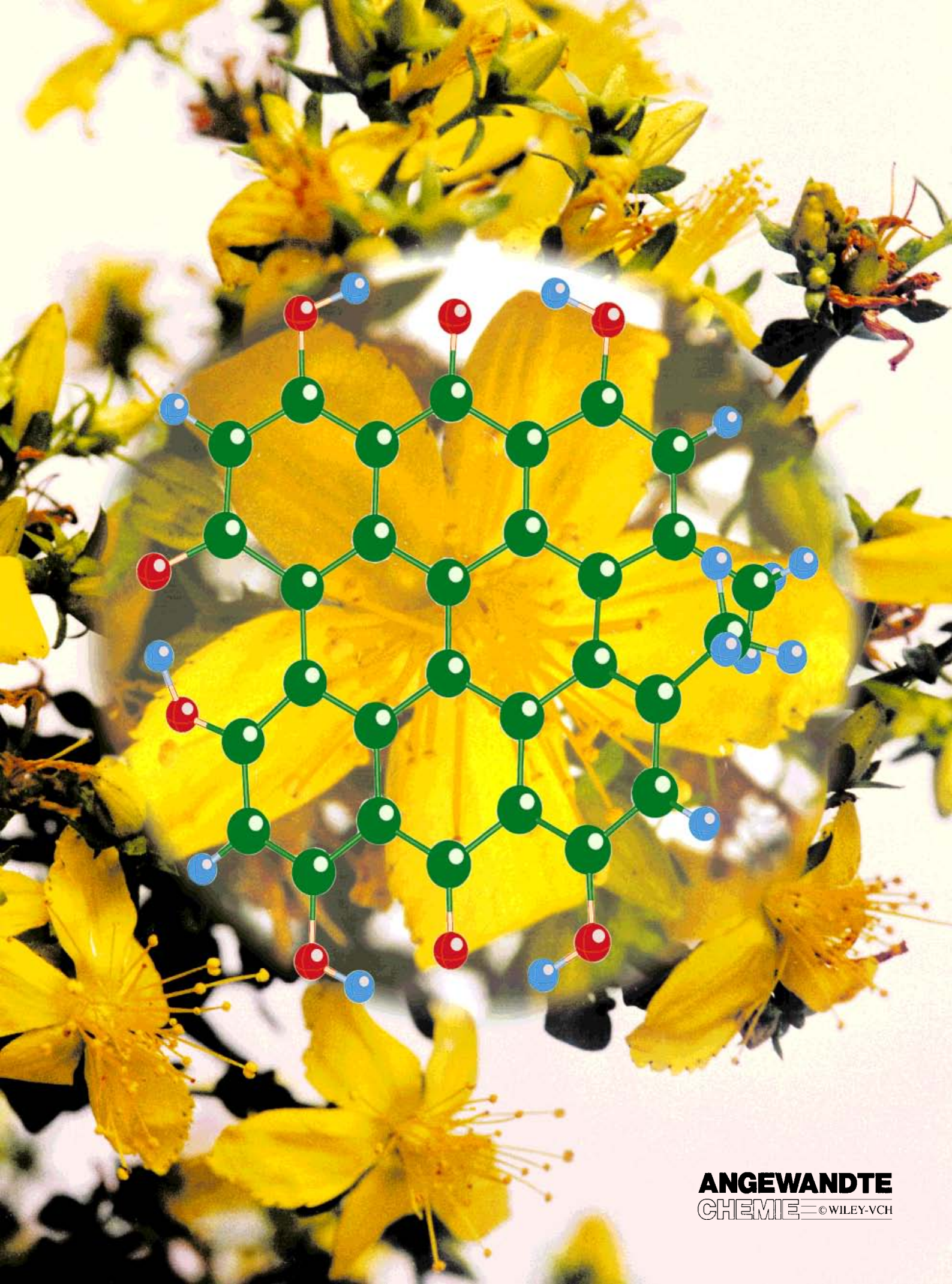




From the Photosensitizer Hypericin to the Photoreceptor Stentorin— The Chemistry of Phenanthroperylene Quinones

Heinz Falk*

The pursuit of the chemistry of natural compounds containing phenanthroperylene quinones substituted with hydroxyl and alkyl groups dates back nearly half a century. It experienced a renaissance within the last decade when it turned out that one of these compounds, hypericin isolated from *St. Johns wort*—a phytotherapeutic drug known since antiquity—does not only exhibit ingestion deterrence, but also antiviral, photodynamically useful, and sedative properties. The fact that this group of phenanthroperylene quinones

also contains the photosensory pigments of protozoa, such as stentorin, has additionally contributed to this new interest in this class of compounds. However, it is also the wealth of chemical and physical problems that spurred the curiosity of scientists to probe the phenanthroperylene quinones in more detail. These problems are mainly a result of the network of tautomerism, dissociation, conformation, and association equilibria and the structural complexity thus caused by them. In keeping with the broad array

of interdisciplinary investigations, which reach from synthetic organic chemistry and spectroscopy to physiology and medicine, this review will focus on a picture of the chemical aspects of this fascinating class of molecules framed by the background of its biological aspects.

Keywords: chirality • natural products • quinones • photochemistry • tautomerism

1. Introduction

- After having ingested a ubiquitous proliferating weed from the genus *Hypericum*, Australian sheep die under a burning sun, bleating miserably.
- A malignant tumor recedes after application of one of the compounds isolated from such plants on irradiation with laser light.
- A protist, such as *Stentor coeruleus*, retreats with vigorous whips of its flagellum after being hit at its photoreceptor system from a sun ray.

The chromophoric system of the phenanthroperylene quinones (**1**; Figure 1) is responsible for all these consequences. Multiple substitution with hydroxyl and partially also with alkyl groups forms the fundamental system of the photosensitizing as well as the photosensory pigments.

As seen from the historical point of view, the roots of our knowledge about these systems date back to antiquity. Even back in those days several species of the genus *Hypericum* were distinguished and used for therapy. The earliest mention

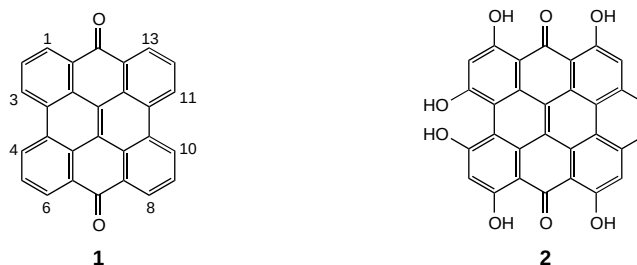


Figure 1. Constitution and numbering of the fundamental phenanthro[1,10,9,8-*opqra*]perylene-7,14-dione (**1**), occasionally named in the literature as “*meso*-naphthodianthrone”, and the constitution of hypericin (**2**).

might date back to Nikandros of Kolophon who lived in the second century B.C. He suggested that “Cheirons root” could be used against intoxication in animals.^[1a] Although *Hypericum* species may be found worldwide, and in particular, in the Mediterranean and in northern Africa, no mention is found that the ancient Egyptians knew or used this plant.^[2] Additional mentions occur in the works of Celsus, Andromachus, and Dioskorides written in the epochs that followed.^[1b] From these Greek and Roman authors through Galenus up to Paracelsus and Matthiolus,^[1c] “*St. Johns wort*” was considered a highly valued drug. Its applications were numerous, and

[*] Prof. Dr. H. Falk
Institut für Chemie der Johannes Kepler Universität
A-4040 Linz (Austria)
Fax: (+43) 732-2468-747
E-mail: hfalk@soft.uni-linz.ac.at

reached from magical applications and its use as an anti-depressant to wound healing.^[1c,d] Since the first pharmacopoeias *Herba hyperici* and later on also *Olio hyperici* it has been valued with respect to applications for various indications.^[1e] Nowadays it is also available in a broad palette of pharmaceutical specialties.^[1a] In most recent times it was also discussed for use against alcohol addiction.

The photodynamic effects of *Hypericum* were linked at the beginning of this century to their causes, which were collectively called the “hypericism” syndrome.^[3] But only in the middle of the century was the compound that caused hypericism, hypericin (**2**; Figure 1), isolated by Brockmann in a pure form from *Hypericum perforatum* and *hirsutum*, and its constitution assigned by total synthesis.^[4] The name hypericin was coined after its first isolation by Cerny in 1911.^[1f] After this “classical period”, investigations of this class of compounds are only scarcely encountered in literature.

The renaissance in the pursuit of phenanthroperylene quinones started about a decade ago when it turned out that **2** had an antiviral effect. Moreover, photoreceptors, such as stentorin and blepharismine, which are responsible for the phototaxis of certain protozoa, display structural analogy with hypericin.^[5a–c] Upon investigating such phenomena of **2** the question of the mechanism of action was raised. It transpired that the fundamental chemistry of the phenanthroperylene quinones was not as simple and clear-cut as could be inferred from a superficial contemplation of the structural formulas of Figure 1. This review will start with an overview of the occurrence and importance of the main members of this class of compounds and then proceed to give mainly a picture of the chemistry of the phenanthroperylene quinones—at the very least to stimulate its further development.

2. Occurrence and Importance of Phenanthroperylene Quinones

2.1. Hypericin and Hypericin Derivatives

Hypericin (**2**) has been identified both in the plant and animal kingdoms. Its widest distribution is found in the more than three hundred species of the genus *Hypericum* of the plant family Guttiferae.^[1a] It is contained in the plants in the form of dark colored granules (Figure 2) and is present in the



Figure 2. *Hypericum perforatum* LINNÉ; bottom left is shown a microscopic view of a dark petal granule (diameter approximately 100 μm) from which a red liquid—its color being due to the hypericinate ion—is extruded upon applying soft pressure.

form of its *bay*-hypericinate, with potassium as the counter-ion.^[6] This fact could be deduced by means of counter-current droplet distribution and contradicted the earlier presumptions that it should occur as a glycoside.^[6a] The content of **2** in dried plant material (< 0.05 %) varies from species to species and is sometimes also found to vary within the same species, being dependent on location and even harvesting time.^[1a] In the first instance, **2** was also assumed to occur in the fungus *Dermocybe austroveneta*.^[7] However, careful isolation in the dark afforded only skyrin (**3**) and protohypericin (**4**; Figure 3), with the latter cyclizing under the influence of light to yield **2**.^[7b] Such intermediates were also observed in *Hypericum*.^[1a] As mentioned above, **2** is used by the plants as an ingestion deterrent, which induces edemas and eventually death of the



Heinz Falk was born in St. Pölten. He studied chemistry at the University of Vienna and completed his PhD in 1966 with Prof. K. Schlögl with a thesis on the configuration of optically active ferrocenes. After a postdoc at the ETH Zürich with Prof. A. Eschenmoser he completed his habilitation at the University of Vienna in 1972 where he worked on stereochemical investigations of chiral metallocenes. From 1975 to 1979 he worked as professor of physical organic chemistry at the University of Vienna and was appointed as full professor of organic chemistry at the Johannes Kepler University Linz in 1979. The research interests in his group focus on synthesis, structure–property relations, and spectroscopic investigations of natural products, such as bile pigments and condensed quinones, relevant in photobiology.

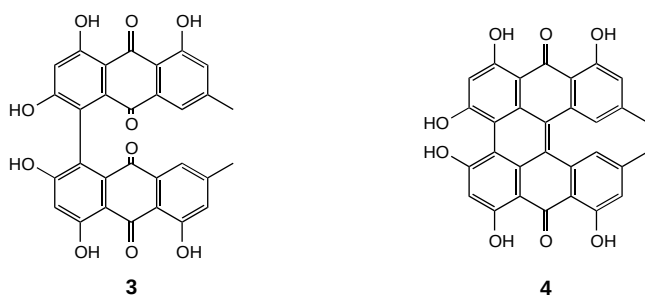


Figure 3. Constitution of skyrin (**3**) and protohypericin (**4**) obtained from the fungus *Dermocybe austroveneta*.

grazing animals under the influence of sunlight (hypericium).^[3] Hypericin (**2**) was also shown to act as an insecticide against the tobacco parasite *Manduca sexta*.^[8] Interestingly enough, several insects, such as *Platynota flavedana*, have developed a strategy that allows them to escape the fatal influence of light. These insects curl up the leaves of *Hypericum* to make them into sunshades.^[8b]

In the animal kingdom **2** was found in the Australian bug *Nipaeococcus aurilanus* MASKELL.^[7a] In this case it is certain that it is genuinely contained in this organism and is not derived from ingested food. The function of **2** in these animals is not known, but it is suspected that it protects the organism against sunlight by contributing to the dark pigmentation of the epidermis!^[7b]

It was clear that the photodynamic activity that **2** displays under the influence of light could be used for therapy. Thus, the light-induced antiviral activity of **2** was recognized and used rather early on.^[9] For example, it turned out that it acted as a virucidal agent against sindbis,^[9b,c,o] cytomegalo,^[9b,c,o] hepatitis B,^[9d] herpes,^[9c,i] equine anemia,^[9j] papilloma,^[9m] and vesicular stomatitis virus.^[9p] This effect can be of interest for the virus-decontamination of transfusion blood and blood derivatives by irradiating them in the presence of **2**.^[10] Hopes that **2** might be an agent for the photodynamic therapy of AIDS, which were spurred on by the in vitro activity against retroviruses, were in vain.^[11] However, the photodynamic therapy of topical cancers has gained an effective weapon in the photosensitizer hypericin (**2**).^[12] Moreover, it was shown that this compound enhances the radiolytic sensitivity of tumor cells,^[12d, 12n] and there are indications that **2** is also effective in the case of T-lymphocyte-mediated diseases, such as multiple sclerosis, myasthenia gravis, rheumatoid arthritis, scleroderma, polymyositis, pemphigus, psoriasis, and transplant rejection.^[13] Results for the molecular basis of all these effects are available from various studies.^[14] Accordingly, for example, it was found that enzymes such as reverse transcriptase,^[11a] monoaminoxidase,^[14a] succinoxidase,^[14c] and several protein kinases were inhibited.^[14b,e,i] The photodynamic action of **2** could either be attributed to the sensitized formation of singlet oxygen or to an acidification by light-induced deprotonation of the pigment.^[14n,o] Interestingly, the electron transfer in the photosystem II of cyanobacteria is inhibited by **2**.^[14k] The hypericium syndrome might be mainly a consequence of photohemolysis.^[14p] For **2** to be used as a drug it was of utmost importance that no genotoxicity could be found.^[15] Recently, several studies on the use of *Hypericum* as

an antidepressant were published.^[16] It is not clear at the moment if, of the several compounds present in this plant, **2** is the active principle. However, since it was shown that **2** interacts with the serotonin and muscarin receptors this might be a good guess.^[16b]

As well as **2**, the ω -hydroxylated hypericin derivative pseudohypericin (**5**; Figure 4) also predominates in several *Hypericum* species.^[17] This pigment also seems to exhibit physiological properties comparable to those of **2**.^[17d]

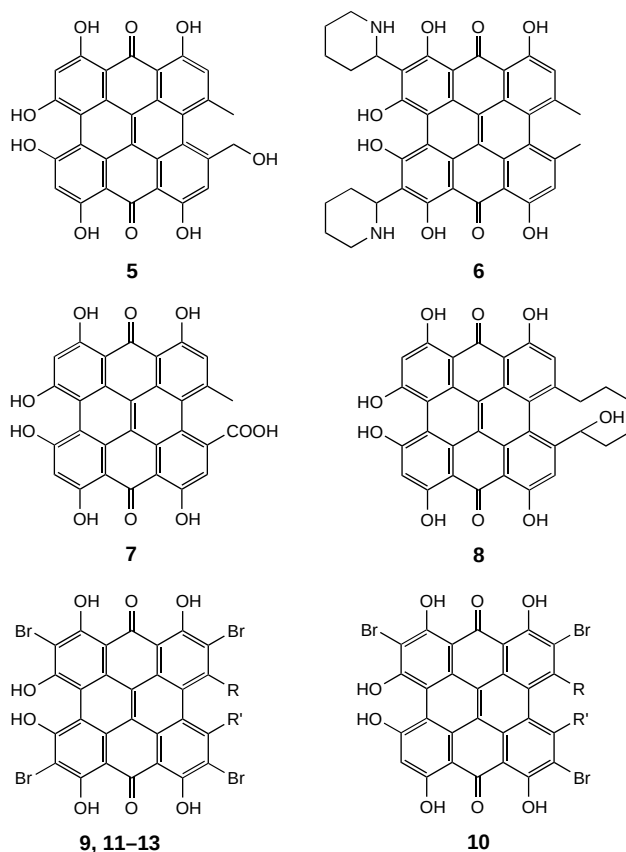
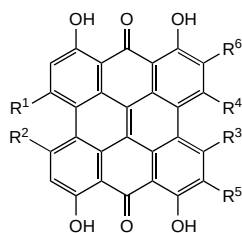


Figure 4. Constitution of pseudohypericin (**5**), fagopyrin (**6**), hypericinic acid (**7**), Lamprometra pigment (**8**), the gymnochromes A–D (**9**: R = (S)-CH(OH)CH₃, R' = (R)-CH(OH)(CH₂)₂CH₃; **10**: R = (S)-CH(OH)CH₃, R' = (R)-CH(OH)(CH₂)₂CH₃ or R' = (S)-CH(OH)CH₃, R = (R)-CH(OH)(CH₂)₂CH₃; **11**: R = (S)-CH(OH)CH₃, R' = (S)-CH(OSO₃H)CH₃; **12**: R = R' = (R)-CH(OSO₃H)(CH₂)₂CH₃), and isogymnochrome D (**13**), the atropisomer of **12**.

In 1943 fagopyrin (**6**; Figure 4) was isolated from the blossoms of the red flowering variety of buckwheat, *Fagopyrum esculentum*, a plant that has been known since 1833 to also induce a light-dependent disease in grazing animals (called fagopyrism).^[18a,b] Its constitution was deduced only in 1979.^[18c] Thereby, it has been one of the longest known natural products of unknown constitution.

Hypericinic acid (**7**; Figure 4) is derived by oxidation of one of the methyl groups of hypericin (**2**). It is found as a by-pigment of **2** in the flour beetle *Nipaeococcus aurilanus* mentioned above.^[7a] The molecular skeleton of hypericin is also found in pigments that occur in sea lilies. Thus, **8** (Figure 4) was isolated from *Lamprometra palmata* gyges

BELL and several other related crinoids.^[19b] In addition, the gymnochromes **9–13** (Figure 4), a family of brominated and ω -substituted hypericin derivatives, were found in the deep sea crinoid *Gymnocrinus richeri*.^[20a,b] Interestingly, other halogen derivatives, such as 2,5-dichloro- and 2,5,9,12-tetrachloro-hypericin, could be isolated from lichens (for example, *Nephroma laevigatum*).^[20c,d] All these compounds, as well as their precursors of biogenesis, seem to function mainly as ingestion deterrents.^[19a]



14–18

Figure 5. Constitution of stentorin (**14**: $R^1 = R^2 = R^3 = R^4 = OH$, $R^5 = R^6 = CH(CH_3)_2$) and of fringelite D (**15**: $R^1 = R^2 = R^3 = R^4 = OH$, $R^5 = R^6 = H$), E (**16**: $R^1 = R^2 = R^4 = OH$, $R^3 = R^5 = R^6 = H$), F (**17**: $R^1 = R^2 = OH$, $R^3 = R^4 = R^5 = R^6 = H$), and H (**18**: $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$).

2.2. Stentorin and Fringelites

The photoreceptor pigment stentorin (**14**; Figure 5), which is responsible for the actions of the flagellated protozoon *Stentor coeruleus* (Figure 6), was discovered in the last century (1873) when searching for the pigment responsible for the “green oysters”, which were then en vogue.^[21a]

The constitution **14** of this pigment, formerly called marennin according to the oysters source, which is attached to a protein was isolated by Song in 1993, and was later on proven by synthesis.^[21b, 23] Despite intensive efforts the molecular basis of the photosensory signal is still an open question.^[22] A photo-induced proton or electron transfer might be regarded as the primary process.^[22d, 22g]

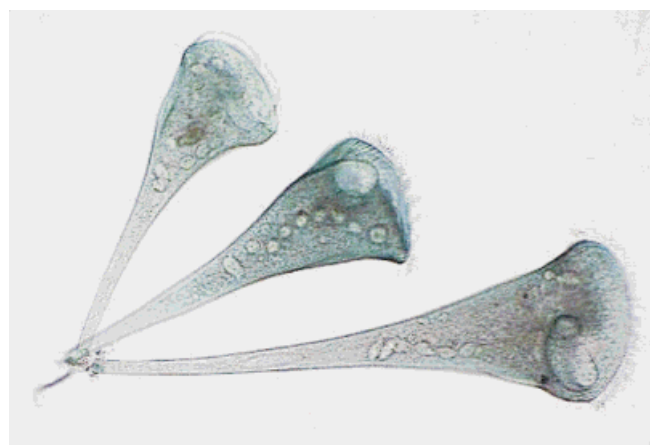


Figure 6. *Stentor coeruleus* (length of the organism approximately 200–400 μ m; picture courtesy of D. C. Wood).

An echo of the chromophoric system of **14** from prehistoric times still reverberates in the fringelites (**15–19**; Figure 5). These pigments were discovered by Blumer in the Jurassic sea lily *Millericrinus munsterianus* ORBIGNY (Figure 7) found in Fringeli in the Swiss Jura hills.^[24] The pigments are, as shown by a screening of fossils, widely distributed with respect to their ages and organisms.^[25] The fringelites, and in particular, fringelite D (**15**), have been found as early as the Devonian

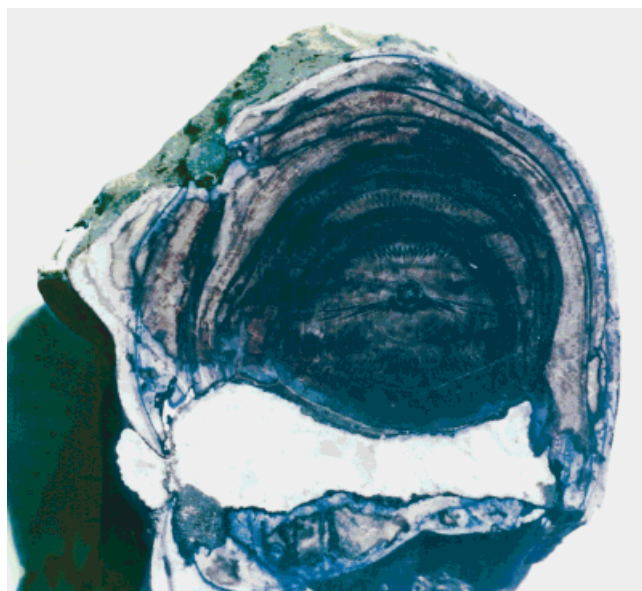


Figure 7. Section through the roots (diameter approximately 5 cm) of the fossilized sea lily *Millericrinus munsterianus* ORBIGNY from the Upper Jurassic of Liesberg/Switzerland.

age in animal as well as plant fossil specimens—a surprising manifestation of the chemical stability of these organic pigments.^[25d] Clearly, they are stabilized against washing out from the fossil material through the formation of their calcium salts and transition metal chelates.^[25c] It is still questionable what the physiological significance of the fringelites or their precursors is. However, their function as ingestion deterrents might not be too far fetched.

2.3. Blepharismins

Most of the almost fifty species of the flagellated protozoan genus *Blepharisma* (Figure 8) contain a pigment, which depending on light intensity may be present as a reddish or

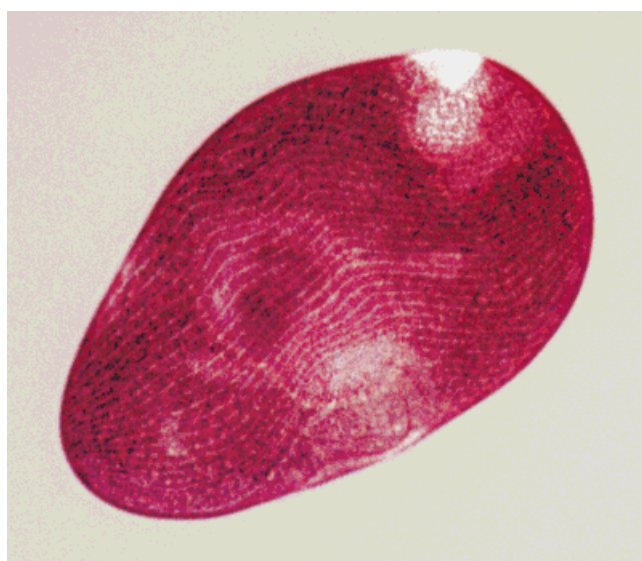


Figure 8. *Blepharisma japonica* (length of the organism approximately 300–400 μ m; picture courtesy of F. Lenci).

blue colored form. The pigment is contained in small membrane-coated granules and is bound there to a protein.^[26] This pigment, called blepharismismin (formerly zoopurpurin), has been known since 1905.^[26a] Analysis with respect to the chromophore of this pigment system revealed that it consisted of at least five constitutionally related, ring-homologous phenanthroperylene quinones. The constitution of the blepharismismin 1–5 (**19**–**23**; Figure 9) was deduced only recently

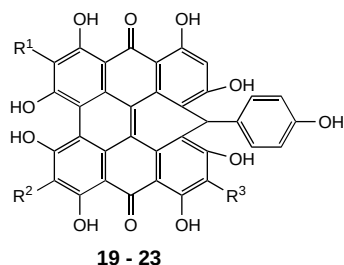


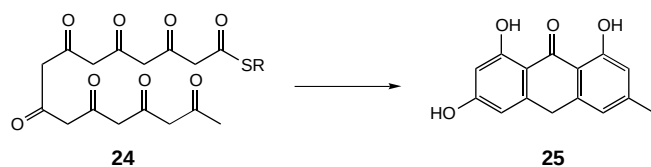
Figure 9. Constitution of blepharismismin 1 (**19**: $R^1 = R^2 = C_2H_5$, $R^3 = H$), 2 (**20**: $R^1 = C_2H_5$, $R^2 = CH(CH_3)_2$, $R^3 = H$), 3 (**21**: $R^1 = R^2 = CH(CH_3)_2$, $R^3 = H$), 4 (**22**: $R^1 = C_2H_5$, $R^2 = CH(CH_3)_2$ or $R^1 = CH(CH_3)_2$, $R^2 = C_2H_5$, $R^3 = CH_3$), and 5 (**23**: $R^1 = R^2 = CH(CH_3)_2$, $R^3 = C_2H_5$); for the systematic nomenclature of the ring system see ref. [27c].

by two research groups; **21** constitutes the main pigment.^[27] The constitution of “oxyblepharismismin” originating from a rearrangement of the blepharismismin was recently assigned. It comprises the 4-hydroxybenzaldehyde-*bay*-acetal of **14**.^[28n]

The photobiology of *Blepharisma* has been investigated thoroughly.^[26b,c, 28] The photosensory signal for the “step-up” photophobic response of the pigment system could originate in a similar manner to the one of stentorin (**14**), with the primary process being a photoinduced proton ejection or an electron transfer reaction.^[28g,k]

3. Biogenesis and Synthesis

Biogenesis of the phenanthroperylene quinones, which was mostly studied for hypericin (**2**), may be viewed as two consecutive reaction cascades. The first one consists of the biosynthesis of the two anthraquinone “halves” of the phenanthroperylene quinone (Scheme 1). For this purpose,

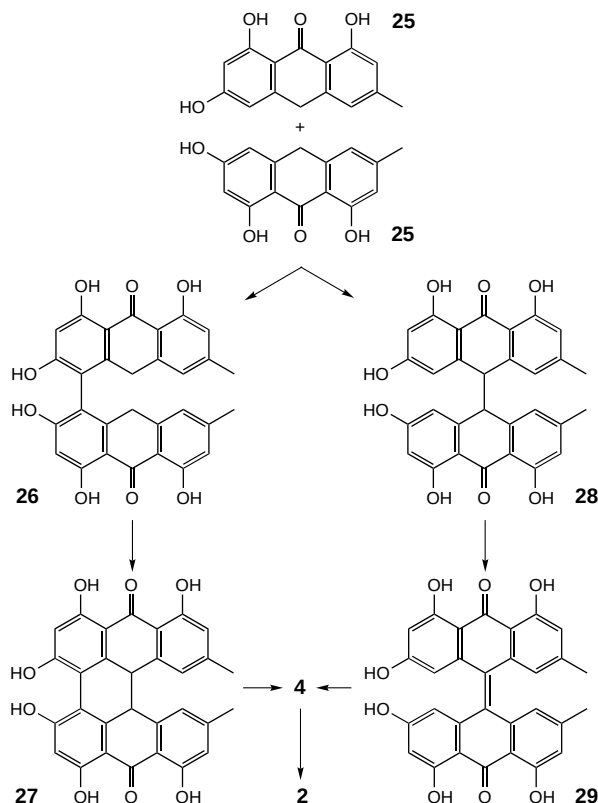


Scheme 1. Biogenesis of emodin anthrone (**25**).

the well understood acetate malonate pathway (1 acetyl coenzyme-A + 7 malonyl coenzyme-A) that occurs in many organisms of the animal and plant kingdoms is used. It is well known with respect to its enzyme systems, and in this case leads to the octaketide **24**.^[29] Multiple aldol cyclization, which was also impressively demonstrated to proceed in chemical synthesis, then results in emodin anthrone (**25**).^[29c-e] This

compound could also be detected in plant material, which documented its role as the precursor of the second reaction cascade.^[30]

In principle, the oxidative dimerization of **25** that forms the second cascade can proceed by two pathways (Scheme 2). In contrast to the well established biogenesis of the precursor,



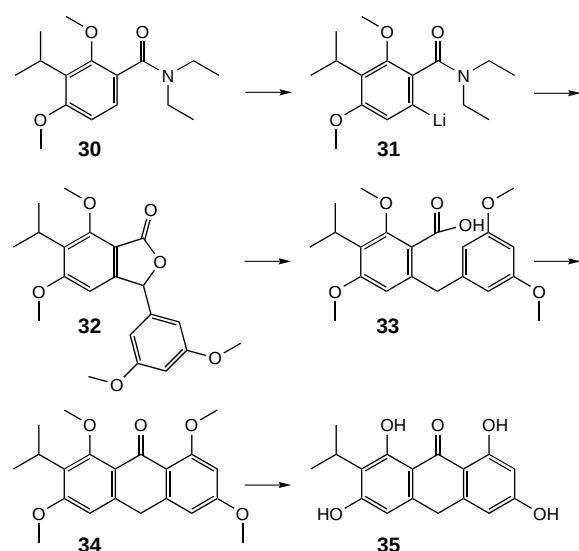
Scheme 2. The two pathways of the biosynthetic dimerization of emodin anthrone (**25**) that yield hypericin (**2**).

the formation of the phenanthroperylene quinone is only speculated.^[4a, 4c, 30] The first possible way starts with a phenol coupling to yield penicillipsin (**26**). This then undergoes a second oxidative coupling to provide the diastereomers of **27**, which is followed by dehydrogenation to give protohypericin (**4**). Photooxidation of **4** eventually leads to hypericin (**2**). However, as shown by the gymnochromes (**9**–**13**; Figure 4),^[20] which originate in the darkness of the oceans, the formation of the phenanthroperylene skeleton can also take place without light. For the second possibility, dimerization starts from the central methylene group of the anthrone **25** and yields the diastereomers of **28**. These undergo dehydrogenation to afford **29**, which is then cyclized by oxidative phenol coupling to provide **4**. Of all these intermediates only **26** and **4** could be isolated from the fungus *Penicillium brunneum*,^[31] and in particular, from the plant *Hypericum*.^[30] As an alternative, skyrin (**3**), identified in *Dermocybe austroveneta*,^[7b] constitutes a possible hypericin precursor molecule. Currently, these rather scarce facts and the chemical (in vitro) syntheses form the basis of hypotheses on the biogenesis of phenanthroperylene quinones from the anthracenoid octaketide precursor. Moreover, the question as to whether these

reactions are catalyzed enzymatically or not is still unanswered. The first results and hypotheses on the biogenesis of the *Stentor* and *Blepharisma* pigments were published recently.^[28n]

The chemical synthesis of the phenanthroperylene quinones follows the pattern of biogenesis. A rich arsenal of methods is available to prepare the anthraquinone or anthrone precursors.^[32] The best strategies for the synthesis of anthracene derivatives substituted in an arbitrary way are based on a Friedel–Crafts cyclization of the correspondingly substituted diphenylmethane carboxylic acid and on a Diels–Alder cycloaddition. This is demonstrated by the example of the two emodin anthrones **35** and **41**, which served as precursors for the synthesis of stentorin (**14**).

To prepare **35** (Scheme 3) the benzamide **30** is regioselectively metalated to provide **31**.^[23c] This method was developed by Snieckus et al. and has also been employed successfully in

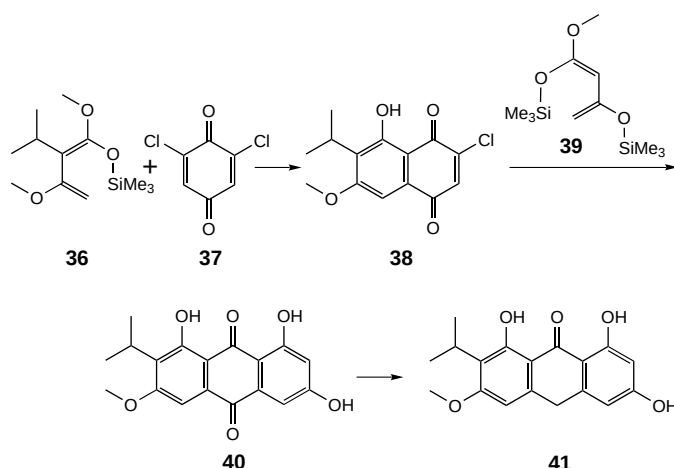


Scheme 3. Synthesis of **35**.

the synthesis of a variety of natural compounds.^[33] The reaction of **31** with 3,5-dimethoxybenzaldehyde yields after work-up the lactone **32**, which is hydrogenated to **33**. This acid is then cyclized by means of a Friedel–Crafts reaction to give **34**. Upon its demethylation the desired anthrone **35** is produced.

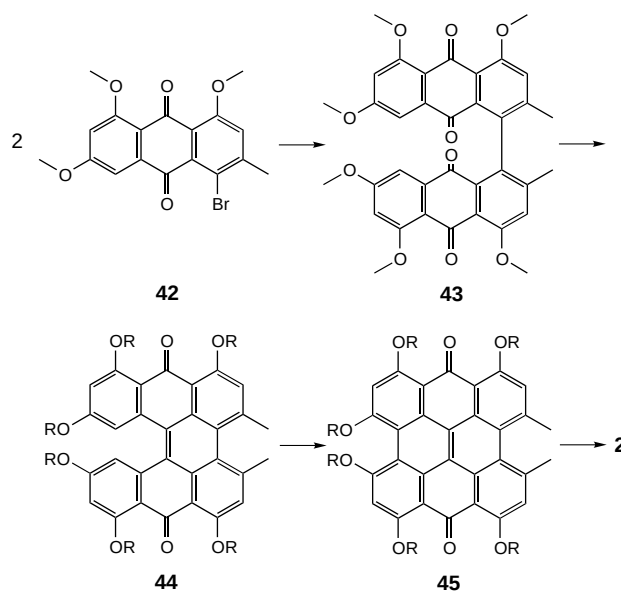
The Diels–Alder pathway leading to **41** (Scheme 4) makes use of the doubly activated ene component of quinone **37**. This is cyclized with the silyl-diene component **36** to give **38** and then this is cyclized with the disilyl derivative **39** to yield the anthraquinone **40**.^[23a,b,d] The regioselective reduction of **40** with Sn/HCl finally provides the anthrone **41**.

Emodin anthrone (**25**), the most favored precursor for the preparation of **2**,^[34a] is obtained from the reduction of emodin. This can be easily isolated from the bark of the breaking buckthorn (*Cortex frangulae*).^[34b] However, the very elegant synthesis sequence corresponding to the biomimetic polyketide formation (Scheme 1)^[29c,d] did not reach importance in the synthesis of anthrones, such as **25**, **35**, and **41**, mainly because of the demanding protecting group strategy needed.



Scheme 4. Synthesis of **41**.

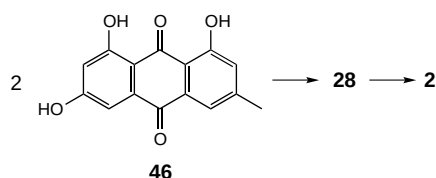
The dimerization of anthraquinone or anthrone precursors to phenanthroperylene quinones may be achieved in several ways. The classical route that led to the first chemical synthesis of hypericin by Brockmann^[4d] is based on the regioselective Ullmann coupling of the bromoanthraquinone **42** to the bianthaquinone **43** (Scheme 5). Its reductive



Scheme 5. Synthesis of hypericin (**2**) by Ullmann dimerization of the bromoanthraquinone **42**. **44**, **45**: $5 \times R = \text{CH}_3$, $1 \times R = \text{H}$.

cyclization to **44** (copper powder in acetic acid/HCl) proceeds smoothly. However, one of the methoxy groups is cleaved in this reaction. Oxidative photocyclization to **45** and demethylation eventually leads to hypericin (**2**). The yields are in most steps satisfactory, however, the disadvantage of this reaction sequence is the demanding and low yielding synthesis of the starting material (**42**). Nevertheless, this methodology was successfully adapted to the synthesis of stentorin (**14**).^[23b]

The dimerization of the anthraquinone precursor emodin (**46**; Scheme 6) under alkaline conditions in the presence of hydroquinone as the reducing agent and under nitrogen and

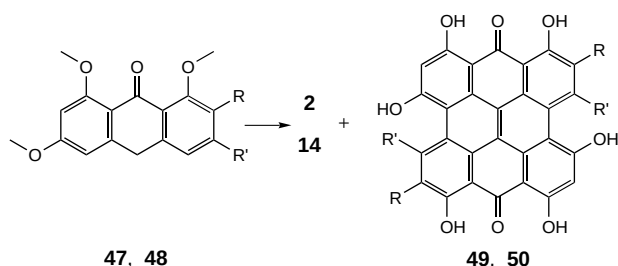


Scheme 6. Synthesis of hypericin (**2**) by dimerization of the anthraquinone **46**.

with the exclusion of light proceeds via the dibenzoperylene derivative **4** (Scheme 2). Photochemical cyclization of the latter then leads to **2**.^[35] This procedure is of principal interest for hypotheses about its biogenesis, however, the reaction conditions (20 days in a sealed tube at 100 °C) and its yield (<30 %) render this method rather unattractive for preparative purposes.

Therefore, procedures relying on the dimerization of anthrone derivatives were used rather early on. Thus, in 1955 Brockmann succeeded in fusing two molecules of emodin anthrone (**25**) through a biomimetic sequence via **28**, **29**, and **4** into **2** (Scheme 2).^[31] This synthesis strategy was improved recently with respect to the reagents (hexacyanoferrate(III),^[36a] pyridine-*N*-oxide/piperidine/iron(II)-sulfate^[36b]) and conditions used. Moreover, several intermediates, such as the diastereomers of **28**, and the bianthrone **29** could be characterized.^[36a] These improvements led to an universally applicable strategy that allowed for the synthesis of a series of hypericin derivatives,^[37] of fringelite D (**15**),^[38] and stentorin (**14**).^[23a,c,d]

The regioselectivity of the primary cyclization of **28** (or **29**) in the case of the unsymmetrically substituted anthrone precursors is caused by the difference in reactivity between the two benzene rings flanking the central moiety.^[36c] Thus, the difference in electronic activation between the methyl and hydroxyl groups in **25** is sufficient to steer the reaction regioselectively to produce **2**. However, starting from the emodin anthrone trimethyl ether (**47**), dimerization after demethylation affords the mixture of hypericin (**2**) and isohypericin (**49**; Scheme 7).^[39] Besides a selective synthesis for the production of isostentorin (**50**),^[23a,d] this route was also used for the synthesis of **50** starting from **48**.^[23c]

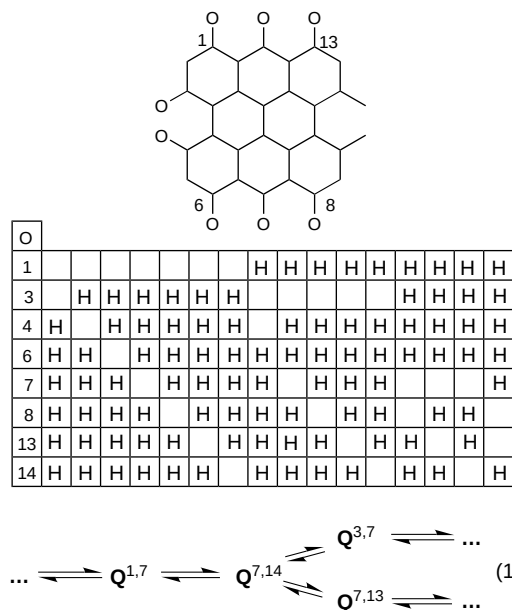


Scheme 7. Synthesis of hypericin (**2**), isohypericin (**49** R = H, R' = CH₃), stentorin (**14**), and isostentorin (**50** R = CH(CH₃)₂, R' = OH) by non-regioselective dimerization of the corresponding trimethoxyanthrone **47** (R = H, R' = CH₃) and **48** (R = CH(CH₃)₂, R' = OH).

4. Structural Complexity Resulting from the Intertwining of Equilibria

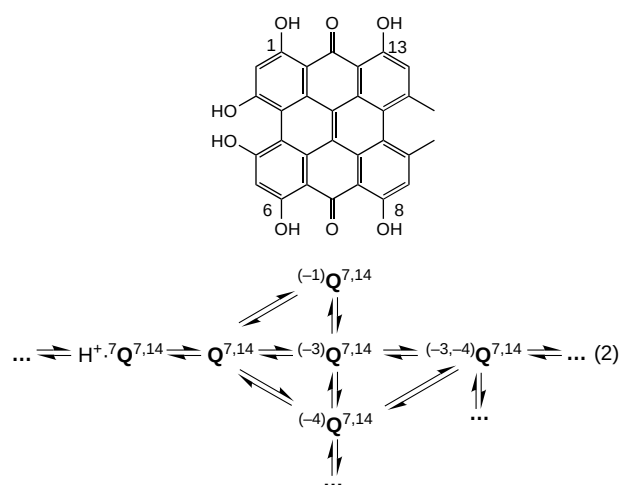
Investigation of the structural aspects of multiple hydroxyl-substituted phenanthroperylene quinones shows that these

compounds are more complicated than their simple structural formulas suggest, and are involved in four correlated equilibria of tautomerism (Scheme 8, equilibrium (1)), dissocia-

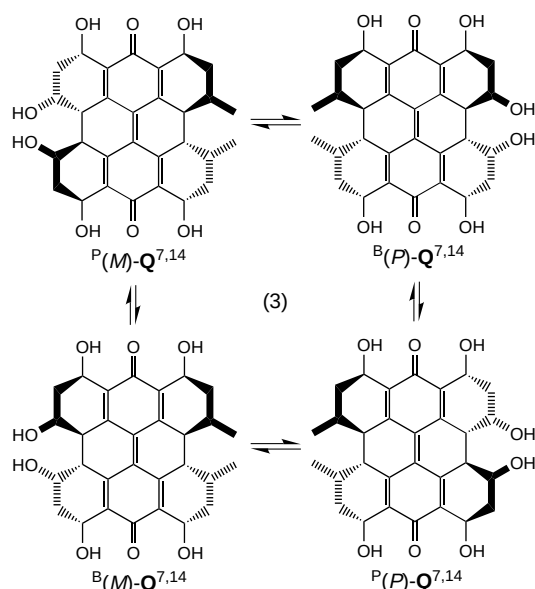


Scheme 8. Partition diagram for the distribution of six protons upon the eight oxygen atoms of hypericin (**2**) and the resulting partial tautomeric equilibrium (1); within this scheme, for example, $Q^{7,14}$ denotes the tautomer with the carbonyl groups in positions 7 and 14—this one corresponds to the last column of the partition diagram.

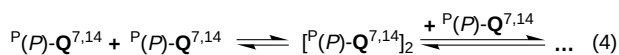
tion (Scheme 9, equilibrium (2)), torsional isomerism (Scheme 10, equilibrium (3)), and homoassociation (Scheme 11, equilibrium (4)), which leads to a high degree of structural complexity. Upon joining these four structural aspects, the example of **2** shows that there are ten tautomers that might in principle all be present as four species (singly protonated, neutral, and the respective energetically most favored single and double deprotonated forms). This adds up



Scheme 9. Protonation and deprotonation equilibria (2) of the tautomer $Q^{7,14}$ of **2**; herein, for example, $(-3)Q^{7,14}$ denotes the tautomer $Q^{7,14}$, which is deprotonated in position 3, and $H^{+} \cdot Q^{7,14}$ then denotes the tautomer $Q^{7,14}$ protonated at the carbonyl group in position 7.



Scheme 10. Conformation equilibrium (3) of the undissociated tautomer $Q^{7,14}$ of **2**; herein, for example, $P(M)-Q^{7,14}$ denotes the propeller conformation of the tautomer $Q^{7,14}$ of configuration (*M*).



Scheme 11. Homoassociation equilibrium (4) of the propeller conformer of configuration (*P*) of tautomer $Q^{7,14}$ of **2**, $P(M)-Q^{7,14}$.

to forty such species. Since every one of these species may occur as four torsional stereoisomers the total number of species reaches 160. Eventually, these species may be involved in oligomerization equilibria, for example, in the form of H- or J-aggregates,^[40] which renders the number of possible species more or less innumerable. The following sections will focus upon experimental as well as semiempirical or quantum chemical results that clarify the important parts or knots in this complex equilibrium system under certain conditions.

4.1. Tautomerism

The ten canonically structured tautomers of hypericin (**2**; see Scheme 8) are involved in a one proton interconversion network, in which one proton at a time is transferred from a hydroxyl oxygen to a carbonyl oxygen atom. This high complexity of the system has so far more or less prohibited an experimental approach. However, as shown in Figure 10, it could be analyzed with respect to its thermodynamic aspects by means of semiempirical molecular modeling. From such calculations, regardless of the method (HMO, MM2 + force field,^[41a] AM1,^[41b,e] ab initio with a 6-31G basis set^[41d,c]), it is found that the tautomer $Q^{7,14}$ (in the gaseous state) is at least 40 kJ mol⁻¹ more stable than all the others. This is a consequence of the stability of its π system; the highest stability as given by the aromaticity index can even be derived by simple graphical theoretical reasoning.^[42] Moreover, the highest number of possible Kekulé structures for all the

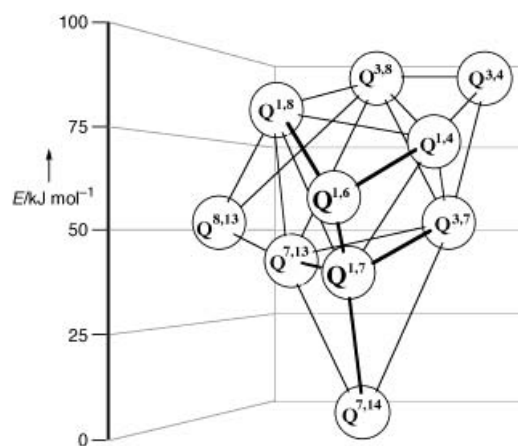


Figure 10. One proton interconversion net and relative binding enthalpies of the tautomers of hypericin (**2**) as deduced from semiempirical (AM1) calculations (for the meaning of designations $Q^{x,y}$ see the legend of Scheme 8).

tautomers of **2** (or of the fundamental system **1**) are derived for the $Q^{7,14}$ tautomer.^[41a,c] The corresponding analyses were also carried out for the ten tautomers of isohypericin (**49**), the sixteen of stentorin (**14**), the fifteen of isostentorin (**50**), and the nine of fringelite D (**15**), and in all cases the pronounced stabilization of the $Q^{7,14}$ tautomer was found.^[43] The activation barrier for the intramolecular transfer of a proton within the *peri* region ($Q^{7,14} \rightarrow Q^{1,7}$) was estimated by means of ab initio calculations on **2** to amount to about 41 kJ mol⁻¹, and for the reverse process approximately 7.5 kJ mol⁻¹.^[41d]

However, experimental evidence for the presence of defined tautomers under certain conditions is scarce. Moreover, the tautomers are strongly related to the state of dissociation, and thus they will be discussed together with the latter phenomenon. (Section 4.5.).

4.2. Dissociation (Protonation and Deprotonation in Ground and Excited States)

With regard to the protonation of hydroxyphenanthroperylene quinones, such as hypericin (**2**; Figure 18), both the hydroxyl and carbonyl groups have in principle to be considered. The latter ones are usually more basic than the first ones, and their protonation leads to a characteristic change in the chromophore (see Section 5.1.). Therefore, one to two protonation steps can be anticipated for such compounds and for aromatic ketones these steps should be found in the region of $pK_a < -5$. In fact, about 70 % aqueous sulfuric acid has to be used in the spectrophotometric titration of the unsubstituted quinones **1** to produce the monoprotonated form, **1-H**⁺. This result corresponds to a pK_a value of -6 , and for the second carbonyl group a $pK_a = -7$ is found.^[44b] The monoprotonation pK_a values are found within the same pK_a region for **2**,^[44a] **14**,^[23c] and **15**.^[38a] The application of a Förster cycle reveals that the basicity of the carbonyl group in the excited state is somewhat higher. Thus, for example, the pK_a^* of **2** is determined as -3.2 .^[44a]

Deprotonation of hydroxyphenanthroperylene quinones is possible in principle at the phenolic hydroxyl groups in the *peri* and *bay* positions. However, these groups were found to display dramatically different acidities. Whereas a *bay*-hydroxyl group with a pK_a value of 1.8 for **2** approximately matches the acidity of picric acid, the *peri*-hydroxyl groups are deprotonated only within or above the region of common phenols, whereby one ($pK_a \approx 9$) to two ($pK_a \approx 12$) deprotonation steps may be observed. This was shown to be the case for phenols in aqueous solvents and water by means of spectrophotometric titrations,^[23c, 38a, 44a, 44c] NMR spectroscopy,^[6, 23c, 41a] electrophoresis,^[44c] electrospray mass spectrometry,^[44d] X-ray structural analysis,^[41a, 45a] and comparison with model compounds partially methylated at the hydroxylic groups.^[44e] Figure 11 summarizes the results of these studies

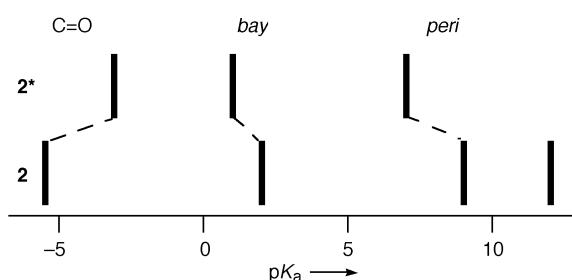


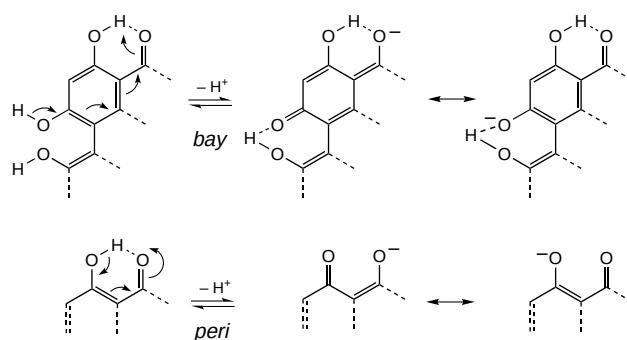
Figure 11. Protonation ($C=O$) and deprotonation steps (*bay* and *peri* region) of hypericin in the ground state (**2**) and excited state (**2***).

for the example of **2**. It should be stressed here that numerous data published for **2** actually refer to the hypericin-3-ate ion since *bay*-hydroxy derivatives are completely dissociated in polar solvents at low concentrations.^[38a, 44c]

The reason for these different acidities of the hydroxyphenanthroperylene quinones in the two regions can be rationalized in the case of their *bay*-ionization by formation of a vinylogous carboxylic acid.^[38a, 44c] The resulting phenolate ion ($^{-3}$)**2** produced in this way is stabilized by a very strong, yet unsymmetrical hydrogen bond.^[37b, 45] This was deduced from the unsymmetrical distribution of $C-C$ bonding distances,^[45a] polarization spectroscopy,^[37b] hole-burning experiments,^[45b] isotope effects,^[45c] and ab initio calculations.^[45c] Proton transfer that leads to the formation of the identical tautomeric *bay*-phenolate ($^{-4}$)**2** is extremely fast in solution. Moreover, as derived from X-ray structural analyses, NMR investigations, and intercepting reactions, the *bay*-hypericinate ion is present in the crystalline state as well as in solution as its $Q^{7,14}$ tautomer.^[6, 23c, 41a, 45a,e] In contrast to this, a phenolate ion in the *peri*-region is destabilized by interaction of the lone pairs on the carbonyl oxygen atoms (Scheme 12). The application of a Förster cycle to the excited state yields an acidification of the *bay*- and *peri*-hydroxylic groups by 1 to 4 pK_a units (Figure 11).^[23c, 38a, 44a]

4.3. Torsional Isomerism

Substitution of the *bay* region of phenanthroperylene quinones with hydroxyl, and in particular with alkyl groups,



Scheme 12. Hydroxyphenanthroperylene quinone: vinylogous carboxylic acid and stabilization upon deprotonation of the *bay* region, and destabilization upon deprotonation of the *peri* region.

as found in the natural products **2–23**, leads to a significant dihedral deformation of the unsubstituted parent compound (**1**), which itself displays an only slightly distorted molecular skeleton. Conformational analysis by means of force field models is shown for hypericin (**2**) in Figure 12.^[37d, 41a, 43a, 43b] Besides two energetically similar ($\pm 5 \text{ kJ mol}^{-1}$), but distinct

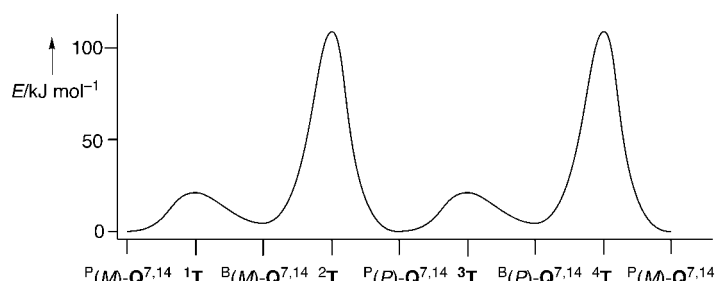


Figure 12. Section through the energy hypersurface of hypericin (**2**); for the designation of the various species see Scheme 10 and Figure 13.

minima pairs, $^P(M)/^P(P)$ and $^B(M)/^B(P)$, two quite different (≈ 30 , $\approx 100 \text{ kJ mol}^{-1}$) extremal pairs, $^1T/^3T$ and $^2T/^4T$ are obtained. The first pair correspond to the propeller and butterfly conformers shown in Figure 10, while the latter ones are highly strained transition conformations between the energy valleys (Figure 13). The principal situation as given in Figure 12 is only slightly modulated by dissociation, tautomerism, and substitution at the aromatic rings and substituents. This is supported by experimental results.

Accordingly, the dihedral propeller symmetry of the skeleton is clearly revealed in the X-ray structure of two crystal forms of pyridinium hypericin-3-ate.^[41a, 45a] The dihedral angles at the hydroxyl and the methyl *bay* regions, $\theta_{3, 3a, 3b, 4}$ and $\theta_{10, 10a, 10b, 11}$, amount to 19.6 and 31.9° , respectively.^[45a] The results of semiempirical,^[41a,b] and in particular from ab initio calculations,^[41c,d] are virtually superimposable with the experimental structural data. Thereby, such calculations expand and extrapolate our knowledge beyond that currently accessible from experimental investigations (for example, despite numerous efforts crystals of hypericin itself that are suitable for X-ray structure determination have not yet been obtained). The three orthogonal images of the hypericin-3-ate ion shown in Figure 14 illustrate the degree of distortion of the phenanthroperylene quinone skeleton.

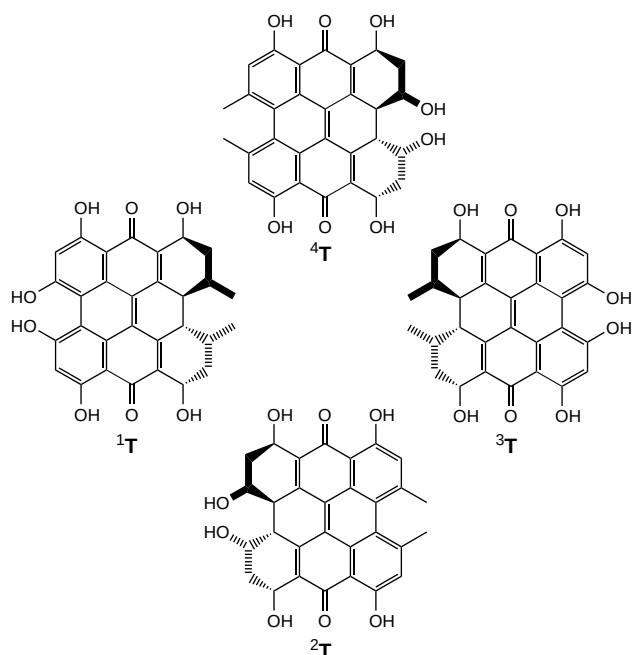


Figure 13. Transition conformations 1^{T} – 4^{T} in the conformational cycle of **2**.

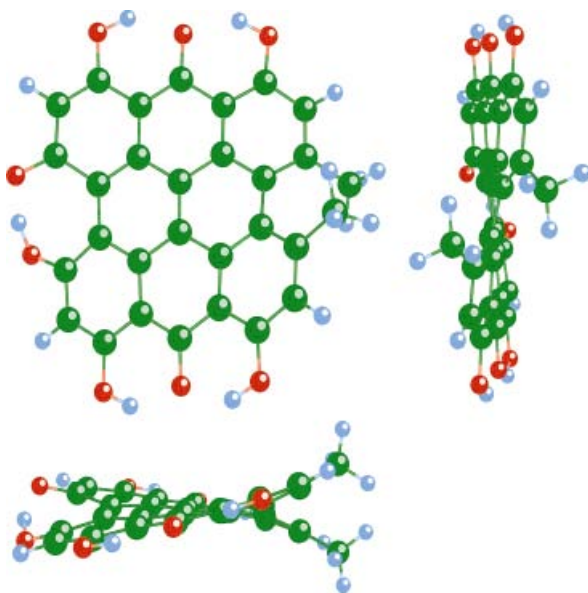


Figure 14. Ball and stick views^[46] of the hypericin-3-ate (results from an ab initio calculation; 6-31G basis set).^[45c]

With respect to the energetic situation of *bay*-substituted phenanthroperylene quinones an estimate of a lower limit of the enantiomerization barrier (2^{T} in Figure 12) of 80 kJ mol^{-1} was determined from the temperature dependent ^1H NMR spectrum of pseudohypericin (**5**).^[41d] Eventually, the synthesis of the two hypericin derivatives **51** and **52** (Figure 15) bearing enantiomerically pure (*R*)-menthyl residues in one or both side chains, respectively, allowed for more significant results to be obtained.^[37d] Measurements of the diastereomerization kinetics of these two thermally easily equilibrating diastereomer pairs at various temperatures afforded Arrhenius activation energies for the inversion of the propeller config-

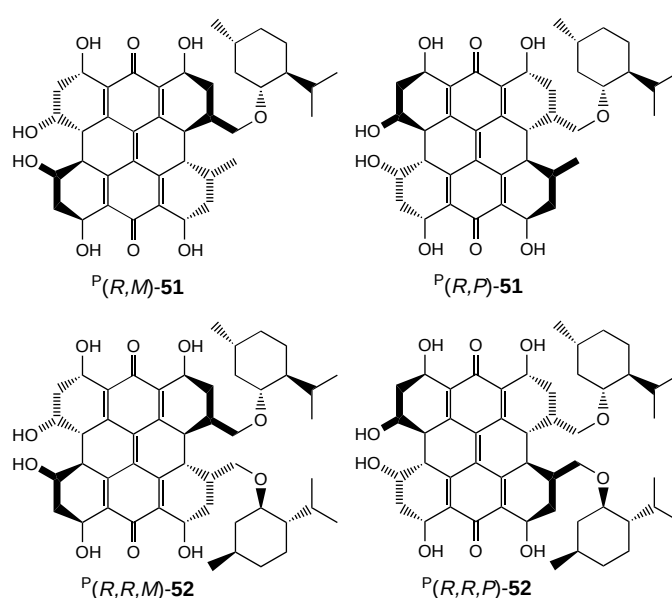


Figure 15. The respective diastereomeric (*R*)-menthylhypericin derivatives **51** and **52**.

urations of 83 ± 3 and $89 \pm 3 \text{ kJ mol}^{-1}$. As is clear from the demanding space requirements of the menthyl moieties of **51** and **52** on the one hand, and the concomitant small difference of their activation barriers on the other hand, the thus derived height of the activation barrier represents the intrinsic barrier of *bay*-alkyl-substituted phenanthroperylene quinones. Moreover, this height is in good agreement with the results of semiempirical calculations, thereby also strengthening their respective results.^[37d, 41] The very strong chiroptical effects observed for these derivatives (see Section 6) provide further evidence of the chromophore helicity and even corroborates its propeller conformation.

4.4. Homoassociation

Besides their dissociation to their *bay*-phenolate ions (see Section 4.3.), hypericin (**2**) and its analogues are monomolecularly dissolved in polar organic solvents, such as dimethylsulfoxide or alcohols. This is proven by compliance with the Beer–Lambert law and results obtained from vapor pressure osmometry.^[47a] Upon addition of water to such solutions a dramatic change in their absorption and emission properties,^[47a] as well as their photodynamic behavior is observed.^[47b] This is a result of the formation of dimers at low concentrations;^[47b] at higher concentrations H-aggregates are formed.^[40, 47a]

By applying the exciton theory to these dimers an arrangement with parallel ring planes and orthogonal dipole axes is derived.^[47b] From measurements of nuclear Overhauser effects (NOE) for strategic ^1H NMR signals and of spin-lattice relaxation times H-aggregates were identified that consisted of at least four molecules with their C_2 axes rotated against each other by about 180° (Figure 16).^[47a] Polymeric aggregates precipitate upon storage of aqueous hypericin solutions, which can even be viewed by means of electron

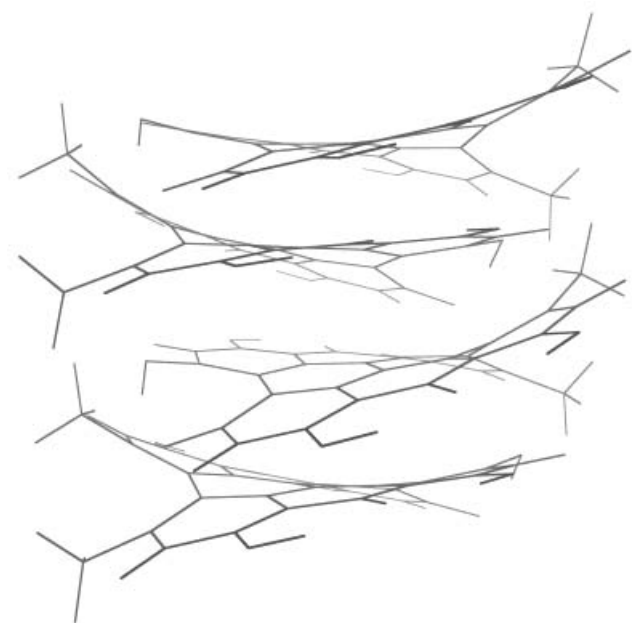


Figure 16. Schematic representation^[46] of a hypericin-3-ate-H-aggregate.

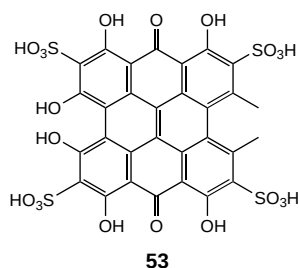


Figure 17. The formation of J-aggregates at concentrations above 10^{-4} M is possible for the water-soluble hypericin derivative **53**.

microscopy.^[47c] The formation of J-aggregates was possible in the case of the water-soluble hypericin derivatives **53** (Figure 17) at concentrations above 10^{-4} M.^[47d]

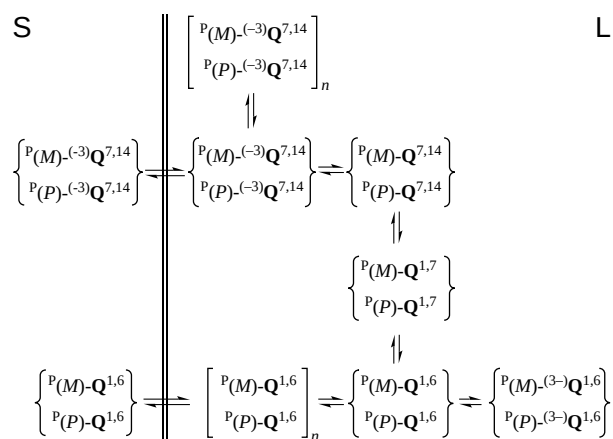
4.5. Synopsis

In conclusion, from these detailed investigations of the complex equilibrium system discussed above for

the phenanthroperylene quinones, particularly for hypericin (**2**), the experimentally determined equilibrium diagram shown in Scheme 13 is obtained. Thus, according to X-ray analysis the hypericin ion is present in the solid state (S) as the racemate $\{P(M)^{-(-3)}Q^{7,14} + P(P)^{-(-3)}Q^{7,14}\}$ of the propeller conformer of the $Q^{7,14}$ tautomer.^[38b, 41a]

In solutions (L) the dissociation and homoassociation equilibria of this system will be dependent on solvent, concentration, and proton concentration, and this will govern the presence of certain species.^[23c, 38a, 44c, 45c,d, 47a] Moreover, high concentrations in aprotic, slightly polar solvents, such as tetrahydrofuran or aliphatic esters, as well as addition of Lewis acids favors tautomerization via the $Q^{1,7}$ tautomer to yield the extremely sparingly soluble $Q^{1,6}$ tautomer. This property may be used to enrich or isolate this tautomer.^[45c, 48a] The latter is also involved in dissociation and association equilibria. In addition, according to several investigations it is very probable that undissociated crystalline **2** is present as its $Q^{1,6}$ tautomer.^[45c, 48a, 48b]

All these results suggest that extreme care should be exercised during investigations of the physiological and



Scheme 13. The complex equilibrium system of phenanthroperylene quinones, from experimental results mainly for **2**. Winged brackets denote racemic mixtures. Square brackets indicate associates of n molecules, S denotes the crystalline state, and L the solution state.

physical properties of the phenanthroperylene quinones with respect to the presence of certain species under certain experimental conditions.

5. Light Absorption and Emission—Excited States

The extended conjugation system of **1** renders its derivatives as colorful dyes that possess unique properties in their excited states. Thus, it is not surprising that nature has selected them during evolution for a variety of functional roles as photosensitizers and photoreceptors.

5.1. Absorption

The singlet absorption band of the fundamental chromophores of **1** at about 420 nm is bathochromically shifted by substitution with hydroxyl and alkyl groups and is observed at about 600 nm for the highly substituted derivatives such as **2** (Figure 18). This absorption band, and also its phenotype, varies in a characteristic way for the various positions of the equilibria within the complex structural system. Tautomerization and conformational changes (torsion resulting from the influence of substituents, butterfly and propeller conformers) have minor influence on the absorption bands, however, deprotonation, protonation, and association may lead occasionally to dramatic changes in the absorption behavior.^[37b, 45c, 48a] Accordingly, protonation and deprotonation normally cause a bathochromic shift. The intensity and form of the second absorption band system around 450 nm (Figure 18) is highly diagnostic for the dissociation of hydroxyl groups. A characteristic feature of H-aggregates is their absorption spectrum, which displays a lower intensity and is hypsochromically shifted relative to the monomer and shows the anticipated exciton splitting (Figure 18).^[47a]

This phenomenological behavior of the light-absorbing properties of phenanthroperylene quinones can be nicely rationalized and understood by means of semiempirical

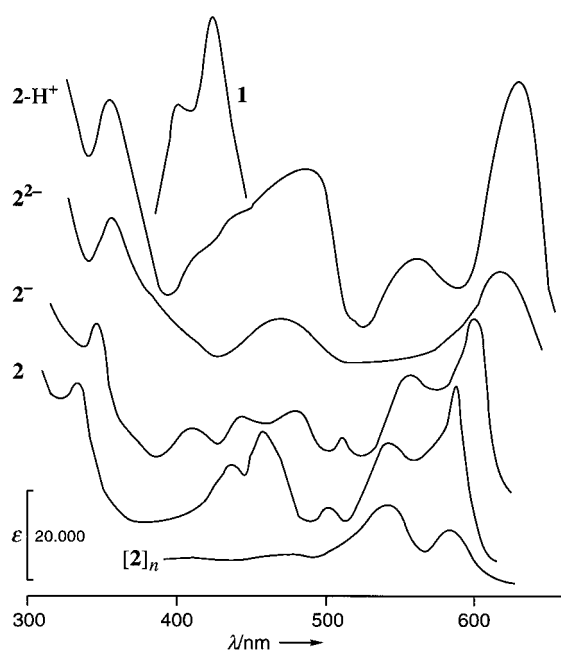


Figure 18. UV/Vis spectra of the fundamental phenanthroperylene quinone (**1**) and of hypericin (**2**) in 80 % ethanol, as well as its protonation (2-H^+ ; 80 % ethanol, $\text{pH} \approx 0.5$), *bay*-deprotonation (2^- ; 80 % ethanol, $\text{pH} \approx 6$), *bay,peri*-dideprotonation product (2^{2-} ; 80 % ethanol, $\text{pH} 12$), and of an H-aggregate ($[2]_n$; H_2O).

quantum chemical calculations of the PPP type.^[37b] The distinct structuring of the absorption bands results from vibrational progressions.^[37b, 49a] The polarization of the absorption bands derived from such calculations are corroborated by an analysis of the emission polarization,^[49b] and moreover, by direct measurements of their polarization.^[37b] For the latter experiment, the hypericin derivative $(-3)\mathbf{54}$ (Figure 19) was incorporated into a polyethylene foil, which after being stretched was investigated by means of polarized light.^[37b] Thus the obtained polarization of the absorption band obtained shows that the short wavelength band system is rather sensitive to changes in the *bay* region.

5.2. Emission

5.2.1. Fluorescence

Solutions of hydroxyphenanthroperylene quinone derivatives display a significant fluorescence with medium to high quantum yields, which is characterized by only small Stokes shifts and pronounced vibrational progression. The fluorescence is slightly dependent on the ionization of the hydroxyl groups or the tautomeric situation.^[23c, 37b,c,d, 38a, 39, 44b, 48a, 50a] However, it is quenched completely upon formation of H-aggregates and it is also dampened by bromine substitution of the aromatic rings.^[47a, 50b] As an illustration the intensely studied *bay*-hypericinatonate ion $(-3)\mathbf{2}$ is used.^[51, 52] Its fluorescence band at 595 nm is Stokes shifted by 5 nm (ethanol), and is followed at room temperature by a second band at 640 nm whose intensity is about 80 % of the first one. As could be expected, the elusive vibrational structure is sharpened at 77 K and complemented by a band at 700 nm.^[52e] Finally, at

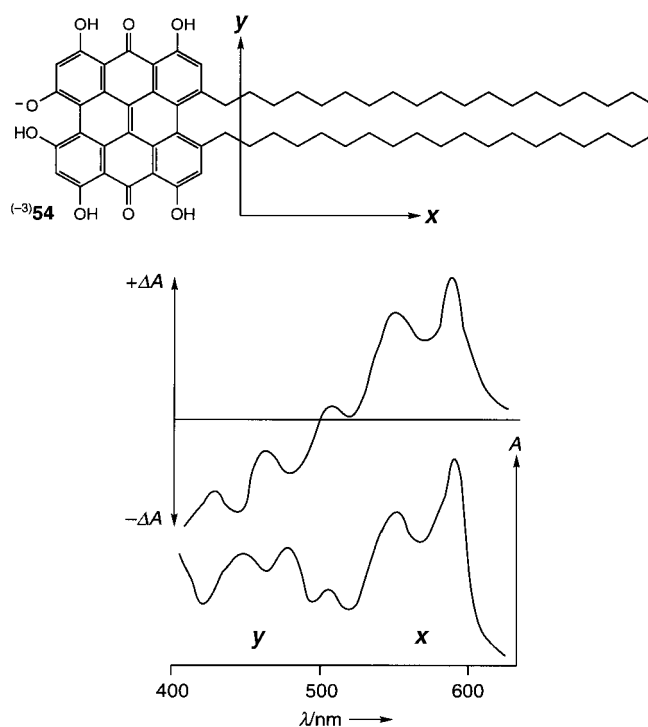


Figure 19. Absorption (A) and polarization spectrum (ΔA) of the hypericin derivative $(-3)\mathbf{54}$ incorporated into polyethylene and then stretched. The polarization curve is obtained by subtracting the absorption obtained with the polarizer oriented perpendicularly to the stretching direction from that of the corresponding parallel orientation. The polarization of the two band systems is then x and y .

1.2 K the vibrational structure is completely developed with sharp bands being observed at 595 (100), 610 (30), 644 (26), 663 (7, shoulder), and 702 (9) nm (relative intensity).^[50a] The quantum yield of the fluorescence amounts to 0.2 to 0.3;^[47a, 53] its monoexponential decay is characterized by a mean lifetime of 5 ns.^[22g, 52a] The fluorescence is self-quenched.^[53b] Moreover, it is also quenched by electron donors and electron acceptors.^[22g, 52d,g] The latter phenomenon stresses the point that this class of compounds may act either as electron acceptors of the quinone type or as electron donors of the aryl ketone type.^[52g] H-aggregates are virtually nonfluorescent.^[47a] The emission of the first singlet state is built up with a delay of 10 ps, which is attributed to an intramolecular proton transfer.^[9k]

5.2.2. Phosphorescence

Information on the phosphorescence and the triplet state of hydroxyphenanthroperylene quinone derivatives is currently only available for the *bay*-hypericinatonate ion $(-3)\mathbf{2}$ and isohypericin (**49**).^[22g, 49b, 50a, 52e, 53a, 54] The band form of the phosphorescence of $(-3)\mathbf{2}$ is similar to that of fluorescence:^[51] at 77 K and 1.2 K a vibrational progression from 755 (100), 779 (70), 836 (33), and 936 (10) nm (relative intensity) is obtained in ethanol.^[52e, 50a] The phosphorescence quantum yield is of the order of $\leq 10^{-3}$.^[53a] The triplet state is very effectively populated from the singlet state with a quantum yield of this intersystem crossing of about 0.7.^[54a] The triplet state decays monoexponentially with a mean lifetime of a few millise-

onds.^[50a, 52e, 53a] The various possibilities of energy transfer originating in the triplet state of $(^{-3})\mathbf{2}$ have been investigated intensely. These results will be discussed in more detail within the discussion of photochemical reactions (Section 10.2.).^[22g, 53a, 54b]

6. Chiroptical Properties

Bay-substituted phenanthroperylene quinones are chiral as a result of the C_1 or C_2 symmetry of their propeller conformers. Thus, in principle, they may be resolved into their antipodes. Since the activation barrier of racemization in many derivatives is rather low, a detailed investigation of their chiroptical properties and an assignment of their absolute configuration had to be postponed until the diastereomers **51** and **52** (Figure 15) became available. These display pronounced opposite Cotton effects in the regions of their two main absorption band systems. These effects are virtually identical for the derivatives $(^{-3})\mathbf{51}$ and $(^{-3})\mathbf{52}$, with the respective two diastereomers of each having a mirror image relation (Figure 20).^[55a] This fact corroborates the assumption

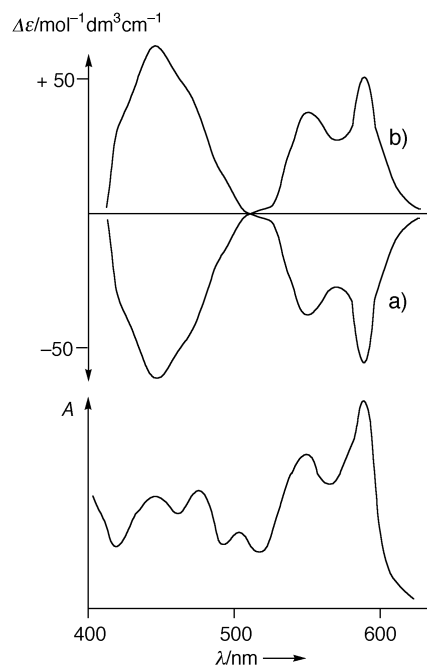


Figure 20. Circular dichroism ($\Delta\epsilon$) and absorption spectra (A ; identical) of the two diastereomers $(R,P)\text{-}(-^3)\mathbf{51}$ (a) and $(R,M)\text{-}(-^3)\mathbf{51}$ (b) in ethanol.

that the observed chiroptical effects are caused by the intrinsic helicity of the phenanthroperylene quinone chromophore and are not induced by the menthyl moieties.

Chromophores with formal or intrinsic C_2 symmetry are properly described by means of the Wagnière C_2 rule.^[56] From its application the diastereomer with a negative Cotton effect of its long wavelength absorption band is assigned the absolute configuration (*P*) (Figure 21).^[55a] Investigations on **51** and **52** under conditions that stabilize certain species of the complex equilibrium system (see Section 4.5.) do not reveal significant changes in the chiroptical signals. This observation

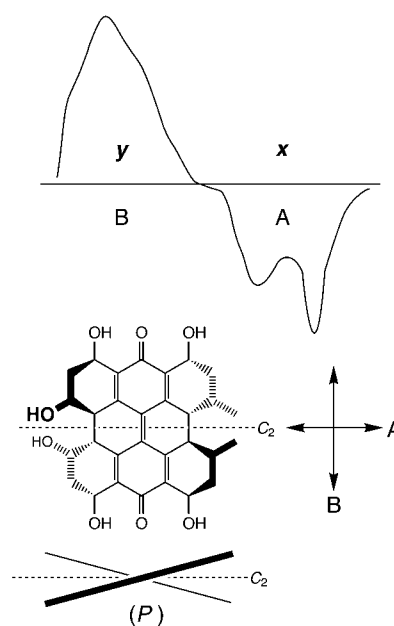


Figure 21. Application of the C_2 rule^[56] to the hypericin chromophore: for x and y polarization of the long and short wavelength band (Figure 19) for the point group C_2 the corresponding transitions are of symmetry A and B. Accordingly, the absolute configuration (*P*) is assigned from the negative Cotton effect of the long wavelength band.^[55a]

indicates that the intrinsic helicity and, accordingly, the chiroptical properties of the chromophore are similar for the *bay*-ionized, nonionized, and tautomeric forms.^[55a] Semi-empirical calculations corroborate the absolute configuration derived by means of the C_2 rule. Moreover, they demonstrate that the intense chiroptical signals have the propeller conformation as a prerequisite^[55a] and that the butterfly conformation would display only marginal chiroptical effects.^[55b]

The absolute configuration thus deduced for the hydroxyphenanthroperylene chromophore allows that of the related stentorin chromophore of **14** (Figure 5) to be deduced. From the observed sequence of positive and negative Cotton effects of the long and short wavelength absorption band systems of the native stentorin protein complex an absolute configuration (*M*) is assigned.^[22f, 55a] Accordingly, the gymnochromes B and D (**10** and **12**;^[20a] Figure 4) are assigned an absolute configuration (*P*) and isogymnochrome D (**13**;^[20a] Figure 4) an absolute configuration (*M*).

7. Vibrational and NMR Spectra

Several infrared spectra of hydroxyphenanthroperylene quinone derivatives may be found in the literature.^[6, 37a,c, 38a, 39, 45d, 47d, 50b] In addition, particularly in the case of hypericin (**2**), Fourier transform resonance Raman spectroscopy (FTRR),^[48b, 57a] fluorescence and fluorescence excitation spectroscopy,^[49a] as well as surface enhanced Raman scattering (SERS) have been used to obtain structurally relevant vibrational data.^[48b, 57b] However, the assignment of all vibrational bands beyond the characteristic hydroxyl and carbonyl vibrations has yet to be achieved. Currently, the 156

and 153 normal vibrations expected for **2** (54 atoms) and its phenolate ion $(^{-3})\mathbf{2}$ (53 atoms), respectively, are mostly unassigned. Nevertheless, vibrational spectroscopy could provide a valuable tool for clarifying structural details of the phenanthroperylene quinones, which are otherwise inaccessible.^[48b]

Although the notoriously low solubility of many phenanthroperylene quinones limits the application of ^1H and ^{13}C NMR spectroscopy to some degree, it is nevertheless an indispensable tool for structural analysis in this class of compounds. Characteristic chemical shifts, as shown for the hypericinate ion $(^{-3})\mathbf{2}$ in Figure 22, as well as two dimen-

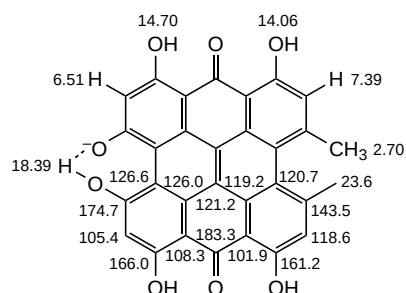


Figure 22. Chemical shifts of the ^1H and ^{13}C nuclei of the hypericinate ion $(^{-3})\mathbf{2}$ in $[\text{D}_6]\text{dimethylsulfoxide}$ (according to data from ref. [6]).

sional correlation spectroscopy can be used successfully to assign constitution, tautomerism, ionization, hydrogen bonding, and exchange processes of hydroxyphenanthroperylene quinone derivatives. This is illustrated with the following examples.

The assignment of constitutions to stentorin (**14**; Figure 5) and isostentorin (**50**; Scheme 7) is achieved unequivocally from a comparison of the ^1H NMR spectra of the two *bay*-diphenolates $(^{-3},-10)\mathbf{14}$ and $(^{-3},-10)\mathbf{50}$: as shown in Figure 23, the

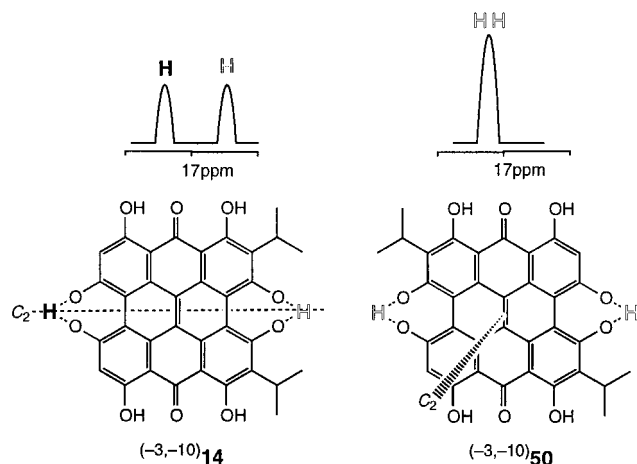


Figure 23. The constitution of stentorin (**14**) and isostentorin (**50**) is derived from the ^1H NMR spectra of their di-*bay*-phenolates.

two hydrogen-bonded *bay* protons of $(^{-3},-10)\mathbf{14}$ undergo fast exchange and are placed on the formal C_2 symmetry axis. Thus, they have two different chemical environments and yield two distinct signals. In contrast to this, a C_2 axis perpendicular to the ring system in $(^{-3},-10)\mathbf{50}$ causes two

identical *bay* protons and accordingly, only one signal is observed.^[23c]

As shown in Figure 24 two dimensional ^1H NOE correlation spectroscopy allows the assignment of the tetramethyl derivative **54**, which was formed by methylation of the $\mathbf{Q}^7$,¹⁴ tautomer.^[44e]

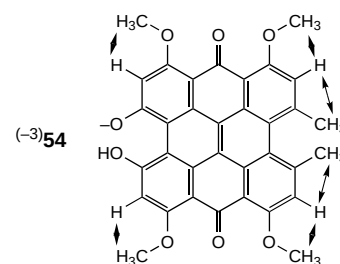


Figure 24. NOE correlations of the protons of **54**.

Finally, the region and number of signals in the ^1H and ^{13}C NMR spectra of the hypericinate ions $(^{-3})\mathbf{2}$ as shown in Figure 22 immediately allows the deduction that the ionization of a hydroxyl group leads to a hydrogen-bonded phenolate, which when viewed through the methods time window is shown to be involved in a very fast exchange. An investigation of secondary isotope effects (H/D) showed the presence of an unsymmetrical *bay* hydrogen bridge in $(^{-3})\mathbf{2}$,^[45c] which is in accord with other results^[37b, 45a,b,c].

8. Heteroassociation

Considering the pronounced tendency of hydroxyphenanthroperylene quinones to undergo homoassociation (see Section 4.4.) it is not surprising that they also display a strong tendency to associate with other molecules. The first effect to mention is specific solvation, which is observed upon addition of benzene to a solution of **2**. As shown by means of ^1H nmr experiments, the benzene molecules associate in stacks above and below the mean plane of the hypericin ring system.^[47a] Whereas strong electron acceptors, such as tetracyanoethylene, are not involved in the formation of donor–acceptor complexes,^[47a] such complexes are encountered in the case of donors, such as duroquinone or ferrocene.^[22g] Interestingly, for the example of hypericin (**2**) or $(^{-3})\mathbf{2}$ two patterns of behavior are observed. On the one hand pigment H-aggregates are solubilized by binding to a host molecule, and on the other hand defined complexes are formed in which the pigment is associated monomolecularly to the host, and might even be associated in a specific orientation.^[47a]

Accordingly, the absorption spectrum together with the absence of fluorescence of **2** and $(^{-3})\mathbf{2}$ in the presence of aqueous solutions of γ -cyclodextrin, lysozyme, basic pancreatic trypsin inhibitor, melittin, polylysine, and DNA displays the characteristic bands of H-aggregates as illustrated in Figure 18 for $[\mathbf{2}]_n$.^[47a] The pronounced solubilization encountered in these cases are interpreted as an association of the H-aggregates to the corresponding host molecule. With lipoproteins, such as HDL and LDL, heteroassociates with very high hypericinate content are found.^[9i]

As inferred from the absorption spectra of several solution systems, monomolecular association occurs in the case of the solubilization of hydroxyphenanthroperylene quinones by means of the formation of micelles and vesicles.^[14n, 53a,b, 58a,b,c] As to whether covalent or noncovalent bonding is present between the apoproteins and the pigments of stentorin and blepharismismin is not yet known with certainty. However, experiments to form Schiff bases between a carbonyl group of hydroxyphenanthroperylene quinones and the ϵ -lysine amino group in analogy to the visual pigments failed.^[58d] Therefore it may be assumed that in the native pigment system a specific, but noncovalent association is formed.

A special situation is encountered in the case of the specific heteroassociation of **2** ($^{(-3)}\mathbf{2}$) to serum albumin, which is of the utmost importance for the transport and availability of this pigment under physiological conditions. The 1:1 complex formed between human serum albumine and $^{(-3)}\mathbf{2}$ (binding constant $K_b = 7.5 \times 10^4 \text{ M}^{-1}$)^[58e] may be easily isolated.^[47] It is easily dissolved in water, and has absorption and fluorescence properties differing only slightly from those of homogeneous solutions of $^{(-3)}\mathbf{2}$. Its fluorescence polarization corresponds to that of solutions of $^{(-3)}\mathbf{2}$ in low temperature glasses or glycerol, which points to a relatively rigid positioning of the chromophore with respect to the albumine molecule.^[47a] With respect to the site of association it was shown by means of competition experiments with diazepam, warfarin, and bilirubin that $^{(-3)}\mathbf{2}$ is selectively bound to the active site of domain IIIA of human serum albumine.^[47a] In addition, resonance Raman and SERS data point to an interaction of the pigment with the tryptophane residue of domain IIA,^[58f] which is close to domain IIIA and forms a common surface.^[59a, 59b] As can be inferred from the X-ray structural analysis of this protein, hydrophobic interactions are mainly responsible for bonding in this case.^[59a,b] Hole-burning experiments point to a relatively flat bonding geometry and a pronounced accessibility of the solvent to the pigment.^[45b] The long wavelength absorption band of bound $^{(-3)}\mathbf{2}$ displays a Cotton effect with $\Delta\epsilon_{600}$ of +19.^[47a] It can be inferred from the chiroptical properties of the chromophore (see Section 6) that there is only a partial preference of the propeller enantiomer with configuration (*M*). Such low partial chiral discrimination was also deduced from hole-burning experiments.^[45b]

Resonance Raman spectroscopy indicated a sequence-specific interaction of $^{(-3)}\mathbf{2}$ with oligonucleotides having a partial sequence corresponding to the HIV “rev” gene resonance.^[47e]

9. Salts and Coordination Complexes

The pronounced acidity of the *bay*-region hydroxyl groups of phenanthroperylene quinones make salt formation a definite possibility. Thus, as mentioned in Section 2.1, hypericin (**2**) is present in the plant material mainly as its potassium salt.^[6a] For **2** salts with monovalent counterions are occasionally prepared because of their enhanced solubility.^[13b, 41a, 45d, 48a, 59c,d] In addition, in the *bay*-hydroxylated fringelites (Figure 5) salt formation with divalent ions, such as

Ca^{2+} , yields polymeric systems, which because of their extreme insolubility are highly stable in fossils.^[25c]

The *peri*-hydroxyl groups situated in the neighborhood of the carbonyl groups display the best prerequisites to form chelates with transition metal ions. Such coordination complexes could be characterized in the case of fringelite D and Zn^{2+} . This binding principle allows for the formation of a network of the just mentioned Ca^{2+} salt chains by coordination with the transition metal ions, which eventually leads to the extreme stability of this organic pigments in fossil material.^[25c] Chelate formation with Al^{3+} , Fe^{3+} , Cu^{2+} , Gd^{2+} , and Tb^{2+} with the *peri*-hydroxyl groups of $^{(-3)}\mathbf{2}$ was inferred from the bathochromic shifts in the corresponding absorption spectra.^[59e]

10. Reactions

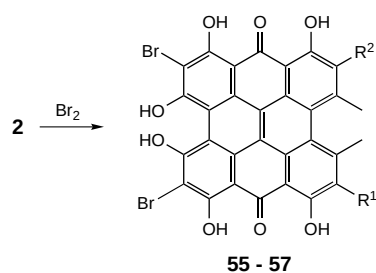
Only a few reactions that are suitable for the derivatization of phenanthroperylene quinones on a preparative scale are known. The two following sections will deal with the most important reactions involving compounds in ground and excited states.

10.1. Reactions of the Ground State

Protonation and deprotonation reactions as viewed from the structural viewpoint were discussed in Section 4.2. Defined reaction products from the chemical or electrochemical reduction or oxidation of hydroxyphenanthroperylene quinones, which would correspond to hydroquinone or bisquinone derivatives, could not be isolated so far. As demonstrated by ESR, electron nuclear double and triple resonance experiments, electrochemical or chemical (metallic potassium) reduction of the hypericinate ion ($^{(-3)}\mathbf{2}$) in aprotic solvents leads to the radical dianion ($^{(-3,-peri)}\mathbf{2}^{\cdot-}$), which is stable for days.^[60b] However, the radical anion ($^{(-3)}\mathbf{2}^{\cdot-}$) derived in the same way from undissociated **2** is short-lived and rapidly forms the aforementioned radical dianion ($^{(-3,-peri)}\mathbf{2}^{\cdot-}$). Reducing cyclic voltammetry between -1.0 and -2.2 V points to a step involving $^{(3-)}\mathbf{2}$ and perhaps also $^{(4-)}\mathbf{2}$.^[60b] A viologen-mediated, photoinduced electron transfer from **2** to a modified gold electrode was documented recently.^[60e] Oxidative cyclic voltammetry of $^{(3-)}\mathbf{2}$ in dimethylsulfoxide displays only a insufficiently defined, nonreversible oxidation process involving several electrons in the region of $+0.9$ V.^[60a]

As could be expected, electrophilic substitution is favored at the aromatic positions of hydroxyphenanthroperylene quinones. Reaction of hypericin (**2**) with bromine thus affords the tetrabromo derivative **57** via the di- and trisubstitution products **55** and **56**, which can be isolated (Scheme 14).^[50b] In analogy, sulfonation of **2** yields the tetrasulfonic acid **53** via the corresponding hypericin di- and trisulfonic acids (Figure 17).^[47d]

Nucleophilic substitution cannot be observed because of the pronounced activation of the aromatic system. However, the phenolic hydroxyl groups, or their respective phenolate ions, may act as nucleophiles. Thereby the *bay*-hydroxyl



Scheme 14. Electrophilic bromination of hypericin to **55** ($R^1 = R^2 = H$), **56** ($R^1 = Br$, $R^2 = H$), and **57** ($R^1 = R^2 = Br$).

groups react preferably in alkylation or acylation reactions.^[39, 44c, 45d] Radical-catalyzed reactions of **2**, for example, the ω -halogenation of methyl groups, were unsuccessful.^[60c] Hypericin **2** was also found to be largely inert in cycloaddition reactions with singlet oxygen, dienes, and dienophiles.^[47a]

The mass spectrometric fragmentation of hydroxyphenanthroperylene quinones, in peculiar those with ionized *bay*-hydroxyl groups, such as $(^{-3})\mathbf{2}$, by electrospray ionization is rather characteristic. The structural aspects and mechanism of the reactions taking place in this case have been discussed in detail,^[60d] but such discussions are beyond the scope of this review.

10.2. Photochemical Reactions

Electron transfer reactions involving the excited singlet state of hydroxylated phenanthroperylene quinones can be verified from fluorescence quenching by electron acceptors and ESR detection of the resulting radical species.^[22g]

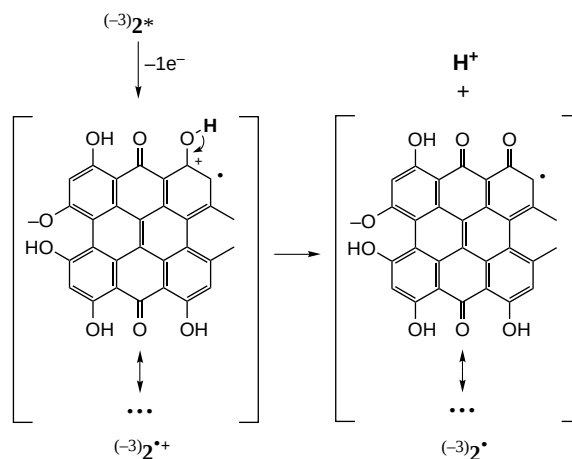
The triplet state is an ideal starting point for chemical processes because of the efficient intersystem transfer. However, the triplet state can function both as the source of excitation transfer, as is typical for quinones and other electron acceptors, and as an electron donor, as is characteristic of phenols. Most of these investigations were carried out using hypericin **2** as an electron acceptor and its *bay*-phenolate ion $(^{-3})\mathbf{2}$ as an electron donor.^[14c,n, 52a, 54c, 58a,b,c, 61] Such reactions are mainly of interest in regard to the application of the phenanthroperylene quinones as agents for photodynamical therapy (Section 2.1.), and moreover, with respect to their function as photoreceptors (Sections 2.2. and 2.3.).

In these cases excitation transfer for the formation of singlet oxygen ($^3\mathbf{2} + O_2 \rightarrow \mathbf{2} + ^1O_2$; quantum yield $\Phi_A \approx 0.4$ ^[61f]) is of utmost importance. This photochemical behavior is classified as a type II reaction of photosensitized reactions.^[62] The photochemically induced disproportionation ($^3\mathbf{2} + \mathbf{2} \rightarrow \mathbf{2}^{\cdot-} + \mathbf{2}^{+\cdot}$) is also possible and has been documented by ESR experiments, and even observed to a small extent in solutions of very high concentration, that is, with homo-aggregates in the ground state.^[61c] This reaction is comparable to the formation of the superoxide radical by direct reaction of the triplet species with oxygen ($^3\mathbf{2} + O_2 \rightarrow \mathbf{2}^{+\cdot} + O_2^{\cdot-}$).^[61c,d] The latter could also be derived from a reaction starting from

the anion radical ($\mathbf{2}^{\cdot-} + O_2 \rightarrow \mathbf{2} + O_2^{\cdot-}$).^[61d] These reactions are classified as photosensitizing reactions of type I.^[61d, 62]

The excited state of hydroxyphenanthroperylene quinones can also act as the source of a light-induced proton transfer, which is of eminent importance for their functional aspects (Sections 2.1.–2.3.). Epifluorescence microscopy investigations on $(^{-3})\mathbf{2}$ incorporated together with a fluorescence pH indicator into a vesicle demonstrated that after excitation a proton is transferred within a few 10 μs to the indicator.^[58c, 63] As indicated by studies on partially O-alkylated hypericin derivatives this proton mainly originates in the *peri* region of the pigment.^[63]

With respect to the reaction mechanism, one can assume that the acidification of the molecule in its singlet or respective triplet state is insufficient to bridge the rather large pK_a gap between the proton donor and acceptor. However, by means of electron transfer from the excited singlet or triplet state $(^{-3})\mathbf{2}^*$ (see above) the cation radical $(^{-3})\mathbf{2}^{+\cdot}$ (Scheme 15) could be formed, which should be much



Scheme 15. Light-induced proton transfer in the hypericin anion $(^{-3})\mathbf{2}$.

more acidic than the ground state of $(^{-3})\mathbf{2}$.^[22g] This is in analogy to the case of tyrosine for which after excitation and electron transfer its acidity was found to be increased by ten orders of magnitude.^[64] The species thus formed is sufficiently long lived to account for the time characteristics observed for this reaction.^[63]

11. Summary and Outlook

Hydroxyl-substituted phenanthroperylene quinones form a fascinating group of natural products. Some of its representatives, such as hypericin or stentorin, display important physiological properties. These reach from therapeutically useful photosensitizations to their function as photoreceptors. Their chemistry is mostly characterized by a complex intertwined network of tautomerism, dissociation, torsional, and association equilibria, which account for their chemical, physical, reactive, and accordingly, also the dependence of their physiological properties on environmental parameters.

Although our knowledge of the chemistry of this class of compounds has expanded considerably in the last decade, there are still many gaps present which have to be bridged as a result of the importance of these molecules for physiology and medicine. Thus, detailed investigations on the structures of the tautomers under physiological conditions are still lacking. The detailed photochemistry of the photosensory pigments is, as is evident from the discussions above, only marginally known. In addition, the bonding of these chromophores to their respective proteins as well as the reaction cascades that lead to the physiological signal are mostly unclear. Further pursuit of the chemistry of the phenanthroperylene quinones still remains a challenge!

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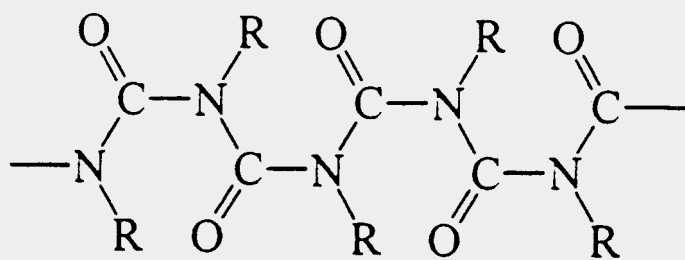
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Deposition of Data from X-Ray Structure Analyses

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In the Chinese language a large number of small forces making a large force expresses the connection between cooperation and amplification. This finds parallel in the chiral properties of the polyisocyanates, a model helical system.



The Macromolecular Route to Chiral Amplification

Mark M. Green,* Ji-Woong Park, Takahiro Sato, Akio Teramoto, Shneior Lifson, Robin L. B. Selinger, and Jonathan V. Selinger

Dedicated to Professors Kurt Mislow and Herbert Morawetz

Polymers show cooperative phenomena for almost all of their properties, and this is no less true for the optical activity of chiral polymers. This phenomena was first observed by the “Italian School” in their early work following the discovery of stereoregular polymerization, and led to observations of nonlinear relationships between enantiomeric characteristics of monomeric materials used in polymerizations and the polymers produced. These observations confirmed the hypothesis that the conformations of these polymers in the melt and dissolved states resembled those found in the solid crystal. In recent years a

version of the Nylons, which failed to make the grade as a fiber, turned out to carry these cooperative properties of chirality to an extreme. Minute chiral forces control the chain properties, allowing experiments in which chirality arising from isotopic substitution, or solvation effects, or even nearly racemic states can be studied. Statistical physics and the one-dimensional Ising model describe the properties of these polymers in quantitative perfection and yield insight into how to manipulate the chirality and the polymer properties to gain even higher amplification of the chiral forces. Through work on such disparate materials as

vinyl polymers and polyisocyanates, we discover the structural boundaries for these observations and therefore which other polymeric and supramolecular systems may behave similarly. This is already being seen. However, these studies also demonstrate that structural theory appears inadequate to interpret the small energies driving these chiral effects, and this has parallels in other areas where equilibrium states are balanced on cooperatively driven forces.

Keywords: asymmetric amplification • chirality • helical structures • polymers

1. Introduction

A large number of small forces adding up to a large force expresses the mutually intertwined ideas of cooperation and amplification (Figure 1). Since polymers are an ideal molecular form for cooperative phenomena, and this manifests itself

across the spectrum of polymer science, it is not surprising that early observations of optical activity in polymers revealed the signature characteristics of chiral amplification. These early observations derived from the possibility of producing stereoregular polymers by the methods of Ziegler and Natta. In these polymers, such as isotactic polypropylene, the pendant groups are connected to the chain through centers of identical configuration, and this uniformity leads to helical conformations for these materials in the crystalline regions of their solid state. It was quickly understood, as most elegantly explained by Mario Farina in Milan,^[1] that although a nearly perfect asymmetric synthesis was necessary to produce identical configurations for these pendant groups, the fact that the chain ends in a very long polymer are indistinguishable led to what Mislow^[2] has termed a cryptochiral state. The



Figure 1. Chinese character for cooperation – amplification.

[*] Prof. M. M. Green, J.-W. Park
Herman F. Mark Polymer Research Institute, Polytechnic University
Six Metrotech Center, Brooklyn, New York 11201 (USA)
Fax: (+1) 718-260-3125
E-mail: mgreen@duke.poly.edu
Prof. T. Sato, Prof. A. Teramoto
Department of Macromolecular Science, Osaka University
Machikaneyama-cho 1-1, Toyonaka, Osaka 560 (Japan)
Prof. S. Lifson
Department of Chemical Physics, Weizmann Institute of Science
Rehovot, 76100 (Israel)
Prof. R. L. B. Selinger
Department of Physics, Catholic University of America
Washington, D.C. 20064 (USA)
Dr. J. V. Selinger
Center for Bio/Molecular Science and Engineering
Naval Research Laboratory
Washington, D.C. 20375 (USA)

Mark M. Green, born in 1937, received his B.Sc. degree at the City College of New York in 1958 and his doctoral degree from Princeton University in 1966, where he worked with Kurt Mislow. He joined Carl Djerassi's group at Stanford University, where he worked on the mechanism of chemical processes in mass spectrometers. In three academic positions over the next thirteen years he used stereochemical methods to investigate the unimolecular chemistry of cation radicals in mass spectrometers. He moved to Brooklyn Poly (now the Polytechnic University) in 1980 and met Herbert Morawetz, which led to research in the area overlapping stereochemistry and the cooperativity inherent in polymers.



M. M. Green

Ji-Woong Park, born in 1965 in Korea, graduated from Seoul National University in 1989. He studied polymer chemistry for an M.S. at the Korea Advanced Institute of Science and Technology (KAIST) under the supervision of Professor Iwhan Cho, and worked in the Korea Research Institute of Chemical Technology (1991–1995) with Dr. Suh Bong Rhee on the development of new polyimides. Since 1995 he has been studying the molecular dynamics of optically active polymers and their small molecule analogues in viscous liquids and polymer glasses as part of his doctoral thesis with Professor Green.



J.-W. Park



T. Sato

Takahiro Sato, born in 1957 in Osaka (Japan), studied macromolecular science and received his D.Sci. in 1985 from Professor H. Fujita at Osaka University. After working with Dr. C. C. Han at NBS, Gaithersburg, MD (USA), as a guest scientist, he was appointed to a position at Osaka University in 1988, where he is now associate professor. His research interests include the physical chemistry of macromolecular solutions.

Akio Teramoto, born in 1933, received his B.S. in 1956 and his Ph.D. in 1961 from Kyoto University. He worked at Osaka University from 1961 to 1997, where he is Professor Emeritus, and is currently Chair Professor at Ritsumeikan University. His research interests include chain conformations and conformational transitions in dilute solution, thermodynamics, and dynamics of polymers solutions, including polymer liquid crystals.



A. Teramoto



S. Lifson

Shneior Lifson, born in 1914 in Tel-Aviv, obtained his M.Sc. degree in physics from the Hebrew University of Jerusalem in 1949. That year he joined the Weizmann Institute of Science, where he has stayed since, receiving his Ph.D. in 1954 and becoming Professor of Chemical Physics at the Weizmann Institute of Science in 1961 and Head of the Department of Chemical Physics in 1963. His long list of research interests includes light scattering of polyelectrolytes, conformations and vibrations of large molecules, and statistical mechanics and conformation analysis of rigid polymers.



R. L. B. Selinger



J. V. Selinger

Robin L. B. Selinger, born in 1962, received her Ph.D. at Harvard University in 1989 and did postdoctoral work at UCLA, University of Maryland, and the National Institutes of Standards and Technology. She is currently assistant professor of Physics at Catholic University in Washington, D.C. Her research involves statistical physics and modeling of soft and hard condensed matter, with a focus on complex fluids and on the fracture and deformation of crystalline solids.

Jonathan V. Selinger, born in 1961, received his doctorate in Physics from Harvard University in 1989. He then did postdoctoral research with a joint appointment at UCLA Department of Physics and Caltech Department of Chemical Engineering. In 1992 he came to the Naval Research Laboratory in Washington, D.C. His research focuses on the statistical mechanics of complex fluids, including polymers, liquid crystals, Langmuir monolayers, and self-assembled lipid microstructures.

isotactic polymer chain is chiral only by virtue of the different chain ends. However, these chain ends in a high molecular weight polymer are an unimportant part of the structure, therefore precluding any manifestation of chirality such as optical activity. The isotactic polymer belongs to a class of molecules in which chirality is buried, that is, resides in a crypt. Optical activity could though be produced in these polymers in another manner.

Italian researchers under the direction of Piero Pino in Pisa in the 1960s began to prepare stereoregular vinyl polymers with chiral, nonracemic pendant groups (for example, from (*R*)- or (*S*)-3-methyl-1-pentene) and discovered that the optical activities of such materials in solution showed nonlinear relationships between the configurational enantiomeric characteristics of the monomer units and the optical activity of the derived polymer. This nonlinear optical activity was difficult to understand except as arising from the chiral units affecting some aspect of the chain conformation. Although the measurements were made in solution rather than with the crystal the results pointed to the presence of a helical conformation. A full understanding was impeded though by the absence of an accessible chromophore, blocking therefore direct observation by circular dichroism of the source of the chiral optical observations. In addition, the magnitude of the effects was limited by the flexibility of the polymers since helical reversal states were relatively easily accessible. Such defects in the helical structure, as we shall see, limited the cooperativity responsible for the nonlinear effects.

In the early 1960s chemists at DuPont had found a route to the simplest Nylon, the addition polymer of organic isocyanates. These different types of Nylon-1, or poly(isocyanates), show unusual dimensional properties which arise from a strongly preferred local helical conformation of the chain. This is consistent with a high persistence in the chain directionality. In other words, if tangents are drawn to the chain at any two points the angle with which they meet, for the same distance along the chain, will be much smaller than for a random coil polymer. The polyisocyanates became an excellent system for testing theories in the area of stiff wormlike polymers and lyotropic liquid crystals.^[3] In addition, these polymers, though helical, were synthesized from achiral monomers, which led to the property that their mirror helical senses were of equal probability. This fact in combination with the expected low population of conformations that reversed the helical sense, consistent with their stiff structure, suggested that a more extreme manifestation of the chiral amplification properties encountered by the group of Pino with the isotactic vinyl polymers would be found in the polyisocyanates. Furthermore, the chromophore of the polymers absorbs light in an accessible region of the spectrum, suggesting that circular dichroism measurements might allow direct observation of the helices whenever the balance between the mirror helical senses is upset. The magnitude of the amplification of chirality of the polyisocyanates has lived up to the expectation and has allowed precise correlations with cooperative models of statistical physics based on one-dimensional Ising models (see Section 3.2), which in turn has offered insight into how to manipulate the chiral amplification. In this review we trace the path of this macromolecular chiral amplification from its

origins in Italy to the present day. Through this work we show the principles involved to be independent of the precise structure of the polymer, and in this way these observations may stimulate similar experiments in other systems which may have their own unique advantages.

2. Stereoregular Vinyl Polymers Synthesized from Chiral Monomers

Driven by questions concerning the conformational properties of isotactic vinyl polymers in solution and the melt, Pino and co-workers used the Ziegler–Natta organometallic methods to polymerize chiral molecules containing 1-alkene moieties.^[4] Highly stereoregular polymers were produced. It was known from earlier studies that increasing isotacticity is correlated to increased crystallinity and therefore to lower solubility, so that samples could be fractionated according to their tacticity by dissolution in increasingly high boiling solvents at higher temperatures. All fractions of the optically active polymers produced in this manner showed increased optical activity compared to the monomer units from which they were made. However, as the isotacticity increased, as evidenced by decreasing solubility, so did the optical activity and its temperature dependence. The original data from this classic work, showing these effects, are presented in Table 1.^[4]

If the isotactic polymer chain exists as a series of blocks of left- and right-handed regions separated by helical reversals, sense can be made of the data in Table 1. In such a model the bias per unit from the chiral side group casting the left- and right-handed helical senses into a diastereomeric relationship must be multiplied by the number of units which take the same helical sense. This is the ultimate source of the amplification and the central idea of all the discussions to follow. This amplified chiral bias will determine the excess of one helical sense over the other and therefore the optical activity, but any factor that interrupts the continuity of the helix will limit this amplification. What can be the nature of these interruptions? Accumulation of energy in the chain can allow the conformation to defect from the helical state and attain higher energy states, which can act to reverse the helical sense. The population of such helical reversals would depend exponentially on the temperature, following Boltzmann statistics, and this could be the source of the strong temperature dependence of the optical activity seen in Table 1. Another source of interruptions in the helical conformation could arise from mistakes in the polymerization mechanism, allowing defects in the stereoregular configurations along the chain. This would be the reason why higher optical activities are observed in the samples which dissolve only in higher boiling solvents and for which the isotactic content is higher (Table 1).

A helical conformation in solution was the central tenet of the interpretation of the data in Table 1.^[4] Although such conformations could be demonstrated in crystals of isotactic vinyl polymers, there was no experimental way to directly address the question in the isotropic state of the melt or in solution. Guiseppe Allegra in Milan took up the question with force field calculations which clearly showed that helical

Table 1. Original table reprinted with permission from reference [4a].

Table 1. Physical properties of poly-(S)-3-methyl-1-pentene fractions having different stereoregularity

Fraction	Sample A ¹⁾ Catalyst: Al(<i>i</i> -C ₄ H ₉) ₃ /TiCl ₄					Sample B ¹⁾ Catalyst: Al(<i>i</i> -C ₄ H ₉) ₃ /TiCl ₃				
	%	[M] _D ²⁾ a) h) (°)	[η] b) (dl./g.)	m.p. (°C.)	$\frac{\Delta[M]_D}{\Delta T}$ a)	%	[M] _D ²⁾ c) h) (°)	[η] b) (dl./g.)	m.p. (°C.)	$\frac{\Delta[M]_D}{\Delta T}$ c)
Acetone sol.	6.3	+29.4	d)	n.d.	−0.08	2.4	+75.8	n.d.	n.d.	n.d.
Acetone insol. diethyl ether sol. ...	2.6	+96.4	0.08	65–75 ^{e)}	−0.23	4.8	+127	0.13	93–96 ^{f)}	n.d.
Diethyl ether insol. isooctane sol. ...	0.9	+120	0.10	135–140 ^{e)}	−0.26	1.5	+146	0.13	187–193 ^{f)}	−0.31
Isooctane insol. benzene sol.	0.4	+158	0.11	175–180 ^{e)}	−0.34	0.5	+157	n.d.	200–210 ^{e)}	−0.39
Benzene insol. decalin sol.	2.0	+161 ^{m)}	0.50	228–232 ^{e)}	−0.36	1.7	+158 ^{m)}	0.60	200–210 ^{e)}	−0.40
Residue	87.8	n.d.	n.d.	271–273 ^{e)}	n.d.	89.1	n.d.	n.d.	265–275 ^{e)}	n.d.

a) In tetralin solution

b) Determined in tetralin at 120°C.

c) In toluene solution

d) Mol.wt. det. by cryosc. in benzene: 1200 ± 100

e) Determined by a KOFLER m.p. apparatus

f) Determined by X-ray method

g) Determined by the capillary method

h) Referred to one monomeric unit

i) Monomer optical purity: 91%

j) Monomer optical purity: 89%

m) ± 10%

conformations were important in isolated chains,^[5] offering strong support for Pino's hypothesis. Later work was to extend this and suggested the ability to roughly estimate the population of the proposed helical reversals and even their possible effect on the overall chain dimensions.^[6] At the time of the initial work though direct experimental evidence was sought through observation by circular dichroism of the helical chromophore, but this could not be probed directly because of its inaccessible wavelength. Seeking other ways to support their hypothesis, Pino and co-workers took the approach^[7] of synthesizing an isotactic copolymer of styrene with a large excess of (*R*)-3,7-dimethyl-1-octene. The large increase in the molar ellipticity of the aromatic chromophore in the polymer compared to the model (Figure 2) was suggested as arising from an extended conformation of the polymer, which they considered to be helical.

The experiments were extended further to isotactic copolymers derived from units offering conflicting information to the helical sense of the chain. In these seminal stereochemistry experiments, a series of copolymers of enantiomers were prepared from three structurally different molecules, namely, (*S*)-5-methyl-1-heptene, (*S*)-4-methyl-1-hexene, and (*R*)-3,7-dimethyl-1-octene. The results are shown in Figure 3.^[8]

When the stereocenter of the chiral side chain is far removed from the backbone we could expect its influence on the helical conformation to be small, so that changes in the enantiomeric excess of the monomer units should scale linearly with optical activity. In this case the optical activity of the polymer would be derived from the chiral side chains and the backbone would be unaffected; that is, there would be equal proportions of left- and right-handed helical segments. Moving the stereocenter closer to the backbone should give an entirely different result though since the asymmetry of the side chains will be coupled to the helical backbone, favoring one sense of the helix. If the minor enantiomer takes part in the helical sense dictated by the major enantiomer, so as to avoid placing many helical reversals along the backbone in response to the changing information from the side groups, we

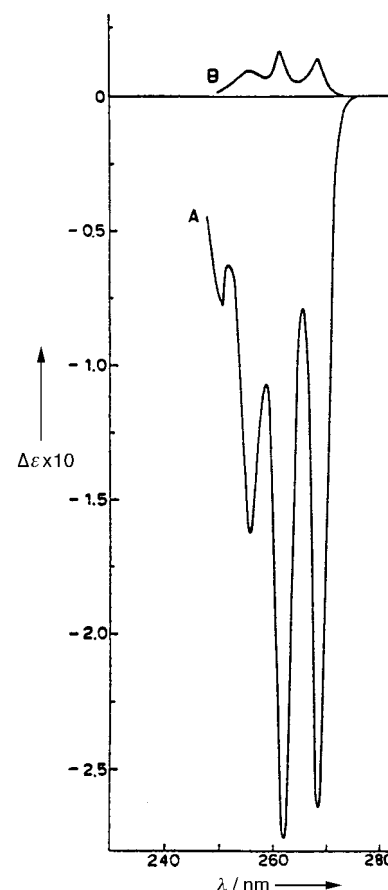


Figure 2. Circular dichroism in chloroform at 25°C of (3*S*,9*S*)-3,9-dimethyl-6-phenylundecane (B) and of the diethyl ether extractable fraction of the styrene-(*R*)-3,7-dimethyl-1-octene copolymer (A); $\Delta\epsilon$ is based on one unit of styrene. Reprinted with permission from reference [7a].

would expect to see a nonlinear response of the optical activity of the polymer to the enantiomeric excess of the side chain groups. This would arise from the strong contribution of the helix to the optical activity. As seen in Figure 3 this is precisely what is found.^[8]

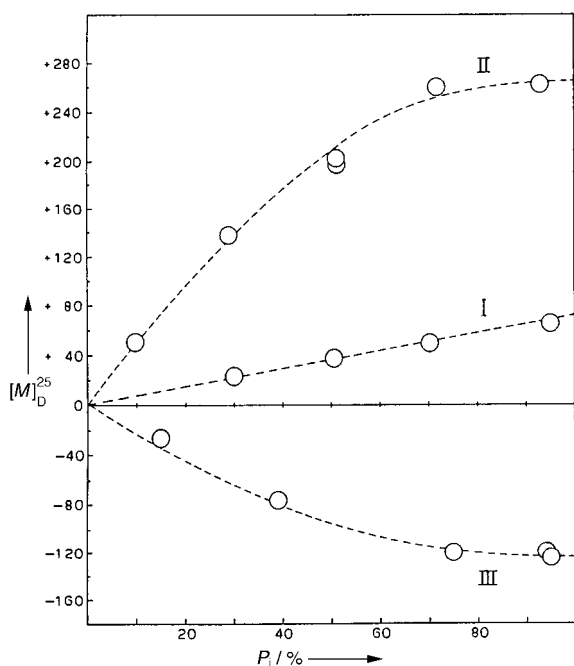


Figure 3. Molar rotatory power ($[M]_D^{25}$), referred to one monomeric unit, in hydrocarbon solution for the unfractionated methanol-insoluble polymers obtained from samples having different optical purity (P_i) of (*S*)-5-methyl-1-heptene (I), (*S*)-4-methyl-1-hexene (II), and (*R*)-3,7-dimethyl-1-octene (III). Reprinted with permission from reference [8].

Alternatively in another kind of experiment, the Italian chemists considered copolymerization of enantiomerically pure chiral units randomly dispersed among achiral units. The constraint of several units taking the same helical sense would require that the chiral units impose their bias on the helical conformations in the region of the chain where the achiral units were pendant. As a control experiment, isotactic homopolymers from two related monomers—one achiral, 4-methyl-1-pentene, and the other chiral, (*S*)-4-methyl-1-hexene—were prepared. Copolymers from the same two monomer units were also synthesized. Figure 4 shows a linear response of the optical activity to the proportion of the chiral

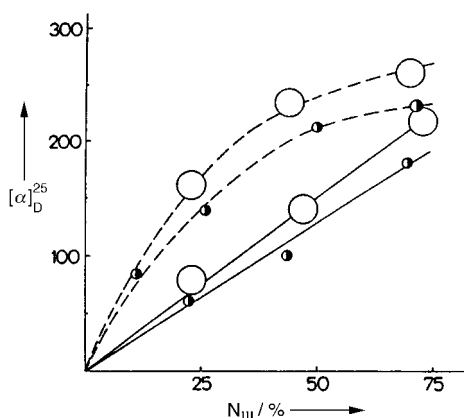


Figure 4. Rotatory power in methylcyclohexane versus mole fraction in units derived from (*S*)-4-methyl-1-hexene (N_{III}) for copolymers of (*S*)-4-methyl-1-hexene with 4-methyl-1-pentene (dashed line) and for mixtures of the two homopolymers (solid line). $\bullet$ fraction extracted with cyclohexane. Reprinted with permission from reference [9].

molecules only in the mixture of the homopolymers. In the copolymer of the chiral and achiral units 50% of the chiral comonomer is enough to yield the full optical activity, and this effect is more extreme in the higher boiling solvent, which favors, as discussed above, polymers with higher isotactic content.^[9]

In this beautifully designed early work in Italy the effects were limited by the random coil nature of the isotactic vinyl polymers. Clearly these chiral, nonlinear relationships could be further amplified in a helical polymer with fewer interruptions in the helical conformation—that is, in a stiffer polymer—and this is the subject of Section 3.

3. Chiral Properties of the Polyisocyanates

3.1. Structural Considerations

Shashoua, working at Dupont in the 1950s, realized that addition polymerization of the isocyanates could produce a material at one extreme of the Nylon structure, the Nylon-1. In this material the amide groups follow each other without interruption (Figure 5), in contrast to the higher Nylons where aliphatic groups intervene.^[10]

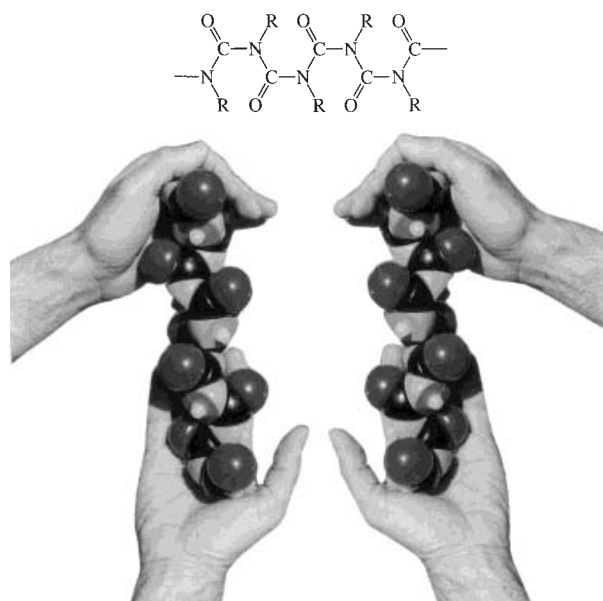


Figure 5. Top: *cis-trans* alternating structure of the polyisocyanate backbone. Bottom: left- and right-handed 8/3 helix constructed of CPK models; only the backbone atoms are shown.

In Figure 5 the chain is first drawn in two dimensions as an extended crankshaft to represent what is now known to be the basic conformation. Reducing steric interactions from the proximity of the carbonyl oxygen atom to the alkyl group on nitrogen requires turning of the structure out of the plane so as to form a helix. In the case of the *n*-butyl side chain X-ray work in Israel on stretched, oriented films showed this helix to take eight units for three turns.^[11] The conjugative requirements between the recurring amide groups combined with this steric effect forces all nonhelical conformations to occupy far

higher energy states, with the consequence that the overall or global dimension of the chain is very large for the molecular weight. Conformations which would change the direction of the chain are low in population and segmental motions are restricted, leading to a stiffening of the chain. Therefore, for the same contour length along the chain backbone the distance between the ends of the chain is far larger than for a random coil polymer. This leads to extremely viscous solutions even at low concentrations, while at high enough concentrations in the dissolved state, lyotropic liquid crystals are formed.^[12] These characteristics, discovered over the years since the first synthesis^[13] have fostered a continuing interest in these polymers.

As in the isotactic vinyl polymers discussed above, polyisocyanates constructed of achiral units allow both helical senses with equal probability intervened by helical reversals. These helical reversals are likely to cause a change in the chain direction. Are the chains long enough so that these changes can be found? What is their nature? Do they contribute to the dimensions of the chain?^[14]

In the first experiments the above questions were studied by light scattering experiments, which showed the chain dimensions of certain optically active polyisocyanates^[15, 16] to be greatly increased over that, for example, in poly(*n*-hexyl isocyanate), where there can be no preference for one helical sense. Unfortunately the chiral pendant naively first investigated^[16] was sterically bulky, so that in addition to excluding the helical reversals by exclusively favoring one helical sense, it forced restrictions on the local segmental motions of the chain. This latter parameter, revealed by NMR line width measurements,^[17] rather than the absence of the helical reversals was responsible for the increased chain dimensions.^[17, 18] A way had to be found to favor one helical sense without changing the segmental characteristics of the chain.

3.2. The Uniform Chiral Field

The concept of a uniform chiral field in a polyisocyanate—namely, of introducing a single stereospecific deuterium substituent in the side chain of every unit—arose from the desire to cast the mirror helical states into a diastereomeric relationship without changing the torsional characteristics of the backbone.^[19] Samples of 1- and 2-deuterio-*n*-hexyl isocyanate (see Figure 6) were synthesized by the key step of yeast-mediated reduction of 1-deuterio-hexanal and 1-deuterio-pentanal. The resulting alcohols, which were chiral only by virtue of the deuterium substitution, were produced in the *S* configuration, as is known for the biochemical reducing agent associated

with the yeast. This was followed by routine functional group transformations that inverted the configuration at the stereocenter and produced the (*R*)-deuterated isocyanates.^[19] While the optical activity at the sodium D line, $[\alpha]_D$, was so small as to be almost unmeasurable—a characteristic of this kind of chirality which impeded its acceptance for many years^[20]—the polyisocyanates produced had very large $[\alpha]_D$ values in the hundreds of degrees and also of opposite sign from the precursor monomers. Clearly the optical activity of the polymer could not be arising simply from the deuterated stereocenter.

The large circular dichroism signal for the helical chromophores of poly(1-deuterio-*n*-hexyl isocyanate) and poly(2-deuterio-*n*-hexyl isocyanate) in Figure 6 is direct evidence for an excess of one helical sense in these polymers and demonstrates a large chiral amplification, since the per unit bias favoring one helical sense arising from the deuterium substitution must be very small, while the intensity of the CD band is consistent with a large, although not complete, excess

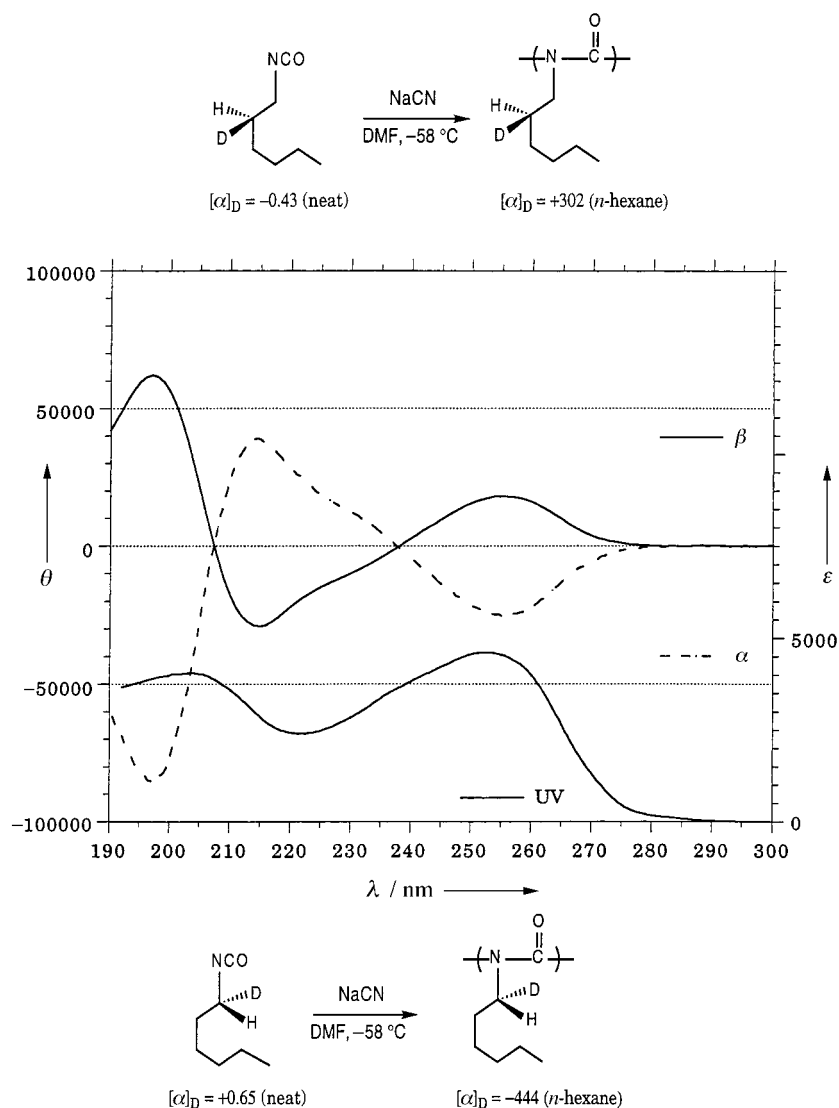


Figure 6. Graph showing the CD and UV spectra of poly(1-deuterio-*n*-hexyl isocyanate) and poly(2-deuterio-*n*-hexyl isocyanate) (reprinted with permission from reference [3]). Also shown are the structures and changes in optical activities in the conversion of the monomers into these polymers. θ = molar ellipticity; ϵ = molar extinction coefficient.

of the preferred helical sense. What is the structural basis of this isotope effect?^[21] Any hope to answer this question must come from knowledge of the energy parameter associated with the preference for one helical sense for the configuration of the deuterated stereocenter. As we shall see statistical physics can be very helpful in this regard.

The polyisocyanate chain with its long blocks of left- and right-handed helical states, interrupted occasionally by helical reversals, provides a model allowing understanding of the amplification factor that can be clearly seen from the effect of the stereospecific placement of the deuterium on the helical sense ratio. Since many units are forced by the low population of helical reversals to take one helical sense, any chiral perturbation favoring one helical sense must be multiplied by the number of these cooperating units. In this way a small effect per unit, which is certainly the situation for the deuterium placement, will be amplified.

In chains that are long enough to contain helical reversals, the amplification will be limited by the number of units between reversals. In chains so short that reversals rarely occur, the number of cooperating units will be the number of units in each chain, that is, the degree of polymerization. In this way the relative lengths of left- and right-handed blocks will reflect the amplified energy. In long chains the number of units of the favored helical sense will be larger than of the unfavored sense, with this ratio depending on the energy difference and the temperature in the usual manner. The helical reversals will interrupt the higher energy helical sense more often. However, the the population of reversals depends exponentially on temperature, and therefore the amplification controlling the energy difference between the left- and right-handed helical states will depend strongly on temperature. In short chains though, as defined above, temperature will play its conventional role in moderating the equilibrium between left- and right-handed helical states since there is no role for the reversal. The degree of polymerization is the amplification factor, and it is fixed.

These qualitative considerations can be expressed in quantitative form, as explained in detail below, by a one-dimensional Ising model for which a partition function can be written and specifically evaluated.^[22] The controlling parameters are temperature, T ; the degree of polymerization, N ; the excess energy of the helical reversal state, ΔG_r ; and the per unit energy favoring one helical state over the other, $2\Delta G_h$. The qualitative picture discussed above is expressed in quantitative terms for the limit of short and long chains by Equations (1) and (2) derived from the partition function.^[22] These equations are valuable in demonstrating in quantitative terms the picture of the amplification mechanism drawn above, although they are simplifications of a more complex equation which was actually used to fit the experimental data.

$$[\alpha] = [\alpha]_m \tanh(\Delta G_h N / RT) \quad (1)$$

$$[\alpha] = [\alpha]_m (L\Delta G_h / RT) / ((L\Delta G_h / RT)^2 + 1)^{1/2} \quad (2)$$

In Equation (1) the optical activity term on the left does not depend on the helical reversal energy ΔG_r . These are short chains and the optical activity will grow in proportion to N and to ΔG_h , the “chiral bias”. On the contrary, in Equation (2) for

long chains, N does not appear as a variable, while the term $L = \exp(\Delta G_r / RT)$ appears, designating the length of the helical sense blocks. As Equation (2) shows, as L becomes very large the observed optical activity $[\alpha]$ will approach the optical activity of a chain of a single helical sense, $[\alpha]_m$.

An intensive research effort produced samples of variable N of the two deuterated polyisocyanate; each sample had a narrow range of molecular weights around N for that sample. This was accomplished by synthesis of highly polydisperse polymers followed by fractionation by gel permeation chromatography. These materials were studied in great detail for the relationships between N , $[\alpha]$, and temperature T , and experiment and theory were shown to be in perfect agreement. The qualitative picture drawn for the polyisocyanates and the understanding of the source of the chiral amplification are supported quantitatively.^[23] The key energy parameters defining the excess energy of the helical reversal and the energetic bias favoring one helical sense arising from the deuterium substitution were revealed.^[23] These results took the work in two unrelated directions based on these different energy terms.

3.3. Chiral Bias

Only a tiny amount of energy, on the order of a single calorie per mole per unit^[23] (approximately $1/600$ of the ambient energy), distinguishes the left- and right-handed helices in the deuterated polyisocyanates, where the R configuration at the α - and β -carbon atoms favors opposing helical senses (Figure 6). In general terms, substitution of deuterium for hydrogen leads to a lower zero-point energy, and the stronger the carbon–hydrogen bond is, the greater is the decrease in the zero-point energy.^[21] The two hydrogens atoms of any methylene unit in the side chain of poly(n -hexyl isocyanate) are diastereotopic and therefore different to some extent in their bond strength. They exchange this difference as the local helix changes from one handedness to the other. If one hydrogen atom of one of the methylene groups is substituted for deuterium, this will favor the helical sense which confers a higher bond frequency on the substituted hydrogen. This is the basis of the approximately one calorie per mole difference we are measuring from the cooperative properties of the polyisocyanates, an energy so small as to be virtually invisible in the absence of the chiral amplification. Understanding the structural basis of the isotope effect, beyond the general considerations outlined above, is far more difficult because of its magnitude. Normally, in chemical phenomena, given the kind of information available to us on the polyisocyanates, we could point to the structural source of observed effects. However, in this case such a small amount of energy is so far within the noise level of any structural theory there is no hope at this time of pointing to the responsible structural features of the polymer. This interesting difficulty can be seen in even more extreme terms for the experiment described below.

When poly(n -hexyl isocyanate) is dissolved in a series of optically active solvents of similar structure, the circular

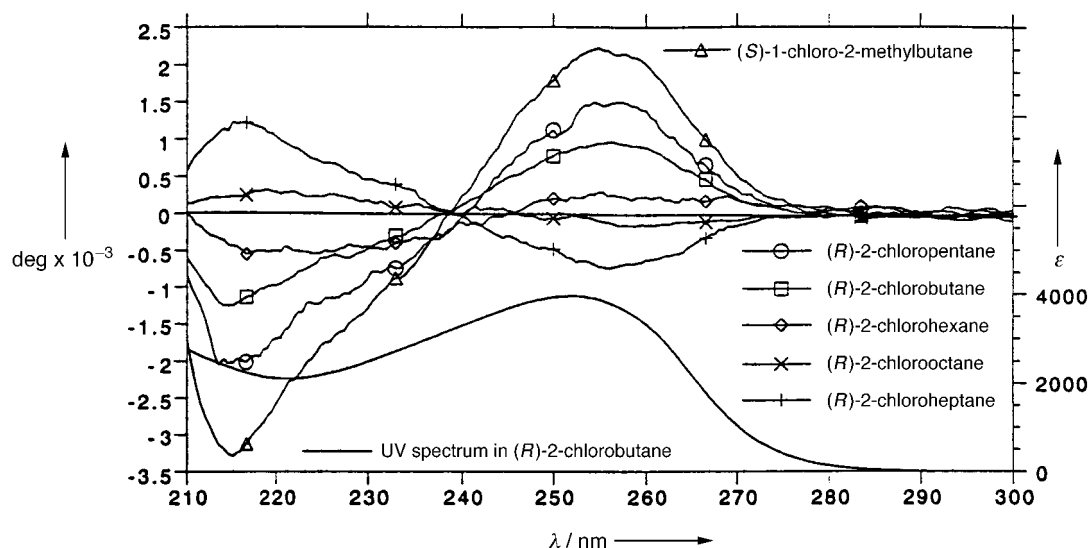


Figure 7. Circular dichroism spectra of poly(*n*-hexyl isocyanate) dissolved in optically active solvents at 20°C. UV spectrum shown only for (*R*)-2-chlorobutane. Continuous lines represent the experimental data; all concentrations of polymer are 1.9 mg mL⁻¹. Reprinted with permission from reference [24].

dichroism spectra (Figure 7) demonstrate that one of the dynamically interconverting helical senses is preferred by each solvent. Fitting this “chiral solvation” in the identical manner to the theory discussed above for the deuterated polyisocyanates^[23] for one of the chiral solvents, 2-chlorobutane, yields a remarkably minute energy. The chiral bias for the units is 0.04 cal mol⁻¹.^[24] Again, as with the isotope effect, we have no structural interpretation of the chiral solvation, and cannot test our speculations of what aspect of the relationship between the polymer chain and the solvent is responsible for the intriguing fact that a change in the length of the alkyl group results in a change in the preference for the helical sense for an otherwise identical stereocenter (Figure 7). As noted above, structural hypotheses are tested by predictions of energy and in this case the magnitude of the energy is beyond our predictive ability. However, there is a way for the experiment to be turned in a manner to allow a correlation with structural theory.

Chiral solvation^[24] opens a new way to look at an interesting phenomenon in the solution properties of both polymers and small molecules. Mixing achiral or racemic solvents with the nonracemic solvents described in Figure 7 allows determination of the contact of the “competing” solvents with the polymer backbone by measuring how the overall solvent composition scales with the chiral optical signal. This solvent–polymer contact is an interesting aspect of this first use of chiral solvation to measure preferential solvation, and differs from other preferential solvation experiments in polymers where, for example, index of refraction increments place ill-defined boundaries on the nature of the solvent surrounding the polymeric solute. Actual contact with the chiral solvent is necessary to cause a discrimination between the helical senses, and this is directly responsible for the magnitude of the circular dichroism signal.^[25] Treatment of the circular dichroism data obtained on mixing various proportions of (*S*)-1-chloro-2-methylbutane with 13 achiral or racemic solvents allowed determination of a series of

equilibrium constants *K* defining the preferential solvation (Table 2).^[25]

Why should the two isomeric alcohols 1- and 2-butanol and 1- and 2-octanol, which are nonsolvents for the polymer and act to precipitate the polymer on addition to a solution in (*S*)-1-chloro-2-methylbutane, preferentially solvate the polymer up to the point of precipitation? In fact the alcohol isomers which are the stronger precipitants are more attracted to the polymer! Why should the highly branched hydrocarbon 2,2,4,4,6,8,8-heptamethylnonane, also a precipitant for the polymer, be strongly attracted to it? Fortunately, in contrast to the isotope and solvation effects on chirality discussed above, these preferential solvation effects are likely associated with solvation energies of a magnitude which can be subjected to theoretical analysis, although this possibly valuable effort has yet to be undertaken.^[26]

Table 2. Preferential solvation of poly(*n*-hexyl isocyanate) by 1-chloro-2-methylbutane in solutions of this solvent with an achiral or racemic cosolvent.

Cosolvent	<i>K</i> ^[a]	Vol. % cosolvent at polymer precipitation
2,2-dimethylbutane	2.90	
octane	2.40	
hexane	2.11	
2,2-dimethylhexane	1.40	
2-chlorobutane	0.99	
2-butanol	0.86	55
tetrahydrofuran	0.84	
1-bromobutane	0.75	
1-butanol	0.75	40
chloroform	0.63	
2-octanol	0.57	50
1-octanol	0.36	25
2,2,4,4,6,8,8-heptamethylnonane	0.27	60

[a] $K = ([PA][I])/([PI][A])$, where [PA] and [PI] are the concentrations of optically active and inactive solvents in contact with the polyisocyanate backbone. [A] and [I] are the concentrations of optically active solvent and inactive solvent.

3.4. Helical Reversal

In hydrocarbon solvents the value of $\Delta G_r^{[22-24]}$ is about $3.8 \text{ kcal mol}^{-1}$ for poly(*n*-hexyl isocyanate), which translates to the low population expected (see Section 3.2), that is, about one helical reversal per about 600 units at 20°C . This energy could be used in concert with an empirical force field to determine the torsional potential along the backbone and to describe the conformational properties of the reversal.^[27]

These insights arising from the empirical force field show that the low number of helical reversals along the chain, about one every 120 nm, and the 50° angular change in the chain direction cannot contribute significantly to the overall chain dimension. This agrees with light scattering and viscosity measurements comparing poly(*n*-hexyl isocyanate) with the deuterated, optically active polyisocyanates described in Figure 6.^[18] The answer to the longstanding question concerning the dimensions of the polyisocyanates, the question which initially drove the inquiry leading to the experiments discussed here, is that this property is controlled by local segmental motions. As predicted originally by Cook,^[17a] small dynamic variations in torsion and bond angle have a far larger effect on the global dimensions and the persistence length than the kinks in the chain associated with the rarely occurring helical reversals.^[17, 18]

The kink in the chain caused by a helical reversal has interesting consequences in situations where the chains are not isolated from each other. This was seen first in aggregates formed by optically active variations of poly(*n*-hexyl isocyanate) in hydrocarbon solvents at low temperature. These aggregates can be detected in dilute solution by light scattering methods^[28] and are revealed in macroscopic dimensions when the aggregates lead to gels which form and unform as a function of temperature, that is, they are thermally reversible. In such gels chain enlargements rather than cross-links maintain the gel structure. When the polyisocyanate chains forming these aggregates consist of unequal populations of left- and right-handed helical blocks separated necessarily by helical reversals, entering the aggregate phase was associated with a strong increase in the optical activity (Figure 8). This must mean a decrease in the number of helical reversals, which makes sense considering that electron microscopy^[28] of the gel state arising from the aggregate shows parallel packing of the chains in fibrous bundles. In such a packing arrangement the kinked helical reversals would interfere, and since they are an equilibrium state their population would be reduced. In chains in which there was an excess of one helical state, the population of the preferred helix would increase, giving rise to an increase in optical activity, as we observe.^[28, 29]

The parallel packing seen in the aggregates of the polyisocyanates has similarities to the parallel arrangements of the mesogenic molecules in liquid crystals,^[31] and in fact the polyisocyanates form lyotropic liquid crystals. What would be the fate of helical reversals in a liquid crystal phase? To address this question, a subject of theoretical interest,^[12, 32-34] a series of copolymers of *n*-hexyl isocyanate with varying proportions of one or the other of the enantiomers of 2,6-dimethylheptyl isocyanate was prepared. In this way we

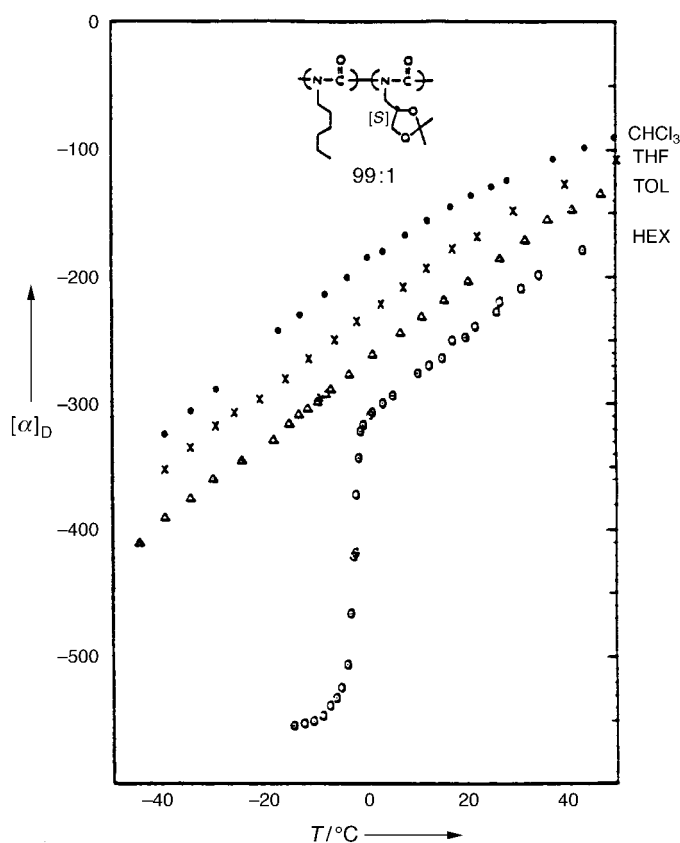


Figure 8. The temperature dependence of the D-line optical activity for a random copolymer of *n*-hexyl isocyanate and a chiral nonracemic isocyanate in chloroform (0.54 mg mL^{-1}), tetrahydrofuran (0.60 mg mL^{-1}), toluene (TOL, 0.82 mg mL^{-1}), and hexane (HEX, 0.54 mg mL^{-1}) in descending order. Reprinted with permission from reference [35].

obtained chains of a single helical sense as well as chains with blocks of opposite sense. Only the latter would contain helical reversals.

Figure 9^[36] is a plot of Xr , a parameter designating the optical rotation in dilute solution at a constant dopant concentration, against a term $2\pi/\text{pitch}$, defining the pitch property of the continuously twisting cholesteric arrange-

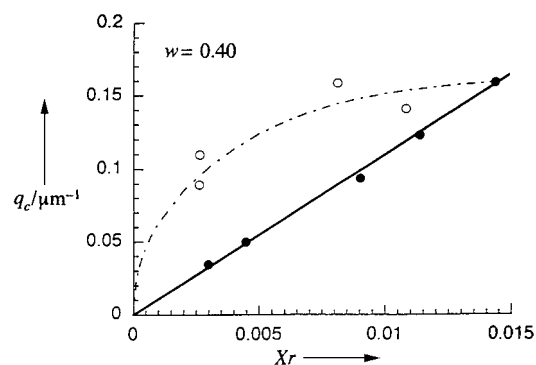


Figure 9. Plot of $2\pi/\text{pitch}$ versus Xr , a parameter related to the ratio of left- and right-handed units in the samples for optically active polyisocyanates used as dopants for the lyotropic liquid crystal formed from poly(*n*-hexyl isocyanate). Open circles are data for polymers with left- and right-handed blocks within each chain, while closed circles are for mixtures of fully left- and fully right-handed chains. The total polymer concentration in toluene is 40%. Reprinted with permission from reference [36].

ment. The plot presents data for the cholesteric liquid crystals formed by doping a nematic phase of poly(*n*-hexyl isocyanate) in toluene with the various polyisocyanates designated. Two variations of the dopants were used for the data in Figure 9. The filled circles represent the results for mixtures of mirror-image chains of a single helical sense with different compositions, while the unfilled circles represent the results for polyisocyanate chains with blocks of helical senses along a single chain. The data clearly show that the cholesteric liquid crystal property (ordinate) scales linearly with the dilute solution property (abscissa) for the dopants which are mixtures of fully left- and fully right-helical chains, whereas identical ratios of left- and right-handed helices within single chains scale nonlinearly with this cholesteric pitch property.

The nonlinearity in the data shown in Figure 9 for polyisocyanates with alternating helical blocks can reasonably arise from the fact that the ratio of left- and right-handed helical units determined from the optical activity of the dilute solution does not represent the ratio in the liquid crystal state. In fact, the data showing tighter twisting (smaller pitch) for the helical block dopants, the open circles in Figure 9, inform us that the enantiomeric excesses in these dopants are higher in the liquid crystal than in dilute solution. The proportion of the favored helical sense is expanding at the expense of the other helical sense, which is expected if the helical reversal population is reduced in the liquid crystal compared to isotropic solution yielding an example of this sought-after phenomenon.^[32, 33, 37]

The details of the helical reversal conformation, as described by the force field calculation,^[27] are shown in Figure 10. The kink in combination with the stiffness of the polyisocyanate chain indicates that movement of the reversal would force many units of the chain on either side of the reversal to move along with it. This would sweep out a large volume,



Figure 10. Molecular mechanics generated helical reversal in a polyisocyanate. Reprinted with permission from reference [3].

which suggests that in a glassy state, where many entanglements offer impediment to motion, the movement of the reversal would be severely impeded or even stopped. Consider spin coating a sample of an optically active polyisocyanate with helical reversals between blocks of left- and right-handed units at a temperature far below the glass transition temperature. On raising the temperature the polyisocyanate would be frustrated in its ability to respond to the increase in thermal energy and, as the glass around it, would fall out of equilibrium. The temperature would be too high for the low population of helical reversals. On reaching the melt state the system would equilibrate and the population of the helical reversals would be suddenly diminished, causing a large reduction in the optical activity.

Successful blending^[38] of certain functionalized polyisocyanates with copolymers of styrene and vinyl phenol allowed this experiment to be carried out. A material was formed without birefringence, allowing measurement of the optical activity properties of the polyisocyanate in the solid state. The results, along with the variation of optical activity with temperature in solution as a comparison,^[39a] are shown in Figure 11. The strong change in optical activity on reaching the glass transition temperature confirms the theoretical picture drawn above and is therefore consistent with the kinked nature of the reversal determined from the force field calculation (Figure 10). We have extended this idea to the motions associated with the racemization of 1,1'-binaphthyls with oligophenyl "paddles" of various lengths attached to

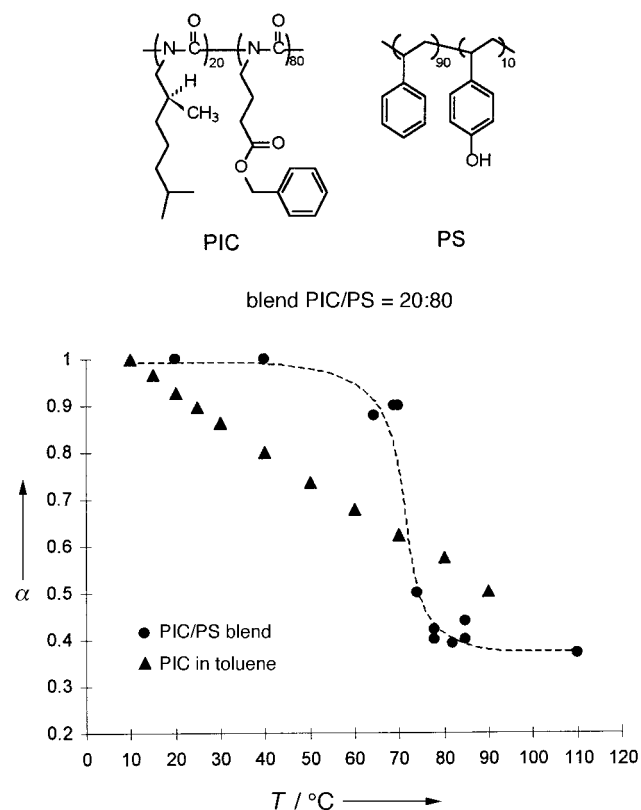


Figure 11. The temperature dependence of the optical properties of a polyisocyanate with unequal proportions of left- and right-handed blocks in dilute solution in toluene and in an amorphous blend with a glass transition temperature near 70 °C. PIC = polyisocyanate; PS = polystyrene.

each ring at the 6- and 6'-positions. We measured the effect of the length of the paddle (number of phenyl units) on the restriction to motion at the glass transition temperature in several polymers; this led to a new way to judge the correlation between length scale and motion in polymeric glassy and melt states.^[39b]

3.5. The Quenched Random Field

When the chiral information distinguishing the helical senses of the polyisocyanate are not distributed uniformly along the chain, as in the case of the deuterium substitution or the chiral solvation discussed in Section 3.3, the Ising model describing the situation is slightly altered, leading to an important change in the partition function derived from it. For this partition function to be evaluated and lead to algebraic expressions such as Equations (1) and (2), every unit of the chain must be identically affected by the chiral information. The Ising model for the uniform chiral influence is seen in Equation (3), while that for a random input of this chiral information is seen in Equation (4).

$$H = -\frac{1}{2}\Delta G_r \sum_{i=1}^{N-1} \sigma_i \sigma_{i+1} - \Delta G_h \sum_{i=1}^N \sigma_i \quad (3)$$

$$H = -\frac{1}{2}\Delta G_r \sum_{i=1}^{N-1} \sigma_i \sigma_{i+1} - \sum_{i=1}^N \Delta G_{h,i} \sigma_i \quad (4)$$

The Ising models described by Equations (3) and (4) are widely used in statistical physics to describe the cooperative properties of one-dimensional magnetic materials. In magnetic systems, σ_i is the spin state representing the localized magnetic moment, which can be +1 or -1. The first term in the Hamiltonian H represents the energy cost of a boundary between domains of opposite spin, and the second term represents the energy of a single spin interacting with the local magnetic field. For polyisocyanates, the spin σ_i corresponds to the local helical sense, the first term in the Hamiltonian represents the energy cost of a helical reversal, and the second term represents the local chiral bias. In the standard Ising notation, the first term in the Hamiltonian has the coefficient J and the second term has the coefficient h . Here, we replace these coefficients by $\frac{1}{2}\Delta G_r$ and ΔG_h , respectively, in order to emphasize the interpretation of these coefficients for polyisocyanates.

The movement of the ΔG_h term from outside the summation term to inside the summation in Equations (3) and (4) represents the nature of the chiral information. In Equation (3), which describes a uniform chiral field, all units of the chain are subjected to an identical influence. In the case of Equation (4) though each unit of the chain may be subject to differing chiral influences, therefore the use of $\Delta G_{h,i}$, which must appear within the summation to allow this higher level of information. Unfortunately, evaluation of the partition function derived from Equation (4) requires specifying the precise input of the chiral information, a factor that will differ according to how the chiral information is arranged along the chain. This is termed a “quenched random field”. In a random copolymer of, for example, chiral and achiral units, each

differing chain would require a different partition function. We cannot therefore for any random system apply the theory developed for the uniform chiral field [Eqs. (1)–(3)]. How can such random systems, which can certainly be synthesized (see below), be theoretically dealt with?

In analogy to the experiments of the Italian researchers where copolymers of enantiomers and of chiral and achiral monomers were synthesized (Figures 3 and 4),^[1, 4, 7–9] polyisocyanates were prepared with different units along the chains. The experimental results for these copolymers in which the chiral information is fixed by the details of the mechanisms of the copolymerizations—that is, in which there is a quenched random chiral field—are found in Figure 12^[35] and Table 3.^[40, 41] As in the Italian work we see the signature characteristics of cooperativity in the nonlinear relationships between the enantiomeric content of the units used in the synthesis and the chiral optical properties of the polymer.

In qualitative terms the data in Table 3 demonstrate that a small proportion of chiral units, shown to be randomly distributed in the chain among achiral units, causes an excess

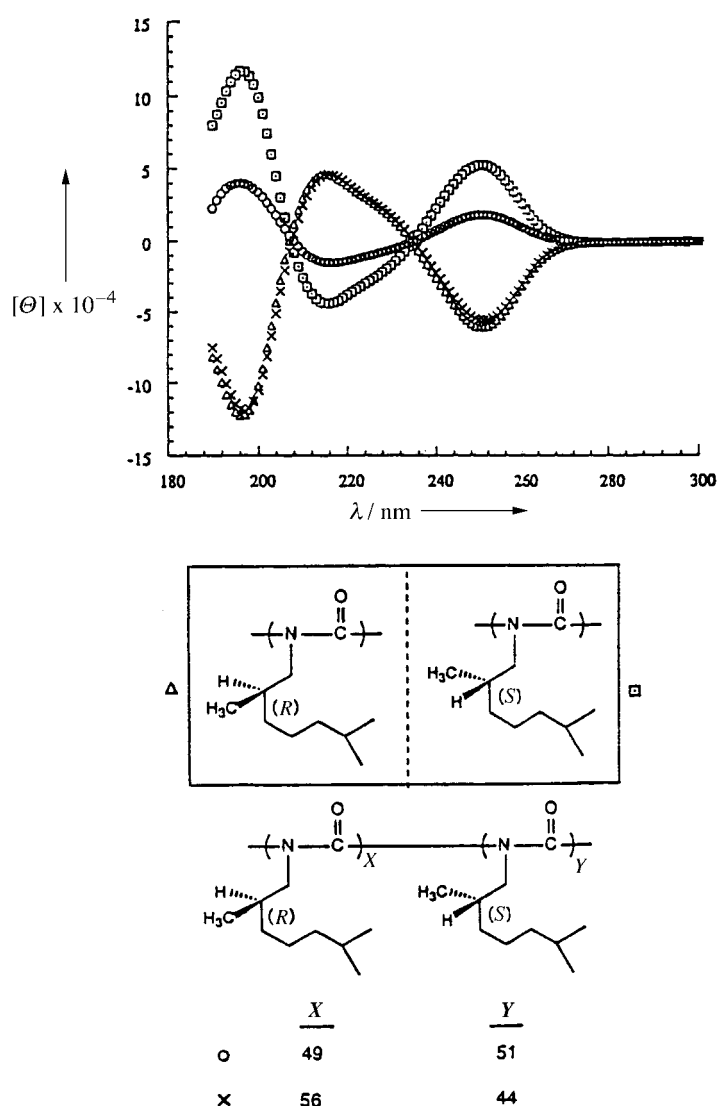
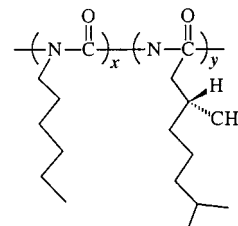


Figure 12. Circular dichroism data for random copolymers of enantiomers. Reprinted with permission from reference [40].

Table 3. Specific rotation of polyisocyanate copolymers.^[a,b] [35]


x	y	$[\alpha]_D^{20}$	$[\alpha]_D^{20}$
100	0	0	0
99.5	0.5	-140	-66
97.7	2.3	-379	-231
85	15	-532	-480
0	100	-514	-500

[a] Measured in CHCl_3 ($c = 0.5 \text{ mg mL}^{-1}$). [b] x = mole percent of *n*-hexyl isocyanate, y = mole percent of 2,6-dimethylheptylisocyanate.

of one helical sense far out of proportion to their population. A chain with 15 % of the chiral units gives essentially the same optical activity as a chain made entirely of the chiral units, while even the presence of 0.5 % of the chiral units provides a large optical activity. In addition the strong temperature dependence of the optical activity for a chain with less than a full preference for one helical sense is consistent with the exponential relationship of the helical reversal population with temperature. That population is reduced at lower temperature, as discussed above for the uniform chiral field work, as a result therefore increasing the domain sizes and the cooperativity and the effect of the chiral units. These experiments have been called the “sergeants-and-soldiers” experiments, the chiral units being sergeants and the achiral units soldiers.^[35]

The results in Figure 12 are also startling. Here a polyisocyanate made up of an isocyanate synthesized from a citronellic acid (3,7-dimethyl-6-octenoic acid) which is considered essentially racemic by Aldrich Chemical Company yields a polymer whose circular dichroism spectrum is identical to that of a polymer synthesized from nearly enantiomerically pure monomers. The enantiomeric excess in the “racemic” monomer turns out to be 12 %. Even a 2 % enantiomeric excess in the monomer units is enough to produce one-third of the circular dichroism signal of the polymer of a single helical sense. This phenomenon has been termed “majority rule” and arises from the minority units taking part in the helical sense of the majority units, presumably to avoid introducing increased numbers of helical reversals.^[40]

These experiments are subject to analysis using the Ising model expressed in Equation (4), and therefore special procedures are necessary to apply the cooperative theory. The effort, as seen below, offers insights into the nature of the cooperativity that are entirely contrary to one’s intuition.

One approach to evaluating the Ising model for the quenched random field is a numerical transfer-matrix calculation,^[42, 43] where one specifies specific arrangements of the groups along the backbone within the random constraint. Each specific realization can then be theoretically evaluated

since the detailed characteristics of the chiral field are specified. If one then averages over all these specific realizations, given that one has chosen enough of them to describe the system realistically, something which is only limited by computer time, the optical activity can be predicted as a function of the energetic parameters and the degree of polymerization. This approach involves a great deal of computation, but correlations with experimental measurements of the relationship between N and $[\alpha]$ yield precise results for the energetic parameters ΔG_r and ΔG_h . Although this information has great value in continuing work in the area, it does not yield qualitative insight into how the various parameters interact with each other to control the properties of the cooperative system.

In an approximate analytical approach developed for the specific situation of a copolymer of achiral and chiral units with proportions r and $1 - r$, respectively (Table 3), the chiral and achiral units have $\Delta G_{h,i} = \Delta G_h$ and $\Delta G_{h,i} = 0$. In this case the characteristic domain size L is determined precisely in the same way as for the uniform chiral field discussed in the analysis of the deuterated polyisocyanates (see Section 3.2)—that is, with $L = \exp(\Delta G_r/RT)$ —except in the situation of small chains, where N may limit the domain size. If we define the chiral order parameter M as the fraction of the optical activity of a chain of a single helical sense, under certain approximations, M for the random copolymer of chiral and achiral units can be expressed by the total chiral field acting on a domain of size L as given by Equation (5).^[42]

$$M = \tanh(rL\Delta G_h/RT) \quad (5)$$

All the energy terms in Equation (5) can be expressed, as discussed above, in terms of ΔG_r and ΔG_h , and so estimation of these values allows predictions of the optical activity as a function of the proportion r of chiral units. In the nature of the hyperbolic tangent the optical activity will scale linearly with low values of r and show saturation at a value of r that depends on the energetic parameters. Saturation at low values of r is seen in the experimental data in Table 3, and a numerical analytical procedure allows fitting of Equation (5) to these data. By this procedure a plot can be constructed which defines a locus of points in the $(\Delta G_h, \Delta G_r)$ plane which fit the experimental findings. By assigning the value of ΔG_r as that obtained from the uniform chiral field, one can determine ΔG_h .^[42] Although Equation (5) offers an accurate view of the cooperative factors in the copolymers of chiral and achiral units, the analysis provides no further insight beyond our qualitative understanding that increase of L and/or ΔG_h and reduction of T must increase the excess of one helical sense and therefore M and the optical activity.

This sergeants-and-soldiers system^[35] has in addition been treated by the numerical transfer-matrix calculation discussed above, and this approach in combination with a large range of samples with molecular weights of narrow dispersity yields accurate values for the two energetic parameters.^[43] The theoretical work leaves little question of the accuracy of the conformational model proposed for this polymer.

Analysis of the quenched random field of the copolymer of enantiomeric units (Figure 12) using the approximate analyt-

ical approach offers two surprises into how the cooperativity works in these copolymers, which has an important impact on how to vary the experimental approach. In the copolymer of enantiomeric units we define proportions of p and $1-p$ for the randomly placed enantiomeric units. If the right-handed units have $\Delta G_{h,i} = +\Delta G_h$ and the left-handed units $\Delta G_{h,i} = -\Delta G_h$, and ΔG_r , as usual, is the energy of the helical reversal, an approximate analytical analysis shows that the domain size L of a single helical sense is determined not only by ΔG_r and the temperature, but as well by ΔG_h in an interesting manner. This is seen in quantitative form in Equations (6)–(8).^[44] As expected, the chiral order parameter M —that is, the excess of one helical sense and therefore the optical activity—will increase as the domain size L increases and as the enantiomeric excess $p - 1/2$ increases.

$$L_{\text{rf}} = (\Delta G_r / 2\Delta G_h)^2 \quad (6)$$

$$1/L = 1/L_{\text{rf}} + 1/L_{\text{th}} + 1/N \quad (7)$$

$$M = \text{erf}[(2L)^{1/2}(p - 1/2)] \quad (8)$$

The error function, erf, can be described in the following manner: If one were to draw a Gaussian function around zero, movement along the abscissa is determined by the right-hand side of Equation (8). From the nature of the Gaussian, small deviations from zero subject a far larger volume under the curve than further away from zero. The volume under the curve subtended determines the value of M , and the sharper the Gaussian, the faster M rises for small increases in enantiomeric excess. The error function therefore causes small increases in enantiomeric excess close to the racemic state to result in far larger changes in optical activity than equivalent changes at higher enantiomeric excesses. The optical activity is predicted to change steeply only near to the racemic state and to reach a value corresponding to a single helical sense far from the enantiomerically pure state.

The term L_{rf} designates the random field domain size that is influenced by the competition among the enantiomeric units for the helical sense of the backbone. This competition, not seen in the uniform field systems or in the quenched random field of chiral and achiral units, is one of the fascinating aspects of the enantiomeric copolymers. Before going into this let us see how the domain that ultimately determines the cooperativity is determined itself. In the sergeants-and-soldiers copolymers or in the deuterated polyisocyanates or in the chiral solvation the cooperative domain, as discussed above, is determined by ΔG_r and T , unless it is limited by N . The cooperative domain though in the copolymers of enantiomers is determined in a far more complex and interesting manner [Eq. (7)].

Under conditions where the degree of polymerization and the thermal domain are large, Equation (7) informs us that the domain size L in Equation (8) will be dominated by the random field domain size. This turns out to be the experimental situation for all of the data in Figure 12.^[44] Under these conditions L in Equation (8) can be replaced by the right-hand side of Equation (6). Since ΔG_r is divided by ΔG_h , and squared, the algebra remarkably predicts that, within

certain limits, *increasing* the chiral bias will *decrease* the influence of the majority enantiomer, giving therefore lower optical activities. This can be understood from the symmetry properties of the system. Any change in ΔG_h will effect the majority and minority units with equal and opposite effects, so that the minority objection will rise in concert with the majority force for its favored helical sense. The physics predicts that the minority objection will override the majority force by limiting the cooperativity. In this most unhuman situation of cooperativity along a one-dimensional polymer chain we encounter a familiar human behavior.

The theory has been applied to the optical activities of polymers obtained from the copolymerization of enantiomers for several enantiomeric excesses, including those in Figure 12. Using the value of ΔG_r obtained from the uniform chiral field work on deuterated polyisocyanates and the value of ΔG_h for the chiral group shown in Figure 12, estimated from a force field calculation,^[27] one can predict the change of optical activity with enantiomeric excess. The prediction fits the experimental data with no adjustable parameters (Figure 13).^[44]

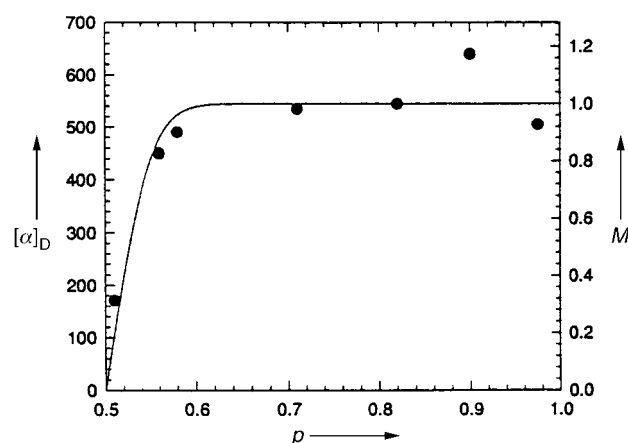


Figure 13. Fit of the theory from the random field Ising model to the data points for the optical activity versus the enantiomeric excess for random copolymers of enantiomers. $[\alpha]_D$ is the optical activity for the random copolymer at the sodium D line as a function of enantiomer concentration p . Solid line: theoretical prediction for the chiral order parameter M from Equation (8), with the domain size $L = 164$. The prediction agrees with the data with no adjustable parameters, other than the relative scale of the vertical axes. Reprinted with permission from reference [44].

Although experiments are in progress to test the prediction about the effect of the magnitude of the chiral bias ΔG_h , the prediction that reduction of the minority objection to the helical sense of the majority units increases the domain size and therefore the optical activity is made in another way. Terpolymerization of mirror-image enantiomers near to the racemic state with an achiral monomer could be used to modify the theory^[45] to produce Equations (9) and (10), which are directly analogous to Equations (6) and (8). Here r is the fraction of the chiral comonomers in the terpolymer. If the

$$L_{\text{rf}} = 1/r(\Delta G_r / 2\Delta G_h)^2 \quad (9)$$

$$M = \text{erf}[(2rL)^{1/2}(p - 1/2)] \quad (10)$$

random field domain dominates the term L , it follows that the right-hand side of Equation (9) can be substituted in Equation (10), and that r cancels out! In other words, if N and the thermal domain size L_{th} are large enough that L_{tr} can be used in the error function equation, dilution of the competing chiral units with achiral units will make no difference to the optical activity. The critical cancellation of r in this case arises qualitatively from the fact that this dilution does not change the number of chiral units within a single cooperative domain. This effect of the dilution of the chiral units with achiral units has now been observed experimentally, with the details in line with the predictions of the theory.^[46]

The possibilities for experiment and the development of new materials are extended also by random copolymerization of enantiomerically pure isocyanates of different structure, where each structure favors the opposite helical sense. Since the chiral biases of each of the competing units differ, in contrast to enantiomers, the helical senses of the polymer will be equally populated at a ratio, a pseudoracemic state, other than when the proportion of the competing chiral units is 50:50. In addition since the temperature dependencies of these chiral biases will differ, again in contrast to enantiomers, this pseudoracemic ratio will depend on temperature. It follows that the proportion of the chiral comonomers, which can be easily varied, determines the temperature at which the optical activity is zero, but below and above that temperature the optical activity increases with opposite sign. This unusual effect, which can also be described by the statistical physical theory discussed above, has been recently observed.^[47]

4. Summary and Outlook

For the phenomena described here, the helical systems associated with biological origins have the disadvantage of a given nonracemic chirality. In this way nature blocks our observations of certain fascinating aspects of the cooperativity of helical arrays, although when it serves a specific purpose “wrong” enantiomers may be inserted in specific places.^[48] In synthetic systems, on the contrary, incorporation of non-racemic chirality is an additional burden, and the work presented here shows that this burden may be considerably alleviated by taking advantage of the amplification of chirality inherent in helical systems. Could it be possible to design a catalytic helical polymer directed to asymmetric synthesis in which the enantiomeric excess of the products were independent, over a wide range, of the enantiomeric excess of the units making up the polymer?^[49] Analogously, could the chromatographic properties of a chiral polymer allow the same separation of enantiomers independent, over a wide range, of the enantiomeric excess of the units making up the polymer?^[50]

Helical arrays are of considerable interest^[51] and several show parallels to the findings discussed here. Hopefully the intense effort we have taken to understand the limits and theoretical basis of these effects may help others to evaluate the limits and opportunities in other materials. The fact that these effects find parallels in materials as disparate as vinyl

polymers and an analogue of the Nylons is encouraging, as is the fact that polypeptides synthesized from mixtures of enantiomers also show a majority rule effect.^[52] In another direction, could the lamella boundaries of helical polymer crystals play the role of the helical reversals, so that annealing could determine the amplification resulting from stereospecific placement of deuterium at, for example, the 3-position of poly(1-butene) and produce excesses of a single helical sense in the crystal?^[53]

The amplification characteristics studied here spotlight the inability of structural theory to deal with the very small energies that entirely control the chiral properties of these helical polymers. Certainly such small forces are widely present in all of chemistry, and likely amplified in many cases,^[54] but their understanding is less critical in systems in which they play a minor role because larger forces are also at work in controlling the equilibrium properties, for example in crystals or in the folding of proteins. This point goes beyond stereochemistry. Such structurally incomprehensible small forces can yield complete control over miscibility in polymer blends such as that between poly(styrene) and poly(vinyl methyl ether). Here deuterium substitution of all the aryl hydrogen atoms considerably helps the miscibility.^[55] Is this due to $C-H \cdots O-R$ hydrogen bonds^[56, 57] between these hydrogen atoms and the ether oxygen atoms, attractive interactions that could have only minor effects in the absence of the amplification associated with large numbers of polymer units in contact?

The work presented here might be relevant to proposals that the circularly polarized light discovered in outer space was responsible for small enantiomeric excesses produced by photoresolution processes that then lead to the origin of homochirality in life. The prerequisite must be chiral amplification, which as shown here requires a stable helix, a conformational state which is common in biological systems.^[58]

This kind of idea has an evolutionary aspect since in such a polymer the minority units residing in the helix sense of the majority, and vice versa, would be of higher energy, as quantitatively discussed in this review. Even a small excess of majority units could therefore lead to a preference for epimerization of the minority units to the configuration of the majority units, which would lead to a fuller excess of the majority helical sense and thus to a cycle of increasing enantiomeric excess of the units making up the chain. The outcome of this cycle, and as well the minimum excess of majority units to initiate the evolutionary process, would depend on the same parameters controlling the one-dimensional cooperativity discussed in this review and could also be described theoretically by a statistical physical model. The decreased entropy of the enantiomerically enriched system opposes the process and enforces the limitations. Within these limits, even in an ensemble of chains with an overall exactly equal proportion of the competing enantiomers, there could be an excess of one or the other mirror-related units in the single chains so that an epimerization mechanism could allow the ensemble to evolve toward a true racemic mixture of chains. The observation of majority rule in certain DL-polypeptides^[52] and the variety of mechanisms for epimeriza-

tion of the amino acid constituents suggests that these ideas may apply to a biologically relevant system.^[59,60]

The interplay of classic stereochemical ideas with cooperativity, a characteristic of large molecular organizations, continues to be rich with research potential.

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Porous Solids from Rigid Colloidal Templates: Morphogenesis**

Christine G. Göltner*

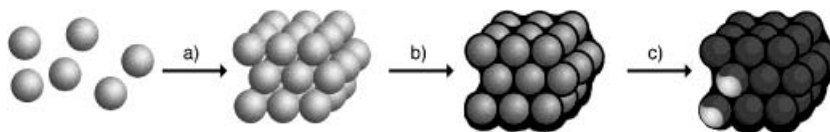
The creation of nanoporous inorganic and organic solids through the exploitation of colloidal objects as templates is a new development in materials science which recently has been receiving great attention and coverage in top-rank journals. The reasons for this trend are obvious: To generate novel materials with improved properties, modern research is increasingly focusing on structuring matter on a nanometer-length scale rather than producing molecularly new species. The formation of porosity on the length scale of a few nanometers is a comparably simple method of creating new properties in old—that is, chemically well known—materials. Furthermore, the exploration of “nanospace” possesses an undeniable aesthetic attraction.

In modern approaches towards porous ceramic nanostructures, surfactants are used to stabilize the interface between inorganic and organic matter; therefore they are superbly suited as structure-directing porogens. The synthetic pathways^[1,2] are now sufficiently understood to allow predictable production of a large variety of inorganic pore systems. This is not always the case for organic porous polymer gels, as the principle of casting the “soft” amphiphile template into an organic polymer gel fails. The dimension of organic pore systems prepared in organized surfactant media is all too often located on the length scale of microns instead of a few nanometers. The successful synthesis of porous organic polymers from supramolecular assemblies has been reported for polymerizable surfactants,^[3] but the templating mechanisms here are far more complicated and sensitive to phase disruption than in the case of inorganic mesoporous nanostructures: Nanostructured polymers are difficult to make by direct templating of supramolecular aggregation structures. The often observed structural phase changes result mainly from macroscopic demixing, because the amphiphile aggregate structure is too soft.

This simple conclusion leads to an equally simple consequence, namely, the use of rigid colloidal templates, where

solid objects of nanoscale dimensions act as structure-directing media. Besides structural integrity throughout the polymerization process, the main prerequisite for a successful templating of a “colloidal crystal” (i.e., the ordered arrangement of particles) is the sufficient compatibility of the template with the polymer precursor. Individual compatibility problems can even be addressed by adding amphiphiles or cosurfactants to stabilize the resulting interface. In this context the use of organic colloidal templates (i.e., polymer latex spheres) has particular potential, because modern heterophase polymerization techniques allow the synthesis of lattices of almost any size and with a rich variety of surface functionalities.

The general method of rigid-colloid templating occurs in three stages (Scheme 1), namely, the assembly of nanosized



Scheme 1. The synthesis of porous solids from rigid colloidal templates occurs in three steps: a) assembly of colloidal particles into a regular array, b) impregnation of template with monomer(s) and polymerization, and c) removal of the template.

spherical objects into a more or less regular array (a), filling the interstitial volumes of this colloidal crystal with a precursor mixture and polymerization (b), and finally removal of the template (c). In contrast to classical procedures, rigid colloidal templating can be applied to the synthesis of inorganic and organic polymers (IP and OP); inorganic as well as organic templates (IT and OT) can be used to prepare ordered porous solids.

The most regular pore systems are produced by the OT–IP approach. Here the interstitial volumes within a layer of monodisperse, densely packed, polymer lattices (between 0.2 and 1 μm in diameter) are filled with a siliceous sol–gel precursor, which solidifies there.^[4] The colloidal crystal is obtained by simply densifying a latex dispersion on a filter membrane. Since in the OT–IP approach the templating colloidal crystal is not intrinsically compatible with the growing inorganic polymer, it is necessary to create compatibility by adsorbing a surfactant layer on the template surface. A similar approach has been reported for the synthesis of other porous ceramic oxides.^[5,6] Here the crystallization of monodisperse latex spheres is achieved by pouring a latex

[*] Dr. C. G. Göltner
Max-Planck-Institute for Colloids and Interfaces
Forschungscampus Golm
Am Mühlenberg, D-14476 Golm (Germany)
Fax: (+49) 331-5679502
E-mail: goeltner@mpikg-golm.mpg.de

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dispersion through a paper-covered filter funnel, where it forms a colloidal crystal. The sol–gel synthesis of titania, zirconia, and alumina within this polymer layer produces a 1:1 cast of the latex assembly. The macropore size is directly related to the diameter of the latex particles used to displace the growth of the inorganic ceramic oxide, commonly between 300 and 400 nm. Achieving compatibility by an additional surfactant is not necessary, as the alcohol formed by the hydrolysis of the ceramic precursor sufficiently mediates between the two materials. This procedure works equally well for the templating of synthetic poly(styrene) opal, which after removal of the organic matter leaves a “crystal of air spheres” in titania.^[7]

But how about using the rigid templates for the generation of organic nanostructures? In addition to structural integrity and compatibility, a further prerequisite to be fulfilled by a suitable template is its facile removal from the organic polymer. And if an organic template can be removed from an inorganic cast, an inorganic template must surely be separable from its organic replica. Indeed, the principle of the rigid colloidal template can be reversed: The production of a cross-linked polymer within the continuous, three-dimensional pore system of a suitable mesoporous silica object (IT–OP) and subsequent dissolution of the inorganic matrix with hydrofluoric acid affords the organic polymer replica without any detectable loss of order.^[8]

The most recent development in colloidal templating, however, is the use of silica spheres as templates for the generation of porous organic polymers.^[9] In analogy to the crystallization of latex spheres, monodisperse silica particles can be assembled into colloiddally crystalline pellets. Slight sintering of the pellet causes the nanosized spherical entities to partially sinter and fuse, thus rendering additional stability to the template. The impregnation of this inorganic template with a mixture of monomer and radical initiator preserves its structure as an organic cast. By this route, it is possible to create rigid as well as flexible porous polymers with pore diameters between 15 and 35 nm. The pore size can be chosen freely through the appropriate chemical composition of a copolymer, because the extent of shrinkage of each copolymer depends linearly on the monomer fraction. Although the control over the pore size is reliable, it is only given for a particular chemistry: Not all monomers will show exactly the same behavior, so that either the chemical composition of the polymer or the pore size can be chosen freely. However, having mapped a master curve, there is a high degree of control of surface functionality and pore size.

By using the OT–OP route, three-dimensional porous poly(urethane) membranes with pore diameters around 0.5 μm are obtained by filling the voids between densely packed poly(styrene) particles with a photocurable prepolymer.^[10] Photopolymerization and subsequent dissolution of the template affords a highly ordered porous polymer film consisting of a three-dimensional network of spherical pores interconnected by circular “windows”: Such films are promising candidates for separation processes and are discussed in context with photonic devices.

Finally, reproduction of the three-dimensional periodicity of colloiddally crystallized silica spheres (opal) in nonpolymer solids has been reported.^[11] Here the production of regularly structured porous carbon morphologies (glassy carbon, graphite, and diamond) was achieved by either steeping the inorganic matrix in a precursor or by chemical vapor deposition (CVD) and subsequent heat treatment. As in the IT–OP approach, the inorganic template can be removed by extraction.

One drawback of rigid colloidal templating may be the fact that only spherical pores can be generated, as the controlled synthesis of nonspherical nanoparticles and their colloidal crystallization is not sufficiently established. Also, the connectivity of these pores cannot be adjusted in order to provide individually designed diffusion pathways. Nevertheless, templating of rigid colloidal aggregates is a versatile alternative for the generation of meso- and macroporous solids, whenever soft amphiphilic aggregate structures fail to do their job.

So far, the main objective of rigid-colloid casting has been morphogenesis, the preparation and utilization of a novel template in order to address still existing problems of porous nanostructure design. Now the question arises: “what now?”. In this context it is to be hoped that the application-orientated future of these beautiful structures is not going to let us wait long. There is a vast number of potential applications ranging from robust catalysts and supports over size- and shape-selective membranes to photovoltaic devices. These materials are the first template-synthesized nanostructures with periodicities in the range of optical wavelengths and are therefore promising candidates as photonic crystals.^[12]

Scientists have established this inventive, simple, and very successful methodology of shaping matter, and this is the time to address the technological aspects and to bench-test the many predicted uses of the “porous nanostructure”. The author has the pleasure of looking forward to finding this documented in top-rank journals soon.

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New Routes to Hydrogen Peroxide: Alternatives for Established Processes?

Werner R. Thiel*

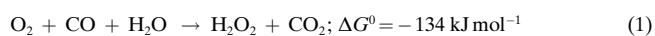
Hydrogen peroxide is produced industrially on a megaton scale. Aqueous solutions (3–85 weight % of H_2O_2) are of technical importance in a series of industrial processes. Most of the hydrogen peroxide is used for ecological reasons to replace chlorine and chlorine oxides in paper production. Further important applications are in the synthesis of fine chemicals, treatment of drinking and waste water, etching and purification in the electronic industry, bleaching of fabrics, and metallurgic processes. The cosmetic and pharmaceutical industries also makes use of its disinfecting properties.^[1] While hydrogen peroxide has been known for more than 180 years, these applications have only been set up during the last few decades.

From 1818, when it was discovered by Thénard,^[2] up to the beginning of the 20th century, solutions containing about 3 % of hydrogen peroxide could only be obtained by the hydrolysis of barium peroxide with sulfuric acid (world production in 1900 was about 2000 t). Investigations on the electrolysis of sulfuric acid, carried out at the Consortium für Elektrochemische Industrie, proved the formation of peroxomono- and peroxodisulfuric acid and finally resulted in a new and economically favorable process for the production of more highly concentrated solutions of hydrogen peroxide with increased purity and stability.^[3] On the basis of the work of Manchot,^[4] Riedel and Pfeleiderer (BASF) developed the anthraquinone process between 1935–45.^[5] This process, which is used at the moment in most of the technical hydrogen peroxide plants worldwide, allows the production of ultrapure and highly concentrated solutions of hydrogen peroxide under economically beneficial conditions. In addition, a series of alternative ideas for the generation of hydrogen peroxide has been worked out: autoxidation of isopropanol, direct reaction of hydrogen and dioxygen in the presence of silent discharges or in the presence of transition metal catalysts, or cathodic reduction of dioxygen. However, there is no alternative to the established anthraquinone process. Although still far from a technical breakthrough, two new routes to hydrogen peroxide have recently begun to attract attention.

Beside its technical potential, hydrogen peroxide also plays an important role in the biosphere. It is formed in small amounts in living organisms as a by-product of autoxidation reactions or during the one-electron reduction of dioxygen. The superoxide and hydroperoxo radicals created in the latter process undergo disproportionation either spontaneously or enzyme catalyzed (superoxide dismutase) to give hydrogen peroxide and dioxygen. As a consequence of its high toxicity, efficient mechanisms for the decomposition of hydrogen

peroxide had to be developed by all organisms. But hydrogen peroxide is also used as an oxidizing agent in the metabolism of the cell. For this purpose it is synthesized enzymatically, often using dioxygen for the oxidation of organic substrates. Recently, two groups succeeded independently in modeling the biological features and function of galactose oxidase by mono- and dinuclear copper complexes.^[6, 7] Since the biochemical importance of these results has already been a matter of discussion here in this journal,^[8] these publications will only be cited in terms of their potential for the biomimetic synthesis of hydrogen peroxide. The broad spectrum of substrates accepted by galactose oxidase not only allows the oxidation of the primary OH group of galactose to give the corresponding aldehyde, but also enables the conversion of a series of simple primary alcohols. This observation is a common feature of the enzyme and the model complexes: oxidation of an alcohol in the presence of dioxygen generates the carbonyl compound and one equivalent of hydrogen peroxide. Primary alcohols are converted with higher rates than secondary alcohols. Only minor amounts of side products (from C-C coupling and over-oxidation) are detected. These biomimetic processes may finally result in a technical application, not only for the selective formation of aldehydes and ketones but also for the generation of hydrogen peroxide, when further ligand optimization leads to catalysts of improved stability and activity.

Ligand optimization had a decisive influence on the success of Bianchi, Ricci, and co-workers.^[9] The idea of using palladium for the synthesis of hydrogen peroxide in a two phase system can be traced back to 1979 with the results of Ermakof et al., who obtained the compound by reacting dioxygen, carbon monoxide, and water in the presence of palladium acetate and triphenylphosphane.^[10] As a result of a rapid oxidation of the phosphane ligands, the turnover numbers of this system were too low for a technical application. A good reason for a reinvestigation of these results may be found in the thermodynamics of Equation (1).

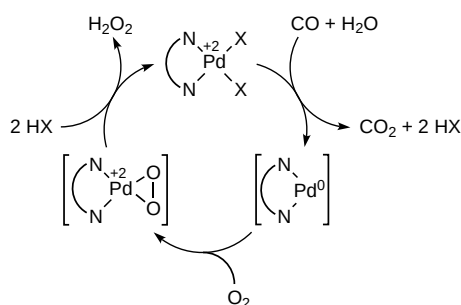


In the new two-phase procedure (1,2,4-trichlorobenzene or toluene, 2-methyl-2-butanol/water) of EniChem, aromatic N,N-chelate ligands such as 1,10-phenanthroline, which are quite inert to oxidation relative to phosphanes, are used to stabilize the palladium catalyst. High pressure (6500–7500 kPa O_2 and 600 kPa CO), a reaction temperature of about 70 °C, and the addition of an excess of acids that form weakly coordinating anions such as CF_3COOH , $\text{C}_7\text{F}_{15}\text{COOH}$, or $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}$ ($[\text{Pd}]:[\text{acid}] = 1:40$) are obligatory for high yields. Optimized conditions give solutions of hydrogen peroxide up to 8 %. Additionally the chemical structure of the chelate ligand ($[\text{Pd}]:[\text{ligand}] = 1:4-1:8$) was found to be crucial for the efficiency of the catalytic system. The best results were obtained using 2,9-dimethyl-4,7-diphenyl-1,10-

[*] Priv.-Doz. Dr. W. R. Thiel
Anorganisch-chemisches Institut
Technische Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-28913473
E-mail: werner.thiel@ch.tum.de

phenanthroline. It seems that the methyl substituents in the 2- and 9-positions prevent the formation of dinuclear, catalytically inactive palladium complexes. It has been found, that electron-withdrawing (Cl) or bulky substituents (*n*-C₄H₉, C₆H₅) in these positions lead to a decreased activity. The pronounced steric effects are quite surprising, since only small reactants (CO, O₂, H₂O) are converted at the palladium center. The palladium complex of 2,9-dimethyl-1,10-phenanthroline is too soluble in the aqueous solution, which leads to a complete loss of activity and further proves that the conversion should take place in the organic phase. This lack of reactivity can either be overcome by the application of the long-chain perfluorooctanoic acid as the co-reagent or by introducing phenyl substituents in the 4- and 7-positions of the chelate ligand.

The formation of palladium peroxo complexes, starting from Pd^{II} precursors, is proposed by the authors as a basis of a mechanistic discussion (Scheme 1). Such complexes, stabilized by phosphane ligands, have been known for a long time.^[11] However, analogous systems bearing nitrogen donors have not yet been reported. The reduction of Pd^{II} to Pd⁰ with carbon monoxide in aqueous systems is known to give CO₂. This reaction is fast in the presence of weakly coordinating anions.^[12]



Scheme 1. Proposed reaction mechanism for the Pd-catalyzed reduction of dioxygen to H₂O₂. X = CF₃CO₂, C₇H₁₅CO₂, CH₃C₆H₄SO₃.

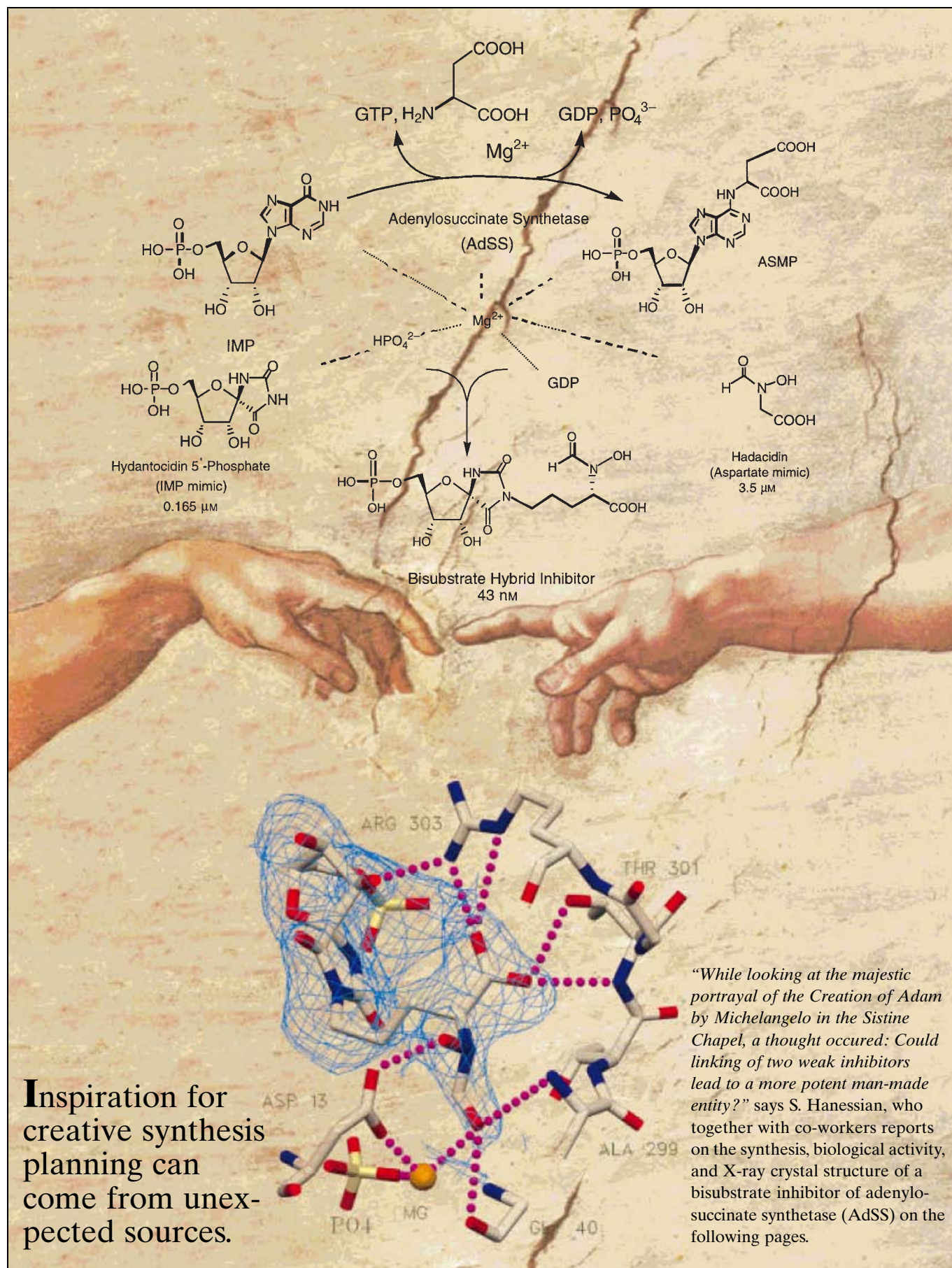
Unfortunately, the authors do not discuss the selectivity of their process. Carbon monoxide^[13] as well as carbon dioxide^[14] undergoes an insertion reaction in the O-O bond of

[(PPh₃)₂Pd(η²-O₂)] and in both cases [(PPh₃)₂Pd(η²-CO₃)] is formed. Insertion of CO₂ probably first leads to the percarbonato complex [(PPh₃)₂Pd(η²-CO₄)], which gives [(PPh₃)₂Pd(η²-CO₃)] by oxidation of PPh₃. In principle, both insertions may be possible for the corresponding N,N-chelate complexes of palladium (CO may be used for the reduction of the percarbonato complex) and would not produce any hydrogen peroxide but only consume carbon monoxide and dioxygen (2CO + O₂ → 2CO₂). The answering of such questions, in combination with a further ligand optimization and mechanistic investigations, are of high importance for a possible technical application of the new hydrogen peroxide process.

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An Enzyme-Bound Bisubstrate Hybrid Inhibitor of Adenylosuccinate Synthetase**

Stephen Hanessian,* Pu-Ping Lu, Jean-Yves Sane  au, Philippe Chemla, Keigo Gohda, Raymonde Fonne-Pfister, Lars Prade, and Sandra W. Cowan-Jacob

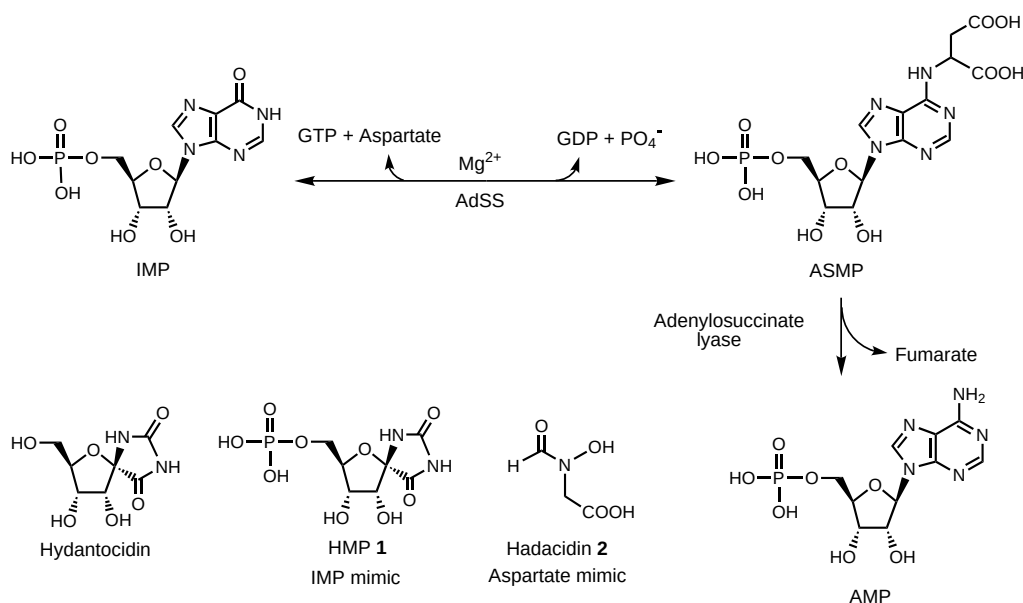
Nature has been a generous provider of a plethora of compounds displaying fascinating structural and functional stereochemical diversity and biological activity. Such compounds are also endowed with intriguing biological activity affecting a wide cross-section of physiological functions in the animal and plant world. Nowhere is this more evident than in the area of drug discovery and the development of therapeutically important medicines.^[1] The great advances in physical methods of structure elucidation such as X-ray crystallography and NMR analysis of proteins have provided the synthetic chemist with powerful tools to creatively design inhibitor molecules on a "rational basis".^[2] Thus, a crystal structure of an organic molecule nestled in the active site of a given enzyme^[3] offers a powerful visual image of critical interactions, which can be used to optimize new structures through chemical modifications. While great efforts have been directed at the exploitation of such approaches in medicinal chemistry, relatively little information is available in the area of plant enzymology with respect to "designed" inhibitors.^[4]

The enzyme adenylosuccinate synthetase (AdSS) is involved in the first step in the conversion of inosine monophosphate (IMP) into adenosine monophosphate (AMP, Scheme 1).^[5] The process is mediated by GTP, magnesium ions, and aspartate, which lead to the aspartylated nucleotide adenylosuccinate monophosphate (ASMP) with release of GDP and phosphate. The enzyme adenylosuccinate lyase then

completes the transformation with the production of AMP and release of fumarate.

Hydantocidin, a unique spirocyclic hydantoin riboside, isolated from *Streptomyces hygroscopicus*,^[6] inhibits AdSS from *E. coli* as well as from the plant. As a pro-herbicide, it is first converted into the 5'-phosphate **1** (hydantocidin monophosphate, HMP; see Scheme 1), and as such, it is believed to mimic IMP or AMP.^[7] Convincing evidence comes from the structure of the cocrystal HMP and AdSS, where the inhibitor molecule has replaced IMP in the active site.^[7c]

An unrelated natural product, hadacidin (*N*-formyl-*N*-hydroxy glycine, **2**; see Scheme 1), which also possesses herbicidal activity, exerts its activity on AdSS as a competitive inhibitor of aspartic acid, thus affecting the enzyme at a different site.^[8] An example of simultaneously capturing and visualizing two different inhibitors with a common enzyme is provided by the crystal structure of AdSS harboring HMP and



Scheme 1. Biosynthesis of AMP and structures of natural inhibitors of adenylosuccinate synthetase (AdSS).

hadacidin.^[9] These two crystallographic studies presented a unique opportunity to probe new aspects of inhibitor design for AdSS.^[7c, 9]

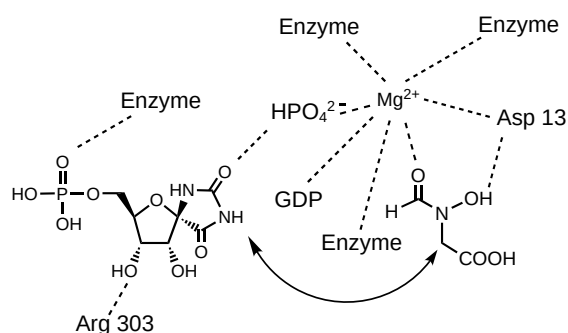
Considering the relative positions of HMP, hadacidin, Mg²⁺, and phosphate (Scheme 2), it occurred to us that the covalent attachment of HMP and hadacidin by a judicious choice of a linker unit would lead to an HMP–hadacidin hybrid with improved binding, hence a more potent herbicidal activity. Molecular modeling and simulated docking experiments revealed that a bisubstrate hybrid with a C₃ methylene bridge ending with an (2*S*)-*N*-formyl-*N*-hydroxy amino acid such as **3** would be a preferred hybrid compared to the 2*R* isomer **4**, or to the C₂-linked variants. We report herein on the validation of this hypothesis through synthesis and X-ray crystal structure analysis in an unequivocal way.

The camphorsultam derivative **5**^[10] was treated with allyl bromide in the presence of powdered zinc in a mixture of aqueous ammonium chloride and THF to produce the (*S*)-

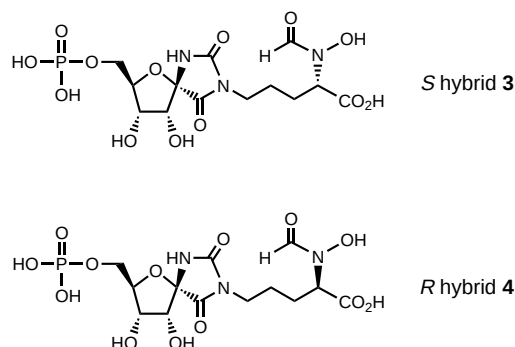
[*] Prof. Dr. S. Hanessian, P.-P. Lu, J.-Y. Sane  au
Department of Chemistry
Universit   de Montr  al
C.P. 6128, Succ. Centre-ville
Montreal, QC, H3C 3J7 (Canada)
Fax: (+1) 514-343-5728
E-mail: hanessia@ere.umontreal.ca
P. Chemla, K. Gohda, R. Fonne-Pfister
Novartis Crop Protection AG, Basel (Switzerland)
L. Prade, S. W. Cowan-Jacob
Novartis Pharma AG, Basel (Switzerland)

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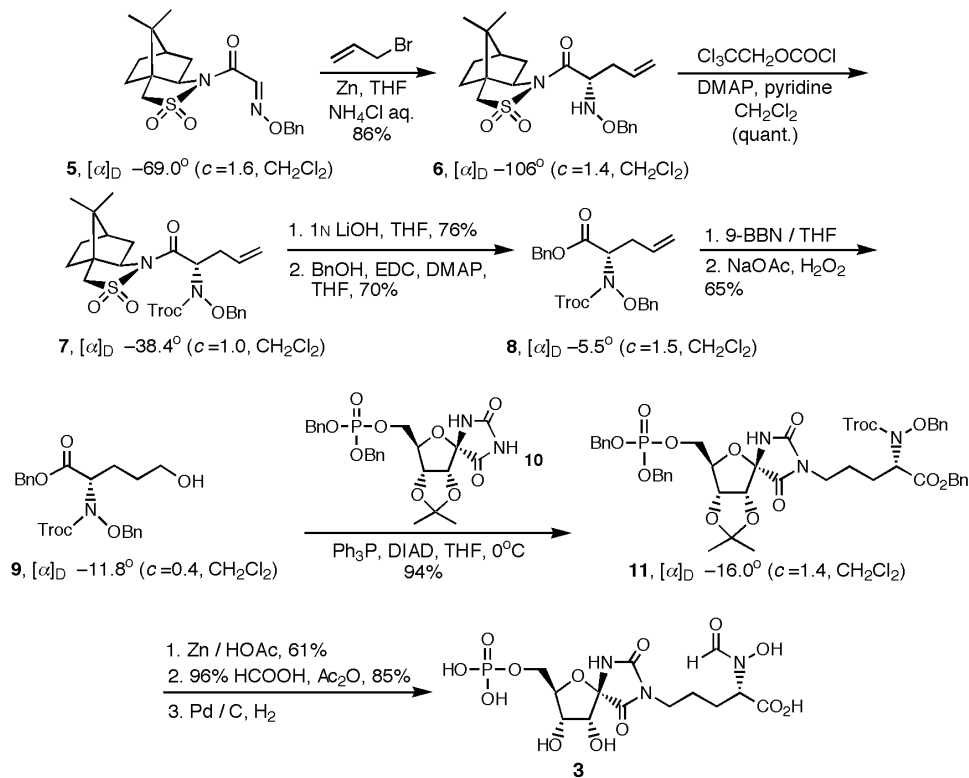
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 2. Interactions of hydantocidin phosphate and hadacidin with AdSS. Structures of bisubstrate hybrids **3** and **4**.



allyl glycine derivative **6** in excellent yield and with high diastereoselectivity (Scheme 3). Protection of the amine group as the *N*-trichlorethoxy-carbonyl derivative **7**, cleavage of the chiral amide motif, and reesterification afforded the



Scheme 3. Synthesis of hybrid **3**. 9-BBN = 9-borabicyclo[3.3.1]nonane, Bn = benzyl, DIAD = diisopropyl azodicarboxylate, DMAP = dimethylaminopyridine, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, Troc = trichlorethoxycarbonyl.

benzyl ester **8** in good overall yield. Hydroboration proceeded uneventfully to give the primary alcohol **9**, which was coupled to the HMP dibenzyl derivative **10** under the conditions of Mitsunobu reaction^[11] to afford the coupled product **11** in excellent yield. Deprotection of the *N*-Troc group followed by *N*-formylation with concomitant hydrolysis of the acetal function afforded an O-benzyl-protected precursor of the target compound. Debenzylation under catalytic hydrogenolysis by careful monitoring gave the hybrid molecule **3** as an amorphous powder. The analogous (*2R*)-amino acid analogue **4** was similarly prepared starting with the other enantiomer of the sultam.

Enzyme inhibition studies proved to be most gratifying: (*2S*)-hybrid **3** inhibited AdSS from *E. coli* and wheat at concentrations of 0.043 and 0.200 μM , respectively, which was much lower than observed for the *2R* isomer **4** and the natural substrates **1** and **2** (Table 1).^[12] Thus, linking two relatively

Table 1. Inhibitory activity of HMP, hadacidin, and bisubstrate hybrids on AdSS from *E. coli* and wheat.

Inhibitor	IC ₅₀ [μM]	
	<i>E. coli</i> AdSS	wheat AdSS
HMP (1)	0.675	1.35
hadacidin (2)	3.5	12
3	0.043	0.200
4	0.665	8.93

weakly active inhibitors to produce a hybrid molecule such as **3** enhanced the enzymatic inhibitory activity significantly compared to the individual natural substrates.

Structural validation of the biological results was secured from X-ray crystallographic data of AdSS complexed with the *2S* and *2R* hybrids individually at a resolution of 2.0 and 2.2 Å, respectively.^[13] The left side of Figure 1 depicts the orientation of the *2S* hybrid **3**, which occupies the sites originally harbored by IMP and aspartate. Magnesium and phosphate are seen at their expected positions, as well as interactions with amino acids. The C₃ methylene chain in **3** adopts a conformation which presumably allows for maximum binding of the HMP and hadacidin counterparts to AdSS.^[14] Curiously the *2R* hybrid **4** also occupies the same relative positions with subtle differences at the amino acid end and in the conformation of the C₃ methylene chain^[14] (right side of Figure 3).

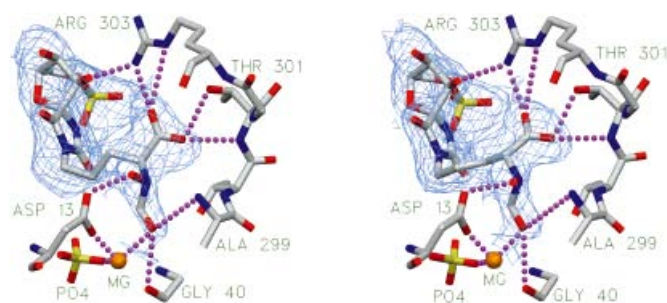


Figure 1. X-ray crystal structures of the complexes formed between AdSS and **3** (left) and **4** (right) showing the electron density at a cutoff of 1σ . Hydrogen bonds with amino acids in AdSS are indicated. Note the different conformations of the C_3 methylene chain in **3** and **4**.^[13]

The C_2 -linked hybrid—readily available from the common intermediate **8** by oxidative cleavage and reduction, then Mitsunobu coupling and deprotection—was also more active than either HMP or hadacidin, but not as active as the C_3 -linked hybrid **3**.^[15] It is possible that in this case, it is the enzyme that must undergo a conformational change to adapt to the inhibitor, rather than the reverse as in the case of **3**.

There are very few examples of successfully linking two entities to achieve a hybrid-type structure that improves enzyme inhibitory activity.^[16] Recently, great strides have been made in this direction, by the ingenious application of structure–activity relationships (SAR) determined from NMR spectroscopy for the discovery of high-affinity ligands.^[17] To the best of our knowledge the design and synthesis of a bisubstrate inhibitor such as **3** is unprecedented in the herbicide field.

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Table 2. Dihedral angles [°] in **3** and **4**.

Angle	3	4
N(hydantoin)-C1-C2-C3	66.4	– 51.9
C1-C2-C3-C α (glycine)	– 166	– 178
C2-C3-C α -CO ₂ H	167	– 150
C2-C3-C α -NH ₂	– 72.8	89.4

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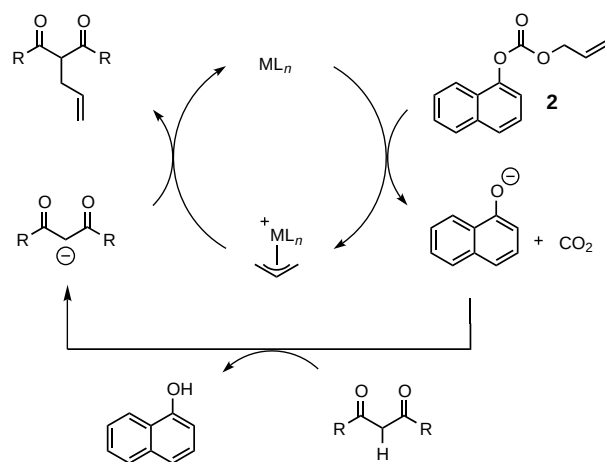
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Discovery of Novel Catalysts for Allylic Alkylation with a Visual Colorimetric Assay**

Olivier Lavastre* and James P. Morken*

Transition metal catalyzed reactions are useful tools for the construction of complex organic molecules.^[1] In this regard, catalytic allylic alkylation represents a particularly powerful method for the formation of carbon–carbon bonds.^[2] While most investigations have focused on the catalytic efficacy of palladium complexes,^[2,3] complexes involving nickel,^[4] rhodium,^[5] iron,^[6] molybdenum,^[7] ruthenium,^[8] tungsten,^[9] and iridium^[10] have also shown promise. Current challenges to this field center on issues of regioselectivity and stereoselectivity, and thereby motivate the development of new catalytic systems. Recently, a number of groups have reported the application of combinatorial chemistry techniques to the development of catalytic processes.^[11] In an effort to develop parallel assays for solution-phase catalysis, recent studies have demonstrated the visual detection of active catalysts by noting the modification of temperature,^[12] color,^[13] or fluorescence^[14] induced by a catalytic reaction. Herein, we report a novel catalyst for allylic alkylation in neutral medium discovered with the aid of a fast, parallel colorimetric screening method.^[15]

Our strategy for detection of allylic alkylation catalysts is described in Scheme 1 and relies on the fact that colorless

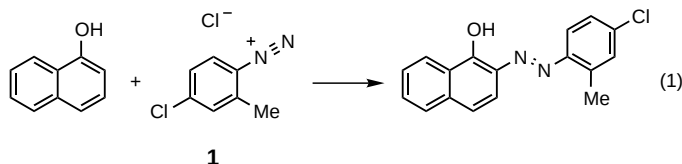


Scheme 1. Schematic representation of the strategy for detection of allylic alkylation catalysts (see text for details).

[*] O. Lavastre
UMR 6509 CNRS-Universite de Rennes 1
Campus de Beaulieu, F-35042 Rennes (France)
Fax: (+33) 2-99-28-69-39
E-mail: lavastre@univ-rennes1.fr
J. P. Morken
Department of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-3290 (USA)
Fax: (+1) 919-962-2388
E-mail: morken@unc.edu

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1-naphthol will undergo electrophilic aromatic substitution with Fast Red diazonium salt^[16] (**1**) to give a bright orange azo product [Eq. (1)]. We envisioned that effective catalysts for allylic alkylation would ionize 1-naphthyl allyl carbonate (**2**) and, after release of CO₂, would furnish the naphthoxide



along with the derived π -allyl metal complex (Scheme 1). For allylic alkylation to occur, the naphthoxide would deprotonate a β -dicarbonyl, which in turn would react with the π -allyl metal complex. Since the naphthol carbonate starting material is less active than 1-naphthol towards aromatic substitution, it does not generate color when treated with Fast Red. Critically, under the reaction conditions naphthyl allyl ether also does not generate color when treated with Fast Red. Thus if naphthoxide directly intercepts the π -allyl complex, no signal will be generated in the assay. Color formation on introduction of Fast Red is indicative only of the presence of 1-naphthol and therefore may be used as an indicator of the extent of allylic alkylation.

Using the colorigenic azo coupling assay we have screened several metal–ligand combinations using a 96-well plate format. In an inert atmosphere glovebox, eight ligands were introduced in rows 1 to 8 of the plate as indicated in Figure 1. Eleven different metal salts were then dispatched into columns 1 to 11 (ligand:metal = 3:1). Metal salt was not added to column 12 in order to ascertain that ligand alone does not generate color on treatment with Fast Red. Subsequently, a solution of diethyl malonate and **2** (substrates:catalyst = 100:1) was added to each well. After two hours a solution of Fast Red in wet THF was added. As can be

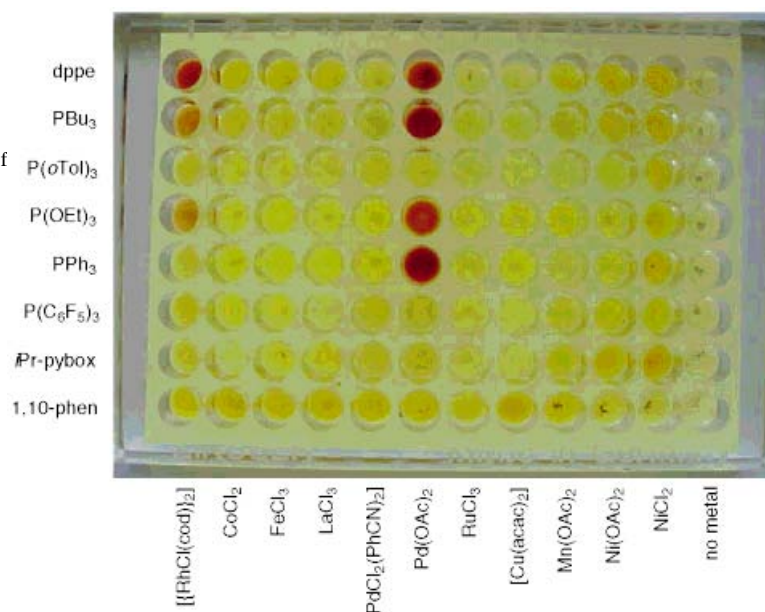


Figure 1. View of the 96-well plate after addition of Fast Red. acac = acetylacetone, oTol = o-tolyl.

seen in Figure 1, red color is generated in several wells and is indicative of allylic alkylation.

While simple visual analysis of the 96-well plate is sufficient to differentiate efficient from inactive catalysts, parallel UV analysis may be used to differentiate catalysts of similar activity and provides a means to subtract background color due to ligand or metal salt. This operation provided the data depicted in Figure 2a which correlates well with that obtained by visual inspection.

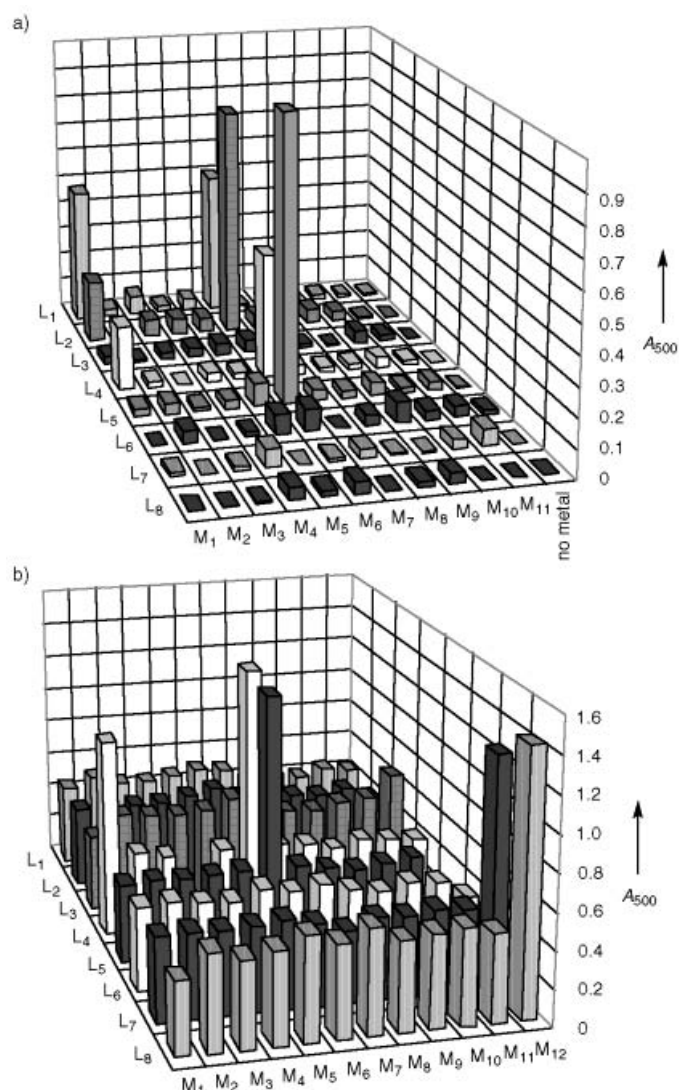


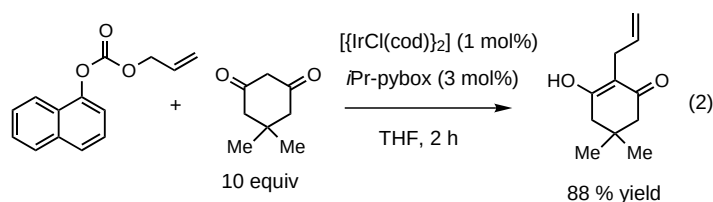
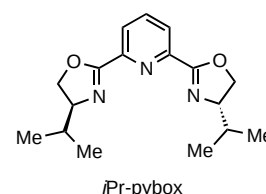
Figure 2. Relative absorbance of each well in the 96-well plate: a) with dimethyl malonate, b) with dimedone. M_1 : $[\text{RhCl}(\text{cod})_2]$, M_2 : CoCl_2 , M_3 : FeCl_3 , M_4 : LaCl_3 , M_5 : $[\text{PdCl}_2(\text{PhCN})_2]$, M_6 : $\text{Pd}(\text{OAc})_2$, M_7 : RuCl_3 , M_8 : $[\text{Cu}(\text{acac})_2]$, M_9 : $\text{Mn}(\text{OAc})_2$, M_{10} : $\text{Ni}(\text{OAc})_2$, M_{11} : NiCl_2 , M_{12} : $[\text{IrCl}(\text{cod})_2]$, L_1 : dppe, L_2 : $\text{P}(\text{Bu}_3)_3$, L_3 : $\text{P}(\text{oTol})_3$, L_4 : $\text{P}(\text{OEt})_3$, L_5 : PPh_3 , L_6 : $\text{P}(\text{C}_6\text{F}_5)_3$, L_7 : *i*Pr-pybox, L_8 : 1,10-phen.

The information in Figures 1 and 2a indicates that $\text{Pd}(\text{OAc})_2$ when combined with diphenylphosphanyleneethane (dppe), $\text{P}(\text{Bu}_3)_3$, $\text{P}(\text{OEt})_3$, or PPh_3 provides an effective catalyst system. Also apparent is that $[\text{RhCl}(\text{cod})_2]$ (cod = 1,5-cyclooctadiene) with either dppe, $\text{P}(\text{Bu}_3)_3$, or $\text{P}(\text{OEt})_3$ as ligand serves as an active catalyst for allylic alkylation. In light of extensive studies with π -allyl palladium complexes,^[2, 3] the results with

$\text{Pd}(\text{OAc})_2$ are not surprising. However, rhodium-catalyzed allylic alkylations in neutral medium are less well developed,^[5a, c] and it is encouraging that this initial proof-of-concept revealed the effectiveness of these rhodium–ligand complexes.

To evaluate the impact of substrate structure on catalyst activity, we examined the use of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) as nucleophile. In this case, we used the experimental procedure as described above and employed the iridium salt $[\text{IrCl}(\text{cod})_2]$ in column 12. The results of this assay are depicted in Figure 2b. While it was found that unchanged dimedone generates a yellow color, it is still possible to identify the most active catalysts. In contrast to reactions involving malonate as nucleophile (Figure 2a), dppe and $\text{P}(\text{Bu}_3)_3$ ligands are not effective with the Rh and Pd complexes for the allylation of the dimedone. In the case of $[\text{IrCl}(\text{cod})_2]$ it is clear that addition of either *i*Pr-pybox or 1,10-phenanthroline (1,10-phen) generates an active catalyst. Additional experiments (data not shown) showed that under the same assay conditions with either malonate or dimedone, none of the metal complexes, in the absence of ligand, generate red color.

The relative activity of the new iridium catalysts for base-free allylation of dimedone was investigated in detail by ¹H NMR spectroscopy. In accord with the colorimetric assay, when PPh_3 is employed as the ligand, no catalytic reaction occurred and the starting materials were recovered. In contrast, when *i*Pr-pybox is employed as the ligand with ten equivalents of dimedone,^[17] ¹H NMR analysis shows quantitative conversion is achieved in two hours. Moreover, the reaction product may be isolated in 88% yield and in purity sufficient to obtain accurate elemental analysis [Eq. (2), see Experimental Section].^[18]



In summary, we have reported an efficient colorimetric strategy for parallel analysis of catalysts for allylic alkylation. The colorimetric assay is simple and inexpensive, and should be applicable to other reactions of interest. While few examples of iridium-catalyzed allylic alkylation are known,^[10] by noting formation of color, the assay revealed the first non-phosphane iridium catalysts for allylic alkylation.

Experimental Section

In THF (6 mL), **2** (91 mg, 0.4 mmol) and dimedone (0.57 g, 4 mmol) were allowed to react in the presence of $[\text{IrCl}(\text{cod})_2]$ (1 mol%) and *i*Pr-pybox (3 mol%) for 2 h. After evaporation of THF the solid residue was purified by silica gel chromatography with ethyl acetate/hexane (1/1) as eluant.

After evaporation of solvent, a white crystalline solid was isolated (63 mg) in 88 % yield. Elemental analysis calcd for $C_{11}H_{16}O_2$: C 73.33, H 8.88; found: C 73.56, H 8.81; m.p. 143 °C (lit.^[19] 143 °C). Spectroscopic data are in accordance with previous reports.^[19]

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Solid-State Coordination Chemistry: The Self-Assembly of Microporous Organic–Inorganic Hybrid Frameworks Constructed from Tetrapyrrolylporphyrin and Bimetallic Oxide Chains or Oxide Clusters**

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

Oxygen is not only the most abundant terrestrial element but it is also highly reactive; consequently, oxides exist for all of the elements with the exceptions of radon and the lighter noble gases.^[1] Inorganic oxides constitute a vast family of materials ubiquitous as both naturally occurring and synthetic materials.^[2–4] The significant contemporary interest in solid-state oxides reflects a structural and compositional diversity that endows these materials with a range of physical properties that yield applications to heavy construction, sorption, catalysis, biomineralization, microelectronics, and solar energy conversion.^[5] However, despite the practical and fundamental importance of inorganic oxides, the designed synthesis of such materials remains an elusive goal.

The synthetic challenge reflects the fact that binary metal oxides, for example, typically possess only one or a few thermodynamically stable modifications, which provides a limited range for design. While such simple oxides possess undeniably useful properties, there is, in general, a correlation between the complexity of the structure of a material and the functionality that it displays. Two general observations provide an insight into the synthesis of structurally complex oxides: a) if the formation of the oxide is carried out at low temperatures, and thus under kinetic control, it is possible to prepare metastable modifications and to influence the reaction process,^[6] and b) organic molecules can dramatically influence the inorganic oxide microstructure, thus offering a powerful tool for the design of novel materials.^[7]

[*] Prof. J. Zubieta, D. Hagrman, P. J. Hagrman
Department of Chemistry, Syracuse University
Syracuse, NY 13244 (USA)
Fax: (+001) 315-443-4070
E-mail: jazubiet@syr.edu

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In organic–inorganic hybrid materials the inorganic oxide substructure contributes to the increased complexity and corresponding functionality through incorporation as one component into a multilevel hierarchical material that combines synergistically interacting organic and inorganic components. The interaction within such organic–inorganic hybrid materials derives from the nature of the interface between the organic component and the inorganic oxide, a feature that drives chemists to elaborate the synthetic and structural characteristics of materials with such an interface in an effort to derive structure–function relationships for such hybrid compositions.^[8]

Four major classes of compounds in which an organic component exerts a major structural influence on the inorganic oxide substructure are zeolites,^[9, 10] mesoporous materials of the MCM-41 class,^[11] biomineralized materials,^[12] and organically templated transition metal phosphates.^[13] More recently, we have described a fifth major class, the organically templated molybdenum oxides.^[14] A subclass of this latter family of materials uses rigid multitopic ligands to bridge oxide monomers, clusters, or chains to form complex two-dimensional networks and three-dimensional frameworks. In an effort to design framework materials that combine the porosity of zeolites with the reactivity of transition metal oxides, pyridyl-substituted porphyrins have been introduced as fourfold connectors that are capable of generating significant void space and of providing ordered supramolecular arrays of functional chromophores.^[15] Following our general synthetic guidelines, we have isolated the first examples of three-dimensional framework materials constructed from metal oxide and porphyrin subunits. The structure of $[\text{Cu}(\text{tpypor})\text{Cu}_2\text{Mo}_3\text{O}_{11}]$ (tpypor = tetrapyridyl-porphyrin (**1**)) consists of a tessellated porphyrin network linked through bimetallic oxide chains into a three-dimensional, covalently connected framework. In assessing the structure-directing role of the metal center ligated with secondary or porphyrin/pyridyl groups, the isolation of $[\{\text{Fe}(\text{tpypor})\}_3\text{Fe}(\text{Mo}_6\text{O}_{19})_2] \cdot x\text{H}_2\text{O}$ (**2**), a material constructed from a three-dimensional $[\{\text{Fe}(\text{tpypor})\}_3\text{Fe}]^{4n+}_n$ framework and isolated $\{\text{Mo}_6\text{O}_{19}\}^{2-}$ polyoxo anions, was effected.

The structure of the hydrothermally synthesized **1** was determined by a single-crystal X-ray diffraction study^[16] and shown to be constructed from $\{\text{Cu}(\text{tpypor})\text{Cu}_2\}^{4+}$ building blocks and $\{\text{Mo}_3\text{O}_{11}\}^{4n-}_n$ chains (Figure 1). This structure appears as a tessellated porphyrin network linked through copper–molybdenum oxide chains when viewed along the crystallographic *c* axis. There are three distinct copper(II) environments: one rests in the porphyrin pocket and displays a square planar CuN_4 coordination geometry while the remaining two exhibit square pyramidal CuN_2O_3 and octahedral CuN_2O_4 ligation through coordination to pyridyl nitrogen atoms from two tpypor groups of one planar network and to three or four oxo groups, respectively, of the $\{\text{Mo}_3\text{O}_{11}\}^{4n-}_n$ chains (Figure 2). Thus, the structure may be described as neutral $[\text{Cu}(\text{tpypor})]$ units linked to bimetallic $[\text{Cu}_2\text{Mo}_3\text{O}_{11}]$ oxide chains. These oxide chains are constructed from a molybdate ribbon of alternating MoO_6 octahedra and MoO_4 tetrahedra in a corner-sharing arrangement and decorated by MoO_4 tetrahedra, which share a single corner with the

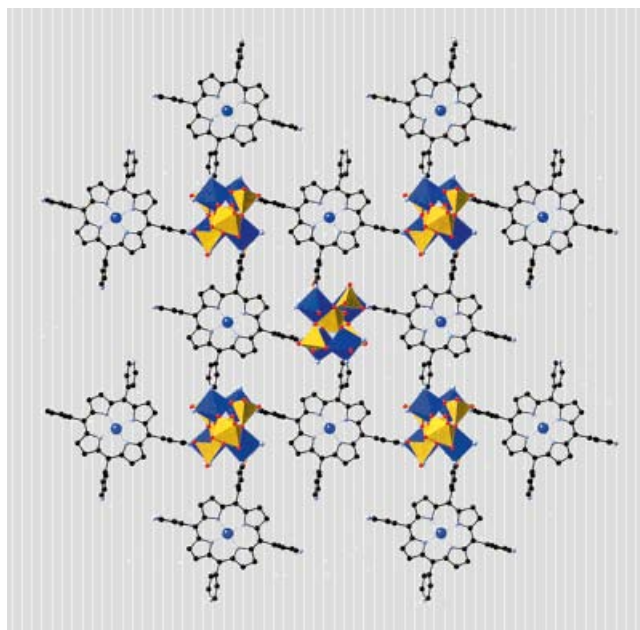


Figure 1. A view of the structure of **1** parallel to the $[\text{Cu}_2\text{Mo}_3\text{O}_{11}]$ chains, illustrating the linking of $\{\text{Cu}(\text{tpypor})\}$ building blocks into a tessellated pattern in the *ab* plane and the stacking of porphyrin groups along the *c*-direction. Cu–N(porphyrin) distances [Å]: 1.988(6), 1.989(6), 1.998(6), 2.003(6).

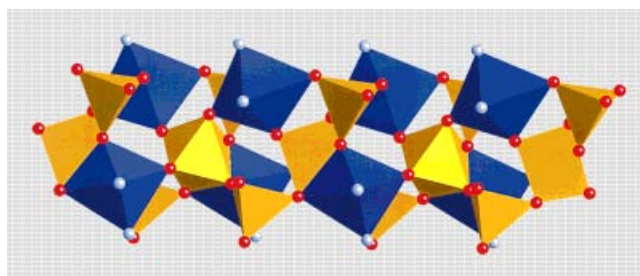


Figure 2. A polyhedral representation of the $[\text{Cu}_2\text{Mo}_3\text{O}_{11}]$ chain of **1**. Selected bond distances [Å]: square-pyramidal Cu site: Cu–Npy: 2.019(7), 2.047(7); Cu–O: 1.937(6), 1.980(6), 2.300(7); octahedral Cu site: Cu–Npy: 1.985(6), 1.989(6); Cu–O: 1.973(5), 2.001(5), 2.156(7), 2.408(6); MoO_4 -tetrahedra: Mo–O range: 1.704(6)–1.882(5); MoO_6 octahedral site: Mo–O: 1.730(6), 1.734(6), 1.770(6), 2.102(5), 2.220(6), 2.265(6).

octahedral Mo sites, and the square pyramidal and octahedral copper centers, which share three and four vertices, respectively, with the molybdate ribbon. One of these copper sites bridges adjacent octahedral MoO_6 sites and one terminal MoO_4 tetrahedron in corner-sharing modes exclusively while the second engages in corner-sharing interactions with a tetrahedral MoO_4 site and edge-sharing interactions with two adjacent MoO_6 octahedra. This polyhedral arrangement is quite distinct from that observed for “naked” copper–molybdate phases.^[17]

The copper molybdate chains of **1** propagate at 90° to the porphyrin planes. Consequently, the porphyrin units stack in a face-parallel fashion, and parallel to the oxide chains with a porphyrin–porphyrin distance of 4.815 Å. Adjacent porphyrin rings in a stack are staggered by approximately 30° .

The structure of **1** reflects not only the rigid geometry of the porphyrin building block, but also the coordination preferences of the Cu^{II} sites that adopt the conventional square

planar and “4+1” and “4+2” coordination geometries. In contrast, iron(II) ions would be expected to adopt a six coordinate geometry with concomitant structural consequences. This expectation has been realized in the structure of **2**.

As shown in Figure 3 the structure of **2**^[18] is constructed from a three-dimensional cationic framework $[\text{Fe}_4(\text{tpyor})_3]_n^{4n+}$ and entrained $\{\text{Mo}_6\text{O}_{19}\}^{2-}$ cluster anions.

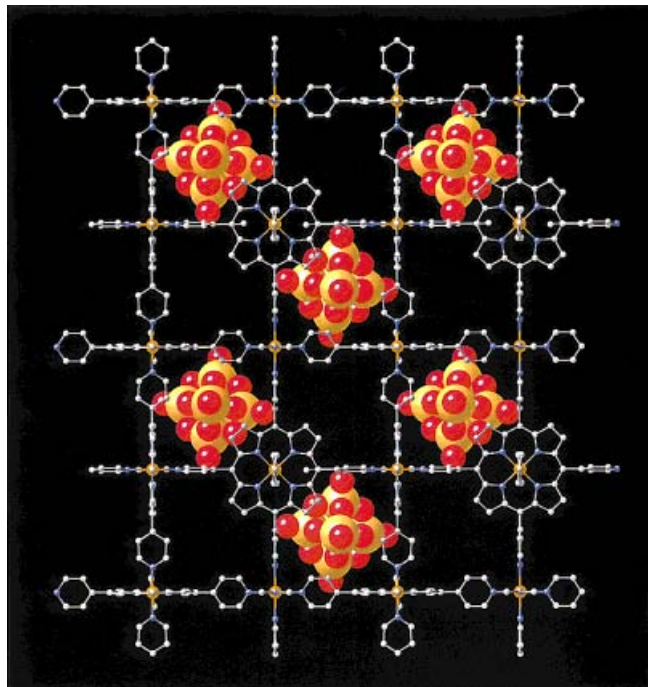


Figure 3. A view of the structure of $[\text{Fe}(\text{tpyor})_3]_n^{4n+}\text{Fe}(\text{Mo}_6\text{O}_{19})_2 \cdot x\text{H}_2\text{O}$ (**2**) parallel to the crystallographic *c* axis.

The cationic matrix consists of cubic building blocks of $[\text{Fe}_8(\text{tpyor})_6]^{8+}$ with an edge dimension of 9.833(1) Å. There are two distinct iron centers in the cationic microstructure: one resides in the heme pocket and is additionally axially coordinated to a pyridyl nitrogen atom from two adjacent $[\text{Fe}(\text{tpyor})]$ units, while the second iron center is octahedrally coordinated to six pyridyl nitrogen donors (Figure 4). The large cavities generated within these iron–porphyrin cubes are alternately populated by $\{\text{Mo}_6\text{O}_{19}\}^{2-}$ clusters and diffuse, disordered water molecules. The hexamolybdate ion is well known^[19] and adopts a charge-compensating and space-filling role in this material. Each cavity occupied by $\{\text{Mo}_6\text{O}_{19}\}^{2-}$ is octahedrally surrounded by water-filled cavities.

While the assembly of porphyrin building blocks into two- and three-dimensional structures has witnessed significant activity,^[20] the structures of **1** and **2** are unique with respect to the secondary metal–porphyrin microstructures, as well as in regard to the role of the molybdenum oxides in structural elaboration. The structures of **1** and **2** illustrate that molybdenum oxide structures may be readily modified by the porphyrin building blocks and appropriate selection of porphyrin ligated metal centers. The synergistic interaction of the various structural components is revealed in the framework of **1** wherein the Cu^{II} ion exhibits its pronounced tendency to associate directly with the molybdate substructure.

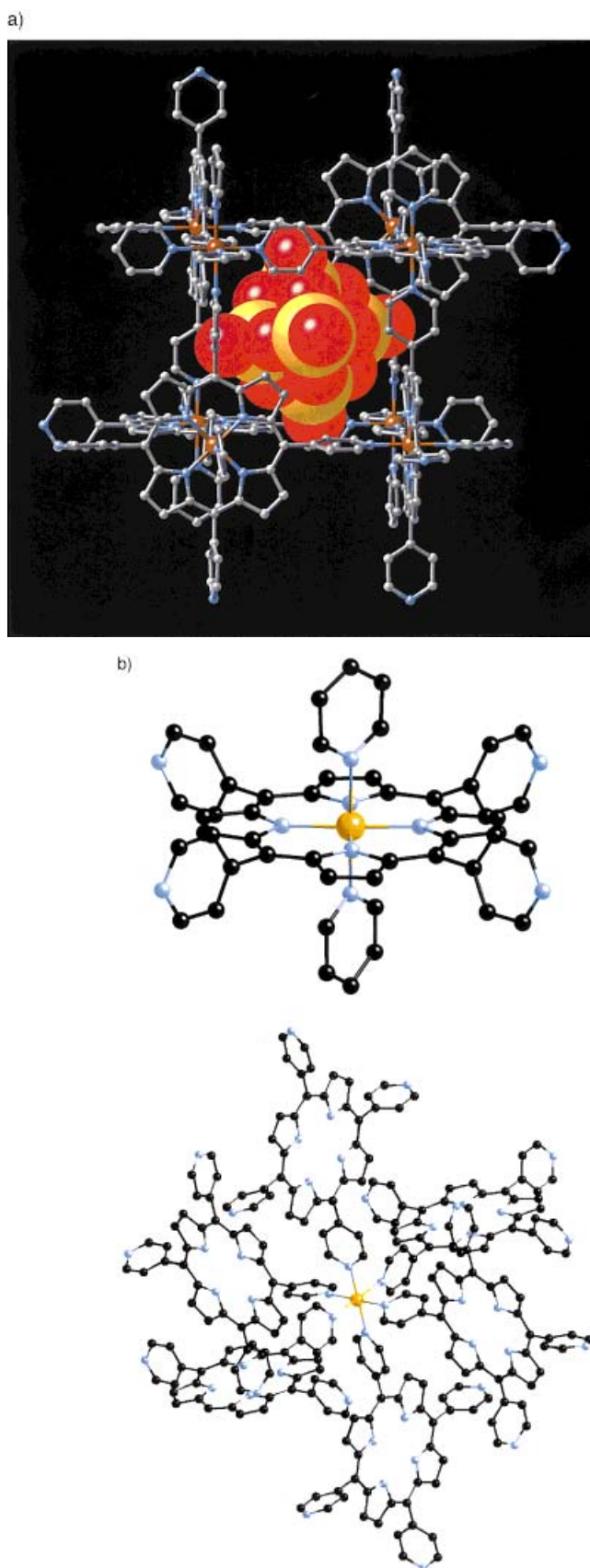


Figure 4. a) A view of the $[\text{Fe}_8(\text{tpyor})_6]^{8+}$ building block of the cationic framework of **2** with the entrained $\{\text{Mo}_6\text{O}_{19}\}^{2-}$ cluster; b) Views of the two Fe sites of **2**. Selected bond lengths [Å]: porphyrin-bound Fe site: Fe–Npor, 1.986(6) × 4; Fe–Npy, 2.050(8) × 2. Pyridyl-bound Fe site: Fe–Npy, 2.165(8) × 6. Mo–O: 1.691(6), 1.869(6), 1.870(6), 1.963(6), 1.979(6), 2.319(1).

ture, in addition to incorporating into the porphyrin pocket. On the other hand, exploitation of the coordination preferences of Fe^{II} ions provides a cationic framework for entrapment of the molybdate oxide substructure; naively this can be considered as a “ship in the bottle” approach to modification of oxide microstructures. These results suggest that oxides and appropriate metal–porphyrin substructures may be fused to produce hybrid bimetallic materials with different metal-containing active sites, framework components providing a variety of pore geometries and dimensionalities, and incipient microporosities. While predictability of product structure remains elusive in view of the paucity of examples, the basic approach is amenable to considerable variation and illustrates not only the ease of modification of oxide microstructure by organic components but also the reciprocal structure-directing influences of anionic oxide constituents on hybrid structures.

Experimental Section

1: Hydrothermal treatment of MoO₃, Cu(NO₃)₂ · 2.5H₂O, tetrapyrrolylporphyrin, and H₂O (1:1.03:0.16:182) for 48 h at 200 °C gives dark purple needles of **1** in approximately 50% yield based on porphyrin. Hydrothermal conditions are required to overcome the differential solubilities of the inorganic starting materials and the porphyrin. Aqueous reactions at room temperature and under reflux conditions proved unproductive for isolating hybrid oxide–porphyrin phases, while organic solvents and appropriate metal precursors such as [Cu^I(CH₃CN)₄]BF₄ and MoO₃ · nH₂O yielded mixtures of [Cu(tpypor)CuBF₄] and unidentified molybdates.

The infrared spectrum of **1** exhibits a strong band at $\tilde{\nu}$ = 794 cm^{−1}, which is associated with the tpypor unit, and multiple bands in the $\tilde{\nu}$ = 890–943 cm^{−1} range, attributed to ν (Mo=O). The electronic spectrum of a suspension of **1** in a gel exhibits a band red-shifted by 10 nm from the Soret absorption of the porphyrin (420 nm) and an extinction coefficient of less than half of that of the native porphyrin. This red shift, reduced extinction coefficient, and a broadening of the Soret half-width indicate some electronic coupling between the porphyrins.^[21]

Compound **1** exhibits magnetic properties that are consistent with a simple paramagnet. A somewhat elevated magnetic moment of 2.20 μ_B at room temperature is consistent with temperature-independent paramagnetism. The temperature dependence is unexceptional for a noninteracting d⁹ ion. Thermogravimetric analysis of **1** exhibits successive 6% weight losses in the ranges 230–250 and 470–480 °C, followed by a 12% weight loss between 500–550 °C. These correspond to the loss of one, one, and two pyridyl groups, respectively. A further weight loss of about 12% in the range 575–650 °C is attributed to the loss of the porphyrin. The final thermolysis product is an amorphous gray powder.

2: The hydrothermal reaction of MoO₃, FeCl₂ · 4H₂O, tetrapyrrolylporphyrin, and H₂O (1:1.02:0.18:1750) at 200 °C for 68.5 h gave **2** in 35% yield based on porphyrin.

The infrared spectrum of **2** exhibits the characteristic tpypor band at $\tilde{\nu}$ = 795 cm^{−1} and a single band at $\tilde{\nu}$ = 925 cm^{−1}, which is attributed to ν (Mo=O) of the symmetric [Mo₆O₁₉]^{2−} cluster. The electronic spectrum again shows a red shift, reduced extinction coefficient, and broadening of the Soret band associated with electronic coupling of the porphyrins.

Thermogravimetric analyses and density measurements are consistent with 19 water molecules per cavity. Preliminary sorption studies on **2** indicate that the material exhibits a Type I water vapor absorption isotherm^[22] and is capable of taking up about 15 wt % water vapor. The material also sorbs alcohols, but excludes hydrocarbons and acetonitrile.

Keywords: composites • crystal engineering • hydrothermal synthesis • polyoxometalates • porphyrinoids

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Epitaxial Electrodeposition of Lead Sulfide on (100)-Oriented Single-Crystal Gold**

Alexey A. Vertegel, Mark G. Shumsky, and Jay A. Switzer*

Single-crystal films are important for device applications because the properties of the material of interest are not affected by the presence of grain boundaries. Epitaxial films are usually synthesized by vapor deposition onto a single crystal substrate, chosen to have a crystal structure and lattice parameter a as close as possible to that of the film. Typically, the lattice mismatch between a film and a substrate ($(a_{\text{film}} - a_{\text{substrate}})/a_{\text{substrate}}$) should not exceed 10–15%. Recently, we reported that epitaxial films of $\delta\text{-Bi}_2\text{O}_3$ can be electrodeposited from an alkaline tartrate solution onto single-crystal Au,^[1] although the lattice mismatch between $\delta\text{-Bi}_2\text{O}_3$ and Au is 35.4%. The large mismatch was accommodated by forming coincidence lattices, in which the $\delta\text{-Bi}_2\text{O}_3$ film was rotated in relation to the gold substrate. Herein, we extend this work to the electrodeposition of epitaxial films of lead sulfide (PbS) onto a single-crystal Au (100) substrate. The epitaxial films were deposited directly from solution precursors and required no subsequent thermal annealing to effect epitaxy. The crystal structures of Au and PbS are shown in Figure 1. Both structures are face centered cubic ($Fm\bar{3}m$) with lattice parameters 0.4079 nm and 0.5933 nm, respectively. The lattice mismatch between the two materials is 45.5%.

Several methods have been used to achieve epitaxial growth from solutions, including chemical bath deposition,^[2] underpotential electrodeposition,^[3] and electrochemical atomic layer epitaxy.^[4] Epitaxial quantum dots of Cd(Se,Te) have been electrodeposited on evaporated Au(111) films.^[5] Epitaxial CdS nanocrystals have been prepared on graphite by a hybrid electrochemical/chemical method.^[6] However, little work has been done on the electrodeposition of epitaxial semiconductor films with thicknesses in the micrometer range. Lincot et al. reported the electrodeposition of epitaxial CdTe films onto InP(111) substrates.^[7] Epitaxial films of PbO_2 have been deposited on TiO_2 and SrTiO_3 substrates by a photoelectrochemical method.^[8] Single-crystal Bi films were deposited on Au-covered, single-crystal Si(100) by electrodeposition with subsequent annealing at 268 °C.^[9]

Lead sulfide is a low band-gap (0.4 eV) semiconductor that is used extensively in IR photodetectors.^[10] Polycrystalline films of PbS have been prepared by precipitation,^[11] vacuum evaporation,^[12] and chemical bath deposition.^[13] Electrodeposition of PbS has been performed by anodic oxidation of S^{2-} on a Pb electrode,^[14] by deposition from an acidic solution of

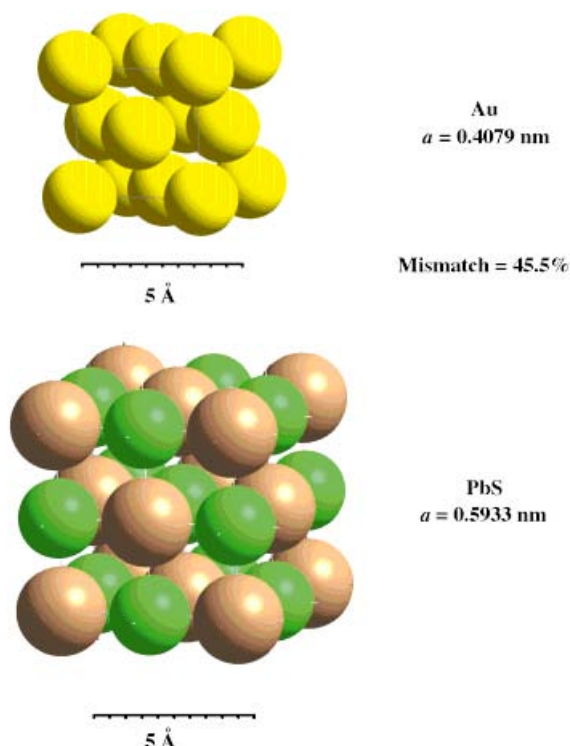


Figure 1. Crystal structures of Au and PbS. Both structures are face-centered cubic, space group $Fm\bar{3}m$, with lattice parameters of 0.4079 and 0.5936 nm, respectively. The lattice mismatch between the two materials is 45.5%. Au atoms are yellow, Pb atoms are brown, and S atoms are green.

$\text{Pb}(\text{NO}_3)_2$ and $\text{Na}_2\text{S}_2\text{O}_3$ ^[15–16] and by co-reduction of Pb^{2+} and elemental sulfur in a suitable nonaqueous solvent.^[17] However, the mobility of carriers in polycrystalline PbS films is two orders of magnitude less than that of the bulk material,^[18] which results in a loss in sensitivity. Epitaxial PbS films should possess higher collection efficiency and better photoconductive properties.

The PbS films were electrodeposited on single-crystal Au(100) at 25 °C from an acidic (pH 4.0) solution of 0.1M $[\text{Pb}(\text{S}_2\text{O}_3)_2]^{2-}$ in an excess of $\text{S}_2\text{O}_3^{2-}$. It should be noted that the authors of refs. [15–16] used lower concentrations of both components (ca. 10^{-3}M), probably to avoid precipitation of PbS_2O_3 . However, the use of low concentrations imposes some limitations on the process conditions. In particular, PbS films were obtained only in the pH range 2.7–2.9.^[16] In our preliminary experiments we did not see such an extreme pH effect. However, since colloidal sulfur may play an important role^[15] the process should be performed at $\text{pH} < 4.5$ to achieve the following partial disproportionation of thiosulfate ions [Eq. (1)].

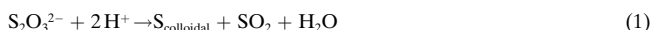


Figure 2 shows the Bragg–Brentano X-ray pattern for a PbS film on Au(100). Only the (200) and (400) peaks of PbS are observed, which indicates its strong out-of-plane orientation. Rocking curves performed on the (200) reflections of both Au and PbS gave full-width at half maximum (FWHM) values of 0.6 and 1.0°, respectively, indicating a high structural perfection of the film. In order to prove the in-plane

[*] Prof. J. A. Switzer, Dr. A. A. Vertegel, Dr. M. G. Shumsky
University of Missouri-Rolla
Department of Chemistry and
Graduate Center for Materials Research
Rolla, MO 65409-1170 (USA)
Fax: (+1) 573-341-2071
E-mail: jswitzer@umr.edu

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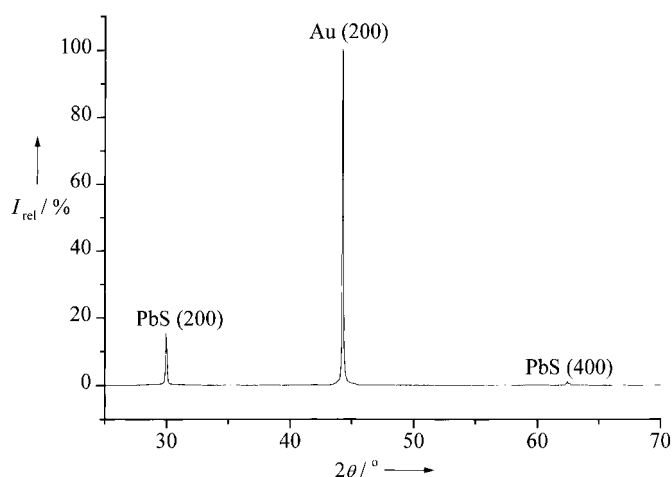
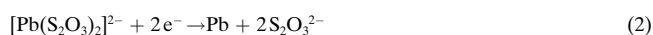


Figure 2. Bragg–Brentano X-ray diffraction pattern probing the out-of-plane orientation of a 1-μm thick PbS film electrodeposited onto single-crystal Au(100). Only the (*h*00) planes are observed in the X-ray pattern for both the film and substrate.

orientation and determine the epitaxial relationship between the film and substrate pole figures of the (111) reflections of PbS and Au were acquired. Figures 3 A and B show the (111) pole figures for Au and PbS. In both cases, the expected fourfold symmetry is observed, with the peaks at a tilt angle $\chi \approx 55^\circ$. This angle corresponds well to the angle between the (111) and (200) planes (54.4°). No diffraction maxima are observed at other angles, which indicates the absence of any other epitaxial relations. The (111) reflections of PbS are observed at the azimuthal angles rotated 45° with respect to those of (111) reflections of Au, as shown in the azimuthal scan (Figure 3 C). This means that although both the film and the substrate adopt the same (100) out-of-plane orientation, the PbS structure is rotated 45° with respect to the Au in the azimuthal plane. An interface model consistent with this rotation is $\text{Au}(100)/(\sqrt{2} \times \sqrt{2}\text{R}45^\circ) - \text{PbS}(100)$, where $\text{R}45^\circ$ denotes the 45° rotation of the overlayer (Figure 4). In this case, the mismatch is only +2.9%. An SEM micrograph of the sample is presented in Figure 5. The film surface consists of square terraces characteristic of a (100) single crystal with a cubic structure. The square features are aligned with each other, and this is also consistent with the in-plane orientation of the film.

Studies of the detailed mechanism of the formation of epitaxial PbS films on Au(100) are currently in progress. Our preliminary results indicate that the primary electrochemical reaction most likely involves the reduction of Pb^{II} as shown in Equation (2).



The freshly deposited lead may then react with elemental sulfur adsorbed on the electrode. Demir and Shannon^[19] showed that sulfur forms a stable $(\sqrt{2} \times \sqrt{2})\text{R}45^\circ$ atomic layer on single-crystal Au(100) during underpotential deposition. Thus, formation of PbS may occur by the deposition of Pb atoms at the unfilled sites on the S/Au lattice, which results in the coincidence lattice that we observed experimentally.

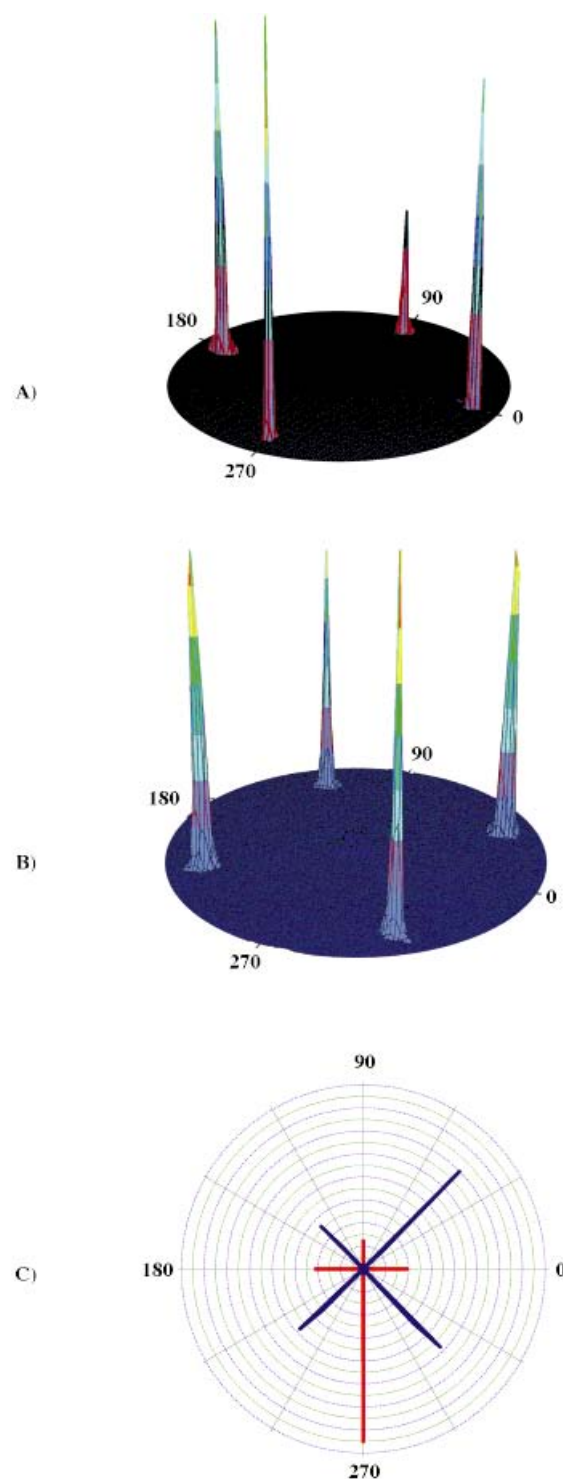


Figure 3. (111) pole figures for A) Au and B) PbS probing the in-plane orientation of the PbS film relative to the Au(100) substrate. The pole figures were obtained by setting 2θ equal to the angle of maximum diffracted intensity for the reflection of interest ($2\theta = 38.184^\circ$ and 25.963° for Au and PbS, respectively) and performing azimuthal scans at tilt angles (χ) from 0 to 70° . No other maxima are observed in either pole figure except for those occurring at $\chi \approx 55^\circ$. C) Azimuthal scans for the (111) reflection of Au (red) and PbS (blue). Each scan represents a cross section of the corresponding pole figure at the fixed tilt angle of 54.4° . This is the angle between the (111) and (200) planes in a cubic lattice. The (111) reflections for PbS are rotated 45° with respect to those of the substrate. The lobes of the azimuthal scan are not of equal intensity because of a slight misorientation of the Au single crystal. The average FWHM for the Au peaks is 1.2° , while the average FWHM for the PbS peaks is 1.8° .

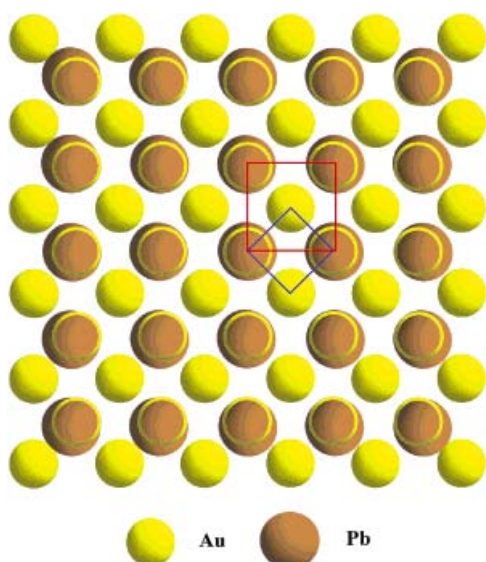


Figure 4. Schematic representation of the $\text{Au}(100)/(\sqrt{2} \times \sqrt{2}\text{R}45^\circ) - \text{PbS}(100)$ coincidence lattice, which is consistent with the X-ray diffraction results. Sulfur atoms are not shown for clarity. The atoms of the adlattice are shown on top of the substrate atoms though they may actually occupy the hollow sites. The Au atoms placed beneath Pb atoms are shown as yellow rings. The red and blue squares indicate unit meshes of PbS and Au surface nets, respectively. The mismatch of the PbS coincidence lattice with the Au is +2.9%.

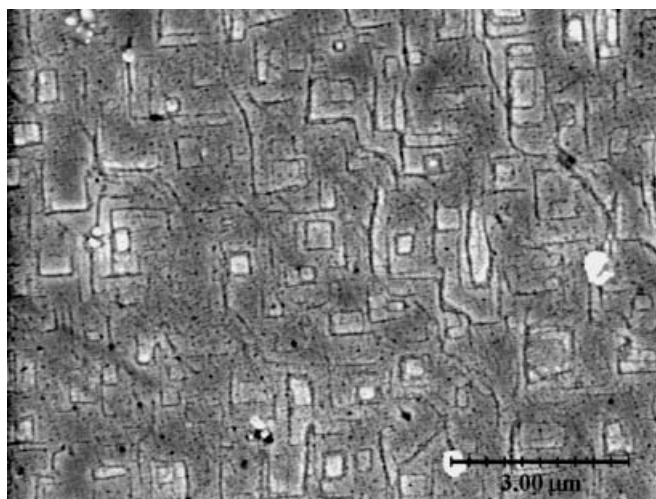


Figure 5. SEM micrograph of the PbS film. Note the square terraces are aligned with each other, which are characteristic of (100) surfaces of cubic single crystals.

Experimental Section

The deposition solution was prepared by adding 1M aqueous $\text{Na}_2\text{S}_2\text{O}_3$ to 0.25M $\text{Pb}(\text{NO}_3)_2$ with vigorous stirring. A white precipitate of PbS_2O_3 is first formed, which then dissolves in the excess of thiosulfate to form $[\text{Pb}(\text{S}_2\text{O}_3)_2]^{2-}$. The concentrations of the components in the final solution were 0.1M Pb^{2+} and 0.6M $\text{S}_2\text{O}_3^{2-}$. This ratio ensures full dissolution of PbS_2O_3 . The final pH of the solution was adjusted to pH 4.0 with 0.5M HNO_3 . HPLC-grade water (Aldrich) was used to prepare the solutions. All other chemicals were reagent grade (Aldrich).

The working electrode consisted of an electropolished $\text{Au}(100)$ single crystal (Monocrystals Company), with a diameter of 10 mm and a thickness of 1 mm. A gold wire was fitted around the edge of the crystal to serve as the electrical contact during deposition. The film was deposited only on one side of the crystal by using the meniscus method. The counter electrode

consisted of a chromel alloy wire. A constant cathodic current density of 0.125 mA cm^{-2} was applied to the working electrode with an EG&G Princeton Applied Research Model 273A potentiostat/galvanostat for 5000s to yield a nominal PbS film of thickness 1 μm .

X-ray diffraction experiments were performed ex-situ in air with a Scintag 2000 diffractometer using $\text{CuK}\alpha$ radiation. The 2θ scan was performed with a step size of 0.03° and a data acquisition time of 1 s per point. Azimuthal scans were obtained by the use of a texture goniometer accessory that had been fashioned in-house for the Scintag 2000 diffractometer. The azimuthal steps were 1° with a data acquisition time of 1 s per point. SEM micrographs were carried out on a Hitachi model S4700 cold-field emission scanning electron microscope.

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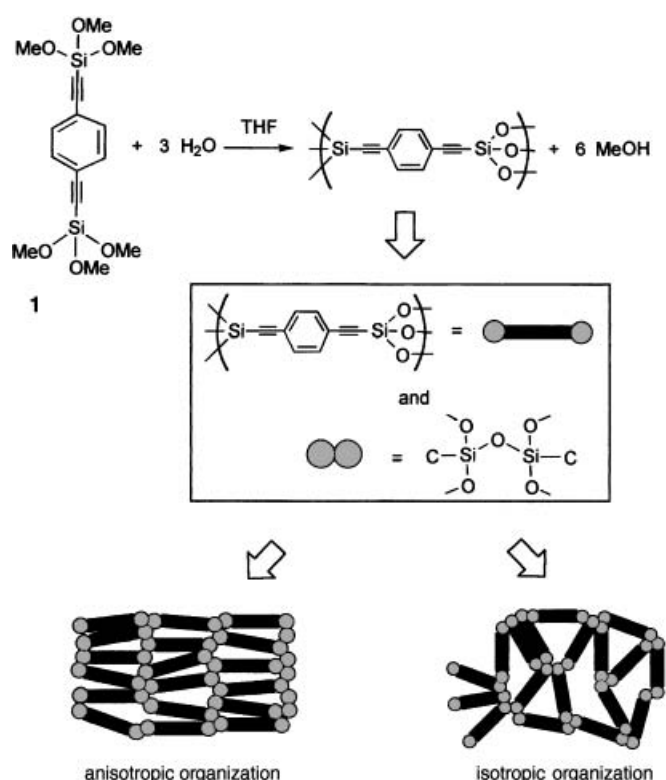
Nanostructured Silica-Based Organic–Inorganic Hybrid Materials—Evidence for Self-Organization of a Xerogel Prepared by Sol–Gel Polymerization**

Bruno Boury, Robert J. P. Corriu,* Valérie Le Strat, Pierre Delord, and Maurizio Nobili

The sol–gel polycondensation is a very convenient method for the preparation of amorphous oxide.^[1] Recently this method was also developed for the preparation of organic–inorganic hybrid materials such as nanocomposites (non-covalently bonded organic groups) and nanostructured hybrid solids (covalently bonded organic groups).^[2–11] The latter can be prepared using a building block of the general formula (MeO)₃Si–R–Si(OMe)₃. Their purity is greatly dependent on both the nature of the organic group and the experimental procedure used to form the gel.^[12–16] These materials are generally considered as amorphous and their organization is still unclear. Two extreme situations can be considered (Scheme 1): a complete isotropic organization with no preferential orientation of the molecule, and the opposite situation with an ordered organization of the organic group that locally mimicks the organization in a liquid crystal.

Chemical evidence of a short-range order in these materials was found when precursors with a rigid, organic core, such as aryl, acetylenic, or thienyl groups, were used. For example, it is possible to induce a selective reaction in these solids, as demonstrated for the electrochemically and chemically induced polymerization of thiophene units in (O)_{1.5}Si–(C₄H₄S)–Si(O)_{1.5},^[17] or the thermal crosslinking reaction of acetylenic units in (O)_{1.5}Si–C≡C–C≡C–Si(O)_{1.5}.^[18] These results demonstrated that the organic groups are in a favorable situation for reaction with each other. Moreover, small-angle X-ray scattering (SAXS) analysis showed a signal at 150 pm in the case of the xerogel (O)_{1.5}Si–(C₆H₄)₃–Si(O)_{1.5}, which, on the basis of a Bragg assumption, was tentatively related to the size of the spacer.^[19] In this case, the formation of aggregates was proposed and modeled in accordance with the ²⁹Si NMR data.^[20]

More recently we reported the use of 1,4-bis[(trimethoxysilyl)ethynyl]benzene (**1**) as a rigid-core precursor for the preparation of such organic–inorganic xerogels.^[21] This precursor was initially chosen because of its well-defined size and geometry and also because of the possibility of selectively



Scheme 1. Possible organization of the molecules in the organic–inorganic xerogel prepared from the rigid rodlike precursor 1,4-bis[(trimethoxysilyl)ethynyl]benzene (**1**).

hydrolyzing the fragile Si–C_{sp} bond using a F[–] catalyst.^[22–24] This property allows organic–inorganic xerogels based on silicon to be prepared, and leads to silica with a narrow pore size distribution after hydrolysis and removal of the organic group.^[21,25,26] The rigidity of the organic group in this precursor has motivated the investigation of the organization of the corresponding gels and xerogels.

These organic–inorganic xerogels are generally obtained by mixing the precursor with solvent in a Schlenk tube in an atmosphere of nitrogen and adding a stoichiometric amount of water. Hydrolysis and polycondensation of the Si–OMe bonds result in the formation of the Si–O–Si network without cleavage of the Si–C_{sp} bond. In an ideal case the polycondensation reaction corresponds to that presented in Scheme 1. In the present case, the gelation occurs within 5 to 10 min without the addition of any catalyst. After aging, washing, and drying, chunks of this xerogel are slightly birefringent when analyzed by polarizing optical microscopy, which indicates a possible self-organization of the organic spacers in the xerogel. We saw the possibility to enhance the birefringence of the xerogel and to better visualize its optical properties by preparing it in closed cells. This procedure is used to study the textures of liquid crystals by promoting the formation of self-organized structures.^[27] Herein we report the preparation of a highly birefringent xerogel by hydrolysis of **1** in closed glass cells treated with oriented teflon.

Two different experimental procedures were used to prepare the xerogel in the cells. The first method (A) is a “static” observation: a homogeneous solution of **1** in THF with a stoichiometric amount of water was prepared and then

[*] Prof. R. J. P. Corriu, B. Boury, V. Le Strat
Laboratoire de Chimie Moléculaire et Organisation du Solide
UMR 5637, Université Montpellier II
Place E. Bataillon, 34095 Montpellier Cedex 5 (France)
Fax: (+33)4-67-14-38-52
E-mail: boury@crit.univ-montp2.fr

P. Delord, M. Nobili
Groupe de Dynamique des Phases Condensées
UMR 5581 Université Montpellier II
Place E. Bataillon, F-34095 Montpellier Cedex 5 (France)

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quickly introduced by capillarity into the cell which is then sealed. The second method (B) is a “dynamic” study: the pure precursor **1** (m.p. = 36 °C) was melted in a nitrogen atmosphere and introduced into the cell by capillarity. The cell was then cooled and the precursor **1** solidified as a microcrystalline solid after a few minutes. The sides of the cell were not sealed and the gelation of **1** was promoted by placing the cell in a dessicator with a 70 % humidity level. This experimental procedure was chosen to limit the dynamics of the gel formation by using a slow diffusion of gaseous water. In both cases, the cells were observed at the different stages of the hydrolysis process by optical microscopy using polarized light.

The 1:THF:H₂O mixture used in method A is initially an optically isotropic solution that always appears dark, no matter what the angle of the crossed polarizer. Gelation occurred a few minutes after the cell was filled. The absence of any induced hydrodynamic movement in the domain when gentle pressure was applied to the glass plate indicated that these bright regions are solid. The gelation time of 7 to 10 mins is similar to the gelation time of the same solution in the Schlenk tube. After a few hours the gel occupied the whole cell and we observed the formation of retracts and cracks, which were attributed to a hydrodynamic process similar to the syneresis process generally observed during sol–gel polycondensation.^[1] This process leads to the formation of birefringent pieces of gel, which are separated by optically isotropic dark cracks (Figure 1 a). In each piece of gel we observed simultaneously the presence of dark and bright regions, with the bright zones changing with the orientation of the sample in the polarized light.^[28] The absence of complete light extinction in the whole piece of gel when using crossed polarizers proves that the orientation of the optical axis inside each piece is not homogeneous. We found from birefringent measurements that in each case the optical axis is parallel to the edge of these pieces. Therefore, the distortion of the optical axis arises from the shape of the piece and its morphology. The birefringent phenomenon suggests a self-organization of the highly polarizable organic spacers. After 48 h, final aging and evaporation of the solvent (THF and methanol produced by the reaction) led to an increase in both the number and the size of the cracks that cut through the gel as it is progressively transformed into a xerogel with similar birefringent properties.

In the experimental procedure used in method B, the whole cell is filled with the crystalline solid precursor, which is easily identified by both its texture and anisotropy. Investigations into the liquid crystalline properties of the precursor have demonstrated that this compound is not mesomorphous. It is a crystalline solid that melts into an isotropic liquid without formation of any mesophases.^[29] The precursor solidified after cooling back to room temperature, and then the cell was placed in the humid atmosphere. In this case, the gelation is closely dependent on the possibility of water reaching and reacting with the crystalline precursor. We observed a slow and continuous process that can be broken down into four steps (Scheme 2).

Initially, the highly birefringent solid **1** (H) occupies the whole cell domain (step 1). After a few minutes the solid (H)

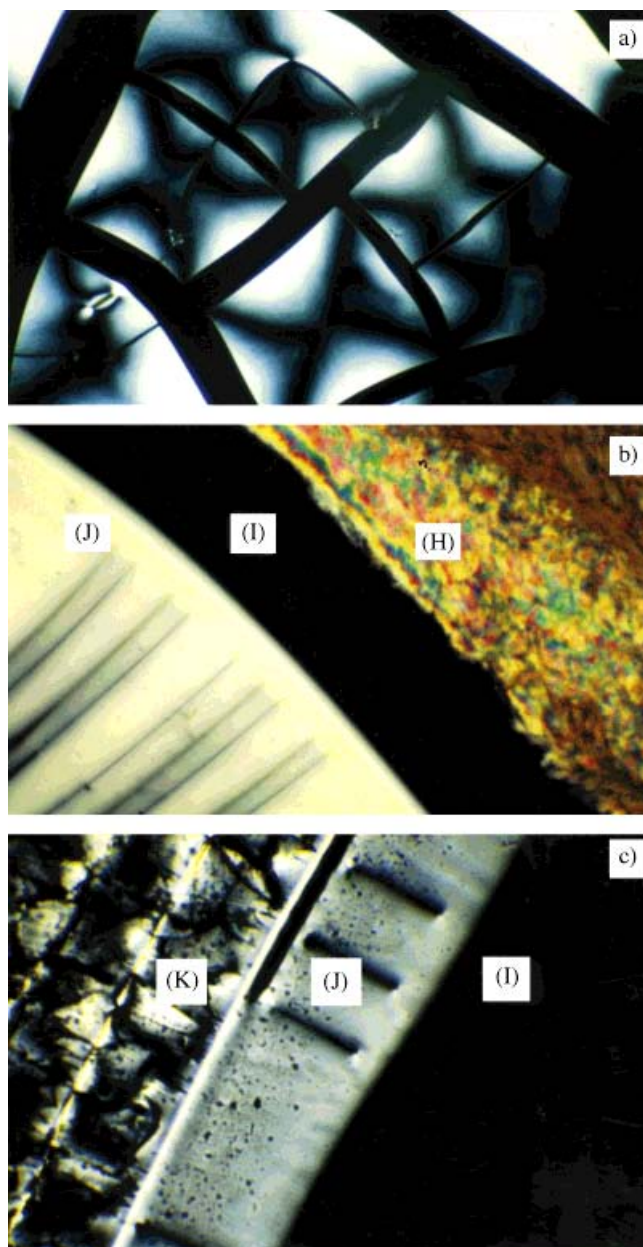
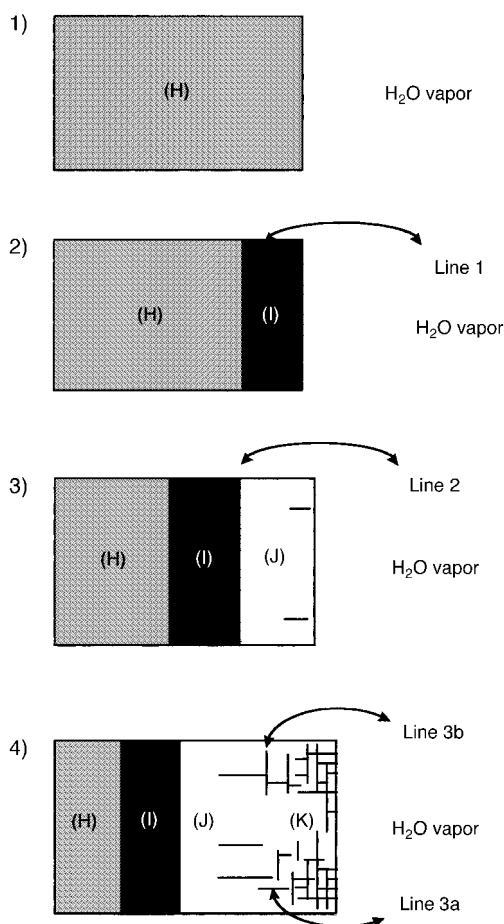


Figure 1. Pictures of the cells of experiment A(a) and experiment B(b,c).

at the edge of the cell was converted into an isotropic liquid (I) that is separated from the pure precursor by line 1 (step 2). In step 3 (I) is formed deeper in the cell at the expense of (H), and at the same time a new birefringent solid (J) appears. This process is initiated at the edges of the cell and leads to the successive transformation of each part of (H) into (I) and then into (J). We also designated a fourth domain (K) related to the evolution of (J) by aging. This domain is characterized by the appearance of dark isotropic lines either perpendicular (line 3a in Scheme 2) or parallel (line 3b) to the fronts of hydrolysis (line 1) and gelation (line 2). These cracks are related to the syneresis and hydrodynamic processes that occur during the aging of the gel. The kinetics of the whole process decreases through time because the water vapor has to diffuse progressively deeper into the cell. After one week,



Scheme 2. Evolution of a part of a cell during the polycondensation process of the pure precursor **1**.

only a small part of the precursor remained in the center of the cell surrounded by birefringent pieces of xerogel that occupied the rest of the cell.

Photographs of the cell give a steady image of the system's evolution (Figure 1 b, c). The pictures obtained using crossed polarizers revealed the four different regions, which could be easily distinguished by their optical properties and morphology. Going from the center of the cells towards the edge we found a microcrystalline birefringent solid (H), an isotropic liquid domain (I), a birefringent gel (J), and a cracked birefringent xerogel (K).

This experimental procedure enables us to trace the history of the xerogel formation through the successive four states: precursor, sol, gel, and xerogel. We assume that hydrolysis and polycondensation reactions of **1** start in domain (I) and produce methanol. The methanol can in turn act as a solvent for the small amount of precursor and partially hydrolyzed precursor. Both species are free to move easily and this accounts for the liquid and isotropic properties of this domain. In this case, this domain can be assimilated to the sol formed during the sol–gel polycondensation of an alkoxysilane.^[1] When reactive species of domain (I) polycondense with Si–OH groups at the surface of the gel (J) their mobility becomes restricted and finally completely suppressed when the aggregate is linked by several Si–O–Si linkages. However, their position is not statistical but occurs with respect to an

organization that leads to the birefringent solid (J). The aging of (J) leads to a syneresis process that is related to the polycondensation, the shrinkage of the xerogel's network, and the expulsion of methanol. The regularity of the dark lines produced, either parallel or perpendicular, to the gel's growth front reinforces the idea of the formation of an organized material by a progressive and diffusive process.

Pieces of the xerogel obtained with method A were powdered and placed in a Lindemann tube for X-ray analysis. A preliminary measurement using a 2D detector showed Bragg's spots forming a ring at $q = 1.5 \text{ \AA}^{-1}$ ($d = 4.16 \text{ \AA}$). Other isolated Bragg's spots were found at $q = 1.67 \text{ \AA}^{-1}$ ($d = 3.76 \text{ \AA}$), $q = 1.87 \text{ \AA}^{-1}$ ($d = 3.36 \text{ \AA}$), and $q = 2.0 \text{ \AA}^{-1}$ ($d = 3.04 \text{ \AA}$). These signals clearly indicate the presence of a crystal order within the material.

This experiment enables us to follow the different steps of the gelation process at a macroscopic scale. In addition, the flat geometry of the pieces of xerogel permits their optical study. In the present case, the formation of a highly cross-linked anisotropic material with a crystal order is observed from a nonmesomorphous precursor. The material's organization is unexpected since neither the precursor nor the oligomeric materials obtained in the first step of the hydrolysis (I) exhibit birefringence. The formation of organized structures from a nonmesomorphous precursor has already been reported in the case of polymeric materials in which the polymeric chains lead to mesophases. As an example, several polysiloxanes with no mesogenic groups^[30–33] are known to form liquid crystalline polymers with smectic structures. However the present case is completely different since the organization of the solid arises from a nonreversible polycondensation in an isotropic solution.

In conclusion, we can state that the formation of a microstructure occurs during the sol–gel polycondensation of a nonmesomorphous precursor. There is an extension from the nanostructure scale previously reported and is certainly the result of the rigid, rodlike structure of the precursor and/or the formation of the siloxane network. However, the influence of the surface treatment also has to be considered.

Experimental Section

Compound **1**, was prepared according to literature methods.^[21, 25] In a typical experiment a homogenous solution was prepared from **1** (0.45 g, 1.24 mmol), THF (0.413 mL), and H₂O (0.67 mL, 3.72 mmol). When the reaction was performed in a Schlenk tube, the gelation time of this mixture was 5–10 min.

The cell's glass was cleaned using ethanol, acetone, sulfochromic acid, and finally water. A thin film of teflon was deposited on one side of each slide by gently applying and rubbing a teflon roller heated at 285 °C onto it. The slides were then assembled with a cellulose acetate glue (CAF4) and using two mylar stripes as spacers; size of the cell 20 × 20 mm. The typical cell thickness was $40 \pm 5 \text{ \mu m}$ as measured by UV/Vis spectroscopy. The amount of xerogel prepared in this condition (< 50 mg) was too low to permit other analyses.

Liquid crystalline properties of the precursor **1** were investigated by heating a teflon-lined cell filled by pure precursor. The melted precursor was introduced into the cell under an atmosphere of nitrogen. The four sides of the cell were sealed with cellulose acetate glue (CAF4). The precursor recrystallized on cooling to room temperature. The cell was then put in an oven (Mettler) and heated from 22 °C to 50 °C at a rate of 0.1 °C min^{-1} . At around 36 °C the crystalline precursor started to break up

and turn into an isotropic liquid without showing any mesophase. When this liquid was cooled at the same rate, the crystal slowly appeared, but formation of mesophase was still not observed.

Optical properties of the material were observed with a Laborlux12POLS polarizing microscope. Photographs were taken with a Leica camera (MPS28). The imaging plate apparatus Rigaku RU 200 equipped with a Marresearch 2D detector was used for the X-ray analysis (the radiation was $\text{Cu}_{\text{K}\alpha}$; $\lambda = 1.542 \text{ \AA}$).

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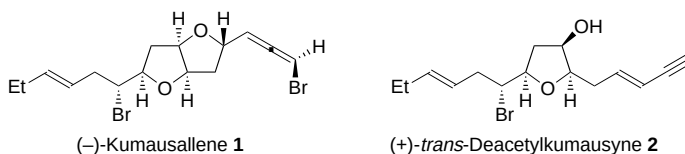
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- [28] See the photographs in the Supporting information. Pictures (a) to (f) were taken with crossed polarizers at every 30° rotation of the sample. Picture (a'), also given in the Supporting information, shows other examples of birefringent pieces of xerogel.
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Enantioselective Total Synthesis of the Nonisoprenoid Sesquiterpene (–)-Kumausallene**

P. Andrew Evans,* V. Srinivasa Murthy, Jamie D. Roseman, and Arnold L. Rheingold

(–)-Kumausallene (**1**) was isolated by Kurosawa and co-workers in 1983 from the red algae *Laurencia Nipponica* Yamada^[1] indigenous to the coast of Hokkaido in Japan, and is a member of a class of halogenated nonisoprenoid sesquiterpenes that contain a *cis*-2,5-disubstituted tetrahydrofuran unit halogenated or oxygenated at C3.^[2–4] In a program directed towards the construction of *cis*-2,5-disubstituted tetrahydrofuran-3-ones using acyl radical cyclizations,^[5–7] we decided to apply this methodology to the enantioselective total synthesis of kumausallene (**1**) and thus confirm the



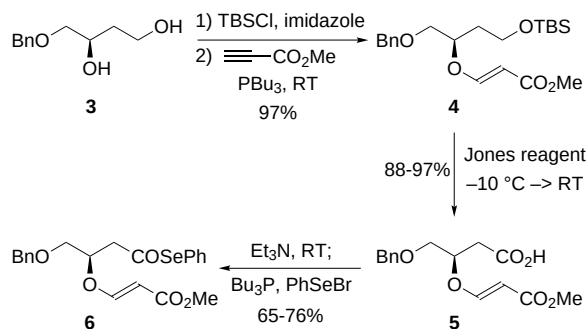
absolute configuration of the bromoallene moiety, which had previously been assigned on the basis of optical rotation data (Lowe's rule).^[1, 8] Furthermore, the proposal that kumausallene (**1**) is biomimetically related to (+)-*trans*-deacetylku-mausyne (**2**)^[9] through an electrophilic cyclization of the C3 hydroxy group onto the enyl side chain^[10] provided an additional incentive to incorporate this feature into the synthetic sequence and determine the suitability of the bromoallene to multistep synthesis. Herein, we describe the first enantioselective synthesis of (–)-kumausallene (**1**) by a

[*] Dr. P. A. Evans, Dr. V. S. Murthy, J. D. Roseman, Dr. A. L. Rheingold
Brown Laboratory, Department of Chemistry and Biochemistry
University of Delaware, Newark, DE 19716 (USA)
Fax: (+1) 302-831-6335
E-mail: paevans@udel.edu

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strategy that can, in principle, be adapted to facilitate the synthesis of related metabolites^[4] and that unequivocally establishes the absolute configuration of the bromoallene.

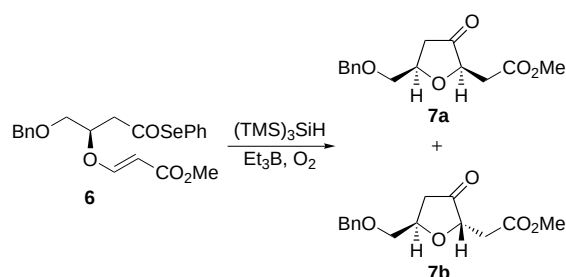
The synthesis of **1** was initiated with the preparation of the acyl selenide **6** by the four-step sequence outlined in Scheme 1. The enantiomerically enriched 1,3-butanediol (**3** (92 % *ee*), prepared by the method reported by Sharpless



Scheme 1. Preparation of the acyl selenide **6**. Bn = benzyl, RT = room temperature.

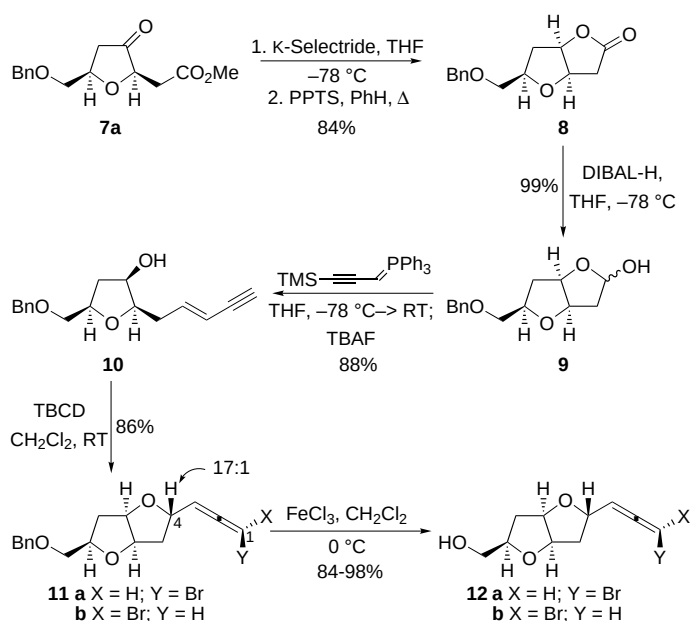
et al.,^[11] was selectively protected as its primary *tert*-butyldimethylsilyl (TBS) ether, and the remaining secondary alcohol was allowed to react with tributylphosphane and methyl propiolate,^[12] giving the vinylogous carbonate **4** in 97% overall yield. Oxidation of the *tert*-butyldimethylsilyl ether **4** with Jones reagent gave the carboxylic acid **5** (88–97%),^[13] which was transformed to the acyl selenide **6** (65–76%) by the Crich protocol.^[14]

The acyl radical cyclization of **6** using tris(trimethylsilyl)silane and triethylborane at –78 °C, in the presence of air, furnished the cyclic ethers **7a** and **7b** (92%) in a 32:1 mixture of diastereoisomers (by HPLC), favoring **7a** (Scheme 2). The analogous reaction at room temperature furnished **7a** and **7b** with only modest diastereoselectivity (8:1), illustrating the role that entropy plays in this type of free radical cyclization.^[15, 16]



Scheme 2. Intramolecular acyl radical cyclization. TMS = trimethylsilyl.

The introduction of the bromoallene at this early juncture in the synthetic sequence offers the advantage of avoiding additional protection/deprotection steps and the possibility of evaluating the biomimetic electrophilic-type cyclization of **10** to give **11** (Scheme 3). Earlier studies suggested that the bromoallene is particularly labile, hence this reaction sequence was expected to determine the stability of the bromoallene, and thus required an orthogonally protected

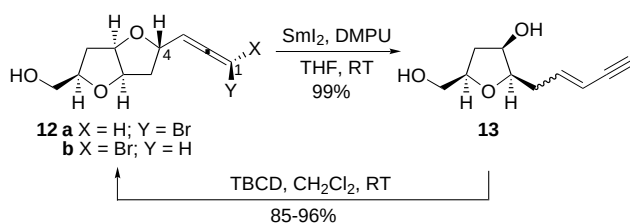


Scheme 3. Introduction of the bromoallene by means of an electrophilic biomimetic-type cyclization.

primary hydroxy group. Treatment of the cyclic ketone **7a** with K-Selectride at –78 °C, followed by pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene, furnished the bicyclic lactone **8** in 84% overall yield. Hence, the strategic lactone **8** required for preparing related metabolites^[4] containing the *cis*-2,5-disubstituted tetrahydrofuran moiety was prepared in 55% overall yield from the 1,3-butanediol **3**. Reduction of the lactone **8** with diisobutylaluminum hydride (DIBAL-H) occurred smoothly to furnish the lactol **9** in nearly quantitative yield. Wittig homologation of **9** using two equivalents of (3-trimethylsilyl-2-propynyl)triphenylphosphorane^[17] led to the formation of the predominantly *trans*-enynyne, which was desilylated in situ with tetra-*N*-butylammonium fluoride (TBAF) to furnish the isomeric enynes **10** (*E/Z* ≈ 10:1) in 88% overall yield. Treatment of **10** with freshly prepared 2,4,4,6-tetrabromocyclohexadienone (TBCD)^[18, 19] gave the bromoallenes **11a** and **11b** (86%) as a 2.5:1 mixture favoring the unnatural C1 epimer, **11b** (kumausallene numbering). Bromoallenes **11a** and **11b** were debenzylated with ferric chloride^[20] to liberate the primary alcohols **12a** and **12b** (84–98%).

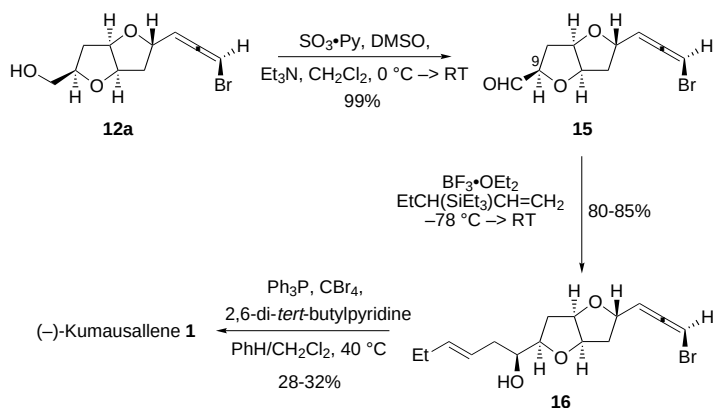
It is gratifying that although the diastereoselectivity in favor of **12a** could not be significantly improved, the undesired diastereoisomer **12b** could be separated by preparative HPLC and recycled by means of the reaction sequence outlined in Scheme 4. Treatment of the bromoallene **12b** with samarium(II) diiodide furnished the enynes **13** (99%) as an almost equal mixture of geometrical isomers (*E:Z* = 1:1.25).^[21] The enynes **13** were then resubjected to the biomimetic electrophilic cyclization, with the primary hydroxy group unmasked, to furnish the bromoallenes **12a** and **12b** (85–96%) as a 1:1 mixture of C1 epimers. The epimers were separated, and the undesired isomer **12b** resubjected to the reaction sequence to furnish **12a** in 78% overall yield after recycling two times.^[22]

The (*E*)-pentenyl appendage was then introduced in a manner analogous to that employed by Overman et al.,^[2] by



Scheme 4. Recycling protocol for the conversion of the epimeric bromoallene. DMPU = 1,3-dimethyl-2-oxohexahydropyrimidine.

using the Sakurai reaction,^[23] albeit in the presence of the relatively labile bromoallene moiety (Scheme 5). Oxidation of alcohol **12a** with sulfur trioxide/pyridine (Py) furnished the



Scheme 5. Completion of the total synthesis of (-)-kumausallene (**1**).

aldehyde **15** with evidence for some equilibration (11:1 by NMR). Treatment of **15** with 3-triethylsilyl-1-pentene^[24] in the presence of boron trifluoride etherate furnished the secondary alcohol **16** (80–85%) as a 14:1 mixture of diastereoisomers. The C10 epimers of **16** were separated by preparative HPLC and the major epimer was converted into (-)-kumausallene (**1**) as outlined in Scheme 5. The spectroscopic data and optical rotation of synthetic kumausallene (**1**) were identical in all respects to the values reported for the natural substance [¹H/¹³C NMR and IR, [α]_D¹⁶ = -145 (c = 0.4 in CHCl₃); lit.^[1] [α]_D²⁰ = -150 (c = 1 in CHCl₃)].

The enantioselective synthesis of the nonisoprenoid sesquiterpene (-)-kumausallene (**1**) was accomplished in 14 steps through the intermediacy of a bicyclic lactone prepared from the optically enriched 1,3-butanediol **3** (92% *ee*). The synthesis demonstrates that the bromoallene is compatible with multiple synthetic operations and provides the unambiguous assignment of the absolute configuration of the bromoallene.

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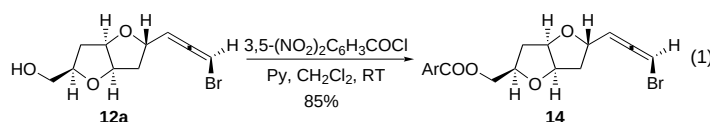
German version: *Angew. Chem.* **1999**, *111*, 3370–3372

Keywords: bromoallenes • natural products • radicals • total synthesis

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the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-12260. 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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Carbon Monoxide and Cyanide Ligands in a Classical Organometallic Complex Model for Fe-Only Hydrogenase**

Erica J. Lyon, Irene P. Georgakaki,
Joseph H. Reibenspies, and Marcetta Y. Darensbourg*

As for the well-characterized [NiFe]hydrogenase,^[1] IR spectroscopic studies^[2] and X-ray crystal structures of Fe-only hydrogenases isolated from *Clostridium pasteurianum*^[3] and *Desulfovibrio desulfuricans*^[4] suggest the active site contains diatomic ligands, CN[−] and CO. The stick drawing representation in Figure 1 embodies features of the diiron site

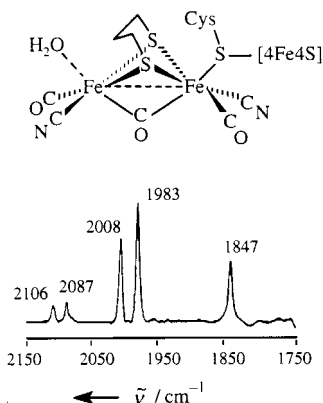


Figure 1. Top) Representation of the dinuclear iron site of Fe-only hydrogenases as an amalgamation of two reported structures, see text.^[3, 4] Bottom) The IR spectrum in the diatomic region as recorded on the oxidized form of the hydrogenase isolated from *Desulfovibrio vulgaris*. (Spectrum reproduced from reference [2].

of both Fe-only H₂ase structures. For example, the former did not refine the S–S bridge as the hydrocarbon link (CH₂)₃,^[3] while the latter did not assign the third bridging ligand as a CO group,^[4] a conclusion which is consistent with IR spectra measured on yet a third Fe-only H₂ase source, *Desulfovibrio vulgaris* (Figure 1, bottom).^[2] While the similarity of peptide sequence at the H-cluster in the different Fe-only H₂ases would support this melding of structures,^[4] the changes in the ν(CO) and ν(CN) IR spectral region with various manipulations of the protein^[2] could indicate the possibility of different forms of the active site dinuclear unit. The development of organometallic complexes as spectroscopic models is hence an important goal as vibrational spectroscopy is a

powerful tool for defining electronic factors that control structure and reactivity in traditional organometallic chemistry.

The surprising and useful similarity between the classical organometallic complex [(η⁵-C₅H₅)Fe(CO)(CN)₂][−] and the iron site of [NiFe]hydrogenase^[5] appears to be equally matched by a homodinuclear organometallic mimic of the unique diiron center in the Fe-only H₂ases. The [(μ-SCH₂-CH₂CH₂S)Fe₂(CO)₆]^[6] complex (hereafter, [(μ-pdt)Fe₂(CO)₆]) is a member of a well-known set of [(μ-SR)₂Fe₂(CO)_{6-x}L_x] complexes which are thermodynamic sinks in low-valent iron–thiolate carbonyl chemistry. Herein we report its molecular structure and studies of CO lability and reactivity resulting in the preparation of spectroscopically relevant mono- and dianionic cyano dimetallic complexes.

Orange platelike crystals of [(μ-pdt)Fe₂(CO)₆] obtained from crystallization from pentane are in the space group P2₁/m.^[7]

The molecular structure of the compound is displayed in Figure 2 (top). Distances and angles are essentially the same

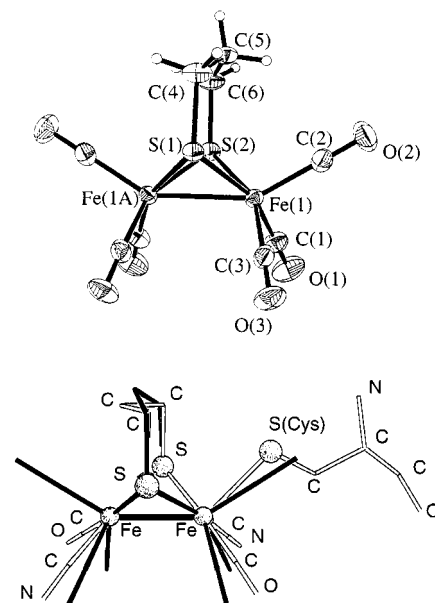


Figure 2. Top) Molecular structure of [(μ-SCH₂CH₂CH₂S)Fe₂(CO)₆] (ORTEP plot, thermal ellipsoids at 50% probability) Selected bond lengths [Å] and angles [°]: Fe(1)–Fe(1A) 2.5103(11), Fe(1)–S(1) 2.2542(10), Fe(1)–S(2) 2.2491(10), S(1)–C(4) 1.823(4), S(2)–C(6) 1.818(4), C(4)–C(5) 1.451(7), C(6)–C(5) 1.470(7), Fe(1)–C(1) 1.801(3), Fe(1)–C(2) 1.802(3), Fe(1)–C(3) 1.797(3), C(1)–O(1) 1.141(4), C(2)–O(2) 1.130(4), C(3)–O(3) 1.136(4); S(1)–Fe–S(2) 85.27(4), Fe(1)–S(1)–Fe(1A) 67.67(4), Fe(1)–S(2)–Fe(1A) 67.85(4), C(1)–Fe–C(2) 97.96(14), C(2)–Fe–C(3) 100.01(13), C(1)–Fe–C(3) 91.02(14), C(1)–Fe–S(1) 160.15(11), C(1)–Fe–S(2) 97.79(11), C(2)–Fe–S(1) 101.75(10), C(2)–Fe–S(2) 103.96(10), C(3)–Fe–S(2) 155.93(10). Bottom) Superposition of the structures of [(μ-SCH₂CH₂CH₂S)Fe₂(CO)₆] with the Fe–Fe dimetallic site of Fe-only hydrogenase using the crystal structure coordinates of the protein as isolated from *Desulfovibrio desulfuricans*.^[4]

in the [(μ-EtS)₂Fe₂(CO)₆]-analogous structure as well as in the two-carbon linked, [(μ-SCH₂CH₂S)Fe₂(CO)₆] complex.^[11, 12] The coordination geometry about each iron center is roughly square pyramidal; the two μ-S atoms, C(1), and C(3) define the base, and C(2), the apical position. The metal is displaced by about 0.38 Å from the base, resulting in the obtuse angles

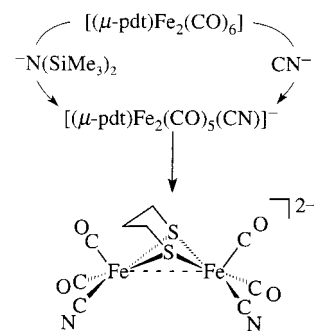
[*] Prof. Dr. M. Y. Darensbourg, E. J. Lyon,
I. P. Georgakaki, Dr. J. H. Reibenspies
Department of Chemistry, Texas A&M University
College Station, TX 77843 (USA)
Fax: (+1) 409-845-0158
E-mail: marcetta@mail.chem.tamu.edu

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between the atoms at apical and basal sites. This edge-shared bi-square pyramidal interpretation differs from earlier structural reports of $[(\mu\text{-SR})_2\text{Fe}_2(\text{CO})_6]$ which represented the $\{\text{Fe}(\text{CO})_3\}$ fragment as part of a face-sharing bioctahedron, the sixth site of which was a shared vertex, the metal–metal bond. The Fe–Fe bond was frequently shown as bent, reflecting the directionality of the overlapping metal orbitals.^[11, 13] While the short Fe–Fe distances of $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_6]$ and those found in the enzyme structures (vide infra) are well within the accepted range for Fe–Fe bonds, and a metal–metal bond is expected to spin pair the 17-electron $\{(\text{RS})_2\text{Fe}(\text{CO})_3\}$ fragments accounting for the observed diamagnetism, the exact nature of the HOMO has not been defined.

Figure 2 (bottom) displays the model complex $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_6]$ overlaid with the Fe–Fe dimetallic site in the hydrogenase isolated from *D. desulfuricans*.^[4] The Fe–Fe distance of 2.510(1) Å in the model complex is 0.1 Å shorter than those reported for the diiron site in the protein structures (2.62 and 2.60 Å).^[3, 4] The root mean square (rms) deviation of the eight atoms, 4Fe and 4S, used to determine the fit, 0.0489 Å, is impressive as is the electron density match of the pdt-bridged diiron site, and the overall coordination of the irons. There is some misalignment in the pdt units, particularly at the central CH₂ group. The slight misfit could imply protein restriction, or, since the S–S linker could not be defined in the *C. pasteurianum* enzyme structure,^[3] give cause to further examine the assignment of the remarkable unit. Interestingly, the limited covalent interactions with the protein has prompted the suggestion that the organodimetallic moiety might have been imported as a preconstructed unit.^[4]

Dissolved in THF, the orange-red $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_6]$ compound exchanged carbonyl ligands slowly with ¹³CO even with photolysis. In contrast, addition of excess cyanide as Et₄CN in solution in CH₃CN or as [15]crown-5-solubilized KCN in THF, resulted in red shifts in the diatomic $\nu(\text{CO})$ region within a few hours, consistent with stepwise substitution of CO by two CN[−] ions. An alternate route to the expected monocyno derivative $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_5(\text{CN})]^-$, that is the reaction of $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_6]$ with sodium bis(trimethylsilyl)amide in THF, demonstrated a coincidence of spectral bands of the intermediate produced by ligand substitution (Scheme 1, Figure 3). A weak band which appeared at 2103 cm^{−1} was assigned to a single $\nu(\text{CN})$ band, resulting from the nucleophilic addition of one N(SiMe₃)₂[−] ion with subsequent loss of the silyl ether (Scheme 1). The $\nu(\text{CO})$ region was



Scheme 1. Ligand substitution in $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_6]$.

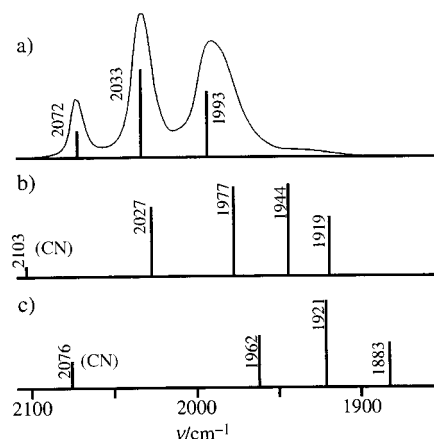


Figure 3. Line drawings of the IR spectra in the diatomic region of a) $[(\mu\text{-SCH}_2\text{CH}_2\text{CH}_2\text{S})\text{Fe}_2(\text{CO})_6]$, b) $[(\mu\text{-SCH}_2\text{CH}_2\text{CH}_2\text{S})\text{Fe}_2(\text{CO})_5(\text{CN})]^-$, and c) $[(\mu\text{-SCH}_2\text{CH}_2\text{CH}_2\text{S})\text{Fe}_2(\text{CO})_4(\text{CN})_2]^{2-}$.

rendered more complicated than that of the $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_6]$ precursor, as expected for the loss of symmetry. Band shifts in the $\nu(\text{CO})$ region as large as 75 cm^{−1} resulted from incorporation of a cyanide ligand, which produced a unit negative charge on one iron.^[14]

While subsequent addition of Na[N(SiMe₃)₂] produced no further reaction,^[15, 16] a second CN[−] was incorporated by the ligand exchange process. A medium to weak broad band appearing at 2076 cm^{−1}, unfortunately coincident with the highest frequency CO band of the neutral starting material, was established by isotopic labeling (using both K¹³CN and K¹⁵N) to be the $\nu(\text{CN})$ band.^[17]

The structural assignment of $[(\mu\text{-pdt})\text{Fe}_2(\text{CO})_4(\text{CN})_2]^{2-}$ is shown in Scheme 1. The line drawing spectrum of the final product (Figure 3c) indicates a relative intensity pattern compatible with a symmetrical placement of two, vibrationally uncoupled (or very weakly coupled), cyanide ligands on adjacent iron centers.^[18] The displacement of vibrationally coupled major $\nu(\text{CO})$ bands by 80–100 cm^{−1} to lower energy from the starting material furthermore suggests symmetrical disubstitution of two carbonyl ligands by cyanide ligands with a unit negative charge on each iron center.

A comparison of the spectra shown in Figure 1 and Figure 3 reveal that the model anionic, cyanoiron(II) species have $\nu(\text{CO})$ bands somewhat lower in frequency than those of the aerobically isolated and presumably oxidized enzyme.^[2] Initial IR studies of the reduced enzyme however find both $\nu(\text{CO})$ and $\nu(\text{CN})$ bands compatible with our anionic cyano Fe^I–Fe^I dinuclear models.^[2] The actual oxidation state of the dinuclear iron site in the enzyme and whether, or how, it changes with various enzymic redox levels is not yet established.

Inorganic and organometallic precedents of CO coordination to iron in higher oxidation states are few and highlight the necessity of good donor ligands such as thiolates and cyanides to stabilize Fe^{II}(CO) or Fe^{III}(CO) as seen in the case of the mononuclear $[\text{Fe}^{\text{II}}(\text{PS}_3)(\text{CO})(\text{CN})]^{2-}$ and $[\text{Fe}^{\text{III}}(\text{PS}_3)(\text{CO})(\text{CN})]^-$ complexes (PS₃H₃ = tris(2-sulfanyphenyl)phosphane) reported by Koch and co-workers.^[19] Furthermore, the $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}^{\text{II}}(\text{CO})(\text{CN})_2]^-$ ion provided a precise match of $\nu(\text{CO})$ and $\nu(\text{CN})$ in the oxidized form of [NiFe]H₂ase, confirming

the proposed oxidation state of Fe^{II} in the [(SCys)₂Ni^{III}(μ-SCys)₂Fe^{II}(CO)(CN)₂] site.^[5] A highly asymmetric model complex which contains [Fe^{II}-(μ-SR)₃-Fe^{II}(CO)₂] shows ν(CO) bands at 2011 and 1957 cm⁻¹, considerably higher than the average ν(CO) band of the reduced Fe-only H₂ase enzyme.^[20] Furthermore, its Fe...Fe distance of about 3.1 Å is typical of Fe^{II}-bridged thiolates.

The structural and spectroscopic matches of the Fe-only H₂ase and the model dinuclear complexes reported herein indicate the possibility of Fe^I in nature, or the achievement of an equivalent electron density about Fe^{II} by the use of anionic cyanide ligands. The ambidentate CN⁻ provides an anchor for the site through H-bonding to the protein, which in turn may tune the amount of negative charge contributed to the iron centers.^[21] Notably, the other component of the "H-cluster", cysteine-S bridged into the dinuclear site, is a 4Fe₄S cube which may serve as an oxidation level buffer. The 2Fe/4Fe₄S site would appear to be electronically versatile and hence complicated, as noted in forerunner spectroscopic studies.^[22]

Experimental Section

Synthesis of [(μ-pdt)Fe₂(CO)₆]: The [(μ-pdt)Fe₂(CO)₆] complex was obtained either from BrCH₂CH₂CH₂Br and [(μ-S₂)Fe₂(CO)₆],^[6, 23] or from reaction of HSCH₂CH₂CH₂SH with Fe₃(CO)₁₂.^[24]

Reaction of [(μ-pdt)Fe₂(CO)₆] with Na[N(SiMe₃)₂]: To a solution containing [(μ-pdt)Fe₂(CO)₆] (ca. 0.16 g, 0.41 mmol) in dry THF (20 mL) was added a solution of Na[N(SiMe₃)₂] (0.134 g, 0.732 mmol) in THF. The ensuing color change from dark orange to deep red brown was accompanied by IR spectral changes (see Figure 3).

Synthesis of [(μ-pdt)Fe₂(CO)₄(CN)₂]²⁻ by ligand substitution: To [(μ-pdt)Fe₂(CO)₆] (0.056 g, 0.15 mmol) dissolved in CH₃CN (15 mL) was added Et₄CN (0.054 g, 0.35 mmol) in CH₃CN (5 mL). Within 6 h the limiting IR spectrum, Figure 3c, was obtained.

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positions and refined using a riding model. Refinement of 97 parameters and 1208 data points converged with residual values of $R(F)$ (all data) = 0.0380, $R(F)[I > 2\sigma(I)]$ = 0.317, $R_w(F^2)$ (all data) = 0.0881, $\Sigma(F^2)$ (all data) = 1.016. The propanedithiolate ligand was located on the mirror plane with four of the five atoms on special positions; the central methylene carbon atom of the ligand was disordered between two positions. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-127014. 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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The 5/2,3/2 Spin Admixture in the Chloroiron(III) Derivative of the Sterically Crowded 2,3,7,8,12,13,17,18-Octaethyl-5,10,15,20-tetraphenylporphyrin**

Volker Schünemann, Michael Gerdan, Alfred X. Trautwein, Najib Haoudi, Dominique Mandon, Jean Fischer, Raymond Weiss,* Alain Tabard, and Roger Guillard

Dedicated to Professor Gottfried Huttner on the occasion of his 62nd birthday

Interest in how nonplanar distortions affect the properties of tetrapyrrole macrocycles, in particular their biological function, has led to the syntheses of and structural studies on a large number of sterically crowded porphyrins.^[1, 2] Important results of these studies are that porphyrins are considerably more flexible than originally suspected, and that conformational variations offer an attractive mechanism for the modulation of a wide range of physical and chemical properties of porphyrins in vitro and in vivo.^[3]

Cheng et al.^[4] recently showed that the chloroiron(III) derivative of the sterically crowded 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetraphenylporphyrin [Fe^{III}Cl(oetpp)] (**1**) displays a nonplanar saddled and slightly ruffled conformation. Owing to the ring distortion this species possesses magnetic properties corresponding to a quantum-mechanically spin-admixed $S = 5/2, 3/2$ state with an effective magnetic moment of $5.2 \mu_B$ in the solid state at 300 K and an EPR spectrum with a $g_{\perp}$ value of 5.2 at 77 K in frozen 2-methyl-tetrahydrofuran (2-MeTHF) solution. According to the Maltempo model, a $g_{\perp}$ value of 5.2 corresponds to an $S = 5/2$ spin state with approximately 40 % $S = 3/2$ spin admixture.^[5, 6]

Several iron(III) complexes of nonsaddled porphyrins that can be regarded as having a spin-admixed 5/2,3/2 state are known.^[7–9] A well-documented case is [Fe^{III}(tpp)]ClO₄ (tpp = 5,10,15,20-tetraphenylporphyrin dianion).^[8] The fact that the spin states of iron(III) porphyrins (high-spin $S = 5/2$, low-spin $S = 1/2$, and mixed intermediate-spin $S = 5/2, 3/2$) can vary in response to subtly changing conditions and can be nearly degenerate depending on the axial ligand(s) and the geometrical environment around the iron center has long been recognized.^[10–12] Five-coordinate ferric complexes which exhibit a strong quantum-mechanically spin-admixed state ($S =$

5/2,3/2) typically exhibit large Mössbauer quadrupole splittings that remain almost unchanged throughout the whole temperature range.^[13–15] At 280 K, the zero-field Mössbauer spectrum of a powder sample of [Fe^{III}Cl(oetpp)] (**1**) synthesized by us consisted of a well-defined quadrupole doublet, which, although asymmetric due to relaxation effects, displayed an isomer shift of $\delta = 0.35 \text{ mm s}^{-1}$ and a quadrupole splitting ΔE_Q of only 0.95 mm s^{-1} , inconsistent with a substantial spin admixture. Therefore, we investigated the X-ray structure and the ¹H NMR, Mössbauer, EPR, and magnetic properties of a sample of [Fe^{III}Cl(oetpp)] (**1**). Here we report the results of these studies.

In spite of having a nonplanar saddled and slightly ruffled conformation similar to that reported by Cheng et al.,^[4] the [Fe^{III}Cl(oetpp)] (**1**) compound synthesized by us showed a quantum-mechanical spin admixture with a contribution from the $S = 3/2$ state of 10 % or less, as opposed to the 40 % found in the [Fe^{III}Cl(oetpp)] studied by Cheng et al.

Compound **1** was prepared by procedures described in the literature.^[16] It was characterized by UV/Vis spectroscopy and mass spectrometry: UV/Vis (CH₂Cl₂): λ_{max} ($\epsilon \times 10^{-3}$) = 397.5 (40.5), 444.5 (37.3), 574 (6.1); MS (EI): m/z (%): 927 (100) [M^+], 892 (8) [$M^+ - \text{Cl}$]. Single crystals suitable for X-ray studies were obtained by slow diffusion of dodecane into a solution of **1** in dichloromethane.^[17a] A projection of the molecular structure of **1** onto the mean plane of the porphyrin core is displayed in Figure 1. Figure 1 also gives the perpendicular displacements of the porphyrin-core atoms relative to

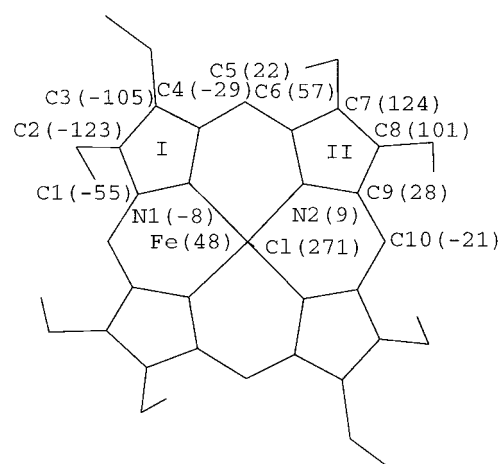


Figure 1. Projection of the structure of **1** (hydrogen atoms are omitted for clarity) on the mean plane of the porphyrin core. The perpendicular displacements (in $10^{-2} \text{ \AA}$) of the atoms relative to the mean plane of the porphyrin core are given. Selected bond lengths [$\text{\AA}$]: Fe–N1 2.053(6), Fe–N2 2.027(6), Fe–Cl 2.234(4).

the mean plane of the porphyrin core. The molecule **1** is located on a twofold axis of the space group $C2/c$; therefore, the crystallographically required symmetry of **1** is C_2 . The oetpp dianion adopts, as in the crystalline form studied by Cheng et al.^[4] (**1'**), a saddled^[18] and slightly ruffled nonplanar conformation. The mean values of the displacements of the geminal β -carbon atoms above and below the mean plane of the porphyrin core are not significantly different in the two

[*] Prof. Dr. R. Weiss, N. Haoudi, Dr. D. Mandon, Prof. Dr. J. Fischer
Institut Le Bel (UMR 7513)
Université Louis Pasteur
4, Rue B. Pascal, 67070 Strasbourg Cedex (France)
Fax: (+33) 388-41-363
E-mail: weiss@chimie.u-strasb.fr

Dr. V. Schünemann, M. Gerdan, Prof. Dr. A. X. Trautwein
Institut für Physik, Medizinische Universität zu Lübeck
Lübeck (Germany)

Dr. A. Tabard, Prof. Dr. R. Guillard
LIMSAG (UMR 9953), Université de Bourgogne
Faculté des Sciences "Gabriel", Dijon (France)

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structures (av 1.133(8) Å in **1**, av 1.153(6) Å in **1'**). Both **1** and **1'** are also slightly ruffled. The ruffling is characterized by the mean value of the displacements of the *meso*-carbon atoms above and below the mean plane of the porphyrin core.^[18] The mean values of 0.216(8) and 0.190(6) Å for **1** and **1'**, respectively, are not significantly different. The difference in the distances of the iron atom from the porphyrin core and from the mean planes of the four pyrrole nitrogen atoms N_p ($\Delta = 0.480(2) - 0.477(2) = 0.003(2)$ Å) is not significant and indicates that these two mean planes are superimposed in **1**. In contrast, in **1'** this difference ($\Delta = 0.434(1) - 0.467(1) = -0.032(1)$ Å) is significant and indicates a slight doming in this structure that is absent from the structure of **1**. Accordingly, the out-of-plane displacements of the iron atoms of 0.480(2) and 0.434(1) Å relative to the corresponding porphyrin mean planes of **1** and **1'**, respectively, are significantly different. However, the distances of 0.477(2) and 0.466(1) Å of the iron atom from the $4N_p$ mean planes of **1** and **1'**, respectively, are again very similar. The mean Fe– N_p bond lengths are 2.040(6) and 2.031(5) Å, and the Fe–Cl bond lengths are 2.233(1) and 2.242(2) Å in **1** and **1'**, respectively.^[17b] All these data indicate that the molecular structures of **1** and **1'** are quite similar, despite their packing in two different space groups ($C2/c$ for **1** and $P2_1/c$ for **1'**).

Four signals ($\delta = 61.8, 57.0, 29.6, 22.5$) are present in the ^1H NMR spectrum of **1** (200 MHz, CD_2Cl_2 , 200 K, TMS), corresponding to the eight methylene protons of the β -pyrrole ethyl substituents. The appearance of these four signals indicates that no inversion of the saddle/ruffle distortion occurs in solution at 200 K. Moreover, the variable-temperature ^1H NMR spectra of **1** in CD_2Cl_2 between 200 and 400 K shows that the coalescence temperature of these four methylene signals lies, as in the variable-temperature ^1H NMR spectrum of **1'** in $C_2D_2Cl_4$,^[4] at about 370 K. Hence, the conformations of **1** and **1'** must also be very similar in solution.

The molar magnetic susceptibility of **1** was measured on a powder sample between 2 and 293 K with a SQUID magnetometer (Quantum Design MPMS). Figure 2 shows the temper-

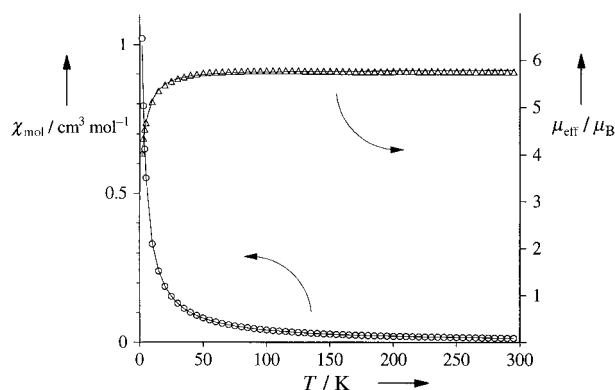


Figure 2. Temperature dependence of the effective magnetic moment μ_{eff} of a powder sample of **1** as derived from the molar magnetic susceptibility χ_{mol} in a field of 1 T. The measured data are corrected for diamagnetic contributions ($\chi_{dia} = -592 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$). The solid line represents a spin-Hamiltonian simulation with a zero-field splitting of $D = 10.2 \text{ cm}^{-1}$, the rhombicity parameter $E/D = 0.025$ (from the EPR analysis), and an isotropic g tensor with $g = 1.954$.

ature dependence of the effective magnetic moment per molecule of **1**. The effective magnetic moment of $5.78 \mu_B$ is only slightly lower than the spin-only value for a pure $S = 5/2$ state ($2(S(S+1))^{1/2} \mu_B = 5.92 \mu_B$). The data were analyzed by means of the spin-Hamiltonian formalism, which gave a zero-field splitting of $D = 10.2 \text{ cm}^{-1}$ and an isotropic g tensor of 1.954. The latter value, being smaller than 2, indicates minor quantum-mechanical mixing of the $S = 5/2$ and $S = 3/2$ spin states.^[19]

The EPR spectra of **1** were recorded with a conventional X-band spectrometer (Bruker 200D SRC) equipped with a helium-flow cryostat (ESR 910, Oxford Instruments). The measurements at 10 K were performed at a frequency of 9.646 GHz, a microwave power of 20 μW , a modulation amplitude of 5 G, and a modulation frequency of 100 kHz. The spectra were analyzed under the assumption of a Lorentzian line shape. Figure 3 shows the EPR spectrum of

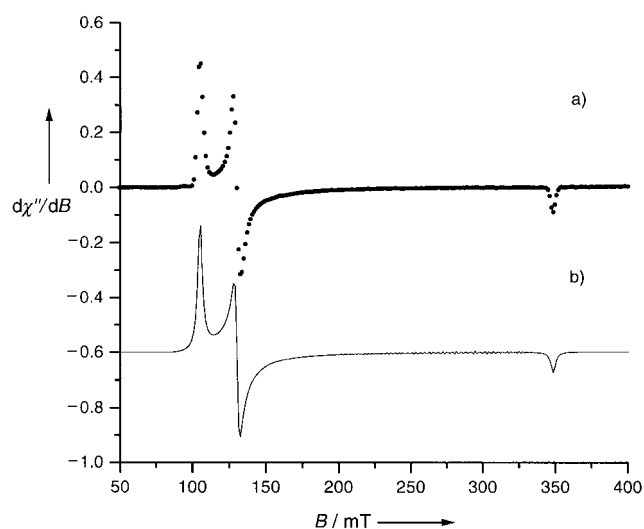


Figure 3. a) EPR spectrum of **1** in 2-MeTHF at $T = 10 \text{ K}$; b) simulated spectrum under the assumption of Lorentzian line shape with $g_y^{eff} = 6.55$, $g_x^{eff} = 5.28$, and $g_z^{eff} = 1.976$ and line widths $\Gamma_y = 3.7 \text{ mT}$, $\Gamma_x = 3.7 \text{ mT}$, and $\Gamma_z = 3.8 \text{ mT}$. Experimental conditions: Microwave frequency 9.646 GHz, modulation frequency 100 kHz, modulation amplitude 10 G, microwave power 20 μW .

1 in frozen 2-MeTHF measured at 10 K (a) and a simulation (b), which yielded the effective g values $g_y^{eff} = 6.55$, $g_x^{eff} = 5.28$ ($g_{\perp}^{eff} = 5.92$), and $g_z^{eff} = 1.976$. A less well resolved spectrum recorded in frozen CH_2Cl_2 yielded by simulation the following effective g values: $g_y^{eff} = 6.34$, $g_x^{eff} = 5.28$ ($g_{\perp}^{eff} = 5.81$), and $g_z^{eff} = 1.992$. The effective g values obtained in both frozen solutions are characteristic for an $S = 5/2$ ground state with a positive zero-field splitting D , a small rhombicity ($E/D = 0.02-0.03$), and a small quantum-chemical admixture of the $S = 3/2$ state. According to Maltempo and Moss,^[6] the reduction of the average $g_{\perp}^{eff}$ value due to quantum-chemical $5/2, 3/2$ spin mixing is given by $g_{\perp}^{eff} = 6(a_{5/2})^2 + 4(b_{3/2})^2$. The coefficient $(a_{5/2})^2$ can be directly expressed in terms of effective $g_{\perp}$ value by $(a_{5/2})^2 = (g_{\perp}^{eff} - 4)/2$. Hence, the degree of spin mixing in **1** lies between 4% in 2-MeTHF ($(a_{5/2})^2 = 0.96$) and 10% in CH_2Cl_2 ($(a_{5/2})^2 = 0.90$).

A Mössbauer spectrum of a powder sample was recorded with a conventional spectrometer in the constant-acceleration mode. Isomer shifts are relative to α -Fe at room temperature. The spectrum was analyzed by a least-squares fit with a Lorentzian line shape. The Mössbauer spectrum of **1** (Figure 4) at 280 K exhibits an asymmetric doublet because of relaxation effects. The Mössbauer parameters ($\delta = 0.35 \text{ mm s}^{-1}$ and $\Delta E_Q = 0.95 \text{ mm s}^{-1}$) compare well with those of other high-spin iron(III) porphyrins, whereas the quadrupole splitting is considerably smaller than those of iron(III) porphyrin complexes which exhibit a substantial $S = 3/2$ admixture.^[13–15, 19]

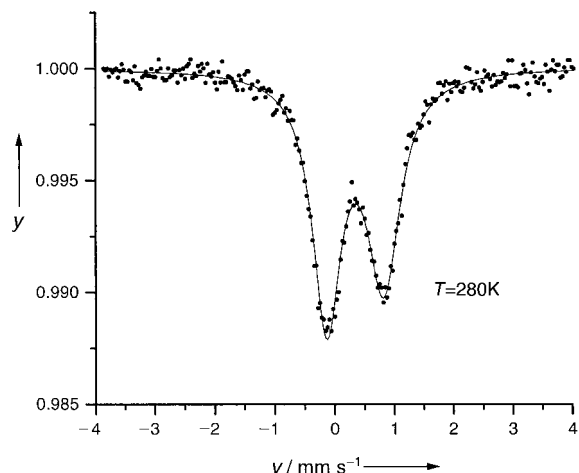


Figure 4. Mössbauer spectrum of a powder sample of **1** at 280 K in a field of 10 mT applied perpendicular to the γ beam. Two single lines of Lorentzian shape were used to fit the asymmetry of the spectrum, which is caused by relaxation effects: $\delta = 0.35 \text{ mm s}^{-1}$, $\Delta E_Q = 0.95 \text{ mm s}^{-1}$, $\Gamma_1 = 0.68 \text{ mm s}^{-1}$, and $\Gamma_2 = 0.57 \text{ mm s}^{-1}$. y = relative transmission, v = velocity.

In conclusion, a significantly smaller quantum-mechanical $S = 3/2$ spin admixture is present in the $[\text{Fe}^{\text{III}}\text{Cl}(\text{oetpp})]$ complex prepared by us (4–10%), as compared to that in the $[\text{FeCl}(\text{oetpp})]$ complex prepared by Cheng et al. (ca. 40%),⁸⁴⁹ despite similar ring deformations in both complexes in solution and in the solid state.

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- [17] a) Crystal data for **1**: $\text{C}_{60}\text{H}_{60}\text{N}_4\text{ClFe}$, $M_r = 928.5$, monoclinic, space group $C2/c$, $a = 17.737(5)$, $b = 24.456(7)$, $c = 15.588(4)$ Å, $\beta = 111.24(2)^\circ$, $V = 6302$ Å³, $Z = 4$, $\rho_{\text{calc}} = 0.978 \text{ g cm}^{-3}$, $\lambda(\text{MoK}\alpha) = 0.7107$ Å, 6791 reflections ($2 < \theta < 26^\circ$) were collected at 20°C on a dark blue crystal of dimensions $0.35 \times 0.30 \times 0.25$ mm. Semi-empirical absorption corrections were applied. A total of 3537 reflections with $I > 3\sigma(I)$ were used in the refinements; 299 refined parameters, $R = 0.073$, $R_w = 0.120$, GOF 1.036, final residual electron density 0.13 Å³; b) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-118960. 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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Transition Metal Induced Pentamerization of a Phosphaalkyne**

Peter Kramkowski and Manfred Scheer*

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

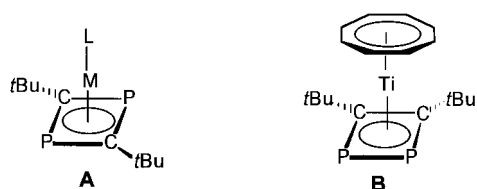
The chemistry of the phosphaalkynes has been intensively investigated over the past 15 years in their various aspects of organoelement chemistry^[1] and coordination chemistry.^[2] The basis for this immense development was the first synthesis of kinetically stabilized $t\text{BuC}\equiv\text{P}$ by G. Becker in 1981^[3, 4] and the improved preparation by M. Regitz and G. Becker.^[5] Most of the studies into the reactivity of phosphaalkynes have been carried out on this compound, whereas the supermesityl-phosphaalkyne $\text{Mes}^*\text{C}\equiv\text{P}$ ($\text{Mes}^* = 2,4,6\text{-}t\text{Bu}_3\text{C}_6\text{H}_2$) and the

[*] Prof. Dr. M. Scheer, Dr. P. Kramkowski
Institut für Anorganische Chemie der Universität
D-76128 Karlsruhe (Germany)
Fax: (+49) 721-661921
E-mail: mascheer@achibm6.chemie.uni-karlsruhe.de

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adamantyl-phosphaalkyne $\text{AdC}\equiv\text{P}$ ($\text{Ad} = \text{C}_{10}\text{H}_{15}$) have only been rarely included in such investigations. Recently Regitz and co-workers were able to synthesize mesityl-phosphaalkyne $\text{MesC}\equiv\text{P}$ ($\text{Mes} = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$) in preparatively useful quantities.^[6]

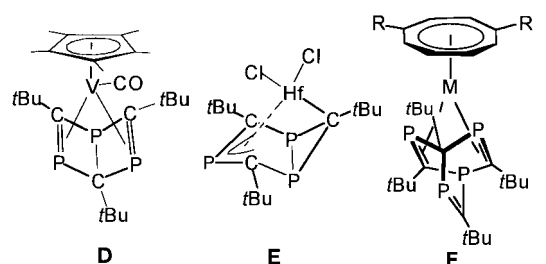
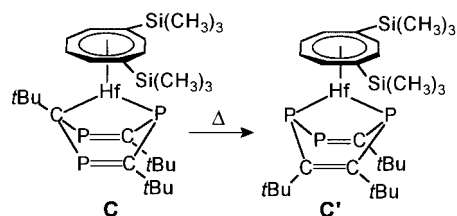
A central aspect of the investigations on the reactivity of phosphalkynes in transition metal compounds is the comparison with the reactivity pattern of isolobal alkynes of the type $\text{RC}\equiv\text{CR}'$ ($\text{R}, \text{R}' = \text{alkyl, aryl}$). The complex chemistry of alkynes is, amongst other factors, characterized by cyclooligomerization processes in the coordination sphere of the transition metal center. Corresponding oligomers of isoelectronic phosphalkynes have been synthesized recently, and products of di-, tri-, and tetramerization on transition metal centers were successfully isolated. Dimerization to 1,3-diphosphete ligands is the preferred reaction in such cases. The head-to-tail dimerization on 14-valence electron (VE) complexes of cobalt,^[7] rhodium,^[8] and iron^[9] and on 12VE fragments of zirconium and hafnium^[10] occurred with the formation of compounds of type **A** ($\text{cot} = \text{cyclooctatetraene}$). In comparison, dimerization to 1,2-diphosphete (complex **B**) is rare, but has been observed in the coordination sphere of titanium complex fragments.^[11]



M = Co, Rh; **L** = $\eta^5\text{-C}_5\text{R}_5$; **R** = H, Me

M = Zr, Hf; **L** = cot

M = Fe; **L** = 3 CO



M = Hf; **R** = SiMe_3

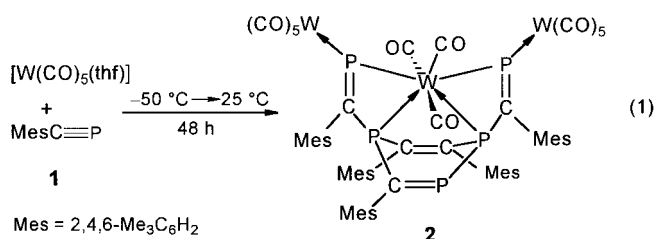
M = Zr; **R** = H

The number of known trimerization products is much smaller than the number of dimers. The synthesis of trimeric phosphalkyne derivatives succeeded with $(\eta^4\text{-butadiene})[\eta^8\text{-1,4-bis(trimethylsilyl)cyclooctatetraene}]$ hafnium as the starting material.^[12] By reaction with $t\text{BuC}\equiv\text{P}$, compound **C** was

obtained initially. Thermolysis of **C** led to an intramolecular rearrangement to form **C'**, whose composition was determined on the basis of $^{31}\text{P}\{\text{H}\}$ NMR spectroscopic data. Furthermore, vanadium complex **D** with a 1,3,5-triphosphadewar-benzene ligand^[13] as well as the hafnium complex **E** with the 1,3,5-triphosphabicyclo[3.1.0]hexene ligands^[14] have also been described. The only known phosphalkyne tetramerization product is the tetraphosphabarrelene complex **F**.^[15]

Here we report the synthesis and characterization of the first pentamerization product from mesityl-phosphaalkyne and $[\text{W}(\text{CO})_5(\text{thf})]$.^[16] These studies are part of our investigations into the formation of complexes with a metal-phosphorus triple bond by three-component reactions between $[(\text{RO})_6\text{W}_2]$ ($\text{R} = t\text{Bu}, 2,5\text{-Me}_2\text{C}_6\text{H}_4$) and the phosphalkyne in the presence of $[\text{M}(\text{CO})_5(\text{thf})]$ ($\text{M} = \text{Cr}, \text{W}$).^[17]

The reaction of $\text{MesC}\equiv\text{P}$ (**1**) with $[\text{W}(\text{CO})_5(\text{thf})]$ at -50°C in THF/*n*-hexane yielded a product mixture from which the pentamerization product **2** was isolated in 10% yield after column chromatographic workup [Eq. (1)]. The separation and characterization of the other products proved to be very complex, although spectroscopic data indicated the presence of compounds with 1,3-diphosphete ligands. Compound **2** is an



orange-red crystalline solid which is stable for a short time in air and which dissolves well in toluene and THF. Solutions of **2** are unstable with respect to thermolysis and photolysis. The molecular structure of **2**^[18] (Figure 1) shows a basic framework of a metalla-norbornadiene formed by the atoms P(3), C(15), P(5), P(4), C(17), C(16), and W(1) and extended by two phosphalkyne units in the 1,4-position. The basic framework is similar to the trimerization product of $t\text{BuC}\equiv\text{P}$ in **C'** and has been structurally verified. The central feature of compound **2** is the tungsten atom W(1),^[19] which is sevenfold coordinated by three CO groups and the phosphorus atoms P(1) to P(4) of the pentamer. The W(1)–P(1) and W(1)–P(2) bond lengths of 2.5398(14) and 2.514(2) Å are within the range of typical W–P bonds, such as in $[\text{Ph}_3\text{P}\{\text{W}(\text{CO})_5\}]$ (2.544 Å).^[20] The bond lengths W(1)–P(3) and W(1)–P(4) with 2.494(2) and 2.459(2) Å are slightly shortened in comparison. The phosphorus atoms P(1) and P(2) are also bonded to $[\text{W}(\text{CO})_5]$ units and to C(18) or C(14). These bond distances (1.707(5) and 1.710(5) Å) lie within the range of slightly elongated P=C bonds.^[21] The metalla-norbornadiene fragment is bonded through P(3) and P(4) to the carbon atoms of the phosphalkyne units, C(14)/P(2) and C(18)/P(1). The bond lengths are 1.801(5) and 1.775(5) Å and are therefore in the range of slightly elongated P–C single bonds (1.84 Å^[22]). Within the boat-shaped six-membered ring, there is a P–P bond between the atoms P(4) and P(5). The bond length of

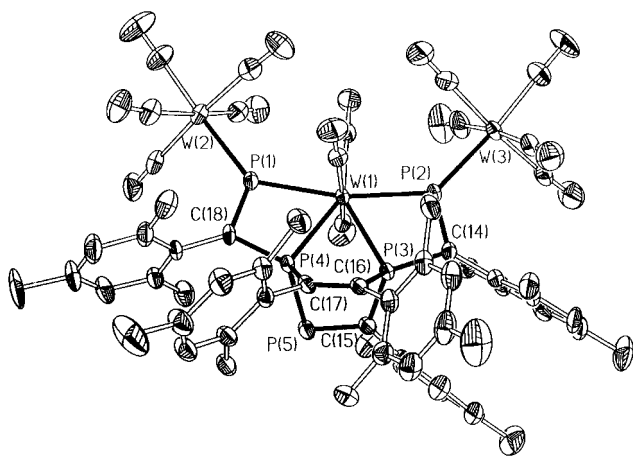


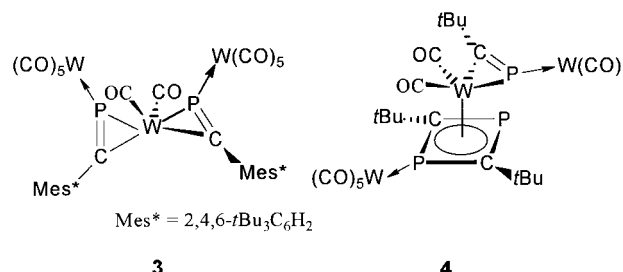
Figure 1. Structure of **2** in the crystal (ORTEP, vibrational ellipsoid with 50% probability, hydrogen atoms omitted). Selected bond lengths [Å] and angles [°]: P(1)–C(18) 1.707(5), P(2)–C(14) 1.710(5), P(1)–W(1) 2.5398(14), P(2)–W(1) 2.514(2), P(1)–W(2) 2.453(2), P(2)–W(3) 2.460(2), P(4)–C(18) 1.775(5), P(4)–C(17) 1.849(6), P(4)–P(5) 2.249(2), P(4)–W(1) 2.459(2), P(5)–C(15) 1.695(5), P(3)–C(14) 1.801(5), P(3)–C(15) 1.872(5), P(3)–C(16) 1.916(5), P(3)–W(1) 2.494(2), C(16)–C(17) 1.359(7); P(3)–C(16)–C(17) 109.0(4), C(17)–C(16)–C(37) 124.4(4), C(37)–C(16)–P(3) 126.6(4), P(3)–C(15)–P(5) 114.6(3), P(3)–C(15)–C(28) 122.1(4), C(28)–C(15)–P(5) 123.1(3), C(14)–P(2)–W(1) 100.4(2), C(18)–P(1)–W(1) 98.9(2).

2.249(2) Å is in the range of a P–P single bond (β -P₄: 2.204 Å^[23]). The distance between P(5) and C(15) is 1.695(5) Å and corresponds to the P–C bond length in phosphalkenes.^[22] There is also a typical C–C double bond of 1.359(7) Å between the atoms C(16) and C(17). The sp² hybridization of the atoms C(15) and C(16) is also confirmed by consideration of the relevant bond angles. The distances between P(3) and C(15) (1.872(5) Å) and between P(3) and C(16) (1.916(5) Å) correspond to P–C single bonds, which is also the case for the bond distance of 1.849(6) Å for P(4)–C(17).

In the ³¹P NMR spectrum of **2**, five groups of signals for the different phosphorus atoms were observed. Two doublets at δ = 497.6 and 456.1 are assigned to P(2) and P(1) with $J(\text{P,P})$ coupling constants of 45 and 42 Hz, respectively. Each doublet has a satellite pair with a coupling constant $^1J(\text{W,P})$ of 190 Hz, which is within the usual range of coupling constants between a phosphorus atom and a tungsten atom of a [W(CO)₅] group. The P–P couplings of these signals are found within the signal groups of P(3) and P(4) at δ = 50.8 and 10.4. These nuclei couple both with each other and with the atom P(5), which displays a large $^1J(\text{P,P})$ coupling constant of 280 Hz as a result of the proximity to P(4). A somewhat larger coupling constant (354 Hz) was obtained for the coupling between the neighboring P atoms in the hafna-norbornadiene complex **C'**.^[12] The coupling constant for coupling between P(4) and the W atom of the central [W(CO)₃] group was determined to be 108 Hz, but it was not possible to resolve the equivalent coupling for P(3).

It was not possible to derive any rules for the degree of oligomerization of phosphalkynes from an examination of the existing complex fragments in **A–F** and **2**. For example, dimerization occurs most commonly in the coordination sphere of 14VE fragments. Although dimerization takes place

to a certain extent with 12VE complex fragments, mainly trimerization, tetramerization, and now also pentamerization are observed. Much more significant than the number of valence electrons of the complex fragment are the steric and electronic properties of the phosphalkyne reactant. The use of Mes* $\text{C}\equiv\text{P}$ in reaction (1) resulted in the formation of complex **3**, in which the phosphalkynes are only coordinated “side-on”.^[24] In contrast, with *t*BuC $\equiv\text{P}$ the cyclodimerization product **4** was obtained exclusively.^[17a] The results presented



here show that a pentamerization product is also accessible with MesC $\equiv\text{P}$. The formation of **2** can be explained by various dimerization, Diels–Alder, and ring-opening reactions. In addition, the ability of [W(CO)₅] groups to eliminate CO to form [W(CO)₆]^[25] ultimately enables the formation of the central [W(CO)₃] complex unit. It can be predicted that the variation of the steric and also the electronic properties of the substituents on the phosphalkyne (e.g. in R₂NC $\equiv\text{P}$ ^[26] and –OC $\equiv\text{P}$ ^[27]) will have a significant influence on the reactivity and thus offer access to further novel products.

Experimental Section

A solution of **1** (162 mg, 1 mmol) in *n*-hexane (20 mL) was cooled to –50 °C. At this temperature, a 0.04 M solution of [W(CO)₅(thf)] (1 mmol) in THF (25 mL) was added, and the reaction solution was reduced to about 20 mL. Then the solution was warmed over a period of 15 h to room temperature and then stirred for a further 48 h. Subsequently all volatile components were removed under vacuum (10^{–3} Torr). Three such batches were combined and purified by column chromatography. After separation of a bright red fraction (*n*-hexane), an orange fraction was eluted with *n*-hexane/toluene (1/1), from which 100 mg (10%) of **2** were isolated. ³¹P{¹H} NMR (101.256 MHz, [D₆]benzene, 298 K, 85% H₃PO₄ ext.): δ = 497.6 (P_A: d; $^2J(\text{P}_A, \text{P}_C)$ = 45, $J(\text{W}, \text{P}_A)$ = 190 Hz), 456.1 (P_B: d; $^2J(\text{P}_B, \text{P}_D)$ = 42, $J(\text{W}, \text{P}_B)$ = 190 Hz), 370.7 (P_E: dd; $^1J(\text{P}_E, \text{P}_D)$ = 280, $^2J(\text{P}_E, \text{P}_C)$ = 35 Hz), 50.8 (P_C: ddd; $^2J(\text{P}_C, \text{P}_A)$ = 45, $^2J(\text{P}_C, \text{P}_E)$ = 35, $^2J(\text{P}_C, \text{P}_D)$ = 15 Hz), 10.4 (P_D: ddd; $J(\text{P}_D, \text{P}_E)$ = 280, $^2J(\text{P}_D, \text{P}_B)$ = 42, $^2J(\text{P}_D, \text{P}_C)$ = 14, $J(\text{W}, \text{P}_D)$ = 108 Hz); ¹H NMR (250.133 MHz, [D₆]benzene, 298 K, TMS): δ = 1.400, 1.422, 1.720, 1.819, 1.838, 1.900, 1.937, 1.979, 2.002, 2.061, 2.113, 2.163, 2.780, 2.864, 3.229 (CH₃, each s, 3H), 6.82–5.71 (arom. CH, 10s, 1H each); FT-IR (Nujol): $\tilde{\nu}(\text{CO})$ = 2075(s), 2065(s), 2041(m), 1987(w), 1962(sh), 1950(vs), 1938(vs), 1931(vs), 1925(vs) cm^{–1}; elemental analysis calcd for C₆₃H₅₅O₁₃P₅W₃ (1726.54): C 43.10, H 3.10; found: C 43.50, H 3.35.

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Facile, Novel Methodology for the Synthesis of Spiro[pyrrolidin-3,3'-oxindoles]: Catalyzed Ring Expansion Reactions of Cyclopropanes by Aldimines**

Phil B. Alper, Christiane Meyers, Andreas Lerchner, Dionicio R. Siegel, and Erick M. Carreira*

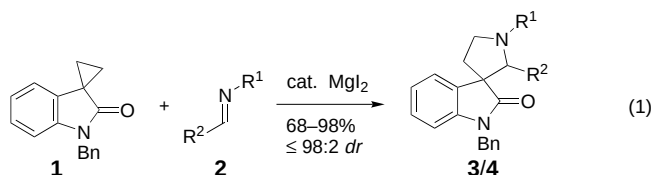
The spiro[pyrrolidin-3,3'-indole] ring system is a recurring structural motif in a number of natural products such as vinblastine and vincristine that function as cytostatics and are of prime importance in cancer chemotherapy.^[1] The related spiro[pyrrolidin-3,3'-oxindole] ring system has been identified in a number of other cytostatic alkaloids, exemplified by spirotryprostatin A and strychnophylline.^[2] Moreover, these structures embody stereochemical and structural complexities that continue to challenge the synthetic chemist.^[3,4] In combination, these factors have driven the development of novel, versatile, and efficient methods aimed at the synthesis of the spiro[pyrrolidin-3,3'-oxindole] moiety and related structures, as exemplified recently in the elegant total synthesis of spirotryprostatin by Danishefsky et al. and of aspidophytine by Corey et al.^[5] We have been interested in the development of a variety of methods for the stereocontrolled synthesis of alkaloids.^[6] Herein we report a novel

[*] Prof. Dr. E. M. Carreira, Dr. P. B. Alper, C. Meyers, A. Lerchner
Laboratorium für Organische Chemie, ETH-Zentrum
Universitätsstrasse 16, CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-13-28
E-mail: carreira@org.chem.ethz.ch
D. R. Siegel
Arnold and Mabel Beckman Laboratory for Chemical Synthesis
California Institute of Technology
Pasadena, CA 91125 (USA)

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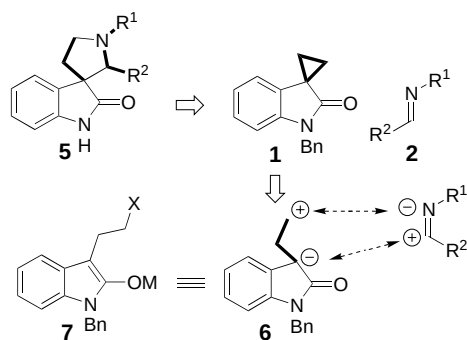
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

approach to the construction of the spiro[pyrrolidin-3,3'-oxindole] ring system from the reaction of spiro[cyclopropan-1,3'-oxindole] **1** and *N*-alkyl as well as *N*-arylsulfonyl aldimines **2** [Eq. (1)]. The successful implementation of the



unprecedented ring-expansion we report is made possible by careful selection of a catalyst (MgI_2) in which the Lewis acidity of the metal center (Mg^{II}) and nucleophilicity of the counterion (I^-) appear to operate in synergy.

The most common approaches to spiro[pyrrolidin-3,3'-oxindoles] commence with tryptamine derivatives and assemble a dihydro- or tetrahydro- carboline by Bischler–Napieralski or Pictet–Spengler annulation reactions.^[7, 8] Oxidative rearrangements of the resulting carbolines then furnish spirocyclic pyrrolidine-3,3'-oxindoles.^[4, 8] We envisioned a more direct, alternate bond-construction strategy to these ring systems. In our retrosynthetic analysis, **5** is disconnected to cyclopropane **1** and aldimine **2** (Scheme 1). As depicted for

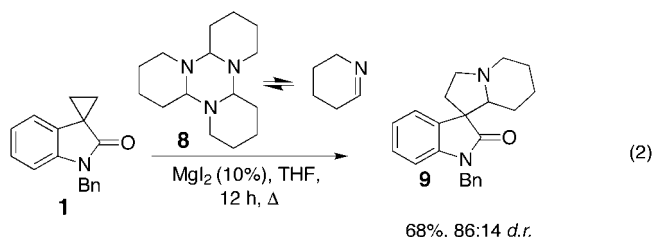


Scheme 1. Retrosynthetic and charge affinity analysis of the spiro[pyrrolidin-3,3'-oxindoles] ring system.

synthon **6**, the charge-affinity pattern of the cyclopropane complements that of an aldimine.^[9] The dissonant charge-affinity pattern of cyclopropanes is manifest in their well-known reactivity, when substituted with electron-withdrawing groups, to serve as homo-Michael acceptors.^[10] Pioneering work by Danishefsky et al. had established the participation of doubly activated cyclopropanes in tandem reactions resulting in ring formation.^[11] By contrast, the strategy depicted in Scheme 1 necessitates nucleophilic ring opening of a singly activated ring system by a weakly nucleophilic aldimine. We speculated that the use of a catalyst exhibiting dual electrophilic and nucleophilic activation would enable the desired reaction. In this regard the selection of a Lewis acidic metal possessing nucleophilic counterions could efficiently lead to ring-opened products **7** possessing the same reactivity pattern of synthon **6**.^[12] As a caveat, the application of dual nucleophilic/electrophilic catalysts to the reaction of imines

and spiro-fused cyclopropanes would lead to the desired spiro[pyrrolidin-3,3'-oxindoles] provided competitive intramolecular cyclization (by O-alkylation) is precluded.

The implementation of the plan depicted in Scheme 1 as a practical alternative to existing strategies to the title ring systems, in part, rests on the accessibility of the starting material (**1**). This oxindole was easily prepared on multigram scale from the known *N*-benzyloxindole and 1,2-dibromoethane (NaH , DMF, 23°C , 73 % yield).^[13] In our initial study, **1** and **8**^[14] were allowed to react in the presence of a number of metal catalysts (e.g. MgBr_2 , $\text{Mg}(\text{OTf})_2$, ZnI_2 , $\text{Zn}(\text{OTf})_2$, LiI (Tf = trifluoromethanesulfonate)), whereupon the use of MgI_2 was identified as optimal [Eq. (2)].^[15] Thus, treatment of **1** and **8** in THF at 125°C in the presence of 5 % MgI_2 gave tetracyclic adduct **9** in 68 % yield as an 86:14 mixture of diastereomers.



The scope of this reaction was explored subsequently by examining aliphatic and aromatic *N*-allyl aldimines along with *N*-*p*-arylsulfonyl aldimines [Eq. (3), (Table 1)]. Treatment of **1** with catalytic amounts of MgI_2 (10 mol %) in THF at 60 – 80°C afforded spiro[pyrrolidin-3,3'-oxindoles] in good yields

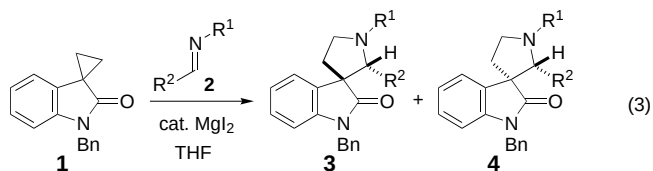


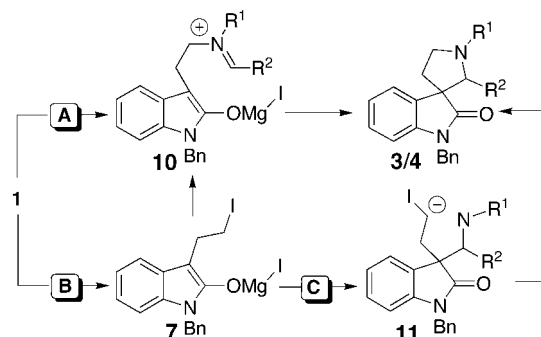
Table 1. Reaction of spiro[cyclopropan-1,3'-oxindole] **1** with aldimines.^[a]

Entry	R ¹	R ²	Yield [%]	3:4
1	–CH ₂ CH ₂ CH ₂ CH ₂ –		68	86:14
2	Allyl	Et	55	91:1
3	Allyl	Me ₂ CH	83	80:20
4	Allyl	Ph	99	79:21
5	Bu	Ph	97	81:19
6	<i>p</i> -TolSO ₂	Ph	97	91:9
7	<i>p</i> -TolSO ₂	2-Me-C ₆ H ₄	89	98:2
8	<i>p</i> -TolSO ₂	4-Me-C ₆ H ₄	96	64:36
9	<i>p</i> -TolSO ₂	2-Br-C ₆ H ₄	82	98:2
10	<i>p</i> -TolSO ₂	4-Br-C ₆ H ₄	92	82:18
11	<i>p</i> -TolSO ₂	4-CF ₃ -C ₆ H ₄	97	84:16
12	<i>p</i> -TolSO ₂	4-OMe-C ₆ H ₄	75	67:33
13	<i>p</i> -TolSO ₂	Furyl	97	85:15
14	<i>p</i> -TolSO ₂	PhCH=CH	62	74:16
15	<i>p</i> -TolSO ₂	PhCH=C(Me)	55	52:48
16	<i>p</i> -TolSO ₂	<i>i</i> Pr ₃ SiC≡C	77	98:2

[a] The assignment of the configuration of the products was established by ¹H NMR spectroscopy and correlation to the major product of entry 5, for which an X-ray structure was obtained (see Supporting Information). The diastereomeric ratios for entries 1–5 were determined from the mass of the separated, purified products. The diastereomeric ratios reported for entries 6–16 were obtained by HPLC analysis.

and useful diastereoselectivities for both classes of electron-rich and electron-deficient aldimines. The *N*-arylsulfonyl imines reacted smoothly at 60 °C, while the more electron-rich *N*-allyl imines required reaction temperatures of 80 °C for product formation. We have observed that the stereoselectivity could be improved by appropriate selection of the *N*-alkyl protecting group on the oxindole or the *N*-arylsulfonyl group of the aldimine. In this regard, the diastereoselectivity of the reaction of the *N*-tosyl imine of *p*-tolualdehyde and **1** (entry 8, 64:36 *dr*) could be improved to 71:29 by utilizing the *N*-benzhydryl rather than a *N*-benzyl protected oxindole. Moreover, the use of the *N*- β -naphthylsulfonyl aldimine derivative of *p*-tolualdehyde with **1** affords adduct in 89:11 *dr*.

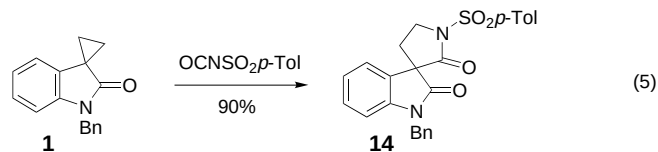
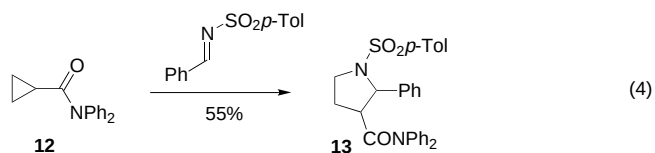
For the process we have delineated, three mechanistic pathways may be postulated that differ in the sequence of C–N and C–C bond-formation and in the nucleophilic ring-opening step (Scheme 2). In the first pathway (A, Scheme 2), the imine nitrogen participates directly in the nucleophilic



Scheme 2. Potential mechanistic pathways leading to the formation of the pyrrolidine ring.

cleavage of the cyclopropyl ring, generating iminium ion **10** which can undergo ring closure (**1** $\rightarrow$ **10** $\rightarrow$ **3/4**). In the second pathway (B, Scheme 2), iodide effects ring opening of the cyclopropane furnishing enolate **7**. The reactivity of this ambiphilic species may be manifest in two distinct ways. *N*-Alkylation of the aldimine furnishes **10** in a route that subsequently converges with A (**1** $\rightarrow$ **7** $\rightarrow$ **10** $\rightarrow$ **3/4**). Alternatively, reaction of enolate **7** with the starting imine furnishes **11** which can in turn undergo alkylative cyclization C (**1** $\rightarrow$ **7** $\rightarrow$ **11** $\rightarrow$ **3/4**). Although a mechanistic study of the process is ongoing, a number of observations lead us to prefer B and C for *N*-allyl and *N*-arylsulfonyl imines. In this regard, the fact that both *N*-alkyl and *N*-arylsulfonyl aldimines are substrates in the reaction argues against the nitrogen moiety functioning directly as a nucleophile as depicted for A. Moreover, when Mg(OTf)₂ was employed the starting materials were recovered unchanged and no product formation could be observed. These results strongly implicate a critical role for the halide in the course of the reaction (cf. **7** and **11**).

Preliminary observations suggest that the catalyzed ring expansion may be general, extending in scope beyond the substrates described above. Carboxamide **12** undergoes ring expansion in the presence of MgI₂ to give **13** [Eq. (4)]. Additionally, the reaction of **1** and *N*-*p*-tolylsulfonyl isocyanate furnishes **14** [Eq. (5)].^[16]



We have described novel methodology which provides direct access to spiro[pyrrolidin-3,3'-oxindoles], a ring system found in many natural products with intriguing biological activity. The reaction process employs readily available spiro[cyclopropan-1,3'-oxindoles] and *N*-alkyl or *N*-arylsulfonyl imines. The successful implementation of the ring expansion strategy involving moderately activated cyclopropanes and aldimines is enabled by selection of MgI₂ as a catalyst possessing dual nucleophilic and electrophilic activity. The observation that simple, singly activated cyclopropanes also participate suggests that the process may be considerably generalized. Further extensions to other reacting partners as well as the use of optically active Mg complexes for the asymmetric synthesis of chiral spiro[pyrrolidin-3,3'-oxindoles] are topics of current investigation and will be reported in due course.

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Specific RNA Dinucleotide Cleavage by a Synthetic Calix[4]arene-Based Trinuclear Metallo(III)-phosphodiesterase**

Peter Molenveld, Johan F. J. Engbersen,* and David N. Reinhoudt*

Dedicated to Professor H. C. Beyerman on the occasion of his 80th birthday

Phosphodiesterase enzymes such as nuclease P1 use three divalent metal ions (e.g. Zn^{II}) in the active site to catalyze the hydrolytic cleavage of phosphate diester bonds in nucleotides like RNA and DNA.^[1] Synthetic catalysts that cleave RNA at

specific sites are of interest, for example, for future application in gene technology.^[2, 3] There are several mononuclear complexes of trivalent metal ions^[3, 4] (e.g. lanthanide(III) and Co^{III}) that efficiently cleave RNA because they are strong Lewis acids. According to previous studies, mononuclear and even dinuclear Zn^{II} complexes^[2, 5, 6] generally exhibit only a moderate catalytic activity in RNA cleavage. Recently, we have shown that synthetic dinuclear and trinuclear^[7] metallo-phosphodiesterases based on calix[4]arenes^[8] exhibit a very high catalytic activity in the transesterification of the RNA model substrate 2-hydroxypropyl-*p*-nitrophenyl phosphate (HPNP).^[6, 9, 10]

Here we report that **1**- Zn_3 efficiently catalyzes the cleavage of RNA dinucleotides (3',5'-NpN) by the cooperative action of the Zn^{II} centers, with high rate enhancement and significant nucleobase specificity. The heterotrimeric complex **1**- Zn_2Cu is even more active; it mimics phosphodiesterases with a heterotrimeric metal cluster including a Zn^{II} center in the active site.^[1]

Catalytic cleavage of the RNA dinucleotides 3',5'-NpN (0.09 mM) by the complexes **1**- M_3 (0.9 mM) was carried out in 35% EtOH/20 mM aqueous HEPES buffer^[11] at $50^\circ C$ and monitored by HPLC. The formation of cyclic ribonucleoside monophosphates (2',3'-cNMP) and the corresponding nucleosides show that the RNA dinucleotides are cleaved by intramolecular transesterification of the hydroxyl group at the 2'-position.^[12] The catalytic activity of **1**- Zn_3 was measured for a series of RNA dinucleotides, namely, GpG, UpU, CpC, GpA, ApG, and ApA (Table 1). The trinuclear complex **1**- Zn_3

Table 1. Observed pseudo-first-order rate constants ($k_{obs}/10^5 s^{-1}$) for the cleavage of RNA dinucleotides.^[a]

Substrate	1 - Zn_3	1 - Zn_2Cu	1 - Cu_3	2 - Zn_2	3 - Zn
GpG	72	88	28	0.45	— ^[b]
UpU ^[c]	8.5	13	1.2	0.45	0.56
CpC	6.1	7.1	1.9	0.58	— ^[b]
GpA	4.6	5.9	— ^[b]	— ^[b]	— ^[b]
ApG	2.7	2.4	— ^[b]	— ^[b]	— ^[b]
ApA ^[d]	0.44	0.46	0.47	0.28	0.31

[a] In 35% EtOH/20 mM HEPES (pH 8.0) at $50^\circ C$; [substrate] = 0.09 mM; **1**- Zn_3 = **1**- Cu_3 = **2**- Zn_2 = 0.9 mM; **1**- Zn_2Cu is a statistical mixture of **1** = 0.9 mM, **2** = 1.8 mM, and **3** = 2.7 mM; ^[15] **3**- Zn = 2.7 mM. [b] Not determined. [c] $k_{uncat} \approx 9.8 \times 10^{-9} s^{-1}$.^[5b] [d] $k_{uncat} \approx 1.7 \times 10^{-9} s^{-1}$.^[13]

exhibits a very high catalytic activity; rate accelerations over the uncatalyzed reactions are on the order of 10^4 – 10^5 .^[5b, 13] Moreover, **1**- Zn_3 is a genuine catalyst that exhibits turnover. A threefold excess of UpU is completely converted, while a reference solution of UpU without catalyst is unaffected. Surprisingly, for different nucleobases in the dinucleotides large differences in rate were observed: GpG $\gg$ UpU $\gg$ ApA (see below).

The dependence of rate on the pH value for the **1**- Zn_3 -catalyzed cleavage of UpU shows a bell-shaped curve with an optimum at pH 8. The apparent pK_a of a Zn^{II} -bound water molecule in **3**- Zn is 7.9;^[9] the value is lower for **1**- Zn_3 due to hydrophobic and cooperative effects.^[9, 10] Therefore, it is likely that at pH 8 one or two Zn^{II} centers in **1**- Zn_3 are coordinated by a hydroxide ion. Furthermore, the activity reaches a

[*] Prof. Dr. J. F. J. Engbersen, Prof. Dr. D. N. Reinhoudt, Dr. P. Molenveld
Laboratory of Supramolecular Chemistry and Technology
MESA+ Research Institute, University of Twente
P.O. Box 217, NL-7500 AE Enschede (The Netherlands)
Fax: (+31) 53-489-4645
E-mail: smct@ct.utwente.nl

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maximum with three equivalents of Zn^{II} per molecule of **1**, which indicates that all three Zn^{II} ions in **1**- Zn_3 are involved in the catalysis. The trinuclear complex **1**- Zn_3 is a factor of 10, 19, and even 160 times more active than the dinuclear complex **2**- Zn_2 for the cleavage of CpC, UpU, and GpG, respectively. These differences in activity are much higher than that observed in the transesterification of the *p*-nitrophenyl-activated phosphate diester HPNP catalyzed by **1**- Zn_3 and **2**- Zn_2 (factor of 1.4).^[9] This can only be due to additional catalytic effects originating from the third Zn^{II} center in the transesterification of the RNA dinucleotides. Since the basicity of the alkanolate leaving group in an RNA dinucleotide is much higher, one of the catalytic centers in **1**- Zn_3 might stabilize this leaving group.

So far, Cu^{II} ions have not been found in the active sites of phosphodiesterases, but they exhibit generally a high hydrolytic activity in abiotic catalysts.^[10, 14] Whereas **1**- Zn_3 is superior to its analogue **1**- Cu_3 (except for the case of ApA), a statistical mixture of **1**, two equivalents of Zn^{II} , and one equivalent of Cu^{II} —to form the heterotrinnuclear analogue **1**- Zn_2Cu as the main species^[15]—shows a higher activity (Table 1, Figure 1). This may be due to synergy of the

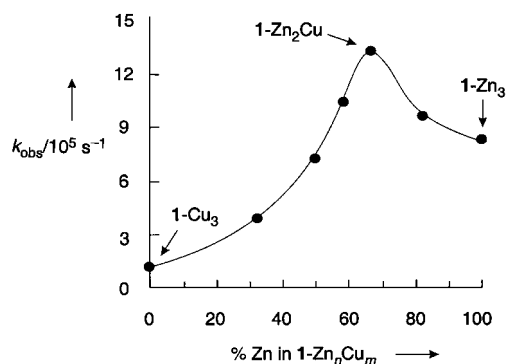
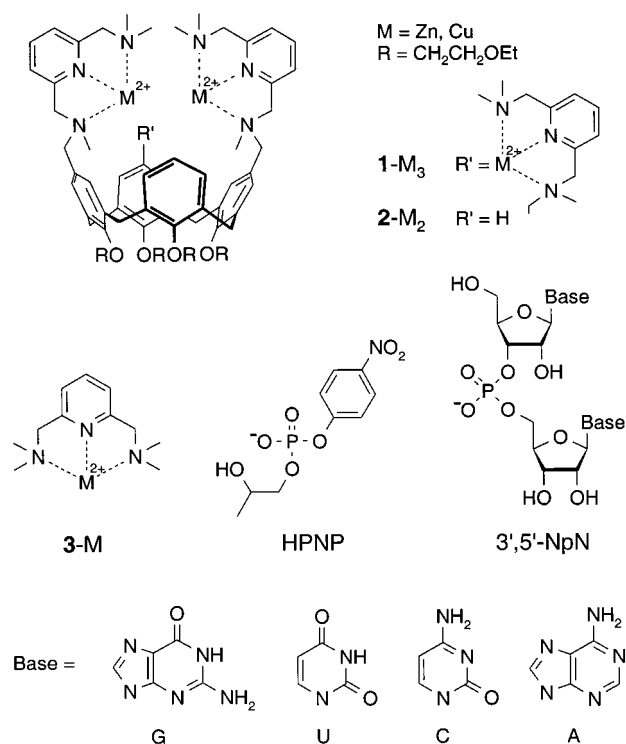


Figure 1. Dependence of the rate k_{obs} for the cleavage of UpU catalyzed by **1**- Zn_nCu_m ($n+m=3$) on the percentage of $\text{Zn}(\text{ClO}_4)_2$ with respect to the total concentration of $\text{M}(\text{ClO}_4)_2$ ($\text{M} = \text{Zn}, \text{Cu}$; 2.7 mM) at a fixed concentration of ligand **1** (0.9 mM) in 35% EtOH/20 mM HEPES buffer (pH 8.0) at 50 °C. At the rate optimum, **1**- Zn_2Cu is the main species in solution.^[15]

favorable properties^[9, 10] of Zn^{II} in the binding (K_{ass})^[16] and Cu^{II} in the conversion (k_{cat}) of the phosphate diester substrate.

The catalytic activities of the trinuclear complexes are dependent on the structure of the nucleobases in the RNA dinucleotides. The activity of **1**- Zn_3 in the cleavage of GpG is a factor of 8.5 higher than of UpU, and even a factor of 160 higher than of ApA. For **1**- Zn_2Cu the selectivities are even more pronounced, that is, factors of 190 and 28 for GpG and UpU over ApA. The mixed dinucleotides GpA and ApG are also more reactive than ApA, but they are far less reactive than GpG. It seems that an adenylyl nucleobase in an RNA dinucleotide reduces the activity of the catalyst **1**- M_3 . Comparison of the activity of **1**- Zn_3 with that of the reference complexes **2**- Zn_2 and **3**- Zn indicates that in the cleavage of ApA the three metal centers in **1**- M_3 do not cooperate in the catalysis (Table 1). This was confirmed when we measured the rates as a function of the concentration of catalyst **1**- Zn_3



(Figure 2). For ApA the rate linearly increases with the catalyst concentration. The small slope ($k_2 = 4.3 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$) suggests that only small amounts of a reactive catalyst–substrate complex are formed. The highly reactive substrates UpU (Figure 2) and GpG show saturation kinetics, indicating

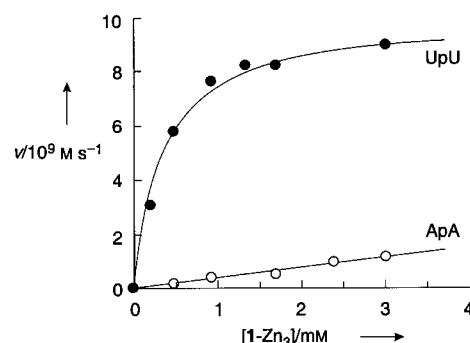


Figure 2. Plot showing the dependence of the rate of cleavage of UpU and ApA (0.09 mM) on the concentration of **1**- Zn_3 in 35% EtOH/20 mM HEPES (pH 8.0) at 50 °C. The experimental data points for cleavage of UpU are fitted to the Michaelis–Menten equation with $K_{\text{m}} = 0.34 \text{ mM}$ and $k_{\text{cat}} = 1.1 \times 10^{-4} \text{ s}^{-1}$. The experimental data for cleavage of ApA are fitted according to second-order reaction kinetics with $k_2 = 4.3 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$.

a strong binding to the catalyst **1**- Zn_3 . The saturation curves obey Michaelis–Menten kinetics and were analyzed by means of Eady–Hofstee plots. Although the binding constant (K_{ass}) is a factor of 3.8 lower for GpG ($7.7 \times 10^2 \text{ M}^{-1}$) than for UpU ($29 \times 10^2 \text{ M}^{-1}$), the catalytic rate constant (k_{cat}) is a factor of 16.4 higher (GpG: $18 \times 10^{-4} \text{ s}^{-1}$; UpU: $1.1 \times 10^{-4} \text{ s}^{-1}$). These studies indicate that the higher activity in the reactions of GpG and UpU than of ApA is due to enhanced binding to **1**- Zn_3 . The higher reactivity of GpG compared with UpU is due to a higher rate of conversion.

The most reactive nucleotides GpG and UpU have an acidic amide NH moiety that can be deprotonated by a Zn^{II} -bound hydroxide group, the resulting anionic nitrogen atom can coordinate to form a stable nucleobase– Zn^{II} complex.^[17] In this way one of the Zn^{II} centers in **1**- Zn_3 might orient the RNA dinucleotide within the catalytic site (Figures 3 and 4).

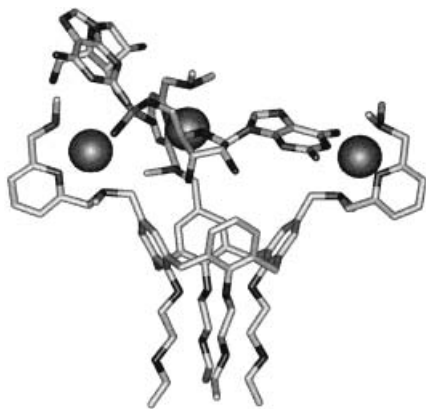


Figure 3. Computer-generated model of the complex between catalyst **1**- Zn_3 and the substrate GpG, formed by coordination of the phosphoryl group and a deprotonated guanosine group to Zn^{II} . Hydrogen atoms are omitted for clarity.

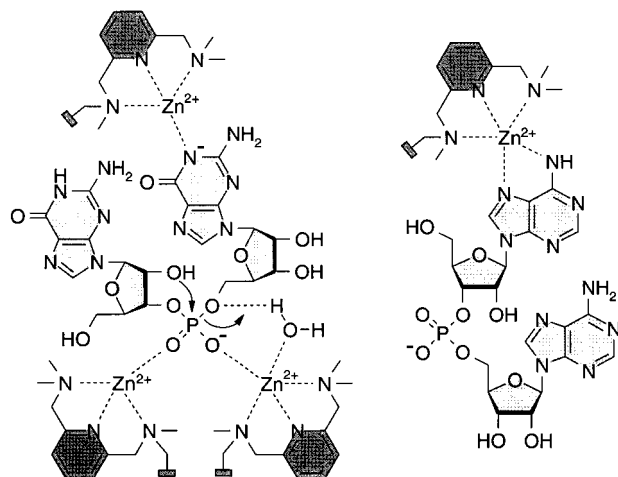


Figure 4. Schematic representations of possible modes of binding of RNA dinucleotides to **1**- Zn_3 . Left: mechanism for GpG cleavage. Right: nonproductive binding mode for ApA.

Subsequently, the two remaining Zn^{II} centers may activate the phosphoryl group by double Lewis acid coordination. Elimination of the leaving group may be assisted by protonation by a Zn^{II} -bound water molecule. The specificity for GpG over UpU might originate from a better fit owing to the different sizes of the nucleobases. The adenyl group has multiple metal ion binding sites, including a bidentate binding site formed by the nitrogen atoms on the 6- and 7-positions. Bidentate coordination of a substrate adenyl group results in a different, less favorable substrate orientation within the catalyst **1**- Zn_3 compared to monodentate binding of a deprotonated uracyl or guanine group (Figure 4).

Preliminary experiments with a 24-mer RNA^[18] show that **1**- Zn_3 and **1**- Zn_2Cu exhibit catalytic activity in the cleavage of

RNA oligonucleotides. This opens possibilities for sequence-selective cleavage of RNA.^[2, 3]

Experimental Section

The synthesis and characterization of the complexes **1**- M_3 , **2**- M_2 , and **3**- M ($\text{M} = \text{Zn}, \text{Cu}$) was described previously.^[9] Solutions for kinetic measurements were made by adding up to 35 % (v/v) EtOH to a 20 mM aqueous buffer solution adjusted with NaOH to the desired pH value.^[11] Aliquots of the reaction mixtures were analyzed by reverse-phase HPLC (Waters) with elution (1.0 mL min^{-1}) with mixtures of 10 mM KH_2PO_4 (pH 4.7 or pH 5.5) and MeOH/ H_2O (3/2) and detection of guanosine, uridine, cytidine, and adenosine at $\lambda = 254, 260, 272$ and 260 nm , respectively. In a typical experiment, the ligand **1** ($10 \mu\text{L}$, 50 mM in EtOH) and $\text{M}(\text{ClO}_4)_2$ ($30 \mu\text{L}$, 50 mM in water) were added to 0.5 mL of the buffer solution and thermostated at 50°C . After a couple of minutes equilibration time, 3',5'-NpN ($10 \mu\text{L}$, 5 mM in water) was injected. Aliquots ($20 \mu\text{L}$) of the reaction mixture were quenched with an excess of tris(2-aminomethyl)amine ($20 \mu\text{L}$, 50 mM in EtOH) and analyzed with HPLC ($2.0 \mu\text{L}$ injection, 25 min elution). Initial rates were determined by analysis of at least four aliquots ($< 10\%$ conversion). The concentration of the formed nucleoside was determined by means of a calibration curve made with commercially obtained nucleoside (correlation coefficient > 0.95). The observed pseudo-first-order rate constants k_{obs} (s^{-1}) were calculated from the initial rates (correlation coefficient > 0.95).

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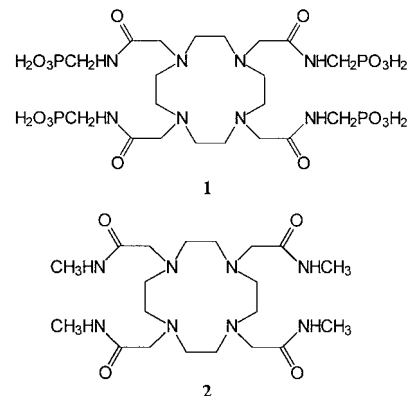
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A Novel pH-Sensitive MRI Contrast Agent**

Shanrong Zhang, Kuangcong Wu, and
A. Dean Sherry*

Most gadolinium complexes enhance relaxation of water protons by rapid exchange of inner-sphere water molecules with bulk solvent.^[1] However, recent kinetic results have shown that the lifetime of an inner-sphere water molecule in Gd^{III} complexes can range from 0.84 ns for aqueous Gd^{III}, 208 ns for [Gd(dota)]⁻, (dota = 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetate) to over 19000 ns in the tetraamide analogue, [Gd(**2**)].^[1d, 2, 3] Recently reported examples of gadolinium-based contrast agents that are sensitive to enzyme activity^[4a] and Ca²⁺^[4b] has stimulated synthesis of new cyclen-based ligands bearing different types of pendant arms. Given that tetraamide derivatives of cyclen have been reported to form both thermodynamically stable and kinetically inert complexes with Gd^{III} in aqueous solution,^[3, 5, 6] we

have been exploring tetraamide-based ligands with extended phosphonate or carboxylate noncoordinating side chains with the intent of generating new systems with specific ion-pairing capabilities. In characterizing one new derivative in this series, we observed that the water proton *R₁* relaxivity of [Gd(**1**)] has



an unusual pH dependence, increasing between pH 4 and 6, reaching a maximum near pH 6, gradually decreasing to a minimum near pH 8.5, then remaining relatively insensitive to pH 10.5 before increasing once again at higher pH values (Figure 1). This feature is quite different from that of [Gd(**2**)] whose *R₁* is essentially independent of pH between 2 and 8 before increasing at higher pH values.^[3] Similarly, the *R₁* of [Gd(dotp)]⁵⁻ (dotp is the tetraphosphonate analogue of dota) is independent of pH over an extended pH range (3–13).^[7]

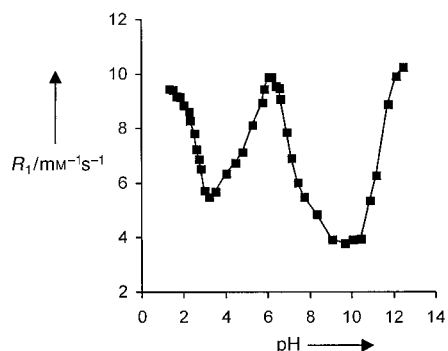


Figure 1. The pH dependence of the water proton relaxivity of [Gd(**1**)] at 20 MHz, 25 °C. The solid line is included to guide the eye and does not represent a fit of these data to theory.

To provide further insight into the unusual relaxation behavior of [Gd(**1**)], we examined the solution structures of various [Ln(**1**)] complexes by NMR spectroscopy. ³¹P NMR spectra of all [Ln(**1**)] complexes (except Gd^{III}) had single resonances with chemical shifts not dramatically different from that of the free ligand. In comparison with the highly shifted ³¹P resonances in the analogous [Ln(dotp)]⁵⁻ complexes,^[8] this indicated that the four phosphonate groups of [Ln(**1**)] are situated relatively far from the paramagnetic center, likely not coordinated to the central ion. ¹H and ¹³C NMR spectra of [Ln(**1**)] were all consistent with one main molecular species having high stereochemical rigidity. The hyperfine shifts of the macrocyclic protons of [Yb(**1**)] mirrored those of [Yb(dotp)]⁵⁻,^[8] [Yb(dota)]⁻,^[9] and

[*] Prof. Dr. A. D. Sherry, S. Zhang, K. Wu
Department of Chemistry
University of Texas at Dallas
P.O. Box 830688, Richardson
TX 75083-0688 (USA)
and
The Rogers Magnetic Resonance Center
Department of Radiology
University of Texas Southwestern Medical Center
5801 Forest Park Road
Dallas, TX 75235-9085 (USA)
Fax: (+1) 972-883-2925
E-mail: sherry@utdallas.edu

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[Yb(dotma)]⁻,^[10] indicating that the Yb³⁺ is chelated by the four amide oxygens and four macrocyclic nitrogens (dotma = 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetra(2-propionate)). After correction for bulk susceptibility effects, no shift was observed in the ¹⁷O NMR resonance of bulk water at 25 °C upon addition of [Dy(1)] but a sizable shift was observed at 75 °C (Figure 2). The slope of the line through

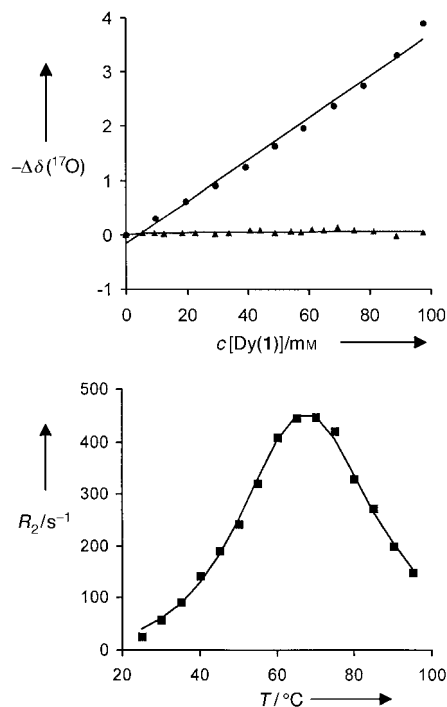


Figure 2. Top: ¹⁷O NMR chemical shift of bulk water as a function of [Dy(1)] at 25 °C (▲) and 75 °C (●). Bottom: ¹⁷O NMR linewidth of the bulk water resonance in the presence of 46 mM [Dy(1)] as a function of temperature at pH 9.5. The curve shows the fit of the data to theory as described in Pubanz et al.^[12]

the 75 °C data indicated that one inner-sphere water molecule in [Dy(1)] was in exchange with bulk water.^[11] The insensitivity of the ¹⁷O water resonance to [Dy(1)] at 25 °C suggests that water exchange is slow at this temperature. The temperature dependence of the ¹⁷O linewidth verified that water exchange in this complex is indeed slow below $\approx 67^\circ\text{C}$ (Figure 2). A fit of that data to theory^[12] gave a water exchange lifetime (τ_M) of $21 \pm 1.2 \mu\text{s}$ for [Dy(1)] at 25 °C, identical to the value reported for [Gd(2)].^[1d, 3] Interestingly, τ_M for water exchange in [Dy(1)] was independent of pH from 5.9 to 9.5, so the changes in R_1 over this pH range do not reflect changes in water molecule exchange.

The water proton relaxivity R_1 of [Gd(1)] increased ≈ 2.6 -fold between pH 10.5 and 12. The R_1 of [Gd(2)] is also pH sensitive in this range,^[3] although in this complex R_1 begins increasing at pH ≈ 8 and increases ≈ 2.2 -fold by pH 11. This has been ascribed to OH⁻-catalyzed prototropic exchange of the bound water protons in this complex.^[3] To quantitatively analyze the R_1 changes above pH 10.5, we followed the lead of Aime et al.^[3] and assumed that τ_M is proportional to $1/(k_1 + k_2[\text{OH}^-])$. Given that $k_1 = 4.76 \times 10^4 \text{ s}^{-1}$ ($= 1/\tau_M$ as determined by ¹⁷O NMR), a fit of the high pH relaxivity data to this

equation gave $k_2 = 8.09 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$. This value is significantly smaller than k_2 reported for [Gd(2)]^[3] ($1.4 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$), showing that higher concentrations of base are necessary to catalyze prototropic exchange in [Gd(1)] than in [Gd(2)]. This may reflect protection of the coordinated water molecule in [Gd(1)] by the extended side-arms of the ligand.

Potentiometric titrations of [Gd(1)] showed that the complex undergoes five protonations between pH 9 and 2 ($\lg K_n = 8.70, 7.28, 6.55, 6.02, \text{ and } 3.38$). In comparison to the protonation constants of uncomplexed ligand **1** in this same pH range ($\lg K_n = 7.30, 6.64, 6.11, \text{ and } 2.39$), it is tempting to assign the highest constant ($\lg K_1 = 8.70$) of the complex to the bound water (the $\text{p}K_a$ of the bound water molecule of [Gd(2)]^[3, 6] is reportedly 7.9). However, the fluorescence lifetime of [Eu(1)] was insensitive to pH in this range and the ³¹P NMR chemical shift of [Eu(1)] showed pH dependent changes consistent with protonation of a phosphonate beginning above pH 9. Thus, the ≈ 2.6 -fold increase in water relaxivity catalyzed by [Gd(1)] over the pH range 9 to 6 seems to largely parallel protonation of the extended phosphonate groups. This suggests that the H-bonding network created by protonation of the phosphonates provides a catalytic pathway for exchange of the bound water protons with protons of bulk water. Interestingly, the maximum in the R_1 curve near pH 6 indicates that prototropic exchange is maximized after ≈ 3 –4 phosphonates are protonated and that further protonation at these sites interferes with the H-bonded exchange network. The subsequent increase in R_1 below pH 3 suggests that strong acid also catalyzes prototropic exchange of the bound water protons, as first suggested by Aime et al.^[3] for [Gd(2)]. Unlike recent data reported for [Gd(2)],^[6] however, we find no evidence for release of free Gd^{III} (as detected by colorimetric indicators) from [Gd(1)] even after storage in 2.5 M HNO₃ for 2 months, so the increase in R_1 below pH 3 does not reflect release of the aqua-ion. Interestingly, the minimum in R_1 observed between pH 8.5–10.5 ($3.8 \text{ mM}^{-1} \text{ s}^{-1}$) does not correspond to pure outer-sphere relaxation typical of other Gd^{III} complexes at this field (ca. 2 – $2.4 \text{ mM}^{-1} \text{ s}^{-1}$). This indicates a small prototropic exchange contribution ($\approx 50\%$) remains in this pH range catalyzed either by partial deprotonation of the bound water molecule or by the fully deprotonated phosphonate groups.

The unique sensitivity of the water relaxivity of [Gd(1)] indicates that this complex could be used in a magnetic resonance imaging (MRI) experiment to monitor changes in pH. T_1 weighted proton images of phantoms containing 0.2 mM [Gd(dtpa)]²⁻ at pH 6 and 9 and [Gd(1)] at pH 6 and 9 were recorded on a 4.7 T imaging system (images not shown). Using a spin-echo sequence and parameters typical of those used for T_1 weighted imaging (TR/TE = 300/12 ms), we observed a 50% increase in average pixel intensity for the [Gd(1)] sample at pH 6 compared to the sample at pH 9, while the average pixel intensity of the corresponding [Gd(dtpa)]²⁻ (dtpa = diethylenetriamine-*N,N,N',N'',N'''*-pentaacetate) samples decreased by $\approx 10\%$. This demonstrates that [Gd(1)] can produce MRI contrast that is exquisitely sensitive to pH. Although other approaches to preparing gadolinium complexes with relaxivities that are sensitive to pH near physiological values have been proposed,^[13] the present

results demonstrate that it may be possible to modulate prototropic exchange by pendant arms in ligands such as **1** to design a series of contrast agents with differing pH sensitivities.

Experimental Section

Diethyl aminomethylphosphonate^[14] was treated with bromoacetyl bromide to give diethyl bromoacetamidomethylphosphonate. The latter compound (2.88 g, 0.01 mol) was stirred with cyclen (0.43 g, 0.0025 mol) and potassium carbonate (1.5 g, 0.011 mol) in acetonitrile (10 mL) at 60–70 °C for 6 h. After removal of salts by filtration, the ester of **1** was isolated as a pale-yellow solid (2.48 g). The ethyl esters were deprotected in 30 % HBr in glacial acetic acid (8 mL) by stirring overnight at room temperature. Pure **1** was precipitated from methanol using diethyl ether to yield a white solid: 0.53 g, 85.5 %. ¹H NMR (D₂O): δ = 3.72 (br., 8H; NCH₂CO), 3.52 (d, 8H; CH₂P), 3.25 (br., 16H; NCH₂CH₂N); ¹³C NMR (D₂O): δ = 170.65 (CO), 56.50 (NCH₂CO), 51.83 (NCH₂CH₂N), 38.24 (d, CH₂P). Satisfactory C, H, N analysis.

[Ln(**1**)] complexes were prepared in water by mixing a LnX₃ solution with ligand **1** at pH ~ 9. All NMR spectra were recorded at 11.7 T on a Varian INOVA 500 spectrometer using either a 5 mm inverse probe (¹H) or a 5 mm tunable broadband probe (¹⁷O, ¹³C and ³¹P). *tert*-Butyl alcohol was used as an internal chemical shift reference for ¹H and ¹³C while 85 % H₃PO₄ was used as an external reference for ³¹P experiments. The sample of [Dy(**1**)] used for the ¹⁷O experiments contained 5 % dioxane for purposes of correcting the observed water shifts for bulk susceptibility shifts. Water proton relaxation measurements were performed under temperature control using a MRS-6 NMR analyzer operating at 20 MHz (Institut Jozef Stefan, Ljubljana, Slovenija). ¹H images were collected using a GE (Bruker) Omega 4.7 T imaging system and a 20 mm Helmholtz coil. Potentiometric titrations were performed in 0.1 M NMe₄Cl at 25 °C under a N₂ atmosphere using an Accumet 925 pH meter, an Orion 8103 Ross combination electrode, and a Brinkmann/Metrohm 665 Dosimat titrator. The resulting activity versus volume titration curves were analyzed by using a spreadsheet program described previously.^[15]

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Gold(II) and Gold(0) Complexes of Phosphinine-Based Macrocycles**

Nicolas Mézailles, Narcis Avarvari, Nicole Maigrot, Louis Ricard, François Mathey,* Pascal Le Floch,* Laurent Cataldo, Théo Berclaz, and Michel Geoffroy*

In the vast majority of gold complexes (organometallic, coordination, and catalytic species) the metal center has an oxidation state from +1 to +3.^[1] Indeed, monomeric zerovalent gold complexes, as their Group 11 congeners (complexes of Cu or Ag),^[2] eluded isolation for a long time, and are still rare.^[3] In any case, these gold(0) complexes appear thermodynamically too unstable to be used in chemical transformations. Carbonyl derivatives [Au(CO)_n] (n = 1–3) were obtained by cryochemical methods and characterized in matrices at low temperatures; they decompose above 77 K.^[4] In this context, the synthesis of new and more stable Au⁰ species is a topical and challenging field of investigation.

Recently, we reported on the synthesis of silacalix[n]phosphinines, a new class of macrocycles incorporating sp²-hybridized phosphorus atoms.^[5] In view of the adequate electronic balance between σ-donating and π-accepting properties in phosphinines, we proposed that these cavities

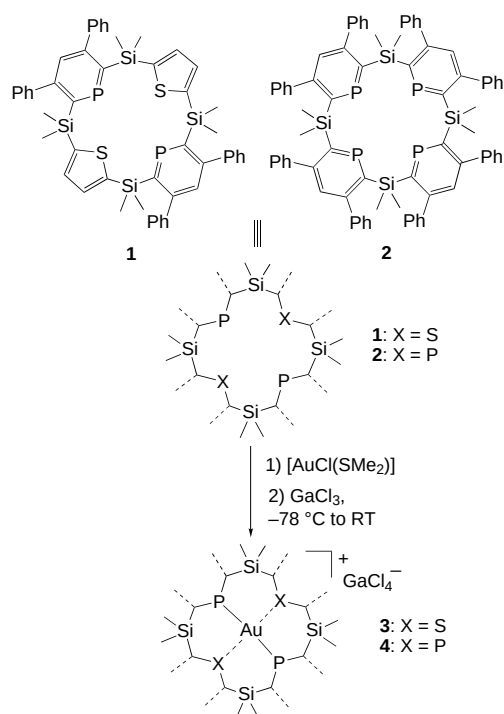
[*] Prof. F. Mathey, Dr. P. Le Floch, Dr. N. Mézailles, Dr. N. Avarvari, Dr. N. Maigrot, Dr. L. Ricard
Laboratoire "Hétéroéléments et Coordination"
Ecole Polytechnique
91128 Palaiseau Cedex (France)
Fax: (+33)1-69-33-39-90
E-mail: lefloch@mars.polytechnique.fr

Prof. M. Geoffroy, Dr. L. Cataldo, Dr. T. Berclaz
Département de Chimie Physique, Université de Genève
30, Quai Ernest Ansermet, 1211 Genève 4 (Switzerland)
Fax: (+41)22-702-61-03
E-mail: michel.geoffroy@chiphys.unige.ch

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might work as a kind of “macrocyclic equivalent” of carbonyl groups and thus provide unusual reduced transition metal species of enhanced thermodynamic stability. To assess this proposal we focused our first studies on the synthesis and the reduction of gold(I) complexes. Here we report on results obtained with two of these macrocycles, namely, the silacalix[4]1,3-bis(phosphinine)-2,4-bis(thiophene) **1** and the silacalix[4]phosphinine **2** (see Scheme 1).^[6]

Complexes **3** and **4** were prepared by allowing one equivalent of the macrocycle (**1** or **2**, respectively) to react with [AuCl(SMe₂)], followed by treatment with GaCl₃ as chloride abstractor, in dichloromethane at –80 °C (Scheme 1).^[7] These two complexes were fully characterized and are, to the best of our knowledge, the first examples of macrocycles coordinated to a gold(I) center.



Scheme 1. Chemical structures of **1** and **2**, and their reaction with [AuCl(SMe₂)] to form Au^I cationic derivatives **3** and **4**.

In both cases, X-ray diffraction studies have been carried out. Only the structure of **4** is reported here (Figure 1).^[8] The four phosphorus atoms lie in the same plane, but only two subunits (P1 and P3) are connected to the Au^I center, the two others (P2 and P4) only showing very weak interactions (P2–Au 2.974, P4–Au 2.905 Å). However, this geometry is not preserved in solution. The ³¹P NMR spectrum of complex **4** consists of a sharp singlet (four magnetically equivalent P nuclei) down to –80 °C, indicating a fluxional behavior. Unfortunately, the complex precipitates out of solution below this temperature, precluding extraction of thermodynamic data. Apart from this feature and the fact that intramolecular phosphinine bond distances are slightly modified by complexation as previously noted,^[9] the structure of **4** deserves no special comment.

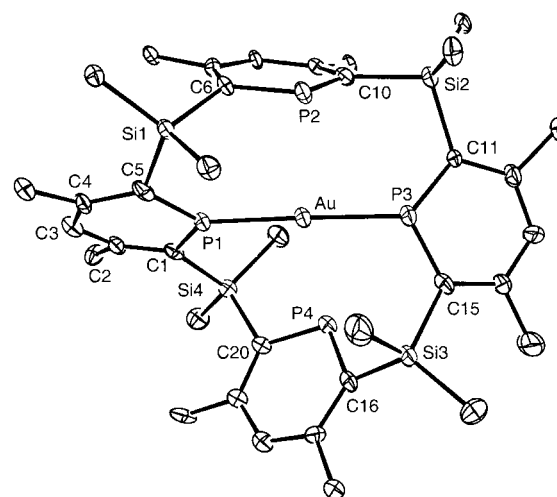


Figure 1. Structure of the cation of **4** in the crystal. Ellipsoids are scaled to enclose 50% of the electronic density. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Au–P1 2.307(2), Au–P2 2.974(2), Au–P3 2.331(2), Au–P4 2.905(3), P1–C1 1.730(8), C1–C2 1.39(1), C2–C3 1.40(1), C3–C4 1.39(1), C4–C5 1.40(1), C5–P1 1.732(8), C1–Si4 1.940(8), Si4–C20 1.892(9); P1–Au–P2 97.27(7), P1–Au–P3 176.48(9), P1–Au–P4 93.60(7), P2–Au–P3 85.49(7), P2–Au–P4 168.01(6), P3–Au–P4 83.46(8), Au–P1–C1 126.3(3), P1–C1–C2 117.1(6), C1–C2–C3 123.3(7), C2–C3–C4 126.8(7), C3–C4–C5 123.1(7), C4–C5–P1 117.0(6), C5–Si1–C6 100.6(3).

The electrochemical reduction of the two complexes was carried out in dichloromethane and reveals important information. First, complex **3** is irreversibly reduced at a peak potential of $E^0 = -1.0$ V (versus saturated calomel electrode, SCE) at a scan rate of 0.05 V s^{–1}, which shows that the generated Au⁰ species is not stable. Increasing the scan rate (up to 100 V s^{–1}) or decreasing the temperature (below 253 K) only led to a weak reversibility of the reduction. On the other hand, complex **4** undergoes a quasi-reversible process at $E^p = -0.80$ V upon scanning at 0.1 V s^{–1} (263 K, Figure 2), indicating the formation of the Au⁰ complex **5** (Scheme 2). This behavior markedly differs from that of the [Au(dppe)₂]⁺[GaCl₄[–]] complex (dppe = diphenylphosphanylene), which is irreversibly reduced at –2.0 V. The lower reduction potential recorded for complex **4** is in full agreement with the strong π -acceptor character of phosphinines, which increases the Lewis acidic character of the Au^I center. The chemical reduction of **4** was thus attempted in THF at –78 °C using sodium naphthalenide (NaNp) as reducing agent. The formation of complex **5** was evidenced by an immediate color change from red to deep purple. Unfortunately, **5** could not be isolated as it starts to decompose when the temperature reaches –20 °C, releasing the free ligand **2** and colloidal gold.

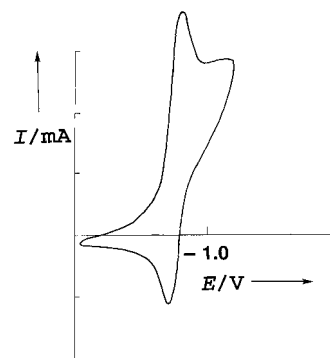
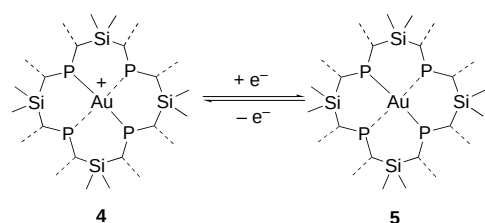


Figure 2. Cyclic voltammogram of complex **4** (2 mM in CH₂Cl₂, 0.3 M *n*Bu₄NBF₄, 263 K) at a gold disk electrode (diameter 0.5 mm, scan rate 0.1 V s^{–1}). *I* = intensity, *E* = potential vs. SCE.



Scheme 2. Electrochemical reduction of complex **4** to form **5**.

Consequently, we attempted to detect the reduction product of **4** by EPR spectroscopy. Solutions of **4** in THF were reduced under vacuum (10–5 Torr) on a mirror of alkali metal (K or Na) in a sealed tube at -80°C . When the experiments were performed with a perfectly degassed solvent, the resulting signal ($g=2.001$) was composed of 20 lines in accordance with a 700-MHz coupling with a nucleus of spin 3/2 (^{197}Au , natural abundance 100 %) and with a 160-MHz coupling with four equivalent nuclei of spin 1/2 (^{31}P , Figure 3). The same observations were made when **4** (largely in excess) was allowed to react with NaNp at -80°C in the absence of contact with air (cryopumping). At 200 K the signal begins to decrease in intensity after 1 h, whereas it rapidly disappears at 230 K.

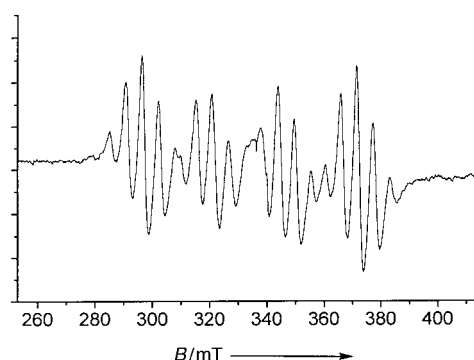


Figure 3. EPR spectrum obtained at 190 K after reaction of **4** in THF with a potassium mirror.

Comparison of the ^{197}Au and ^{31}P isotropic coupling constants with the corresponding atomic parameters (2876 MHz for ^{197}Au , 13306 MHz for ^{31}P) indicates that 24 % of the spin is confined in a gold s orbital and 1 % in an s orbital of each phosphorus atom.^[10] The Au s-spin density is considerably smaller than the value reported for Ag^0 solvated by four acetonitrile molecules ($\rho_s=0.70$)^[11] or for the $[\text{Au}(\text{C}_6\text{H}_6)]$ complex ($\rho_s=0.90$).^[12] Recording the spectrum at 77 K does not considerably modify the position of the lines, but affects their intensity distribution. Under these conditions, simulation could hardly determine to what extent the slight anisotropy of the signal is due to the g value or ^{197}Au hyperfine tensors. However, it shows that the ^{31}P hyperfine anisotropy is small and that the observed isotropic coupling is too large to result from inner shell polarization only. Experiments are planned to study the temperature dependence of the signal between 4 and 77 K and to check if the equivalence of the four phosphorus atoms does not result from a dynamic process which would subsist even at liquid nitrogen temperature.

In conclusion, we have shown that silacalix[4]phosphinine macrocycles may serve, at least in the case of Au^0 , as a kind of “CO-like matrix”. Studies aimed at determining whether this property can be extended to other reduced metallic centers are currently underway.

Experimental Section

3: A solution of GaCl_3 (0.022 g, 0.12 mmol) in CH_2Cl_2 (2 mL) was added to a solution of **1** (0.09 g, 0.10 mmol) and $[\text{AuCl}(\text{SMe}_2)]$ (0.03 g, 0.10 mmol) in CH_2Cl_2 (3 mL) at -80°C . The reaction mixture was then slowly warmed to room temperature. After evaporation of Me_2S and a part of the solvent, **3** was precipitated with hexanes (10 mL). After filtration and drying, **3** was isolated as a pale yellow solid (0.12 g, 91 %). Crystals suitable for X-ray analysis were obtained at room temperature from slow diffusion of hexanes in a solution of **3** in chloroform. Elemental analysis calcd for $\text{C}_{50}\text{H}_{50}\text{AuCl}_4\text{GaP}_4\text{Si}_4$: C 46.27, H 3.88; found: C 46.65, H 3.92; ^{31}P NMR (200 MHz, CD_2Cl_2 , 25°C): $\delta=234.50$ (s); ^1H NMR (CD_2Cl_2 , 25°C): $\delta=0.30$ (brs, 24H; SiMe_2), 7.45–7.62 (m, 26H; Ph, CH of thiophene rings, and H4 of phosphinines); ^{13}C NMR (200 MHz, CD_2Cl_2 , 25°C): $\delta=3.8$ (brs; SiMe_2), 130.3–131.6 (m; Ph and C4 of phosphinines), 135.1 (virtual t, $\Sigma J(\text{C},\text{P})=36.4$ Hz; C3, C3' of thiophene rings), 140.6 (s; C2, C2' of thiophene rings), 142.0 (brs; C3, C3' of Ph), 146.0 (virtual t, $\Sigma J(\text{C},\text{P})=12.1$ Hz; C3, C3' of phosphinines), 161.4 (virtual t, $\Sigma J(\text{C},\text{P})=13.9$ Hz; C2, C2' of phosphinines).

4: A solution of GaCl_3 (0.017 g, 0.10 mmol) in CH_2Cl_2 (2 mL) was added to a solution of **2** (0.10 g, 0.082 mmol) and $[\text{AuCl}(\text{SMe}_2)]$ (0.024 g, 0.082 mmol) in CH_2Cl_2 (4 mL) at -80°C . The reaction mixture was then slowly warmed to room temperature. After evaporation of Me_2S and a part of the solvent, **4** was precipitated with hexanes (10 mL). After filtration and drying, **4** was isolated as a red solid (0.12 g, 90 %). Crystals suitable for X-ray analysis were obtained at room temperature from slow diffusion of hexanes in a solution of **4** in CH_2Cl_2 . Elemental analysis calcd for $[\text{C}_{76}\text{H}_{68}\text{AuCl}_4\text{GaP}_4\text{Si}_4]$: C 56.14, H 4.21; found: C 56.45, H 4.18; ^{31}P NMR (200 MHz, CD_2Cl_2 , 25°C): $\delta=241.45$ (s); ^1H NMR (CD_2Cl_2 , 25°C): $\delta=0.05$ (brs, 24H; SiMe_2), 7.10–7.41 (m, 44H; Ph and H4 of phosphinines); ^{13}C NMR (200 MHz, CD_2Cl_2 , 25°C): $\delta=4.0$ (s; SiMe_2), 127.3–129.0 (m; Ph), 134.3–134.9 (virtual t, $\Sigma J(\text{C},\text{P})=28.6$; C4 of phosphinines), 143.8 (s; C3, C3' of Ph), 157.0 (s; C3, C3' of phosphinines), 158.2–159.0 (m, $\Sigma J(\text{C},\text{P})=40.7$; C2, C2' of phosphinines).

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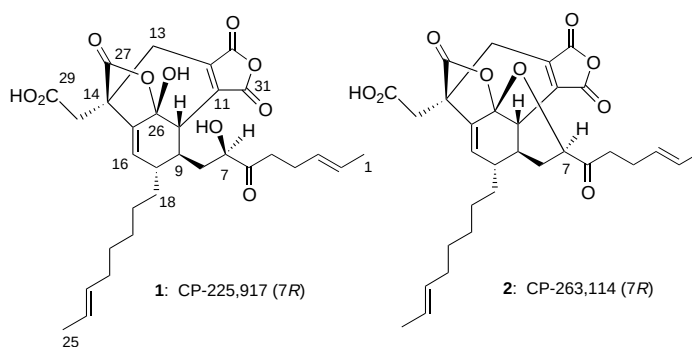
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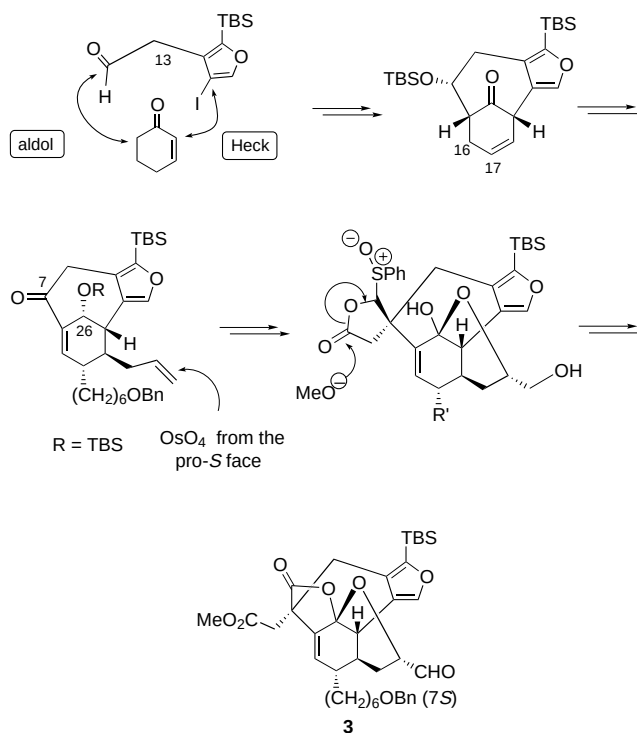
Discovery Through Total Synthesis— Epimerization at C7 in the CP Compounds: Is (7S)-CP-263,114 a Fermentation Product?*

Dongfang Meng, Qiang Tan, and
Samuel J. Danishefsky*

The goal of accomplishing the total syntheses of CP-225,917 (**1**) and CP-263,114 (**2**) has attracted the active participation of a variety of research groups.^[1–3] These substances inhibit farnesyltransferase and squalene synthase activity. While the



biological potential, if any, of agents that combine both activities is far from demonstrated, chemists have been attracted to this challenge by the novel molecular architecture of these target compounds. Elsewhere, we have described an approach to the synthesis of the CP series that delivered compound **3**, with the full framework to reach the target structure (Scheme 1).^[3c]



Scheme 1. Synthesis of **3**.^[3c]

We noted that the stereochemistry we were assigning at C7 (*S*)^[4] of our synthetic structure was not the same as that assigned by the Pfizer discovery group to CP-263,114 (*7R*).^[5, 6] However, one could not then be sure that the assignment to the natural product was necessarily correct. Some preliminary attempts on our part to epimerize aldehyde **3** were not successful and were attended by extensive decomposition. Accordingly, we undertook the installation of the remaining functionality required to go from **3** to the CP compounds (neglecting the issue of the C7 stereochemistry) in the hope of settling this question. Pentenylation of **3** followed by the oxidation of the resultant carbinol afforded **4** (Scheme 2).

[*] Prof. S. J. Danishefsky,^[+] D. Meng,^[+] Q. Tan
Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: s-danishefsky@ski.mskcc.org

[+] Further address:
Department of Chemistry, Columbia University
Havemeyer Hall, New York, NY 10027 (USA)

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Fortunately, we could deprotect the primary hydroxyl group on the C4 side chain with dichlorodicyanobenzoquinone (DDQ) to afford alcohol **5**. Oxidation of **5** provided aldehyde **6**. The direct coupling of the compound with 1,1-diodoethane^[7] gave rise to **7**. NMR spectral analysis continued to suggest that our compounds had the 7*S* configuration.^[4, 8] At this stage we were in a position to exploit the fused 2-(*tert*-butyldimethylsilyl)furan moiety. Treatment of this compound, as previously described in our model studies^[3b] indeed gave rise to the hemiacetal **8** as an anomeric mixture.^[9] Oxidation with tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) produced the internal carboxylic anhydride **9**.

Definitive proof of the configuration of the natural series at C7^[4] would require comparison with the methyl ester of CP-263,114, an unknown compound at the time. Of course, the obvious possibility of hydrolyzing **9** to its corresponding acid did not escape our attention. However, in practice, the attempted base-induced saponification of the methyl-ester

linkage is superseded by other interesting chemistry (see below).

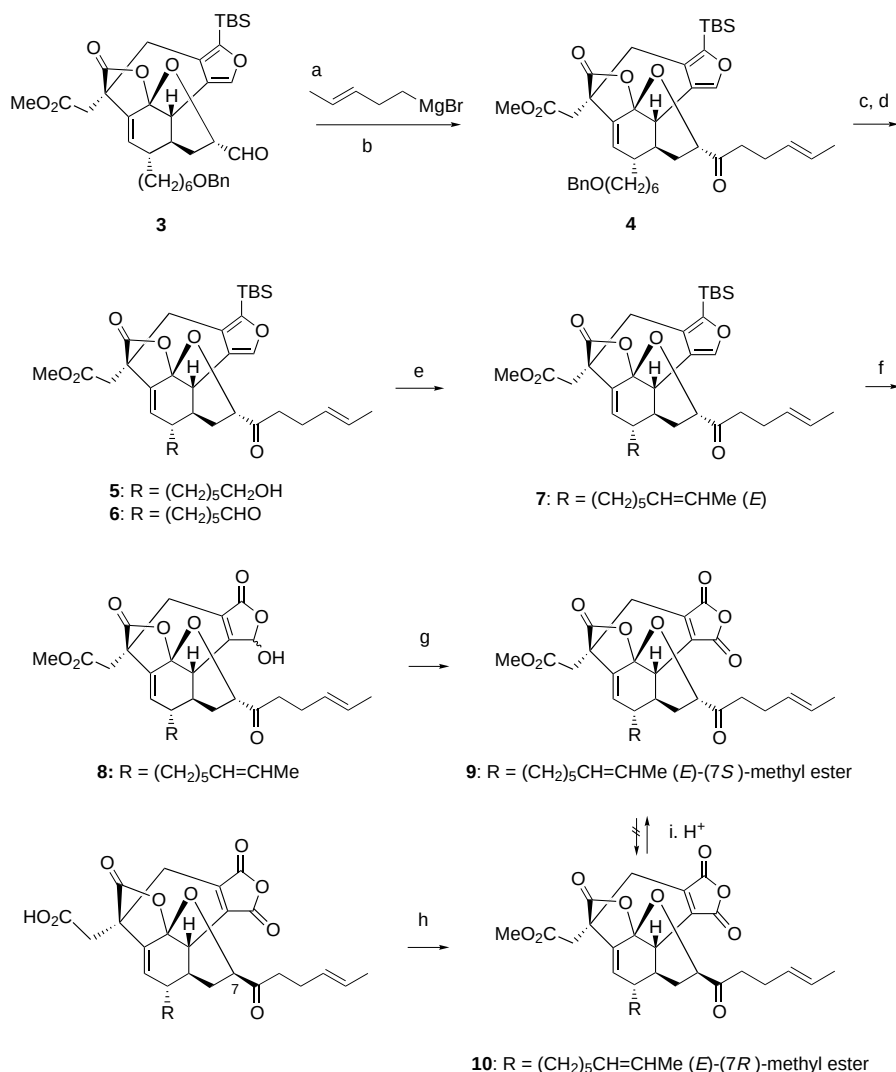
We were able to convert small reference samples of the acid **2**, made available to us from fermentation,^[10] into its methyl ester through the action of diazomethane under carefully controlled conditions.^[11] It was clear that the methyl ester **9**^[12] obtained from synthesis was similar to, *but not the same as* that derived from **2**. Accordingly, we were obliged to conclude that the natural CP-derived ester indeed corresponds to structure **10**,^[13] with the 7*R*^[4] configuration in accordance with the assignment of Kaneko and colleagues.^[5, 6] Correspondingly, the ester derived from total synthesis was, as we had surmised, **9** with 7*S* configuration.^[3c]

At this point, we recorded a most surprising observation: following esterification of various trace specimens of **2**, provided by Pfizer scientists from various fermentation broths^[10]—with **9** used as a reference sample—we could readily detect significant quantities (between 5 and 30 %) of the synthetically derived 7*S* system **9** in addition to the major

product **10**.^[14] This finding raised the possibility that the 7*S* product may *also* be naturally occurring. We set this question aside and probed whether epimerization at C7 would be possible in the ester series. Interestingly, when a purified sample of **10**, prepared from the methylation of **2** with diazomethane, was subjected to the action of various strong acids such as trifluoroacetic acid (TFA) or, preferably methanesulfonic acid (MSA), there was clear epimerization at C7 leading to a mixture of **9** and **10**. With time, the mixture significantly favored **9**. A precise statement of the ratio is not possible, since some side reactions were occurring as “equilibration” was in progress. We note that after treatment with MSA for one week the ratio **9**:**10** is approximately 3:1. However, equilibrium had not yet been reached.

Unfortunately, attempted equilibration of **9** and **10**, starting with **9**, using TFA or MSA, was attended by serious decomposition in the case of the former acid and essentially no reaction with the latter reagent. These experiments show that the 7*S* compound, **9** is substantially more stable than the 7*R* compound **10** in the ester series.^[4] More extensive investigations of the situation at C7 in the CP-225,917 series are described below.

While the full range of possible acid-catalyzed experiments or other epimerization strategies starting in the manifold of the “closed” 7-*epi*



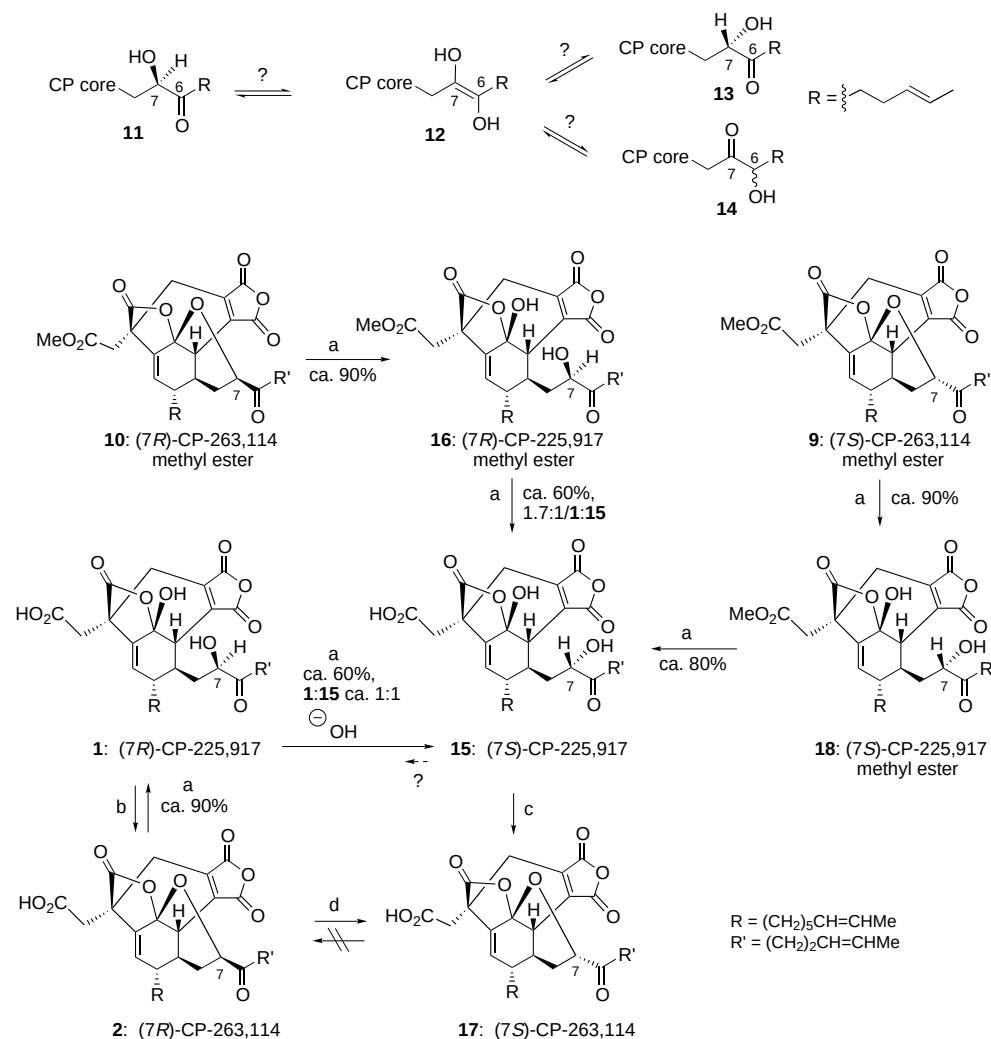
Scheme 2. a) Diethyl ether, -78°C (80–90 % conversion); b) Dess–Martin periodinane, CH_2Cl_2 , 60 % over two steps; c) DDQ, H_2O , CH_2Cl_2 , 60 %; d) Dess–Martin periodinane, CH_2Cl_2 , 80 %; e) 1,1-diodoethane, CrCl_2 , THF, 70 %; f) $h\nu$, O_2 , rose Bengal, $i\text{Pr}_2\text{EtN}$, CH_2Cl_2 , 0°C ; g) TPAP, NMO, CH_2Cl_2 , ca. 50 % over two steps; h) CH_2N_2 , diethyl ether, > 90 %; i) CF_3COOH or MeSO_2OH , CDCl_3 .

series has not yet been pursued, we posed the question as to whether base-catalyzed epimerization at C7 in the “open” CP series (see structure **1**; where “closed” and “open” refer to the presence and absence, respectively, of an ether bridge between C7 and C28) might be possible (Scheme 3). Such an epimerization could be pictured in terms of the C7-C8 enediols (see partial structure **12**). Clearly, this approach was not without its own attendant risks. In addition to C7 protonation to produce the two stereoisomeric alcohols at C7, there loomed the possibility that ketonization could occur at C7 (partial structure **14**), resulting in a new line of CP congeners that could not readily be “rehabilitated” in our total synthesis venture.

We first probed this question indirectly by starting with a specimen reference sample of the “open” CP acid **1**. In the event, treatment of this compound with lithium hydroxide, generated an approximate 1:1 mixture of **1** and a new acid **15**,^[15] which we assumed to be the 7-epimer of **1**. Remarkably, the mixture seemed to be substantially confined to epimers at C7.^[16] Thus, starting with **1**, crossing of the C7R-C7S boundary was possible without significant wandering into the structurally isomeric ketol terrain ($\rightarrow$ **14**).^[16] The lithium

hydroxide experiment was also conducted starting with the 7R methyl ester **10** of the natural series. The process was closely monitored by HPLC and ¹H NMR spectroscopy. The fastest step is that of cleavage of the δ -lactol, which is initiated by a reversible opening of the γ -lactone under formation of the open-chain methyl ester **16**. Concurrently, a slower epimerization at C7 was accompanied by hydrolysis of the methyl ester. After 24 h the ester linkage had been cleaved and the resultant mixture of acids, somewhat richer in **1** relative to **15**,^[15] could be separated. Given the fact that the hydroxide-induced conversion of **10** $\rightarrow$ **16** occurs much more rapidly than hydrolysis of the ester, the critical role postulated by Nicolaou et al. of free carboxylate being a crucial element in a presumed “cascade” process to achieve the opening of the γ -lactone, as judged by cleavage of the δ -lactol, is open to considerable question.^[2] In our case, clearly no such participation is involved in the hydroxide-driven opening of the γ -lactone since there are no free carboxylate groups.

Because of some attendant decomposition we cannot quote a precise equilibrium ratio of **1** and **15**. However, we were able to interconnect the open (CP-225,917) and closed (CP-263,114) systems in the 7S series by taking advantage of the cyclization reaction with methanesulfonic acid, initially discovered by the Pfizer scientists^[6, 7] starting with the natural 7R isomer. Compound **1** was indeed converted into **2** exactly as they reported. Similarly, **15** was converted into **17**, the 7S analogue of **2**. In each case the cyclization reaction occurred without noticeable epimerization at C7. Long-term treatment of **2** with MSA did result in epimerization at C7. Thus, an 8:1 mixture of **17**:**2** was obtained from **2** after one week.^[15, 16] Clearly, the 7S acid is substantially more stable than the 7R acid **2**, which is in keeping with our findings in the case of the corresponding esters **9** and **10**.



Scheme 3. a) LiOH (0.1M):THF, 1:4; b) MeSO₂OH (1 equiv), CDCl₃, ca. 90%; c) MeSO₂OH (3 equiv), CDCl₃, ca. 90%; d) MeSO₂OH (15 equiv), CDCl₃, ca. 90%, **17**:**2** = 8:1.

tained between 5–30% of **17**. Without an authentic sample such as we had available through total synthesis, it would be quite understandable for the minor 7*S* version of **2** to be overlooked in an isolation program. We also note that the HPLC separation of **2** and its 7*S* epimer is quite difficult.^[15]

We then explored the possibility of entering the natural series (7*R*) by base-catalyzed equilibration starting with the 7*S* epimers that could be derived from total synthesis. Remarkably, treatment of **15** with lithium hydroxide followed by acidification gave recovered starting material in addition to some general decomposition. At best, we could detect only trace quantities (about 5%) of **1** by HPLC. However, with the amounts of **15** available to us, fully homogenous CP-225,917 (**1**) was not secured from a total synthesis route.

In summary, the total syntheses of the 7*S*-CP systems has been accomplished. This program, initially directed at the total syntheses of **1** and **2**, has served to broaden our understanding of the chemistry of the CP-225,917 (open) and 263,114 (closed) series and to identify the 7*S* closed isomer **17** in the latter case as a very likely fermentation product. In the closed case a very powerful thermodynamic advantage favoring the 7-epi series (**9/10** and **17/2**) was discovered. We attribute this striking stability differential to the fact that in the epi series (**9** and **17**) the hexenoyl side chain projecting from C7 is *exo* with respect to the bicyclo-[3.3.1]nonane substructure. By contrast, in the naturally prevalent 7*R* series, the hexenoyl moiety is *endo* and substantially more hindered (Figure 1). A similar conclusion

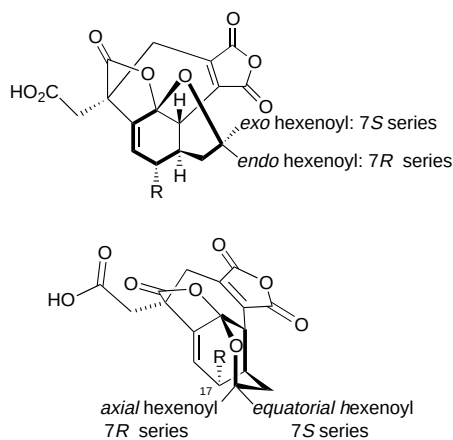


Figure 1. Positioning of the hexenoyl groups in the 7*R* and in the 7*S* series (for further information see the text).

arises from examining the two series from the sterical perspective of the tetrahydropyran ring. If this ring is in a chair conformation, then the hexenoyl group is equatorial in the 7*S* series while it is axial in the 7*R* case (Figure 1). Alternatively, the pyran ring may adapt an energetically costly boatlike conformation in the 7*R* case, to avoid placement of the large hexenoyl group in a 1,3-diaxial relationship to C17. In any case, dynamic equilibration apparently does not lead to detectable conversion of 7*S* into 7*R* diastereomer in the closed systems.

Surprisingly, the preference for the 7*S*-configured system, while perhaps less overwhelming, extends to the open CP-

225,917 stereoisomers (**15** and **1**). Here it was initially felt that given free rotation in the open structures, the stability margins between the 7*R* and 7*S* isomers would have been markedly reduced. Instead, we again found (at least in the context of the systems where, in addition to the free CH₂CO₂[−], the internal anhydride has been opened to form a disodium salt) a strong preference for the 7*S* configuration. Apparently, even in the “open” series, there are rigidifying influences—possibly arising from intramolecular hydrogen bonds—which favor the 7*S* diastereomers. Whether the preference for the 7*S* configuration extends to “open” systems that lack the array of lithium carboxylates, remains to be established. Such matters, as well as the biological properties of the newly fashioned and recognized 7*S* compounds, are the subjects of continuing investigation.

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- [11] Use of trimethylsilyldiazomethane leads to a trimethyl ester as the product from a ring opening of the anhydride. Some diazomethane methylations required 2-pentene as cosolvent to prevent side reactions at the two side-chain olefins.
- [12] **9**: IR(film): $\tilde{\nu}$ = 2921, 1798, 1767, 1736 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 5.81 (s, 1H), 5.45–5.39 (m, 4H), 4.21 (dd, J = 12.2, 3.0 Hz, 1H), 3.71 (s, 3H), 3.29 (s, 1H), 3.25 (d, J = 17.5 Hz, 1H), 3.08 (d, J = 8.3 Hz, 1H), 2.95 (d, J = 17.5 Hz, 1H), 2.64 (dd, J = 19.2, 2.2 Hz, 1H), 2.29–2.20 (m, 3H), 2.04–2.00 (m, 3H), 1.94–1.89 (m, 3H), 1.64–1.62 (m, 6H), 1.25–1.14 (m); HR-MS (FAB) calcd for $\text{C}_{32}\text{H}_{38}\text{O}_9\text{Na}$ [$M+\text{Na}$] $^+$: 589.2413, found: 589.2391.
- [13] **10**: IR(film): $\tilde{\nu}$ = 2927, 1792, 1768, 1740 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 5.66 (d, J = 1.9 Hz, 1H), 5.50–5.30 (m, 4H), 4.54 (t, J = 8.1 Hz, 1H), 3.73 (s, 3H), 3.53 (s, 1H), 3.25 (d, J = 17.4 Hz, 1H), 3.08 (d, J = 19.5 Hz, 1H), 2.93 (d, J = 17.4 Hz, 1H), 2.74–2.69 (m, 3H), 2.53 (m, 1H), 2.35–2.25 (m, 4H), 2.12 (dd, J = 13.6, 8.8 Hz, 1H), 1.94–1.91 (m, 2H), 1.64–1.62 (m, 6H), 1.25–1.14 (m); HR-MS (FAB) calcd for $\text{C}_{32}\text{H}_{38}\text{O}_9\text{Na}$ [$M+\text{Na}$] $^+$: 589.2413, found: 589.2415.
- [14] The trace fermentation acid samples came from several different sources which differed in the amount of the 7S system **17** (and subsequently its methyl ester **11**). The ratio of **2**:**17** did not change following storage of the samples in our premises for five months at -78°C .
- [15] Separation conditions of **1**, **2**, **15**, and **17**: Reversed-phase HPLC column: Metachem Inertsil 5 μ ODS2, 0.002 % H_3PO_4 : CH_3CN = 4:6. Retention time: **15** (16 min), **1** (17 min), **2** (32 min), **17** (34 min). It is also crucial to inject the sample in a 1/1 mixture of 0.1 % H_3PO_4 in CH_3CN . We note also that the chromatography per se does not effect the homogeneity of the samples. Hence, we are confident that the 7S isomer we detected was present in the original samples.
- [16] Another pathway not invoking enediol **12** would involve a reversible C6-C7 α -ketol shift with an intervening rotation about the C6-C7 σ bond. This step would effectively epimerize C7 without the necessary scrambling of the ketol. For this “ketol-shift” pathway, as well as the enediol pathway, to be viable, it would be crucial that the 7-hydroxy-6-ketone be much more stable than the 6-hydroxy-7-ketone isomers in both the 7R and 7S series.
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Electron Microscopy Reveals the Nucleation Mechanism of Zeolite Y from Precursor Colloids**

Svetlana Mintova, Norman H. Olson, and Thomas Bein*

Zeolites are crystalline, porous solids whose intricate pore and channel systems in the molecular size range of 0.3 to about 1.5 nm are the basis for their immense importance in catalysis, separations, and ion exchange.^[1–4] Although numerous studies have addressed the preparation of zeolites, it has been very difficult to model the complex mechanism by which they assemble from framework constituent precursor species under hydrothermal synthesis conditions.

An improved understanding of the synthesis mechanism is pivotal for the design of new zeolites (only about 100 structures are known so far), and for the preparation of novel zeolitic assemblies such as zeolite thin films for membrane reactors, monoliths, or functional nanostructures.^[5] Here we report direct, high-resolution electron microscopic evidence for the nucleation mechanism of zeolite Y (faujasite structure type; FAU) in nanoscale amorphous aluminosilicate gel particles, followed by full conversion of the gel aggregates into 25–35 nm large single crystals of zeolite Y. Further crystallization of the colloidal zeolite Y suspension is mediated by soluble aluminosilicate species.

Different mechanisms have been discussed regarding nucleation and crystallization of zeolites, based on experimental evidence obtained with various methods such as X-ray diffraction and scattering, solid-state NMR spectroscopy, atomic force microscopy, and electron microscopy.^[6–22] These include transformation of the precursor gel phase, aggregation and realignment of preassembled building blocks containing template molecule/(alumino)silicate clusters, and assembly of soluble small species from solution. Most of the above techniques give information about the final crystalline product; however, imaging the initial stage of zeolite formation has not previously been possible.

Several molecular sieves, including zeolite A, Y, L, ZSM-5, silicalite-1, TS-1, and $\text{AlPO}_4\text{-5}$ can be made in colloidal form with particle sizes in the nanometer range.^[23–28] Recently, we reported a detailed study of the very early stages of zeolite A

[*] Prof. T. Bein, Prof. S. Mintova^[+]
Department of Chemistry, Purdue University
West Lafayette, IN 47907 (USA)

New Address:
Institut für Physikalische Chemie der Universität
D-81377 München (Germany)
Fax: (+49) 89-2180-7624
E-mail: tbein@cup.uni-muenchen.de

Dr. N. H. Olson
Department of Biology, Purdue University
West Lafayette, IN 47907 (USA)

[+] On leave from:
Central Laboratory of Mineralogy and Crystallography
Bulgarian Academy of Science, 92 Rakovski Street
1000 Sofia (Bulgaria)

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crystal growth at room temperature, where amorphous gel particles were converted into nanoscale single crystals.^[28]

Zeolite Y can be viewed as the archetype zeolite owing to its enormous importance in catalysis (hydrocracking of petroleum) and its large stable pore structure, which makes it an ideal host for novel nanocomposites.^[1] In this study we examined the entire process of gel formation, nucleation, and crystal growth of this important zeolite at 100 °C in a colloidal model system. The structural evolution of these species was followed at different time intervals with high-resolution transmission electron microscopy (HR-TEM) at reduced dose in the field-emission mode. To complement the HR-TEM studies, X-ray diffraction, dynamic light scattering (DLS), thermogravimetric analysis (TGA), and IR spectroscopy were used to monitor the crystallization process.

The aggregates in the freshly prepared colloidal solution at room temperature are shown to be amorphous by X-ray diffraction (Figure 1 a). The TEM image reveals the presence of 25–35 nm large amorphous gel particles having sharp edges (Figure 2 a). These gel particles are the precursors for the nucleation stage of the FAU crystals. The start of crystallization of zeolite Y from this colloidal solution requires heating at 100 °C in excess of 24 h—representing the well-known “induction period” in zeolite synthesis. After 24 h at 100 °C, the XRD pattern shows

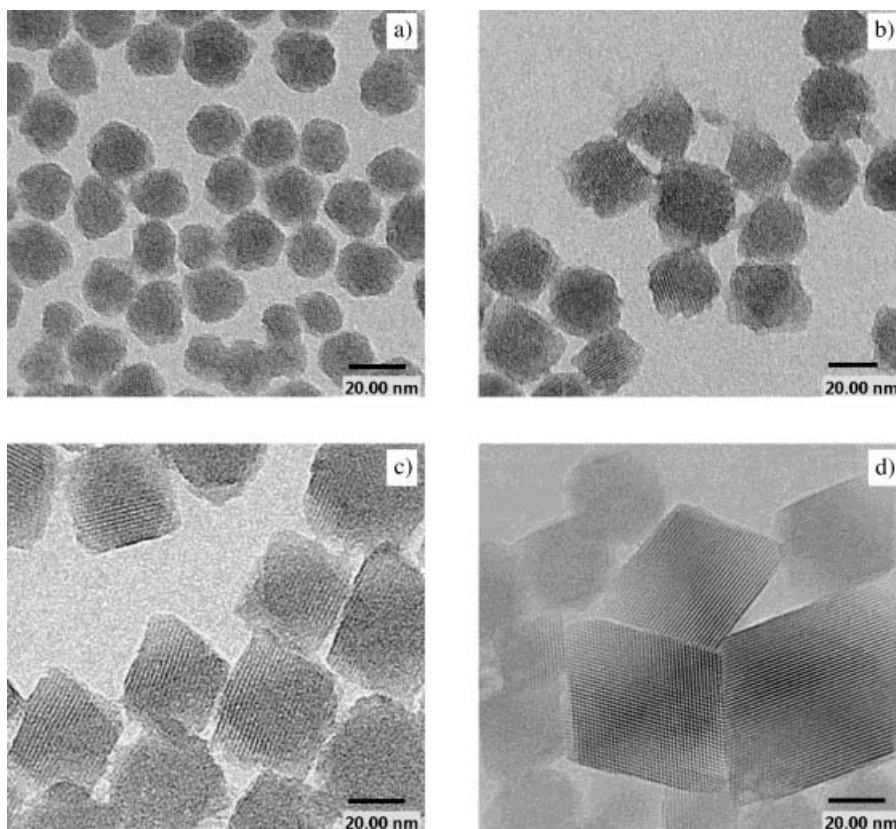


Figure 2. Particles in a) freshly prepared aluminosilicate solution for the synthesis of zeolite Y and after hydrothermal treatment at 100 °C for b) 28, c) 48, and d) 75 h.

that the resulting aluminosilicate consists of amorphous material only (Figure 1 b). The TEM image of this sample is similar to that for the freshly prepared synthesis mixture. A complementary IR study was performed of both freshly prepared solutions and samples heated for 24 h (Figure 3 a, b). The IR spectra contain only a band at 470 cm⁻¹, which is assigned to structure-insensitive T–O bending modes of tetrahedral TO₄ units (T=Si or Al), and confirm the amorphous nature of the above sample.

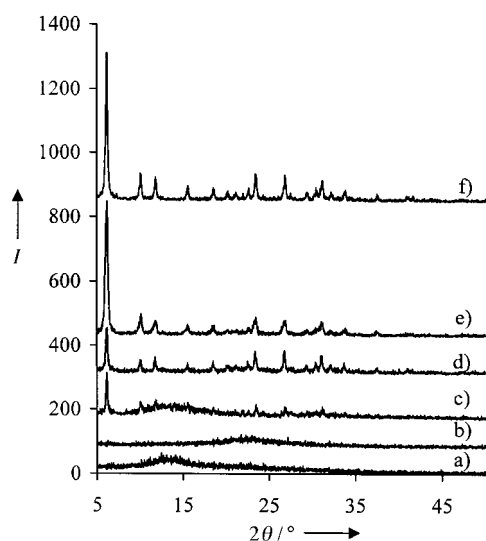


Figure 1. Powder diffraction patterns of a) the freshly prepared solution for the synthesis of zeolite Y (containing all reagents) and after hydrothermal treatment for b) 24, c) 28, d) 38, e) 55, and f) 75 h.

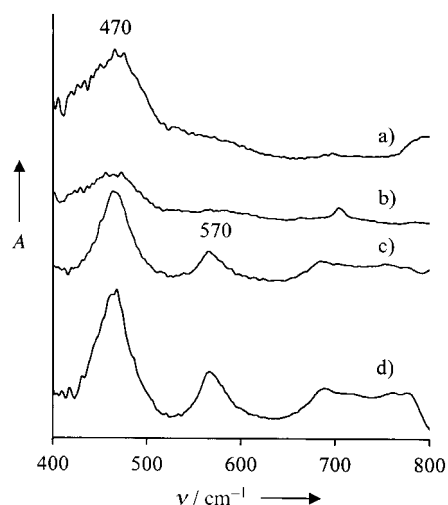


Figure 3. IR spectra of a) the freshly prepared solution for the synthesis of zeolite Y and after hydrothermal treatment for b) 24, c) 28, and d) 55 h. Samples were isolated by centrifugation and prepared as KBr pellets.

Crystalline zeolite Y emerged after 28 h of hydrothermal treatment of the initial solution, and diffraction lines began to appear (Figure 1c). The HR-TEM images of this sample show crystalline nanoparticles of approximately 10 to 20 nm in size (Figure 2b). The linear size of these crystals corresponds to only 7, 9, and 15 unit cells (Figure 4). These particles show a

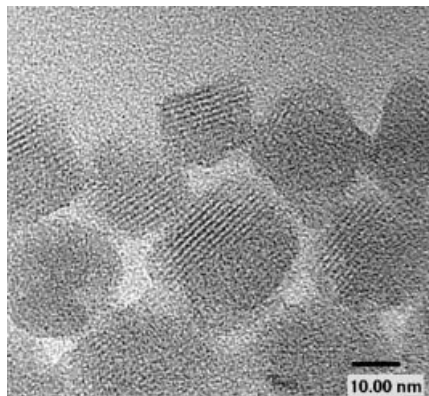


Figure 4. HR-TEM image of FAU crystals grown in the amorphous gel aggregates after hydrothermal treatment for 28 h at 100 °C.

lattice spacing of 14 Å attributed to the (111) planes of the FAU structure.^[29] Strikingly, the crystals always nucleate on the periphery of the amorphous gel aggregates (Figure 4). Our observations provide strong evidence for one of the nucleation mechanisms of zeolite X (FAU structure type with a lower Si/Al ratio than Y) discussed by Lechert et al.^[21] It was assumed that the gel phase causes the formation of structural elements such as six-rings that may act as precursors for the nucleation events. This may occur preferably at the gel–liquid interface, where precursor structures can be formed by transport of small species from solution, or by structural reorganization within the surface region (for example, by partial hydrolysis and rearrangement of surface-bound rings).^[21]

The next stages observed during the synthesis were after hydrothermal treatment for 38, 48, 55, and 75 h. The TEM images revealed that while increasing the crystallization time from 28 h (Figure 2b) to 48 h (Figure 2c), the amorphous aggregates were consumed and crystalline particles of FAU-type zeolites were obtained. All crystals have the typical octahedral morphology of the FAU-type zeolite. Close examination of the images taken at different crystallization times indicates that all crystals are single, and that the particle size is rather uniform. This implies that only one nucleus was present in each gel particle. To ascertain the representative nature of the HR-TEM samples, different stages of crystallization were examined with DLS. Particles with sizes of 25–35 nm were present in the initial synthesis mixture and in the products obtained after heating up to 28, 38, 48, and 55 h. In situ DLS measurements and TEM results are therefore in good agreement. The data show that as crystallization time increases, the overall size of the zeolite-gel particles remains approximately constant, suggesting that the nutrients for the crystal growth were primarily supplied by the gel particles. This is confirmed by the stable mass balance of the solutions

1) containing the amorphous precursor gel particles two hours after mixing, 2) after two days of aging at RT, and 3) after hydrothermal treatment at 100 °C for 48 h (1.7 ± 0.1 wt % solid content throughout).

The XRD patterns show that all products obtained after 38 h are highly crystalline FAU zeolite (Figure 1d–f). Further evidence for the emerging FAU structure in the early stages of particle growth is provided by IR spectroscopy. The IR spectra of FAU samples after 28 and 55 h contain a band at approximately 570 cm^{-1} in addition to the band at 470 cm^{-1} (Figure 3c, d). The appearance of the band at 570 cm^{-1} , first evident after 28 h, is associated with the FAU structure (this band is not observed for amorphous silica; see Figure 3b).

To probe the association of the organic template with the primary gel aggregates existing in the initial solutions and in the zeolite crystals (heated for 48 h), thermogravimetric analysis (TGA) of washed samples was performed. The TGA data for the gel aggregates show the presence of large quantities of organic template, decomposing at around 236 °C in air (ca. 32 wt % based on calcined gel, after water desorption, Figure 5). The FAU sample also contains the organic TMA template, but it decomposes in two steps at higher temperatures (335 and 487 °C), suggesting different local environments of the template (ca. 10 wt % total, the remainder is adsorbed water).

After keeping the initial mixture at 100 °C for an extended period (75 h), well-defined octahedral crystals with sizes of about 50 nm were formed (Figure 2d). Since no gel particles remained in the solution after 48 h, the nutrients for this extended growth must have been the colloidal zeolites themselves. The important point is that the FAU zeolite crystals can continue to grow through solution transport over macroscopic distances.

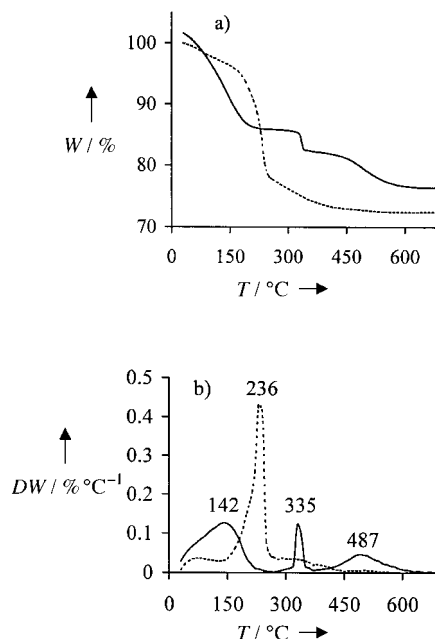


Figure 5. a) Thermogravimetric (TG) and b) derivative TG curves of TMA-containing primary gel aggregates present in the initial solution before heating (dotted line) and of the FAU nanocrystals obtained after 48 h of heating at 100 °C (solid line; heating rate 10 °C min^{-1} in air).

The direct evidence obtained here with high-resolution electron microscopy reveals the mechanism of FAU zeolite nucleation and crystal growth at elevated temperatures (Figure 6). FAU crystals are nucleated in amorphous gel

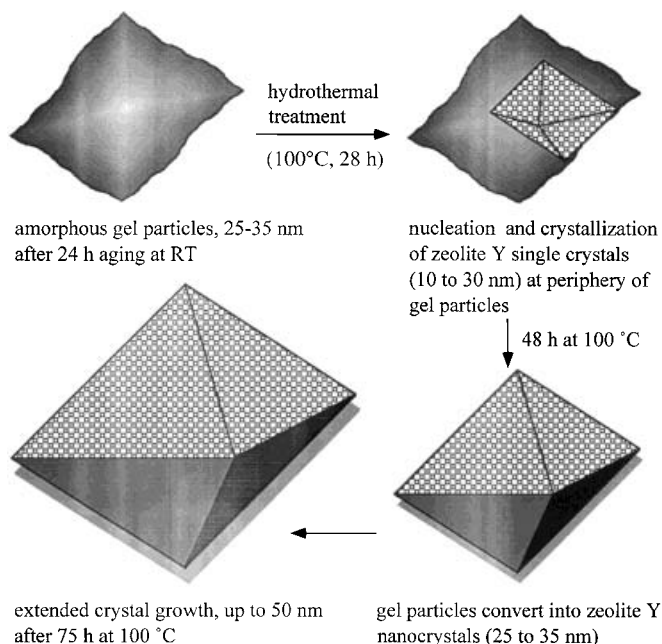


Figure 6. Proposed reaction scheme for the zeolite growth mechanism in colloidal solution.

aggregates existing in the colloidal aqueous solution after 28 h. Each amorphous aggregate nucleates only one single zeolite crystal, with nucleation always beginning at the gel–solution interface. Our results confirm a previously proposed nucleation mechanism for this type of zeolite, where structural elements at the periphery of the gel phase act as precursors for the nucleation events. The aggregates are completely converted into crystalline zeolite Y within 48 h at 100 °C. Solution mass transfer is the dominant mechanism for the substantial crystal growth of FAU crystals after prolonged crystallization times.

Experimental Section

The synthesis of FAU from a clear aqueous solution with a molar composition of 0.15 Na₂O:5.5 (TMA)₂O:2.3 Al₂O₃:10 SiO₂:570 H₂O was performed at 100 °C. Tetramethylammonium hydroxide pentahydrate (TMAOH · 5H₂O; Aldrich) was added to an aqueous solution of aluminum isopropoxide (Aldrich) to give a clear solution. Then silica sol (30%, 5 nm, pH 10, Aldrich) was added while stirring, and the mixture was further stirred for about 30 min. Crystallization was carried out in Teflon-lined stainless steel autoclaves at 100 °C. Prior to analysis all samples were purified three times by high-speed centrifugation, removal of the mother liquor, and redispersion in water.

The XRD data were collected on a Scintag XDS 2000 diffractometer using CuK α radiation. The TG measurements were performed with a 951 DuPont Instruments Analyzer. The samples were examined with a Philips 200 FEG TEM operated at 200 kV. The grid covered with colloidal suspension was dried and scanned at low magnification to search for the crystals. Focusing and astigmatism correction were performed at the working magnification on an area about 2.5 μ m from the area of interest to decrease the amount of beam damage to the specimen. The beam was then automatically translated

back to the previous area before the image was captured by a Gatan 794 multiscan charge-coupled device camera.

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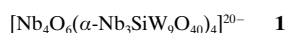
Keywords: colloids • crystal growth • zeolites

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A Supramolecular Tetra-Keggin Polyoxometalate $[\text{Nb}_4\text{O}_6(\alpha\text{-Nb}_3\text{SiW}_9\text{O}_{40})_4]^{20-}$ **

Gyu-Shik Kim, Huadong Zeng, Don VanDerveer, and Craig L. Hill*

The self-assembly of modular and multicomponent inorganic systems into larger structures or materials with useful properties remains an intense focus of current research.^[1] In this context, the formation of giant polyoxometalates (POMs) with catalytic, magnetic, and antiviral properties in part attributable to their structures, is of interest.^[2] Herein we explore the acid-induced formation of Nb-O-Nb linkages between Nb-containing POM units to generate supramolecular poly(POM) species,^[3-6] and report the synthesis and characterization of a structurally novel tetrameric Keggin complex, **1**. The stability of this complex is also evaluated under physiological conditions, because the corresponding well-studied monomer **2** and dimer **3**^[3] are some of the least toxic and most potent antiviral agents of the 300+ POMs investigated biologically and pharmacologically.^[7-12]



Reaction of $\text{Nb}_6\text{O}_{19}^{8-}$ and aqueous peroxide H_2O_2 with solid $\alpha\text{-SiW}_9\text{O}_{34}^{10-}$ forms **1** in 51 % yield. If the Keggin units used in the synthesis already contain the requisite three Nb atoms, the yield of **1**, not surprisingly, is higher. For example, reaction of $\text{Nb}_6\text{O}_{19}^{8-}$ and aqueous H_2O_2 with the triperoxo compound $\alpha\text{-Cs}_6\text{H}[(\text{NbO}_2)_3\text{SiW}_9\text{O}_{37}]$ (**Cs-4**) as a solid affords **1** in 81 % yield. Both reactions proceed with vigorous evolution of O_2 . The attempt to prepare **1** by initial construction of the $\text{Nb}_4\text{O}_6^{8+}$ unit (controlled hydrolysis of $\text{Nb}(\text{OEt})_5$ under acidic conditions) followed by addition of **4** produces only the known tri- μ -oxo dimer **3**.^[3] The stoichiometry, selection of appropriate POM synthons (tectons), and good structural fit between the $\text{Nb}_4\text{O}_6^{8+}$ unit and the Keggin POM units appear to be responsible in part for the successful synthesis. The

$n\text{Bu}_4\text{N}$ salt of **1** is easily prepared by metathesis of the Cs salt at low pH.

Single crystals of **Cs-1** were found to be suitable for X-ray crystallography;^[13] Figure 1 shows the structure of the C_2 tetra-Keggin polyanion **1** and its $\text{Nb}_4\text{O}_6^{8+}$ core. Each of the

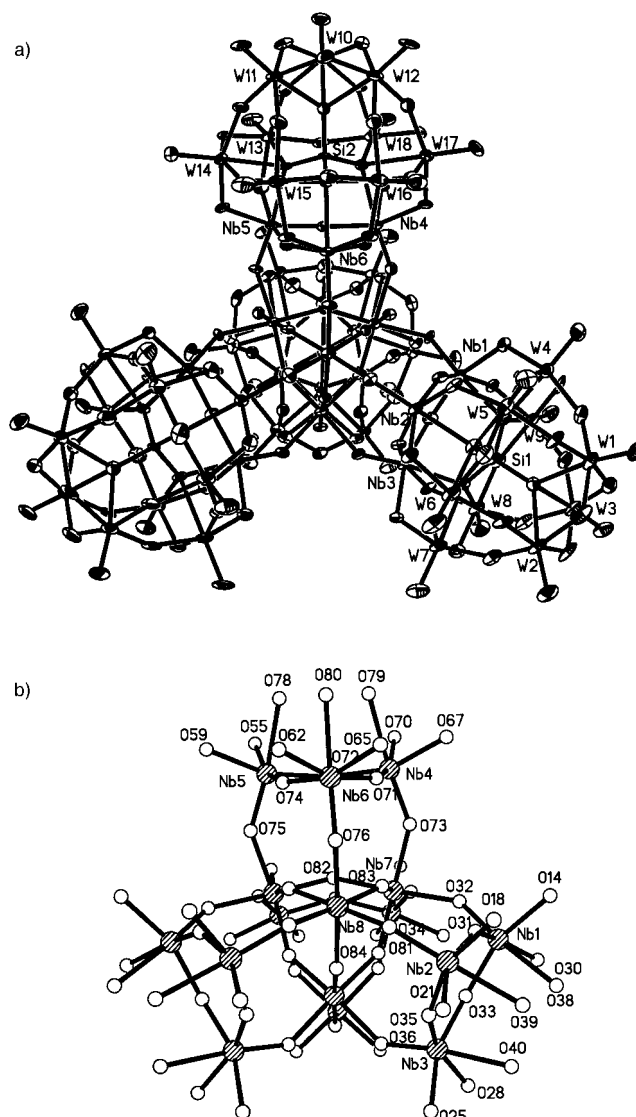


Figure 1. ORTEP drawings of the structure of **Cs-1**. a) View down the pseudo- C_3 axis of **1**. b) View of the $\text{Nb}_{16}\text{O}_{66}$ core. Selected average bond lengths [Å] and angles [°]: $\text{Nb}(\text{K})\text{-O}_{\text{b1}} 1.84(1)$, $\text{Nb-O}_{\text{b2}} 1.93(1)$, $\text{Nb-O}_{\text{b3}} 2.02(1)$, $\text{Nb}(\text{C})\text{-O}_{\text{b1}} 2.06(1)$, $\text{Nb-O}_{\text{b4}} 1.94(1)$; $\text{Nb-O}_{\text{b1}}\text{-Nb} 139.7(7)$, $\text{Nb-O}_{\text{b2}}\text{-Nb} 148.5(5)$, $\text{Nb-O}_{\text{b4}}\text{-Nb} 141.5(9)$; where O_{b1} is a doubly bridging oxygen atom between the Keggin unit and the Nb_4O_6 core; O_{b2} is a doubly bridging oxygen atom between Nb atoms in the Keggin unit; O_{b3} is a doubly bridging oxygen atom between Nb and W atoms in the Keggin unit; O_{b4} is a doubly bridging oxygen atom between Nb atoms in the Nb_4O_6 core; Nb(K) are Nb atoms in the Keggin unit, and Nb(C) are Nb atoms in the Nb_4O_6 core.

four $\alpha\text{-}[\text{Nb}_3\text{SiW}_9\text{O}_{40}]^{7-}$ Keggin units are linked by three Nb-O-Nb bonds to one $[\text{Nb-O}]_3$ face of the $\text{Nb}_4\text{O}_6^{8+}$ tetrahedral core. A crystallographically imposed C_2 axis passes through two O atoms (O82 and O84) in the $\text{Nb}_4\text{O}_6^{8+}$ core; nonetheless, **1** and $\text{Nb}_4\text{O}_6^{8+}$ approach the maximum possible T_d symmetry. The M_4O_6 adamantanoid unit has been reported in several complexes,^[14-18] and in one Nb_4 complex, $[(\text{Cp}^*\text{Nb})_4\text{O}_4]$

[*] Prof. Dr. C. L. Hill, Dr. G.-S. Kim,^[+] H. Zeng
Department of Chemistry, 1515 Pierce Drive, Emory University
Atlanta, GA 30322 (USA)
Fax: (+1) 404-727-6076
E-mail: chill@emory.edu
Dr. D. VanDerveer
School of Chemistry and Biochemistry
Georgia Institute of Technology, Atlanta, GA 30332 (USA)

[+] Permanent address:
Department of Science Education, 192-1 Hyoja-2-dong
Kangwon National University
Chunchon, 200-701 (Republic of Korea)

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(Cp* = C₅Me₅).^[16] However, the latter contains Nb^{IV} (d¹) centers unlike the Nb^V (d⁰) centers in **1**. Alternatively, **1** may be viewed as four α -SiW₉O₃₄¹⁰⁻ units supported on Nb₁₆O₃₀²⁰⁺, the largest isopolyoniobate unit observed in a discrete molecule.

This tetrahedral complex of four Keggin units completes a structural series of increasing dimensionality and nuclearity: the double Keggin structure exemplified by tri- μ -oxo dimer **3** (a one-dimensional motif), the triple Keggin structure, exemplified only by [Ni₉(OH)₃(H₂O)₆(HPO₄)₂(PW₉O₃₄)₃]¹⁶⁻^[19] and a partially characterized Co analogue^[20] (a two-dimensional motif), and **1**, a quadruple Keggin structure (a three-dimensional motif).

Four lines of direct or indirect evidence are consistent with maintenance of the solid-state structure of **1** (Figure 1) in aqueous solution (Figure 2). First, the ²⁹Si NMR spectrum

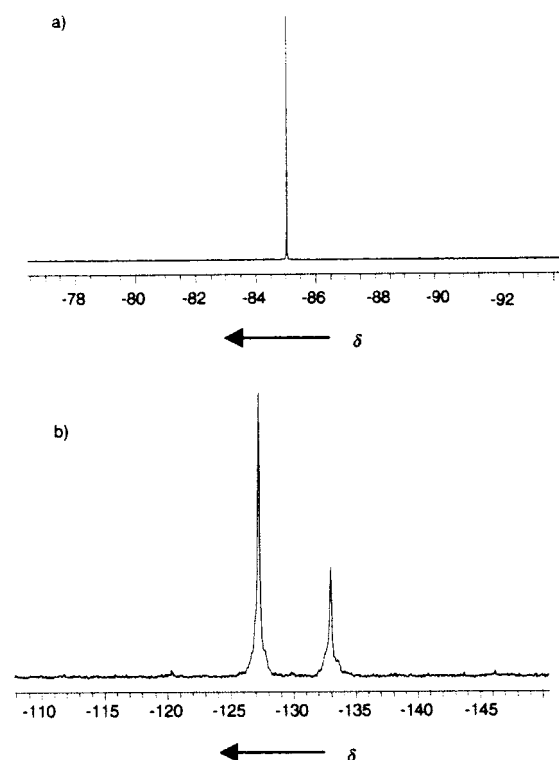


Figure 2. ²⁹Si NMR (a) and ¹⁸³W NMR (b) spectra of Li₂₀[(Nb₄O₆)(α -Nb₃SiW₉O₄₀)₄] in D₂O (72 mm, pD = 0.6).

(sharp singlet at $\delta = -85.04$) and the ¹⁸³W NMR spectrum (two singlets at $\delta = -127.6$ and -132.8 in a 2:1 integration ratio) are consistent with the approximate overall *T_d* symmetry of **1** and the local *C_{3v}* symmetry of each of the four pendant Keggin units (Figure 1). Second, the FT-IR spectrum of **1** in D₂O (35 mm Li-**1**) and in the solid state (Cs-**1** in KBr) are similar, and both exhibit a medium to strong Nb-O-Nb stretch at about 723 ± 13 cm⁻¹ which precludes the presence of only monomer (see Figure S1 in the Supporting Information).^[21] Third, the ¹⁸³W NMR chemical shifts of **1** are quite distinct from those of the monomer **2** and the dimer **3** under similar conditions, and fourth, both the ¹⁸³W NMR and FTIR spectra indicate that titration of **1** with the 24 equivalents of hydroxide forms **2** quantitatively (see Figure S2 in the Supporting Information).

¹⁸³W NMR and FTIR establish that at pD values of 1.0, 4.2, and 6.0, respectively, **1** equilibrates to the following POMs: 100% **1**, 70% **1** plus 30% **2**, and 100% **2**. The cyclic voltammetric behavior of these Nb₃SiW₉-based species (**1**, **2**, and **3** all give quasi-reversible cyclic voltammograms at glassy carbon electrodes) is also consistent with the same pH-dependent speciation. These results make it clear that while **1** is thermodynamically stable at the pH of the stomach (pH 1–2), it is not at the pH of human serum (pH ~7.3).

The reduction potentials of **1** (pH = 0), **2** (pH = 4), and **3** (pH = 0) are -518 , -706 , and -664 mV versus Ag/AgCl, respectively. Neither H₂S nor NH₂NH₂ reduces **1** under anaerobic conditions at 25 °C in aqueous solution, and unlike several heteropoly anions, including the Nb-containing compounds [Nb₃P₂W₁₅O₆₂]⁹⁻ and [Nb₂W₄O₁₉]⁴⁻,^[22] **1** does not catalyze the aerobic oxidation of sulfide (H₂S + $\frac{1}{2}$ O₂ $\rightarrow$ $\frac{1}{8}$ S₈ + H₂O).^[23]

Experimental Section

α -Cs-4: To a stirred solution of K₇HNb₆O₁₉ · 13 H₂O^[24] (1.91 g, 1.39 mmol) dissolved in aqueous H₂O₂ (250 mL of a 0.5 M solution) was added dropwise aqueous HCl (20 mL of a 1.0 M solution) followed by solid α -Na₁₀SiW₉O₃₄ · 23 H₂O (7.82 g, 2.72 mmol). To the resulting solution was added solid CsCl (25.0 g, 149 mmol). After 15 min of stirring, the orange-yellow precipitate was removed by filtration, washed with diethyl ether (2 × 20 mL) and dried in air to give 9.11 g of yellow powder (86.9% yield based on Nb₆O₁₉⁸⁻). FT-IR (KBr pellet): $\tilde{\nu}$ [cm⁻¹]: 994 (w), 957 (m), 903 (vs), 868 (sh), 789 (vs), 673 (vw), 592 (w), 534 (w), 482 (vw); elemental analysis (%) calcd for Cs₆H[(NbO₂)₃SiW₉O₃₇] · 8 H₂O: H 0.48, Si 0.78, Cs 22.2, Nb 7.76, W 46.1; found: H 0.44, Si 0.62, Cs 21.9, Nb 7.50, W 46.5.

Cs₂₀ salt of **1:** To a solution of K₇HNb₆O₁₉ · 13 H₂O (0.76 g, 5.5 mmol) in aqueous H₂O₂ (150 mL of a 0.5 M solution) was added HCl (20 mL of a 6.0 M solution). To this yellow solution was added α -Cs-**4** (12.76 g, 3.552 mmol) and LiClO₄ (2.47 g, 6.54 equiv) in HCl (35 mL of a 0.8 M solution) followed by removal of the CsClO₄ (0.10 g). The resulting mixture was refluxed for 3 h until the yellow color disappeared. After cooling to ambient temperature, CsCl (20.3 g) was added. After 30 min, the white precipitate was removed by filtration, washed with methanol (2 × 20 mL) and diethyl ether (2 × 20 mL), and dried in air overnight to give 10.46 g of a colorless crystals (81.0% yield based on α -Cs-**4**). FTIR (KBr pellet): $\tilde{\nu}$ [cm⁻¹]: 1003 (w), 963 (m), 920 (s), 785 (vs), 710 (s, Nb-O-Nb), 534 (w), 425 (vw); (in D₂O, AgBr windows): 1003 (w), 965 (m), 934 (s), 915 (s), 884 (vw, sh), 803 (s), 735 (m, Nb-O-Nb). ²⁹Si NMR (79.456 MHz, 0.8 M HCl/D₂O, + LiClO₄, - CsClO₄, 1.6 M NaTMSPA (TMSPA = trimethylsilylpropionate in D₂O standard): $\delta = -85.04$ (fwhh = 0.99 Hz); ¹⁸³W NMR (16.662 MHz, 0.8 M HCl/D₂O, + LiClO₄, - CsClO₄, 2.0 M Na₂WO₄ in D₂O standard): $\delta = -127.6$ (s, 24 W), -132.8 (s, 12 W); elemental analysis (%) calcd for Cs₂₀[Nb₄O₆(Nb₃SiW₉O₄₀)₄] · 70 H₂O: H 0.95, Cs 18.0, Nb 10.1, W 44.7; found: H 1.01, Cs 18.4, Nb 9.82, W 44.2.

Cs₁₅H₃ salt (Cs-1**):** Concentration of a saturated solution of the Cs₂₀ salt in 0.8 M HCl by evaporation in air over three days at 25 °C afforded colorless crystalline Cs-**1**. The FT-IR and ¹⁸³W NMR spectra of the Cs₂₀ salt of **1** and Cs-**1** are identical. Elemental analysis (%) calcd for Cs₁₅[H₃Nb₄O₆(Nb₃SiW₉O₄₀)₄] · 50 H₂O: H 0.77, Cs 14.5, Nb 10.8, W 48.1; found: H 0.76, Cs 14.5, Nb 10.7, W 48.0.

nBu₄N⁺ salt (TBAH₈-1**):** TBAHSO₄ (5.75 g) dissolved in HCl (20 mL of a 0.8 M solution) was added to the Cs₂₀ salt of **1** (1.5 g) in HCl (100 mL of a 0.8 M solution). The resulting white powder (yield = 99.6%) was recrystallized from CH₃CN using diethyl ether diffusion to provide 1.37 g of product. FT-IR (KBr pellet): $\tilde{\nu}$ [cm⁻¹]: 1005 (w), 967 (m), 915 (s), 800 (vs), 698 (s, Nb-O-Nb), 602 (w), 540 (vw); elemental analysis (%) calcd for TBAH₈[Nb₄O₆(Nb₃SiW₉O₄₀)₄]: C 16.7, H 3.22, N 1.22, Nb 10.8, W 48.0; found: C 16.5, H 3.11, N 1.23, Nb 10.6, W 47.9.

Cyclic voltammograms of **1**, **2**, and **3** were recorded using a glassy carbon working electrode, a Pt wire counter electrode and a Ag/AgCl (3 M NaCl)

reference electrode as Cs salts in aqueous 0.1M NaClO₄ under Ar at 24 °C with sweep rates of 100 mV s⁻¹. HClO₄ was used to adjust the pH.

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Cerium(IV)-Catalyzed Deprotection of Acetals and Ketals under Mildly Basic Conditions**

István E. Markó,* Ali Ates, Arnaud Gautier, Bernard Leroy, Jean-Marc Plancher, Yannick Quesnel, and Jean-Christophe Vanherck

Dedicated to Professor Heinz G. Viehe on the occasion of his 70th birthday

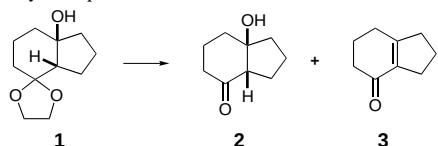
The protection–deprotection sequence is probably the most frequently encountered functional-group transformation in organic synthesis.^[1] Amongst the plethora of groups typically employed for protecting aldehydes and ketones, cyclic acetals and ketals enjoy a cardinal position, as exemplified by the numerous and ingenious methods devised for their attachment and removal.^[2] Unfortunately, these protocols usually require harsh acidic conditions that are unsuitable for sensitive substrates.

A recently investigated example of this transformation is the deprotection of β -hydroxy ketal **1**^[3] to give the corresponding highly acid-labile β -hydroxy ketone **2** (Table 1).^[4] A variety of Brønsted and Lewis acids were ineffective and provided almost exclusively the α,β -unsaturated ketone **3**.

[*] Prof. Dr. I. E. Markó, A. Ates, Dr. A. Gautier, B. Leroy, J.-M. Plancher, Dr. Y. Quesnel, J.-C. Vanherck
Université catholique de Louvain, Département de Chimie
Laboratoire de Chimie Organique
Batiment Lavoisier, Place Louis Pasteur 1
B-1348 Louvain-la-Neuve (Belgium)
Fax: (+32) 10-472788
E-mail: marko@chor.ucl.ac.be.

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Table 1. Catalytic deprotection of ketal **1** with CAN.



Entry	Conditions	Yield [%] ^[a]	Ratio 2:3 ^[b]
1	3 mol % CAN/1.5 equiv NaBrO ₃ MeCN/H ₂ O (1/1), 60 °C	91	100:0
2	3 mol % CAN/borate–HCl buffer (pH 8) MeCN/H ₂ O (1/1), 60 °C	93	100:0

[a] Yields of pure, isolated compounds. [b] The ratios were measured by NMR spectroscopy, both on the crude reaction product and on the purified material.

During these studies, we discovered that cerium ammonium nitrate (CAN, 2.5 equiv) afforded the desired aldol product **2**, though in a modest yield of 53 %.^[5] However, this procedure suffered from serious drawbacks. First, acid-catalyzed epimerization occurred when sensitive substrates were subjected to the deprotection reaction. Second, the large quantities of CAN required for this transformation (2.5 equiv) precluded its application to large scale transformations.

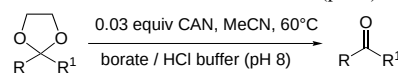
Inspired by reports of the oxidation of a range of functional groups with catalytic amounts of CAN in conjunction with stoichiometric quantities of inexpensive oxidants,^[6] we attempted deprotection of ketal **1** with 3 mol % of CAN and 1.5 equivalents of NaBrO₃.^[7] Gratifyingly, the reaction proceeded smoothly and afforded ketone **2** as the sole product in a much improved yield of 91 % yield (Table 1, entry 1). To our surprise, the diol by-product could also be isolated from the reaction mixture, and this implied that CAN did not act as an oxidant. This unexpected observation prompted us to examine the deprotection of **1** in the absence of NaBrO₃. To safeguard our acid-labile product, the oxidant was replaced with a mildly basic aqueous buffer solution. Remarkably, catalytic amounts of CAN (3 mol %) in the presence of a borate–HCl buffer (pH 8) and without any added cooxidant transformed **1** into **2** in excellent yield (Table 1, entry 2).

To the best of our knowledge, this is the first report that a simple cyclic ketal could be efficiently removed under neutral or mildly basic conditions with a catalytic amount of a Lewis acid. This novel protocol was applied to a range of acetals and ketals (Table 2).

A variety of cyclic acetals and ketals can be removed efficiently and in high yield. Furthermore, the reaction even tolerates a range of functional groups, including unprotected secondary and tertiary alcohols, ketones, enones, and triisopropylsilyl (TIPS) ethers.^[8] It is noteworthy that aldehydes, formed by deprotection of acetals, are stable under these conditions and do not undergo oxidation to the corresponding carboxylic acids.^[9] In sharp contrast to the procedure with 2.5 equivalents of CAN,^[10] the conditions of this catalytic system are so mild that no epimerization occurs in the case of acid-labile substrates (Table 2, entry 8).

Other cyclic ketals **4–6** are also smoothly deprotected.^[11] The total inertness of the pinacol-derived ketal **7** under these reaction conditions suggests that the cerium catalyst is highly

Table 2. CAN-catalyzed deprotection reactions with 3 mol % CAN at 60 °C in a 1:1 MeCN/borate–HCl buffer solution (pH 8).



Entry	Substrate	Product	Yield [%] ^[a]	Time
1			95	30 min
2			92	25 min
3			91 ^[b]	45 min
4			95	48 h
5			99	1.5 h
6			86 ^[c]	1.5 h
7			95	2.5 h
8			96 ^[b]	20 min

[a] Yields of pure, isolated products. [b] The reaction was carried out in the presence of 1.5 equivalents of NaBrO₃. [c] Performed with 4 mol % CAN.

4	5	6	7
(97%; 15 min)	(96%; 25 min)	(95%; 20 min)	(0%; 300 min)

sensitive to steric hindrance in the ketal protecting group and/or in its immediate vicinity.^[12] This property is further demonstrated by the prolonged reaction time required for the deprotection of a decalone derivative (Table 2, entry 4).

To gain some insights into the mechanism of this novel catalytic reaction, the deprotection of **1** was monitored by cyclic voltammetry. The only cerium species that was detected throughout the deprotection reaction possesses the Ce^{IV} oxidation state. These experiments clearly confirm that, under our catalytic conditions, CAN acts as a highly selective and efficient Lewis acid that activates the acetal or ketal protect-

ing group towards hydrolysis but does not behave as a redox catalyst. Such behavior appears to be unique to CAN.^[13]

In summary, we have developed a highly efficient, catalytic protocol for the deprotection of acetals and ketals. This is the first time that such deprotections could be carried out under neutral to slightly basic conditions.

Experimental Section

Typical experimental procedure: Deprotection of 1,4-dioxadispiro-[4.0.5.3]tetradecan-7-one (Table 2, entry 6): Solid cerium ammonium nitrate (18 mg, 4 mol%) was added to a stirred solution of 1,4-dioxadispiro[4.0.5.3]tetradecan-7-one (237 mg, 1.13 mmol) in MeCN (3.5 mL) and borate–HCl buffer (Merck, pH 8, 3.5 mL). The faintly yellow solution was heated at 60 °C for 1.5 h. After cooling to room temperature, H₂O (10 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂ (2 × 15 mL). The combined organic extracts were dried over MgSO₄ and filtered, and the solvents were removed in vacuo. The crude product was further purified by column chromatography on silica gel with EtOAc/hexane (3/7; R_f = 0.58) as the eluant. Spiro[4.5]decane-1,6-dione was obtained as a colorless liquid (144 mg, 86 %). ¹H NMR (CDCl₃, 300 MHz): δ = 2.7 (m, 2H), 2.42 (dt, J = 14.1, 5.1 Hz, 1H), 2.31 (dt, J = 8, 1.7 Hz, 2H), 2.2 to 1.6 (m, 9H); ¹³C{¹H} NMR (CDCl₃, 75.5 MHz): δ = 18.9, 21.0, 26.6, 33.7, 35.9, 38.4, 39.7, 64.3, 207.9, 215.5; IR (film): ν̄ = 1734, 1700 cm⁻¹; MS (70 eV): m/z (%): 166 (92) [M⁺], 167 (100) [M⁺ + 1].

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- [10] With 2.5 equivalents of CAN, epimerization takes place, affording a near thermodynamic mixture of axial and equatorial product (60:40).
- [11] Deprotection of ketal **6** with 2.5 equivalents of CAN resulted in quantitative formation of *tert*-butylcyclohexanone. However, no 1,2-octanediol could be isolated in this experiment. In contrast, removal of the dioxolane protecting group with 3 mol % CAN in borate buffer

(pH 8) afforded not only the desired ketone (95 %) but also 1,2-octanediol (97 %); hence, a different mechanism operates in these two reactions.

- [12] Chemoselective deprotections can thus be realized by using dioxolane protecting groups with different steric demands.
- [13] Indeed, Ce(NO₃)₃, Ce(OTf)₄, and other lanthanide salts were inert under our reaction conditions.

Fluorescent Indicators for Imaging Nitric Oxide Production**

Hirotatsu Kojima, Yasuteru Urano, Kazuya Kikuchi, Tsunehiko Higuchi, Yasunobu Hirata, and Tetsuo Nagano*

Nitric oxide (NO) is a signal transmitter in vivo.^[1] However, many of the functions proposed for NO remain controversial owing to the lack of direct evidence. The use of NO-reactive fluorescent indicators which allow bioimaging of NO with high spatial and temporal resolution in conjunction with fluorescence microscopy should overcome this problem. A reaction that traps NO directly is essential for developing probes for NO, but NO itself shows low reactivity towards organic compounds. Further, a nitroso or nitro group will generally quench fluorescence when dyes react with NO to generate these functional groups. Therefore, few reactions are suitable for this purpose. Recently, fluorescent probes for NO, FNOCTs, were reported.^[2] They react with NO to yield nonfluorescent compounds that are reduced by biological compounds, such as ascorbic acid, to afford fluorescent derivatives. However, they have not yet been applied in biological experiments.

We have developed diaminofluoresceins (DAFs), such as DAF-2 (Scheme 1), as fluorescent indicators for NO.^[3, 4] The DAFs react not with NO itself but with NO⁺ equivalents, such as nitric anhydride (N₂O₃), which are formed by autoxidation of NO. Under aerobic conditions, DAFs can trap NO to yield highly fluorescent triazolo fluoresceins (DAF-Ts) by nitrosation and dehydration. This mechanism is convenient because it does not interfere with signal transduction, but is

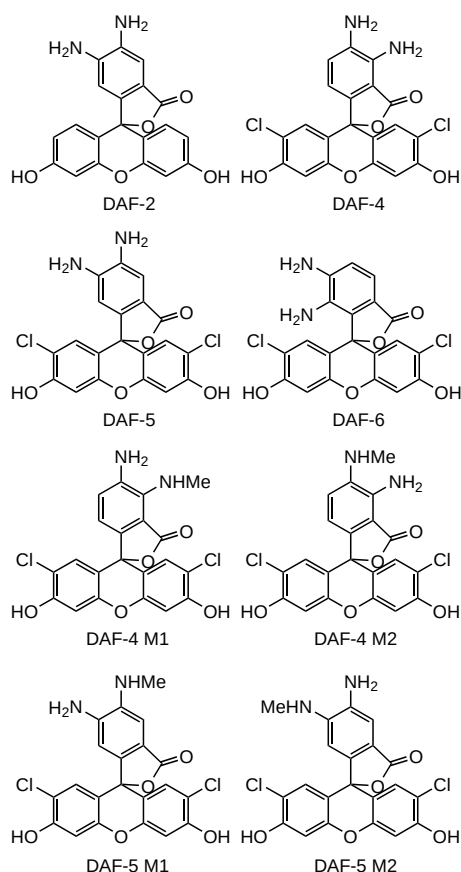
[*] Prof. T. Nagano, H. Kojima, Dr. Y. Urano, Dr. K. Kikuchi, Dr. T. Higuchi

Graduate School of Pharmaceutical Sciences
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5841-4855
E-mail: tlong@mol.f.u-tokyo.ac.jp

Dr. Y. Hirata
The Second Department of Internal Medicine, Faculty of Medicine
The University of Tokyo (Japan)

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



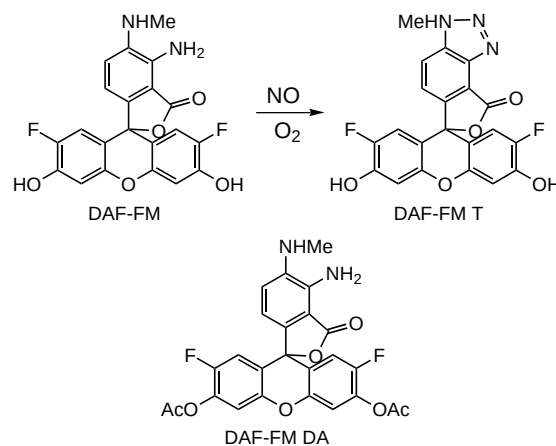
Scheme 1. Chemical structures of the fluorescent NO indicators. DAF-2 and DAF-4 were previously reported.^[3]

disadvantageous from the viewpoint of sensitivity. Under physiological conditions, DAF-Ts are not formed in the absence of NO, which is why DAFs can be used for direct detection of NO produced by cells. However, during the application of DAF-2 for NO imaging in vascular endothelial cells, we encountered the problem of pH dependency of the fluorescence intensity of DAF-Ts, which makes it difficult to monitor small changes in intracellular NO levels after a stimulus that shifts the intracellular pH level. For example, it was reported that stimulation with bradykinin lowers the pH value in vascular endothelial cells to 6.5.^[5] Since we had anticipated this problem, we synthesized dichloro derivatives of DAF (DAF-4, DAF-5, and DAF-6; Scheme 1).

The chlorine atoms lower the pK_a value of the adjacent phenolic OH group due to their electronegativity. However, they were unexpectedly less useful than DAF-2 owing to their unstable fluorescence intensity around neutral pH. The instability may arise from a triazole proton, so we introduced a methyl group (DAF-4 M1, DAF-4 M2, DAF-5 M1, and DAF-5 M2; Scheme 1). Derivatives of DAF-6 were not synthesized due to the low chemical yield and the low sensitivity of DAF-6 in comparison with DAF-1–DAF-5. The sensitivities of these new dyes to NO were determined by using the NO-releasing compound NONOate.^[6] After 1 h of incubation at 37 °C with NONOate (half-life: 13.7 min at 22 °C), the fluorescence intensity at the appropriate wavelengths of 10 μ M DAF-4, DAF-5, DAF-4 M1, DAF-4 M2, DAF-5 M1, and DAF-5 M2 increased by 380, 339, 75, 417, 195,

and 196 units, respectively. Thus, DAF-4 M2 was the most sensitive to NO. The fluorescence intensity of the triazole form of DAF-4 M2 was stable above pH 5.8.

It was reported that fluorinated fluorescein derivatives are more resistant to photobleaching than fluorescein and can be efficiently excited with the 488-nm spectral line of the argon-ion laser used in confocal laser scanning microscopes.^[7] Therefore, we prepared DAF-FM (Scheme 2), in which the



Scheme 2. Structures of fluorinated DAFs, and the synthesis of the triazole form DAF-FM T.

chlorine atoms of DAF-4 M2 are replaced by fluorine atoms. Photobleaching was examined in sunlight. The fluorescence intensity of the triazole form of DAF-FM (DAF-FM T) was reduced to 94, 63, and 28% of the initial intensity after 1, 2, and 3 h, respectively, while that of DAF-2 T decreased to 58, 11, and 1%, and that of DAF-4 T to 81, 45, and 20%.

The effect of pH on the fluorescence intensity of DAF-FM T was also examined. The pK_a value of the phenolic OH group of DAF-FM was 4.38 ± 0.05 . The fluorescence intensity was stable above pH 5.8 (Figure 1). The absorbance and

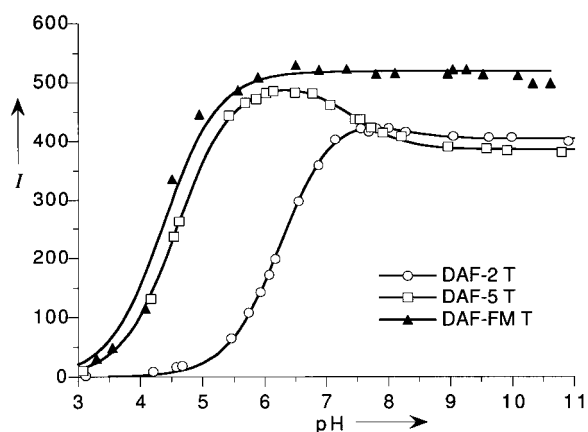


Figure 1. Effect of pH on the fluorescence intensity I of DAF-Ts. Triazole forms of DAF-2, DAF-5, and DAF-FM (1 μ M) were added to sodium phosphate solution adjusted to various pH values. The pH was measured after mixing. The fluorescence intensities of DAF-2T, DAF-5T, and DAF-FMT were determined at 515, 520, and 515 nm with excitation at 495, 505, and 495 nm, respectively. The curves were fitted to the following equations: DAF-2T: $I = 460/(1 + 10^{6.27-pH}) - 55.6/(1 + 10^{7.94-pH})$, $R = 1.00$; DAF-5T: $I = 505/(1 + 10^{4.59-pH}) - 119/(1 + 10^{7.41-pH})$, $R = 1.00$; DAF-FM T: $I = 518/(1 + 10^{4.38-pH})$, $R = 0.994$.

fluorescence properties of the DAFs are summarized in Table 1. As expected, the peak wavelengths of DAF-FM do not differ from those of DAF-2, unlike those of DAF-4. The augmentation of the fluorescence intensity of DAF-FM upon

Table 1. Absorbance and fluorescence properties of dyes.^[a]

Dye	Extinction coefficients [$\times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$], absorption maxima [nm]		Fluorescence maximum of triazole form [nm]	Relative quantum efficiencies	
	diamine	triazole		diamine	triazole
DAF-2	7.9, 486	7.3, 491	513	0.005	0.92
DAF-4	9.7, 501	9.2, 505	530	0.002	0.75
DAF-FM	8.4, 487	7.3, 495	515	0.005	0.81

[a] All data were obtained at 20 °C in 0.1 M sodium phosphate buffer (pH 7.4).

addition of NO is shown in Figure 2. Judging from NO standard curves calibrated with 7 μM DAF-FM, the detection limit of NO was 3 nM. The sensitivity of DAF-FM was 1.4 times higher than that of DAF-2. It is considered that this increase in sensitivity results from the higher rate of the reaction with NO^+ equivalents due to the electron-donating effect of the methyl group.

For the bioimaging of NO, we synthesized DAF-FM DA (Scheme 2), which permeates well into cells and is quickly transformed into water-soluble DAF-FM by esterases in the cytosol, where the dye can remain for a long time. The indicator DAF-FM DA was applied to the imaging of NO in

cultured bovine aortic endothelial cells by using a fluorescence microscope. The cells were incubated with 10 μM DAF-FM DA for 1 h at 37 °C for dye loading. The fluorescence images before and after stimulation of the cells with 0.1 μM bradykinin are shown in Figure 3. Line A in Figure 4 shows the corresponding data. After stimulation, the fluorescence

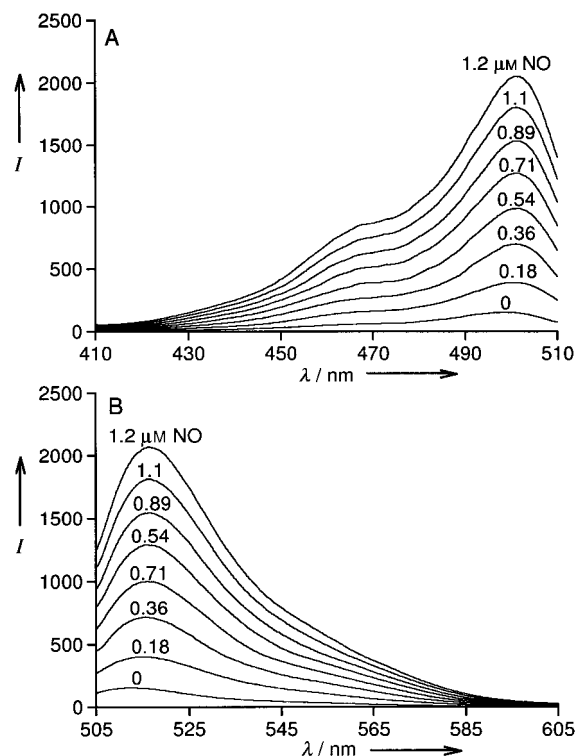


Figure 2. Excitation (A) and emission (B) spectra of DAF-FM at 37 °C in 0.1 M sodium phosphate buffer (pH 7.4) with NO concentrations ranging from 0 μM to 1.2 μM . A solution of NO was added to 7 μM DAF-FM solution under aerobic conditions. The spectra were obtained from an average of five repeated measurements 15 min after the addition of NO solution. A) Determined with emission at 515 nm. B) Determined with excitation at 500 nm.

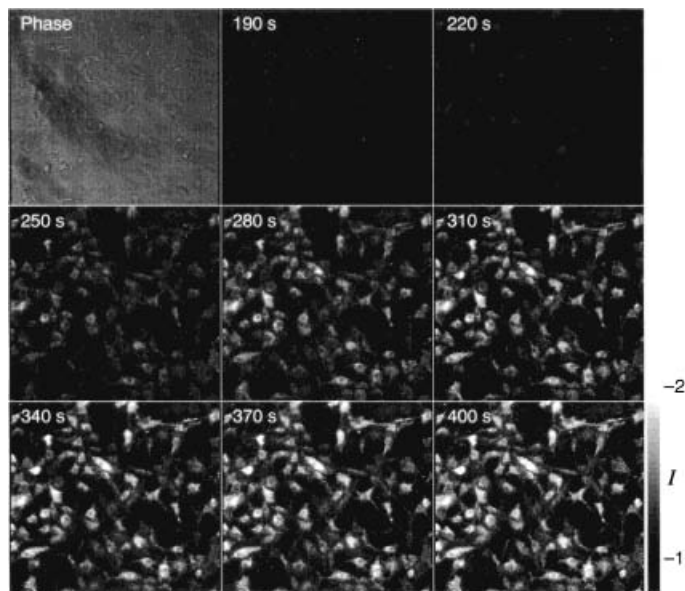


Figure 3. Bright-field and fluorescence images of cultured bovine aortic endothelial cells loaded with DAF-FM DA. Times from the start of measurement are shown. At 200 s, bradykinin (0.1 μM) was added. The fluorescence images are shown as ratio images on the basis of the initial intensity at the start of measurement and correspond to the fluorescence intensity data in Figure 4 (line A).

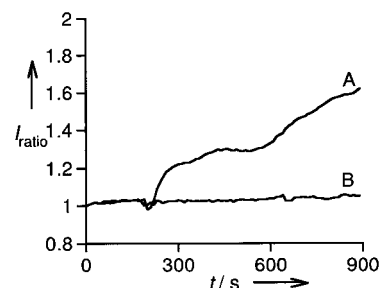


Figure 4. Fluorescence response of DAF-FM DA-loaded cultured bovine aortic endothelial cells, reflecting NO production in response to the addition of 0.1 μM bradykinin at 200 s. Fluorescence was measured at 10-s intervals. A) Ratio of fluorescence intensity I_{ratio} of the cells corresponding to Figure 3. B) Ratio of fluorescence intensity of the cells in the presence of the NO synthase inhibitor L-NAME (1 mM). The lines show mean values of the average fluorescence intensity in seven areas containing a cell.

intensity in the cells increased, and that in the cytosol increased more than that in the nucleus. Nitric oxide is believed to be produced in the cytosol, where NO synthase exists. This observation implies that little of the produced NO diffuses into the nucleus, or, if it does diffuse into the nucleus, little of it is oxidized there. Line B in Figure 4 shows the control data, for which the augmentation of the fluorescence intensity was suppressed by the NO synthase inhibitor L-nitroarginine methyl ester (L-NAME).

In conclusion, we suggest that DAF-FM is a useful tool for visualizing the temporal and spatial distribution of intracellular NO.

Experimental Section

The synthesis of the indicators is described in the Supporting Information. Fluorescence spectroscopy: The DAFs were dissolved in DMSO to obtain 10 mM stock solutions. Relative quantum efficiencies of fluorescence of DAFs and DAF-Ts were obtained by comparing the area under the corrected emission spectrum of the test sample upon excitation at 492 nm with that of a solution of fluorescein in 0.1 M sodium hydroxide, which has a quantum efficiency of 0.85.^[8] Bleaching of dyes (10 μ M) was determined in 0.1 M sodium phosphate buffer (pH 7.4). The solutions in 30-mL vials were placed in full sunlight on a fine day in November in Tokyo and were sampled every 1 h.

Imaging: Primary cultured endothelial cells from bovine aorta were passaged in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum and antibiotics. Cells between the 13th and 16th passages were used for these experiments. The cells were incubated for 1 h at 37 °C in PBS(+) (PBS = phosphate buffered saline) containing 10 μ M DAF-FM DA (0.2% DMSO) for loading, and washed with PBS(+). They were mounted on an inverted fluorescence microscope (Olympus IX70, Tokyo, Japan) equipped with an objective lens ($\times 20$), an excitation filter (490 nm), a dichroic mirror (505 nm), and a long-pass emission filter (515 nm). The air temperature was maintained at 37 °C with a warming box (IX-IBM, Olympus). Optical signals were recorded with an Argus 50 (Hamamatsu Photonics, Shizuoka, Japan), which is an imaging system including a cooled charge-coupled device (CCD) camera. Bradykinin and L-NAME were purchased from Sigma (St. Louis, MO, USA).

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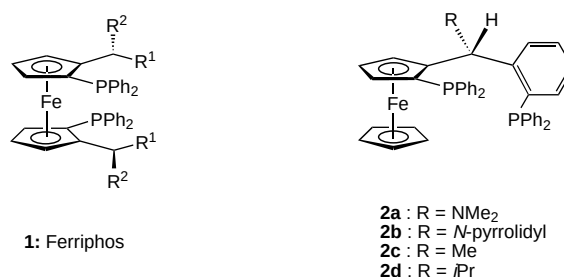
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Ferrocenyl Ligands with Two Phosphanyl Substituents in the α,ϵ positions for the Transition Metal Catalyzed Asymmetric Hydrogenation of Functionalized Double Bonds**

Tania Ireland, Gabriele Grossheimann, Catherine Wieser-Jeunesse, and Paul Knochel*

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

Chiral ferrocene ligands have found numerous useful applications in asymmetric catalysis.^[1] Recently, we described a new family of C_2 -symmetrical ferrocenyl ligands called Ferriphos **1**, which proved to be efficient catalysts for the hydrogenation of α -acetoamidoacrylic acid derivatives.^[2, 3] We have now discovered another class of chiral diphosphanylferrocenyl derivatives **2a–d** which are excellent ligands for the enantioselective hydrogenation of various functionalized double bonds and carbonyl groups. The relatively broad area

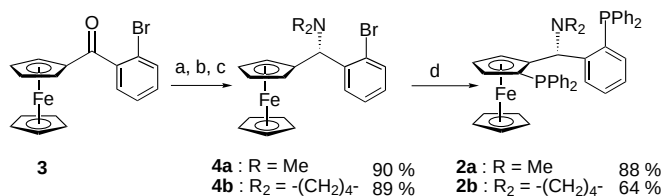


of application of this new class of α,ϵ -diphosphanes in asymmetric catalysis as well as their short synthesis makes these ligands especially attractive. The modular approach to their synthesis means that a variety of substituents R (alkyl or amino groups) can be introduced in the benzylic position. As shown later, the nature of R is crucial to the enantioselectivity observed with these ligands.

The ferrocenyl derivatives **2** are readily prepared in five steps starting from ferrocene (Scheme 1). Thus, a Friedel–Crafts acylation of ferrocene with 2-bromobenzoyl chloride furnishes the ferrocenyl ketone **3** in 80% yield. The Corey–Bakshi–Shibata (CBS) reduction^[4] of **3** affords the corresponding ferrocenyl alcohol in 95% yield and 96% *ee*. This

[*] Prof. Dr. P. Knochel, Dipl.-Chem. T. Ireland, Dr. G. Grossheimann, Dr. C. Wieser-Jeunesse
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
and
Institut für Organische Chemie der Universität
Butenandtstrasse 5–13, D-81377 München (Germany)
Fax: (+49)89-2180-7680
E-mail: Paul.Knochel@cup.uni-muenchen.de

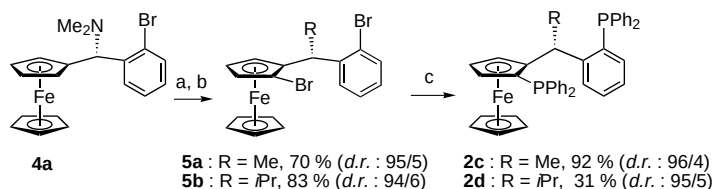
[**] We thank the DFG (SFB 260, Graduiertenkolleg, Leibniz-Programm) and the Fonds der Chemischen Industrie for financial support. We thank Dr. Klaus Harms for the crystal structure analysis as well as Degussa-Hüls AG and Chemetall GmbH for the generous donation of chemicals. C.W.-J. thanks the Alexander-von-Humboldt-Stiftung for a stipendium.



Scheme 1. a) CBS catalyst (0.3 equiv), BH₃-Me₂S, 0 °C, 2 h; b) Ac₂O, pyridine, 12 h; c) HNR₂, CH₃CN, H₂O, 12 h; d) *t*BuLi (3.5 equiv), -78 °C to room temperature (RT), 1 h; then ClPPh₂ (2.5 equiv), -78 °C to RT, 1 h.

alcohol is obtained almost enantiomerically pure (99.5 % *ee*) after recrystallization from heptane. Acylation of the alcohol gives the intermediate acetate in a quantitative yield, which is converted into the corresponding amino derivatives **4a** and **4b** by treatment with dimethylamine or pyrrolidine, respectively. These are then converted into **2b** and **2c**, respectively, in approximately 97 % *ee* by the reaction with *t*BuLi followed by the addition of ClPPh₂.

Finally, **4a** was dilithiated with *t*BuLi and converted into the corresponding dibromide by reaction with Cl₄Br₂C₂ (80 % yield, 97.5 % *ee*; Scheme 2), which can then be directly substituted with various organozinc reagents (Me₂Zn and



Scheme 2. a) *t*BuLi (3.5 equiv), -78 °C to RT, 1 h; then Cl₄Br₂C₂ (2.2 equiv), -78 °C to RT, 1 h, 80 % yield, 97.5 % *ee*; b) CH₃COCl (2 equiv), R₂Zn (4 equiv), THF, -78 °C to RT, 12 h; c) *n*BuLi (2.2 equiv), -78 °C, 15 min, then ClPPh₂ (2.3 equiv), -78 °C to RT, 1 h.

*i*Pr₂Zn) using acetyl chloride as a promotor. This process leads to the substitution products **5a** and **5b** with high retention of configuration (*d.r.* > 94:6). The diphosphanes **2c** and **2d** were obtained in 92 and 31 % yield, respectively, after exchange of the bromine atoms with lithium and reaction with ClPPh₂.

Remarkably, the ligands **2a–d** are highly efficient for the asymmetric hydrogenation of various β -ketoesters of type **6** (Table 1).^[5, 6] The hydrogenation reactions were performed using the standard conditions of [Ru(cod)(C₄H₇)₂]/HBr^[7] (0.5 mol %; cod = cycloocta-1,5-diene, C₄H₇ = 2-methylallyl) and ligands **2a–d** (0.5 mol %) in EtOH at 50 °C and under H₂ (50 bar).

The same configuration for the hydrogenated products **7** are obtained using the ligands **2a**, **2b**, and **2d**, while the β -hydroxyesters having the opposite configuration (*ent*-**7**) result from the use of **2c** (R = Me) (92–96 % *ee*; entries 4, 6, and 9 in Table 1).

The hydrogenation can be applied successfully to cyclic ketoesters such as ethyl 2-oxocyclopentane carboxylate^[8] to give (1*R*,2*R*)-ethyl 2-hydroxy-1-cyclopentane carboxylate (**8**) with 98 % *de* and 90.9 % *ee* after complete conversion ("Ru"/**2a** (0.5 mol %), H₂ (50 bar), CH₂Cl₂/EtOH 1/10, 50 °C, 65 h). The enantiomeric product (1*S*,2*S*)-*ent*-**8** is obtained with 90.5 % *de* and 91.6 % *ee* from **2c** ("Ru"/**2c** (0.5 mol %),

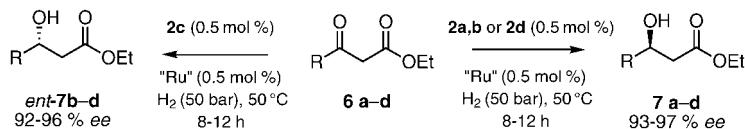


Table 1. Enantioselective hydrogenation of β -ketoesters with the "Ru"^[a] chiral ligand catalytic system.

Entry	Substrate	R	Ligand	Product	% <i>ee</i> ^[b]
1	6a	Me	2a	7a	95.5 (93.2) ^[c]
2	6a	Me	2d	7a	95.9
3	6b	<i>n</i> Pr	2a	7b	96.5
4	6b	<i>n</i> Pr	2c	<i>ent</i> - 7b	92.7
5	6c	<i>i</i> Pr	2a	7c	95.9
6	6c	<i>i</i> Pr	2c	<i>ent</i> - 7c	96.5
7	6d	Ph	2a	7d	95.0
8	6d	Ph	2d	7d	96.0
9	6d	Ph	2c	<i>ent</i> - 7d	93.7

[a] [Ru(cod)(C₄H₇)₂]/HBr; [b] Determined by GC on a chiral phase (Chirasil-L-Val) or by HPLC on a chiral phase (Daicel Chiralcel OD, OJ, or AD columns). The absolute stereochemistry was established by comparison with the literature. [c] Reaction performed with a substrate to catalyst ratio of 5000 to 1.

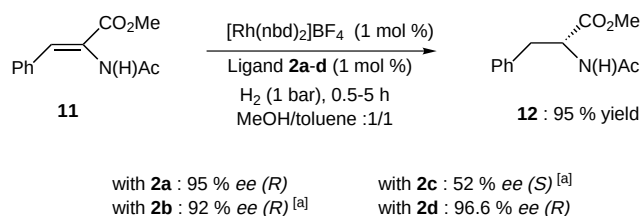
Table 2. Enantioselective hydrogenation of various β -dicarbonyl compounds.

Entry	Product	Ligand	<i>de</i> (%) ^[a]	<i>ee</i> (%) ^[a,b]
1		2a	98.2	90.9 (1 <i>R</i> ,2 <i>R</i>)
2	<i>ent</i> - 8	2c	90.5	91.6 (1 <i>S</i> ,2 <i>S</i>)
3		2a	98.0	98.2 (1 <i>S</i> ,3 <i>S</i>)
4	<i>ent</i> - 9	2c	98.8	98.8 (1 <i>R</i> ,3 <i>R</i>)
5		2a	97.2	98.4 (1 <i>S</i> ,3 <i>R</i>)
6	<i>ent</i> - 10	2c	99.4	91.8 (1 <i>R</i> ,3 <i>S</i>)

[a] Determined after complete conversion. [b] See Table 1.

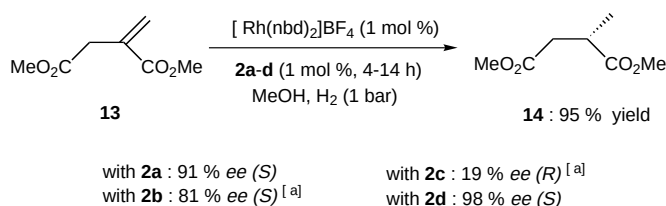
H₂ (50 bar), EtOH, 25 °C, 21 h; Table 2). Dibenzoylmethane undergoes a double reduction using **2a** ("Ru"/**2a**, H₂ (50 bar), EtOH, 50 °C, 10 h) to produce the C₂-symmetrical 1,3-diol (*S,S*)-**9** with 98.2 % *ee*. The opposite enantiomer (*R,R*)-*ent*-**9** can be obtained in 98.8 % *ee* using **2c** with the same reaction conditions. Unsymmetrical β -diketones such as 1-phenyl-1,3-butanedione^[9] is diastereoselectively reduced to (1*S*,3*R*)-1-phenyl-1,3-butanediol **10** with 98.4 % *ee* using **2a** and (1*R*,3*S*)-1-phenyl-1,3-butanediol (*ent*-**10**) in 91.8 % *ee* using **2c** ("Ru"/**2a** or **c**, H₂ (50 atm), EtOH, 50 °C, 10 h). Thus excellent enantioselectivities are obtained with a broad range of β -dicarbonyl compounds.^[11]

We also found in preliminary experiments that (*Z*)- α -methylacetamido cinnamate (**11**) is smoothly hydrogenated^[5, 10] in the presence of 1 mol % of catalyst (H₂ (1–5 bar), RT, 0.5–5 h) to give the amino acid derivative **12** with enantioselectivities up to 96.6 % (Scheme 3).^[12] Interestingly,



Scheme 3. Enantioselective reduction of methyl α -acetamido cinnamates (**11**) to the amino acid derivatives **12**. [a] Reaction performed under H_2 (5 bar).

the ligand **2d** also gives the best results for the hydrogenation of dimethyl itaconate (**13**)^[5, 10] (H_2 (1 bar), MeOH, 14 h; > 95 %; 98 % *ee*; Scheme 4).



Scheme 4. Enantioselective reduction of dimethyl itaconate (**13**). [a] Reaction performed in MeOH/toluene (1/1).

The complex $[Rh(nbd)2a]BF_4$ (**15**, nbd = norbornadiene) was isolated and characterized by X-Ray crystallography (Figure 1).^[13] Remarkably, the ligand **2a** acts as a tridentate ligand and forms two six-membered metallocycles with an unusual pentacoordinated Rh^I atom. The coordination of the amino group seems not to be important to the catalytic hydrogenation since the ligand **2d** (R = *i*Pr) gives similar enantioselectivities.

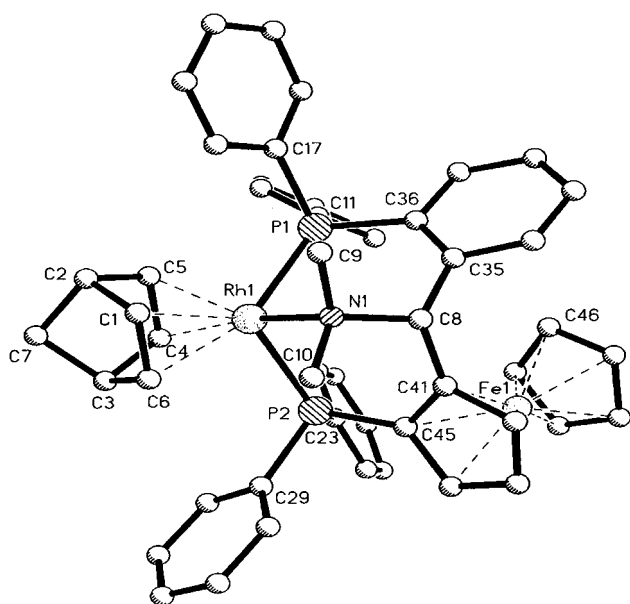


Figure 1. Structure of the complex cation $[Rh(nbd)(2a)]^+$ in the crystal (the hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Rh-P1 2.337(1), Rh-P2 2.433(1), Rh-N1 2.233(4); P1-Rh-P2 107.53(4), N1-Rh-P1 86.86(10), N1-Rh-P2 91.65(9).

It is interesting to note the difference in the enantioselectivity observed in the hydrogenation reactions using **2c**. In an attempt to explain these results, the complexes formed between $[Rh(nbd)_2]BF_4$ and **2a–d** were isolated. All these complexes are monomers according to FAB measurements although the ^{31}P NMR spectrum of the $[Rh(nbd)2c]BF_4$ complex shows a smaller Rh,P coupling constant than the other three complexes.^[14] It seems that the presence of the α -benzylic methyl group induces a particular space arrangement of the chelating diphosphanes.

In summary, we have developed a new family of ferrocenyl ligands (**2**) with two phosphane substituents. These ligands gave good to excellent enantioselectivities in the reduction of various functionalized double bonds and β -dicarbonyl compounds. Interestingly, the two opposite configurations of the reduced products can be obtained just by modifying the substituent R in the benzylic position. Further ligand modifications and applications in asymmetric catalysis are currently underway.

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- However, preliminary experiments show that 2-substituted β -dicarbonyl compounds give moderate diastereoselectivities but also excellent enantioselectivities under our conditions. Hydrogenation of ethyl 2-methyl-3-oxo-butylate with ligand **2a** affords ethyl 3-hydroxy-2-methyl-butylate with 40% *de*, 91.4% *ee* (2*R*,3*S*), and 86.0% *ee* (2*S*,3*S*).
- Enantiomeric excesses were determined by GC or HPLC on a chiral phase (Chirasil-L-Val, and Diacel Chiralcel columns OD, OJ, AD).

- [13] Crystal data for **15**: $M_r = 1001.44$, monoclinic, space group $P2_1$, $a = 1073.7(1)$, $b = 2317.0(2)$, $c = 1756.3(1)$ Å, $\beta = 97.03(1)^\circ$, $V = 4336.4(6)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.534$ Mg m⁻³, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å), $\mu = 0.847$ mm⁻¹. Data were collected on a STOE IPDS system at 193 K. The structure was solved by direct methods and refined on F_o^2 by full-matrix least-squares methods (SHELXS-97, SHELXL-97, SHELDRICK, 1997). All non-hydrogen atoms were refined anisotropically. $\omega R2 = 0.0893$ (all unique data), $R1 = 0.0367$ for data with $I > 2\sigma(I)$. 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-134965. 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).
- [14] Selected ³¹P NMR data (81 MHz, CDCl₃) of the phosphane ligands **2** and their complexes with Rh^I: **2a**: $\delta = -16.7$ (d, $J_{\text{PP}} = 19.1$ Hz), -23.2 (d, $J_{\text{PP}} = 19.1$ Hz); [Rh(nbd)(**2a**)]BF₄: $\delta = 23.1$ (dd, $J_{\text{PP}} = 22.0$, $J_{\text{PRh}} = 129.7$ Hz), 8.6 (dd, $J_{\text{PP}} = 22.0$, $J_{\text{PRh}} = 117.6$ Hz); **2b**: $\delta = -17.1$ (d, $J_{\text{PP}} = 20.3$ Hz), -22.4 (d, $J_{\text{PP}} = 20.3$ Hz); [Rh(nbd)(**2b**)]BF₄: $\delta = 24.4$ (dd, $J_{\text{PP}} = 30.5$, $J_{\text{PRh}} = 155.1$ Hz), 5.1 (dd, $J_{\text{PP}} = 30.5$, $J_{\text{PRh}} = 153.2$ Hz); **2c**: $\delta = -12.9$ (d, $J_{\text{PP}} = 18.4$ Hz), -22.4 (d, $J_{\text{PP}} = 18.4$ Hz); [Rh(nbd)(**2c**)]BF₄: $\delta = 17.9$ (dd, $J_{\text{PP}} = 23.5$, $J_{\text{PRh}} = 101.9$ Hz), 16.0 (dd, $J_{\text{PP}} = 23.5$, $J_{\text{PRh}} = 101.9$ Hz); **2d**: $\delta = -17.8$ (d, $J_{\text{PP}} = 26.7$ Hz), -22.8 (d, $J_{\text{PP}} = 26.7$ Hz); [Rh(nbd)(**2d**)]BF₄: $\delta = 24.8$ (dd, $J_{\text{PP}} = 31.1$, $J_{\text{PRh}} = 155.1$ Hz), 12.3 (dd, $J_{\text{PP}} = 31.1$, $J_{\text{PRh}} = 155.1$ Hz).

Dendritic Iron Porphyrins with Tethered Axial Ligands: New Model Compounds for Cytochromes**

Philipp Weyermann, Jean-Paul Gisselbrecht, Corinne Boudon, François Diederich,* and Maurice Gross

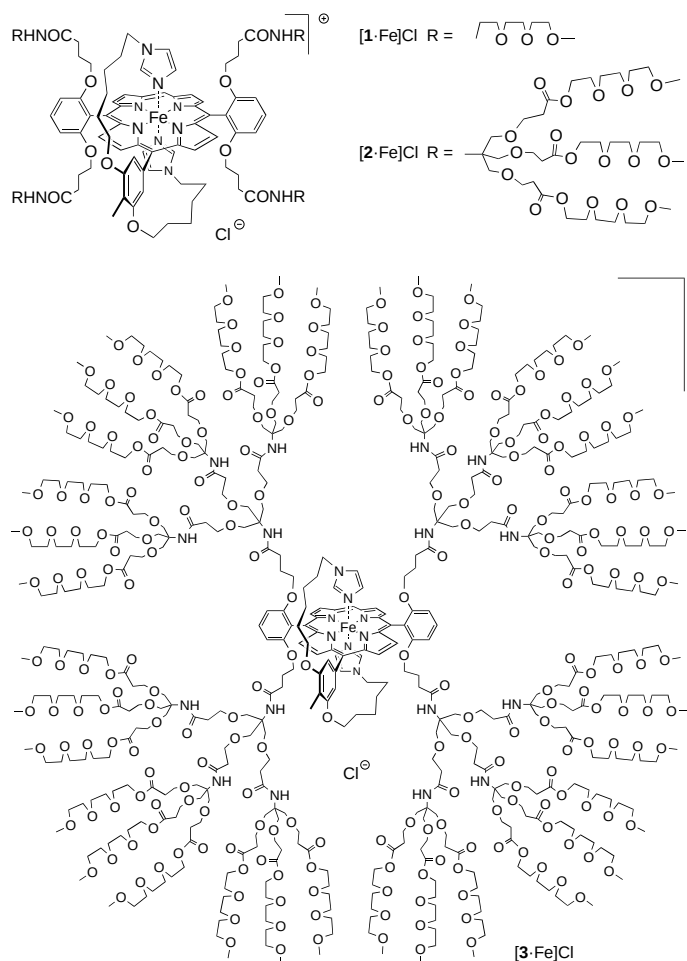
Dedicated to Professor Jean-Marie Lehn
on the occasion of his 60th birthday

The most intriguing characteristics of the cytochrome family of electron transfer proteins is the very broad range of redox potentials featured by the Fe^{III}/Fe^{II} couple at the electroactive heme core.^[1] A variety of model studies have identified a dependency of this potential from the nature of substituents at the porphyrin ring,^[2] axial ligation to the iron center,^[3] hydrogen bonding to the axial ligands,^[4] and ruffling of the porphyrin macrocycle.^[5] In contrast, the influence of environmental effects such as heme solvation,^[6] polarity of the heme microenvironment,^[7] and the nature of the surrounding

protein shell^[8] have not been intensively investigated using model compounds and are less well understood.

We have already reported the use of dendritic iron porphyrins^[9, 10] as model compounds for cytochromes in which the protein shell around the buried electroactive core is mimicked by the dendritic superstructure. These investigations revealed a strong correlation between the redox potential and the degree of dendritic branching. In these early systems, however, the nature of the axial ligation to the iron center, which is known to have a very strong influence on the redox properties^[3] was not controlled. Therefore, the observed shifts in redox potential caused by the dendritic shell could not be quantified independently from axial ligation effects and no general conclusions concerning the effects of the dendritic superstructure could be drawn.

We now present a new series of dendritic cytochrome mimics, which contain a defined and stable axial ligation pattern. This allows, for the first time, a quantitative evaluation of the effect of an insulating dendritic shell on the redox properties of the embedded iron porphyrin core. The three novel dendrimers of generation zero ([**1**·Fe]Cl), one ([**2**·Fe]Cl), and two ([**3**·Fe]Cl) feature controlled axial ligation at the iron center by two imidazoles tethered to the porphyrin core. This stable ligation pattern, which is kinetically inert towards coordinating solvents, is found in the cytochrome b₅ family of electron transfer proteins.^[11] The optimal length of the alkyl tethers between the iron-coordi-



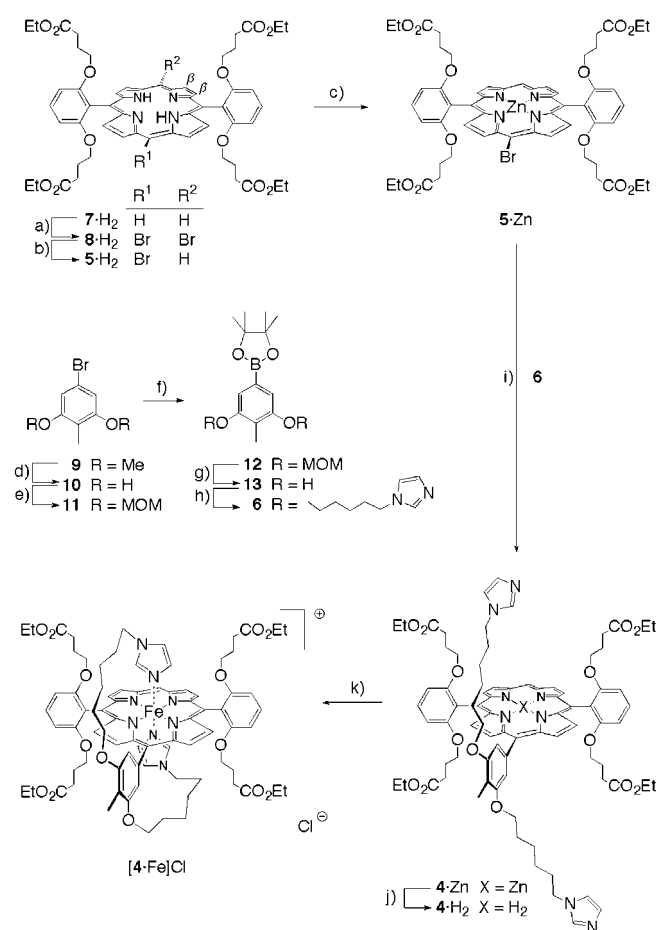
[*] Prof. Dr. F. Diederich, Dipl.-Chem. P. Weyermann
Laboratorium für Organische Chemie, ETH-Zentrum
Universitätstrasse 16, CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-1109
E-mail: diederich@org.chem.ethz.ch

Dr. J. P. Gisselbrecht, Dr. C. Boudon, Prof. Dr. M. Gross
Laboratoire d'Electrochimie et de Chimie Physique du Corps Solide
Faculte de Chimie, Universite Louis Pasteur and CNRS, UMR
no. 7512
4, rue Blaise Pascal, F-67000 Strasbourg (France)

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nating imidazoles and the phenyl ring at the porphyrin core was designed with the help of molecular modeling.^[12] The second-generation compound [**3**·Fe]Cl (11 719 Da) is comparable in mass to typical single-heme cytochromes such as cytochrome c (tuna, 11 384 Da),^[13] or cytochrome b₅ (bovine, 15 198 Da).^[11] With their triethyleneglycol monomethyl ether surface groups, the three dendritic mimics are soluble in solvents of widely differing polarity.

The key intermediate in the synthesis of the dendritic porphyrins was the bis-imidazole-appended zinc porphyrin **4**·Zn, which was obtained in high yield by a Suzuki coupling between the brominated zinc porphyrin **5**·Zn and the bis-imidazole-appended phenylboronic ester **6** (Scheme 1). The *meso*-bromoporphyrin **5**·Zn was obtained from precursor **7**·H₂^[9c] by dibromination with *N*-bromosuccinimide (NBS) to



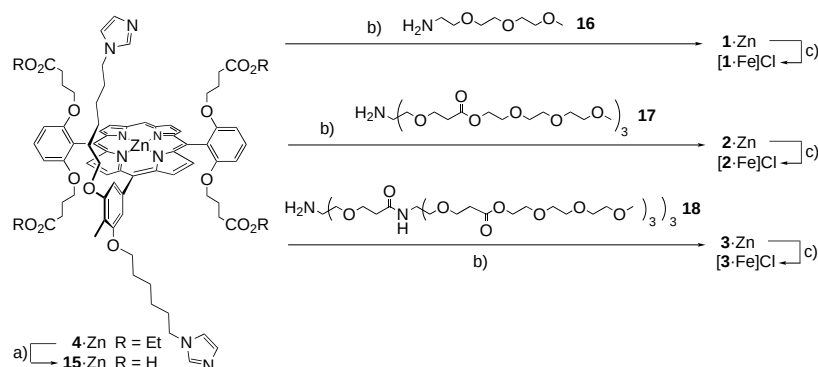
Scheme 1. Synthesis of the bis-imidazole-ligated Fe^{III} porphyrin core [**4**·Fe]Cl. a) NBS (2.0 equiv), CHCl₃, RT, 30 min, 91%; b) *n*Bu₃SnH (1.5 equiv), AIBN (0.1 equiv), PhH, reflux, 4 h, 45%; c) Zn(OAc)₂ (10.0 equiv), CHCl₃/MeOH, RT, 4 h, 98%; d) conc. HI (excess), AcOH, reflux, 6 h, 95%; e) MOM-Cl (4.0 equiv), K₂CO₃ (8.0 equiv), MeCN, 0 °C, 30 min, 98%; f) *n*BuLi (1.6 equiv), TMEDA (1.6 equiv), THF, −78 °C, 60 min, then B(OMe)₃ (5.0 equiv), RT, 2 h, then pinacol (10.0 equiv), PhH, reflux, 12 h, 96%; g) conc. HCl (excess), THF/MeOH, RT, 3 d, 66%; h) **14** (5.0 equiv), Cs₂CO₃ (10.0 equiv), DMF, RT, 4 h, 49%; i) **6** (2.0 equiv), [Pd(PPh₃)₄] (0.1 equiv), Cs₂CO₃ (8.0 equiv), PhMe, 90 °C, 4 h, 82%; j) CF₃COOH (excess), CHCl₃, 0 °C, 5 min, 78%; k) FeCl₂ (10.0 equiv), 2,6-lutidine (10.0 equiv), THF, reflux, 2 h, then 1% HCl in CHCl₃ (excess), RT, 5 min, then “proton sponge” (excess), THF, RT, 15 min, 66%. AIBN = *azobisisobutyronitrile*; MOM = methoxymethyl; TMEDA = *N,N,N',N'*-tetramethylethylenediamine; DMF = *N,N*-dimethylformamide; “proton sponge” = 1,8-bis(dimethylamino)naphthalene.

give *meso*-dibromoporphyrin **8**·H₂, partial reduction with *n*Bu₃SnH to give monobromoporphyrin **5**·H₂, and metalation. Phenylboronic ester **6** was prepared from 4-bromo-2,6-dimethoxytoluene **9**^[14] by cleavage of the methyl ethers (conc. HI; →**10**) re protection of the phenolic hydroxy groups with chloromethyl methyl ether (MOM-Cl; →**11**), metalation (*n*BuLi) and boronic ester formation (B(OMe)₃), then pinacol; →**12**), cleavage of the MOM protecting groups (HCl; →**13**), and alkylation with 1-(6-bromohexyl)imidazole (**14**).^[15] The Fe^{III} complex [**4**·Fe]Cl was obtained from **4**·Zn by acid-induced demetallation (→**4**·H₂) and subsequent insertion of Fe^{II} (FeCl₂), followed by air oxidation.

Comparison of the Fe^{III} complex [**4**·Fe]Cl with the six-coordinate Fe^{III} complex [**7**·Fe(*N*-MeIm)₂]Cl^[16] (*N*-MeIm = 1-methylimidazole) unambiguously showed complete intramolecular axial coordination of the two tethered imidazoles under formation of a paramagnetic low-spin complex. The UV/Vis^[17] and EPR spectra^[18] as well as the magnetic moments,^[19] determined by the Evans–Scheffold method^[20] of both compounds compared very well with those of other bis-imidazole-coordinated Fe^{III} porphyrins. Reduction of [**4**·Fe]Cl, similar to that of [**7**·Fe(*N*-MeIm)₂]Cl, with Na₂S₂O₄ produced a diamagnetic low-spin complex with a hemochrome absorption spectrum which was readily identified as that of a six-coordinate Fe^{II} species.^[21]

For the preparation of the dendritic porphyrins of generation zero (**1**·Zn), one (**2**·Zn), and two (**3**·Zn), the core tetraacid **15**·Zn, obtained by hydrolysis of **4**·Zn, was coupled to the corresponding dendritic wedges **16**–**18**,^[22] respectively, using HATU as coupling reagent (Scheme 2). They were purified by preparative gel permeation chromatography (GPC, Biorad Biobeads SX-1, CH₂Cl₂) and fully characterized by standard spectroscopic methods (Table 1). In the Zn^{II} porphyrin derivatives, one imidazole is complexed to the metal ion forming a dynamic five-coordinate species. Demetallation to the highly air- and light-sensitive free-base porphyrins and iron insertion finally yielded the target compounds [**1**·Fe]Cl, [**2**·Fe]Cl, and [**3**·Fe]Cl which were purified by GPC (Biorad Biobeads SX-3, CH₂Cl₂) and shown by MALDI-TOF mass spectrometry to be free of any structural defects. According to UV/Vis and EPR spectroscopy, they are six-coordinate low-spin complexes with double axial imidazole ligation (Table 1). Reduction with Na₂S₂O₄ in various solvents led instantaneously to typical low-spin Fe^{II} porphyrin absorption spectra, regardless of the size of the dendrimer.

The redox properties of [**1**·Fe]Cl–[**3**·Fe]Cl were first investigated in the rather nonpolar solvent CH₂Cl₂ using cyclic (CV) and steady-state voltammetry (SSV). All three compounds showed a reversible one-electron reduction step (Figure 1) which was clearly assigned to the Fe^{III}/Fe^{II} couple by spectroelectrochemical methods: the UV/Vis spectra of the electrochemically reduced species were identical to those obtained by chemical reduction, and well defined isosbestic points evolved during controlled potential electrolysis. The generation zero complex [**1**·Fe]Cl exhibited a redox potential of −0.21 V (vs. SCE; Table 2). This is in the expected range for a bis-imidazole-ligated iron porphyrin complex.^[23] In the higher generation compounds [**2**·Fe]Cl (+0.08 V) and



Scheme 2. Synthesis of the dendritic cytochrome mimics [1·Fe]Cl–[3·Fe]Cl. a) NaOH (excess), dioxane/H₂O, RT, 3 d; b) **16**, **17**, or **18** (12.0 equiv), HATU (6.0 equiv), Et₃N (24.0 equiv), DMF, 0°C, 24 h, 85% (**1·Zn**); 3 d, 65% (**2·Zn**); 7 d, 42% (**3·Zn**); all yields starting from **4·Zn**; c) TFA (excess), CHCl₃, 0°C, 5 min, then FeCl₂ (10.0 equiv), 2,6-lutidine (10.0 equiv), THF, reflux, 4 h, then 1% HCl in CHCl₃ (excess), RT, 5 min, then “proton sponge” (excess), THF, RT, 15 min, 68% ([**1·Fe**]Cl); 73% ([**2·Fe**]Cl); 78% ([**3·Fe**]Cl). HATU = O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

Table 1. Selected physical and spectroscopic data of **3·Zn** and [**3·Fe**]Cl.^[a]

3·Zn: Viscous purple oil. *R*_f = 0.48 (SiO₂, CH₂Cl₂/MeOH 90:10); UV/Vis (CHCl₃): λ_{max}(ε) = 595 (5100), 559 (20700), 520 (4200), 427 (544900), 408 (sh, 63600), 311 nm (22500); IR (CHCl₃): ν̄ = 2880m, 1735s, 1670m, 1580w, 1520m, 1460m, 1380w, 1355w, 1325w, 1245m, 1185s, 1110s, 1030w, 990w, 950w, 855m, 810w, 620w cm^{−1}; ¹H NMR (500 MHz, [D₅]pyridine, 300 K): δ = 10.20 (s, 1H), 9.47 (d, *J* = 4.0 Hz, 2H), 9.28–9.32 (m, 4H), 9.23 (d, *J* = 4.0 Hz, 2H), 8.05 (br. s, 2H), 8.02 (t, *J* = 7.9 Hz, 2H), 7.52 (s, 2H), 7.49 (d, *J* = 7.9 Hz, 4H), 7.40 (br. s, 2H), 7.31 (br. s, 2H), 6.30 (br. s, 16H), 4.48–4.52 (m, 4H), 4.41–4.45 (m, 4H), 4.32–4.40 (m, 72H), 4.10–4.22 (m, 8H), 3.47–4.05 (m, 576H), 3.29 (s, 108H), 2.69 (t, *J* = 6.2 Hz, 72H), 2.67 (s, 3H), 1.55–1.73 (m, 24H), 1.42–1.54 (m, 4H), 1.21–1.32 (m, 4H); ¹³C NMR (125 MHz, [D₅]pyridine, 300 K): δ = 172.4, 171.7, 171.4, 160.6, 155.9, 151.3, 151.2, 150.3, 150.2, 142.8, 136.7, 132.0, 132.0, 131.9, 131.4, 130.7, 128.3, 122.1, 120.6, 120.3, 113.2, 113.1, 113.0, 106.2, 105.3, 72.3, 70.8, 70.8, 70.7, 69.7, 69.7, 69.3, 68.7, 68.4, 68.2, 67.3, 64.0, 60.6, 60.6, 58.7, 47.4, 37.3, 35.2, 32.1, 31.1, 29.4, 26.4, 25.9, 24.9, 9.2; MALDI-TOF-MS (2-(4'-hydroxyphenylazo)benzoic acid): *m/z* (%): 11750.8 (100, [*M* + Na]⁺, calcd for C₅₃₃H₉₁₈N₂₄O₂₅₀Zn·Na⁺: 11750.9),^[b] 11729.5 (37, *M*⁺, calcd for C₅₃₃H₉₁₈N₂₄O₂₅₀Zn⁺: 11727.9).^[b]

[**3·Fe**]Cl: Viscous brown oil. *R*_f = 0.32 (SiO₂, CH₂Cl₂/MeOH 90:10); UV/Vis (CHCl₃): λ_{max}(ε) = 543 (10200), 415 (128000), 313 nm (25400); IR (CHCl₃): ν̄ = 2915s, 2880s, 1735s, 1670m, 1580w, 1515m, 1460m, 1380w, 1350w, 1320w, 1240m, 1185s, 1110s, 1030w, 995w, 950w, 850w, 620w cm^{−1}; EPR (X-Band, CHCl₃, 77 K): *g*_x = 1.558, *g*_y = 2.321, *g*_z = 2.890; MALDI-TOF-MS (2-(4'-hydroxyphenylazo)benzoic acid): *m/z* (%): 11719.2 (100, [*M* − Cl]⁺, calcd for C₅₃₃H₉₁₈N₂₄O₂₅₀Fe⁺: 11718.9).^[b]

[a] All new compounds were fully characterized by ¹H and ¹³C NMR (except Fe complexes), IR, UV/Vis and FAB or MALDI-TOF mass spectra as well as by elemental analysis or high-resolution mass spectra. For all Fe complexes, EPR spectra were recorded and in some cases magnetic moments were calculated by the method of Evans and Scheffold. [b] Calculated highest peak in the isotope pattern.

[**3·Fe**]Cl (+0.10 V), the Fe^{III} → Fe^{II} reduction becomes greatly facilitated, with the largest change in potential occurring between generation zero and one.

CV measurements in MeCN, a solvent of intermediate polarity, showed a similar trend: upon changing from generation zero (−0.24 V) to two (+0.09 V), reduction of Fe^{III} becomes increasingly favored (by 330 mV) with the largest change in potential again occurring at the stage of the generation one dendrimer (−0.01 V).

In H₂O, the redox process could only be monitored electrochemically for the generation zero complex, with the

generation one dendrimer showing a very weak spread-out reduction step and the second-generation compound being electrochemically silent.^[10a] Therefore, we changed to chemical methods to determine the redox potential for the Fe^{III}/Fe^{II} couple in this solvent. UV/Vis spectroscopic investigations showed that equilibria with solutions of suitable reducing agents were rapidly established after mixing with the porphyrin dendrimers. This allowed an accurate, highly reproducible determination of the redox potentials from equilibrium measurements using [Fe(ox)₃]^{−4}/[Fe(ox)₃]^{−3}^[24a, b] or [Fe(CN)₆]^{−4}/[Fe(CN)₆]^{−3}^[24c, d] (Figure 2), as it is commonly done with proteins.^[25] The potentials measured for [**1·Fe**]Cl by chemical and electrochemical methods were in excellent agreement. In contrast to the results obtained in the organic solvents, the potential of the Fe^{III}/Fe^{II} couple hardly shifts upon

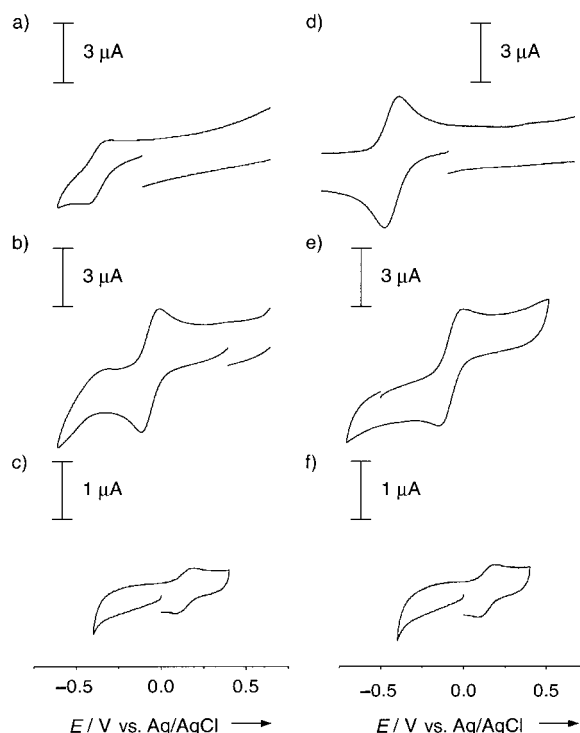


Figure 1. Cyclic voltammograms showing the first reduction step of [**1·Fe**]Cl (a, d), [**2·Fe**]Cl (b, e), and [**3·Fe**]Cl (c, f) in CH₂Cl₂ (left) and MeCN (right). For the conditions, see Table 2.

changing from generation zero (−0.29 V) to one (−0.25 V) but a dramatic increase is observed upon changing to the generation two dendrimer [**3·Fe**]Cl (+0.09 V) (see Table 2). For comparison, the Fe^{III}/Fe^{II} redox potential of cytochrome b₅ in H₂O was determined as +0.24 V vs. SCE.^[11b]

The results of the redox studies in the three solvents are summarized in Figure 3: 1) In all solvents, the redox potential of the Fe^{III}/Fe^{II} couple becomes more positive with increasing dendritic generation. Remarkably, the potential of the

Table 2. Redox potentials (in V vs. SCE) of the $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ couple of $[\mathbf{1} \cdot \text{Fe}] \text{Cl}$ – $[\mathbf{3} \cdot \text{Fe}] \text{Cl}$ in different solvents.

Porphyrin	CH_2Cl_2 ^[a]	$E(\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}})$ MeCN ^[a]	H_2O
$[\mathbf{1} \cdot \text{Fe}] \text{Cl}$	–0.21	–0.24	–0.29 ^[b]
$[\mathbf{2} \cdot \text{Fe}] \text{Cl}$	+0.08	–0.01	–0.25 ^[b]
$[\mathbf{3} \cdot \text{Fe}] \text{Cl}$	+0.10	+0.09	+0.09 ^[c]

[a] Values from CV approximated as $E_{1/2} = (E_{\text{pa}} - E_{\text{pc}})/2$; supporting electrolyte 0.1M Bu_4NPF_6 ; glassy carbon working electrode, Ag/AgCl reference electrode, platinum wire counter electrode; $T = 298 \text{ K}$; scan rate = 0.1 V s^{-1} ; typical concentration $5 \times 10^{-4} \text{ M}$; ferrocene was used as an internal standard, and the redox potentials referenced against the standard calomel electrode (SCE) using published values for the Fc/Fc^+ couple in CH_2Cl_2 (0.46 V vs. SCE; N. G. Connelly, W. E. Geiger, *Chem. Rev.* **1996**, *96*, 877–910) and MeCN (0.45 V vs. SCE; W. G. Barrette, Jr., H. W. Johnson, Jr., D. T. Sawyer, *Anal. Chem.* **1984**, *56*, 1890–1898). [b] Values from equilibrium measurements with $[\text{Fe}(\text{ox})_3]^{-4}/[\text{Fe}(\text{ox})_3]^{-3}$ (ox = oxalate) as reference compound.^[26] [c] Values from equilibrium measurements with $[\text{Fe}(\text{CN})_6]^{-4}/[\text{Fe}(\text{CN})_6]^{-3}$ as reference compound.^[26]

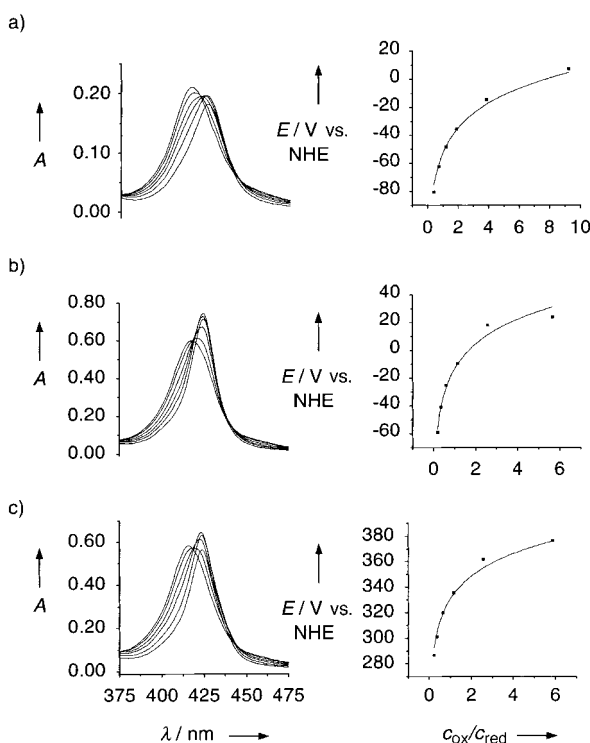


Figure 2. Redox equilibria in H_2O between $[\text{Fe}(\text{ox})_3]^{-4}/[\text{Fe}(\text{ox})_3]^{-3}$ and $[\mathbf{1} \cdot \text{Fe}] \text{Cl}$ (a) and $[\mathbf{2} \cdot \text{Fe}] \text{Cl}$ (b) and between $[\text{Fe}(\text{CN})_6]^{-4}/[\text{Fe}(\text{CN})_6]^{-3}$ and $[\mathbf{3} \cdot \text{Fe}] \text{Cl}$ (c). Spectral evolution of the Soret band region in the UV/Vis spectrum during reductive titration (left) and nonlinear least-squares fit of the titration data to the Nernst equation, yielding the redox potential (right). For the conditions, see Table 2. $c_{\text{ox}}/c_{\text{red}}$ is the concentration ratio of oxidized and reduced porphyrin.

second-generation complex $[\mathbf{3} \cdot \text{Fe}] \text{Cl}$ is, within experimental error, identical in all three solvents (of extremely different polarity), which clearly demonstrates that the dendritic branching creates a unique local microenvironment around the isolated electroactive core. Therefore, the dendritic shell fully mimics the protecting peptide shell which modulates the redox potential of the $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ couple in a similar way in cytochromes.^[7a,b] 2) In the two organic solvents, the largest

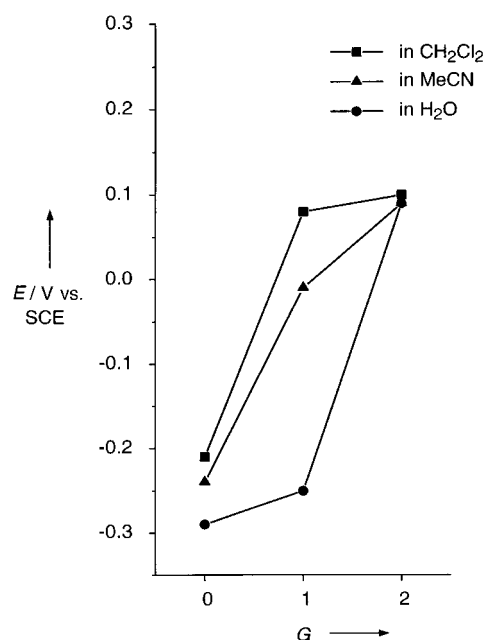


Figure 3. Plot of the redox potentials (in V vs. SCE) of the $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ couple in $[\mathbf{1} \cdot \text{Fe}] \text{Cl}$ – $[\mathbf{3} \cdot \text{Fe}] \text{Cl}$ in CH_2Cl_2 , MeCN and H_2O vs. dendrimer generation G .

shift to more positive potential occurs upon changing from the generation zero to the generation one complex. Clearly, the special microenvironment is already largely created by the first generation branching in these solvents. 3) In sharp contrast, the redox potential in H_2O does not vary much upon passing from the generation zero to the generation one complex. Solvation effects are much more pronounced in H_2O , and, as we had previously suggested,^[9b,c] the relatively open dendritic branches in $[\mathbf{2} \cdot \text{Fe}] \text{Cl}$ do not impede access of bulk solvent to the central core for stabilization of the Fe^{III} state. However in $[\mathbf{3} \cdot \text{Fe}] \text{Cl}$, the dendritic superstructure is sufficiently dense to prevent the contact between the porphyrin and the external bulk solvent, thereby creating the same, unique core microenvironment as in the organic solvents.

This model study confirms the large contributions of the densely packed protein shell to the strong positive shifts of the $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ potential in cytochromes^[7a,b] and firmly establishes well-designed dendrimers as powerful mimics for globular proteins.

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Novel U-Shaped Systems Containing an Imide-Functionalized Cleft for the Study of Solvent-Mediated Electron Transfer and Energy Transfer: Synthesis and Binding Studies**

Nicholas J. Head, Anna M. Oliver, Kai Look, Nigel R. Lokan, Garth A. Jones, and Michael N. Paddon-Row*

One of the most intensively investigated issues of long-range electron transfer (ET) and energy transfer (EnT) is how the electronic coupling for these processes depends on the nature of the intervening medium between a pair of chromophores.^[1] Using structurally well-defined systems, considerable progress has been made in delineating the characteristics of electronic coupling involving saturated hydrocarbon bridges,^[1a–c] protein-like pathways,^[1d] and the π stacks of base pairs in DNA molecules.^[1e]

By contrast, solvent-mediated electronic coupling remains a vexing issue, owing to the dynamic, jostling nature of the solvent molecules which blur the electronic coupling pathways. Progress has recently been made by using novel rigid U-shaped multichromophoric systems, represented by Class I in Figure 1,^[2] in which the terminal chromophores face each other across a “rigid” cavity within which a certain number of solvent molecules are present (in a dynamic sense). However, because these systems still do not address the problem of

[*] Prof. M. N. Paddon-Row, Dr. N. J. Head, Dr. A. M. Oliver, Dr. K. Look, N. R. Lokan, G. A. Jones
School of Chemistry
University of New South Wales
Sydney, N.S.W., 2052 (Australia)
Fax: (+61)2-9385-6141
E-mail: m.paddonrow@unsw.edu.au

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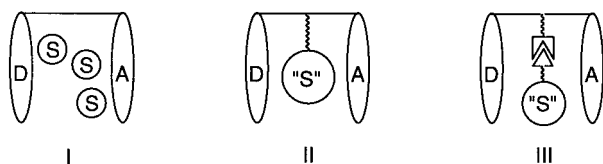


Figure 1. Modes of solvent inclusion within a U-shaped cavity. Class I: Unconstrained solvent; Class II: Covalently attached; Class III: Non-covalently bound. D: Donor, A: Acceptor, S: Solvent.

solvent mobility, both the number of solvent molecules occupying the molecular cavity and the electronic coupling pathways remain ill-defined. This problem may be ameliorated by “freezing” the solvent molecule within the cavity, either by covalent attachment (Class II), or by noncovalent recognition forces, such as H-bonding (Class III).

We describe herein the synthesis of three representative members of a novel cavity-functionalized U-shaped system, **1–3** (Figure 2; see Table 1 for melting points and NMR data), which offer the exciting potential for acting as Class II and Class III systems in solvent-mediated ET and EnT studies. The key attribute of these molecules is the presence of the imide functionality within the cavity. Class II models are realized by covalent attachment of the “solvent” molecule to the imide nitrogen atom, in which case it has, at the most, only one rotational degree of freedom. Three-point H-bonding of a guest molecule to the imide functionality results in a Class III system in which all rotational degrees of freedom are frozen.

The AM1-optimized geometries of **1–3** (Figure 2) and the H-bonded complex, **5**, between **1** and 2,6-bis(hexanoylamino)pyridine **4** (Figure 3) are revealing. The interchromophore separation in these systems ranges between 7 and 10.5 Å, and the chromophores are proximal to the intervening “solvent” molecules, thereby ensuring reasonably strong chromophore–solvent electronic coupling.

The synthesis of **1** is summarized in Scheme 1, the key to which proved to be the correct selection of a protecting group for the imide functionality that would impart both suitable solubility to the system during the synthesis and ease of removal when the free imide group was required. Precedent^[3] suggested the use of the *p*-methoxybenzyl (PMB) protecting group which may be removed using cerium(IV) ammonium nitrate (CAN).^[4] Anhydride **6**^[5] was treated with *p*-methoxybenzylamine to afford the corresponding amic-acid which was

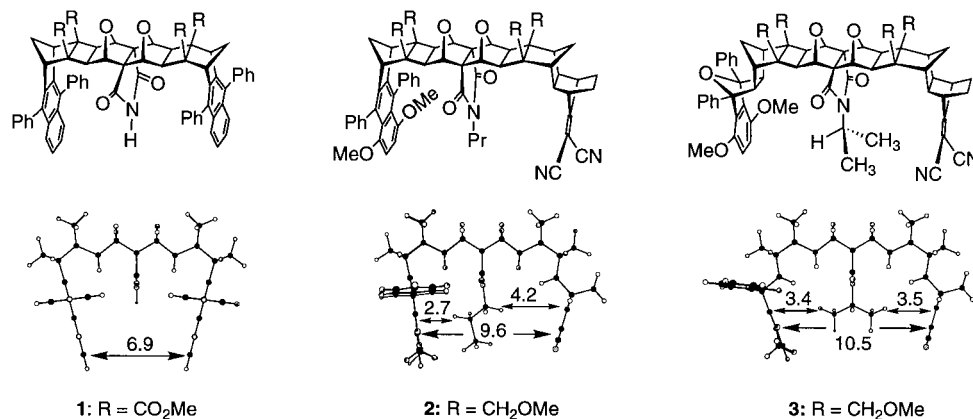


Figure 2. AM1-optimized structures for **1–3**. Distances in Å.

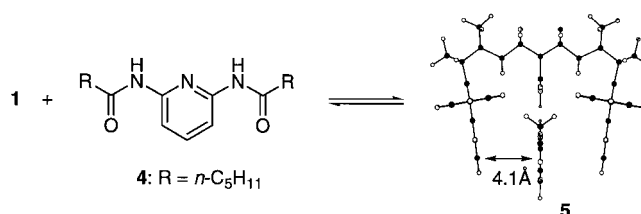
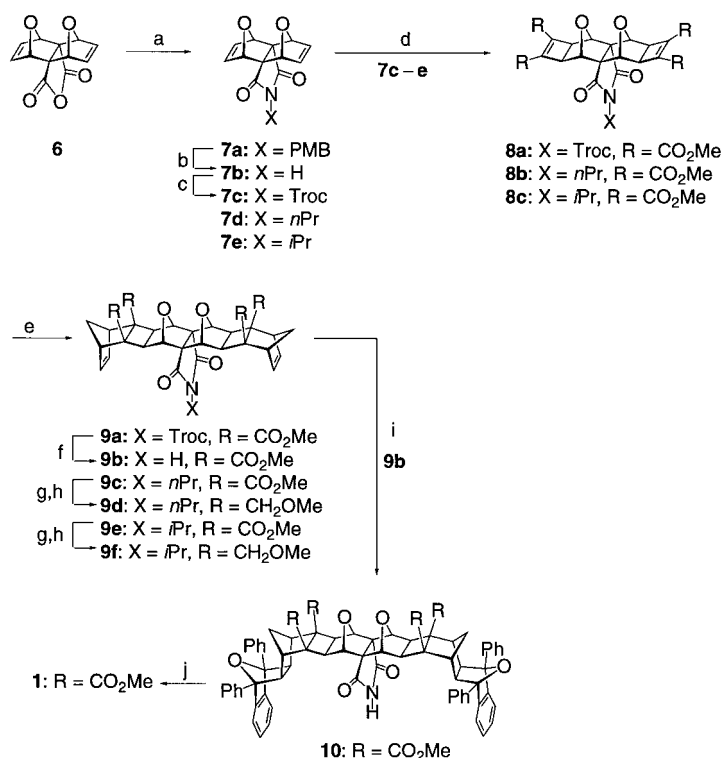


Figure 3. AM1-optimized structure for the H-bonded complex **5**.



Scheme 1. a) 1. XNH_2 ($X = p\text{-MeOC}_6\text{H}_4\text{CH}_2$ (PMB), $n\text{Pr}$, $i\text{Pr}$), 2. NaOAc , Ac_2O ; b) CAN ; c) NaH , DMF , $\text{CCl}_3\text{CH}_2\text{O}_2\text{CCl}$; d) DMAD , $[\text{RuH}_2\text{-CO}(\text{PPh}_3)_3]$; e) C_5H_6 ; f) Zn , dioxane, AcOH ; g) LiAlH_4 ; h) 1. NaH , 2. MeI ; i) DPEBF , dioxane, 120°C ; j) TFA , C_6H_6 .

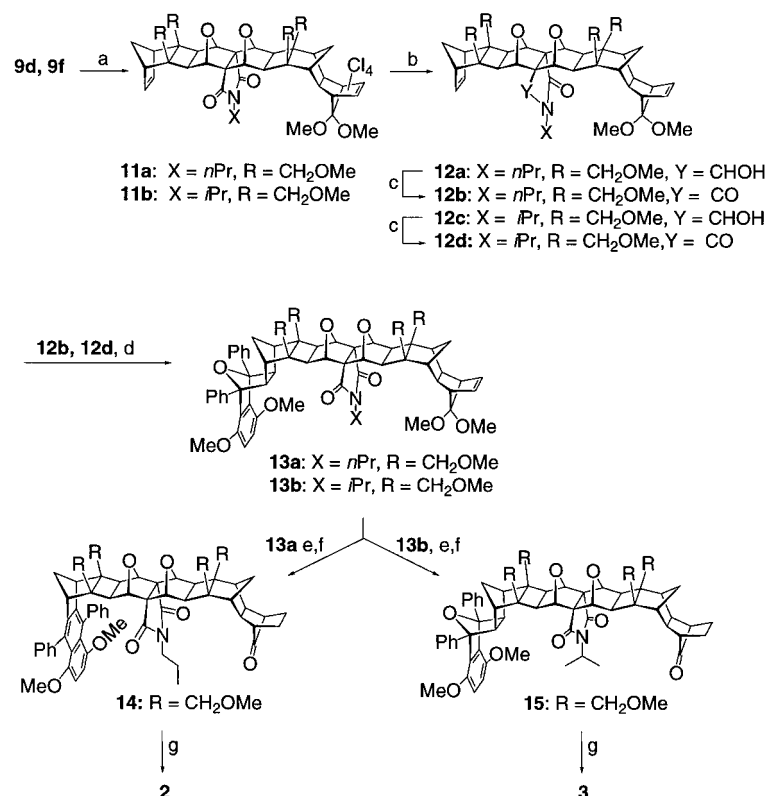
cyclized to give the imide **7a** in 42% yield. Although treatment of **7a** with CAN resulted in ready removal of the PMB group, to give **7b**, oxidative removal of this group at latter stages of the synthesis was problematical. The more readily removable trichloroethoxycarbonyl (Troc) group^[6] was therefore used and was introduced by NH deprotonation of **7b**, followed by quenching with 2,2,2-trichloroethylchloroformate, to give **7c**. The imide **7c** was converted into the tetraester **8a** by ruthenium-catalyzed [2+2] cycloaddition with dimethyl acetylenedicarboxylate (DMAD)^[7] and then into the diene **9a** by Diels–Alder addition with cyclopentadiene.^[8] The Troc group was cleanly removed in essentially quantitative yield upon treatment with zinc to give the bridge system **9b**.^[6]

The system **9b** possesses two terminal norbornene double bonds to which a number of useful chromophores may be attached.^[1b,9] For our initial studies we elected to attach simple diphenylnaphthalene groups and this was readily accomplished by Diels–Alder addition of 1,3-diphenylisobenzofuran (DPIBF) to the double bonds^[5b] of **9b** at 120 °C, followed by acid-catalyzed dehydration of the oxo-bridged bisadduct **10** to give **1**.

The binding abilities of the free imide systems **1**, **9b**, and **10** were assessed by determining their association constants K_a with the guest molecule **4**, from the complexation-induced ¹H NMR shifts of the imide proton (in CDCl₃). The K_a values for **1**, **9b**, and **10** are 946, 121, and 119 M^{−1}, respectively. The association constant for **1** is significantly larger than that typically reported for complexation between 2,6-bis(acylamino)pyridines with succinimides ($K_a = 50–500$ M^{−1}),^[10] and is most likely due to enhanced stabilization of the complex by π -stacking interactions between the guest molecule and the proximal naphthalene groups.

Scheme 2 illustrates how the synthesis may be extended to systems possessing different cavity sizes and having chromophores suitable for ET studies. In these systems, *n*-propyl and isopropyl “solvent” molecules have been covalently linked to the imide group.

The bridge ester groups of **9c** and **9e** (Scheme 1) were converted into the less chemically reactive methoxyethers **9d** and **9f**, respectively.^[8] Diels–Alder reaction of dimethoxytetrachlorocyclopentadiene (DMTC)^[11] with **9d** and **9f** gave the respective monoadducts **11a** and **11b**, together with unconverted starting material and some of the bisadducts.



Scheme 2. a) DMTC, 120 °C; b) Na, *i*PrOH; c) MnO₂; d) DMIBF, *o*-C₆H₄Cl₂, 120 °C; e) H₂, Pd/C; f) TFA, C₆H₆; g) CH₂(CN)₂, NH₄OAc, AcOH.

Reductive dechlorination of **11a** and **11b** (Na, *i*PrOH)^[11] was accompanied by reduction of the imide groups to give the hydroxylactams **12a** and **12c**, respectively, oxidation of which gave the imides **12b** and **12d** in greater than 90 % yield for both steps.

Diels–Alder addition of 4,7-dimethoxy-1,3-diphenylisobenzofuran (DMIBF)^[12] to **12b** and **12d** slowly gave the respective adducts **13a** and **13b**. The naphthalene–ketone **14** was obtained from **13a** by catalytic hydrogenation, followed by trifluoroacetic acid (TFA) catalyzed simultaneous dehydration and deacetalization. In contrast, hydrogenation of **13b**, followed by TFA treatment, gave only deacetalized material **15**, without causing dehydration to form the naphthalene ring. Failure to effect aromatization in this system is due to the increased degree of steric congestion within the molecular cavity caused by the bulky *i*Pr group. Knoevenagel condensation of the ketones **14** and **15** with malononitrile afforded **2** and **3**, respectively.^[11]

Cyclic voltammetry and UV spectroscopy of suitable model compounds indicate that both the diphenyldimethoxynaphthalene and dimethoxybenzene groups should be suitable donor chromophores for effecting photoinduced ET to the dicyanovinyl (DCV) acceptor.^[13] Indeed, preliminary steady-state fluorescence studies on **2** and **3** in acetonitrile revealed quenching of the naphthalene fluorescence, to the extent of 92 % and 49 %, respectively.^[14] These results strongly indicate that photoinduced ET is occurring in these systems and that it is particularly efficient in **2**.

In summary, we have demonstrated a viable synthetic route to novel U-shaped systems of the type **1–3** which offer considerable scope in exploring a variety of neighboring group interactions under structurally well-defined conditions. In particular, their deployment in photophysical investigations should provide valuable insight into the mechanism of solvent-mediated ET and EnT processes. Efforts are currently being directed towards synthesizing a range of systems, based on architectural principles described above, which contain covalently linked “solvent” groups, particularly aromatic units.

Table 1. Melting point and NMR data for **1–3**.

1: M.p. > 300 °C; ¹ H NMR (300 MHz, CDCl ₃): δ = 1.84 (s, 4H), 2.05 (d, J = 10.2 Hz, 2H), 2.38 (d, J = 10.2 Hz, 2H), 3.59 (s, 16H), 5.08 (s, 4H), 7.16 (d, J = 7.5 Hz, 4H), 7.27–7.35 (m, 8H), 7.42–7.53 (m, 8H), 7.54–7.64 (m, 8H); ¹³ C NMR (75.5 MHz, CDCl ₃): δ = 45.7, 49.3, 51.9, 52.4, 58.1, 70.9, 81.3, 125.2, 126.7, 127.5, 128.5, 128.8, 129.9, 130.1, 131.5, 134.0, 137.2, 141.0, 171.1, 173.8.
2: M.p. > 300 °C; ¹ H NMR (500 MHz, CDCl ₃): δ = 0.72 (t, J = 7.3 Hz, 3H), 0.98–1.18 (m, 2H), 1.21–1.29 (m, 2H), 1.62 (s, 2H), 1.62–1.68 (m, 2H), 1.79 (d, J = 9.7 Hz, 1H), 1.88 (d, J = 12.2 Hz, 1H), 1.92–1.99 (m, 2H), 1.99–2.04 (m, 2H), 2.20 (s, 2H), 2.28 (s, 2H), 2.37 (s, 2H), 2.80 (d, J = 8.9 Hz, 2H), 2.97 (s, 2H), 3.00 (d, J = 9.3 Hz, 2H), 3.13 (s, 6H), 3.23 (s, 2H), 3.23 (s, 6H), 3.35 (s, 6H), 3.63 (d, J = 8.9 Hz, 2H), 3.65 (d, J = 9.3 Hz, 2H), 4.75 (s, 2H), 4.78 (s, 2H), 6.74 (s, 2H), 7.17 (t, J = 8.0 Hz, 4H), 7.27 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H); ¹³ C NMR (75.5 MHz, CDCl ₃): δ = 11.3, 20.4, 21.6, 24.4, 33.5, 38.6, 38.7, 40.0, 44.2, 44.8, 45.4, 45.5, 50.2, 51.1, 52.8,

57.0, 58.7, 58.9, 69.5, 69.8, 70.7, 73.3, 81.3, 108.3, 110.9, 124.8, 125.3, 126.6, 127.1, 128.3, 128.4, 131.3, 142.7, 144.1, 151.9, 173.7, 191.9.

3: M.p. >300 °C; ¹H NMR (300 MHz, CDCl₃): δ = 0.57 (d, *J* = 10.6 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 6H), 1.30 (d, *J* = 12.0 Hz, 1H), 1.68 (d, *J* = 8.7 Hz, 2H), 1.93 (d, *J* = 12.0 Hz, 1H), 2.00 (d, *J* = 8.7 Hz, 2H), 2.19 (d, *J* = 10.6 Hz, 1H), 2.34 (s, 2H), 2.39 (s, 2H), 2.44 (s, 2H), 2.46 (s, 2H), 2.47 (s, 2H), 2.60 (d, *J* = 9.0 Hz, 2H), 2.79 (s, 2H), 2.87 (d, *J* = 9.0 Hz, 2H), 3.04 (s, 2H), 3.16 (s, 6H), 3.29 (s, 6H), 3.33 (s, 6H), 3.59 (d, *J* = 9.0 Hz, 2H), 3.68 (d, *J* = 9.0 Hz, 2H), 4.10 (sept, *J* = 6.8 Hz, 1H), 4.79 (s, 2H), 4.83 (s, 2H), 6.53 (s, 2H), 7.33 (t, *J* = 7.1 Hz, 2H), 7.43 (t, *J* = 7.1 Hz, 4H), 7.80 (d, *J* = 7.1 Hz, 4H); ¹³C NMR (75.5 MHz, CDCl₃): δ = 0.93, 17.79, 21.69, 31.36, 33.51, 38.60, 40.10, 40.26, 43.31, 44.57, 44.82, 45.44, 48.92, 51.00, 52.94, 56.46, 58.69, 58.88, 69.57, 70.29, 73.66, 81.63, 81.91, 90.32, 110.93, 113.21, 126.89, 127.09, 128.23, 137.11, 138.36, 147.15, 173.84, 191.59.

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- [13] Diphenyldimethoxynaphthalene: *E*_{ox}(CH₂Cl₂) = 0.99 eV, *E*₀ = 3.4 eV. Dimethoxybenzene: *E*_{ox}(CH₃CN) = 1.33 eV, *E*₀ = 3.95 eV. DCV: *E*_{red}(CH₃CN) = −1.7 eV. From these data, the driving forces for photoinduced ET from locally excited aromatic donor to DCV acceptor in **2** and **3** are estimated to be 0.8 and 0.9 eV, respectively.
- [14] The fluorescence quantum yields for **2** and **3** were obtained relative to appropriate model systems lacking the DCV acceptor group.

Ruthenium-Catalyzed Intermolecular Hydroamination of Terminal Alkynes with Anilines: A Practical Synthesis of Aromatic Ketimines**

Makoto Tokunaga, Markus Eckert, and Yasuo Wakatsuki*

Aromatic ketimines are an important class of compounds widely used for the preparation of a variety of nitrogen-containing chemicals, such as tertiary^[1a] or secondary amines,^[1b–d] nitrogen heterocycles,^[1e, 2e,g] carboxylic amides,^[1f, 2f] β-enamino esters,^[1g] amino alcohols,^[1h] α-sulfinyl ketimines,^[1i] and many others.^[1j–l] Although the condensation of ketones with primary amines is a textbook route to ketimines, the procedure is sometimes not practical for the synthesis of aromatic ketimines because aromatic ketones react much more slowly than aliphatic ketones or aldehydes, and methyl ketones are sensitive to aldol-type side reactions.^[2a] Therefore synthesis of imines from acetophenone often gives unsatisfactory results (for example, 40–55% maximum yields from reactions with aniline^[2b,d–f, 3]). Another practical route to aromatic ketimines is therefore desired to supplement the classical ketone–amine condensation pathway.

We thought that the hydroamination of phenylacetylene and its derivatives should be a convenient way to synthesize the compounds, and it deserved special attention in terms of its efficiency of atom utilization since it avoids the formation of stoichiometric amounts of by-products.^[4] Compared to intramolecular cyclizations,^[5] however, the intermolecular hydroaminations of alkynes^[6] is more difficult, and only a few approaches exist.^[4] Besides the established stoichiometric aminomercuration/reduction method,^[7] the only catalytic reactions known are those with mercury or thallium,^[6a,b] and metallocenes of zirconium,^[6c] lanthanide,^[6d,f] and actinide.^[6e] These catalysts or precursors, though interesting in their own right, have problems associated with environmental protection, low activity, and/or air and moisture sensitivity.

Herein we disclose an efficient synthesis of aromatic ketimines based on the regioselective hydroamination of terminal alkynes with anilines using a ruthenium carbonyl catalyst. The incorporation of late transition metals in catalysts have an advantage over early transition metals, lanthanide, and actinide metals in that their low oxophilicity permits the use of many substrates for catalysis that are excluded in the systems with highly oxophilic metals. Yet, to the best of our knowledge, intermolecular hydroamination of alkynes by late transition metals other than mercury has not appeared in the literature. This situation is probably because of their very low activity (and small turnover numbers

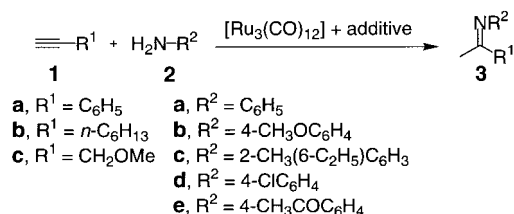
[*] Dr. Y. Wakatsuki, Dr. M. Tokunaga, Dr. M. Eckert^[†]
The Institute of Physical and Chemical Research (RIKEN)
Wako-shi, Saitama, 351-0198 (Japan)
Fax: (+81)48-462-4665
E-mail: waky@postman.riken.go.jp

[†] Present address:
Bayer AG, D-51368 Leverkusen (Germany)

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(TON)).^[8] The present breakthrough constitutes the effect of a small amount of additive in the catalytic system on attaining a very high activity of the ruthenium catalyst: in many cases 0.1 mol % of the catalyst concentration may be employed. Furthermore, the reaction can be carried out in the open air under solvent-free conditions, and does not require an inert gas atmosphere or strict anhydrous conditions.

We started to explore a practical catalyst system for the hydroamination using the addition of aniline (**2a**) to phenylacetylene (**1a**) as the standard reaction (Scheme 1). Ruthenium phosphane complexes that had been successfully



Scheme 1. Ruthenium-catalyzed hydroamination of terminal alkynes with anilines.

employed for anti-Markovnikov hydration^[9a] or homodimerization^[9b] of alkynes, and dehydrogenative silylation of alkenes^[9c] showed poor activity. Only slightly better results were obtained with the ruthenium carbonyl cluster $[\text{Ru}_3(\text{CO})_{12}]$.^[10] However, we found a dramatic rate enhancement when the cluster was used in the presence of a small amount of acid or its ammonium salt. For example, the reaction was completed in 12 h at 100 °C with only 0.1 mol % $[\text{Ru}_3(\text{CO})_{12}]$ and 0.3 mol % NH_4PF_6 and gave a 84 % yield (GC) of the product **3**, while only a 2.6 % yield of the product was obtained under the same conditions but without the additive. The effect of the additives as judged by the GC yields of **3** is compared in Table 1.

Table 1. Hydroamination of **1a** with **2a** catalyzed by $[\text{Ru}_3(\text{CO})_{12}]$ and additives.^[a]

Additive [mol %]	Yield [%] ^[b]	Additive [mol %]	Yield [%] ^[b]
–	1.6	NH_4BF_4 (0.3)	56
$\text{NH}_4(\text{CF}_3\text{SO}_3)$ (0.3)	44	$\text{BF}_3 \cdot \text{OEt}_2$ (0.3)	71
aq HPF_6 (0.3)	78	$\text{H}_2\text{SO}_4 \cdot 2\text{PhNH}_2$ (0.15)	14
NH_4PF_6 (0.1)	19	NH_4I (0.3)	4.2
NH_4PF_6 (0.2)	53	aq HCl (0.3)	9.6
NH_4PF_6 (0.3)	52	aq HCl (3.0)	4.2
NH_4PF_6 (0.3)	84 ^[d]	NH_4Cl (0.3)	9.3
NH_4PF_6 (0.3)	92 ^[e]	$\text{HCl} \cdot \text{PhNH}_2$ (0.3)	7.7
NH_4PF_6 (0.6)	50	MeSO_3H (0.3)	48
NH_4PF_6 (1.5)	53	CF_3COOH (0.3)	26
NH_4PF_6 (3.0)	49	ClCH_2COOH (0.3)	17
KPF_6 (0.3)	1.5	NH_4F (0.3)	4.5
NMe_4PF_6 (0.3)	1.5	$\text{HF} \cdot \text{PhNH}_2$ (0.3)	29
$\text{NMe}_4\text{PF}_6 + \text{HCl}$ (0.3)	19	aq HF (0.3)	11
aq HBF_4 (0.1)	24	aq HF (excess)	46
aq HBF_4 (0.2)	64	PhCOOH (0.3)	2.7
aq HBF_4 (0.3)	67		

[a] Reactions were carried out with 1 g of **1a**, 1.1 equivalents of **2a**, 0.1 mol % $[\text{Ru}_3(\text{CO})_{12}]$, and additives in CH_3OH (1 mL) at 100 °C. [b] GC yield after 3 h, unless otherwise stated. [c] Reference experiment with NH_4PF_6 in the absence of $[\text{Ru}_3(\text{CO})_{12}]$ yielded no detectable product. [d] After 12 h. [e] Yield of the isolated product from a 50-g scale reaction without solvent, see Experimental Section.

The strong acids HPF_6 and HBF_4 and their ammonium salts were the most effective additives,^[11] and the reactions with them gave 50–78 % yields in 3 h at 100 °C. A decrease in the effect was observed with a decrease in the acidity of the additives: MeSO_3H , CF_3COOH , ClCH_2COOH , and PhCOOH gave yields of 48, 26, 17, and 2.7 %, respectively. However, the effect of the additives is not a simple function of their acidity since aqueous HCl , NH_4Cl , and NH_4I showed only a very small rate enhancement. Moreover, although NH_4F accelerated the reaction only slightly as a consequence of its poor solubility, the effect of hydrogen fluoride and its salts is larger than that for the chloride and iodide. Interestingly, KPF_6 and NMe_4PF_6 gave no effect at all. Addition of HCl to NMe_4PF_6 restored the effect and afforded a better result than those obtained by each additive alone.

The effect of the amount of additives on the reaction yield was examined with NH_4PF_6 and HBF_4 . As shown in Table 1, only 0.2 mol % of additive and 0.1 mol % of $[\text{Ru}_3(\text{CO})_{12}]$ was necessary to achieve the maximum rate; a further addition of these additives did not lead to any further improvement.

In regard to the solvent, the reactions in methanol, 2-propanol, toluene, and THF all gave similar results. It was found that the solvent-free system exhibited the highest reaction rate. It appears that the use of a small excess of **1a** (1.2 equiv) to **2a** often gives better results than a strictly equivalent ratio. We also found that it did not matter whether the reaction was carried out under argon or in air.

On the basis of these findings, a 50-g-scale reaction was carried out to test the practicability of the present system. Neat substrates, 0.1 mol % $[\text{Ru}_3(\text{CO})_{12}]$, and 0.3 mol % NH_4PF_6 were placed in an open 100-mL one-necked flask. After the mixture had stirred for 3 h at 100 °C, the product **3** was simply distilled directly from the same flask to give the imine of > 99 % purity in 92 % yield (TON 300 per Ru atom).

The present hydroamination system was also found to be applicable to the reactions of substituted anilines with phenylacetylene (Table 2, entries 1–4).^[12] Aniline (**2b**), with an electron-donating substituent, reacts smoothly, but a sterically hindered aniline (**2c**), or one with electron-withdrawing substituents (**2d, e**) requires higher loadings of the

Table 2. Hydroamination of **1** with **2** catalyzed by $[\text{Ru}_3(\text{CO})_{12}]$ and additives.

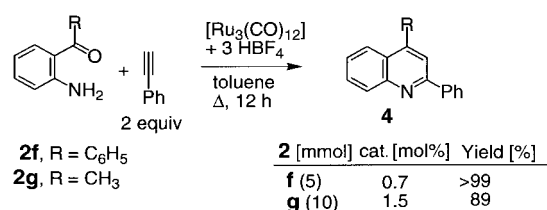
Entry	Alkyne [mmol]	Amine [mmol]	Catalyst ([mol %]) additive ([mol %])	Solvent [mL]	T [°C] t [h]	Yield [%]
1	1a (12)	2b (10)	$[\text{Ru}_3(\text{CO})_{12}]$ (0.1) NH_4PF_6 (0.3)	–	100 3	95 ^[b]
2	1a (28)	2c (20)	$[\text{Ru}_3(\text{CO})_{12}]$ (0.7) $\text{HBF}_4/\text{OEt}_2$ (2.1)	–	100 12	89 ^[a]
3	1a (24)	2d (20)	$[\text{Ru}_3(\text{CO})_{12}]$ (0.2) NH_4PF_6 (0.6)	–	100 3	88 ^[a]
4	1a (15)	2e (5)	$[\text{Ru}_3(\text{CO})_{12}]$ (1.0) $\text{HBF}_4/\text{OEt}_2$ (3.0)	–	100 12	80 ^[c,d]
5	1b (30)	2a (20)	$[\text{Ru}_3(\text{CO})_{12}]$ (0.5) NH_4PF_6 (1.5)	MeOH (3.0)	100 12	63 ^[a]
6	1c (10)	2c (5)	$[\text{Ru}_3(\text{CO})_{12}]$ (1.0) $\text{HBF}_4/\text{OEt}_2$ (3.0)	toluene (0.7)	100 12	41 ^[c]

[a] Isolated by distillation. [b] Isolated by recrystallization. [c] Determined by GC analysis. [d] 3:2 mixture of geometrical isomers: ^1H NMR (CDCl_3): $\delta = 1.77, 2.47$ (s, 1.2H), 2.16, 2.51 (s, 1.8H); ^{13}C NMR (CDCl_3): $\delta = 165.4, 167.0, 196.8, 196.9$.

catalyst. It is noteworthy that the aromatic imine prepared here from **1a** and **2e** is apparently difficult to synthesize by the ordinary dehydrative condensation of acetophenone and **2e**; a self-condensation of **2e** to form a polymer occurs.

The preparation of nonaromatic ketimines by use of aliphatic 1-alkynes was moderately successful (Table 2, entries 5, 6). The aliphatic acetylenes **1b**, **c** were found to be less reactive than **1a** towards aniline and prolonged reaction times resulted in the partial decomposition of the imine formed. Nevertheless, the utility was demonstrated for the preparation of the imine from **1c** and **2c** (Table 2, entry 6), which is a synthetic intermediate of Metolachlor,^[13] one of the most intensively used herbicides.

As an application of the present catalytic system to form aromatic ketimines, a new two-component synthesis of quinolines (Scheme 2) was examined. The quinoline nucleus



Scheme 2. Ruthenium-catalyzed two-component synthesis of 2,4-disubstituted quinolines.

is present in a variety of natural products, pharmaceuticals, and dyes,^[14a] and the synthesis of this important structure has been a steady topic.^[14b] The 2,4-disubstituted quinolines **4** were formed in good to quantitative yields by the reaction of *o*-benzoyl- (**2f**) or *o*-acetylaniline (**2g**) with two equivalents of **1a**. The yields obtained by this method (Scheme 2) are superior to the corresponding Friedländer synthesis, which uses *o*-acylanilines and ketones.^[15]

The reaction mechanism of the present hydroamination reaction, in particular the reason for the remarkable enhancement effect of the additives, remains to be clarified. The observation that NH_4PF_6 and aqueous HPF_6 are quite efficient additives while NMe_4PF_6 is totally ineffective suggests that protons play an important role. However, the conjugated base must also be important since aqueous HCl has only a very small acceleration effect. It has been reported by Lavigne et al. that halides and related salts can promote substitution reactions of $[\text{Ru}_3(\text{CO})_{12}]$.^[16]

Experimental Section

Special care does not need to be taken with the catalytic reaction to remove air and moisture from the system.

Acetophenone-*N*-phenylimine: A mixture of phenylacetylene (36.8 g, 0.360 mol), aniline (27.9 g, 0.300 mol), $[\text{Ru}_3(\text{CO})_{12}]$ (0.192 g, 0.300 mmol), and NH_4PF_6 (0.147 g, 0.900 mmol) was stirred at 100 °C for 3 h, then distilled under reduced pressure^[17] to give the imine (bp. 90–95 °C, 0.1 Torr; 53.7 g, 0.275 mol, 92 %).

2,4-Diphenylquinoline: A mixture of phenylacetylene (1.02 g, 10.0 mmol), 2-aminobenzophenone (0.986 g, 5.00 mmol), $[\text{Ru}_3(\text{CO})_{12}]$ (22.4 mg, 0.035 mmol), 48 % aqueous HBF_4 (14 μL , 0.105 mmol), and toluene (3 mL) was stirred at 160 °C for 12 h. Water was removed by azeotropic

dehydration. The products were separated by column chromatography on silica gel (hexane/ CH_2Cl_2 3/1) to give 2,4-diphenylquinoline (1.41 g, 5.00 mmol, >99 %).

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Chemically Triggered Assembly of Chiral Triangular Metallomacrocycles**

Tassilo Haberer, Marcus Warchhold, Heinrich Nöth, and Kay Severin*

Dedicated to Professor Theodore Severin on the occasion of his 70th birthday

Self-assembly processes that are based on interactions between transition metals and ligands are among the most elegant methods for the construction of large macrocyclic compounds. In recent years a variety of amazingly complex structures have been built in this way.^[1] The focus of interest has been on two-dimensional polygons such as squares and rectangles, but three-dimensional polyhedra^[2] and possible applications are now beginning to be explored.^[1, 3] In comparison with rectangular assemblies there have been relatively few reports on triangular metallomacrocycles.^[4–6] This is especially true for complexes with rigid heterocyclic ligands, a class of compounds that was very successfully employed for the construction of other polynuclear assemblies. A possible explanation, as suggested by Stang et al.,^[1b] is the fact that the

required 60° turning angle is quite uncommon in transition metal chemistry.^[7]

Herein we describe the synthesis and crystal structure of two chiral, triangular macrocycles in which half-sandwich complexes of iridium(III) and ruthenium(II) occupy the corner positions. The heterocyclic bridging ligand is the dianion of 3-hydroxy-2-methyl-4(1*H*)-pyridone. This ligand^[8] as well as *N*-substituted derivatives^[9] are easily synthesized from commercially available 3-hydroxy-2-methyl-4-pyrone (maltol). These ligands have received considerable attention since they are good chelators of various metal ions, especially iron(III).^[10] Recently, we reported the first examples of organometallic complexes with *N*-alkyl and *N*-aryl pyridones.^[11] During the course of the work we realized that the unsubstituted 3-hydroxy-2-methyl-4(1*H*)-pyridone should be an ideal candidate for the synthesis of well defined oligonuclear transition metal assemblies. The starting point of our investigations was the chiral pentamethylcyclopentadienyl (Cp^*) iridium(III) complex **1**. This compound was obtained as a racemic mixture from $[\{\text{Cp}^*\text{IrCl}_2\}_2]$ and 3-hydroxy-2-methyl-4(1*H*)-pyridone in the presence of one equivalent of base.

In accordance with previous studies on transition metal pyridone complexes it was assumed that the mesomeric form B (Figure 1) contributes significantly to the electronic structure of **1**.^[11, 12] We therefore anticipated that the proton bound

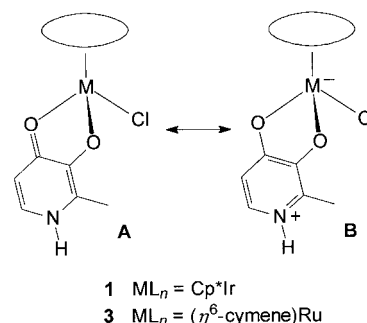


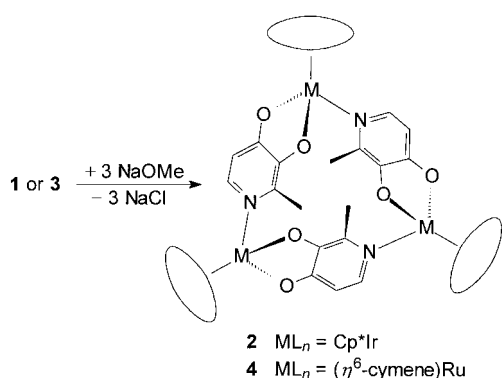
Figure 1. Mesomeric forms that contribute to the electronic structure of **1** and **3**.

at the nitrogen atom should be acidic. Simultaneously the chloride ligand was expected to be labile. Combining these two characteristics should allow a base-induced oligomerization of **1**. In fact, if **1** was stirred with one equivalent of NaOMe (or NEt_3) in methanol the yellow complex **2** was obtained in quantitative yield (Scheme 1).^[13] Alternatively, **2** can be prepared directly from $[\{\text{Cp}^*\text{IrCl}_2\}_2]$, the pyridone ligand, and NaOMe (molar ratio 1:2:4).

The ^1H NMR spectrum of **2** was indicative of a highly symmetrical structure: only one signal was observed for the Cp^* protons and only one set of signals was detected for the pyridone protons. It is known that the symmetry of supramolecular assemblies based on metal–ligand interactions is strongly biased by the geometric requirements of the ligand as well as the transition metal.^[1a,b] The geometry of half-sandwich complexes can be described as pseudo-octahedral with angles between the three “piano-stool legs” approaching 90° (for example, $\text{Cl-Ir}(\mu\text{-Cl}) = 88.49^\circ$ in $[\{\text{Cp}^*\text{IrCl}_2\}_2]$ ^[14]). Since the heterocyclic ligand is nearly planar our initial guess

[*] Dr. K. Severin, Dipl.-Chem. T. Haberer, Dipl.-Chem. M. Warchhold, Prof. Dr. H. Nöth, Institut für Anorganische Chemie der Universität Butenandtstrasse 5–13, D-81377 München (Germany) Fax: (+49)89-2180-7866 E-mail: kse@cup.uni-muenchen.de

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Scheme 1. Base-induced formation of chiral triangular metallomacrocycles.

for the molecular structure of **2** was a square geometry with four iridium atoms in the corner.^[15] The mass spectrum of **2**, however, showed no peak with the expected mass but showed a peak at m/z 1352, which is indicative of a trinuclear complex.^[16] This conclusion was confirmed by the result of a single-crystal X-ray structure analysis.^[17] The structure of one enantiomer of the cyclic trimer in the crystal is shown in Figure 2. As expected, the bridging pyridone ligand acts as an

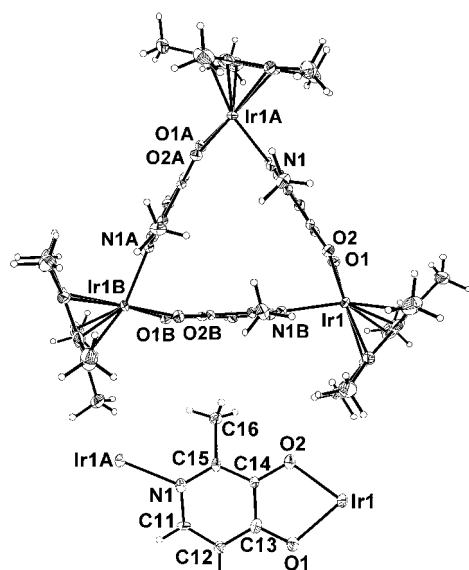


Figure 2. Structure of **2** in the crystal (top) and side view of the bridging pyridone ligand (bottom); selected bond lengths [Å] and angles [°]: Ir(1)–O(1) 2.118(7), Ir(1)–O(2) 2.085(7), Ir(1)–N(1) 2.141(8), O(1)–C(13) 1.319(11), O(2)–C(14) 1.328(10), C(13)–C(14) 1.437(14), C(14)–C(15) 1.380(12), N(1)–C(11) 1.340(12), N(1)–C(12) 1.335(12), C(11)–C(12) 1.374(13), C(12)–C(13) 1.389(13); O(1)–Ir(1)–N(1) 82.4(3), O(2)–Ir(1)–N(1) 85.0(3), O(2)–Ir(1)–O(1) 79.6(3).

O,O'-chelate and simultaneously coordinates through the nitrogen atom in position 4 to another iridium atom. The C–O bond length as well as the bond lengths within the six-membered ring are in agreement with an aromatic structure as depicted in Scheme 1. The iridium atoms are 7.24 Å apart from each other. Contrary to other “molecular triangles”, which show a concave^[6] or distorted^[4a,b] geometry, the bridging ligands in **2** (as well as the Cp* ring) are almost orthogonal to the plane defined by the metal atoms forming a

trigonal prism. This geometry requires that the O,O'-chelate is coordinated in a slightly bent fashion. Thus, a torsion angle of C(13)–C(14)–O(2)–Ir(1) = 16.2° is observed, as opposed to other pyridone complexes that show a linear arrangement.^[11, 12]

We were especially interested in the diastereoselectivity of the self-assembly process since three stereogenic centers were produced simultaneously. Both the NMR data and the result of the X-ray structure analysis indicated that only one diastereoisomer was formed (as a racemate) in which all metal centers had the same configuration. Nevertheless it would have been possible that in solution epimerization was fast on the NMR time scale and consequently the other diastereoisomer was not detected. To exclude this possibility we tried to incorporate the structurally related $\{(\eta^6\text{-cymene})\text{Ru}^{\text{II}}\}$ fragment into the macrocycle. The *i*Pr-methyl groups of the cymene ligand provide an excellent spectroscopic probe for the configurational stability of the adjacent metal center in $\{(\eta^6\text{-cymene})\text{Ru}^{\text{II}}\}$ complexes: if epimerization is slow on the NMR time scale they appear as two separate doublets, otherwise only one doublet should be observed.

When the reactions were carried out using $\{[(\eta^6\text{-cymene})\text{-RuCl}_2]_2\}$ instead of $\{[\text{Cp}^*\text{IrCl}_2]_2\}$ the new ruthenium complexes **3** and **4** were obtained. Again, only the signals of one isomer was observed in the ¹H NMR spectrum of the trimeric compound **4**. Furthermore, epimerization was shown to be slow even in polar organic solvents at elevated temperatures (CD₃OD, 50 °C). We therefore conclude that the assembly process is completely diastereoselective.^[18] The monomeric complex **3**, on the other hand, was unstable towards epimerization (on the ¹H NMR time scale) even in less polar solvents such as CD₂Cl₂. The remarkable configurational stability of the chiral metal centers in **4** can be explained by the rigidity of the cyclic complex.

Single crystals of **4** suitable for X-ray structure analysis were obtained by the slow diffusion of pentane into a solution of **4** in tetrahydrofuran.^[17] The structure is very similar to that of **2** though **4** shows no C₃ symmetry in the crystal (Figure 3). Again, the pyridone ligand is coordinated to the ruthenium

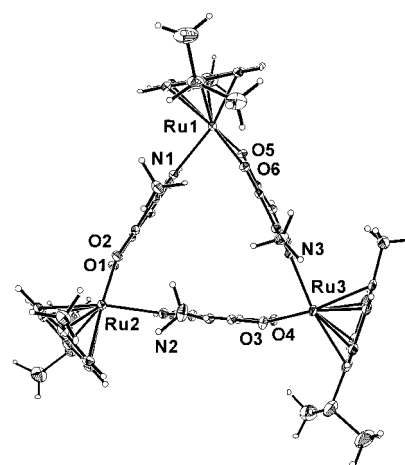
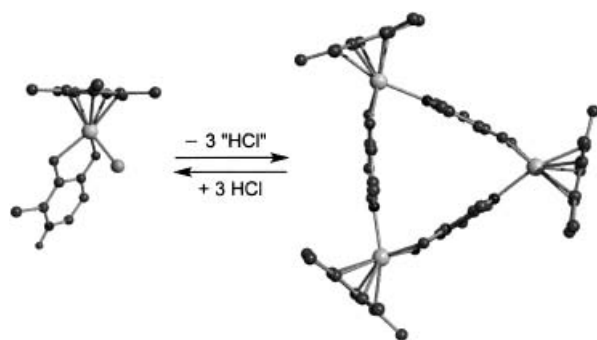


Figure 3. Structure of **4** in the crystal; selected bond lengths [Å] and angles [°]: Ru(1)–O(5) 2.066(2), Ru(1)–O(6) 2.063(3), Ru(1)–N(1) 2.169(3), O(5)–C(45) 1.322(4), O(6)–C(46) 1.345(4), O(6)–Ru(1)–N(1) 83.29(11), O(5)–Ru(1)–N(1) 83.11(11), O(6)–Ru(1)–O(5) 80.07(10).

atoms through both oxygen atoms (in a bent fashion: C(34)–C(33)–O(1)–Ru(2) = 14.2°) and the nitrogen atom. All bond lengths and angles lie within the expected range. The distance between the ruthenium atoms (7.24 Å) is exactly the same as for the iridium atoms in **2**.

There are very few reports on the controlled disassembly of polynuclear macrocyclic complexes such as molecular “squares” or cages.^[19] Chemical or physical means that trigger the assembly–disassembly process are nevertheless highly desirable because of the possible applications in host–guest chemistry. The organometallic macrocycles **2** and **4** can be transformed quantitatively into their constituent monomeric complexes by adding three equivalents of HCl (0.6 M in ethyl acetate). Thus, macrocyclization can be induced *and* reversed by addition of appropriate amounts of base or acid, respectively (Scheme 2).



Scheme 2. The assembly–disassembly process can be triggered by addition of acid or base, respectively.

We have shown that triangular organometallic macrocycles can be obtained with the dianion of 3-hydroxy-2-methyl-4(1*H*)-pyridone as the bridging ligand. The assembly process, which proceeds in virtually quantitative yields, is absolutely diastereoselective and can be reversed chemically. The strategy for the construction of such “molecular triangles” appears to be rather general since different half-sandwich complexes can be incorporated. Utilization of other fragments such as {Cp**Rh*^{III}} or {Cp**Ru*^{II/III}} therefore seems possible. Because of the shape of these macrocycles they are potential hosts for small organic and inorganic molecules.

Experimental Section

1: A 2.3 M solution of NaOMe in methanol (0.2 mmol) was added to a suspension of 3-hydroxy-2-methyl-4(1*H*)-pyridone (25 mg, 0.2 mmol) in methanol (10 mL). [{Cp**Ir*Cl₂]₂] (80 mg, 0.1 mmol) was added to the resulting clear solution and the mixture was stirred for 2 h. After removal of the solvent in vacuo the product was extracted with a mixture of dichloromethane/diethyl ether (30 mL, 2/1). Subsequent addition of hexane (20 mL) and evaporation of the solvent under reduced pressure gave a yellow powder which was dried in vacuo. Yield: 84 %; IR (KBr): ν = 3236 cm^{−1} (m, NH), 3130 (m, NH), 1588 (m), 1523 (s), 1493 (s); ¹H NMR (270 MHz, CD₂Cl₂): δ = 1.61 (s, 15H; Cp*), 2.09 (s, 3H; CH₃), 6.23 (d, ³*J* = 5.8 Hz, 1H; CH, pyridone), 7.00 (d, ³*J* = 5.7 Hz, 1H; CH, pyridone); ¹³C NMR (68 MHz, CD₂Cl₂): δ = 8.80 (CH₃, Cp*), 13.41 (CH₃, pyridone), 81.77 (C(CH₃)₂), 109.35, 128.29, 131.36, 160.99, 177.17 (pyridone); *M*_{calcd} = 487.02, MS (FAB): (*m/z*): 452.1 [*M* − Cl]⁺; elemental analysis calcd for C₁₆H₂₁IrNO₂: C 39.46, H 4.35, N 2.88; found: C 40.05, H 4.76, N 2.94.

2: A 2.3 M solution of NaOMe in methanol (0.8 mmol) was added to a suspension of 3-hydroxy-2-methyl-4(1*H*)-pyridone (50 mg, 0.4 mmol) in methanol (10 mL). [{Cp**Ir*Cl₂]₂] (159 mg, 0.2 mmol) was added to the resulting clear solution and the mixture was stirred for 1.5 h. After removal of the solvent in vacuo the product was extracted with dichloromethane (100 mL). A yellow powder was obtained after evaporation of the solvent under reduced pressure and drying in vacuo. Yield: 78 %; IR (KBr): ν = 1578 cm^{−1} (s), 1540 (m), 1483 (s), 1450 (m); ¹H NMR (400 MHz, CD₂Cl₂ + 10 % CD₃OD): δ = 1.53 (s, 15H; Cp*), 2.43 (s, 3H; CH₃), 5.88 (d, ³*J* = 6.1 Hz, 1H; CH, pyridone), 6.90 (d, ³*J* = 6.3 Hz, 1H; CH, pyridone); ¹³C NMR (101 MHz, CD₂Cl₂ + 10 % CD₃OD): δ = 10.43 (CH₃, Cp*), 19.95 (CH₃, pyridone), 83.87 (C(CH₃)₂), 111.43, 142.51, 144.86, 161.32, 170.73 (pyridone); *M*_{calcd} = 1351.68, MS (FAB): (*m/z*): 1352.1 [*M*]⁺; elemental analysis calcd for C₄₈H₆₃IrN₃O₆ · CH₂Cl₂: C 40.97, H 4.35, N 2.92; found: C 40.81, H 4.26, N 2.59.

3: The synthesis was performed analogous to **1** using [(η^6 -cymene)-RuCl₂]₂. Orange powder, yield: 81 %; IR (KBr): ν = 3230 cm^{−1} (m, NH), 3123 (m), 1587 (m), 1523 (s), 1492 (s); ¹H NMR (270 MHz, CD₂Cl₂): δ = 1.23 (d, ³*J* = 6.7 Hz, 6H; CH(CH₃)₂), 1.99 (brs, 3H; CH₃), 2.18 (s, 3H; CH₃), 2.78 (sept, ³*J* = 7.0 Hz, 1H; CH(CH₃)₂), 5.14 (d, ³*J* = 5.9 Hz, 2H; CH, cymene), 5.38 (d, ³*J* = 6.0 Hz, 1H; CH, cymene), 6.13 (brs, 1H; CH, pyridone), 6.82 (brs, 1H; CH, pyridone); ¹³C NMR (68 MHz, CD₂Cl₂): δ = 13.39, 18.23, 22.05 (CH₃), 31.09 (CH(CH₃)₂), 77.74, 79.68 (CH, cymene), 95.38, 98.56 (C, cymene), 108.78, 128.11, 130.61, 159.07, 175.83 (pyridone); *M*_{calcd} = 394.86, MS (FAB): (*m/z*): 360.0 [*M* − Cl]⁺; elemental analysis calcd for C₁₆H₂₀NO₂Ru: C 48.67, H 5.11, N 3.55; found: C 48.52, H 5.91, N 3.40.

4: The synthesis was performed analogous to **3** using [(η^6 -cymene)-RuCl₂]₂. Orange powder, yield: 82 %; IR (KBr): ν = 1576 cm^{−1} (s), 1539 (m), 1482 (s), 1445 (m); ¹H NMR (400 MHz, CD₂Cl₂): δ = 1.20 (d, ³*J* = 7.3 Hz, 3H; CH(CH₃)₂), 1.27 (d, ³*J* = 7.3 Hz, 3H; CH(CH₃)₂), 1.98 (s, 3H; CH₃), 2.34 (s, 3H; CH₃), 2.68 (s, ³*J* = 7.2 Hz, 1H; CH(CH₃)₂), 4.96 (d, ³*J* = 5.7 Hz, 1H; CH, cymene), 4.98 (d, ³*J* = 5.8 Hz, 1H; CH, cymene), 5.15 (d, ³*J* = 5.8 Hz, 1H; CH, cymene), 5.31 (d, ³*J* = 5.8 Hz, 1H; CH, cymene), 5.60 (d, ³*J* = 6.3 Hz, 1H; CH, pyridone), 6.78 (d, ³*J* = 6.0 Hz, 1H; CH, pyridone); ¹³C NMR (68 MHz, CD₂Cl₂): δ = 17.55, 22.10, 22.28, 22.41 (CH₃), 31.08 (CH(CH₃)₂), 78.92, 79.38, 79.65, 80.18 (CH, cymene), 94.58, 99.52 (C, cymene), 107.67, 139.85, 141.96, 157.60, 167.93 (pyridone); *M*_{calcd} = 1075.20, MS (FAB): (*m/z*): 1074.9 [*M*]⁺; elemental analysis calcd for C₄₈H₅₇N₃O₆Ru₃ · THF: C 54.44, H 5.71, N 3.66; found: C 53.91, H 5.64, N 3.51.

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- [17] Crystal structure analysis: General: Siemens CCD area detector, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$, semiempirical absorption correction with SADABS. The structure was solved with direct methods (SHELXS-97, Sheldrick, 1990). 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-127378 (**2**) and CCDC-127377 (**4**). 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). Crystal structure analysis of **2**· 0.5CHCl_3 : crystal size $0.02 \times 0.01 \times 0.01 \text{ mm}$. The crystal was mounted in perfluoropolyether oil, $T = 173 \text{ K}$, yellow prism, hexagonal, space group $R\bar{3}$, $a = b = 19.6202(6)$, $c = 21.9013(9) \text{ \AA}$, $V = 7301.4(4) \text{ \AA}^3$, $Z = 6$, $\rho_{\text{calcd}} = 1.926 \text{ Mg m}^{-3}$, $\mu = 8.313 \text{ mm}^{-1}$. Data collection: 2θ from 3.04 to 59.02 , $-25^\circ \leq h \leq 25$, $-24 \leq k \leq 24$, $-28 \leq l \leq 24$, 14 799 reflections collected, 3515 independent reflections, 2590 observed reflections ($F > 4\sigma(F)$), max./min. transmission 0.9215/0.8514, $R_1 = 0.0471$, $wR_2 = 0.1038$ ($F > 4\sigma(F)$), $\text{GOF}(F^2) = 1.047$, residual electron density $5.080/-2.994 \text{ e \AA}^{-3}$, the weighting scheme is $w^{-1} = \sigma^2 F_o^2 + (0.0477P)^2 + 221.7031P$ with $P = (F_o^2 + 2F_c^2)/3$. A riding model was employed for the hydrogen atoms. There is a high electron density near the Ir atom ($0.78 \text{ \AA}$, $5.08 \text{ e \AA}^{-3}$). The solvent molecule is only partially occupied ($\text{GOF} = 0.1666$). Crystal structure analysis of **4**·THF: crystal size $0.20 \times 0.10 \times 0.10 \text{ mm}$. The crystal was mounted in perfluoropolyether oil, $T = 183 \text{ K}$, red prism, monoclinic, space group $C2/c$, $a = 35.694(2)$, $b = 14.6090(7)$, $c = 22.456(1) \text{ \AA}$, $\beta = 123.527(1)^\circ$, $V = 9761.3(8) \text{ \AA}^3$, $Z = 8$, $\rho_{\text{calcd}} = 1.550 \text{ Mg m}^{-3}$, $\mu = 0.970 \text{ mm}^{-1}$. Data collection: 2θ from 3.10 to 58.60 , $-44 \leq h \leq 44$, $-18 \leq k \leq 18$, $-27 \leq l \leq 28$, 28 663 reflections collected, 9848 independent reflections, 6759 observed reflections ($F > 4\sigma(F)$), max./min. transmission 0.9092/0.8296, $R_1 = 0.0356$, $wR_2 = 0.0797$ ($F > 4\sigma(F)$), $\text{GOF}(F^2) = 0.943$, residual electron density $1.013/-0.786 \text{ e \AA}^{-3}$, weighting scheme $w^{-1} = \sigma^2 F_o^2 + (0.0488P)^2 + 0.0000P$ with $P = (F_o^2 +$

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Inhibition of Angiogenesis In Vivo by *ets-1* Antisense Oligonucleotides—Inhibition of *Ets-1* Transcription Factor Expression by the Antibiotic Fumagillin**

Nicolas Wernert,* Antje Stanjek, Serafim Kiriakidis, Anja Hügel, Hem Chandra Jha, Ralph Mazitschek, and Athanassios Giannis*

Dedicated to Professor Konrad Sandhoff
on the occasion of his 60th birthday

The formation of new blood capillaries from preexisting ones (angiogenesis or neovascularization; Scheme 1) is a fundamental aspect of many physiological and pathological processes^[1] such as reproduction, embryonic development, wound healing, chronic inflammation, and malignant growth. Folkman's view of the early 1970s^[2] that an appropriate blood supply is necessary for tumor growth has been confirmed meanwhile. Furthermore, subsequent investigations have shown that not only tumor growth but also tumor metastasis is dependent on angiogenesis.^[3] For these reasons anti-angiogenesis became an attractive strategy for the treatment of neoplastic diseases.^[4–7] Angiogenesis inhibitors are likewise useful for the treatment of other frequent angiogenesis-dependent diseases such as diabetic retinopathy^[8] and rheumatoid arthritis.^[9]

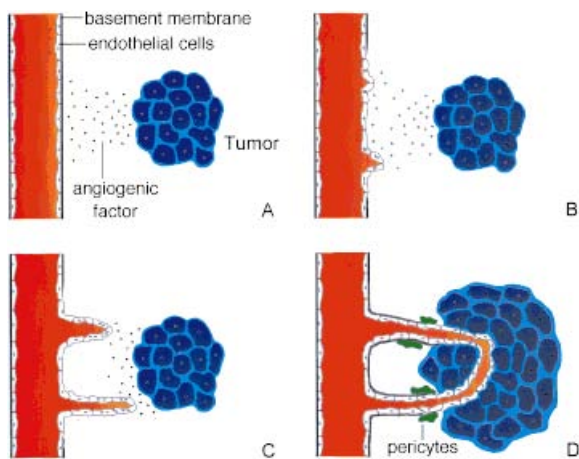
The mechanisms of angiogenesis have been intensively investigated during the last years, and several endogenous regulators have been identified.^[10] Vascular endothelial

[*] Prof. Dr. N. Wernert, Dr. A. Hügel
Institut für Pathologie der Universität
Postfach 2120, D-53011 Bonn (Germany)
Fax: (+49) 228-287-50-30
E-mail: wernert@mail.meb.uni-bonn.de

Prof. Dr. A. Giannis, Dr. A. Stanjek,
Dipl.-Chem. R. Mazitschek
Institut für Organische Chemie der Universität
Richard-Willstätter-Allee 2, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-608-7652
E-mail: giannis@ochhades.chemie.uni-karlsruhe.de

Dr. S. Kiriakidis, Dr. H. C. Jha
Institut für Physiologische Chemie der Universität Bonn (Germany)

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Scheme 1. The complex process of angiogenesis comprises the following steps: A) Activation of the endothelial cell by growth factors. B) Degradation of the basement membrane of the blood vessels by proteinases (collagenases, plasminogen activator). C) Migration and proliferation of endothelial cells towards the angiogenic stimulus. Matrix metalloproteinases are recruited for extracellular matrix remodeling during this step. D) Formation of a new basement membrane around the immature blood vessels and merging of the ends of two outgrowing blood vessels (anastomosis). In general, tumor vascularization also stimulates tumor growth. Modified according to ref. [5, 33].

growth factor (VEGF), a protein with several isoforms, is considered to be the most important stimulator of angiogenesis.^[11] The different VEGF isoforms bind to two tyrosine kinase receptors, VEGF-R1 (*flt-1*) and VEGF-R2 (*flk-1*), both of which are almost exclusively present on the plasma membrane of endothelial cells.^[12] Activation of VEGF receptors leads by the Ras-Raf-MAP-kinase pathway to the expression^[11] of proteinases (serine proteinases, cysteine proteinases, and matrix metalloproteinases) and of specific integrins on endothelial cell surfaces, and finally initiates the proliferation and the migration of these cells towards the angiogenic stimulus. The Ets-1 transcription factor^[13, 14] plays an important role for the regulation of neovascularization. Some of the genes which encode the above-mentioned proteinases contain within their promotor sequences Ets binding sites with the central core motif GGAA/T. Ets-1 binds to these regulatory control regions through a helix–turn–helix motif and enhances the expression of these proteinases.

We were able to show that the expression of Ets-1 proteins is stimulated during tumor-induced angiogenesis.^[15, 16] Recently it has also been reported that stimulation of human endothelial cells with VEGF leads to an induction of Ets-1 expression.^[17] Interestingly enough, the Ets-1 protein is also involved as a positive regulatory factor in the transcriptional control of the gene encoding VEGF-R1 (*flt-1*).^[18] However, the importance of Ets-1 for in vivo angiogenesis has not been demonstrated yet.

Here we report for the first time that *ets-1* antisense oligodeoxynucleotides (ODN) effectively reduce the formation of new blood vessels on the chick chorioallantois membrane (CAM-assay^[19]). Additionally, we show that the potent angiogenesis inhibitor fumagillin (**3**) strongly inhibits Ets-1 expression.

To block Ets-1 expression in the CAM assay we used the phosphorothioate antisense ODN 5'-AGATC-

GACGGCCGCCTTCAT-3' (**1**), which inhibits Ets-1 expression in cultured endothelial cells.^[17] This 20-mer is complementary to the AUG initiation codon and a short "downstream" sequence of the *c-ets-1* mRNA. We used the sense phosphorothioate 5'-ATGAAGGCGGCCGTCGATCT-3' (**2**) as a negative control. We directly applied three different concentrations of either antisense or sense ODNs (2.5, 5, and 10 µg per egg; the ODNs were dissolved in 5 µL of 150 mM NaCl and 5 µL of transfection solution,^[20] respectively) on the chicken chorioallantois membrane on day 5 of development and evaluated the results on day 7. A drastic reduction of angiogenesis was observed after application of 5 µg of antisense ODN **1** (seven embryos compared to eight embryos of the sense control group). Both the number and the diameter of blood vessels were significantly reduced (Figure 1 c–g). No effect was detected in either the antisense group (two embryos) or in the sense group (three embryos) after application of 2.5 µg of ODN. All six embryos in the antisense group and five of six embryos in the control group had died by day 7 following the application of 10 µg of sense or antisense ODN. We observed no inhibition of angiogenesis when using the transfection solution alone (Figure 1 h).

Since the biosynthesis rate of the Ets-1 transcription factor is greatly enhanced during angiogenesis under both physio-

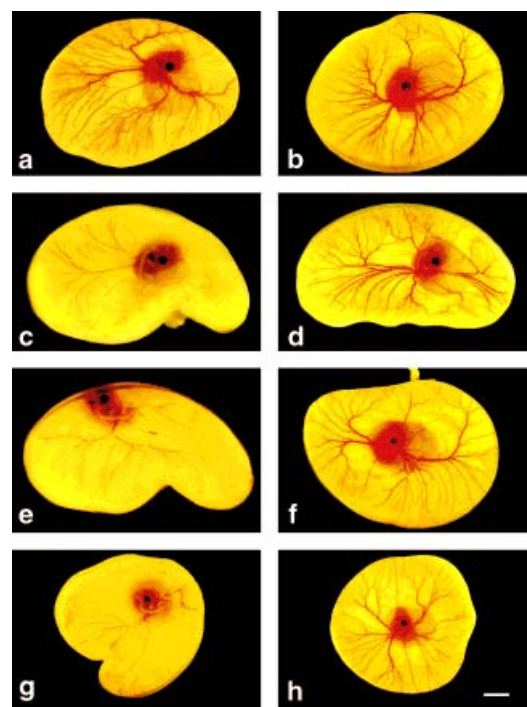


Figure 1. Inhibition of blood vessel development on the chick chorioallantois membrane by *ets-1* antisense ODN **1**. No angiostatic effect was detected after application of 2.5 µg of antisense ODN in 10 µL of transfection solution (a) or of 2.5 µg of sense ODN in 10 µL of transfection solution (b). In contrast, a strong inhibition of angiogenesis was observed after application of 5 µg of antisense ODN in 10 µL of transfection solution (c, e, g; examples of different embryos). Compared to the sense control group (d, f; in each case 5 µg of sense ODN in 10 µL of transfection solution), both the number and the diameter of blood vessels were significantly reduced. No angiostatic effect was observed after application of the transfection solution alone (h, bar = 1 cm). The oligodeoxynucleotides were purchased from Applied Biosystems, Weiterstadt (Germany), and the transfection solution was purchased from Euromedex, Strasbourg (France).

logical and pathological conditions, a participation of Ets-1 in in vivo blood vessel formation has strongly been suggested. When angiogenesis is finished, Ets-1 expression is downregulated again.^[21] The results obtained in the present study prove for the first time the in vivo role of the Ets-1 transcription factor in neovascularization. This is further supported by investigations in cultured endothelial cells^[17] in which inhibition of Ets-1 expression by the antisense ODN **1** not only diminishes cell proliferation and migration but also the production of urokinase-type plasminogen activator and collagenase I. Both enzymes are necessary for extracellular matrix remodeling during angiogenesis.^[5, 22, 23]

In view of these findings the Ets-1 transcription factor represents a promising target in experimental cancer therapy.^[13] In addition to antisense strategies, low molecular weight compounds which inhibit Ets-1 expression seem particularly useful. We assumed that the fungal metabolite fumagillin (**3**),^[24] which strongly inhibits both endothelial cell proliferation in vitro and angiogenesis in vivo, could exert its effects by modulating Ets-1 expression. To investigate this hypothesis, we stimulated human umbilical vein endothelial cells (HUVEC) with VEGF in the absence or in the presence of fumagillin and subsequently investigated Ets-1 expression by Western blotting. Four hours after application of VEGF (150 ng) we observed a significant increase of both the p51 and the p39 Ets-1 proteins.^[25] Upon simultaneous application of VEGF and fumagillin (0.15 nM) we found a nearly complete inhibition of the biosynthesis of both proteins (Figure 2). As expected, fumagillin also inhibits in vivo angiogenesis in the CAM assay (Figure 3).

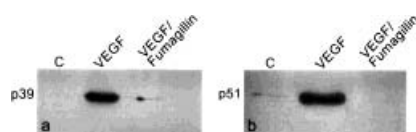


Figure 2. Inhibition by fumagillin (**3**) of VEGF-induced Ets-1 expression in cultured human umbilical vein endothelial cells (HUVEC). The HUVEC cells were cultured in Medium 200 (TEBU) with low serum growth supplement (LSGS, TEBU). After confluence, cells were maintained in LSGS-free medium for four hours and then stimulated for four hours with VEGF (150 ng) with or without fumagillin (0.15 nM). Proteins were extracted with Trizol,^[34] separated electrophoretically by means of SDS-PAGE, and blotted onto a nitrocellulose membrane. Ets-1 proteins were demonstrated by ELISA. For the detection of Ets-1 proteins a polyclonal rabbit antibody (directed against amino acids 422–441, Santa Cruz, CA) and a monoclonal mouse antibody (directed against amino acids 122–288, Transduction Laboratories) were used. Bands were visualized with the BM Chemoluminescence Western Blotting Kit (Boehringer Mannheim, Germany). VEGF strongly induced both p39 (a, polyclonal rabbit antibody) and p51 (b, monoclonal mouse antibody) Ets-1 proteins (lane 2 in (a) and (b)). This induction was nearly completely inhibited by fumagillin (lane 3).

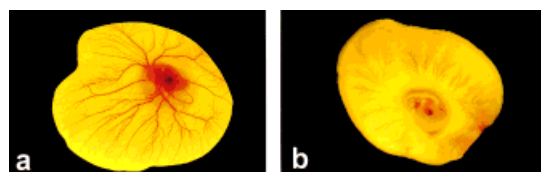
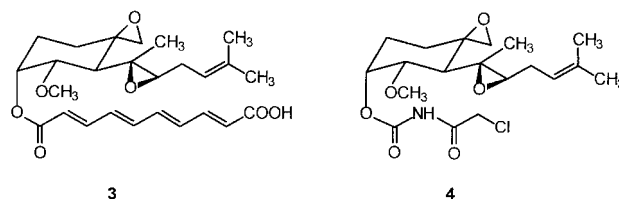


Figure 3. Inhibition of blood vessel development on the chick chorioallantoic membrane (CAM) by fumagillin (**3**). A methylcellulose plate^[19] (diameter about 2 mm) containing 10 µg of fumagillin was applied on the outer one-third of the CAM on day 5 of development. The results were evaluated after 48 h. Fumagillin caused a significant and generalized inhibition of angiogenesis (b) compared to the negative control (a).

The bisepoxide **3** is one of the most potent angiostatic agents. Its synthetic analogue TNP-470 **4** was the first angiostatic drug in clinical trials.^[26]



It has already been shown that fumagillin is a covalent inhibitor of the enzyme methionine aminopeptidase type 2 (MetAP-2).^[27] The crystal structure of the fumagillin–MetAP-2 complex has recently been published.^[28] However, the link between MetAP-2 inhibition and the angiostatic effect is not yet clear. The cobalt-dependent enzyme MetAP-2 is responsible for the removal of N-terminal methionine residues from specific proteins,^[29] which are essential for cell-cycle progression of endothelial cells. It has been supposed that these proteins participate in the signal transduction cascade triggered by VEGF.^[30] Our results suggest that inhibition of Ets-1 expression by fumagillin is an important aspect of the angiostatic effect of this natural compound. The way in which this inhibition is achieved is not yet clear. Both a fumagillin-mediated decrease of Ets-1 biosynthesis or a stimulation of Ets-1 degradation are conceivable. In addition, MetAP-2 might participate in the regulation of Ets-1 transcription factor activity.^[31] In this context it is noteworthy that Ets-1 contains a N-terminal methionine group^[32] and is therefore a potential MetAP-2 substrate.

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A Robust, Environmentally Benign Catalyst for Highly Selective Hydroformylation**

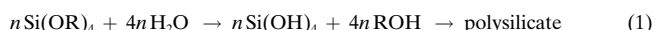
Albertus J. Sandee, Lars A. van der Veen,
Joost N. H. Reek, Paul C. J. Kamer, Martin Lutz,
Anthony L. Spek, and Piet W. N. M. van Leeuwen*

The hydroformylation of olefins to aldehydes is an important example of an efficient and clean process, because of its potentially 100% atom economy.^[1] In the industrial production of C₄ and C₅ aldehydes, where regioselectivity towards the more valuable linear aldehyde product is critical, rhodium–triphenylphosphane complexes are used as catalysts. The products are separated from the catalyst by distillation, which results in catalyst decomposition as an undesirable side reaction. Furthermore, distillation techniques are not suitable for the production of heavier products or fine chemicals because of the high boiling points.

The use of an aqueous biphasic system, in which the water phase contains the dissolved catalyst, affords a straightforward separation of the organic products. To this end, a process using the water-soluble catalyst [HRhCO(TPPTS)₃] (TPPTS = triphenylphosphanyl trisulfonate) has been developed by Ruhrchemie/Rhône-Poulenc for the hydroformylation of propene.^[2] This process meets all the requirements for an environmentally benign process. The applicability of the aqueous biphasic system is, however, strictly limited to substrates that are slightly soluble in water, such as propene and but-1-ene.

A widely investigated approach to facilitate catalyst–product separation is the attachment of the catalyst to a polymeric resin.^[3] To date, immobilized catalysts of industrial importance are still unknown: Metal leaching^[4] and low catalyst selectivity are the insurmountable problems.

The hydroformylation catalyst that we present here is covalently anchored to a silicate matrix by the sol–gel technique.^[5] This material can be prepared by a simultaneous cocondensation of tetraalkoxysilanes and functionalized trialkoxysilanes [Eq. (1)].^[6] The sol–gel technique is an ideal method to immobilize catalysts because of its diversity^[7] and



[*] Prof. Dr. P. W. N. M. van Leeuwen, A. J. Sandee, L. A. van der Veen, Dr. J. N. H. Reek, Dr. P. C. J. Kamer
Institute of Molecular Chemistry, Nieuwe Achtergracht 166
1018 WV Amsterdam (The Netherlands)
Fax: (+31)20-525-6456
E-mail: pwnm@anorg.chem.uva.nl
Dr. M. Lutz, Dr. A. L. Spek
Bijvoet Center for Biomolecular Research
Utrecht (The Netherlands)

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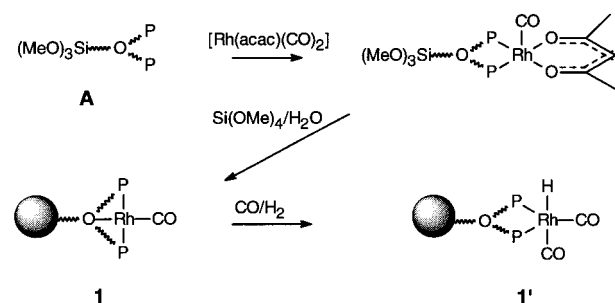


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its mildness (recently lipases were successfully immobilized using the sol–gel technique).^[8] The few examples, however, of sol–gel-immobilized hydroformylation catalysts reported so far show considerable amounts of metal leaching^[9] and low selectivity of the catalyst.^[10]

Diphosphanes with a large natural P–M–P bite angle have a beneficial influence on the regioselectivity of homogeneous hydroformylation catalysts.^[11] In our group xanthene-based ligands (P–M–P $\approx 110^\circ$) were especially designed for this purpose.^[12] Overall selectivities of 93 % for the linear aldehyde were obtained.^[13] A novel xanthene-based ligand, *N*-(3-trimethoxysilane-*n*-propyl)-4,5-bis(diphenylphosphanyl)-phenoxazine (siloxantphos, **A**), was synthesized and immobilized as a rhodium–diphosphane complex in a sol–gel.^[14]

On stirring a solution of siloxantphos, [Rh(acac)(CO)₂] (acac = acetylacetonate), and tetramethyloctosilicate (TMOS) in THF/H₂O, the cationic complex [Rh(siloxantphos)CO]⁺ (**1**, Scheme 1) was formed, which was immobilized in the silica (Figure 1). Interestingly the gelation of these



Scheme 1. Schematic illustration of the preparation of sol–gel-immobilized [HRh(siloxantphos)(CO)₂].

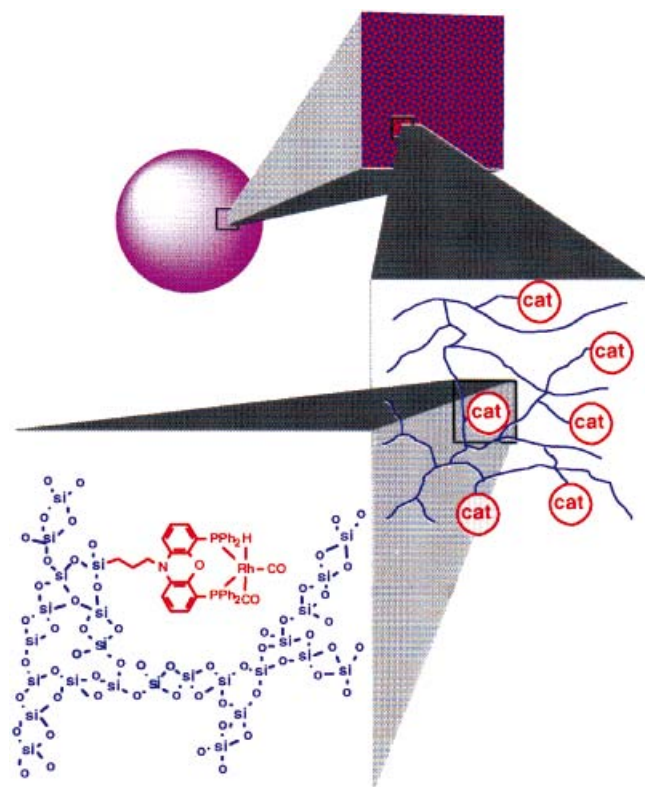
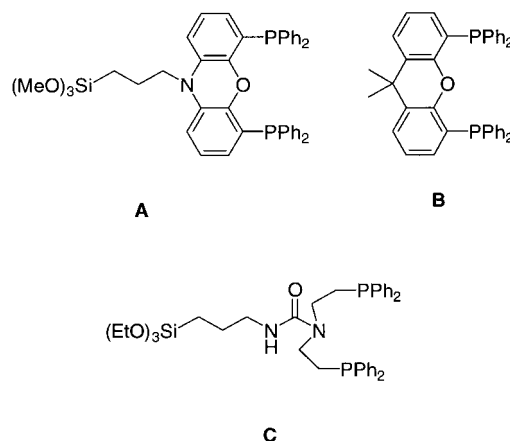


Figure 1. A schematic representation of the sol–gel-immobilized catalyst [HRh(siloxantphos)(CO)₂].

mixtures takes place within one hour without the use of an additive to catalyze the polycondensation of the silica monomers. This suggests that the rhodium–xanthenediphosphane complex acts as a catalyst in this process (the same mixture without **A** has a gelation time of about seven days, even with a large excess of acetylacetone). We observed the formation of the cationic complex by monitoring the sol–gel process of a mixture of 9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (xantphos, **B**) and [Rh(acac)(CO)₂] by



liquid-state ³¹P NMR spectroscopy. (Nonimmobilized complexes can easily be studied during the sol–gel process by means of liquid-state NMR spectroscopy. This is not possible for the immobilized rhodium–siloxantphos complex.^[15]) After [Rh(xantphos)(acac)CO] is formed, this complex quantitatively turns into [Rh(xantphos)CO]⁺ (**2**) during the gelation process. Probably, acidic silanols, formed during the hydrolysis of TMOS, protonate the acetylacetonate to acetylacetone. As a consequence **2** is formed having a silicate counterion (it cannot be excluded that acac[−] is the counterion of these cationic rhodium–diphosphane–carbonyl complexes).

On exposing the gel containing **2** to one atmosphere of CO/H₂ (1/1), the color of the gel changes from orange to yellow. NMR studies showed the transformation from **2** to [HRh(xantphos)(CO)₂] (**2'**), which is the key intermediate for a selective hydroformylation catalyst in a homogeneous phase.^[12]

System **1** was characterized by means of solid-state ³¹P MAS NMR and FT-IR spectroscopy, and both the phosphorus chemical shift and the carbonyl vibration were in good agreement with the fully characterized (homogeneous) complexes **2**(OTf) (Tf = F₃CSO₂) and **2**(BF₄) (Table 1).^[16] Using

Table 1. Spectroscopic data for immobilized [Rh(siloxantphos)CO]⁺ (**1**) and homogenous analogues.^[a]

	1	2 (OTf)	2 (BF ₄)
³¹ P-NMR:			
δ (<i>J</i> _{P-Rh} [Hz])	38 (br) ^[b]	36 (br), ^[b] 37.4 (d, 122) ^[c]	37.2 (d, 122) ^[c]
FT-IR:			
$\tilde{\nu}$ (CO) [cm ^{−1}]	2011	2003	1998

[a] For more details see the Experimental Section. [b] Obtained by means of MAS solid-state NMR spectroscopy; *J*_{P-Rh} is too small for detection in the solid state. [c] Obtained by means of liquid-state NMR spectroscopy.

X-ray photoelectron spectroscopy (XPS) we evidenced that rhodium is present purely in the oxidation state I. The binding energies of the rhodium 3d electrons in **1** were found to be 312 and 317 eV with a relative intensity of 3.3 and 2. For **2**(BF₄) similar binding energies of 311 and 316 eV were determined with a relative intensity of 3.2 and 2 (Figure 2). This is in good agreement with the twofold degenerated energy levels of the rhodium 3d electrons known for rhodium(I) compounds.^[17] No traces of metallic rhodium(0) were found in the samples.

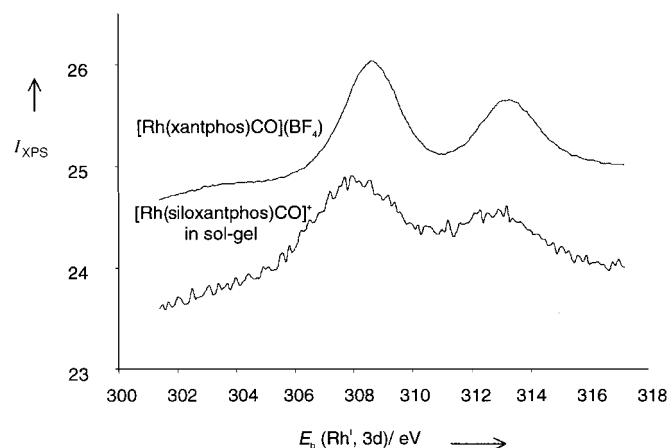


Figure 2. Binding energy of rhodium 3d electrons determined by means of XPS.

The porous nanostructure of the functionalized silica **1** was visualized by means of transmission electron microscopy (TEM) (Figure 3). From the TEM experiments, which were performed without using staining techniques, it was concluded that no clustered rhodium particles were present in the material.^[18] This substantiates the results obtained from the XPS experiments.

The crystal structure of **2**(BF₄) shows that in the cationic complex the xanthene ligand coordinates in a tridentate

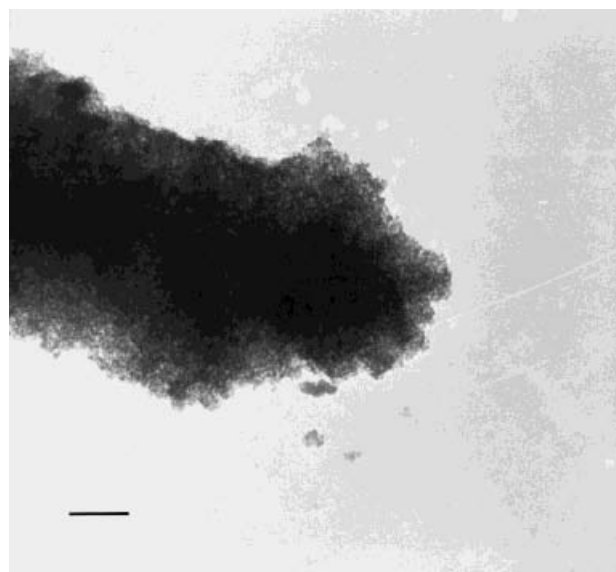


Figure 3. Electron micrograph of an aqueous suspension of sol-gel-immobilized [Rh(siloxantphos)CO]⁺. The bar represents 100 nm.

fashion, with the phosphane groups in a *trans* coordination and the ether oxygen atom as a hemilabile donor atom (Rh–O 2.126(3) Å; Figure 4).^[19] This POP chelate coordination on rhodium, earlier found for 1,5-bis(diphenylphosphanyl)-3-oxapentane,^[20] is likely an important stabilizing factor for the complex during the sol–gel process.^[6]

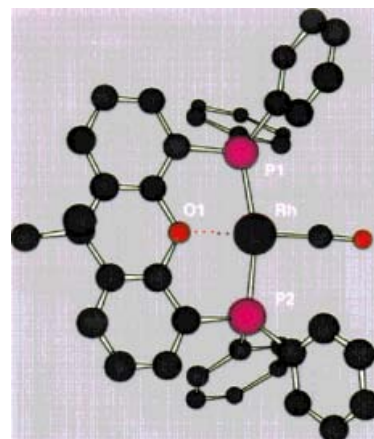


Figure 4. The X-ray structure of [Rh(xantphos)CO](BF₄) (**2**(BF₄)) (hydrogen atoms and the BF₄[−] counterion are omitted for clarity). Selected bond distances [Å] and angles [°]: Rh–P1 2.266(11), Rh–P2 2.282(11), Rh–O1 2.126(3), Rh–C(O) 1.798(5); P1–Rh–P2 164.42(4), O1–Rh–C(O) 175.33(19), O1–Rh–P1 83.41(8), O1–Rh–P2 83.68(8).

The catalytic performance of **1** in the hydroformylation of 1-octene was studied in a batch process using 1 g of silica containing 1×10^{-5} mol of rhodium. The selectivity of **1** was as high as 93 % towards the linear aldehyde, which is similar to the value for the homogeneous catalyzed reaction (Table 2, entries 1 and 9). In the absence of the xanthene ligand the selectivity is lowered dramatically (Table 2, entry 8; 26 % *n*-nonanal).

The high selectivity of **1** is induced by the large natural P–Rh–P bite angle. This was proven on comparing **A** (bite angle 108° in **1'**) with a ligand having a much smaller bite angle (93°): *N*-(3-triethoxysilane-*n*-propyl)-*N,N'*-bis[2-(diphenylphosphanyl)ethyl]urea (siloxPNP, **C**).^[14, 21] This ligand was sol–gel processed in the same way as **A** (Scheme 1), and immobilized [Rh(siloxPNP)CO]⁺ (**3**) obtained was subsequently tested in the hydroformylation of 1-octene. The linear-to-branched product ratio using **3** is 15 times lower than for **1** (Table 2, entry 10). This proves that indeed the large P–Rh–P bite angle, as we already reported for the homogeneous systems, plays a key role in the regioselectivity of immobilized systems.

The recyclability of catalyst **1** was studied by performing a series of consecutive runs (Table 2, entries 1–5). We observed no deterioration of the catalytic performance in at least eight cycles. The linear-to-branched ratio remained very high during all experiments and only 2 % of isomers of 1-alkene was formed. The decrease in rate in successive catalytic cycles is very small, indicating that ligand **A** retains the rhodium quantitatively in the solid state. This is confirmed by rhodium analysis on the product by means of atomic emission spectroscopy. No rhodium traces were detected in any of the experiments using **1** and **3**.

Table 2. Results from the hydroformylation of 1-octene at 80 °C and 50 bar CO/H₂.

Entry	Catalyst (cycle) ^[a]	Con- version [%]	TOF ^[b]	Linear aldehyde ^[c] [%]	Branched aldehyde ^[c] [%]	Alkene isomerization ^[c] [%]	<i>n</i> -Aldehyde hydrogenation ^[c] [%]	Linear: branched ^[c]	Rh leach- ing ^[d] [%]
1	1 (1)	69	35	92.8	3.0	1.7	2.5	32:1	< 1
2	1 (2)	69	36	94.1	2.7	2.0	1.2	36:1	< 1
3	1 (3)	69	36	94.0	2.7	2.3	1.0	35:1	< 1
4	1 (4)	67	35	94.5	2.7	2.2	1.3	35:1	< 1
5	1 (8)	63	33	95.0	2.6	2.0	0.5	37:1	< 1
6	1 ^[e]	92	32 ^[f]	95.5	2.3	1.6	0.6	43:1	< 1
7	1 ^[g]	63	287	95.5	2.4	1.9	0.3	40:1	< 1
8	[Rh(acac)(CO) ₂] in sol-gel ^[h]	64	175	26.3	16.3	57.4	0.0	1.6:1	> 50
9	A /[Rh(acac)(CO) ₂] (homogeneous)	19	283	93.3	2.9	3.7	0.0	32:1	–
10	3	72	119	70.0	28.9	1.0	0.1	2.4:1	< 1

[a] The ligand-to-rhodium ratio is 10:1; the catalysis was performed in toluene/*n*-propanol (13/1) using 1 mL of 1-octene. [b] Initial turnover frequencies (TOF) were calculated as the amount of aldehyde formed [mol h⁻¹] per mole of catalyst at 10–20% conversion. [c] Determined by means of GC analysis using decane as an internal standard. [d] Determined by means of atomic emission spectroscopy. [e] 3 mL of 1-octene were used. [f] Average turnover frequency. [g] In 14 mL of 1-octene and 1 mL of *n*-propanol. [h] No ligand was used.

Compound **1** is remarkably stable under catalytic conditions. We were able to use the catalyst for more than two weeks without loss of activity and selectivity. Even a three-day run, leaving only a few percent of the substrate unconverted, does not affect the performance of **1** (Table 2, entry 6). This long-term stability indicates that very high turnover numbers can be achieved with this system.

The rate of hydroformylation of 1-octene using **1** has a first-order dependency in substrate concentration, and the exact rate under these specific conditions was determined to be 0.038[octene].^[22] As a consequence we found a high rate of hydroformylation when the reaction was performed in pure octene (initial turnover rate of 287 mol h⁻¹ per mol of catalyst; Table 2, entry 7). This rate is about the same as that of the homogeneous catalyzed reaction (283 mol h⁻¹ per mol of catalyst) which was performed in toluene (Table 2, entry 9).

Complex **1** is the most selective immobilized hydroformylation catalyst to date. With **1**, the almost ideal situation is reached in that a product, which may have any boiling point or polarity, is isolated in 95% purity after only one simple filtration. Moreover, this system is one of the first examples of a heterogenized catalyst that is free of metal leaching. These features make this novel catalyst perfectly suitable for application in the production of fine chemicals. Furthermore, waste streams are expected to be relatively small because: 1) we find only small amounts of side products, 2) there is no solvent needed, and 3) the catalyst is stable for a long time and shows no metal leaching. It can be concluded that **1** is an interesting environmentally benign catalyst for the selective hydroformylation towards linear aldehydes.

Experimental Section

Synthesis of polysiloxane-bound [Rh(siloxantphos)CO]⁺: A mixture of [Rh(acac)(CO)₂] (5 mg, 0.01946 mmol) and siloxantphos (138.7 mg, 0.1946 mmol) was dissolved in THF (6 mL). H₂O (2 mL) and TMOS (2 mL) were subsequently added, and a red-brown two-phase system formed. MeOH was added until a clear red-brown solution was formed. Gelation took place within 1 h. After 36 h the gel was carefully dried under reduced pressure. The dried gel was powdered and thoroughly washed with MeOH, THF, and Et₂O. The resulting pink-red silicas were stored at

–20 °C. FT-IR (KBr): $\tilde{\nu}(\text{CO})$ 2011 cm⁻¹; ³¹P MAS NMR (121.4 MHz, NH₄H₂PO₄ ($\delta = 0.8$)): $\delta = 38$ (br, phosphane), 26 (br, some phosphane oxide), 51 (protonated phosphane).

The recycling experiments were performed as follows. A stainless steel 50-mL autoclave—equipped with a mechanical stirrer, a substrate vessel, a cooling spiral, and a sample outlet—was charged with 1 g of silica, containing 1 × 10⁻⁵ mol of rhodium catalyst, in toluene (10 mL) and *n*-propanol (1 mL). The suspension was incubated for 1 h at 80 °C under 20 bar CO/H₂ (1/1). A mixture of 1-octene (1 mL) and decane (1 mL) in toluene (3 mL) was added, and the CO/H₂ pressure was brought to 50 bar. The mixture was stirred for 24 h. The autoclave was cooled down to 10 °C, and the pressure was reduced to 1.8 bar. With the small overpressure the liquid was slowly removed from the catalyst with a 1.2-mm syringe. After the catalyst was washed with toluene (5 mL), toluene (10 mL) was added, and the pressure was brought to 20 bar. Finally the mixture was heated to 80 °C and the second cycle was performed.

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Visualization of Surface Gelation Processes in a Doped Sol–Gel Glass

Germain Puccetti* and Roger M. Leblanc

Sol–gel materials present an alternative to organic polymers and have the advantage of operating at room temperature. This makes them particularly interesting for doping with biological materials.^[1, 2] Much work on the chemistry of sol–gel materials aims at adjusting the initial sol composition to control the hydrolysis and condensation reactions according to the desired application of the end material. In situ studies of the evolution of a sol–gel in thin films are based on the optical (for example, fluorescence, interferometry) or mechanical properties (for example, stress) and yield macroscopic information from which the material evolution is inferred.^[3–5] Thin-film fabrication is particularly sensitive to the initial chemistry because of the strong influence of environmental constraints over the large exposed surface (air humidity, solvent evaporation).^[6–8]

[*] Dr. G. Puccetti, Prof. Dr. R. M. Leblanc
Center for Supramolecular Science and Department of Chemistry
University of Miami
P.O. Box 249118 Coral Gables, FL 33124–0431 (USA)
Fax: (+1) 305-284-1880
E-mail: gpuccetti@umiami.ir.miami.edu

The present work reports the first depth-resolved, in situ measurements of the near-surface regions of a material during its evolution from the sol to the gel states. The organic dye molecule β -carotene serves as a probe for the chemical changes that occur during the sol–gel evolution. Depth analysis evidences a clearly distinct chemical evolution at the surface of the material relative to the bulk. This is attributed to the exposition of the surface to air.

Photoacoustic spectroscopy (PAS) relies on optical excitation of a material and measurement of the induced heat release. Despite its simple basic principles, PAS covers a broad range of phenomena that occur during the process of converting absorbed light into the release of heat. Several information factors can be identified that influence, directly or indirectly, the energy conversion process: a) the light absorption coefficient; b) the molecular-level de-excitation process; c) the excitation/heat transfer to the molecular environment; d) heat propagation; and e) the spatial distribution of microscopic heat sources inside the sample. The characterization of any material by PAS is governed by three main material properties: 1) the light absorption distribution (Beer's law); 2) the thermal diffusion; and 3) the thickness of the material being investigated.^[9, 10]

The relative importance of the aforementioned information factors can be modified by choosing sample conditions so as to eliminate some of them.^[11] In the present study, thin samples and a low dopant concentration allow us to neglect three out of the five factors. Two dominant information factors influence the response signal: energy transfer from β -carotene to its microscopic environment (c) and variable thermal properties of the sample (d). However, a previous study has shown that the changes in the thermal property of the sample (during the sol to gel evolution) are small with respect to the energy transfer factor.^[11] The measured signal is therefore dominated by changes in the efficiency of heat transfer from β -carotene molecules to their immediate molecular environment. This dopant molecule was chosen because of its very good stability in sol–gel materials and its near unit thermal de-excitation conversion yield.^[12–14]

A thicker sample (about 1 mm) was used initially to simulate bulk sol–gel material during its chemical aging. The depth-dependent heat emission that was extracted from the time response signal, obtained from pulsed photoacoustic spectroscopy (PPAS), versus time of aging is given in Figure 1b. The classical PPAS signal ($\Delta p_{\text{max}}, t_{\text{max}}$) is added for comparison (Figure 1a). Studies of the dopant dynamics of a tetramethoxysilane (TMOS)/dimethylaminopyridine (DMAP) sol–gel have shown that the sol phase is characterized by an increase in length of polymers with time which results in an increasing viscosity of the medium.^[15] Macroscopic gelation occurs when the longer polymer species are consumed to form the long-distance network. This process results in a temporary decrease in hindrance (local viscosity) around dopant molecules and β -carotene experiences a sudden return to a solventlike environment.

The depth-resolved signal (Figure 1b) reveals two distinct time evolutions: near the sample surface (less than 11 μm) and in its bulk (greater than 11 μm). These were not apparent on the global response signal (Figure 1a) as obtained by classical

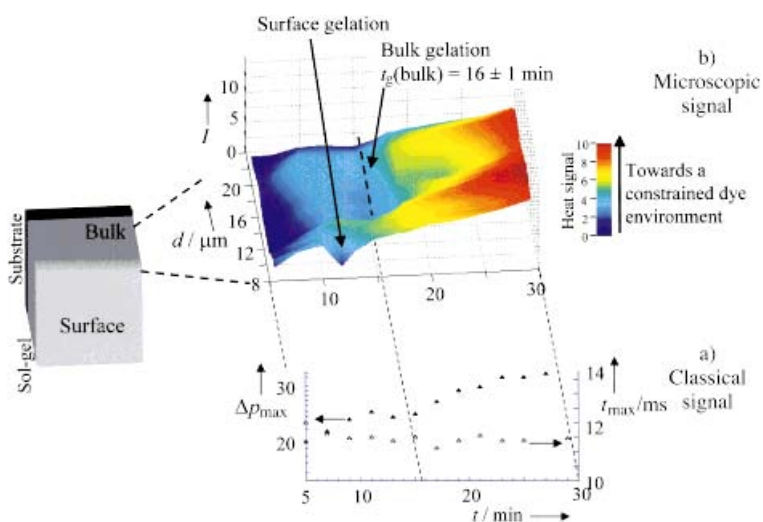


Figure 1. Surface and bulk sol–gel processes in a thick sample: A massive material. a) The classical PPAS response signal ($\Delta p_{\max}$ and $t_{\max}$) is presented versus time; b) the depth-analyzed signal extracted from the PPAS responses of (a) is given versus time t and depth d (also μ_D) in the upper part of the figure. In the sample view on the left the bulk material is represented by dark gray and the environment-influenced surface layer of the material by light gray.

PPAS. A faster evolution is observed near the sample surface (gelation time $t_g = 12 \text{ min}$) than in its bulk ($t_g = 16 \text{ min}$). This result is a consequence of solvent (alcohol) evaporation at the surface, which depletes the amount of methanol and results in a higher precursor concentration (equivalent to a higher initial molar ratio). A faster surface evaporation is therefore consistent with a higher reactivity as a result of a local increase in the concentration of the precursor. The gelation remains quite constant with depth in the bulk region (depths greater than $12 \mu\text{m}$) of the sol–gel. This observation is consistent with a pure interfacial effect and shows that the solvent evaporation affects only a surface layer of about 10 – $12 \mu\text{m}$ thickness. The absence of any gelation transition for a depth around $11 \mu\text{m}$ could be the result of a solvent concentration gradient as the inside of the gel plays the role of reservoir in supplying the surface regions, driven by high evaporation rates. The depression occurring near a depth of 14 – $18 \mu\text{m}$ and at times of 18 – 24 min could be attributed to solvent accumulation resulting from the dense silicon surface.

In a second experiment, a thin sample (about $80 \mu\text{m}$, Figure 2) was chosen to reduce the contribution of the bulk gelation and enhance the signal contribution from the surface. The low viscosity of the initial sol meant that a simple drop deposition of the sol on the sapphire substrate could be used for the preparation of a homogeneous layer. Because of its reduced bulk content, this second sample is also expected to limit solvent effects. For a better time resolution, the evolution was slowed down by halving the DMAP concentration. Contrary to the previous massive sample, the film sample shows one clear transition near the surface. The depth analysis with time (Figure 2b) shows a well contrasted surface evolution ($t_g = 13 \text{ min}$). A residual bulk gelation can be slightly observed around 42 min (also obtained from observation of a laboratory experiment carried out in a vial), which confirms our hypothesis of a film sample, that is, independent of a bulk component. The similar values of both surface

gelation processes indicates that its chemistry is dominated by a precursor densification effect. The absence of transition in deeper layers indicates few chemical changes occurring after the first instants. The very fast depletion of solvent molecules induces a solidlike environment for dopant molecules. The classical response signal amplitude $\Delta p_{\max}$ (Figure 2a) shows a similar increase with time of aging as observed for the massive sample. This is due to a progressive solid network formation that leads to an improved propagation of heat from the inside to the surface.^[8]

The present results show that information hidden by the total signal evolution can be extracted from a simplified model and converted into a depth profile of the microscopic heat emission. This analysis has revealed a completely different surface evolution that is driven mainly by a densification of the precursor molecules. This is, to our knowledge, the first in situ observation of clearly separate surface and bulk gelation processes in a sol–gel material.

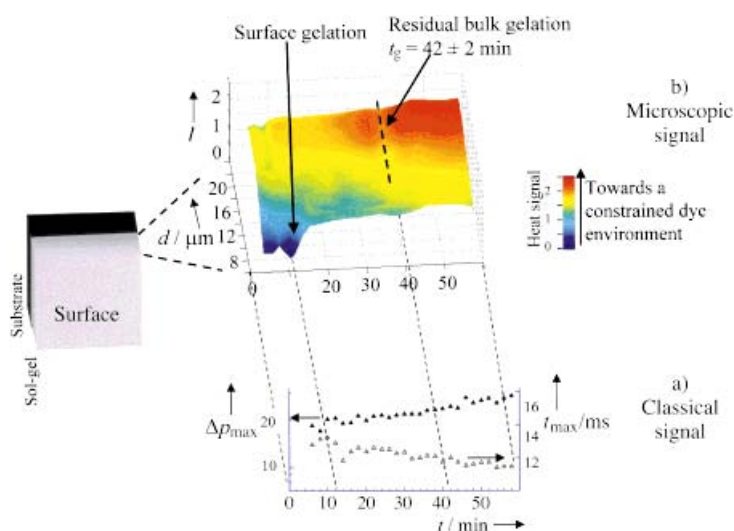


Figure 2. Surface dominated sol–gel materials: The case of a thin sample. a) The classical PPAS response signal ($\Delta p_{\max}$ and $t_{\max}$) is presented versus time; b) the depth-analyzed signal extracted from the PPAS responses of (a) is given versus time t and depth d (also μ_D) in the upper part of the figure. The sample is represented by a dominant light gray shade to show that the material evolution is influenced by surface effects.

An in situ monitoring could be particularly important for applications of thin films of sol–gel materials such as in integrated optics or for enzymes entrapped in biosensor films.

Experimental section

The sol–gel materials were composed of tetramethoxysilane/water/ethanol/dimethylaminopyridine with respective molar ratios $1:7:4:x$, where x was doped with β -carotene at the concentration of 10^{-4} M in the solution state. By adjusting x to 0.002 or 0.001 gels within $t_g(\text{bulk}) = 16$ or 42 min were obtained. The procedure was reported elsewhere.^[16] We chose the drop-deposition technique for the thick-film sample because it can be prepared in the measurement cell and allows for measurements at very short times. The deposition reliability, hence the measurement reproduci-

bility, were insured by performing deposition of a 60 μL drop (by a calibrated micropipet) onto an inclined PAS cell. A small reservoir around the slightly protruding sapphire window collects the excess sol liquid and helps ensure a reproducible film thickness. This method of deposition was compared to dip coating of the sol onto a thin quartz plate and was found to give information at earlier times as a result of the limited handling time involved. Temperature and humidity conditions were kept similar between experiments (19°C and 60% relative humidity, respectively).

Pulsed photoacoustic spectroscopy (PPAS) was used for time resolution by exciting samples with 532 nm radiation. We chose a sample thickness (1 mm) and a dopant concentration (10^{-4}M) to characterize our material as a thermally thick and optically transparent case. Fourier spectra obtained from the PPAS response pulses showed a $1/f$ dependence (f = Fourier frequency). The PAS response signal in Fourier space is also proportional to the yield for the conversion of the energy of absorbed light into released heat η integrated over the thickness $z(f)=\mu_D(f)$ of material being detected.^[10, 17, 18]

It is then possible to infer the local signal contribution at a given depth $z_i+\delta z/2$ by differentiation of the PAS signals corresponding to the two neighbor layers of thicknesses $z_i=\mu_D(f_i)$ and $z_i+\delta z=\mu_D(f_{i+\delta i})$ ($0<\delta z\ll z_i$, $f_i>f_{i+\delta i}$) [Eq. (1)] by using a mixture law for $\eta(f_{i+\delta i})$ and $\eta(f_i)$ (Figure 3).

$$\eta(\delta z) = \frac{1}{\Delta\mu_D} \mu_D(f_{i+\delta i}) (\eta(\Delta p(f_{i+\delta i}), f_{i+\delta i}, \rho_{i+\delta i}, k_{i+\delta i}, C_{i+\delta i}) - \frac{\mu_D(f_i)}{\mu_D(f_{i+\delta i})} \eta(\Delta p(f_i), f_i, \rho_i, k_i, C_i)) \quad (1)$$

Several steps are involved in the determination of the depth profile: conversion of the time signal into a frequency-dependent signal ($\Delta p(f)$) by Fourier transformation, extraction of the local heat signal η by differentiation between neighboring layers (Figure 3), and relating the Fourier frequency f to the depth μ_D by using the thermal properties of the material ($\mu_D(f)=(k/\rho C f)^{0.5}$).

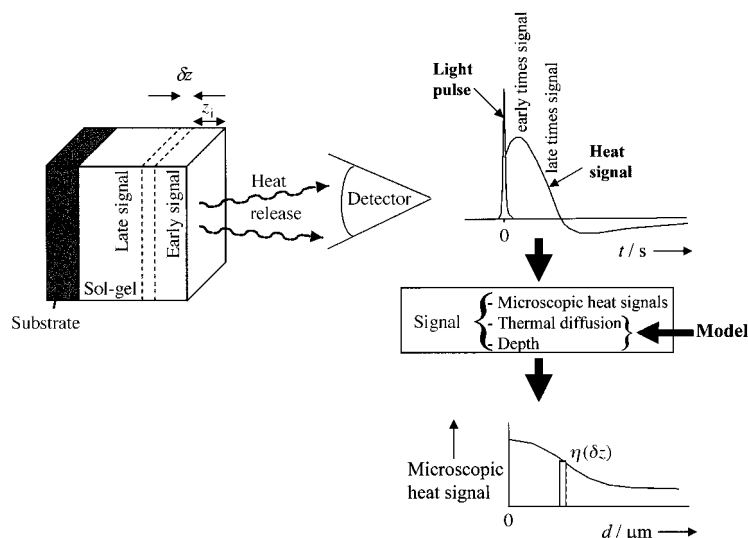


Figure 3. Schematic representation of the dependence of the signal on the depth of heat release inside the sol-gel. The global signal is converted, by fast Fourier transform (FFT) and a model, into a microscopic heat signal versus depth d . The local depth-resolved signal from a layer at a depth $z_i+\delta z/2$ results from the differentiation of signals from the two surrounding layers of thicknesses z_i and $z_i+\delta z$.

The signal analysis was performed using a sample with a mixed methanol/alkoxide composition (density $\rho=0.9\text{ g mL}^{-1}$, heat capacity $k=2.5\text{ mW cm}^{-1}\text{ K}^{-1}$, and thermal conductivity $C=2.0\text{ J g}^{-1}\text{ K}^{-1}$). The resulting local heat release (microscopic signal) is presented versus the depth, as calculated from thermal diffusion lengths. Modifications of thermal parameters, for example, resulting from a surface gradient, were found to have a negligible effect on the observed effects. For comparison the global PPAS response signals ($\Delta p_{\text{max}}(t)$ and the time delay of the pulse maxima t_{max}) were added to these figures as a function of time.^[11]

The influence of depth-dependent thermal properties on the signal was also investigated by using an exponential variation (between a dominant alkoxide composition and the previous mixed one) over a thickness of 12 μm (inferred from the previous analysis). Results showed little changes with respect to the first representation and are therefore not included here. Finally, any increase in light absorption near the surface of the sample as a result of increased dopant concentration was found to be negligible, as evident from the previous observation that no major variations in signal amplitude versus depths occur (Figure 1).

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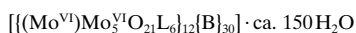
Archimedean Synthesis and Magic Numbers: “Sizing” Giant Molybdenum-Oxide-Based Molecular Spheres of the Keplerate Type**

Achim Müller,* Sabyasachi Sarkar, Syed Qaiser Nazir Shah, Hartmut Bögge, Marc Schmidtman, Shatarupa Sarkar, Paul Kögerler, Björn Hauptfleisch, Alfred X. Trautwein, and Volker Schünemann

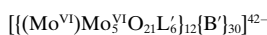
Dedicated to Professor Sir Harold Kroto

It has long been the chemist’s endeavor to vary the size of highly symmetrical molecular objects according to a pre-determined plan (“sizing”). For spherical objects using, for example, different types of linkages between pentagons, this dream has now become reality. Pentagons play an important role in the cultural and intellectual history of mankind as well as in modern science—beginning with the Pythagoreans, then later from Archimedes, Kepler, and Dürer, to Goethe’s Faust, and finally to Weyl and Penrose.^[1, 2] For the chemist, pentagons are especially attractive, but it was not possible to control these units up to now. The most challenging task for us was to synthesize spherical objects (the most symmetrical objects in Euclidean space) from pentagons in accordance with the early geometric knowledge of Archimedes of Syracuse.^[2] Here we report on the first construction of giant molecular spheres of the Keplerate type with different sizes which is achieved by varying the type of linkage between the pentagons by means of various spacers or linkers.^[3–5] Incidentally, the linkers span an Archimedean solid with icosahedral symmetry.^[13]

The yellow compound **1** was synthesized in high yield by the reaction of FeCl₃ with the {Mo₁₃₂} cluster anion **2a**,^[5] a Keplerate which contains the {(Mo)Mo₅}-type pentagons. The reaction is essentially based on the substitution of the {Mo₂^Y} spacers in **2a** by aqua-ligand-Fe^{III} polyhedra. Compound **1** was characterized by elemental analysis (including cerimetric titration to exclude the presence of Mo^V and Fe^{II} centers), thermogravimetry (to determine the amount of water of crystallization), magnetochemistry, spectroscopy (IR, Raman, UV/Vis, ESR, and ⁵⁷Fe Mössbauer spectroscopy), X-ray structure analysis, and bond valence sum (BVS) calculations (e.g. to differentiate between the positions of terminal oxygen atoms and H₂O ligands).^[6–9] The starting compound, the Keplerate anion **2a**, is also readily accessible in high yield.^[5, 10]

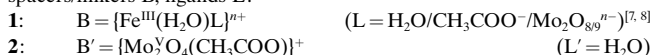


1



2a

spacers/linkers B, ligands L:



Compound **1**, which crystallizes in the space group $R\bar{3}$,^[9] contains discrete, neutral, spherical clusters **1a** (Figure 1). Each sphere contains twelve pentagonal fragments of the type {(Mo)Mo₅}, that is, {(Mo)Mo₅O₂₁} with a central bipyramidal MoO₇ group which is linked by edge-sharing to five MoO₆ octahedra. These pentagonal fragments are connected by the

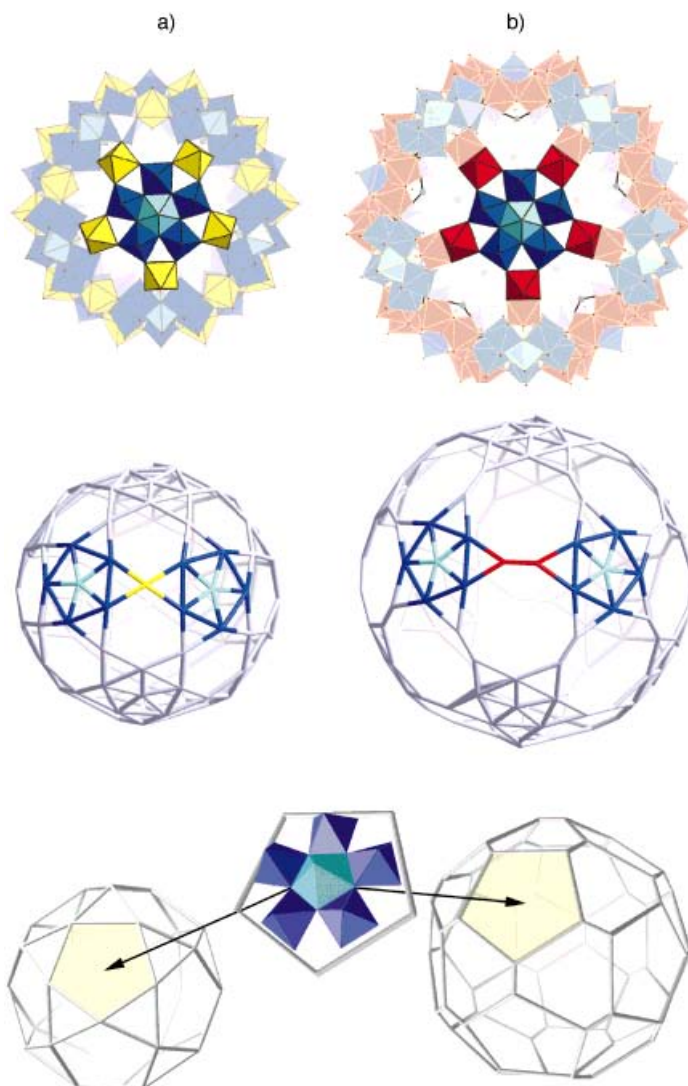


Figure 1. Top: polyhedral representation of **1a** (a) and **2a** (b) viewed along a C₅ axis showing five of the openings formed by the (Mo₉O₉) (accessible for very small molecules) and (Mo₃Fe₃O₆) rings. {(Mo)Mo₅} units: blue; central MoO₇ unit: turquoise; linkers {Fe} and {Mo₂^Y}: yellow and red, respectively). Center: comparison of the spherical {Fe₃₀Mo₇₂} fragment (**1a**) (a) and the {Mo₁₃₂} fragment (**2a**) (b) with the corresponding basic fragments {(Mo)Mo₅} and {Fe} in **1a** (a) as well as {(Mo)Mo₅} and {Mo₂^Y} in **2a** (b) (color code as above; viewed along a C₂ axis). Bottom: structures spanned by the fundamental spacer units (Archimedean solids) of **1a** and **2a** with one of the 12 capping {(Mo)Mo₅} pentagons: the Fe₃₀ icosidodecahedron (12 pentagons and 20 triangular faces) in **1a** and a truncated {Mo₂^Y}₃₀ icosahedron (12 pentagons and 20 hexagons with trigonal symmetry) in **2a** (b).

[*] Prof. Dr. A. Müller, Prof. Dr. S. Sarkar, Dipl.-Chem. S. Q. N. Shah, Dr. H. Bögge, M. Schmidtman, Sh. Sarkar, Dipl.-Chem. P. Kögerler, Dipl.-Chem. B. Hauptfleisch
Lehrstuhl für Anorganische Chemie I der Universität
Postfach 100131, D-33501 Bielefeld (Germany)
Fax: (+49) 521-106-6003
E-mail: a.mueller@uni-bielefeld.de

Prof. Dr. A. X. Trautwein, V. Schünemann
Institut für Physik, Medizinische Universität
Ratzeburger Allee 160, D-23562 Lübeck (Germany)

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polyhedral Fe^{III} spacers so that the overall shape of **1a** has (approximately) icosahedral symmetry and the 102 metal atoms as well as their (terminal) ligands (O or H₂O), which are directed outwards, lie in two concentric spherical shells. Each Fe polyhedron is connected to two MoO₆ octahedra of two neighboring pentagons. While the centers of the 12 pentagons, that is, the central Mo atoms of the MoO₇ bipyramids, span an icosahedron, the 30 Fe centers span one of the 13 Archimedean solids, namely, an icosidodecahedron with 20 triangles and 12 pentagons (from this point of view these “open electrophilic” pentagons are capped by 12 nucleophilic {(Mo)Mo₅} pentagons with a rotation of 360/10 = 36°; see Figure 1, bottom).

The Raman spectrum of **1** in concentrated aqueous solution (heating necessary!) corresponds approximately to the solid-state spectrum. (Interestingly, the solutions are acidic as a result of partial deprotonation of the H₂O ligands attached to the Fe centers.) The weak yellow color is in agreement with the presence of polyoxomolybdate(vi) fragments and Fe^{III} centers (the band at about 370 nm corresponds to that of [Fe(H₂O)₆]Cl₃) which are either nonabsorbing or only weakly absorbing in the visible region. The magnetic measurements also indicate the presence of a strong molecular magnet with high-spin Fe^{III} centers, between which, however, there are weak antiferromagnetic exchange interactions. The value of $\chi_{\text{mol}}T = 130 \text{ emu K mol}^{-1}$ measured at room temperature corresponds to 30 nearly uncorrelated centers with $S = 5/2$ —this is the largest number of paramagnetic centers found in a discrete cluster until now; furthermore the ⁵⁷Fe Mössbauer spectrum (4.2 K, $\delta = 0.52 \pm 0.01 \text{ mm s}^{-1}$, $\Delta E_Q = 0.70 \pm 0.01 \text{ mm s}^{-1}$) also confirms these results: the presence of Fe^{III} centers in a weakly distorted octahedral environment of O atoms.

The structure of the spherical cluster anion **1a** (and correspondingly of **2a**) is remarkable, since it can be built up from the 12 pentagons characteristic for spherical polyhedral objects (Figure 1, bottom). The fact that the pentagons in **2a** are linked by the larger (binuclear) spacers (they give a truncated icosahedron) leads to the notable expansion of this spherical cluster relative to **1a**, which has correspondingly 20 large openings formed by the (Mo₉O₉) rings (Figure 1). Although the icosahedron more closely resembles the spherical construction than the other Platonic solids, one can nevertheless come to a better approximation of this spherical shape by a combination of hexagons and 12 pentagons. In general, spherical polyhedral structures (pseudoicosahedra)

can be optimally constructed from exactly 12 pentagons and different sets of hexagons. In agreement with Euler's polyhedral law, the numbers of vertices, edges, and faces V , E , and F amount to $V = 20T$, $E = 30T$, and $F = 10T + 2$ (the latter is identical to the so-called “magic number” of Table 1); the “triangulation” number T ($T = h^2 + hk + k^2$), according to Caspar and Klug, is used to classify spherical viruses which are structurally similar to **1a** and **2a**.^[5, 11] $60T$ corresponds to the number of protein units (in the strict sense of the term quasiequivalence a $T = n$ virus should contain n conformations of the capsid protein). The relationships between T or the magic number $10T + 2$ on the one hand, and the number of building blocks in these spherical clusters on the other (Table 1), could tempt one to speak of Pythagorean harmony following a related quotation by Aristotle (see ref. [11]).

The geometrical relationship between the five solids with icosahedral symmetry, that is the dodecahedron, the icosahedron, the two truncated (Archimedean) solids derived from these, and the (Archimedean) icosidodecahedron (Figures 2 and 3), is particularly interesting for the following reasons: 1) The 12 pentagons of **1a** can be formally assigned to the icosahedron (namely, its corners) as well as to the dodecahedron (namely, its faces). 2) In **2a** the 30 spacers of the type {Mo₂} span a (distorted) truncated icosahedron ($T = 3$),^[5] while in **1a** the 30 Fe^{III} spacers span an icosidodecahedron. 3) The two latter Archimedean solids can be differentiated by the fact that the pentagons “present” are either “condensed” (like in **1a**) or “isolated” (like in **2a**).^[12] Remarkably, the spherical structural motif of both Archimedean solids is generated by the pentagonal units, in the sense of the title of this article.

Experimental Section

1: To a stirred orange-red solution of FeCl₃·6H₂O (1.1 g, 4.1 mmol) and CH₃COONa·3H₂O (1.1 g, 8.1 mmol) in H₂O (75 mL), the NH₄⁺ salt of **2a**^[5] (1.4 g, 0.05 mmol) was added. The resulting mixture was vigorously stirred in an open 100-mL Erlenmeyer flask (wide-necked) for 24 h. After acidification with HCl (1M, 1 mL) and addition of NaCl (2.0 g), the stirred reaction mixture was heated to 90–95 °C and then filtered whilst still hot. The golden yellow filtrate was cooled to 20 °C, and yellow, rhombic crystals of **1** formed over a period of 2–3 d (compare the space group $R\bar{3}$! which corresponds to the space-group relevant habit). The crystals were collected by filtration through a glass frit, washed twice with a little iced water (to remove the adhering NaCl), and dried in air. Yield: 0.5–0.6 g (33–39% based on **2a**). Characteristic IR bands for **1** (KBr pellet): $\tilde{\nu} = 1620$ (m, $\delta(\text{H}_2\text{O})$), 1533 (m, $\nu_{\text{as}}(\text{COO})$), 1406 (s-m, $\nu_s(\text{COO})$), 968 (m, $\nu(\text{Mo=O})$), 854 (m), 778 (s), 623 (m), 568 (s), 438 cm^{−1} (m); characteristic Raman bands ($\lambda_e = 1064 \text{ nm}$): $\tilde{\nu} = 950$ (s), 908 (w) ($\nu(\text{Mo=O})$), 835 (s), 510 (m), 445 (w),

Table 1. Relationship between the so-called magic numbers $10T + 2$ for spherical viruses and the structural units of polyhedral spherical objects of the Keplerate type, that is, in the present case with 12 pentagons and an Archimedean solid spanned by spacers.

Magic number $10T + 2$	{Mo ₁₃₂ } (20 hexagons)	Cluster/Molecule {Mo ₇₂ Fe ₃₀ } (20 triangles)	Triangulation number $T = [h, k] = h^2 + hk + k^2$
12	12 central {(Mo)Mo ₅ } pentagons (icosahedral structure)	12 central {(Mo)Mo ₅ } pentagons (icosahedral structure)	1 [1, 0]
32	32 faces of the {Mo ₂ ^{VI} } ₃₀ – (spacer) polyhedron (truncated icosahedron)	32 faces of the {Fe ₃₀ } – (spacer) polyhedron (icosidodecahedron)	3 [1, 1]
42	42 (12 + 30) building blocks ^[a] (and charge of the cluster)	42 (12 + 30) building blocks ^[a]	4 [2, 0]
72	72 Mo ^{VI} centers (and negative charge of the 12 pentagons ^[b])	72 Mo ^{VI} centers	7 [2, 1]
132	132 Mo atoms	–	13 [3, 1]

[a] 12 {(Mo)Mo₅} units + 30 {Mo₂^{VI}} or 30 {Fe} spacers. [b] {(Mo^{VI})Mo₃^{VI}O₂₁}^{6−}.

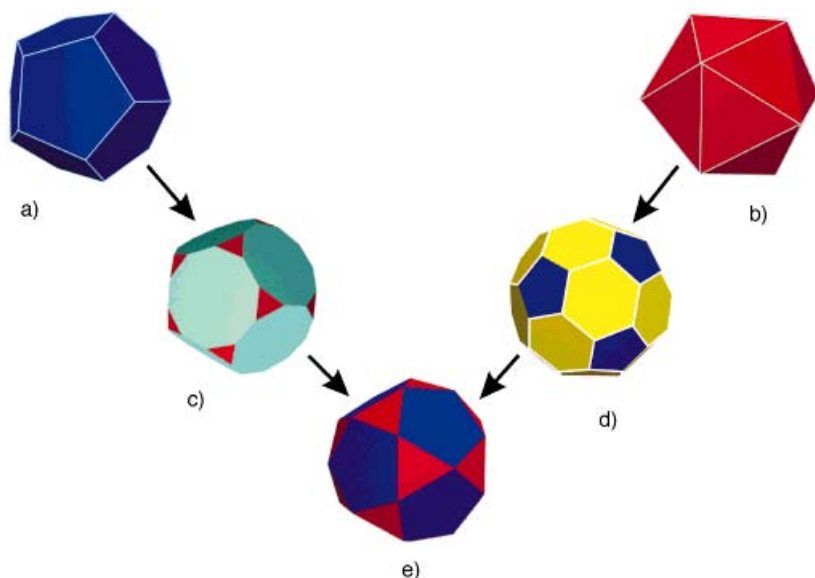


Figure 2. Relationships between solids with icosahedral symmetry: the dodecahedron (a) and icosahedron (b), the two corresponding truncated Archimedean solids (in c and d; as the $\{\text{Mo}_2\}_{30}$ fragment in the case of **2a**) as well as the Archimedean icosidodecahedron (e; corresponding to the $\{\text{Fe}_{30}\}$ fragment in the case of **1a**).^[13] It is interesting that the solids in (d) and (e) are distinguishable by a different degree of truncation and the related size. This corresponds to the relative sizes of **1a** and **2a**.

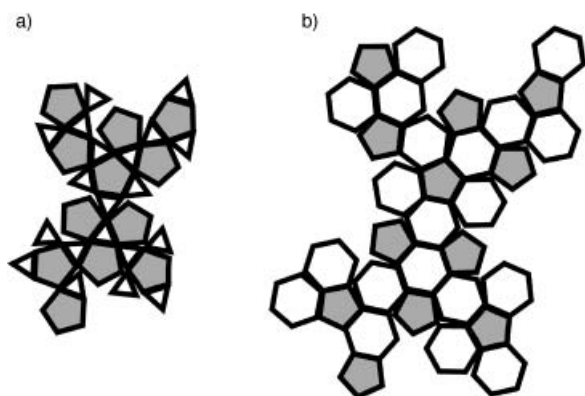


Figure 3. The nets ("Netzabwicklung") a) of the icosidodecahedron and b) of the "Ikosaedron truncum" (see ref. [1g]) to clarify the relationship between the two Archimedean solids of Figure 2d and 2e, which are spanned by the spacers.

370 (m), 238 cm^{-1} (m-w); UV/Vis (measured against cellulose as white-standard): $\lambda \approx 370$ nm. The IR and UV/Vis measurements of **2** were carried out under the same conditions and not under those given erroneously in ref. [5].

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[1] Pentagons are of particular interest in numerous scientific areas: for the mathematician (to construct one of the five regular solids given in Euclid's famous work "Elements (Book XIII)", to which Dürer also refers), for the architect and the art theorist or felix aestheticus (in the sense of Fuller's geodesic domes and with respect to the "Golden Section"), for the solid-state physicist (with regard to the fascinating quasicrystals), for the virologist (because of the structure of spherical viruses), for the classical morphologist amongst the biologists (in particular because of the numerous plant organisms (blossoms) with

fivefold symmetry), more recently for the cosmologist (because of a planetary nebula with a fullerene structure), and naturally for the chemist, who can use them to design harmonic molecular constructions. Pythagoras even associated physical well-being with the five-pointed star, which was the symbolic sign of his school, and he wanted—obviously with not very altruistic intentions—to keep secret the existence of the dodecahedron derived from it. a) A. L. Mackay, *Crystals and Fivefold Symmetry in Quasicrystals, Networks, and Molecules of Fivefold Symmetry* (Ed.: I. Hargittai), VCH, Weinheim, **1990**, pp. 1–18; b) H. W. Kroto, K. Prassides, A. J. Stace, R. Taylor, D. R. M. Walton in *Buckminsterfullerenes* (Eds.: W. E. Billups, M. A. Ciufolini), VCH, Weinheim, **1993**, pp. 21–57; c) K. Miyazaki, *Polyeder und Kosmos: Spuren einer mehrdimensionalen Welt*, Vieweg, Braunschweig, **1987**, pp. 69–75 (chap.: Fünfecke und Fünfstern); d) R. Penrose in *Hermann Weyl, 1885–1985: Centenary Lectures* (Ed.: K. Chandrasekharan), Springer, Berlin, **1986**, pp. 23–52; e) H. S. M. Coxeter, *Regular Polytopes*, Macmillan, New York, **1963** (in particular the various chapters with "historical remarks"); f) H. Weyl, *Symmetry*, Princeton University Press, Princeton, NJ, **1952**, pp. 41–80 (chap.: Translatory, rotational, and related symmetries); g) E. Schröder, *Dürer, Kunst und Geometrie: Dürers künstlerisches Schaffen aus der Sicht seiner "Unterweisung"*, Birkhäuser, Basel, **1980**; h) L. Liljas, *Prog. Biophys. Mol. Biol.* **1986**, *48*, 1–36; i) V. I. Arnol'd, *Huygens and Barrow, Newton and Hooke: Pioneers in mathematical analysis and catastrophe theory from evolvents to quasicrystals*, Birkhäuser, Basel, **1990**, pp. 62–66 (chap. 3, paragraph 16: The icosahedron and quasicrystals); j) S. Hildebrandt, A. Tromba, *Kugel, Kreis und Seifenblasen: Optimale Formen in Geometrie und Natur*, Birkhäuser, Basel, **1996**; k) A. Dress, D. Huson, A. Müller in *Muster des Lebendigen: Faszination ihrer Entstehung und Simulation* (Ed.: A. Deutsch), Vieweg, Wiesbaden, **1994**, pp. 183–202; l) A. Stückelberger, *Einführung in die antiken Naturwissenschaften*, Wiss. Buchgesellschaft, Darmstadt, **1988**, p. 12.

[2] Mackay states in the chapter: "What Is Special about Fivefold Symmetry?"^[1a] "Five is, in a sense, the first "interesting" integer in that given five points in space all cannot be identically related to all the others [...]" This has then the well-known consequences for the generation of structures in three-dimensional space or in a plane (cf. the tiling problem^[1a]). Even Archimedes had recognized the importance of pentagonal patterns for the construction of spherical structures (cf. book 5 of the "Collectiones" of Pappos of Alexandria (around 320 AD), the last famous mathematician of that epoch).

[3] For the topologists under the mathematicians it is of particular interest that the Keplerates discussed here are based on the 12 pentagons essential for the construction of optimal spherical polyhedral structures; pentagons are present (in the "magic number" of 12), along with a variable but defined number of hexagons in all such formations, even in the largest known spherical polyhedral objects such as the Fuller domes. A Keplerate should define a spherical species—with part of its atoms located at the sphere spanning a Platonic solid—for example in which the 12 centers of the pentagonal units forming an icosahedron lie on a spherical shell, whereby the spacers span a relevant Archimedean solid (that is, with appropriate symmetry; see Table 1). In the first reported Keplerate there are 132 molybdenum atoms located on a spherical shell^[5] and in the present Keplerate 102 metal atoms, and in both cases 12 of them span an icosahedron in an arrangement corresponding to Kepler's early speculative model of the cosmos.

[4] With regard to the synthesis of **1**, it is important to note that the Fe^{III} spacers used here, in addition to those of the VO^{2+} type, are particularly suitable for the linkage of nucleophilic molybdate fragments (see: A. Müller, W. Plass, E. Krickemeyer, S. Dillinger, H. Bögge, A. Armatage, A. Proust, C. Beugholt, U. Bergmann, *Angew. Chem.* **1994**, *106*, 897–899; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 849–851; A. Müller, J. Meyer, E. Krickemeyer, C. Beugholt, H. Bögge, F. Peters, M. Schmidtman, P. Kögerler, M. J. Koop, *Chem. Eur. J.* **1998**, *4*, 1000–1006; A. Müller, W. Plass, E. Krickemeyer, R. Sessoli, D. Gatteschi, J. Meyer, H. Bögge, M. Kröckel, A. X. Trautwein, *Inorg. Chem. Acta* **1998**, *271*, 9–12).

- [5] A. Müller, E. Krickemeyer, H. Bögge, M. Schmidtman, F. Peters, *Angew. Chem.* **1998**, *110*, 3567–3571; *Angew. Chem. Int. Ed.* **1998**, *37*, 3360–3363.
- [6] See, for example: A. Müller, S. Q. N. Shah, H. Bögge, M. Schmidtman, *Nature* **1999**, *397*, 48–50; A. Müller, F. Peters, M. T. Pope, D. Gatteschi, *Chem. Rev.* **1998**, *98*, 239–271; A. Müller, H. Reuter, S. Dillinger, *Angew. Chem.* **1995**, *107*, 2505–2539; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2328–2361, and references therein.
- [7] The elemental analyses show that **1a** is, within the error limit of our data, a neutral cluster (uncertainty only exists in the number and/or kinds of ligands/fragments). Compound **1** contains, according to numerous analytical values and also, according to the IR spectrum, no Cl^- , Na^+ , and NH_4^+ ions; however there are 12 CH_3COO^- ligands and “additionally” three negatively charged $\text{Mo}_2\text{O}_{8/9}$ “ligand” fragments with a total charge of -6 , which are necessary for the neutrality of the cluster. Clearly, the positively charged hypothetical cluster formed by the complete replacement of the spacers in **2a** by those in **1a** is not stable under the present conditions. (The $\{(\text{Mo}^{\text{VI}})\text{Mo}_5^{\text{VI}}\text{O}_{21}\}_{12}\text{Fe}_{30}^{\text{III}}$ cluster fragment, structurally unambiguously identified, has a charge of $+18$.) The $\text{Mo}_2\text{O}_{8/9}$ fragments, which are derived from the $\{\text{Mo}_2\}$ units of the starting compound and which function as a type of ligand on the inside of the cluster (in a similar manner to H_2O and CH_3COO^-), are strongly disordered due to the highly symmetrical space group, whereby the occupation factors of the Mo positions of the $\text{Mo}_2\text{O}_{8/9}$ fragments, found in the X-ray structural analysis add up to about six. The position of the twelve strongly disordered acetate ligands could not be unambiguously determined, mainly because of the numerous possible positions (≥ 120). However, this problem did not arise in a related compound (*Cmca*; $a = 36.8148$, $b = 34.4029$, $c = 35.0556$ Å) which crystallizes in a space group of lower symmetry and in which the clusters **1a** are linked by Fe–O–Fe bonds into layers. Because of the markedly less disorder, the positions of the $\{\text{Mo}_2\}$ fragments as well as (some) of the acetate ligands were resolved.^[8]
- [8] The $\text{Mo}_2\text{O}_{8/9}$ “ligand” fragments in this compound have the following structures: $\{(\text{O}_{\text{br}})_2\text{O}=\text{Mo}^{\text{VI}}(\text{OH})_2(\text{H}_2\text{O})\text{Mo}^{\text{VI}}=\text{O}(\text{O}_{\text{br}})_2\}^{2-}$ and $\{(\text{O}_{\text{br}})_2\text{O}=\text{Mo}^{\text{VI}}\text{O}(\text{H}_2\text{O})\text{Mo}^{\text{VI}}=\text{O}(\text{O}_{\text{br}})_2\}^{2-}$ with octahedral and square-pyramidal coordination of the Mo centers, respectively, whereby the atoms of the $\{\text{Mo}_2^{\text{VI}}\}$ ligands designated formally as $(\text{O}_{\text{br}})_2$ (br = bridging) are coordinated to the Mo atoms of the spherical shell in a similar manner to those of the H_2O and CH_3COO^- ligands. Correspondingly, in the above formula all three types of ligands are denoted as L.
- [9] Crystal structure analysis of **1**: Space group $R\bar{3}$, $a = 55.1306(14)$, $c = 60.193(2)$ Å, $V = 158439(8)$ Å³, $Z = 12$, $\rho = 2.346$ g cm⁻³, $\mu = 2.70$ mm⁻¹, $F(000) = 108\,744$, crystal dimensions: $0.25 \times 0.25 \times 0.15$ mm³. Crystals of **1** were removed from the mother liquor and immediately measured at 153(2) K on a Bruker-axs-SMART diffractometer (three-circle goniometer with a 1K-CCD detector, $\text{MoK}\alpha$ radiation, graphite monochromator). Measurements were performed on a hemisphere with 0.3° ω -scans in three runs with 606, 435, and 230 frames ($\phi = 0, 88, \text{ and } 180^\circ$) based on a detector distance of 5 cm. Of the 274 226 reflections measured ($1.57 < \theta < 24.99^\circ$), 61 998 were independent ($R(\text{int}) = 0.0659$) and were used in the refinement. An empirical absorption correction on the basis of symmetry-equivalent reflections was carried out with the help of the program SADABS. The structure was solved and refined with the programs SHELXS-97 and SHELXL-97 to $R = 0.082$ for 34 204 reflections with $I > 2\sigma(I)$; max./min. residual electron density: 2.97 and -3.26 e Å⁻³ (SADABS, SHELXS/L by G. M. Sheldrick, Universität Göttingen, Germany, **1997**; structural graphics with DIAMOND 2.1 from K. Brandenburg, Crystal Impact GbR, **1999**). Several individual crystals were measured in which the same type and number of strongly disordered $\text{Mo}_2\text{O}_{8/9}$ fragments bound to the inside of the spherical shell could be localized. 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-132027. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [10] Some basic comments on the synthesis of giant clusters based on polyoxomolybdates: in contrast to the synthesis of the Keplerate clusters, which can be readily obtained in high yield, the synthesis of the extremely soluble molybdenum blue compounds based on giant ring-type structures caused considerable problems in the past. However, these are now also readily accessible in the presence of a high electrolyte concentration which destroys the hydration shell that stabilizes the structures in solution (A. Müller, M. Koop, H. Bögge, M. Schmidtman, C. Beugholt, *Chem. Commun.* **1998**, 1501; A. Müller, S. K. Das, V. P. Fedin, E. Krickemeyer, C. Beugholt, H. Bögge, M. Schmidtman, B. Hauptfleisch, *Z. Anorg. Allg. Chem.* **1999**, *625*, 1187–1192; A. Müller, S. K. Das, H. Bögge, C. Beugholt, M. Schmidtman, *Chem. Commun.* **1999**, 1035–1036; A. Müller, C. Beugholt, M. Koop, S. K. Das, M. Schmidtman, H. Bögge, *Z. Anorg. Allg. Chem.* **1999**, *625*, in press).
- [11] H. S. M. Coxeter in *A Spectrum of Mathematics: Essays Presented to H. G. Forder* (Ed.: J. Butcher), Oxford University Press, Oxford, **1967**, pp. 98–107; I. Stewart, *Spiel, Satz und Sieg für die Mathematik*, Birkhäuser, Basel, **1990**, pp. 95–114.
- [12] Within the context of the Pythagorean knowledge of geometry (from about 500 BC) and the knowledge given in the first book written on natural philosophy, the epochal *Timaios*, it is demonstrated very impressively that the elementary building blocks of nature, such as these polygons, have to “find” each other, metaphorically speaking, in Euclidean space for the joint construction of complex, and in particular, unusual and harmonic structures (see, for example, ref. [1k]).
- [13] Further information on Archimedean solids in chemistry can be found in a recent review: L. R. MacGillivray, J. L. Atwood, *Angew. Chem.* **1999**, *111*, 1080–1096; *Angew. Chem. Int. Ed.* **1999**, *38*, 1018–1033.

“Open and Shut” for Guests in Molybdenum–Oxide-Based Giant Spheres, Baskets, and Rings Containing the Pentagon as a Common Structural Element

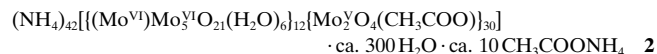
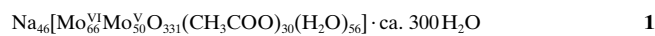
Achim Müller,* Sebastian Polarz, Samar K. Das, Erich Krickemeyer, Hartmut Bögge, Marc Schmidtman, and Björn Hauptfleisch

In memory of Frank Hellweg

The synthesis of very large molecular containers^[1] or host systems—for problem-solving use—presents an enormous challenge for modern chemistry. Here, we report on the formation of a giant molecular basket which is generated by “opening” a giant molybdenum–oxygen sphere (“Keplerate”),^[2] and on the option of exchanging the contents of the spheres in a variable and controlled manner. Our prediction—based on the isolation of the first giant molecular Keplerate spheres^[2]—that a novel supramolecular chemistry, or in other words a defined Keplerate chemistry would develop^[2] has now been confirmed with this article. A kind of Pythagorean harmony^[3] is evident in this type of chemistry and is of particular interest in this context since the structural unit which is responsible for the curvature in the spherical and ring-shaped giant clusters, to which the common formula $\{\text{Mo}_{11}\}_n$ can be given, is the same.

[*] Prof. Dr. A. Müller, Dipl.-Chem. S. Polarz, Dr. S. K. Das, E. Krickemeyer, Dr. H. Bögge, M. Schmidtman, Dipl.-Chem. B. Hauptfleisch
Lehrstuhl für Anorganische Chemie I
Fakultät für Chemie der Universität
Postfach 100 131, D-33501 Bielefeld (Germany)
Fax: (+49) 521-106-6003
E-mail: a.mueller@uni-bielefeld.de

Compound **1**, with the aforementioned giant molecular basket **1a** as its anion, which is clearly important for the understanding of the exchange reaction of the ligands in the spherical Keplerate clusters described here, precipitates from solutions that contain the Keplerate anion **2a**^[2] on standing for some time in air (Figure 1). (Compound **1** has not yet been



isolated free of side products.) The addition of anions with (bidentate) ligand function (e.g. perchlorate, sulfate, sulfite, phosphate, hypophosphite, or phenylphosphonate ions) to freshly synthesized solutions of **2** gave compounds with the correspondingly substituted Keplerate clusters, which have identical spherical shells, in a pure form and in relatively high yield. In the resulting compounds, the CH_3COO^- ligands, which were originally coordinated to the $\{\text{Mo}_2^{\text{V}}\text{O}_4^{2+}\} \equiv \{\text{Mo}_2^{\text{V}}\}$ groups of **2a**,^[2] have been either completely exchanged (as in the case of the phosphate and hypophosphite) or partially exchanged (as in the case of the sulfate). Compounds **3** and **4** are described here.^[4]

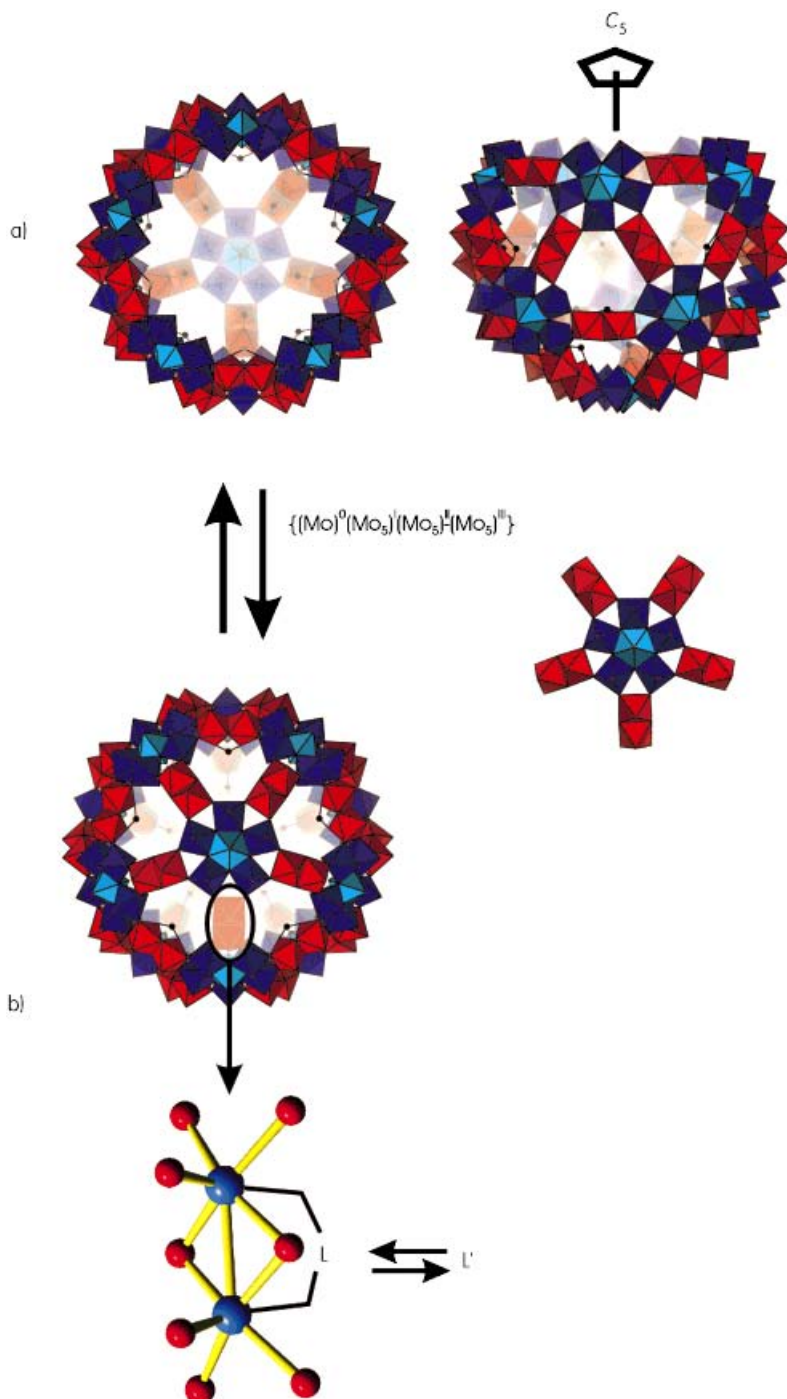
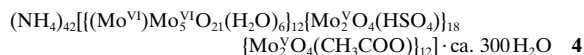
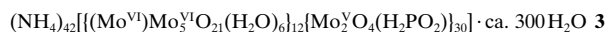


Figure 1. Structure of **1a** (viewed along the C_5 axis and perpendicular to it) a) and **2a** b). The position where the ligand exchange reactions take place in **2a** is circled and a separate $\{\text{Mo}_2^{\text{V}}\text{L}\}$ unit is given below. The $\{\text{Mo}_{16}\}$ motif ("lid" of the basket **1a**) is separately represented ($\{(\text{Mo})\text{Mo}_5\}$ pentagons: blue; $\{\text{Mo}_2^{\text{V}}\}$ fragments: red).

Compounds **1**, **3**, and **4** were characterized by elemental analysis (including cerimetric titration to determine the number of Mo^{V} centers), thermogravimetry (to determine the amount of water of crystallization), spectroscopy (IR, Raman, UV/Vis), single-crystal X-ray structure analysis,^[5] and bond valence sum (BVS)^[6] calculations (to determine the positions of the H_2O molecules as well as to differentiate between the Mo^{VI} and Mo^{V} centers).

Compound **1**, which has a basket-shaped anion, crystallizes in the space group $Pmn2_1$.^[5] Compounds **3** and **4** are isostructural or pseudoisostructural, respectively, to the corresponding compounds with a giant spherical structure of the type $\{\text{Mo}_{132}\}$, which contain acetate^[2] (space group $Fm\bar{3}$) or formate ligands,^[7] respectively (space group $R\bar{3}$) at the $\{\text{Mo}_2^{\text{V}}\}$ groups. The structure of the basket-shaped giant cluster **1a** can be formally derived from the giant sphere **2a**^[2] (Figure 1) ($\{\text{Mo}_{11}\}_{12} \equiv \{(\text{Mo})^0(\text{Mo}_5)^{\text{I}}\{[\text{Mo}_2^{\text{V}}]_{5/2}\}^{\text{III}}\}_{12}$) by the "removal" of a $\{(\text{Mo})^0(\text{Mo}_5)^{\text{I}}\{(\text{Mo}^{\text{V}})^{\text{II}}-(\text{Mo}^{\text{V}})^{\text{III}}\}_5\}$ motif (Figure 1). During the reaction, however, the distribution of the acetate ligands concentrated at the "edge of the basket" changes somewhat—including their coordination to the $\{(\text{Mo})\text{Mo}_5\}$ units, which are not abundant in **2a**. The relative number of Mo^{V} centers in **1a** is less than that of **2a**, so that the reaction (with regard to **1a** and **2a**) can formally be considered as a partial oxidation.

Product **1**, with its basket-shaped anion **1a**, which is formed after "opening" the giant molecular sphere **2a**, is much more soluble in H_2O than **2**, whose anion **2a** has mainly terminal oxygen ligands on the surface of the sphere. The reason for this difference in solubility lies in the easy access of the solvent to the hydrophilic interior of **1a**, which has a large number of H_2O ligands positioned *trans* to the terminal O atoms. Therefore, crystallization of **1** only takes place after the equilibrium has shifted extensively in the direction of the basket-type species, whereby the solution must be kept diluted in order to ensure that the less soluble spherical cluster **2a** remains long enough in solution. But if the

work is carried out in the presence of a high sodium acetate concentration (this causes salting out as a result of the destruction of the hydrate shell) or even in the presence of NH_4^+ ions, which reduce the solubility of the relevant salt, then our goal to obtain **1** will not be achieved and **2** precipitates instead.

To understand the remarkable guest/ligand exchange in the reaction of **2a** to **3a** or **4a**, the following points should be considered:

1) The ligand exchange should not occur through the “molecular windows” found on the C_3 axes of **2a** (at least when dealing with rigid $\{\text{Mo}_9\text{O}_9\}$ rings), since these are too small for the negatively charged ions.

2) The isolation of **3** and **4** takes place at a time when the reaction medium still contains a considerable amount of spherical anions.

3) It follows from (1) that either the ligands which “approach” the sphere **2a** lead to its “opening” or that in solution there is an equilibrium between the corresponding basket-shaped object and “closed” spherical-shaped species—with the possibility of direct ligand exchange. In the latter case, one can easily understand the facile crystallization of the compounds **3** and **4** (i.e., after ligand exchange and equilibrium readjustment) which contain the corresponding cluster spheres **3a** and **4a**, since they are—due to the lower hydrophilicity of the surface of the sphere relative to **1a**—less soluble than the corresponding basket species, with which they are in equilibrium. Further evidence for the presence of an equilibrium is provided by the fact that from a solution which was produced exclusively from the basket compound **1** the spherical cluster anion **2a** (corresponding to **2**) can be isolated (the reverse is also valid). In these considerations, one cannot assume that the $\{\text{Mo}_{16}\}$ fragment/lid is present as a relatively stable unit in solution.

The fact that during the transformation sphere $\rightarrow$ basket a fragment of the type $\{(\text{Mo}_{11})\text{Mo}_5\}$ is “dislodged” stimulates ideas concerning the relevance of pentagonal building blocks in structural chemistry. The star-shaped basic motif $\{(\text{Mo})^0(\text{Mo}_5)^{\text{II}}(\text{Mo}_5)^{\text{III}}\}$ (cf. Figure 2b), comprising several formal (motif-) “generations”, can be clearly recognized in Figure 1, which shows the structure of **2a** along the direction of the fivefold axis. The existence of the pentagonal pattern clearly correlates with the controlling/symmetry-determining influence of the central pentagonal MoO_7 bipyramid (“zero generation”) which is connected to the five MoO_6 octahedra of the “first generation”. The five MoO_6 octahedra are then connected to those of the “second generation” are then connected to those of the first by corners, whereby the former build up the neighboring relatively stable $\text{Mo}^{\text{V}}\text{—}\text{Mo}^{\text{V}}$ dumbbells of the $\text{Mo}_2^{\text{V}}\text{O}_4^{2+}$ type with further MoO_6 polyhedra.

It must be emphasized that this motif-related view does not correlate directly with the real formation process of these structures; however, it is very useful to elucidate the structural chemistry.

In this context it is certainly remarkable that, on the one hand the $\{\text{Mo}_{11}\} \equiv \{(\text{Mo})^0(\text{Mo}_5)^{\text{I}}(\text{Mo}_5)^{\text{II}}\}$ fragments/motifs can generate not only the giant spheres, but they are also the basic motif for various ring-shaped polyoxomolybdate structures of the type $\{\text{Mo}_{11}\}_n$ ($n = 14, 16$) (Figure 2 and 3). Only in the case

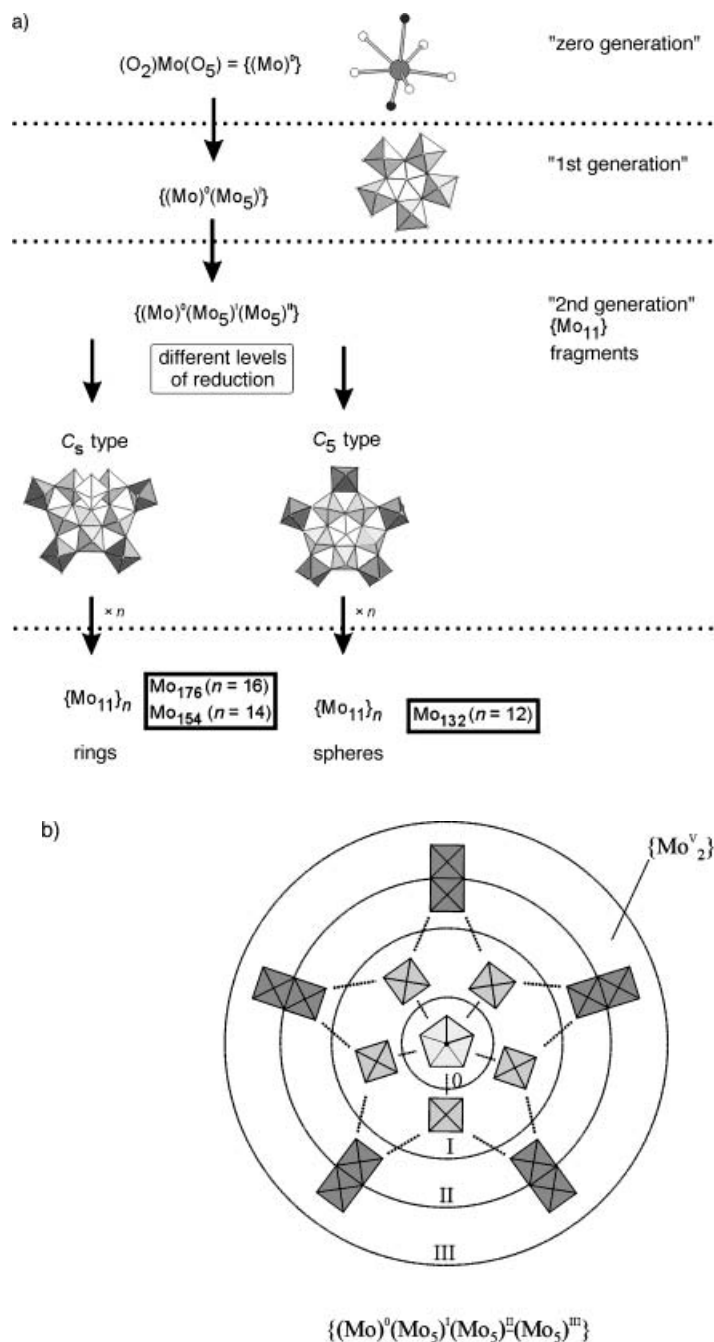


Figure 2. a) Schematic (formal) relationship between the basic structural elements and/or the motifs of giant molecular spheres and rings as well as b) the formal relationship to the $\{(\text{Mo})^0(\text{Mo}_5)^{\text{I}}(\text{Mo}_5)^{\text{II}}(\text{Mo}_5)^{\text{III}}\} \equiv \{\text{Mo}_{16}\}$ motif (“lid” of the giant sphere).

of stronger reducing conditions, as in the present case, are the $\{(\text{Mo}_5)^{\text{II}}\}$ centers equivalent and this ultimately leads to an arrangement with C_5 symmetry. (The above-mentioned bidentate ligands are, however, necessary for the formation of the present type of spherical structures that are produced by linking 12 of these regular $\{\text{Mo}_{11}\}$ pentagons). If this is not the case—that is, under less reducing conditions—then a shift of a MoO_6 octahedron and a C_s - $\{\text{Mo}_{11}\}$ fragment with lower symmetry results, (Figure 2a and 3), and consequently ring-shaped species of the $\{\text{Mo}_{154}\}$ and $\{\text{Mo}_{176}\}$ type^[8, 9] (related stoichiometry $(\text{Mo}_{11})_{14}$ and $(\text{Mo}_{11})_{16}$ are formed, respectively.

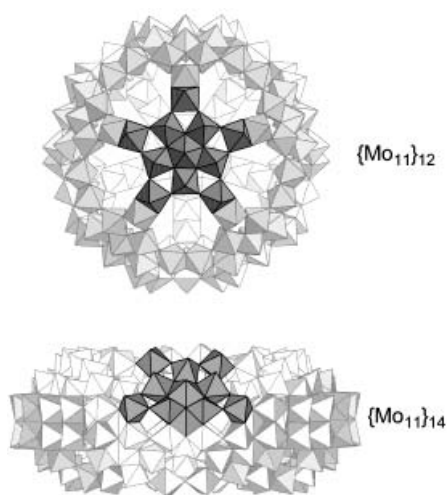


Figure 3. Structural comparison of the ring-shaped and spherical clusters $\{Mo_{11}\}_{14}$ and $\{Mo_{11}\}_{12}$, respectively, each with a highlighted $\{Mo_{11}\}$ unit.

We believe that the results reported here point the way towards a novel type of supramolecular nanochemistry. The synthesized “vessels” allow not only the inclusion but also the common (!) transport of various molecular and/or ionic collectives. Since the exchange of acetate ligands described here is also possible with many other guests/ligands—for example, those with even larger organic groups—it is possible to construct new tailored surface structures on the inside of the sphere, particularly with amphiphilic ligands. Additionally, by the control of the reaction conditions, such as by the use of ligands that do not coordinate too strongly, the extent of substitution of the acetate ligands can be varied. With a smaller ligand than that used in **2a** (e.g. $HCOO^-$ instead of CH_3COO^-) it is even possible to generate an onion-shaped arrangement of the enclosed van der Waals clusters, for example with a $(H_2O)_n$ collective or cluster.^[7] In this case only the spherical cluster shell influences the type of organization of the central guest collective in the hollow interior of the Keplerate clusters. Additionally, there is the possibility that smaller guests, such as very small organic molecules, can be “smuggled” into **2a** through the 20 openings formed by the $\{Mo_9O_9\}$ rings, which have a diameter of about 0.35 nm. Corresponding investigations are currently underway.

In any case, there are still many exciting novelties to be discovered in the field of polyoxometalate chemistry (see also refs. [8, 9]), and certainly we can expect a (topological) variety comparable to that of the fullerenes.^[10]

Experimental Section

1: A stirred solution of $Na_2MoO_4 \cdot 2H_2O$ (7.67 g, 31.7 mmol) and $CH_3COONa \cdot 3H_2O$ (12.50 g, 91.9 mmol) in H_2O (250 mL) was treated with $N_2H_4 \cdot H_2SO_4$ (0.80 g, 6.2 mmol) and 50 % CH_3COOH (65 mL). The mixture was stirred for 10 min (gradual color change to green whilst $N_2H_4 \cdot H_2SO_4$ slowly reacted; pH value ca. 4.0). After addition of NaCl (5.00 g, 85.6 mmol), the reaction solution was left in an open beaker (400 mL, wide-neck) for 3–4 weeks (under the fume hood), whereby the volume of the solution reduced to about 50 mL. During this time the initial product **2a** was partially oxidized: within the first hours the color of the solution slowly changed to dark brown with simultaneous evolution of gas. On concentration of the mixture, several fractions precipitated: first, a dark brown precipitate

(filtration at a volume of about 150 mL), then orange-brown crystals of $Na_{10}[H_4Mo_{10}O_{56}Mo_5O_{56}(CH_3COO)_2] \cdot ca. 34 H_2O \cdot 3 CH_3COONa$,^[11] followed by a mixture of colorless crystals and black-brown, columnar crystals of **1**. The mixture of crystals was separated from the oily dark brown mother liquor by filtration through a glass frit (D2). The mixture was washed several times with an aqueous sodium acetate buffer solution (see below) followed by 2-propanol, and finally dried over $CaCl_2$. The individual crystal fractions could only be separated mechanically from one another. Total yield: ca. 3.5 g (ca. 35 % **1**, ca. 15 % $Na_{10}[H_4Mo_{10}O_{56}Mo_5O_{56}(CH_3COO)_2] \cdot ca. 34 H_2O \cdot 3 CH_3COONa$, and ca. 50 % colorless crystals). Compound **1** is very soluble in H_2O . Characteristic IR bands (KBr pellets; 1800–500 cm^{-1}): $\tilde{\nu} = 1628$ (m, $\delta(H_2O)$), 1543 (s, $\nu_{as}(COO)$), 1447 (m), 1412 (m) ($\delta(CH_3)$, $\nu_s(COO)$), 971 (s), 937 (w-m) ($\nu_{as}(Mo=O)$), 854 (s), 795 (vs), 724 (s), 627 (w), 566 cm^{-1} (s); characteristic Raman bands (solid and solution; $\lambda_e = 1064$ nm; 1000–200 cm^{-1}): $\tilde{\nu} = 953$ (w-m), 934 (w-m) ($\nu(Mo=O)$), 874 (s), ca. 845 (sh), 371 (m), 313 cm^{-1} (w-m); UV/Vis (solid-state spectrum measured against cellulose as white-standard: $\lambda = ca. 440$ (br), ca. 600 nm (br). The spectroscopic data are almost identical with those of **2** (the same sample techniques were also used in ref. [2] and not those given there erroneously).

Preparation of the sodium acetate buffer solution for washing: A stirred and cooled aqueous solution of CH_3COOH (50 %; 500 mL) was treated with an aqueous solution of NaOH (20 %) until the pH was 4.0–4.2.

3: A stirred solution of **2**^[2] (1.0 g, 0.04 mmol) in H_2O (50 mL) was treated with $NaH_2PO_4 \cdot H_2O$ (1.0 g, 9.43 mmol) and 50 % H_3PO_4 (ca. 0.8 mL, pH = 2.0). The mixture was stirred for 24 h at 20 °C, NH_4Cl (2.0 g, 37.4 mmol) was added, and the mixture was cooled to 15 °C. The dark brown, rhombohedral crystals of **3** slowly precipitated from the dark brown solution over a period of 4 d, were filtered over a glass frit and dried in air. Yield: 0.55 g (56 % based on **2**). Characteristic IR bands (KBr pellets; 1800–500 cm^{-1}): $\tilde{\nu} = 1620$ (m, $\delta(H_2O)$), ca. 1425 (sh), 1402 (s) ($\delta_{as}(NH_4^+)$), 1118 (m), 1075 (w), ca. 1033 (w) (H_2PO_4), 973 (s), ca. 940 (w) ($\nu(Mo=O)$), 857 (s), 801 (s), 724 (vs), 630 (m), 572 cm^{-1} (s); characteristic Raman bands (solid and solution; $\lambda_e = 1064$ nm; 1000–200 cm^{-1}): $\tilde{\nu} = 939$ (m, $\nu(Mo=O)$), 881 (s), ca. 850 (sh), 374 (m), 304 cm^{-1} (m); UV/Vis (solid-state spectrum measured against cellulose as white-standard): $\lambda = ca. 450$ (br), ca. 600 nm (br).

4: A stirred solution of **2**^[2] (0.50 g, 0.018 mmol) in H_2O (25 mL) was treated with Na_2SO_4 (0.35 g, 2.5 mmol) and hydrochloric acid (15 %, ca. 1 mL). The stirred reaction solution (pH $\approx$ 4.5) was kept in an oil bath at 30 °C for 48 h. (The crystals used for the data collection were obtained in suitable quality by heating the solution to 90 °C for a short time prior to the addition of NH_4Cl .) After addition of NH_4Cl (0.4 g, 7.5 mmol) and cooling to 18 °C, dark brown, rhombohedral crystals of **4** slowly precipitated from the dark brown solution over a period of 4 d. These crystals were collected by filtration using a glass frit and dried in air. Yield: 0.2 g (40 % based on **2**). Compound **4** is very soluble in H_2O and moderately soluble in EtOH. Characteristic IR bands (KBr pellet; 1800–500 cm^{-1}): $\tilde{\nu} = 1625$ (m, $\delta(H_2O)$), 1540 (w, $\nu_{as}(COO)$), ca. 1425 (sh), 1401 (s) ($\delta_{as}(NH_4^+)$), 1187 (m), 1132 (m), 1044 (w-m) ($\nu_{as}(SO_3)$), 970 (s), 936 (w-m) ($\nu(Mo=O)$), 855 (s), 798 (s), 726 (m), 632 (w-m), 572 cm^{-1} (m); characteristic Raman bands (solid and solution; $\lambda_e = 1064$ nm; 1000–200 cm^{-1}): $\tilde{\nu} = 942$ (m) ($\nu(Mo=O)$), 879 (s), ca. 845 (sh), 375 (m), 312 cm^{-1} (w-m); UV/Vis (solid state spectrum measured against cellulose white-standard): $\lambda = ca. 450$ (br), ca. 600 nm (br).

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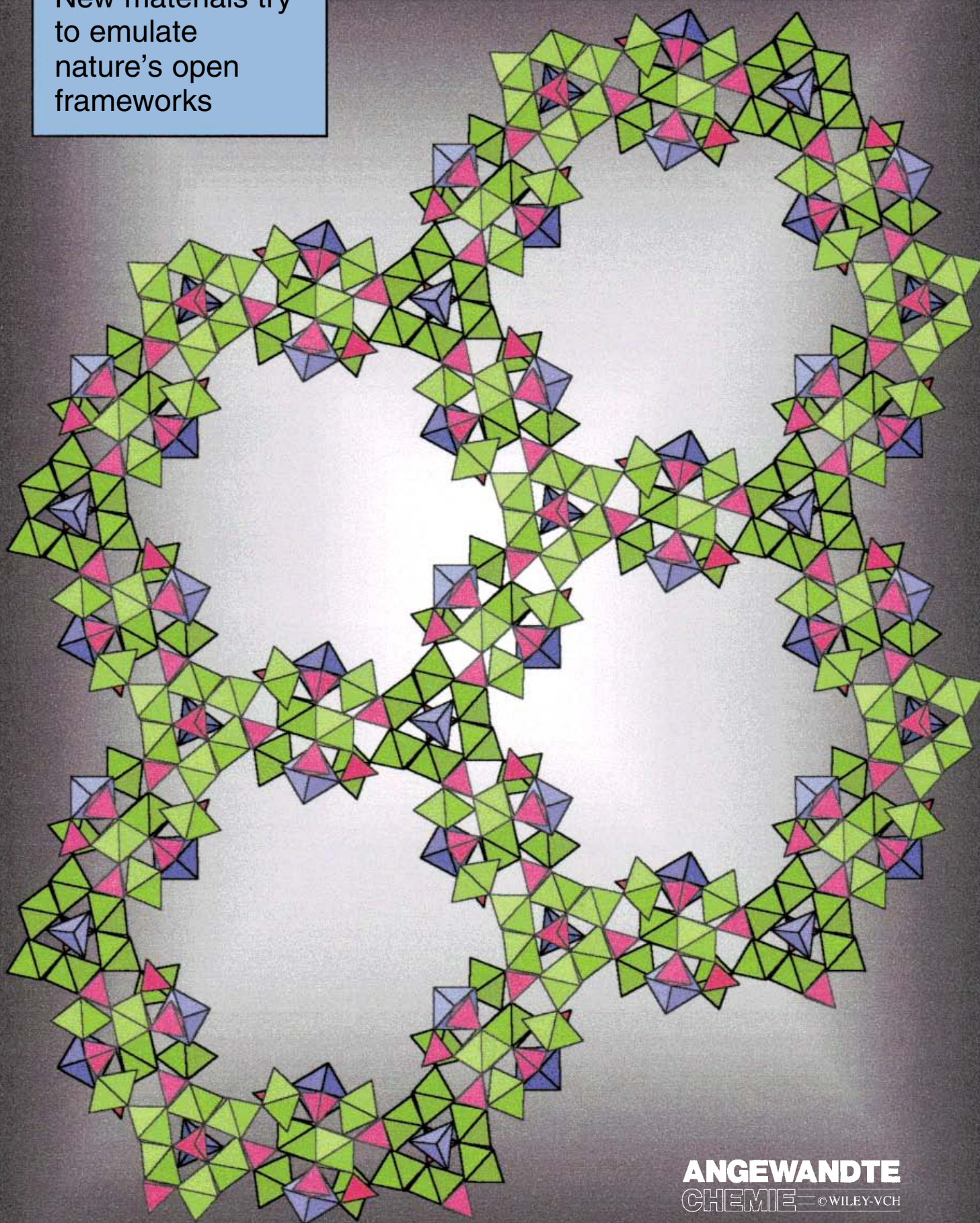
Keywords: cage compounds • cluster compounds • polyoxometalates • structure elucidation • supramolecular chemistry

[1] The title of this article refers to an interesting contribution by P. C. H. Mitchell (“Open and shut case for anions”, *Nature* **1990**, *348*, 15–16; section: News and Views), which in turn refers to one of our earlier publications on a related host/guest chemistry (A. Müller, M. Penk, R. Rohlfing, E. Krickemeyer, J. Döring, *Angew. Chem.* **1990**, *102*, 927–929; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 926–927). In our opinion,

the given title is now completely justified in the present work, because only closed hosts were described in our work at that time. The term "open and shut" can also be applied to the giant wheel-type clusters (A. Müller, S. Q. N. Shah, H. Bögge, M. Schmidtman, *Nature* **1999**, 397, 48–50).

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- [3] The Pythagoreans believed that the world order, its harmony, and symmetry could be defined by numbers: Aristotle wrote in his famous book *Metaphysics* that according to the Pythagoreans—contrary to his own beliefs—the elements of numbers are the elements of all things and various types of structures could be differentiated by different numbers (see: A. Stückelberger, *Einführung in die antiken Naturwissenschaften*, Wiss. Buchgesellschaft, Darmstadt, **1988**, p. 12).
- [4] The extent of the exchange of the acetate ligands depends on the nucleophilicity of the added ligand and the pH value of the solution. The exchange with the phosphate and hypophosphite ions (at least at low pH values) is complete at room temperature; however, only partial exchange with the sulfate ion was observed under the present conditions. We will not report any details here on the phosphate-Keplerate since our investigations have indicated an interesting result which must be discussed separately: the relative uptake of HPO_4^{2-} and H_2PO_4^- ions can be nicely controlled by changing the pH value.
- [5] **1**: Space group $Pmn2_1$; $a = 49.117(4)$, $b = 34.898(3)$, $c = 25.223(2)$ Å, $V = 43\,234(7)$ Å³; $Z = 2$; 207 015 reflections obtained at 183 K from 1271 frames, each of which covered 0.3° in ω scans ($2\theta_{\text{max}} = 50^\circ$); structure solution with direct methods, $R = 0.0896$ for 35 329 independent reflections ($F_o > 4\sigma(F_o)$). **3**: Space group $R\bar{3}$; $a = 32.719(1)$, $c = 73.567(2)$ Å, $V = 68\,205(3)$ Å³; $Z = 3$; 134 487 reflections obtained at 183 K from 1271 frames, each of which covered 0.3° in ω scans ($2\theta_{\text{max}} = 54^\circ$); structure solution with direct methods, $R = 0.0457$ for 24 569 independent reflections ($F_o > 4\sigma(F_o)$). **4**: Space group $R\bar{3}$; $a = 32.695(1)$, $c = 73.529(3)$ Å, $V = 68\,069(3)$ Å³; $Z = 3$; 134 980 reflections obtained at 183 K from 1271 frames, each of which covered 0.3° in ω scans ($2\theta_{\text{max}} = 54^\circ$); structure solution with direct methods, $R = 0.0409$ for 23 684 independent reflections ($F_o > 4\sigma(F_o)$). The crystals were taken directly from their reaction solutions and measured immediately on a Bruker-axs-SMART diffractometer to prevent the loss of water of crystallization. The measurement of several individual crystals led to the same results. The structures were solved with the program SHELXS-97, refined with the programs SHELXL-93 and SHELXL-97, and the absorption corrections were performed with the program SADABS (G. M. Sheldrick, Universität Göttingen, **1997** and **1993**). Disorder problems occurred in the following cases: 1) all of the smaller lattice components, 2) the acetate ligands at various positions in **1** and **4**, 3) terminal MoO groups with the appended *trans*-positioned H₂O ligands in **4**, 4) the H₂PO₂[−] ligands in **3** and HSO₄[−] ligands in **4**. Problems (1) and (4) give rise to a related error limit in the formulae. The structural graphics were generated with the program DIAMOND 2.1 (K. Brandenburg, Crystal Impact GbR, **1999**). Further details of the crystal structure investigation of **3** may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de) on quoting the depository number CSD-410885. Crystallographic data (excluding structure factors) for the structures of **1** and **4** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-132028 and CCDC-132029, respectively. 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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- [11] Space group $P\bar{1}$; $a = 12.1293(5)$, $b = 15.2523(6)$, $c = 15.2852(6)$ Å, $\alpha = 114.911(1)$, $\beta = 94.227(1)$, $\gamma = 101.647(1)^\circ$, $V = 2471.4(2)$ Å³; $R = 0.0358$ for 12 491 independent reflections ($F_o > 4\sigma(F_o)$).

New materials try
to emulate
nature's open
frameworks



Open-Framework Inorganic Materials

Anthony K. Cheetham,* Gérard Férey,* and Thierry Loiseau

In memory of Jean Rouxel

The field of open-framework inorganic materials has expanded dramatically during the last decade. The scope of such materials is no longer limited to aluminosilicate zeolites, aluminum phosphates and related systems, but now embraces frameworks based upon as many as 25 elements of the periodic table. These include a large number of main block phosphates, such as those of gallium, indium, and tin, as well as several transition metal phosphates,

including systems based upon vanadium, molybdenum, cobalt, and iron. In addition to oxide-containing phases, open frameworks are now being found in the realm of sulfides, chlorides, and nitrides, as well as in coordination compounds. Applications of open-framework materials continue to be dominated by the aluminosilicate zeolites, which are noted for their stability and which find utility in catalysis, separations, and ion-exchange, but at-

tempts are being made to exploit some of the exciting properties of the newly discovered systems. The review discusses the synthesis and structures of this growing class of materials, as well as some of their properties and applications.

Keywords: host–guest chemistry • microporosity • solid-state structures • zeolite analogues • zeolites

1. Introduction

There has been an enormous growth in the chemical diversity of open-framework inorganic materials during the 1990s. Prior to the early 1980s, when the nanoporous aluminum phosphates were first reported by Flanigen and co-workers, the aluminosilicate zeolites and closely related systems represented the predominant class of open-framework materials with three-dimensional crystalline structures. The extent of the change during the last 16 years can be judged from the fact that as many as 25 chemical elements of the main block and the transition series are now known to participate as major components of such frameworks, and the number is increasing rapidly. Most are based upon oxygen-containing materials, especially phosphates, but there is a growing list of examples based upon other chemistries, such as

oxyfluorides, nitrides, and sulfides. The range of systems has also increased in another sense: whereas the zeolites and early aluminophosphates were based entirely upon corner-sharing tetrahedra ($[\text{SiO}_4]$, $[\text{AlO}_4]$ etc.), many of the newer architectures involve other polyhedra such as octahedral $[\text{XO}_6]$, pentacoordinated $[\text{XO}_5]$, or pyramidal $[\text{XO}_4]$ or $[\text{XO}_3]$ units. These exciting developments will gradually have an impact on the applications of such materials. The traditional applications of aluminosilicate zeolites are in the areas of ion-exchange, separations, and catalysis, but the new generation of materials offers a wider range of chemical and physical properties that are only just beginning to be explored.

The scope of the present review is restricted for practical purposes to three-dimensional open-framework inorganic structures, thus excluding a large range of related materials such as clays, layered phosphates, and organic frameworks such as clathrates and cyclodextrins. Nor shall we discuss pillared layer structures since these are probably better treated in the context of clays. Our coverage is also limited to crystalline open frameworks, rather than nonperiodic porous systems such as xerogels and aerogels. It does, however, embrace both true nanoporous materials—those that show some reversible adsorption and desorption behavior—and open inorganic frameworks from which it has not yet proven possible to remove the contents of the channels without loss of crystallinity and collapse of the framework; this is a common problem that will no doubt be overcome by

[*] Prof. Dr. A. K. Cheetham,^[+] Prof. Dr. G. Férey, Dr. T. Loiseau
Institut Lavoisier
Université de Versailles St. Quentin
45 Avenue des Etats Unis, F-78035 Versailles Cedex (France)
Fax: (+33) 1-3925-4358
E-mail: ferey@chimie.uvsq.fr

[+] Permanent address:
Materials Research Laboratory
University of California
Santa Barbara, CA 93106 (USA)
Fax: (+1) 805-893-8797
E-mail: cheetham@mrl.ucsb.edu

more subtle chemical treatments. The review also includes reference to the “mesoporous”, surfactant-mediated structures, albeit in less detail.

The discussion will follow an approximately chronological sequence, beginning, of course, with the zeolites and finishing with a short discussion of the growing number of open-framework coordination compounds. Between these extremes, we shall explore a wide range of chemical systems, including phosphates, oxides, nitrides, chalcogenides, and halides. To a considerable extent, the sequence is also one of decreasing thermal stability. For example, the extensive occurrence of aluminosilicate zeolites and their widespread utility in industry depends heavily upon the thermodynamic and kinetic stability of the constituent aluminosilicate framework (it should be noted that the open frameworks of zeolites are thermodynamically slightly less stable than the corresponding condensed structures, into which they will transform during severe thermal treatment). The challenge with many of the newer materials is that their stability with respect to transformation into alternative condensed structures is considerably lower. Nevertheless, there are many surprises in this respect, such as the unusual stability of the Sn^{II} phosphates and rare-earth dicarboxylates.

Given the huge literature in this burgeoning area, we shall not attempt to give a comprehensive coverage, but we shall endeavor to highlight the important general trends and to give an eclectic selection of illustrative examples and references.

More recent developments will be given greater emphasis since they have not been reviewed in detail elsewhere.

2. Aluminosilicate Zeolites and Related Materials

The aluminosilicate zeolites of general formula $\text{A}_{x/n}[\text{Si}_{1-x}\text{Al}_x\text{O}_2] \cdot m\text{H}_2\text{O}$, where A is typically a metal cation of valence n , were the first class of nanoporous materials to be recognized. They occur quite extensively in nature, and synthetic examples were made as early as the mid 19th century.^[1] Such has been the rate of development in this area during the second half of the 20th century that as many as 100 different architectures are now known,^[2] all of which are based upon vertex-sharing $[\text{SiO}_4]$ and $[\text{AlO}_4]$ tetrahedra, as in the example shown in Figure 1.^[*] The Si/Al ratio can range from a minimum of 1 (where the Si and Al would be in strict alternation) to infinity (see below). The nomenclature is often confusing, in spite of the fact that the International Zeolite Association has assigned a three-letter code to each structure type. A typical example would be FAU, which represents the family of materials with the faujasite-type structure. Never-

[*] All black-and-white figures are shown on approximately the same scale in order to facilitate comparisons between their pore dimensions.

Tony Cheetham obtained his Ph.D. at the University of Oxford in 1971 and was a member of the chemistry faculty at Oxford from 1974 to 1991. In 1991 he moved to the University of California at Santa Barbara to become Professor in the Materials Department. In 1992 he also became Professor of Chemistry at UCSB and Director of the newly created Materials Research Laboratory. His research interests concern the synthesis and characterization of in-

organic materials, especially nanoporous solids and magnetic oxides. He is a Fellow of the Royal Society, and recently held a Chaire Internationale de Recherche, Blaise Pascal, in Paris.



T. Cheetham



G. Férey



T. Loiseau

G rard F rey studied chemistry in Caen (France). In 1977, he obtained his Ph.D. and became Professor in the group of R. de Pape in Le Mans. In 1996 he moved to the new University of Versailles to create the Institut Lavoisier (UMR CNRS 8637). His research interests moved from structure and frustrated magnetic properties of crystalline and amorphous transition metal fluorides to synthesis and characterization of new porous oxyfluorinated solids and hybrid open frameworks. Professor F rey is a Corresponding Member of the French Academy of Sciences.

Thierry Loiseau was born in 1968 in Angers, France. He is an engineer in Materials Sciences (ISITEM, Nantes). He received his Ph.D. at the University of Maine in Le Mans in 1994 under the supervision of Professor G. F rey and Dr. F. Taulelle from the University of Strasbourg, and became Charg  de Recherche CNRS. In 1996 he moved to the Institut Lavoisier (UMR CNRS 8637) at the newly created University of Versailles. His research interests are in the area of hydrothermal synthesis and structural chemistry of microporous phosphate-like materials.

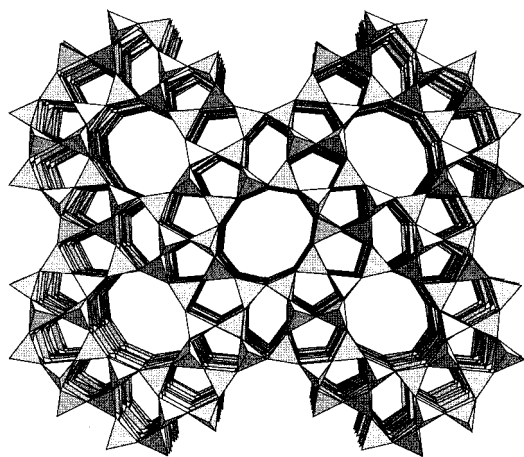


Figure 1. A perspective view of the structure of zeolite ZSM-5 (MFI), viewed down the straight channel; no cations are shown. The tetrahedra are shaded for clarity.

theless, many materials are more commonly known by acronyms chosen by the laboratories in which they were discovered. Pore sizes range from about 2.5 Å in the case of sodalites (SOD), in which the largest channel has rings containing 6 Si/Al sites (i.e. 6-rings), to about 10 Å in so-called UTD-1 which has a 14-ring channel^[3] (Figure 2). Some common examples are given in Table 1. Zeolitic materials, of course, are well known to exhibit large pore volumes that are associated with very low tetrahedral (T) site densities (< 20 T atoms/1000 Å³, T = Si, Al). The majority of the systems with large channels contain rings with even numbers of T sites, for example 8-, 10-, 12- or 14-rings, but a recent X-ray diffraction study found both 7- and 9-rings in the high-silica zeolite SSZ-23.^[4]

Industrial interest in these materials has been driven by their excellent ion-exchange properties in the hydrated state, and by the exciting adsorption and catalytic properties exhibited by their dehydrated forms. Indeed, it is for this

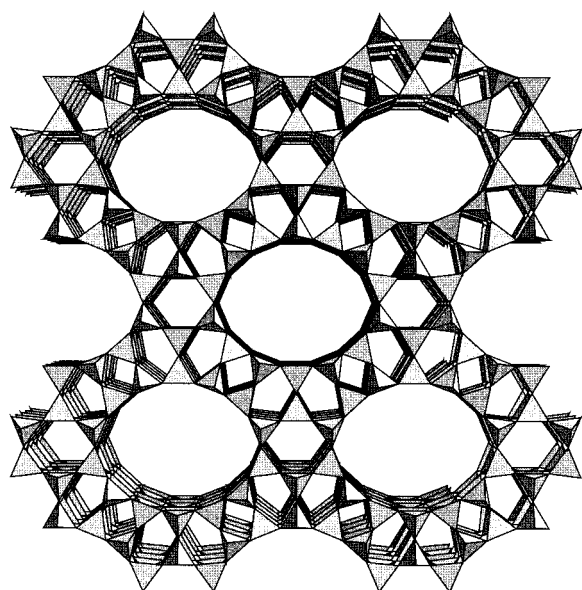


Figure 2. A perspective view of the structure of zeolite UTD-1; no cations are shown.

Table 1. Examples of nanoporous aluminosilicates, with the three-letter IZA designations and a brief description of the pore systems.

System	Pore system
sodalite family (SOD) (e.g. mineral and synthetic sodalites)	3-dimensional; 6-ring channels
zeolite A family (LTA) (e.g. zeolites A, ZK-4; no mineral analogue)	3-dimensional; 8-ring channels
chabazites (CHA) (e.g. mineral chabazites, SSZ-13)	3-dimensional; 8-ring channels
ZSM-5 (MFI) (e.g. mineral murataite, silicalite)	2-dimensional; 10-ring channels
ferrierites (FER) (e.g. mineral and synthetic ferrierites)	2-dimensional; 10 and 8-ring channels
faujasites (FAU) (e.g. mineral faujasite, zeolites LSX, X, Y, US-Y)	3-dimensional; 12-ring channels

reason that many of the most eye-catching synthetic discoveries have been made in industrial laboratories, such as those of Mobil, Union Carbide (now UOP), British Petroleum, and Chevron. Table 2 summarizes some of the most important actual and prospective applications. Commercial production of zeolites was approximately one million tons in 1995, most of which was accounted for by applications in catalytic cracking, xylene isomerization, and detergents. This pattern is gradually changing, however, as new applications are developed.

Table 2. Some important applications of aluminosilicate zeolites.

Well-established:
ion-exchange with hydrated zeolites detergency (e.g. zeolites Na-A and Na-P) water softeners animal feeds radwaste remediation (e.g. Cs, Sr with clinoptilolite)
molecular sieving with dehydrated zeolites air separation (N ₂ from O ₂ with Li-LSX) drying agents (e.g. double glazing, air conditioning) sulfur removal from natural gas separation of HFCs (CFC substitutes)
catalysis with dehydrated zeolites catalytic cracking (gasoline production)—zeolite-Y derivatives xylene isomerization (for polyesters)—H-ZSM-5 butene isomerization—H-FER methanol to gasoline—H-ZSM-5 phenol to hydroquinone—titanosilicates denox reactions—Cu-ZSM-5, Co-FER
Future possibilities include:
nano-composites for electro-opticals sensors with zeolite thin films stereoselective polymerization contrast enhancement in MRI (e.g. Gd-Y)

Hydrated low-silica zeolites (Si/Al < 2), such as synthetic sodium zeolite A (LTA), are used widely for ion-exchange applications where their high cation content leads to high exchange capacities. Many other factors, such as cost, good kinetics, and selectivity, are also important. Consequently, cheap naturally occurring materials with somewhat higher Si/Al ratios (3–5), for example clinoptilolite (HEU) and

phillipsite (PHI), may be used for certain large-scale applications. Dehydrated forms of the large-pore low-silica zeolites, such as zeolite X (FAU), are used in adsorption and separation applications, including noncryogenic air separation (Li-zeolite LSX). The interactions between the under-coordinated cations and the sorbate molecules are a crucial feature of such processes. In air separation, for example, it is the affinity of the lithium for the dinitrogen molecule, which has a quadrupolar moment three times bigger than that of dioxygen, that provides the basis for the separation.^[5] The low-silica materials are relatively unstable at high temperatures, so materials with high Si/Al ratios are preferred for catalytic applications. These include high-silica faujasite types such as ultrastabilized Y, and ZSM-5. Most of the catalytic processes are based upon acid-catalyzed reactions in which the exchangeable cation of the zeolite is replaced by a proton that provides Brønsted acidity. In addition, the shape and size of the zeolite cavities leads to selectivity in the reaction, hence the term “shape-selective catalysis”. This is the case in the hydrocarbon cracking catalysts used in gasoline manufacture and the isomerization catalysts used in *p*-xylene production for polyester manufacture. Some of the new titanosilicates, such as TS-1 (MFI) which contains framework titanium, exhibit redox activity and are being used for partial oxidation reactions involving phenols and hydrogen peroxide.^[6]

Naturally occurring zeolites normally have quite low Si/Al ratios, typically three or less, and it is often quite easy to make synthetic analogues of these materials under hydrothermal conditions. For example, synthetic analogues of the mineral faujasite (FAU) can be made from reactions between sodium silicate and sodium aluminate under basic conditions at 60–150 °C. Variations in the temperature, charge-compensating cation, time of reaction, and the pH value, amongst other variables, yield a variety of low-silica aluminosilicate zeolites, although all such reactions are carried out under basic conditions. Post-synthesis modifications, such as steaming or treatment with silicon tetrachloride, have been developed to increase the Si/Al ratios of these materials to render them stable during high-temperature use. A major breakthrough in respect of the direct synthesis of high-silica materials took place in the late 1960s with the development of synthetic routes involving the hydroxides of quaternary ammonium ions or organic amines in place of the normal alkali metal bases. These organic nitrogen compounds, which act as template molecules or structure-directing agents, are incorporated into the final product where they replace the usual charge-compensating cations. They play two important roles: 1) the size and shape of the quaternary amine can lead to the creation of new pore structures which cannot be made in other ways; 2) the large sizes of these cations, when compared with traditional metal cations, means that they can only compensate for a relatively low framework charge, thus leading to the formation of high-silica materials. The organic cations can normally be removed from the zeolite by calcination, leaving behind the acid form of the zeolite (see above). A classical example is zeolite ZSM-5 (Figure 1), which is made in the presence of tetrapropylammonium cations, TPA (it should be noted that organic templates are not always essential for the

synthesis of high-silica zeolites; for example, ZSM-5 itself can be prepared by a template-free method). Curiously, over 20 years after its full characterization in the laboratory,^[7] a natural analogue of ZSM-5, known as murataite, has recently been discovered.^[8] It has a Si/Al ratio of 7.6, which is the highest found in any natural zeolite.

In addition to the aluminosilicates zeolites, some synthetic analogues, such as borosilicates, gallosilicates, and ferrisilicates have also been explored. The borosilicates are more difficult to prepare, probably because the much smaller boron atom, with its tendency towards planar threefold coordination, is not such an obvious substitute for the aluminum. Gallium- and iron(III)-containing materials, however, are well known and usually have properties similar to those of the aluminosilicates. There is evidence, nevertheless, for some unique behavior with gallosilicates, as in their ability to catalyze cyclization reactions and to activate methane.^[9] Other silicate-based systems include the eye-catching titanosilicates, mentioned earlier, and an unusual zincosilicate (VPI-7) which contains tetrahedral Zn^{2+} .^[10]

Another interesting development has been the direct synthesis of pure silica materials with no exchangeable cations. The synthesis of the silica polymorphs, which include silicalite-1 (MFI)^[11] and siliceous ferrierite (FER),^[12] requires template molecules or structure-directing agents, and there is an interesting question as to how the charge of the quaternary ammonium ions is compensated in the absence of framework aluminum. The use of fluoride ion during these reactions is often desirable, and it is known that it can play a variety of roles, for example as a mineralizing agent. Its use is even more widespread in the case of phosphates, as described in Section 3. Since the silica polymorphs should be completely ordered once the organic molecule has been removed, they provide excellent vehicles for detailed characterization by ^{17}O and ^{29}Si NMR spectroscopic studies,^[13] as well as for computer simulation studies.^[14] They are also very interesting candidates in the context of low-dielectric materials for integrated circuit manufacturing,^[15] since they can be made defect-free and have up to nearly 50 % pore volume.

There remains considerable interest in the synthesis of new zeolite architectures that may offer unique catalytic or other applications, and much of the synthetic effort lies in the area of the use of novel quaternary ammoniums ions as structure-directing agents. In this respect, the most eye-catching discovery in the last ten years has been the successful use of self-assembling surfactant cations, such as $(\text{C}_{16}\text{H}_{33})(\text{CH}_3)_3\text{N}^+$, in such reactions by scientists at Mobil.^[16] This can lead to the formation of lamellar, hexagonal, or cubic phases, known collectively as the M41S family, and which are closely related to the lyotropic phases formed by simple halide salts of these cations in aqueous solution. Calcination of the hexagonal and cubic phases has yielded thermally stable porous materials with pores that are much larger (approx. 30–100 Å) than those of conventional zeolites. Although these materials are periodic in terms of their pore structures and therefore give rise to coherent X-ray diffraction, the silica walls are disordered and more resemble the structure of a glass. There has been a lot of discussion concerning the mechanism of the formation of the M41S materials^[17] and their possible

applications. Unlike conventional zeolites they do not exhibit strong acidity, but they do show promise as supports in other types of catalytic reactions, such as olefin polymerizations.^[18] Recent reviews of the area^[19, 20] also discuss the extension of this type of chemistry to other chemical systems, where a large number of analogues have now been reported (e.g. mesoporous AlPO_4 , TiO_2 , Al_2O_3 , metallic platinum, and so on).

It has been shown both experimentally^[21] and theoretically^[14] that open structures are less stable than their condensed analogues, but the differences are quite small, about 15 kJ mol^{-1} between siliceous faujasite and α -quartz for example. The remarkable thermal stability of silica-based nanoporous materials, therefore, stems from the strength of their T–O bonds (e.g. $\text{Si–O} \approx 466 \text{ kJ mol}^{-1}$) which render them stable with respect to framework rearrangement. As we look at other chemical systems in the following sections, we shall see that this kinetic stability is less evident as the framework bonds become weaker. Consequently, whereas it is now practicable in many systems to make open-framework materials with organic cations in the channels, it is often very difficult to remove these guests without inducing the collapse of the host structure. The vast majority of the systems that we shall describe cannot therefore be rendered nanoporous. One family that approaches the stability of the silicates, however, is the aluminum phosphates (AlPO_4), which are discussed in the following section.

3. Aluminum Phosphates, Gallium Phosphates, and Related Materials

3.1. Aluminum Phosphates

Following the extensive development of synthetic, microporous aluminosilicates, research has gradually shifted towards the exploration of new families of three-dimensional frameworks. Based on crystal chemistry principles, the aluminophosphates (AlPO_4) were considered first. They are isoelectronic with SiO_2 and can be regarded as III–V analogues. Seven allotropic forms of AlPO_4 that correspond to condensed silica polymorphs are known (α - and β -quartz, α -, β -, and γ -tridymite, and α - and β -cristobalite).^[22] In these materials, aluminum and phosphorus are observed in tetrahedral coordination, as is silicon in the silicas. From these considerations, Flanigen and co-workers at Union Carbide Corporation discovered a new generation of microporous materials, aluminophosphate $\text{AlPO}_4\text{-}n$ (n refers to a structural type), at the beginning of the 1980s.^[23] These materials, and related ones made subsequently, are the subject of this section.

The synthetic procedure^[24] is similar to that used for zeolites: the aluminophosphates are prepared hydrothermally under autogenous pressure in the temperature range $100\text{--}250^\circ\text{C}$. They are typically obtained from a mixture of aluminum oxyhydroxide or alkoxide and phosphoric acid in water, leading to the formation of an aluminophosphate gel. An amine or quaternary ammonium salt, which plays a templating or structure-directing role, is then added to the mixture. These reactions are typically carried out in the

following molar proportions: $x\text{R}:1\text{Al}_2\text{O}_3:1.0 \pm 0.2\text{P}_2\text{O}_5:y\text{H}_2\text{O}$ ($0 < x < 10$, $40 < y < 400$), where R is the structure-directing species. The crystallization time depends on multiple variables such as temperature, reactant composition, and structural type, and ranges from several hours to several weeks. The pH of the reaction, which is less than that observed in zeolite synthesis, varies within the range from 3 to 10 and tends towards the neutral value at the end of the reaction. The organic molecule, which is trapped within the pores, plays a critical role in producing the microporous framework. In the absence of such a molecule, only dense AlPO_4 or $\text{AlPO}_4 \cdot n\text{H}_2\text{O}$ hydrates are formed. The thermal stability of the open-framework solids is similar to that obtained for zeolites and the template can often be removed by calcination in air at $500\text{--}600^\circ\text{C}$. Some compounds exhibit stable structures up to 1000°C . In the $\text{AlPO}_4\text{-}n$ series, the Al/P ratio is 1 and the frameworks are electrostatically neutral.

Investigations were then performed on the incorporation into the AlPO_4 frameworks of elements with different valences in order to modify the chemical properties for catalysis, ion-exchange, and so on. This led the Union Carbide researchers to synthesize several new series of materials, in particular the silicoaluminophosphates ($\text{SAPO-}n$),^[25] metal-aluminophosphates ($\text{MAPO-}n$) and metasilicoaluminophosphates ($\text{MAPSO-}n$).^[26] The strategy was first to explore divalent cations which are able to adopt tetrahedral coordination (e.g. $\text{M} = \text{Mg}^{2+}$, Mn^{2+} , Fe^{2+} , Co^{2+} , and Zn^{2+}). The weakly acidic pH of the reaction prevents the precipitation of the metal as hydroxide or oxide and facilitates its partial incorporation into the inorganic framework. These phases have framework compositions of the general formula $(\text{Si}_x\text{M}_w\text{Al}_z\text{P}_z)\text{O}_2$, where x varies from 0 to 0.20 and w from 0 to 0.25. The silicon substitutes preferentially at the phosphorus site whereas the metal substitutes exclusively for the aluminum. The introduction of these elements renders the frameworks negative and therefore charge-compensating cations are required, as in the aluminosilicate zeolites. When these cations are protons, the materials exhibit acid catalytic properties which vary as a function of the structural type and the nature of the substituting element.^[27] The incorporation of other elements, such as monovalent (Li), divalent (Be), trivalent (B, Cr, Fe, Ga), tetravalent (Ti, Ge), and pentavalent elements (As), into the AlPO_4 framework has also been reported (e.g. $\text{AlAsPO-}n$).^[28]

From the structural point of view, the microporous aluminophosphate-based compounds include more than 40 different framework types. As in the zeolites, the three-dimensional structure is delimited by channels and cavities where the templating agent is located. However, there are some differences compared with the topologies encountered in the zeolite family. The majority of the aluminum phosphate based solids exhibit (4,2)-connected networks with alternating Al and P on tetrahedral sites. This rule limits the structural possibilities because rings must be formed by an even number of T atoms, which prevents the occurrence, for example, of 5-ring units. Thus, while the aluminophosphate analogues of the aluminosilicate zeolites, erionite (ERI) or sodalite (SOD), are known ($\text{AlPO}_4\text{-}17$ and $\text{AlPO}_4\text{-}20$, respectively^[2]), no AlPO_4 exists with the MFI type structure, which contains

5-ring units. In the last issue of the *Atlas of Zeolite Structure Types*,^[2] 16 structural types were reported for both the silicate and phosphate families.

During the last decade, the synthesis of microporous aluminophosphate-based materials has led to the discovery of numerous novel topologies, some of them exhibiting extra-large pores delimited by more than 12 T atoms (until recently, the pore sizes found in aluminosilicates ranged only up to 12-rings, but the synthesis of the silicate UTD-1 pushed the limit to 14; see Section 2). For the AlPO_4 s, this trend was initiated at the end of the 1980s by Davis and co-workers with the synthesis of the aluminophosphate VPI-5 (VFI).^[29] This molecular sieve contains one-dimensional circular channels with an 18-membered ring aperture and possesses a free diameter of 12–13 Å (Figure 3). The VFI network can be viewed as the insertion of two adjacent 4-ring units between the 6-ring units of AlPO_4 -tridymite. The structure of AlPO_4 -8 (AET),^[30] which contains 14-ring channels, is a close relative of the VPI-5 network.

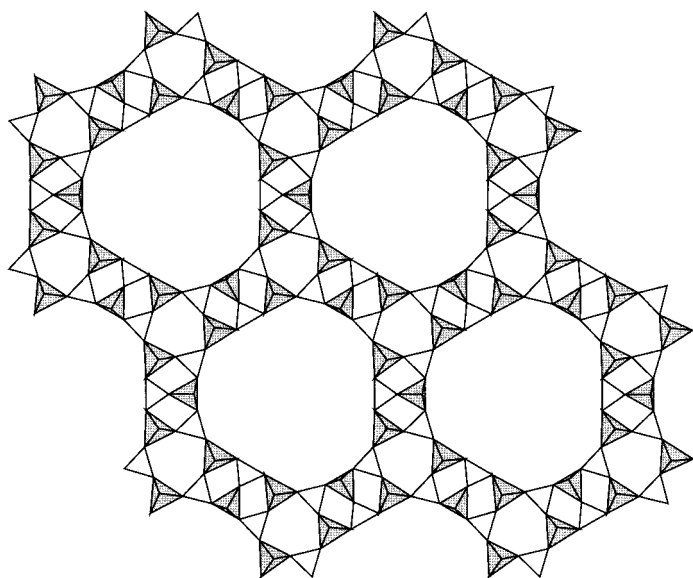


Figure 3. A plan view of the structure of the aluminophosphate VPI-5 (VFI).

The occurrence of coordination numbers greater than four for the aluminum is another feature of the phosphate-based solids in comparison with the zeolites. For example, in some phases aluminum adopts fivefold (trigonal bipyramidal) or sixfold coordination (octahedral). In these cases, water groups or anionic species such as hydroxide complete the coordination sphere of the aluminum, which leads to connection modes already encountered in mineral aluminum phosphates^[31] in which $[\text{AlO}_n]$ polyhedra may share corners or edges through Al-O-Al linkages. It also results in the formation of odd-numbered rings, as in, for instance, AlPO_4 -14A^[32] and AlPO_4 -21 (Figure 4).^[33] In these examples, the channel size appears to be limited as a consequence of the increase of the aluminum coordination, which thus seems to be a drawback for the production of large pores.

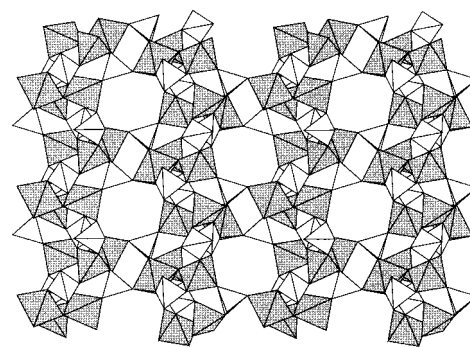


Figure 4. A plan view of the structure of AlPO_4 -21.

3.2. Gallium Phosphates—Early Developments

In the mid-1980s, research was extended to microporous phosphates in which other elements completely replaced aluminum. For example, Parise^[34–36] described the synthesis of several gallophosphates related to the AlPO_4 - n family. Following this idea, Xu and co-workers^[37–40] undertook a systematic study in the gallium system to produce a series named GaPO_4 -C n ($n = 1–12$). Some of them are identical to the AlPO_4 - n materials; for example, GaPO_4 -C7^[39] is isostructural with the hydrated gallium phosphate $\text{GaPO}_4 \cdot 2\text{H}_2\text{O}$ ^[41] and the AlPO_4 -15^[42] type, and corresponds to the structure of the iron phosphate mineral, leucophosphite.^[43] However, a new framework called GaPO_4 -C3,^[37] previously reported as GaPO_4 - α by Wilson et al.,^[44] has been shown to exhibit an open structure containing 8-ring channels. In this program,^[40] some alumi- and galloarsenates with new topologies were also described (AlAsO_4 -1,^[45] AlAsO_4 -2^[46] and GaAsO_4 -2^[47]). These examples indicate that gallium can be found in four-, five- and sixfold coordination in its phosphates, as is the case for aluminum in the aluminum compounds. However, there is a general trend for the coordination numbers to be higher than those of aluminum.

The micropores of these early phosphate and arsenate frameworks are limited to 8-ring channels, except for the gallium arsenate GaAsO_4 -2^[47] which has tunnels delimited by ten polyhedra (but see Section 3.4). A deviation from the normal Ga/P stoichiometry of 1 is shown in the hydrated gallophosphate $\text{Na}_3\text{Ga}_5(\text{PO}_4)_4\text{O}_2(\text{OH})_2 \cdot 2\text{H}_2\text{O}$.^[48] The pores of the structure contain sodium cations and water molecules, and the latter can be desorbed to give rise to pores with an aperture diameter of 4 Å.

3.3. Reactions in Nonaqueous Solvents

All of the phosphate compounds described so far were synthesized with water as the main solvent. Several studies (principally by the groups of Xu of Jilin, China, and Thomas of the Royal Institution, London) have explored the solvent effect under hydrothermal conditions for the feasibility of making open frameworks and for the control of the crystal quality.^[49] The tested solvents were mainly alcohols (butanol, triethylene glycol, etc.) and improved crystallization is gen-

erally observed, which is helpful for X-ray structural characterization. Several known aluminophosphates, including $\text{AlPO}_4\text{-5}$, $\text{AlPO}_4\text{-11}$, and $\text{AlPO}_4\text{-21}$, have also been synthesized from nonaqueous systems.^[50] In many cases, however, low-dimensional AlPOs and GaPOs^[51] were obtained, corresponding to several series of layered and chain solids, with P/Al or P/Ga ratios ranging from 4/3 to 2/1, in which the interlamellar or interchain space is occupied by organic cations. In a recent examination of the formation of aluminophosphates under nonaqueous conditions, Ozin and co-workers^[52] have suggested that intermediates based upon one-dimensional chains could be involved in the crystallization of two-dimensional porous layers and finally the three-dimensional open-framework materials. The condensation scheme is believed to depend upon the hydrolysis rate determined by the water concentration present in the reaction mixture.

The utilization of organic solvents has nevertheless allowed for the discovery of several new three-dimensional structural types. An aluminophosphate known as JDF-20,^[53] $[\text{Al}_5\text{P}_6\text{O}_{24}\text{H}]^{2-} \cdot 2[\text{N}(\text{C}_2\text{H}_5)_3\text{H}]^+ \cdot 2\text{H}_2\text{O}$, has been obtained from a mixture of triethylene glycol and triethylamine. Its framework is three-dimensional and contains 20-rings with elliptical apertures with a free diameter of 6.2 by 14.5 Å (Figure 5). The other feature is the P/Al ratio, which differs from 1, as is sometimes the case in other microporous aluminophosphates. All of the $[\text{AlO}_4]$ tetrahedra share their vertices, but this is not the case for the phosphate groups, some of which exhibit terminal P–OH bonds to give rise to an interrupted framework. The utilization of ethanolamine instead of pure amine was reported for the synthesis of the microporous aluminophosphate $\text{AlPO}_4\text{-JDF}$,^[54] analogous to $\text{AlAsO}_4\text{-1}$,^[45] in the presence of a large variety of alcohols. The use of alcoholic solvents has continued to yield interesting AlPO_4 materials, as shown by the recent preparation of $\text{AlPO}_4\text{-HDA}$.^[55]

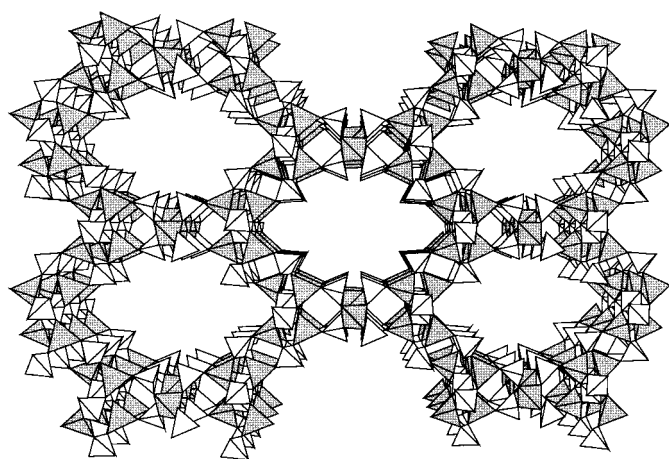


Figure 5. A perspective view of the structure of JDF-20.

The first gallium phosphates prepared from predominantly nonaqueous solvents were the two GaPO_4 materials, $\text{GaPO}_4\text{-M1}$ and $\text{GaPO}_4\text{-M2}$, obtained by variation of the methylamine content in ethylene glycol.^[56] The structure of $\text{GaPO}_4\text{-M2}$ ^[57] is unique and consists of 8-ring channels with the methylammonium cations in the cavities. Another compound,

$[\text{Me}_2\text{NH}(\text{CH}_2)_2\text{NHMe}_2]^{2+} [\text{Ga}_4\text{P}_5\text{O}_{20}\text{H}]^{2-} \cdot \text{H}_2\text{O}$,^[58] presents an open framework with large elliptical pores characterized by puckered windows (16.50×6.65 Å) made of 16 Ga/P atoms.

3.4. The Fluoride Method

The fluoride method, previously mentioned in Section 2, was first used in the elaboration of phosphate-based compounds by Kessler and co-workers.^[59, 60] Beside its mineralizing effect, fluoride seems to have a catalytic role: for example, the presence of fluoride ions is necessary for the formation of the phase $\text{AlPO}_4\text{-14A}$,^[61] although it is not incorporated into the network. However, when fluoride is present in the structure, it can adopt specific configurations in which AlPO_4 structural types are essentially preserved. For example, in $\text{AlPO}_4\text{-5}$ (AFI)^[62] the fluoride is located between two 4-rings in the 4-ring columns. It is linked to two aluminum atoms with rather long distances (Al–F 2.19 Å). In the aluminophosphate analogues of the zeolites chabazite (CHA)^[60, 63] and gismondine (GIS),^[64] two fluoride atoms bridge two aluminum atoms across the 4-ring units, rendering them octahedrally coordinated rather than tetrahedrally coordinated as in the aluminosilicate forms. Double octahedral entities, $[\text{Al}_2\text{O}_8\text{F}_2]$, are thus generated with a common F–F edge (Figure 6a).

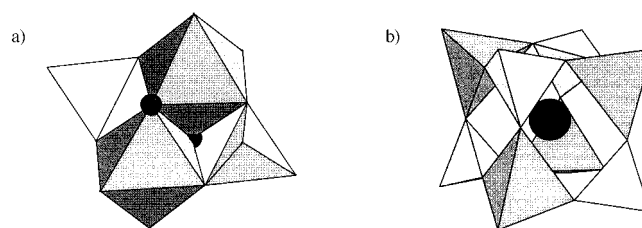


Figure 6. a) A representation of the unit $[\text{M}_2(\text{PO}_4)_2\text{F}_2]$ (fluorides are shown as filled circles). b) A representation of a D4R cage with an encapsulated fluoride anion (fluoride is shown as a filled circle).

The most exciting feature of the fluoride method is its use in the synthesis of new alumi- and gallophosphate architectures which incorporate fluorine atoms into the open framework. Two situations are found for the fluoride. First, it seems to stabilize the double-4-ring (D4R) cage, which is a cube with the corners occupied by $[\text{TO}_4]$ tetrahedra. The fluoride is trapped within this cavity (Figure 6b) and Kessler has suggested that such fluoride ions could play a structure-directing role. This case is encountered in GaPO-LTA ,^[65] but the major breakthrough was the discovery of cloverite (Figure 7),^[66] a gallophosphate with extra-large pore openings comprising 20 $[\text{TO}_4]$ units and a three-dimensional channel system similar to that in faujasite-type zeolites.^[2] The expected pore size is 13.2 Å, but the effective diameter is limited by the presence of terminal hydroxy groups that point towards the centers of the windows. The basic building unit is the D4R cage with an occluded fluoride atom. It is noted that the presence of fluoride strongly modifies the surroundings of the gallium atoms, leading to an increase of the coordination to fivefold (elongated trigonal bipyramid).

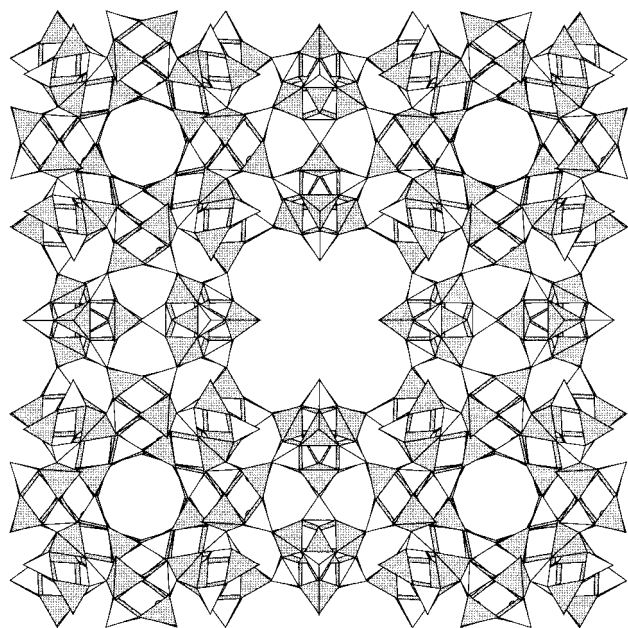


Figure 7. A plan view of the structure of cloverite (CLO).

The resulting Ga–F distances indicate that the fluoride is weakly linked to the gallium atom (Ga–F 2.3–2.6 Å). The occurrence of this octameric unit is also found in aluminophosphates such as $\text{AlPO}_4\text{-16}$ (AST)^[67] synthesized in the presence of hydrofluoric acid. This building unit has also been prepared as an isolated cluster in Mu-1^[68] and as linear chains in Mu-3.^[69]

Alternatively, fluorine can participate more directly in the coordination sphere of the metal and increase the coordination number from five to six. This is seen in the case of the phosphate CJ2,^[70, 71] in which Al or Ga atoms adopt both fivefold and sixfold coordinations. Studies performed by Férey and co-workers^[72, 73] in Le Mans gave rise to a new series of oxyfluorinated phosphates called ULM-*n*. In this family, the basic building units can be either tetramers, as is usually found in the crystal chemistry of phosphates,^[74] or hexamers (Figure 8a). For the tetramers, the connection of the metal atom is by means of corner- (Figure 8b) or edge-sharing fluorine

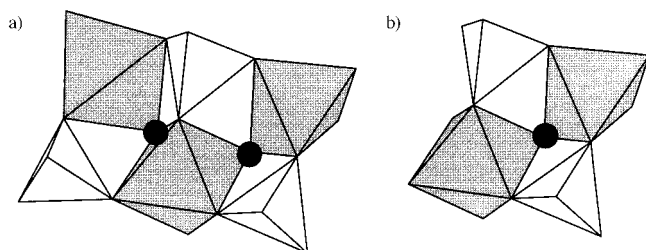


Figure 8. Polyhedral representations of a) the $[\text{M}_3\text{P}_3]$ hexamer, and b) the $[\text{M}_2\text{P}_2]$ tetramer.

atoms (Figure 6a). The hexameric unit is quite common in fluorinated materials. It is composed of a central octahedrally coordinated Al or Ga linked to two Al or Ga atom with trigonal-bipyramidal coordination, through fluorine. This trimer is capped by three phosphate groups. The connection of these hexamers generates different packing structures,^[75]

such as ULM-3 or ULM-4 where the channels are delimited by 10-ring windows. The galloarsenate, $\text{GaAsO}_4\text{-2}$,^[47] exhibits an open framework closely related to that of ULM-4. The hexameric unit can be found with other building blocks, such as the D4R cage in ULM-5 (Figure 9) or the double crankshaft chain in ULM-16 (Figure 10). In the last two compounds, the addition of these other building units leads to the production of extra-large channels with 16-ring windows. The other feature of fluorinated materials is that fluorine in the framework creates anchoring points for the NH groups of the amines as a result of strong hydrogen bonding.

Synthesis from a predominantly nonaqueous system in the presence of a mixture of HF/pyridine and tris-(2-aminoethyl)-amine (tren) yields another example of a hexameric-based phosphate phase, TREN-GaPO.^[76] The structure contains

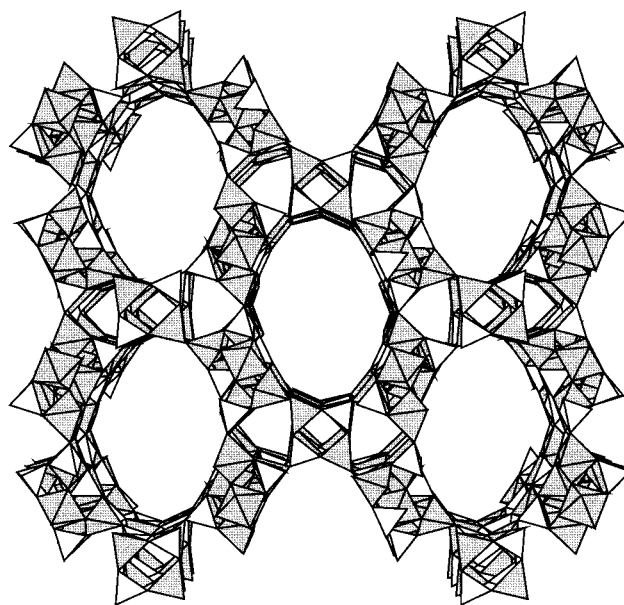


Figure 9. A perspective view of the structure of ULM-5 (without template molecules).

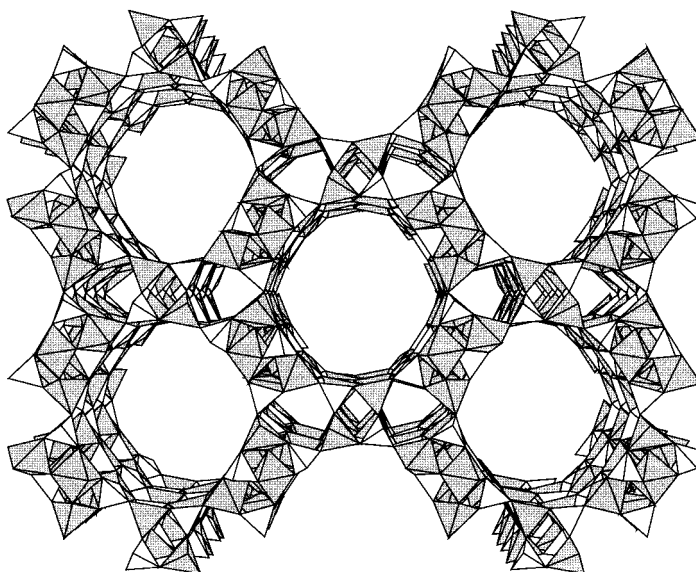


Figure 10. A perspective view of the structure of ULM-16 (without template molecules).

adjacent and parallel 12-ring and 8-ring channels and a segregation is observed between the two amine molecules: the tren molecule is located in the larger channels whereas the pyridine molecule resides in the 8-ring pores (Figure 11). The combined nonaqueous/fluoride reaction strategy, which was first used by Ozin in the synthesis of siliceous zeolite ferrierite,^[12] is very versatile. In the gallium system, for example, the use of 1,6-diaminohexane instead of tren led to the formation of a 14-ring channel compound.^[77] It should be noted that the pure hexameric-based phosphates were also obtained with aluminum^[78] or iron (see Section 5.3) in place of gallium.

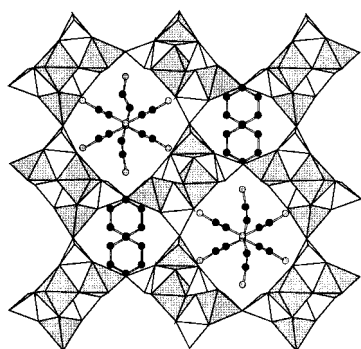


Figure 11. A plan view of the structure of TREN-GaPO (note the pyridine and tren molecules in the small and large channels, respectively). Octahedral $[\text{GaO}_6]$ and pentacoordinated $[\text{GaO}_5]$ units are shown as shaded polyhedra.

The effect of the fluorine source has also been investigated. Whereas the use of ammonium fluoride leads to the formation of small-pore compounds (e.g. $\text{AlPO}_4\text{-CJ2}$,^[70] $\text{NH}_4[\text{Ga}_2(\text{PO}_4)_2(\text{OH})(\text{H}_2\text{O})] \cdot \text{H}_2\text{O}$ ^[79]), reactions made with a combination of hydrofluoric acid and alkali fluorides (NaF, KF) with alkylammonium hydroxides as organic templates result in the preparation of new phases with larger pores (the $\text{UiO-}n$ series).^[80] For example, UiO-6 (OSI) ,^[81] synthesized with tetraethylammonium hydroxide and NaF or KF, contains one-dimensional 12-ring channels (free aperture 6.2 Å). The alkali cations and fluorine atoms are located in the small pores as in the zeolites, and the fluorine–alkali cation interactions seem to be essential for the formation of this new phase. Without an alkali cation, the use of tetramethylammonium hydroxide leads to a new framework, UiO-7 (ZON) ,^[82] with a two-dimensional 8-ring channel system.

3.5. Synthesis in the Presence of Transition Metal Coordination Complexes

Recently, transition metal coordination complexes have been tested as structure-directing agents in the synthesis of aluminophosphates. This type of complex is very versatile, and offers a range of unique conformations that are not found with organic amine molecules. Many exhibit chiral character, which might lead to the formation of chiral frameworks for use in enantioselective heterogeneous catalysis or separation processes. Different tris(diamine) cobalt(III)

complexes have been tested and a few chiral layered aluminophosphates have already been reported.^[83, 84] Only one three-dimensional framework gallophosphate has been obtained with such cobalt complexes^[85] and consists of a diamondlike network composed of tetrahedral $[\text{GaO}_4]$ units linked to $[\text{PO}_4]$ units. The complex remains intact during the reaction and is found trapped within the pores. Metallocene molecules, which were used in the synthesis of the large-pore zeolite, UTD-1, have also been used for the production of $\text{AlPO}_4\text{-5}$ and $\text{AlPO}_4\text{-16}$.^[86] From these and other results, it has been shown that cobalt complexes are usually quite stable under hydrothermal conditions. However, similar experiments carried out with a tris(1,3-diaminopropane) nickel(II) complex^[87] resulted in decomposition during hydrothermal treatment which led to the formation of a three-dimensional open-framework aluminophosphate with the ULM-3 structural type.

3.6. Methyl Phosphonates

Interest in open-framework aluminum phosphonates, as distinct from phosphates, was stimulated by the recent discovery of two microporous aluminum methylphosphonates, $\text{AlMePO-}\alpha$ and $\text{AlMePO-}\beta$, prepared by Maeda and co-workers.^[88–90] These two structures, with the stoichiometry $\text{Al}_2(\text{PO}_3\text{CH}_3)_2$, are polymorphs and have unidimensional hexagonal channels composed of 18-rings. Aluminum is found in both tetrahedral and octahedral sites, and the methyl groups, which are covalently linked to the phosphorus atoms, protrude into the channels and reduce the pore size to around 6 Å. Layered aluminophosphonates have also been reported,^[91] as expected by analogy with other areas of phosphonate chemistry.

3.7. Indium Phosphates

The aluminum and gallium phosphates confirm that it is possible to produce open three-dimensional architectures with metallic atoms in four-, five- or sixfold coordination. Indium, therefore, represents an interesting case since, by comparison with the smaller Al or Ga which can adopt three types of coordination, In is only expected to occur with octahedral coordination. This has been confirmed in several examples. In the first report of an organically templated indium phosphate, Haushalter^[92] described a new open-framework material, $\text{H}_3\text{NCH}_2\text{CH}_2\text{NH}_3[\text{In}_2(\text{HPO}_4)_4]$, obtained with ethylenediamine. This work was followed by several other examples which incorporated various amine molecules,^[93–95] including a pillared layer structure obtained with imidazole (Figure 12).^[93] Other structures, analogous to known minerals, have been isolated: a hydrated indium phosphate, $\text{InPO}_4\text{-1}$,^[96] related to the variscite type, and $\text{InPO}_4\text{-2}$,^[97] related to the leucophospite type. These compounds are characterized by small pores delimited by eight polyhedra.

In the presence of HF, three fluorinated indium phosphates have been obtained so far. One structure is lamellar^[98] and is

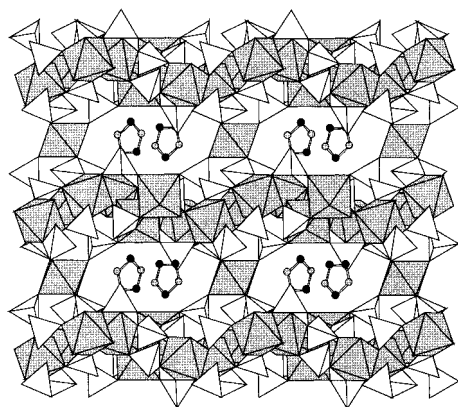


Figure 12. A view of the structure of imidazole-templated indium phosphate (see text). $[\text{InO}_6]$ octahedra are shown as shaded polyhedra.

isostructural with ULM-11 or $\text{AlF}(\text{HPO}_4) \cdot \text{en}$,^[73] the second structure, $\text{In}_5(\text{PO}_4)_4\text{F}_3(\text{H}_2\text{O})_2 \cdot \text{en}_3$,^[98] is three-dimensional with 10-ring channels which are spanned by ethylenediamine bridges between two opposite indium atoms. In both compounds, the nitrogen atoms of the template molecule are directly connected to indium atoms, and fluorine atoms are shared between indium atoms. A third phase, with the framework formula $[\text{In}_9(\text{PO}_4)_6(\text{HPO}_4)_2\text{F}_{16}]$,^[99] is characterized by a high fluorine content. The three-dimensional network is composed of large elliptical cavities resulting from 14-ring channels adjacent to 8-ring channels. The fluorine atoms are found in either bridging or terminal positions.

3.8. Boron Phosphates

Surprisingly few studies have been reported the synthesis of microporous boron phosphates. From a crystal chemistry point of view, BPO_4 possesses the same dense structures as those of silica and AlPO_4 ,^[100] and one might assume that it would be relatively easy to produce open-framework BPO_4 architectures. Boron is commonly found in trigonal or tetrahedral surroundings and it should be a good candidate for the preparation of solids based on (4;2)-connected networks, as in zeolites. It would seem that this is not the case. Boron has been incorporated to a small extent (less than 1 %) into the AlPO_4 -5 framework,^[101] where it substitutes for aluminum, but there are no reports to date of open-framework BPO_4 structures. However, a complex borophosphate has been described by Sevov;^[102] this is a mixed cobalt–boron phosphate, $\text{CoB}_2\text{P}_3\text{O}_{12}(\text{OH}) \cdot \text{C}_2\text{H}_{10}\text{N}_2$ or BPO-1, in which the boron is found in tetrahedral coordination. The connection of the $[\text{BO}_4]$ units to $[\text{PO}_4]$ tetrahedra and $[\text{CoO}_6]$ octahedra by corner sharing generates 8-ring channels where the occluded ethylenediamine plays the role of the template.

3.9. New Open Frameworks in Metal-Containing AlPO and GaPO Materials

Interest in the incorporation of metal ions into the frameworks of aluminophosphates was initiated by researchers at

Union Carbide with the discovery of the MAPO-*n* series (Section 3.1).^[25] A number of new structural types have been found in this area, several of them having unique frameworks with no pure AlPO_4 analogue. For example, MAPO-36 (ATS)^[2] can only be obtained in the presence of small amounts of a metal such as Mg, Mn, Zn, Co,^[25] or Ti.^[103] Other examples include magnesium-containing aluminophosphates such as DAF-1^[104] or STA-*n*,^[105] which have been prepared by the use of decathonium hydroxide and linear diquinuclidine, respectively, as templates. The structure of DAF-1 (DFO) possesses two parallel unidimensional channel systems containing puckered 12-rings in one case (ca. 6.1 Å) and planar 12-rings in the other (ca. 7.5 Å). It has been shown to be catalytically active for the acid-catalyzed conversion of isobutane to butenes and propene.^[106] The structure of STA-1 (SAO) has large-pore channels delimited by 12-rings (ca. 6.6 Å and 7.2 Å) which run along two perpendicular directions, but without straight connections between them. In these compounds, the magnesium is partially substituted into the tetrahedrally coordinated aluminum framework sites. Chippindale and co-workers have described several examples of mixed cobalt(II)–gallium phosphates, some of which are analogous to known zeolites. For example, $(\text{C}_5\text{H}_5\text{NH})\text{[CoGa}_2(\text{PO}_4)_3]$ ^[107] and $(\text{C}_4\text{NH}_{10})\text{[CoGa}(\text{PO}_4)_2]$ ^[108] have the LAU and GIS framework topologies, respectively. The laumontite structure type has also been obtained with iron or manganese replacing cobalt atoms in the framework.^[109] By contrast, CoGaPO-5 (CGF)^[110] exhibits a novel framework topology based on alternating $[\text{PO}_4]$ and $[\text{MO}_4]$ ($\text{M} = \text{Ga}, \text{Co}$) tetrahedra. It consists of two sets of channels delimited by 8- and 10-rings perpendicular to 8-ring channels, similar to the system encountered in heulandite.^[2]

Very recently, Stucky and co-workers^[111, 112] reported an extensive study of microporous cobalt–aluminum and cobalt–gallium phosphates materials, of general formula $(\text{R})\text{Co}_x\text{M}_{1-x}\text{PO}_4$ ($\text{R} = \text{organic template}$, $\text{M} = \text{Al}, \text{Ga}$). This study was based on the concept of template–framework charge matching, rather than the steric hindrance of the structure-directing agent: the negative charge of the framework, which depends on the $\text{Co}^{2+}/\text{M}^{3+}$ ratio, is counterbalanced by the positive charge of the organic species. By varying the organic charge/volume ratio, cobalt can be incorporated more or less extensively into the framework. Several zeolite analogues were synthesized, as well as new frameworks that had been predicted previously. For example, the compound ACP-1 (ACO), which has a structure built up from the connection of D4R cages to form three-dimensional 8-ring channels, has not yet been observed in aluminosilicates. This work was then extended to other divalent cations, such as Mg^{2+} , Zn^{2+} , and Mn^{2+} , and several materials designated UCSB-*n*, were obtained, three with frameworks characterized by multidimensional 12-ring channels. UCSB-10 (SBT) and UCSB-6 (SBS) exhibit three-dimensional 12-ring channel systems and their structures, built up from cancrinite-like cages, are related to that of faujasite (FAU) and its hexagonal polymorph (EMT). In this description, the sodalite cages of FAU and EMT types are replaced by cancrinite cages. These frameworks differ in the packing of the cancrinite cages, and large cavities bounded by three, four, or five 12-rings are

produced. The architecture of UCSB-8 (SBE) consists of two sets of perpendicular 12-ring channels interconnected with 8-ring channels. At the intersection, this results in large cavities bounded by 64 T atoms (four 12-rings and two 8-rings).

In all the above phases, the metal is incorporated into the network in a tetrahedral site. However, there are a few examples where cobalt adopts octahedral coordination, as in the ammonium cobalt–gallium phosphate $\text{NH}_4[\text{CoGa}_2(\text{PO}_4)_3(\text{H}_2\text{O})_2]$ ^[113] and the cobalt–aluminum phosphate $\text{CoAl}(\text{PO}_4)_2 \cdot \text{en}$.^[114] In the latter, the coordination of the cobalt atom is completed by five oxygen atoms and one nitrogen atom of the ethylenediamine. In the manganese–gallium phosphate, $(\text{C}_6\text{N}_2\text{H}_{14})[\text{MnGa}(\text{HPO}_4)(\text{PO}_4)]$ or MnGaPO-2 ,^[115] the manganese ion is in a five-coordinated site with square-pyramidal geometry.

4. Other Main Block Open Frameworks

4.1. Beryllium and Zinc Compounds

In addition to the study of novel open frameworks with metals substituting into zeolites, aluminophosphates and so on, there have been numerous recent publications concerning the synthesis of open frameworks which contain exclusively metallic ions in combination with phosphate. In much of this work, the strategy has been to choose elements that can adopt tetrahedral coordination in the solid state. At the beginning of the 1990s, the groups of Meier^[116] and Stucky^[117] described the synthesis of beryllo- and zincophosphates and arsenates, denoted as BePO , ZnPO , BeAsO and ZnAsO . Most of these compounds were prepared under hydrothermal conditions, although some of them were obtained from milder reactions at temperatures ranging from -20 to 70°C . Their structures consist of vertex-sharing networks of $[\text{MO}_4]$ ($\text{M} = \text{Zn}^{2+}$, Be^{2+}) and $[\text{XO}_4]$ ($\text{X} = \text{P}$, As) tetrahedra, corresponding to anionic frameworks, $[\text{MXO}_4]^-$, that are equivalent to those encountered in aluminosilicates of composition $[\text{AlSiO}_4]^-$. By the use of alkaline cations for charge compensation, several zeolite analogs have been obtained, for example ZnPO , ZnAsO , BePO , and BeAsO sodalites,^[118, 119] ZnPO and BePO faujasites,^[120] BePO and BeAsO RHO,^[121] and the ZnPO , ZnAsO , BePO , and BeAsO ABW.^[117, 122] New topologies were also found, including the berylllophosphate $\text{Na}_{0.5}\text{K}_{0.5}\text{BePO}_4$ (BPH),^[123] the chiral framework, $\text{NaZnPO}_4 \cdot \text{H}_2\text{O}$ (CZP),^[124] and the $\text{A}_3\text{Zn}_4\text{O}(\text{XO}_4)_3 \cdot n\text{H}_2\text{O}$ ($\text{A} = \text{alkaline}$, $\text{X} = \text{P}$, As) series^[125] in which both Zn–O–P and Zn–O–Zn linkages occur.

Certain of the zincophosphates contain tetrahedral units with terminal hydroxy groups (HPO_4^{2-} or/and H_2PO_4^-), thereby limiting the connection of these units to other $[\text{MO}_4]$ tetrahedra. Consequently, several three-dimensional topologies with interrupted networks have been prepared.^[126–132] With the exception of $\text{H}[\text{Zn}_4(\text{PO}_4)_3] \cdot \text{H}_2\text{O}$ and $(\text{NH}(\text{CH}_3)_3)[\text{Zn}_4(\text{H}_2\text{O})(\text{PO}_4)_3]$,^[132] the Zn/P ratio in these compounds is very often less than 1. A higher Zn content implies some Zn–O–Zn linkages, the bridging oxygen atom being in trigonal coordination with a link to a phosphorus atom. This is a situation where metal–oxygen–metal connec-

tivities occur with the metal in tetrahedral surroundings. This is not usually observed in aluminosilicates, nor in AlPOs unless the coordination of aluminum is increased to five or six. More recently, Harrison and Phillips^[133, 134] have described the synthesis of a series of zincophosphates prepared with the nitrogen-rich guanidinium cation; a molecule with trigonal planar geometry. Despite the small size of this organic species, the open frameworks of these compounds exhibits large pores bounded by 12-ring^[134] or 18-ring channels.^[133] Although the Zn/P ratio is greater than 1, there is no Zn–O–Zn bonding in this structure; only terminal Zn–OH₂ bonds occur, as was also observed in the zincophosphate templated by the DABCO molecule.^[127] In $\text{N}(\text{CH}_3)_4[\text{ZnH}_3(\text{PO}_4)_2]$,^[135] the three-dimensional network contains 12-ring channels but the tetrahedral framework is characterized by one of the lowest framework densities observed so far for a microporous compound ($10.1 \text{ T atoms}/1000 \text{ \AA}^3$). A mixed zinc–aluminum phosphate, denoted ZAPO-M1 (ZON),^[136] has also been reported and is isostructural with the fluorinated aluminophosphate UiO-7.^[82] Other zinc derivatives, including a zincoborate^[137] and a zincocarbonate,^[138] have also been mentioned and present alternatives systems for the elaboration of open frameworks.

Another feature of beryllium and zinc phosphate chemistry is the formation of topologies which contain 3-ring units as a basic building block. This feature is observed, for example, in the beryllsilicate mineral, lovdarite.^[2] Brunner and Meier^[139] found a linear correlation between the occurrence of small ring sizes and the framework density. From Brunner and Meier's concept, one strategy to obtain materials with low framework density is to synthesize beryllium- and zinc-based materials, but, due the toxicity of the beryllium, efforts concentrated mainly on the study of the zinc compounds. Several new topologies based on three-membered ring units have thus been reported: VPI-7 (VSV),^[10] VPI-9 (VNI), and RUB-17 (RSN).^[140]

4.2. Borates and Germanates

Although open-framework borosilicates (Section 2) and borophosphates (Section 3.8) have attracted a certain amount of attention, many other borate systems still remain to be explored. In the light of the enormous literature on condensed borates, this surely represents an interesting opportunity for future research. One interesting family that has been reported is the boron sodalites, such as $\text{Zn}_4\text{O}(\text{BO}_2)_6$.^[141] These comprise a framework based exclusively upon tetrahedral $[\text{BO}_4]$ units, the zinc atoms being located in extra-framework cation positions.

Equally surprisingly, open-framework structures based upon germanates have not been extensively studied in comparison with the huge effort that has been expended on silicates and phosphates. However, one versatile family of composition $\text{M}_{4-x}\text{H}_x\text{Ge}_7\text{O}_{16} \cdot n\text{H}_2\text{O}$ has been known for many years^[142] and several structural variants are known.^[143–145] The framework structure of these materials is composed of a central cluster of four face- and edge-sharing $[\text{GeO}_6]$ octahedra; these clusters are linked to each other through $[\text{GeO}_4]$

tetrahedra. This coordination behavior is consistent with the larger size of germanium compared to silicon. These germanates are reported to exhibit useful ion-exchange behavior and ionic conductivity,^[146] but we are not aware of any work relating to other properties.

A quite different germanate architecture has been described recently by Cascales et al.^[147] As with the system discussed above, $(\text{NH}_4)_2\text{Ge}_7\text{O}_{15}$ contains both tetrahedral and octahedral $[\text{GeO}_n]$ units, but their connectivities are quite different, and give rise to a rare example of a 9-ring window. Given the occurrence of both tetrahedral and octahedral coordination with germanium, it could be of great interest to explore mixed Si,Ge systems. Similarly, recent work on the gallium- and aluminum-containing germanate frameworks, UCBS-9 and UCSB-11,^[148] has revealed a tendency for the formation of 3-ring units, as is also found in certain beryllium- and zinc-containing systems (Section 4.1).

4.3. Tin(II) Phosphates

Very recently, some open-framework tin(II) phosphates templated with organic molecules have been prepared by Cheetham and Natarajan.^[149–151] Since tin in the 2+ oxidation state is associated with a lone pair of electrons, its presence in the structure results in unique building units for open frameworks. Tin(II) is mainly found in threefold coordination, connected to three phosphorus atoms by bridging oxygens located at the vertices of a trigonal pyramid (Figure 13). The lone pair occupies the fourth vertex of a hypothetical tetrahedron. For three-dimensional systems based on the alternation of $[\text{PO}_4]$ tetrahedra and $[\text{SnO}_3]$ trigonal pyramids,^[149, 150] this yields a framework of general formula $[\text{Sn}_4\text{P}_3\text{O}_{12}]^-$ with pores in which the organic amine species

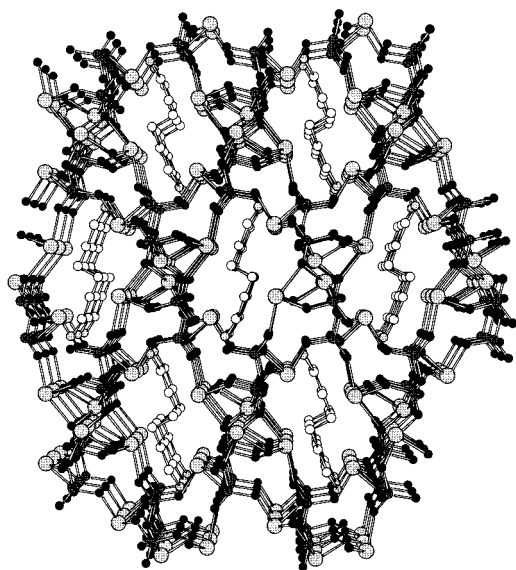


Figure 13. A perspective view of the structure of a Sn^{II} phosphate, with 1,6-diaminohexane in the channels (Sn: large shaded spheres; P: medium shaded spheres; O: small black spheres; C: small white spheres; N: small shaded spheres). Note that the lone pairs on tin(II) point into the channels.

are occluded. The channels found to date include both 8- and 12-rings, but the effective size for accessibility is smaller than anticipated due to the hindrance of the lone pair of electrons that point towards the centers of the channels. In the oxophosphate phase, SnOPO -1,^[151] the Sn/P ratio is 2 and tin atoms are connected together by a common oxygen atom which coordinates three tin atoms. The three-dimensional framework encapsulates ammonium cations and star-shaped 10-ring channels are generated. In a system with a Sn/P ratio of 3/2, the presence of both trigonal-pyramidal $[\text{SnO}_3]$ and square-pyramidal $[\text{SnO}_4]$ units also results in Sn-O-Sn linkages.^[152] As in the AlPO systems, monomeric,^[153] chain,^[154] layered^[155] and three-dimensional chiral^[156] structures have also been observed, and there is evidence that a simple tetramer, $[\text{Sn}_2\text{P}_2\text{O}_8]$, may be a fundamental building unit in many of these structures.

5. Transition Metal Phosphates

Following the successful introduction of transition metals into the zeolitic AlPOs and GaPOs and the discovery of open-framework solids with coordination numbers larger than four, several groups attempted to synthesize phosphates containing exclusively transition metals. Such materials offer a great deal of scope, since they may contain metals in different valence states and/or different coordination numbers, and the anionic framework may be all oxide or oxide and fluoride. The presentation will follow a chronological sequence.

5.1. Molybdenum Phosphates

Several years after the discovery of MoOPO_4 by Kierkegaard and Westerlund,^[157] the reduced molybdenum phosphates were studied simultaneously by the Raveau and Haushalter groups.^[158, 159] They initially focused on solid-state synthesis techniques at temperatures above 750°C , the reaction mixture being alkali metal phosphate or MoO_3 , a phosphate source (P_2O_5 or metal phosphate) and Mo metal, which were heated together in an evacuated quartz ampoule. The resulting molybdenum phosphates had a Mo/P ratio lower than 1.

In this series of high-temperature materials, inorganic cations are accommodated into condensed frameworks with various topologies. Costentin et al. proposed^[158] a classification of these phases according to the connectivity of the molybdenum polyhedra. Class I involves structures in which the $[\text{MoO}_6]$ octahedra are isolated from each other, which means they share five of their corners with $[\text{PO}_4]$ tetrahedra, the sixth oxygen, corresponding to the very short $\text{Mo}=\text{O}$ bond, being terminal. This family, the largest in the series, mainly corresponds to Mo/P ratios of 1/2 and 2/3, and gives rise to many different topologies, principally with $[\text{Mo}_2\text{P}_3\text{O}_{13}]_\infty$ frameworks. Class II is characterized by infinite $[\text{MoO}_{6/2}]_\infty$ octahedral chains in which short $\text{Mo}-\text{O}$ bonds ($\approx 1.65 \text{ \AA}$) alternate with long bonds ($\approx 2.5 \text{ \AA}$) along the axes of the chains. This second family does not exhibit any free apices;

the four available apices are shared with $[\text{PO}_4]$ tetrahedra. The typical structure of this class is MoOPO_4 .^[157] An interesting example that combines class I and class II is $\text{AgMo}_5\text{P}_8\text{O}_{33}$ ^[160] which gives rise to 10- and 8-rings, the latter containing the Ag^+ ions (Figure 14). Class III has a few representatives with $\text{Mo/P} < 1$. It concerns structures that exhibit units with a limited number of molybdenum octahedra, for example in $\text{K}_2\text{Mo}_2\text{P}_2\text{O}_{11}$ where the framework is built

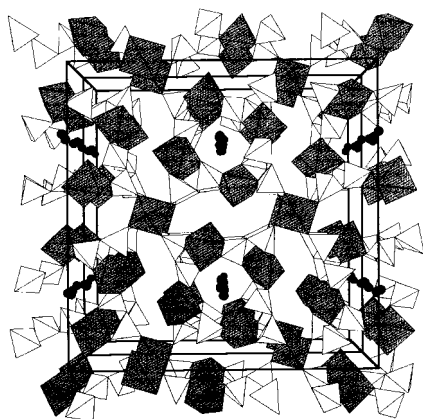


Figure 14. A perspective view of the structure of $\text{AgMo}_5\text{P}_8\text{O}_{33}$ (Ag: small spheres; $[\text{MoO}_6]$ polyhedra are dark shaded; $[\text{PO}_4]$ tetrahedra are light shaded)

from corner-sharing $[\text{Mo}_2\text{P}_2\text{O}_{15}]$ tetramers. In the latter, two Mo octahedra share a vertex, and two tetrahedra are grafted on to the Mo dimer by corner sharing. An increase of the Mo/P ratio implies a further condensation of the Mo octahedra and leads to structures in which these polyhedra share edges and faces. The building units which describe the frameworks are often octameric, with four Mo and four P atoms arranged in three different ways. This was first observed by Haushalter^[159] in $\text{Cs}_3\text{Mo}_4\text{P}_3\text{O}_{16}$, which is isotypic with the mineral pharmacosiderite;^[161] it contains octameric $[\text{Mo}_4\text{P}_4]$ clusters linked by corners. These clusters comprise a central tetramer of MoO_6 octahedra, each of them sharing three edges with the others; six phosphate groups cap the Mo tetramer by shared corners.

All of these high-temperature MoPOs show very poor ion-exchange properties. In order to form materials with significant internal micropore volume, it is necessary to use hydrothermal techniques and to try to incorporate large removable cations. With this approach, Haushalter et al.^[159] successfully prepared some MoPOs with open frameworks by allowing a molybdenum source ($\text{MoO}_3 + \text{Mo}$ or MoCl_5) to react with phosphoric acid and an organic cationic template in an autoclave in the temperature range 200–400 °C. The first MoPO, $(\text{Me}_4\text{N})_{1.3}(\text{H}_3\text{O})_{0.7}[\text{Mo}_4\text{O}_8(\text{PO}_4)_2] \cdot 2\text{H}_2\text{O}$,^[162] is built up from another type of tetramer, close to that of pharmacosiderite, with the same central tetramer of Mo octahedra, but with only four phosphate groups. Such a cluster can present different connectivities to form various frameworks that lead to different pore openings and different cavity diameters (2.8–7 Å). Several other open-framework solids were also synthesized in this way by changing the nature of the template; they contain a third form of octameric unit, already

described in leucophosphate^[162] and speniscidite,^[163] in which the central tetramer is composed of two edge-sharing octahedra on the edge of which are grafted two other octahedra over shared corners. Finally, another open-framework topology was obtained when a mixture of organic and inorganic cations is used during the synthesis. It derives from the MoOPO_4 structure in the sense that the bridging oxygen atoms between two layers are replaced by phosphate groups.^[164]

5.2. Vanadium Phosphates

Interest in this family of materials stemmed initially from the catalytic applications of vanadyl pyrophosphate $(\text{VO})_2\text{P}_2\text{O}_7$ in the selective oxidation of butane to maleic anhydride.^[165, 166] As with the MoPOs described above, the VPOs were synthesized by the use of both high-temperature solid-state reactions with inorganic cations and low-temperature hydrothermal techniques with amines as templates. The association of different vanadium valence states (v, iv, iii) with their various polyhedra (tetrahedra, square pyramids, distorted and regular octahedra) leads to a very large diversity for the resulting structures. For the solid-state approach, which will not be described in detail here, the major contributors were the groups of Haushalter and Jacobson in USA, Raveau in France, Lii in Taiwan, and Beltran-Porter in Spain. A good list of references to the corresponding works can be found in ref. [167]. As with the condensed molybdenum phosphates, several situations occur for the vanadium subnetwork: isolated polyhedra and corner- and edge-sharing chains (these are connected to each other by $[\text{PO}_4]$ tetrahedra, but their connections always leave small tunnels inside which cationic exchange is difficult).

The success obtained with MoPOs with hydrothermal techniques and organic templates led Haushalter^[168] and Férey^[169] to investigate the corresponding V-P-O systems. Two eye-catching results originate from this research: a) the first evidence of an inorganic double helix in $[(\text{CH}_3)_2\text{NH}_2]\text{K}_4[\text{V}_{10}\text{O}_{10}(\text{H}_2\text{O})_2(\text{OH})_4(\text{PO}_4)_7] \cdot 4\text{H}_2\text{O}$ ^[168] and b) the existence of giant voids in the two square-pyramidal–tetrahedral framework vanadium phosphates $\text{Cs}_3[\text{V}_5\text{O}_9(\text{PO}_4)_2] \cdot x\text{H}_2\text{O}$ and $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{NH}]\text{K}_{1.35}[\text{V}_5\text{O}_9(\text{PO}_4)_2] \cdot x\text{H}_2\text{O}$.^[170] In the double-helix compound, the structure is built up from two crystallographically independent V_5P_4 enneamers. These oligomers can be described as a linear trimer of *trans* corner-sharing octahedra in which long and short $\text{V}=\text{O}$ bonds alternate along the axis of the chain. Each of the two outer octahedra of the trimer share one edge perpendicular to the axis of the trimer with a square pyramid, thus forming pentameric building units. The four $[\text{PO}_4]$ tetrahedra share two of their oxygen atoms with those of the basal plane of each octahedron of the trimer. These pentamers are arranged so as to form spirals, with four pentamers per spiral of unit cell length along $[001]$. These spirals are intertwined to give the two strands of a double helix. Some of the remaining phosphate groups connect the strands to one another, and others bond one double helix to another. The strands and double helices intergrow with each

another in an extremely complicated manner. This arrangement generates different cavities in which K^+ and protonated dimethylamines are inserted. The K^+ ions lie in the more polar regions of the cavities and are solvated by water. At very low temperatures (<2.5 K), the solid exhibits antiferromagnetic properties.

The structures of $Cs_3[V_5O_9(PO_4)_2] \cdot xH_2O$ and its homologue with DABCO and potassium (Figure 15)^[170] are characterized by a very unusual pentameric unit of square-pyramidal coordinated vanadium atoms $[V_5O_9(PO_4)_{4/2}]$, in the shape of a spiked helmet; the V_5 pentamers consist of a central $[VO_5]$ square pyramid which shares its four basal edges with those of the four satellite square-pyramidal vanadium centers. The four phosphate tetrahedra each link

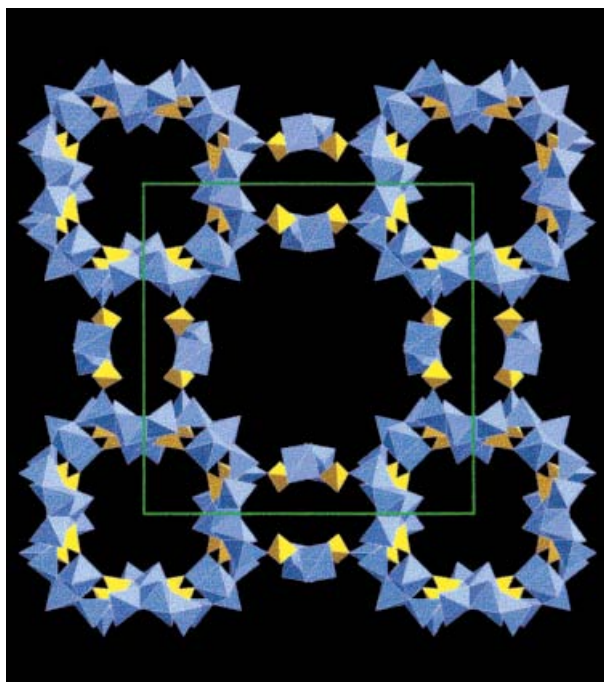


Figure 15. A view of the open framework of $Cs_3[V_5O_9(PO_4)_2] \cdot xH_2O$. The Cs and H_2O are not shown.

two satellites by corners. Such an arrangement was already encountered in molecular chemistry with the famous vanadium clusters described by Müller.^[171] The curvature of these pentamers explains the formation of very large cavities. Each cavity, which could contain a sphere of ca. $13 \text{ \AA}$ diameter, is occupied by 12 DABCO molecules, 32 K^+ cations and some water of crystallization. At its maximum diameter, it displays an enormous 32-ring window and connects over 16-ring windows with the other supercages. These materials possess one of the lowest framework densities ($9.3 \text{ metal atoms}/1000 \text{ \AA}^3$) and the largest cavities observed so far in open-framework materials.

Beside these two original compounds, a mixed-valence material must also be mentioned owing to its very interesting structure: $(H_2en)_3[V^{III}(H_2O)_2(V^{IV}O)_8(OH)_4(HPO_4)_4(PO_4)_4 \cdot (H_2O)_2] \cdot 2H_2O$. It may be described^[172] as undulating layers constructed of corner-sharing V^{IV} square pyramids and

phosphate tetrahedra; these layers are then connected by single $[V^{III}(H_2O)_2]$ centers to form a framework which exhibits elliptical channels (ca. $7 \times 18 \text{ \AA}$). Furthermore Beltrán-Porter et al. showed that it was possible to substitute V^{III} by Fe^{III} in this structure type.^[173]

All of the above compounds are oxides. The application of the fluoride route already described (Section 3.4) for $AlPO_4$ s and $GaPO_4$ s has showed that it is also possible to obtain open-framework structures containing fluoride. This led to the discovery by Riou and Férey^[174] of the first open-framework vanado(v)fluorophosphate, ULM-7 or $(H_3N(CH_2CH_2)NH_3)[(V^VO_2)_2(PO_4)F]$, in which the building units are V_2P trimers. Vanadium exhibits both octahedral and square-pyramidal coordination, and a fluoride ion, which belongs to both polyhedra, is shared between them. Each V polyhedron shares an oxygen with the phosphate group of the trimer. The three-dimensional network generated by corner sharing of these trimers exhibits 10-rings in which diprotonated amines are inserted. Two new vanadofluorophosphates have recently been reported;^[167] one is mixed valence V^{III}/V^{IV} while the other contains only V^{IV} .

5.3. Iron Phosphates

In the mineral kingdom, iron phosphates are among the most important materials besides silicates and aluminates. Many phases, with a large number of both open and dense octahedral–tetrahedral frameworks, have been described in the Fe–P–O and the M–Fe–P–O (M = alkaline; alkaline-earth) systems.^[175, 176] The most striking example of an open-framework iron phosphate is provided by the mineral caxogenite,^[177] $[AlFe_{24}(OH)_{12}(PO_4)_{17}(H_2O)_{24}] \cdot 51H_2O$, (Figure 16) which contains cylindrical tunnels occupied by water molecules, with a free diameter of $14.2 \text{ \AA}$. The first synthetic materials, analogues of the minerals hureaulite and alluaudite, were described by Corbin et al. in 1986^[178] and opened the way for synthetic open-framework iron phosphates whose applications in catalysis could be very important. For example, dense

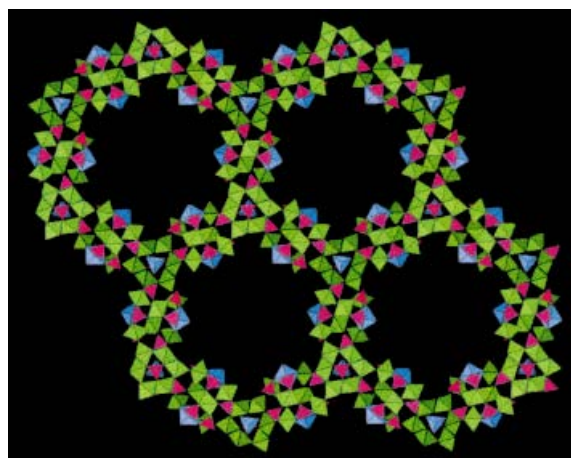


Figure 16. A view of the structure of the mineral caxogenite showing the channels running along the c axis. The relative size of this Figure is 1.5 times smaller than for the remaining Figures. Unfortunately, the framework collapses on dehydration.

iron phosphates are used as selective catalysts during the oxidative dehydrogenation of isobutyric acid into methacrylic acid.

Paradoxically, and at variance with the other families, the first synthetic, open-framework iron phosphates containing organic cations in the pores were not pure oxides, but oxide–fluorides obtained by the use of the fluoride route already described. Indeed, the hypothesis for the formation of the ULM solids proposed by Férey^[73] advanced the possibility of obtaining hitherto unknown iron phosphates with open frameworks. The first of them, ULM-12 or $\text{N}_2\text{C}_6\text{H}_{14}[\text{Fe}_4(\text{PO}_4)_4(\text{H}_2\text{O})_3\text{F}_2]$, was discovered in 1996.^[179] Other oxyfluorinated compounds followed, but the first all-oxide homologues were synthesized in 1997 in the group of Lii in Taiwan.^[180] A complete description of these oxidic phases is given elsewhere^[180] and will not be discussed here. However, we would like to draw attention to the building units that often appear in these phases. Whereas the majority of the units which appear in the ULM series (fluorinated medium) are M_3P_3 hexamers, when fluorine is absent from the synthesis most of them are M_4P_4 octamers. Moreover, these octamers are very close to the D4R cages encountered in cloverite and LTA, with a central oxygen replacing fluorine in the cages. The following section will be devoted to the Fe-ULM series.

From the chemical point of view, all the ULM phases in the system Fe–P–O–F–amine have very slow kinetics of formation, and many intermediate phases appear before those corresponding to thermodynamic equilibrium are formed. As a function of pH, temperature, and concentration, the resulting compounds are either pure Fe^{III} or mixed-valence $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ solids. Among the ten phases already characterized, many are iron analogues of gallium compounds. However, three of them are of particular interest. In ULM-12, which was already introduced above, the three-dimensional structure (Figure 17) arises from the corner sharing of two types of building blocks, one a hexamer with Fe–F–Fe–F–Fe bonds, similar to those encountered in the Ga-ULM series (Section 3.4), and one a dimer corresponding to the monophosphate aqua complex of iron. In the hexamer, two of the three iron ions are octahedrally, including a water molecule in the coordination, while in the dimer, a square-pyramidal coordination of Fe is

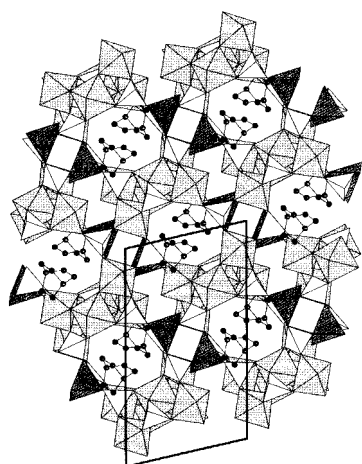


Figure 17. A view of the structure of the fluorinated ferric phosphate, ULM-12, showing the DABCO templates encapsulated in the 8-ring cages.

observed with just one aqua ligand. The corner-sharing assembly of these oligomers defines 8-ring channels in which DABCO ions are housed. The irreversible dehydration of ULM-12 yields ULM-19, whose structure is close to that of ULM-12 and corresponds to the loss of the water molecules that were in the coordination polyhedra. This leads to a drastic change in the nature of the polyhedra since the structure of ULM-19 exhibits one iron octahedron, two trigonal bipyramids and one tetrahedron instead of three octahedra and one square pyramid.

ULM-15 (Figure 18) obtained with 1,3-diaminopropane,^[181] has a singular structure built up from dimers and infinite *trans* chains of Fe^{III} octahedra linked by phosphate groups to form corrugated planes. The three-dimensional character is provided by single tetrahedra which link two consecutive planes, and leads to 16-ring ovoid windows with dimensions of ca. $12 \times 7 \text{ \AA}$.

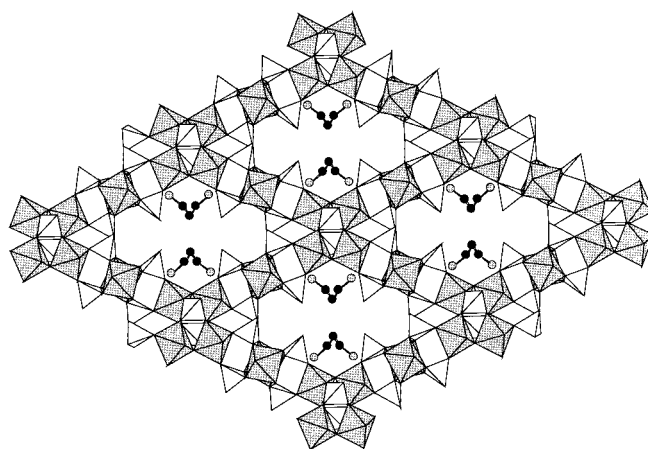


Figure 18. A view of the structure of the fluorinated iron phosphate, ULM-15, templated by ethylenediamine.

The main interest in these ferrofluorophosphates concerns their magnetic properties. Despite the existence of isolated clusters linked by phosphate groups, three-dimensional magnetic ordering takes place in the range 15–40 K, with either antiferro- or ferrimagnetic properties. They open the way to a new class of open-framework solids that combine the well-known sieving properties with magnetic properties; these might be used for magnetic separation if the ordering temperatures reached are sufficiently high.

5.4. Cobalt(II) and Manganese Phosphates

Cobalt(II) has a special place in the open-framework family because it is one of the few transition metal cations that easily exhibits tetrahedral coordination in addition to five- and sixfold coordination. Moreover, magnetic coupling can give rise to interesting magnetic properties, similar to those described above for iron. Finally, it is well known that Co^{2+} doping enhances the catalytic performance of certain zeolites and related compounds. This property has led^[182, 111] to many reports of Co^{2+} -doped aluminophosphates and related compounds. For instance, CoAPO-5 and CoAPO-11 have been used for the autoxidation of cyclohexane^[183] and *p*-cresol.^[184]

Recently, a substantial effort was made to synthesize pure cobalt phosphates with an open framework with either inorganic or organic templates. The first success^[185] concerned the pseudo tetragonal three-dimensional material $\text{CoPO}_4 \cdot 0.5\text{C}_2\text{H}_{10}\text{N}_2$. The framework consists of three systems of channels with 8-ring windows limited by Co and P tetrahedra in strict alternation. The dimensions are $3.9 \times 4.7 \text{ \AA}$, and the compound becomes antiferromagnetic at 2 K. The three-dimensional character exists only with ethylenediamine. As soon as the length of the carbon chain increases (e.g. 1,3-diaminopropane and 1,4-diaminobutane), the solids become two-dimensional^[186] with planes built up from corner-sharing *trans* chains of Co^{2+} tetrahedra linked by phosphate groups.

One of the main contributions to the CoPOs has been made by Stucky's group.^[187] Being aware that the tremendous success with the aluminophosphate system was in part due to the initial recognition of structural analogies between AlPO_4 and SiO_4 , they sought to determine if the same analogies also exist between cobalt phosphates and aluminosilicate minerals. This design approach led them to characterize, with alkali metal ($\text{M} = \text{Na}, \text{K}, \text{Rb}$) and NH_4^+ ions, chiral tetrahedral MCoPO_4 cobalt phosphates. These exhibit either the zeolite Li-ABW structure type^[2] with NH_4^+ and Rb^+ , or a hexagonal structure, intermediate between the ABW and tridymite structures, with Na^+ , K^+ , and NH_4^+ cations. The latter contains 6-ring channels. This paper clearly indicates the difficulty of the corresponding chemistry and underlines the drastic influence of pH and the nature of the solvent on the synthesis of the desired products. Despite the usually antiferromagnetic behavior of these CoPO_4 materials, the sodium compound is ferromagnetic at 2 K.

Manganese phosphates with an open framework are very scarce. The chemistry of new phases in this area is emerging with some recent attempts by Kaucic et al.^[188] and Rziha et al.^[189] In the case of nickel phosphates there is again little to report, though we have recently discovered a large-pore nickel phosphate (VSB-1 (Versailles/Santa Barbara-1)) which has very interesting sorption and magnetic properties.^[190] Further work is clearly merited in these and other systems such as chromium and copper phosphates.

5.5. Zirconium and Titanium Phosphates

With tetravalent cations, synthesis often leads to two-dimensional phosphates, as is clearly shown by the work of Clearfield on the zirconium phosphates.^[191] However, the fluoride route has very recently led to the first zirconium phosphates with three-dimensional open-framework structures.^[192, 193] For example, $[(\text{enH}_2)_{0.5}][\text{Zr}_2(\text{PO}_4)_2(\text{HPO}_4)\text{F}] \cdot \text{H}_2\text{O}$ exhibits 8-ring tunnels formed by strict Zr–P alternation. The Zr octahedra are of two types: ZrO_6 and ZrO_5F , the Zr–F bond being terminal.

The same method, applied to titanium, very recently led^[194] to a mixed-valence fluorinated titanium phosphate with 7-ring channels. In non-fluorinated medium, a new phosphate, ρ -TiP, has been also found,^[195] with three types of tunnels (4-, 6-, 8-rings).

6. Chalcogenides, Halides, and Nitrides

6.1. Sulfides and Selenides

The known classes of open-framework materials are overwhelmingly dominated by oxide or mixed oxide/fluoride matrices. In 1989, however, Bedard and co-workers of UOP^[196] proposed to extend this class of materials to metal sulfide compounds. Metals and semimetals exhibiting tetrahedral coordination in sulfides were considered first in order to imitate the crystal chemistry of the microporous zeolites and aluminophosphates. In the original paper, only germanium(IV) and tin(IV) sulfides were described, but the preparation of antimony(III)^[197] and indium(III)^[198] sulfides was subsequently reported by Parise. A new nomenclature was adopted corresponding to the generic name $\text{R-M'MS-}n$, where R indicates the organic template, M' is a 3d (or 4d) metal, M represents germanium (noted G), tin (Sn), antimony (Sb) or indium (In) and n corresponds to a structural type. These compounds are obtained under hydrothermal conditions in a similar way to zeolites and other derivatives. The reaction is carried out with a mixture of metal sulfide (or metal + sulfur) and an amine or quaternary alkylammonium species which is heated at temperatures from 25 to 180 °C for several days. In some preparations, the organic template is used in the carbonate or hydrosulfide (HS^-) form, rather than the hydroxide; this appears to give rise to a mineralizer effect. By changing the nature of the organic species, new open frameworks have been isolated and different configurations of building units have been observed, depending on the elements (Ge, Sn, Sb, or In).

The reaction of germanium sulfide with organic amines frequently leads to the formation of amine germanium sulfides which contain clusters of $[\text{Ge}_4\text{S}_{10}]^{4-}$ which may be found isolated or in low-dimensional compounds such as DPA-GS-8.^[199] This kind of tetrameric unit is quite common in germanium sulfide chemistry and is related to the structure of adamantane (Figure 19). The four germanium atoms are tetrahedrally coordinated by sulfur atoms and are connected by shared corners. This unit can be viewed as a tetrahedron in which germanium occupies each corner and is reminiscent of the tetrahedral units $[\text{SiO}_4]^{4-}$ observed in silicates. The formation of three-dimensional networks is achieved by the use of a metal that furnishes the connection between the $[\text{Ge}_4\text{S}_{10}]$ adamantane units. The utilization of several metals, including Mn, Fe, Co, Ni, Cu, Zn, and Ga,^[196, 200] has been reported.

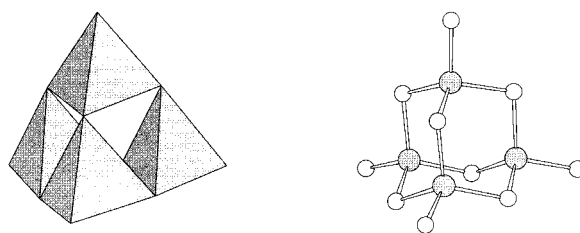


Figure 19. Tetrahedral basic building unit $[\text{Ge}_4\text{S}_{10}]^{4-}$ usually described in the microporous germanium sulfides. Ge: large grey spheres, S: small white spheres.

Yaghi and co-workers^[201] have proposed an alternative route for the synthesis of these sulfides. They were able to obtain crystals from the diffusion of an aqueous solution of the 3d metal into a solution of an amine– $[\text{Ge}_4\text{S}_{10}]$ complex at room temperature. In the case of copper(I), the $[\text{Ge}_4\text{S}_{10}]$ tetrahedral clusters are bridged by the Cu^+ cations which can be in linear twofold coordination ($[\text{CuS}_2]$)^[202] or trigonal planar threefold coordination ($[\text{CuS}_3]$).^[203] An example of metal–metal linking is found in the mixed silver–copper germanium sulfide, $(\text{CH}_3)_4\text{N}[(\text{Ag}_2\text{Cu}_2)\text{Ge}_4\text{S}_{10}]$.^[204] The open framework is built up from the connection of the $[\text{Ge}_4\text{S}_{10}]$ unit by metal–metal bonds of the type $[\text{Ge}(\mu\text{-S})]_2\text{M-M}[\text{Ge}(\mu\text{-S})]_2$ ($\text{M} = \text{Cu}, \text{Ag}$). New topologies have been discovered with very low framework densities. For instance, the structure of the M'GS-2 type is composed of puckered 12-ring channels which contain organic species and has a framework density of $7.27 \text{ T}/1000 \text{ \AA}^3$, which is much less than that encountered in oxide frameworks (e.g. $12.7 \text{ T}/1000 \text{ \AA}^3$ for the FAU type). For some frameworks, the arrangement of the tetrahedral $[\text{Ge}_4\text{S}_{10}]$ units resembles that occurring in the diamond^[201, 202] or blende^[204] types. With manganese, a germanium sulfide^[205] has been obtained with a structure analogous to that of zeolite Li-ABW (Figure 20).

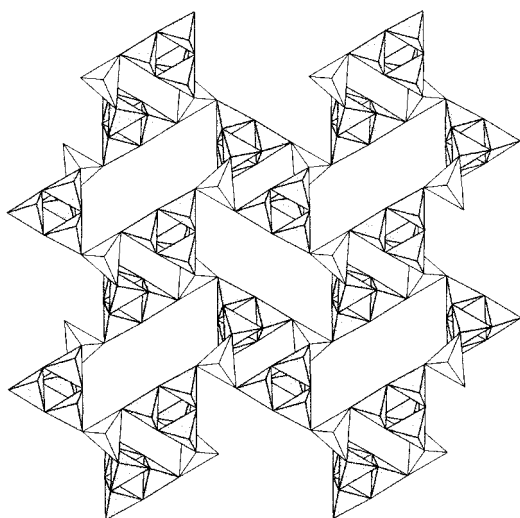


Figure 20. Representation of the open framework of $\text{MnGe}_4\text{S}_{10} \cdot \text{C}_6\text{H}_{14}\text{N}_2 \cdot 3\text{H}_2\text{O}$ analogous to zeolite Li-A(BOW). Manganese polyhedra, $[\text{MnS}_4]$, are indicated by white tetrahedra, germanium polyhedra, $[\text{GeS}_4]$, are indicated by gray tetrahedra. Amines have been omitted for clarity.

Very few compounds with three-dimensional open frameworks have been prepared with tin chalcogenides. The structures of the pure tin sulfides are most often lamellar and several studies have been reported on the structure types R-SnS-1^[196, 206, 207] and R-SnS-3,^[207–209] with $[\text{Sn}_3\text{S}_7]^{2-}$ and $[\text{Sn}_4\text{S}_9]^{2-}$ network compositions, respectively. The R-SnS-1 structure type can also be obtained with selenium instead of sulfur.^[210] The inorganic layers of these compounds are composed of $[\text{Sn}_3\text{S}_4]$ broken-cube building units linked together by double-bridging $\text{Sn}(\mu\text{-S})\text{Sn}$ sulfur bonds (Figure 21). The resulting polyhedral coordination for tin corresponds to trigonal bipyramid SnS_5 instead of the tetrahedral geometry of the germanium compounds. The layer contains

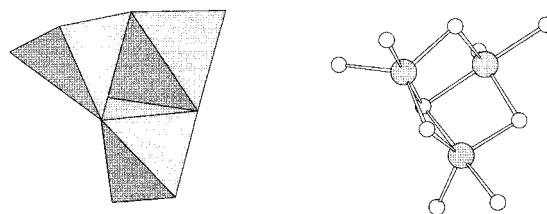


Figure 21. Representation of the broken cube cluster, Sn_3S_4 , for R-SnS-1. Sn: large grey spheres, S: small white spheres.

hexagonal 12-ring apertures for R-SnS-1 (Figure 22) and elliptical 16-ring apertures in R-SnS-3. In the latter compound, the tin atoms are in fourfold (tetrahedral) and fivefold (trigonal bipyramid) coordination, whereas they are in fivefold coordination exclusively in R-SnS-1. Studies have been undertaken concerning the mechanism of the formation of these two phases.^[211] Three types of intermediates have been isolated during the condensation process and it is thought that

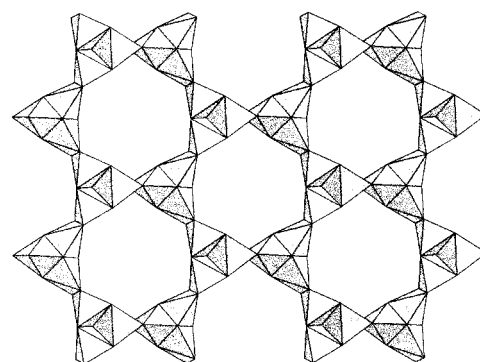


Figure 22. A view of the inorganic layer of R-SnS-1.

the framework may be formed from the dimeric precursor $[\text{Sn}_2\text{S}_6]^{4-}$, which is in solution. Another layered phase of composition $[\text{Sn}_5\text{S}_{12}]^{4-}$ has also been mentioned by Parise.^[212] The situation for tin is different since it is found in both five- and sixfold coordination in a layer that consists of edge-linked tin polyhedra.

In contrast to the tin sulfides, a three-dimensional framework has been found with a tin oxysulfide.^[213] The structure is built up from clusters of composition $[\text{Sn}_{10}\text{S}_{20}\text{O}_4]^{8-}$ connected by sulfur bridges (Figure 23). This unit can be described as a super tetrahedron composed of four $[\text{Sn}_4]$ tetrahedra. Each node of the four tetrahedra is occupied by one tin atom. The tin atoms are coordinated by one oxygen atom and four sulfur

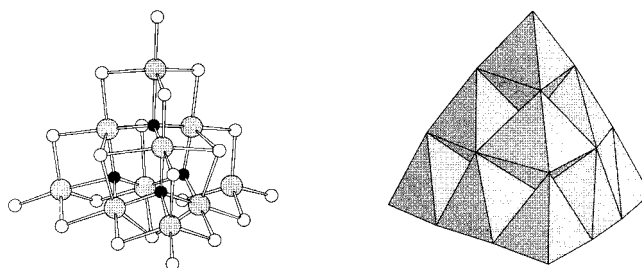


Figure 23. Representation of the tetrahedral building unit $[\text{Sn}_{10}\text{S}_{20}\text{O}_4]$. Sn: large grey spheres, S: small white spheres, O: small black spheres.

atoms to give rise to a distorted trigonal bipyramid. Each oxygen atom is linked to four tin atoms whereas the sulfur atoms connect two or three tin atoms together. The arrangement of the super tetrahedra blocks is related to that of the $[\text{SiO}_4]$ units in the cristobalite-type structure. A lamellar phase built up from similar decameric units was also isolated.^[210]

The structures of the germanium and tin sulfides consist of a few well-defined building units that are for the most part based on tetrahedral geometries, as in the zeolites and many phosphate derivatives. The synthesis of antimony sulfides has yielded completely different geometries, probably due to the influence of the lone pair of electrons of antimony(III). Several different situations are observed. In the phase synthesized with tetramethylammonium, $(\text{Me}_4\text{N})[\text{Sb}_2\text{S}_5]$,^[214] the antimony atom is surrounded by four sulfur atoms with a pseudo-trigonal-bipyramidal configuration; the lone pair forms the fifth vertex and is located in the trigonal plane of this polyhedron. The three-dimensional network is entirely built up from edge-shared bipyramids, ψ - $[\text{SbS}_4]$ (ψ corresponds to a missing ligand as a result of the lone pair of antimony). However, in other compounds,^[215, 216] the coordination of antimony may vary from 3 to 5 and the corresponding polyhedra may be ψ - $[\text{SbS}_3]$ tetrahedra, or ψ_2 - $[\text{SbS}_4]$ and ψ - $[\text{SbS}_5]$ octahedra. In general, these polyhedra share edges and corners to form infinite ribbons, and the interconnection of the ribbons generates open frameworks with different systems of channels in which the organic molecules are located. As observed in the tin phosphates (see Section 5.3), the lone pairs point towards the centers of the channels. Similar structural features have been reported in lamellar antimony sulfides.^[217]

Very recently, one example of an indium sulfide has been described by Parise and co-workers.^[198] The open framework is based on corner-linked supertetrahedral $[\text{In}_{10}\text{S}_{20}]^{10-}$ clusters. The same building-block configuration was obtained with the tin oxysulfide,^[213] but the indium atom is tetrahedrally coordinated by sulfur. The connection of these tetrahedral units is related to two interpenetrating, nonintersecting diamondlike lattices.

Little is known about the properties and potential applications of the open-framework chalcogenides, though Jiang and co-workers^[218] have recently described the adsorption and spectroscopic properties of some of the layered tin sulfides that belong to this family of materials. Furthermore, the very recently discovered indium sulfides, ASU-31 and ASU-32, which are large-pore systems based upon linked supertetrahedra containing 10 $[\text{InS}_4]$ units, exhibit interesting ion-exchange properties.^[219]

6.2. Halides

In 1997, Martin and Greenwood^[220] introduced a new generation of microporous compounds which utilized halides as replacements for the normal oxygen or chalcogenide anions. New materials were formed from metal halides such as zinc dichloride and copper chloride; Zn and Cu are both known to exhibit tetrahedral geometries with chlorine. Three compounds, named CZX-*n*, have been synthesized under

hydrothermal conditions (160 °C) in benzene solution. The framework of CZX-1 is isostructural with the aluminosilicate sodalite (SOD), while CZX-2 and CZX-3 adopt new framework topologies. All three structures are based on ZnCl_4 and CuCl_4 tetrahedra sharing corners, as in the aluminosilicate zeolites, and the organic molecules are trapped in the micropores. One interesting property of these microporous halides is their high capacity to adsorb methanol into the framework. They can adsorb up to three equivalents per framework unit, but the addition of more methanol results in dissolution of the structure and the formation of a colloidal solution.

6.3. Nitrides

The existence of condensed framework structures based upon ceramic nitrides, such as the silicon nitrides of composition Si_3N_4 , led to the idea that the synthesis of open-framework nitrides might also be feasible. The first success in this area was the preparation of the phosphorus nitride, $\text{Zn}_7[\text{P}_{12}\text{N}_{24}]\text{Cl}_2$, by Schnick in 1992.^[221a] This was achieved by means of a high-temperature (700–800 °C) solid-state reaction between ZnCl_2 and HPN_2 , and yielded a small-pore open framework with the sodalite structure. A similar reaction, in which a source of oxygen ($\text{OP}(\text{NH}_2)_3$) was also included in the reaction mixture, has very recently led to the discovery of a phosphorus oxonitride with the same structure.^[221b] The preparation of open-framework silicon nitrides requires more severe conditions, but Schnick successfully achieved this objective in 1997 with the synthesis of the small-pore zeolitic $\text{Ba}_2\text{Nd}_7\text{Si}_{11}\text{N}_{23}$.^[222] In this instance, reaction between the metals and silicon diimide, $\text{Si}(\text{NH})_2$, under a nitrogen atmosphere in an RF furnace operating at temperatures between 900 and 1650 °C, was necessary. By analogy with the progress in other areas, it seems probable that much milder reaction conditions will be necessary if the preparation of large-pore nitrides is to be achieved.

7. Binary Metal Oxides

Whereas the development of crystalline, open frameworks based upon silicates, phosphates, and related materials has progressed at an ever-increasing pace, the synthesis of simple binary oxides with periodic open structures has been less successful to date. An obvious exception to this generalization, however, is the case of MnO_2 , which is known to exhibit small channels up to about 7 Å in diameter in the minerals hollandite, cryptomelane, and todorokite. Synthetic analogues of these minerals have been made^[189, 223] in the presence of metallic cations (M) such as Mn^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} . They are based upon a structural principle in which octahedral $[\text{MnO}_6]$ units share edges and the metallic cations occupy the channels, and correspond to a stoichiometry of $\text{M}_x\text{MnO}_2 \cdot n\text{H}_2\text{O}$ in the as-synthesized form. As a consequence, these are mixed-valence materials with a manganese oxidation state typically in the range 3.5–3.8, and they show a variety of interesting electronic, magnetic, and catalytic

properties.^[224, 225] A small concentration of manganese vacancies is often observed, and a limited amount of manganese substitution is also possible. The water of hydration can be removed at temperatures up to about 500 °C, to yield nanoporous materials that will adsorb small organic molecules such as cyclohexane.

The existence of these stable open frameworks in the specific case of manganese is presumably related to the high ligand stabilization energy associated with the t_{2g}^3 electronic configuration of Mn^{4+} . This should render the materials kinetically stable with respect to their collapse into more condensed phases. It is also, no doubt, the reason why it has been possible to make stable mesoporous phases based upon MnO_2 , and indeed to remove the surfactant templates in order to access their porosity.^[226]

8. Open-Framework Coordination Compounds

In a domain where the challenge is often to increase and modulate the sizes of the pores for selective adsorption and other applications, purely inorganic systems have their limitations owing to the relatively small sizes of the polyhedral centers and their limited means of connection. As an alternative strategy for achieving this end, it is possible again to use organic molecules, but this time in the skeleton rather than within the pores. This has led to a new chemistry that we can consider to be “non templated”, since the holes are not occupied by the usual templates of the zeolite-related chemistry. Some aspects of this area have recently been reviewed.^[227]

Two approaches have been developed since the beginning of the 1990s. The first concerns the modification of previously known porous solids by replacement of the phosphate groups with other chelating agents in the structure, mainly organic phosphonates and carboxylates. Most of these organic linkages are reasonably flexible. This will be discussed in the first section. The second starts from rigid organic moieties, with a preselected shape, which are then connected, either by strong ionocovalent bonds with metallic centers or by appropriate hydrogen bonding.

8.1. Organically Modified Inorganic Open Frameworks

The initial idea in this area was to replace phosphates by phosphonates to produce open frameworks. This strategy was originally used for layered compounds by Alberti^[228] in order to increase the interlayer spacing in such materials. The approach took advantage of monophosphonates, which acted as spacers between the layers, with no possibility of connection between them.

In the context of building open three-dimensional frameworks, it is possible to create connections between layers by the use of diphosphonates or functionalized monophosphonates. This idea, initiated by Johnson and Jacobson,^[229] is currently used by several groups (e.g. Zubietta in USA,^[230] Bujoli^[231] and Férey^[232, 233] in France) and leads to three-dimensional transition metal phosphonates with various top-

ologies,^[234] the two most spectacular examples being $[M(O_3PCH_2NH(C_2H_4)_2NHCH_2PO_3)] \cdot H_2O$ ($M = Mn, Co$) and $[NH_4]_4[(V^{IV}O)_3(O_3PCH_2PO_3)_4(H_2O)_4] \cdot 4H_2O$. The first^[230] is made from tetrameric $[Co_2P_2]$ entities linked by $CH_2NH(C_2H_4)_2NHCH_2$ groups in three directions. The long connections between the tetramers lead to very large, ellipsoidal 44-rings ($4.7 \times 18 \text{ \AA}$) which contain water molecules. The second,^[232] using vanadium, leads to clover-like windows (Figure 24) in which ammonium ions and water molecules lie. Such an approach, successful with the 3d transition metals, is also valuable for lanthanides.^[233] A whole series of lanthanide phosphonates has recently been characterized, thus underlining the generality of the method.

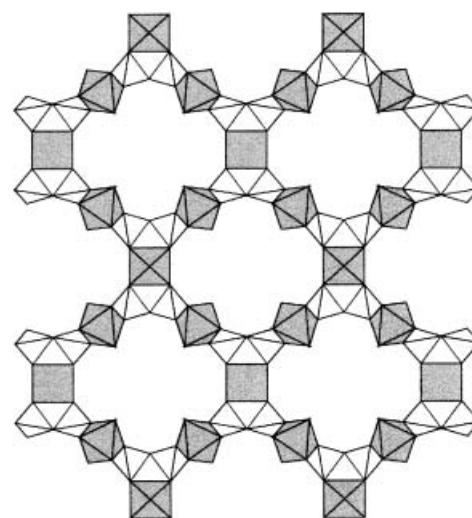


Figure 24. Projection of the structure of $(VO)_2VO(H_2O)_4\{O_3P-CH_2-PO_3\}_4$, MIL-2.

However, the use of diphosphonates turns out not to be essential in order to make an open framework, since a few examples show that this can even be achieved with monophosphonates. Thus, three-dimensional zeolite-like phosphonates have been reported for β -Cu(O_3PCH_3),^[235] $Zn(O_3PC_2H_4NH_2)$,^[236] and β -Al $_2$ (CH_3PO_3) $_3 \cdot H_2O$,^[90] the latter having unidimensional 18-ring channels with a 5.8 Å cross-section (see Section 3.6).

A new variant of this approach, which uses carboxylates instead of phosphonates, has led to new lanthanide(III) glutarates and Co^{II} succinates with open frameworks.^[237] In the first, parallel chains of edge-sharing polyhedra of Ln are connected in the other two directions by glutarate bridges, thus generating voids that can be occupied by water; the water can be removed and readsorbed, reversibly, on heating and cooling.^[237c] In the second, layers of edge-sharing Co^{II} octahedra with 12-ring windows are pillared by succinate chains.

The carboxylate approach has very recently been extended by utilizing benzene-1,3,5-tricarboxylate (TMA) to link dimeric copper units to form a highly porous metal coordination polymer known as HKUST-1.^[238] The framework is stable up to 240 °C and exhibits promising adsorption properties. It is believed that the pores can be chemically functionalized by replacement of the aqua ligands that are attached to

the copper ions. Since the TMA is a fairly rigid organic link, HKUST-1 could also be considered in the context of the following Section 8.2.

The simplest members of the dicarboxylate class of materials are the oxalates, which are also capable of forming open frameworks, both with rare-earth elements^[239] and with tin(II).^[240] The latter example is particularly interesting, since it involved the use of an organic template, guanidinium, for the first time in this area. In another variation on the carboxylate theme, an open-framework Co^{II} system containing a mixed carboxylate–phosphonate ligand has also been reported recently.^[241]

8.2. Open Frameworks with Rigid Organic Links

The development of this area can be traced back to the work of Graverneau, Garnier, and Hardy in Poitiers in the late 1970s, in which zeolitic materials exhibiting ion-exchange properties were made by the linkage of hexacyanoferrates units with (tetrahedrally coordinated) Zn²⁺ cations.^[242] Charge balance is provided by sodium ions. The concept gained fresh impetus in 1994 with the work of Robson^[243] and J. Moore.^[244] In a general way, and even if their approaches were different, their aim was to recreate the topologies of zeolites and related open frameworks in organic and metal–organic solids in order to create large and adjustable cavities. The latter might be used for therapeutic applications, such as the selection, in a single step, of the active form of a drug.

Compared to inorganic open frameworks in which strong semi-ionic bonds govern the structure, this approach has the advantage of harnessing a diversity of bonding types (semi-ionic, covalent, and hydrogen bonding) to modulate the topology. Starting from this idea—the use of pre-selected organic moieties—one can, however, distinguish two main classes of compounds based on the linking modes between them. The linkage can occur either over strong bonds (often M–N bonds) of metallic centers of appropriate coordination, or by weak hydrogen bonds. In both cases, the stability is typically less than that found in most inorganic open frameworks.

Robson^[243] choose as a geometrical/topological model one of a number of simple three-dimensional nets such as diamond, α -Po, and PtS, and then tried to devise ways of chemically linking together the building blocks with a functionality and a stereochemistry appropriate to the chosen parent net. Using this approach, he linked metalloporphyrines like [Cu^{II}(tcp)] or [Cu^{II}(tpp)] by means of Cu^I complexes to generate open frameworks of ca. 24 × 20 Å diameter, the tunnels being occupied by disordered molecules of solvent (tcp = 5,10,15,20-tetrachloro porphinate, tpp = 5,10,15,20-tetraphenyl porphinate). The first success of Lee and Moore^[244] concerned [Ag(TCB)(CF₃SO₃)] (TCB = 1,3,5-tricyanobenzene). TCB has threefold symmetry and its terminal nitrogen atoms serve as ligating groups for the soft Ag^I cation. The combination of TCB and Ag^I triflate leads to a honeycomb lattice in which tricoordinated Ag links three TCB units with dimensions of ca. 10 Å to form cavities, in the centers of which are the triflate anions. The layers are stacked in an ABCABC manner. An extension of the concept with more complicated molecules has been described.^[245]

A similar methodology has been developed simultaneously by Yaghi.^[246] In this instance, he used 4,4'-bipyridine as the organic component, using the two nitrogen atoms of the molecule for ligation. This led to three-dimensional compounds with interpenetrating subnetworks; the cations used were Cu₂Cl₂ dimers, Cu and Ag.^[247] The same principle was applied to Zn associated with SiF₆.^[248] It is noteworthy that the cavities generated in this family of compounds accommodate either solvent molecules or, more often, anions, at variance to the situation in zeolites.

The second approach used hydrogen bonding between organic moieties. The most beautiful example was provided by Wuest et al.^[249] who used a tetrahedral tecton with Si surrounded by four pyridone rings, to produce a framework built up from hydrogen bonding between these tectons. The same principle was applied by Moore^[244] to synthesize an organic solid with wide channels based on hydrogen bonding between macrocycles composed of six phenol groups linked by six acetylenic bonds. Solvent molecules occupy the centers of the macrocycles.

9. Future Developments

Whatever future discoveries may lie ahead, we can look back and see that there was clearly a watershed with the synthesis of open-framework aluminum phosphates by Flanigen and colleagues in 1982.^[23] The impact was not felt immediately, except in the context of AlPO₄s and GaPO₄s, but this discovery gradually led to the realization that the aluminosilicate zeolites might only be the tip of the iceberg in the field of nanoporous crystalline materials. The growing chemical and structural diversity of open-framework materials is amply illustrated by the many examples cited in the preceding sections. In terms of phosphate-based materials, for example, the list is already very impressive, with at least as many as fourteen elements now known to form open-framework structures. This pattern of behavior is underpinned by the strength of the P–O bond, which is broadly comparable with those of Si–O and Al–O, so the relative stabilities within this family of M–P–O materials are probably determined by the M–O bond strengths. As the size and coordination number of M increases, the M–O bond energy decreases, so it is not surprising that the AlPO₄s, especially those that contain tetrahedral Al, show good stability compared with say, GaPO₄s and InPO₄s. However, some interesting materials have yet to be synthesized. For example, Cr^{III}PO₄s would surely show excellent kinetic and thermodynamic stability, given the large ligand field stabilization energy of octahedrally coordinated Cr^{III}, and similar predictions could be made with respect to some of the heavier transition metals, such as Pt^{II} or Rh^{III}. The same argument could be applied to other compounds of these stable transition metal ions, such as their binary oxides, as is already apparent in the case of open frameworks based upon MnO₂ (Section 7).

The recent discovery of new materials based upon transition metal ions inspires us to contemplate the possibility of making open frameworks that exhibit some of the remarkable electronic properties of condensed transition metal com-

pounds. What sort of exciting applications, for example, might be possible with nanoporous crystalline materials that exhibit ferromagnetism, metal-semiconductor transitions, giant magnetoresistance, ferroelectricity, combined ionic/electrical conductivity, or even superconductivity? Some of these developments will surely be seen in the not-too-distant future. Similarly, whilst the overwhelming majority of the known oxide-containing open frameworks are transparent insulators, we are beginning to see narrow band gap materials, and perhaps even metals, in the case of the chalcogenides (Section 6.1). We can also be encouraged by the news that open frameworks containing rare-earth ions are also possible (Section 8.1), and here we could speculate about the possible existence of nanoporous optical and magnetic materials, such as open-framework analogues of the Nd-YAG (yttrium aluminum garnet) lasers and YIG (yttrium iron garnet) permanent magnets. Even the possibility of nanoporous actinide compounds now seems within reach in view of the recent discovery of an open-framework uranium oxyfluoride.^[250]

The scope of this field is not limited by nature itself, since the number of hypothetical, three-dimensional framework topologies is infinite,^[251] but it is limited by the creativity of the synthetic chemist. New preparative strategies continue to appear, such as the use of different solvent systems,^[49, 50] the synthesis of new organic template molecules,^[252] and the construction of open frameworks from molecular building blocks (Section 8). The use of computational methods in the design of organic templates for the synthesis of novel architectures is also of great interest.^[253] And at the opposite end of the spectrum, automated combinatorial methods, which have been successfully applied in other areas,^[254] are now being applied to the synthesis of open frameworks, which would allow as many as 1000 samples to be prepared in a single experiment.^[255]

In conclusion, it is clear that a vast field of new and exciting materials is rapidly emerging from the world of aluminosilicate zeolites. In the industrial environment, the emphasis for the time-being will continue to be on the use of aluminosilicates for ion exchange, separation, and catalysis, but we can look forward to a future in which the materials and their applications will be far more diverse.^[256] Indeed, in dedicating this review to the memory of our friend, Jean Rouxel, it is not unreasonable to expect that the rich tapestry of transition metal chalcogenides that he discovered and elucidated will soon find their parallel in the realm of open-framework materials.

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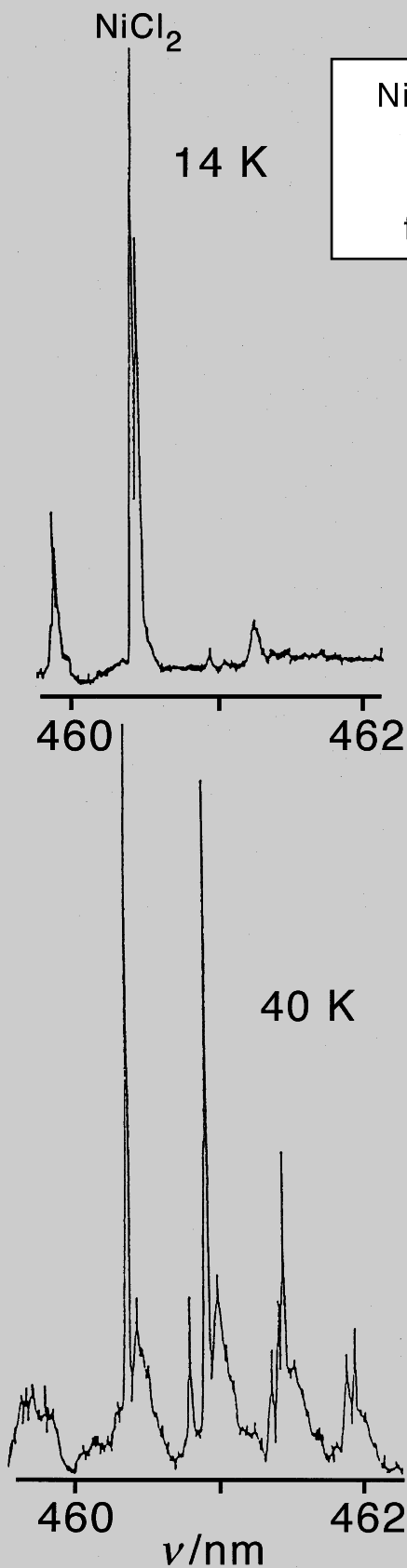
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Structure and Spectra

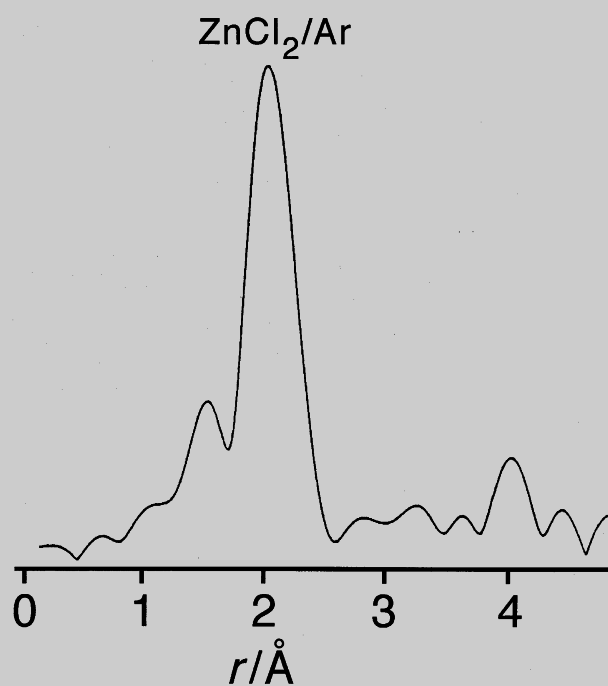
of s-, d-, and f-block halides, oxides, and hydrides.
Presented here are data for two dichlorides.

cold molecular beam
laser-induced fluorescence



Ni-Cl = 2.05607(13) Å
for the ground state
= 2.0958(15) Å
for the excited state

matrix
EXAFS Fourier transform



r = interatomic distance

Zn-Cl = 2.053(2) Å in Ar
= 2.081(2) Å in N₂

A Critical Appraisal of the Experimental Data on the Molecular Structure and Spectra of Halides, Oxides, and Hydrides of the s-, d-, and f-Block Elements

Ian R. Beattie*

An understanding of the electronic structure of small molecules is of importance in many areas of chemistry. It enables theoreticians to improve methods and databases, and experimentalists to interpret more complex systems. Many simple compounds of the s-, d- and f-block elements are rather involatile solids or unstable under normal conditions. Hence, gas-phase data are difficult to obtain. Electron diffraction at high temperatures has been used extensively on the more stable compounds, notably the halides. However, for reasons outlined below this technique is sometimes open to criticism. High-resolution

spectroscopy can be applied at temperatures up to about 700 °C for molecules with larger rotational constants. Alternatively, electronic spectra can be recorded at very high resolution by using "cold" molecular beams, but interpretation of the data is by no means simple. Microwave spectroscopy requires the presence of a permanent electric dipole, and many of the molecules of interest are not thought to be polar. For these reasons, many studies use matrix-isolation techniques. Of these, matrix-isolation IR spectroscopy with partial isotopic substitution has been the most widely used (and is perhaps the easiest from an

experimental point of view). However, energy levels are affected by the surrounding matrix, and even the noble gases can cause changes in molecular geometry. This review attempts to put conflicting strands of evidence in context and suggests new experiments for determining the electronic structure and detailed molecular geometry of key molecules.

Keywords: electronic structure • gas-phase chemistry • laser spectroscopy • matrix isolation • structure elucidation

1. Introduction

A knowledge of the geometry and electronic spectra of small molecules of the s-, d-, and f-block elements is an essential prerequisite to understanding their chemistry. There are many experimental and theoretical papers on this topic. This review attempts to select experimental studies that enable clear-cut conclusions to be drawn. It is biased towards compounds that are not easily studied in the gas phase and those whose structures can be regarded as anomalous (that is, other than linear, trigonal-planar, or tetrahedral for MX_2 , MX_3 , and MX_4 , respectively).

1.1. Matrix Isolation

The isolation of reactive molecules in an inert matrix at cryogenic temperatures allows their study by a variety of

physical techniques. The resulting spectra are greatly simplified compared with gas-phase data because all the molecules are in their ground vibrational and electronic states and rotational motion is effectively quenched. An important source of reference for such experiments up to 1985 is a bibliography by Ball et al.,^[1] which is currently being updated. Almond and Downs^[2] give a detailed tabulation covering mainly 1977–1986 and include a survey of the techniques that can be applied to species isolated in cryogenic matrices. Similar information is given in a review by Perutz,^[3] who commented that "one of the key deficiencies...is the lack of bond length information". Since then (1985) it has been shown that for the dichlorides of Cr, Fe, Ni, and Zn, extended X-ray absorption fine structure (EXAFS) analysis can determine bond lengths in dilute matrices to an accuracy of about one-tenth that obtained in routine single-crystal X-ray studies.^[4]

Infrared spectra of matrix-isolated molecules enable the identification of individual isotopomers, and this leads to information on bond angles and molecular symmetry. Optical spectroscopy has been less extensively used. A study^[5] on CuCl_2 isolated in neon elegantly demonstrates the presence of three distinct matrix sites and illustrates the strengths and weaknesses of this approach. The ESR spectra of matrix-

[*] Prof. I. R. Beattie
The Physical and Theoretical Chemistry Laboratory
South Parks Road
Oxford OX1 3QZ (UK)
Fax: (+44) 1865-275410
E-mail: beattie@physchem.ox.ac.uk

isolated species might be expected to reveal the ground-state electronic configuration of molecules with one or more unpaired electrons, provided the transitions occur within the range of the spectrometer. However, for linear molecules only Σ states are observed in matrices; Weltner and co-workers have summarized much of the available data.^[6]

1.2. Matrix Effects

In matrix-isolation spectroscopy the effects of the medium can be appreciable, and electronic states are usually affected more than vibrational states. Jacox^[7] has tabulated the ground-state vibrational fundamentals of many diatomic molecules in the gas phase and in solid matrices. As examples, the alkali metal halides in argon matrices show red shifts of 6.3–11.2% relative to their gas-phase values. In a nitrogen matrix the shift for LiBr is 24.5%, which in many systems would be taken as evidence of complex formation.

In 1985 Perutz^[3] pointed out that there was only one claim^[8] for a violation of the principle that molecular symmetry should not be altered by changing the matrix: “CsUF₆ which appears to have Cs⁺ bound to one face of the UF₆[−] octahedron in argon, but to an edge in nitrogen matrices”. This work was extended^[9] to CsNbF₆, whereby the strength of the matrix interaction was “calibrated” by observing the splitting of the antisymmetric stretching band of ClO₄[−] in molecular KClO₄ isolated in each of the matrix gases under study. It was proposed for CsNbF₆ that edge binding occurs in nitrogen and carbon monoxide, but facial binding in neon, argon, and oxygen (Figures 1 and 2). Both forms occur in xenon. As the molecules concerned are fluoro derivatives of heavy elements, no data on isotopomers are available. There are many other papers in which site effects, molecular orientation, and dependence of shape on the matrix gas are discussed. Examples include LaF₃,^[10] WO₂,^[11] ScF₂,^[12] BaCl₂,^[13] NbX₅ and TaX₅ (X = Cl, Br),^[14a] NiCl₂,^[15] and NiBr₂.^[16] In 1984 Arthers and Beattie^[17] showed that the IR spectrum of thorium tetrachloride in a neon matrix could be interpreted on the basis of the expected *T_d* molecular symmetry, while the spectrum in krypton indicated a substantial distortion.

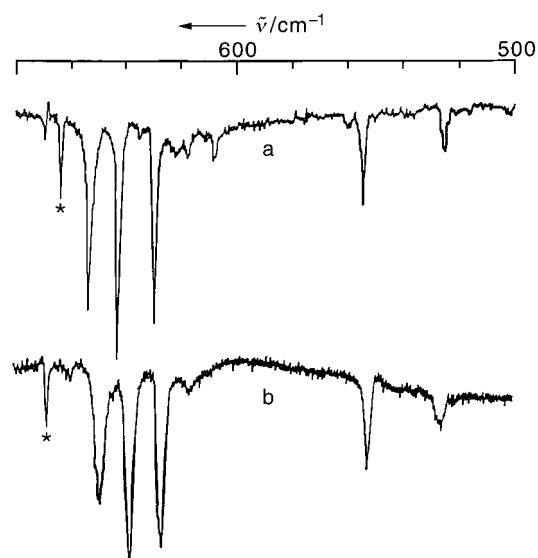


Figure 1. The IR spectrum (500–680 cm^{−1}) of CsNbF₆ isolated in nitrogen a) and carbon monoxide b).^[9] * = matrix isolated CO₂. Reproduced with the permission of The Royal Society of Chemistry.

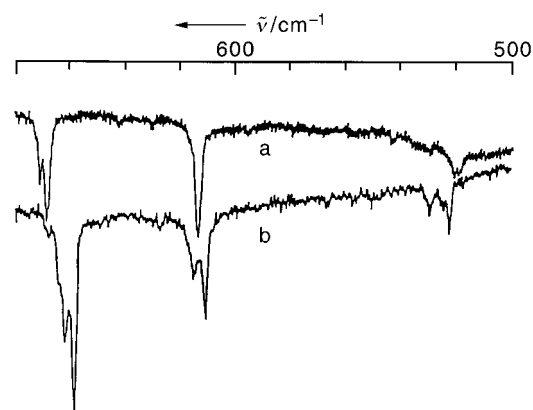
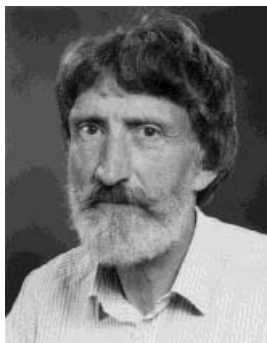


Figure 2. The IR spectrum (500–680 cm^{−1}) of CsNbF₆ isolated in neon a) and argon b).^[9] The apparent splitting of the highest frequency band in (a) arises from an inverse CO₂ band. Reproduced with the permission of The Royal Society of Chemistry.

1.3. Gas-Phase Studies

Electron diffraction can give A–B interatomic distances for AB_{*n*} species, but at higher temperatures the B–B



Until recently Ian Beattie was a Professor at Southampton University. Prior to this he was at the Inorganic Chemistry Laboratory and Oriel College in Oxford. He has now returned to Oxford, but this time to the Physical and Theoretical Chemistry Laboratory. His research has mainly been concerned with molecular species derived from compounds that are solids or are polymeric under ambient conditions (examples include CsClO₃, NiCl₂, WOF₄). This has necessitated the use of many spectroscopic techniques together with the development of a vibrational analysis programme (SOTONVIB) applicable to crystals and molecules. There was still time to look for interesting species such as XeI⁺ (in 1957) and most recently mercury in an oxidation state higher than +2—both unsuccessful! Currently he is working with Professor J. M. Brown on high-resolution spectroscopy of small inorganic molecules in molecular beams.

distances are less reliable as the raw data is averaged over all thermal vibrations. Essentially, angles are more easily deformed than chemical bonds. A review by Hargittai^[18] on the molecular geometry of gas-phase metal halides covers electron diffraction up to 1988 and includes spectroscopic data in the gas phase and in matrices.

Similarly, absorption or emission spectra of the vapors above heated solids are complicated by the occupation of many rotational, vibrational, and even electronic energy levels, and the bands tend to be broad complexes made up of a forest of individual lines. Problems occur for isothermal cells with containment, window materials, and gaskets. In the case of Raman spectroscopy, which can be carried out routinely in fused silica ampoules up to about 1000 °C, the strong Q branches can lead to narrower bands than those in the corresponding IR spectra.^[19] However silica (like many materials) is relatively reactive at high temperatures,^[20] and species such as ThCl_4 can lead to the generation of SiCl_4 as a substantial impurity.

Nevertheless, rotationally resolved spectra can be obtained from hot gases. Limiting features include background luminescence, the rotational constant of the molecule under study, and Doppler and pressure broadening. In 1991 Frum et al.^[21] reported "...the first complete rotational analysis of a dihalide molecule" by the use of IR emission spectroscopy. The molecule was BeF_2 and the temperature about 700 °C. Under assumption of a linear molecule, the Be–F bond length (r_e) was 1.37297(9) Å. Only one rotational constant is available as both Be and F are monoisotopic.

Electronic absorption spectra can usually be obtained at appreciably lower pressures than those needed to obtain IR spectra. However, by far the most sensitive technique at these shorter wavelengths is fluorescence spectroscopy, which is dependent on the quantum yield and the fourth power of the wavelength. By using tunable narrow-linewidth laser excitation and high-resolution spectrometers to disperse the resultant fluorescence it is possible to obtain rotationally resolved spectra from species such as CuCl_2 even at temperatures as high as 750 °C.^[22] In essence, one rovibronic transition is excited in these experiments.

Microwave spectroscopy has not been extensively used owing to the need for a permanent molecular electric dipole. However, there is some elegant work by Törring et al. on the molecules KCN (T-shaped)^[23] and LiNaF_2 (cyclic)^[24] at high temperature. These techniques give at most three rotational constants. Any further information on geometry can only be obtained by isotopic substitution of an effective atom in the molecule.

An elegant way of examining high-temperature molecules at cryogenic temperatures in the gas phase is to make use of "cold" molecular beams.^[25] In our experiments a pressure of about 2 atm of an inert gas (normally argon) is maintained in contact with the sample in an alumina tube. The argon, seeded with the molecule under

examination, is allowed to expand through an orifice (ca. 250 μm in diameter) into a rapidly pumped chamber at a residual pressure of about 0.2 Torr.^[26] In this way rotational temperatures on the order of 10 K can be obtained for molecules vaporized at about 1000 °C. After leaving the nozzle, the molecules rapidly enter a collision-free zone, so that their trajectories are essentially linear, with velocities in the region of 500 m s^{-1} , and are translationally cooled to about 1 K. This can lead to the virtual elimination of Doppler broadening. Since vibrations are more difficult to freeze the vibrational temperatures are usually on the order of 100–200 K. Fluorescence is usually the chosen technique for detection because of the low number density in the beam. By crossing the molecular beam with a tunable narrow-band laser and monitoring the total fluorescence as a function of excitation frequency it is possible to obtain rotationally resolved laser-induced fluorescence (LIF) or excitation spectra (similar to absorption spectra). The main disadvantage of the technique, when only the total fluorescence is measured, is that it gives information on the excited state rather than the ground state. If the fluorescence is dispersed, again at rotational resolution, ground-state data can be obtained. However, the fluorescence is frequently weak, and the signal to noise ratio may not be high enough to give the required resolution.

FeCl_2 ,^[27] CoCl_2 ,^[27] NiCl_2 ,^[26, 28] and CuCl_2 ^[29] were studied in molecular beams by LIF. Figure 3 shows the R branches and part of the P branches of $^{58}\text{NiCl}_2$ and $^{60}\text{NiCl}_2$ in the LIF spectrum of natural-abundance NiCl_2 . This is thought to be a $^3\Sigma \rightarrow ^3\Sigma$ transition of the linear molecule involving one quantum of the symmetric stretch and three quanta of the bend. There is no Q branch because there is no change in angular momentum. Earlier information obtained from matrix isolation^[30] or gas-phase^[31] electronic (including fluorescence) spectra can be of value in interpreting high-resolution electronic spectra and in selecting appropriate molecules for study.

Cavity ringdown spectroscopy^[32] allows absorption experiments to be performed on molecular beams and enables the study of energy levels that are not observed by fluorescence

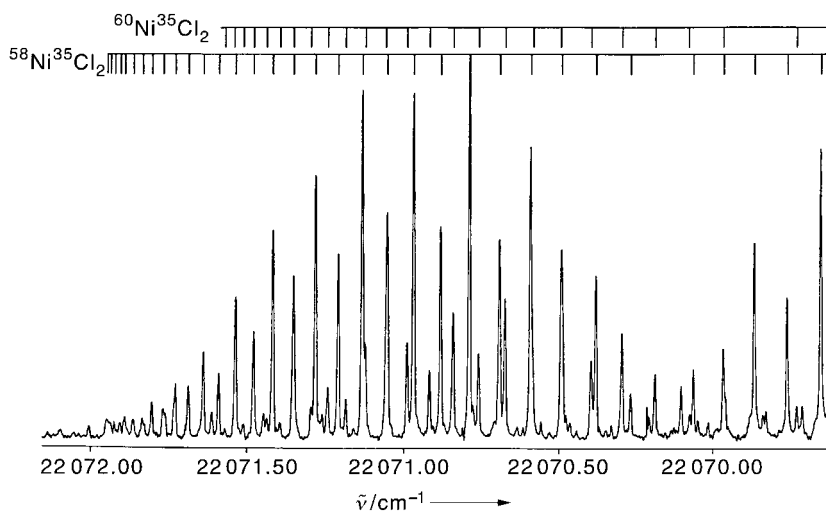


Figure 3. Part of the electronic (LIF) spectrum of jet-cooled NiCl_2 at rotational resolution.^[28b]

spectroscopy. In principle, it yields ground-state constants directly. A recent paper^[33] reports the use of this technique in the infrared at a number density of only about 10^{12} cm^{-3} . Finally, the development of very sensitive electron diffraction techniques may allow the molecules of interest here to be studied in cold molecular beams.^[34]

2. Halides

Halides occupy a major portion of this review because in many cases their vaporization occurs at a relatively low temperature to give mainly monomers. In the first-row transition series pressures of about 1 Torr can be obtained for CrCl_2 at around 850°C and as low as 700°C for NiCl_2 . With Ti and V disproportionation is a serious problem, and CuCl_2 readily loses chlorine.

2.1. Dihalides

2.1.1. Determination of Bond Angles

Since ^{19}F and ^{127}I are the only naturally occurring isotopes of fluorine and iodine and the shift from ^{79}Br to ^{81}Br is only two mass units in eighty this discussion concentrates on the chlorides. Note that ^{45}Sc , ^{55}Mn , and ^{59}Co are monoisotopic, while ^{51}V is 99.75% abundant. For a matrix-isolation experiment the presence of ^{35}Cl and ^{37}Cl enables the number of chlorine ligands to be established; a characteristic 9:6:1 triplet demonstrates the presence of two equivalent chlorine atoms if natural-abundance chlorine is present.

The bond angle 2θ in XY_2 can be calculated from Equation (1)^[35]

$$\left(\frac{\tilde{\nu}_3}{\tilde{\nu}_{3i}}\right)^2 = \left(\frac{1}{M_y} + \frac{2}{M_x} \sin^2\theta\right) / \left(\frac{1}{M_{yi}} + \frac{2}{M_{xi}} \sin^2\theta\right) \quad (1)$$

where i refers to an isotopomer and $\tilde{\nu}_3$ is the antisymmetric stretching frequency. Using the observed frequencies rather than the harmonic frequencies of the isotopomers inevitably leads to errors, but by making reasonable assumptions^[36] it can be shown that substitution at X in XY_2 leads to a lower limit for the bond angle, while substitution at Y leads to an upper limit. The effects of anharmonicity can be appreciable, as is demonstrated for the diatomic molecule NiO isolated in argon matrices.^[37] Four isotopomers were examined, and the following differences between calculated (without corrections for anharmonicity) and observed isotope shifts determined (the second figure in each case is the total shift): 0.12, 2.86 ($^{58/60}\text{Ni}^{16}\text{O}$); 0.06, 3.06 ($^{58/60}\text{Ni}^{18}\text{O}$); 0.45, 36.32 ($^{58}\text{Ni}^{16/18}\text{O}$); 0.40, 36.52 cm^{-1} ($^{60}\text{Ni}^{16/18}\text{O}$). For a polyatomic molecule such differences could lead to large errors in the bond angle calculated with Equation (1).

For an XY_2 molecule, the $\sin\theta$ function becomes less sensitive to changes in θ as the bond angle nears 180° , and this makes the assignment of linearity or nonlinearity increasingly difficult. This is illustrated in Figure 4 on the basis of calculations with Equation (1). The effect of increasing the mass of the central atom X is also clear. With bands of the

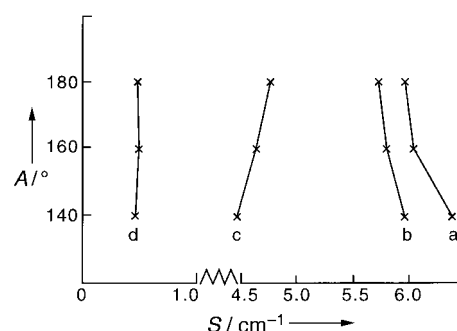


Figure 4. Calculated shifts S of ν_3 for an XY_2 molecule with an isotopic mass change of two units as a function of bond angle A . a) $^{56}\text{Fe}^{35/37}\text{Cl}_2$; b) $\text{Yb}^{35/37}\text{Cl}_2$; c) $^{56/58}\text{Fe}^{35}\text{Cl}_2$; d) $^{172/174}\text{Yb}^{35}\text{Cl}_2$. (ν_3 for $^{56}\text{Fe}^{35}\text{Cl}_2$ taken^[40] as 493 cm^{-1} ; ν_3 for $\text{Yb}^{35}\text{Cl}_2$ taken^[39] as 296 cm^{-1} ; arbitrary mass change for Yb from 172 to 174).

order of 1 cm^{-1} full width at half-height, which frequently may not be fully resolved, attainment of the required accuracy is by no means easy.

If the symmetry of MCl_2 in the all- ^{35}Cl or all- ^{37}Cl form is $D_{\infty h}$ or C_{2v} , ν_3 and ν_1 (the symmetric stretch) have different symmetries and do not interact. However, for the $^{35}\text{Cl}^{37}\text{Cl}$ isotopomer the symmetry is lowered to $C_{\infty v}$ or C_s . This means that the ν_3 and ν_1 modes of $\text{M}^{35}\text{Cl}^{37}\text{Cl}$ can interact. As the mass of the central atom increases, the difference between ν_3 and ν_1 becomes smaller, and the vibrational coupling becomes stronger. As $\tilde{\nu}_3$ is generally higher than $\tilde{\nu}_1$, the central component ($\text{M}^{35}\text{Cl}^{37}\text{Cl}$) of the ν_3 triplet is shifted to a higher frequency, while the central component of the ν_1 triplet is shifted to lower frequency. This behavior can be used to determine whether the observation of two stretching frequencies is due to two matrix sites or the presence of bands for both ν_1 and ν_3 in the IR spectrum. If ν_1 and ν_3 can both be unambiguously identified, the relative intensities of their bands can also be used to obtain information on bond angles^[38] [Eq. (2)], provided no interaction occurs with the bending mode and the change in dipole moment is along the bond axis.

$$\frac{I_{\nu_3}}{I_{\nu_1}} = \tan^2\theta (M_X + 2M_Y \sin^2\theta) / (M_X + 2M_Y \cos^2\theta) \quad (2)$$

A combination of isotope shifts and the ratio of the intensities of the ν_1 and ν_3 bands was used to show that YbCl_2 is nonlinear,^[39] with an estimated bond angle of $126 \pm 5^\circ$. The authors commented (1983) that "...as far as we are aware this is the first unambiguous result showing nonlinearity for a transition element dichloride molecule". We might add "in an argon matrix".

On the subject of linearity of dichlorides the behavior of NiCl_2 , which is almost certainly linear in the gas phase, will be considered. In very careful experiments in argon matrices, Green et al.^[40] determined a bond angle of 161° , although the observed shifts in $\tilde{\nu}_3$ for isotopic substitution of chlorine, which give an upper limit for the angle, were only 0.04 ($^{58}\text{Ni}^{35/37}\text{Cl}_2$) and 0.03 cm^{-1} ($^{60}\text{Ni}^{35/37}\text{Cl}_2$) relative to those calculated for a linear molecule. A later paper^[15] reported similar results in argon, but in nitrogen a major shift of over 90 cm^{-1} occurred in the position of ν_3 , and a bond angle of

130° was reported. In this work separate samples of Ni³⁵Cl₂ and Ni³⁷Cl₂ were simultaneously vaporized to obtain the frequencies of these components without the added complication of an intense Ni³⁵Cl³⁷Cl peak. Similar results were obtained for NiBr₂ in nitrogen by Young,^[16] who used both EXAFS (145°) and isotope shift (125°) to obtain the bond angle. Again the difference between $\bar{\nu}_3$ in argon and $\bar{\nu}_3$ in nitrogen was large.

2.1.2. The Elements Calcium to Zinc

In 1979 Drake and Rosenblatt^[41] wrote a comprehensive review entitled “Trends in Structures and Vibrational Frequencies of MX₂ and MX₃ High Temperature Halide Vapors”. At that time TiF₂ was a key molecule as it was thought to be strongly nonlinear,^[42] with a bond angle of about 120°. However, as deduced by Beattie et al.,^[43] the bands in the IR spectrum of TiF₄ were incorrectly^[42] attributed to TiF₃, and bands due to TiF₃ were assigned to TiF₂. Thus the derived bond angle of about 120° referred to TiF₃, not TiF₂. The error resulted from the ready disproportionation of TiF₃, which leads to the quite volatile TiF₄ and an involatile solid, together with the lack of data for fluorine isotopes, which meant that the number of ligands could not be determined from isotopomer distribution patterns. The remaining evidence for nonlinearity in TiF₂ arises from the ESR spectrum in a matrix, which shows that the molecule is not rigorously cylindrical.^[44] It appears that a similar error arose in the VF₃/VF₂ system, for which data on isotopes are unavailable for both metal and ligand.^[45]

These results emphasize the care that is necessary in interpreting data on fluorides when more than one oxidation state of the metal may be involved. Even when relevant mass spectrometric data are available, the differences between the pressures used in mass spectrometers (<10⁻⁷ Torr), matrix-isolation IR spectroscopy (ca. 10⁻³ Torr), and conventional electron diffraction (ca. 1 Torr) make comparisons difficult. Changes in vaporization conditions can lead to alterations in the composition of the gas phase, as can expansion through an orifice from a higher pressure to a lower pressure. An additional problem, notably with fluorides, is the frequent loss of one (or more) ligands during ionization, so that the parent ion may not be observed in the mass spectrum.

Two other cases of apparent nonlinearity arose from electron diffraction studies^[46] on VCl₂ and CrCl₂, which gave bond angles in the region of 110°. However, the results are in doubt because of the possibility of disproportionation and/or oligomers in the gas phase, as shown by subsequent matrix-isolation experiments.^[47, 48] From a review on the molecular geometry of gas-phase metal halides^[18] it appears that renewed analysis of the electron diffraction data does not give clear evidence for the nonlinearity of these two dichlorides.

Inspection of Figure 4 shows that the bond angles of 161°, 157°, and 161° reported^[40] for FeCl₂, CoCl₂, and NiCl₂, respectively, cannot be reliably differentiated from linearity. We are then left with very little evidence of nonlinearity in the first-row transition element dihalides. The bond angle of 152° found for NiF₂^[49] in an argon matrix represents a lower limit.

In 1988 Bukhmarina et al.^[50] assigned this molecule a linear *D*_{∞h} geometry on the basis of a combination of IR and Raman spectroscopy in neon and argon matrices. This leaves a) the ESR spectrum of TiF₂ in neon, which shows that the molecule does not have cylindrical symmetry^[44] and b) a suggestion, based on the third law entropy, that CrCl₂ is nonlinear.^[51] However this is at best an indirect method,^[52, 53] and the linearity found in matrix studies appears to be more reliable.^[48]

Even with gas-phase rotational data the proof of exact linearity for an XY₂ molecule is by no means easy, as may be seen from a recent paper on CuCl₂,^[29] in which the bond angle determined from extensive experiments is 173°. Under the assumption of linearity, the bond length (*r*_e) in the ²π_{g(3/2)} ground state was 2.0353 Å, and values of 371.693(2) and 525.897(4) cm⁻¹ were obtained for ω₁ and ω₃ of the ⁶³Cu³⁵Cl₂ isotopomer.

With regard to the calcium halides, there seems to be no doubt that CaF₂ is nonlinear in a neon matrix^[54] (and several other matrices), although the angle of 140° represents a lower limit as the isotopic substitution was at calcium. At the other end of the transition series, there is little evidence for nonlinearity of the zinc dihalides.^[55] Finally, anyone who wishes to appreciate the problems of matrix-isolation vibrational spectroscopy on compounds of this type is referred to an excellent paper by Lesiecki and Nibler on MgF₂.^[56]

2.1.3. Heavier Elements

SrF₂, like CaF₂, was reported to be strongly bent, with a bond angle of 108° in krypton,^[57] although the isotope data were taken from two different spectra because of band overlap. In the case of SrCl₂ the bond angle is slightly greater (120°), again in a krypton matrix.^[58] A report^[59] on the surprising stability of YF₂ showed that earlier matrix studies incorrectly identified this molecule as YF₃, which was reduced by the tantalum cell.

There is much less work on the second- and third-row transition series, mainly because of the lack of simple dihalides. The lanthanides Sm, Eu, and Yb form rather stable species in the +2 oxidation state, and there is evidence that the dichlorides are strongly bent.^[13, 39, 60] However in only one case^[39] was the identification of ν₁ confirmed by isotopic shift data for both ν₁ and ν₃, while for Sm^[60] and Eu^[13] isotope data could only be obtained in nitrogen, which is known to cause bending in NiCl₂^[15] and NiBr₂^[16].

2.2. Trihalides

For the trihalides of the lighter transition elements there is little evidence of structures other than *D*_{3h}, except for one very recent paper^[61] entitled “The Structure of the Free MnF₃ Molecule—A Beautiful Example of the Jahn–Teller Effect”, in which a C_{2v} structure was proposed on the basis of the electron diffraction data of the gas. Although this work and the related^[62] matrix-isolation IR and Raman studies appear to have been carried out with great care, many of the problems discussed above also apply to these experiments.

In the case of the lanthanide trihalides, the situation is extremely confusing, as is shown by a collection of literature data by Molnár and Hargettai.^[63] In particular, work by Hastie, Hauge, and Margrave^[10, 64] appears in a number of instances to be in direct conflict with that by De Kock et al.^[65, 66] An added complication in these studies is the orientation of the molecule in the matrix.^[10, 67]

2.3. Tetrahalides

The tetrahalides are a particularly interesting group as any distortion from T_d symmetry results in at least a partial lifting of the triple degeneracy of ν_3 and ν_4 , the antisymmetric stretching and bending vibrations, respectively. As the bands in matrix spectra are usually quite narrow, this is a sensitive way of studying distortions. A detailed study of thorium tetrachloride with a variety of $^{35}\text{Cl}/^{37}\text{Cl}$ isotopomer distributions demonstrated that even the inert gas krypton could have major effects on the vibrational spectrum.^[17, 68] In krypton matrices excellent agreement between calculated and observed spectra was found for a C_{2v} model with bond angles of 110° and 160° (Figure 5). However, in a neon matrix the data could be interpreted in terms of the expected T_d model, with ν_1 and ν_3 effectively coincident, and partial occupation of a second type of site. There is thus unambiguous evidence for a change of symmetry between two noble gas matrices.

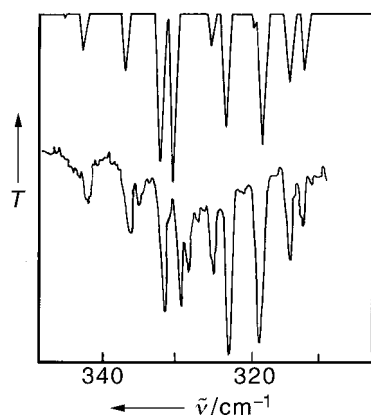


Figure 5. Calculated (upper trace) and observed (lower trace) IR spectra of ThCl_4 ($^{35}\text{Cl}/^{37}\text{Cl}$ ratio 1:2) in a krypton matrix.^[68] T = transmission.

The presence of more than one type of site is a major problem in matrix-isolation spectroscopy, notably when a decision on stereochemistry relies on the observation of a totally symmetric mode in the IR spectrum. Although the tetrahalides often give IR bands that apparently show at least partial resolution of a degeneracy,^[69] there do not appear to be any cases where this cannot be explained by “matrix effects”. A possible exception is UF_4 , which has been carefully examined^[70] in terms of a Jahn–Teller distortion. The situation is again somewhat complicated by the orientation of the molecule within the matrix.^[71]

2.4. Pentahalides

The greater volatility of the pentahalides means that conventional gas-phase techniques can be applied to many of these molecules, and they are therefore of less interest in this review. However, for the pentafluorides very strong association can occur through fluorine bridges to give oligomers which are not easily broken down to the monomers even in the gas phase.^[72] Recently it was shown that NbCl_5 , NbBr_5 , TaCl_5 , and TaBr_5 adopt a square-pyramidal geometry in nitrogen matrices, while a variety of conformers are found in argon matrices.^[14a] Species such as UF_5 and MoF_5 apparently adopt a square-pyramidal geometry in these matrices.^[73, 74]

3. Oxides

Vaporization of metal oxides frequently requires high temperatures and in many cases results in the loss of oxygen and the formation of metal atoms and/or diatomic MO as the gaseous species. The precise behavior is critically dependent on the oxygen partial pressure. In certain cases the desired gaseous oxide may be obtained by passing oxygen over the metal or a lower oxide. Examples include Ag_2O ,^[75] PtO_2 ,^[76] CrO_3 ,^[77] and OsO_3 .^[78] Easily vaporized oxides often give polymeric vapors, and examples that demonstrate the tendency towards tetrahedral coordination include V_4O_{10} ^[79] and $(\text{MO}_3)_n$ ($\text{M} = \text{Cr},^{[77]} \text{Mo}, \text{W}$).^[80] Although matrix-isolation IR spectroscopy is particularly attractive for oxides because of the large relative mass change from ^{16}O to ^{18}O and the high frequency of most metal oxygen vibrations, generating gaseous oxides in a systematic fashion analogous to the work on the halides is difficult. Also, there are fewer ligands in oxides than in halides for a given formal charge of the metal atom, so that matrix interactions may be more important.

The rate of reaction of gaseous metal atoms of the first-row transition series with (di)oxygen has been studied^[81] and correlated with the presence of a $d^n s^1$ configuration. For Sc, Ti, and V, transfer of oxygen atoms occurs, while for Cr ($d^5 s^1$) the reaction shown in Equation (3) is observed.



It is not clear whether OCrO is formed, and no LIF data could be obtained. Cobalt, which has a low-lying s^1 ($3d^8 4s, ^4F$) state, reacts slowly, while Ni has some 22 % population of an s^1 ($3d^9 4s, ^3D$) state at room temperature. An alternative approach to obtain information on the energy levels of the neutral molecule^[82, 83] is to use negative ion photoelectron spectroscopy (NIPES). The resolution is not high, so no information on bond angles is available (for example, for CrO_2 $\bar{\nu}_1 = 895 \pm 20$, $\bar{\nu}_2 = 220 \pm 20 \text{ cm}^{-1}$). There are few papers dealing with electronic spectra of oxides in matrices, and even less information is available for the gas phase.^[84]

3.1. Dioxides

Recent work, notably by Andrews et al., has dramatically altered our knowledge of dioxides. For example, reliable high-

quality IR spectroscopic data are now available for all the dioxides from calcium through to zinc. The results were obtained by reaction of laser-ablated metal atoms with oxygen followed by cocondensation with argon to give a matrix that could be studied by spectroscopy. The resulting bond angles (given here without error ranges) show an interesting dependence on the central element: Ca^[85] 140°, Sc^[86] 128°, Ti^[87] 113°, V^[88] 118°, Cr^[89] 128°, Mn^[90] 135°, Fe^[91] 158°, the rest (Co^[92], Ni^[93], Cu^[94], Zn^[95]) linear. There is, not unexpectedly, a dramatic change in the simple valence force field (SVFF) stretching force constant derived from $\tilde{\nu}_3$ for CaO₂ through ScO₂ to TiO₂ (1.4 to 3.1 to 5.4 in units of 10² Nm⁻¹). Overall, the value of this force constant for Ti through to Ni is around 5.6. It starts to fall at CuO₂ (4.2) and is 3.5 for ZnO₂, which resembles CaO₂ in having a maximum likely metal oxidation state of +2. The decrease in the metal–oxygen distance from calcium to zinc presumably leads to the higher force constant.

For a nonlinear molecule XY₂^[35] [Eq. (4)]

$$4\pi^2\nu_3^2 = \left(\frac{1}{M_Y} + \frac{2}{M_X} \sin^2\theta \right) k \quad (4)$$

where k is the SVFF stretching force constant, and 2θ the bond angle. For ν_1 , neglecting interaction with the deformation ν_2 , a similar expression holds in which $\sin^2\theta$ is replaced by $\cos^2\theta$. For a bond angle of 90°, the ν_1 and ν_3 bands [according to Eqs. (2) and (4)] will have the same intensity and frequency since $\sin^2\theta = \cos^2\theta$. Figure 6 shows the dramatic change in the

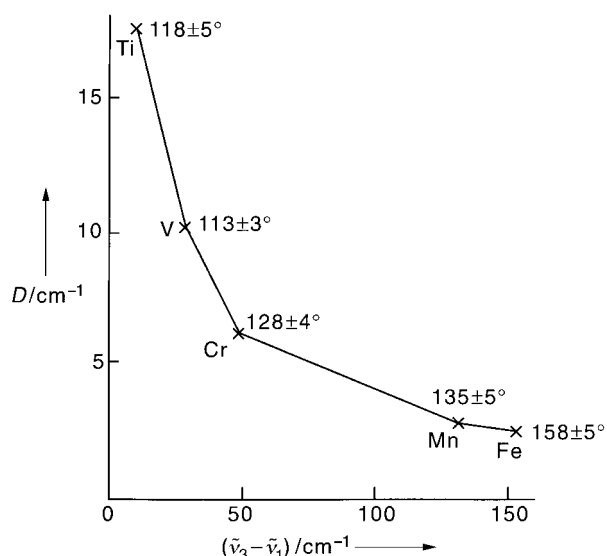


Figure 6. The effect of the O-M-O bond angle on the stretching frequency of metal dioxide molecules (D = difference between the frequency of the M¹⁶O¹⁸O component of ν_3 and that calculated from the mean of the M¹⁶O₂ and M¹⁸O₂ frequencies).

difference between $\tilde{\nu}_3$ and $\tilde{\nu}_1$ from CrO₂ to MnO₂, which is associated with a decrease in the difference between the observed position of the M¹⁶O¹⁸O component and that calculated from the mean of the M¹⁶O₂ and M¹⁸O₂ positions. Both of these effects are brought about principally by changes in bond angle.

Passing now to the second- and third-row transition elements, the earlier members are, like those of the first

row, strongly nonlinear: Zr and Hf (113°),^[87] Nb (108°), Ta (106°),^[96] Mo (122°), and W (124°).^[97] It is noteworthy that in the case of molybdenum, with seven isotopes of natural abundance greater than 9%, it was possible to use 16 (symmetrical) ¹⁶O₂ or ¹⁸O₂ species to calculate an upper limit to the angle (125°), and more than 40 isotopomers to calculate a lower limit (119°). RuO₂ was reported^[98] to have a bond angle of 149°, and if RhO₂ and IrO₂ are linear, as indicated by ESR measurements,^[99] then the general pattern for the second- and third-row transition element dioxides appears to be similar to that established for the first row.

Several lanthanide oxides can be vaporized at very high temperatures to give gas-phase MO₂, and this behavior appears to correlate with the value of the fourth ionization potential of the metal. Both CeO₂ and TbO₂ (d⁰f⁰ and d⁰f⁷) have spherically symmetrical inner shells and are nonlinear (146 ± 2° and 121 ± 2°).^[100] Although the angle for CeO₂ (isoelectronic with BaF₂) is large and the assignments of two IR bands reverse those in an earlier paper,^[101] the authors present a consistent argument for nonlinearity. Praseodymium dioxide, which has a central atom with a partially filled f shell, is a linear molecule.^[100]

In the case of the actinides ThO₂ (d⁰f⁰) is nonlinear (122.5 ± 2°),^[100] while UO₂^[102] and PuO₂^[103] both have partially filled shells and are linear. This work on the lanthanides and actinides is mainly from the group at Argonne National Laboratory, and the IR spectra are of high quality. There are laser ablation experiments by Wilson and Andrews, analogous to those on the first row transition element dioxides, which confirm the earlier work on CeO₂ and indicate that PrO₂, NdO₂ (similar to UO₂), and SmO₂ (similar to PuO₂) are linear. However, EuO₂ and GdO₂ were found to be nonlinear surprisingly, with acute angles of approximately 90° and 97°, respectively.^[104]

3.2. Trioxides

Of the trioxides, MoO₃ was reported^[105] to be pyramidal (C_{3v}). However the ¹⁶O₂ to ¹⁸O₂ frequency shift of the assumed ν_3 band in this difficult experiment was only shifted 0.2 cm⁻¹ from that calculated for a planar molecule (neglecting interaction with the E' bend). Further, the assignment of ν_1 has been questioned.^[97] If MoO₃ were planar this would agree with data on WO₃^[11] and RuO₃,^[98] both reported as D_{3h}. UO₃ is exceptional in that it is apparently T-shaped in argon matrices and, as a result, has been extensively studied.^[102]

4. Hydrides

The situation with regard to hydrides is perhaps the least satisfactory, although as a group they are the most tractable from the point of view of theoretical calculations and spectroscopic rotational analysis. The terms $\left(\frac{2}{M_X} \sin^2\theta \right)$ and $\left(\frac{2}{M_X} \cos^2\theta \right)$ for ν_3 and ν_1 in Equation (4) are small compared

with $1/M_Y = 1$ or 0.5 . Essentially the ν_1 and ν_3 bands of MH_2 and the ν_{M-H} band of HMD will all lie within a narrow frequency range, well separated (by a factor of about $\sqrt{2}$) from the corresponding bands of MD_2 and HMD . Hence, isotopic shift data are usually not useful in determining bond angles. For the dihydrides the determination of bond angle therefore relies on the relative intensities of the ν_1 and ν_3 bands [ca. $\tan^2\theta$ according to Eq. (2)]. The occupation of two different matrix sites by a linear MH_2 molecule also leads to two bands in the stretching region. However, the difficulty is resolved because in this case each MHD molecule gives rise to two stretching vibrations, so that a total of four bands is observed for the mixed isotopomer, rather than the two expected for a nonlinear molecule in a single matrix site.

This approach gave a tentative value of 168° for CaH_2 ,^[106] however, the spectroscopic data are very complex. In the case of TiH_2 Chertihin and Andrews^[107] report a value for $\tilde{\nu}_3$ but note that a band previously assigned^[108] to ν_1 was of variable intensity in their spectra. It is thus possible that TiH_2 is linear. There is disagreement about VH_2 . Van Zee, Li, and Weltnier^[109] find “no indications of VH_2 being nonlinear” by ESR spectroscopy, although a previous paper^[108] reported a strongly bent molecule ($127 \pm 5^\circ$). The situation with CrH_2 is equally confused as the HD species were observed as doublets in the latest paper,^[110] while MnH_2 is probably linear.^[111, 112] Fortunately, at this point some definitive experiments were performed. In 1996 groups in Bonn and Oxford announced the identification of FeH_2 in the gas phase by IR spectroscopy.^[113] FeH_2 was produced in a dc electric discharge through helium doped with hydrogen and iron pentacarbonyl. The discharge was probed with a CO laser by Zeeman modulation of the energy levels of FeH_2 . This laser magnetic resonance experiment characterized the molecule as linear in its ground electronic state ($^5\Delta$) with a ν_3 fundamental frequency of $1674.7196(4) \text{ cm}^{-1}$ and an $Fe-H$ distance of $1.665 \text{ \AA}$. The bending vibration of FeD_2 occurred at 229 cm^{-1} .^[114] The latest matrix IR results^[115] also indicate a linear molecule in argon, in contrast to earlier work in xenon,^[116] which gave a bond angle of “around 117° ”. In the cases of CoH_2 ^[117] and ZnH_2 ,^[106, 118] IR data show them to be close to linear or linear in a matrix, although for CoH_2 the ESR spectrum was interpreted^[119] in terms of a strongly bent molecule. However, there is one very interesting result. From IR studies in argon matrices doped with hydrogen, it has been reported^[120] that nickel atoms insert directly into H_2 to give NiH_2 , with a bond angle close to 90° . For most other metals only excited atoms react with H_2 , again the preferred mechanism being insertion. The bending frequency of NiH_2 is high (771 cm^{-1}), comparable to that of linear ZnH_2 (631 cm^{-1}) but more than twice those of FeH_2 and CoH_2 (335 and 380 cm^{-1}) all in argon matrices. The anomalous behavior of this molecule is further emphasized in Figure 7, which plots the SVFF force constants of MH_2 [from ν_3 in Eq. (4)] for the elements Ca to Zn (except Sc and Cu). By contrast, photodetachment spectroscopy on MnH_2^- , FeH_2^- , CoH_2^- , and NiH_2^- led to the suggestion that all the neutral dihydrides are linear.^[121]

A number of higher and heavier hydrides has been reported.^[122] However, in view of the difficulties outlined

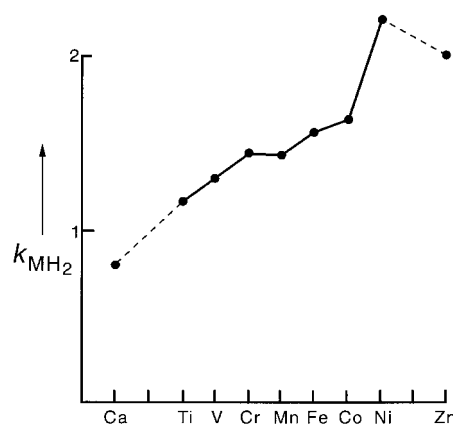


Figure 7. Plot of the stretching force constant k for the dihydrides of elements Ca to Zn (without Sc and Cu). Values refer to argon matrices, except for CaH_2 , which was studied in krypton.

above and the lack of systematic studies, it is not possible to make any useful comments other than to note that several of the heavier ones appear to be nonlinear (MH_2) or pyramidal (MH_3).

5. Summary and Outlook

In 1989^[43] we wrote a paper entitled “Do Any AB_n Molecules Have Anomalous Shapes?” The title was intended to be provocative and to emphasize the potential importance of host–guest interactions in matrices. In 1988^[68] we wrote: “Guests likely to be strongly affected by the host matrix would be those where the central atom is co-ordinatively unsaturated and where bonding forces are not highly directional in character.”

Table 1 summarizes the bond angles found for metal dioxides (OMO) isolated in argon matrices for which well-resolved IR spectra were obtained for the $^{16}O/^{18}O$ molecules. In their experiments on the dioxides of the metals from Ca to Zn,^[85–95] Andrews et al. found a gradual change from CaO_2 at about 140° (similar to CaF_2 in argon) through ScO_2 at 128° to TiO_2 at 113° . This decreasing angle is reflected in the increase in formal charge from $+2$ to $+4$ and possibly represents

Table 1. Bond angles [$^\circ$] of MO_2 species in argon matrices determined by means of O^{16}/O^{18} substitution^[a]

Sc	Ti	V	Cr	Mn	Fe	Co to Zn		
128	113	118	128	135	158	180		
Y	Zr	Nb	Mo	Tc	Ru			
	113	108	122		149			
La	Hf	Ta	W	Re	Os			
	113	106	124					
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb
	146	180	180		180	ca. 90	ca. 97	121
Ac	Th	Pa	U	Np	Pu			
	122		180		180			

[a] Of the dihalides, $^{40/44}CaF_2^*$ (Ne, Ar, Kr, $143-139^\circ$), $^{86/88}SrF_2^*$ (Kr, 108°), $^{86/88}Sr^{35/37}Cl_2$ (Kr, 120°), and $Yb^{35/37}Cl_2$ (Ar, 126°) are nonlinear; of the dihydrides, NiH_2 is nonlinear (Ar, ca. 90° ; an asterisk denotes the lower limit of an angle).

increasing interaction with the matrix. As the electronegativity difference between the metal and oxygen decreases, the bond angle widens up to CoO₂, and all subsequent dioxides up to and including ZnO₂ are linear. Again, one of many possible explanations is that the bending is induced by the matrix, although it could equally well be argued that these strongly bound molecules are unlikely to be appreciably affected by their surroundings. A comment by Lessen and Brucat^[123] is apposite: “the potential well depth of VAr⁺ is sufficiently strong as to be similar to the more chemically relevant solvent water”. As expected the binding energy of such species increases with the polarizability of the inert gas.^[124] It is also interesting that in the sequence FeCl₂, CoCl₂, NiCl₂ in nitrogen matrices^[125] there appears to be a gradual decrease in bond angle from 150° in FeCl₂ to 130° in NiCl₂. As these molecules are all thought to be linear in argon, this again suggests a gradual change in matrix interactions. Against this view, calculations by Andrews and co-workers frequently show excellent agreement between theory and experiment for the first-row transition element dioxides.

This leaves the question of which experiments are most likely to resolve these controversies. For the first-row transition metal dihalides, the only molecule that shows evidence of a nonlinear structure is TiF₂.^[44] A laser ablation experiment on titanium, seeded in an argon stream doped with fluorine, followed by cocondensation and IR spectroscopy could settle this point. The spectra of TiF (gas), TiF₃, and TiF₄ (in matrices) are all known, and titanium has several naturally occurring isotopes. For the halides of Ca, Sr, and Ba, a high-temperature gas-phase microwave spectrum of SrClF could establish whether it is worth pursuing the pure dihalides. This technique could also be used for the lanthanide dihalides, notably YbClF.

In the case of oxides the difficulty of obtaining species in the gas phase means that, unless an alternative approach is found, it may be necessary to work at the very high temperatures required to generate vapors of, for example, CeO₂ or UO₃, with all the attendant problems that this entails.

Of the dihydrides, NiH₂ is the most interesting in that it shows both high force constants and a strongly nonlinear molecule. A reaction analogous to that used to generate gaseous FeH₂, but with [Ni(CO)₄] instead of [Fe(CO)₅], is being actively pursued.

Most of this review has been concerned with ground-state molecules. Matrix-isolation techniques allow the synthesis of many interesting species, and their IR spectra frequently give information on molecular geometry. Gas-phase studies are much more difficult both in the formation of the required molecule and in the recording and analysis of the spectra. However, it is only by obtaining detailed information on molecular energy levels and geometry that comparison with increasingly reliable^[126] theoretical calculations will be possible. In particular density functional theory (which is nearly as old as quantum mechanics) is establishing a reputation for speed and reliability for compounds of the transition elements.^[127] It is also salutary to recall that although the ground and several excited electronic states of CaOH are linear,^[128] “the F state is bent, the first bent and strongly covalent state of CaOH to be observed”.

Perhaps as a finale to this review a quote by Friedman-Hill and Field^[129] is relevant: “Truly heroic analyses of the spectra of these molecules have still left many questions unanswered...” and they were referring to diatomic gases.

Addendum

Several relevant papers have been published since submitting this Review. One of these represents a major advance: the recording of the microwave spectrum of ZrO₂ giving a bond length of 1.7710 ± 0.0007 Å and a bond angle of $108.11 \pm 0.08^\circ$ for the ground-state molecule in the gas phase.^[130] As the corresponding matrix-isolation experiment^[87] gave an upper limit of $113 \pm 5^\circ$ for the bond angle while that calculated was 112° , the value of 108° gives confidence in both the matrix data and the calculations on similar strongly bonded dioxides.

The value of 128° used in Table 1 of this Review for ScO₂ is now thought^[131] to be due to ScO₂[−] (isoelectronic with CaF₂). IrO₂,^[132] RhO₂,^[133] and PtO₂^[134] are all reported as linear, while the more weakly bound YO₂ and LaO₂ are nonlinear^[135] with ν_1 showing an anomalously high intensity and frequency relative to ν_3 . There are now data on all the lanthanide dioxides apart from Pm, Er, and Lu.^[136] This work (which agrees with earlier data on Ce, Pr, and Tm) gives Nd, Sm, Dy, and Yb as linear while Eu, Gd, Ho, and Tm are strongly bent (from isotopic data or intensity measurements on ν_1 and ν_3). Finally the low-lying electronic states of WO₂ have been probed using NIPES,^[137] while the vibrational and electronic energy levels of many oxides and hydrides have been tabulated by Jacox.^[138]

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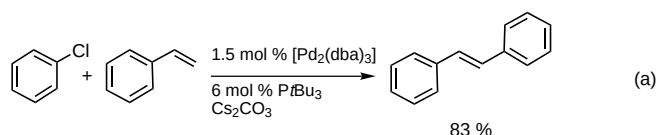
Take the Right Catalyst: Palladium-Catalyzed C–C, C–N, and C–O Bond Formation on Chloroarenes

Rainer Stürmer*

Chlorinated arenes are cheap to manufacture and therefore play a vital role as intermediates in the chemical industry. However, in contrast to their—much more expensive—brominated and iodinated counterparts, chloroarenes are quite unreactive in subsequent reactions. Classical functionalizations of the C–Cl bond in nonactivated arenes usually require harsh conditions, and side reactions may produce environmentally hazardous oxygenated chloroarenes. This leads to considerable problems in using these compounds as intermediates in the synthesis of more highly functionalized biologically active molecules, such as agrochemicals and pharmaceuticals.

Due to recent developments in catalysis, former problems might be overcome: The groups of S. L. Buchwald, G. C. Fu, J. F. Hartwig, and others reported significant improvements in C–C, C–N, and C–O bond formation on chloroarenes. For all of these bond formations the right choice of catalyst is crucial for success. In other words: By ligand tuning, all three bond forming reactions can be realized through palladium catalysis. The following account focuses on recent work, since the subject has been already reviewed.^[1]

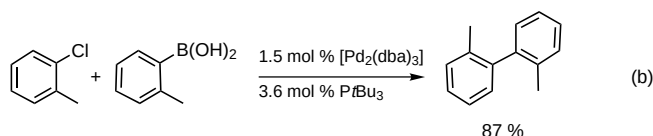
Heck- and Suzuki-type couplings have been described by Fu et al.^[2] The reaction of chlorobenzene and styrene in refluxing dioxane in the presence of $[\text{Pd}_2(\text{dba})_3]$ (dba = di-benzylideneacetone) and the electron-rich, sterically hindered tri-*tert*-butylphosphane gives rise to *trans*-stilbene in 83 % yield [Eq. (a)]. Besides the choice of the ligand—aryl phosphanes, tri-*n*-butylphosphane, and tricyclohexylphosphane show no conversion—the base is also crucial for



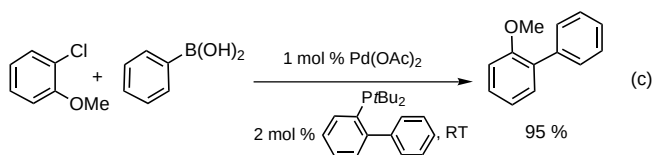
success. Cesium carbonate gives the best results, although the cheaper potassium phosphate gives comparable yields. Under the same conditions the sterically more demanding 2-chlorotoluene is coupled in 70 % yield. However, longer reaction

times are necessary. Acceptor as well as donor substituents are tolerated under these conditions.

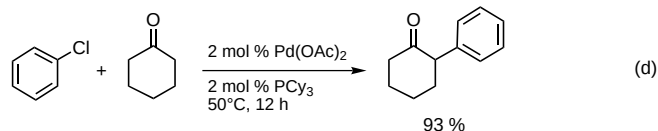
Tri-*tert*-butylphosphane is the ligand of choice in Suzuki couplings^[3] as well: 2-Chlorotoluene reacts with 2-methylphenylboronic acid to provide 2,2'-disubstituted biphenyl in 87 % yield [Eq. (b)]. Another contribution from Fu et al.^[4] describes the Stille coupling of chloroarenes in which vinyl, allyl, phenyl, and even alkyl groups can be transferred in the presence of cesium fluoride.



An improved variation of Suzuki couplings was recently described by Buchwald et al.^[5] By use of 2-(di-*tert*-butylphosphanyl)biphenyl as ligand, palladium acetate and potassium carbonate facilitate couplings at room temperature [Eq. (c)]. Catalyst concentrations may be kept quite low (0.02–0.05 mol %).



In a similar context Hartwig et al.^[6] published a screening method based on a fluorescence assay aimed at the rapid identification of efficient ligands in Heck-type couplings. Arylations of ketones and malonates with aryl chlorides [Eq. (d)] have been recently published by the same group.^[7] Electron-rich phosphanes are used to secure good conversions.

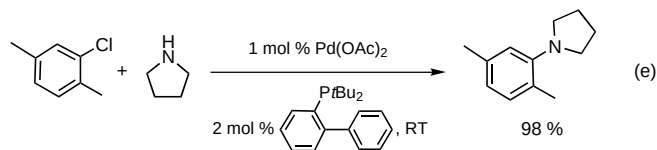


2-(Di-*tert*-butylphosphanyl)biphenyl has been used by Buchwald et al.^[5] as the most efficient ligand in the palladium-catalyzed amination of aryl chlorides. 2-Chloro-4-

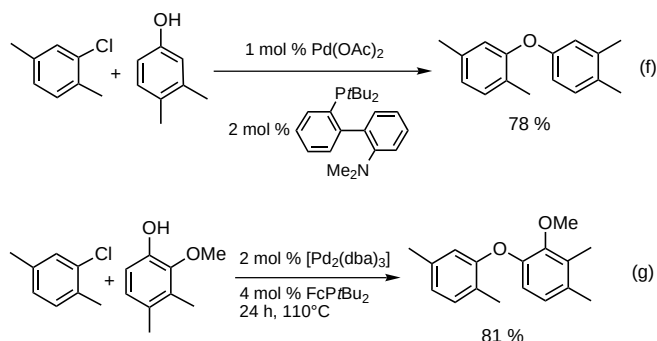
[*] Dr. R. Stürmer

BASF AG, Hauptlaboratorium, ZHF/D, A30
67056 Ludwigshafen (Germany)
Fax: (+49) 621-60-20440
E-mail: rainer.stuermer@basf-ag.de

methyltoluene can be aminated with pyrrolidine in 98 % yield using sodium *tert*-butoxide [Eq. (e)]. These reactions went to completion at room temperature within 15–20 h; donor and acceptor substituents are tolerated.



Palladium-catalyzed C–O bond forming reactions were performed by Buchwald et al.^[8] with 2-dimethylamino-2'-di-(*tert*-butylphosphanyl)biphenyl as ligand. 3,4-Dimethylphenol can be arylated smoothly with 2-chloro-4-methyltoluene in the presence of sodium hydride [Eq. (f)]. Hartwig et al.^[9] developed a novel ferrocene-based dialkylphosphane ligand for this arylation: 2-Methoxy-3,4-dimethylphenol is arylated with 2-chloro-*p*-xylene in 81 % yield [Eq. (g)].



For quite a long time chloroarenes were considered as too unreactive for catalysis. However, significant improvements in various coupling reactions of chloroarenes by the use of electron-rich phosphanes have rendered this statement as no longer valid. The use of these cheap intermediates as coupling partners in the synthesis of more highly functionalized molecules of industrial relevance is now within reach. Since some of these ligands are commercially available already, it is

probably only a question of time until we see the first industrial applications of these improved procedures.

Recent work from Lipshutz et al.^[10] even shows the replacement of the rather expensive palladium with nickel, at least in C–C bond formations. Chloroarenes are coupled with organozinc compounds under nickel(0) catalysis.^[11]

German version: *Angew. Chem.* **1999**, *111*, 3509–3510

Keywords: aminations • cross-coupling • homogeneous catalysis • palladium

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The First Nitride Spinel—New Synthetic Approaches to Binary Group 14 Nitrides**

Wolfgang Schnick*

The discovery of novel element allotropes^[1] as well as the synthesis and structure elucidation of new binary compounds are usually recognized as important landmarks in chemistry. In the case of binary compounds the structural-chemical properties of the constituent elements and especially their mutual behavior is clearly revealed.

Owing to their limited number, only rarely have novel representatives of basic solid-state compounds like binary oxides or nitrides been discovered or their hitherto unknown structures elucidated.^[2] For these reasons it is remarkable that very recently binary tin(IV) nitride, Sn_3N_4 ,^[3] as well as the high-pressure polymorphs $\gamma\text{-Si}_3\text{N}_4$ ^[4] and $\gamma\text{-Ge}_3\text{N}_4$ ^[5] have been synthesized and structurally investigated. All three compounds are isotypic and crystallize in a spinel structure type that previously has not been found for nitrides (Figure 1). Though Si, Ge, and Sn are three homologous elements and the three nitrides are isotypic, the motivation of these research projects and the synthetic procedures used differ substantially. With respect to its chemical, thermal, and mechanical properties, silicon nitride is remarkably resistant. Therefore this compound gained significance as the most important non-oxidic ceramic material.^[6] In contrast the homologous tin(IV) nitride was expected to show a much lower stability, and until recently no proof for the existence of Sn_3N_4 had been obtained.^[7]

Under ambient conditions the binary oxides SiO_2 and GeO_2 are made up of MO_4 tetrahedra ($\text{M} = \text{Si, Ge}$). Their high-pressure chemistry has been studied in detail, and both finally crystallize in the rutile structure type. An essential feature of this transformation is the increase in coordination number and the formation of MO_6 octahedra. Recently, spectacular materials properties have been observed for stishovite, a high-pressure polymorph of SiO_2 that also occurs as a mineral: Microhardness investigations have proved that this material is the hardest oxidic material known so far, and together with diamond and cubic boron nitride it is among the three hardest materials.^[8] Thus the oxides MO_2 ($\text{T} = \text{Si, Ge, Sn, Pb}$) follow the pressure-homologues rule,^[9] because under high-pressure conditions the lighter homologues (SiO_2 , GeO_2) adopt exactly the structure type (rutile) that is observed for the heavier homologues (SnO_2 , PbO_2) under ambient conditions.

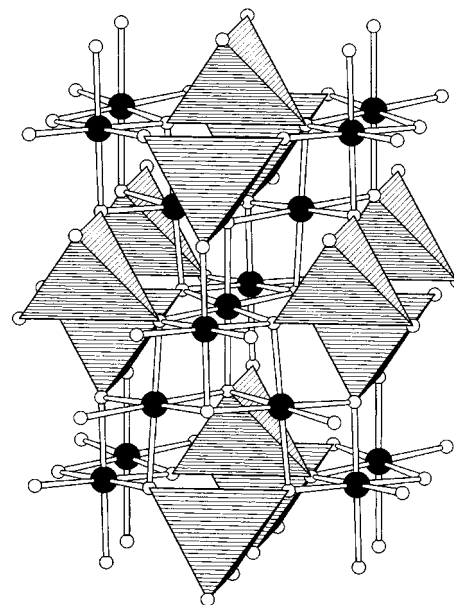


Figure 1. Tin(IV) nitride, Sn_3N_4 , as well as the high-pressure polymorphs $\gamma\text{-Si}_3\text{N}_4$ and $\gamma\text{-Ge}_3\text{N}_4$ crystallize in the spinel structure type, which until now has predominantly been observed for oxides like MgAl_2O_4 or Fe_3O_4 . Here the anions (white circles) form a cubic closest sphere packing, whereas the metal cations (black spheres and centers of the closed polyhedra) occupy one-half of the octahedral and one-eighth of the tetrahedral voids in an ordered manner. According to Pauling's rules the remaining empty voids of the spinel type, in the case of ionic compounds, may not be occupied due to an electrostatic blockade.

The recent high-pressure investigations on Si_3N_4 ^[4] have been targeting fields of application as well. The sintered silicon nitride ceramics are usually manufactured under the influence of high temperatures and pressures. In this context numerous investigations have been published in the material scientific literature. However investigations above a pressure of 9 GPa have not been reported so far. Already the normal-pressure polymorphs $\alpha\text{-Si}_3\text{N}_4$ and $\beta\text{-Si}_3\text{N}_4$ are desired materials owing to their mechanical hardness and stability. For the high-pressure polymorph of silicon nitride even more advanced materials properties and a mechanical hardness comparable to that of stishovite are expected.^[4]

The novel high-pressure polymorph $\gamma\text{-Si}_3\text{N}_4$ was synthesized from the elements or from N_2 and Si_3N_4 at 2000 K and 15 GPa using a laser-heated diamond anvil cell.^[4] The amount of sample obtained by this procedure was extremely small, and thus only sufficient for vibration spectroscopy and electron microscopy investigations. The spinel structure for $\gamma\text{-Si}_3\text{N}_4$ was derived from the cubic metric determined by electron diffraction and the observed extinction conditions.^[4] In retrospect the increase in coordination number for Si in $\gamma\text{-Si}_3\text{N}_4$ caused by high pressure sounds plausible, because recently $\text{Ce}_{15}\text{Si}_{16}\text{O}_6\text{N}_{32}$ was discovered as the first compound

[*] Prof. Dr. W. Schnick
Institut für Anorganische Chemie der Universität
Butenandtstrasse 5–13 (Haus D), D-81377 München (Germany)
Fax: (+49) 89-2180-7440
E-mail: wsc@cup.uni-muenchen.de

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to contain SiN_6 octahedra.^[10] SiN_6 octahedra have also been found in spinel-type $\gamma\text{-Si}_3\text{N}_4$. According to $(\text{Si}^{[6]})_2[\text{Si}^{[4]}\text{N}_4]$ one third of the Si atoms are still tetrahedrally coordinated, forming SiN_4 units. The latter coordination solely occurs in $\alpha\text{-Si}_3\text{N}_4$ and $\beta\text{-Si}_3\text{N}_4$.^[7] According to Liebau^[11] $\gamma\text{-Si}_3\text{N}_4$ thus might be classified as disilicon nitridosilicate.

Homologous $\gamma\text{-Ge}_3\text{N}_4$ was obtained under similar conditions (14 GPa),^[5a] but in the meantime larger amounts of this polymorph (ca. 100 mg) were synthesized at 1000–1200 °C and 12 GPa utilizing a multianvil high-pressure cell.^[5b] Rietveld refinement of the X-ray powder diffraction data confirmed the postulated spinel structure. Therefore $\gamma\text{-Si}_3\text{N}_4$ should also be accessible on a preparative scale by this method; then the missing X-ray diffraction investigations could be performed and the predicted materials properties^[4] of this compound may be experimentally proved.

In the past the existence of Sn_3N_4 or Pb_3N_4 was extremely doubtful. Therefore a prediction of the high-pressure polymorphs $\gamma\text{-Si}_3\text{N}_4$ and $\gamma\text{-Ge}_3\text{N}_4$ using the pressure–homologues rule was not possible. However, simultaneous to the discovery of $\gamma\text{-Si}_3\text{N}_4$ and $\gamma\text{-Ge}_3\text{N}_4$, Jacobs et al. successfully synthesized and structurally characterized Sn_3N_4 .^[3] Although a high-pressure, high-temperature synthesis starting from the elements (analogous to the synthesis of $\gamma\text{-Si}_3\text{N}_4$ and $\gamma\text{-Ge}_3\text{N}_4$) might lead to the formation of Sn_3N_4 , Jacobs et al. chose a simpler synthetic approach: Crystalline Sn_3N_4 is obtained as a by-product from the reaction of SnI_4 or SnBr_4 with KNH_2 in liquid NH_3 with subsequent careful thermal treatment at 573 K in vacuum. In contrast to the high-pressure procedures described above, Sn_3N_4 was obtained in preparative amounts. Consequently, X-ray and neutron powder diffraction experiments as well as ^{119}Sn MAS solid-state NMR measurements were performed, and the results unequivocally confirmed the spinel structure of Sn_3N_4 .^[3]

The results described so far represent an important scientific breakthrough in the investigation of main group nitrides. However, there are still open questions: The existence and the properties of carbon(IV) nitride, C_3N_4 , are still under controversial discussion, though a huge number of investigations have been published focusing on these topics. According to theoretical considerations C_3N_4 was expected to exhibit a spectacular mechanical hardness exceeding that of diamond.^[12] In the absence of reliable data the structure of C_3N_4 was assumed to be isotopic with $\beta\text{-Si}_3\text{N}_4$ or with willemite II (Zn_2SiO_4). The spinel structure, which according to the results discussed above may also be appropriate, has not been considered for C_3N_4 so far.^[4]

Furthermore, the question arises if at higher pressure the nitrides M_3N_4 ($\text{M} = \text{Si}, \text{Ge}, \text{Sn}$) show a phase transformation to a polymorph with an even higher density. Such an ultra-high-pressure polymorph may solely contain M atoms with a higher coordination number (> 4), like Zr_3N_4 ,^[13] which crystallizes in a distorted Eu_3O_4 structure type. Another candidate with an octahedral coordination of the M atoms is represented by the Mg_3NF_3 structure type,^[14] which is a defect variant of NaCl . For tungsten nitride, W_3N_4 ,^[15] which has only been poorly characterized so far, the latter structure has been postulated.

At first glance the different coordination numbers of Si in $\gamma\text{-Si}_3\text{N}_4$ (octahedrally and tetrahedrally coordinated $\text{Si}^{[6]}$ and $\text{Si}^{[4]}$ with a molar ratio of 2:1) seem to be unusual. However, in $\text{La}_2(\text{O}^{[4]})_2\text{O}^{[6]}$ a similar situation occurs: One third of the O atoms are tetrahedrally and the others are octahedrally coordinated by La.^[16] Therefore in solid $\gamma\text{-Si}_3\text{N}_4$ and La_2O_3 the possibility of ternary substitution variants is apparent, and this has already been found for La_2O_3 (e.g. $\text{La}_2\text{O}_2\text{S}^{[17]}$ or the anti-type $\text{CaMg}_2\text{N}_2^{[18]}$). Consequently ternary nitride spinels may be possible.

The question concerning the existence of lead(IV) nitride remains unanswered. With respect to the observation that Sn_3N_4 is much less stable than Ge_3N_4 , the synthetic limits have probably been reached in the case of Pb_3N_4 . Accordingly its existence remains unclear.

German version: *Angew. Chem.* **1999**, *111*, 3511–3512

Keywords: main group elements • nitrides • solid-state structures

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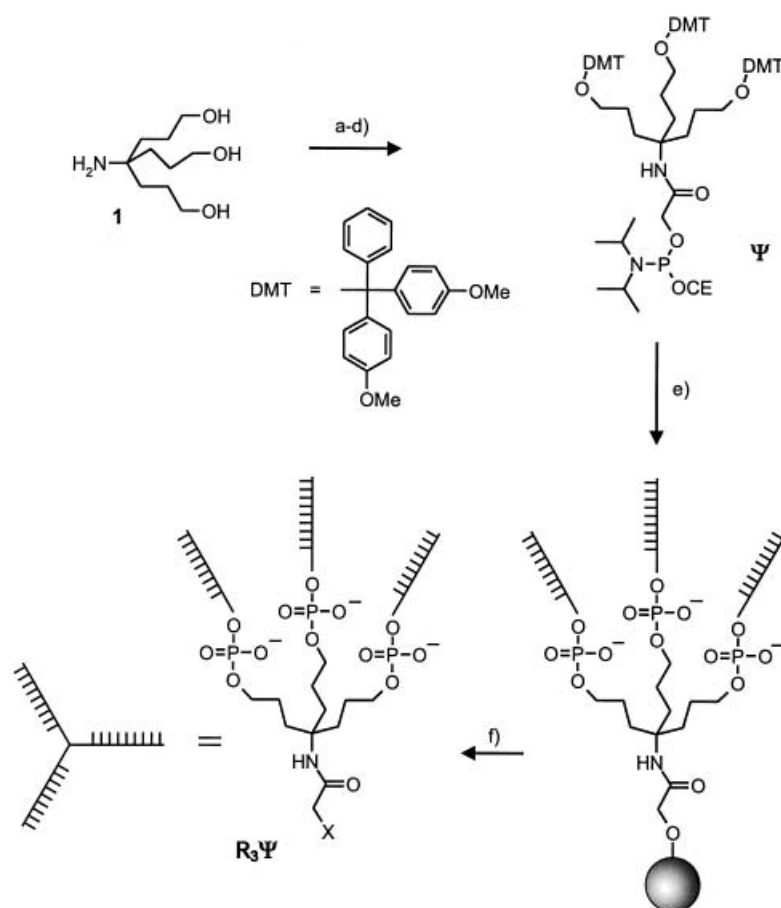


Self-Assembly of Trisoligonucleotides: The Case for Nano-Acetylene and Nano-Cyclobutadiene**

Matthias Scheffler, Axel Dorenbeck, Stefan Jordan, Michael Wüstefeld, and Günter von Kiedrowski*

DNA as well as DNA-like materials enable sequence-addressed self-assembly and thus supramolecular information processing in a unique way. Since the pioneering experiments of Seeman,^[1] the potential of using DNA as construction material for synthetic nanometer-sized objects has been recognized within bioorganic and supramolecular chemistry. Wire-frame-type molecular objects were synthesized from three-way or four-way junctions which are themselves composed of three or four linear oligonucleotides.^[2] Recently, Shi and Bergstrom reported on the assembly of nanometer-sized macrocycles from complementary V-shaped molecules in which the 3'-ends of two oligonucleotides were attached to a bifunctional linker.^[3] Further approaches within DNA nanotechnology focus on the oligonucleotide-addressed spatial positioning of molecular objects such as metal clusters that are covalently attached to single-stranded, linear oligonucleotides.^[4]

We here report on the synthesis and sequence-addressed self-assembly of trisoligonucleotides, a novel class of branched oligonucleotides in which a trifunctional linker connects three oligonucleotide strands through their 3'-termini. Our concept of synthesizing DNA nanostructures is related to that of Seeman; it is, however, solely based on self-assembly, thus avoiding covalent ligation steps in order to enable future approaches towards the self-replication of such nanostructures. Trisoligonucleotides based on the linker Ψ (Scheme 1) were synthesized by solid-phase phosphoramidite chemistry as early as 1993,^[5a] but the lack of proper analytical methods for the identification of these molecules prevented an early publication. Table 1 presents the sequences and selected analytical data of the trisoligonucleotides.^[5b] Linker phosphoramidite Ψ was obtained from Newkome's dendrimer synthon **1** by a four-step transformation sequence in 50% overall yield (Scheme 1).^[6]



Scheme 1. Synthesis of trisoligonucleotides $R_3\Psi$. a) 4,4'-dimethoxytrityl chloride, pyridine; b) acetoxyacetic acid chloride, triethylamine, toluene; c) 0.5N NaOH/THF (1/1); d) 2-(cyanethoxy)-bis-*N,N*-(diisopropylamino)phosphane, dichloromethane; e) standard phosphoramidite protocol for oligonucleotide synthesis on 500 Å CPG, except during coupling of Ψ , where the reaction time was extended to 3×15 min; f) NH_3 (aq) at 85°C for 2 h in a pressure-tight tube; note that under these cleavage conditions the amido functionality at the 3'-termini of the linker is not affected, so that the leader base(s) X from the solid phase is incorporated into the trisoligonucleotides. – CE = cyanethoxy.

UV-titration data allowed us to determine the stoichiometry of different trisoligonucleotidyl complexes. Mixtures of trisoligonucleotidyls with their linear complements showed always a 1:3 stoichiometry (Figure 1a), whereas mixtures of complementary trisoligonucleotidyls showed always a 1:1 stoichiometry (Figure 1b). The UV melting curves of complexes between complementary linear oligonucleotides and between complementary trisoligonucleotidyls as well as of the above-mentioned 1:3 complexes were barely distinguishable at concentrations adjusted to obtain equal UV extinction E .^[5b] Transitions were monophasic in all cases, even when varying the heating rate between 0.1 and 2 K min^{-1} . Obviously, trisoligonucleotidyls undergo self-assembly as efficiently as their linear counterparts.

The size distribution of trisoligonucleotidyl complexes was visualized by means of agarose gel electrophoresis. Immobile high molecular weight aggregates were obtained from complementary trisoligonucleotidyls when a standard hybridization protocol was employed, in which the sample is denatured at 95°C and then slowly cooled to the annealing temperature (0.1 K min^{-1} to $20\text{--}25\text{ K below } T_m$). The formation of these

[*] Prof. Dr. G. von Kiedrowski, Dr. M. Scheffler, A. Dorenbeck, M. Wüstefeld
Lehrstuhl für Bioorganische Chemie der Universität
D-44780 Bochum (Germany)
Fax: (+49) 234-7094-355
E-mail: kiedro@ernie.orch.ruhr-uni-bochum.de
Dr. S. Jordan
Bayer AG, 51366 Leverkusen (Germany)

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

Table 1. Sequence and analytical data of the trisigonucleotidyls $\mathbf{R}_3\Psi$ (Scheme 1).^[a]

$\mathbf{R}_3\Psi$ ^[b]	Sequence	X ^[c]	M_{calcd}	M_{found} ^[d]	t_m [min] ^[e]	t_r [min] ^[f]	Yield [nmol] ^[g]
$\mathbf{A}_3^*\mathbf{Y}$	ATTGGCGCCAAT	pTA	11990	11981.7	17.89	17.55	22.50
$\mathbf{B}_3\mathbf{Y}$	AATGCCGCCAAT	pTC	11882	11878.3	19.33	16.04	52.00
$\mathbf{C}_3\mathbf{Y}$	ATTGGCGGCATT	pTC	12068	12064.4	19.58	17.23	56.45
$\mathbf{D}_3^*\mathbf{Y}$	AATTGGCGCCAATT	pTC	13827	13833.5	20.15	17.06	34.20
$\mathbf{E}_3\mathbf{Y}$	AAATGCCGCCAAAT	pTA	13785	13780.9	20.68	16.51	33.00
$\mathbf{F}_3\mathbf{Y}$	ATTTGGCGGCATTT	pTA	13917	13929.6	21.42	17.56	53.75
$\mathbf{G}_3^*\mathbf{Y}$	ATAATGGCGCCATTAT	pTT	15679	15700.9	22.50	18.22	13.45
$\mathbf{H}_3\mathbf{Y}$	AATCAGCCGCCACAAT	pC	15192	15185.2	22.81	16.63	78.74
$\mathbf{I}_3\mathbf{Y}$	ATTGTGGCGGCTGATT	pC	15562	15554.9	23.35	16.62	86.23
$\mathbf{J}_3^*\mathbf{Y}$	ATTGGACCGCGTCCAAT	pC	17236	17238.2	–	17.40	8.20
$\mathbf{K}_3\mathbf{Y}$	AATCCTCCGCGTCCAAT	pTA	17201	17226.3	26.42	17.02	33.10
$\mathbf{L}_3\mathbf{Y}$	ATTGGACGGCGGAGGATT	pTA	17922	17938.1	24.59	17.47	27.45
$\mathbf{M}_3^*\mathbf{Y}$	ATTGGGACCGCGTCCAAT	pC	19107	19123.2	–	16.38	10.10
$\mathbf{N}_3\mathbf{Y}$	AATCCCTGCCGCCTCCAAT	pTC	18913	18926.8	29.25	16.94	24.70
$\mathbf{O}_3\mathbf{Y}$	ATTGGGAGGCGGCAGGGATT	pTC	19873	19887.7	29.37	17.89	32.70

[a] The materials were purified by denaturing polyacrylamide gel electrophoresis (PAGE, 10–16% acrylamide) followed by desalting on NAP (NAP) columns (APB). Characterization was carried out with capillary electrophoresis (CE), HPLC, and MALDI-TOF-MS. [b] An asterisk indicates a self-complementary sequence. [c] p denotes a phosphodiester linkage. [d] Determined by MALDI-TOF-MS: 3-hydroxypicolinic acid, acetonitrile/H₂O (1/1). [e] t_m is the time of migration as determined by CE on eCAP-cartidge (27 cm, 0.1M tris-borate buffer, 7M urea, 10 kV). [f] t_r is the time of retention as determined by HPLC on Lichrocart C-18 (Merck; eluent A: 0.2M triethylammonium acetate, 2% acetonitrile (pH 7); eluent B: acetonitrile; gradient: eluent A for 5 min, 0→25% eluent B within 25 min, 25→50% eluent B within 3 min). [g] Yield after purification from a 1.3-μmol scale.

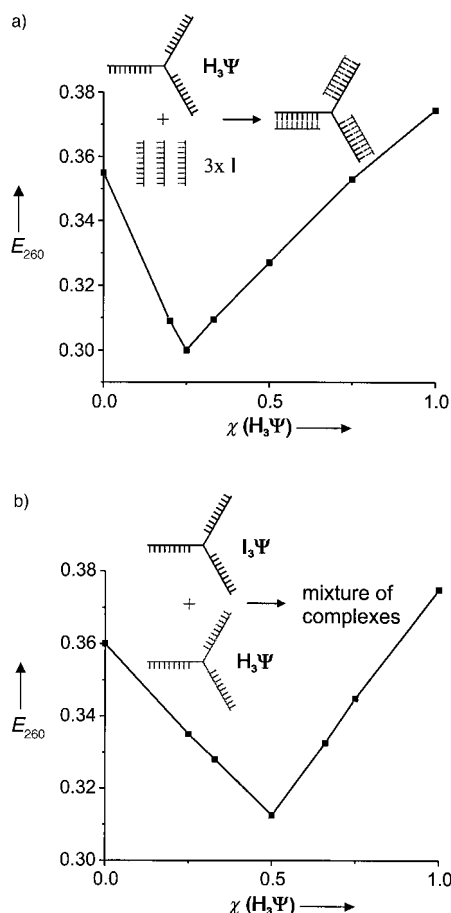


Figure 1. Determination of the stoichiometry of the trisigonucleotidyl complexes by UV-titration. The UV-extinction E at $\lambda = 260$ nm was measured as a function of the mole fraction χ of $\mathbf{H}_3\Psi$. a) Mixing curve for $\mathbf{H}_3\Psi^*\mathbf{I}$ showing a 1:3 stoichiometry; b) mixing curve for $\mathbf{H}_3\Psi^*\mathbf{I}_3\Psi$ revealing a 1:1 stoichiometry. All experiments were carried out under extinction equivalence in the presence of 100 mM NaCl, 0.5 mM EDTA, and 10 mM phosphate buffer (pH 7.5) and at 25 °C. The concentration of $\mathbf{H}_3\Psi$ was 0.333 μM at $\chi = 1$.

polymeric aggregates depends on the concentration of the trisigonucleotidyls and has been observed, for example, for the case $\mathbf{H}_3\Psi/\mathbf{I}_3\Psi$ at $c > 1$ μM. Discretely resolved bands could, however, be made visible after changing the hybridization strategy (see the Supporting Information). The new protocol starts with denaturation at 95 °C followed by rapid cooling to 0 °C (1.8 Ks⁻¹ between 95 and 50 °C, see the Supporting Information), where the sample is maintained for 5 min. Afterwards, the sample is heated to the sequence-dependant annealing temperature. The rationale for the new hybridization strategy is to favour kinetically controlled association processes. This is comparable to a crystallization process where rapid cooling usually leads to high nucleation rates, resulting in smaller crystals.

Figure 2 shows a typical gel from a hybridization study in which the ratio between linear oligonucleotides $\mathbf{H}$, $\mathbf{I}$ and trisigonucleotidyls $\mathbf{H}_3\Psi$, $\mathbf{I}_3\Psi$ was varied. The composition of the samples applied to lanes 1–9 is given in Table 2. As expected, the linear duplex $\mathbf{H}^*\mathbf{I}$ (lane 8) shows the highest mobility among the double-stranded complexes. The 1:3 complexes $\mathbf{H}_3\Psi^*3\mathbf{I}$, and $\mathbf{I}_3\Psi^*3\mathbf{H}$ lead to single bands exhibiting equal mobility (lanes 6, 7). Lane 1 shows the distribution of complexes arising from a 1:1 mixture of trisigonucleotidyls $\mathbf{H}_3\Psi$ and $\mathbf{I}_3\Psi$. The pattern of bands is also visible in lanes 2–5, where the relative amount of linear oligonucleotides $\mathbf{H}$, $\mathbf{I}$ increases. Basically, an overlap of the band patterns in lanes 1 and 6–8 is observed. The band having the highest mobility in lane 1 moves slightly faster than that in lanes 6 and 7, emphasizing that the underlying complex is structurally more compact than the 1:3 complexes. The latter was independently confirmed by size-exclusion chromatography (see the Supporting Information). The above-mentioned band is weakly visible for 14-mers $\mathbf{E}_3\Psi$ and $\mathbf{F}_3\Psi$, but dominates in the case of 20-mers $\mathbf{N}_3\Psi$ and $\mathbf{O}_3\Psi$ ^[5b] its intensity critically depends on the presence of magnesium ions (5 mM) during hybridization (see the Supporting Information).^[5b] In

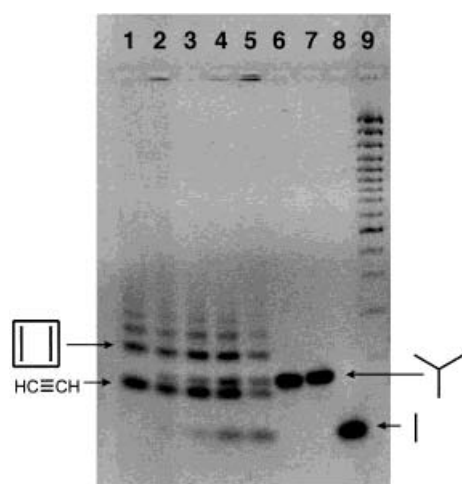


Figure 2. Oligonucleotide complexes on a 2% agarose gel (SeaKem LE; FMC) after electrophoresis and staining with ethidium bromide. The topology of the complexes is described employing hydrocarbon nomenclature as introduced in the text. The composition of the samples applied to lanes 1–9 is given in Table 2; all samples contained 100 mM NaCl, 5 mM MgCl₂, and 10 mM phosphate buffer (pH 7.5). The samples were denatured at 95 °C, cooled to 0 °C with an initial slope of 1.8 K s⁻¹ and after 5 min brought to an annealing temperature of 40 °C^[5b]. Electrophoresis was carried out using an ice bath for cooling.

Table 2. The composition of the samples applied to lanes 1–9 in Figure 2.

lane	H ₃ Y [mM]	I ₃ Y [mM]	H [mM]	I [mM]
1	3.33	3.33	–	–
2	3.12	3.12	0.625	0.625
3	3.00	3.00	1.75	1.75
4	2.75	2.75	1.75	1.75
5	2.50	2.50	2.50	2.50
6	–	3.33	10.00	–
7	3.33	–	–	10.00
8	–	–	10.00	10.00
9[a]	–	–	–	–

[a] Molecular weight standard: GeneRuler 100 bp DNA Ladder Plus, MBI Fermentas.

any case, the mobility data are consistent with the assumption of a bimolecular complex. Such a bimolecular complex may contain one, two, or three double-stranded linkages (Figure 3). To distinguish between the different binding situations, digestion experiments using mung-bean 5'-exonuclease were carried out (see the Supporting Information).^[5b] Under conditions where single-stranded oligonucleotide **I** as well as trisiliconucleotidyl **H₃Ψ** were completely digested, the bands in lane 1 did not show any change, even when the reaction times were twice as long and the concentration of the enzyme was doubled.^[5b] This supports the conclusion that all structures underlying the bands in lane 1 (Figure 2) are completely paired, thus removing possibilities a and b shown for the 1:1 complex in Figure 3. Further support for complete pairing was derived from scavenger experiments (see the Supporting Information). When either **H** or **I** was added to the mixture of **H₃Ψ** and **I₃Ψ** after the annealing procedure at 10 °C, no change of lane 1 (Figure 2) could be observed; that is, no single-stranded components exist in the complexes.^[5b]

For the sake of simplicity, we may now introduce a simple notation for the structures under discussion. We conceive a

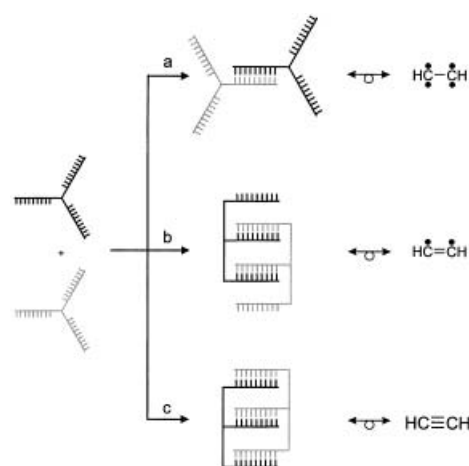


Figure 3. Possible topologies for a bimolecular complex from two complementary trisiliconucleotidyls. Each DNA double strand is described as a chemical C–C bond and each unpaired oligonucleotide as an unpaired electron.

single-stranded oligonucleotide as a free (unpaired) electron and a double-stranded oligonucleotide as a C–C bond. The complexes shown in Figure 3 may then be termed ethane-1,1,2,2-tetrayl (a), ethene-1,2-diyl (b), and acetylene (c). Complementary trisiliconucleotidyls, when processed according to the above-mentioned annealing protocol, always give rise to a series of bands whose mobilities linearly decrease with the logarithm of complex molecularity.^[5b] Thus, if the band of highest mobility is assigned to nano-acetylene, the next band is consistent with nano-cyclobutadiene. Beginning with the third band, there are no longer single possibilities for the assignment of completely paired complexes, as, for example, 3:3 complexes may adopt either the topology of nano-benzene, or of nano-Dewar-benzene, or of both. Even more possibilities arise for higher complexes such as 4:4 complexes, among which nano-cubane and nano-cyclooctatetraene may exist. In any case, the first two members of the series remain rather safe to assign and are illustrated in Figure 4. Molecular modeling studies on the complex **H₃Ψ*****I₃Ψ** at least suggest that the case for nano-acetylene is possible, both geometrically and energetically (see the Supporting Information).



Figure 4. Models of complementary trisiliconucleotidyls (left), nano-acetylene (center), and nano-cyclobutadiene (right).

The gel of self-complementary trisiliconucleotidyls shows an alternating pattern of band intensities (Figure 5). Obviously, complexes from an even number of molecules are more highly populated than those from an odd number of mole-

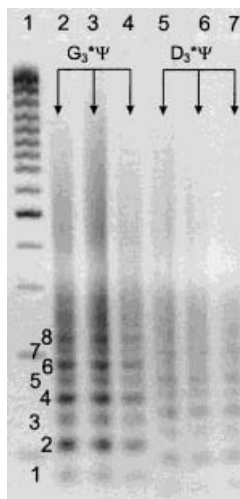


Figure 5. Agarose gel of self-complementary trisligonucleotidyls $G_3^*\Psi$ (lanes 2, 3, 4; 3.34, 2.20, 1.67 μM , respectively) and $D_3^*\Psi$ (lanes 5, 6, 7; 3.34, 2.20, 1.67 μM , respectively) after annealing in 100 mM NaCl, 5 mM MgCl_2 , and 10 mM phosphate buffer (pH 7.5), following the rapid hybridization protocol for complementary trisligonucleotidyls. Bands with high intensities are assigned to fully paired complexes from an even number of trisligonucleotidyls.

cules. When comparing the intensity profiles for 14-mer and 16-mer trisligonucleotidyls, $D_3^*\Psi$ and $G_3^*\Psi$, respectively (Figure 5), it becomes evident that the difference between the intensities becomes more pronounced with an increase in the chain length.^[5b] Finally, self-complementary tris-18-mers $J_3^*\Psi$ behave like mixtures of complementary tris-18-mers and show only bands for even-numbered complexes.^[5b] These data again underline our previous interpretation assuming maximal interstrand pairing, which can only occur in even-numbered complexes. Self-complementary sequences may formally also exhibit intrastrand or intramolecular pairing, such as hairpins or loops. Such behaviour was considered in the design of the sequences which were selected to bear always a CG-rich central core, thus favouring interstrand pairing at the cost of intrastrand pairing. In any case, the number of pairing possibilities for such complexes exceeds that for complementary systems. As such, it is not possible to assign any binding topology, at least for the odd-numbered complexes.

We have shown that trisligonucleotidyls are suitable building blocks for the noncovalent synthesis of superstructures based on DNA double-strand linkages. Similar experiments may be carried out using DNA-based molecules that were synthesized by other linking and branching strategies.^[7] Indeed, most recently, Shchepinov et al. reported a UV-melting study and claimed the formation of bimolecular complexes from complementary oligonucleotide dendrimers.^[8] Nanometer-sized objects of more complex topologies and structures, even irregularly shaped, should be addressable if one starts from a multicomponent mixture of trisligonucleotidyls in which each member consists of three or more individual sequences.^[5b] Those objects, when linked to other functional units, may find applications in DNA nanowiring and electronics.^[9] In any case, further experiments are needed to give more detailed insight into the structure of

such nanocomplexes. As conventional spectroscopic techniques are difficult to apply for such large systems, we will report on approaches towards their direct visualization in due course.

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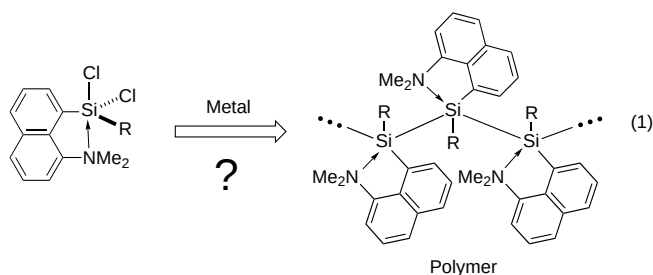
Keywords: DNA structures • hydrogen bonds • nanostructures • supramolecular chemistry

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Reaction of Hypercoordinate Dichlorosilanes Bearing 8-(Dimethylamino)-1-naphthyl Group(s) with Magnesium: Formation of the 1,2-Disilaacenaphthene Skeleton**

Kohei Tamao,* Masahiro Asahara, Tomoyuki Saeki, and Akio Toshimitsu*

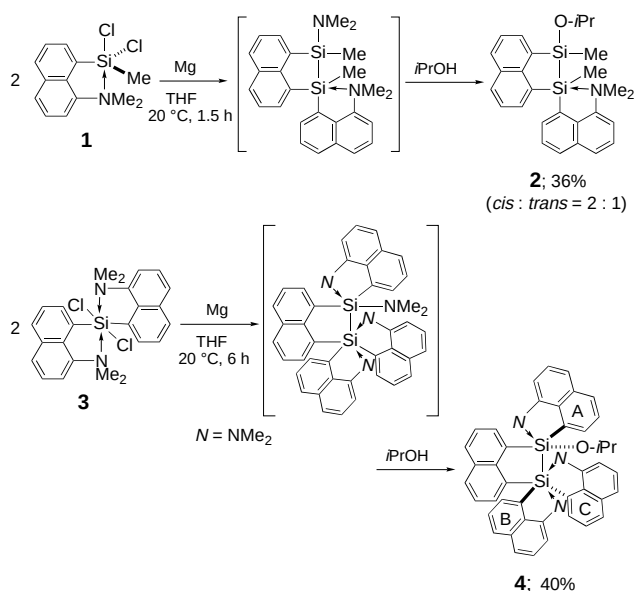
Recently, we found that a pentacoordinate monochlorosilane containing the 8-dimethylamino-1-naphthyl group undergoes reductive coupling with magnesium to form an Si–Si bond, which provided a new procedure for the direct interconnection of pseudo-pentacoordinate silicon atoms.^[1] We anticipated that a similar magnesium reduction of a pentacoordinate dichlorosilane containing the same aminonaphthyl group would give polysilanes in which all the silicon atoms are pentacoordinate^[2] [Eq. (1)]. However, contrary to



our expectation, the reaction actually afforded no polysilanes but only a dimeric product that contained a 1,2-disilaacenaphthene skeleton arising from Si–Si and Si–C bond formation and amino group migration from the naphthyl carbon atom to a silicon atom (Scheme 1).

The pentacoordinate dichlorosilane **1** bearing an 8-(dimethylamino)-1-naphthyl group was treated with two equivalents of magnesium. After quenching with isopropyl alcohol, the dimerized product 1-isopropoxy-1,2-disilaacenaphthene (**2**) bearing only one 8-(dimethylamino)-1-naphthyl group was obtained as a mixture of stereoisomers (*cis:trans* = 2:1). The structure of this unexpected product was confirmed by X-ray crystallography on *cis*-**2** (Figure 1)^[4a] and by ¹H, ¹³C, and ²⁹Si NMR spectra of *cis*- and *trans*-**2**. It is noteworthy that the coordination number of one of the two silicon atoms is lowered from five to four.

Hexacoordinate dichlorosilane **3** bearing two 8-(dimethylamino)-1-naphthyl groups also reacted with magnesium to afford, after treatment with isopropyl alcohol, 1-isopropoxy-1,2-disilaacenaphthene (**4**), which bears three 8-(dimethylamino)-1-naphthyl groups, as the major product (Scheme 1).



Scheme 1. Formation of the disilaacenaphthenes **2** and **4** from **1** and **3**.

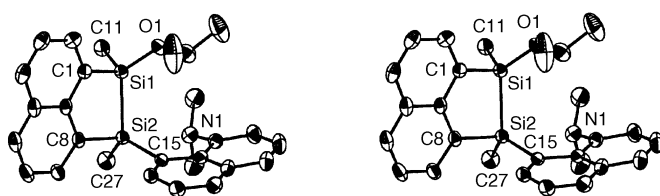


Figure 1. X-ray structure of *cis*-**2** drawn in stereoview at 30% probability level. All hydrogen atoms are omitted for clarity. Selected distances [Å] and angles [°]: Si1–Si2 2.3469(8), Si2...N1 2.828(2); N1...Si2–C8 177.16(8) Si1–Si2–C8 89.43(8), Si1–Si2–C15 113.56(7), Si1–Si2–C27 119.14(9), Si2–Si1–O1 122.01(7), Si2–Si1–C1 93.75(7), Si2–Si1–C11 114.07(9).

The structure of this crowded molecule was also determined by X-ray crystallography (Figure 2).^[4b] One silicon atom is again pentacoordinate while the other is hexacoordinate.^[2] Compound **4** is the first disilane composed of hexacoordinate and pentacoordinate silicon centers.

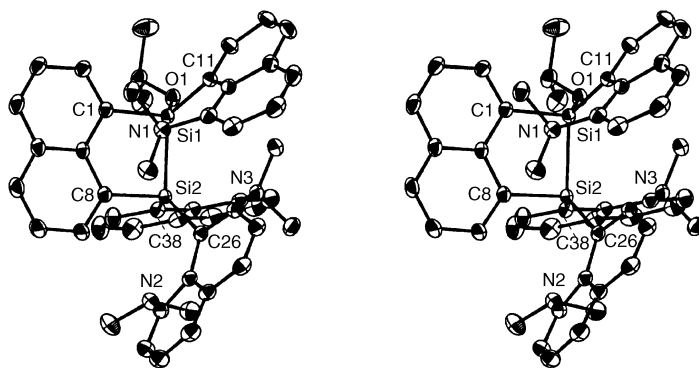


Figure 2. X-ray structure of **4** drawn in stereoview at 30% probability level. All hydrogen atoms are omitted for clarity. Selected distances [Å] and angles [°]: Si1–Si2 2.3641(6), Si1...N1 3.078(2), Si2...N2 3.147(2), Si2...N3 2.970(2); O1–Si1...N1 168.06(6), Si2–Si1–O1 107.17(5), Si2–Si1–C1 94.35(6), Si2–Si1–C11 127.54(6), Si1–Si2...N2 171.97(4), N3...Si2–C8 175.84(7), Si1–Si2–C8 89.14(6), Si1–Si2–C26 122.15(6), Si1–Si2–C38 104.17(6).

[*] Prof. Dr. K. Tamao, Dr. A. Toshimitsu, Dr. M. Asahara, T. Saeki
Institute for Chemical Research, Kyoto University
Uji, Kyoto, 611-0011 (Japan)
Fax: (+81) 774-38-3186
E-mail: tamao@scl.kyoto-u.ac.jp
akiot@scl.kyoto-u.ac.jp

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Interestingly, in these reactions, one silicon atom became bonded to the naphthyl carbon atom that bore the amino group. The amino group migrated to the coordinated silicon atom to afford an aminosilane with a lower coordination number and was finally substituted by the isopropoxyl group during workup with isopropyl alcohol.

Two types of reactions of hypercoordinate dihalosilanes with alkali or alkali earth metals have been reported. One is the conventional silicon–silicon bond formation observed by Belzner et al. in the reaction of a hypercoordinate dichlorosilane bearing 2-[(dimethylamino)methyl]phenyl group(s) with magnesium to afford the corresponding cyclic trisilane.^[5] The other is cyclization by Si–C_{benzyl} bond formation and migration of the amino group from the benzyl carbon atom to the silicon atom without silicon–silicon bond formation. Thus, Corriu, Auner et al. reported the reaction of a pentacoordinate difluorosilane bearing the 8-[(dimethylamino)methyl]-1-naphthyl group with lithium or lithium naphthalenide to afford a 1-silaacenaphthene derivative.^[6] Both silicon–silicon bond formation and amino-group migration proceeded concomitantly and selectively in the reaction of **1** and **3** with magnesium to afford 1-amino-1,2-disilaacenaphthene derivatives. These results indicate that the course of the reaction depends on the structure of the aminoaryl groups and suggest the possibility of developing new types of reactions by the introduction of new intramolecular coordinating groups.

Some structural aspects of the new 1,2-disilaacenaphthene derivatives **2** and **4** are as follows: The Si1–Si2 bond lengths (2.3469(8) in **2** and 2.3641(6) Å in **4**) are shorter than expected and comparable to that of 2.338(2) Å in 1,1,2,2-tetramethyl-1,2-disilaacenaphthene, which contains two tetravalent silicon centers,^[7] presumably because the Si–Si bonds are incorporated in the rather rigid five-membered ring of the acenaphthene skeleton.

One of the silicon atoms in **2** (Si2) is pentacoordinate, as indicated by the Si2⋯N1 distance of 2.828(2) Å, the N1⋯Si2–C8 angle of 177.16(8)°, and the pentacoordinate character %TBP_c and %TBP_a of 77% and 54%, respectively (see ref. [8] for details of definitions of %TBP_c and %TBP_a). Although Si2 in **2** bears no electronegative ligand, these parameters are similar to those of pentacoordinate silicon compounds bearing the same aminoaryl group and a fluorine or oxygen atom.^[9] The Si1–Si2–C8 bond angle of 89.43(8)° in the 1,2-disilaacenaphthene skeleton^[7] of **2** seems suitable to occupy the axial/equatorial positions in the trigonal bipyramidal geometry and thus favors the coordination of the amino group.

In **4**, two aminonaphthyl groups *cis* to each other (labeled A and B in Scheme 1) are highly distorted, as evidenced by the large Si–C1⋯C8–N and C1–C2–C3/C6–C7–C8 dihedral angles^[10] of 29.3 and 13.1°, respectively, in group A, and of 34.1 and 14.7°, respectively, in group B. The coordination of the nitrogen atoms to the silicon centers is weak, as shown by Si⋯N distances of 3.078(2) Å at the pentacoordinate silicon center bearing group A and 3.147(2) Å at the hexacoordinate silicon center bearing group B. These structural features may be ascribed to steric hindrance. In contrast, aminonaphthyl group C is free of distortion,^[11] as shown by the small Si–C1⋯

C8–N and C1–C2–C3/C6–C7–C8 dihedral angles^[10] of 4.5 and 5.8°, respectively. Regardless of the hexacoordination of this silicon center, the Si2⋯N3 distance (2.970(2) Å) is shorter than that of the pentacoordinate silicon center (Si1⋯N1 3.078(2) Å) described above.

Mechanistic studies on this reaction are now in progress.^[12]

Experimental Section

2: A solution of **1** in benzene (1.61 mmol g^{−1}, 0.62 g, 1.0 mmol) was added to a suspension of magnesium powder (49 mg, 2.0 mmol) in THF (2 mL) at 20 °C under a nitrogen atmosphere. After stirring for 1.5 h at this temperature, triethylamine (0.28 mL, 2.0 mmol) and isopropyl alcohol (0.46 mL, 6.0 mmol) were added, and the resulting mixture was stirred for 2 h. [In another experiment, the ¹H NMR spectrum of this mixture with triphenylsilane as internal standard indicated the presence of *cis*- and *trans*-**2** in 52% yield (*cis:trans* ≈ 2:1), dimethylaminonaphthalene in about 20% yield, and very weak signals of an unidentified compound(s).] After concentration under reduced pressure, hexane was added to the residual oil, and the precipitate thus formed was removed by filtration. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel with hexane/ethyl acetate (10:1; R_f = 0.48) as eluent to afford crude **2**. Further purification by HPLC with hexane/ethyl acetate (50/1) as eluent afforded *cis*-**2** (49 mg, 0.11 mmol, 22% yield) and *trans*-**2** (30 mg, 0.068 mmol, 14% yield). *cis*-**2**: m.p. 172–173 °C (from hexane/ethyl acetate (50/1)); ¹H NMR (270 MHz, C₆D₆): δ = 0.59 (s, 3H), 0.59 (d, ³J(H,H) = 5.9 Hz, 3H), 0.83 (s, 3H), 0.89 (d, ³J(H,H) = 5.9 Hz, 3H), 2.61 (s, 3H), 2.75 (s, 3H), 3.77 (sept, ³J(H,H) = 5.9 Hz, 1H), 7.15–7.24 (m, 2H), 7.34 (d, ³J(H,H) = 7.6 Hz, 1H), 7.50–7.59 (m, 3H), 7.67 (d, ³J(H,H) = 7.8 Hz, 1H), 7.82–7.91 (m, 3H), 7.96 (d, ³J(H,H) = 6.5 Hz, 1H), 8.15 (d, ³J(H,H) = 7.0 Hz, 1H); ¹³C NMR (67.94 MHz, C₆D₆): * denotes two overlapping signals: δ = 0.26, 0.44, 25.40, 25.90, 45.77, 50.61, 66.73, 117.02, 125.66, 125.92*, 126.19, 126.26, 128.52, 129.87, 130.39, 131.45, 132.67, 133.41, 134.02, 135.44, 135.60, 138.17, 141.10, 146.36, 148.32, 153.30; ²⁹Si NMR (53.67 MHz, C₆D₆, TMS): δ = −37.55, 4.33; elemental analysis calcd (%) for C₂₇H₃₁NOSi₂: C 73.42, H 7.07, N 3.17; found: C 73.42, H 6.90, N 3.09. *trans*-**2**: m.p. 142–143 °C (from hexane/ethyl acetate (50/1)); ¹H NMR (270 MHz, C₆D₆): δ = 0.36 (s, 3H), 0.91 (s, 3H), 1.09 (d, ³J(H,H) = 5.9 Hz, 3H), 1.20 (d, ³J(H,H) = 5.9 Hz, 3H), 2.60 (s, 3H), 2.73 (s, 3H), 4.04 (sept, ³J(H,H) = 5.9 Hz, 1H), 7.05 (t, ³J(H,H) = 7.4 Hz, 1H), 7.15 (d, ³J(H,H) = 7.3 Hz, 1H), 7.33 (t, ³J(H,H) = 7.7 Hz, 1H), 7.48 (t, ³J(H,H) = 7.4 Hz, 1H), 7.52–7.62 (m, 3H), 7.82–7.92 (m, 5H); ¹³C NMR (67.94 MHz, C₆D₆): * denotes two overlapping signals: δ = 1.05, 1.10, 26.12*, 47.09, 48.76, 66.83, 116.70, 125.83*, 126.01, 126.15, 126.28, 128.50, 129.71, 130.10, 131.34, 132.22, 133.23, 133.73, 135.48, 135.71, 138.01, 141.59, 146.04, 148.38, 153.05; ²⁹Si NMR (53.67 MHz, C₆D₆, TMS): δ = −37.35, 6.11; elemental analysis calcd (%) for C₂₇H₃₁NOSi₂: C 73.42, H 7.07, N 3.17; found: C 73.44, H 7.28, N 3.16.

4: After the reaction of magnesium powder (24 mg, 1.0 mmol) with **3** (0.23 g, 0.5 mmol) in THF (1 mL) at 20 °C for 6 h, the products were quenched with triethylamine (0.14 mL, 1.0 mmol) and isopropyl alcohol (0.23 mL, 3.0 mmol) at 20 °C for 1.5 h as described above. [In another experiment, the ¹H NMR spectrum of this mixture with triphenylsilane as internal standard indicated the presence of **4** in 70% yield and dimethylaminonaphthalene in 30% yield.] After workup as described above, recrystallization of the residual solid from hexane afforded pure **4** (74 mg, 0.10 mmol, 40% yield). **4**: m.p. 270–271 °C (from hexane/ethyl acetate (50/1)); ¹H NMR (270 MHz, C₆D₆): δ = −0.17 (d, ³J(H,H) = 5.1 Hz, 3H), 0.51 (s, 3H), 0.72 (s, 3H), 1.13 (d, ³J(H,H) = 5.9 Hz, 3H), 1.18 (s, 3H), 1.64 (s, 3H), 2.52 (s, 3H), 2.54 (s, 3H), 3.77 (sept, ³J(H,H) = 5.9 Hz, 1H), 6.56 (dd, ³J(H,H) = 7.8 Hz, 7.0 Hz, 1H), 6.74 (dd, ^{3,4}J(H,H) = 4.9, 0.8 Hz, 1H), 6.90 (dd, ³J(H,H) = 8.0, 6.6 Hz, 1H), 7.15–7.40 (m, 6H), 7.47–7.64 (m, 7H), 7.67 (dd, ^{3,4}J(H,H) = 8.0, 0.9 Hz, 1H), 7.72 (dd, ^{3,4}J(H,H) = 8.4, 1.4 Hz, 1H), 7.77 (dd, ^{3,4}J(H,H) = 8.2, 0.9 Hz, 1H), 7.83–7.94 (m, 3H), 8.22 (dd, ^{3,4}J(H,H) = 6.8, 1.4 Hz, 1H), 9.03 (dd, ^{3,4}J(H,H) = 7.3, 1.4 Hz, 1H); ¹³C NMR (67.94 MHz, C₆D₆): * denotes two overlapping signals: δ = 24.05, 26.40, 41.17, 43.28, 49.58, 50.12, 51.04, 51.29, 66.92, 117.04, 117.25, 120.42, 124.73, 125.22, 125.29, 124.45, 125.54*, 125.65, 125.72, 125.77, 126.31, 127.14, 128.74, 129.10, 129.15, 129.76, 130.75, 132.40, 133.19, 133.44, 134.04, 134.60, 135.08, 135.38, 135.74, 135.89, 136.07, 136.19, 137.09, 137.88, 139.12,

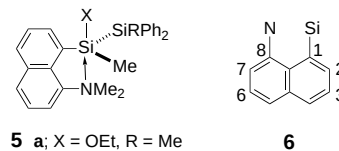
139.54, 140.81, 146.31, 147.41, 154.22, 154.38, 154.71; ^{29}Si NMR (53.67 MHz, C_6D_6 , TMS): $\delta = -21.54$, -11.52 ; elemental analysis calcd (%) for $\text{C}_{49}\text{H}_{49}\text{N}_3\text{OSi}_2$: C 78.25, H 6.57, N 5.59; found: C 78.27, H 6.55, N 5.49.

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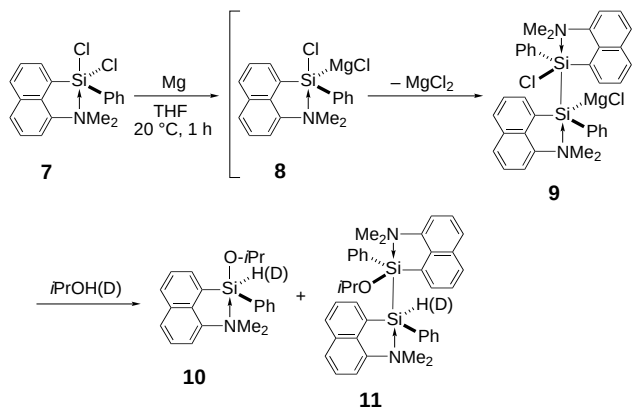
Keywords: heterocycles • hypervalent compounds • magnesium • silicon • rearrangements

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- [4] 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-120868 and 120869. 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). a) Crystal data for *cis*-**2**: $\text{C}_{27}\text{H}_{31}\text{NOSi}_2$, $M_r = 441.72$, crystal dimensions $0.5 \times 0.4 \times 0.3$ mm, monoclinic, space group $P2_1/n$ (no. 14), $a = 8.7570(3)$, $b = 36.023(1)$, $c = 8.8050(2)$ Å, $\beta = 118.604(2)^\circ$, $V = 2438.5601$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.20$ g cm⁻³, $\mu(\text{MoK}\alpha) = 1.64$ cm⁻¹, $2\theta_{\text{max}} = 50.2^\circ$. A Rigaku RAXIS-IV imaging plate area detector with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71070$ Å) at $T = 293$ K was used. A total of 3771 reflections was collected. The data were corrected for Lorentzian and polarization effects. A correction for secondary extinction was applied (coefficient = 4.40260×10^{-7}). The structure was solved by direct methods (SIR92) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included but not refined. The final cycle of the full-matrix least-squares refinement was based on 3271 observed reflections ($I > 3\sigma(I)$) and 281 variable parameters with the teXsan crystallographic software package. The structure was refined to a GOF of 1.47 and final residuals of $R_1 = 0.053$ and $wR_2 = 0.090$. The max./min. peaks on the final difference Fourier map corresponded to $0.50/-0.25$ e Å⁻³. b) Crystal data for **4**: $\text{C}_{49}\text{H}_{49}\text{N}_3\text{OSi}_2$, $M_r = 752.12$, crystal dimensions $0.6 \times 0.4 \times 0.3$ mm, monoclinic, space group $P2_1/n$ (no. 14), $a = 11.283(2)$, $b = 17.446(3)$, $c = 20.793(3)$ Å, $\beta = 99.562(8)^\circ$, $V = 4036.3000$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.238$ g cm⁻³, $\mu(\text{MoK}\alpha) = 1.29$ cm⁻¹, $2\theta_{\text{max}} = 55.2^\circ$. A Rigaku RAXIS-IV imaging plate area detector with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71070$ Å) at $T = 293$ K was used. A total of 8250 reflections was collected. The data were corrected for Lorentzian and polarization effects. A correction for secondary extinction was applied (coefficient = 6.56940×10^{-7}). The structure was solved by direct methods (SIR92) and expanded by using Fourier techniques (DIRDIF94). The non-hydrogen atoms were anisotropically refined. Hydrogen atoms were isotropically refined. The final cycle of the full-matrix least-squares refinement was based on 6100 observed reflections ($I > 3\sigma(I)$) and 693 variable parameters with the teXsan crystallographic software package. The structure was refined to a GOF of 1.27 and final residuals of $R_1 = 0.038$ and $wR_2 = 0.055$. The max./min. peaks on the final difference Fourier map corresponded to $0.28/-0.27$ e Å⁻³.
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- [10] For the numbering of naphthyl carbon atoms used to denote the dihedral angles, see formula **6**.
- [11] Note that the aminonaphthyl group in **2** is somewhat distorted, as shown by the Si-C1...C8-N and C1-C2-C3/C6-C7-C8 dihedral angles^[10] of 19.3 and 8.1°.
- [12] A similar reaction of phenyl-substituted pentacoordinate dichlorosilane **7** with magnesium followed by quenching with *i*PrOH(D) afforded not the disilaacenaphthene derivative but the pentacoordinate monosilane **10** and disilane **11**, each of which bears an *i*PrO group and an H(D) atom in yields of 30 and 29%, respectively. The ^{29}Si NMR spectrum of the reaction mixture before quenching showed three signals at $\delta = -45.89$, -40.23 , and -23.87 , which were assigned to precursors of **10** and **11**, most probably the silylenoid **8** and its self-condensation^[13] product **9**, on the basis of the high-field shift^[14] of the signals relative to the dihalide **7** ($\delta = -23.22$) and the unsymmetrical structure of the precursor of **11**. Similar species may also be involved in the reactions of **1** and **3** with magnesium as well.



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Organotitanium Fluorides as Matrices for Trapping Molecular ZnF_2 and MeZnF^{**}

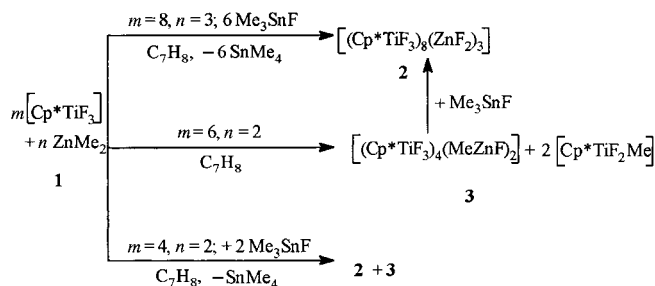
Peihua Yu, Peter Müller, Herbert W. Roesky,*
Mathias Noltemeyer, Alojz Demsar, and Isabel Usón

Dedicated to Professor Marianne Baudler

The understanding of forming single crystals from solution is still in its infancy. Moreover it is very often precisely this step which is rate-determining for the progress of the research work. Therefore we became interested in studying the behavior of "molecular solids". A leading strategy in our investigations is the HSAB (hard soft acid base) concept of Pearson.^[1] In recent years organometallic fluorides from metals of Group 4 have been extensively employed to act as complexing agents for inorganic compounds such as LiF , NaF , MgF_2 , CaF_2 , and Li_2O , which are insoluble in organic solvents. This gives rise to solids that are soluble in organic solvents. In these solids not only hard cations of Group 4, but also those of the alkali and alkaline earth metals are connected to the hard base fluoride.^[2–7] Hitherto it was not known whether organometallic fluorides for Group 4 metals could also complex the transition metal fluorides that are insoluble in organic solvents, and in which the cations have the characteristics of a soft acid. Herein we report on the first aggregates containing ZnF_2 and MeZnF soluble in organic solvents.

Although ZnF_2 does not react directly with organotitanium fluorides due to its high lattice energy and insolubility in organic solvents, zinc difluoride, prepared in situ from dimethylzinc and trimethyltin fluoride, has now been successfully trapped by $[\text{Cp}^*\text{TiF}_3]$ (**1**) ($\text{Cp}^* = \text{C}_5\text{Me}_5$)^[8] to form $[(\text{Cp}^*\text{TiF}_3)_8(\text{ZnF}_2)_3]$ (**2**) in moderate yield. The reaction of **1**, Me_3SnF , and ZnMe_2 in a molar ratio of 8:3:6 in toluene followed by removal of SnMe_4 and the solvent and recrystallization from toluene afforded red crystals of **2** at 0°C . If **1** was allowed to react with ZnMe_2 in a molar ratio of 3:1 in toluene, a red solution was formed immediately, and orange crystals of composition $[(\text{Cp}^*\text{TiF}_3)_4(\text{MeZnF})_2]$ (**3**) could be isolated. However, the reaction of **1**, ZnMe_2 , and Me_3SnF in a molar ratio of 4:2:2 in toluene only resulted in a mixture of **2** and **3**. Evidently, **3** is the intermediate for the formation of **2**. In the first step one fluorine atom of **1** is rapidly exchanged by one methyl group of ZnMe_2 to form **3** and the by-product $[\text{Cp}^*\text{TiF}_2\text{Me}]$. Subsequently, the remaining methyl groups at Zn in **3** can be easily exchanged by Me_3SnF to afford **2** (Scheme 1).

Compounds **2** and **3** are soluble in toluene and chloroform, however only slightly soluble in benzene and *n*-hexane. The melting points of **2** (155°C) and **3** (121°C) were found to be lower than that of the starting material **1** (189°C). In the gas phase only the ion $[(\text{Cp}^*\text{TiF}_3)]^+$ was observed (m/z 240) by



Scheme 1.

mass spectrometry for **2** and **3**. The ^1H NMR spectra display seven proton signals for **2** ($\delta = 2.07$ – 2.13 (Cp^*)) and two resonances for **3** ($\delta = 1.95$ (Cp^* , broad), -0.71 (MeZn)). The ^{19}F NMR spectrum of **2** in C_7D_8 gives seven resonances for the terminal fluorines ($\text{Ti}-\text{F}_\text{t}$) in the range from $\delta = 371.1$ to 305.8 and thirteen signals for the bridging fluorines ($\text{Ti}-\text{F}_\text{b}-\text{Ti}$ and $\text{Ti}-\text{F}_\text{b}-\text{Zn}$) in the range from $\delta = 178.1$ to 49.9 , while the ^{19}F NMR spectrum of **3** in C_6D_6 exhibits four signals for the fluorine atoms ($\delta = 121.8$ (TiF_b , broad), 83.8 ($\text{Ti}(\mu\text{-F})\text{Ti}$), -20 ($\text{Ti}(\mu\text{-F})\text{Zn}$), -40.0 ($\text{Ti}(\mu_3\text{-F})\text{Zn}$)). The ^{19}F NMR data indicate that the structures of **2** and **3** in solution are in accordance with those in the solid state.

The structures of **2** and **3** have been determined by X-ray single-crystal analysis; the central inorganic core of **2** and the molecular structure of **3** are shown in Figure 1 and Figure 2, respectively. Compounds **2** and **3**^[9] crystallize in the triclinic and monoclinic space group $P\bar{1}$ and $P2_1/n$, respectively. There is a pseudo-mirror plane in **2** that passes through the atoms $\text{Ti}(4)$, $\text{Ti}(5)$, $\text{F}(11)$, $\text{F}(13)$, $\text{F}(26)$, $\text{F}(15)$, and $\text{Zn}(2)$ (mean deviation $0.0179 \text{ \AA}$), excluding the seven terminal fluorine atoms ($\text{F}(1)$, $\text{F}(4)$, $\text{F}(7)$, $\text{F}(17)$, $\text{F}(21)$, $\text{F}(24)$), and containing the thirteen bridging fluorines. The whole molecule of **2** is in an asymmetric arrangement. The eight $[\text{Cp}^*\text{TiF}_3]$ molecules completely enclose three ZnF_2 molecules in such a way that each titanium atom is coordinated to five fluorine atoms and one Cp^* group to complete a distorted octahedral geometry. With the exception of $\text{Ti}(5)$ each titanium atom has a terminal fluorine atom. Moreover each zinc atom of **2** is coordinated to six fluorine atoms forming a distorted octahedral geometry. This geometry compares well with the rutile structure of ZnF_2 .^[10] The molecular structure of **3** shows the dimeric

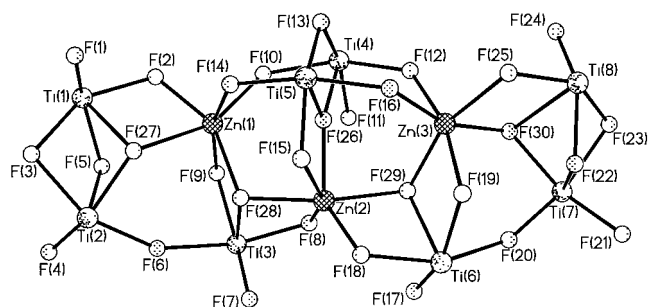


Figure 1. Structure of the inorganic core of **2** in the crystal. For clarity the Cp^* groups at Ti are omitted. Selected bond lengths [$\text{\AA}$]: $\text{Ti}-\text{F}_\text{t}$ 1.836* (1.823–1.849), $\text{Ti}-\text{F}_\text{b}$ 2.034* (1.912–2.317), $\text{Zn}-\text{F}$ 2.047* (1.924–2.260), $\text{Ti}(1)-\text{F}(2)$ 1.912, $\text{Ti}(1)-\text{F}(3)$ 2.008, $\text{Ti}(1)-\text{F}(5)$ 1.973, $\text{Ti}(1)-\text{F}(27)$ 2.257, $\text{Ti}(2)-\text{F}(27)$ 2.027(2), $\text{Ti}(3)-\text{F}(28)$ 2.139, $\text{Ti}(4)-\text{F}(26)$ 2.120, $\text{Ti}(5)-\text{F}(26)$ 2.132, $\text{Ti}(6)-\text{F}(29)$ 2.152, $\text{Ti}(7)-\text{F}(30)$ 2.030, $\text{Ti}(8)-\text{F}(30)$ 2.317. The values marked with a * are average values.

[*] Prof. Dr. H. W. Roesky, Dr. P. Yu, Dipl.-Chem. P. Müller,
Dr. M. Noltemeyer, Dr. A. Demsar, Dr. I. Usón
Institut für Anorganische Chemie der Universität
Tammannstrasse 4, D-37077 Göttingen (Germany)
Fax: (+49) 551-39-3373
E-mail: hroesky@gwdg.de

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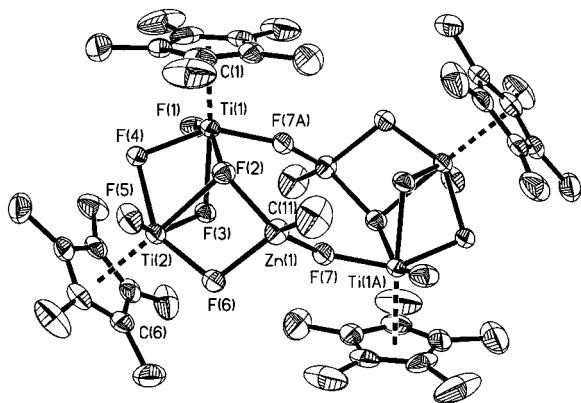


Figure 2. Molecular structure of **3** in the crystal. Selected bond lengths [Å] and angles [°]: Ti(1)–F(1) 1.820, Ti(2)–F(5) 1.823, Ti(1)–F(7A) 1.925, Ti(1)–F(4) 2.008, Ti(1)–F(2) 2.035, Ti(1)–F(3) 2.160, Ti(2)–F(6) 1.934, Ti(2)–F(4) 2.007, Ti(2)–F(3) 1.951, Ti(2)–F(2) 2.302, Zn(1)–F(7) 1.973, Zn(1)–F(6) 2.053, Zn(1)–F(2) 2.035, Zn(1)–C(11) 1.937; F(1)–Ti(1)–F(7A) 93.88, F(1)–Ti(1)–F(4) 92.47, F(4)–Ti(1)–F(7A) 148.24, F(1)–Ti(1)–F(2) 149.28, F(2)–Ti(1)–F(7A) 83.48, F(1)–Ti(1)–F(3) 80.25, F(5)–Ti(2)–F(3) 145.27, F(5)–Ti(2)–F(6) 89.74, F(5)–Ti(2)–F(4) 87.16, F(4)–Ti(2)–F(6) 143.59, F(3)–Ti(2)–F(6) 88.10, F(2)–Zn(1)–F(6) 77.97, F(2)–Zn(1)–F(7) 105.92, F(7)–Zn(1)–F(6) 89.54, Ti(2)–F(6)–Zn(1) 109.96, Ti(1)–F(2)–Zn(1) 143.97, Ti(1)–F(4)–Ti(2) 99.84, Ti(1A)–F(7)–Zn(1) 141.18, C(11)–Zn(1)–F(2) 118.32, C(11)–Zn(1)–F(6) 136.92, C(11)–Zn(1)–F(7) 119.14.

character of the $[(\text{Cp}^*\text{TiF})_2(\mu\text{-F})_4(\mu_3\text{-F})(\text{ZnMe})]$ units that are connected by two $\text{Ti}(\mu\text{-F})\text{Zn}$ bridges. Therefore, compound **3** is a centrosymmetric molecule with a center of inversion in the centroid of the eight-membered $\text{Ti}_2\text{F}_4\text{Zn}_2$ ring. The distorted tetrahedral environments of the Zn atoms in **3** are very different from those in **2**. The coordination sphere at Zn is formed by three of the bridging fluorines and one terminal methyl group. The titanium atoms in **3**, however, are similarly connected to those found in **2**, they are coordinated to five fluorine atoms and one Cp^* ligand to complete a distorted octahedral geometry. The average terminal Ti–F_b bond lengths (1.84 Å for **2** and 1.82 Å for **3**) are shorter than the bridging Ti–F_b distances (2.10 Å for **2** and 2.04 Å for **3**), in which the average μ_3 -bridging Ti–(μ_3 -F_b) distances (2.17 Å for **2** and 2.15 Å for **3**) are slightly longer than the μ -bridging Ti–(μ -F_b) ones (2.07 Å for **2** and 2.00 Å for **3**). The average Zn–F_b bond lengths (2.05 Å and 2.02 Å for **2** and **3**, respectively) are comparable to that found in CaZnF_4 (Zn–F, 1.93 Å).^[11]

In summary, we have demonstrated for the first time that ZnF_2 and MeZnF can be trapped as molecular solids. In compound **2** the Zn atoms are surrounded by six fluorine atoms as in the solid-state structure of ZnF_2 . Moreover, the small molecule MeZnF was isolated and characterized for the first time as an adduct.

Experimental Section

2: ZnMe_2 (0.5 mL, 1 mmol, 2.0 M solution in toluene) was added dropwise by syringe to a mixture of **1** (0.65 g, 2.7 mmol) and Me_3SnF (0.37 g, 2 mmol) suspended in toluene (40 mL) at room temperature. The bright red solution was stirred overnight until all the solid disappeared. All volatiles were removed under vacuum and the residue was recrystallized in toluene (15 mL) at room temperature to give red crystals of compound **2**, which were isolated at 0 °C in 40% yield (0.30 g) (based on **1**). M.p. 154–156 °C; EI-MS: m/z (%): 240 (30) [Cp^*TiF_3], 135 (100) [Cp^*]; ^1H NMR ($[\text{D}_8]\text{toluene}$): δ = 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13 (Cp^*); ^{19}F NMR ($[\text{D}_8]\text{toluene}$): δ = 371.1, 370.1, 353.6, 349.3, 326.5, 313.8, 306.1 (Ti–F), 188.7, 169.2,

149.2, 143.8, 140.1, 138.3, 131.2, 120.6, 115.8, 108.4, 103.7, 73.4, 49.9 (Ti–F_b–Ti, Ti–F_b–Zn); elemental analysis for $\text{C}_{80}\text{H}_{120}\text{F}_{30}\text{Ti}_8\text{Zn}_3$: calcd C 43.0, H 5.4, F 25.6; found: C 43.3, H 5.8, F 26.0.

3: ZnMe_2 (0.5 mL, 1 mmol, 2.0 M solution in toluene) was added dropwise by syringe to a solution of **1** (0.72 g, 3 mmol) in toluene (20 mL) at room temperature, and the resulting mixture was stirred for 12 h. The color changed from orange to bright red. After partial removal of the solvent, the solution was kept at –20 °C for several days, and red crystals of compound **3** could be isolated in a 30% yield (0.18 g) (based on **1**). M.p. 120–122 °C; EI-MS, m/z (%): 240 (40) [Cp^*TiF_3], 135 (100) [Cp^*]; ^1H NMR ($[\text{D}_8]\text{toluene}$): δ = 1.98 (s, 60H, Cp^*), –0.71 (s, 6H, ZnMe); ^{19}F NMR (C_6D_6): δ = 121.8 (s, 4F, Ti–F), 83.8 (s, 4F, Ti–F_b–Ti), –20 (s, 4F, Ti(μ -F)Zn), –40.0 (s, 2F, Ti(μ_3 -F)Zn); elemental analysis for $\text{C}_{42}\text{H}_{66}\text{F}_{14}\text{Ti}_4\text{Zn}_2$: calcd C 43.5, H 5.7, F 23.0; found C 43.7, H 5.6, F 22.8.

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- Crystal structure analyses: a) **2**: $\text{C}_{80}\text{H}_{120}\text{F}_{30}\text{Ti}_8\text{Zn}_3 \cdot 2\text{C}_7\text{H}_8 \cdot 0.5\text{C}_6\text{H}_6$, $M_r = 2230.95 + 2 \times 92.14 + 0.5 \times 78.11$, crystal size: $0.50 \times 0.30 \times 0.30 \text{ mm}^3$, triclinic, space group $P\bar{1}$, $a = 13.260(3)$, $b = 14.217(3)$, $c = 28.568(6)$ Å, $\alpha = 83.39(3)^\circ$, $\beta = 83.31(3)^\circ$, $\gamma = 86.06(3)^\circ$, $V = 5305.1(2)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.537 \text{ Mg m}^{-3}$, $F(000) = 2514$, $\lambda = 0.71073$ Å, $T = 133$ K, $\mu(\text{MoK}\alpha) = 1.327 \text{ mm}^{-1}$. The crystal was mounted on a glass fiber in a rapidly cooled perfluoropolyether.^[12] Diffraction data of **2** were collected on a Stoe-Siemens-Huber four-circle-diffractometer coupled to a Siemens CCD area-detector at 133(2) K, with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å), performing φ - and ω scans. Total number of reflections measured 52524, of which 14965 unique ($R_{\text{int}} = 0.0441$). Data/restraints/parameters: 14965/4589/1297, data collection range: $2.15 \leq \theta \leq 23.26^\circ$. Final R indices: $R1 = \Sigma |F_o| - |F_c| / \Sigma |F_o| = 0.0379$, $wR2 = [\Sigma_w(F_o^2 - F_c^2)^2 / \Sigma_w F_o^4]^{1/2} = 0.0814$ on data with $I > 2\sigma(I)$ and $R1 = 0.0528$, $wR2 = 0.0887$ on all data; goodness of fit $S = [\Sigma_w(F_o^2 - F_c^2)^2 / \Sigma(n-p)]^{1/2} = 1.069$; largest difference peak and hole: 0.610 and –0.396 e Å^{–3}. b) **3**: $\text{C}_{42}\text{H}_{66}\text{F}_{14}\text{Ti}_4\text{Zn}_2 \cdot \text{C}_7\text{H}_8$, $M_r = 1251.42$, crystal size: $0.70 \times 0.60 \times 0.50 \text{ mm}^3$, monoclinic, space group $P2_1/n$, $a = 9.7634(10)$, $b = 20.654(3)$, $c = 13.636(2)$ Å, $\beta = 94.457(11)^\circ$, $V = 2741.5(7)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.516 \text{ Mg m}^{-3}$, $F(000) = 1284$, $\lambda = 0.71073$ Å, $T = 153$ K, $\mu(\text{MoK}\alpha) = 1.495 \text{ mm}^{-1}$. The diffraction data of **3** were collected on a Stoe-Siemens-AED2 four-circle-diffractometer at 153(2) K, using $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å), performing $2\theta/\omega$ scans. Total number of reflections measured 9538, of which 4776 unique ($R_{\text{int}} = 0.0316$). Data/restraints/parameters: 4768/0/340, data collection range: $3.59 \leq \theta \leq 24.93^\circ$. Final R indices: $R1 = \Sigma |F_o| - |F_c| / \Sigma |F_o| = 0.0314$, $wR2 = [\Sigma_w(F_o^2 - F_c^2)^2 / \Sigma_w F_o^4]^{1/2} = 0.0819$ on data with $I > 2\sigma(I)$ and $R1 = 0.0379$, $wR2 = 0.0905$ on all data; goodness of fit $S = [\Sigma_w(F_o^2 - F_c^2)^2 / \Sigma(n-p)]^{1/2} = 1.042$; largest difference peak and hole: 0.410 and –0.309 e Å^{–3}. c) The structures were solved by direct methods using the program SHELXS-97^[13] and refined against F^2 on all data by full-

matrix least squares with SHELXL-97.^[14] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. 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 125050 and CCDC 125051. 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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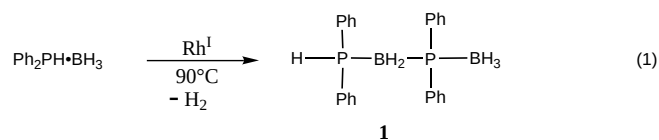
Rhodium-Catalyzed Formation of Phosphorus–Boron Bonds: Synthesis of the First High Molecular Weight Poly(phosphinoborane)**

Hendrik Dorn, Ryan A. Singh, Jason A. Massey, Alan J. Lough, and Ian Manners*

Virtually all currently known and commercially available polymers are based on extended catenated structures containing mainly carbon atoms together with a few other elements such as oxygen and nitrogen. In contrast, the development of extended structures based on atoms of other elements has been much less successful, and their synthesis still represents a substantial challenge.^[1, 2] Nevertheless, the relatively few inorganic polymers such as poly(siloxanes) (silicones) $[\text{R}_2\text{Si}-\text{O}]_n$, polyphosphazenes $[\text{R}_2\text{P}=\text{N}]_n$, polysilanes $[\text{R}_2\text{Si}]_n$, and more recently poly(silynes), poly(stannanes), sulfur-containing polymers, poly(metallocenes), and other metallocopolymers illustrate the potential for accessing materials with fascinating and unexpected properties as well as significant applications.^[1–5] As part of a continuing program to develop novel extended chain structures based on main group elements we have explored compounds with skeletons comprising four-coordinate phosphorus and boron atoms. We were encouraged by previous reports that known cyclic compounds such as the six-membered ring $[\text{Me}_2\text{P}-\text{BH}_2]_3$ show considerable thermal and hydrolytic stability.^[6]

Thermally induced dehydrocoupling of phosphane–borane adducts $\text{R}_2\text{PH}\cdot\text{BH}_3$ at elevated temperatures (150–200 °C) has been previously used to prepare cyclic phosphinoborane species (mainly six-membered rings of the type $[\text{R}_2\text{P}-\text{BH}_2]_3$).^[6] In addition, in a few cases low yields of “polymeric” materials have been claimed, but none have been convincingly structurally characterized (by present day standards) and, where reported, the molecular weights were very low.^[7, 8] We have reinvestigated this “dehydrocoupling chemistry” (coupling with elimination of hydrogen) with the idea that if lower temperatures could be used and more efficient coupling reactions identified, then linear, high polymeric structures might indeed result.^[9, 10]

The phosphane–borane adduct $\text{Ph}_2\text{PH}\cdot\text{BH}_3$ undergoes dehydrocoupling at 180–190 °C to exclusively and quantitatively yield the cyclic trimer $[\text{Ph}_2\text{P}-\text{BH}_2]_3$.^[11] However, on addition of about 0.3 mol % of a Rh^{I} catalyst such as $[\text{Rh}(1,5\text{-cod})][\text{OTf}]$ or $[\{\text{Rh}(\mu\text{-Cl})(1,5\text{-cod})\}_2]$ (1,5-cod = cycloocta-1,5-diene) dehydrocoupling of the neat adduct is observed at 90 °C over 14 h to form a white, crystalline, air-stable product [Eq. (1)]. A ^{31}P NMR spectrum of the new compound showed



the presence of two different phosphorus environments ($\delta = -3.3$ and -17.7). Additional characterization by ^{11}B and ^1H NMR spectroscopy, mass spectrometry, and single-crystal X-ray diffraction (Figure 1) identified the product as the

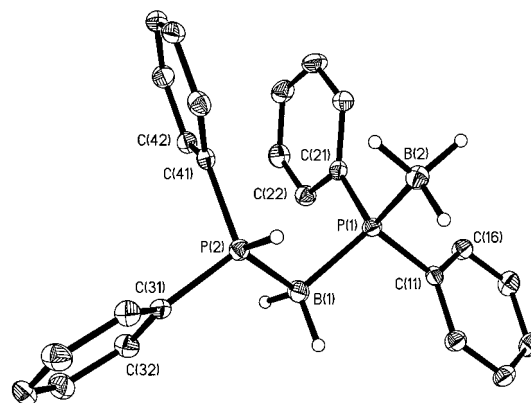


Figure 1. Molecular structure of **1** (thermal ellipsoids at the 30% probability level). Selected bond lengths [Å] and angles [°]: P(1)–B(2) 1.932(2), P(1)–B(1) 1.944(2), P(2)–H(1P) 1.349(19), P(2)–B(1) 1.923(2); B(2)–P(1)–B(1) 113.01(11), H(1P)–P(2)–B(1) 112.6(8), P(2)–B(1)–P(1) 109.23(12).

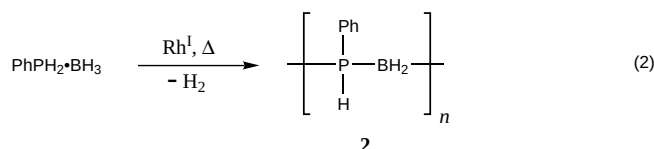
novel linear dimer **1**.^[12, 13] Notably, the P–B bonds in **1** (1.92–1.94 Å) are long compared to carbon–carbon bonds (ca. 1.54 Å) and have lengths typical of single bonds between four-coordinate phosphorus and boron centers.

Encouraged by this result and based on our view that the prospective polymer $[\text{Ph}_2\text{P}-\text{BH}_2]_n$ might be insoluble and that the anticipated steric congestion at phosphorus in the case

[*] Prof. I. Manners, Dr. H. Dorn, R. A. Singh, J. A. Massey, Dr. A. J. Lough
 Department of Chemistry, University of Toronto
 Toronto, M5S 3H6 Ontario (Canada)
 Fax: (+1) 416-978-6157
 E-mail: imanners@alchemy.chem.utoronto.ca

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described above [Eq. (1)] could disfavor polymer formation, we moved on to explore the dehydrocoupling of the analogous primary phosphane–borane adduct $\text{PhPH}_2 \cdot \text{BH}_3$.^[14] In this case, dehydrocoupling occurred in solution in refluxing toluene (110 °C, 14 h, ca. 0.3 mol % $[\text{Rh}(1,5\text{-cod})_2][\text{OTf}]$). An off-white polymeric product was isolated by precipitation into hexanes and was subsequently identified as poly(phenylphosphinoborane) [**2**; Eq. (2)].



Thus, the ^{31}P NMR spectrum of **2** showed a broad singlet at $\delta \approx -48.9$, which split into a doublet ($J_{\text{PH}} = 360$ Hz) in the ^1H -coupled spectrum and is characteristic of a single hydrogen substituent at phosphorus (Figure 2). The ^1H NMR spectrum of **2** was also consistent with the assigned structure: It contains

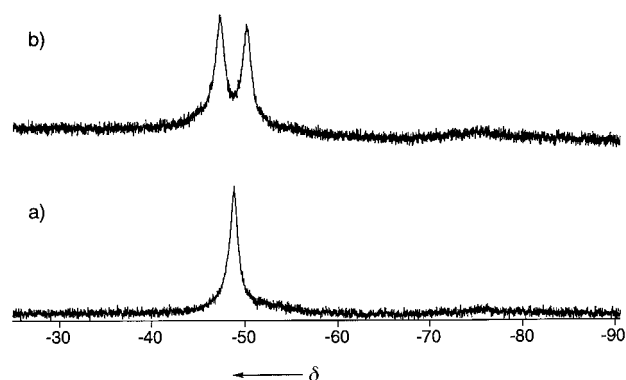


Figure 2. ^{31}P NMR spectra of polymer **2** (121 MHz) in CDCl_3 : a) ^1H -decoupled; b) ^1H -coupled, $J_{\text{PH}} = 360$ Hz.

broad peaks for the phenyl group ($\delta = 6.65\text{--}7.90$) and the BH_2 protons ($\delta = 0.65\text{--}2.20$) as well as a broad doublet at $\delta = 4.25$ ($J_{\text{PH}} = 360$ Hz) for the PH group. The ^{11}B NMR spectrum of **2** showed a single broad resonance at $\delta = -34.7$, which is characteristic for a four-coordinate boron center attached to two phosphorus atoms.^[15] Further characterization of **2**, which is air- and moisture-stable, was achieved by ^{13}C NMR and IR spectroscopy as well as elemental analysis, which also afforded data consistent with the assigned structure.

The absolute weight average molecular weight (M_w) of **2** prepared by this solution method was determined by static light scattering in THF and was found to be relatively low ($M_w = 5600$), corresponding to a weight average degree of polymerization (DP_w) of 46.^[16] To obtain higher molecular weights by increasing the extent of reaction, $\text{PhPH}_2 \cdot \text{BH}_3$ and a Rh^I catalyst were heated in the absence of solvent at slightly elevated temperatures (3 h at 90 °C and 3 h at 130 °C). This yielded a polymeric product **2** which was spectroscopically identical to that prepared in toluene. However, in this case the high molecular weight nature of **2** was confirmed by static light scattering, which afforded an absolute value of $M_w = 31\,000$, corresponding to $DP_w = 254$ (Figure 3).^[16]

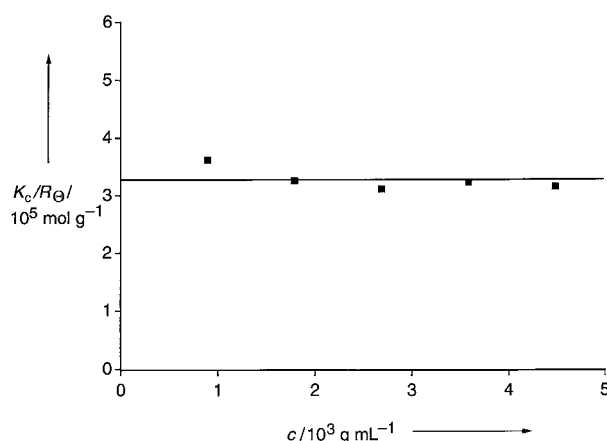


Figure 3. Low-angle laser light scattering plot for **2** in THF at 22 °C (K = optical constant, c = concentration, R_θ = Rayleigh ratio). The absolute molecular weight M_w is determined as the inverse of the intercept on the y axis.^[17]

In contrast to the situation for $\text{Ph}_2\text{PH} \cdot \text{BH}_3$, the dehydrocoupling of $\text{PhPH}_2 \cdot \text{BH}_3$ proceeds at a similar temperature in the absence of added catalyst. However, the rate is substantially slower and the observed molecular weights were considerably lower, which indicates that P–B chain formation is much less efficient than in the catalyzed process.^[14]

In summary, novel and facile transition metal catalyzed P–B bond formation reactions have been discovered and the first, well-characterized, high molecular weight poly(phosphinoborane) (**2**) has been isolated as an air and moisture stable solid. Future work will focus on the further development of this new area of inorganic high polymer chemistry and on the dehydrocoupling mechanism. In addition, detailed studies of the physical properties of polymers such as **2**, which can be regarded as an analogue of polystyrene with a phosphorus–boron backbone, should be very revealing from a fundamental perspective, and useful properties such as flame retardancy and oxidative stability may emerge.

Experimental Section

Reactions were performed under nitrogen using dry solvents. Workup of **2** was carried out in air. Light scattering experiments were carried out in THF at 22 °C and were performed as described in detail elsewhere.^[17] The refractive index increment (dn/dc) for **2** was determined to be 0.24 mL g^{-1} . Low-angle laser light scattering experiments were performed on solutions in THF that had been left undisturbed for 24 h.

Synthesis of 1: Neat $\text{Ph}_2\text{PH} \cdot \text{BH}_3$ (0.625 g, 3.12 mmol) and $[\text{Rh}(1,5\text{-cod})_2][\text{OTf}]$ (ca. 4 mg, 0.3 mol %) were heated at 90 °C for 14 h. The reaction mixture became liquid upon heating and solidified when cooled to room temperature. Recrystallization from diethyl ether (10 mL) gave colorless crystals of air-stable **1**. Yield 0.530 g (85 %). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.68\text{--}7.17$ (m, 20H, aromatic), 6.71 (dm, 1H, $J_{\text{PH}} = 397$ Hz, PH), 2.24 (br, 2H, BH_2), 1.01 (br q, 3H, $J_{\text{BH}} = 75$ Hz, BH_3); $^{11}\text{B}\{^1\text{H}\}$ NMR (160 MHz, CDCl_3): $\delta = -33.2$ (br, BH_2), -37.3 (br, BH_3); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3): $\delta = -3.3$ (br, Ph_2PH), -17.7 (br, Ph_2P); MS (EI, 70 eV): m/z (%): 395 (16) [$M^+ - 3\text{H}$], 384 (100) [$M^+ - \text{BH}_3$].

Synthesis of low molecular weight 2: In a typical experiment $\text{PhPH}_2 \cdot \text{BH}_3$ (1.025 g, 8.27 mmol) and $[\text{Rh}(1,5\text{-cod})_2][\text{OTf}]$ (ca. 10 mg, 0.3 mol %) were dissolved in toluene (15 mL), and the resulting solution was refluxed for 14 h. The reaction mixture was then concentrated under vacuum to ca. 5 mL, filtered, and precipitated into 120 mL of hexanes. The off-white polymeric product **2** was washed with hexanes, decanted, and dried in

vacuo. Yield 0.678 g (67%). Static light scattering (THF): $M_w = 5600$, $DP_w = 46$; the second virial coefficient A_2 was found to be zero. ^1H NMR (300 MHz, CDCl_3): $\delta = 6.65\text{--}7.90$ (br, Ph), 4.25 (br d, $J_{\text{PH}} = 360$ Hz, PH), 0.65–2.20 (br, BH_2); $^{11}\text{B}\{^1\text{H}\}$ NMR (160 MHz, CDCl_3): $\delta = -34.7$ (brs); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): $\delta = 132.5$ (br, *o*-Ph), 129.3 (br, *p*-Ph), 128.2 (br, *m*-Ph); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3): $\delta = -48.9$ (brs); ^{31}P NMR (121 MHz, CDCl_3): $\delta = -48.9$ (br d, $J_{\text{PH}} = 360$ Hz); IR (nujol): $\tilde{\nu}(\text{B-H}) = 2417, 2378\text{ cm}^{-1}$, $\tilde{\nu}(\text{P-H}) = 2213\text{ cm}^{-1}$; elemental analysis calcd for $\text{C}_6\text{H}_8\text{BP}$: C 59.1, H 6.6; found: C 58.9, H 6.5.

Synthesis of high molecular weight **2**: In a typical experiment, neat $\text{PhPH}_2 \cdot \text{BH}_3$ (1.22 g, 9.84 mmol) and $[\text{Rh}(\mu\text{-Cl})(1,5\text{-cod})]_2$ (ca. 15 mg, 0.3 mol %) were heated for 3 h at 90°C and for a further 3 h at 130°C . After cooling to room temperature, the yellow solid was dissolved in CH_2Cl_2 (15 mL), and the solution was filtered and precipitated into hexanes (250 mL). The off-white polymeric product was washed with hexanes, decanted, and dried under vacuum at 50°C for 48 h. Yield 0.90 g (75%). The ^1H , ^{11}B , and ^{31}P NMR and IR spectra are as described above. Static light scattering (THF): $M_w = 31\,000$, $DP_w = 254$; the second virial coefficient A_2 was found to be zero.

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Preparation of a Completely Oriented Molecular Sieve Membrane

Takayuki Ban,* Takafumi Ohwaki, Yutaka Ohya, and Yasutaka Takahashi*

It would be of significant interest if the microstructure of materials could be controlled by modification of the molecular structures of the starting materials. It has been shown that organic compounds influence the crystallization of zeolites.^[1–7] For instance, the addition of triethanolamine (TEA) to the reaction mixture for the synthesis of LTA-type zeolite ($\text{NaAlSi}_3\text{O}_8 \cdot x\text{H}_2\text{O}$) allows the growth of giant crystals^[4–7] as a result of modification of the molecular structure of the Al species by TEA.^[6,7] Zeolites are especially interesting because they can provide unique molecular selectivity to devices such as chemical sensors and catalyst membranes.^[8–11] If a continuous zeolite coating with oriented channels were realized, a novel device in which the oriented channels could effectively control the access of molecules to the underlying surface could be constructed. So far, most zeolite films and membranes have random or partial orientation^[12–23] or large voids between oriented particles.^[24–26] The control of nucleation and crystal growth of zeolites is of great importance for the preparation of continuous oriented zeolite films and membranes. This objective may be achieved by introducing organic compounds that modify the molecular structure of the starting materials and lead to better control of crystallization.

Here we show that a completely oriented and continuous LTA-type zeolite membrane can be prepared by intergrowth of oriented seed crystals, which were attached to a glass plate by dip-coating from a suspension of seed crystals (Figure 1). An organic ligand was then used to preferentially enhance the growth of the seeds.

The seed crystals of LTA-type zeolite were prepared from an aqueous mixture of NaAlO_2 , $\text{Na}_2\text{SiO}_3 \cdot 9\text{H}_2\text{O}$, and

$\text{N}(\text{C}_2\text{H}_4\text{OH})_3$ (TEA) by hydrothermal treatment. Only loose crystals were formed when the aqueous mixture was used without addition of an organic ligand such as TEA. The addition of TEA led to the formation of crystals with a cubic morphology. The size distribution of the particles was uniform, and the average edge length of the cubes was about 10 μm . The powder X-ray diffraction (XRD) pattern of the product (see Figure 3a) was consistent with that of LTA-type zeolite.

The seed crystals were attached to a glass substrate (Corning #1737) by the dip-coating method. The substrate was dipped into an aqueous suspension of seed crystals with a concentration of 180 g L^{-1} , withdrawn at a rate of 2 cm min^{-1} , and then dried at 110 $^\circ\text{C}$ for 10 min. To increase the number of crystals attached to the plate and thus maximize the coverage of the plate, the dip coating was conducted on a tilted substrate as shown in Figure 1. Figure 2 shows optical micrographs of seed layers that were dip-coated onto substrates

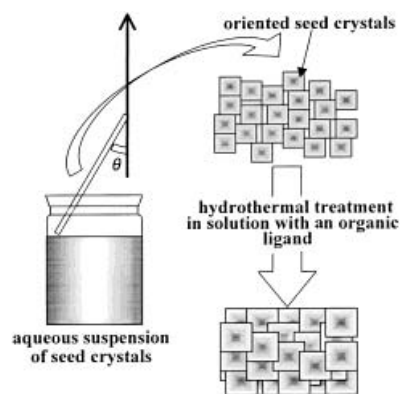


Figure 1. Schematic diagrams of the attachment of seed crystals to the substrate and the growth of oriented seeds to give a completely oriented molecular sieve membrane.

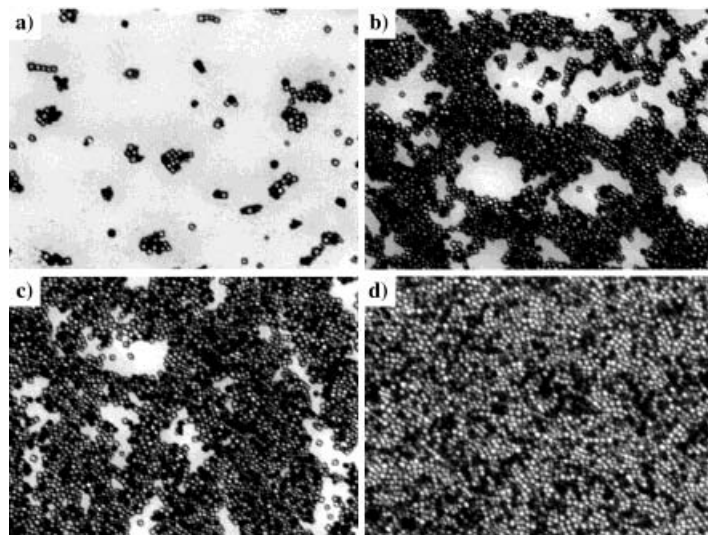


Figure 2. Variation of the amount of seed crystals attached to the substrate with the tilt angle of the substrate in the dip coating process. a) 0 $^\circ$, b) 15 $^\circ$, c) 30 $^\circ$, and d) 45 $^\circ$. Scale bar: 300 μm .

tilted by 0 to 45 $^\circ$. The number of seeds attached to the substrates increased with increasing tilt angle of the substrate. Large interparticle voids were no longer observed at a tilt angle of 45 $^\circ$. Attachment of the seeds occurred only on the upper side of the substrate. Therefore, the substrate was coated once on each side. In the second coating step, no seeds were removed from the lower surface of the substrate. Scanning electron microscopy (SEM) showed that a single layer of seeds was attached to the substrate with good orientation of the (100) plane parallel to the substrate surface. This indicates that the bonding between the substrate and the seeds is much stronger than that between the seeds. As shown in Figure 3b, the XRD pattern of the seed-coated substrate exhibited only the peaks with (*h*00) plane indices; this supports the above observations. The LTA-type zeolite has a channel in the (100) direction, which is perpendicular to the (100) plane due to the cubic symmetry of LTA-type zeolite.^[27]

[*] Dr. T. Ban, T. Ohwaki, Dr. Y. Ohya, Prof. Y. Takahashi
Department of Chemistry, Gifu University
1-1 Yanagido, Gifu 501-1193 (Japan)
Fax: (+81) 58-230-1893
E-mail: ban@apchem.gifu-u.ac.jp
takahashi@apchem.gifu-u.ac.jp

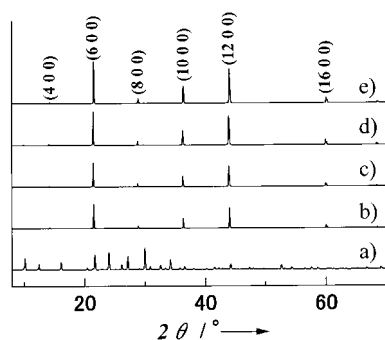


Figure 3. XRD patterns of the seed crystals (a), of the seed crystals attached to the substrate (b), and of the specimens heat-treated in the suspension with bis-tris/Al ratios of 0 (c), 2 (d), and 4 (e).

Therefore, in such an arrangement of the seed crystals on the substrate, the channels are normal to the surface.

The substrates with oriented seeds were hydrothermally treated in the aqueous reaction mixture to fill the spaces between the seeds by intergrowth. The chemical composition of the synthesis mixture was the same as that of the seeds, except that instead of TEA, 2,2-bis(hydroxymethyl)-2,2',2''-nitrilotriethanol (bis-tris) was used as the organic ligand. The bis-tris/Al molar ratio was varied from 0 to 4. Our preliminary study showed that the addition of bis-tris to the starting mixture led to greater growth of zeolite particles than TEA because the ability of bis-tris to form an aluminum complex is greater. This result was confirmed by liquid-state NMR measurements on a suspension containing the precipitate of silica gel. After the precipitate had settled, the seeded substrate was placed horizontally and was hydrothermally treated without stirring at 90 °C for one week. On the upper side of the substrate, deposition of the particles that formed in solution onto the substrate prevented the growth of the attached seed crystals.

Figures 3c–e show the XRD patterns of the lower surfaces of the hydrothermally treated substrates. All patterns exhibited intense peaks for (*h*00); this indicates that the orientation of the zeolite was retained. The intensities of the (*h*00) peaks increased with increasing amount of bis-tris; hence the addition of bis-tris facilitated the growth of the seed crystals. For the specimens obtained with bis-tris/Al ratios of 0 and 2, peaks due to planes other than (*h*00) and products other than LTA-type zeolite were observed, though they were very weak.

Figures 4a–c show the SEM images of the lower surfaces of the substrates treated hydrothermally at different bis-tris/Al ratios, and Figure 4d shows the image of the fractured cross section for the specimen obtained with a bis-tris/Al ratio of 4. For the specimen obtained with a bis-tris/Al ratio of 0, very limited growth of the seed crystals occurred, and some aggregates of very small randomly oriented zeolite particles were observed on and between the oriented zeolite crystals, probably due to the occurrence of homogeneous nucleation and deposition of the crystals in the solution. Although some growth of seeds occurred at a bis-tris/Al ratio of 2, spherical secondary particles also were observed on the substrate surface between the oriented zeolite crystals. On the basis of the XRD data, these particles are not LTA-type zeolite, and

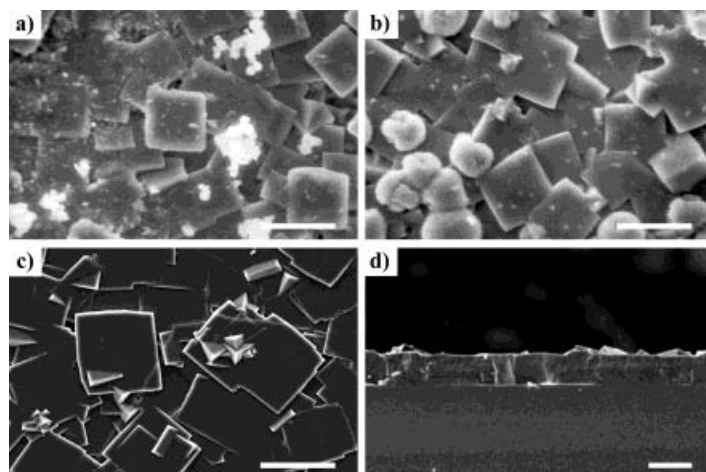


Figure 4. SEM images of the surface of the specimens heat-treated in the suspension with bis-tris/Al ratios of 0 (a), 2 (b), and 4 (c) and the fractured cross section of the specimen with bis-tris/Al = 4 (d). All scale bars: 20 μm.

they may have formed by leaching of the substrate under the strongly alkaline conditions. With a bis-tris/Al ratio of 4, well-developed continuous films consisting exclusively of intergrown oriented zeolite crystals were obtained (Figure 4c). Despite the growth of faces other than (100), the orientation was maintained. Neither other products nor voids were observed in the interparticle spaces. As shown in Figure 4d, the membrane is uniform, continuous, and about 15 μm thick. This suggests that intergrowth of the oriented seeds was rapid enough to prevent leaching of the substrate.

In conclusion, we have discovered a new technique to prepare completely oriented and continuous zeolite membranes having channels normal to the surface of substrate. Controlled crystallization of LTA-type zeolite enabled both the preparation of seed crystals suitable for oriented attachment and homoepitaxial growth of the seeds. Organic ligands such as bis-tris and TEA decrease the degree of supersaturation of $[\text{Al}(\text{OH})_4]^-$ and thus facilitate homogeneous nucleation of the zeolite by an equilibrium reaction such as Equation (1).^[6, 7] Recently, Boudeau et al.^[28, 29] attempted to



prepare continuous oriented LTA-type zeolite films by the intergrowth of seed crystals with a method similar to that described here. However, they used starting solutions without organic ligands for seed preparation and intergrowth, and the films had a rough surface due to multiple coating of seeds^[28] or a partially random orientation due to insufficient intergrowth.^[29]

Gouzinis and Tsapatsis^[30] and Lovallo et al.^[31] prepared continuous and oriented membranes of MFI-type zeolite. Although the straight and sinusoidal channels were parallel to the substrate surface, highly selective gas permeation was exhibited. Our LTA-type zeolite membrane with channels normal to the substrate surface may have similar properties. Investigations on selective gas sensing and permeation are in progress. For application to other zeolite types, our method may require modification, because unlike LTA-type zeolite,

which is homogeneously nucleated,^[32] some other zeolites are nucleated inhomogeneously.^[33]

The materials prepared in this study could offer applications such as controlled access of molecules with selected size and shape to a sensor surface, membranes for catalysis and for separations with true molecular selectivity, and orientation of molecules for nonlinear optical applications.

Experimental Section

The seed crystals of LTA-type zeolite were prepared from an aqueous mixture of NaAlO₂, Na₂SiO₃·9H₂O, and N(C₂H₄OH)₃ by hydrothermal treatment. Before mixing the starting materials, the aqueous solution of NaAlO₂ was filtered through a membrane filter with pore size of 0.2 µm to remove impurities such as Fe(OH)₃. The other reagents were used as received. The composition of the aqueous mixture was adjusted to Na₂O:Al₂O₃:SiO₂:TEA:H₂O = 1.88:1:0.88:8:106. During mixing, precipitates formed. The resulting suspension was transferred to a teflon-lined stainless steel autoclave and heated at 110 °C under autogenous pressure for one week. The product was filtered, washed with 1000 mL of distilled water, and dried at 70 °C in air for 12 h.

The chemical composition of the solid component in the starting suspension was derived from that of the liquid component and the initial composition. The chemical composition of the liquid component was determined by ICP analysis (JICP-PS-1000UV·AT, Leeman Labs). The samples were diluted with milli-Q water.

The crystalline phase and the orientation in the specimens were examined by X-ray diffraction measurements (Rigaku Geigerflex) with graphite-monochromated Cu_{Kα} radiation at a scan rate of 2° min⁻¹ in the range 5 < 2θ < 70°.

The microstructure of the membranes was observed by SEM (Philips XL30) at an acceleration voltage of 10 kV after deposition of a carbon layer with a thickness of about 15 nm on the specimen.

The formation of complexes from Al compounds and alkanolamines was examined by ¹H, ¹³C, ²³Na, ²⁷Al, and ²⁹Si NMR spectroscopy (JEOL α400) at 20 °C and 9.4 T.

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Nickel-Assisted Carbon–Fluorine Bond Activation of 2,4,6-Trifluoropyrimidine: Synthesis of New Pyrimidine and Pyrimidinone Derivatives**

Thomas Braun, Simon P. Foxon, Robin N. Perutz,* and Paul H. Walton

Several methods have been described for the activation of carbon–fluorine bonds of fluoroaromatic and fluoroaliphatic compounds by reaction at transition metal centers.^[1–3] One of the most striking is the fast oxidative addition of pentafluoropyridine at a nickel center to give *trans*-[NiF(2-C₅F₄N)-(PEt₃)₂].^[3] Here we report 1) the activation of a carbon–fluorine bond of 2,4,6-trifluoropyrimidine by a nickel center under mild conditions, 2) the conversion of the nickel fluoride compound into a bifluoride complex, and 3) the selective substitution of the 4-fluoro substituent of 2,4,6-trifluoropyrimidine by a hydroxyl group through reaction at nickel.

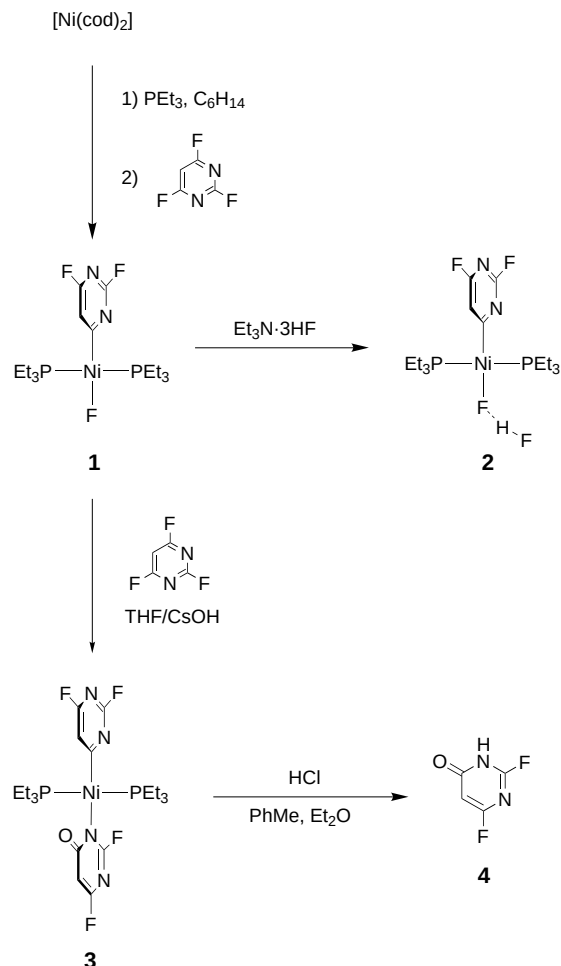
[*] Prof. R. N. Perutz, Dr. T. Braun, S. P. Foxon, Dr. P. H. Walton
Department of Chemistry, University of York
Heslington, York YO10 5DD (UK)
Fax: (+44)1904-432-516
E-mail: rnp1@york.ac.uk

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We show that nickel-supported C–F activation provides an unusual opportunity for the functionalization of fluorinated heterocyclic compounds.

The stepwise treatment of $[\text{Ni}(\text{cod})_2]$ (cod = 1,5-cyclooctadiene) with PEt_3 and 2,4,6-trifluoropyrimidine in hexane results in the fast and regioselective formation of the C–F activation product **1** (Scheme 1). The proposed structure is



Scheme 1. Synthesis and reactions of **1**.

supported by ^1H , ^{31}P , ^{19}F , and ^{13}C NMR spectroscopic data (Table 1). The ^{31}P NMR spectrum displays a doublet at $\delta = 13.6$ ($J = 47.6$ Hz) for the two equivalent phosphorus nuclei coupled to the metal-bound fluorine nucleus. The ^{19}F NMR spectrum shows a signal at $\delta = -361.66$ for the nickel fluoride ligand.^[3] Two other resonances ($\delta = -46.31$, -73.10) indicate the presence of the pyrimidyl ligand.

Addition of $\text{Et}_3\text{N} \cdot 3\text{HF}$ to **1** at room temperature gave the bifluoride complex **2** (Scheme 1). This reagent was recently employed as a mild source of HF for the synthesis of ruthenium and palladium bifluoride complexes from hydride and hydroxide precursors, respectively.^[4, 5] Few other stable adducts of metal fluorides and HF have been reported, and none for a first-row transition metal.^[4, 6, 7] The presence of a bifluoride unit in **2** is revealed by two signals in the ^{19}F NMR spectrum at 233 K at $\delta = -180.35$ (brd, $^1J_{\text{FH}} \approx 390$ Hz, Ni–F–H–F) and -332.61 (brs, 1 F, NiF), and a broad doublet in the

^1H NMR spectrum at $\delta = 11.36$ ($^1J_{\text{FH}} \approx 430$ Hz). The ^{31}P NMR spectrum displays a doublet at $\delta = 13.2$ ($^2J_{\text{PF}} = 43.2$ Hz).

Treatment with $\text{CsOH} \cdot \text{H}_2\text{O}$ converted **2** into **1** and a second compound **3** (Scheme 1), which has four inequivalent fluorine atoms according to its ^{19}F NMR spectrum. The reaction was incomplete, and the ^{31}P NMR spectrum of the crude solution also revealed the presence of free phosphane. Attempts to separate the products by fractional crystallization led to the isolation of single crystals that contain **2** and **3** as independent molecules in the unit cell (Figures 1 and 2).^[8] Both compounds exhibit a square-planar geometry with two *trans* phosphane ligands. The Ni–F bond length of 1.908(3) Å in **2** is significantly longer and the Ni–C bond length of 1.844(3) Å is shorter than the corresponding distances in *trans*- $[\text{NiF}(\text{2-C}_5\text{NF}_3\text{H})(\text{PEt}_3)_2]$ (1.856(2) and 1.869(4) Å, re-

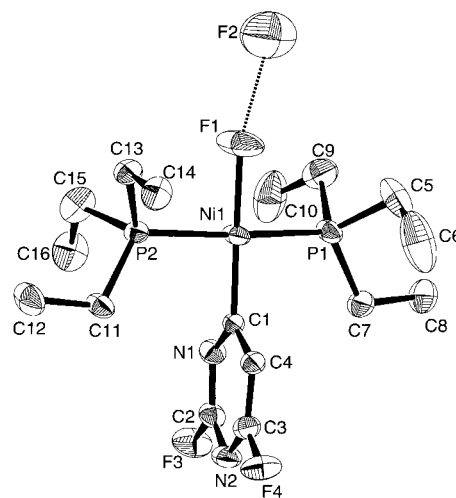


Figure 1. Molecular structure of **2** (ORTEF plot) in the crystal. Selected distances [Å] and angles [°]: Ni1–C1 1.844(4), Ni1–F1 1.908(3), F1...F2 2.400(6); C1–Ni1–F1 177.63(18), P1–Ni1–P2 171.82(5), Ni1–F1–F2 156.7(2).

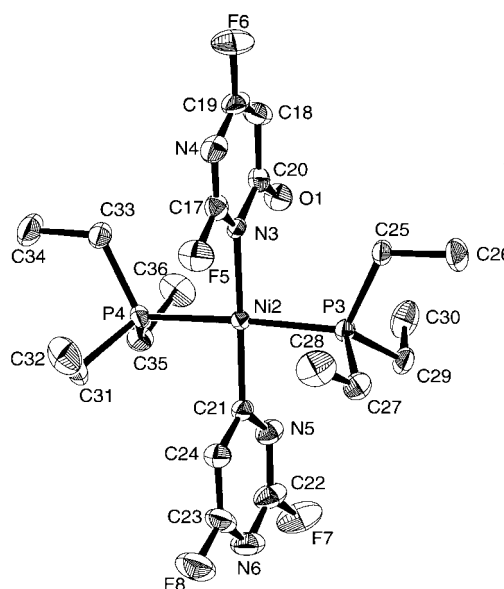


Figure 2. Molecular structure of **3** (ORTEF plot) in the crystal. Selected bond distances [Å] and angles [°]: Ni2–C21 1.877(3), Ni2–N3 1.949(3), O1–C20 1.241(4), N3–C17 1.322(4), N3–C20 1.407(4), N4–C17 1.303(5), N4–C19 1.352(5), C18–C19 1.348(6), C18–C20 1.435(5); C21–Ni2–N3 175.83(14), P4–Ni2–P3 173.27(4).

spectively).^[3] The F...F distance of 2.400(6) Å is clearly longer than that of 2.276(8) Å in *trans*-[RuH(FHF)(dmpe)₂]^[4] or in bifluoride salts MHF₂ (M = Na, K, NH₄).^[9] but it is comparable to that of 2.389(6) Å in [WF(H)₂(FHF)](PMe₃)₄.^[7] The interaction in **2** is best described, therefore, as a hydrogen bond between the NiF moiety and HF.^[7] Complex **3** contains an N(3)-metalated pyrimidin-4-one unit *trans* to a 2-pyrimidyl ligand (Scheme 1, Figure 2).

Treatment of **1** or **2** with CsOH·H₂O in the presence of excess 2,4,6-trifluoropyrimidine in THF resulted solely in the regioselective formation of **3** (NaOH may be used instead of CsOH). The NMR data for **3** (Table 1) are consistent with the crystal structure. Assignments are based partly on ¹³C–¹H and ¹³C–¹⁹F COSY spectra. The most characteristic features in the ¹³C NMR spectra are the signals for the nickel-bound carbon atom at δ = 215.8 and for the C=O group at δ = 174.6 (t, *J* = 11.5 Hz).

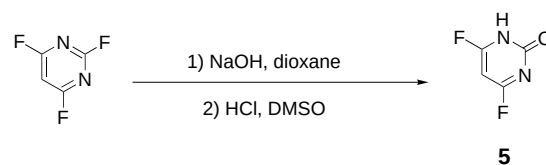
Table 1. Selected spectroscopic data for **1**–**5**.^[a]

1 : ¹ H NMR (C ₆ D ₆): δ = 7.04 (brs, 1 H, CH); ¹⁹ F NMR (C ₆ D ₆): δ = –46.31 (brs, 1 F, CF), –73.10 (brs, 1 F, CF), –361.66 (br, 1 F, NiF); ³¹ P NMR (C ₆ D ₆): δ = 13.6 (d, ² <i>J</i> _{PF} = 47.6 Hz)
2 : ¹ H NMR ([D ₈]toluene, 223 K): δ = 11.36 (brd, ¹ <i>J</i> _{FH} ≈ 427, 1 H, FHF), 6.96 (brs, 1 H, CH); ¹⁹ F NMR ([D ₈]toluene, 223 K): δ = –44.43 (s, 1 F, CF), –76.62 (s, 1 F, CF), –180.35 (brd, ¹ <i>J</i> _{FH} ≈ 392 Hz, 1 F, FHF), –332.61 (br, 1 F, NiF); ³¹ P NMR ([D ₈]toluene, 223 K): δ = 13.2 (d, ² <i>J</i> _{PF} = 43.2 Hz)
3 : IR (Nujol) $\tilde{\nu}$ = 1644 cm ^{–1} (C=O); ¹ H NMR (C ₆ D ₆): δ = 7.57 (brs, 1 H, CH of R ^C), 5.69 (d, <i>J</i> _{FH} = 2.5 Hz, 1 H, CH of R ^N); ¹⁹ F NMR (C ₆ D ₆): δ = –45.41 (s, 1 F, CF), –45.50 (s, 1 F, CF), –70.46 (s, 1 F, CF), –70.82 (s, 1 F, CF); ¹³ C NMR (C ₆ D ₆): δ = 215.8 (m, <i>ipso</i> -C of R ^C), 174.6 (t, 11.5 Hz, CO), 173.2 (dd, ¹ <i>J</i> _{CF} = 247.8, ³ <i>J</i> _{CF} = 22.5 Hz, CF of R ^N), 166.3 (dd, ¹ <i>J</i> _{CF} = 260.4 Hz, ³ <i>J</i> _{CF} = 35.0 Hz, CF of R ^C), 161.3 (dd, ¹ <i>J</i> _{CF} = 220.2 Hz, ³ <i>J</i> _{CF} = 28.9 Hz, CF of R ^N), 158.2 (dd, ¹ <i>J</i> _{CF} = 222.7 Hz, ³ <i>J</i> _{CF} = 15.7 Hz, CF of R ^C), 111.3 (d, <i>J</i> _{CF} = 20.5 Hz, CH of R ^C), 88.2 (dd, <i>J</i> _{CF} = 27.6, <i>J</i> _{CF} = 8.2 Hz, CH of R ^N); ³¹ P NMR (C ₆ D ₆): δ = 9.9 (s)
4 : ¹ H NMR (C ₆ D ₆): δ = 13.5 (brs, 1 H, NH), 5.87 (d, ³ <i>J</i> _{FH} = 2.5 Hz, 1 H, CH); ¹⁹ F NMR (C ₆ D ₆): δ = –45.47 (s, 1 F, CF), –61.89 (s, 1 F, CF); MS (EI): <i>m/z</i> (%): 132 (53.8) [M ⁺]
5 : ¹ H NMR (C ₆ D ₆): δ = 10.47 (brs, 1 H, NH), 5.03 (t, <i>J</i> _{FH} = 1.3 Hz, 1 H, CH); ¹⁹ F NMR (C ₆ D ₆): δ = –56.61 (s, CF); ¹³ C NMR (C ₆ D ₆): δ = 173.14 (AXX' system; apparent coupling constants: <i>J</i> = 260, <i>J</i> = 21 Hz, CF), 164.77 (t, ³ <i>J</i> _{CF} = 23.4 Hz, CO), 84.58 (t, ² <i>J</i> _{CF} = 35.7 Hz, CH)

[a] R^C = C₄N₂F₂H, R^N = C₄N₂F₂HO; ¹H 500 MHz, ¹⁹F 470.4 MHz, ³¹P 202.4 MHz, ¹³C 125.8 MHz.

Treatment of **3** with a solution of HCl in diethyl ether resulted in cleavage of the Ni–N bond and formation of *trans*-[NiCl(C₄N₂F₂H)(PEt₃)₂] and the previously unknown pyrimidin-4-one **4** (Scheme 1). The two compounds can be separated by sublimation of **4**. The ¹⁹F NMR spectrum of **4** displays two signals at δ = –75.47 and –61.89 for the two inequivalent fluorine atoms. The ¹H NMR spectrum has one signal in the nonaromatic region at δ = 5.90, assigned to the ring proton, and a broad singlet at δ ≈ 13.5 for the nitrogen-bound proton.^[10]

In contrast, the reaction of 2,4,6-trifluoropyrimidine with NaOH and then HCl afforded the pyrimidin-2-one **5**, an isomer of **4** (Scheme 2). The ¹H NMR spectrum of **5** shows one resonance in the nonaromatic region at δ = 5.03 but only one ¹⁹F signal at δ = –55.52 for the fluorine atoms, which are equivalent on the NMR time scale.^[10b] We also treated 2,4,6-trifluoropyrimidine with CsOH·H₂O and showed that the



Scheme 2. Synthesis of **5**.

cesium salts of **4** and **5** are formed in a 1:3 ratio. Fluorinated pyrimidinones are of general interest as building blocks in agrochemicals and because of their antitumor activity.^[11]

Experimental Section

1: A suspension of [Ni(cod)₂] (120 mg, 0.36 mmol) in hexane (5 mL) was treated with PEt₃ (142 μL, 9.60 mmol). The solution was stirred for 5 min at room temperature until the color changed from red-purple to yellow. After addition of 2,4,6-trifluoropyrimidine (58 μL, 0.65 mmol), the solution was stirred for 10 min, and the volatile components were removed under vacuum. The orange residue was dissolved in hexane (5 mL), and the resulting yellow solution filtered and concentrated to about 1 mL. Complex **1** was crystallized as a yellow solid on cooling overnight at –20 °C. Yield 135 mg (72 %).

2: A solution of **1** (68 mg, 0.15 mmol) in hexane (5 mL) was treated with a solution of Et₃N·3 HF in THF (98 μL, 0.10 mmol). After stirring for 5 min at room temperature, the solvents were removed under vacuum. The residue was dissolved in hexane (3 mL), and the suspension was filtered. Orange crystals of **2** precipitated at –20 °C. Yield 44 mg (62 %).

3: A solution of **2** (120 mg, 0.27 mmol) in THF (20 mL) was treated with CsOH·H₂O (100 mg, 0.60 mmol) and 2,4,6-trifluoropyrimidine (500 μL, 5.59 mmol). After stirring for 20 h at room temperature, the volatile components were removed under vacuum. The residue was extracted with hexane (20 mL), the extract was filtered, and the filtrate was concentrated to about 3 mL in vacuo. Complex **3** precipitated as a yellow powder. Yield 97 mg (67 %).

4: A solution of **3** (220 mg, 0.41 mmol) in toluene (5 mL) was treated with a solution of HCl in diethyl ether (430 μL, 0.43 mmol). After stirring for 1 min, the volatile components were removed under vacuum. Sublimation of the residue at 2.6 × 10^{–3} mbar and 50 °C afforded **4** as a white solid. Yield 11 mg (20%; not optimized).

5: A solution of NaOH in water (339 mg, 8.47 mmol) was added to a solution of 2,4,6-trifluoropyrimidine (1.1 g, 8.20 mmol) in 1,4-dioxane (50 mL). After stirring for 4 h, the solution was concentrated to 2 mL under vacuum. The product was recrystallized from boiling water. The white product was collected by filtration, dried over anhydrous silica, and dissolved in DMSO. After treatment of the solution with a solution of HCl (4.50 mL, 4.40 mmol) in diethyl ether, the volatile components were removed under vacuum. The residue was extracted with benzene (20 mL), the extract filtered, and the solvent removed in vacuo to give **5** as a white powder. Yield 325 mg (30%; not optimized).

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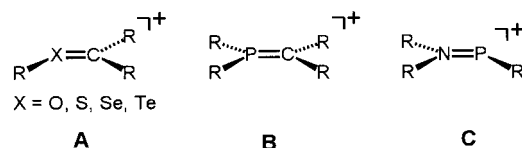
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- [8] Crystal data for **2** + **3**: $C_{36}H_{64}F_8N_6Ni_2OP_4$ ($M_r = 990.2$): crystal dimensions $0.8 \times 0.4 \times 0.4$ mm; triclinic; space group $P\bar{1}$; $a = 14.682(7)$, $b = 18.359(5)$, $c = 9.197(5)$ Å, $\alpha = 100.90(3)$, $\beta = 101.37(4)$, $\gamma = 78.32(3)^\circ$, $Z = 2$, $V = 2351.2(19)$ Å³, $\rho_{\text{calcd}} = 1.817$ g cm⁻³; $T = 150(2)$ K; $\theta_{\text{max}} = 27.99^\circ$; of 11450 reflections collected, 11013 were unique ($R_{\text{int}} = 0.0279$); Rigaku AFC6S diffractometer; graphite-monochromated MoK α radiation ($\lambda = 0.71069$ Å); Lorentz and empirical absorption corrections (ψ scan, min. transmission 84.9%). The structure was solved by direct methods (DIRDIF) and refined by full-matrix least-squares methods on F^2 ; $R_1 = 0.0443$, $wR_2 = 0.1109$ (for 7642 reflections with $I > 2\sigma(I)$); GOF on F^2 1.070; data-to-parameter ratio 20.9; max./min. residual electron density +1.387/–0.924 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-122712. 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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Strong P=P π Bonds: The First Synthesis of a Stable Phosphanyl Phosphenium Ion**

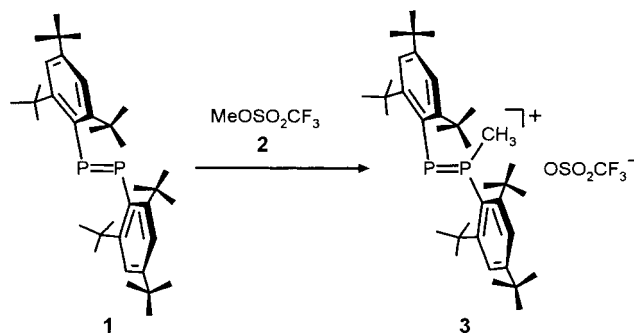
Sandra Loss, Christoph Widauer, and Hansjörg Grützmacher*

Dedicated to Professor Hans Bock
on the occasion of his 71st birthday

α -Heteroatom-substituted carbenium ions **A** ($X = S, Se, Te$),^[1] methylene phosphonium ions **B**,^[2] and amino phosphonium ions **C**^[3] can be formally described as donor–acceptor π -bond systems. In context with our investigations on these quite polar bond systems (i.e., $(X,P)^{\delta+}, C^{\delta-}$ in **A**, **B**; $N^{\delta-}, P^{\delta+}$ in **C**), we became interested in an ion analogous to **C** in which only third-row elements are involved in π bonding. The plan



for the synthesis appeared simple: Protonation or alkylation of a diphosphene, $R-P=P-R$, should give a phosphanyl phosphenium ion, $[R_2P=PR]^+$, in which a phosphanyl group, R_2P , serves as π -electron donor towards an electron-deficient phosphenium unit, PR^+ .^[4] Others have attempted this approach in condensed phase; however, these ions have never been detected.^[5] In the gas phase these species are observed as fragmentation products of $[R_2P-PR_2]^{++}$ radical cations.^[6] Calculations show the planar $[H_2P=PH]^+$ ion to be the global minimum on the $[H_3,P_2]^+$ singlet potential energy surfaces.^[7] Our own efforts to obtain $[Mes^*MeP=PMes^*]^+$ (**3**; $Mes^* = 2,4,6\text{-}t\text{Bu}_3C_6H_2$) were initially frustrating since no reaction occurred when diphosphene **1**^[8] was treated with stoichiometric amounts of methyl trifluoromethanesulfonate (methyl triflate, **2**) in CH_2Cl_2 . However, in the presence of a 35-fold excess of **2**, the methylated cation **3** was formed quantitatively (Scheme 1).



Scheme 1. Synthesis of phosphanyl phosphenium ion **3**.

Only two doublets at $\delta = 237$ (Mes^*MeP) and 332.2 (Mes^*P ; $^1J_{PP} = 633$ Hz) were observed in the ^{31}P NMR spectrum. Note that the creation of a positive charge causes a considerable low-frequency shift of both ^{31}P NMR resonances ($\Delta\delta(P1) = 258$; $\Delta\delta(P2) = 163$) when compared to neutral **1** ($\delta(^{31}P) = 495$). The $n \rightarrow \pi^*$ ($\lambda = 364$ nm) and $\pi \rightarrow \pi^*$ transitions ($\lambda = 249$ nm) of the $P=P$ chromophore are shifted to shorter wavelengths by 98 and 92 nm, respectively.

Since **3** proved to be particularly unstable in nonpolar organic solvents, crystals suitable for an X-ray analysis were grown within five minutes by diffusion of diethyl ether into a solution of **3** in CH_2Cl_2 under a microscope. A rapidly formed small yellow platelet was selected and mounted on the diffractometer, and the resulting structure of **3** is shown in Figure 1.^[9]

The phosphorus center P1 in **3** is trigonal-planar coordinated. The O2 center of the triflate anion is in line with the $P=P$ vector and has a long contact with the two-coordinate phosphorus atom P2 ($P2-O2$ 3.148(3) Å; $P1-P2-O2$ 175.6°), without causing a structural perturbation. There is no twist around the $P=P$ bond; the central skeleton of the cation is

[*] Prof. Dr. H. Grützmacher, Dipl.-Chem. S. Loss, Dipl.-Chem. C. Widauer
Laboratory of Inorganic Chemistry, ETH-Zentrum
Universitätsstrasse 6, CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-10-90
E-mail: gruetz@inorg.chem.ethz.ch

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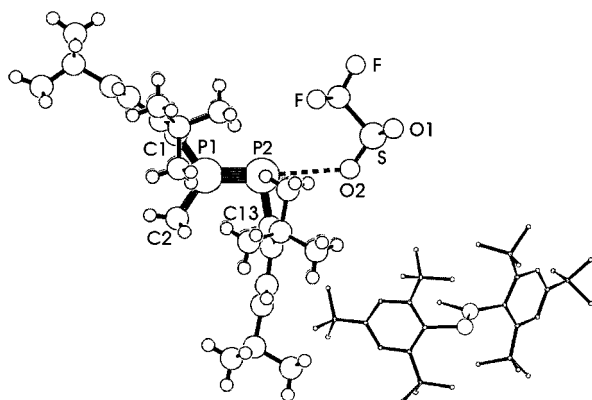
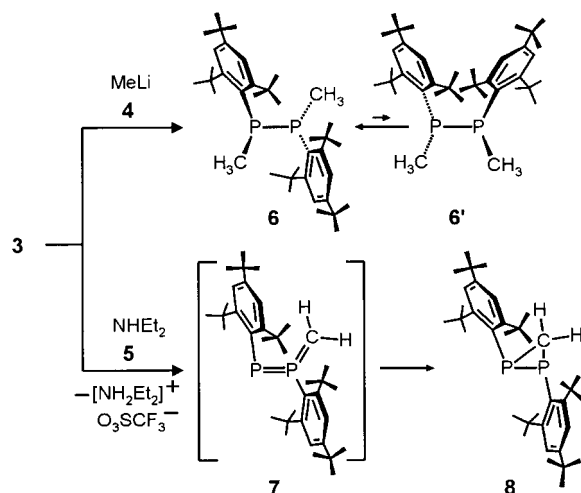


Figure 1. Two different views of the molecular structure of **3**. Left: The mirror plane running through S, O2, P2, P1, C13, C2, C1 coincides with the plane of the page; right: view showing the planar arrangement of the central skeleton. Selected bond lengths [Å] and angles [°]: P1–P2 2.024(2), P1–C1 1.817(5), P1–C2 1.799(4), P2–C13 1.866(4); C1–P1–C2 111.7(3), C1–P1–P2 123.1(2), C2–P1–P2 125.2(2), C13–P2–P1 99.4(2).

perfectly planar ($\tau(\text{C1-P1-P2-C13}) = 0^\circ$). The P1=P2 bond (2.024(2) Å) is not significantly shorter than that in diphosphene **1** (2.034(2) Å). The only notable structural difference between the diphosphene **1** and **3** concerns the $\text{C}_{\text{isopropyl}}\text{-P-P}$ angle, which opens from 102.8° in **1** to $123.1(2)^\circ$ in **3**.

The $[\text{Mes}^*\text{P}=\text{P}(\text{Mes}^*)\text{-CH}_3]^+$ cation in **3** can be regarded as a λ^5, σ^3 -analogue of a λ^5, σ^4 -methylphosphonium ion, $[\text{R}_3\text{P-CH}_3]^+$. Since these salts are deprotonated by strong bases to give Wittig ylides, $\text{R}_3\text{P=CH}_2$, **3** was treated with MeLi (**4**) at low temperatures. However, the products are the diastereomeric diphosphanes **6** and **6'**, which arise from addition of the methanide ion (Scheme 2).^[10]

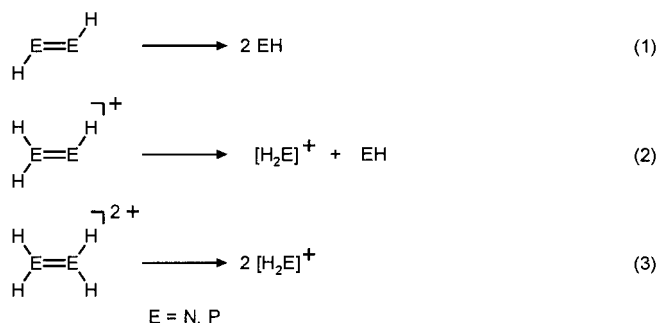


Scheme 2. Synthesis of diphosphanes **6** and **6'** as well as diphosphirane **8**.

Addition of diethylamine (**5**) to **3** leads to clean deprotonation and subsequent electrocyclic ring closure to afford **8**. This compound can be obtained as yellow crystals. As previously suggested,^[11] the methylenephosphanyl phosphorane **7** is assumed as intermediate. No 1,2-addition products are formed; furthermore, *t*BuOH does not react with **3**.

It is interesting to ask whether the P=P bond is strengthened or weakened upon protonation or alkylation.^[12] To this end,

we have calculated the bond dissociation energies for HP=PH (**9**), $[\text{H}_2\text{P=PH}]^+$ (**10**), and $[\text{H}_2\text{P=PH}_2]^{2+}$ (**11**; Scheme 3 and Table 1).^[13] For comparison, the corresponding energies for the analogous nitrogen compounds diazene, HN=NH (**12**), diazenium, $[\text{H}_2\text{N=NH}]^+$ (**13**), and $[\text{H}_2\text{N=NH}_2]^{2+}$ (**14**) were calculated as well (Table 1).



Scheme 3. Dissociation reactions of E_2H_2 , $[\text{E}_2\text{H}_3]^+$, and $[\text{E}_2\text{H}_4]^{2+}$ ($\text{E} = \text{N}, \text{P}$).

Table 1. Calculated dissociation energies ΔE_{Diss} [kcal mol⁻¹] of **9–14** and singlet–triplet excitation energies $\Delta E_{(\text{s} \rightarrow \text{T})}$ [kcal mol⁻¹] of EH and $[\text{H}_2\text{E}]^+$ fragments ($\text{E} = \text{N}, \text{P}$).^[a]

E	ΔE_{Diss} [Eq. (1)]	ΔE_{Diss} [Eq. (2)]	ΔE_{Diss} [Eq. (3)]	$\Delta E_{(\text{s} \rightarrow \text{T})}(\text{EH})$	$\Delta E_{(\text{s} \rightarrow \text{T})}([\text{H}_2\text{E}]^+)$
N	+109.7	+146.3	+7.2	–46.6	–31.5
P	+69.1	+87.3	–47.8	–30.3	+16.5

[a] Calculated at the CCSD(T)/6-311G(2d,2p)//MP2/6-31G(d,p) level.

As is the case for the N=N bond, the P=P bond becomes stronger upon protonation. This finding is supported by the observation of an absorption at 638 cm^{-1} in the IR spectrum of **3**, which is assigned to the P=P stretching vibration ($\tilde{\nu}_{\text{calcd}}([\text{H}_2\text{P=PH}]^+) = 714$,^[7a] 636 cm^{-1} at the MP2/6-31G(d,p) level). This vibration appears at lower wavenumbers in the resonance Raman spectrum of **1** ($\tilde{\nu}_{\text{exp}}([\text{Mes}^*\text{P=P}(\text{Mes}^*)]) = 610 \text{ cm}^{-1}$, $\tilde{\nu}_{\text{calcd}}([\text{HP=PH}]) = 614 \text{ cm}^{-1}$ at the MP2/6-31G(d,p) level).^[14] The slightly smaller increase of the E=E dissociation energy upon protonation ($\text{E} = \text{P}$: 26%; $\text{E} = \text{N}$: 33%) is (at least in part) due to the different electronic ground states of the product fragments $[\text{H}_2\text{P}]^+$ (singlet) and $[\text{H}_2\text{N}]$ (triplet; Table 1). The double bond energy in $[\text{H}_2\text{P=PH}]^+$ (**10**) is diminished by the excitation energy $\Delta E_{(\text{s} \rightarrow \text{T})}$ of the $[\text{H}_2\text{P}]^+$ fragment. However, the sum of the singlet–triplet excitation energies ($\Sigma \Delta E_{(\text{s} \rightarrow \text{T})} = -13.8 \text{ kcal mol}^{-1}$ for $[\text{H}_2\text{P}]^+$ and HP) is still negative. Thus the inequality $\Sigma \Delta E_{(\text{s} \rightarrow \text{T})} < \frac{1}{2}E(\sigma + \pi)$ is fulfilled, and the “classical” planar structures seen in **3** or **10** are expected according to the Carter–Goddard–Malrieu–Trinquier (CGMT) model.^[15] In this respect, although only third row elements are involved in double bonding, phosphanyl phosphonium ions **3** have a higher double bond quality than methylene phosphonium ions **B**, for which the difference between $\Sigma \Delta E_{(\text{s} \rightarrow \text{T})}$ and $\frac{1}{2}E(\sigma + \pi)$ is smaller. However, the data in Table 1 also show that double protonation of diphosphene **9** leads to the unstable dication $[\text{H}_2\text{P=PH}_2]^{2+}$ (**11**).^[16a] which suffers from Coulombic explosion, while the analogous nitrogen dications (**14**) are stable and derivatives have been detected by cyclic voltammetry.^[16b]

Experimental Section

3: Methyl triflate (**2**, 5 g, 30.5 mmol) was added to a saturated solution of **1** (485 mg, 0.88 mmol) in CH₂Cl₂. Evaporation of solvent and excess **2** led to a yellow residue, which was dissolved in CH₂Cl₂. After addition of hexane, **3** precipitated as an analytically pure, microcrystalline powder, which was isolated by filtration and dried under vacuum (442 mg, 0.62 mmol, yield: 70%). Crystals suitable for an X-ray structure analysis could be obtained by layering a saturated solution of **3** in CH₂Cl₂ with diethyl ether. After 5 min sufficiently large platelets appeared, which had to be removed at once from the mother liquor to avoid decomposition. M.p. 118 °C (decomp.); UV/Vis: λ = 249.4 ($\pi \rightarrow \pi^*$, P=P), 283.7 ($\pi \rightarrow \pi^*$, aryl), 364.2 ($n \rightarrow \pi^*$, P=P); ³¹P NMR (CD₂Cl₂): δ = 237.0 (d, ArCH₃P), 332.2 (d, ¹J_{PP} = 633 Hz, ArP); ¹H NMR (CD₂Cl₂): δ = 1.38 (s, 9H, *p*-*t*Bu), 1.40 (s, 9H, *p*-*t*Bu), 1.55 (d, ⁵J_{PH} = 2.44 Hz, 18H, *o*-*t*Bu), 1.60 (s, 18H, *o*-*t*Bu), 1.86 (dd, ³J_{PH} = 19.80, ⁵J_{PH} = 4.87 Hz, 3H, CH₃), 7.66 (dd, ⁴J_{PH} = 1.83, ⁵J_{PH} = 1.83 Hz, 2H, aryl-H), 7.70 (d, ⁴J_{PH} = 5.18 Hz, 2H, aryl-H).

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Polyoxometalates as Reduction Catalysts: Deoxygenation and Hydrogenation of Carbonyl Compounds**

Vladimir Kogan, Zeev Aizenshtat, and Ronny Neumann*

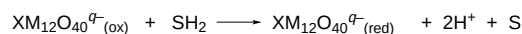
Investigations concerning the use of polyoxometalates as catalysts in both liquid and gas-phase reactions have intensified significantly over the last decade. These catalytic applications in acid catalysis^[1] and oxidation^[2] have taken advantage of the strong Brønsted acidity of heteropoly acids and the inherent stability of the polyoxometalate framework to oxidative degradation in the presence of strong oxidants and at high temperatures. Although a few examples of

[*] Prof. Dr. R. Neumann, V. Kogan, Prof. Dr. Z. Aizenshtat
Casali Institute of Applied Chemistry
Graduate School of Applied Science
The Hebrew University of Jerusalem
Jerusalem, 91904 (Israel)
Fax: (+972) 2-6528250
E-mail: ronny@vms.huji.ac.il

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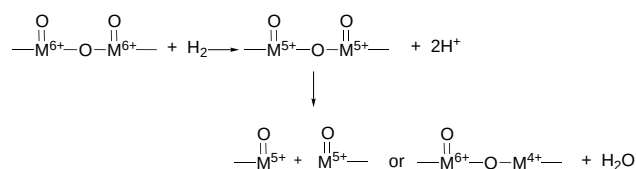
reductions catalyzed by noble metals (Pt, Pd, Rh, and Ir) in the presence of polyoxometalates have been reported,^[3] the use of polyoxometalates alone as reduction catalysts has yet to be disclosed.

The redox activity of polyoxometalates, especially of the Keggin type, has often been utilized, whereby the polyoxometalate in the oxidized form oxidizes a substrate (SH₂) that by definition is a reducing agent (Scheme 1). The reduced



Scheme 1. Oxidation of a substrate SH₂ with a polyoxometalate as well as reduction of the polyoxometalate. X = P, Si; M = W, Mo, V.

form is subsequently reoxidized, commonly by oxygen, to complete the catalytic cycle. Importantly, in this reaction mode the substrate may also be hydrogen.^[4] Thus, at 250–300 °C reduction of polyoxometalates by hydrogen (Scheme 2) has been reported.



Scheme 2. Reduction of a polyoxometalate—represented schematically by M(O)—O—M(O)—with hydrogen.

Here we report on the activation of hydrogen by Keggin-type polyoxometalates and the utilization of the reduced polyoxometalate species for the catalytic deoxygenation of ketones and aldehydes, a reaction classically carried out by the Clemmensen and Wolff–Kishner reactions. The products formed from the polyoxometalate-catalyzed deoxygenation depend strongly on the type of polyoxometalate used (tungstate or vanadomolybdate). The reaction does not appear to involve a carbinol intermediate, and the polyoxometalate was shown to be structurally stable under the reaction conditions.

The polyoxometalate catalysts (as potassium salts) were used supported on γ -alumina (surface area $\approx 200 \text{ m}^2 \text{ g}^{-1}$); reactions were run without solvent in a 300-mL Parr autoclave at 300 °C. γ -Alumina and potassium heteropoly salts (pH 6 in aqueous solution), prepared by cation exchange from the original heteropoly acids, were used to reduce acidity and thus minimize cracking and other acid-catalyzed reactions. In the first stage, the catalytic activity of various polyoxometalates was compared using benzophenone as substrate (Table 1). Two trends were observed. The order of catalytic activity was $[\text{SiW}_{12}\text{O}_{40}]^{4-} < [\text{PW}_{12}\text{O}_{40}]^{3-} < [\text{PMo}_{12}\text{O}_{40}]^{3-} < [\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$, which correlates with the reducibility with H₂ and the oxidation potentials of the polyoxometalates.^[5] For $[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$ the conversion into diphenylmethane was quantitative. In other words, the more facile the activation of H₂ as outlined in Scheme 2, the higher the conversion. For transition metal substituted polyoxometalates $[\text{SiM}(\text{H}_2\text{O})\text{W}_{11}\text{O}_{39}]^{q-}$, the most stable series, a positive affect

Table 1. Reduction of benzophenone by various polyoxometalates.^[a]

Catalyst	Conversion [mol %]
K ₄ SiW ₁₂ O ₄₀ /Al ₂ O ₃	41
K ₆ SiCo(H ₂ O)W ₁₁ O ₃₉ /Al ₂ O ₃	48
K ₆ SiCu(H ₂ O)W ₁₁ O ₃₉ /Al ₂ O ₃	83 ^[b]
K ₆ SiNi(H ₂ O)W ₁₁ O ₃₉ /Al ₂ O ₃	34
K ₅ SiCr(H ₂ O)W ₁₁ O ₃₉ /Al ₂ O ₃	46
K ₃ PW ₁₂ O ₄₀ /Al ₂ O ₃	70
K ₃ PMo ₁₂ O ₄₀ /Al ₂ O ₃	95
K ₅ PV ₂ Mo ₁₀ O ₄₀ /Al ₂ O ₃	100

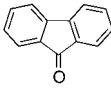
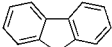
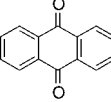
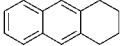
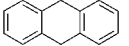
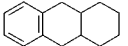
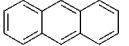
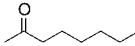
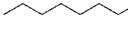
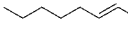
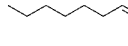
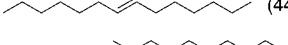
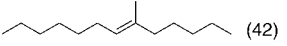
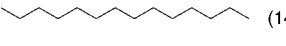
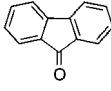
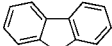
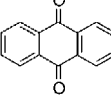
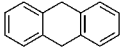
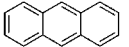
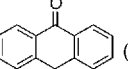
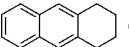
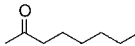
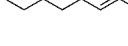
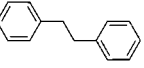
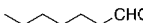
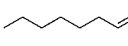
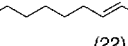
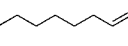
[a] Reaction conditions: 0.5 g (2.75 mmol) of benzophenone, 1 g of catalyst (50 mg (16–20 μmol) of polyoxometalate), 23 atm H₂, $T = 300^\circ\text{C}$, $t = 200$ min. Unless stated otherwise, the sole product was diphenylmethane. [b] 1,1,2,2-Tetraphenylethane was a by-product (6–7 %).

was observed for substitution with Cu^{II}, while Co^{II}, Cr^{III}, and Ni^{II} had no significant influence.

After observing the high activity in benzophenone deoxygenation, we investigated the reductive deoxygenation of various other benzylic, cyclic, and acyclic ketones and aldehydes (Table 2). The differences between supported $[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$ and $[\text{SiW}_{12}\text{O}_{40}]^{4-}$ as catalysts are striking. As in the case of benzophenone, K₅PV₂Mo₁₀O₄₀/Al₂O₃ was significantly more active than K₄SiW₁₂O₄₀/Al₂O₃. For simple benzylic ketones such as benzophenone, fluorenone, and acetophenone, the sole products for both $[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$ and $[\text{SiW}_{12}\text{O}_{40}]^{4-}$ were the simple methylene derivatives, formally formed by deoxygenation and addition of hydrogen. However, other substrates, especially aliphatic ketones and aldehydes, provided very different product selectivities. For 9,10-anthraquinone, use of $[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$ leads to formation of mostly the more highly reduced species, tetra- and octahydroanthracene, along with dihydroanthracene and anthracene but no anthrone, while $[\text{SiW}_{12}\text{O}_{40}]^{4-}$ yielded for the most part less highly reduced products. In the case of cycloheptanone and 2-octanone, it was observed again that $[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$ catalyzed formation of mostly saturated compounds (cycloheptane/ethylcyclopentane and octane, respectively). In contrast, upon use of $[\text{SiW}_{12}\text{O}_{40}]^{4-}$ only alkenes (cycloheptene/methycyclohexene and octenes) and a rearranged alkene (norbornane) were detected. These alkenes were not significantly reduced even after extended reaction periods of 48 h. In the case of benzaldehyde, toluene was the major product for both catalysts, although the formation of a small amount of dibenzyl in the presence of $[\text{SiW}_{12}\text{O}_{40}]^{4-}$ is mechanistically significant. The most unusual reactivity was viewed upon use of an aliphatic aldehyde, *n*-heptanal, as substrate. $[\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^{5-}$ catalyzed a deoxygenation–coupling reaction to yield a mixture of tetradecene isomers and the saturated *n*-tetradecane; no C₇ products were observed. On the other hand, use of $[\text{SiW}_{12}\text{O}_{40}]^{4-}$ yielded mostly formation of the aldol condensation product (presumably due to the acidity of γ -alumina) and some tetradecene isomers, but again no C₇ products or saturated tetradecane.

It is worthwhile to present a preliminary working hypothesis concerning the reaction mechanism. As reported^[4] and shown in Scheme 2, reduction of a Keggin-type polyoxometalate with H₂ at 250–300 °C yields a deoxygenated polyoxometalate that probably contains M^{IV}. Such reduced species are effective even at room temperature for oxygen atom transfer

Table 2. Reduction of ketones and aldehydes catalyzed by $K_3PV_2Mo_{10}O_{40}$ and $K_4SiW_{12}O_{40}$.^[a]

Substrate	Conversion	Conditions	Products ^[b]
$K_3PV_2Mo_{10}O_{40}/Al_2O_3$			
	100	3.5 h, 34 atm	 (100)
	100	3.5 h, 23 atm	 (100)
	100	3.5 h, 34 atm	 (54)  (25)  (16)  (5)
	100	3.5 h, 54 atm	 (48)  (15)  (18)  (5)  (4)  (10)
	96	20 h, 54 atm	 (82) E + Z  (15)  (3)
	62	3.5 h, 23 atm	 (100)
	85	3.5 h, 23 atm	E + Z  (44)  (42)  (14)
$K_4SiW_{12}O_{40}/Al_2O_3$			
	21	3.5 h, 500 psi	 (100)
	80	3.5 h, 23 atm	 (100)
	96	3.5 h, 34 atm	 (66)  (10)  (10)  (14)
	48	3.5 h, 54 atm	 (71)  (19)  (10)
	74	20 h, 54 atm	E + Z  (100)
	85	3.5 h, 23 atm	 (96)  (4)
	69	3.5 h, 23 atm	 (60) $C_5H_{11}CHO$ E + Z  (22)  (18)

[a] Reaction conditions: 2.75 mmol of substrate, 1 g of catalyst (50 mg (16–20 μ mol) of polyoxometalate), $T = 300^\circ C$, H_2 pressure and time are give in the Table. [b] The amount of product as a percentage of the total product is given in parentheses.

from an organic substrate (such as a sulfoxide) to a M^{IV} polyoxometalate.^[6] A similar deoxygenation of a carbonyl compound can thus be contemplated. A simple experiment to test whether such a deoxygenation pathway is operative as opposed to the common hydrogenation mechanism via carbinol intermediates as observed in “hydride chemistry”^[7] was carried out using 1-heptanol as substrate. With $[PV_2Mo_{10}O_{40}]^{5-}$ at 24 atm H_2 and $300^\circ C$ mostly diheptyl ether and a little 1-heptene but no coupled products (i.e., tetradecenes) were formed. In the case of benzylic carbonyl compounds, formal addition of two hydrogen atoms after deoxygenation leads to the reduced product. For aliphatic ketones, a fast hydrogen shift after deoxygenation will lead to an alkene as initial product. In the

case of $[SiW_{12}O_{40}]^{4-}$ as catalyst, this alkene is not reduced although rearrangement reactions (thermal and/or catalytic) lead to the observed product mixture. For $[PV_2Mo_{10}O_{40}]^{5-}$, there are two possibilities to explain the formation of hydrogenated products: 1) The initial alkene formed is hydrogenated in a separate reaction or 2) addition of hydrogen occurs before the hydrogen shift. The reactivity observed for aldehyde deoxygenation also supports our working hypothesis. After deoxygenation, coupling reactions instead of hydrogen shifts are dominant for 1-heptanal but were also observed for benzaldehyde. The mechanism of this coupling is not clear, but the approximately 1:1 product ratio for 7-tetradecene:6-methyl-6-tridecene is conspicuous.

The integrity of the Keggin polyoxometalates $K_4SiW_{12}O_{40}$ and $K_5PV_2Mo_{10}O_{40}$ under the reaction conditions was also proven by IR spectroscopy and X-ray diffraction studies. A finely powdered sample of the polyoxometalate was treated under the reaction conditions (0.5 g of benzophenone, 50 mg of polyoxometalate, 23 atm H_2 , $T = 300^\circ C$, $t = 200$ min). After cooling, the autoclave was opened and the polyoxometalate was isolated by filtration. The catalyst first appeared brown-blue, but after exposure to air the color turned lighter. The IR spectra and X-ray powder patterns before and after the reaction were identical, indicating that the structure of the polyoxometalates was unchanged. A room-temperature ESR spectrum of the $PV_2Mo_{10}O_{40}^{5-}$ catalyst after reaction showed the typical eight-line spectrum of the two-electron-reduced compound.^[8] That no leaching of the polyoxometalate from the support occurred was indicated by atomic absorption measurements of the organic phase after extraction with water.

We have demonstrated a new application of Keggin polyoxometalates as deoxygenation and hydrogenation catalysts for the reduction of carbonyl compounds. The $[PV_2Mo_{10}O_{40}]^{5-}$ polyoxometalate, which is most active for the activation (oxidation) of H_2 , is the most active catalyst. The product selectivity shows that the reduced polyoxometalates deoxygenate ketones and aldehydes; carbinols are not intermediates. Use of $[PV_2Mo_{10}O_{40}]^{5-}$ tends to lead to formation of saturated compounds, whereas for $[SiW_{12}O_{40}]^{4-}$ alkenes are preferred initial products.

Experimental Section

Solutions of $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$, and $H_5PV_2Mo_{10}O_{40}$ ^[9] were treated on an Amberlyst 120 (K^+ form) ion-exchange column to prepare the polyoxometalates $K_3PW_{12}O_{40}$, $K_3PMo_{12}O_{40}$, $K_4SiW_{12}O_{40}$, and $K_5PV_2Mo_{10}O_{40}$. $K_6SiM(H_2O)W_{11}O_{39}$ ($M = Co^{II}$, Cu^{II} , Ni^{II}) and $K_5SiCr^{III}(H_2O)W_{11}O_{39}$ were prepared by the literature procedure.^[10] The polyoxometalates were wet impregnated from water on γ -alumina at a 5 wt % loading and dried at $100^\circ C$ overnight. Reactions were run in a stirred Parr autoclave at $300^\circ C$ and 23–54 atm H_2 . Specific conditions are given in the Table legends. The reaction products were analyzed by GC and GC-MS using an apolar methylsilicone column.

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Total Synthesis of Everninomicin 13,384-1— Part 1: Synthesis of the $A_1B(A)C$ Fragment**

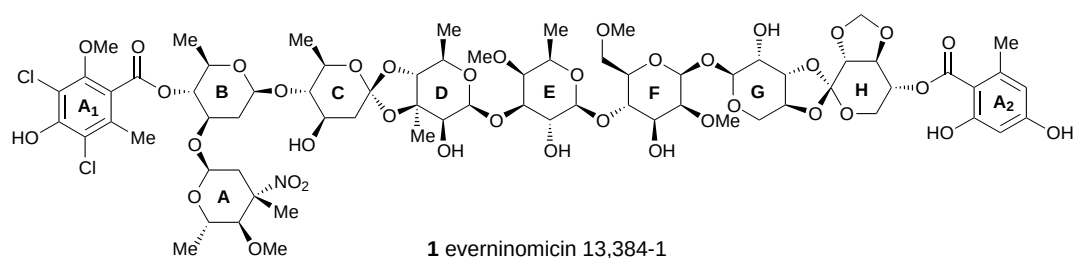
K. C. Nicolaou,* Helen J. Mitchell, Hideo Suzuki, Rosa Maria Rodríguez, Olivier Baudoin, and Konstantina C. Fylaktakidou

*Dedicated to Dr. A. K. Ganguly
on the occasion of his 65th birthday*

Drug-resistant bacteria are currently causing considerable concern because of the serious and constant threat they pose to human health and their potential to cause widespread epidemics. Even vancomycin,^[1] whose effectiveness against such resistant bacterial strains provided the last line of defense, is showing signs of weakness in the face of the evolution of aggressive bacteria. Everninomicin 13,384-1 (Ziracin) (**1**),^[2] a member of the orthosomicin class of antibiotics^[3] and currently in clinical trials, is a promising new weapon against drug-resistant bacteria, including methicillin-resistant staphylococci and vancomycin-resistant streptococci and enterococci.^[4] Isolated from *Micromonospora carbonacea* var. *africana* (found in a soil sample collected from the banks of the Nyiro River in Kenya), everninomicin 13,384-1 (**1**) possesses a novel oligosaccharide structure containing two sensitive orthoester moieties and terminating with two highly substituted aromatic esters. In addition, **1** contains a 1→1'-disaccharide bridge, a nitrosugar (everni-

[*] Prof. K. C. Nicolaou, H. J. Mitchell, Dr. H. Suzuki, Dr. R. M. Rodríguez, Dr. O. Baudoin, Dr. K. C. Fylaktakidou
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

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trose), thirteen rings, and thirty five stereogenic centers within its structure.^[5] Certainly, **1** constitutes a formidable challenge to organic synthesis^[6] because of its unusual connectivity and polyfunctional and sensitive nature. In this and the following two communications^[7, 8] we report the total synthesis of everninomicin 13,384-1 (**1**) through a number of novel synthetic strategies and methods. Herein we lay out the overall strategy and describe the construction of the A₁B(A)C fragment of the target molecule.

Figure 1 outlines, in retrosynthetic format, the strategy utilized in the present total synthesis. As a consequence of its

extreme sensitivity to acidic conditions^[2] the CD orthoester moiety was disassembled first, leading to phenylseleno fluoride **2** (the A₁B(A)C fragment) and diol **3** (the DEF-GHA₂ fragment). The larger fragment **3** was further disconnected at the EF glycosidic bond to give fragments **4** (DE) and **5** (FGHA₂) as potential key intermediates for its construction. Returning to fragment **2**, disconnection at the indicated sites (two glycosidic and one ester bonds) defined building blocks **6–9** as the requisite starting materials. Crucial to this plan were the 1,2-phenylseleno and 1,2-phenylthio migrations^[9] that set the stage for the stereocontrolled constructions of the CD and GH orthoesters and β -2-deoxy B-C glycoside bonds. The stereocontrolled synthesis of building blocks **6–9** and their assembly to the A₁B(A)C fragment **2** is described below.

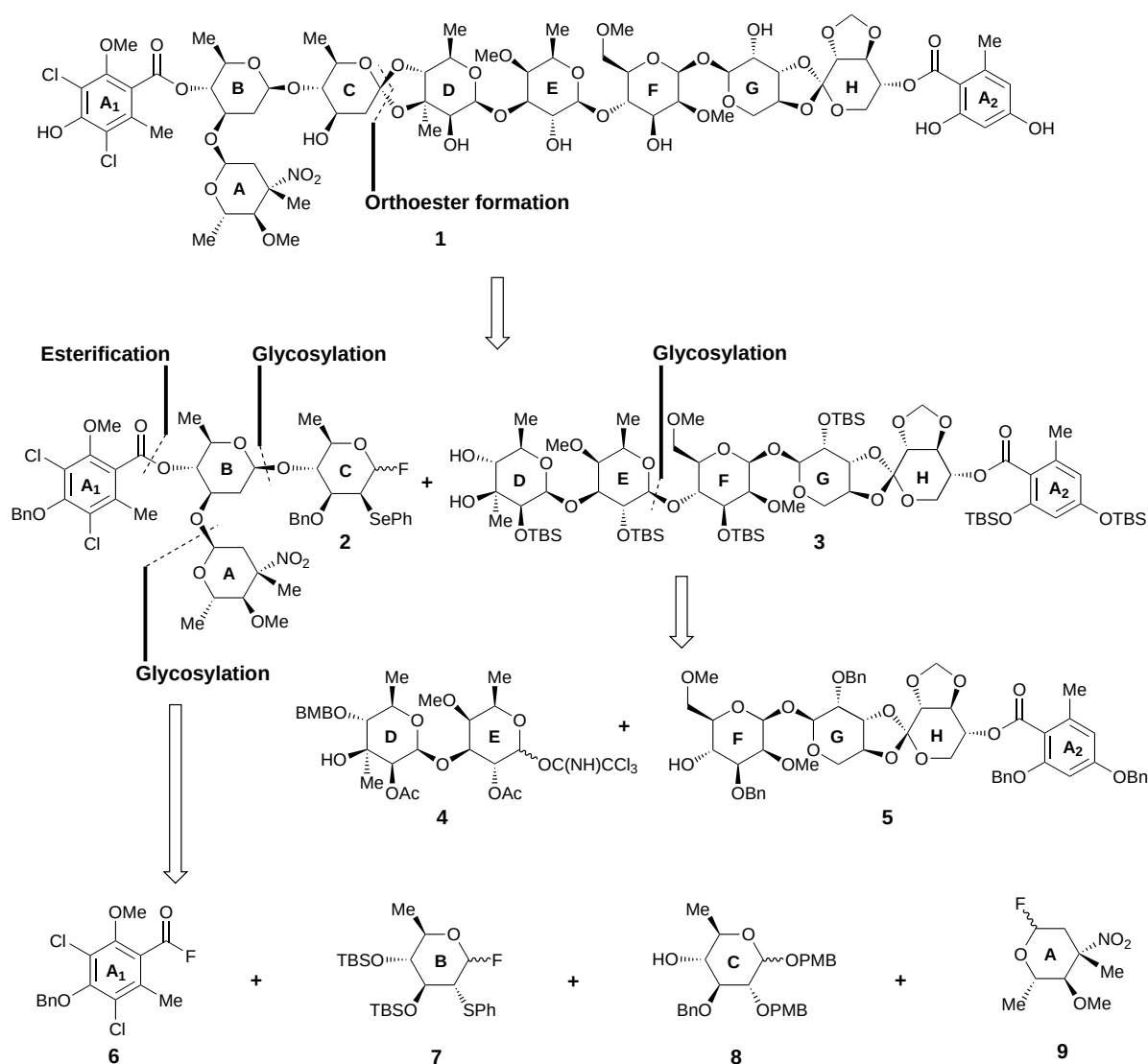
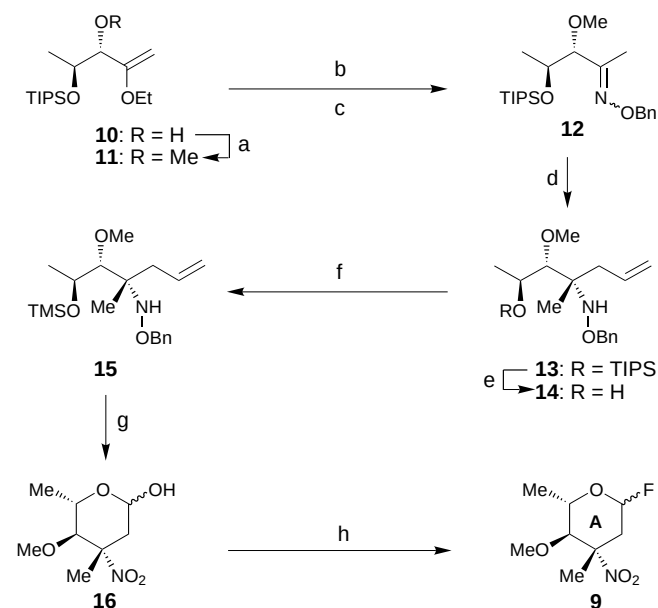


Figure 1. Retrosynthetic analysis of everninomicin 13,384-1 (**1**). Ac = acetyl; Bn = benzyl; PMB = *p*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl.

The construction of the evernitrose donor **9** (Scheme 1) involved an improved sequence along the lines of our original synthesis^[10] of both evernitrose and vancosamine. Thus, methylation of alcohol **10** with NaH and MeI gave, in 96 % yield, the methoxy compound **11**, which was hydrolyzed to the



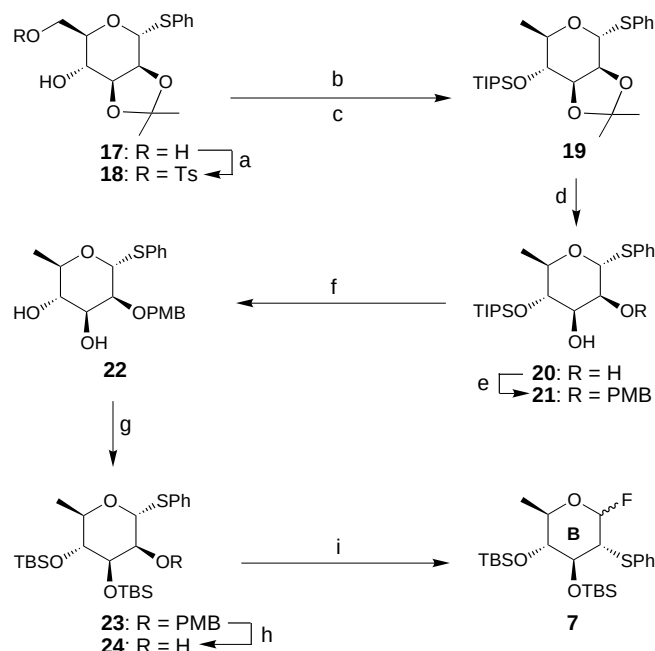
Scheme 1. Synthesis of nitrosugar A (**9**). a) 1.1 equiv NaH, 1.3 equiv MeI, THF, 0 → 25 °C, 4 h, 96 %; b) 0.1 N HCl, THF/H₂O (4/1), 25 °C, 0.5 h, 100 %; c) 1.1 equiv BnONH₂·HCl, py, 0 → 25 °C, 2 h, 91 % (*E:Z* ca. 4:1); d) 2.5 equiv allylMgBr, Et₂O, −35 °C, 1 h, 87 %; e) 1.1 equiv *n*Bu₄NF, THF, 25 °C, 1 h, 92 %; f) 5.0 equiv (TMS)₂NH, 0.1 equiv TMSCl, 25 °C, 0.5 h, 100 %; g) 1. O₃, *i*C₈H₈/CCl₄ (2/1), −78 °C, 1 h; 2. 2.0 equiv TFA, −78 → 25 °C, 1 h; 3. 2.0 equiv Ph₃P, −78 → 25 °C, 12 h, 82 % over three steps (*α:β* ca. 1.8:1); h) 1.5 equiv DAST, CH₂Cl₂, 0 °C, 20 min, 100 %. DAST = (diethylamino)sulfur trifluoride; py = pyridine; TFA = trifluoroacetic acid; TIPS = triisopropylsilyl; TMS = trimethylsilyl.

corresponding ketone with aqueous HCl and converted into oxime **12** by condensation with *O*-benzylhydroxylamine (ratio of *E:Z* isomers approximately 4:1; 91 % over 2 steps). Addition of allylmagnesium bromide to **12** in diethyl ether at −35 °C afforded **13** (87 % yield), which after an exchange of silyl groups (*n*Bu₄NF, 92 %; (TMS)₂NH, TMSCl, 100 %) gave the more labile trimethylsilyl ether **15** via the hydroxy compound **14**. Ozonolysis of **15** followed by sequential exposure to TFA and Ph₃P resulted in aldehyde and nitro group formation, desilylation, and ring closure and the generation of lactol **16**. Finally, treatment of lactol **16** with DAST^[11] led to its rapid conversion into glycosyl fluoride **9** in quantitative yield (an approximate 8:1 mixture of *α*- and *β*-anomers).

Despite our original model studies^[12] and success in constructing rings B and C from a common intermediate, we now required a more demanding orchestration of protecting groups and glycosylation tactics for an eventual total synthesis. After considerable design and experimentation, we finally discovered the winning combination of TBS and PMB groups on rings B and C, respectively.

Furthermore, the adopted constructions of rings B (**7**) and C (**8**) took independent paths and started from thioglycoside

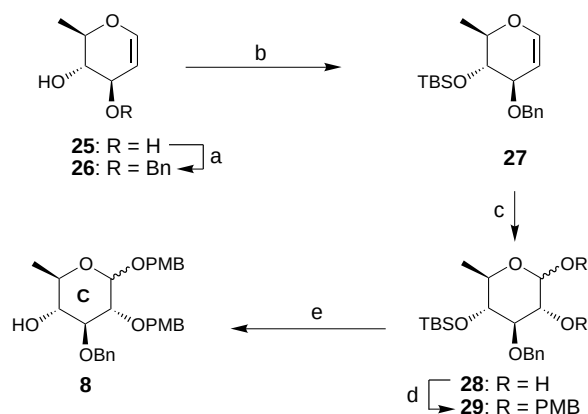
17 (Scheme 2) and glucal **25** (Scheme 3), respectively. The synthesis of building block **7** is summarized in Scheme 2. Thus, tosylation of the primary hydroxyl group of the known intermediate **17**^[13] with TsCl/py furnished tosylate **18** (93 %), which was silylated (TIPSOTf/2,6-lutidine, 90 %) and reduced with LAH (90 %) to afford compound **19**. Acidic methanolysis (TsOH/MeOH) of the acetonide group in **19** gave diol **20** (80 %), whose exposure to *n*Bu₂SnO^[14] and subsequent



Scheme 2. Synthesis of carbohydrate building block B (**7**). a) 1.1 equiv TsCl, py, 0 → 25 °C, 12 h, 93 %; b) 1.1 equiv TIPSOTf, 1.5 equiv 2,6-lutidine, CH₂Cl₂, 0 → 25 °C, 0.5 h, 90 %; c) 2.5 equiv LAH, THF, 0 → 45 °C, 6 h, 90 %; d) 0.5 equiv TsOH, 2.5 equiv (CH₂OH)₂, MeOH, 25 °C, 10 h, 80 %; e) 1.1 equiv *n*Bu₂SnO, toluene, 110 °C, 3 h; 1.5 equiv PMBCl, 0.2 equiv *n*Bu₄NF, 25 → 110 °C, 83 %; f) 2.5 equiv *n*Bu₄NF, THF, 25 °C, 2 h, 91 %; g) 2.2 equiv TBSOTf, 4.0 equiv 2,6-lutidine, CH₂Cl₂, 0 → 25 °C, 0.5 h, 93 %; h) 1.5 equiv DDQ, CH₂Cl₂/H₂O (10/1) 0 → 25 °C, 1 h, 91 %; i) 1.5 equiv DAST, CH₂Cl₂, 0 °C, 20 min, 100 % (*α:β* ca. 10:1). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; LAH = lithium aluminum hydride; Tf = trifluoromethanesulfonyl; Ts = *p*-toluenesulfonyl.

reaction with PMBCl/*n*Bu₄NF furnished **21** in 83 % overall yield. Removal of the TIPS group was induced by *n*Bu₄NF to give diol **22** (91 %), whose treatment with TBSOTf and 2,6-lutidine furnished the bis-TBS derivative **23** (93 %). Finally, DDQ deprotection of **23** gave hydroxy compound **24** (91 %), which on exposure to DAST resulted in the desired 1,2-migration^[9] of the thiophenyl group (with inversion of the C2 stereochemistry) and implantation of the fluoride group at C1 (100 %, approximate 10:1 mixture of *α*- and *β*-anomers) leading to the targeted glycosyl fluoride **7**.

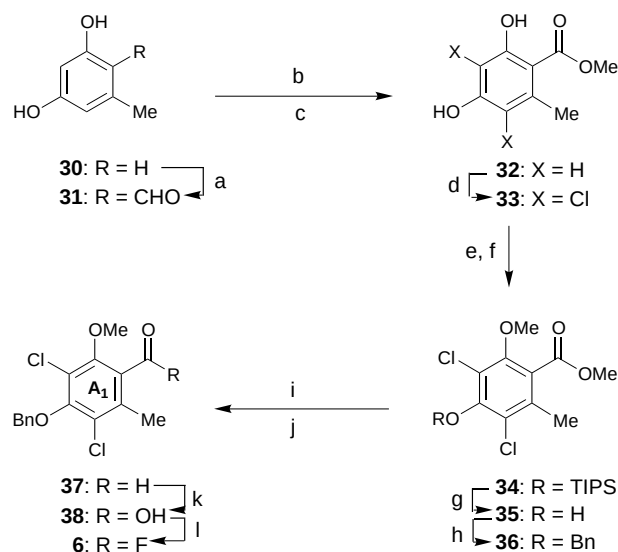
Building block **8** was constructed in five steps from the readily available glucal **25**^[15] as shown in Scheme 3. Thus, tin acetate mediated benzylation of **25** (*n*Bu₂SnO, BnBr/*n*Bu₄NF) resulted in the selective protection at C3 in 83 % yield. Further protection, now at C4, with TBSCl/imidazole led to compound **27** whose exposure to OsO₄/NMO furnished diol **28** in 97 % yield (approximate 1:1 mixture of anomers). Protection of both hydroxyl groups of **28** as PMB ethers



Scheme 3. Synthesis of carbohydrate building block **8**. a) 1.1 equiv $n\text{Bu}_2\text{SnO}$, toluene, 110°C , 3 h, 1.5 equiv BnBr , 0.2 equiv $n\text{Bu}_4\text{NI}$, $25 \rightarrow 110^\circ\text{C}$, 5 h, 83 %; b) 1.5 equiv TBSCl , 2.5 equiv imidazole, $0 \rightarrow 25^\circ\text{C}$, 3 h, 93 %; c) 1.1 equiv NMO , 0.05 equiv OsO_4 , $\text{Me}_2\text{CO}/\text{H}_2\text{O}$ (10/1), 25°C , 8 h, 97 %; d) 2.4 equiv NaH , 3.0 equiv PMBCl , 0.2 equiv $n\text{Bu}_4\text{NI}$, DMF , $0 \rightarrow 25^\circ\text{C}$, 3 h, 95 %; e) 1.1 equiv $n\text{Bu}_4\text{NF}$, THF , 25°C , 1 h, 95 % ($\alpha:\beta$ ca. 1:1). $\text{NMO} = N\text{-methylmorpholine } N\text{-oxide}$.

($\text{NaH}/\text{PMBCl}/n\text{Bu}_4\text{NI}$, 95 %) led to **29** (approximate 1:1 mixture of anomers) and exposure to $n\text{Bu}_4\text{NF}$ generated the desired building block **8** in 95 % yield. The stereochemistry at C1 is inconsequential as it will be destroyed at a later stage.

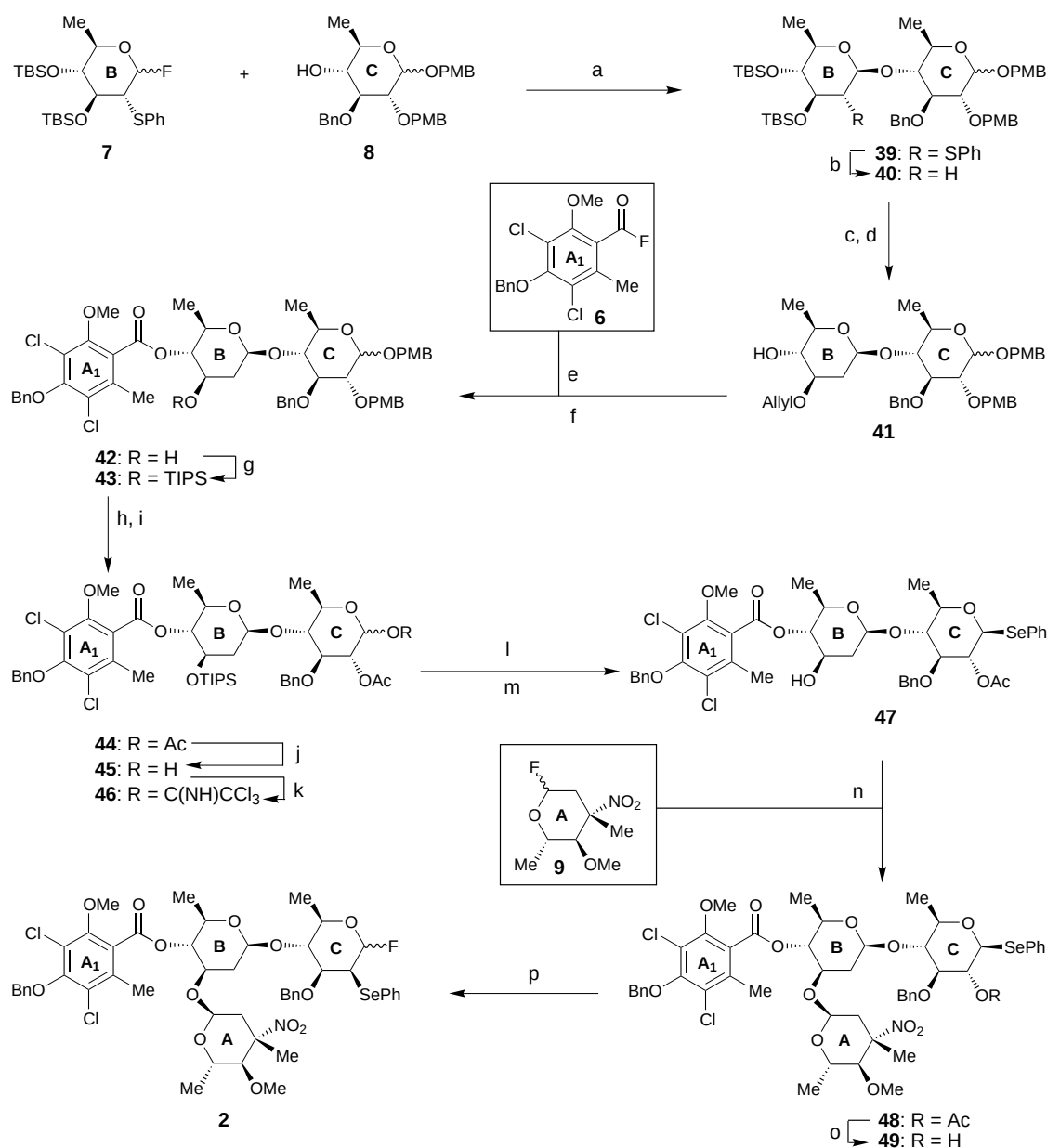
A more efficient synthesis than the one previously reported^[12] for the aromatic fragment **6** was developed and is summarized in Scheme 4. Thus, Gatterman formylation of



Scheme 4. Synthesis of aromatic ring A_1 (**6**). a) 1.5 equiv $\text{Zn}(\text{CN})_2$, 2.4 equiv AlCl_3 , HCl(g) , 0°C , 3 h; 2. H_2O , $0 \rightarrow 100^\circ\text{C}$, 30 min, 92 %; b) 2.4 equiv NaClO_2 , 2.5 equiv NaH_2PO_4 , DMSO , 0°C , 12 h, 80 %; c) 2.0 equiv MeI , 1.2 equiv NaHCO_3 , CH_2Cl_2 , 25°C , 12 h, 90 %; d) 2.5 equiv SO_2Cl_2 , CH_2Cl_2 , 35°C , 3 h, 95 %; e) 1.1 equiv TIPSOTf , 1.3 equiv 2,6-lutidine, CH_2Cl_2 , -78°C , 0.5 h, 90 %; f) 4.0 equiv Ag_2O , 4.0 equiv MeI , Et_2O , 30°C , 12 h, 91 %; g) 1.3 equiv $n\text{Bu}_4\text{NF}$, THF , 25°C , 2 h, 96 %; h) 1.5 equiv BnBr , 3.0 equiv K_2CO_3 , Me_2CO , 70°C , 92 %; i) 1.2 equiv DIBAL , CH_2Cl_2 , -78°C , 1 h, 90 %; j) 3.0 equiv PDC , 3 Å MS , CH_2Cl_2 , 25°C , 3 h, 90 %; k) 3.0 equiv NaClO_2 , 3.0 equiv NaH_2PO_4 , 2-methyl-2-butene (2.0 M in THF , 4.0 equiv), $t\text{BuOH}$, H_2O , 25°C , 3 h, 95 %; l) 1.5 equiv $(\text{Me}_2\text{N})_2\text{CF}^+\text{PF}_6^-$, 2.0 equiv $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 2 h, 97 %. $\text{DIBAL} = \text{diisobutylaluminum hydride}$; $\text{DMSO} = \text{dimethylsulfoxide}$; $\text{PDC} = \text{pyridinium dichromate}$.

orcinol (**30**) with $\text{Zn}(\text{CN})_2/\text{AlCl}_3$ gave aldehyde **31** (92 %), which was oxidized to the corresponding carboxylic acid (NaClO_2 , 80 %) and methylated ($\text{MeOH}/\text{NaHCO}_3$) to give methyl ester **32** (90 %). Chlorination of **32** with SO_2Cl_2 led to dichloride **33** in 95 % yield, while sequential protection of the phenolic groups proceeded smoothly and regioselectively upon treatment with $\text{TIPSOTf}/2,6\text{-lutidine}$ (90 %) and $\text{Ag}_2\text{O}/\text{MeI}$ (91 %) to furnish compound **34**. The TIPS group was then exchanged for a Bn group ($n\text{Bu}_4\text{NF}$, 96 %; $\text{K}_2\text{CO}_3/\text{BnBr}$, 92 %) to give **36** via **35**. The resistance of the methyl ester in **36** towards hydrolysis led to a three-step protocol for its conversion into carboxylic acid **38** (DIBAL reduction, 90 %; PDC oxidation, 90 %; NaClO_2 oxidation, 95 %) involving aldehyde **37** as an intermediate. Finally, exposure^[16] of **38** to $(\text{Me}_2\text{N})_2\text{CF}^+\text{PF}_6^-$ gave the desired acyl fluoride **6**, which withstood chromatographic purification on silica gel (97 % yield).

Having constructed all four requisite building blocks (**6–9**), their assembly became the next task at hand. Scheme 5 summarizes their stereoselective coupling to form the $\text{A}_1\text{B(A)C}$ fragment **2**. Thus, the SnCl_2 -mediated coupling of glycosyl fluoride **7** with alcohol **8** under mild conditions (4 Å MS , $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{Me}_2\text{S}$ (1/1/1), -10°C)^[9] gave disaccharide **39** in 71 % yield and as a single stereoisomer. Having performed its β -directing duty, thus ensuring the desired stereochemical outcome in this glycosylation reaction, the 2-thiophenyl group was now ready for reductive cleavage with Raney-nickel. This procedure led smoothly from **39** to **40**. The latter intermediate (**40**) was then modified for its coupling with acyl fluoride **6** by bis-desilylation ($n\text{Bu}_4\text{NF}$, 78 % over two steps) and selective monoallylation ($n\text{Bu}_2\text{SnO}/\text{allyl bromide}$, 93 %) to convert it into **41** (Table 1). Upon activation of the hydroxyl group of **41** ($n\text{BuLi}$, THF , $-78 \rightarrow 0^\circ\text{C}$) followed by addition of acyl fluoride **6**, the corresponding ester was formed in 99 % yield, from which the allyl group was removed with Wilkinson's catalyst/ DABCO and OsO_4/NMO to afford **42** (81 % yield). A TIPS group was then installed on ring B ($\text{TIPSOTf}/2,6\text{-lutidine}$, 93 %) to afford compound **43**. These particular choices of protecting groups were necessary for optimum esterification yields and subsequent chemistry. Experimentation with future steps in the total synthesis dictated the introduction of the selenium group before the attachment of the evernitro fragment, and therefore the following sequence was adopted. Thus, the PMB groups were removed from **43** by exposure to PhSH and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (83 %) and acetate groups were installed in their place ($\text{Ac}_2\text{O}/\text{Et}_3\text{N}/4\text{-DMAP}$, 98 %) to afford diacetate **44**. Exposure of **44** to $n\text{BuNH}_2$ led to the selective cleavage of the C1 acetate and the liberation of lactol **45** (91 %), which was then converted into trichloroacetimidate **46**^[17] by treatment with CCl_3CN in the presence of DBU . Addition of PhSeH ^[18] to **46** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave the desired β -phenylseleno glycoside as expected with participation of the C2 acetate ($\alpha:\beta$ approximately 1:9, 78 % over two steps). Removal of the TIPS group from this product with $n\text{Bu}_4\text{NF}$ furnished the phenylseleno glycoside **47** (91 % yield), which was ready for the next coupling. Indeed, attachment of the evernitro fragment **9** onto the A_1BC chain **47** proceeded smoothly under the influence of SnCl_2 to furnish the desired



Scheme 5. Construction of A₁B(A)C fragment **2**. a) 1.0 equiv **7**, 1.1 equiv **8**, 1.8 equiv SnCl₂, 4 Å MS, CH₂Cl₂/Et₂O/Me₂S (1/1/1), −10 °C, 3 h, 71 %; b) ca. 1.0 equiv Raney-Ni (w/w), EtOH/THF (1/1), 90 °C, 8 h; c) 2.2 equiv *n*Bu₄NF, 25 °C, 2 h, 78 % over two steps; d) 1.1 equiv *n*Bu₂SnO, toluene, 110 °C, 3 h; 1.5 equiv allylBr, 0.2 equiv *n*Bu₄NI, 25 → 110 °C, 93 %; e) 1.1 equiv *n*BuLi, THF, −78 → 0 °C, 1 h; 1.2 equiv **6**, THF, 25 °C, 99 %; f) 1.5 equiv DABCO, 0.05 equiv [(Ph₃P)₃RhCl], EtOH/H₂O (10/1), 90 °C, 2 h; **2**: 1.1 equiv NMO, 0.05 equiv OsO₄, Me₂CO/H₂O (10/1), 25 °C, 8 h, 81 %; g) 1.2 equiv TIPSOTf, 1.5 equiv 2,6-lutidine, CH₂Cl₂, 0 → 25 °C, 1 h, 93 %; h) 8.0 equiv PhSH, 4.0 equiv BF₃·Et₂O, CH₂Cl₂, −30 °C, 2 h, 83 %; i) 2.5 equiv Ac₂O, 4.0 equiv Et₃N, 0.2 equiv 4-DMAP, CH₂Cl₂, 0 → 25 °C, 1 h, 98 %; j) 1.3 equiv *n*BuNH₂, THF, 25 °C, 5 h, 91 %; k) 5.0 equiv CCl₃CN, 0.05 equiv DBU, CH₂Cl₂, 0 °C, 0.5 h; l) ca. 2.0 equiv PhSeH, 0.2 equiv BF₃·Et₂O, CH₂Cl₂, −78 → 0 °C, 1 h, 78 % over two steps (α:β ca. 1:9); m) 1.2 equiv *n*Bu₄NF, THF, 25 °C, 1 h, 91 %; n) 2.0 equiv **9**, 1.2 equiv SnCl₂, CH₂Cl₂/Et₂O (1/1), 0 → 25 °C, 1 h, 80 %; o) 0.3 equiv NaOH, MeOH, 25 °C, 1 h, 91 %; p) 1.5 equiv DAST, CH₂Cl₂, 0 °C, 20 min, 90 % (α:β ca. 8:1). DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; 4-DMAP = 4-dimethylaminopyridine.

assembly **48** (80 %) in which the newly formed glycoside bond (A → B, α-anomer) was fully controlled by the anomeric effect.

Finally, basic hydrolysis (NaOH/MeOH) of the acetate group from **48** led to the C2 hydroxy compound **49** (91 % yield), whose treatment with DAST produced the targeted 2-phenylselenoglycosyl fluoride **2** in excellent yield (90 %) and with an inversion of the stereochemistry at C2 of ring C (approximate 8:1 mixture of α- and β-fluoride anomers).^[19] In

the following communication^[7] we describe the construction of the desired FGHA₂ fragment of everninomicin 13,384-1 (**1**).

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Table 1. Selected physical and spectroscopic data of compounds **41**, **42**, and **49**.

41: $R_f = 0.25$ (silica, 70 % Et₂O in hexanes); $\alpha_D^{25} = -23.4$ ($c = 0.80$, CHCl₃); IR (thin film): $\tilde{\nu}_{\max} = 3387, 2955, 2908, 2861, 1608, 1584, 1455, 1355, 1302, 1249, 1173, 1091, 1044, 926, 814, 732$ cm⁻¹; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.41-7.24$ (m, 7H, ArH), 7.17 (d, $J = 8.5$ Hz, 2H, PMB), 6.88 (d, $J = 8.5$ Hz, 2H, PMB), 6.79 (d, $J = 8.5$ Hz, 2H, PMB), 5.90 (dddd, $J = 17.0, 10.5, 6.0, 5.5$ Hz, 1H, OCH₂CHCH₂), 5.28 (dd, $J = 17.0, 1.5$ Hz, 1H, OCH₂CHCH₂), 5.19 (dd, $J = 10.5, 1.0$ Hz, 1H, OCH₂CHCH₂), 4.92 and 4.83 (AB, $J = 11.0$ Hz, 2H, CH₂Ar), 4.88 and 4.59 (AB, $J = 11.5$ Hz, 2H, CH₂Ar), 4.81 and 4.61 (AB, $J = 10.5$ Hz, 2H, CH₂Ar), 4.70 (dd, $J = 9.5, 2.0$ Hz, 1H, B-1), 4.47 (d, $J = 8.0$ Hz, 1H, C-1), 4.11 (dd, $J = 12.5, 5.5$ Hz, 1H, OCH₂CHCH₂), 3.94 (dd, $J = 12.5, 6.0$ Hz, 1H, OCH₂CHCH₂), 3.80 (s, 3H, OMe (PMB)), 3.77 (s, 3H, OMe (PMB)), 3.54 (t, $J = 8.5$ Hz, 1H, C-3), 3.44 (t, $J = 8.5$ Hz, 1H, C-2), 3.41–3.35 (m, 2H, C-4, C-5), 3.30–3.22 (m, 1H, B-3), 3.21–3.10 (m, 2H, B-4, B-5), 2.64 (d, $J = 2.0$ Hz, 1H, OH), 2.30 (ddd, $J = 12.5, 4.5, 2.0$ Hz, 1H, B-2), 1.46 (td, $J = 12.5, 9.5$ Hz, 1H, B-2), 1.35 (d, $J = 5.0$ Hz, 3H, C-6), 1.24 (d, $J = 5.5$ Hz, 3H, B-6); ¹³C NMR (125 MHz, CDCl₃): $\delta = 159.2, 159.0, 138.9, 134.5, 130.5, 130.0, 129.7, 129.7, 129.5, 129.4, 128.1, 127.5, 127.2, 117.3, 113.7, 113.5, 102.1, 100.0, 94.8, 83.1, 82.0, 81.8, 81.6, 80.4, 79.4, 78.5, 75.4, 75.2, 71.8, 70.8, 69.8, 55.1, 36.2, 18.0, 17.8$; HR-MS (FAB), calcd for C₃₈H₄₈O₁₀Cs [$M + Cs^+$]: 797.3202, found: 797.2287

42: $R_f = 0.24$ (silica, 70 % Et₂O in hexanes); $\alpha_D^{25} = +12.0$ ($c = 0.20$, CHCl₃); IR (thin film): $\tilde{\nu}_{\max} = 3425, 2931, 2884, 1731, 1614, 1544, 1138, 1326, 1302, 1249, 1120, 1073, 938, 820, 749$ cm⁻¹; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.57$ (d, $J = 6.9$ Hz, 2H, ArH), 7.43–7.28 (m, 10H, ArH), 7.16 (d, $J = 8.6$ Hz, 2H, PMB), 6.88 (d, $J = 8.6$ Hz, 2H, PMB), 6.79 (d, $J = 8.6$ Hz, 2H, PMB), 5.03 (brs, 2H, CH₂Ar (A₁)), 4.93 and 4.83 (AB, $J = 10.9$ Hz, 2H, CH₂Ar), 4.88 and 4.59 (AB, $J = 11.5$ Hz, 2H, CH₂Ar), 4.81 and 4.59 (AB, $J = 11.5$ Hz, 2H, CH₂Ar), 4.78 (t, $J = 9.4$ Hz, 1H, B-4), 4.74 (dd, $J = 9.7, 1.8$ Hz, 1H, B-1), 4.47 (d, $J = 7.9$ Hz, 1H, C-1), 3.87 (s, 3H, OMe), 3.85–3.72 (m, 1H, B-3), 3.81 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.55 (brt, $J = 9.0$ Hz, 1H, C-3), 3.43 (dd, $J = 9.0, 7.9$ Hz, 1H, C-2), 3.41–3.36 (m, 2H, C-4, C-5), 3.33 (dq, $J = 9.4, 6.2$ Hz, 1H, B-5), 2.66 (d, $J = 4.4$ Hz, 1H, OH), 2.36 (s, 3H, Me (A₁)), 2.40–2.30 (m, 1H, B-2), 1.72 (td, $J = 12.2, 9.7$ Hz, 1H, B-2), 1.35 (d, $J = 5.3$ Hz, 3H, C-6), 1.23 (d, $J = 6.2$ Hz, 3H, B-6); ¹³C NMR (150 MHz, CDCl₃): $\delta = 166.4, 159.3, 159.1, 153.0, 151.8, 139.0, 138.9, 133.2, 130.5, 130.1, 129.8, 129.7, 129.6, 129.5, 129.2, 128.5, 128.2, 127.5, 127.3, 126.4, 125.5, 121.4, 113.8, 113.6, 102.2, 100.3, 84.2, 82.9, 81.9, 79.5, 75.3, 74.9, 74.5, 70.9, 70.8, 69.8, 69.6, 65.8, 62.4, 55.2, 39.3, 34.2, 30.3, 29.5, 21.1, 18.0, 17.6, 17.4, 15.2$; HR-MS (FAB), calcd for C₅₁H₅₆Cl₂O₁₃Na [$M + Na^+$]: 969.2995, found: 969.2998

49: $R_f = 0.20$ (silica, 50 % Et₂O in hexanes); $\alpha_D^{25} = -36.1$ ($c = 0.40$, CHCl₃); IR (thin film): $\tilde{\nu}_{\max} = 3476, 2939, 1732, 1542, 1453, 1391, 1251, 1128, 1032, 911, 736$ cm⁻¹; ¹H NMR (600 MHz, CDCl₃): $\delta = 7.64$ (d, $J = 7.0$ Hz, 2H, ArH), 7.57 (d, $J = 7.0$ Hz, 2H, ArH), 7.45–7.27 (m, 11H, ArH), 5.06 and 5.03 (AB, $J = 10.2$ Hz, 2H, CH₂Ar), 4.98 and 4.83 (AB, $J = 11.3$ Hz, 2H, CH₂Ar), 4.94 (brdd, $J = 5.0, 1.8$ Hz, 1H, A-1), 4.89 (t, $J = 9.4$ Hz, 1H, B-4), 4.72 (d, $J = 9.6$ Hz, 1H, C-1), 4.67 (dd, $J = 9.7, 1.8$ Hz, 1H, B-1), 3.89–3.83 (m, 1H, B-3), 3.86 (s, 3H, OMe (A₁)), 3.65 (d, $J = 9.4$ Hz, 1H, A-4), 3.53–3.32 (m, 6H, A-5, B-5, C-2, C-3, C-4, C-5), 3.36 (s, 3H, OMe (A₁)), 2.49 (brs, 1H, OH), 2.46 (dd, $J = 13.8, 5.0$ Hz, 1H, A-2), 2.39 (s, 3H, Me (A₁)), 2.29 (ddd, $J = 12.9, 5.1, 1.8$ Hz, 1H, B-2), 2.02 (dd, $J = 13.8, 1.8$ Hz, 1H, A-2), 1.72–1.65 (m, 1H, B-2), 1.68 (s, 3H, Me (A-3)), 1.34 (d, $J = 5.9$ Hz, 3H, B-6 or C-6), 1.33 (d, $J = 6.2$ Hz, 3H, B-6 or C-6), 0.84 (d, $J = 6.2$ Hz, 3H, A-6); ¹³C NMR (150 MHz, CDCl₃): $\delta = 165.5, 153.2, 153.1, 138.7, 135.8, 135.1, 134.7, 129.0, 128.6, 128.5, 128.3, 128.2, 127.6, 127.5, 126.3, 125.9, 125.4, 99.7, 99.0, 92.4, 89.9, 84.3, 84.2, 83.0, 81.7, 76.7, 76.1, 75.0, 74.9, 73.1, 72.3, 71.0, 66.2, 61.9, 90.7, 40.0, 36.4, 31.5, 30.2, 22.6, 19.3, 18.3, 18.2, 18.0, 17.6, 14.1$; HR-MS (FAB), calcd for C₄₉H₃₇Cl₂NO₁₄SeCs [$M + Cs^+$]: 1166.1378, found: 1166.1319

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Total Synthesis of Everninomicin 13,384-1— Part 2: Synthesis of the FGHA₂ Fragment**

K. C. Nicolaou,* Rosa María Rodríguez,
Konstantina C. Fylaktakidou, Hideo Suzuki, and
Helen J. Mitchell

In the preceding paper,^[1] we described the construction of the A₁B(A)C fragment of everninomicin 13,384-1 (**1**). Herein we report the synthesis of the FGHA₂ fragment (**2**) of this

target molecule (Figure 1). The novelty of this oligosaccharide fragment (**2**), which contains the challenging features of a 1 → 1'-disaccharide unit, a highly sensitive orthoester moiety, and a *trans*-methylene acetal, forced us into a somewhat linear, but nevertheless efficient, strategy.

Figure 1 outlines the retrosynthetic analysis upon which the successful strategy towards subtarget **2** was based. Thus, disconnection of the ester and orthoester bonds in **2** led to fragments **3** and **4**. Further disconnection of **3** at the indicated glycoside bond revealed diol **5** and 2-phenylselenoglycosyl

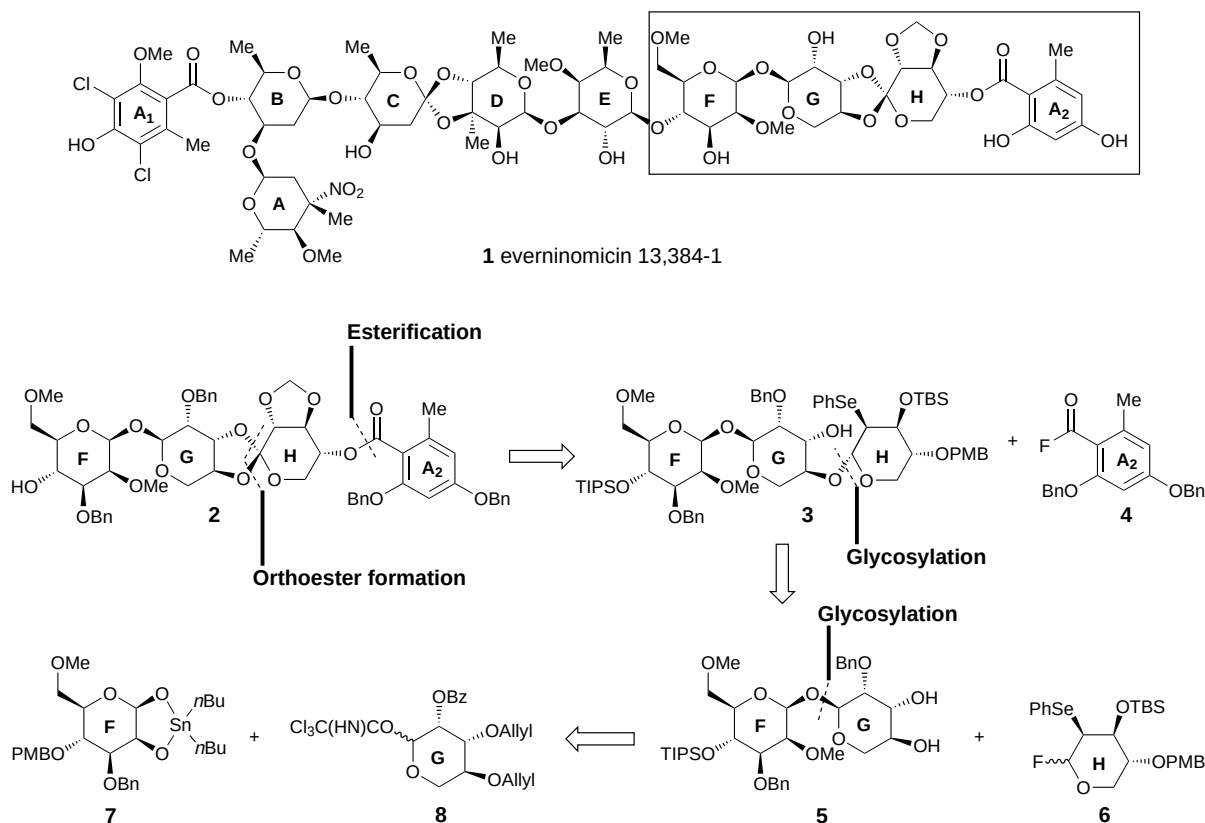


Figure 1. Retrosynthetic analysis of FGHA₂ fragment (**2**). Bn = benzyl; Bz = benzoyl; PMB = *p*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl.

[*] Prof. K. C. Nicolaou, Dr. R. M. Rodríguez,
Dr. K. C. Fylaktakidou, Dr. H. Suzuki, H. J. Mitchell
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

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fluoride **6** as potential precursors. A selenium-assisted coupling of **5** with **6** was expected to furnish regio- and stereo-selectively trisaccharide **3**, which would be poised for the formation of a Sinaÿ-type orthoester.^[2] The success of this scheme depended on the stereoselectivity of this reaction (see Figures 2 and 3). Final disassembly of **5** led to tin acetal **7** and trichloroacetimidate **8** as starting building blocks for this disaccharide. The stereoselective construction of the 1 → 1'-disaccharide bridge of **5** from **7** and **8** was assured from our previous studies on model systems that culminated in an efficient new method^[3] for accomplishing this task.

The construction of the individual building blocks are presented in Schemes 1–4. Building block F (**7**) was synthesized from the readily available phenylthioglycoside **9**^[4] as follows (Scheme 1). Selective silylation of the primary hydroxyl group of **9** (TBSOTf/2,6-lutidine, 97 %) gave silyl ether **10**, which was sequentially exposed to NaH/PMBCl/*n*Bu₄NI (95 % yield) and *n*Bu₄NF (95 % yield) to afford primary

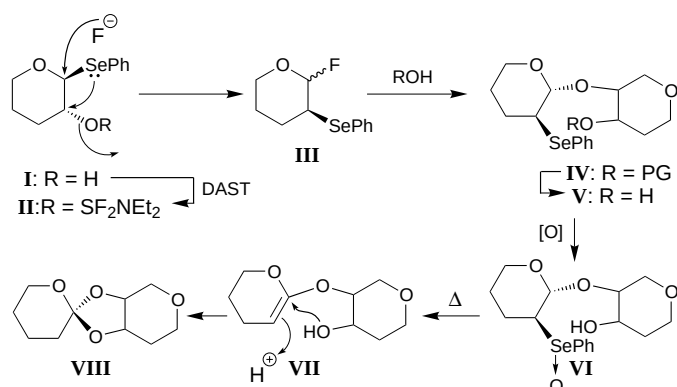
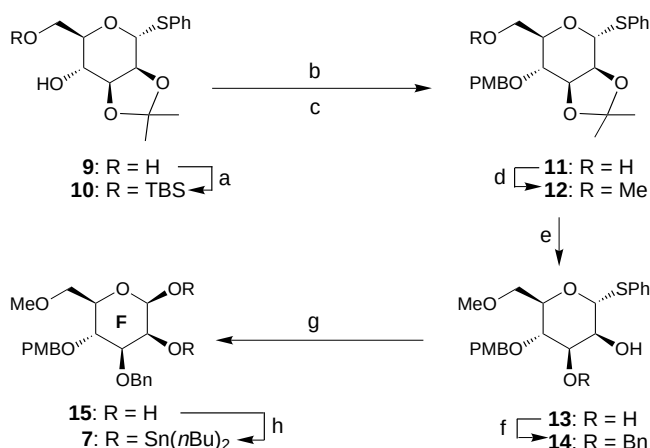


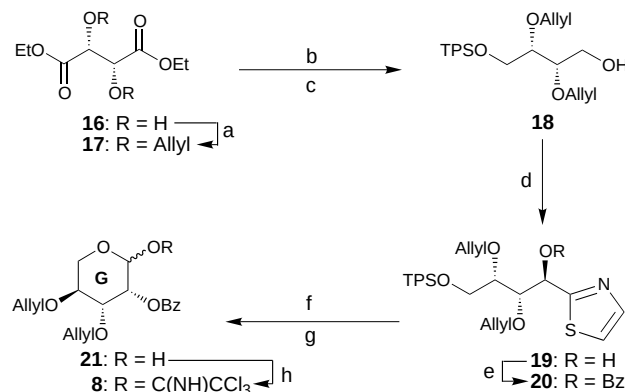
Figure 2. Orthoester formation via 1,2-migration of the phenylseleno group followed by glycosylation (I→II→III→IV)^[10] and ring closure after syn-elimination (V→VI→VII→VIII).^[2] DAST = diethylaminosulfur trifluoride; [O] = oxidant; PG = protecting group.



Scheme 1. Synthesis of carbohydrate building block F (7). a) 1.2 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH₂Cl₂, 0→25°C, 1 h, 97%; b) 1.1 equiv NaH, 1.3 equiv PMBCl, 0.2 equiv nBu₄NI, DMF, 0→25°C, 4 h, 95%; c) 1.2 equiv nBu₄NF, THF, 25°C, 1 h, 95%; d) 1.1 equiv NaH, 1.3 equiv MeI, DMF, 0→25°C, 1 h, 95%; e) 0.2 equiv TsOH, 2.5 equiv (CH₃OH)₂, MeOH, 25°C, 5 h, 85%; f) 1.1 equiv nBu₂SnO, toluene, 110°C, 3 h; 1.5 equiv BnBr, 0.2 equiv nBu₄NI, 25→110°C, 5 h, 89%; g) 1.5 equiv NBS, Me₂CO/H₂O (10/1), 0→25°C, 2 h, 97%; h) 1.1 equiv nBu₂SnO, MeOH, 90°C, 3 h, 100%. NBS = *N*-bromosuccinimide; Tf = trifluoromethanesulfonyl; Ts = *p*-toluenesulfonyl.

alcohol 11. Methylation of 11 (NaH/MeI) then furnished methoxy compound 12 in 95% yield. Acidic methanolysis (TsOH/MeOH) of the acetonide group from 12 led to diol 13 (85% yield), which was selectively benzylated at C3 using the tin acetal technology^[5] (nBu₂SnO/BnBr/nBu₄NI, 89%) to afford 14. Rupture of the thiophenyl group from 14 with NBS/H₂O furnished lactol 15 (97% yield), which was converted into the desired tin acetal 7 by exposure to nBu₂SnO in refluxing MeOH (100% yield).

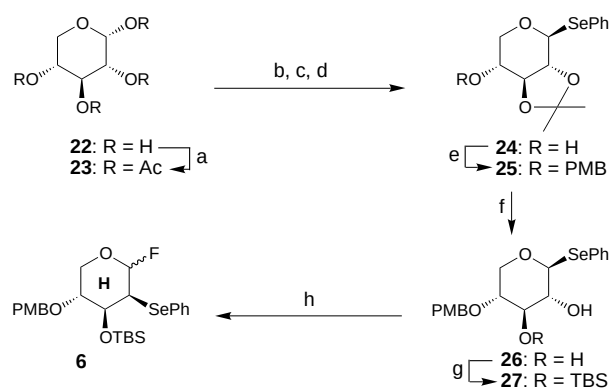
Scheme 2 summarizes the synthesis of the ring G trichloroacetimidate 8 starting from diethyl-L-tartrate (16). Thus, bis-allylation of 16 was effected by treatment with NaH/allyl bromide to afford 17 (93% yield). Reduction of both ester groups of 17 with LAH in refluxing diethyl ether (93%) was followed by monosilylation (NaH/TPSCl) to furnish hydroxy silyl ether 18 in 90% yield. Swern oxidation ((COCl)₂/DMSO/Et₃N)^[6] of 18 led to the corresponding aldehyde, which was



Scheme 2. Synthesis of carbohydrate building block G (8). a) 2.1 equiv NaH, 2.1 equiv allylBr, 0.1 equiv nBu₄NI, 0.1 equiv [18]crown-6, THF, 0→25°C, 4 h, 93%; b) 2.6 equiv LAH, Et₂O, 25→35°C, 93%; c) 1.0 equiv NaH, 1.1 equiv TPSCl, 0.1 equiv nBu₄NI, THF, 0→25°C, 4 h, 90%; d) 1. 2.0 equiv (COCl)₂, 2.5 equiv DMSO, −78°C, 2 h; 2. 4.0 equiv Et₃N, −78→−40°C, 2 h; 3. TMS/thiazole, −40→0°C; 4. 1.5 equiv PPTS, MeOH, 0→25°C, 91% (1:1 mixture of diastereoisomers); e) 1.1 equiv BzCl, 1.5 equiv Et₃N, 0.2 equiv 4-DMAP, CH₂Cl₂, 0→25°C, 2 h, 98%; f) 1.2 equiv MeOTf, MeCN, 25°C, 0.5 h; 2. 2.4 equiv NaBH₄, MeOH, 0→25°C, 0.5 h; 3. 1.2 equiv CuCl₂, 8.0 equiv CuO, MeCN/H₂O (5/1), 25°C, 2 h; g) 1.5 equiv nBu₄NF, THF, 25°C, 2 h, 81% over four steps; h) 5.0 equiv CCl₃CN, 0.05 equiv DBU, CH₂Cl₂, 0→25°C, 0.5 h, 85%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; 4-DMAP = 4-(dimethylamino)pyridine; DMSO = dimethylsulfoxide; LAH = lithium aluminum hydride; PPTS = pyridinium *p*-toluenesulfonate; TMS = trimethylsilyl; TPS = *tert*-butyldi-phenylsilyl.

exposed to TMS/thiazole according to the method of Dondoni et al.^[7] to afford, after acidic workup (PPTS/MeOH), the homologated chain 19 (91% yield, approximate 1:1 ratio of epimeric alcohols). It is interesting to note here that when we used the acetonide counterpart of the bis-allyl aldehyde derived from 18 we observed a ratio of more than 10:1 of the desired:undesired alcohols in the Dondoni reaction. However, subsequent difficulties with protecting group manipulation led to the adoption of the less selective sequence described above, whose efficiency was improved by recycling the wrong isomer (oxidation/reduction). Benzoylation of the chromatographically pure alcohol 19 (BzCl/Et₃N/4-DMAP, 98%), followed by thiazole rupture (MeOTf; NaBH₄; CuO; one-pot reaction)^[7] and desilylation (nBu₄NF) led to lactol 21 (81% overall yield) via benzoate 20. Finally, formation of the trichloroacetimidate 8^[8] was easily accomplished by exposure to CCl₃CN in the presence of DBU (85% yield).

Scheme 3 presents the synthesis of ring H as the 2-phenylselenoglycosyl fluoride 6 from D-xylose (22). Peracetylation of 22 (Ac₂O/Et₃N/4-DMAP, 98% yield) followed by treatment with PhSeH/BF₃·Et₂O^[9] led to a mixture of α- and β-glycosides (α:β approximately 1:5, 93% yield). The desired β-glycoside was subjected to basic methanolysis (K₂CO₃/MeOH) and the resulting triol was exposed to CH₃(CH₃O)C=CH₂/TFA to afford predominantly the 2,3-acetonide 24 (74% yield over two steps). The remaining hydroxyl group in 24 was then protected as a PMB ether (NaH/PMBCl/nBu₄NI, 95% yield) and the acetonide was removed under acidic conditions (PPTS/MeOH) to furnish diol 26 (96% yield). The next task was to protect the C3 hydroxyl group of 26, an objective that was achieved by exposure of the latter compound to TBSOTf/2,6-lutidine in

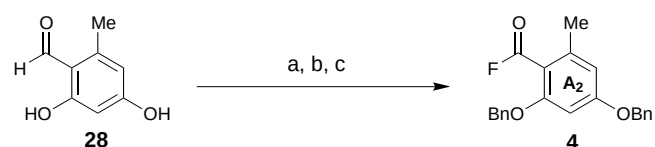


Scheme 3. Synthesis of carbohydrate building block **H** (**6**). a) 5.0 equiv Ac_2O , 8.0 equiv Et_3N , 0.2 equiv 4-DMAP, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 2 h, 98%; b) ca. 2.0 equiv PhSeH , 0.2 equiv $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 4 h, 93% ($\alpha:\beta$ ca. 1:5); c) 0.3 equiv K_2CO_3 , MeOH , 25°C , 5 h; d) 1.5 equiv $\text{CH}_3(\text{CH}_3\text{O})\text{C}=\text{CH}_2$, 0.2 equiv TFA, DMF , 45°C , 3 h, 74% over two steps; e) 1.1 equiv NaH , 1.3 equiv PMBCl , 0.2 equiv $n\text{Bu}_4\text{NI}$, DMF , $0 \rightarrow 25^\circ\text{C}$, 2 h, 95%; f) 0.2 equiv PPTS, MeOH , $0 \rightarrow 25^\circ\text{C}$, 2 h, 96%; g) 1.1 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 0.5 h, 91%; h) 1.5 equiv DAST, CH_2Cl_2 , 0°C , 20 min, 100%. DMF = dimethylformamide; TFA = trifluoroacetic acid.

THF at -78°C to give **27** in 91% yield. Parenthetically, and interestingly, treatment of **26** with the same silylating reagent in CH_2Cl_2 , instead of THF, led to the C2 derivative (96%), an

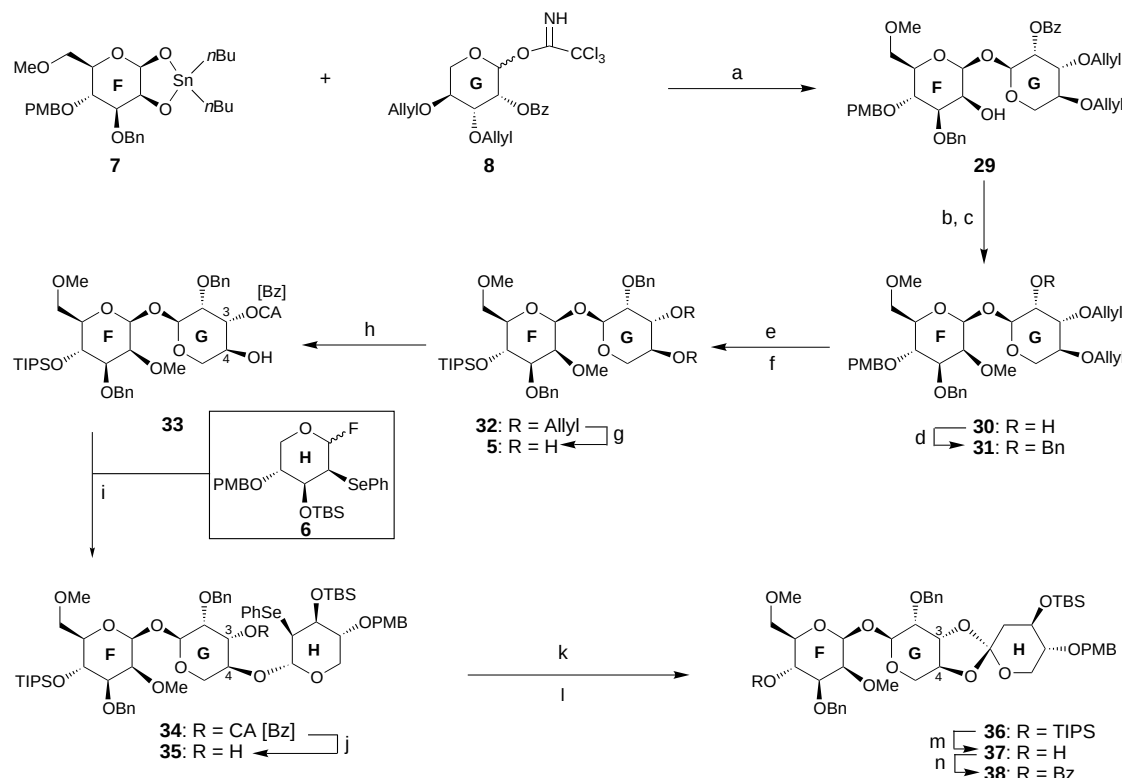
observation that has to await an explanation. Having set the stage for the 1,2-migration,^[10] the targeted 2-phenylselenoglycosyl fluoride **6** was then formed by simple treatment of **27** with DAST (100% yield). This maneuver represents a new reaction^[11] in carbohydrate chemistry and played a crucial role in the success of this total synthesis.

The construction of the aromatic fragment A_2 (**4**) is depicted in Scheme 4. Thus, benzylation of **28**^[1] ($\text{K}_2\text{CO}_3/\text{BnBr}$, 92%) followed by oxidation (NaClO_2 , 80% yield) and fluorination of the resulting carboxylic acid ($(\text{Me}_2\text{N})_2\text{CF}^+\text{PF}_6^-$, 80% yield)^[12] furnished the desired acyl fluoride **4** in high overall yield.



Scheme 4. Synthesis of aromatic ring A_2 (**4**). a) 2.5 equiv BnBr , 4.0 equiv K_2CO_3 , Me_2CO , 70°C , 92%; b) 2.4 equiv NaClO_2 , 2.5 equiv NaH_2PO_4 , DMSO , 0°C , 12 h, 80%; c) 1.5 equiv $(\text{Me}_2\text{N})_2\text{CF}^+\text{PF}_6^-$, 2.0 equiv $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 2 h, 80%.

The assembly of building blocks **4**–**8** to form the targeted intermediate **2** is presented in Schemes 5 and 6. The first task was to construct stereoselectively the $1 \rightarrow 1'$ -trehalose-type



Scheme 5. Assembly of FGH fragment **38**. a) 1.0.3 equiv TMSOTf, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 8 h; 2.0.3 equiv PPTS, MeOH , 25°C , 1 h, 74% over two steps; b) 1.1 equiv NaH , 1.3 equiv MeI , DMF , $0 \rightarrow 25^\circ\text{C}$, 1 h, 87%; c) 0.3 equiv NaOH , MeOH , 25°C , 1 h, 95%; d) 1.1 equiv NaH , 1.3 equiv BnBr , 0.2 equiv $n\text{Bu}_4\text{NI}$, DMF , $0 \rightarrow 25^\circ\text{C}$, 4 h, 90%; e) 1.5 equiv DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10/1), $0 \rightarrow 25^\circ\text{C}$, 1 h, 91%; f) 1.2 equiv TIPSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 1 h, 97%; g) 1.2.5 equiv DABCO, 0.1 equiv $[(\text{Ph}_3\text{P})_3\text{RhCl}]$, $\text{EtOH}/\text{H}_2\text{O}$ (10/1), 90°C , 2 h; 2.2.2 equiv NMO, 0.05 equiv OsO_4 , $\text{Me}_2\text{CO}/\text{H}_2\text{O}$ (10/1), 25°C , 8 h, 81%; h) 1.1 equiv $n\text{Bu}_2\text{SnO}$, toluene, 110°C , 3 h; 1.5 equiv ACl , $0 \rightarrow 25^\circ\text{C}$, 1 h, 97% (1:1 mixture of regioisomers); i) 2.0 equiv **6**, 1.8 equiv SnCl_2 , $0 \rightarrow 25^\circ\text{C}$, Et_2O , 3 h, 92%; j) 0.2 equiv K_2CO_3 , MeOH , 25°C , 1 h, 98%; k) 10.0 equiv NaIO_4 , 8.0 equiv NaHCO_3 , $\text{MeOH}/\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (3/2/1), 25°C , 2 h; l) vinyl acetate/toluene/diisopropylamine (2/2/1), sealed tube, 140°C , 16 h, 81%; m) 1.1 equiv $n\text{Bu}_4\text{NF}$, THF, 0°C , 2 h, 95%; n) 1.2 equiv BzCl , 1.8 equiv Et_3N , 0.2 equiv 4-DMAP, CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 2 h, 97%. CA = chloroacetyl; DABCO = 1,4-diazabicyclo[2.2.2]octane; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; NMO = *N*-methylmorpholine *N*-oxide.

linkage between rings F and G, a challenge that was solved by applying our recently developed methodology for 1 → 1'-disaccharide construction. Thus, the coupling of tin acetal **7** with trichloroacetimidate **8** (Scheme 5) proceeded smoothly under the catalytic influence of TMSOTf in CH₂Cl₂ leading, after PPTS-induced cleavage of the intermediate TMS ether, to disaccharide **29** in 74 % overall yield. As expected from our previous findings^[3] the 1 → 1'-disaccharide linkage was formed in a completely stereocontrolled fashion, furnishing **29** as a single isomer. The free hydroxyl group in **29** was methylated (NaH/MeI, 87 % yield) and the benzoyl group at C2 of ring G, which played a crucial role in directing the stereochemical outcome of the glycosylation reaction, was removed by treatment with NaOH in MeOH to afford alcohol **30** (95 % yield). For strategic reasons, a benzyl group was installed on the hydroxyl group of **30** (NaH/BnBr/*n*Bu₄NI, 90 % yield) to afford **31**, and the PMB group of ring F was replaced with a TIPS group (DDQ, 91 % yield; TIPSOTf/2,6-lutidine, 97 % yield) to furnish compound **32**. Removal of the allyl protecting groups from **32** required initial treatment with Wilkinson's catalyst and DABCO, followed by cleavage of the resulting enol ethers with OsO₄/NMO, to furnish **5** in 81 % overall yield. Despite the nonselective differentiation of the two hydroxyl groups of **5**—even with the tin acetal technology,^[5] which led to hydroxychloroacetate **33** (*n*Bu₂SnO/CaCl₂, 97 % yield) and its regioisomer (approximately 1:1 ratio)—an efficient pathway to the next stage was secured. Thus, while the indicated regioisomer (**33**) was used directly as a carbohydrate acceptor in a glycosidation reaction with glycosyl fluoride **6** (SnCl₂, Et₂O) to give trisaccharide **34** (92 % yield) stereoselectively, its regioisomer required further manipulation prior to being used in the forward sequence. Specifically, the C4 regioisomer of **33**, was benzoylated (BzCl/Et₃N/4-DMAP, 94 %) and the chloroacetate group was removed (Et₃N/MeOH (1/3), 90 % yield) leading to the C3 benzoate counterpart of **33**. This compound was then subjected to the same coupling procedure with **6** to afford the benzoate analogue of trisaccharide **34** (90 % yield). Cleavage of the ester group from **34** (or its benzoate analogue) with K₂CO₃ in MeOH led to alcohol **35** in 98 % yield (Table 1), which was now poised for a Sinaÿ orthoester formation.^[2] Thus, having assisted in the construction of the glycoside bond linking rings G and H, the 2-phenylseleno group was now utilized to prepare the ground for the formation of the second C–O bond between these two rings. To ensure the stereochemistry of the expected orthoester bond between rings G and H, we had to rely on the anomeric effect,^[13] which is maximized in the sequence adopted for the formation of the two C–O bonds (see Figure 3). Extensive model studies demonstrated that the correct orthoester stereochemistry could only be obtained by first attaching the H ring to the C4 oxygen atom of ring G and then constructing the second oxygen bridge (C3), rather than the other way around (which leads to the opposite orthoester stereochemistry, see Figure 3). Thus, oxidation of the phenylseleno group with NaIO₄ followed by heating the crude selenoxide in a mixture of vinyl acetate/toluene/diisopropylamine (2/2/1) in a sealed tube at 140 °C effected sequential *syn*-elimination at the anomeric position and ring closure^[2] to furnish orthoester **36** in 81 %

Table 1. Selected physical and spectroscopic data of compounds **35**, **44**, and **2**.

35: R_f = 0.18 (silica gel, 50 % EtOAc in hexanes); $\alpha_D^{25} = -22.7$ (c = 2.7, CHCl₃); IR (thin film): $\tilde{\nu}_{\max} = 3451, 3051, 2930, 2863, 1612, 1582, 1513, 1463, 1383, 1357, 1304, 1251, 1110, 1031, 942, 885, 883$ cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 7.55 (d, J = 7.1, 2H, ArH), 7.39–7.25 (m, 12H, ArH), 7.15 (t, J = 7.8 Hz, 2H, ArH), 7.06 (t, J = 7.3 Hz, 1H, ArH), 6.86 (d, J = 8.6, 2H, ArH (PMB)), 5.16 (d, J = 1.7, 1H, G-1), 4.87 and 4.69 (AB, J = 12.2 Hz, 2H, CH₂Ar), 4.80 (d, J = 9.1, 1H, H-1), 4.69 and 4.40 (AB, J = 11.1 Hz, 2H, CH₂Ar), 4.66 (s, 1H, F-1), 4.61 and 4.47 (AB, J = 12.1 Hz, 2H, CH₂Ar), 4.30 (brs, 1H, H-3), 4.01–3.92 (m, 5H, G-4, F-4, H-5, H-5, G-2), 3.83–3.79 (m, 1H, G-3), 3.80 (s, 3H, OMe (PMB)), 3.71–3.68 (m, 2H, G-5, F-6), 3.61 (dd, J = 9.1, 2.7 Hz, 1H, H-2), 3.56 (dd, J = 10.5, 6.1 Hz, 1H, F-6), 3.51 (d, J = 2.6 Hz, 1H, F-2), 3.47 (s, 3H, OMe (F-2)), 3.33–3.31 (m, 2H, F-3, F-5), 3.32 (s, 3H, OMe (F-6)), 3.22 (brs, 1H, H-4), 3.15 (t, J = 10.9 Hz, 1H, G-5), 1.02–0.96 (m, 21H, (<i>i</i>Pr)₃Si), 0.90 (s, 9H, <i>t</i>BuSi), 0.14 (s, 3H, MeSi), –0.07 (s, 3H, MeSi); ¹³C NMR (150 MHz, CDCl₃): δ = 159.4, 138.4, 138.0, 131.6, 131.6, 129.6, 129.4, 128.5, 128.4, 128.2, 128.1, 127.6, 127.5, 127.4, 127.4, 127.2, 126.0, 113.9, 102.8, 95.6, 95.2, 82.2, 78.9, 77.4, 76.8, 76.3, 74.4, 73.6, 72.9, 71.9, 70.8, 70.5, 70.1, 68.0, 63.4, 61.5, 60.3, 59.0, 55.2, 48.4, 25.7, 18.2, 18.0, 18.0, 18.0, 13.2, 13.0, –4.4, –4.8; HR-MS (FAB), calcd for C₆₁H₉₀O₁₄SeSi₂CS [M + Cs]: 1315.4089, found: 1315.4022
44: R_f = 0.34 (silica gel, 50 % EtOAc in hexanes); $\alpha_D^{25} = -19.2$ (c = 0.12, CHCl₃); IR (thin film): $\tilde{\nu}_{\max} = 3448, 2943, 2861, 1725, 1614, 1514, 1455, 1372, 1308, 1255, 1108, 1079, 1032, 843, 779$ cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 8.04 (d, J = 7.1, 2H, ArH), 7.61 (t, J = 7.4 Hz, 1H, ArH), 7.47 (t, J = 7.9 Hz, 2H, ArH), 7.37–7.29 (m, 10H, ArH), 7.12 (d, J = 8.6, 2H, PMB), 6.75 (d, J = 8.6, 2H, PMB), 5.42 (t, J = 9.2 Hz, 1H, H-3), 5.34 (s, 1H, G-1), 4.87 and 4.66 (AB, J = 11.6 Hz, 2H, CH₂Ar), 4.67 (s, 1H, F-1), 4.63 and 4.56 (AB, J = 11.5 Hz, 2H, CH₂Ar), 4.53 and 4.50 (AB, J = 11.0 Hz, 2H, CH₂Ar), 4.48 (ddd, J = 10.5, 10.5, 4.5 Hz, 1H, G-4), 4.33 (brs, 1H, G-2), 4.11 (dd, J = 9.6, 4.5 Hz, 1H, G-5), 4.00 (dd, J = 10.2, 2.3 Hz, 1H, G-3), 3.90 (dd, J = 11.4, 5.4 Hz, 1H, H-5), 3.87 (t, J = 9.0 Hz, 1H, F-4), 3.82–3.76 (m, 3H, H-2, H-4, G-5), 3.76 (s, 3H, OMe (PMB)), 3.69 (t, J = 10.7 Hz, 1H, H-5), 3.62 (dd, J = 10.4, 1.8 Hz, 1H, F-6), 3.55 (dd, J = 10.8, 5.3 Hz, 1H, F-6), 3.52 (s, 3H, OMe (F-2)), 3.49 (brs, 1H, F-2), 3.33 (s, 3H, OMe (F-6)), 3.29–3.27 (m, 2H, F-3, F-5), 2.49 (d, J = 8.3 Hz, 1H, OH), 0.86 (s, 9H, <i>t</i>BuSi), 0.04 (s, 3H, MeSi), 0.03 (s, 3H, MeSi); ¹³C NMR (150 MHz, CDCl₃): δ = 167.1, 159.4, 137.9, 137.8, 133.4, 129.9, 129.5, 129.5, 128.4, 128.3, 128.3, 127.8, 127.7, 127.7, 127.6, 119.3, 113.8, 95.7, 82.0, 81.7, 77.1, 76.7, 75.8, 73.6, 73.4, 72.7, 71.9, 71.4, 71.4, 69.7, 67.5, 63.3, 62.5, 61.8, 59.0, 55.2, 29.7, 25.9, 18.1, –3.7, –5.1; HR-MS (FAB), calcd for C₅₅H₆₈O₁₆SiNa [M + Na⁺]: 1011.4174, found: 1011.4205
2: R_f = 0.21 (silica gel, 60 % EtOAc in hexanes); $\alpha_D^{25} = -5.7$ (c = 0.14, CHCl₃); IR (thin film): $\tilde{\nu}_{\max} = 3448, 2955, 2919, 2872, 1725, 1602, 1449, 1378, 1255, 1155, 1108, 1049, 932, 738$ cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 7.39–7.23 (m, 20H, ArH), 6.43 (s, 2H, ArH (A₂)), 5.44 (ddd, J = 9.7, 9.7, 5.5 Hz, 1H, H-4), 5.33 (d, J = 0.8 Hz, 1H, G-1), 5.18 (s, 1H, OCH₂O), 5.05 (s, 1H, OCH₂O), 5.02 (s, 2H, CH₂Ar (A₂)), 5.00 (s, 2H, CH₂Ar (A₂)), 4.77 and 4.61 (AB, J = 11.7 Hz, 2H, CH₂Ar), 4.75 and 4.66 (AB, J = 11.9 Hz, 2H, CH₂Ar), 4.69 (s, 1H, F-1), 4.54 (ddd, J = 10.5, 10.5, 4.5 Hz, 1H, G-4), 4.29 (brs, 1H, G-2), 4.18 (dd, J = 9.7, 4.6 Hz, 1H, G-5), 4.12 (dd, J = 11.3, 5.4 Hz, 1H, H-5), 4.05 (dd, J = 10.2, 2.4 Hz, 1H, G-3), 3.94 (t, J = 9.8 Hz, 1H, H-3), 3.88 (t, J = 9.5 Hz, 1H, F-4), 3.82 (dd, J = 10.6, 10.6 Hz, 1H, G-5), 3.70 (dd, J = 10.5, 3.7 Hz, 1H, F-6), 3.63 (dd, J = 10.5, 5.1 Hz, 1H, F-6), 3.61–3.59 (m, 2H, F-2, H-2), 3.60 (s, 3H, OMe (F-2)), 3.56 (dd, J = 11.3, 9.7 Hz, 1H, H-5), 3.37 (s, 3H, OMe (F-6)), 3.36–3.34 (m, 2H, F-3, F-5), 2.72 (brs, 1H, OH), 2.32 (s, 3H, Me (A₂)); ¹³C NMR (150 MHz, CDCl₃): δ = 166.8, 160.6, 157.3, 138.7, 137.7, 137.5, 136.3, 136.3, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.5, 127.4, 127.0, 119.1, 115.8, 108.1, 98.2, 96.7, 96.0, 96.0, 81.3, 81.0, 77.4, 75.6, 74.9, 73.2, 72.4, 71.8, 70.3, 70.1, 70.1, 69.6, 67.8, 63.4, 63.4, 61.8, 59.3, 53.8, 29.6, 29.6, 27.7, 20.0, 14.1, 14.0; HR-MS (FAB), calcd for C₅₅H₆₀O₁₇CS [M + Na⁺]: 1015.3728, found: 1015.3735

yield and with a diastereoselectivity of approximately 8:1. The stereochemistry of the orthoester linkage in this series of compounds was determined by NMR spectroscopic techniques and correlation with a structure of one such isomer determined unambiguously by X-ray crystallographic analysis

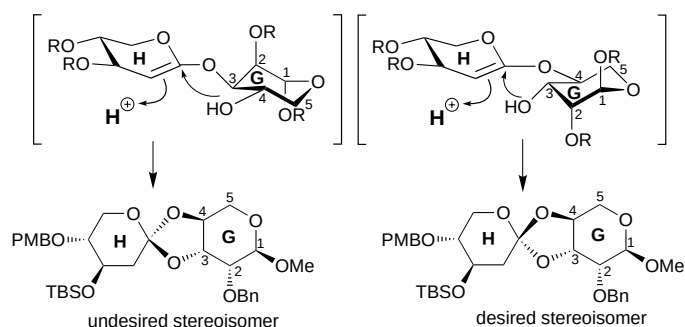


Figure 3. Transition states illustrating the stereoselective formation of the GH orthoester. The joining of rings G and H through the C4 oxygen atom followed by ring closure was crucial for the formation of the desired orthoester stereoisomer. A C3 linked disaccharide leads predominantly to the undesired orthoester stereoisomer.

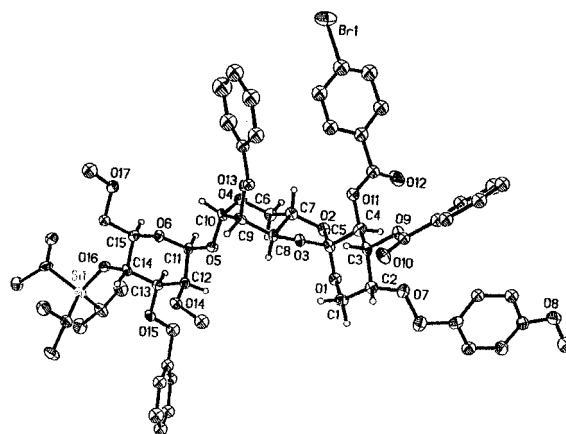
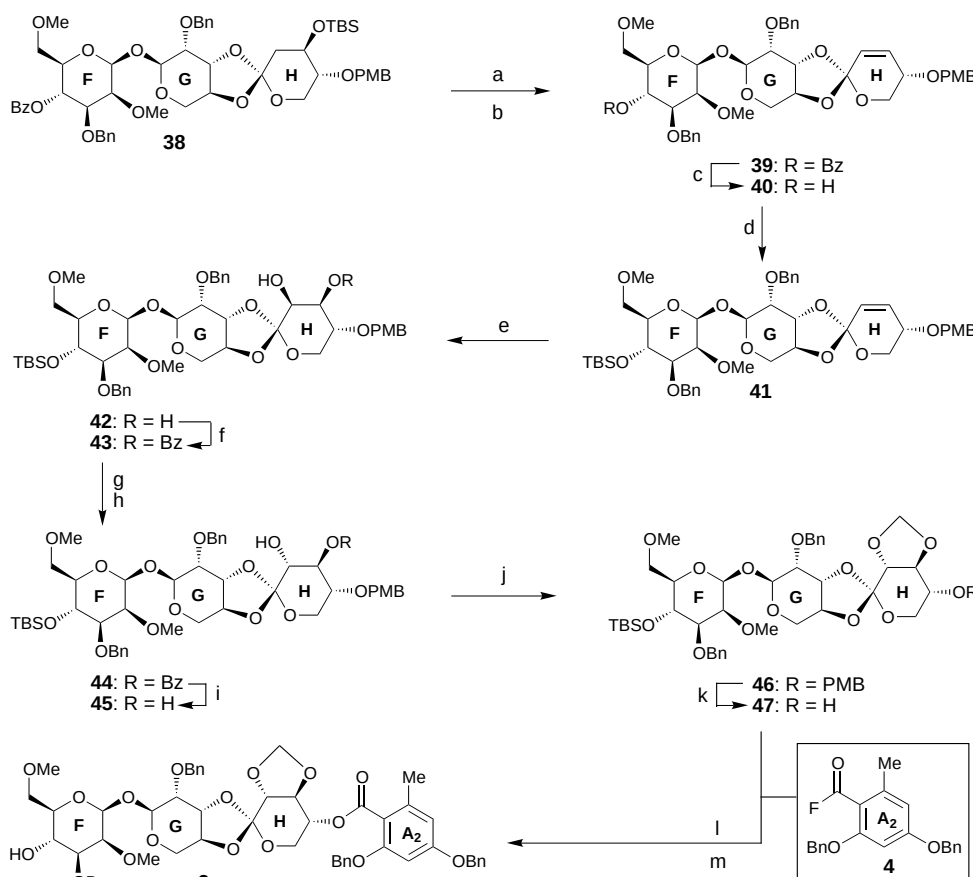


Figure 4. ORTEP drawing of orthoester **A** derived from an X-ray crystallographic analysis.^[20]

(Figure 4). Subsequent findings dictated a need for an exchange of protecting group at this stage for the C4 hydroxyl group of ring F. Thus, exposure of **36** to $n\text{Bu}_4\text{NF}$ in THF led exclusively to alcohol **37** (95 % yield). It is worth noting here that whereas treatment of **35** with $n\text{Bu}_4\text{NF}$ removed the TBS group selectively, the same reagent proved selective for the removal of the TIPS group from **36**, presumably as a consequence of a conformational change and/or the absence of the free OH group in going from **35** to **36**. A benzoate group was then installed on the free hydroxyl group of ring F of **37** ($\text{BzCl}/\text{Et}_3\text{N}/4\text{-DMAP}$) to furnish **38** (97 % yield).

The next task was the installment of an α -hydroxyl group at the C2 position of ring H. To this end, the TBS group of **38** (Scheme 6) was removed from ring H ($n\text{Bu}_4\text{NF}/\text{AcOH}/\text{THF}$, 95 % yield) and the resulting alcohol was dehydrated by treatment with Martin sulfurane^[14] in the presence of catalytic amounts of Et_3N to give olefin **39** (85 % yield), thus setting the stage for a dihydroxylation reaction. Before that operation, however, it was found necessary to exchange the benzoate group on ring F for a TBS group to ensure the success of subsequent steps. Thus, compound **39** was debenzoylated with $\text{K}_2\text{CO}_3/\text{MeOH}$ (90 % yield) and the resulting alcohol was exposed to TBSCl in the pres-



Scheme 6. Completion of the synthesis of the FGHA_2 fragment **2**. a) 1.5 equiv $n\text{Bu}_4\text{NF}$, 0.2 equiv AcOH , THF, 25 °C, 1 h, 95 %; b) 4.0 equiv Martin sulfurane, 0.05 equiv Et_3N , CHCl_3 , 50 °C, 2 h, 85 %; c) 0.5 equiv K_2CO_3 , MeOH , 25 °C, 6 h, 90 %; d) 6.0 equiv of NaH , 12 equiv TBSCl, 1.0 equiv [18]crown-6, THF, 0 $\rightarrow$ 25 °C, 4 h, 80 %; e) 2.2 equiv NMO, 0.5 equiv OsO_4 , 1.0 equiv quinuclidine, $\text{Me}_2\text{CO}/\text{H}_2\text{O}$ (10/1), 25 °C, 36 h, 70 % (8:1 mixture of diastereoisomers); f) 1.1 equiv $n\text{Bu}_2\text{SnO}$, MeOH , reflux, 3 h; 1.5 equiv BzCl , 1,4-dioxane, 15 °C, 0.5 h, 97 % (5:1 mixture of regioisomers); g) 4.0 equiv Dess–Martin periodinane, 20 equiv NaHCO_3 , CH_2Cl_2 , 25 °C, 1 h; h) 1.1 equiv $\text{Li}(\text{tBuO})_3\text{AlH}$, Et_2O , -10°C , 1 h, 80 % over two steps; i) 0.2 equiv NaOH , MeOH , 25 °C, 1 h, 98 %; j) 3.0 equiv $n\text{Bu}_4\text{NBr}$, CH_2Br_2 /50 % aqueous NaOH (1/1), 65 °C, 2 h, 90 %; k) 1.5 equiv DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10/1), 0 $\rightarrow$ 25 °C, 1 h, 85 %; l) 1.0 equiv NaH , THF, 0 $\rightarrow$ 25 °C; then 1.5 equiv **4**, 2 h, 96 %; m) 1.2 equiv $n\text{Bu}_4\text{NF}$, THF, 25 °C, 1 h, 90 %.

ence of NaH and [18]crown-6 (80% yield), to furnish compound **41** via alcohol **40**. Reaction of the highly sensitive olefinic orthoester **41** with NMO/OsO₄ in the presence of quinuclidine led to 1,2-diol **42** as the major product (70% yield, in an approximate 8:1 ratio with its diastereoisomer). The chromatographically purified diol **42** was then regioselectively converted into the monobenzoate **43** by treatment with *n*Bu₂SnO/BzCl (97% yield, in an approximate 5:1 ratio with its regioisomer).^[15] After chromatographic separation **43** was oxidized (Dess–Martin periodinane)^[16] and reduced with Li(*t*BuO)₃AlH to afford, via the corresponding ketone, the desired hydroxy compound **44** (80% overall yield for the last two steps). Having successfully installed the required α -hydroxy group at C2 of ring H, it was now time to remove the benzoate group from the C3 oxygen atom of ring H and to transform the resulting *trans*-1,2-diol system into the desired methylene acetal functionality. To accomplish this goal, benzoate **44** was treated with NaOH in MeOH and the resulting diol (**45**, 98% yield) was converted into methylene acetal **46**, in 90% yield, by slowly adding it to a mixture of aqueous NaOH, CH₂Br₂, and *n*Bu₄NBr at 65 °C.^[17] The remaining steps for the completion of the synthesis of the FGHA₂ fragment **2** involved the DDQ-induced removal of the PMB group from ring H of **46** to afford **47** (85% yield), esterification of the latter compound with acyl fluoride **4** in the presence of NaH in THF (96% yield), and removal of the TBS group from ring F of the obtained ester (*n*Bu₄NF, 90% yield; Scheme 6). The following communication^[18] describes the construction of the required DE fragment and the completion of the total synthesis of everninomicin 13,384-1 (**1**).^[19]

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Total Synthesis of Everninomicin 13,384-1— Part 3: Synthesis of the DE Fragment and Completion of the Total Synthesis**

K. C. Nicolaou,* Helen J. Mitchell, Rosa María Rodríguez, Konstantina C. Fylaktakidou, and Hideo Suzuki

In the preceding communications,^[1, 2] we described the synthesis of the A₁B(A)C and FGHA₂ fragments of everninomicin 13,384-1 (**1**, Figure 1). Herein, we report the construction of the remaining DE fragment and the completion of the total synthesis of **1**. Figure 1 depicts the retrosynthetic excision of the DE fragment from **1** as the appropriately functionalized key intermediate **2**, and its further disconnection to building blocks **3** and **4**. The protecting groups on **2** were carefully defined so as to be compatible not only with its assembly, but also with its incorporation into the structure of the final target. The two main issues that had to be addressed for the synthesis of **2**

[*] Prof. K. C. Nicolaou, H. J. Mitchell, Dr. R. M. Rodríguez, Dr. K. C. Fylaktakidou, Dr. H. Suzuki
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

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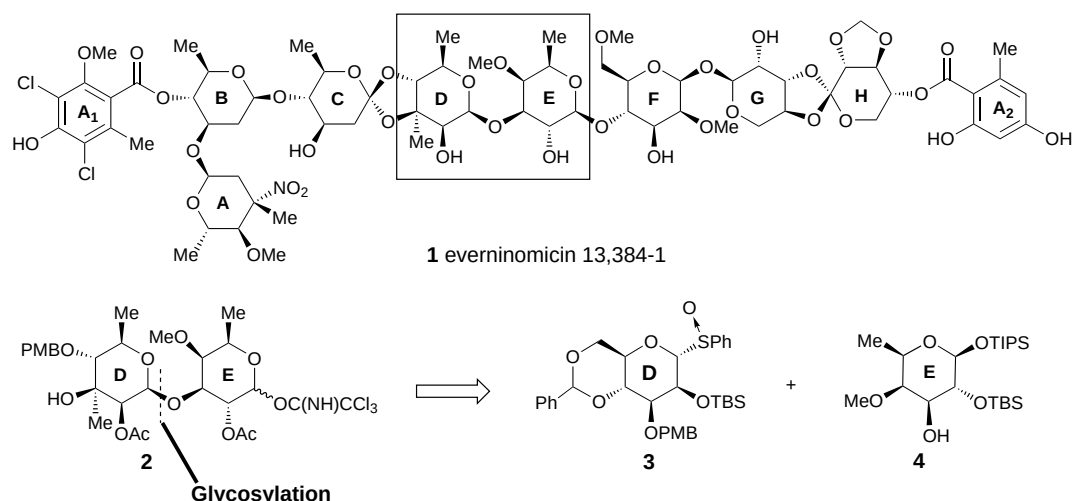
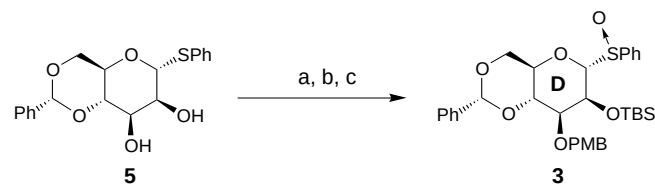


Figure 1. Retrosynthetic analysis of the DE fragment **2**. Ac = acetyl; PMB = *p*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl.

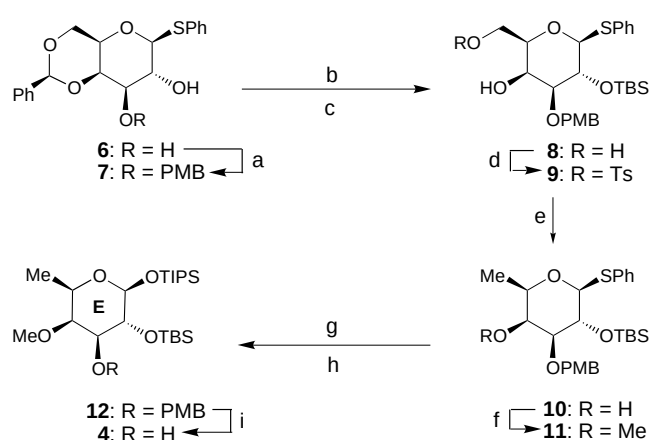
were the following: 1) construction of the β -mannoside linkage and 2) installment of the tertiary center on ring D. We chose the sulfoxide-based glycosidation reaction of Kahne et al.^[3] as the coupling procedure for **3** and **4** and designed the benzylidene ring^[4] in **3** to ensure the stereocontrolled formation of the β -mannoside bond. The introduction of the methyl group at C3 of ring D was postponed until after the coupling to avoid unfavorable 1,3-diaxial interactions^[5] during the planned nucleophilic attack (see below).

Scheme 1 summarizes the construction of building block D (**3**), which proceeded smoothly from the known intermediate **5**.^[6] Thus, the regioselective tin acetal mediated monoprotection of **5** as a PMB ether ($n\text{Bu}_2\text{SnO}$ -PMBCl/ $n\text{Bu}_4\text{NI}$, 83 % yield) was followed by TBS introduction at the C2 hydroxyl group (TBSOTf/2,6-lutidine, 93 % yield) and oxidation of the sulfur group with *m*CPBA (92 % yield) to afford the desired sulfoxide **3** (approximate 4:1 mixture of separable diastereoisomers).



Scheme 1. Synthesis of carbohydrate building block D (**3**). a) 1.1 equiv $n\text{Bu}_2\text{SnO}$, toluene, 110 °C, 3 h; 1.5 equiv PMBCl, 0.2 equiv $n\text{Bu}_4\text{NI}$, 25 $\rightarrow$ 110 °C, 83 %; b) 1.2 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2 , 0 $\rightarrow$ 25 °C, 0.5 h, 93 %; c) 1.1 equiv *m*CPBA, CH_2Cl_2 , -20 $\rightarrow$ 0 °C, 2 h, 92 % (ca. 4:1 mixture of diastereoisomers). *m*CPBA = *m*-chloroperoxybenzoic acid; Tf = trifluoromethanesulfonyl.

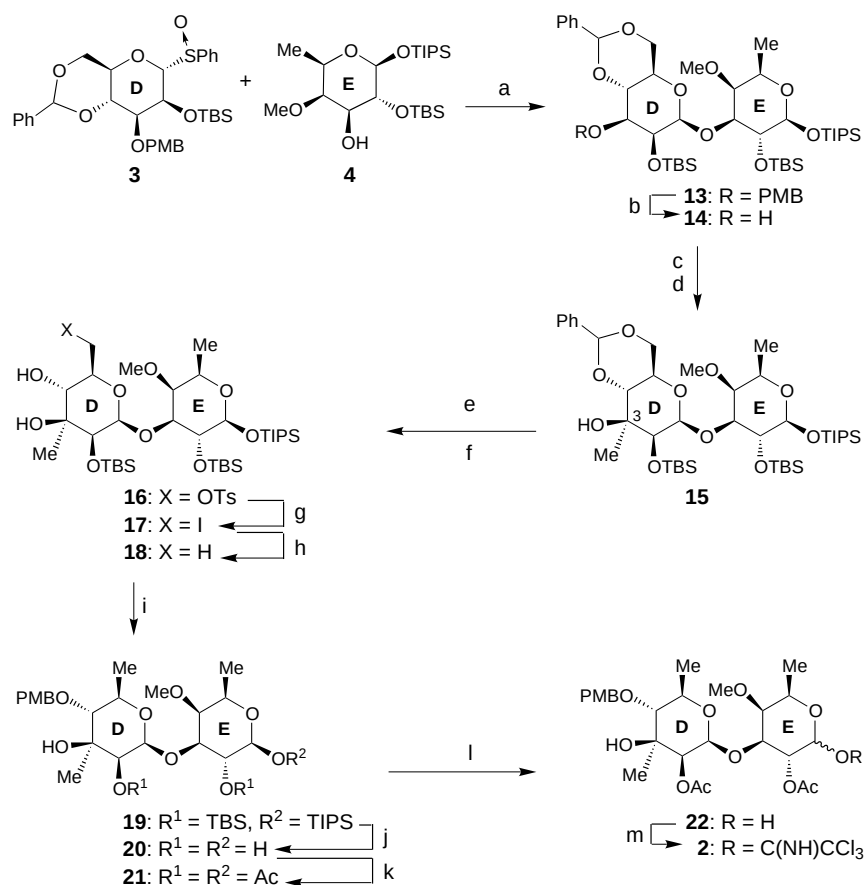
The synthesis of the other requisite fragment, ring E (**4**), is shown in Scheme 2. The tin acetal technology^[7] was again used to facilitate the PMB monoprotection of the starting material **6**^[8] ($n\text{Bu}_2\text{SnO}$ /PMBCl/ $n\text{Bu}_4\text{NI}$, 87 % yield) and furnish the C3 protected intermediate **7**. TBS protection of the C2 hydroxyl group (TBSOTf/2,6-lutidine, 97 % yield) followed by cleavage of the benzylidene group with $\text{Zn}(\text{OTf})_2/\text{EtSH}$ (77 %) afforded diol **8**. Selective tosylation of the



Scheme 2. Synthesis of carbohydrate building block E (**4**). a) 1.1 equiv $n\text{Bu}_2\text{SnO}$, toluene, 110 °C, 3 h; 1.5 equiv PMBCl, 0.2 equiv $n\text{Bu}_4\text{NI}$, 25 $\rightarrow$ 110 °C, 2 h, 87 %; b) 1.2 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2 , 0 $\rightarrow$ 25 °C, 1 h, 97 %; c) 2.5 equiv $\text{Zn}(\text{OTf})_2$, 20 equiv EtSH, CH_2Cl_2 , 0 °C, 2 h, 77 %; d) 1.1 equiv TsCl, py, 0 $\rightarrow$ 25 °C, 12 h, 97 %; e) 1.6 equiv LAH, THF, 45 °C, 3 h, 90 %; f) 1.1 equiv NaH, 1.3 equiv MeI, DMF, 0 $\rightarrow$ 25 °C, 1 h, 94 %; g) 1.5 equiv NBS, $\text{Me}_2\text{CO}/\text{H}_2\text{O}$ (10/1), 0 $\rightarrow$ 25 °C, 2 h, 95 %; h) 1.2 equiv TIPSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2 , 0 $\rightarrow$ 25 °C, 6 h, 97 % (α/β ca. 1:2); i) 1.5 equiv DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10/1), 0 $\rightarrow$ 25 °C, 1 h, 98 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMF = dimethylformamide; LAH = lithium aluminum hydride; NBS = *N*-bromosuccinimide; py = pyridine; THF = tetrahydrofuran; Ts = *p*-toluenesulfonyl.

primary hydroxyl group of **8** (TsCl/py, 97 %) followed by LAH reduction led to derivative **10** (90 %), which was methylated (NaH/MeI, 94 % yield) at C4 to afford methoxy compound **11**. Finally, cleavage of the thiophenyl group from **11** with NBS/ H_2O (95 % yield) followed by silylation (TIPSOTf/2,6-lutidine, 97 %) afforded compound **12** (β/α ratio approximately 2:1), from which the PMB group was oxidatively removed (DDQ, 98 % yield) to furnish the desired building block **4**.

The construction of key intermediate **2** from fragments **3** and **4** is summarized in Scheme 3. This assembly began with the stereoselective coupling of sulfoxide **3** with acceptor **4** in the presence of Tf_2O and di-*tert*-butyl-4-methyl pyridine (DTBMP) to afford the β -mannoside **13** (glycosidation with



Scheme 3. Assembly of DE fragment **2**. a) 1.3 equiv **3**, 1.3 equiv Tf₂O, 2.2 equiv DTBMP, CH₂Cl₂, −78 °C; 1.0 equiv **4**, −78 → 0 °C, 2 h, 71 %; b) 1.3 equiv DDQ, CH₂Cl₂/H₂O (10/1), 0 → 25 °C, 2 h, 95 %; c) 1.5 equiv NMO, 0.05 equiv TPAP, CH₂Cl₂, 25 °C, 2 h; d) 1.4 equiv MeLi, Et₂O, −78 °C, 1 h, 88 % over two steps; e) H₂, 0.2 equiv 10 % Pd/C (w/w), EtOAc, 25 °C, 2 h, 97 %; f) 1.2 equiv TsCl, py, 0 → 25 °C, 12 h, 87 %; g) 5.0 equiv LiI, DMF, 80 → 100 °C, 2 h, 86 %; h) 3.0 equiv *n*Bu₃SnH, 0.01 equiv AIBN, PhH, 80 °C, 0.5 h, 97 %; i) 1.1 equiv *n*Bu₂SnO, toluene, 110 °C, 10 h; 1.5 equiv PMBCl, 0.2 equiv *n*Bu₄NI, 25 → 110 °C, 8 h, 63 %; j) 4.0 equiv *n*Bu₄NF, THF, 25 °C, 6 h; k) 2.5 equiv Ac₂O, 4.0 equiv Et₃N, 0.2 equiv 4-DMAP, CH₂Cl₂, 0 → 25 °C, 1 h, 90 % over two steps; l) 1.3 equiv *n*BuNH₂, THF, 25 °C, 5 h, 86 %; m) 5.0 equiv CCl₃CN, 0.05 equiv DBU, CH₂Cl₂, 0 °C, 0.5 h, 89 % (α:β ca. 30:1). AIBN = 2,2'-azobisisobutyronitrile; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; 4-DMAP = 4-dimethylaminopyridine; DTBMP = di-*tert*-butyl-4-methylpyridine; NMO = *N*-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate.

S_N2 inversion)^[3,4] in 71 % yield. The PMB group was then removed from ring D (DDQ, 95 % yield), the resulting alcohol was oxidized to the corresponding ketone with the aid of TPAP/NMO, and the latter compound was treated with MeLi in Et₂O at −78 °C. To our delight, the latter reaction produced the desired tertiary alcohol **15** in 88 % overall yield (from **14**) and as a single stereoisomer (determined by NOE/NMR experiments). Figure 2 depicts the presumed confor-

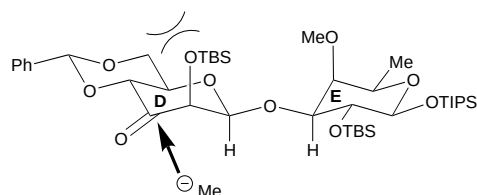
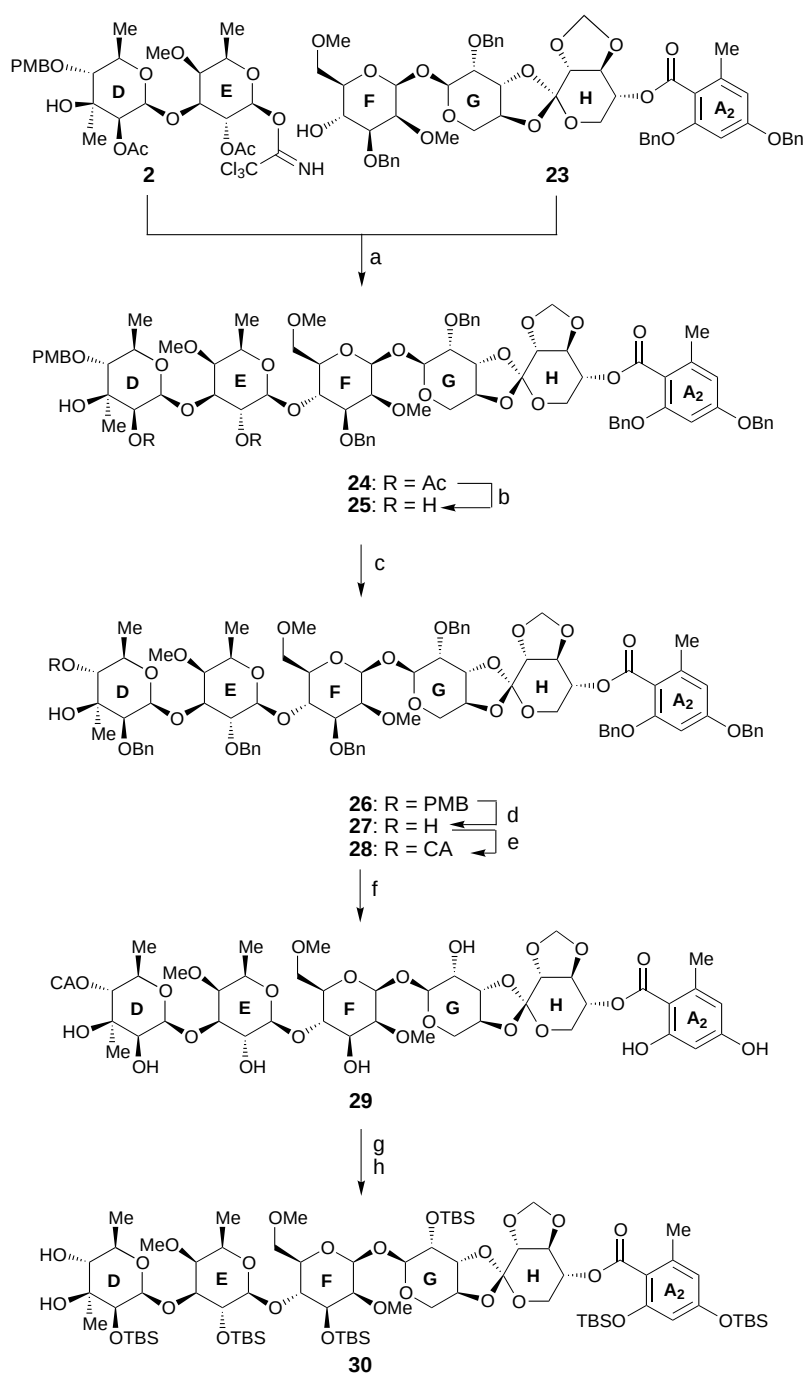


Figure 2. Illustration of the preferential α-attack of MeLi on the C3 carbonyl group of ring D during the formation of compound **15**.

mation of ring D of **14** and the trajectory of the reagent leading to the desired product. Thus, in contrast to a monosaccharide unit D carrying a 1-α substituent in which the reagent would have encountered repulsive 1,2- or 1,3-interactions, the β-mannoside disaccharide system containing the bulky and axially orientated TBS group at C2 proved ideal for setting the tertiary stereocenter on ring D. Difficulties with protecting the highly hindered tertiary alcohol in **15** led us to the conviction that we could leave it free for the rest of the sequence without much interference—a prediction that turned out both correct and fortunate. The next task was to deoxygenate the C6 position of ring D, suitably protect the C4 hydroxyl group of ring D, and activate the C1 carbon atom of ring E. To this end, the benzylidene group of **15** was removed by hydrogenolysis (H₂/10 % Pd/C, 97 % yield) and the primary hydroxyl group so generated was tosylated selectively over the secondary hydroxyl group (TsCl/py, 87 % yield) to afford **16**. Difficulties with the direct reduction of this tosylate forced us to proceed through iodide **17** (LiI, 86 % yield), which was smoothly reduced with *n*Bu₃SnH/AIBN to afford the desired compound **18** in 97 % yield. Protection at C4 of ring D was effected with *n*Bu₂SnO/PMBCl/*n*Bu₄NI leading to **19** (63 % yield), which was completely desilylated (*n*Bu₄NF) and tris-acetylated (Ac₂O/Et₃N/4-DMAP) to afford triacetate **21** in 90 % overall yield (ratio of α- and β-anomers approximately 1:1) via the tetraol **20**. Finally, the anomeric acetate was selectively removed from the latter compound (**22**) by the mild action of *n*BuNH₂ in THF to give lactol **22**, whose conversion into trichloroacetimidate **2** was accomplished by

exposure to CCl₃CN and DBU (89 %, α:β ratio approximately 30:1).

The coupling of the key intermediates **2** and **23** and the elaboration of the resulting fragment to the next advanced key intermediate, **30** is shown in Scheme 4. Thus, reaction of the trichloroacetimidate **2** with hydroxy fragment **23** in the presence of BF₃·Et₂O in CH₂Cl₂ at −20 °C furnished oligosaccharide **24** with the desired β-glycoside linkage (between rings E and F) and in 55 % yield. In addition to **24**, this reaction also produced a small amount of the corresponding α-glycoside (5 % yield) and an as of yet unidentified isomer of **24** (β-glycosidic linkage between rings E and F, 18 % yield). The sensitivity of these advanced intermediates and our intention to prepare them in a suitable form for their pending union with the A₁B(A)C fragment as well as for the overall strategy towards the final target molecule prompted a number of protecting group exchanges



Scheme 4. Completion of the synthesis of the DEFGHA₂ fragment (**30**). a) 1.6 equiv **2**, 0.5 equiv BF₃·Et₂O, CH₂Cl₂, –20 °C, 2 h, 55% yield of desired β-anomer, 18% of unknown compound (β-anomer) and 5% yield of α-anomer (α:β ca. 1:9); b) 0.5 equiv K₂CO₃, MeOH, 25 °C, 2 h, 85%; c) 2.5 equiv NaH, 3.0 equiv BnBr, THF, 0 → 25 °C, 2 h, 95%; d) 1.3 equiv DDQ, CH₂Cl₂/H₂O (10/1), 0 → 25 °C, 2 h, 95%; e) 1.5 equiv (CA)₂O, 3.0 equiv Et₃N, 0.2 equiv 4-DMAP, CH₂Cl₂, 0 → 25 °C, 1 h, 98%; f) 0.5 equiv 10% Pd/C (w/w), EtOAc, 25 °C, 4 h, 85%; g) 8.0 equiv TBSOTf, 20 equiv 2,6-di-*tert*-butylpyridine, CH₂Cl₂, 0 → 25 °C, 8 h, 65%; h) 0.2 equiv K₂CO₃, MeOH, 25 °C, 15 min, 85%. CA = chloroacetyl.

at this stage. Three sets of protecting groups on fragment DEFGHA₂ were tested before a final forward path was found.

We initially targeted the hexabenzylated diol **27** (Scheme 4) as a potential partner in the projected final coupling reaction with the A₁B(A)C fragment. With this objective in mind,

compound **24** was deacetylated (K₂CO₃/MeOH) to furnish triol **25** (85% yield), which was then cleanly dibenzylated with NaH/BnBr in THF (90% yield) to give hexabenzyl ether **26**^[9] in which the tertiary alcohol on ring D remained free. The removal of the PMB group from **26** with DDQ proceeded in 95% yield to furnish the desired diol **27**. This compound, however, proved unsuitable for further elaboration. Problems associated with **27** included low glycosidation yields with the A₁B(A)C fragment and rupture of the highly sensitive C–D orthoester moiety upon attempted debenzylation. We then opted for the hexaacetylated counterpart of **27** (details will be reported in a later paper), but again we encountered poor coupling yields with the same A₁B(A)C partner. Our third generation strategy involved the adoption of the hexa-TBS derivative **30** (Scheme 4) as the DEFGHA₂ coupling partner, and this time we were successful. To reach **30** we proceeded from **27** as follows: Selective formation of the secondary chloroacetate on ring D (CA₂O/Et₃N/4-DMAP, 98% yield) led to **28**, which was subjected to hydrogenolysis (H₂/10% Pd/C) to afford heptaol **29** (85% yield). Six TBS groups were then installed on **29** through exposure to excess TBSOTf in the presence of 2,6-di-*tert*-butylpyridine to afford a hexa-TBS derivative (with a free tertiary OH group on ring D, 65% yield), from which the chloroacetate group was removed with K₂CO₃ in MeOH to give the targeted intermediate **30** (85% yield; Table 1).

The final assembly of the everninomicin 13,384-1 (**1**) skeleton and the final stages of the total synthesis are shown in Scheme 5. Thus, coupling of the A₁B(A)C glycosyl fluoride donor **31**^[1] with the DEFGHA₂ hexa-TBS diol acceptor **30** in the presence of SnCl₂ in Et₂O proceeded smoothly, and with complete stereocontrol,^[10] to afford the 2-phenylseleno glycoside **32** (70% yield). Formation of the remaining orthoester site was then accomplished with equal facility under the Sinaï conditions^[11] (NaIO₄ oxidation to the selenoxide in MeOH/CH₂Cl₂/H₂O (3/2/1) followed by heating in a sealed tube at 140 °C in toluene/vinyl acetate/diisopropylamine (2/2/1)) to afford the fully protected everninomicin 13,384-1 derivative **33** in 65%

yield and as a single stereoisomer. Generation of everninomicin 13,384-1 (**1**) from **33** entailed the following two steps: a) hydrogenolysis (H₂/10% Pd/C, NaHCO₃, *t*BuOMe) to remove the two benzyl ethers and b) desilylation (*n*Bu₄NF/THF) to cleave all six TBS groups (75% overall yield). Synthetic everninomicin 13,384-1 (**1**) was identical by the

Table 1. Selected physical and spectroscopic data of compounds **2**, **30**, and **33**.

2: R_f = 0.60 (silica, 80% EtOAc in hexanes); IR (thin film): $\bar{\nu}_{\max}$ = 3495, 3331, 2928, 2951, 2884, 1743, 1678, 1614, 1508, 1455, 1373, 1243, 1091, 1049, 844, 791 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 8.54 (s, 1H, NH), 7.27 (d, J = 8.5 Hz, 2H, PMB), 6.87 (d, J = 8.5 Hz, 2H, PMB), 6.47 (d, J = 3.7 Hz, 1H, E-1), 5.28 (dd, J = 10.6, 3.7 Hz, 1H, E-2), 4.99 (s, 1H, D-2), 4.81 (s, 1H, D1), 4.81 and 4.56 (AB, J = 11.0 Hz, 2H, CH_2Ar), 4.16–4.12 (m, 2H, E-3, E-5), 3.79 (s, 3H, OMe (PMB)), 3.59 (s, 3H, OMe (E-4)), 3.57 (brs, 1H, E-4), 3.42 (dq, J = 9.6, 5.9 Hz, 1H, D-5), 3.32 (d, J = 9.6 Hz, 1H, D-4), 2.14 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.37 (s, 3H, Me (D-3)), 1.35 (d, J = 6.0 Hz, 3H, D-6), 1.26 (d, J = 6.6 Hz, 3H, E-6); ^{13}C NMR (125 MHz, CDCl_3): δ = 170.1, 170.0, 161.1, 159.0, 130.5, 129.8, 114.4, 98.5, 94.3, 91.6, 82.5, 81.7, 76.1, 75.0, 74.3, 71.0, 69.4, 65.5, 61.5, 55.5, 30.2, 21.2, 21.0, 20.3, 18.2, 16.3

30: R_f = 0.27 (silica, 40% Et₂O in hexanes); α_D^{25} = –29.1 (c = 0.10, CHCl_3); IR (thin film): $\bar{\nu}_{\max}$ = 3495, 2955, 2919, 2861, 1737, 1602, 1467, 1361, 1255, 1073, 838, 779 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 6.29 (d, J = 1.7 Hz, 1H, ArH (A_2)), 6.16 (d, J = 1.8 Hz, 1H, ArH (A_2)), 5.33 (dt, J = 10.1, 10.1, 5.6 Hz, 1H, H-4), 5.18 (s, 1H, OCH_2O), 5.06 (s, 1H, OCH_2O), 5.05 (brs, 1H, F-1), 5.01 (s, 1H, G-1), 4.68 (s, 1H, D-1), 4.39 (dt, J = 10.3, 10.3, 2.5 Hz, 1H, G-4), 4.24 (brs, 1H, G-2), 4.17 (dd, J = 11.1, 5.4 Hz, 1H, H-5), 4.12 (brs, 1H, F-3), 4.08 (d, J = 7.4 Hz, 1H, E-1), 4.05 (dd, J = 9.4, 4.8 Hz, 1H, G-5), 4.00 (dd, J = 10.1, 2.2 Hz, 1H, G-3), 3.96 (dd, J = 9.4, 9.4 Hz, 1H, G-5), 3.95 (t, J = 9.4 Hz, 1H, H-3), 3.89 (dd, J = 8.3 Hz, 1H), 3.84 (brs, 1H), 3.78–3.76 (m, 1H), 3.77 (s, 1H, D-2), 3.64 (dd, J = 8.0, 8.0 Hz, 1H, E-2), 3.59 (dd, J = 10.0, 10.0 Hz, 1H, H-5), 3.58 (d, J = 9.5 Hz, 1H, H-2), 3.53 (s, 3H, OMe (E-4)), 3.52–3.51 (m, 1H, D-5 or E-5), 3.49–3.37 (m, 4H, F-2), 3.40 (s, 3H, OMe (F-2)), 3.33–3.29 (m, 2H, D-5 or E-5), 3.30 (s, 3H, OMe (F-6)), 2.44 (s, 1H, OH), 2.24 (s, 3H, Me (A_2)), 1.93 (brs, 1H, OH), 1.29 (d, J = 5.9 Hz, 3H, D-6 or E-6), 1.27 (d, J = 6.5 Hz, 3H, D-6 or E-6), 1.16 (s, 3H, Me (D-3)), 0.96 (s, 9H, $t\text{BuSi}$), 0.95 (s, 9H, $t\text{BuSi}$), 0.92 (s, 9H, $t\text{BuSi}$), 0.90 (s, 9H, $t\text{BuSi}$), 0.90 (s, 9H, $t\text{BuSi}$), 0.89 (s, 9H, $t\text{BuSi}$), 0.28 (s, 3H, MeSi), 0.21 (s, 3H, MeSi), 0.18 (s, 3H, MeSi), 0.18 (s, 3H, MeSi), 0.14 (s, 3H, MeSi), 0.10 (s, 3H, MeSi), 0.10 (s, 3H, MeSi), 0.10 (s, 3H, MeSi), 0.09 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.07 (s, 3H, MeSi); ^{13}C NMR (125 MHz, CDCl_3): δ = 167.4, 157.3, 153.9, 137.9, 119.0, 118.9, 114.9, 108.4, 103.5, 101.6, 97.2, 96.4, 84.8, 82.4, 81.1, 77.3, 76.7, 76.4, 75.1, 73.9, 72.7, 71.3, 70.6, 70.5, 70.0, 69.5, 65.8, 63.3, 63.0, 62.4, 58.4, 29.3, 28.0, 25.8, 25.6, 19.8, 18.4, 18.2, 18.1, 18.0, 17.1, 16.3, 15.3, –3.4, –3.7, –3.9, –4.2, –4.3, –4.4, –4.6, –4.9, –4.9, –5.0, –5.2; HR-MS (FAB): calcd for $\text{C}_{77}\text{H}_{144}\text{O}_{25}\text{Si}_6\text{Na}$ [$M + \text{Na}^+$]: 1659.8509, found: 1659.8452

33: R_f = 0.32 (silica, 60% Et₂O in hexanes); α_D^{25} = –19.5 (c = 0.20, CHCl_3); IR (thin film): $\bar{\nu}_{\max}$ = 2955, 2919, 2861, 1737, 1602, 1543, 1455, 1384, 1255, 1108, 1067, 1038, 838, 779 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 7.57 (d, J = 7.1 Hz, 2H, ArH), 7.43–7.31 (m, 8H, ArH), 6.29 (d, J = 1.8 Hz, ArH (A_2)), 6.16 (d, J = 1.8 Hz, ArH (A_2)), 5.35 (dt, J = 9.9, 9.9, 5.5 Hz, 1H, H-4), 5.18 (s, 1H, OCH_2O), 5.07 (brs, 1H, F-1), 5.06 (s, 1H, OCH_2O), 5.05 and 5.02 (AB, J = 10.2 Hz, 2H, CH_2Ar), 5.00 (s, 1H, G-1), 4.95 (dd, J = 4.6, 1.4 Hz, 1H, A-1), 4.88 (t, J = 9.4 Hz, 1H, B-4), 4.86 (s, 1H, D-1), 4.75 (brd, J = 9.8 Hz, 1H, B-1), 4.68 and 4.57 (AB, J = 11.0 Hz, 2H, CH_2Ar), 4.39 (dt, J = 10.5, 10.5, 4.8 Hz, 1H, G-4), 4.23 (brs, 1H, G-2), 4.17 (dd, J = 11.4, 5.7 Hz, 1H, H-5), 4.14 (brs, 1H, F-3), 4.09 (s, 1H, D-2), 4.07 (d, J = 7.4 Hz, 1H, E-1), 4.04 (dd, J = 9.2, 4.4 Hz, 1H, G-5), 4.01 (dd, J = 10.1, 2.6 Hz, 1H, G-3), 3.97 (dd, J = 10.1, 9.2 Hz, 1H, G-5), 3.93 (t, J = 9.6 Hz, 1H, H-3), 3.89 (brt, J = 8.3 Hz, 1H), 3.86–3.80 (m, 5H, B-3, C-3, D-4, E-5, F-4), 3.82 (s, 3H, OMe (A_1)), 3.72 (dq, J = 6.2, 4.0 Hz, 1H, D-5), 3.65 (dd, J = 9.2, 9.2 Hz, 1H, E-2), 3.64 (d, J = 9.7 Hz, 1H, A-4), 3.59 (t, J = 11.0 Hz, 1H, H-5), 3.59 (d, J = 9.2 Hz, 1H, H-2), 3.56 (s, 3H, OMe (E-4)), 3.53–3.50 (m, 4H, C-5), 3.48–3.46 (m, 1H, A-5), 3.47 (dd, J = 9.2, 3.1 Hz, 1H, E-3), 3.43 (t, J = 3.5 Hz, 1H, F-2), 3.39 (s, 3H, OMe (F-2)), 3.35 (s, 3H, OMe (A-4)), 3.34–3.33 (m, 2H, B-5, F-5), 3.30 (s, 3H, OMe), 2.51 (dd, J = 12.5, 8.5 Hz, 1H, C-2), 2.45 (dd, J = 13.7, 4.9 Hz, 1H, A-2), 2.38 (s, 3H, Me (A_1)), 2.29 (brdd, J = 12.4, 8.6 Hz, 1H, B-2), 2.26 (s, 3H, Me (A_2)), 2.01 (dd, J = 13.7, 1.6 Hz, 1H, A-2), 1.90 (t, J = 12.1 Hz, 1H, C-2), 1.70–1.66 (m, 1H, B-2), 1.68 (s, 3H, Me, A-3), 1.34 (s, 3H, Me, D-3), 1.32 (d, J = 6.4 Hz, 3H, B-6), 1.31 (d, J = 6.2 Hz, 3H, D-6), 1.28 (d, J = 6.6 Hz, 3H, E-6), 1.26 (d, J = 6.8 Hz, 3H, C-6), 0.96 (s, 9H, $t\text{BuSi}$), 0.95 (s, 9H, $t\text{BuSi}$), 0.94 (s, 9H, $t\text{BuSi}$), 0.90 (s, 9H, $t\text{BuSi}$), 0.89 (s, 18H, $t\text{BuSi}$), 0.83 (d, J = 6.2 Hz, 3H, Me (A-6)), 0.21 (s, 6H, MeSi), 0.19 (s, 3H, MeSi), 0.18 (s, 6H, MeSi), 0.14 (s, 3H, MeSi), 0.10 (s, 6H, MeSi), 0.10 (s, 3H, MeSi), 0.09 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.06 (s, 3H, MeSi); ^{13}C NMR (125 MHz, CDCl_3): δ = 167.1, 165.6, 157.3, 153.9, 152.3, 153.2, 138.7, 137.9, 135.9, 134.8, 128.6, 128.6, 128.5, 127.5, 126.4, 126.0, 121.7, 120.1, 119.0, 119.0, 114.9, 108.5, 103.5, 102.3, 100.2, 97.2, 96.4, 92.6, 89.9, 84.3, 82.8, 82.4, 81.5, 81.1, 79.0, 77.3, 76.1, 75.1, 74.9, 74.1, 73.5, 72.8, 72.4, 71.8, 71.6, 71.1, 70.5, 70.4, 70.0, 69.1, 68.3, 66.2, 63.3, 63.0, 62.5, 62.0, 60.8, 58.4, 46.2, 40.1, 38.8, 36.4, 29.7, 26.2, 26.0, 25.8, 25.6, 25.6, 19.8, 19.3, 19.2, 18.4, 18.3, 18.3, 18.1, 18.1, 18.0, 18.0, 17.6, 16.2, 11.6, –3.7, –3.8, –3.9, –4.2, –4.3, –4.4, –4.4, –4.5, –4.5, –4.9, –5.0, –5.2; MS (electrospray ionization): calcd for $\text{C}_{120}\text{H}_{195}\text{O}_{38}\text{Cs}$ [$M + \text{Cs}^+$]: 2496/2497, found: 2498/2499

usual criteria (TLC, ^1H NMR, ^{13}C NMR, IR, MS, α_D^{25}) with an authentic sample.^[12]

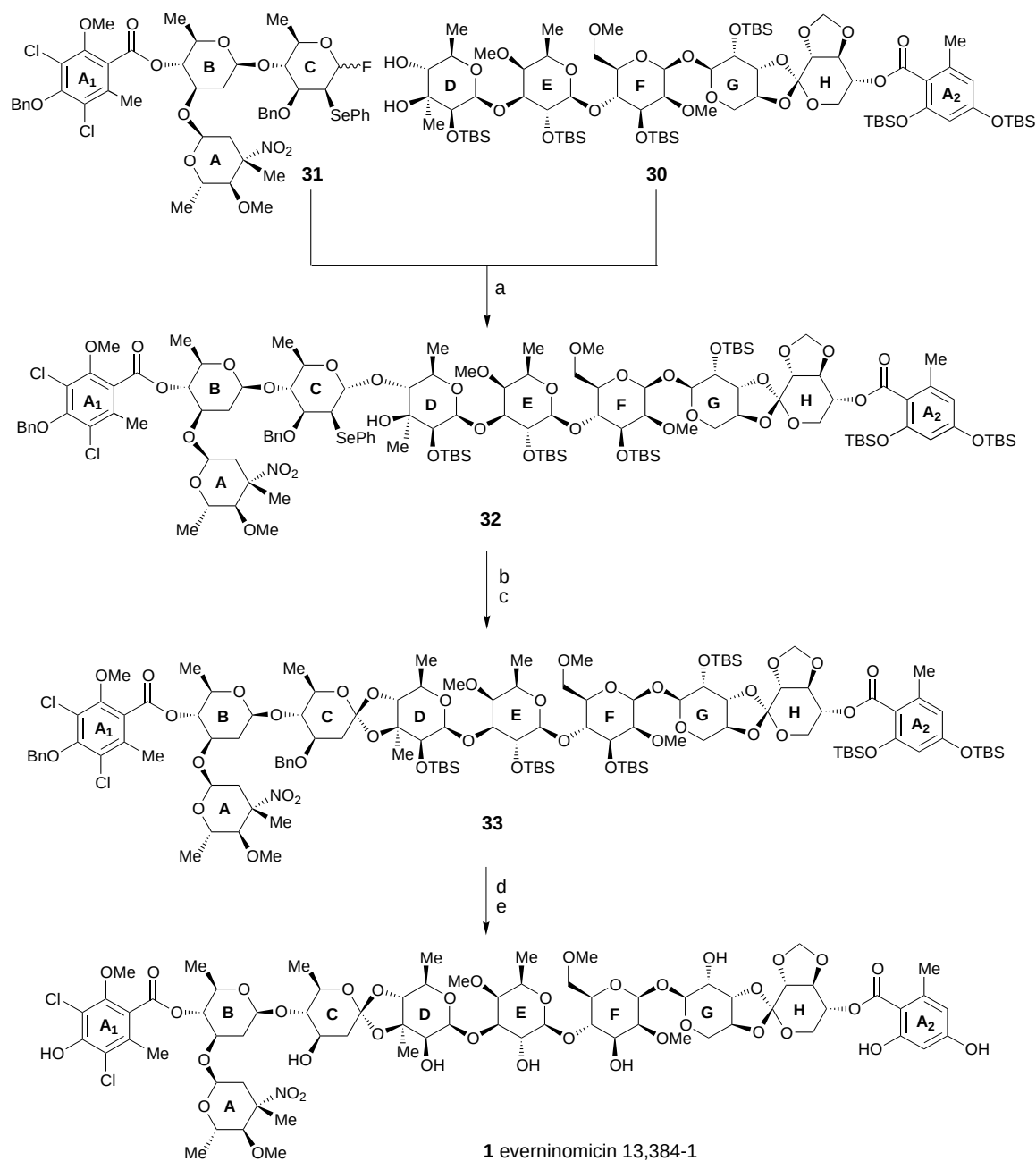
The reported total synthesis of everninomicin 13,384-1 (**1**) constituted an adventurous journey during which we have demonstrated the power of novel synthetic reactions both from our own and other laboratories. Most notable of these methods are the 1,2-phenylthio^[10] and the 1,2-phenylseleno migrations on carbohydrate templates and their use in stereocontrolled glycosidation reactions; the tin acetal based stereocontrolled construction of 1→1'-disaccharides;^[13] the use of acyl fluorides for the formation of sterically hindered esters; the Sinaï orthoester protocol formation;^[11] the sulf-oxide-based β -mannoside forming glycosidation by Kahne et al.;^[3, 4] the trichloroacetimidate glycosidation method of Schmidt and Michel;^[14] the glycosyl fluoride methodology of Mukaiyama et al.;^[15] and the tin acetal technology^[7] for differentiating 1,2-diols. Furthermore, a great deal of knowledge regarding selectivity in manipulating protective groups was gathered and considerable light was shed on conformational effects on selective functionalization of carbohydrate templates. Most importantly and as a result of this synthesis, the stage is now set for further advances in the antibiotics field, including semisynthesis of designed analogues, solid-

phase synthesis, combinatorial chemistry, and chemical biology studies.^[16]

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Scheme 5. Completion of the total synthesis of everninomicin 13,384-1 (**1**). a) 2.0 equiv **31**, 1.8 equiv SnCl₂, Et₂O, 0 → 25 °C, 6 h, 70%; b) 10 equiv NaIO₄, 8.0 equiv NaHCO₃, MeOH/CH₂Cl₂/H₂O (3/2/1), 25 °C, 4 h; c) vinyl acetate/toluene/diisopropylamine (2/2/1), sealed tube, 140 °C, 16 h, 65% over two steps; d) H₂, 0.1 equiv 10% Pd/C (w/w), 4.0 equiv NaHCO₃, *t*BuOMe, 25 °C, 1 h; e) 10.0 equiv *n*Bu₄NF, THF, 25 °C, 10 h, 75% over two steps.

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- [16] All new compounds exhibited satisfactory spectral and exact mass data.

Shaping Solid-State Supramolecular Cavities: Chemically Induced Accordionlike Movement of γ -Zirconium Phosphate Containing Polyethylenoxide Pillars**

Giulio Alberti,* Ernesto Brunet, Chiara Dionigi,
Olga Juanes, María José de la Mata,
Juan Carlos Rodríguez-Ubis, and Riccardo Vivani*

Layered zirconium phosphate derivatives containing organic pillars are very promising materials because the size, shape, and chemical function of free interpillar spaces may be designed by choosing the appropriate organic moieties and controlling the degree of pillaring.^[1–3] Among the different zirconium phosphates, the α phase is less suitable for this purpose because, owing to the flexibility of the α layer, a random distribution of pillars in the interlayer region is not usually obtained, and special pillars (pillars with bases) must be used to create interpillar microporosity.^[4] In contrast, the high rigidity of the lamellae of γ -zirconium phosphate ($[\text{ZrPO}_4\{\text{O}_2\text{P}(\text{OH})_2\}] \cdot 2\text{H}_2\text{O}$; γ -ZrP) allowed us to prepare stable phases with a low extent of pillaring, making the use of pillars with bases no longer necessary.^[5] The utilization of diphosphonic acid derivatives of crown ethers led to pillared materials with the ability to recognize cations.^[6]

More recently, the behavior of γ -ZrP pillared with nonrigid alkyl chains was investigated. The presence or absence of solvent in the cavities of these pillared materials induced conformational changes of the alkyl chains and gave rise to an accordionlike movement of the layers.^[7] This research led to the conclusion that appropriate functionalization of the pillars would allow the chemical control of this anisotropic movement.

With the aim of creating tailor-made supramolecular cavities in interlayer spaces, in which certain molecular species could be selectively inserted, a systematic study on the preparation and properties of γ -ZrP materials containing polyethylenoxide pillars of different length was initiated in our laboratories. This research showed that γ -ZrP derivatives containing these pillars in various densities in the interlayer space can be easily prepared by topochemical reactions, thus confirming that supramolecular interpillar cavities can indeed be tailored. In the course of this study it was also found that the oxygen atoms of the pillars played a decisive role in the chemically induced accordionlike movements of the layers.

Preparation procedures, compositions, model structures as well as the chemical and recognition properties of γ -ZrP

containing a variety of polyethylenoxide chains at various interpillar distances will be reported elsewhere. Here our attention will be focused on the chemically induced accordionlike movement of these derivatives. Only compounds of general composition $\text{ZrPO}_4[\text{O}_2\text{P}(\text{OH})_2]_{0.76}(\text{O}_2\text{P}(\text{OH})-\text{R}-(\text{OH})\text{PO}_2)_{0.12} \cdot n\text{H}_2\text{O}$, where the pillar R can be diethylene glycol (DEG) or pentaethylene glycol (PEG), will be considered. This kind of pillaring can be seen as a process in which each diphosphonate molecule acts as a tetradentate ligand and replaces two bidentate $\text{O}_2\text{P}(\text{OH})_2$ ligands belonging to two adjacent lamellae of the original γ -ZrP.^[8]

The interlayer spaces of the DEG- and PEG-pillared derivatives after centrifugation from the mother liquors were 15.7 and 17.6 Å, respectively. When these samples were dehydrated at 80 °C, the interlayer distances decreased to 13.2 and 13.3 Å, respectively, with the loss of one mole of water per mole of zirconium. The initial hydrated phases were obtained again by rehydration in water, showing that the dehydration–rehydration process was reversible. The fact that the interlayer space of the anhydrous phases is independent of the chain length indicates that the pillars must lie almost parallel to the plane of the layer. Taking the average thickness of a γ layer and the polyethylenoxide chains as 9.3 and 4 Å, respectively, the experimental interlayer space agrees satisfactorily with the value expected when a stratum of heavily inclined pillars is interposed between layers (Figure 1).

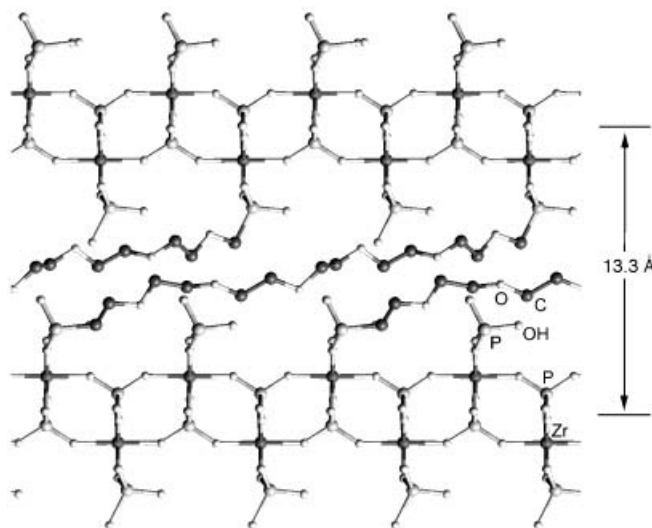


Figure 1. The structure of the anhydrous PEG-pillared derivative of γ -zirconium phosphate.

In derivatives with 25 % pillaring the total free area for each pillar is four times that of the free area available for each phosphorus atom (i.e., $4 \times 33.3 = 133 \text{ Å}^2$). Therefore, the formation of a monolayer containing heavily inclined pillars is largely compatible with the total free area available in derivatives with 25 % pillaring, even in the case of very long pillars. For example, one PEG pillar should occupy an area approximately equal to the product of its cross section and its length (i.e., $4 \times 27.5 = 110 \text{ Å}^2$). The differences between the interlayer spaces of the hydrated and anhydrous phases for

[*] Prof. Dr. G. Alberti, Dr. R. Vivani, Dr. C. Dionigi
Dipartimento di Chimica, Università di Perugia
Via Elce di Sotto 8, I-06123 Perugia (Italy)
Fax: (+390) 75-585-5566
E-mail: alberti@unipg.it

Prof. Dr. E. Brunet, Prof. Dr. O. Juanes, M. J. de la Mata,
Prof. Dr. J. C. Rodríguez-Ubis
Departamento de Química Orgánica, Facultad de Ciencias C-I
Universidad Autónoma de Madrid, 28049-Madrid (Spain)

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DEG and PEG derivatives are 2.5 and 4.3 Å, respectively. Considering that DEG contains 11 chain atoms (8C and 3O), while PEG contains 20 chain atoms (14C and 6O), the average increment per chain atom is about the same for the two derivatives (0.23 and 0.22 Å, respectively). Thus, assuming that the chains are in their extended conformation, this small increment corresponds to an average inclination angle α of the chain to the plane of the hydrated γ -ZrP sheets of about 10°.

The pronounced inclination of the chains, even in the hydrated forms, suggests a low tendency of these derivatives to incorporate water in the interpillar region. This fact seems to be in contrast with the results previously obtained with alkyl pillars, where, despite their much lower hydrophilicity, several water molecules entered freely into the interpillar space, thus forcing the alkyl chains to assume a position almost perpendicular to the layers.^[7] A reasonable explanation of this apparent contradiction is that the hydrophilic oxygens present in the pillars also have a strong affinity for the surface of the γ -ZrP lamellae, probably due to the formation of hydrogen bonds with the unexchanged $\text{O}_2\text{P}(\text{OH})_2$ groups. The pillars could therefore be obliged to take a position almost parallel to the layers. Furthermore, the water molecules may be also well organized in the interlayer space. Composition data seem to indicate that one water molecule is present for each unexchanged $\text{O}_2\text{P}(\text{OH})_2$ group, while the remaining water may be coordinated to the pillar chain (about one molecule per ethylenoxide monomer). On this assumption, molecular modeling reproduces reasonably well the water content and the increment of the interlayer distance when the DEG and PEG derivatives become hydrated.

To increase the number of water molecules in the interpillar space, we tried to break these hydrogen bonds between the pillars and the $\text{O}_2\text{P}(\text{OH})_2$ groups by titrating the derivatives with various bases and checked whether the pillars could be forced to align perpendicular to the layers. The best results were obtained with methylamine (see Experimental Section). Elemental and thermogravimetric analysis as well as X-ray powder diffraction (XRD) patterns of samples titrated with methylamine showed that 0.76–0.78 moles of the amine (one molecule for each unexchanged $\text{O}_2\text{P}(\text{OH})_2$ group) and additional 1.7 moles of water per mole of zirconium were taken up in the interlayer space. The interlayer distance of the DEG and PEG derivatives greatly increased to 21.6 and 26.7 Å, respectively.

We also tested whether the large variations in the interlayer spaces obtained with methylamine titration were reversible. After titration, the derivatives were suspended again in water and then 0.1M HCl was added to pH 2.5. The compounds were centrifuged, and their XRD patterns recorded. The resulting interlayer distance had decreased to 15.7 and 17.6 Å, respectively. This clearly demonstrates the reversibility of the process schematically shown in Figure 2 for the DEG derivative. In the case of the titrated DEG derivative, the interlayer separation of 21.6 Å is almost the maximum possible because it corresponds to an α angle very close to 90°.

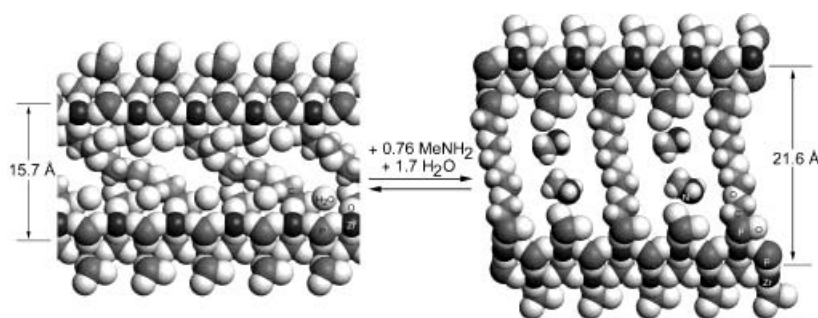


Figure 2. Schematic representation of the reversible enlargement–shortening of the interlayer space of the DEG-pillared derivative following intercalation–deintercalation of methylamine and additional water.

In the case of the PEG derivative a more spectacular variation of the interlayer space was observed (ca. 9 Å). However, this is still shorter than the maximum possible value predicted when the chains are in a completely extended conformation (ca. 33 Å). A plausible explanation could be that, owing to the interactions with water molecules, the long polyethylenoxide chains tend to assume a helicoidal conformation, as recently shown by IR measurements in solution.^[9]

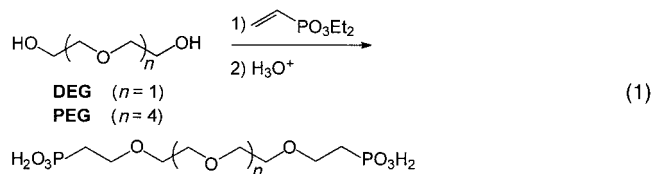
We also analyzed the stages of the methylamine titration of the DEG derivative. Detailed studies are in progress to determine the methylamine and water content of the above phases, but preliminary results clearly show that the passage from the initial to the final interlayer distance is reached through many intermediate steps; at least five different intermediate phases were identified. Thus, an almost continuous variation of the interlayer distance between 15.7 and 21.6 Å can be obtained by gradual addition of methylamine. We conclude that in the presence of methylamine, a progressive, reversible accordionlike movement of this pillared compound can be simply induced by a gradual change in the pH value of the solution. This is the first time, to the best of our knowledge, that the size and shape of the cavities of a pillared material can be finely tuned by chemical means.

Upon dehydration, the interlayer space of DEG and PEG derivatives loaded with methylamine decreased to 14.9 and 16.6 Å respectively. Since the original interlayer spaces are recovered when rehydrated, the phenomenon of the reversible elongation–shortening of the interlayer space induced by hydration–dehydration of the interlayer region seems to be similar to that already described for γ -derivatives pillared with alkyl chains.^[7]

The possibility of engineering an accordionlike movement by simply controlling the pH value of the external solution is fascinating. The easy preparation of γ -ZrP derivatives containing polyethylenoxide phosphonates in which the length of the pillars, their conformation, and their distances to one another in the interlayer space can be modulated over a wide range is very promising for the realization of shaped interpillar spaces. The creation of these molecular vessels would allow the specific adsorption of different species with which selective reactions might be carried out. Additional studies are in progress to clarify the details of the conformational changes of the pillars when the corresponding derivatives are titrated with methylamine, other amines, or metal hydroxides and salts.

Experimental Section

The DEG and PEG diphosphonic acids were prepared by Michael-type double addition of the corresponding diol to diethyl vinyl phosphonate and final acid hydrolysis of the resulting tetraethyl phosphonic diester [Eq. (1)].



The pillaring procedure was performed by first exfoliating γ -ZrP (0.5 g) in water/acetone (1/1, 60 mL) at 80 °C. This dispersion of exfoliated lamellae was then mixed with a 0.015 M solution (20 mL) of DEG or PEG bisphosphonic acids in water/acetone (1/1) at 80 °C overnight.

Average values from elemental analysis and ^{31}P NMR spectroscopy^[10] were used to determine the composition of the solids. Water content was derived by thermogravimetry with a Stanton STA750 thermoanalyzer. The interlayer distances were taken from the first reflection in the XRD patterns.

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Laser-Induced “Regeneration” of Colloidal Particles: The Effects of Thermal Inertia on the Chemical Reactivity of Laser-Heated Particles**

Thomas E. McGrath, Andrew C. Beveridge, and Gerald J. Diebold*

Colloidal suspensions of metal particles frequently display surprising colors,^[1, 2] the most striking examples being perhaps the deep red of colloidal gold and the light yellow-green of colloidal silver. Irradiation of colloidal carbon^[3, 4] or colloidal metal solutions^[5, 6] by a high-power, pulsed laser causes a reduction in the diameters and the dispersion of the suspended particles, resulting in dramatic changes in their optical properties that are easily discernible by the unassisted eye. We show here that the mechanism of change in several colloidal metal solutions involves rapid production of ions as a result of laser heating, followed by diffusion and chemical reduction on a long time scale to form new small-diameter colloidal particles. A result of the experiments is that large particles are differentially consumed relative to small ones. The recently reported method^[7, 8] of forming colloidal suspensions through irradiation of solid metal surfaces submerged in water is also shown here to involve formation of ionic species.

When an aqueous suspension of particulate carbon, known as “India ink”, is irradiated with a high-power, pulsed laser it rapidly becomes transparent as a result of carbon consumption through the carbon–steam reaction: Heating of the carbon particles on absorption of the laser radiation^[3, 4] converts carbon and water into hydrogen and carbon monoxide, gradually reducing both the diameter of the carbon particles and the total amount of carbon in suspension. The recently reported observation of the same effect of size reduction in colloidal silver and gold suspensions^[5, 6] suggests examination of the possibility of chemical reactions, albeit of an altogether different character than in the case of carbon in water, as playing some role in the mechanism of change. The first experiments carried out here sought to determine if Au^{3+} ions were generated by pulsed laser irradiation of a gold sol.

An aqueous suspension of gold particles of 100 nm diameter^[9] has a surface plasmon resonance^[1] at 566 nm, which is a result of collective oscillations of the electrons in small particles, giving the sol its distinctive color, as is evidenced by the absorption spectrum (inset of Figure 1). Irradiation of the suspension for 2 min at 10 Hz and 330 mJ per pulse with the unfocused output (532 nm, 15 ns) of a frequency-doubled Nd:YAG laser results in the formation of smaller gold particles, as is found from transmission electron microscope measurements^[10] and as further evidenced in

[*] Prof. Dr. G. J. Diebold, T. E. McGrath, A. C. Beveridge
Department of Chemistry, Brown University
Providence, RI 02912 (USA)
Fax: (+1) 401-863-2594
E-mail: gerald_diebold@brown.edu

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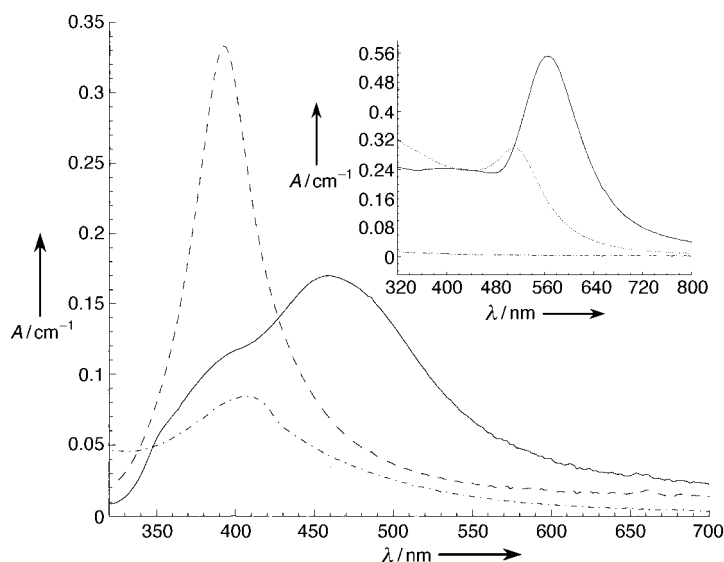


Figure 1. Optical absorbance A versus wavelength λ for a silver sol before irradiation (—), after irradiation (---), and after irradiation but with KI present (- · -). The I^- ion reacts with Ag^+ to form AgI . Inset: Optical absorbance versus wavelength for a gold sol before irradiation (—), after irradiation (····), and after irradiation with CN^- present (- · - ·).

Figure 1 by a shift of the plasmon resonance to 512 nm. Experiments to investigate the possibility of ion formation as a step in size reduction of particles employed $SnCl_2$, which acts as a color indicator for the presence of Au^{3+} ions. Following irradiation of a 0.2 mM sol of 100-nm gold particles, an equal volume of 2 mM $SnCl_2$ was added to the sol. The solution immediately turned to a deep purple color known as the "Purple of Cassius",^[11] indicating a positive test for the presence of Au^{3+} . In a second experiment, CN^- , known to react with Au^{3+} to form $[Au(CN)_4]^-$, was introduced into a suspension of 100-nm colloidal gold particles before irradiation to determine the effect of scavenging Au^{3+} on the size-reduction process. A solution 1 mM in $NaCN$ and 0.1 mM in colloidal gold was irradiated under the same conditions as in the previous experiment. The flat, featureless absorption spectrum taken after irradiation has neither of the plasmon resonances at 566 or 512 nm (inset of Figure 1), indicating consumption of 100-nm gold particles without the formation of new, smaller diameter colloidal particles. Similar experiments using Cl^- , which also scavenges Au^{3+} , gave absorption spectra devoid of peaks characteristic of gold surface plasmon resonances, again indicating that ion formation is an essential step in the mechanism that leads to size reduction of irradiated particles.

The particles of colloidal silver used in the experiments here,^[9] as shown by transmission electron microscopy, were not uniform in diameter, or even, in general, spherical; the absorption of the sol is thus spread over a wide spectral region.^[1] As shown in Figure 1, when such a silver colloid is irradiated with the frequency-doubled output of a Nd:YAG laser, the normally translucent solution, which has a broad, weak absorption from 350 to 550 nm, takes on a light green color that arises from a strong absorption of a surface plasmon resonance at 397 nm from particles with diameters on the order of 5 to 15 nm. Experiments analogous to those

described above with gold were done with 26 mM silver sols using 2 mM I^- to precipitate any Ag^+ ions formed by absorption of laser radiation. Instead of showing a large increase in the absorption at the surface plasmon resonance at 397 nm after irradiation with 532-nm radiation, as is the case with neat silver sol, the suspension showed a decrease in absorption at 397 nm as well as a strong decrease in absorbance in the visible spectral region (Figure 1). Again, the profound effect of the presence of an anion that reacts with the metal cation of the colloid gives strong evidence that ion production is the primary route in the process of size reduction.

The time scales for destruction and reformation of the colloidal particles were also investigated. The absorption of the broad surface plasmon resonance of silver was monitored as a function of time after firing of the Nd:YAG laser using an Ar^+ laser probe beam (488 nm). The probe beam and the 532-nm beam were directed nearly colinearly into a 1-cm² cuvette. The decrease in absorption of the suspension at 488 nm (inset of Figure 2) takes place on a microsecond time scale and

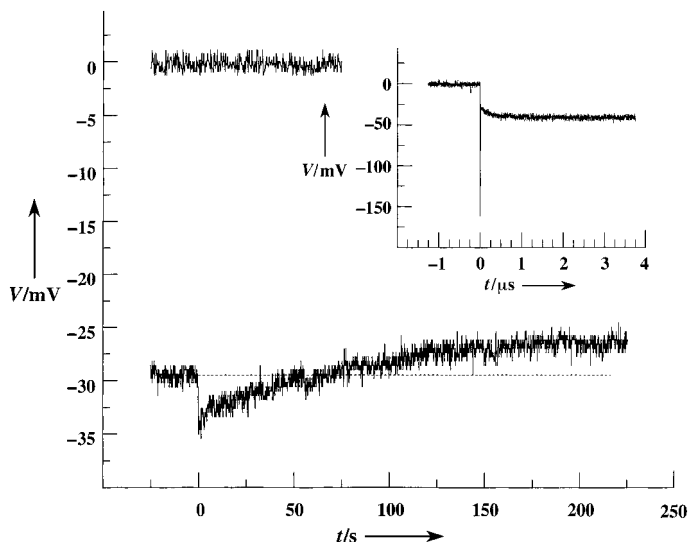


Figure 2. Lower trace: Photodiode output voltage V versus time t showing the change in transmission of a silver suspension at 422 nm following irradiation of the cuvette with a single pulse of radiation (15 ns, 532 nm). Upper trace: Photodiode baseline taken with the probe laser beam blocked. The finite transmission of the solution before firing of the Nd:YAG laser, marked with a straight dotted line, can be attributed to scattering and absorption from large particles. Inset: Photomultiplier output voltage V versus time t showing the change in transmission of the broad continuum absorption in a silver suspension monitored at 488 nm following irradiation with 532-nm laser radiation. After the 330-mJ burst of 532-nm light, seen as a sharp spike at $t=0$, the photomultiplier shows an increase in optical transmission.

corresponds to an overall decrease in absorption of the solution over a wavelength span of several hundred nanometers caused by reduction in the mean size of the particles. In a second experiment, the growth of the plasmon resonance at 397 nm was monitored by recording the absorption of a 422-nm probe laser beam. The initial decrease in absorbance of the suspension at 422 nm (Figure 2) can be attributed to a decrease in absorbance of the suspension over a wide wavelength span. The increase in absorbance corresponding to the formation of new particles takes place over a period of

hundreds of seconds and can vary significantly depending on irradiation conditions such as the laser fluence and the number of shots fired. Analogous experiments carried out with a gold sol showed nearly identical time scales for the destruction and reformation of the gold particles. The results of these two experiments are consistent with a mechanism whereby metallic particles are partially converted into ions, which diffuse outwardly from the particles, and are later chemically reduced forming new small-diameter colloidal particles. The time evolution of the absorption of the surface plasmon resonance from the newly formed particles reflects a dynamic process as is typically seen in the chemical formation of colloids.^[12, 13]

Transient grating experiments to investigate the time evolution of particles irradiated by intense laser radiation were carried out as well. In the transient grating technique^[14] a laser beam is split into two equal-intensity beams that are recombined, giving an interference pattern in space with nodes and antinodes in the electric field. Formation of the interference pattern in a weakly absorbing liquid results in a sinusoidal deposition of heat in space. The result of the heat deposition is thermal expansion at the antinodal regions and the consequent launching of a standing acoustic wave, which owing to the density variations in the acoustic wave acts as a diffraction grating. The time evolution of the ultrasonic wave is typically recorded by directing a probe laser beam at the Bragg angle to the grating and recording the intensity of the diffracted light, which shows a waveform that varies with time and whose period is governed by the speed of sound in the fluid and the fringe spacing of the grating. Theoretical calculations^[3, 15] have shown that the consumption of energy through chemical reaction results in what appears as a doubled frequency for the transient grating signal. The effect was first reported in carbon suspensions,^[3] where the endothermic carbon–steam reaction is initiated by laser heating.

Transient grating experiments with colloidal gold showed a frequency-doubled signal for particles with diameters of 100, 40, and 20 nm, but not for particles with 5 nm diameter. With gold particles of 100 nm diameter, and the laser operating at 532 nm with an output of 50 mJ, a frequency-doubled signal was observed that diminished over the course of 250 laser shots, giving only the usual signal corresponding to the fringe spacing of the grating (Figure 3). On increasing the output energy to 200 mJ, the frequency-doubled signal reappeared, again gradually disappearing to give only the signal at the calculated frequency. The same effect could be initiated again by increasing the output energy to 330 mJ. The appearance of a frequency-doubled signal and its recurrence with increasing laser power suggests first that an endothermic reaction—namely, the desorption and ionization of atomic gold to produce Au^{3+} and three solvated electrons—is initiated by the laser heating, and, second, that the ability of the laser radiation to cause reaction depends on the laser fluence and the diameter of the particles in suspension. It is noteworthy that neither a suspension of gold particles with 5 nm diameter nor a filtered^[16] carbon suspension gives a frequency-doubled signal; only a signal corresponding to the optical fringe spacing is seen.

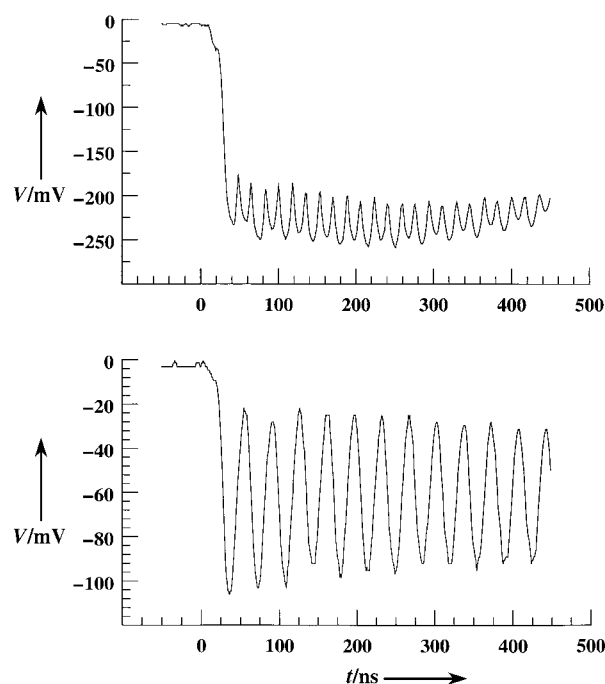


Figure 3. Photomultiplier output voltage V versus time t showing the evolution of the diffracted light signal. The initial transient grating signal (upper plot) decreases in amplitude and appears after 250-laser shots (lower plot) at the frequency corresponding to the optical fringe spacing of the grating.

The question of whether the process leading to ion formation is linearly related to the laser intensity was addressed by studying the formation of the plasmon resonance at 397 nm in silver sol by reducing the intensity of the laser but keeping the total amount of energy absorbed in the cell constant by increasing proportionately the number of laser shots. Experiments performed over a range of laser intensities using 532-nm radiation showed that an intensity threshold exists for changing the absorption spectrum of the colloid: A large number of low-intensity laser pulses is not equivalent to a small number of high-intensity pulses. Similar experiments done with gold sols gave the same result. These findings are consistent with a thermal mechanism of size reduction. Although the experiments do not delineate the details of the first step following absorption of radiation, it is likely that electrons are ejected^[17, 18] from the particle surface, which in turn leads to ion emission and size reduction, the time scale for which depends on irradiation parameters. The presence of electrons following flash photolysis has been reported; however, the evidence is not incontrovertible.^[19, 20] Hydrated electrons which would react on a short time scale, OH^- ions which reduce Ag^+ on a longer time scale and which are known to be formed by reaction of electrons with water,^[21] are likely candidates as reducing agents.^[13]

It has recently been shown that metal colloids can be produced by irradiation of bulk metal targets immersed in water using the 1.06- μm output of a Nd:YAG laser.^[7, 8] Irradiation of a silver target with 700 mJ from an unfocused Nd:YAG laser produces a colloidal suspension whose absorption is easily visible to the eye after only a few seconds. Experiments conducted using an ion-selective electrode that

responded to Ag^+ showed a strong ion signal after a few firings of the laser.^[22] The presence of ions in the experiments with irradiation of bulk metal argues for the same final step in colloid production that is operative in the size reduction of colloids, namely, diffusion followed by chemical reduction and particle formation.

That the first step in size reduction is a thermal phenomenon is evidenced by a lack of any dependence of the reduction phenomenon on laser wavelength. Experiments with colloidal suspensions of C, Au, Ag, Pt, Fe, and Ni showed no significant difference in absorption spectra after irradiation for excitation at 355, 532, and 590 nm—all three wavelengths gave the same result.^[23] From the theory of Mie scattering^[1, 2] it is known that spherical particles whose diameter is smaller than the wavelength of the incident radiation absorb radiation and are heated uniformly throughout their volume. In the absence of any heat-loss mechanisms, such particles reach the same final temperature irrespective of their diameter. However, it can be shown^[24] that when heat conduction takes place and when the time scale for heat conduction is commensurate with the laser pulsewidth, a particle that is large, but still smaller than the wavelength of the exciting radiation, is heated to a higher temperature and maintains that temperature longer than a small one. Large particles can be thought of as having a greater “thermal inertia” than small ones: For any heat-loss mechanism dependent on the surface area of the particle, large particles will maintain their temperature longer than small ones as a result of the volume-to-surface ratio, which increases as the first power of the radius. In the case of a polydisperse suspension of particles in a chemically reactive environment, a general principle for reactivity can be thus formulated: The largest particles in a laser-irradiated suspension, owing to their higher thermal inertia, reach a higher final temperature and maintain that temperature longer. They undergo chemical reaction to a greater extent than their smaller counterparts, giving, in effect, a size-dependent chemical reactivity. The failure of laser irradiation to effect changes in suspensions of small-diameter gold and carbon, the power dependence of the doubled frequency in the transient grating signals in colloidal gold, and the reduction in size and dispersity of large-diameter gold, silver, platinum, nickel, and iron sols can be explained by reactivity dependent on thermal inertia.

Although phrased somewhat differently in medical science, the above principle is clearly the operative mechanism in laser removal of, for instance, port wine stain, where large epithelial blood vessels are coagulated preferentially over small ones.^[25] The application of the principle in experiments with metal sols clearly shows that the size and dispersity of colloidal particles can be controlled by irradiation with a pulsed laser. The size-reduction phenomenon itself is perhaps a first demonstration of the possibilities of laser manipulation of the physical or chemical properties of colloidal particles.

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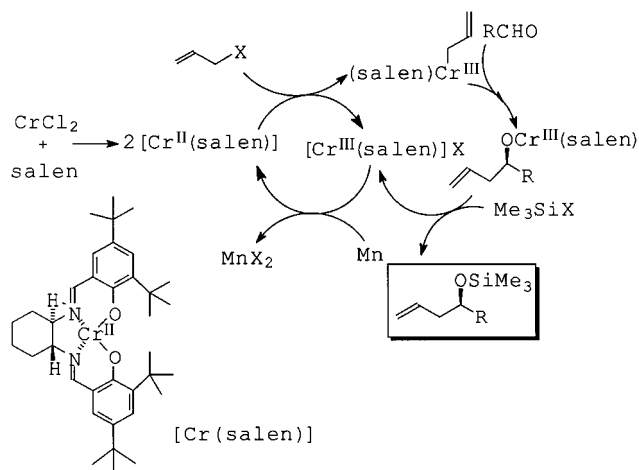
The First Catalytic Enantioselective Nozaki–Hiyama Reaction**

Marco Bandini, Pier Giorgio Cozzi,* Paolo Melchiorre, and Achille Umani-Ronchi*

In recent years, catalytic redox reactions have become more important in organic synthesis since they represent environmentally friendly processes. Titanium,^[1a] samarium,^[1b] vanadium,^[1c] and chromium^[1d,2] catalytic redox processes have been recently applied to C–C bond-forming reactions. Among them, the Nozaki–Hiyama reaction^[2] performed by Fürstner with catalytic amounts in chromium is of high importance.^[3] The crucial points of this catalytic redox cycle are the use of commercial Mn as the stoichiometric reducing agent and Me₃SiCl as the scavenger. Herein we describe the first effective catalytic enantioselective allylation reaction (Nozaki–Hiyama reaction)^[4] performed using a catalytic amount (10 mol %) of chiral chromium complex.

Catalytic asymmetric allylation methodologies have been recognized as important synthetic tools for the stereoselective preparation of homoallylic alcohols and amines.^[5] In all the previous reactions described allylstannanes or allylsilanes were used as nucleophiles; however, our enantioselective redox process utilizes allyl halides and the inexpensive and commercially available (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (salen, **1**) as the chiral ligand (Scheme 1).^[6]

In the course of our work, several types of chiral ligands were tested in the reaction of allylchromium complexes with

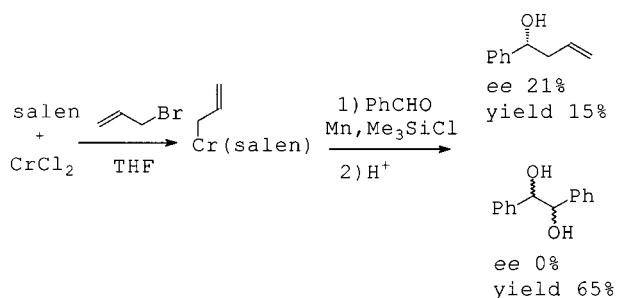


Scheme 1. A tentative mechanism for the catalytic enantioselective Nozaki–Hiyama reaction.

[*] Dr. P. G. Cozzi, Prof. Dr. A. Umani-Ronchi, Dr. M. Bandini, P. Melchiorre
Dipartimento di Chimica “G. Ciamician”, Università di Bologna
Via Selmi 2 I-40126 Bologna (Italy)
Fax: (+390)51-2099456
E-mail: pgcozzi@ciam.unibo.it
umani@ciam.unibo.it

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benzaldehyde.^[7] However, a promising level of enantioselectivity (21 % *ee*) was only obtained by using **1**. The chiral organometallic allyl-Cr(salen) complex was prepared “in situ” by adding anhydrous CrCl₂ to a solution of **1** in THF followed by treatment with allyl bromide. Nevertheless, the subsequent addition of Mn, Me₃SiCl, and benzaldehyde at room temperature gave the silylated homoallylic alcohol in low yield (15 %); the main product was the pinacol (Scheme 2). We found that this side reaction can be minimized by using CH₃CN as solvent. Optimal reaction conditions require the preparation of the [Cr(salen)] complex in



Scheme 2. Allylation of benzaldehyde mediated by [Cr(salen)] complex, prepared by using CrCl₂.

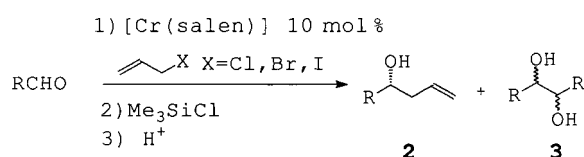
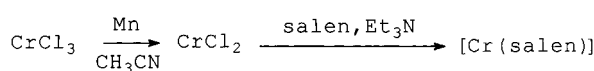
CH₃CN and in the presence of a base (20 mol %, that is 1 equiv base per HCl formed) capable of deprotonating the salen ligand. In fact the *ee* of the homoallylic alcohol significantly increased by adding both inorganic and organic bases such as K₂CO₃, (2,6-di-*tert*-butyl)pyridine, and Et₃N (Table 1).^[8]

Table 1. Influence of bases on the enantioselective addition of allyl bromide to PhCHO catalyzed by [Cr(salen)] complex.

Entry	Base ^[a]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	–	56	21
2	K ₂ CO ₃	51	47
3	K ₂ CO ₃ ^[d]	52	25
4	Et ₃ N	65	65
5	Et ₃ N ^[e]	50	50
6	(<i>t</i> Bu) ₂ Py	20	58

[a] All the bases were added to a suspension of salen and CrCl₂ in CH₃CN. All the reactions, except for that in entry 1, were carried out with 20 mol % of base. [b] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [c] The *ee* value was evaluated with a cyclodextrin Megadex 5.25 mt chiral column. The absolute configuration of the isolated homoallylic alcohol was assigned by comparison of the GC analysis trace with that of the known product.^[5a] [d] The reaction was carried out at 40 °C. [e] 10 equivalents of Et₃N were employed.

The procedure was further improved by avoiding the manipulation of highly air-sensitive CrCl₂; instead the reduction of anhydrous CrCl₃ with an excess of Mn was employed. The Cr^{II} species was complexed to the salen ligand in the presence of Et₃N (20 mol %) to afford the chiral [Cr(salen)] complex in situ.^[9] The resulting chiral catalyst was employed in 10 mol % with allyl halide, Me₃SiCl, and PhCHO (Scheme 3).



Scheme 3. Enantioselective allylation of aldehydes mediated by $[\text{Cr}(\text{salen})]$ complex, prepared by the in situ reduction of CrCl_3 .

Using the above-mentioned procedure, we screened several allyl halides and the results are summarized in Table 2. Up to 84% *ee* was obtained in the reaction of benzaldehyde with

Table 2. Enantioselective addition of various allyl halides to PhCHO catalyzed by $[\text{Cr}(\text{salen})]$ complex.

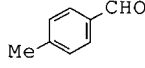
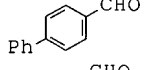
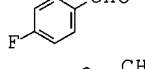
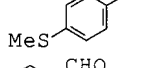
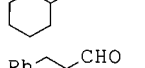
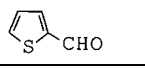
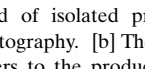
Entry	RX	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1		67	84 (<i>R</i>)
2		65	65 (<i>R</i>)
3		70	0
4		62	42 (<i>R</i>) ^[c]
5		60	43 (<i>R</i>) ^[c]
6		85	70 (nd) ^[d]

[a] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [b] Determined with a cyclodextrin Megadex 5.25 mt chiral column. The absolute configuration of the isolated homoallylic alcohol was assigned by comparison of the GC analysis trace with that of the known product.^[5a] [c] Determined with a cyclodextrin Megadex 5.25 mt chiral column on the corresponding O-methyl ether. The absolute configuration was assigned by comparing the optical rotation with that of the known product: $[\alpha]_{\text{D}} = +6.3$ ($c = 0.51$ in C_6H_6); literature value: *R* isomer, $[\alpha]_{\text{D}} = +50.2$ ($c = 1.16$ in C_6H_6).^[11a]

allyl chloride (Table 2, entry 1), while a racemic product was isolated by using the allyl iodide, probably due to its direct reaction with Mn affording an achiral allylating species (Table 2, entry 3). Other substituted allyl halides were successfully employed (entries 4–6). Different silylating agents did not have any significant influence on the asymmetric induction of the process.^[10] The optimal conditions (Scheme 3) were employed for a variety of aliphatic and aromatic aldehydes showing the generality of our method (Table 3).

The high enantioselectivity (89% *ee*) obtained with the cyclohexanecarbaldehyde is also remarkable (Table 3, entry 5). Higher yields were achieved with aromatic aldehydes substituted in the *para* position with weak electron-releasing groups, while substitution with electron-withdrawing groups gave lower yields with comparable enantioselectivity (Table 3, entry 3). In all cases by-products derived from the pinacol coupling or reduction of the aldehydes were observed. In summary, the reported chromium(salen) allylation represents the first example of an effective enantioselective reaction controlled by the catalytic amount of chromium and the chiral

Table 3. Enantioselective addition of allyl chloride to aldehydes catalyzed by $[\text{Cr}(\text{salen})]$ complex.

Entry	R'CHO	Yield of 2 [%] ^[a]	Yield of 3 [%] ^[b]	<i>ee</i> of 2 [%] ^[d]
1		67	16	78 (<i>R</i>) ^[e]
2		54	35	82 (<i>R</i>) ^[e]
3		41	40	77 (<i>R</i>) ^[e]
4		46	40	78 (<i>R</i>) ^[e]
5		42 ^[c]	0 ^[h]	89 (<i>R</i>) ^[f]
6		45 ^[c]	13	77 (<i>S</i>) ^[g]
7		40	40	65 (<i>R</i>) ^[e]

[a] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [b] The products **3** were obtained in racemic form. [c] Refers to the product obtained after desilylation ($\text{Bu}_4\text{NF}/\text{THF}$) and flash chromatography. [d] Determined with a cyclodextrin Megadex 5.25 mt chiral column. [e] The absolute configuration of the isolated homoallylic alcohol was assigned by analogy to the results obtained with PhCHO. [f] The absolute configuration of 1-cyclohexyl-3-buten-1-ol was determined by comparison of the chiral GC analysis trace with that of the known product.^[5a] [g] The absolute configuration was assigned by comparison of the optical rotation with that of the known product $[\alpha]_{\text{D}} = -14.8$ ($c = 0.68$ in CHCl_3); literature value: *R* isomer, $[\alpha]_{\text{D}} = +12.2$ ($c = 1.00$ in CHCl_3).^[11b] The *ee* value was determined by HPLC analysis, column: Chiracel OD, eluent: hexane/isopropyl alcohol (95:5), flow rate: 0.5 mL min^{-1} , retention time: 16.6 min (*R*) and 25.0 min (*S*). [h] In this case 40% yield of (hydroxymethyl)cyclohexane was detected by GC analysis.

ligand. This reaction allows one to obtain homoallylic alcohols in moderate yields and with good to high enantioselectivity starting from aliphatic and aromatic aldehydes.^[12] The synthetic utility of this C–C bond-forming reaction is obvious because the features of the chromium(III) salen complex make the preparation of a large variety of chiral chromium(III) reagents possible.

Experimental Section

Typical experimental procedure: CrCl_3 (8 mg, 0.05 mmol) and Mn (83 mg, 1.5 mmol) were added to anhydrous CH_3CN (2 mL), and the mixture was left to stand for about 5–8 min. Then it was stirred until a green-white precipitate was observed. The ligand **1** (27 mg, 0.05 mmol) was introduced followed by dry triethylamine (14 μL , 0.1 mmol), and the resulting brown solution was stirred at room temperature for 1 h. The solution was treated with allyl chloride (58 μL , 0.75 mmol) and the resulting red solution was stirred for 1 h at room temperature. Finally, PhCHO (51 μL , 0.5 mmol) and Me_3SiCl (95 μL , 0.75 mmol) were added, and the mixture was stirred until consumption of the aldehyde was complete. After quenching with a saturated solution of NaHCO_3 , the reaction mixture was filtered through celite, and the CH_3CN was evaporated under reduced pressure. The residue was extracted with Et_2O , the organic phases were collected, and the solvent was evaporated under reduced pressure. The resulting oil was dissolved in THF (2 mL) and treated with 1N HCl (0.5 mL). The mixture was stirred to complete desilylation (monitored by TLC). After evaporation of the THF, the residue was extracted with Et_2O . The organic phases were collected, dried over Na_2SO_4 , and concentrated in vacuo to give a brown residue, which was purified by flash chromatography (silica gel, cyclohexane/ Et_2O

(4/1), $R_f = 0.3$). The (*R*)-1-phenyl-3-buten-1-ol was isolated as a light yellow oil (50 mg, 67% yield) in 84% *ee*.

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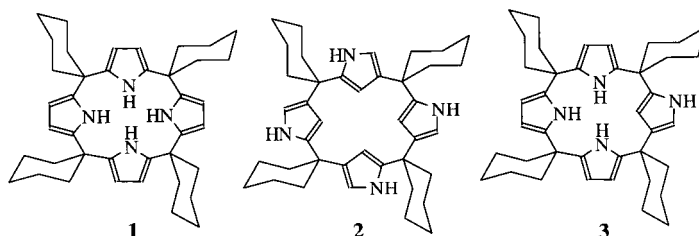
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- [8] Bases such as pyridine and *N*-methyl imidazole were screened as well, but in these cases the homoallylic alcohol was isolated in very low yields, probably due to a complexation of the Cr species by the bases.
- [9] The use of $[\text{Cr}(\text{salen})]$ complex following Jacobsen's protocol in the addition of allyl bromide to benzaldehyde afforded the desired homoallylic alcohol in 52% yield and 38% *ee*.
- [10] By replacing Me_3SiCl with $\text{ClMe}_2\text{Si}(\text{CH}_2)_3\text{CN}$ or $\text{ClMe}_2\text{SiCH}_2\text{CH}_2\text{SiMe}_2\text{Cl}$ in the allylation of the benzaldehyde we obtained 76% *ee* and 78% *ee*, respectively.
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N-Confused Calix[4]pyrroles**

Stefaan Depraetere, Mario Smet, and Wim Dehaen*

In recent years, calix[4]pyrroles^[1] have attracted a lot of attention because of their properties as binders of anions,^[2] transition metals,^[3] and neutral substrates.^[4] However, these compounds have been known for over a century.^[5] Their synthesis is straightforward and amounts to a [4+4] cyclocondensation of pyrrole and a ketone, analogous to the first steps of the Rothemund porphyrin synthesis. In the synthesis of porphyrins, the N-confused isomers (isomers in which one or more of the pyrrole units has the nitrogen atom at the exterior of the macrocycle) can be observed in low yields under certain conditions, as shown recently by a number of authors.^[6]

There is one report in the literature^[7] where the condensation of cyclohexanone and pyrrole, catalyzed by *p*-toluenesulfonic acid in benzene, was claimed to yield a mixture of the expected calix[4]pyrrole **1** and an isomer which was assigned the structure **2**. Because of the limited solubility of **2**, no NMR spectra were taken, so this assignment should be regarded as



tentative. On the other hand, **1** was the only product claimed when hydrochloric acid was used as the catalyst in ethanol. We decided to reinvestigate this reaction in a systematic manner in order to find out the best conditions to obtain N-confused calix[4]pyrroles, which may be of importance as novel host systems.

Mixtures of equimolar pyrrole and cyclohexanone were heated for 4 h in several solvents at reflux temperature with different acid catalysts. For each reaction the mixture was evaporated to dryness, taken up in chloroform, filtered, and purified by chromatography to yield two different calix[4]pyrroles **1** and **3**. A third, chloroform-insoluble calix[4]pyrrole isomer **4** (see Figure 1) was present in some cases. The results are summarized in Table 1.

In most cases the major product is the expected isomer **1** (up to 80% yield, m.p. 271–272 °C, m/z 588). The D_4 symmetry is apparent from the ^1H NMR spectrum (CDCl_3), which is identical with that reported.^[8] In all cases a significant amount (6–22%) of an isomer **3**, having much lower

[*] Prof. W. Dehaen, S. Depraetere, M. Smet
Department of Chemistry
Katholieke Universiteit Leuven
Celestijnenlaan 200F
BE-3001 Heverlee (Belgium)
Fax: (+32)16-32-79-90
E-mail: wim.dehaen@chem.kuleuven.ac.be

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Table 1. Results of the condensation of cyclohexanone and pyrrole at reflux temperature (4 h) in several solvents with variation of the acid catalyst. Product **1** is the normal calix[4]pyrrole, **3** the N-confused calix[4]pyrrole, and **4** the doubly N-confused calix[4]pyrrole.

Entry	Solvent	Catalyst	Yield [%]			
			total	1	3	4
A	ethanol	conc. HCl	74	62	12	0
B	ethanol	CH ₃ SO ₃ H	87	66	22	0
C	ethanol	BF ₃ · Et ₂ O	94	73	21	0
D	ethanol	CF ₃ COOH	97 (87) ^[a]	80 (77) ^[a]	18 (10) ^[a]	0 (0) ^[a]
E	ethanol	<i>p</i> -CH ₃ C ₆ H ₄ SO ₃ H	91	69	17	5
F	ethanol	ZnCl ₂	44	31	13	0
G	— ^[b]	CH ₃ SO ₃ H	34	12	22	0
H	CHCl ₃	CF ₃ COOH	87	80	3	4
I	CHCl ₃	<i>p</i> -CH ₃ C ₆ H ₄ SO ₃ H	90 (70) ^[a]	53 (9) ^[a]	5 (4) ^[a]	32 (57) ^[a]
J	benzene	<i>p</i> -CH ₃ C ₆ H ₄ SO ₃ H	94	54	6	35
K	toluene	<i>p</i> -CH ₃ C ₆ H ₄ SO ₃ H	64	18	11	36
L	toluene ^[b]	CF ₃ COOH	90	77	16	1
M	petroleum ether	CH ₃ SO ₃ H	53	42	11	0
N	ethanol	CF ₃ COOH	91 ^[c]	65 ^[c]	26 ^[c]	0

[a] Yields in brackets for heating at reflux for 60 h. [b] No solvent was used. Stirring became difficult because of immediate precipitation of the calixpyrrole mixture. The reaction was worked up at this point. [c] Condensation of acetone and pyrrole.

solubility in chloroform, was formed. This product (m.p. 223.2–223.6 °C, *m/z* 588) is clearly different from the compound found by Tsuge et al. (m.p. 302 °C).^[7] The ¹H NMR spectrum (CDCl₃) and appropriate decoupling experiments showed unambiguously that only one of the four pyrrole rings was connected through the 2,4-positions, while the other three had the normal 2,5-connectivity. The fourfold symmetry, clearly present for **1**, is totally absent according to the ¹H and ¹³C NMR spectra of **3**. The coupling constant between the β- and α-hydrogen atoms of the confused pyrrole in **3** has a typical value of 1.97 Hz. Signals for the α-pyrrole hydrogen (1H) and β-pyrrole hydrogen (1H) of the 2,4-disubstituted pyrrole appear at δ = 6.42 and 5.50, respectively, well apart from those of the β-hydrogens atoms (6H) of the 2,5-disubstituted pyrroles (δ = 6.03–5.82). In the ¹³C NMR spectrum of **3**, a new peak at δ = 112.8 appears, which can be assigned (confirmed by 2D experiment) to the α-CH moiety of the confused pyrrole.

Under the conditions of Tsuge et al.^[7] (entry J in Table 1) and other conditions (entries E, H–L) we found next to **1** and **3** (total 13–86 %) small to fair amounts (1–36 %) of a third isomer **4** (m.p. 312–313 °C, *m/z* 588), which is, as reported, highly insoluble in common organic solvents. We assume this product to be identical with the Tsuge product (m.p. 302 °C). A ¹H NMR spectrum of **4** could be taken at low concentration using [D₆]DMSO as the solvent. This showed the structure to correspond to a “doubly N-confused” calix[4]pyrrole **4** (see Figure 1) and not to the “all-confused” calix[4]pyrrole **2** as assigned by Tsuge et al. The signals for the α-pyrrole hydrogen atom (2H at δ = 6.35) are again well separated from those for the β-hydrogen atoms (6H, δ = 5.70–5.54). The NH protons appear as two groups of signals (each 2H) corresponding to the 2,4- and 2,5-connected pyrroles. Although the concentration of **4** in [D₆]DMSO was too weak to obtain a satisfactory ¹³C NMR spectrum, the two signals at δ = 112.8 and 113.2, corresponding to the α-CH carbon atoms, are another proof for a doubly N-confused structure. There are five different possible ways **4a–e** in which the 2,4- and 2,5-substituted pyrroles can be connected (Figure 1), and indeed

the ¹H NMR spectrum may correspond to a mixture of isomers, with most of the signals overlapping. However, due to the extremely low solubility of **4**, it is not possible to determine which isomers **4a–e** are formed or to separate them at this point. The pyrrole parts (δ = 10.2–5.4) of the

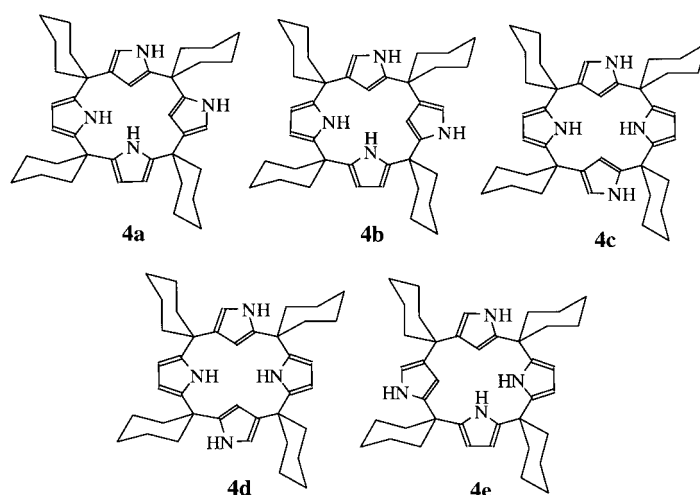


Figure 1. Schematic representation of the different ways in which the 2,4- and 2,5-connected pyrroles can be arranged in **4**.

¹H NMR spectra of compounds **1**, **3**, and **4** (all taken in [D₆]DMSO for comparison) are compiled in Figure 2.

When the reaction is run for longer times (entries D and I in Table 1), the total yield decreases. The amount of the N-confused isomer **3** decreases, whereas that of the less soluble **4** increases (up to 57 % when *p*-toluenesulfonic acid is used as the catalyst, entry I). These findings indicate that the reactants and products are in equilibrium, and displacement of the equilibrium may occur owing to the lower solubility of **4**. The N-confused calixpyrroles **3** and **4** have a free pyrrole α-position, which makes these products unstable in solution. In particular we have noticed that the singly N-confused **3**

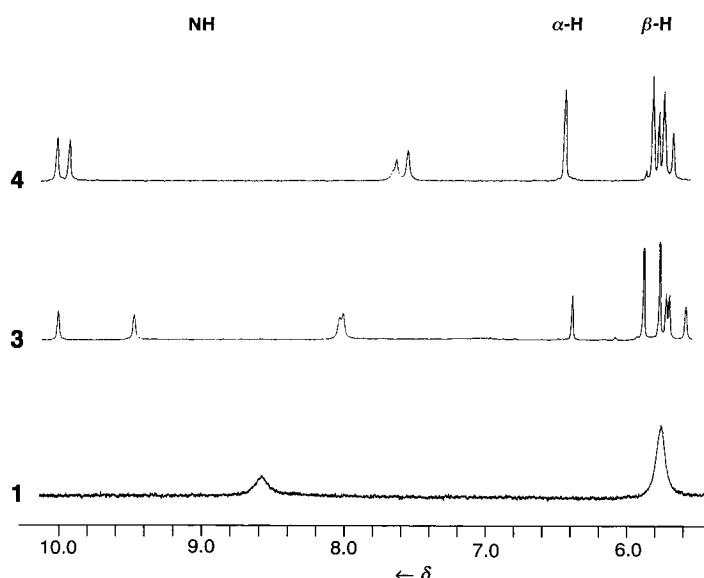


Figure 2. The pyrrole region of the ^1H NMR spectrum (400 MHz, $[\text{D}_6]\text{DMSO}$) of calix[4]pyrrole **1**, N-confused calix[4]pyrrole **3**, and doubly N-confused calix[4]pyrroles **4a–e**.

deteriorates in chloroform, giving a darkly colored, complex mixture. This may have been the reason why **3**, which is present in appreciable amounts in the reaction mixtures leading to calix[4]pyrroles, has so far remained undetected. However, the compounds **3** and **4** are perfectly stable in the solid phase.

From our systematic study we can conclude that trifluoroacetic acid/ethanol is the best catalyst/solvent system (total yield of 97%, entry D in Table 1). The condensation of acetone and pyrrole under these conditions (entry N) gives the octamethyl analogues of **1** and **3** in a total yield of 91%.

Experimental Section

General procedure for the condensation reactions: To a solution of pyrrole (15 mmol) and cyclohexanone (15 mmol) in the solvent of choice (5 mL) is added the appropriate acid catalyst (typically around 1 mmol) in a dropwise manner or with a spatula. In most cases an exothermic reaction results. The mixture was heated at reflux for a further 4 h and evaporated. The residue was taken into chloroform, and the solution filtered and purified by chromatography over silica gel with chloroform as the eluent to give **1** and **3**. The residue from the filtration contains **4a–e**.

1: M.p. 271–272 °C; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 1.47 (m, 24H; cyclohexyl), 1.92 (m, 16H; cyclohexyl), 5.90 (d, $^3J(\text{H,H})$ = 3 Hz, 8H; pyrrole β -H), 7.04 (br, 4H; pyrrole NH); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 22.8, 26.0, 37.2, 39.6, 103.4 (pyrrole β -CH), 136.4 (pyrrole α -CH); MS (70 eV, %): m/z 589 ($[\text{MH}]^+$, 100).

3: M.p. 223.2–223.6 °C; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 1.20–1.60 (m, 24H, cyclohexyl), 1.70–2.10 (m, 16H, cyclohexyl), 5.50 (br, 1H; pyrrole β -H), 5.82 (m, 2H; pyrrole β -H), 5.97 (br, 2H; pyrrole β -H), 6.03 (br, 2H; pyrrole β -H), 6.42 (d, $^3J(\text{H,H})$ = 1.97 Hz, 1H; pyrrole α -H), 7.10 (br, 2H; pyrrole NH), 7.44 (br, 1H; pyrrole NH), 7.63 (br, 1H, pyrrole NH); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 22.8, 25.9, 26.0, 26.4, 36.6, 37.2, 37.5, 37.7, 38.4, 39.4, 39.8, 39.9, 101.3, 102.2, 103.9 (3 $\times$ pyrrole β -CH), 112.8 (pyrrole α -CH), 130.1 (pyrrole β -C), 133.7, 134.6, 136.5, 137.8, 139.1, 140.3 (pyrrole α -C); MS (70 eV, %): m/z 589 ($[\text{MH}]^+$, 100).

4a–e: M.p. 312–313 °C; ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$, 25 °C, TMS): δ = 1.20–1.60 (m, 24H; cyclohexyl), 1.70–2.10 (m, 16H; cyclohexyl), 5.54 (br, 1H; pyrrole β -H), 5.60–5.70 (m, 5H; pyrrole β -H), 6.35 (br, 2H;

pyrrole α -H), 7.51 (br, 1H pyrrole NH), 7.96 (br, 1H; pyrrole NH), 9.98 (br, 1H; pyrrole NH), 10.07 (br, 1H; pyrrole NH), MS (70 eV, %): m/z 589 ($[\text{MH}]^+$).

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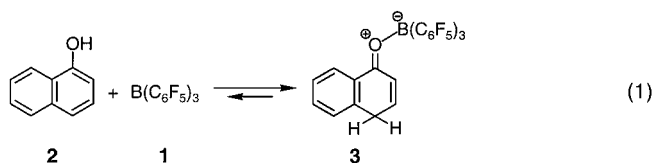
Treatment of Naphthols with $B(C_6F_5)_3$: Formation and Characterization of the Lewis Acid Adducts of Their Keto Isomers**

Dominik Vagedes, Roland Fröhlich, and Gerhard Erker*

Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday

The formation of kinetically persistent nonstabilized enols from simple aldehydes and ketones is difficult, but has been achieved in several cases.^[1] It is equally problematic to generate the keto tautomers of the phenols and related “aromatic enols” (except in specific instances^[2b]) and stabilize them under ambient conditions. This has been achieved in a number of cases by π complexation of, for example, the cyclohexadienone isomers of phenol and phenol derivatives with a variety of late transition metal complex fragments.^[2, 3] We have now found that the keto tautomers of a number of naphthol derivatives can be obtained and isolated as stable κ -O-adducts by treatment with the strong Lewis acid tris(pentafluorophenyl)borane (**1**).^[4]

A suspension of $B(C_6F_5)_3$ (**1**) and α -naphthol (**2**; 1:1) in pentane was stirred for 12 h at room temperature. The resulting solid was collected by filtration, and a sample was crystallized from toluene at 4 °C. The single crystals obtained were suitable for an X-ray crystal structure analysis, which revealed that the $B(C_6F_5)_3$ adduct **3** of the 1-naphthol tautomer benzocyclohexadiene was obtained [Eq. (1)].



In **3** the borane Lewis acid is attached to the carbonyl oxygen atom (B–O: 1.547(3) Å, C1–O: 1.273(3) Å, angle C1–O–B: 130.9(2)°). The cyclohexadienone part of the adduct molecule features the expected long-long-short-long-long-short array of carbon–carbon bonds along the six-membered ring (Figure 1). The annelated aromatic C_6H_4 ring is devoid of this alternation. Its C–C bond lengths are between 1.40 and 1.37 Å, with the typical tendency of a slight bond lengthening of the “inner” more highly substituted carbon–carbon bonds. The hydrogen atoms at the $C_{10}H_8O$ nucleus were located in the early stages of the structure solution.^[5a] Two hydrogen atoms are attached to C4, and the angle C3–C4–C4a (116.2(3)°) is the smallest observed inside the framework.

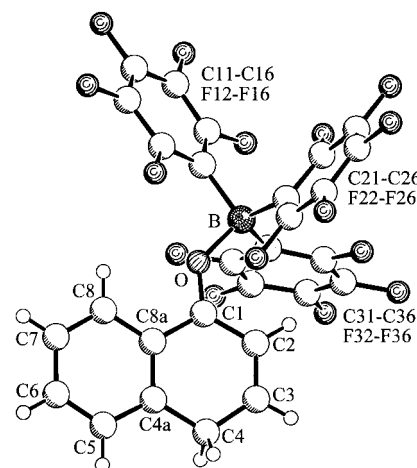
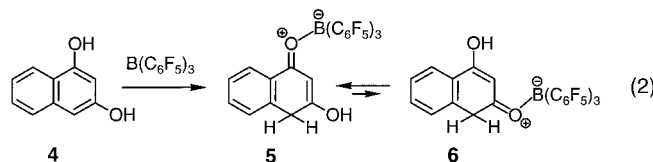


Figure 1. Molecular structure of **3**. Selected bond lengths [Å] and angles [°]: C1–O 1.273(3), C1–C2 1.432(4), C1–C8a 1.452(4), C2–C3 1.338(4), C3–C4 1.456(5), C4–C4a 1.488(5), C4a–C8a 1.396(4), C4a–C5 1.402(5), C5–C6 1.367(6), C6–C7 1.376(6), C7–C8 1.375(4), C8–C8a 1.397(4), O–B 1.547(3), B–C11 1.634(4), B–C31 1.636(3), B–C21 1.638(4); O–C1–C2 123.7(2), O–C1–C8a 115.9(2), C2–C1–C8a 120.4(2), C3–C2–C1 119.6(3), C2–C3–C4 123.8(3), C3–C4–C4a 116.2(3), C8a–C4a–C5 118.0(3), C8a–C4a–C4 120.0(3), C5–C4a–C4 122.0(3), C6–C5–C4a 120.9(3), C5–C6–C7 120.8(3), C8–C7–C6 119.8(4), C7–C8–C8a 120.2(3), C4a–C8a–C8 120.3(3), C4a–C8a–C1 119.5(3), C8–C8a–C1 120.2(2), C1–O–B 130.9(2).

The solid product was dissolved in $[D_6]$ benzene. The NMR analysis revealed that compound **3** is persistent in solution, but that there is an equilibrium (ca. 75:25) between the benzocyclohexadienone– $B(C_6F_5)_3$ adduct and the free naphthol/ $B(C_6F_5)_3$ mixture [Eq. (1)]. The rate of the equilibration is sufficiently low on the NMR time scale, so that sharp signals for the components are observed. Typically, the ^{13}C NMR resonances for C1 and C4 of 1-naphthol are found at $\delta = 145.4$ and $\delta = 120.8$, respectively, and the ^1H NMR signal for OH is at $\delta = 4.26$. The tautomer adduct **3**, in contrast, exhibits clearly distinguished resonances for C1 ($\delta = 189.9$) and C4 ($\delta = 33.7$). The adduct shows a ^{11}B NMR resonance at $\delta \approx 0$ ($w_{1/2} \approx 380$ Hz; $B(C_6F_5)_3$: $\delta \approx 60$) and a set of ^{19}F NMR signals ($\delta = -128.7$ (o), -151.8 (p), -158.6 (m)) that are distinguishable from the corresponding $B(C_6F_5)_3$ signals ($\delta = -124.4$ (o), -138.5 (p), -155.5 (m)) in the mixture.

1,3-Dihydroxynaphthalene was treated with $B(C_6F_5)_3$ in an analogous manner. Again, a solid adduct was isolated. Recrystallization from toluene gave single crystals of the $B(C_6F_5)_3$ adduct of the corresponding 1-keto-3-hydroxy tautomer **5** [Eq. (2)]. The X-ray crystal structure analysis



(Figure 2) shows the presence of only a single intact C_6H_4 ring, which is annelated to the keto tautomer of the *m*-dihydroxyarene. $B(C_6F_5)_3$ is attached at the resulting C=O group^[6, 7] (B–O: 1.553(5) Å, C1–O: 1.276(5) Å, angle C1–O–B: 129.6(3)°). The adjacent C1–C8a bond in **5** is rather long (1.463(6) Å), as in **3**. The C1–C2 bond is much shorter

[*] Prof. Dr. G. Erker, Dipl.-Chem. D. Vagedes, Dr. R. Fröhlich^[+]
Organisch-Chemisches Institut der Universität
Corrensstrasse 40, D-48149 Münster (Germany)
Fax: (+49) 251-8336503
E-mail: erker@uni-muenster.de

[+] X-ray crystal structure analyses.

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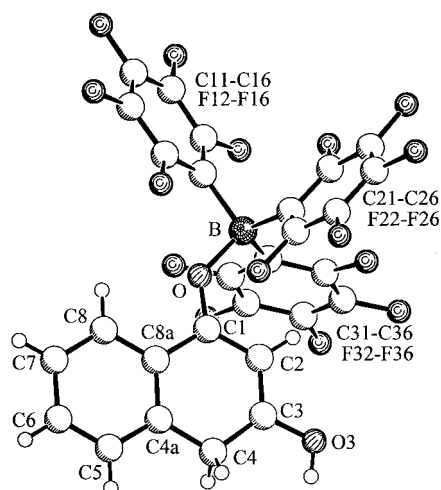
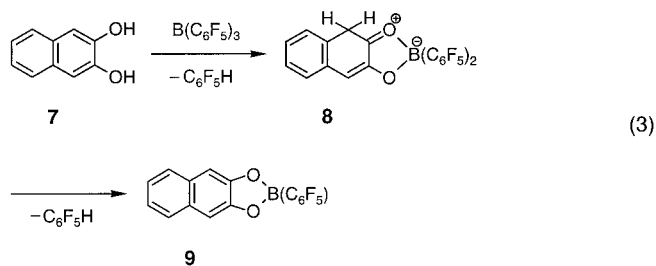


Figure 2. Molecular structure of **5**. Selected bond lengths [Å] and angles [°]: C1–O 1.276(5), C1–C2 1.392(6), C1–C8a 1.463(6), C2–C3 1.357(6), C3–O3 1.321(5), C3–C4 1.468(7), C4–C4a 1.477(7), C4a–C5 1.387(6), C4a–C8a 1.398(6), C5–C6 1.362(7), C6–C7 1.382(7), C7–C8 1.396(6), C8–C8a 1.382(6), O–B 1.553(5), B–C31 1.634(6), B–C21 1.634(6), B–C11 1.639(6); O–C1–C2 124.6(4), O–C1–C8a 115.3(4), C2–C1–C8a 120.2(4), C3–C2–C1 120.5(4), O3–C3–C2 118.1(4), O3–C3–C4 118.2(4), C2–C3–C4 123.7(4), C3–C4–C4a 114.8(4), C5–C4a–C8a 118.9(4), C5–C4a–C4 120.0(4), C8a–C4a–C4 121.1(4), C6–C5–C4a 120.4(5), C5–C6–C7 121.5(5), C6–C7–C8 118.8(5), C8a–C8–C7 120.0(5), C8–C8a–C4a 120.3(4), C8–C8a–C1 120.2(4), C4a–C8a–C1 119.5(4), C1–O–B 129.6(3).

(1.392(6) Å), now being part of a W-shaped 1,3-diketone mono-enol tautomer.^[8] Both the C4a–C8a (1.398(6) Å) and the C2–C3 enol double bonds (1.357(6) Å) are short (C3–O3(H): 1.321(5) Å), and C4, which bears two hydrogen atoms, is approaching sp^3 hybridization (C4–C4a: 1.477(7) Å, C3–C4: 1.468(7) Å, angle C3–C4–C4a: 114.8(4)°).

The solid was dissolved in $[D_6]$ benzene and shown by NMR spectroscopy to consist of a 70:30 mixture of the two regioisomeric keto tautomer adducts **5** and **6** [Eq. (2)]. In this case we did not detect free 1,3-dihydroxynaphthalene in the equilibrium mixture. The major regioisomer corresponds to the structure found in the solid state (see above and Figure 2). It shows the ^1H NMR signals of the free enol moiety at $\delta = 5.88$ (2-H) and 4.98 (OH). The newly formed CH_2 group shows ^1H ^{13}C NMR features at $\delta = 2.18$ (4-H, H') and 33.6 (C4), respectively. The ^{13}C NMR resonance of the boron-activated C=O group of **5** occurs at $\delta = 189.4$ (C1), whereas the enolate carbon signals are observed at $\delta = 102.6$ (C2) and 185.9 (C3). The minor isomer (**6**) also shows the typical NMR signals of the C4 methylene group (^1H : $\delta = 3.31$; ^{13}C : $\delta = 39.6$) as part of a clearly distinguished set of $^1H/^{13}C$ NMR features (for details, see the Experimental Section). The ^{19}F and ^{11}B NMR signals of the isomers **5** and **6** could not be observed separately.

The reaction of $B(C_6F_5)_3$ with 2,3-dihydroxynaphthalene takes a slightly different course. When carried out in $[D_6]$ benzene under direct NMR control, the immediate formation of pentafluorobenzene was observed.^[9] A reactive intermediate was produced, to which we assign the structure of **8** [Eq. (3); ^1H NMR: $\delta = 2.90$ (1-H, H'); ^{13}C : $\delta = 203.4$ (C2), 155.0 (C3), 125.5 (C4), 29.9 (C1)]. The reaction rapidly proceeds further with formation of the stable product **9**. This



compound was also prepared on a preparative scale (isolated in ca. 30% yield) and characterized by X-ray diffraction (Figure 3).

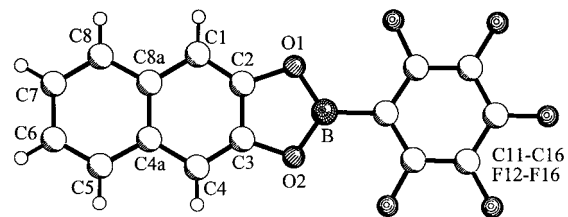
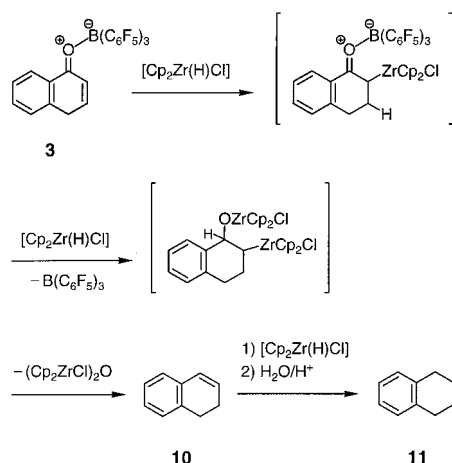


Figure 3. Molecular structure of **9**. Selected bond lengths [Å] and angles [°]: C1–C2 1.355(2), C1–C8a 1.418(2), C2–O1 1.383(2), C2–C3 1.403(2), C3–C4 1.353(2), C3–O2 1.390(2), C4–C4a 1.424(2), C4a–C5 1.417(2), C4a–C8a 1.430(2), C5–C6 1.368(2), C6–C7 1.406(2), C7–C8 1.361(2), C8–C8a 1.413(2), O1–B 1.378(2), O2–B 1.381(2), B–C11 1.550(2); C2–C1–C8a 116.99(13), C1–C2–O1 128.59(14), C1–C2–C3 122.57(15), O1–C2–C3 108.84(13), C4–C3–O2 128.45(13), C4–C3–C2 122.93(14), O2–C3–C2 108.60(13), C3–C4–C4a 116.67(13), C4–C4a–C8a 120.45(14), C1–C8a–C4a 120.37(14), B–O1–C2 105.20(12), B–O2–C3 104.89(12), O1–B–O2 112.44(14), O1–B–C11 122.92(14), O2–B–C11 124.60(14).

Synthetic applications are still to be developed, but we have found a first reaction out of the $2 + 1 \rightarrow 3$ equilibrium mixture where the $B(C_6F_5)_3$ adduct **3** of the benzocyclohexadienone tautomer is involved. Treatment of the α -naphthol/ $B(C_6F_5)_3$ reaction mixture with the hydrozirconation reagent $[Cp_2Zr(H)Cl]$ in benzene resulted in complete consumption of the starting material with formation of μ -oxo-bis(zirconocene chloride) (identified by spectroscopy and X-ray diffraction^[10]) and a mixture of the following organic products, which were identified spectroscopically: 1,2-dihydronaphthalene (**10**; ^1H NMR: $\delta = 6.39$ ($^3J = 9.6$ Hz, 4-H), 5.81 ($^3J = 9.6$, 4.5 Hz, 3-H), 2.59 (1-H), 1.98 (2-H)), 1,2,3,4-tetrahydronaphthalene (**11**; ^1H : $\delta = 2.57$ (1-H, 4-H), 1.52 (2-H, 3-H)), and α -naphthol in a 1.6:4.5:1.0 ratio. The hydrozirconation route^[11] schematically depicted in Scheme 1, which starts from the $B(C_6F_5)_3$ adduct **3**, readily explains the straightforward formation of these observed organic and organometallic products.^[12] This shows that $B(C_6F_5)_3$ adduct formation may open new routes to generate and eventually utilize the keto tautomers of the hydroxyarenes synthetically. Such studies are presently being pursued in our laboratory.

Experimental Section

3: A Schlenk tube was charged with **2** (288 mg, 2.00 mmol) and **1** (1.02 g, 2.00 mmol). At 0 °C pentane (20 mL) was added. The suspension was warmed to room temperature with stirring and then stirred for 12 h. The solid was collected by filtration, washed with pentane (5 mL), and dried in



Scheme 1. Hydrozirconation of **3** and subsequent reactions.

vacuo to yield **3** (1.17 g, 89%) as a slightly green solid, m.p. 134 °C. Elemental analysis (%) calcd for $C_{28}H_{18}OBF_3$ (656.15): C 51.25, H 1.23; found: C 51.16, H 1.59. Diffusion of pentane vapor into a solution of **3** in toluene at 40 °C over 3 d furnished single crystals that were suitable for X-ray crystal structure analysis.^[5a] IR (KBr): $\tilde{\nu}$ = 3587, 1646, 1621 cm^{-1} . The NMR spectra showed the presence of an equilibrium mixture (**2** + **1** $\rightleftharpoons$ **3**; 25:75) in solution. **3**: ^1H NMR ($[D_6]$ benzene, 599.8 MHz): δ = 8.43 (d, ^3J = 8.1 Hz, 1H, 8-H), 6.94 (m, 1H, 6-H), 6.87 (m, 1H, 7-H), 6.78 (d, ^3J = 10.0 Hz, 1H, 2-H), 6.40 (d, ^3J = 7.8 Hz, 1H, 5-H), 6.26 (m, 1H, 3-H), 2.31 (br., 2H, 4-H); ^{13}C NMR ($[D_6]$ benzene, 150.8 MHz): δ = 189.9 (C1), 162.4 (C3), 145.4 (C4a), 136.0 (C6), $\approx$ 129 (C7, C8a), 128.3 (C5), 123.3 (C2), 33.7 (C4), $B(C_6F_5)_3$ signals at 148.4 ($^{1J}_{CF}$ = 247 Hz), 140.7 ($^{1J}_{CF}$ = 256 Hz), 137.7 ($^{1J}_{CF}$ = 254 Hz) (*o*-, *p*-, *m*-CF); ^{11}B NMR ($[D_6]$ benzene, 64.2 MHz): δ = 0.1 ($w_{1/2}$ = 380 $\pm$ 20 Hz); ^{19}F NMR ($[D_6]$ benzene, 282.4 MHz): δ = -128.7, -151.8, -158.6 (*o*-, *p*-, *m*-F).

5 and **6**: The reaction of **4** (100 mg, 625 μ mol) with $B(C_6F_5)_3$ (320 mg, 625 μ mol) in pentane (20 mL) was carried out analogously to that of **1** and **2** to yield **5** (400 mg, 95%) as an off-white solid, m.p. 78 °C. Elemental analysis (%) calcd for $C_{28}H_{18}O_2BF_3$ (672.16): C 50.03, H 1.20; found: C 49.61, H 1.98; IR (KBr): $\tilde{\nu}$ = 3563, 1646, 1609 cm^{-1} . Single crystals were obtained from toluene/pentane by the diffusion method.^[5b] In solution the NMR signals of a 70:30 mixture of the regioisomers **5** (major product) and **6** (minor product) were observed. **5**: ^1H NMR ($[D_6]$ benzene, 599.8 MHz): δ = 8.37 (d, ^3J = 7.5 Hz, 1H, 8-H), 6.90 (m, 1H, 6-H), 6.88 (m, 1H, 7-H), 6.19 (d, ^3J = 7.2 Hz, 1H, 5-H), 5.88 (s, 1H, 2-H), 4.98 (s, 1H, OH), 2.18 (s, 2H, 4-H); ^{13}C NMR ($[D_6]$ benzene, 150.8 MHz): δ = 189.4 (C1), 185.9 (C3), 137.8 (C4a), 134.7 (C6), 128.7 (C7), 128.1 (C8), $\approx$ 128 (C5, C8a), 102.6 (C2), 33.6 (C4), $B(C_6F_5)_3$ signals at 148.5 ($^{1J}_{CF}$ = 241 Hz), 140.5 ($^{1J}_{CF}$ = 246 Hz), 137.7 ($^{1J}_{CF}$ = 248 Hz), 118.8 (br) (*o*-, *p*-, *m*-, *ipso*-C of C_6F_5); ^{19}F NMR ($[D_6]$ benzene, 282.4 MHz): δ = -133.6, -157.0, -163.8 (*o*-, *p*-, *m*-F); ^{11}B NMR ($[D_6]$ benzene, 64.2 MHz): δ = -0.6 ($w_{1/2}$ = 400 $\pm$ 20 Hz). **6**: ^1H NMR ($[D_6]$ benzene, 599.8 MHz): δ = 7.21 (d, ^3J = 8.1 Hz, 1H, 8-H), 6.81 (m, 1H, 6-H), 6.68 (m, 1H, 7-H), 6.31 (d, ^3J = 8.0 Hz, 1H, 5-H), 5.52 (s, 1H, 2-H), 5.36 (s, 1H, OH), 3.31 (s, 2H, 4-H); ^{13}C NMR ($[D_6]$ benzene, 150.8 MHz): δ = 199.6 (C3), 179.5 (C1), 139.1 (C4a), 134.2 (C6), 128.1 (C5), 127.9 (C7), 125.8 (C8), 123.6 (C8a), 101.7 (C2), 39.6 (C4); $B(C_6F_5)_3$ signals are undistinguishable from those of **5**.

9: A mixture of **7** (160 mg, 1.00 mmol) and **1** (512 mg, 1.00 mmol) was dissolved in toluene (15 mL) at 0 °C. The solution was warmed to room temperature and then allowed to stand at that temperature for 2 d. The supernatant solution was decanted from the precipitated green product. The solid was washed with pentane (5 mL) and dried in vacuo to give **9** (104 mg, 31%), m.p. 261 °C. Elemental analysis (%) calcd for $C_{16}H_8O_2BF_5$ (336.02): C 57.19, H 1.80; found: C 56.93, H 2.04. Single crystals of **9** were obtained from a solution in benzene after 2 d at room temperature.^[5c] ^1H NMR ($[D_8]$ THF, 599.8 MHz): δ = 7.69 (dd, ^3J = 6.2 Hz, ^4J = 3.3 Hz, 2H, 6-H, 7-H), 7.34 (s, 2H, 1-H, 4-H), 7.26 (dd, ^3J = 6.2 Hz, ^4J = 3.3 Hz, 2H, 5-H, 6-H); ^{13}C NMR ($[D_8]$ THF, 150.8 MHz): δ = 150.8 (C2, C3), 131.5 (C4a, C8a), 127.8 (C6, C7), 124.4 (C5, C8), 106.9 (C1, C4), $B(C_6F_5)_3$ signals at 150.0 ($^{1J}_{CF}$ = 252 Hz), 142.8 ($^{1J}_{CF}$ = 255 Hz), 138.3 ($^{1J}_{CF}$ = 252 Hz) (*o*-, *p*-, *m*-C of C_6F_5 ; *ipso*-C not observed); ^{19}F NMR ($[D_8]$ THF, 282.4 MHz): δ =

-128.5, -151.2, -161.2 (*o*-, *p*-, *m*-F); ^{11}B NMR ($[D_8]$ THF, 64.2 MHz): δ = 19.0 ($w_{1/2}$ = 260 $\pm$ 20 Hz); IR (KBr): $\tilde{\nu}$ = 3063, 1655, 1531 cm^{-1} . The reaction of **7** with **1** was also directly monitored by NMR spectroscopy. This led to the detection of the product C_6F_5H and the intermediate **8**: ^1H NMR ($[D_6]$ benzene, 599.8 MHz): δ = 6.83 (m, 2H, 6-H, 7-H), 6.64 (d, ^3J = 7.4 Hz, 1H, 8-H), 6.49 (s, 1H, 4-H), 6.35 (d, ^3J = 7.3 Hz, 1H, 5-H), 2.90 (s, 2H, 1-H); ^{13}C NMR ($[D_6]$ benzene, 150.8 MHz): δ = 203.4 (C2), 155.0 (C3), 131.0 (C8a), 129.6 (C4a), 128.2 (C6, C7), 128.1 (C8), 127.1 (C5), 125.5 (C4), 29.9 (C1), $B(C_6F_5)_3$ signals at 148.3 ($^{1J}_{CF}$ = 248 Hz), 146.0 ($^{1J}_{CF}$ = 248 Hz), 137.6 ($^{1J}_{CF}$ = 256 Hz) (*o*-, *p*-, *m*-CF), 113.7 (br, *ipso*-C of C_6F_5); ^{11}B NMR ($[D_6]$ benzene, 64.2 MHz): δ = 14.4 (br, $w_{1/2}$ = 260 $\pm$ 20 Hz); ^{19}F NMR ($[D_6]$ benzene, 282.4 MHz): δ = -135.1, -154.4, -162.9 (*o*-, *p*-, *m*-F).

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- a) X-ray crystal structure analysis of **3**:^[5d] $C_{28}H_{18}OBF_3$, M_r = 656.15, colorless crystal, $0.40 \times 0.30 \times 0.30$ mm, a = 12.560(1), b = 10.444(1), c = 19.857(1) Å, β = 102.88(1)°, V = 2539.2(3) Å³, ρ_{calcd} = 1.716 g cm⁻³, $F(000)$ = 1296 e, μ = 16.29 cm⁻¹, absorption correction with ψ scan data ($0.562 \leq T \leq 0.641$), Z = 4, monoclinic, space group $P2_1/n$ (no. 14), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans; of 4533 reflections collected ($-h, -k, \pm l$), $[(\sin \theta)/\lambda]_{\text{max}}$ = 0.55 Å⁻¹, 4319 were independent and 3787 observed [$I \geq 2\sigma(I)$]; 407 refined parameters, R = 0.065, wR^2 = 0.176, max./min. residual electron density 0.49/−0.47 e Å⁻³;

hydrogen atoms were calculated and refined as riding atoms. The data set was collected with a Enraf Nonius CAD4 diffractometer. Programs used: data reduction: MolEN (K. Fair, Enraf Nonius B. V., 1990), structure solution: SHELXS-86 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473), structure refinement: SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1997), graphics: SCHAKAL (E. Keller, Universität Freiburg, 1997). b) X-ray crystal structure analysis of **5**:^[5d] C₄₂H₂₄O₂BF₁₅, *M_r* = 856.42, crystal size 0.40 × 0.30 × 0.25 mm, *a* = 10.436(1), *b* = 14.121(1), *c* = 14.438(1) Å, *α* = 66.74(1), *β* = 71.45(1), *γ* = 77.15(1)°, *V* = 1841.7(3) Å³, *ρ*_{calcd} = 1.544 g cm^{−3}, *F*(000) = 864 e, *μ* = 1.46 cm^{−1}, absorption correction with SORTAV (0.944 ≤ *T* ≤ 0.965), *Z* = 2, triclinic, space group *P*1̄ (no. 2), *λ* = 0.71073 Å, *T* = 198 K, *ω* and *φ* scans; of 18063 reflections collected (±*h*, ±*k*, ±*l*), [(sin *θ*)/*λ*]_{max} = 0.59 Å^{−1}, 6348 were independent and 3592 observed [*I* ≥ 2σ(*I*)], 544 refined parameters, *R* = 0.078, *wR*² = 0.183, max./min. residual electron density 0.39/−0.34 e Å^{−3}; hydrogen atoms were calculated and refined as riding atoms. The structure contains two toluene molecules in the asymmetric unit. The data set was collected with a Nonius KappaCCD diffractometer on a rotating anode generator (FR 591). Programs used: data acquisition: COLLECT (Nonius B. V., 1998), data reduction: Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326), absorption correction: SORTAV (R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33–37; R. H. Blessing, *J. Appl. Cryst.* **1997**, *30*, 421–426), structure solution: SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473), structure refinement: SHELXL-97, graphics: SCHAKAL-92. c) X-ray crystal structure analysis of **9**:^[5d] C₁₆H₆O₂BF₅, *M_r* = 336.02, crystal size 0.30 × 0.25 × 0.05 mm, *a* = 11.110(1), *b* = 8.344(1), *c* = 13.876(1) Å, *β* = 93.19(1)°, *V* = 1284.3(2) Å³, *ρ*_{calcd} = 1.738 g cm^{−3}, *F*(000) = 672 e, *μ* = 1.61 cm^{−1}, absorption correction with SORTAV (0.953 ≤ *T* ≤ 0.992), *Z* = 4, monoclinic, space group *P*₂/c (no. 14), *λ* = 0.71073 Å, *T* = 198 K, *ω* and *φ* scans; 9733 reflections collected (±*h*, ±*k*, ±*l*), [(sin *θ*)/*λ*] = 0.71 Å^{−1}, 3885 were independent and 2941 observed [*I* ≥ 2σ(*I*)], 217 refined parameters, *R* = 0.051, *wR*² = 0.112, max./min. residual electron density 0.33/−0.22 e Å^{−3}; hydrogen atoms were calculated and refined as riding atoms. The data set was collected with a Nonius KappaCCD diffractometer on a rotating anode generator (FR 591). d) 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-120955 (**3**), -120956 (**5**), and -120957 (**9**). 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).

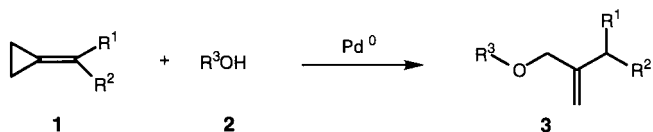
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Palladium-Catalyzed Hydroalkoxylation of Methylenecyclopropanes

Drexel H. Camacho, Itaru Nakamura, Shinichi Saito, and Yoshinori Yamamoto*

The activation of heteroatom–hydrogen bond or carbon–hydrogen bonds by transition metal catalysts is becoming an increasingly important method in organic synthesis.^[1–4] The palladium-catalyzed addition of carbon pronucleophiles to an olefinic bond—that is, hydrocarbonation^[1]—enabled the formation of C–C bonds to unsaturated hydrocarbons. Likewise, hydroamination,^[2] hydrocarboxylation,^[3] and hydrosulfination^[4] of unsaturated carbon–carbon bonds have also been developed.

The transition metal catalyzed addition of alcohols to olefins to form a C–O bond—that is, hydroalkoxylation—is also an important synthetic method. The addition reactions of alcohols to dienes^[5] or allenes^[6] presumably proceed via cyclic palladium intermediates,^[5c] where dimerization of the acceptors occurs. These processes are therefore different from pronucleophilic additions. In our continuing study of pronucleophiles, we concentrated on the addition of alcohols to nonconjugated olefins. We report herein that the palladium-catalyzed reaction of alcohols **2** with methylenecyclopropanes **1** affords the hydroalkoxylation products **3** regioselectively and in good yields (Scheme 1).



Scheme 1. Palladium-catalyzed synthesis of **3**. Reaction conditions: 1 equiv of **1** and **2** (0.5 mmol), 5 mol % [Pd(PPh₃)₄], 10 mol % P(*o*-tolyl)₃, THF, 100 °C, 3 d.

The results are summarized in Table 1. In the presence of catalytic amounts of tetrakis(triphenylphosphane)palladium (5 mol %) and tri-*o*-tolylphosphane (10 mol %) the reaction of octylidenecyclopropane (**1a**) with benzyl alcohol (**2a**) in THF at 100 °C gave the hydroalkoxylated product **3a** in 69 % yield (entry 1). No addition product or ring opening of **1a** was observed in the absence of palladium catalyst. Other catalysts such as [Pd₂(dba)₃]·CHCl₃ (dba = dibenzylideneacetone), Pd(OAc)₂, and [(*η*³-C₃H₅)PdCl]₂ in combination with P(*o*-tolyl)₃ and 1,3-bis(diphenylphosphanyl)propane (dppp) did not promote the reaction at all. The use of [Pd(PPh₃)₄] without P(*o*-tolyl)₃ ligand gave **3a** in lower yield (46 %). The combination of [Pd(PPh₃)₄] with other ligands such as bis(diphenylphosphanyl)methane (dppm), 1,2-bis(diphenylphosphanyl)ethane (dppe), dppp, 1,4-bis(diphenylphosphanyl)butane (dppb), 1,1'-bis(diphenylphosphanyl)ferro-

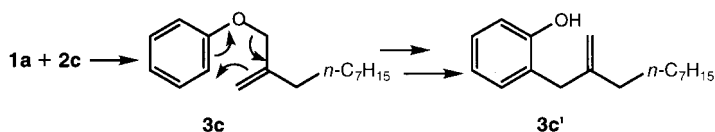
[*] Prof. Dr. Y. Yamamoto, D. H. Camacho, I. Nakamura, Dr. S. Saito
Department of Chemistry, Graduate School of Science
Tohoku University
Sendai 980–8578 (Japan)
Fax: (+81) 22-217-6784
E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp

Table 1. Palladium-catalyzed addition of alcohols **2** to methylenecyclopropanes **1**.^[a]

En-try	1	2	3 (yield [%]) ^[b]
1	1a (R ¹ = <i>n</i> -C ₇ H ₁₅ ; R ² = H)	PhCH ₂ OH (2a) ^[c]	3a (69)
2	1a	CF ₃ CH ₂ OH (2b)	3b (68)
3	1a	PhOH (2c) ^[c]	3c (67) ^[c] 3c' (56) ^[d]
4	1a	2,4,6-trimethylphenol (2d)	3d (67) ^[c]
5	1a	<i>n</i> -butanol (2e) ^[f]	3e (63)
6	1a	<i>sec</i> -butanol (2f) ^[f]	3f (24)
7	1a	<i>tert</i> -pentanol (2g) ^[f]	3g (25)
8	1a	H ₂ C=CHCH ₂ OH (2h) ^[f]	3h (35)
9	1a	Et ₃ SiOH (2i)	3i (49)
10	1b (R ¹ = PhCH ₂ CH ₂ ; R ² = H)	2a ^[c]	3j (67)
11	1c (R ¹ = R ² = PhCH ₂ CH ₂)	2a ^[c]	3k (80)

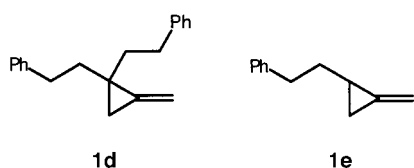
[a] Unless otherwise specified, all reactions were carried out in a microreactor in 1:1 molar ratio of the substrates (0.5 mmol) with 5 mol % [Pd(PPh₃)₄] and 10 mol % P(*o*-tolyl)₃ in THF at 100 °C for 3 d. [b] Yield of isolated product. [c] The solvent used was toluene. [d] See text. [e] The reaction was carried out at 70 °C. [f] The alcohol was used as the solvent.

cene (dppf), or PPh₃ yielded trace amounts of **3a**. The reaction of 2,2,2-trifluoroethanol (**2b**) with **1a** gave **3b** in 68 % yield (entry 2). The reaction of phenol (**2c**) and **1a** also proceeded smoothly (entry 3), but the product **3c'** was formed. We assumed that **3c'** was formed by the Claisen rearrangement of the initial product **3c** (Scheme 2). The reaction of 2,4,6-trimethylphenol (**2d**) with **1a** proceeded



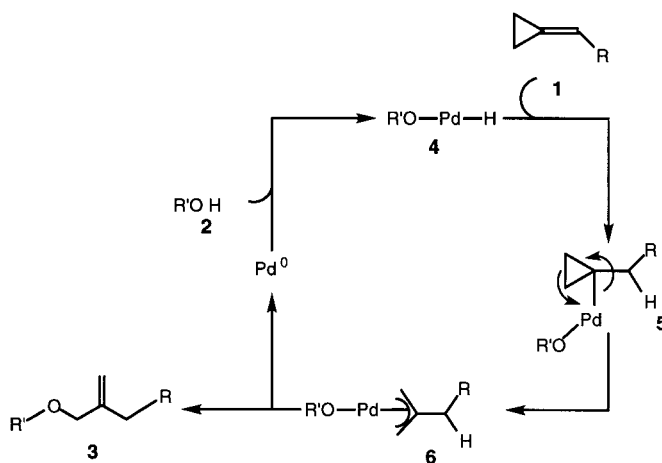
Scheme 2. The Claisen rearrangement of **3c** to **3c'**.

smoothly to give the allyl ether product **3d** in 67 % yield (entry 4). An excess amount of *n*-butanol (**2e**) reacted with **1a** to afford **3e** in 63 % yield (entry 5). The use of one equivalent of **2e** gave **3e** in poor yield, indicating that a normal aliphatic alcohol is less reactive than **2a–d**. Similarly the use of the bulky alcohols **2f** and **2g** as solvents afforded **3f** and **3g**, respectively (entries 6 and 7). The use of allyl alcohol as an oxygen pronucleophile also gave the desired product (entry 8). The low yield of **3h** could be attributed to the possible elimination of the allyl moiety in **3h** by palladium. Triethylsilanol (**2i**) also reacted with **1a** to afford **3i** in moderate yield (entry 9). The methylenecyclopropanes **1b** and **1c** with a 2-phenethyl substituent at the exocyclic methylene carbon atom also underwent hydroalkoxylation reactions with **2a** to give **3j** and **3k**, respectively (entries 10 and 11). However, the reactions of **1d** or **1e** with either **2a** or **2b** did not give the desired hydroalkoxylation products at all.

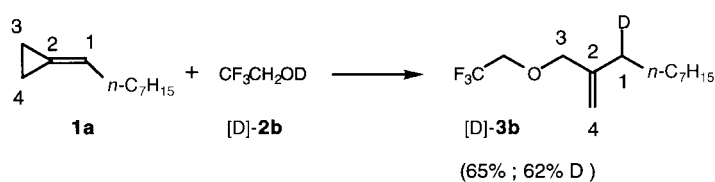


We propose the mechanism shown in Scheme 3 to explain the observed reaction. Oxidative addition of Pd⁰ into the O–H bond of alcohol **2** would produce the alkoxohydrido-palladium species **4**.^[7] The hydropalladation of methylenecyclopropane **1** with **4** would afford the alkylpalladium complex **5** by a Markovnikov-type addition. The distal bond cleavage of **5** would afford the π -allylpalladium species **6** by rearrangement. Reductive elimination of Pd⁰ from **6** would produce **3** and regenerate Pd⁰.

The proposed mechanism is in accordance with the palladium-catalyzed hydrocarbonylation^[1c] and hydroamination^[2f] of methylenecyclopropanes. The reaction of deuterated trifluoroethanol ([D]-**2b**) with **1a** (Scheme 4) substantiated the proposed hydroalkoxylation mechanism. Under the same conditions as above, the reaction gave [D]-**3b** in 65 % yield; the deuterium content at C1 was 62 %. Deute-



Scheme 3. Proposed mechanism for the addition of alcohols **2** to methylenecyclopropanes **1**.



Scheme 4. Reaction of methylenecyclopropane **1a** with deuterated trifluoroethanol ([D]-**2b**). See Scheme 1 for reaction conditions.

rium incorporation did not occur at the other carbon atoms of **1a**. The result supports the mechanism of Markovnikov hydropalladation and distal bond cleavage.

In summary, palladium-catalyzed addition of alcohols to methylenecyclopropanes has been achieved. Distal bond cleavage is characteristic of this reaction, making it highly regioselective. This reaction differs considerably from palladium-catalyzed hydrostannation^[8] and rhodium-catalyzed hydrosilylation,^[9] where proximal bond cleavage is observed. The high regioselectivity as well as the wide scope of alcohols

that can undergo hydroalkoxylation with methylenecyclopropanes make this reaction a versatile process in organic synthesis.

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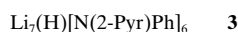
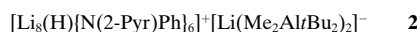
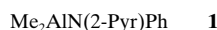
Keywords: alcohols • allyl ether formation • hydroalkoxylation reaction • methylenecyclopropanes • palladium

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The First Molecular Main Group Metal Species Containing Interstitial Hydride**

David R. Armstrong, William Clegg, Robert P. Davies, Stephen T. Liddle, David J. Linton, Paul R. Raithby, Ronald Snaith, and Andrew E. H. Wheatley*

As part of an ongoing study^[1] into the mechanism by which “mixed” organolithium/organoaluminum reagents promote conjugate addition to α,β -unsaturated ketones, we attempted to synthesize $\text{Me}_2(\text{tBu})\text{Al}[\text{N}(2\text{-Pyr})\text{Ph}]\text{Li}$ (2-Pyr = 2-pyridyl) by treating dimethyl(2-pyridylanilido)aluminum (**1**) with one equivalent of *t*BuLi. Remarkably, however, this reaction in toluene afforded in reasonable yield (over 40%) the ion-separated compound **2**, neither component of which contains any Al–N bonds. Rather, the anion is an unprecedented lithium bis(aluminate) while the cation, equally unprecedented, contains a hydride anion within a distorted $(\text{Li}^+)_8$ cubic cage. Treatment of the reaction mixture with THF results in removal of one Li^+ ion from this cage to give **3**.



Treatment of **1** in toluene at -78°C with one equivalent of *t*BuLi gave a suspension which can be dissolved in further toluene, the resultant solution affording colorless crystals of **2** as the only isolable product. Superior yields were obtained by using 1.5 equivalents of *t*BuLi (see Experimental Section). X-ray crystallography^[2] showed that in the solid state **2** is a remarkable mixed aggregate which incorporates both an unprecedented lithium bis(aluminate) anion and a hydride-containing lithium amide cation. The $[\text{Li}(\text{Me}_2\text{AltBu}_2)_2]^-$ ion (Figure 1) contains two Al centers arranged such that two methyl substituents on each are tetrahedrally disposed about Li(5) to afford an $\text{Al}(\mu\text{-C})_2\text{Li}(\mu\text{-C})_2\text{Al}$ motif. This is one of the few examples of an alkali metal containing anion.^[3] This molecular motif is related to the repeat unit of polymeric lithium tetra(alkyl)aluminates, and the mean Li–($\mu\text{-C}$) and Al–($\mu\text{-C}$) distances of 2.25 and 2.07 Å, respectively, are comparable to those of 2.30 and 2.02 Å in LiAlEt_4 .^[4]

[*] Dr. A. E. H. Wheatley, Dr. R. P. Davies, D. J. Linton, Dr. P. R. Raithby, Dr. R. Snaith
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
Fax: (+44) 1223-336-362
E-mail: aehw2@cam.ac.uk

Dr. D. R. Armstrong
Department of Pure and Applied Chemistry
University of Strathclyde, Glasgow G1 1XL (UK)
Prof. W. Clegg, S. T. Liddle
Department of Chemistry, University of Newcastle
Newcastle upon Tyne NE1 7RU (UK)

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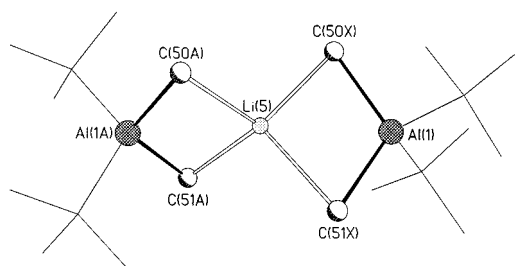


Figure 1. Molecular structure of the $[\text{Li}(\text{Me}_2\text{Al}t\text{Bu}_2)_2]^-$ anion of **2**; hydrogen atoms and minor disorder omitted for clarity.

The $[\text{Li}_8(\text{H})\{\text{N}(2\text{-Pyr})\text{Ph}\}_6]^+$ part of **2** (Figure 2) is based on an unusual $(\text{Li}^+)_8$ cubic cage whose six faces are straddled by the N–C–N backbones of the six pyridylamide moieties. Each

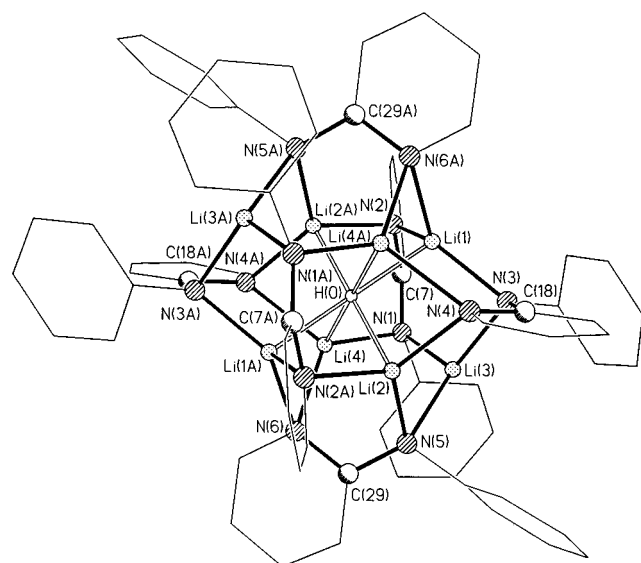


Figure 2. The hydride-containing $[\text{Li}_8(\text{H})\{\text{N}(2\text{-Pyr})\text{Ph}\}_6]^+$ component of **2**; hydrogen atoms excluded for clarity.

N atom coordinates to two Li^+ centers such that this dication adopts C_i symmetry (mean Li–N 2.047 Å). However, while six of the cations each interact with one amido group and two pyridyl N centers, Li(3) and Li(3A) bond only to three deprotonated N centers each (N(1), N(3), and N(5) for Li(3)). Because of the resulting distortions in the $(\text{Li}^+)_8$ core, the distances between nonbonding metal centers that involve the centers with tetragonally elongated geometry [Li(3) and Li(3A)] are longer (mean Li(3)⋯Li 2.701 Å) than those which do not (mean Li⋯Li 2.488 Å).

The presence of the central hydride anion in the cation is consistent with its refinement from crystallographic data, with the Li–H distances, and with the ratio of $[\text{Li}(\text{Me}_2\text{Al}t\text{Bu}_2)_2]^-$ to $[\text{Li}_8\{\text{N}(2\text{-Pyr})\text{Ph}\}_6]^{2+}$. It is unprecedented in main group chemistry.^[5] The different coordination of Li(3) and Li(3A) and the resulting extension of the Li⋯Li distances involving them are in accord with the adoption by the hydride anion of an octahedral coordination sphere (mean Li–H(0) 2.015 Å) since neither Li(3) nor Li(3A) bonds with the interstitial ion (Li(3)⋯H(0) 2.828(9) Å). Preliminary results from ab initio molecular orbital calculations (6-31G* basis set at the SCF

level) on models of the cation of **2** lend support to these structural assignments. A viable and stable species resulted from the insertion of H^- into the Li_8 cavity of a cube-based structure of type $[\text{Li}_8\{\text{N}(\text{H})\text{CH}_2\text{NH}_2\}_6]^{2+}$. Moreover, this optimized structure reproduces features seen in the structure of the cation of **2**: Two of the Li^+ ions are significantly extruded (Li⋯H 3.45 Å), whilst the other six are bonded to the H^- anion (Li–H 2.11 Å).

The solvent dependency of interstitial hydride formation is revealed by treatment of the reaction mixture with THF (see Experimental Section). The resultant solution yields a crystalline mixture of the lithium amide **3** and $[\text{Li}(\text{thf})_4]^+[\text{Li}(\text{Me}_2\text{Al}t\text{Bu}_2)_2]^-$ (**4**). X-ray crystallography^[6] showed **3** to be the new hydride-containing cluster $\text{Li}_7(\text{H})\{\text{N}(2\text{-Pyr})\text{Ph}\}_6$ (Figure 3). The lithium amide monocation part of **3** adopts a

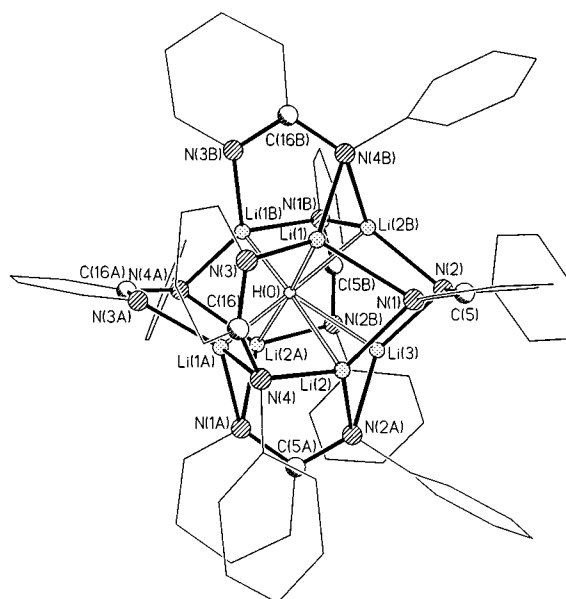


Figure 3. Molecular structure of **3**; hydrogen atoms omitted for clarity.

similar motif to the cage dication component of **2**, except that one vertex of the cubic cage is absent. It is worth noting that the relative orientations of the organic ligands in **3** (resulting in the adoption of C_3 symmetry) are incompatible with its formation by the simple THF-induced extrusion of a metal ion from **2**. Owing to the absence of a single Li^+ ion, three of the six pyridyl N centers (N(3), N(3A), N(3B)) each interact with one (Li(1), Li(1A), Li(1B)) rather than two metal ions, while the lithium ion Li(3) *trans* to the vacant site bonds to three amido N centers (N(2), N(2A), N(2B)). Accordingly, there are now three distinct nonbonding Li⋯Li distances in the $(\text{Li}^+)_7$ core (mean 2.565 Å); those involving the unique Li(3) are of intermediate length (2.586(8) Å). Atom Li(3) shows an extended Li⋯H distance (2.49(3) Å). This relatively long interaction renders the interstitial hydride pseudo-seven-coordinate, Li(3) capping one face of a distorted octahedral coordination shell. The remaining metal–hydride interactions are comparable to those of **2** (mean Li–H(0) 2.06 Å).

While there are several examples of transition metal clusters containing interstitial hydrido ligands,^[5] we know of

no molecular main group metal analogues. (The macrostructure of, for example, lithium hydride (Li-H 2.04 Å^[7]) could be considered to contain metal-encapsulated hydride anions.) Hence, the structures of **2** and **3** are unprecedented. Probably the closest analogues are various O^{2-} -containing lithium species,^[8] although these have traditionally been viewed as containing Li_2O , formed by the admission of moisture during the synthesis. More recently,^[9] various dicationic $[\text{Li}_2\text{Mg}_2(\text{amide})_4]^{2+}$ rings ("inverse crowns") have been shown to capture both O^{2-} and O_2^{2-} , and the compound $\text{Li}[(t\text{BuCH}_2\text{O})_5\text{Al}_3\text{H}_5] \cdot \text{OEt}_2$ has been described as including molecular LiH that lies above the Al atoms of an Al_3O_3 chair.^[10] Aside from the incorporation of hydride or other anions within molecular metal compounds, **2** and **3** are also unique in being based on polyhedral $(\text{Li}^+)_n/\text{X}$ frameworks ($n=8$, $\text{X}=\text{H}^-$ for **2**; $n=7$, $\text{X}=\text{H}^-$ for **3**). To our knowledge, all other reported alkali metalated organic compounds (amides, but also imides, alkoxides, enolates, alkyls, aryls, etc.) have structures based on rings.^[9, 11]

In spite of the crystallographic evidence for interstitial hydride ions in **2** and **3**, the ^1H NMR spectra of neither compound afforded a signal attributable to hydride. These compounds are soluble only in polar solvents, and the identical signals of the aromatic groups (in spite of the various crystallographic symmetries of the amide anions in **2** and **3**) in the ^1H NMR spectra indicate that the cages of **2** and **3** are deaggregated in such media. It follows that the difficulty in observing the hydride ion in solution results from fragmentation of the cage, accompanied by liberation and reaction of H^- . This is consistent with the observation of significant effervescence on dissolution of **2** and **3**. Preliminary IR spectroscopic studies also point to the existence of interstitial hydride anion. The spectrum of **2** shows a band at 583 cm^{-1} (cf. 588 cm^{-1} for $(\text{LiH})_\infty$ ^[12]). The spectra of the parent amine $[\text{HN}(2\text{-Pyr})\text{Ph}]$ and of the lithium amide $[\text{LiN}(2\text{-Pyr})\text{Ph}]$, which show essentially the same fingerprint bands as **2**, both lack this signal.

We are attempting to elucidate the mechanism by which these compounds are formed. Preliminary experiments suggest that the formation of hydride-containing amidolithium polyhedral clusters requires the presence of a pyridylamide or similar heterocyclic anion and an excess of an organolithium compound that can undergo β elimination of LiH .^[13] On the last count, for example, reactions of **1** with $n\text{BuLi}$ or $s\text{BuLi}$ followed by recrystallization from THF gave **3** and analogues of **4**, that is, $[\text{Li}(\text{thf})_4]^+[\text{Li}(\text{Me}_2\text{AlR}_2)_2]^-$ ($\text{R}=n\text{Bu}, s\text{Bu}$); in contrast, **1** reacts with MeLi to afford only the expected lithium aluminate $\text{Li}[\text{AlMe}_3\{\text{N}(2\text{-Pyr})\text{Ph}\}]$.

Experimental Section

2: Trimethylaluminum (0.5 mL, 2.0 M in toluene, 1.0 mmol) was added to 2-pyridylaniline (0.17 g, 1.0 mmol) in toluene (2 mL) at -78°C under N_2 . The resultant yellow solution was stirred at this temperature until effervescence subsided and then at room temperature for 1 h. *tert*-Butyllithium (0.88 mL, 1.7 M in hexanes, 1.5 mmol) was added at -78°C , and the mixture was warmed to room temperature, giving a yellow suspension. The addition of toluene (5 mL) followed by filtration gave a yellow solution. Storage at room temperature for 2 d afforded colorless crystals of **2**. Yield 42% (based on *t*BuLi consumed), m.p. $268-270^\circ\text{C}$. Elemental analysis calcd for $\text{C}_{86}\text{H}_{103}\text{Al}_2\text{Li}_9\text{N}_{12}$: C 72.68, H 7.25, N 11.83, Li

4.44; found: C 72.07, H 7.34, N 12.69, Li 3.99; ^1H NMR (500 MHz, $[\text{D}_8]\text{THF}$): $\delta=7.48$ (dd, 6H, 6-Pyr), 6.85 (dd, 12H, 3-Ph), 6.79 (ddd, 6H, 4-Pyr), 6.75 (d, 12H, 2-Ph), 6.51 (d, 6H, 3-Pyr), 6.35 (t, 6H, 4-Ph), 5.69 (dd, 6H, 5-Pyr), 0.67–0.55 (m, 36H, *t*Bu), -1.46 (sext., $^2J(\text{H},\text{Al})=5.9\text{ Hz}$, 12H, Me).

Cosyntheses of **3** and **4:** As for **1**, but with dissolution at room temperature by the addition of THF (0.2 mL). Filtration and storage of the orange solution at 5°C for 2 d afforded a colorless cocrystalline mixture of **3** and **4**, m.p. $307-311^\circ\text{C}$. Elemental analysis calcd for **3** ($\text{C}_{66}\text{H}_{55}\text{Li}_7\text{N}_{12}$): C 73.32, H 5.69, N 13.55, Li 3.71; found (for manually separated **3**): C 74.44, H 5.17, N 15.79, Li 4.61; ^1H NMR (500 MHz, $[\text{D}_8]\text{THF}$): $\delta=7.58$ (d, 6H, 6-Pyr), 6.95 (dd, 12H, 3-Ph), 6.90 (ddd, 6H, 4-Pyr), 6.86 (d, 12H, 2-Ph), 6.61 (d, 6H, 3-Pyr), 6.46 (t, 6H, 4-Ph), 5.80 (dd, 6H, 5-Pyr), 3.59 (m, 1H, 0.25 THF), 1.75 (m, 1H, 0.25 THF), 0.77–0.66 (m, 1.5H, 0.2 *t*Bu), (sext., $^2J(\text{H},\text{Al})=5.6\text{ Hz}$, 0.5H, 0.2 Me).

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- [6] Crystal data for **3**: $\text{C}_{66}\text{H}_{55}\text{Li}_7\text{N}_{12}$, $M_r=1064.8$, rhombohedral, space group $R\bar{3}$, $a=14.383(2)$ Å, $a=85.822(3)^\circ$ (primitive axes), $V=2952.8(7)$ Å³, $Z=2$, $\rho_{\text{calcd}}=1.198\text{ g cm}^{-3}$; $\text{MoK}\alpha$ radiation, $\lambda=0.71073$ Å, $\mu=0.071\text{ mm}^{-1}$; $T=160\text{ K}$. A total of 12479 reflections

(3475 unique reflections, $R_{\text{int}} = 0.1492$, $\theta < 25.0^\circ$) were collected on a Bruker SMART CCD diffractometer. The structure was solved and refined as for **2**:^[2a] $wR2 = 0.1147$, conventional $R = 0.0494$ for F values of 1407 reflections with $F_o^2 > 2\sigma(F_o^2)$, and $S = 0.802$ for 259 parameters. Isotropic H atoms bonded to C were constrained. Max./min. residual electron density: 0.15/−0.16 e Å^{−3}.^[2b]

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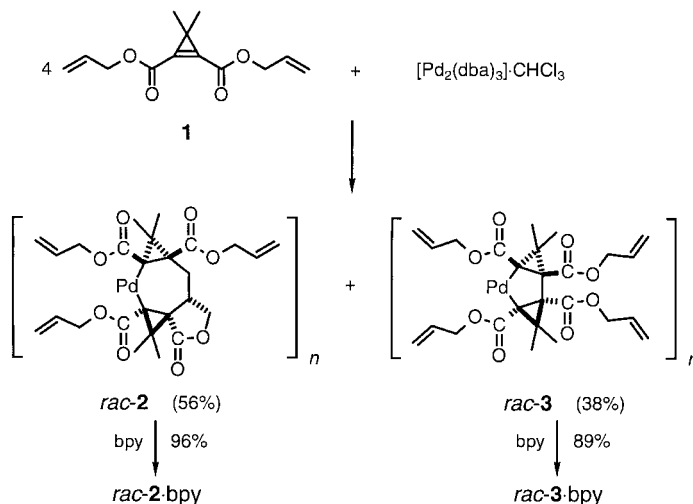
First and Highly Diastereoselective Synthesis of Palladepanes**

A. Stephen K. Hashmi,* Andreas Rivas Nass, Jan W. Bats, and Michael Bolte

Although many palladium-catalyzed reactions are supposed to proceed via palladacyclo[n]alkanes,^[1] such species have, with one singular exception, never been isolated or detected for compounds with more than five ring atoms! The high tendency of such intermediates to form the corresponding cyclo[$n-1$]alkanes by a fast reductive elimination is probably responsible for this observation. The exception mentioned above is a diphosphane complex of a nine-membered palladacycloalkane derivative that was formed in the reaction of 3,3-dimethylcyclopropene with a Pd⁰ precursor.^[2] Here we report the first synthetic approach to palladacycloheptane derivatives.

Since several of our efforts to achieve an intermolecular “mixed” oxidative cyclization between a cyclopropene and another unsaturated organic molecule at a Pd⁰ center failed,

we prepared **1**, which offered a terminal double bond as an intramolecular reaction partner at an appropriate distance. In the reaction of **1** with [Pd₂(dba)₃]·CHCl₃, two products were formed. The minor product could be identified as the palladatricyclo[4.1.0.0^{2,4}]heptane (PTH) derivative *rac*-**3** (Scheme 1). We had observed this mode of reaction many



Scheme 1. Cyclization of cyclopropene **1**. bpy = 2,2'-bipyridyl, dba = dibenzylideneacetone.

times before for cyclopropene-1,2-dicarboxylates.^[3] The major product turned out to be the seven-membered palladacycloalkane derivative *rac*-**2**. As reported before for the PTHs, the palladacycloalkanes *rac*-**2** and *rac*-**3**, which would be coordinatively unsaturated, are stabilized by the formation of coordination polymers. The PTHs that possess no olefinic side chains are readily dissolved in coordinating solvents like acetone or acetonitrile, and complexes with two molecules of these easily exchangeable solvents were obtained.^[3b,c] In contrast, the ¹H NMR spectra of *rac*-**2** and *rac*-**3** in these solvents showed that they are still aggregated (probably through intermolecular coordination of the olefin moieties). As PTHs are known to form stable complexes with bidentate ligands,^[3a,d,e] the 2,2'-bipyridyl (bpy) ligand was used to prepare the monomeric complexes *rac*-**2**·bpy (Table 1) and *rac*-**3**·bpy from *rac*-**2** and *rac*-**3**.

An X-ray crystal structure analysis was carried out for *rac*-**2**·bpy (Figure 1).^[4] Thus the connectivity as well as the stereochemical assignment was proven unambiguously. We could not detect the other diastereomer of *rac*-**2** possessing a *cis* arrangement of the two three-membered rings annelated to the central seven-membered ring. The high yields of *rac*-**2** and *rac*-**3** (sum 94%) clearly showed that other processes which one could have feared to occur with the allyl ester moieties of the molecules (formation of π -allyl–Pd^{II} species with the stoichiometric amount of Pd⁰, like in the Tsuji–Trost reaction)^[5] were of no significance under these conditions.

We then tested whether the double bond of the allyl ester is capable of directing the regioselectivity of the cyclization. The cyclopropene **4** bearing methyl and allyl ester moieties led to the maximum number of constitutional isomers one could expect. As PTHs the three isomers *rac*-**7**, *rac*-**8**, and *rac*-**9** were formed (Scheme 2). While *rac*-**8** could easily be assigned by its

[*] Priv.-Doz. A. S. K. Hashmi, Dipl.-Chem. A. Rivas Nass, Dr. J. W. Bats, Dr. M. Bolte
Institut für Organische Chemie der Universität
Marie-Curie-Strasse 11, D-60439 Frankfurt (Germany)
Fax: (+49) 69-79829464
E-mail: hashmi@chemie.uni-frankfurt.de

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Table 1. Selected spectroscopic data for *rac-2*·bpy and *rac-13*.

rac-2·bpy: IR (NaCl, film): $\tilde{\nu}$ = 3142, 3082, 2935, 1754, 1714, 1682 cm^{-1} ; ^1H NMR (400 MHz, $[\text{D}_6]\text{acetone}$): δ = 1.54 (s, 3H), 1.61 (s, 3H), 1.69 (s, 3H), 1.74 (s, 3H), 2.39–2.51 (m, 3H), 4.13–4.23 (m, 4H), 4.33–4.38 (m, 1H), 4.40–4.41 (m, 1H), 4.43–4.48 (m, 1H), 4.48–4.61 (m, 1H), 4.79–4.83 (m, 1H), 4.84–4.88 (m, 1H), 5.13–5.22 (m, 3H), 5.29–5.35 (m, 1H), 5.68–5.78 (m, 2H), 5.91–6.01 (m, 1H), 7.73–7.77 (m, 2H), 8.16–8.21 (m, 2H), 8.31–8.34 (m, 2H), 9.17–9.22 (m, 2H); ^{13}C NMR (62.9 MHz, $[\text{D}_6]\text{acetone}$): δ = 20.7 (q), 21.2 (q), 26.8 (q), 27.7 (q), 33.9 (s, 2C), 34.3 (s), 34.7 (s), 35.1 (t), 37.4 (d), 45.3 (s), 48.6 (s), 64.2 (t), 64.6 (t), 65.6 (t), 74.7 (t), 116.1 (t), 116.3 (t), 118.0 (t), 122.9 (d), 123.0 (d), 126.3 (d), 126.4 (d), 134.1 (d), 134.7 (d), 134.8 (d), 139.9 (d, 2C), 153.6 (d), 153.8 (d), 155.9 (s), 156.0 (s), 173.1 (s), 174.0 (s), 174.2 (s), 177.0 (s); FAB-MS (positive ion, *m*-nitrobenzyl alcohol): m/z (%): 734 (1, $[\text{M}^+]$), 677 (3, $[\text{M}^+ - \text{C}_3\text{H}_5\text{O}]$), 512 (2), 157 (100); elemental analysis calcd for $\text{C}_{36}\text{H}_{40}\text{N}_2\text{O}_8\text{Pd}$ (735.1): C 58.82, H 5.48, N 3.81; found: C 58.54, H 5.53, N 3.95

rac-13: IR (NaCl, film): $\tilde{\nu}$ = 2920, 1752, 1724, 1676, 1396, 1281, 1232, 1153 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.41 (d, J = 14.7 Hz, 2H), 2.93–2.99 (m, 2H), 3.50–3.55 (m, 2H), 4.04 (dd, J = 9.6 Hz, 3.9 Hz, 2H), 4.53 (t, J = 4.7 Hz, 2H), 4.72–4.75 (m, 4H), 5.26–5.37 (m, 4H), 5.91–6.01 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ = 38.7 (t), 40.1 (d), 66.7 (t), 72.3 (t), 119.5 (t), 131.3 (d), 131.4 (s), 143.0 (s), 167.3 (s), 168.3 (s); elemental analysis calcd for $\text{C}_{20}\text{H}_{20}\text{O}_8$ (388.4): C 61.85, H 5.19; found: C 61.61, H 5.20

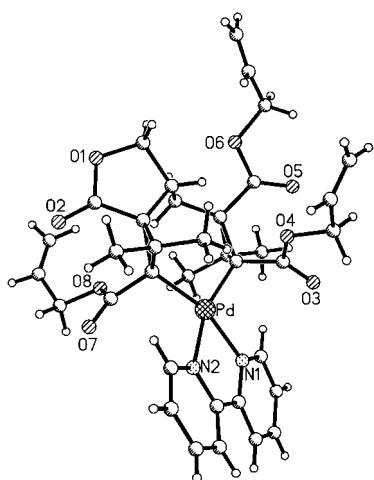
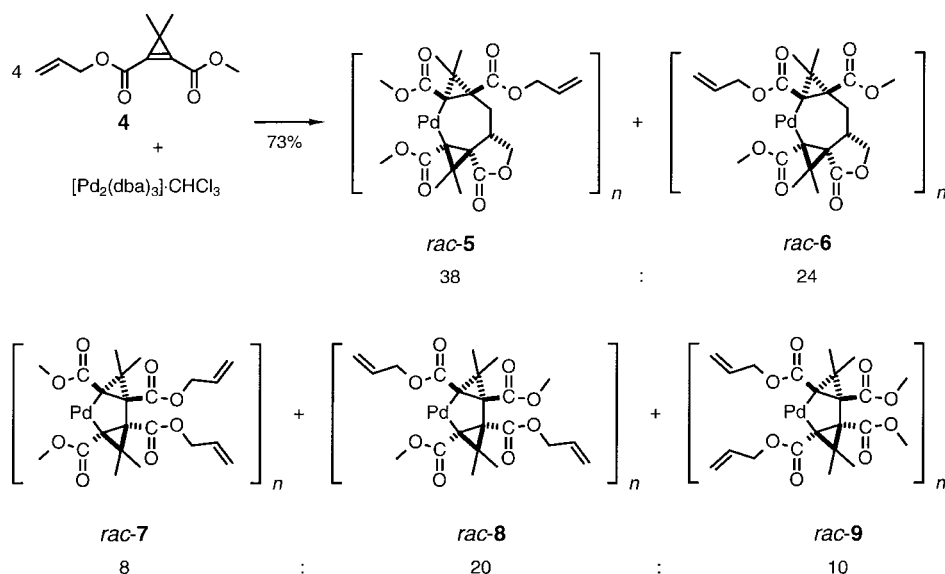


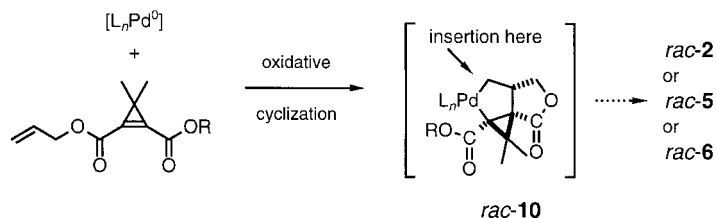
Figure 1. X-ray crystal structure of *rac-2*·bpy (ORTEP plot).



Scheme 2. Cyclization of cyclopropene 4.

C_1 symmetry, *rac-7* and *rac-9* were C_2 -symmetrical. We again prepared the bpy complexes *rac-7*·bpy, *rac-8*·bpy, and *rac-9*·bpy, and from the latter obtained crystals suitable for a crystal structure analysis.^[6] Therefore, the assignments for *rac-7* and *rac-9* were possible. The relative yields of *rac-7*, *rac-8*, and *rac-9* (see Scheme 2) basically reflected the statistical ratio one could expect, so no directing effect of the vinyl group in the side chain was observed with the PTHs. As palladacycloheptane derivatives, *rac-5* and *rac-6* could be isolated. For a clean structural assignment the complexes *rac-5*·bpy and *rac-6*·bpy were prepared and investigated by crystal structure analysis.^[6] Interestingly the major product was the one with the allyl group far away from Pd; again, both complexes showed the *trans* arrangement of the two cyclopropyl rings annelated to the palladacycle. The relative yields of the isolated products *rac-5*–*rac-9* corresponded well to the relative ratios determined in the crude product by HPLC.

How were the products *rac-2*, *rac-5*, and *rac-6* formed? It was reasonable to assume that first the strained cyclopropene coordinates to palladium, and then the vinyl group reacts as an intramolecular partner in an oxidative cyclization. Then the intermediate *rac-10* would be formed (Scheme 3) con-

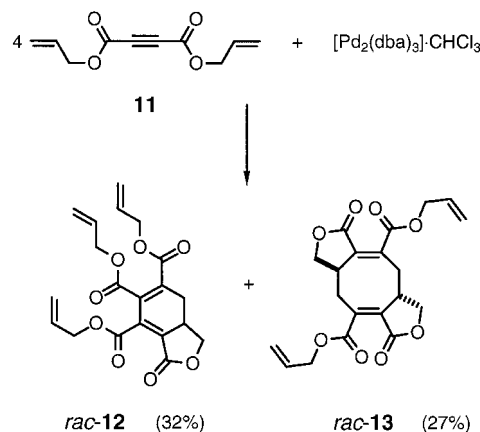


Scheme 3. Intermediate in the cyclization of cyclopropenes with allyl ester substituents. L = dba or solvent; R = $\text{CH}_2\text{CH}=\text{CH}_2$, CH_3 .

taining two different Pd–C bonds. A second (reactive) cyclopropene molecule then inserts only into the Pd– CH_2 bond and not into the Pd–cyclopropyl bond (in this step the diastereoselection also takes place). This would be in accordance with the behavior of the PTHs, where we observed that additional cyclopropene (as well as other olefins)^[3c] did not insert into the Pd–cyclopropyl bonds of the five-membered palladacycloalkanes.^[3c] The end products *rac-2*, *rac-5* or *rac-6* then contain two Pd–cyclopropyl bonds that seemed to be quite stable (kinetically and/or thermodynamically). In neither the seven-membered palladacycloalkanes *rac-2* and *rac-6* nor the five-membered palladacycloalkanes *rac-8* and *rac-9* did we observe another insertion of the vinyl group offered intramolecularly. These compounds were perfectly stable

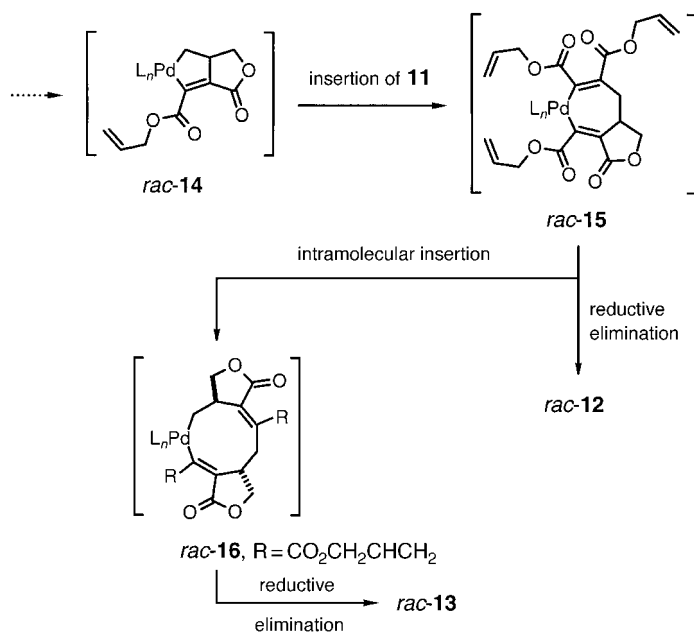
up to 50 °C! Therefore, it might not be a coincidence that the only other known palladacycloalkane with more than five ring atoms also has two Pd–cyclopropyl bonds.

To test this concept we treated the analogous diallyl acetylenedicarboxylate **11** (we considered PTHs to be “bishomo” palladoles) with Pd⁰ under the same conditions (which are also the standard conditions for the formation of the analogous palladoles).^[7] In this case no palladacycles could be isolated; only the two products *rac*-**12** and *rac*-**13**^[6] (Table 1) were obtained (Scheme 4).



Scheme 4. Cyclization of acetylenedicarboxylate **11**.

The formation of these products can be explained by an intermediate *rac*-**15**, which corresponds to *rac*-**2**, *rac*-**5**, and *rac*-**6**. An initial oxidative cyclization would form *rac*-**14**, and then insertion of a second alkyne into the Pd–CH₂ bond would give the seven-membered ring *rac*-**15**. Subsequent reductive elimination would lead to *rac*-**12**, whereas intramolecular (regio- as well as diastereoselective!) insertion of the alkene into the nine-membered ring would provide *rac*-**16**, which then reductively eliminates *rac*-**13** (Scheme 5). Both



Scheme 5. Intermediates in the cyclization of **11**. L = dba or solvent.

steps—the reductive elimination of *rac*-**15** to *rac*-**12** and the insertion that transforms *rac*-**15** into *rac*-**16** (or, in other words, the fact that no palladacycles were isolated)—demonstrated that the Pd–C bonds in *rac*-**14**, *rac*-**15**, and *rac*-**16** are more reactive than in the stable palladacycles *rac*-**2**, *rac*-**5**, and *rac*-**6**.

The synthesis of palladacycloheptanes reported here will now allow the investigation of the reactivity of this new class of organometallic compounds. The stability of such metallacycles formed from cyclopropenes might also allow the isolation of analogous intermediates involved in transition metal catalyzed reactions of alkenes or alkynes.

Experimental Section

rac-**2**·bpy: A solution of **1** (330 mg, 1.40 mmol) in acetone (4 mL) was added to a well-stirred solution of [Pd₂(dba)₃]·CHCl₃ (300 mg, 290 μmol) in acetone (70 mL) at room temperature. After 1 h the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (eluent: hexanes/acetone 2/1) to give *rac*-**2** (187 mg, 56 %) and *rac*-**3** (127 mg, 38 %). Derivative *rac*-**2** (187 mg, 322 μmol) was dissolved in MeCN (20 mL) and CH₂Cl₂ (4 mL). 2,2'-Bipyridyl (54.2 mg, 347 μmol) was added in one portion, and after 10 min the solvent was removed in vacuo. Column chromatography on silica gel (eluent: hexanes/acetone 4/1) provided *rac*-**2**·bpy (227 mg, 96 %). Crystals for the structure analysis were grown from hexane/ethyl acetate at 4 °C.

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- [4] Crystal structure analysis of *rac*-**2**·bpy: Siemens CCD three-circle diffractometer, MoK_α radiation (λ = 0.71073 Å), ω scans, empirical absorption correction with SADABS (G. M. Sheldrick, a Program for Absorption Correction of Area Detector Data, Universität Göttingen, Germany, **1996**), the structure was solved by direct methods and refined with SHELXL-97 (G. M. Sheldrick, a Program for the Refinement of Crystal Structures, Universität Göttingen, Germany, **1997**) by full-matrix least-square methods against F². Hydrogen atoms were placed on ideal positions and refined with fixed isotropic displacement parameters using a riding model. C₄₀H₄₈N₂O₁₀Pd·CH₃CO₂CH₂CH₃: 0.9 × 0.45 × 0.45 mm, triclinic, space group P1̄; a = 12.5620(8), b = 13.1135(11), c = 13.4805(13) Å, α = 117.697(8), β = 94.107(7), γ = 97.666(8)°; V = 1925.9(3) Å³, Z = 2; ρ_{calcd} = 1.420 g cm⁻³; μ = 0.541 mm⁻¹, min./max. transmission 0.862/1.000; 2θ_{max} = 62.9°; 143(2) K; of 34 664 measured reflections, 10 828 were independent; 476 parameters refined; R1 = 0.055, wR2 = 0.182; min./max. residual electron density 1.533/–1.221 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-127844. 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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Stereoselective Mukaiyama–Michael/Michael/Aldol Domino Cyclization as the Key Step in the Synthesis of Pentasubstituted Arenes: An Efficient Access to Highly Active Inhibitors of Cholesteryl Ester Transfer Protein (CETP)**

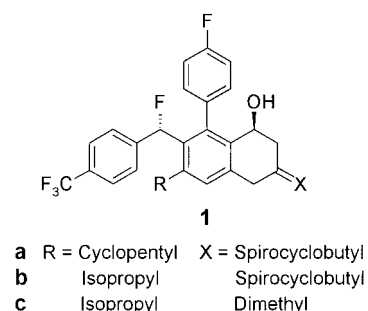
Holger Paulsen,* Stefan Antons, Arndt Brandes, Michael Lögers, Stephan Nicholas Müller, Paul Naab, Carsten Schmeck, Stephan Schneider, and Jürgen Stoltzfuß

Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday

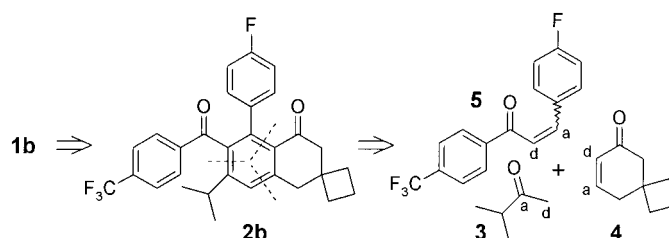
In spite of a number of successes, the treatment of arteriosclerosis is still a challenge for medicine. In addition to a high LDL-C (low density lipoprotein cholesterol) level, a low HDL-C (high density lipoprotein cholesterol) level is a further, main independent risk factor for coronary heart disease. Whereas the regulation of the LDL-C level by blockade of cholesterol biosynthesis with HMG-CoA reductase (3-hydroxy-methylglutaryl coenzyme A) inhibitors^[1] is established medical practice, the increase in HDL-C levels offers a new and promising therapeutic principle. HDL absorbs cholesterol from the periphery, including the coronary arteries, and carries it to the liver for metabolic degradation. The action of cholesteryl ester transfer protein (CETP) leads to a transfer of cholesteryl ester molecules from HDL to LDL in a triglyceride exchange. The disadvantageous net effect is a reduction in HDL-C level and an increase in LDL-C level.^[2]

Compounds of structure **1** have been identified as highly active CETP inhibitors (IC₅₀ ≤ 3 nmol L⁻¹).^[3] The complexity of this class of structures and the substance requirements for

further testing demanded an efficient synthesis in order to pave the way for applying this innovative principle. We have tried a number of different strategies and with the example of **1b** we present here a multigram synthesis which features a new domino reaction as the key step.



Three structural elements are the main contributors to the complexity of **1b**: the spirocyclobutyl system, two stereocenters in sterically demanding positions, and a central, pentasubstituted benzene ring. The first retrosynthetic transformation consisted of interconversion of the stereocenters to a diketone system. Diketone **2b** thus becomes a key intermediate (Scheme 1). Disconnection of the central benzene ring into approximately equally large fragments gives the greatest possible simplification of **2b**. The Mukaiyama–Michael addition is recognized as one of the most reliable



Scheme 1. Retrosynthesis of **1b**.

methods for the synthesis of 1,5-diketones.^[4a] In addition to the obvious 1,5-diketo structure, **2b** contains a strategic carbonyl group concealed behind a “Kekulé double bond” of the central arene. The translation of the resulting synthones into starting materials with alternating acceptor–donor polarization leads to the reagents **3**, **4**, and **5** (Scheme 1).

The enolate formed by the Mukaiyama–Michael addition has already been trapped with aldehydes, acetals, and orthoformates, or by a second, intramolecular Michael acceptor.^[4b,c, 5] An intermolecular Mukaiyama–Michael/Michael/aldol cascade has to our knowledge not been previously published. The underlying domino concept has already been realized,^[6] but the example illustrated here is unique in the degree of substitution and the steric hindrance of the acceptor components, especially **4**.

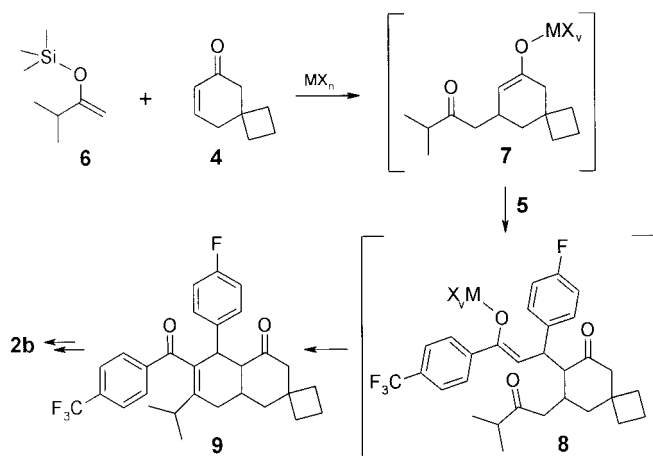
The following concept (Scheme 2) was devised for **2b**: silyl enol ether **6** and **4** yield the enolate **7** under Mukaiyama conditions. Its selective intermolecular 1,4-addition to the chalcone **5** leads to the enolate **8**, which gives **9** in an intramolecular aldol condensation. The cyclization ends a

[*] Dr. H. Paulsen, Dr. A. Brandes, Dr. M. Lögers, Dr. S. N. Müller, Dr. P. Naab, Dr. C. Schmeck, Dr. S. Schneider, Dipl.-Ing. J. Stoltzfuß
Bayer AG, Pharmaforschung
PH-R-CF Chemisch-wissenschaftliches Laboratorium
D-42096 Wuppertal (Germany)
Fax: (+49)202-364061
E-mail: holger.paulsen.hp@bayer-ag.de

Dr. S. Antons
Bayer AG, PH-OP-CE Verfahrensentwicklung

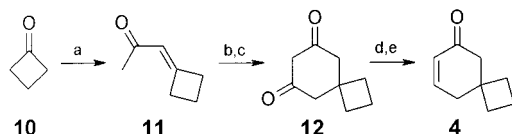
[**] We thank Dr. J. Benet-Buchholz for the X-ray structure analysis and colleagues of PH-R-Strukturchemie for providing the analytical data.

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



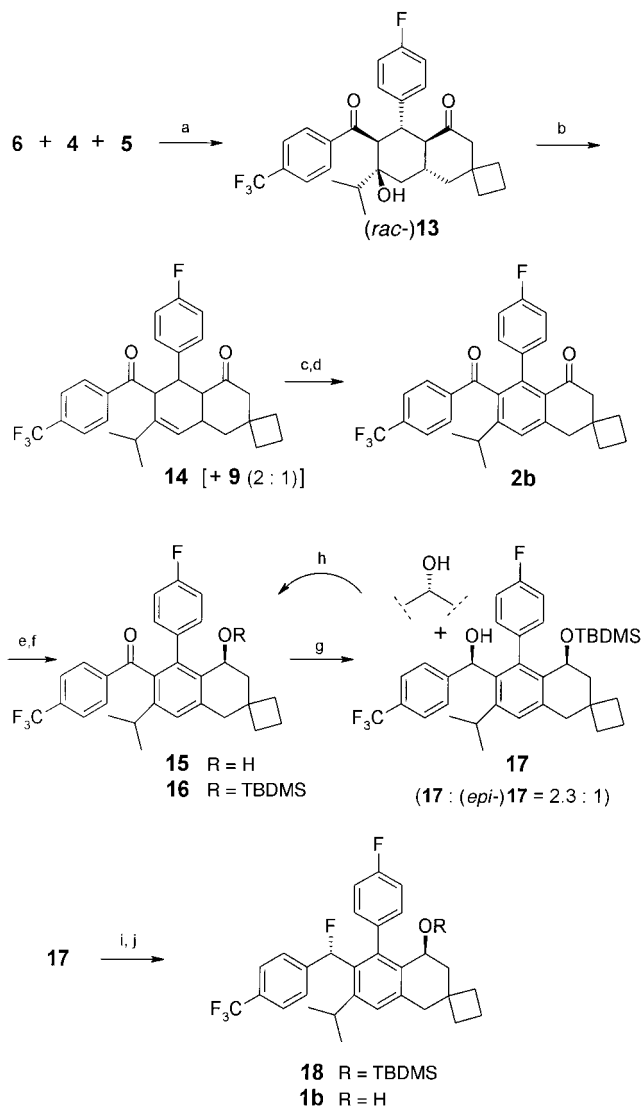
Scheme 2. Concept for the synthesis of the key compound **2b**.

reaction sequence in which the complete carbon framework of **2b** is constructed. The silyl enol ether **6** was formed from ketone **3** in the usual manner.^[7] The (*E*)-chalcone **5** was obtained in 95 % yield by the acid-catalyzed aldol condensation of 4-(trifluoromethyl)acetophenone and 4-fluorobenzaldehyde. Following preliminary investigations with cyclohexenone the sterically demanding spiro compound **4** was synthesized (Scheme 3). To this effect, the cyclobutanone **10** was first transformed into the enone **11** in a Wittig reaction.



Scheme 3. Synthesis of **4**. a) $\text{Ph}_3\text{P}=\text{CHCOCH}_3$, silicon oil, 100 °C, cat. PhCO_2H , 87 %; b) $\text{CH}_2(\text{CO}_2\text{Me})_2$, NaOMe, MeOH, 65 °C; c) aq. KOH, reflux, 20 % hydrochloric acid, pH 3–5, 99 %; d) isobutanol, toluene, cat. *p*-TsOH, azeotropic distillation; e) RedAl (65 % in toluene), 40–50 °C, 77 % relative to **12**. Ts = 4-methylphenylsulfonyl, RedAl = sodium bis-(2-methoxyethoxy)aluminum hydride.

The addition of dimethyl malonate and cyclization by Claisen condensation followed by hydrolysis and decarboxylation gave the dimedone analogue **12**. Enol ether synthesis and an ensuing reduction with RedAl gave the desired starting material **4**. In the key reaction, **6** and **4** in dichloromethane at about –5 °C were transformed into *rac*-**13** by successive addition of four equivalents of $\text{TiCl}_3(\text{O}i\text{Pr})$ in dichloromethane and **5** (Scheme 4).^[8] After aqueous workup, the product is readily isolated diastereomerically pure in 42 % yield by simple crystallization from petroleum ether. The all-equatorial arrangement of the substituents and the axial position of the hydroxyl functionality were confirmed by X-ray structure analysis.^[9] Until now the formation of only one additional diastereoisomer was detected to an extent of 10 % or less.^[10] The aldol condensation to **9** illustrated in Scheme 2 was not observed in spite of the antiperiplanar arrangement of the hydroxyl group and the H atom α to the carbonyl group.^[9] The correct establishment of the required connectivities was all that was needed to be achieved. Therefore, the excess of molecular complexity which was produced with the stereo-



Scheme 4. Synthesis of **1b**: a) $\text{TiCl}_4/\text{Ti}(\text{O}i\text{Pr})_4$ (3/1; i.e., 4 equiv of $\text{TiCl}_3(\text{O}i\text{Pr})$), dichloromethane, –5 °C, 42 %; b) pyridine, SOCl_2 , 0 °C, 83 %; c) NCS, cat. $(\text{PhCO}_2)_2$, dichloromethane, RT, 85 %; d) DBU, dioxane, 5, 96 °C, 64 %; e) (1*R*,2*S*)-1-aminoindan-2-ol (0.3 equiv), $\text{BH}_3\text{--NEt}_2\text{Ph}$ (3 equiv), THF, RT, 78 %; 94 % *ee* for the crude product; f) TBDMSCl, NEt_3 , DMAP, DMF, 70 °C, 80 %; g) LAH, THF, 0 °C → RT, 55 % **17**, > 99 % *ds*; h) MnO_2 , dichloromethane, RT, 77 % **16**; i) DAST (Et_2NSF_3), toluene, –70 °C → –60 °C, 75 %; j) TBAF, THF, RT, 87 %, > 99 % *ee*, > 99 % *ds*. NCS = *N*-chlorosuccinimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBDMS = *tert*-butyldimethylsilyl, DMAP = 4-(dimethylamino)pyridine, LAH = lithium aluminum hydride, TBAF = tetra-*n*-butylammonium fluoride.

selectively generated stereopentad was dismantled by subsequent aromatization with removal of all stereocenters. The sterically highly loaded cyclohexanol derivative **13** was thus subjected to a double halogenation–elimination sequence with subsequent oxidation at the cyclohexadiene stage (see Scheme 4).

The system resisted shorter aromatization strategies, for example the catalytic dehydrogenation at the cyclohexene stage, because of the all-*trans* arrangement of the hydrogen atoms and the large increase in steric interactions. Only reaction in a sulfur melt also afforded the arene **2b** successfully.

A mixture of the elimination products **14** and **9** was obtained rapidly and in high yield by treatment of *rac*-**13** with thionyl chloride in pyridine. Allylic halogenation gave a regioisomeric mixture which provided **2b** after elimination in the presence of an oxidizing agent. To introduce the stereocenters **2b** was next regio- and enantioselectively reduced to the oxoalcohol **15**. A variant of the Corey–Bakshi–Shibata (CBS) reduction makes use of *cis*-1-aminoindane-2-ol as the source of chirality.^[11] With this procedure, the tetralone system in the highly sterically hindered **2b** was reduced with high enantioselectivity (94% *ee* in the crude product) and yield (78% of **15** after crystallization) with complete differentiation of the two oxo groups. After protection of the hydroxyl functionality as the TBDMS ether (**16**) the internal 1,5-induction of the stereocenter mediated by the biphenyl system permitted a diastereoselective reduction of the second oxo function with LAH in favor of the desired isomer **17** (**17:epi-17** = 2.3:1). This was isolated from the mixture by crystallization. The alcohols remaining in the mother liquor, **17** and *epi*-**17**, could be reconverted into **16** by oxidation of the double benzylic position with manganese dioxide. By reaction of the unprotected hydroxyl functionality with DAST (Et₂NSF₃) **17** is converted with inversion into the fluoro compound **18**. The final deprotection with TBAF yields the target compound **1b** in diastereomeric and enantiomeric pure form (> 99% *ds*, > 99% *ee* after crystallization).

The present synthesis of **1b**, in its longest linear sequence 14 steps, can be carried out without any chromatographic purification and can be converted in a kilogram-scale process. The way is thus open for the in-depth evaluation of CETP inhibition as a therapeutic principle.

Experimental Section

rac-**13**: To a solution of **6** (72 mmol) and **4** (60 mmol) in dichloromethane (40 mL) are added simultaneously TiCl₄ (183 mmol) and Ti(O*i*Pr)₄ within 30 min under argon at –7 to –1 °C. After 5 min solid **5** (60 mmol) is added, during which time the temperature increases to 3 °C. The reaction mixture is stirred for 5 min with cooling, then for 2 h at room temperature. After workup with 1N hydrochloric acid, washing with water, drying over sodium sulfate, and removal of the solvent the residue is crystallized from petroleum ether. The product *rac*-**13** is obtained in 42% yield.

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- [8] Because of the oxygen-containing functional groups 2–4 equivalents of titanium reagent are necessary. According to reference [4a], cyclohexenone and **6** are labile towards titanium tetrachloride. TiCl₄(O*i*Pr), on the other hand proved to be too weak an inducing agent for the desired reaction. TiCl₃(O*i*Pr) can be freshly prepared by the (exothermic) mixing of TiCl₄ and Ti(O*i*Pr)₄ in a ratio of 3:1 or by parallel addition of both components. A modification of this reaction has meanwhile been carried out on a kilogram scale.
- [9] The C–OH und C=O bonds are almost parallel. In addition, the IR and ¹H NMR spectra suggest a hydrogen bond between the two groups (low-field shift and W-coupling of the OH hydrogen atom with an H atom of the neighboring AB system). By complexation with titanium this conformation should be maintained in the reaction mixture. Thus, the π orbitals of the carbonyl group and the σ C–H bond in the α position are almost orthogonal to each other. Therefore, acidification of the α H atom lacks conjugative stabilization. In addition, elimination leads to greater steric hindrance of the neighboring substituents.
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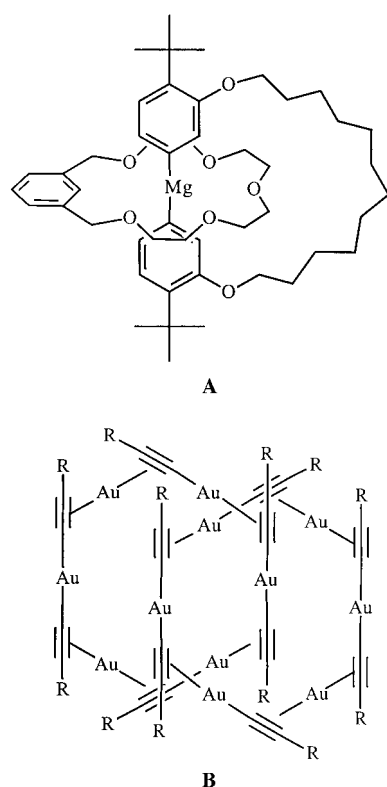
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[3] Significant HDL-C increase in hamsters and hCETP mice at doses of <1 mg kg^{–1} p.o. (p.o. = per os, oral administration).

Controlled Self-Assembly of Cyclic Gold(I) Complexes: The First Family of Organometallic Catenanes**

Christopher P. McArdle, Michael J. Irwin,
Michael C. Jennings, and Richard J. Puddephatt*

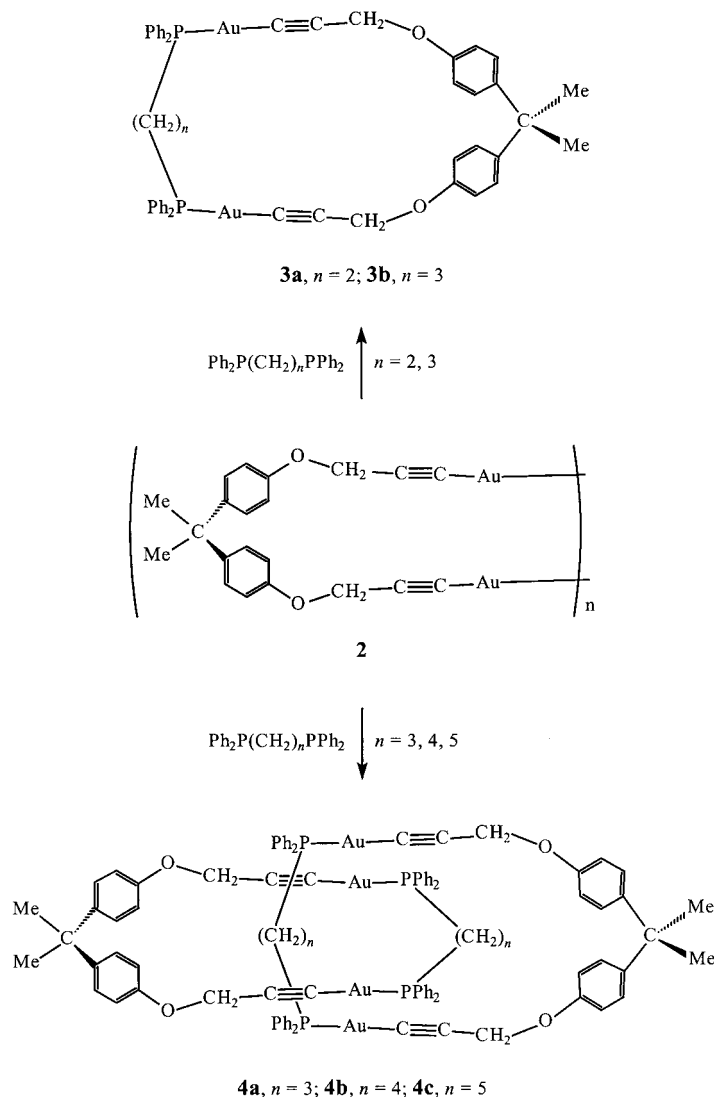
The synthesis of catenanes for potential application in molecular devices has been achieved through several very clever strategies,^[1, 2] such as “metal ion templating”,^[3, 4] and methods have recently been devised for synthesis of catenanes with metal atoms incorporated into the macrocycles.^[5] However, there appear to be only two isolated examples in which organometallic centers are present, namely the organomagnesium compound **A** (with metal in one ring only) and the gold(I) acetylide **B** ($R = t\text{Bu}$).^[6, 7] For different reasons, neither



synthetic method is easily adapted to the planned synthesis of a wide range of catenanes, but the method reported below leads to easy self-assembly of organometallic catenanes with different ring sizes and so allows systematic study of such complexes.

We have previously reported the synthesis of digold(I) diacetylide complexes $[(\text{AuC}\equiv\text{C}-\text{R}-\text{C}\equiv\text{CAu})_x]$ **1**, having

linear spacer groups R (e.g. $R = \text{C}_6\text{H}_4$), and their use as precursors for the preparation of rigid-rod polymers or organogold ring complexes.^[8] However, the complexation of **1** with neutral bidentate ligands such as diphosphanes gives ring complexes with cavities that are too small to allow formation of catenanes.^[8] The digold(I) diacetylide complex **2** is longer and more flexible than **1** and so can form rings having a larger cavity; **2** reacts with the diphosphane ligands $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$ ($n = 2-5$) to give the interesting ring structures **3** and **4** (Scheme 1). The new ring complexes **3** and [2]catenanes **4** are formed in good yield; they are colorless, air-stable solids which are soluble in organic solvents such as dichloromethane.^[9]



Scheme 1. Synthesis of the new ring complexes **3a** and **3b** and the new catenane complexes **4a–c**. See Supporting Information for experimental details.

The beauty of the synthetic method shown in Scheme 1 is that the ring size can be varied easily by changing the number of methylene spacer groups in the diphosphane ligand $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$. As n increases, the cavity size increases and then catenanes can form by simple self-assembly. Thus, the reaction of **2** with $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$ yields only the simple

[*] Prof. R. J. Puddephatt, Dr. C. P. McArdle,
Dr. M. J. Irwin, Dr. M. C. Jennings
Department of Chemistry, University of Western Ontario
London, ON N6A 5B7 (Canada)
Fax: (+1) 519-661-3022
E-mail: pudd@uwo.ca

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ring complex **3a** when $n = 2$, and only the catenanes **4b** and **4c** when $n = 4$ or 5, respectively. The crossover between these reaction types occurs when $n = 3$ where a mixture of the simple ring complex **3b**, the catenane **4a**, and a third "isomer" of undetermined structure is formed.^[10] Slow crystallization of this mixture gives pure **4a** which reverts to the above mixture of isomers over a period of days when dissolved in CD_2Cl_2 , as monitored by NMR spectroscopy.^[9] The catenane formation is clearly reversible in this case.

The new compounds were characterized by their spectroscopic properties and by structure determinations for **3a**, **4a**, and **4b**.^[9, 11] Complex **3a** is shown to be formed as a single isomer by the observation of a single sharp resonance at $\delta = 40.26$ in the ^{31}P NMR spectrum. The complex exists as a simple ring (Figure 1, top), which is strongly puckered as a

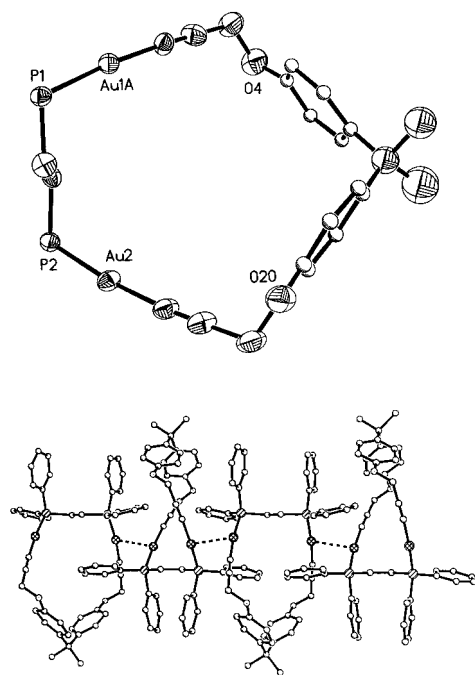


Figure 1. Top) A view of the structure of **3a**, showing the single ring form. Phenyl groups are omitted and other aryl carbon atoms are shown as small spheres for clarity. Bottom) A part of the infinite chains formed by intermolecular $\text{Au} \cdots \text{Au}$ bonding. Note the twisted ring conformation.

result of the need to bring the two gold atoms close enough together that they can be bridged by the ligand $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$ with its relatively small bite distance. The molecular packing within the crystal lattice is interesting; adjacent molecules, which are held together by short $\text{Au} \cdots \text{Au}$ contacts,^[12] adopt an *anti* arrangement to minimize steric interactions. The intermolecular gold–gold distance of $2.9668(8) \text{ \AA}$ indicates that there is a significant aurophilic attraction between neighboring gold(i) centers and results in a loose polymeric structure (Figure 1, bottom).

The structures of the organometallic catenanes **4a** and **4b** are shown in Figure 2, with phenyl substituents removed to show the interlocking rings more clearly. In each case, the rings interlock symmetrically across the polymethylene chain of the diphosphane ligand, but there are also significant differences between the two structures. For **4a** the large unit cell contains two inequivalent catenanes; in one of these there

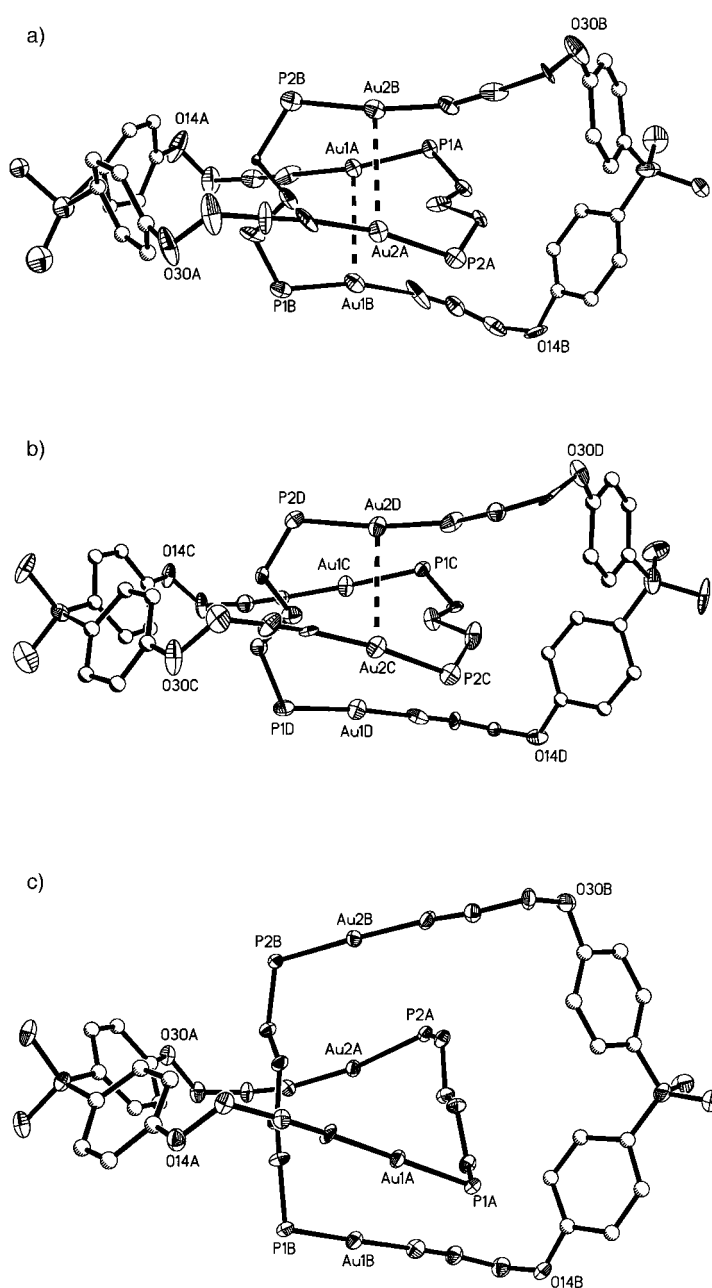


Figure 2. A view of the structures of the [2]catenanes with inter-ring $\text{Au} \cdots \text{Au}$ interactions indicated by dotted lines. Phenyl groups are omitted and other aryl carbon atoms are shown as small spheres for clarity. a) and b) the independent molecules of **4a**; c) the complex **4b**. Note the larger cavity of **4b** compared to **4a** and the absence of $\text{Au} \cdots \text{Au}$ bonding in **4b**.

are two close inter-ring $\text{Au} \cdots \text{Au}$ contacts ($3.216(2) \text{ \AA}$ and $3.357(2) \text{ \AA}$), while in the other there is only one $\text{Au} \cdots \text{Au}$ distance that is short enough to be considered an aurophilic interaction ($3.231(2) \text{ \AA}$), as the other $\text{Au} \cdots \text{Au}$ distance ($3.686(2) \text{ \AA}$) is outside the normal range of $2.75\text{--}3.40 \text{ \AA}$ for such bonds. The structure of **4b** differs most obviously from **4a** by having no short $\text{Au} \cdots \text{Au}$ contacts. The shortest distances are $\text{Au1A} \cdots \text{Au1B}$ $4.993(1)$ and $\text{Au2A} \cdots \text{Au2B}$ $5.219(1) \text{ \AA}$, and these are both beyond the range for any bonding interaction. The reason for this difference is clear by examination of Figure 2. In **4a** the short trimethylene chain leads to a small 24-membered ring and, in turn, this leads to

significant steric congestion and to short inter-ring Au...Au distances; since the Au...Au interaction is attractive,^[12] it is naturally present. However, in **4b** the longer tetramethylene chain leads to a 25-membered ring, and the observed conformation with the tetramethylene chains passing through the ring centers naturally leads to minimum steric congestion but longer Au...Au distances than in **4a**. The complex could distort to give shorter Au...Au distances but this would cause greater steric hindrance; the steric effects are clearly dominant in this case.

In summary, it is established that gold(I) catenanes with diacetylide and diphosphane ligands can be formed easily by self-assembly, that the transition from simple ring to [2]catenane can be controlled by simple ligand design and that, in at least one case, it is possible for the simple ring and [2]catenane to interconvert. While aurophilic attractions may enhance catenane formation they are clearly not a necessary feature, and the low steric hindrance associated with the linear gold(I) acetylide units appears to be more important in allowing the easy formation of catenanes. Attractive inter-aryl forces also favor catenane formation. It follows that the principles outlined here may also be useful in the design of more complex molecular topologies, such as rotaxanes and knots with organometallic functionality, and that these systems are well suited for studies of the mechanisms and energetics of catenane formation.

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- [9] Synthetic procedures are similar to those described in ref. [8], with gold complexes protected from light by using darkened flasks throughout. Selected data: **2**: Yield: 94% from [AuCl(SMe₂)]. IR (Nujol): $\tilde{\nu}$ = 2000 (w, C≡C) cm⁻¹. **3a**: Yield: 70%. IR (Nujol): $\tilde{\nu}$ = 2130 (w, C≡C) cm⁻¹; ¹H NMR (CD₂Cl₂, 25 °C): δ = 1.65 (s, 6H; 2 CH₃), 2.51 (m, 4H; 2 CH₂), 4.75 (s, 4H, 2 OCH₂), 7.01 (m, 4H; 2 C₆H₄), 7.23 (m, 4H; 2 C₆H₄), 7.42–7.52 (m, 20H; 4 C₆H₅); ³¹P NMR (CD₂Cl₂, 25 °C):

δ = 40.26 (s). **4a**: Yield of mixture with **3b** and third isomer: 81%. Recrystallization from CH₂Cl₂/Et₂O gave pure **4a**. ³¹P NMR (CD₂Cl₂, 25 °C): δ = 31.67 (s); IR (Nujol): $\tilde{\nu}$ = 2132 (w, C≡C) cm⁻¹. **3b**: ³¹P NMR (CD₂Cl₂, 25 °C): δ = 35.61 (s). Third isomer: ³¹P NMR (CD₂Cl₂, 25 °C): δ = 34.56 (s), 34.47 (s). **4b**: Yield 68%; IR (Nujol): $\tilde{\nu}$ = 2132 (w, C≡C) cm⁻¹; ³¹P NMR (CD₂Cl₂, 25 °C): δ = 38.73 (s). **4c**: Yield 70%; IR (Nujol): $\tilde{\nu}$ = 2130 (w, C≡C) cm⁻¹; ³¹P NMR (CD₂Cl₂, 25 °C): δ = 37.36 (s).

- [10] The identity of the third isomer is not established at this stage. It could be a more complex catenane or an oligomer. Note that the bulky Ph₂P groups will act as a barrier to prevent free motion of interpenetrating rings.
- [11] X-ray data; Enraf-Nonius diffractometer equipped with a CCD detector; refinement used SHELX software; crystals were small and of only adequate quality but the structures are well-defined; partial occupation of lattice vacancies by solvent molecules is responsible for the unusual stoichiometries: Complex **3a** · 0.75 CH₂Cl₂: C_{47.75}H₄₃Au₂Cl_{1.50}O₂P₂, M_r = 1157.87, T = 293 K, monoclinic, $P2_1/n$, a = 17.9418(7), b = 14.4752(6), c = 20.1253(6) Å, β = 111.736(2)°, V = 4855.1(3) Å³, Z = 4, ρ_{calcd} = 1.584 Mg m⁻³, μ = 6.218 mm⁻¹, 33 078 reflections, 9880 independent reflections, θ_{max} = 26.41°, refinement by full-matrix least-squares on F^2 , 505 parameters, $R1$ = 0.0817, $wR2$ = 0.1091. Complex **4a** · 0.125 C₂H₄Cl₂: C_{48.25}H_{44.5}Au₂Cl_{1.025}O₂P₂, M_r = 1121.07, T = 150(2) K, λ = 0.71073 Å, monoclinic, $P2_1/n$, a = 12.4526(3), b = 45.006(2), c = 30.538(1) Å, β = 98.570(2)°, V = 16924(1) Å³, Z = 16, ρ_{calcd} = 1.760 Mg m⁻³, μ = 7.056 mm⁻¹, 27 409 reflections, 18 686 independent reflections, θ_{max} = 26.38°, refinement by full-matrix least-squares on F^2 , 1450 parameters, $R1$ = 0.0889, $wR2$ = 0.1726. Complex **4b** · 2.5 CHCl₃: C_{50.25}H_{47.25}Au₂Cl_{3.75}O₂P₂, M_r = 1271.94, T = 200(2) K, λ = 0.71073 Å, triclinic, $P\bar{1}$, a = 15.7561(4), b = 16.1929(5), c = 21.2826(7) Å, α = 106.545(1), β = 97.842(1), γ = 102.660(1)°, V = 4962.5(3) Å³, Z = 4, ρ_{calcd} = 1.702 Mg m⁻³, μ = 6.209 mm⁻¹, 70 232 reflections, 34 852 independent reflections, θ_{max} = 32.70°, 1103 parameters, $R1$ = 0.0957, $wR2$ = 0.2390. 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-120855–120857. 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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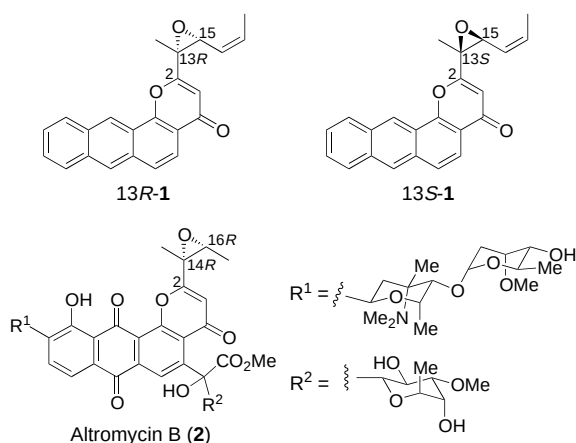
Specific Alkylation of Guanine Opposite to a Single Nucleotide Bulge: A Chemical Probe for the Bulged Structure of DNA

Kazuhiko Nakatani,* Akimitsu Okamoto, and Isao Saito*

Drug interactions at nucleotide bulges have been intensively studied because the stabilization of the bulged structure by intercalators is thought to enhance frameshift mutation of DNA.^[1] Furthermore, the drugs bound to RNA bulges has

[*] Prof. Dr. K. Nakatani, Prof. Dr. I. Saito, Dr. A. Okamoto
Department of Synthetic Chemistry and Biological Chemistry
Faculty of Engineering, Kyoto University
and
CREST, Japan Science and Technology Corporation
Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-5676
E-mail: nakatani@sbchem.kyoto-u.ac.jp
saito@sbchem.kyoto-u.ac.jp

recently been shown to prevent binding of the Tat protein to the *trans*-activating region (TAR).^[2] Chemical modifications of DNA and RNA bulges by intercalating and cleaving drugs occurred primarily near the bulge as a result of the much more efficient formation of an intercalated complex at the bulge than at an intrinsic site for the drug.^[3, 4] Herein we report that the chiral DNA-alkylating intercalator **13R-1** is a remarkable drug that specifically alkylates guanine (G) opposite a bulge and can be used as a chemical probe for the detection of a bulged structure.



The DNA-alkylating agent **1**^[5, 6] was designed as an aglycon model for altromycin B (**2**),^[7] a pluramycin antibiotic^[8] that intercalates into the DNA base pairs by a threading mode and alkylates guanine at the N7 position by an electrophilic attack by the epoxide.^[9] We recently demonstrated that one enantiomer **13S-1**, which possesses a 13*S* epoxide, alkylates guanine of 5'-GG-3' sequences with high 5'-G selectivity, whereas the other enantiomer **13R-1** exhibited only a very low reactivity.^[5] On the basis of molecular modeling and ab initio calculation experiments we have established that the alkylation of guanine by **13S-1** proceeds by a threading intercalation at the 3'-side of the alkylated guanine residue, and the preferential intercalation into the GG step is the origin of the high GG sequence selectivity. The poor reactivity of **13R-1** was rationalized by assuming that the orientation of the epoxide in the intercalated complex is not well suited for the S_N2-type ring opening by 5'- or 3'-guanine residues.^[10] To gain further insight into the significance of the precovallent intercalation in DNA alkylation we investigated the alkylation of guanine residues in oligodeoxynucleotides (ODNs) containing a single nucleotide bulge.

The oligonucleotides used in this study were designed to contain a single nucleotide bulge just opposite the GG step, which is the most efficiently alkylated site for **1**.^[5] A 35-mer ODN 5'-d(TTT TTG TTA TTG₁₂ **G₁₃G₁₄T TG₁₇G₁₈ TTG₂₁ **G₂₂G₂₃T TG₂₆G₂₇ TTG TTT TT**) (ODNP) contains two GG doublets and two GGG triplets (shown in bold face), and a single nucleotide bulge was created on the complementary strand opposite the G₁₇G₁₈, G₂₁G₂₂, and G₂₂G₂₃ steps by annealing it with bulge-forming oligomers ODN2, ODN3, and ODN4, respectively (Figure 1). These ODNs possess a 5'-**

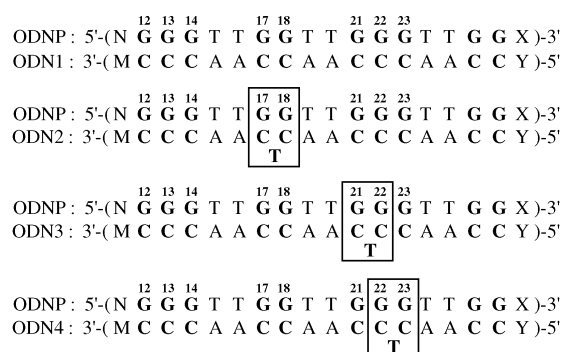


Figure 1. Sequences of ODNP and ODN1–ODN4. GC base pairs at normal and bulged sites are shown in bold face. Bulged sites are also boxed. N = TTTTGTATT, M = AAAACAATAA, X = TTGTTT, Y = AACAAA.

CTC-3' sequence instead of the 5'-CC-3' sequence in fully complementary ODN1. ODNP in which the 5'-end was labeled with ³²P was annealed with ODN1–ODN4 and the duplex was treated with **13S-1** or **13R-1**. Alkylated guanine residues were detected as cleavage bands by treatment with hot piperidine followed by polyacrylamide gel electrophoresis (PAGE) analysis. Autoradiograms of the gel are shown in Figure 2.

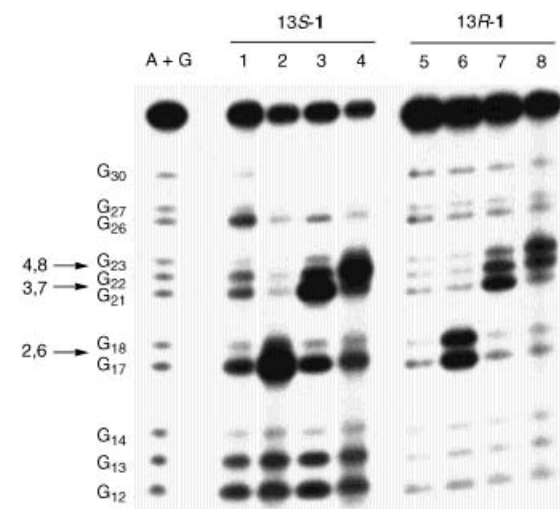


Figure 2. Guanine alkylation in the duplex DNAs containing a single bulge by **13S-1** and **13R-1**. ODNP in which the 5'-end was labeled with ³²P was annealed with ODN1–ODN4. The duplexes were treated with **13S-1** and **13R-1** (50 μM) for 5 h at 37 °C in Tris-HCl buffer (pH 7.6, 50 mM) in the presence of calf thymus DNA (10 μM). Alkylated ODNs were separated by precipitation with ethanol. Alkylated G residues were detected as cleavage bands by heating with piperidine (90 °C, 30 min) followed by electrophoresis on the denaturing sequencing gel (15% polyacrylamide and 7 M urea) and autoradiography. Lanes 1 and 5: ODN1; lanes 2 and 6: ODN2; lanes 3 and 7: ODN3; lanes 4 and 8: ODN4; A + G, Maxam–Gilbert A + G sequencing reactions. Lanes 1–4: **13S-1** and lanes 5–8: **13R-1**. For clarity the bulged sites are shown by arrows with the lane numbers.

Guanine alkylation of the fully complementary duplex ODNP–ODN1 by **13S-1** selectively occurred at the 5'-G of the 5'-GG-3' sequence (lane 1). The 5'-G (G₁₂ and G₂₁) and middle G (G₁₃ and G₂₂) were selectively alkylated in the 5'-GGG-3' sequence, which indicates that **13S-1** preferentially intercalates into the GG step and alkylates 5'-G at the

intercalated site. Guanine alkylation occurred more readily at bulged sites than at normal GG sites in the duplexes containing a single nucleotide bulge (lanes 2–4). Alkylation at G₁₇G₁₈ in ODNP–ODN2 (lane 2) and G₂₁G₂₂ in ODNP–ODN3 (lane 3) in a bulged structure was enhanced 2.5- and 3.6-fold, respectively, relative to the cleavage of the normal strand (lane 1).^[11] Almost same 5'-G selectivity as observed for the normal GG doublets was detected. Enhanced alkylation susceptibility of guanine residues opposite the bulge is well rationalized in terms of the increased stability of the intercalated complex of 13S-1.^[4]

In sharp contrast to the nearly negligible guanine alkylation of the fully complementary duplex ODNP–ODN1 by 13R-1 (lane 5), strong cleavage bands at guanine residues opposite a bulge were observed (lanes 6–8). Alkylation at G₁₇G₁₈ in ODNP–ODN2 (lane 6) and G₂₁G₂₂ in ODNP–ODN3 (lane 7) was enhanced 13- and 25-fold, respectively.^[12] Both the 5'- and 3'-side guanine residues of the 5'-GG-3' sequence in the bulge are almost equally alkylated, in sharp contrast to the high 5'-G selectivity observed for 13S-1 (lanes 6 and 2, respectively). Since the alkylation at the normal G and GG sites by 13R-1 is quite inefficient (lane 5), the marked enhancement of the reactivity of guanine alkylation should be ascribable to the formation of a unique intercalated complex of 13R-1 that is only attainable in the bulged structure.

Having established that 13R-1 selectively alkylates guanine opposite a bulge, we carried out molecular modeling studies for the complex of bulge-containing simplified model oligomer d(CATG₄G₅TAC/GTAC₁₂T₁₃C₁₄ATG) with 13R-1.^[13] These simulations showed that the alkylation at G₄ seems to proceed smoothly only when 13R-1 intercalates into the G₄G₅ step through a threading mode and the intercalated complex is stabilized by stacking with G₅ and with T₁₃ of the complementary strand (Figure 3a). The average nonbonding

distance between C15 of 13R-1 and N7 of G₄ in the molecular dynamic simulation for 100 ps at 300 K was 3.37 Å. An alternative intercalated complex for G₅ alkylation where 13R-1 strongly stacks with both G₄ and T₁₃ was also feasible (Figure 3b).

In general, DNA-cleaving intercalators are known to exhibit enhanced reactivity in cleaving DNA at bulges as a result of the increased stability of the intercalated complex. In contrast, 13R-1 specifically alkylates guanine opposite a T bulge, not only because of the increased complex stability as is generally observed for most intercalating drugs, but also because of the formation of the uniquely oriented complex in which the S_N2-type ring opening of the epoxide is highly facilitated by the neighboring guanine residue. Such designed DNA-cleaving drugs that possess extremely high bulge selectivity can be used as a chemical probe for bulged structure in DNA and RNA.

Experimental Section

Molecular modeling of a bulge-containing oligomer with 13R-1 was carried out as follows. An oligomer containing a single T-bulge d(CAT G₄G₅TAC/GTA CTC ATG) was produced from a fully complementary B-form duplex d(CAT GAG TAC/GTA CTC ATG) by removing dA monophosphate from the GAG sequence. The sugar–phosphate backbone between the two guanine residues was connected manually. The structure of this oligomer was stored as a nonminimized bulge. Compound 13R-1 was manually inserted into the hole of the bulged site by a threading mode, and the complex was energy minimized.^[13] Manual docking of 13R-1 into the nonminimized bulge was repeated with various geometries of 13R-1 relative to the bulge. With these operations two complexes were obtained with a reasonable nonbonding distance between the epoxide carbon atom (C15) and the guanine N7 (Figures 3a and b). Molecular dynamic simulation was carried out with these complexes as a starting geometry for 100 ps at 300 K.

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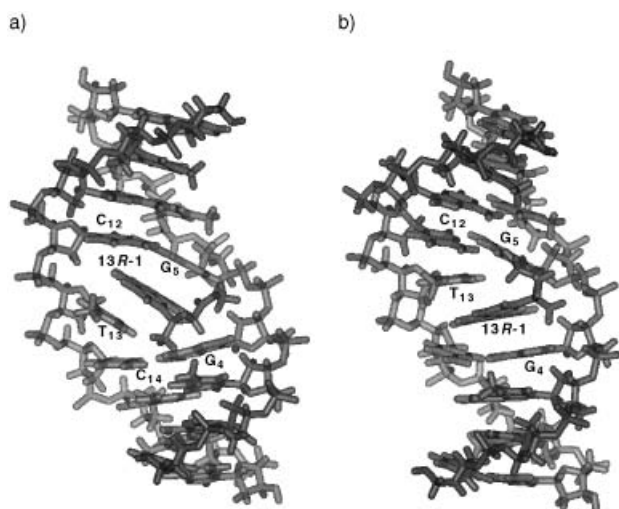


Figure 3. Energy-minimized structures for the complex of d(CATG₄G₅TAC/GTAC₁₂T₁₃C₁₄ATG) with 13R-1. The complexes viewed from a major groove are shown. a) 13R-1 intercalates into the G₄G₅ step by a threading mode and stacks with G₅ and with T₁₃ of the complementary strand. The epoxide carbon atom C15 is close to N7 of G₄ (3.44 Å). b) 13R-1 intercalates into the G₄G₅ step; but this time it stacks with G₄ and with T₁₃ of the complementary strand. The epoxide carbon atom is close to N7 of G₅ (3.51 Å).

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- [10] It should be noted that altromycin B (**2**) possesses an epoxide with the same absolute configuration as that of 13R-**1** and alkylates the 3'-G at the intercalated site. DNA–sugar interactions that would change the orientation of the epoxide relative to the 3'-G have a crucial effect on the efficiency of the epoxide ring opening.
- [11] The relative intensity of the cleavage bands at $G_n G_m$ and at $G_{12} G_{13} G_{14}$ in the same strand for the normal ODNs and for those with a bulge, $I_{\text{normal}(n,m)}$ and $I_{\text{bulge}(n,m)}$, respectively, was measured by densitometric analysis: $I_{\text{normal}(17,18)}$ (lane 1) 0.87; $I_{\text{normal}(21,22)}$ (lane 1) 0.59; $I_{\text{bulge}(17,18)}$ (lane 2) 2.2; $I_{\text{bulge}(21,22)}$ (lane 3) 2.1. The enhanced alkylation susceptibility at the bulge $I_{\text{bulge}(n,m)}/I_{\text{normal}(n,m)}$ was thus calculated as 2.5 (2.2/0.87) at the $G_{17} G_{18}$ step and 3.6 (2.1/0.59) at the $G_{21} G_{22}$ step.
- [12] $I_{\text{normal}(17,18)}$ (lane 5) 1.8; $I_{\text{normal}(21,22)}$ (lane 5) 1.1; $I_{\text{bulge}(17,18)}$ (lane 6) 23; $I_{\text{bulge}(21,22)}$ (lane 7) 28.
- [13] Molecular mechanic calculations were carried out using the Amber* force field with the GB-SA solvation model of water implemented in the molecular modeling software MacroModel version 6.0. Molecular dynamic simulations were performed at 300 K for 100 ps. The intermediate structure during the MD simulations was sampled every 1 ps.

Ga₂₂[Si(SiMe₃)₃]₈: The Largest Atom-Centered Neutral Main Group Metal Cluster**

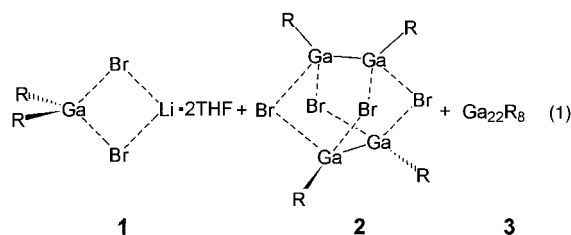
Andreas Schnepf, Edgar Weckert, Gerald Linti, and Hansgeorg Schnöckel*

*Dedicated to Professor Reinhart Ahlrichs
on the occasion of his 60th birthday*

Until recently, clusters of metal atoms were limited to transition metals.^[1] With the synthesis of an Al₇₇ cluster,^[2] which was the largest metal atom cluster hitherto that has

been characterized by X-ray analysis, we have developed a new route to the synthesis of this type of compound.^[3] We started from metastable AlX/GaX solutions (X = Cl, Br, I), which disproportionate, even under mild conditions, into the corresponding metal and trihalide (e.g.: 3 GaBr → 2 Ga + GaBr₃).^[4] However, by substituting the halide with suitable ligands, this process can be delayed so that the compounds that contain clusters of metal atoms can be captured as intermediates before they form the metals; in some cases they can even be crystallized. Since the preparation of the necessary metastable subhalide solutions requires special apparatus,^[5] this method has only been used by our research group up to now. We expect, however, that the successful synthesis of unusual species will lead to a widespread use of this technique in the future. We report here on a gallium cluster in which a central gallium atom exhibits a coordination number of 13, which is very unusual even for “real” metals.

Cocondensation of molecular GaBr, which is thermodynamically stable only at high temperatures (about 1000 °C) and low pressures (about 10^{−2} mbar), with a mixture of toluene and THF at −196 °C followed by warming to −78 °C afforded a metastable GaBr solution which already disproportionated above −20 °C into gallium and GaBr₃. However, treating this solution at −78 °C with tris(trimethylsilyl)silyllithium (hypersilyllithium) in toluene leads, upon slow warming, to an initially dark red solution, which later turns dark brown to almost black and is stable at room temperature [Eq. (1)].



After removal of the solvent mixture under vacuum and extraction of the residual solid with pentane, a dark red-brown solution was obtained from which colorless crystals of **1** precipitate as a first product. In addition to this product, which is formed by oxidation of the original Ga^I species, **2** is observed as a second oxidation product under certain conditions.^[6] Compound **2** is isostructural with the corresponding chloro derivative [GaClSi(SiMe₃)₃]₄.^[7] After separation of the oxidized species **1** and **2**, a reduced, metal-rich species should therefore be present in which gallium has an oxidation number less than 1. Indeed, upon concentration of the pentane extract, such a compound, **3**, is obtained as black crystals in the form of cubes and rods. Its ESR spectrum shows that it is a diamagnetic compound. The results of the X-ray structural analysis are presented in Figure 1.

The core of the gallium cluster can be described as follows: A central gallium atom is surrounded by 13 gallium atoms at a large distance (average value 294.2 pm). This shell of thirteen atoms, within which the average distance between the gallium

[*] Prof. Dr. H. Schnöckel, Dipl.-Chem. A. Schnepf, Priv.-Doz. Dr. G. Linti
Institut für Anorganische Chemie der Universität (TH)
Engesserstraße, Geb. 30.45, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4854
E-mail: hg@achpc9.chemie.uni-karlsruhe.de
Priv.-Doz. Dr. E. Weckert
Institut für Kristallographie der Universität (TH)
Engesserstraße, Geb. 30.45, D-76128 Karlsruhe (Germany)

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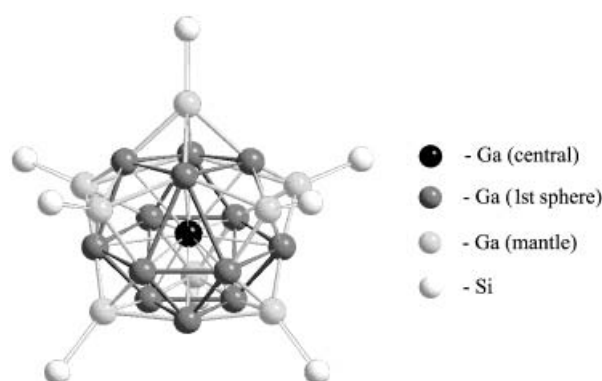


Figure 1. X-ray structural analysis of **3**. All the trimethylsilyl groups have been omitted for clarity. Average value of the bond lengths [pm] in the individual areas of **3**: Ga(central)–Ga(1st sphere) 294.2(5), Ga–Ga (within the 1st sphere) 286.7(7), Ga(1st sphere)–Ga(mantle) 267.3(6), Ga(mantle)–Si 242.6(5).

atoms is 286.7 pm, shows great similarity to the cuboctahedral coordination (coordination number 12) of metals (M_3 – M_6 – M_3), whereby one of the triangular M_3 faces is substituted by a square Ga_4 face (Figure 2).

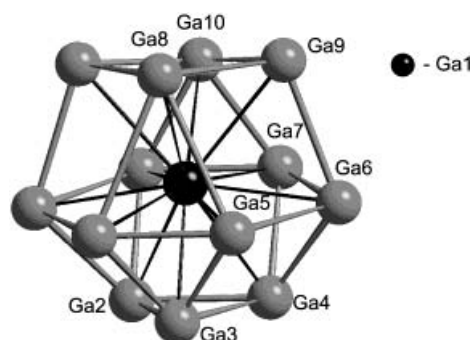


Figure 2. First coordination sphere and the central atom in **3**: Selected bond lengths [pm] and angles [°]: Ga1–Ga5 284.3(3), Ga1–Ga10 291.1(5), Ga1–Ga6 297.6(2), Ga1–Ga9 308.3(4), Ga1–Ga8 312.9(2), Ga9–Ga8 289.1(6), Ga9–Ga6 294.9(5), Ga8–Ga5 336.1(6), Ga6–Ga7 301.6(8), Ga6–Ga5 290.0(7), Ga6–Ga4 272.2(5), Ga4–Ga3 275.5(5); Ga2–Ga3–Ga4 60.9(2), Ga3–Ga5–Ga8 114.5(1), Ga5–Ga6–Ga7 114.2(1), Ga4–Ga6–Ga9 118.5(2), Ga8–Ga9–Ga10 90.3(1).

As a consequence of this alteration, there are eight square faces in the 13-atom shell. Each of these faces is capped by a ligand-bearing gallium atom at an average distance of 267.3 pm. These eight outer gallium atoms form a slightly distorted square antiprism (Figure 3), while the eight hyper-silyl groups form a closed ligand sphere about the gallium cluster built of a total of 22 atoms. This complete shielding of the metal cluster is probably the main reason for the unusual coordination number of 13, because a cuboctahedral arrangement with six rectangular faces and six ligands would provide only an incomplete encapsulation.

In addition to the purely steric explanation of the structure of the Ga_{22} cluster, an argumentation based on electronic factors can also be considered. Thus, preliminary calculations with density functional theory (DFT) on Ga_{22}^{8+} ^[8] showed that

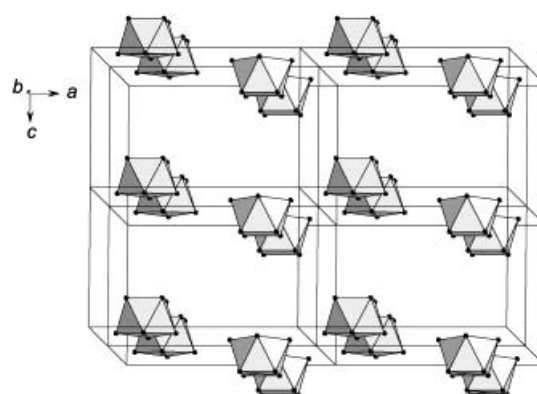


Figure 3. Arrangement of the Ga_{22} units in the crystal. The eight outer gallium atoms are depicted in a polyhedral representation.

the 20 low-lying molecular valence orbitals are assigned to energetically similar groups so that they can be described by the jellium model.^[9] A first indication of such an electronic stabilization is provided by a simple count of the valence electrons: If the eight outer gallium atoms are counted as Ga^I , then a total of 58 skeletal electrons ($14 \times 3 + 8 \times 2 = 58$) results. This corresponds to a “stable” jellium state.^[10]

It is particularly remarkable that in **3** the central gallium atom is forced to take up a “metallic” coordination with 13 gallium atoms at understandably large distances, although gallium in its elemental state would rather prefer nonmetallic coordination (coordination number: 6 + 1 (275 pm, 245 pm) in α -gallium).

Thus the structure and formation of **3** provide evidence that gallium can also take up a previously unknown metallic structure with a high coordination number. Similar to the situation in the Al_{77} cluster,^[2] the inner and the outer Ga atoms in **3** have different geometric environments, and therefore different electronic properties can be expected. The inner gallium atoms would have a more metallic character and the outer gallium atoms a more molecular character (2e–2c bonds). The shortening of the Ga–Ga distances on going from the center to the outer mantle of 8 gallium atoms is chemically plausible; however, to the best of our knowledge, such a trend has up to now not been found or discussed for the few clusters built of transition metal atoms which have a known structure (e.g. $Au_{39}Cl_6(PPh_3)_{14}Cl_2$ ^[11]).

In the crystal, the Ga_{22} units are arranged to give a distorted primitive cubic structure in which the “cubes” of Ga_{22} clusters are tilted against each other to form undulating layers (Figure 3).

Now that the synthetic potential of GaX and AlX solutions has been proved by the formation of an Al_{77} cluster as well as by the Ga_{22} cluster described here, our future work will focus on the variation of the steric and electronic properties of the ligands in an attempt to synthesize tailored cluster species. Additionally, by improving the synthesis conditions we will try to increase the yields of these compounds so that physical measurements (e.g. the electrical conductivity and the magnetic susceptibility) can be undertaken on crystals of **3**, in which each Ga_{22} unit is surrounded by 32 Si atoms and 72 methyl groups.

Experimental Section

To a solution of $(\text{SiMe}_3)_3\text{SiLi} \cdot 2\text{THF}$ (1 g, 2.5 mmol, 1 equiv) in toluene (20 mL) placed in a 250-mL round-bottomed flask was added a 0.3 M solution of GaBr (9.2 mL, 2.76 mmol, 1.1 equiv) in toluene/THF at -78°C . The reaction mixture was slowly warmed to room temperature, and the solution changed color from dark red to black. The solvent was removed under vacuum, and the reaction products were extracted with pentane. The first crystals which precipitated from the dark brown pentane extract were colorless crystals of **1**. These crystals were removed by filtration and the pentane extract was concentrated to give black crystals of **3** (ca. 30 mg, 10%).

1: ^1H NMR (250 MHz, $[\text{D}_6]\text{benzene}$, 25°C): $\delta = 0.54$ (s); ^{13}C NMR (63 MHz, $[\text{D}_6]\text{benzene}$, 25°C): $\delta = 5.07$ (CH_3); ^{29}Si NMR (50 MHz, $[\text{D}_6]\text{benzene}$, 25°C): $\delta = -6.65$; MS (70 eV): m/z (%): 644 (3, $M^+ - \text{LiBr} \cdot 2\text{THF}$), 629 (19, $M^+ - \text{LiBr} \cdot 2\text{THF} - \text{CH}_3$), 316 (100, $\text{GaSi}(\text{SiMe}_3)_3$).

2: ^1H NMR (250 MHz, $[\text{D}_6]\text{benzene}$, 25°C): $\delta = 0.421$ (s), 0.472 (s); ^{13}C NMR (63 MHz, $[\text{D}_6]\text{benzene}$, 25°C): $\delta = 4.394$ (CH_3), 4.679 (CH_3); ^{29}Si NMR (50 MHz, $[\text{D}_6]\text{benzene}$, 25°C): $\delta = -7.94$ (3Si), -123.08 (1Si); MS (70 eV): m/z (%): 1335 (4, $M^+ - \text{Si}(\text{SiMe}_3)_3$), 1320 (2, $M^+ - \text{Si}(\text{SiMe}_3)_3 - \text{CH}_3$), 1262 (2, $\text{Ga}_4\text{Br}_3(\text{Si}(\text{SiMe}_3)_3)_3$), 715 (5, $\text{Ga}_2\text{Br}(\text{Si}(\text{SiMe}_3)_3)_2$), 316 (100, $\text{GaSi}(\text{SiMe}_3)_3$).

The structures of **1–3** were solved by direct methods and all the observed reflections were refined against F^2 . Programs used: SHELXS and SHELXTL (G. M. Sheldrick, Universität Göttingen (Germany)).

Crystal structure analysis of **1**: $\text{GaBrSi}_4\text{LiO}_2\text{C}_{26}\text{H}_{70}$, $M_r = 710.42$. Crystal dimensions $0.73 \times 0.36 \times 0.15$ mm, monoclinic, space group $P2(1)/c$, $a = 13.595(3)$, $b = 17.070(3)$, $c = 20.687(4)$ Å, $\beta = 104.69(3)^\circ$, $V = 4643.7(16)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.270$ g cm⁻³, $\mu_{\text{Mo}} = 2.541$ mm⁻¹, $2\theta_{\text{max}} = 50.04^\circ$, 8186 measured reflections, 8186 independent reflections, absorption correction: semiempirical (min./max. transmission 0.3517/0.5328), $R_1 = 0.0635$, $wR_2 = 0.1381$. Stoe-Stadi 4 diffractometer ($\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, 150 K).

Crystal structure analysis of **2**: $\text{GaBrSi}_4\text{C}_9\text{H}_{27}$, $M_r = 397.30$. Crystal dimensions $0.2 \times 0.57 \times 1.15$ mm, tetragonal, space group $P4_2(1)c$, $a = 18.018(3)$, $b = 18.018(3)$, $c = 14.481(3)$ Å, $V = 4701.3(14)$ Å³, $Z = 8$, $\rho_{\text{calc}} = 1.123$ g cm⁻³, $\mu_{\text{Mo}} = 3.056$ cm⁻¹, $2\theta_{\text{max}} = 48^\circ$, 8252 measured reflections, 2954 independent reflections, absorption correction: numerical (min./max. transmission 0.344/0.553), $R_1 = 0.0486$, $wR_2 = 0.1405$. Stoe-Stadi 4 diffractometer ($\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, 150 K).

Crystal structure analysis of **3**: $\text{Ga}_{22}\text{Si}_{32}\text{C}_{72}\text{H}_{216}$, $M_r = 3515.17$. Crystal dimensions $0.2 \times 0.4 \times 0.6$ mm, orthorhombic, space group $Pnmm$, $a = 23.741(3)$, $b = 24.557(2)$, $c = 15.9999(12)$ Å, $V = 9328.1(14)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.252$ g cm⁻³, $\mu_{\text{Mo}} = 3.347$ cm⁻¹, $2\theta_{\text{max}} = 44.80^\circ$, 37953 measured reflections, 6333 independent reflections, absorption correction: numerical (min./max. transmission 0.25142/0.34044), $R_1 = 0.0716$, $wR_2 = 0.2371$. Stoe-IPDS diffractometer ($\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, 200 K).

The structure refinement of **3** indicated that the inner Ga_{14} core is present in two intermeshing orientations (distribution 50:50), which can be interconverted through a mirror plane. This disordering seems plausible if account is taken of the fact that the Ga_8R_8 mantle (square antiprismatic) shows a higher symmetry than the Ga_{14} core, so that within the mantle there are two orientations for the Ga_{14} core (Ga_{14} , Ga_{14}') and their average leads to a 50:50 disordering. Structural analysis in space groups of lower symmetry ($P2(1)mn$, $Pm2(1)n$, $P2(1)2(1)2$, and Pn) also led to the same disordering so that this interpretation seems to be conclusive. However, the disordering does not appear to be completely statistical since a more exact analysis of the measured data showed additional reflections of lower intensity in which about 10% of the total intensity is localized. If a superlattice structure is assumed, then this would lead to a sevenfold increase in the c axis ($c = 111.95$ Å). However, if this holds true, entire planes in the reciprocal space would create reflections with no measurable intensity, and therefore we cannot decide whether there is a superlattice present or perhaps an incommensurable modulation along c . A more accurate examination of this situation is not possible with the given experimental possibilities. Therefore, the structure was initially refined as a disordered structure in the small cell with $c = 15.999$ Å. We assume that this result corresponds to the averaged structure. In future investigations we will attempt to discover which phenomenon is responsible for the additional reflections.

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-125675 (**1**), CCDC-125676 (**2**), and CCDC-125677 (**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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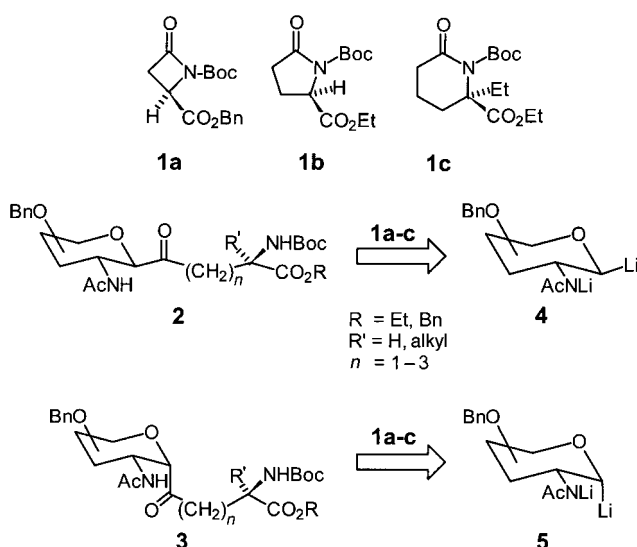
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Diastereoselective Synthesis of C-Glycosylated Amino Acids with Lactams as Peptide Building Blocks**

Bernhard Westermann,* Armin Walter, and Nicole Diedrichs

Glycopeptides are of growing interest with regard to the elucidation and utilization of their numerous biological properties.^[1, 2] However, these natural products are of low metabolic and chemical stability, and their synthesis often requires complex sequences. Therefore, recent research has been focussed on the efficient synthesis of glycopeptide mimics with a stable linkage of the glycosyl and peptide moieties. Whereas natural glycopeptides bear metabolic labile O- and N-glycosidic bonds, C- and S-glycosylated mimics offer the possibility to circumvent this drawback.^[3] Despite numerous contributions for the synthesis of C-glycosylated amino acids in recent years, these methods often involve a lot of steps and are of low diastereoselectivity.^[4, 5]

Here we present the diastereoselective synthesis of C-glycosylated amino acids **2** and **3** by utilizing enantiomerically pure lactams **1a–c** as peptide building blocks. Lactams **1a–c** can be ring-opened with the easily generated glycosyl dianions **4** and **5** (Scheme 1).^[6] The lactams used in this study can be obtained from the chiral pool or synthesized by enzyme-catalyzed kinetic resolution of appropriate precursors. Therefore, they offer an easily accessible source of peptide building blocks.^[7] Furthermore, for the formation of



Scheme 1. Strategies for the synthesis of C-glycosides starting from lactams **1**.

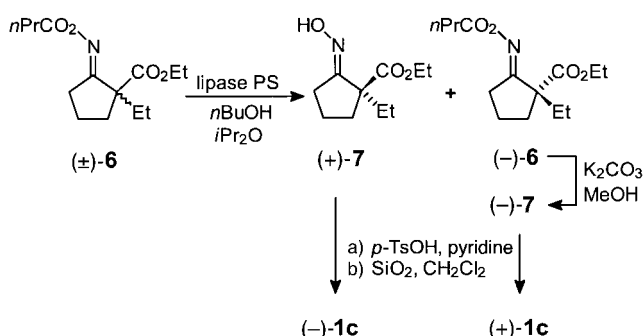
[*] Priv. Doz. Dr. B. Westermann, Dipl.-Chem. A. Walter, Dr. N. Diedrichs
Fachbereich für Chemie und Chemietechnik
der Universität-Gesamthochschule
Warburgerstrasse 100, D-33098 Paderborn (Germany)
Fax: (+49) 5251-603245
E-mail: bw@chemie.uni-paderborn.de

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the glycosidic bond no racemization of the aglycon has to be taken into account upon utilization of **1a–c**.^[8]

In addition it will be shown that following this strategy, C-glycosylated α,α' -disubstituted α -amino acids can be prepared. When incorporated into oligopeptides, certain secondary peptidic structures like β turns can be adjusted through use of these conformationally restricted amino acids.^[9]

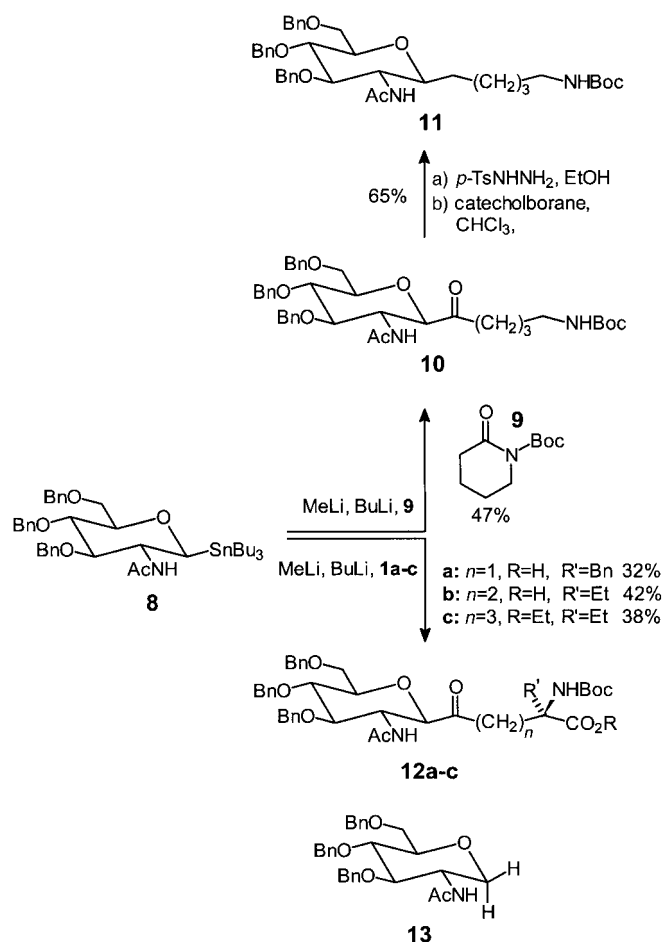
We showed earlier that *N*-Boc-protected lactams can be easily ring-opened by nucleophiles to afford α,α' -disubstituted amino acids.^[10] Although lactams **1a, b** can be taken from the chiral pool,^[11] others such as lactam **1c** can be obtained enantiomerically pure by a lipase-catalyzed kinetic resolution. When ($\pm$)-**6**^[12] is submitted to lipase-catalyzed transacylation in the presence of *n*-butanol, (+)-**7** and (–)-**7** (from (–)-**6** after cleavage of the butyrate moiety with K_2CO_3 /methanol) can be obtained in high enantiomeric excess and high yields. The enantiomeric excess was determined to be 93% *ee* for (+)-**7** and 98% *ee* for (–)-**7**.^[13] This, to our knowledge, is the first example of successful kinetic resolution of oxime esters by an enzyme-catalyzed transacylation.^[14] A stereospecific Beckmann rearrangement and protection of the lactam led to the desired lactams (+)-**1c** and (–)-**1c** (Scheme 2). As shown earlier, no racemization takes place during this rearrangement.^[10]



Scheme 2. Lipase-catalyzed transacylation of oxime esters ($\pm$)-**6** to (+)-**7** and (–)-**6** as well as Beckmann rearrangement to **1c**. Ts = tosyl = toluenesulfonyl.

To prove our approach for the synthesis of C-glycosylated amino acids from **1**, a model reaction using *N*-Boc-protected, unsubstituted valerolactam **9** was carried out (Scheme 3). Starting from the β -configured stannyl derivative **8**, the glycosyl dianion **4** was generated at $-78^\circ C$ by subsequent addition of one equivalent each of MeLi and BuLi, and then allowed to react with **9**. The C-glycoside **10** was obtained in 47% yield as the only diastereoisomer. The product was of β -configuration, as determined by extensive NMR experiments. Reduction of **10** to **11** was accomplished by synthesis of the tosyl hydrazone and subsequent reduction with catecholborane in 65% overall yield.^[15]

In analogy, the reactions of **8** with lactams **1a–c** were carried out as described above. The C-glycosylated amino acids **12a–c** could be isolated in satisfactory yields (**12a**: 32%; **12b**: 42%; **12c**: 38%). The investigation of the configuration at the anomeric center and a possible racemization of the stereogenic center of the peptidic moiety was of high interest. To prove that no racemization occurred, the



Scheme 3. Nucleophilic ring opening of lactams **1a–c** and **9** by reaction with glycosyl dianions.

pyroglutamic derivative **1b** was employed enantiomerically pure, (+)-**1b** and (–)-**1b**, and as a racemate, (±)-**1b**. The ^1H NMR spectra for the products obtained from (+)-**1b** and (–)-**1b** revealed only one singlet for the *tert*-butyl moiety, whereas the ^1H NMR spectra for the product from (±)-**1b** showed two baseline-separated singlets.^[16] Therefore, it can be concluded that no racemization took place during the nucleophilic ring opening of the enantiomerically pure lactams.

To obtain α -configured glycosylated amino acid **3**, glycosyl dianion **5** was used. To date, this reaction has not been carried out successfully; only **13** could be isolated as the sole product. We believe that steric reasons are responsible for this failure.

The results presented above clearly indicate that lactams are suitable, easily obtainable building blocks for the synthesis of C-glycopeptides. The products are orthogonally protected. Thus, by incorporation of these conformationally restricted amino acids in oligopeptides new hybrids can be synthesized that stabilize secondary structural elements in the peptide moiety and, in addition, contain a glycosidic adhesion ligand through a metabolic stable linkage.^[17]

Experimental Section

(+)-**12b**: Stannane **8** (250 mg, 0.33 mmol) was dissolved in THF (10 mL) and cooled to -78°C . Within 5–10 min MeLi (0.33 mL, 0.33 mmol, 1 M in

hexane) was added, followed by warming to -65°C and addition of BuLi (0.30 mL, 0.45 mmol, 1.5 M in hexane) in 5–10 min. After addition of (+)-**1b** (105 mg, 0.43 mmol) the dark red reaction solution became colorless. After 30 min of stirring, a saturated NH_4Cl solution was added to stop the reaction. The reaction mixture was warmed to room temperature in an ultrasound bath, and extracted with ethyl acetate (2×20 mL). The extract was dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography on silica gel (petrol ether/ethyl acetate 1/1) yielded **12b** (97 mg, 42%) as a colorless oil. $R_f = 0.27$; $[\alpha]_D^{20} = +24.3$ ($c = 0.82$ in CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3): $\delta = 1.26$ (t, $J = 7.2$ Hz, 3 H, CH_3), 1.42 (s, 9 H, CH_3), 1.78 (s, 3 H, CH_3), 2.09–2.14 (m, 2 H, CH_2), 2.61–2.87 (m, 2 H, CH_2), 3.48–3.51 (m, 1 H, 5-H), 3.55–3.64 (m, 2 H, 4-H, 2-H), 3.70 (d, $J = 2.9$ Hz, 2 H, 6-H), 3.89 (d, $J = 10.1$ Hz, 1 H, 1-H), 3.97–4.03 (m, 1 H, 3-H), 4.17 (q, $J = 7.1$ Hz, 2 H, OCH_2), 4.10–4.21 (m, 1 H, CH_n), 4.51–4.85 (m, 6 H, PhCH_2), 5.29 (d, $J = 8.6$ Hz, 1 H, BocNH), 5.72 (d, $J = 7.6$ Hz, 1 H, NH), 7.18–7.35 (m, 15 H, arom. CH); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 14.57, 23.57, 25.72, 28.76, 33.37, 52.97, 54.26, 61.74, 69.32, 73.85, 75.12, 75.39, 79.34, 79.57, 80.57, 81.83, 83.21, 128.12, 128.25, 128.37, 128.43, 128.52, 128.84, 128.91, 129.04, 133.32, 133.42, 133.82, 151.11, 166.34, 167.99, 201.88$.

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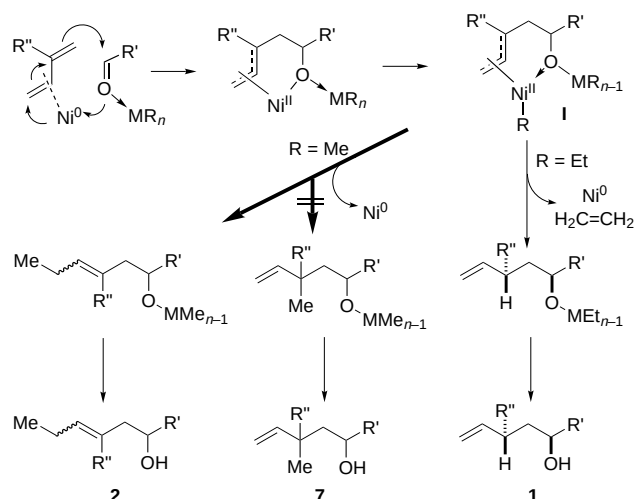
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Nickel(0)-Catalyzed Three-Component Connection Reaction of Dimethylzinc, 1,3-Dienes, and Carbonyl Compounds**

Masanari Kimura, Shintaro Matsuo, Kazufumi Shibata, and Yoshinao Tamaru*

Since the discoveries of the thermal [4+2] cycloaddition reaction by Diels and Alder and nickel-catalyzed oligomerization by Wilke,^[1] 1,3-dienes have been recognized to be among the most useful synthetic blocks in organic synthesis. Significant expansion of their synthetic utility has been brought about by recent studies on transition metal catalyzed cyclizations^[2] and 1,2-/1,4-difunctionalization of 1,3-dienes (H, B,^[3] H, Si;^[4] H, Sn;^[5] B, B;^[6] B, Si;^[7] B, Sn;^[8] C, Si;^[9] Si, Si;^[10] Sn, Sn;^[11] etc.).^[12] In most cases, the products of the latter reactions are allylic metalloids that are capable of regio- and stereoselective allylation of carbonyl compounds.

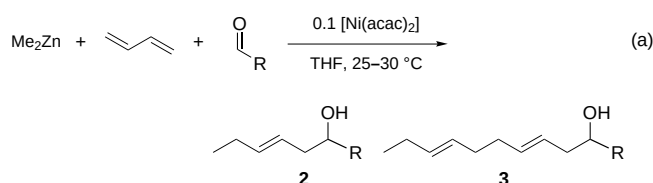
We previously reported that, in the presence of a catalytic amount of $[\text{Ni}(\text{acac})_2]$ (acac = acetylacetonato) and a stoichiometric amount of triethylborane or diethylzinc, 1,3-dienes serve as a homoallyl anion equivalent and react with a wide range of carbonyl compounds to furnish bishomoallyl alcohols **1** in high yields and with high regio- and stereoselectivities^[13] (Scheme 1). A proposed mechanism involves nucleophilic addition of diene–nickel(0) complexes to carbonyl compounds coordinated by MR_n ($\text{MR}_n = \text{Et}_2\text{Zn}$ or Et_3B) and ethyl group migration from M to Ni^{II} to yield an intermediate **I** ($\text{R} = \text{Et}$). This is followed by β -dehydronickelation and



Scheme 1. Nickel-catalyzed coupling of 1,3-dienes with alkylmetal reagents and carbonyl compounds.

reductive elimination to furnish **1** and ethylene and regenerate Ni^0 .

This sequence of reactions suggested to us that if dimethylzinc were used in place of diethylzinc, the β -dehydronickelation in the final step might be inhibited, and the intermediates **I** ($\text{R} = \text{Me}$) would undergo reductive elimination to provide homoallyl alcohols **2** or bis-homoallyl alcohols **7**. In fact, when dimethylzinc (4.8 mmol), 1,3-butadiene (8.0 mmol), and benzaldehyde (2.0 mmol) were exposed to $[\text{Ni}(\text{acac})_2]$ (0.2 mmol) in dry THF (5 mL) at room temperature for 2 h under N_2 , the methyl group was transferred selectively to the distal allylic terminus, and homoallyl alcohol **2a** ($\text{R}' = \text{Ph}$, $\text{R}'' = \text{H}$ in Scheme 1) was obtained in almost quantitative yield [Eq. (a), $\text{R} = \text{Ph}$; Table 1, entry 1]. In the product mixture, the corresponding regioisomeric product **7** ($\text{R}' = \text{Ph}$, $\text{R}'' = \text{H}$) was not detected at all.^[14]



A number of nickel-catalyzed three-component connection reactions between organometallic compounds, alkynes (or strained alkenes), and carbonyl compounds have been reported;^[15] however, the present reaction, to the best of our knowledge, is the first example that utilizes conjugated dienes as the unsaturated hydrocarbon component.^[16] Although CrCl_2 also mediates a similar coupling reaction of alkyl iodides, 1,3-dienes, and carbonyl compounds, this reaction displays contrasting regioselectivity: The alkyl and carbonyl groups combine with 1,3-dienes at the C1 and C2 positions, respectively, to provide 2-alkylmethyl-3-buten-1-ols.^[17]

Intrigued by the synthetic possibilities and the facility with which dimethylzinc, 1,3-butadiene, and benzaldehyde combine with one another linearly in this sequence under very mild conditions with catalysis by Ni^0 in the absence of any

[*] Prof. Dr. Y. Tamaru, Dr. M. Kimura, S. Matsuo, K. Shibata
 Department of Applied Chemistry
 Faculty of Engineering, Nagasaki University
 1-14 Bunkyo-machi, Nagasaki 852-8521 (Japan)
 Fax: (+81)958-47-9008
 E-mail: tamaru@net.nagasaki-u.ac.jp

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Table 1. Nickel(0)-catalyzed coupling reaction of dimethylzinc, 1,3-dienes, and carbonyl compounds.^[a]

Entry	Carbonyl compound	1,3-Diene	T [°C]/t [h]	Yield [%] ^[b, c]	
				1:1:1 product ^[d]	1:2:1 product ^[e]
1	PhCHO	butadiene	25 (2)	2a : 99	3a : 0
2	Ph-CH ₂ -CHO	butadiene	25 (1)	2b : 83	3b : 3
3		butadiene	25 (1)	2c : 73	3c : 17
4	<i>t</i> BuCHO	butadiene	25 (3)	2d : 75	3d : 20
5		butadiene	30 (3)	2e : 0	3e : 89
6	PhCHO	isoprene	25 (5)	4a : 92 (<i>E</i> : <i>Z</i> = 2.2:1)	5a : 0
7	Ph-CH ₂ -CHO	isoprene	30 (1)	4b : 40 (<i>E</i> : <i>Z</i> = 3.8:1)	5b : 10
8		isoprene	30 (1)	4c : 62 (<i>E</i> : <i>Z</i> = 4.0:1)	5c : 11
9	<i>t</i> BuCHO	isoprene	25 (3)	4d : 57 (<i>E</i> : <i>Z</i> = 2.4:1)	5d : 8
10		isoprene	30 (3)	4e : 69 (<i>E</i> : <i>Z</i> = 2.5:1)	5e : 10

[a] A mixture of [Ni(acac)₂](0.2 mmol), 1,3-butadiene or isoprene (8.0 mmol), an aldehyde or a ketone (2.0 mmol), and Me₂Zn (4.8 mmol, 1M in hexane) in dry THF (5 ml) was stirred at the indicated temperature under N₂ [Eqs. (a), (b)]. [b] Yields refer to the isolated materials. All products were characterized by ¹H NMR (400 MHz), ¹³C NMR (100 MHz), and IR spectroscopy, high-resolution mass spectrometry, and/or elemental analysis. [c] In addition to **2**–**5**, 1-methyl-3-phenylpropan-1-ol (15%, entry 2), 1-cyclohexylethan-1-ol (10%, entry 3), 1-methyl-3-phenylpropan-1-ol (48%, entry 7), or 1-cyclohexylethan-1-ol (20%, entry 8) was obtained. [d] The *E*:*Z* ratios are determined on the basis of ¹H and ¹³C NMR spectroscopy. [e] Compound **3** contains a small amount of an isomer (<10%),

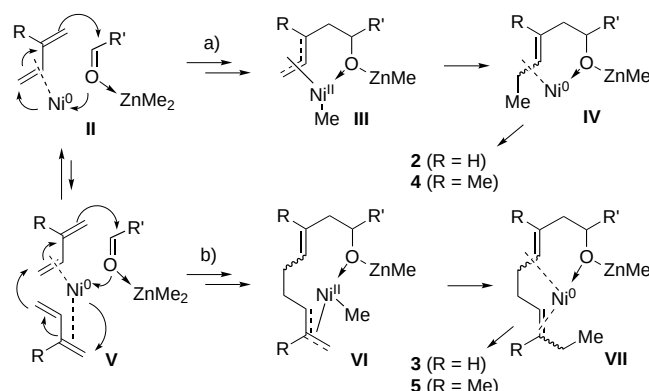
tries 6–10]. Isoprene selectively affords the 1:1:1 adducts **4**. In contrast to 1,3-butadiene, isoprene even reacts with ketones to give **4** as the major product (entry 10). All the products **4** are regiochemically homogeneous; this indicates that isoprene selectively reacts at C1 with carbonyl compounds and at C4 with dimethylzinc. However, compounds **4** proved to be mixtures of stereoisomers ((*E*)- and (*Z*)-**4** in a ratio of 2:1–4:1). As is apparent from ¹H and ¹³C NMR spectra, **5** consists of more than three stereoisomers. However, close examination of three alcoholic fragments derived from **5** by ozonolysis and reduction of the reaction mixture with NaBH₄ revealed that **5** bears regiochemically homogeneous methyl groups at the C3 and C8 positions [Eq. (b)]; hence, isoprene molecules selectively combined with each other in a tail-to-tail manner.

The reaction mechanism remains speculative at present. One likely scenario is outlined in Scheme 2. The 1,3-butadiene–nickel(0) complex may

phosphane ligands, we examined the scope of the present reaction by varying the type of carbonyl compound (Table 1, entries 1–5). Dihydrocinnamaldehyde furnished the expected **2b** in 83% yield; however, the unexpected product **3b** (the 1:2:1 coupling product of dimethylzinc, 1,3-butadiene, and the aldehyde) was also obtained as a minor product in 3% yield (entry 2). Interestingly, the relative amount of **3** to **2** gradually increased as the steric bulk around the carbonyl moiety increased (entries 3 and 4). Indeed, acetone gave **3e** as the sole product (entry 5).

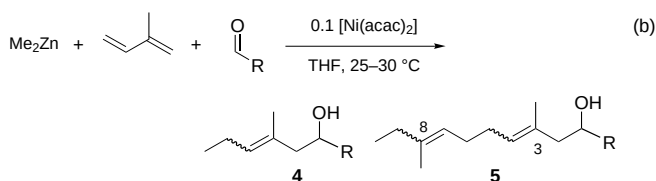
The products **2** are regio- and stereochemically homogeneous; all possess the common structural features of (*E*)-3-hexen-1-ol (see Experimental Section). The (*E,E*)-3,7-decadien-1-ol structure of **3**^[18] was elucidated from spectroscopic data: In the ¹H NMR spectrum (400 MHz, CDCl₃) the olefin proton signals (multiplets) separated into signals integrating for 1H (dt, *J* = 15.5, 6.0 Hz), 1H (dt, *J* = 15.5, 6.0 Hz), and 2H (m) in the presence of [Eu(fod)₃] (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato); the ¹³C NMR (100 MHz, CDCl₃) chemical shifts are in good agreement with the calculated values;^[19] and the IR spectrum contains a band at $\tilde{\nu}$ = 970 cm^{−1} (s).

We next examined the reaction of isoprene with carbonyl compounds under similar conditions [Eq. (b); Table 1, en-



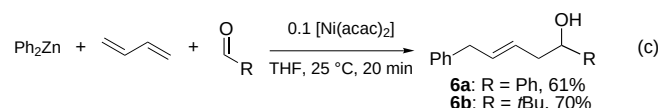
Scheme 2. Possible mechanism for the formation of **2/3** and **4/5**.

react with carbonyl compounds by path a to give the 1:1:1 adducts **2**.^[20] An intermediate **III** (R = H) with a *syn*- π -allylnickel(II) structure^[21] would undergo reductive elimination^[22] in such a way as to deliver the methyl group to the distal site, so that coordination of Ni⁰ with both Zn–O (nonbonding electron pair) and *trans*-CH=CH is better maintained.^[23] For less reactive carbonyl compounds, the potential of **II** to undergo oxidative cyclization might be insufficient to lead to **III**; hence, a small equilibrium concentration of bis-butadiene–nickel(0) complex **V** would then lead to **VI**. In this case, **V** is assumed to display higher reactivity than **II** owing to its greater polarizability (path b). Isoprene might react selectively by path a, irrespective of the type (reactivity) of carbonyl compound, since path b might be



unfavorable owing to steric congestion in **V** (R = Me). A higher electron density on C1 of isoprene than on C4 might contribute to the selective nucleophilic C1 addition of isoprene to carbonyl compounds.

Organozinc compounds with no accessible β -hydrogen atoms can similarly undergo a three-component connection reaction. For example, as illustrated in Equation (c), diphenylzinc [1.2 mmol, from ZnCl_2 (1.2 mmol) and PhMgBr (2.4 mmol)] reacted with 1,3-butadiene (4.0 mmol) and benzaldehyde (1.0 mmol) to furnish (*E*)-1,5-diphenyl-3-penten-1-ol (**6a**) in 61 % yield of isolated product.^[24] No 1:2:1 adducts were detected, even for the reaction with pivalaldehyde, from which **6b** was isolated as the sole product [Eq. (c)].



Experimental Section

(*E*)-1-phenyl-3-hexen-1-ol (**2a**): To a homogeneous solution of $[\text{Ni}(\text{acac})_2]$ (51.2 mg, 0.2 mmol) in dry THF (5 mL) were added 1,3-butadiene (670 μL , 8.0 mmol), benzaldehyde (212 mg, 2.0 mmol), and dimethylzinc (4.8 mL, 1 M in hexane). The mixture was stirred at room temperature for 2 h under N_2 and then quenched by adding 2 M HCl (5 mL). The mixture was extracted with ethyl acetate ($2 \times 20 \text{ mL}$), and the organic extracts were combined, washed with saturated NaHCO_3 , dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (64/1) to give **1a** in 99 % yield. R_f = 0.42 (hexane/ethyl acetate, 8/1); IR (neat): $\tilde{\nu}$ = 3400 (s), 1500 (s), 1460 (s), 1050 (s), 970 (s), 760 cm^{-1} (s); ^1H NMR (400 MHz, CDCl_3 , TMS): δ = 0.98 (t, J = 7.3 Hz, 3H), 1.86 (brs, 1H), 2.05 (br dq, J = 6.2, 7.3 Hz, 2H), 2.39 (m, 1H, coalesces to br dd, J = 8.1, 13.9 Hz on irradiation at δ = 5.40), 2.47 (m, 1H, coalesces to br dd, J = 4.8, 13.9 Hz on irradiation at δ = 5.40), 4.68 (dd, J = 4.8, 8.1 Hz, 1H), 5.40 (ddm, J = 6.2, 15.4 Hz, 1H), 5.63 (br dt, J = 15.4, 6.2 Hz, 1H), 7.24–7.29 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3 , TMS): δ = 13.7, 25.6, 42.7, 73.5, 124.5, 125.8, 127.3, 128.3, 136.6, 144.1; HR-MS calcd for $\text{C}_{12}\text{H}_{16}\text{O}$: 176.1201; found (%): 176.1195 (2) [M^+], 107 (100), 77 (23), 69 (3).

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Intermolecular Hydroamination of Alkynes Catalyzed by Dimethyltitanocene**

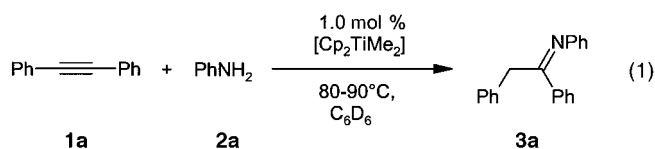
Edgar Haak, Igor Bytschkov, and Sven Doye*

Dedicated to Professor Ekkehard Winterfeldt

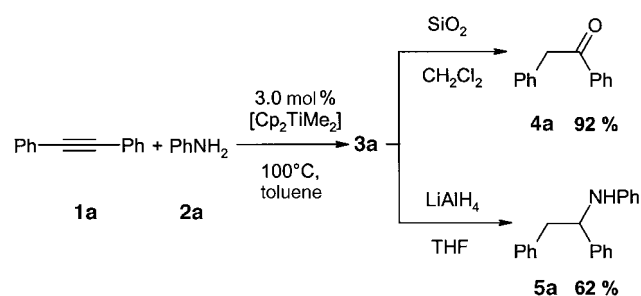
The synthesis of alcohols, ethers, ketones, and aldehydes by acid- or metal-catalyzed addition of water or alcohols to alkenes and alkynes is a well-established reaction in organic chemistry. Many regio- and stereoselective modifications of these addition reactions are known. In contrast, the formal analogous addition of ammonia or primary and secondary amines to nonactivated alkenes and alkynes does not have a comparable significance, in spite of extensive research efforts.^[1] This reaction, the hydroamination, offers a very interesting pathway to primary, secondary, and tertiary amines, imines, and enamines by converting inexpensive alkenes and alkynes into the desired more highly substituted products in a single reaction without any formation of side products. In connection with this, the intermolecular reaction of amines with alkenes and alkynes represents the greatest challenge. Catalysts used so far for the intermolecular hydroamination of alkynes include mercury and thallium compounds,^[2] as well as complexes of zirconium,^[3] the lanthanoids,^[4] uranium, and thorium.^[5] However, these catalysts have big disadvantages with respect to their limited range of application, price, handling, and toxicity. We report here for the first time on a catalyst system for the intermolecular hydroamination of alkynes that is nontoxic, inexpensive, and simple to use.

In 1992 Bergman et al. reported that the bisamide complex $[\text{Cp}_2\text{Zr}(\text{NH}-2,6\text{-Me}_2\text{C}_6\text{H}_3)_2]$ catalyzes the hydroamination of alkynes with 2,6-dimethylaniline.^[3] Unsymmetrically substituted alkynes preferentially gave the anti-Markovnikov products.^[3b] Unfortunately, this reaction could not be applied to other less sterically hindered amines. At about the same time, Livinghouse et al. demonstrated that $[\text{CpTiCl}_3]$ catalyzes the intramolecular hydroamination of aminoalkynes;^[6] however, intermolecular hydroaminations using this catalyst were not successful. In both cases metal-imido complexes were assumed to be the catalytically active species. Inspired by these interesting results, we started to synthesize compounds derived from $[\text{Cp}_2\text{Zr}(\text{NH}-2,6\text{-Me}_2\text{C}_6\text{H}_3)_2]$ and to investigate their performance as hydroamination catalysts. In preliminary experiments, we discovered that bisamide complexes of titanium, such as $[\text{Cp}_2\text{Ti}(\text{NH}-\text{C}_6\text{H}_5)_2]$,^[7] are very good hydroamination catalysts. However, to obtain a useful general catalyst and to avoid the isolation of titanium-bisamide complexes, we used the known and readily available dimethyltitanocene, $[\text{Cp}_2\text{TiMe}_2]$, as catalyst in all further experi-

ments.^[8] In the presence of an arbitrary amine, $[\text{Cp}_2\text{TiMe}_2]$ should lose methane to give the catalytically active titanium-bisamide or titanium-imido complexes. Therefore, $[\text{Cp}_2\text{TiMe}_2]$ would be a suitable general catalyst precursor. Indeed, $[\text{Cp}_2\text{TiMe}_2]$ catalyzes the hydroamination of alkynes very efficiently: Diphenylacetylene (**1a**) reacted smoothly with aniline (**2a**) in the presence of 1.0 mol % $[\text{Cp}_2\text{TiMe}_2]$ in C_6D_6 at 80–90 °C to give *N*-(1,2-diphenylethylidene)aniline (**3a**), which was detected by ¹H NMR spectroscopy [Eq. (1)].



On a preparative scale, **3a** was isolated in 52% yield by crystallization from methanol. In all subsequent experiments, the initially formed imines were not isolated owing to their potential susceptibility to hydrolysis. Instead, the hydroamination products were detected indirectly: The imines were either hydrolyzed with SiO_2 to the stable ketones or reduced with LiAlH_4 or H_2 on Pd/C to the stable amines. Thus, the reaction of **1a** with **2a** in the presence of 3.0 mol % $[\text{Cp}_2\text{TiMe}_2]$ gave 1,2-diphenylethanone (**4a**) in 92% yield. The amine **5a** was obtained by reduction with LiAlH_4 in 62% yield (Scheme 1).



Scheme 1. In situ hydrolysis and reduction of the hydroamination product **3a**.

Since reliable workup procedures were available, we investigated the scope of the reaction. For this, **1a** was treated with various amines in the presence of $[\text{Cp}_2\text{TiMe}_2]$ followed by a hydrolytic or reductive workup [Eq. (2), Table 1].

As can be seen in Table 1, both aryl- and alkylamines can be coupled with **1a** at 100 °C in toluene with 0.5–3.0 mol % $[\text{Cp}_2\text{TiMe}_2]$ as catalyst. Sterically hindered arylamines, such as 2,6-dimethylaniline (**2b**), as well as sterically less hindered, such as aniline (**2a**), can be coupled in comparable yields. Whereas the coupling product of *p*-fluoroaniline (**2c**) is obtained in yields of 93% or 63%, depending on the workup procedure, the reaction with pentafluoroaniline (**2d**) gave much lower yields. In the case of alkylamines, a significant decrease in the obtained yield was observed for sterically less hindered *n*-alkylamines. While the use of *tert*-butylamine (**2e**) and cyclohexylamine (**2f**) still gave yields of 91% and 65%, respectively, for the formation of **4a**, the yield dropped to 19% for *n*-hexylamine (**2g**). The reaction with benzylamine (**2h**) caused particular problems. No reaction was observed at

[*] Dr. S. Doye, Dipl.-Chem. E. Haak, Dipl.-Chem. I. Bytschkov
Institut für Organische Chemie der Universität Hannover
Schneiderberg 1B, D-30167 Hannover (Germany)
Fax: (+49) 511-762-30-11
E-mail: sven.doye@oci.uni-hannover.de

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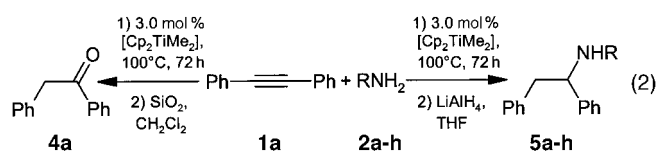


Table 1. $[\text{Cp}_2\text{TiMe}_2]$ -catalyzed hydroamination of diphenylacetylene (**1a**) with various amines [Eq. (2)].

Amine	R	Yield of 4a	Yield of 5
2a	Ph	92 % 75 % ^[a, b]	5a 62 %
2b	2,6-Me ₂ C ₆ H ₃	89 %	5b 68 %
2c	<i>p</i> -C ₆ H ₄ F	93 %	5c 63 %
2d	C ₆ F ₅	23 % ^[b]	
2e	<i>t</i> Bu	91 %	5e 86 % ^[c]
2f	Cy	65 %	5f 86 % ^[c]
2g	<i>n</i> -Hex	19 % ^[b]	
2h	Bn	5 % ^[b, d] 14 % ^[b, e]	5h 3 % ^[b, e]

[a] 0.5 mol % $[\text{Cp}_2\text{TiMe}_2]$. [b] Incomplete reaction. [c] Reduction with 1 bar of H₂ and 5 mol % Pd/C instead of LiAlH₄. [d] 110 °C. [e] 130 °C.

100 °C. At temperatures above 110 °C, the product was formed slowly.

In addition to alkyne **1a**, further alkynes were treated with **2a** in the presence of $[\text{Cp}_2\text{TiMe}_2]$ [Eq. (3)]. The results of the hydrolytical workup are presented in Table 2.

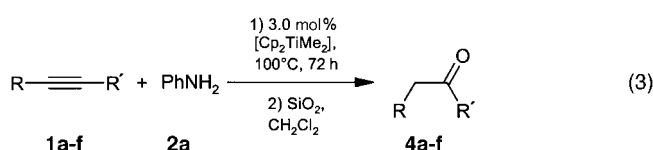


Table 2. $[\text{Cp}_2\text{TiMe}_2]$ -catalyzed hydroamination of various alkynes with aniline (**2a**) [Eq. (3)].

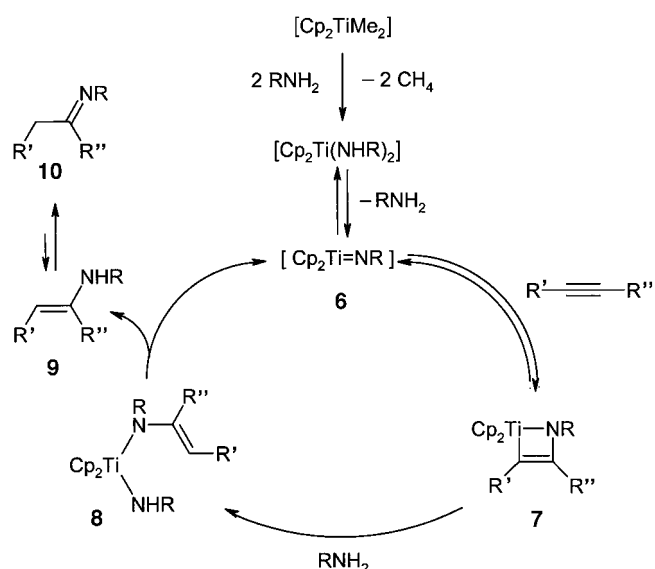
Alkyne	R	R'	Yield of 4
1a	Ph	Ph	4a 92 %
1b	C ₂ H ₅	C ₂ H ₅	4b 30 % ^[a-c]
1c	Ph	CH ₃	4c 99 % ^[d, e]
1d	Ph	C ₂ H ₅	4d 73 % ^[b, d]
1e	Ph	C ₃ H ₇	4e 35 % ^[b]
1f	C ₁₀ H ₂₁	H	4f (detected by NMR)

[a] Yield determined by gas chromatography (GC) with an internal standard. [b] Incomplete reaction. [c] Isolation of the corresponding amine by reduction with LiAlH₄ in 27 % yield. [d] 40 h. [e] 1.0 mol % $[\text{Cp}_2\text{TiMe}_2]$.

Symmetrically substituted bisaryl- and bisalkylalkynes, such as **1a** and 3-hexyne (**1b**), provided access to the corresponding ketones after hydrolysis; however, after the same reaction time the yield for the bisarylalkyne **1a** was 92 %, which is considerably higher than that for the bisalkylalkyne **1b** (30 %). For unsymmetrically substituted alkynes, the regioselectivity of the amine addition was particularly interesting. In the presence of 1.0 mol % catalyst, the alkylarylalkyne 1-phenylpropyne (**1c**) reacted to give a single regioisomer, the anti-Markovnikov product 1-phenylpropan-2-one (**4c**), in 99 % yield. 1-Phenylbutyne (**1d**) and 1-phenylpentyne (**1e**) also gave the anti-Markovnikov products 1-phenylbutan-2-one (**4d**) and 1-phenylpentan-2-one (**4e**) exclusively. How-

ever, the reaction was much slower than that of **1c**. The reaction of terminal alkynes is also possible. In preliminary catalytic experiments with 1-dodecyne (**1f**), followed by hydrolysis with SiO₂, we were able to detect dodecanal (**4f**) in the ¹H NMR spectrum. However, it has not yet been possible to isolate **4f**. In contrast, phenylacetylene (**1g**) and 1-naphthylamine (**2i**) were successfully coupled in the presence of 3.0 mol % catalyst. After subsequent reduction, the anti-Markovnikov addition product 1-*N*-(2-phenylethyl)aminonaphthalene was isolated in 23 % yield; the isomeric 1-*N*-(1-phenylethyl)aminonaphthalene was not detected.

The proposed mechanism of the $[\text{Cp}_2\text{TiMe}_2]$ -catalyzed hydroamination is shown in Scheme 2. It is based on mechanistic studies on the reactivity of zirconocene-imido complexes;^[3] however, it has not yet been verified by experimental data.



Scheme 2. Postulated mechanism of the $[\text{Cp}_2\text{TiMe}_2]$ -catalyzed hydroamination of alkynes.

We assume that $[\text{Cp}_2\text{TiMe}_2]$ reacts with the amine to form the catalytically active titanium-imido complex **6**, which then undergoes a [2+2] cycloaddition with the available alkyne. The resulting azatitanacyclobutene **7** is then irreversibly protonated by further amine to form the bisamide **8**, which is then thermally cleaved into enamine **9** and the catalytically active species. Finally, enamine **9** is converted into imine **10** under the reaction conditions.

In conclusion, dimethyltitanocene is a widely applicable, inexpensive catalyst of low toxicity that can be used in intermolecular hydroamination reactions of alkynes. With this catalyst, primary aryl- and alkylamines can be coupled to symmetrically and unsymmetrically substituted alkynes. In the case of unsymmetrically substituted alkynes, the reaction occurs with high regioselectivity, forming the anti-Markovnikov products exclusively. Further work to optimize the reaction is currently underway. These studies will include the use of substrates bearing various functional groups.

Experimental Section

All experiments were carried out under argon with the exclusion of air and moisture in Schlenk tubes sealed by Teflon stopcocks. The chemicals used were dried and purified according to the standard procedures and stored under argon. $[\text{Cp}_2\text{TiMe}_2]$ was synthesized according to ref. [8]. All the products were identified by comparison with authentic samples (^1H NMR, MS, TLC). PE: light petroleum (b.p. 40–60 °C), EA: ethyl acetate.

Reaction of **1a** with **2a**: Alkyne **1a** (513 mg, 2.88 mmol) and amine **2a** (224 mg, 2.40 mmol) were dissolved in toluene (2.0 mL) under argon. After addition of a solution of $[\text{Cp}_2\text{TiMe}_2]$ (0.48 mL, 0.15 mol L⁻¹, 0.072 mmol, 3.0 mol %) in toluene the mixture was heated at 100 °C for 72 h in a closed Schlenk tube.

a) Isolation of the imine **3a**: The dark brown reaction solution was concentrated under vacuum. The residue was taken up in the minimum amount of methanol and then filtered. The light yellow filtrate was cooled to -30 °C, and light yellow crystals of **3a** precipitated. Yield: 341 mg (1.26 mmol, 52 %).

b) Isolation of the ketone **4a**: The reaction solution was treated with CH_2Cl_2 (10 mL) and silica gel (4.0 g). The mixture was stirred for 2 h at room temperature and then filtered. The filtrate was then concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel (PE:EA, 10:1) to give **4a**. Yield: 432 mg (2.20 mmol, 92 %).

c) Isolation of the amine **5a**: At 0 °C, the reaction solution was carefully added to a suspension of LiAlH_4 (137 mg, 3.61 mmol) in THF (10 mL) and the mixture was refluxed for 3 h. After cooling to 0 °C, the excess LiAlH_4 was hydrolyzed with iced water and the precipitate was dissolved by dropwise addition of NaOH (2.0 M). The mixture was then extracted three times with CH_2Cl_2 . The combined organic phases were washed with water, dried (MgSO_4), and concentrated on a rotary evaporator. Column chromatography of the residue on silica gel (PE:EA, 10:1) gave **5a**. Yield: 406 mg (1.49 mmol, 62 %).

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Catalytic, Regiospecific End-Functionalization of Alkanes: Rhenium-Catalyzed Borylation under Photochemical Conditions**

Huiyuan Chen and John F. Hartwig*

The end-functionalization of alkanes remains an important, unsolved problem in chemistry.^[1, 2] Although C–H bond activation by transition metals has been known for decades, there are few reactions that selectively functionalize alkanes using catalytic amounts of transition metals. For example, metal-catalyzed oxidations are notoriously unselective with linear alkanes.^[3, 4] Photochemical carbonylations can give high, but not exclusive, selectivity for terminal products when catalyzed by $[\text{RhCl}(\text{CO})(\text{PMe}_3)_2]$,^[5, 6] and the product yields are limited by unfavorable thermodynamics.^[5] Most recently, terminal olefins have been generated as the dominant product of dehydrogenation with a sacrificial hydrogen acceptor at early reaction times,^[7] but this chemistry provides mixtures of alkenes at high conversions in the absence of acceptor.^[8, 9]

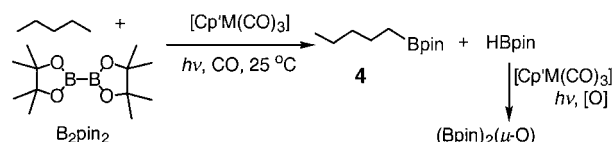
We have previously reported that monoboryl complexes of tungsten functionalize alkanes stoichiometrically.^[10] Regeneration of the boryl complex from the accompanying metal hydride and dimeric metal carbonyl products in this system requires several steps and external reagents, which prohibits catalytic functionalization. Thus, we have sought a related but alternative approach to catalytic borylation of alkanes. We report here a rhenium-catalyzed process that produces terminal organoborane products from alkanes and 4,4',4'',5,5',5''-octamethyl-2,2'-bi-1,3,2-dioxaborolane (B_2pin_2) under photochemical conditions. Organoboranes are established, versatile synthetic intermediates that can be converted into alcohols, amines, halocarbons, aldehydes, and alkylarenes without loss of regiochemistry.^[11]

Our initial studies employed stoichiometric amounts of $[\text{Cp}'\text{M}(\text{CO})_3]$ (**1**: $\text{Cp}' = \text{C}_5\text{H}_4\text{Me}$, $\text{M} = \text{Mn}$; **2**: $\text{Cp}' = \text{C}_5\text{H}_5$, $\text{M} = \text{Re}$; **3**: $\text{Cp}' = \text{C}_5\text{Me}_5$ (Cp^*), $\text{M} = \text{Re}$) to determine whether alkane functionalization would occur with these complexes and whether the reaction would consume the starting complex or regenerate it to allow for catalysis. Irradiation of B_2pin_2 alone in neat pentane with a 450-Watt medium-pressure Hanovia mercury arc lamp gave no reaction, but irradiation of B_2pin_2 in the presence of complexes **1**, **2**, or **3** produced 1-pentylboronate ester **4** (Scheme 1), the product of alkane functionalization in the terminal position.^[12] HBpin, which decayed to $(\text{Bpin})_2(\mu\text{-O})$ during the reaction, was the accompanying product. Yields of HBpin were determined by addition of benzaldehyde to form the pinacol benzyloxyl-

[*] Prof. J. F. Hartwig, Dr. H. Chen
Department of Chemistry, Yale University
P.O. Box 208107, New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-6144
E-mail: john.hartwig@yale.edu

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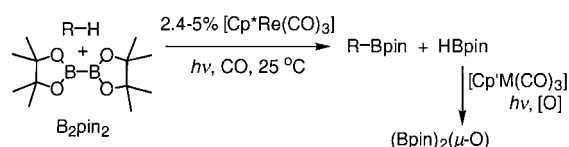
 Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 1. Stoichiometric reaction of B_2pin_2 with $[Cp^*M(CO)_3]$ in pentane. $Cp^* = C_5H_5$, C_5H_4Me , C_5Me_5 ; $M = Mn$, Re .

borate, which was quantified by ^1H NMR spectrometry. Although the formation of **4** from these reactions was encouraging, the functionalized product was produced in only 35% yield for reactions with manganese complex **1** and in 50% yield for those with rhenium complex **2**. Reactions using Cp^* complex **3** produced **4** in quantitative yields, but only 17% of the rhenium complex was regenerated.

The presumed $[Cp^*Re(CO)_n]$ intermediates that would result from extrusion of the borane products are known to form stable bridging carbonyl dimers.^[13] Thus, we conducted reactions under CO in hopes of regenerating $[Cp^*Re(CO)_3]$ instead of forming catalytically inactive species. Indeed, irradiation of B_2pin_2 in pentane under 2 atm of CO in the presence of 2.4 mol % of **3** produced **4** in 95% yield (NMR spectroscopy; isolated in 65% yield; Scheme 2, $R = n-C_5H_{11}$).^[12a] Entries 1–3 of Table 1 show the results for



Scheme 2. Reaction of B_2pin_2 in pentane catalyzed by $[Cp^*Re(CO)_3]$. $Cp^* = C_5H_5$, C_5H_4Me , C_5Me_5 ; $M = Mn$, Re ; $R = n-C_5H_{11}$, $i-C_5H_{11}$, $CH_2C_6H_{11}$.

reactions of B_2pin_2 with a variety of alkanes catalyzed by $[Cp^*Re(CO)_3]$ to produce primary alkylboronate esters. In the absence of added CO, the reaction of B_2pin_2 in pentane with 5% $[Cp^*Re(CO)_3]$ produced **4** in only 22% yield; 72% of the B_2pin_2 remained, and all of the catalyst had been consumed.

Table 1. Regiospecific, catalytic functionalization of alkanes, alkyl ethers, and benzene.^[a]

En- try	Substrate	Catalyst (amount [%])	t [h]	Conv. of B_2pin_2 [%]	Yield [%] RBpin	HBpin
1	<i>n</i> -pentane	3 (2.4)	56	94	95 (4)	32
2	2-methylbutane	3 (3.4)	55	89	83 ^[b]	24
3	methylcyclohexane	3 (5.0)	60	88	75 (6)	27
4	di- <i>n</i> -butyl ether	3 (5.0)	45	100	100 (7)	23
5	<i>tert</i> -butyl ethyl ether	3 (4.9)	46	100	82 (8)	26
6	benzene	1 (10)	36	97	76 (9)	23
7	<i>n</i> -pentane	10a (2.5)	56	92	97 (4)	31

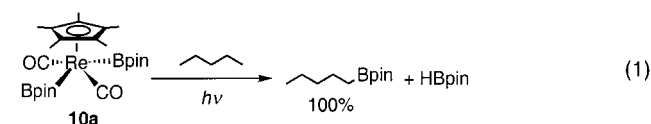
[a] A solution in pentane containing $[Cp^*Re(CO)_3]$, dodecahydrotriphenylene (internal standard), B_2pin_2 , and CO (2 atm) was irradiated with a Hanovia medium-pressure mercury arc lamp. Yields were determined by GC or ^1H NMR spectroscopy, and yields of isolated products were determined after purification by chromatography on silica gel eluting with pentane or pentane/diethyl ether.

[b] The two terminal regioisomers **5a** and **5b** were obtained in a 3.6:1 ratio.

All reactions of B_2pin_2 with alkanes were remarkable in their regiospecificity for the functionalization of primary sites. Reaction with pentane produced a single functionalized product **4**. None of the internal isomers, which were prepared by independent synthesis, were detected by GC/MS. Reaction with isopentane also produced only terminal substitution products, 3-methyl-1-butylboronate ester (**5a**, 65%) and 2-methyl-1-butylboronate ester (**5b**, 18%).^[14] Reaction with methylcyclohexane produced 1-cyclohexyl-1-methylboronate ester (**6**) in 75% yield. Some regioisomeric products were observed in this case, but taken together they constituted less than 1% yield. The low reactivity of these catalysts for secondary C–H bonds was underscored by the rhenium-catalyzed reaction of B_2pin_2 with cyclohexane, which gave no alkylboronate ester and only a trace amount of HBpin.

Ether substrates also underwent borylation at the termini of aliphatic substituents (Table 1, entries 4, 5). The photochemical reaction of B_2pin_2 in *n*-butyl ether with 5% catalyst produced the 4-butoxy-1-butylboronate ester **7** in quantitative yield (NMR spectrometry; isolated in 55% yield). A similar reaction with the unsymmetrical *tert*-butyl ethyl ether produced product **8** in 82% yield (NMR spectroscopy; isolated in 75% yield) from functionalization at the terminal position of the ethyl group. The selectivity toward other regioisomers was greater than 350:1. The reaction of benzene with B_2pin_2 was effectively catalyzed by manganese complex **1** under 2 atm of CO to form the phenylboronate ester **9** in good yield (Table 1, entry 6).

trans- $[Cp^*Re(CO)_2(Bpin)_2]$ (**10a**) was isolated from the reaction of B_2pin_2 with $[Cp^*Re(CO)_3]$ in cyclohexane; *cis*- $[Cp^*Re(CO)_2(Bpin)_2]$ (**10b**) was observed at early reaction times. Both pure **10a** and mixtures of the *cis* and *trans* isomers catalyzed the photochemical borylation of pentane in the same manner as $[Cp^*Re(CO)_3]$ (Table 1, entry 7). Moreover, the stoichiometric reaction of **10a** in pentane led to the regiospecific formation of boronate ester **4** in quantitative yield [Eq. (1)]. These results suggest that the reaction



involves initial oxidative addition of the diboron compound followed by C–H activation and functionalization of the alkane (Scheme 3). After photochemically induced CO dissociation,^[15] the C–H activation of pentane by **10a** or **10b** could occur by oxidative addition to generate a Re^V intermediate or by σ -bond metathesis involving Re^{III} (as shown in Scheme 3).^[16] An alternative catalytic cycle could involve initial oxidative addition of the alkane and subsequent reaction of the alkylrhenium hydride with B_2pin_2 . This pathway is not ruled out by our data, but is less likely considering the isolation of **10a** and **10b**, their conversion into the products of the catalytic process, and the known thermal instability of $[Cp^*Re(CO)_2(H)(CH_3)]$.^[17]

Preliminary studies to determine the origin of the regio-specificity were conducted. Specifically, we probed for metal-catalyzed conversion of internal activation products into the

more thermodynamically stable terminal products.^[18] To do so, we added the pinacol ester of 2-butylboronic acid to the catalyzed reaction of B_2pin_2 with pentane. The 2-butylboronate ester remained unchanged during the formation of **4**, ruling out isomerization of products formed from initial functionalization of the secondary C–H bonds to end-functionalized products. Therefore, the terminal boronate esters are kinetic products, and the selective functionalization most likely results from a regiospecific reaction of the rhenium bis-boryl complex with the alkane primary C–H bond. Higher reactivity of primary over secondary C–H bonds has been observed in stoichiometric oxidative addition and σ -bond metatheses.^[16, 19]

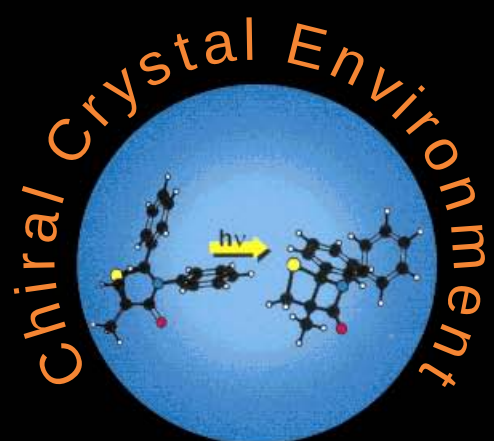
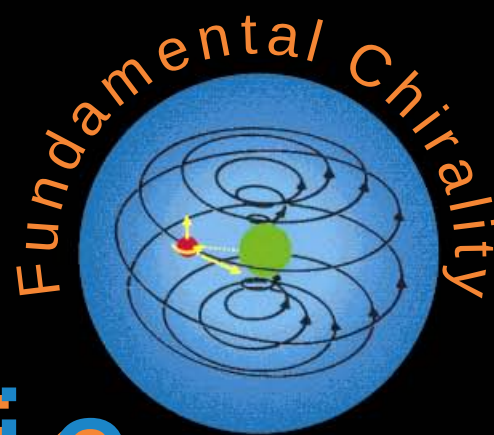
Experimental Section

benzaldehyde in toluene and placed into an NMR tube. The solution was frozen, the system was evacuated, and the sample tube was flame-sealed before heating at 100 °C for 10 h. HBpin was quantitatively converted into pinacol benzoyloxylborate, whose yield was determined by ¹H NMR spectroscopy (32 % for the reaction of B₂pin₂ with pentane). Product **4** was isolated in 65 % yield by chromatography on silica gel of a reaction mixture generated by a similar procedure using 5 mol % catalyst.

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Absolute Asymmetric Synthesis



Absolute Asymmetric Synthesis: The Origin, Control, and Amplification of Chirality

Ben L. Feringa* and Richard A. van Delden

Dedicated to Professor Hans Wynberg

One of the fundamental and intriguing aspects of life is the homochirality of the essential molecules. From the early days of stereochemistry, the origin of chirality in biological systems has been a challenge to the chemical sciences and numerous theories and experiments have been reported. Despite the great progress in asymmetric synthesis, there are only a few genuine absolute asymmetric syntheses known

today. Novel approaches based on the interplay of molecular biology, organic chemistry, and supramolecular sciences have resulted in synthetic molecules that show amplification, autocatalysis, or self-replication and these systems are pertinent to the question as to how to amplify a small stereochemical bias. In this review absolute asymmetric synthesis—including many failures towards this goal—will be dis-

cussed with the emphasis on photochemistry with circularly polarized light and conversions in chiral crystals. Amplification mechanisms through autocatalytic systems, liquid crystalline materials, and polymers will also be described.

Keywords: asymmetric amplification
• asymmetric synthesis • autocatalysis
• chirality • circularly polarized light

1. Introduction

“...do not let your left hand know what your right hand is doing, so that your giving may be a secret...”

Matthew 6:3

Most confrontations with chirality (Greek: *χείρ* (cheir) = hand) in daily life, such as putting on one's shoes or shaking hands, enjoying the taste of an artificial sweetener in a soft drink, or admiring the right-handed spiral of a snail or the bindweed in the garden, go unnoticed. Although there is no apparent direct relationship between this macroscopic chirality and chirality at the molecular level it is generally accepted that homochirality of the essential molecules is one of the most fundamental aspects of life on the Earth.^[1]

The sugars such as deoxyribose and ribose in DNA and RNA, respectively, that contain and transfer the genetic information are all right-handed and the 20 amino acids (except for glycine) that form the proteins that are essential for the structure and chemical transformations in cells also

share a common relative configuration.^[2] Without uniform chirality in the monomeric units that build the biopolymers, the enzymes that catalyze the chemical conversions in the organism and the numerous chiral compounds that are involved in recognition or information processing, such as hormones, current life forms could not exist. The realization of the essential role of supramolecular chirality (and the information content) associated with the DNA helix or the α -helix of proteins makes it difficult to comprehend how the biopolymers composed of D and L monomers could function.

Despite the fact that 150 years have past since Louis Pasteur conducted his famous experiments on the resolution of tartaric acids^[3, 4] the origin of chirality in biomolecules is still one of the great current mysteries.^[5, 6] The fundamental problems with the generation of asymmetry at the molecular level as well as the expression at the supramolecular and macromolecular level are usually associated with the quest for molecular evolution and the origin of life.^[7] Homochirality is thus displayed at the molecular level with large terrestrial excesses of L-amino acids and D-sugars over their enantiomers. The questions as to where biomolecular chirality, or rather biomolecular homochirality, originates from and at what stage in the evolutionary process homochirality took over, have however not yet been answered.^[5-8]

Several theories have been proposed that explain the chirality of biomolecules on physical grounds. Attempts to mimic the terrestrial chemical composition at a prebiotic stage

[*] Prof. Dr. B. L. Feringa, Drs. R. A. van Delden
Department of Organic and Molecular Inorganic Chemistry
University of Groningen
Nijenborgh 4, 9747 AG Groningen (The Netherlands)
Fax: (+31) 50-3634296
E-mail: feringa@chem.rug.nl
delden@chem.rug.nl

on a laboratory scale do not show any evolution of homochirality whatsoever, because of the short time scales studied and also because of the difficulties associated with these type of experiments.^[9] A model system for the scrupulous experimental demonstration of the naturallike selection of L-amino acids and D-sugars remains to be developed.^[10] Nevertheless, despite a good mechanistic knowledge, many attempts were, and are increasingly, made to imitate nature's ability to induce homochirality from scratch. Pasteur tried to grow chiral crystals in a magnetic field following Faraday's discovery of magnetically induced optical activity.^[11, 12] The negative results did not discourage him from trying related experiments, such as attempts to induce optical activity by performing reactions in a centrifuge or even rotating growing plants, to modify the optical activity of natural products that were produced. Although all these attempts failed to form enantiomerically enriched products from achiral precursors, he stressed the essence of optical activity and molecular dissymmetry for life and beyond:

"L'univers est dissymétrique"

With the stereochemical analysis of Le Bel and Van't Hoff as a basis,^[13] it was Emil Fischer who demonstrated that a "dissymmetric force" is not required to generate optically active molecules in living organisms.^[14] It was shown that the asymmetry inherent in an optically active molecule can control the asymmetry in subsequent reactions and the proposal was made that in the conversions of chiral compounds the "lock and key" principle provides a mechanism for stereochemical selection in nature.^[15] Despite the fact that with this landmark achievement the transfer of chiral

information within one molecule or from one molecule to the other is rationalized, it did not provide answers to the following questions: a) what is the origin of the biomolecular chirality; b) why is there a chiral bias for L-amino acids and D-sugars; and c) how can an amplification of an apparently small initial enantiomeric excess be achieved? The formation of enantiomerically enriched products from achiral precursors without the intervention of pre-existing optical activity, namely absolute asymmetric synthesis and the amplification of chirality, is still a challenging opportunity for many scientists.

In this review we summarize the current status of absolute asymmetric synthesis with a focus on recent enantioselective conversions of organic molecules. Excellent reviews and book chapters on various aspects of the origin of chirality in nature and earlier work on absolute asymmetric synthesis and self-replication and amplification have been published.^[4–9] Recently, the physical aspects of absolute asymmetric synthesis were reviewed.^[16] Herein, main features will be discussed as well as new developments in autocatalysis and amplification mechanisms pertinent to absolute asymmetric synthesis.

2. Chirality in Nature

2.1. Terrestrial Origin

Until 1957 it was thought that nature was symmetric at the atomic level. Biochemical homochirality was therefore assumed to be generated by spontaneous symmetry breaking, with the naturally observed preference for L-amino acids and D-sugars being purely coincidental. An alternative explanation for biochemical homochirality was provided by the

Ben L. Feringa received his PhD degree from the University of Groningen in 1978 with Professor Hans Wynberg. He was a research scientist with Royal Dutch Shell, both at the research center in Amsterdam and at the Shell Biosciences Laboratories at Sittingbourne, UK, from 1978 to 1984. He joined the department of chemistry at the University of Groningen in 1984 as a lecturer and was appointed professor at the same university in 1988. He was visiting professor at the University of Leuven, JSPS fellow, and 1997 recipient of the Pino gold medal of the Italian Chemical Society. His research is mainly focused on stereochemistry and his present research interests include organic synthesis, homogeneous (asymmetric) catalysis, molecular switches, self-assembly, and new organic materials.



B. L. Feringa



R. A. van Delden

Richard A. van Delden was born in 1974. He started his studies in the group of Professor B. L. Feringa at the University of Groningen in 1994 on the excited-state properties of chiroptical molecular switches based on sterically overcrowded alkenes. In 1996 he spent six months in the group of Professor M. M. Green, Brooklyn Polytechnic University, performing research on the chiral properties of binaphthalene solubilized in aqueous polymer solutions. On the basis of these projects he received his B. A. in organic chemistry with honors in 1997. In the same year he started a PhD study under the guidance of professor B. L. Feringa on aspects of chirality in different helical-shaped molecules both in solution as well as in organized media, with the chiroptical molecular switches as a basis. His research interests include physical properties, such as circular dichroism and fluorescence, of organic molecules and organic molecular devices in the broadest sense—from total synthesis to application.

action of an external dissymmetric force and Le Bel and van't Hoff had already made the suggestion of asymmetric photosynthesis through irradiation with circularly polarized light (CPL).^[13, 17]

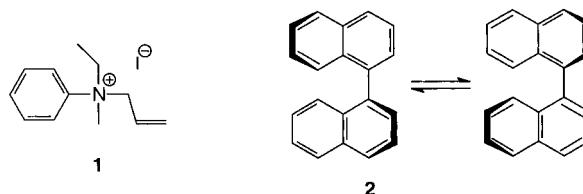
Bonner considers “random mechanisms” and “determinate mechanisms” to distinguish the random generation of either enantiomer of a chiral compound or a process that yields a single enantiomer with a predetermined handedness.^[18] But irrespective of the mechanism that created a chiral bias in nature, a fundamental question is at what stage in evolution did molecular asymmetry become a crucial factor. Were primitive life forms, with both D- and L-building blocks available, developed first and did homochirality provide a distinct advantage during the next stage in early biological evolution, or was homochirality a consequence of chemical evolution and a requirement for the evolution of life? In the first case it is conceivable that enantiomorphous primitive life forms could have developed at different places and that in the course of the evolutionary process these became extinct.

It is now generally accepted that homochirality did not have a biogenic origin.^[18, 19] Homochirality of the monomers is a prerequisite to form the folded structures of a peptide (for example, the α -helix) essential for the catalytic function of enzymes and the double helix of DNA that is essential for replication. In a number of experiments it has been demonstrated that the formation of oligonucleotides and of polypeptide α -helices only proceed effectively and in a stereoregular manner with enantiomerically pure monomers. For instance, it was recently shown by Eschenmoser et al., using pyranoside nucleotides, that the corresponding tetranucleotide cyclophosphates can assemble into oligomers of 36 nucleotides in length.^[20] Oligomers that have the same chirality as the template are exclusively joined leading to a stereoselective oligomerization. When a D-ribopyranosyl unit at any position of the homochiral tetramer was replaced by the corresponding L-unit a reduction in the rate of oligomerization by two orders of magnitude was observed. These findings imply that the “per force” generation of homochiral states is well feasible.

There is considerable experimental evidence for the random generation of optical active organic molecules. Spontaneous generation of optical activity without any chiral bias has been observed in the spontaneous resolution of various racemic compounds and in the preferred crystallization of one of two rapidly interconverting enantiomers from solution.^[21] In the first case, the racemic compound forms a conglomerate, that is mixtures of equal amounts of the crystals of the enantiomers.^[22] Preferential crystallization of one form or any other mechanism for separation might lead to a certain enantiomeric excess. The normally entropically disfavored generation of optical activity is made possible by the enthalpy gained in going from a homogeneous to a heterogeneous system. It was, for example, shown that NaClO₃ forms chiral crystals and when strong stirring was used crystals showing exclusively one optical rotation were obtained.^[23]

Preferential enantiomorphous crystallization might result in single enantiomers provided inversion of configuration is fast relative to the rate of crystallization. In a pioneering contribution Havinga described the “spontaneous asymmetric

synthesis” in the crystallization of allylethylmethylphenylammonium iodide (**1**).^[24] A high bias for one enantiomer was obtained because of a simultaneous interconversion between both stereoisomers in solution. One of the most striking and experimentally useful examples of spontaneous generation of optical activity is the production of enriched binaphthalene (**2**) by suddenly cooling a small portion of its melt, where racemization of the compound is rapid.^[25]



Spontaneous resolution by chiral crystal formation from achiral molecules has been reported for divinylbenzene, dibenzobarrelene, diacylperoxide, and tri-*o*-thymotide.^[26] It should be noted that in all these cases the chiral selection of one of the two enantiomers is purely a matter of chance.

Throughout the years, the stereoselective adsorption of one of the enantiomers of racemic compounds on quartz has been advocated as a mechanism to generate a chiral bias in nature. Many prior results have proved to be erroneous, but the experimental proof for asymmetric absorption of racemic amino acids on quartz was given by Bonner et al.^[27] As the abundance of left- and right-handed quartz on the earth is equal, the preferential chiral absorption seems an unlikely mechanism to explain prebiotic homochirality.^[28] Of course, this racemic net distribution of terrestrial quartz does not preclude the absolute asymmetric synthesis on a single site.

Despite the fact that these types of mechanisms of spontaneous resolution very inefficiently account for the genesis of materials of nature with a single sense of chirality (for example, no preference for one of two possible enantiomers is expected), the experiments show that a dissymmetric force need not to be present to generate optical activity. Spontaneous chiral crystallization can provide an explanation for biohomochirality. Another possible explanation assumes chiral symmetry exists at the fundamental level and concerns symmetry breaking as a result of an autocatalytic mechanism based on a fluctuating racemic state (see below). One could question whether this would eventually lead to homochirality. It should be noted that recently Siegel reported a paper that places in perspective how natural fluctuations from a perfect racemic state in combination with evolutionary pressures eventually could lead to homochiral molecules.^[29]

2.2. Extraterrestrial Origin

In recent years there has been a growing notion that the deposition of nonracemic materials from extraterrestrial origin on the Earth might have been the source that led to the uniform homochiral compounds essential in prebiotic evolution. Most notable in this respect is the isolation of L-alanine with a significant enantiomeric excess from the

Murchison meteorite that landed on Australia in 1969.^[30] Recently, optically active α -alkylated (unnatural) amino acids were also isolated from the meteorite, thus providing strong evidence against terrestrial contamination.^[31] By combining these findings with the exciting discovery of intense sources of circular-polarized radiation in the cosmos,^[32] one realizes that it is highly feasible that asymmetric photolysis of organic material in interstellar clouds produces enormous quantities of optically active molecules. Even if further experimental proof can be obtained, the question of the preferred handedness in nature still remains. For extensive discussions on the extraterrestrial origin of homochirality the reader is referred to several papers and monographs.^[5, 6, 18, 33]

3. The Weak Force

3.1. Parity Violation

In 1957 parity violation (namely, a different probability for the occurrence of a process and its mirror image), as proposed by Lee and Yang,^[34] was discovered in the weak nuclear force (the fourth type of force, next to gravity, electromagnetism, and the strong nuclear force, through which elementary particles interact with each other).^[35] This discovery led to the experimental observation that the β -particles emitted from radioactive nuclei have an intrinsic asymmetry: left-handed (*L*)-electrons are preferentially formed relative to right-handed (*R*)-electrons.^[36] The major consequence of this finding is that chirality exists at the level of elementary particles. Until the late 1960s it was assumed that parity violation was confined to nuclear reactions, but then a theory was developed that unified the weak and electromagnetic forces.^[37] According to this theory, an electro-weak force between the electrons on one hand and the protons and neutrons of an atom on the other, which does not conserve parity, exists (the *Z* force). It is predicted that the weak nuclear force should be able to discriminate between mirror images not only through the weak charged currents (*W* force) responsible for the observed nonconservation of parity in β -decay, but also through weak neutral currents (*Z* force). This situation is indeed found.^[38] The *W* force is zero for (*R*)-electrons and nonzero for (*L*)-electrons, while β -decay produces mostly (*L*)-electrons as shown by experiment (measurements on positrons, the positively charged analogues of electrons, show mostly (*R*)-positrons being produced).^[39] For the *Z* force, the (*L*)- and (*R*)-electrons have charges of opposite sign and nearly equal magnitude. This difference in sign causes (*R*)-electrons to be attracted to the nucleus and (*L*)-electrons to be repelled.

Two important consequences of the weak *Z* force between electrons and nuclei that pertain to our discussion are: a) all atoms are chiral and b) a chiral molecule exists in a lower or higher energy state relative to its enantiomer. This parity violation results in an energy difference between two species, which for practical reasons are considered to be enantiomers. The concept of enantiomers, however, implies precise mirror images and the true enantiomer of a chiral compound is in fact a compound with the opposite absolute configuration that is

composed of antiparticles; this compound then has exactly the same energy as the original molecule.^[40] There is no fundamental rationale as to why chirality at such an elementary level is present.

3.2. Absolute Asymmetric Synthesis Using Fundamental Chirality

A few ways by which the parity violating weak force can cause enantioselectivity, which might eventually pave the way to the origin of bihomochirality, have been proposed, although not supported experimentally.^[41] Firstly, the excess (*L*)-electrons produced by β -decay emit left-handed electromagnetic radiation and this could cause the preferential decomposition of one stereoisomer in a racemate and leave a net excess of its enantiomer.^[42] Secondly, β -particles themselves can decompose chiral molecules directly. Calculations as well as experiments,^[43, 44] however, showed that enantiomeric excesses of less than one part in 10^9 are obtained with such decompositions. A third possibility would be that the *Z* force itself affects the production of either *D*- or *L*-amino acids by stabilizing one enantiomer over the other. Calculations show that the magnitude of the parity violation energy (E_{pv} , the difference in the parity violation energy between two enantiomeric structures as a consequence of the *Z* force) is about $5.2 \times 10^{-16} \text{ J mol}^{-1}$ for steroid analogue **3** and 1.04×10^{-13} for a 10° twisted ethylene (**4**; Figure 1).^[45]

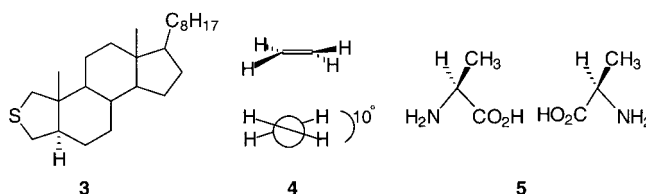


Figure 1. Structures for which E_{pv} has been calculated.

Furthermore a value of $6.5 \times 10^{-14} \text{ J mol}^{-1}$ was found for a specific conformation of alanine (**5**) in water with the naturally abundant *L* enantiomer having the lower energy.^[46] An enantiomeric excess of about one in 10^{17} is expected from this energy difference. Although this value is smaller than a random deviation from a racemic state, it is striking that the *Z* force clearly governs a small bias for the naturally occurring *L*-amino acid. A direct estimate for the energy difference (E_{pv}) for sugars has not yet been reported, but it should be noted that the naturally occurring *D*-sugars are chemically correlated to the *L*-amino acids through the conversion of *D*-glucosamine to *L*-alanine.^[47]

Some attempts were made to perform absolute asymmetric syntheses (in fact degradation) using the fundamental chirality of β -decay.^[48] Initial results of ten different radiolysis reactions with a variety of β -emitters, however, showed no optical activity in the products.^[49] These negative results are presumably a result of very low polarization at higher wavelengths since the degree of circular polarization of β -rays falls off with an increase in wavelength.^[50] Subsequent experiments with longitudinally polarized electrons from a

linear accelerator showed a slight preference in the degradation of the D isomer of racemic leucine.^[51] A chiral discrimination of up to 1.4 % is observed. The chirality induced by β -decay will only be significant for absolute asymmetric synthesis if it can be combined with an amplification mechanism (see below). Any future application of these techniques on a laboratory time scale therefore does not seem very likely.

4. Physical Forces

4.1. Absolute Asymmetric Synthesis Using Physical Forces

Numerous attempts to induce absolute asymmetric synthesis using a physical force have been described. Experiments to induce photochemical asymmetric synthesis using linearly polarized light in the presence of a magnetic field were reported as early as 1939.^[52] The very low optical yields found in these reactions were however shown to be irreproducible.^[53] This actually has been the case all through this century, as no unequivocally absolute asymmetric synthesis using chiral field effects (except for circularly polarized light, see below) has yet been described. Dougherty and co-workers performed absolute asymmetric epoxidations of isophorone using hydrogen peroxide in vessels rotating in the Earth's gravitational field and found optical rotations in the range of 0.001 – 0.017° .^[54] These optical rotations were dependent on the rotation rate of the vessel and were only found when vertical rotations were employed. Clockwise and counterclockwise rotation resulted in opposite optical rotations of the epoxide.

This research group also performed an absolute asymmetric epoxidation of stilbene and a reduction of 1-bromo-1-methyl-2,2-diphenylcyclopropane in a magnetic field oriented in various orientations relative to the Earth's gravitational field that gave optical rotations of maximal 0.01° .^[55] Their data were, however, later refuted on theoretical grounds (see below).^[56] Later attempts to achieve absolute asymmetric synthesis as well as preferential crystallization in this kind of chiral gravitational field (using strong stirring either clockwise or counterclockwise in the Earth's gravitational field) showed no optical activity in the products.^[57] Honda and Hada did find optical activity of a J-aggregate of the 1,1'-diethyl-2,2'-cyanine chloride product in a reaction induced by conical swirling,^[58] but the observed optical activity was later attributed to an artifact.^[59]

Perhaps the most discussed chiral physical field in the context of potential use in absolute asymmetric synthesis is a magnetic field parallel to an electric field. In 1893 Curie stated that a magnetic field parallel to an electric field appears to generate chirality because the indistinguishable parallel and antiparallel arrangements are interconverted by the operation of parity (space inversion) just like mirror-image forms of a molecule.^[60] In 1975 Gerike reported the first example of such an absolute asymmetric synthesis.^[61] Six different reactions were tested in both stationary and alternating magnetic and electric fields and all attempts gave some optical rotation that seemed to be opposite in sign for parallel and antiparallel

arrangements of the fields, but according to the author this might have been coincidental. Furthermore, the optical rotations that were observed could not be reproduced. Gerike's results were also later rejected on theoretical grounds; no combination of a uniform and constant electric and magnetic field can induce an asymmetric bias into reactions going to completion (see below).^[62]

This is only one example of a disputed absolute asymmetric synthesis in magnetic fields. In 1986 Takahashi and co-workers claimed an asymmetric electrochemical reduction in a magnetic field in the case of the conversion of phenylglyoxylic acid into mandelic acid using NADH.^[63] An excess of D-mandelic acid (up to 21 %, depending on pH) was found in all cases. Surprisingly, this was independent of the orientation of the magnetic field and proportional to the magnetic flux density. As a consequence of the failure of the reversal of the magnetic field to reverse the asymmetric effect (which is completely without theoretical explanation) Bonner decided to try to reproduce these results and was not successful. It was concluded that Takahashi's results must be a result of an experimental artifact.^[64]

More recently a spectacular example of an enantioselective reaction in a static magnetic field was reported by Zadel and co-workers.^[65] Enantiomeric excesses ranging from 11 up to 98 % were claimed in a static magnetic field of 0.43 – 2.1 T for the reactions of aromatic aldehydes and ketones with Grignard reagents and LiAlH_4 , respectively. It was however unpredictable as to which enantiomer predominated in each experiment. Intrigued by the high levels of enantioselectivity and the simplicity of the asymmetric synthesis using some of the most common organic reactions, several groups engaged in experiments to reproduce the stereoselectivity. All attempts to reproduce these results failed and it turned out that the observed enantiomeric excesses were a result of the deliberate seeding of the reaction mixtures with an optically active compound before work-up.^[66, 67]

4.2. Chirality Aspects of Physical Forces

To see whether or not it is possible to perform absolute asymmetric synthesis using physical forces it is necessary to take a close look at the chirality aspects of these forces. In 1977 it was already stated that a simultaneous application of a uniform and constant electric and magnetic field can not affect the equality of the enantiomeric population (50:50) in a racemic mixture at equilibrium.^[62, 68] This argument is based on symmetry operations of the system. It appears that even though a colinear arrangement of electric and magnetic fields is chiral in the sense that it has a mirror image in which it is converted by space inversion, both arrangements can also be interconverted by time reversal. In 1986 Barron proposed a more general theory about chirality by stating that there are physical systems that exist as two mirror images yet are not truly chiral in a fundamental sense because dissymmetric systems are not necessarily chiral when motion is concerned.^[69] Barron introduced the terms "true" and "false" chirality to indicate time-invariant and time-noninvariant enantiomorphism, where "true" chirality is only possessed by

systems that exist in two distinct enantiomeric states that are interconverted by space inversion but not by time reversal combined with any proper spatial rotation. This distinction is illustrated for a simple system of rotating cones in Figure 2.

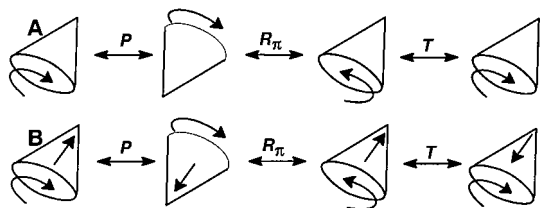


Figure 2. Representation of "True" (B) and "false" chirality (A). (From reference [69].)

A rotating cone (A) exists as two mirror-image states interconverted by space inversion (P). Time reversal (T) combined with a 180° spatial rotation (R) also interconverts these two states, which indicates "false" chirality. When this rotating cone also displays a translation motion (B) along the axis of spin the two mirror-image states that exist are again interconverted by P . In this case, however, a combined application of T and R does not interconvert these two states, which indicates "true" chirality. This explanation is of course not restricted to conical shapes and is valid for all combinations of translation and rotation as long as the translation is along the spin axis.

The same argument holds for a parallel arrangement of an electric field E —a time-even polar vector—and a magnetic field B —a time-odd axial vector. The time-even polar E vector changes sign under space inversion but is time-invariant, while the time-odd axial B vector is time-non-invariant but does not change sign under space inversion (Figure 3). In this case time reversal combined with a 180° spatial rotation has the same effect as space inversion, which indicates "false" chirality.

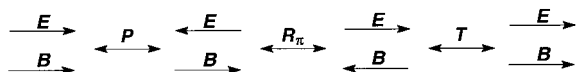
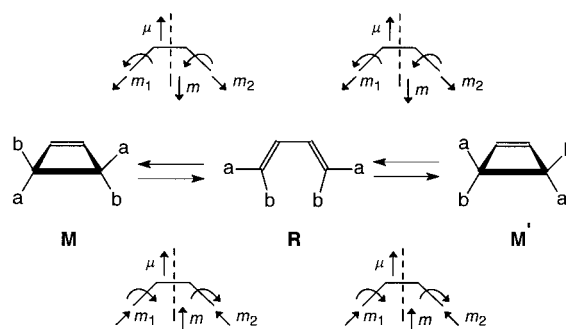


Figure 3. "False" chirality of a parallel combination of a magnetic (B) and an electric field (E).^[69]

A crucial distinction between a truly and falsely chiral influence is that only under the former the energy of a chiral molecule will be different from that of its mirror image. Chiral enantiomers will remain strictly degenerate in the presence of a falsely chiral influence.^[70] A falsely chiral influence (for example, a colinear electric and magnetic field) can however act as a chiral catalyst since it modifies the potential energy barriers that change the relative rates of formation of enantiomeric products without affecting the equilibrium thermodynamics. In theory, a falsely chiral influence can induce absolute asymmetric synthesis for reactions far from thermodynamic equilibrium. One theoretical example using the breakdown of microscopic reversibility is illustrated below for the conrotatory interconversion of butadiene with two enantiomeric chiral cyclobutenes (Scheme 1).^[71] During the entire process the molecule preserves its twofold rotation (C_2)



Scheme 1. Relative orientation of the transient electric and magnetic dipole moments during the conrotatory interconversion of a butadiene and two enantiomeric chiral cyclobutenes. (from reference [71].)

axis. Symmetry arguments show that there will be an electric dipole moment (μ) parallel to this C_2 axis and, to a good approximation, μ will have the same magnitude and sense during the entire process. The rotational motion of the a and b groups will generate transient magnetic moments (m_1 and m_2) parallel to the local rotation axis.

From Scheme 1 it can be seen that this magnetic moment (m) is opposite for the forward and back reaction in both cases ($R \rightleftharpoons M$ and $R \rightleftharpoons M'$), but the same for the ring closure $R \rightleftharpoons M$ and the ring opening $M' \rightleftharpoons R$ and vice versa. An electric field will partially align the molecules while a parallel magnetic field will result in different energies of the antiparallel and parallel rearrangements of μ and m resulting in a potential energy profile as depicted in Figure 4. This system can thus develop an enantiomeric excess during the reaction that is under the influence of a falsely chiral combination of physical fields as long as no thermodynamic equilibrium is established. It should be emphasized however that this is a purely theoretical example; in practice the motion of molecules in solution is isothermal and according to transition-state theory all states are in equilibrium.^[72]

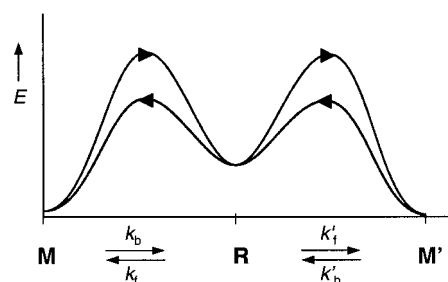


Figure 4. Energy diagram for the conrotatory interconversion of two enantiomeric chiral cyclobutenes (k_f = rate of forward reaction; k_b = rate of back reaction). (From reference [74].)

The enantiomeric excesses formed in a reaction under a falsely chiral influence will ultimately disappear if thermodynamic equilibrium is established. Similarly, a falsely chiral influence cannot generate an enantiomeric excess in a racemic mixture. However, some reservations should be made involving enantio-differentiating reactions in a falsely chiral field since non-uniform fields or forces could be present or the reacting species might be partially aligned on the walls of the reaction vessel.^[73] In a thought provoking article entitled "Can a magnetic field induce absolute asymmetric synthesis"

Barron predicted that asymmetric induction might take place in a magnetic field provided the prochiral molecules are pre-aligned (on a surface, in a crystal or at an interface) and the system is far from equilibrium.^[74] The experimental proof for such a magnetic field induced asymmetric synthesis still remains an intriguing challenge.

Let us consider the physical forces used in the absolute asymmetric syntheses mentioned above and investigate their chirality. Firstly, linearly polarized light together with a magnetic field will be discussed. A static magnetic field (B) parallel to the direction of propagation of an incident, arbitrarily polarized light beam (k) used in the earliest examples of absolute asymmetric synthesis is, in principle, a truly chiral influence (parallel and antiparallel arrangements of B and k are true chiral enantiomers because they cannot be interconverted by time-reversal since k , unlike E , is time-odd; see Figure 3) and is thus a candidate for asymmetric synthesis.^[75] Although the attempted absolute asymmetric synthesis was irreproducible, the truly chiral influence of a magnetic field parallel to the propagation vector of arbitrarily polarized light has been shown experimentally. This combination of forces can induce a difference in the refractive index (magnetic field induced dispersion difference, MIDD) and correspondingly, the absorption coefficient (magnetic field induced absorption difference, MIAD) of enantiomers. The shift, independent of the polarization of the light beam, changes sign either on replacing the chiral molecule by its mirror image or on reversing the relative directions of the magnetic field or propagation direction of the light beam.^[76] It should be noted that, because of the very small effects involved, there is no foreseen practical application of MIDD and MIAD.

Secondly, rotations in gravitational fields are close analogues of electric and magnetic fields (false chirality). The spinning vessel has a time-odd axial angular momentum vector (such as E), while the gravitational field is a time-even polar vector (such as B); thus the system displays “false” chirality. In this case, an enantiomeric excess can only be established under kinetic control and the enantiomers are strictly degenerate.

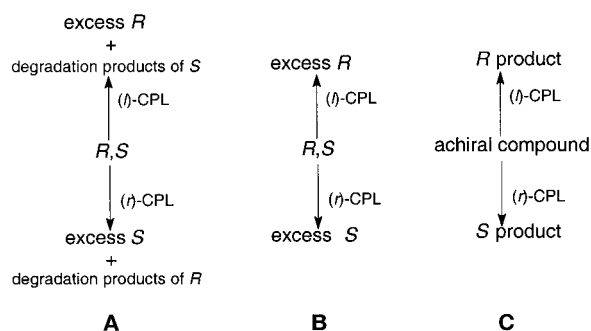
Thirdly, a conical swirl is definitely a truly chiral system. Yet no enantiomeric excess in any process is expected as a result of a condition reported in 1930, but often ignored.^[77] For an absolute asymmetric synthesis to occur the externally applied truly chiral forces must actually cause the reaction. This means that the applied field must be capable of either changing the rate of the reaction or generate a pair of diastereomeric transition states of different energies that lead to the products. Because of this, absolute asymmetric synthesis using rotating vessels in the Earth’s gravitational field can be discarded in advance, irrespective of whether the force field is truly chiral or not.

5. Absolute Asymmetric Synthesis with Circularly Polarized Light

Circularly polarized light (CPL) is without doubt truly chiral electromagnetic radiation in the sense described above

and therefore CPL should in theory be able to induce absolute asymmetric synthesis.^[78] The only basic requirement is that the molecules to be converted should absorb visible or UV light. Since circular dichroism (CD) arises from a difference $\Delta\epsilon$ in the absorption of right- and left-circularly polarized light by an optically active molecule, right- and left-handed CPL should preferentially interact with one enantiomer of substances that exhibit circular dichroism. In addition, irradiation of a prochiral molecule with CPL might preferentially convert the ground state of molecules into an excited state with a certain chirality that can lead to a preference for the formation of one enantiomer. Three types of enantioselective conversions effected by CPL irradiations can be distinguished (Scheme 2):

- Preferential photodestruction in which one of the enantiomers of a racemate is preferentially converted and the other remaining stereoisomer is enriched; this process is irreversible.
- Photoresolution, namely a deracemization process of photochemically interconvertible enantiomers.
- Asymmetric photosynthesis, namely an enantioselective photochemical formation of an optically active compound from a prochiral starting material.



Scheme 2. Three ways of using CPL for enantio-differentiating reactions. For further information see the text.

Early work on enantio-differentiating reactions by CPL has been reviewed by Izumi and Tai as well as Inoue.^[79, 88] In considering the possibility that CPL can induce biomolecular homochirality we should point out that a very small portion of the light that comes to the earth is circularly polarized, probably as a result of scattering by particles in the atmosphere. Other sources that have been suggested are reflection to surfaces such as quartz crystals. It should be emphasized that there is no chiral bias as a tiny excess of either (l) -CPL or (r) -CPL can be observed depending on the time and place on the earth.^[5, 48, 80] Therefore natural asymmetric synthesis with CPL seems to be only a feasible mechanism to generate homochirality if a high local intensity of CPL were created. In such a case a strong amplification mechanism is also necessary to explain homochirality since high ee values can only be obtained directly for molecules with high anisotropy factors or optical-rotatory powers, which is usually not the case for biomolecules. Absolute asymmetric synthesis using CPL is certainly interesting from the point of view of laboratory applicability since circularly polarized light is readily generated from linearly polarized light in combination with a quarter wavelength plate.^[79, 81]

5.1. Photodestruction

As early as the 19th century Le Bel and Van't Hoff recognized the potential use of (*r*)- and (*l*)-CPL in photochemical reactions for the production of an excess of a particular enantiomer from a racemic substrate.^[13] Cotton was the first to test this idea by attempting enantio-differentiating photolysis of an alkaline solution of copper tartrate.^[82] It was known that copper tartrate exhibits unequal absorptions for right- and left-handed CPL in the red region of the spectrum. However, no rotation was detected after photolysis owing to insufficient energy of the light employed, as was later shown by Byk.^[83] Kuhn and co-workers succeeded in performing an enantio-differentiating reaction with circularly polarized light in the UV region, namely the photodestruction of the racemic dimethylamide of α -azidopropionic acid.^[84] In this first unequivocal asymmetric photolysis, the final optical rotation could be correlated very well with the anisotropy factor of the substrate derived from CD experiments.

Soon after this finding a study by Mitchell appeared that reported optical rotation in the product after irradiation of the sesquiterpene humulene with CPL.^[85] Enantio-differentiating photochemical reactions employing CPL have, however, not been extensively explored. As photodestruction involves the preferential conversion of one of the enantiomers of a racemate, that is, kinetic resolution, a high *ee* value might be achieved provided the reaction is run to high conversions.

Thus Kagan and co-workers^[86] reported optical purities of 20% (Kuhn anisotropy factor $g = 0.09$ at 310 nm; see Section 5.2) for camphor and 30% ($g = 0.24$ at 313 nm) for *trans*-bicyclo[4.3.0]nonan-8-one, at 99% photodestruction of the racemates. These are among the highest stereoselectivities reported so far, but the very low yield of the remaining optically active material is illustrative of the disadvantages associated with this kinetic resolution method.

Although the obtained *ee* values are considerably lower, a very important aspect is the asymmetric photolysis of (*R,S*)-leucine using laser-induced circularly polarized UV light.^[87] Bonner and co-workers obtained leucine with about 2% *ee* after irradiation of a racemic sample of the amino acid with a circularly polarized laser beam (212.8 nm, 180 J). This direct way of enriching an amino acid is of course of major importance in the study of the origin of biomolecular homochirality.

5.2. Photoresolution

Next to photodestruction, partial photoresolution comprises a second mechanism by which enantio-differentiating reactions using circularly polarized light can operate in a reversible manner.^[88] For instance, irradiation of racemic chromium oxalate solutions in water with CPL gradually resulted in an optical-rotary power without affecting the chromium oxalate contents.^[89] The CPL selectively excites one of the two enantiomers of chromium oxalate and from this excited state racemization takes place, the other enantiomer, which is hardly affected, will accumulate in solution until an equilibrium is reached. Stevenson and Verdick as

well as Norden reported a similar partial resolution of octahedral bidentate Cr^{III} complexes.^[90]

In a photoresolution process irradiation of a racemate with (*l*)-CPL will cause the formation of an excess of the *R* enantiomer whereas irradiation with (*r*)-CPL will lead to an excess of the *S* enantiomer (or the reverse enantioselectivity takes place; see Scheme 2). The selectivity that can be expected in such a process is governed by the Kuhn anisotropy factor g where $g = \Delta\epsilon\epsilon^{-1}$.^[91] The enantiomeric excess in the photostationary state (*ee*_{PSS}) is given by Equation (1). For most compounds the anisotropy factor seldom exceeds 1% and therefore *ee* values below 0.5% are to be expected from CPL photoresolution. Notable exceptions are for instance chiral lanthanide complexes that show g values up to 3% and chiral bicyclic ketones with anisotropy factors of about 1% (see below).

$$ee_{PSS} = \frac{g}{2} = \frac{\Delta\epsilon}{2\epsilon} \quad (1)$$

The research group of Schuster has studied a large variety of axially chiral (arylmethylene) cycloalkanes (Figure 5) in their search for a liquid crystal phototrigger based on CPL (see Section 7).^[92] Typically, irradiation of methyl ester (*R*)-**6** at 254 nm resulted in complete and selective racemization.

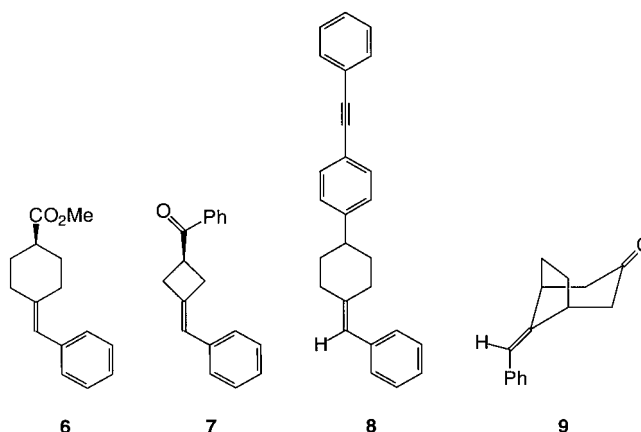


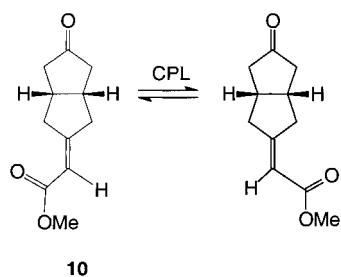
Figure 5. Axial chiral (arylmethylene)cycloalkanes for photoresolution.

This points to a stable system since irradiation of the enantiomerically pure compound should exclusively lead to racemization and no decomposition should occur with a photobistable compound if it is to be suitable for a fully reversible photoresolution experiment. With related compounds this requirement was not always fulfilled and considerable photodecomposition often accompanied photoracemization. Anisotropy factors could be enhanced from $g_{251} = 7.5 \times 10^{-5}$ for **6** to $g_{361} = 10^{-2}$ for ketone **7** by tuning the exciton interactions between the chromophores through structural modifications. Although optically active **7** shows complete racemization in one minute and an enantiomeric excess of 5×10^{-3} was calculated for the photostationary state based on the g factor, no successful photoresolution was described.

In an alternative approach the photoresolvable group was part of the mesogenic compound itself. For this purpose

axially chiral 1-benzylidene-4-(phenylethynylphenyl)cyclohexanes (for example, **8**) were prepared, but again the anisotropy factor g proved to be too small.^[93] Slow photo-resolution was observed for the axially chiral bicyclo[3.2.1]octan-3-one **9** ($g_{313} = 0.0502$, $ee_{\max} = 2.5\%$), which led to an enantiomeric excess of 1.6%.^[94]

In 1995 Schuster and co-workers reported the first reversible photoderacemizations, that is the reversible formation of an excess of one enantiomer after irradiation of a racemate with CPL.^[95] The observed ee value was 0.4%, again using axially chiral bicyclic ketones (Scheme 3). The ketone chromophore exhibits a high g factor since the $n\text{-}\pi^*$ transition is forbidden. The absorption of the substituted acrylic ester moiety **10** has no overlap with that of the ketone group, and the relatively rigid bicyclo[3.3.0]octane skeleton is used to link the chromophores in order to avoid averaging of the CD spectra by strong coupling. These features resulted in a g value of about 10^{-2} . Irradiation of **10** with unpolarized light leads to efficient photoracemization by isomerization around the double bond.



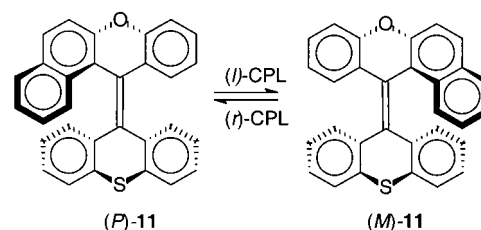
Scheme 3. Reversible photoderacemization of a rigid bicyclo[3.3.0]octanone with CPL.^[95]

Our interest in the control of chirality by circularly polarized light stems from the challenge to develop a chiroptical molecular switch based on CPL.^[96] The switching process we envisioned involves the interconversion of the P and M enantiomers of helical-shaped inherently dissymmetric alkenes. Despite the fact that two enantiomers represent two different states (0 and 1) in a binary system, they have the same properties and switching with light, independent of the wavelength, will result in a racemic mixture. Theory predicts that the ratio of enantiomers in a racemic photoresponsive material can however be modulated by irradiation at a single wavelength by changing the handedness of the light, such as in the examples discussed above. The possible photoisomerization steps are the following (Scheme 4): 1) After irradiation with CPL one of the enantiomers (P or M) will be formed in small excess when one starts with a racemate (M,P). 2) Irradiation with light at one wavelength, but alternating (l)- and (r)-CPL, will result in a modulation between a P and a M helix. 3) The racemic mixture can be obtained again after irradiation with linearly polarized light (LPL).



Scheme 4. Photoisomerizations based on irradiation with circularly polarized light (CPL) and linearly polarized light (LPL).

Out of a large number of sterically overcrowded chiral alkenes that were synthesized and resolved, helical-shaped alkene **11** meets the requirements for a useful switch (Scheme 5). Decisive factors for a successful CPL switch are: 1) a selective interconversion of enantiomers by CPL without any photodestruction; 2) a high g factor; 3) thermally stable enantiomers; 4) a high quantum efficiency for photoderacemization, since the rate of photoresolution depends exponentially on this quantity.



Scheme 5. Photochemical interconversion of P (right handed) and M (left handed) helices of **11** upon irradiation with (l)- or (r)-CPL.^[96]

The enantiomers of **11** are stable at ambient temperatures ($\Delta G_{\text{rac}}^\ddagger = 25.9 \pm 0.2 \text{ kcal mol}^{-1}$) and fatigue resistant. Stereo-specific photoisomerization takes place that reverses the helicity of the molecules. Thus irradiation of (P)-**10** with unpolarized light at 300 nm resulted in rapid photoracemization without notable degradation and with a high quantum yield ($\Phi_{\text{rac}} = 0.40$ in n -hexane). Furthermore large CD absorptions and optical rotations, similar to those seen in helicenes, are found, which are useful for detecting the rather small change in chirality upon CPL irradiation.

We took into consideration that for practical purposes the photoresponsive system should exhibit sufficiently large g values at wavelengths above 300 nm. The experimental g value for **11** is -6.4×10^{-3} (313 nm), which indicates that an ee value of 0.3% might be expected under ideal conditions. Irradiation of (P,M)-**11** with (l)-CPL indeed resulted in photoderacemization. Successive irradiation for 30 min with (l)- and (r)-CPL at the same wavelength led to a modulation of the chirality as detected by CD measurements and no deterioration of the CD signal was observed during eight cycles. Typical switching cycles are shown in Figure 6. Switching occurs between photostationary states with small excess of P and M helices and an ee value of 0.07% and -0.07% , respectively. The ee values are smaller than anticipated but by

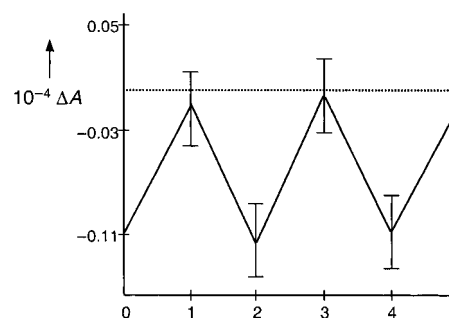


Figure 6. The difference in CD absorption at 313 and 400 nm ($\Delta A_{313} - \Delta A_{400}$) for a solution of **11** in n -hexane after alternating irradiation with (l)- and (r)-CPL at 313 nm.^[96]

taking into account that the light is 90% circularly polarized at best and that the band width was 10 nm *ee* values no greater than 0.1–0.2 are realistic.

The demonstration of a chiroptical molecular switching process based on photomodulation of helicity using CPL is not only interesting from a fundamental point of view but also offers intriguing possibilities for molecular optical devices, which we briefly mention here. The two forms of the bistable molecule with opposite helicity constitute a memory element in a binary logic system—a requirement for reversible optical data storage. In the system described here, although still a very primitive version, the chirality is modulated and as a consequence so are the chiroptical properties and the three-dimensional structure. The principle of a potential data storage system is depicted in Figure 7. Irradiation of a racemate (*M,P*) using (*r*)- or (*l*)-CPL for the writing process generates *P*-enriched or *M*-enriched regions, respectively.

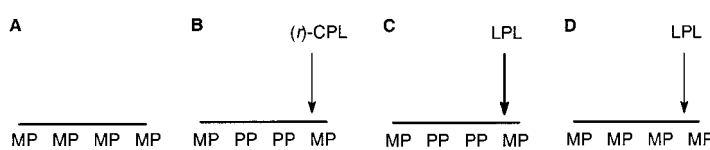


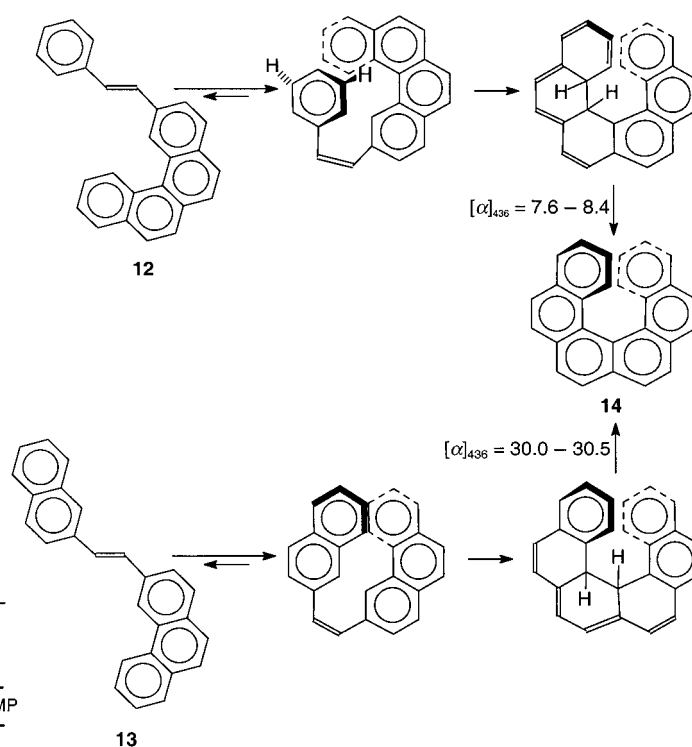
Figure 7. Proposed optical data storage system based on the chiroptical molecular switch **11**. Writing is done with CPL while reading and erasing is done with LPL. A: unwritten; B: write; C: read; D: erase.

Detection (read-out) is achieved with LPL outside the absorption band (for example, optical rotation), whereas written information can be erased by LPL (or unpolarized light) at the original wavelength, which generates the racemate (*M,P*) again. In principle, this photoresolution constitutes a three position—(*P,M*), *P*-enriched, and *M*-enriched—switch, with the distinct advantage that all switching processes can be performed at a single wavelength merely by changing the chirality of the light.

5.3. Asymmetric Photosynthesis

An early attempt to test the idea of using CPL as a means of performing absolute asymmetric synthesis was an irradiation experiment of an asymmetrically substituted triphenylmethyl radical, but no unequivocal optical activity was observed.^[97] Suitable systems to prove the concept of CPL-controlled asymmetric synthesis are helicenes, which are known to have an extremely strong optically rotatory power and are produced by a photochemical ring closure and subsequent oxidation of a diarylethylene in the presence of iodine. Indeed the groups of Kagan and Calvin independently succeeded in a CPL-induced enantioselective synthesis of helicenes (Scheme 6).^[98, 99]

When 1-(2-benzo[*c*]phenanthryl)-2-phenylethylene (**12**) or 1-(2-naphthyl)-2-(3-phenanthryl)-ethylene (**13**) were irradiated with CPL in the wavelength range of 310–410 nm optically enriched hexahelicene (**14**) was obtained via a dihydrohelicene intermediate. The optical rotations of the synthesized helicene ($[\alpha]_{436}$) were 7.6–8.4 starting from **12** and 30.0–30.5

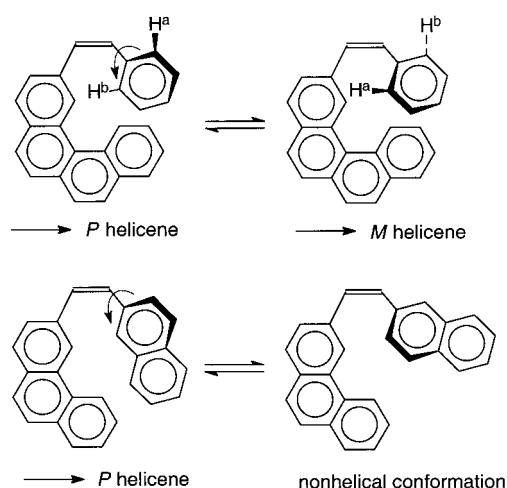


Scheme 6. Absolute asymmetric synthesis of hexahelicene from **12** and **13** using CPL.^[99, 100]

starting from **13** (positive optical rotations were obtained with (*l*)-CPL). Accordingly, 1-(2-naphthyl)-2-(2-benzo[*c*]phenanthryl)-ethylene, 1-(3-phenanthryl)-2-(2-benzo[*c*]phenanthryl)-ethylene and 1,2-bis-(2-benzo[*c*]phenanthryl)-ethylene under the same conditions gave optically active hepta-, octa-, and nonahelicene.

A mechanism involving the formation of racemic helicene followed by partial photoresolution was rejected by the observation that photoresolution of racemic hexahelicene gave resolved material with opposite optical rotations compared to the helicene product of the photochemical reaction. Partial photoresolution probably does compete with absolute asymmetric synthesis and as a consequence lowers the optical yield.

The photochemical reaction takes place from the lowest excited singlet state of the *cis* alkene. Circularly polarized light will preferentially excite the ground-state molecules to an excited state with a certain helical sense, which leads to a certain optical rotation in the final product. In this excited singlet state however, rotation around the aryl–ethylene bond requires little energy. In the case of **12**, such a bond rotation would cause equilibration of the two unequally excited enantiomers and therefore result in a decrease in the optical activity of the final product (Scheme 7). A comparable bond rotation for **13** will result in a nonhelical conformation that will not lead to the helicene product and therefore this bond rotation does not influence the enantiomeric excess of the helicene **14** formed. This explains the large difference in optical rotations found for **14** starting with **12** or **13**. Experiments using substituted analogues of **12** confirm this mechanistic rationale.

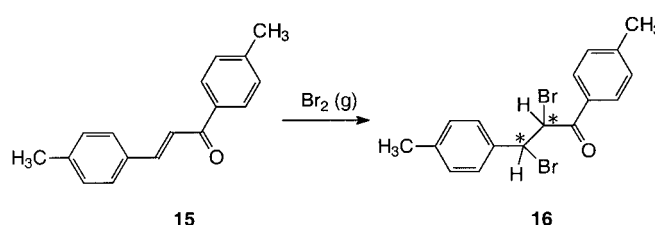


Scheme 7. Effect of bond rotation on the formation of hexahelicene.

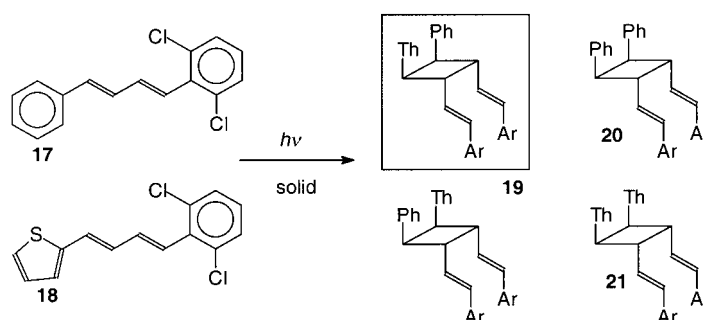
6. Photochemistry in Chiral Crystals

A different approach to absolute asymmetric synthesis is the use of a chiral crystal field in topochemically controlled solid-state reactions. Asymmetric synthesis has been reported by doping achiral compounds in a crystal of a chiral compound and using chiral inclusion phenomena, but this is not an *absolute* asymmetric synthesis.^[100, 101] Chiral compounds always crystallize in chiral space groups but also a number of achiral compounds are known to form chiral crystals.^[22] Most achiral molecules are known to adopt interconverting chiral conformations (a feature that might have more general implications in asymmetric synthesis than we tend to realize), which could lead to a unique conformation upon crystallization. Green, Lahav, and Rabinovich already noted from a viewpoint of asymmetric synthesis that stereocontrol is exerted during crystallization in the chiral form; it is only necessary to lock the chirality in a configurationally stable product by a subsequent solid-state reaction.^[102] Unfortunately, it is not easy to arrange achiral molecules in a chiral form in the crystal. Molecules with a C_2 -symmetry axis tend to crystallize in chiral structures, according to Jacques and co-workers, but despite impressive work on crystal engineering, predictions on a correlation between crystal symmetry and molecular structures are still hard to make.^[22, 103] The asymmetric crystallization of achiral compounds is stimulated by autoseeding with the first crystal formed. Although the chiral sense of the spontaneously formed crystal cannot be predicted, seed crystals of the preferred chirality can be added in a more practical procedure to obtain one enantiomorph of a crystal. Achiral compounds that crystallize in a chiral one-component crystal form are compiled in the JCPDS crystal data series and the Cambridge Crystallographic Data Centre.^[104]

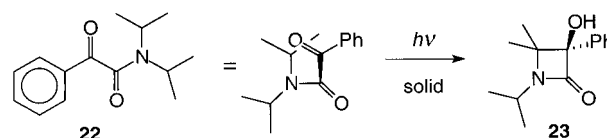
Penzien and Schmidt reported the first absolute asymmetric transformation in a chiral crystal.^[105] The enone 4,4'-dimethylchalcone (**15**) was found to crystallize in the chiral space group $P2_1'2_1'2_1'$ with a highly twisted conformation. Reaction with bromine provided the dibromide **16** with optical purities of 6–25% (Scheme 8).

Scheme 8. First example of absolute asymmetric synthesis using the chiral crystal environment of 4,4'-dimethylchalcone.^[105]

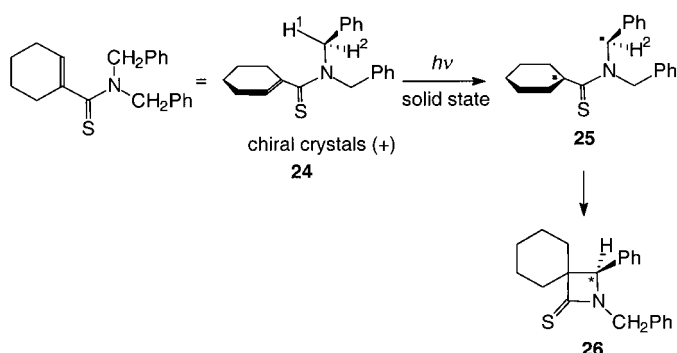
For early work on the (attempted) asymmetric synthesis in chiral crystals, the reader is referred to a review by and the work of Green, Lahav, and Rabinovich.^[102, 106] As detailed discussions on photochemistry in organized media, enantioselective solid-state reactions of the enantiomorphs of chiral crystals, and stereochemistry of solid-state organic reactions have appeared^[107] we will restrict ourselves to some recent findings. Photochemical conversions in the solid state are well known and stereochemical control can be excellent. It was found that upon irradiation of homochiral mixed crystals of butadienes **17** and **18** a [2+2] photodimerization takes place yielding heterodimer **19** with an optical yield of 70%.^[108] Formation of the achiral homodimers **20** and **21** was prevented by tuning the ratios of heterodimer (**19**) and homodimers (**20** and **21**) by selective excitation of the thiophene derivative. As expected, some crystals gave left-handed and others right-handed cyclobutanes (Scheme 9).

Scheme 9. Enantioselective hetero-dimerization in a two-component homochiral mixed crystal of two butadienes.^[108]

Many examples of solid-state photochemical reactions that use the chiral crystal environment of an otherwise achiral compound to induce an optically enriched product have been reported in recent years.^[109] A remarkable case—the photocyclization of the diisopropyl amide **22**—was reported by Toda et al. (Scheme 10).^[110] A helical conformation is found in the chiral crystal as a consequence of a twisting around the CO–CO bond, and this conformation is locked by photocyclization to afford β -lactam **23** with 93% *ee*. A prominent

Scheme 10. Formation of chiral β -lactam **23** by photocyclization of **22** in the crystal.^[110]

example is also the formation of optically active (*R*)-(+)-thiolactam **26** with enantiomeric excesses of 81–97 % by intramolecular [2+2]-photocyclization of one enantiomorphous form of achiral α,β -unsaturated thioamide **24** via diradical **25** using the chiral crystal environment (Scheme 11).^[111]

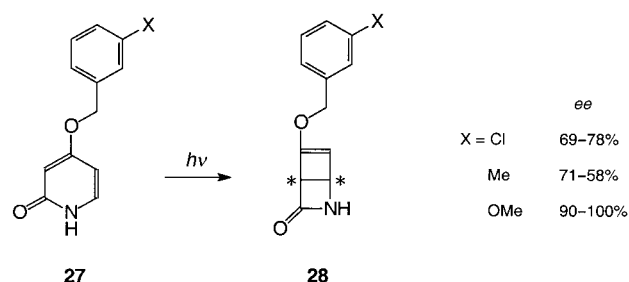


Scheme 11. Absolute asymmetric synthesis by photocyclization of **24** in the crystal.^[111]

Although the photocyclization gives a very large enantiomeric excess, a decrease in selectivity is observed at higher conversion (the above mentioned 81 % *ee* is obtained after 100 % conversion, while 97 % *ee* was obtained after 20 % conversion). This is attributed to an increased disorder in the packing of the crystal as a result of the accumulation of product and the local melting of the crystals by excess radiation energy.^[112] However, no melting was observed after 20 % conversion, which resulted in the relatively high *ee* values.

The major drawbacks of the crystal-field method, which prevent it from becoming a general method for absolute asymmetric synthesis, are the unpredictability of the crystallization of the achiral substrates, which as indicated can be circumvented by manual seeding, and the fact that achiral substrates seldomly crystallize in chiral space groups. It was shown that it is possible to regulate this chiral crystallization by crystal engineering. In the case of the formation of the β -lactam (Scheme 12), it was shown that the ability of a compound to crystallize in a chiral space group was increased by using compounds with *meta*-substituted aryl groups such as **27** instead of their *ortho*- and *para*-substituted analogues; the absolute asymmetric photocyclization of the *m*-chloro-substituted oxoamide **27** resulted in **28** with 100 % *ee*.^[113]

Despite the fact that the benzyloxy moiety is rather remote the photocyclization led to β -lactams with high *ee* values. The



Scheme 12. Effect of *meta*-substituent X on the enantioselectivity of an absolute asymmetric cyclization of different 2-pyridones.^[113]

remarkable enantioselectivity is attributed to intermolecular interactions in the solid state that discriminate between the two possible electrocyclization pathways. If the observations that *meta*-substituted arenes prefer to crystallize in non-centrosymmetric space groups, in comparison to the *ortho*- and *para*-isomers, have some generality^[114, 115] then *meta*-substitution in an achiral compound could be an important structural motif in the design of new absolute asymmetric synthesis and to make it more predictable.

It should be emphasized that an achiral compound can show polymorphism. In the case of bis(biphenylmethylene)-*N*-methylsuccinimide only the solid-state photocyclization of the chiral form, in which the molecule adopts a helical conformation, provides optically active (*ee* = 64 %) product.^[116]

Absolute asymmetric synthesis using the chiral crystal field has also been demonstrated for other cycloadditions and photoreactions such as Norrish Type II photocyclization and di- π -methane-type photorearrangements.^[117–119] The use of chiral bimolecular crystals,^[120] chiral bimolecular charge-transfer complexes, and specific reactions on one face of an achiral crystal have also been demonstrated for absolute asymmetric synthesis.^[121, 122]

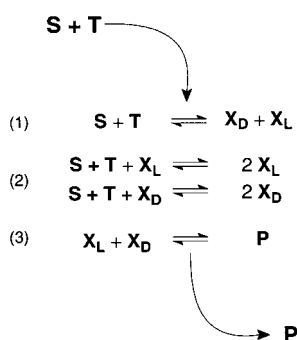
7. Amplification of Chirality

7.1. Autocatalysis and Nonlinear Effects

With the notable exception of asymmetric synthesis in enantiomorphous crystals and a few cases of CPL reactions the observed enantiomeric excesses in absolute asymmetric synthesis are extremely small. This means that an amplification mechanism is absolutely essential to enhance the initial chiral bias.

Also in light of the origin of biomolecular chirality, it is clear that observable consequences of the difference in the parity violating energy between enantiomeric molecules require some amplification mechanism. One possible method of amplification, based on a model for spontaneous symmetry breaking by Frank, is an autocatalytic system with competitive reactions of two enantiomers that are mutually inhibitory and form inactive products in a dynamic metastable system that is sensitive to small perturbations.^[123] The reaction of two achiral compounds leads to two enantiomeric products that each catalyze their own formation, namely autocatalysis occurs. Simultaneously, each enantiomer reduces the activity of the other (mutual inhibition) resulting in a strong asymmetric amplification. Calculations on such a model system that is thermodynamically far from equilibrium show that this system can evolve spontaneously into a chirally asymmetric state.^[124] In Scheme 13 a mechanism is depicted in which two enantiomeric forms of **X** (**X_L** and **X_D**) are produced from achiral substrates (**S** and **T**) directly through Reaction (1) and autocatalytically through Reaction (2). By irreversible removal of the products (**P**) by Reaction (3) the system can be driven far from thermodynamic equilibrium.

A detailed study of the reaction rates show that the balance between autocatalysis and mutual annihilation is unstable,



Scheme 13. Chemical model system for the synthesis of chiral compounds from achiral precursors.^[124]

with $\lambda = [S][T]$ being the critical parameter. When λ is increased past a critical value (λ_c) the system will switch to a state where X_L ($\alpha = [X_L] - [X_D] > 0$) or X_D ($\alpha < 0$) is favored. The state that is reached without any chiral bias is of course completely random (such as in the case of the spontaneous asymmetric crystallization described above) but spontaneous symmetry breaking indeed occurs as was shown by computational simulation (Figure 8).^[124] When the situation was biased, for instance by giving a slight preference for X_L over X_D (analogous to the possible effect of the Z force), the system almost always followed the branch where X_L dominated (Figure 8, right). It was predicted that in such a system

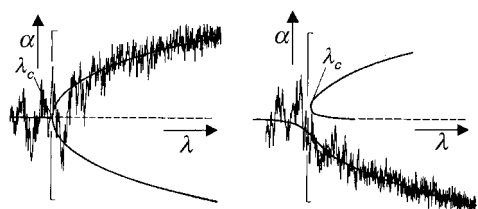
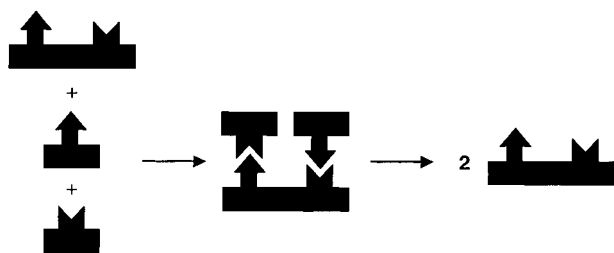


Figure 8. Evolution of chiral asymmetry (α) with time, without chiral bias (left) and with chiral bias (right). (From reference [124].)

the weak nuclear force should be capable, over a period of 50 000–100 000 years, to create a situation with at least a 98 % chance that nearly all molecules will be left-handed, as observed for terrestrial amino acids. This kind of system could provide a possible explanation for the origin of biomolecular asymmetry although it will not be easy to obtain experimental proof.

Self-replication and autocatalysis are among the most fascinating areas in chemistry today. In a self-replicating system, a molecule should function as a template for components that are bound by noncovalent interactions and are organized in such a way that they can react to form a copy of the original template molecule. In this way an autocatalytic synthesis is accomplished (Scheme 14). Following the pioneering work of the group of Orgel, who demonstrated the template-directed synthesis of complementary oligonucleotides,^[125] von Kiedrowski reported the first example of a



Scheme 14. Schematic representation of autocatalysis.

nonenzymatic self-replicating system that is based on the autocatalytic formation of a self-complementary hexanucleotide **29** (Figure 9).^[126] The square root law of autocatalysis^[127] was obeyed, as shown by the observed rate of the autocatalytic reaction being proportional to the square root of the concentration of the template.

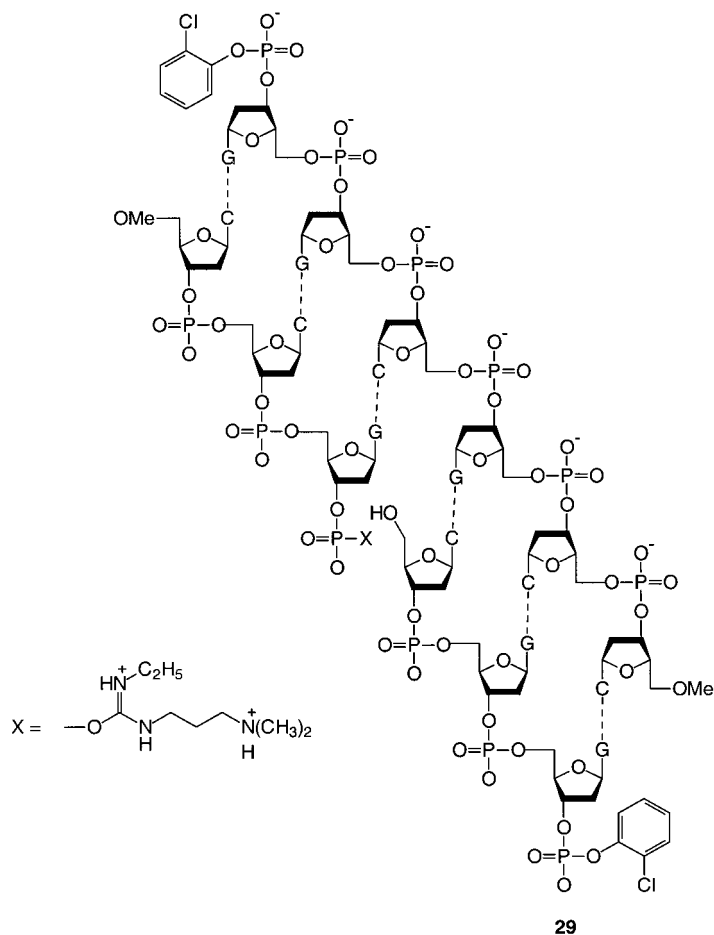


Figure 9. Nonenzymatic self-replication.^[126]

As a result of the efforts of the groups of Orgel, Rebek, von Kiedrowski, Nicolaou, and others a number of genuine self-replicating and autocatalytic systems are known today.^[128] Figure 10 shows two synthetic models (**30** and **31**) that function as artificial self-replicators.^[129, 130] Recently, Ghadiri et al. reported the first example of a self-replicating peptide.^[131] A α -helical 32mer peptide with a sequence that is similar to the leucine-zipper domain of the yeast transcription factor GCN4 acts as a template for its own autocatalytic formation by coupling 15- and 17-oligopeptide residues.

In light of the discovery of enriched amino acids from extraterrestrial source (Section 2.2) and the stereoselection in oligopeptide formation (Section 7.2), the proposal that self-replicating peptide sequences should be considered in the early evolution of living systems is intriguing.

Asymmetric autocatalysis and nonlinear effects provide two mechanisms that can lead to amplification of chirality. A few early reports on the effect of chiral products on the stereochemical course of organometallic reactions and the

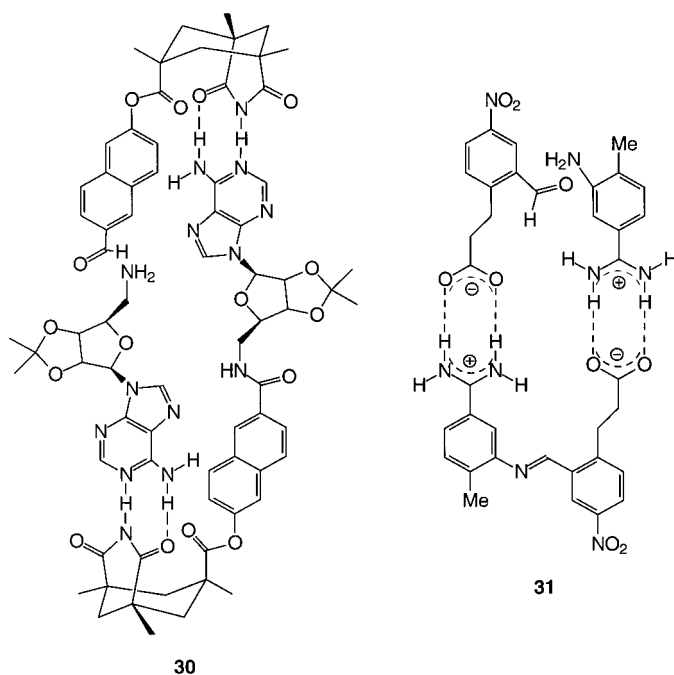
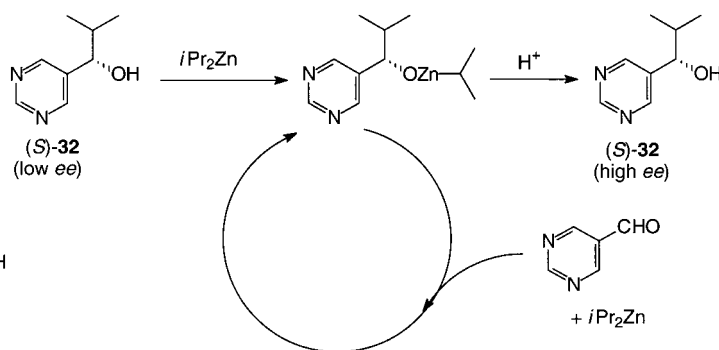


Figure 10. Synthetic models that function as artificial self-replicating systems.

observation of enantioselective autoinduction should be mentioned in this context.^[132] A decade ago Wynberg advocated asymmetric autocatalysis as the major challenge in future asymmetric synthesis.^[133] In 1990 Soai et al. found that the optically active pyridyl alcohol formed from pyridine-3-carbaldehyde and isopropylzinc is a chiral catalyst for its own formation.^[134] Up until that time all systems resulted in a decrease of the *ee* value of the product. Soon after this first example of asymmetric autocatalysis, Danda et al. reported a strong asymmetric amplification of an optically active product by a co-catalytic effect in an addition of HCN to 3-phenoxybenzaldehyde catalyzed by a cyclic dipeptide.^[135] This is an intriguing case of an asymmetric synthesis where the chiral product affects the chiral catalyst for the reaction and results in a strongly improved catalyst while simultaneously governing the absolute stereocontrol of its own formation.

A major breakthrough in this field was the finding by Soai et al. of catalytic asymmetric automultiplication in the addition of the dialkylzinc reagents to pyrimidine aldehydes without a decrease in the optical purity of the product.^[136] These discoveries formed the basis for the first autocatalytic system that showed asymmetric amplification (Scheme 15).^[137] The 1,2-addition in the presence of (*S*)-**32** with 2% *ee* gave additional (*S*)-**32** with 10% *ee* and further cycles enhanced the *ee* value to 88% with over a 900-fold increase in product formation. This represents an asymmetric autocatalytic amplification system in accordance with Frank's model. Recently, Soai et al. reported a similar autocatalytic reaction of pyrimidyl aldehydes using slightly enriched amino acids as the only chiral bias.^[138] By this approach an *ee* value of up to 51% could be obtained. Interestingly from the point of view of the origin of chirality is the fact that the initial *ee* value of the amino acids used was equal to the *ee* value that could be obtained from asymmetric photolysis, as discussed above.^[87]



Scheme 15. Proposed reaction scheme of asymmetric catalysis of **32** with enhancement of enantiomeric excess.

Highly relevant for amplification of the enantiomeric excess of the product of an absolute asymmetric synthesis is the so-called “nonlinear effect”. Horeau found a strong deviation between optical purity, as determined by specific optical rotation, and the actual *ee* value of chiral succinic acids.^[139] The nonlinear effect was attributed to diastereomeric association through hydrogen-bond formation. In 1976 Wynberg and Feringa discovered the so-called antipodal effects.^[140] For instance, the diastereoselectivity in the LiAlH_4 reductions of camphor were found to depend on the *ee* value of the starting material, which pointed to a nonlinear effect in stoichiometric asymmetric synthesis. In 1986 Kagan was the first to observe significant nonlinear effects in three catalytic asymmetric reactions, namely asymmetric sulfoxidation, Sharpless epoxidation, and (*S*)-proline-catalyzed aldol cyclization.^[141] Since then a variety of catalytic enantioselective reactions have been reported that show nonlinear behavior.^[142] Kagan and Girard have extensively discussed the principles and important observations regarding nonlinear effects and we will focus only on the essential aspects of amplification.^[143]

A linear relationship in an asymmetric catalytic reaction implies that the *ee* value of the product is proportional to the *ee* value of the chiral auxiliary, for instance a chiral ligand. The linear relationship is shown in Figure 11 and is given by Equation (2) for $g = 1$.^[144]

$$ee_{\text{product}} = \left(ee_0 \frac{1 + \beta}{1 + g\beta} \right) ee_{\text{aux}} \quad (2)$$

If diastereomeric associations between chiral species occur in nonhomochiral systems, deviation from the linear relationship [Eq. (2)] can occur leading to a positive nonlinear effect ($g < 1$; curve B in Figure 11) or a negative nonlinear effect ($g > 1$; curve C in Figure 11). For instance, the use of (–)-DAIB **33** as a chiral ligand in the ligand-accelerated catalytic addition of diethylzinc to benzaldehyde (Scheme 16), reported by Noyori et al., results in a dramatic nonlinear effect as is evident from Figure 12.^[145] The asymmetric 1,2-addition of organozinc reagents has been studied in depth and the strong amplification is attributed to the formation of a stable (and therefore ineffective) heterochiral dimer **35** of the Zn-complex of the chiral ligand (Scheme 16).

Several models have been proposed to explain nonlinear effects in asymmetric catalysis.^[143, 145–148] One model that

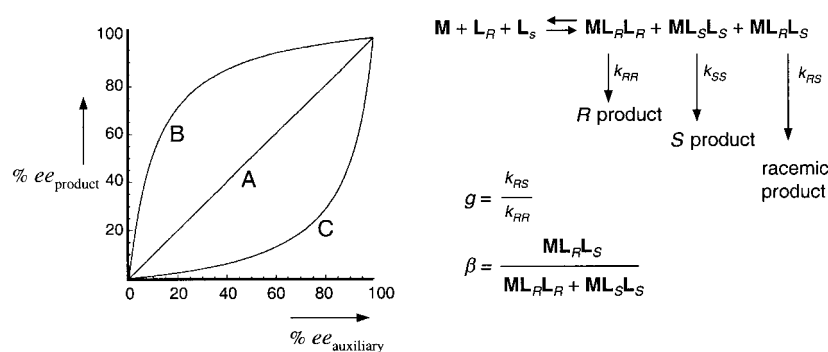
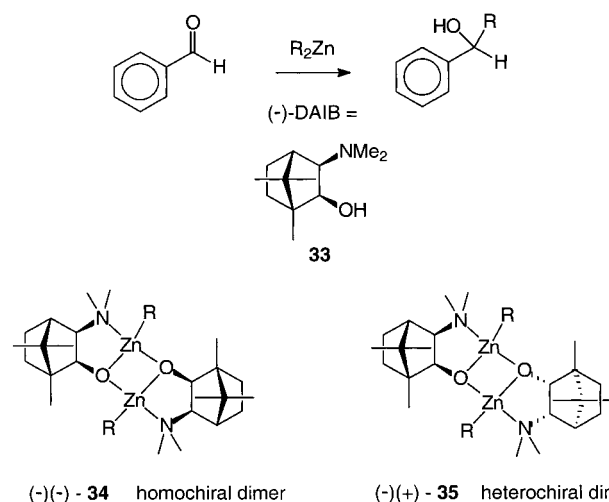


Figure 11. A) Linear relationship between the *ee* value of the chiral auxiliary and *ee* value of the product; B) positive nonlinear effect; C) negative nonlinear effect. (From reference [143].)



Scheme 16. (–)-DAIB-catalyzed addition of dialkylzinc to benzaldehyde. (From reference [145].)

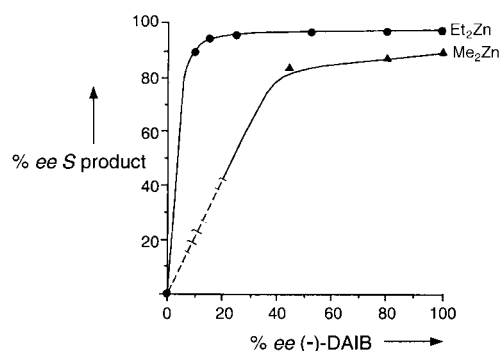


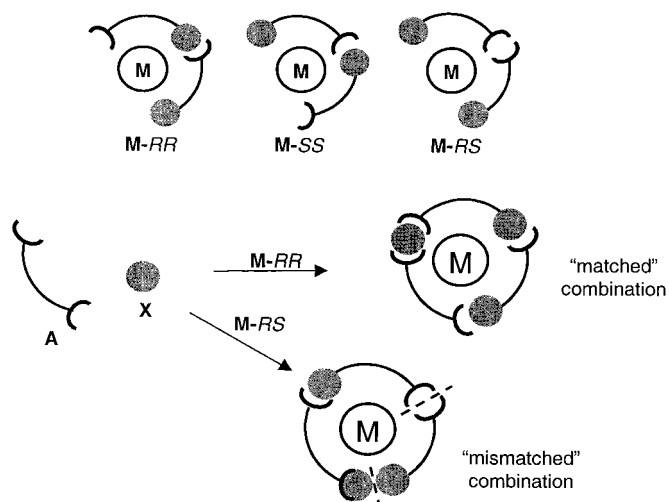
Figure 12. Observed nonlinear effects for the diethylzinc and dimethylzinc additions to benzaldehyde using (–)-DAIB as a catalyst. (From reference [145].)

provides a rational for asymmetric amplification is a catalyst model proposed by Bailey for a simple autocatalytic self-replicating system.^[149] It comprises a metal complex, with two product molecules as the chiral ligand, that can only efficiently catalyze the formation of chiral product through the “matched” homochiral ligand combination (Scheme 17).

An amplification can be expected in two cases when a nonlinear effect is operating (Figure 11):^[143] a) when the *meso*-catalyst is less reactive than the homochiral catalyst; b) when part of the chiral ligand is removed from the

catalytically active species by the formation of inactive complexes that lead to an enhancement of the initial *ee* value of the chiral ligand. Optically active products will be produced by the homochiral catalyst while the *meso*-catalyst will lead to racemic product. Similar analyses apply for other metal–ligand combinations and non-metal-based chiral catalysts.

Nonlinear effects are a prominent feature of many catalytic asymmetric reactions and the self-amplification in the autocatalytic system reported by Soai et al. can be explained accordingly.



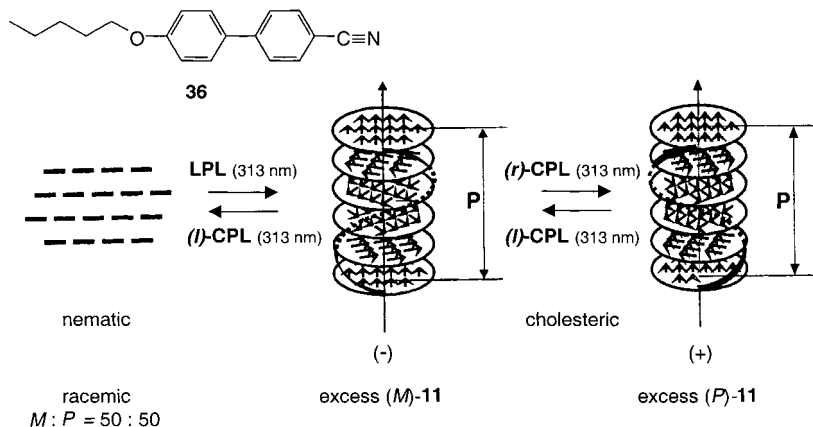
Scheme 17. Mechanisms for the asymmetric amplification in metal–ligand autocatalytic system (from reference [149]).

7.2. Amplification in Macromolecules and Supramolecular Assemblies

A delicate balance of noncovalent interactions, stereochemical features, and conformational flexibility is usually inherent in the successful assembly of large supramolecular structures.^[150] This notion also implies that some of these systems are highly sensitive to chiral perturbations, in particular this is the case for liquid crystalline materials. It is well established that small amounts of an optically active guest molecule added to a nematic host could induce a cholesteric phase and that the helical organization in the mesoscopic system is very sensitive to modifications in the chiral guest molecule. The development of a switching and amplification system in which light can transform a nematic (achiral) liquid crystalline phase to a cholesteric (chiral) phase is appealing,^[151] and in particular of interest for new information storage and display systems.^[152]

The control and modulation of the chirality of the liquid crystalline mesophase was studied in our laboratory with the chiroptical molecular switch (Scheme 6).^[96] Doping of the mesogen 4'-(pentyloxy)-4-biphenylcarbonitrile (**36**) with (*P,M*)-**11** (about 20 wt %) established a nematic phase, which upon irradiation at 313 nm with (*I*)- or (*r*)-CPL was converted

into a cholesteric phase. The photoresolution of guest **11** in the nematic host results in a small (0.07 %) *ee* value and, as a consequence a small helical twisting power and large pitch are observed. Furthermore, irradiation of the cholesteric phase containing excess (*M*)-**11**, obtained after CPL irradiation, with linearly polarized light (LPL) at 313 nm resulted in a nematic phase as a consequence of the formation of a 50:50 ratio of *P* and *M* helices of **11**, namely photoracemization occurs. The photochemical switching processes of the liquid crystalline phases are completely controlled by the changes in the chirality of the light at a single wavelength. The changes in liquid crystalline phases and dopant are shown in Scheme 18. Switching between LPL and CPL results in a nematic to



Scheme 18. Switching between three different liquid crystalline states after irradiation at one wavelength. For further information see the text.

cholesteric modulation. Switching between (*I*)-CPL and (*r*)-CPL modulates the chirality of the cholesteric phase (that is left- and right-handed, respectively). The low efficiency and the rather high dopant concentrations that are required in the current system need further improvement through structural modification of the photoresponsive guest molecule. It is fascinating to establish for the first time that an extremely small bias for a particular molecular chirality sense, induced by CPL photoresolution, can cause a major effect on the chiral organization of large ensembles of molecules and that this control of chirality is fully reversible.

Another possible mechanism for the amplification of an initial small enantiomeric excess in L-amino acids was proposed in which amplification occurs during the polymerization to proteins. A small difference in the activation parameters of enantiomeric monomers, effective at each stage of the polymerization, or an enhancement of the formation of an α -helical secondary protein structure by the employment of a single configuration of the amino acid can result in a relatively large enantiomeric excess of one of the homochiral polymers.^[153] It was shown experimentally that the helical structure of poly(benzyl-L-glutamate) was progressively weakened when configuration randomness was introduced by substitution of L-glutamate units by their D-enantiomers.^[154] Polymerization of leucine with 31.1 % *ee* (*L* > *D*) gave polyleucine with 45.4 % *ee*.^[155] When this polyleucine of 45.4 % *ee* is subsequently partially hydrolyzed the residual

monomer shows a lower *ee* value of 30.5 to 43.7 %, while the residual unhydrolyzed polymer shows an enhancement of 49.5 to 54.9 % *ee*.^[156] According to these results a repeated cycle of polymerization and hydrolysis could be an efficient method of enhancing an initial small enantiomeric bias. It was suggested that environmental dry/wet cycles on the primitive Earth might have caused repeated polymerization/hydrolysis cycles that permitted the eventual evolution of optical purity from a small abiotic *ee* value in amino acids.^[155]

Cooperative responses to chiral information and magnification effects can also be extremely large in helical polymers.^[157] Pioneering studies show that polyalkylisocyanates such as polyhexylisocyanate form left- and right-handed helices although the monomers themselves are achiral.^[158] Green et al. demonstrated that helical reversals along the chain are highly sensitive to chiral effects. Incorporation of a small number of units with pendant chiral groups, for example **37**, in co-polymers with hexylisocyanate, results in the control of helical reversals that forces large numbers of polymer chain units to cooperate in directing the chirality of the polymer. On the basis of these findings Green et al. formulated a majority rule and the so-called “sergeants and soldiers” principle. A tiny majority of *R* over *S* monomers or a small amount of chiral units (sergeants) incorporated within the achiral units (soldiers), for example, hexylisocyanate units in polymer **38**, can dictate the helical sense (Figure 13). This powerful amplification mechanism is highly attractive for the magni-

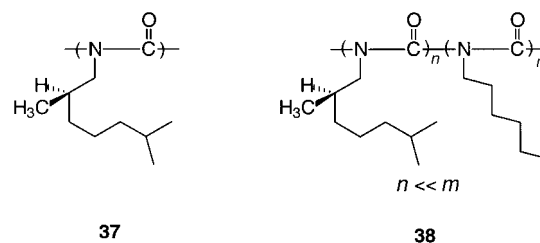


Figure 13. Optically active polyisocyanates.

fication of the small chiral bias that is reached with CPL photoresolution.

Recently, an approach that incorporates a photoresponsive racemic unit into a polyisocyanate and uses CPL resolution of such a trigger element to control the helical sense of the polymer (and to amplify the chiral bias) has been successful.^[159] These types of amplification mechanisms will attract considerable interest in the coming years as similar effects have been observed in other helical polymers^[160] and dynamic aggregates of disc-shaped molecules.^[161]

Finally, it should be emphasized that chirality at a molecular level is not a prerequisite to observe chirality at the macroscopic level, that is, it is not essential to have chiral molecules as building blocks. An illustrative example is shown in Figure 14. Achiral bisurea compounds (low molecular weight

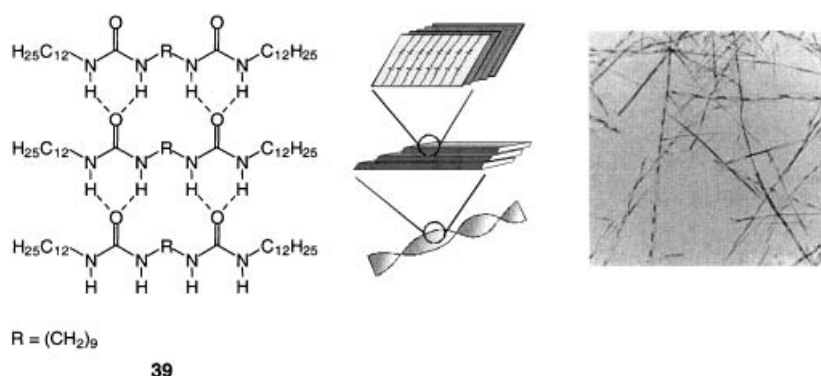


Figure 14. Chiral aggregates formed from achiral bisurea building blocks.

gelators, for example, **39**) undergo efficient and spontaneous self-assembly to form micrometer-long fibers with strong helical twisting.^[162] Apparently, strong anisotropic growth and small distortions cause the macroscopic helicity. Clearly, there is no stereochemical bias as both left- and right-handed helices are formed.

8. Summary and Outlook

There are few areas in chemistry that have experienced the pace of progress seen in asymmetric synthesis in the last decade. It is remarkable that since the early days of organic stereochemistry in the last century the challenge and excitement to perform absolute asymmetric synthesis was felt. Despite the numerous attempts and some remarkable achievements, in particular using circularly polarized light for photochemical conversions and with solid-state reactions in the last few years, the challenge remains as strong as ever. It is doubtful if absolute asymmetric synthesis will be of much use to our synthetic repertoire for the preparation of homochiral compounds. More important is the experimental proof of absolute asymmetric synthesis in the context of the origin of biomolecular chirality and the ways chiral information can be transferred from a molecular level to supra- and macromolecular levels. New discoveries that might point to a potential extraterrestrial origin of chirality and theoretical models for the spontaneous resolution and symmetry breaking are highly intriguing in this respect.

Mechanisms associated with the amplification of chirality and autocatalytic and self-replicating systems are pertinent to this field. The amplification of a small stereochemical bias resulting from absolute asymmetric synthesis remains a major goal, although the first examples in which chiral amplification is demonstrated in autocatalytic and supramolecular systems, such as liquid crystalline materials, look highly promising.

Since absolute asymmetric synthesis and the origin of chirality are intimately related to asymmetric autocatalysis, self-replicating systems, and molecular amplification mechanisms several exciting discoveries are ahead of us—most probably on the trail of the origin of chemical evolution itself.

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Concomitant Polymorphs

Joel Bernstein,* Roger J. Davey, and Jan-Olav Henck

Chemists who encounter polymorphism for the first time are often unaware of its existence and baffled by its manifestations. Experimental problems might include, for example, variable or diffuse melting point, crystal batches with inconsistent physical properties (electrical or thermal conductivity, filtering, drying, flow, tableting, dissolution), or two (or more) different colored or different shaped crystals in the same batch of (chemically) "pure" material. These problems arise because the conditions of the particular crystallization have led to the production of a number of polymorphs, which are present in the crystallizing medium or vessel at the time the crystals are harvested. The fact that polymorphs of a substance can appear concomitantly has long

been recognized but rarely noted or studied. Is the phenomenon of concomitant polymorphs a curse or a blessing? It can be both. It is a curse for the chemist seeking a pure substance and a robust procedure to repeatedly and consistently produce the pure material, and the existence of concomitant polymorphs corrupts that procedure. It is a blessing, however, because (the recognition of) the existence of polymorphs in general, and concomitant polymorphs in particular, can provide the information and the opportunity to gain control over the crystallization process, and to achieve the desired specificity and robustness. An understanding of the competing thermodynamic and kinetic factors that govern the crystallization of polymorphs in general, or of a particular

substance in particular, facilitates the control over the production of the desired polymorph, to the exclusion of undesired ones. Such control has important implications in a variety of industrial applications, of which pharmaceutical production and formulation is but one important example. This review covers the factors that govern competitive polymorphic crystallization and the rationale behind concomitantly crystallizing polymorphs, followed by a survey of concomitant polymorphs of a variety of chemical systems and a variety of crystallization procedures and conditions.

Keywords: concomitant polymorphs • crystallization • kinetics • polymorphism • thermodynamics

You can observe a lot just by watching.

Yogi Berra

1. Introduction

Even the title of this paper^[1] requires close examination: are we referring to a description of the phenomenon of polymorphs that crystallize simultaneously or is this meant to be a practitioner's recipe for obtaining two or more polymorphs at the same time? The intent is the former, but in

describing the phenomenon we certainly can provide hints on how one might accomplish the crystallization of polymorphs, if that were the desired experimental goal.

A polymorph has been defined as "a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state".^[2] Different polymorphs have different structures and hence, in effect, each is a unique material with its own physical and chemical properties. Every student learns early on that crystallization is one of the principal methods of purification, and indeed most industrial processes that lead to solid products rely on this technique almost exclusively to prepare active materials which meet the regulatory and market demands of reproducibility and purity. In a polymorphic system, crystallization can result in the production of more than one material, in fact a mixture of materials; hence a knowledge of the processes that govern nucleation, crystal growth, and phase transformation in these systems is essential, on the one hand, for process control and, on the other hand, to ensure that maximum data and understanding are generated from experiments. This review

[*] Prof. Dr. J. Bernstein

Department of Chemistry

Ben-Gurion University of the Negev

P.O. Box 653, Beer Sheva, 84105 (Israel)

Fax: (+972) 7-647-2943

E-mail: joel@bgumail.bgu.ac.il

Prof. Dr. R. J. Davey

Department of Chemical Engineering, UMIST

P.O. Box 88, Manchester M60 1QD (United Kingdom)

Dr. J.-O. Henck

Institut für Pharmakognosie der Universität Innsbruck

Josef-Moeller-Haus, Innrain 52, 6020 Innsbruck (Austria)

deals with a particular phenomenon which is not widely recognized but is associated with crystallization in polymorphic systems—namely that of concomitant crystallization of polymorphic crystal forms. We shall show that this is of particular relevance on two counts. First, from a scientific point of view, experiments that simultaneously yield crystals of different polymorphic structures potentially offer both structural and thermodynamic information not available when only one phase crystallizes. Second, from a commercial perspective, process conditions that result in concomitant crystallization are to be strenuously avoided since they lead to variable materials that do not meet prescribed specifications. We will address a number of questions related to this phenomenon:

- 1) Why do different polymorphs crystallize concomitantly?
- 2) How can concomitant polymorphic crystallization be achieved or avoided?
- 3) What information can be obtained by the observation and study of such systems?

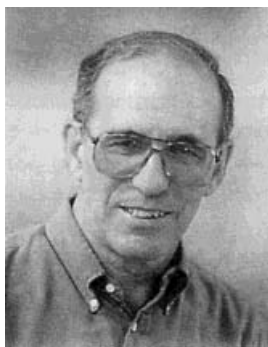
- 4) What use can be made of such information?
- 5) What examples of concomitant polymorphs are available?

Although in the course of addressing these questions a number of examples will be given in demonstration, this paper is not intended to be exhaustive or comprehensive. It is meant to provide an introduction and an entry to a generally unrecognized phenomenon which, when properly recognized and studied, can provide useful information for a variety of disciplines.

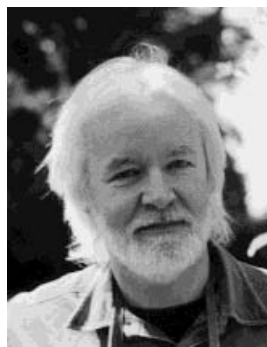
2. Why do Polymorphs Crystallize Concomitantly?—The Qualitative Picture

Crystallization is a remarkable process that brings approximately 10^{20} molecules or ions into an essentially ordered array, and results in the same structure—or limited number of structures, in the case of polymorphism—for every crystal, in every laboratory, and, in principle, every time it is done. There

Joel Bernstein was born in Cleveland, Ohio, in 1941. After obtaining a BA degree at Cornell University, he earned a PhD degree in physical chemistry at Yale University for research on the solid-state spectroscopy of organic compounds. Following two-year postdoctoral stints in X-ray crystallography with the late Ken Trueblood at UCLA and in organic solid-state chemistry with the late Gerhardt Schmidt at the Weizmann Institute of Science in Rehovoth, Israel, he joined the faculty of the newly established Ben-Gurion University of the Negev, where he is now Professor of Chemistry. His research interests center on the organic solid state, with particular emphasis on understanding and utilizing polymorphism, structure–property relationships, hydrogen-bonding patterns and graph sets, and organic conducting materials. His career has been punctuated by visiting professorships at the University of Illinois, Cornell University, and the University of Minnesota, and as a visiting scientist at the Cambridge Crystallographic Data Centre.



J. Bernstein



R. Davey



J.-O. Henck

Roger Davey graduated as a chemist from Bristol University. He earned a PhD degree on crystal-habit modification with Professor J. W. Mullin at University College London and spent four years studying the growth of molecular crystals at the ETH in Zurich, Switzerland. He then joined ICI at their Corporate Laboratory in Cheshire where he became a Company Research Associate, eventually transferring to ZENECA's Process Studies Group at Huddersfield. He joined UMIST in 1995 and now holds the Chair in Molecular Engineering in the Department of Chemical Engineering and leads the Department's activities in the area of colloids, crystals, and interfaces. His research interests in solid-state and surface chemistry form the basis for a range of activities in crystallization, precipitation, phase transitions, and the design of surface-active molecules.

Jan-Olav Henck obtained his Diplom in chemistry from the Universität Essen (Germany) in 1993. During the experimental work on his master thesis on phase transitions of drug substances under pressure, at the pharmaceutical division of Bayer AG in Wuppertal-Elberfeld (Germany), he came in contact with the topic of polymorphism of drug substances. For further studies in this research field he moved to the University of Innsbruck (Austria), where he received his PhD degree at the Institute of Pharmacognosy with Prof. Dr. Artur Burger in 1996. His thesis on conformational polymorphism of *n*-butyl-substituted drug substances was awarded the State Capitol Prize from the city of Innsbruck for scientific research at the University of Innsbruck. During 1996–1997 he was an Alexander von Humboldt Foundation Postdoctoral Fellow (Feodor Lynen Program) with Prof. Joel Bernstein at the Ben-Gurion University of the Negev in Israel.

are exceptions, but it is these characteristics of the crystallization process that make it so attractive as a purification technique. As generations of chemists have learned, it is possible to define experimentally for any substance the solvent, temperature, rate of evaporation or cooling, and other conditions under which a material will crystallize.^[6] This has been termed the *occurrence domain*.^[7] This domain exists for any substance, but rarely, if ever, are its contents completely known. The contents of the occurrence domain for any material—in the present context, any polymorph—are not necessarily unique. In regions in which there is overlap of domains, one may expect that two or more polymorphs would crystallize under essentially identical conditions, thus leading to the phenomenon discussed in this review.

3. Polymorphism—Some Fundamentals

Like most chemical processes, crystallization in polymorphic systems is governed by a combination of thermodynamic and kinetic factors. We shall see in this and the following Section that it is in fact the interplay between thermodynamics and kinetics that makes concomitant crystallization possible. This section deals with the essentials of the thermodynamic processes involved. More detailed accounts may be found elsewhere.^[8–13]

3.1. Thermodynamic and Kinetic Stability Amongst Polymorphs

Thermodynamic theory tells us that crystallization must result in an overall decrease in the free energy of the system. This means that, in general, the crystal structures that appear will be those with the greater (negative) lattice (free) energies. In polymorphic systems there are evidently a number of possible structures with similar lattice energies.

This drive towards free energy minimization will be balanced, as in all chemical changes, by the kinetic tendency of the system to crystallize as quickly as possible to relieve the imposed supersaturation. From the molecular point of view, the process of crystallization is one of supramolecular assembly in which the building blocks of the crystal assemble through the utilization of molecular recognition forces involving an array of intermolecular interactions as well as stereochemical packing constraints. If some structures are able to form more quickly than others then the system may, in the short term, settle for less than the maximum energy decrease, providing such a situation can be achieved at speed. A secondary transformation to a lower energy state can take place later.

The distinction between thermodynamic and kinetic influences is often demonstrated using the example of the graphite and diamond forms of carbon. The former is the thermodynamically preferred crystalline form, but kinetic factors (in particular, a high activation barrier) make the rate of transformation from diamond to graphite infinitely slow.^[14]

3.1.1. Energy versus Temperature Diagrams

The energy versus temperature (E/T) diagram was introduced into crystallography by Buerger^[15] in 1951 without application to any specific example. The theoretical derivation and practical application of this diagram have been described and discussed by Burger and Ramberger^[11, 12] and by Grunenberg et al.^[13] For simplicity we will limit the discussion to two polymorphic solids, although the extension to a larger number is based on the same principles.

The relative stability of two polymorphs depends on their free energies, the more stable polymorph having a lower free energy. The Gibbs free energy of a substance is expressed as Equation (1), where G and H are clearly functions of temper-

$$G = H - TS \quad (1)$$

ature and this variation may be plotted for one possible relationship between the two polymorphs and the melt (liquid) as in Figure 1. Such diagrams contain a great deal of information in a compact form, and provide a visual and readily interpretable summary of the often complex relationships among polymorphs.

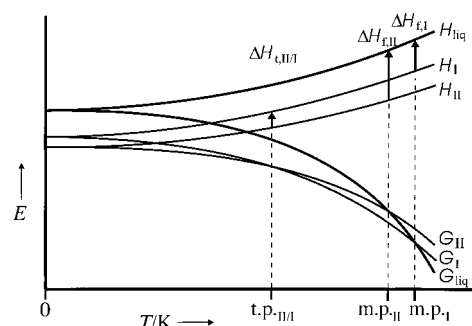


Figure 1. Energy versus temperature (E/T) diagram of a dimorphic system. G is the Gibbs free energy and H is the enthalpy. The Roman numerals indicate the two polymorphs; m.p. is the melting point and t.p._{II/I} is the transition point between the two polymorphs. This diagram represents the situation for an enantiotropic system, in which form II is the stable form below the transition point. (Reprinted from ref. [13] with permission.)

At absolute zero, TS vanishes so that the enthalpy is equal to the Gibbs free energy. As a consequence, at absolute zero, the most stable polymorphic modification should have the lowest Gibbs free energy. As mentioned above, at absolute zero the entropy term will play a role which may differ for the two polymorphs so that the free energy as a function of the temperature follows a different trajectory for the two polymorphs, as represented by the G_I and G_{II} curves in Figure 1. The two curves cross at the thermodynamic transition point t.p._{II/I}, but since the enthalpy of II is lower than that of I, a quantity of energy $\Delta H_{t,II/I}$ is required to be input for the phase transition, which must be endothermic for the transition above t.p. and exothermic below t.p. for the situation that is depicted in Figure 1. The endothermic solid-to-liquid transitions at the melting points may be understood in the same way, with $\Delta H_{f,I}$ and $\Delta H_{f,II}$ denoting the respective enthalpies of fusion. Figure 1 represents an *enantiotropic* situation, since

$t.p._{II/I}$ lies at a temperature below the melting points for the two polymorphs.

The *monotropic* situation is represented in Figure 2. In this case, there is no transition point below the melting points of the two polymorphs. The phenomenological manifestation of enantiotropism is that there can be a reversible transition from one phase to another without going through the gas or liquid phase. If the thermodynamic relationship is one of

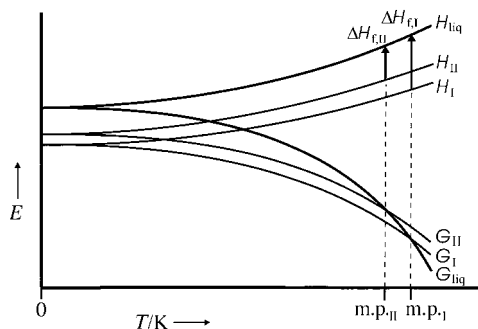


Figure 2. The E/T diagram of a monotropic dimorphic system. All symbols have the same meaning as in Figure 1. (Reprinted from ref. [13] with permission.)

monotropism the two modifications are not interconvertible.^[16] In the context of simultaneously crystallizing polymorphs, the thermodynamic aspects are clear. First, only at thermodynamic transition points can two forms have the same stability and hence coexist as mixtures at equilibrium. At any other temperature there will be a thermodynamic tendency to transform to the more stable structure. This implies that mixtures of polymorphs will have limited lifetimes, except at the thermodynamic transition point, with transformation kinetics playing a role in those lifetimes.

3.1.2. Vapor Pressure versus Temperature Diagram

Another common representation of phase relationships is the pressure versus temperature (p/T) diagram. Figure 3 shows prototypical p/T plots for the enantiotropic and monotropic cases. These are best understood by traversing along various curves, which represent equilibrium situations between two phases. The liq./v. line in the high-temperature region of Figure 3a is the boiling point curve for the (common) melt of the two polymorphs. Moving to lower temperatures along that line, one encounters the II/v. line, which is the sublimation curve for form II. The intersection is the melting point for form II. Under thermodynamic conditions form II would crystallize out at this point and the solid part of the II/v. line would govern the behavior. However, if kinetic conditions prevail (for example, if the temperature is lowered rapidly) the system may proceed along the broken liq./v. line to the intersection with the I/v. line, at which point form I would crystallize. Continuing downward along the solid part of the II/v. curve, the crossing point with the I/v. sublimation curve is the transition point between the two polymorphic phases. Once again, if thermodynamic conditions prevail, form II will transform to form I. Under kinetic conditions form II may continue to exist (even indefinitely in

some cases) along the II/v. sublimation curve. Figure 3a represents the enantiotropic case because the transition point between the two phases is found at a temperature below the melting point of form II, while Figure 3b represents the monotropic situation, in which the transition point is above the melting points of both forms.

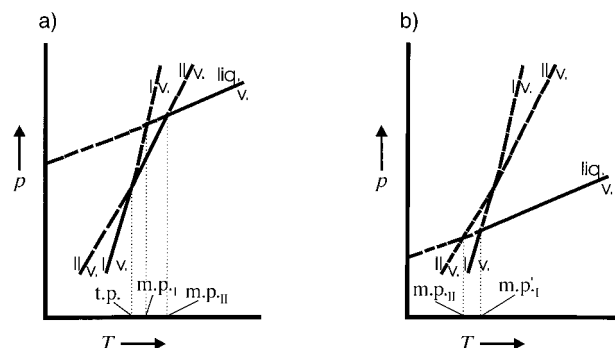


Figure 3. Pressure versus temperature plots: I/v. and II/v. represent sublimation curves, liq.v. is the boiling point curve. Broken lines represent regions which are thermodynamically unstable or inaccessible. a) Enantiotropic system; b) monotropic system. The labeling corresponds to that of Figures 1 and 2 to indicate that form I is stable at room temperature, which is below the transition point in the enantiotropic case. (Adapted from ref. [2] with permission.)

3.2. Some Practical Aspects of Relative Stabilities of Polymorphs

Knowledge of the enantiotropic or monotropic nature of the relationship between polymorphs can be used to steer crystallization processes to obtain a desired polymorph at the exclusion of an undesired one. For a dimorphic system there are four possibilities:

- 1) The thermodynamically stable form in a monotropic system: no transformation can take place to another form, and no precautions need be taken to preserve that form or to prevent a transformation.
- 2) The thermodynamically stable form in an enantiotropic system: precautions must be taken to maintain the thermodynamic conditions (temperature, pressure, relative humidity, etc.) at which the G curve for the desired polymorph is below that for the undesired one.
- 3) The thermodynamically metastable form in a monotropic system: a kinetically controlled transformation may take place to the undesired thermodynamically stable form. To prevent such a transformation it may be necessary to employ drastic conditions to reduce kinetic effects (e.g. very low temperatures, very dry conditions, storage in the dark).
- 4) The thermodynamically metastable form in an enantiotropic system: the information for obtaining and maintaining this form is essentially found in the E/T diagram.

Therefore, it is of practical importance (e.g. preformulation studies of a drug substance^[10, 13]) to determine whether a system of concomitant polymorphs is monotropic or enantiotropic to enable the choice of and control over the desired

polymorphic form. The combination of experience with polymorphic systems and the accumulation of sufficient thermodynamic and structural data have permitted the development of some useful “rules” for determining the relative positions of the G and H isobars, as well as the enantiotropic or monotropic nature of the relationship between polymorphs.^[11–13]

3.2.1. Heat-of-Transition Rule^[11]

If an endothermic phase transition is observed at a particular temperature, this experimental transition temperature lies above the thermodynamic transition temperature. An endothermic phase transition is observed if two modifications are enantiotropically related and is represented in the E/T diagram by the intersection point of the G isobars of two modifications. If the phase transition is exothermic, there is no thermodynamic transition point below the experimentally observed transition temperature. This is generally observed if two modifications are monotropically related. Exceptions to this rule were discussed by Burger and Ramberger.^[12]

3.2.2. Entropy-of-Fusion Rule

The entropy of fusion is easily accessible by means of differential scanning calorimetry (DSC), since the enthalpy of fusion and the melting point of a crystal can be obtained in one experiment ($\Delta H_f/T_f = \Delta S_f$). At the melting point, the difference between the Gibbs free energy of a modification and its melt is zero. If a modification with the higher melting point has the lower entropy of fusion, the two forms are enantiotropic. Monotropism is realized if the lower melting form shows the lower entropy of fusion.^[13]

3.2.3. Enthalpy-of-Sublimation Rule

The enthalpy of sublimation of a particular crystal form is the sum of its enthalpy of fusion and enthalpy of vaporization. The latter is identical for all polymorphs of a compound. Therefore the enthalpy of transition for the transformation of one modification into another is the same as the difference in their enthalpies of sublimation^[9] and their enthalpies of fusion. Thus, if the modification with the higher melting point has the lower enthalpy of sublimation, the two forms are enantiotropic. Monotropism is realized if the lower melting form shows the lower enthalpy of fusion.

3.2.4. Density Rule^[11]

If a particular modification exhibits a lower density than another one at ambient conditions, then it may be assumed that, at absolute zero, this form is thermodynamically metastable. The energetically most favorable packing of molecules in a crystal has the strongest interactions between the molecules and hence the greatest density. The best possible packing also corresponds to thermodynamic stability.

This energetically favorable modification requires more energy than any other modification to melt. At absolute zero, the form with the greatest density is thermodynamically stable. This approximation assumes that there is no great variation in the density of solids over a wide range of temperature. The two modifications are monotropically related if the higher melting modification shows the higher density. Otherwise they are enantiotropically related. Exceptions to this rule (e.g. resorcinol^[17] or acetazolamide^[18]) are discussed by Burger and Ramberger.^[11]

3.2.5. Heat-Capacity Rule^[13]

If the higher melting modification shows a higher heat capacity at a given temperature than another modification, these two crystal forms are enantiotropically related. Otherwise the two modifications are monotropically related.

3.2.6. Solubility and Dissolution Rates

In addition to differences in melting points, heats of fusion, entropies of fusion, densities, heat capacities, and virtually every chemical and physical property, different modifications can also exhibit different solubilities and dissolution rates. Since the solubility is directly proportional to the free energy of a modification, determination of solubility curves is the most reliable method of assessing the relative free energies of polymorphs. The difference in solubility of two polymorphs is a direct measure of the ΔG between them. It is important to note that although the absolute solubility (and hence the dissolution rate) of a polymorph will be solvent dependent, the relative solubility of different forms will not depend on the solvent used.

As discussed in Sections 4 and 5, the situations in which polymorphs concomitantly crystallize are determined by the experimental conditions in relation to both the free energy–temperature relationships and the relative kinetic factors. These situations may arise either because specific thermodynamic conditions prevail or because the kinetic processes have equivalent rates. In thermodynamic terms we have seen that polymorphs can only exist in true equilibrium at the thermodynamic transition temperature (where the G curves cross). The chance of carrying out a crystallization precisely at such a temperature must be small, with the inevitable conclusion that kinetics play at least some role in the overall process. The final consequence of this, of course, is that a system of concomitantly crystallizing polymorphs will be subject to change in the direction that favors the formation of the most stable structure. If the crystals have grown from and remain in contact with solution, the most likely route for this transformation is via the solution by dissolution and recrystallization.^[2, 19] If the crystals have formed from the melt or vapor phase or have been isolated from their mother phase, solid-state transformation is possible.^[20] Either way, keen observation is vital to recognize the phenomenon, as discussed in Section 5.

4. Why do Polymorphs Appear Together?—Kinetic Factors

The starting point for a discussion of the kinetic factors is the traditional energy–reaction coordinate diagram in Figure 4. This shows G_0 , the free energy per mole of a solute in a supersaturated fluid which transforms by crystallization into one of two crystalline products, I or II, in which II is the more stable ($G_{\text{I}} > G_{\text{II}}$). Associated with each reaction pathway is a transition state and an activation free energy which is implicated in the relative rates of formation of the two structures. Unlike a chemical reaction, crystallization is complicated by the nature of the activated state since it is not a simple bi- or trimolecular complex as would be expected for a process in which a covalent bond is formed; rather it relates to a collection of self-assembled molecules with not only a precise packing arrangement but which also exist as a new separate solid phase.

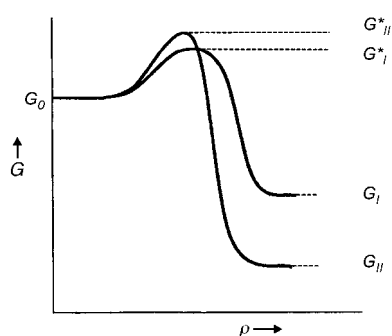


Figure 4. Schematic representation of the reaction coordinate ρ for crystallization in a dimorphic system to show the activated barriers for the formation of polymorphs I and II.

It is the existence of the phase boundary that complicates matters since this is associated with an increase in free energy of the system which must be offset by the overall loss of free energy. For this reason the magnitudes of the activated barriers are dependent on the size (i.e., the surface-to-volume ratio of the new phase) of the supramolecular assembly (crystal nucleus). This was recognized in 1939 by Volmer in his development of the kinetic theory of nucleation from homogeneous solutions which remains our best guide to-day.^[21]

One of the key outcomes of this theory is the concept of critical size which an assembly of molecules must have in order to be stabilized by further growth. The higher the operating level of supersaturation, the smaller this size is (typically a few tens of molecules). In Figure 4, the supersaturation with respect to I is simply $G_0 - G_{\text{I}}$ and is lower than $G_0 - G_{\text{II}}$ for structure II. However, it can now be seen that if the critical size is lower for I than for II for a particular solution composition then the activation free energy for nucleation is lower and kinetics will favor form I. Ultimately form I will have to transform to form II, a process that we discuss later. Overall we can say that the probability that a particular form i will appear is given by Equation (2) in which

$$P(i) = f(\Delta G, R) \quad (2)$$

ΔG is the free energy for forming the i th polymorph and R is the rate of some kinetic process associated with the formation of a crystal by molecular aggregation. Thus, for example, if we follow the above reasoning we could equate the rate process with J , the rate of nucleation of the form. If all polymorphs had the same rates of nucleation then their appearance probability would be dominated by the relative free energies of the possible crystal structures.

The rates of nucleation as expressed by the classical expression of Volmer are related to various thermodynamic and physical properties of the system such as bulk and surface free energy (γ), temperature (T), degree of supersaturation (σ), solubility (hidden in the preexponential factor A_n) which will not be the same for each structure but will correctly reflect the balance between changes in bulk and surface free energies during nucleation. This is seen in Equation (3), which relates the rate of nucleation to the above parameters (v is the molecular volume).

$$J = A_n \exp(-16\pi\gamma^3 v^2 / 3k^3 T^3 \sigma^2) \quad (3)$$

From this analysis it can be seen that the tradeoff between kinetics and thermodynamics is not at all obvious. Consider a monotropic, dimorphic system (for simplicity) whose solubility diagram is shown schematically in Figure 5. It is quite clear that for the occurrence given by solution compositions and temperatures that lie between the form I and II solubility curves, only polymorph II can crystallize. However, the outcome of an isothermal crystallization that follows the crystallization pathway indicated by the vector in Figure 5 is not so obvious since the initial solution is now supersaturated with respect to both polymorphic structures, with thermodynamics favoring form II and kinetics form I.

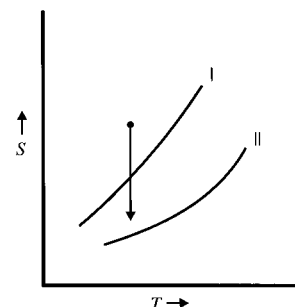


Figure 5. Schematic solubility diagram for a dimorphic system (polymorphs I and II) showing a hypothetical crystallization pathway at constant temperature.

Experimentally, the reality of this overall scenario of kinetic versus thermodynamic control was known long before the development of nucleation theory and is encompassed by Ostwald in his Rule of Stages in 1897.^[22, 23] The German scientific literature between 1870 and 1914 contains many examples from organic and inorganic chemistry in which crystallization from melts and solutions yields an initial metastable form which is ultimately replaced by a stable structure, and Ostwald was led to conclude that “when leaving a metastable state, a given chemical system does not seek out the most stable state, rather the nearest metastable one that can be reached without loss of free energy”.^[24] Figure 6 shows an example of Ostwald’s rule for potassium nitrate. It shows a group of rhombic (β form) crystals in contact with their mother liquor and their solution-mediated conversion to the more stable needle morphology (α form) by means of dissolution and recrystallization.

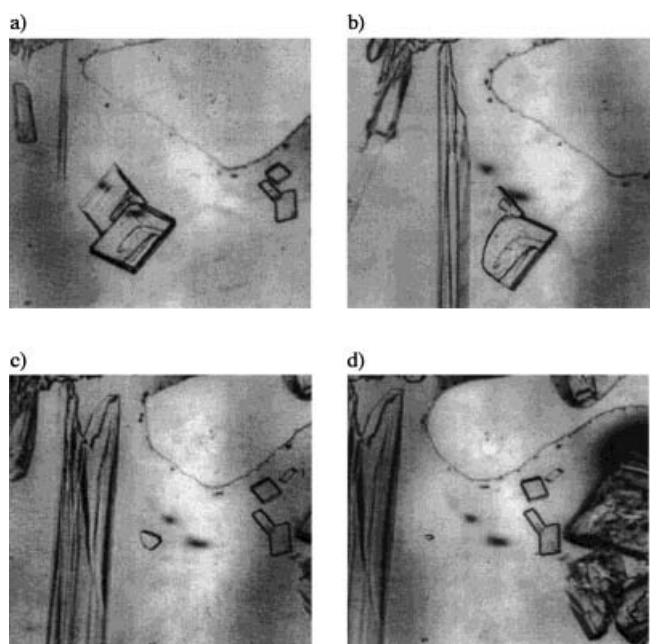


Figure 6. Time-lapse micrographs ($\times 50$) of the crystallization of potassium nitrate from aqueous solution at room temperature. a) After 1 min, showing well formed rhombs and a single needle (upper left quadrant); b) after 5 min—note the rounded edges of the rhombs due to dissolution and the enlargement of the needle; c) and d) after 10 and 15 min—note the further dissolution of the rhombs and growth of the needle.

Of course this conclusion is significantly flawed: when a crystallization experiment yields only a single form there is no way of knowing whether it contradicts the rule or whether the material is simply not polymorphic. There is no way of answering this question. However, a sufficient number of cases of successively crystallizing polymorphic forms have been observed to warrant consideration of the principles behind Ostwald's rule as guidelines for understanding the phenomenon.

By making use of Volmer's equations, some attempts have been made by Becker and Döring, Stranski and Totomanov, and Davey to explain the rule in kinetic terms.^[25] In doing so it becomes apparent that the situation is by no means as clear cut as Ostwald might have led us to believe. Figure 7 shows the three possible simultaneous solutions of the nucleation equations which indicate that, by careful control of the occurrence domain, there may be conditions in which the nucleation rates of the two forms are equal and hence their appearance probabilities are nearly equal. Under such conditions we might expect the polymorphs to crystallize concomitantly.

5. How Can Concomitant Polymorphs be Recognized?

Most cases of concomitant polymorphs have been recognized visually simply by a combination of curiosity, thoroughness, and keen observation. In the first years following the discovery of polymorphism by Mitscherlich in 1822,^[26] the principal method of the study of crystals was observation and

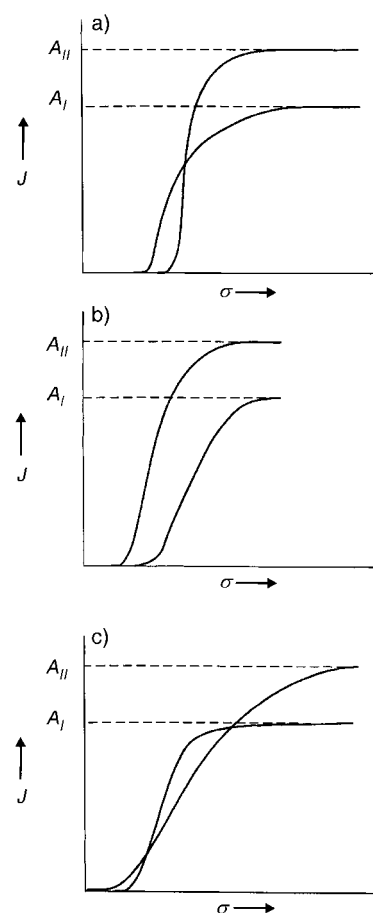


Figure 7. The rates of nucleation as functions of supersaturation for the dimorphic system defined in Figure 5. The three diagrams a, b, and c represent the three possible solutions for the simultaneous nucleation of two polymorphs each of which follows a rate equation of the form of Equation (3). Note that solutions a and c both allow for simultaneous nucleation of the forms at supersaturation levels corresponding to the crossover of the curves.

measurement on the microscope, particularly the polarizing microscope, and the measurement of interfacial angles on an appropriate goniometer. Differences in habit are indicative (but not necessarily conclusive) evidence of polymorphism, which could be confirmed by physical measurements such as index of refraction, melting behavior (including, of course, the melting point itself) and others. Groth's landmark compilation of such data contains many examples of polymorphism.^[27] He was apparently also intrigued by the instances of concomitant crystallization of polymorphs, and compiled a list of examples in his book on chemical crystallography in 1904.^[28]

With the emergence of X-ray diffraction and the development of more sophisticated methods of analysis, the discovery of concomitant polymorphs should have become more frequent—provided one is aware of the phenomenon. Even a variable melting point may be a sign of concomitant polymorphs since mixtures of different polymorphic composition can result from the crystallization, but also a peak on a DSC scan, or a broadening or doubling of lines in a solid-state IR or solid-state NMR spectrum may be signs for the existence of concomitant polymorphs. Still, probably the best

method for discovering them is careful thermomicroscopic examination on the hot-stage polarizing microscope,^[29, 30] and three examples of the facility with which concomitant polymorphs may be observed on the hot-stage polarizing microscope are given in Figure 8.

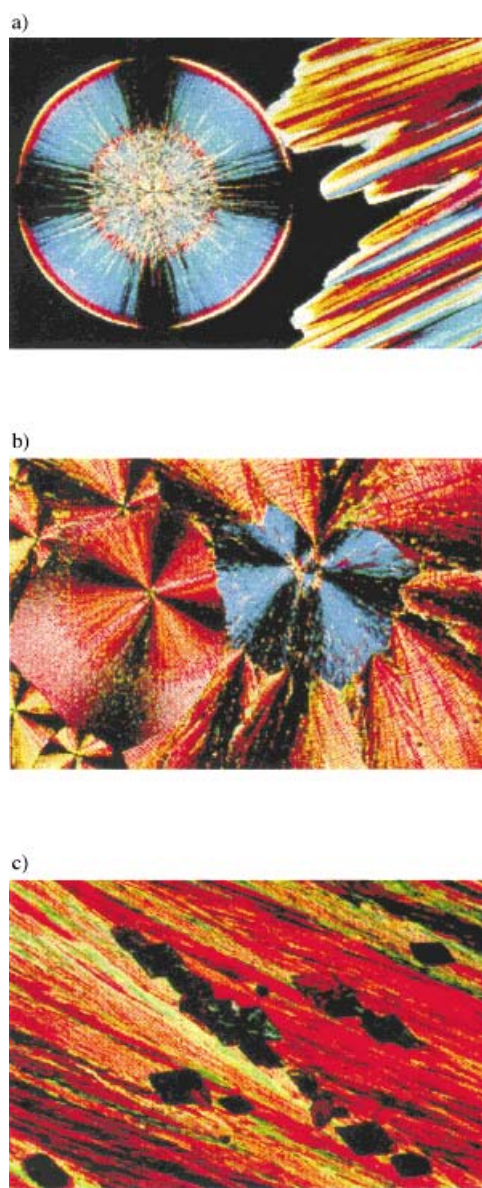


Figure 8. Cocrystallizing polymorphs as observed on the hot-stage microscope. a) Two crystal modifications of phenobarbital; b) three crystal modifications of nicotinamide; c) growth of the stable (diamond-shaped) crystals of sulfethidole from the unstable form. (Reprinted from ref. [30] with permission.)

6. What Are Concomitant Polymorphs Good For?

Polymorphs are of general interest because they represent special situations for the study of structure–property relations in systems with limited numbers of variables. They are also of interest since they provide unique data on the factors that govern molecular packing. Finally they are, as pointed out earlier, of extreme interest to those involved in the large-

scale preparation of solid forms of specialty chemical and pharmaceutical materials.

Thus, if concomitant crystallization occurs, it offers the crystallographer the chance to maximize the data from a single crystallization experiment. It offers the formulation chemist the chance to measure physical properties and hence to select the structure that best matches the needs of the product. It gives the process chemist and chemical engineer a choice of which morphology might separate more effectively and also a warning that the process will have to be robust if a single polymorph is to be consistently isolated. For these reasons we believe that chemists should be aware of this phenomenon and maximize the information it offers.

Finally, we comment that since concomitant polymorphs are very nearly energetically equivalent structures, they provide excellent and demanding benchmarks for the validation of lattice energy programs^[31] and so-called “polymorph predictor” programs.^[32, 33] The programs and the force fields employed in those programs must reproduce the near equivalency of the crystal energetics, even if the absolute lattice energy is not reproduced or even not known.^[34]

7. Examples of Concomitant Polymorphs

Apart from the above-mentioned section in Groth’s book we are not aware of any other attempt to collect and document examples of concomitant polymorphs. It is a daunting, perhaps even impossible task to systematically extract additional instances from the literature.^[35] Most examples given here were taken from our own experience, from chance encounters of descriptions of crystal growth procedures in the experimental sections of papers in the literature^[24] or from responses to appeals by the authors at scientific meetings for testimonial cases from colleagues. One of the objects of this paper is to increase awareness of the phenomenon so it can become a keyword for indexing and abstracting, to enable future workers to take advantage of the useful information to be extracted from situations in which polymorphs crystallize concomitantly.

7.1. The Earliest Reported Concomitant Polymorphs

The first recognized example of a polymorphic organic substance was also an example with concomitant polymorphs. In 1832 Wöhler and Liebig described the dimorphism of benzamide.^[36] They synthesized the material for the first time and initially found a melting point of 115 °C (later called modification II).^[37] Reexamination led to a melting point of 128 °C (modification I). The lower melting modification crystallizes in featherlike needles while the higher melting modification shows blocks (Figure 9). It is of interest that if a hot saturated aqueous solution of benzamide is allowed to cool rapidly, one is able to observe by microscopy that the two modifications crystallize concomitantly, and in accord with Ostwald’s rule. With increasing time the blocks of modification I grow at the expense of the feathery needles.

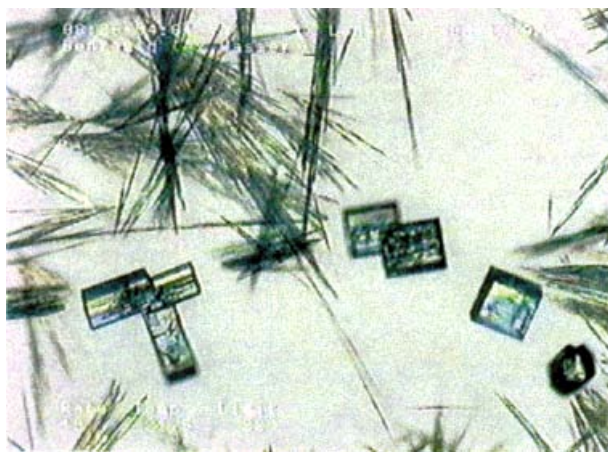
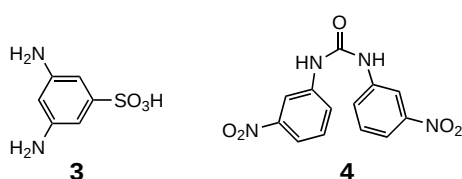
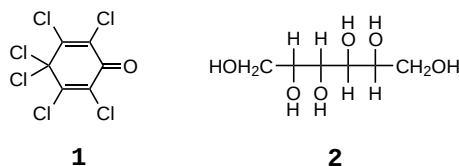


Figure 9. Photograph of the two forms of benzamide growing in aqueous solution. Form I are the blocklike crystals which grow at the expense of the featherlike needles of the less stable form II.

7.2. Groth's Collection

As noted above, Groth was apparently the first to collect a number of cases of the phenomenon of concomitant polymorphism from the literature until roughly the turn of the 20th century.^[28] He noted that concomitant crystallization can occur for an enantiotropic system such as sulfur as well as in a monotropic dimorphous material such as “hexachloro-ketodihydrobenzene, C_6Cl_6O ” (**1**). He characterized the phenomenon as a “peculiarity” which is “analogous to the...indifference towards direct transformation” between polymorphic forms.



Groth presents examples across a wide range of compound types, but what appears to be common among these examples is that keen observation was combined with considerable time and effort to study and characterize the compounds. Among the inorganic examples cited by Groth are telluric acid (H_6TeO_6),^[38] ammonium fluorosilicate $(NH_4)_2SiF_6$,^[39] sodium beryllium fluoride (Na_2BeF_4) ,^[40] rubidium dichromate $(Rb_2Cr_2O_7)$,^[41] and ammonium paratungstate $(NH_4)_{10}W_{12}O_{41} \cdot H_2O$,^[42] while the organic examples include mannitol $C_6H_{14}O_6$ (**2**),^[43, 44] *m*-diaminobenzenesulfonic acid ($C_6H_3(NH_2)_2SO_3H$) (**3**),^[45] and di-*m*-nitro-*s*-diphenylcarbamide $CO(NHC_6H_4NO_2)_2$ (**4**).^[46] An organometallic salt exhibiting the phenomenon is dimethylammonium chloroplatinate $[NH_2(CH_3)_2PtCl_6]$.^[47]

7.3. *m*-Nitrophenol: 120 Years of History

In spite of their generally keen powers of observation, the giants of 19th and early 20th century chemical microscopy and morphology certainly could have been aided by modern technology in the discovery of concomitant polymorphs. *m*-Nitrophenol is a case in point. The description of the material appears in Groth's book.^[48] The two melting points quoted by Groth, 96 °C^[49] and 93 °C,^[50] and the description of the crystals might have suggested that the phase was not pure but the difference was within the acceptable range for different determinations. Groth himself had determined the interfacial angles in 1875, and Barker^[51, 52] and Steinmetz^[50] obtained similar results, with no hint of polymorphism.

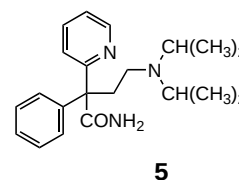
In 1934 Davis and Hartshorne^[53, 54] determined indices of refraction as a technique for the identification of organic solids, including *m*-nitrophenol. They did note “occasional individuals (of crystals) with more or less rhombic outlines” amid monoclinic prismatic crystals (m.p. 96 °C) from water and benzene.

In 1972 Shigorin and Shipulo^[55] reported that the compound exhibited a strong second harmonic generation (SHG), an effect known to require a non-centrosymmetric space group,^[56] but Groth's morphological description indicated a centrosymmetric space group. In an attempt to resolve this discrepancy, Pandarese et al. carried out the crystal structure determination of the material described by Groth and others on crystals grown from the melt and from benzene.^[57] The crystals were indeed centrosymmetric, in the common space group $P2_1/n$.

With the dilemma not resolved, they carefully reexamined many individual crystals from the benzene-grown batch, and discovered that approximately 20% belonged to the non-centrosymmetric orthorhombic space group $P2_12_12_1$, thus explaining the source of the SHG. A method for purifying *m*-nitrophenol and growing single crystals was developed by Wojack and Marqueton in 1989^[58] and the structure of the orthorhombic form was published in 1996.^[59]

7.4. Similar and Dissimilar Solubilities

One example from our own collection of concomitant polymorphs from solution is the dimorphic drug substance disopyramide **5**. Crystallization from *n*-hexane at 25 °C led to both modifications simultaneously. Gunning et al.^[60] have described the solubility behavior and dissolution rates of two modifications of this material. They found no significant differences in the solubilities and the dissolution rates of the crystal forms at 37 °C. No thermodynamic or structural studies have been published until now.



We prepared single crystals of the two forms, determined their thermodynamic properties, and solved their structures, which will be published in a separate contribution. The two crystal forms are enantiotropically related with a t.p. at about

40 °C. Modification II (m.p. 86 °C) crystallizes in rough blocks, while modification I (m.p. 96 °C) shows a needlelike habit. This example shows that similar solubilities and dissolution rates favor concomitant crystallization of different modifications.

The recent report of work on a neutral copper complex reveals some possible additional features of concomitant crystallization. Kelly et al.^[61] prepared blue crystals of **6**, which precipitate from “reasonably concentrated (acetonitrile) solutions” with square-planar coordination geometry around the copper center (Figure 10). When the precipitate was filtered off and the remaining mother liquor treated with diethyl ether, followed by cooling in a freezer, concomitant crystallization of the blue crystals with green crystals occurred, in which the molecular structure exhibits pseudotetrahedral coordination geometry around the copper center.

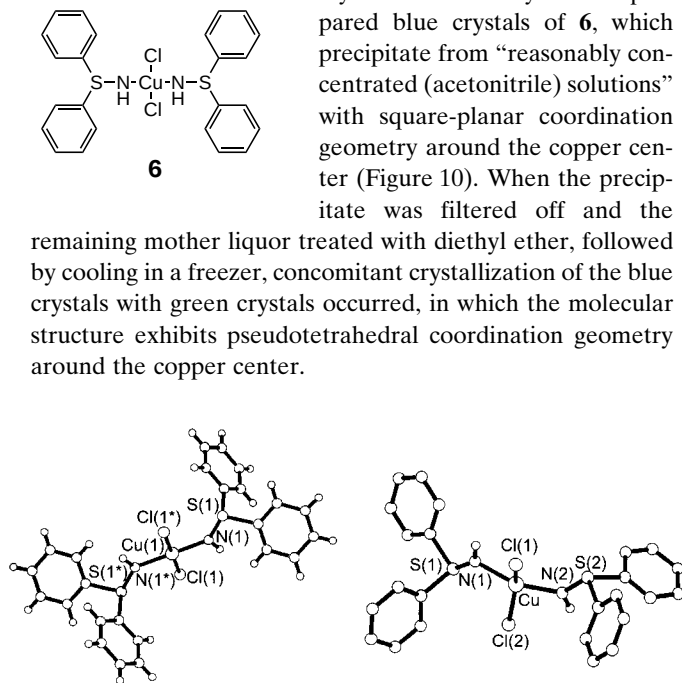


Figure 10. Molecular structure of the concomitant polymorphs of **6**. Left: the square-planar geometry found in the blue crystals. Right: The pseudotetrahedral geometry found in the green crystals. (Reprinted from ref. [61] with permission.)

There is ample evidence that this also is a genuine case of polymorphism. The blue square-planar form can be dissolved to obtain the green tetrahedral one; indeed the authors state that the two form intergrowths, which apparently grow coincidentally. The green form is obtained only from dilute solutions, and once it is obtained the blue form cannot be regenerated. The sequence of events and the experimental conditions are compatible with Ostwald's Rule of Stages: the slight thermodynamic preference for the green form over the blue one (at least in dilute solutions—the melting points are essentially identical) and the phenomenon of “disappearing polymorphs”.^[62] Once seeds of the (even slightly) preferred green form are present in the immediate environment, the blue form cannot be obtained.

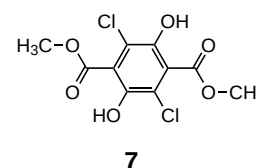
7.5. Trimorphic Concomitant Crystallization

The “diphenylcarbamide” **4** is, in fact, a urea derivative, and was recently studied by Etter et al. for apparently entirely different reasons.^[63] As a symmetrically substituted urea derivative it was expected to exhibit a tendency to form polar chains,^[64] while the substituents may be considered derivatives of *m*-nitroaniline and therefore might exhibit the known

tendency of such compounds to avoid a centrosymmetric structure.^[56, 65] However, it is the concomitant trimorphic crystallization behavior of this compound, which was extensively studied almost a century ago, that is of interest here.

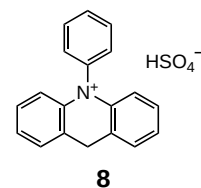
The three reported forms are α , yellow prismatic needles; β , white needles; and γ , yellow tablets. Upon crystallization from 95 % ethanol in the range 30–75 °C, the α and β forms always crystallize concomitantly, even in the presence of seeds of one form. The relative amounts can be regulated by varying the temperature; α is preferred at higher temperatures. Upon evaporation of the mother liquor at “the ordinary temperature (13 °C)” γ crystallizes out alone; warming the same mother liquor leads also to some crystals of β ; at 40 °C γ no longer appears, but small amounts of α appear. The authors conclude that on the basis of the experiments with 95 % alcoholic solutions, γ is the stable form at room temperature (considerably lower than room temperature today), and with increasing temperature, β and then α are the stable forms. However, this behavior may be modified by solvent. This is clearly a rich system with a very delicate balance between the relative stabilities of the three forms, as well as the kinetic factors that govern their appearance.

There are other examples of trimorphic concomitant crystallizations, generally recognized by differences in color. One, also originating in the early literature,^[66] but on which a great deal of work has subsequently been done is methyl 2,5-hydroxy-3,6-dichloroterephthalate (**7**). The white and yellow forms were reported by Hantzsch in 1916^[66] and studied by Byrn et al. in 1972,^[67] but it was not until a thorough study was undertaken in 1989 that a third light yellow form was discovered by Dunitz and co-workers.^[68] As the latter authors point out, visual observation during heating often reveals changes that are not detected by instrumental analytical methods, and it was this observation that led to the discovery of the previously undetected form.



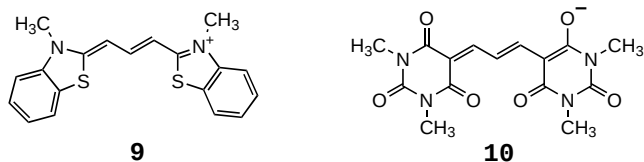
Crystallization of the dibromo derivative of **7** from concentrated ethanolic solutions yields first polymorphic modification I, which transforms over a period of a week to a second modification II, upon which small crystals of the first form adhere. Crystals of both modifications are recognizable and separable by their morphology and color: the first are colorless blocks or plates, while the second are colorless on some faces and light violet on others.^[69]

The term coined by Hantzsch^[70] for polymorphs that exhibit different colors is *chromoisomerism*, recently discussed in historical perspective by Kahr and co-workers.^[71] An example given by Kahr, which is also one of concomitant polymorphs, is that of 9-phenylacridinium hydrogen sulfate (**8**) which yields equal masses of red and green forms from acetonitrile/DMSO (10/1). The physical basis for the color difference remains an enigma.



7.6. Concomitant Crystallization of Multicomponent Systems

Concomitant crystallization is not limited to single component systems. For the remarkable cyanine/oxonol system (**9**/**10**) at least fourteen different polymorphs or solvates have been identified.^[72] Two of these, a gold and a red form (each containing a molecule of CHCl_3 solvent per 1:1 complex, and



hence true polymorphs) crystallize concomitantly and have been structurally characterized.^[72] Three of these polymorphs are shown in Figure 11. Despite the fact that both of these dyes are known to be individually self-aggregating,^[73] the two

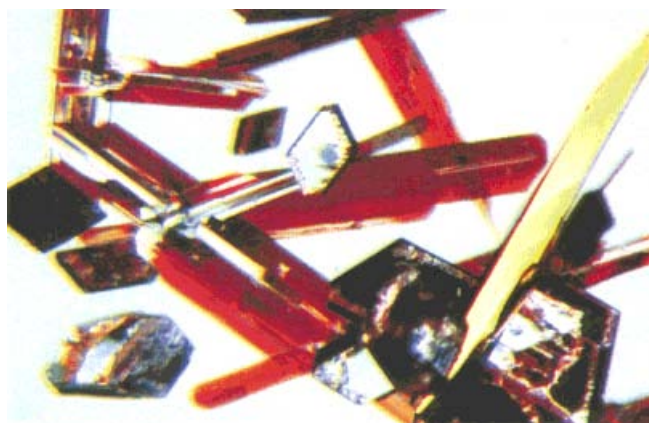


Figure 11. Three of the concomitant polymorphs of the cyanine/oxonol dyes **9** and **10**. The gold (by reflection; otherwise red by transmission) and red forms mentioned in the text are easily distinguishable. The third form is purple, normally diamond shaped as on the middle right, but many of these crystals are undergoing conversion, as indicated by varying degrees of mottled surfaces.

structures exhibit mixed stacks, with very significant differences in the relative orientation of neighboring molecules along the stack (Figure 12): in the case of the gold structure the molecular long axes are oriented nearly perpendicular to each other, while in the red polymorph the molecular long axes are very nearly parallel. Recently Bonafede and Ward have shown how edge-directed epitaxy on single crystal succinic acid substrates may be used for the selective nucleation and growth of the less stable red polymorph.^[74]

The often serendipitous nature of the discovery of concomitant polymorphs is illustrated by another recent example of a two-component system, pyromellitic acid (**11**) and 2,4,6-trimethylpyridine (**12**).^[75] The first polymorph (A) was

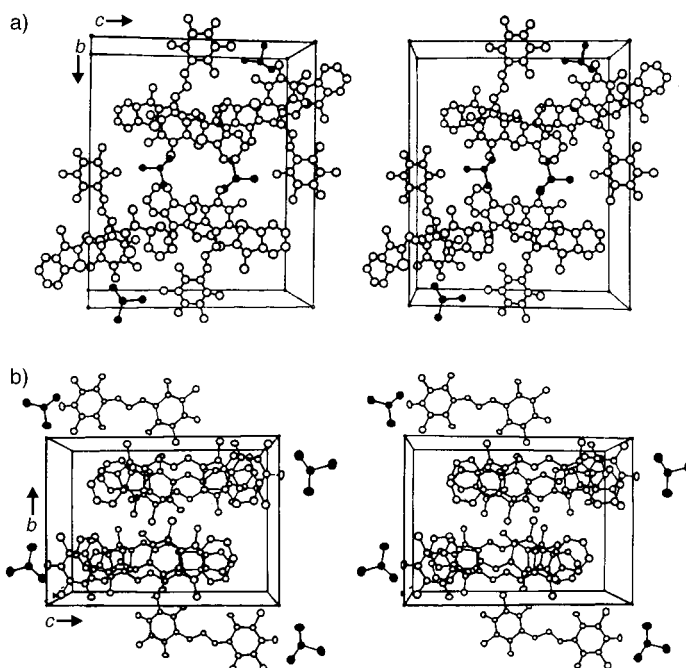
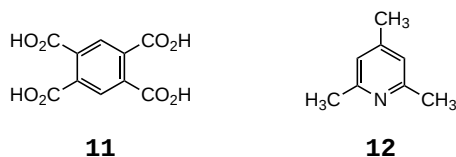
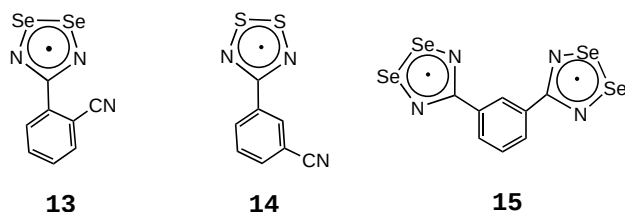


Figure 12. Stereoviews of the unit cells of the gold (a) and red (b) forms of the salt of **9** and **10**. a) View along [100] of the entire cell. Chloroform molecules of solvation (shaded black in the figure) fill (010) planes of the structure, providing stabilization by hydrogen-bond interaction with the oxonol dye. b) [100] view of the entire cell of the red form. Chloroform molecules represented in a similar manner. Both figures are viewed down the stack axis and indicate the relative orientation of cation and anion which is one feature of the overall packing. (Reprinted from ref. [72] with permission.)

obtained by the reaction of **11** with four equivalents of **12** in a methanolic solution. When **12** was used as the solvent, a second polymorph (B) crystallized in fifteen minutes. Form A was found to have crystallized as well in the same reaction vessel after about 24 hours. These two polymorphs are not readily distinguishable by their morphology. However, the authors point out that the experimental evidence indicates that form B is the kinetically controlled one, while form A is the thermodynamically preferred one.

7.7. Concomitant Crystallization by Sublimation

Concomitant crystallization is by no means limited to crystallization from solution, nor to preservation of constant molecular conformation. As noted in Section 3.1.2, the classic p/T phase diagram for two solid phases (Figure 3) of one material exhibits two lines corresponding to the solid/vapor equilibrium for each of two polymorphs. At any one temperature one would expect the two polymorphs to have different vapor pressures. This, in fact, is the basis for purification of solids by sublimation. Nevertheless there are examples where the two have nearly equal vapor pressures at a particular temperature and cosublime. For instance, the two compounds **13** and **14** both yield two phases upon vacuum sublimation.^[76] For **13** slow sublimation at 140°C and 0.1 Torr led to a mixture of a “few feathery needles” (m.p. $192\text{--}193^\circ\text{C}$) among the main product of “lustrous coppery blocks” (m.p. $220\text{--}223^\circ\text{C}$),



which could be separated manually for further characterization. Compound **14** was also purified/crystallized by vacuum sublimation (120°C, 10⁻² Torr) to yield manually separable deep red needles (α phase, m.p. 157–160°C) and blocks (β phase 165–168°C). The crystal structure determinations of the two phases of **14** indicated significantly different molecular geometry (Figure 13), a cofacial dimer in the α phase, and a *trans* antarafacial dimer in the β phase.^[77]

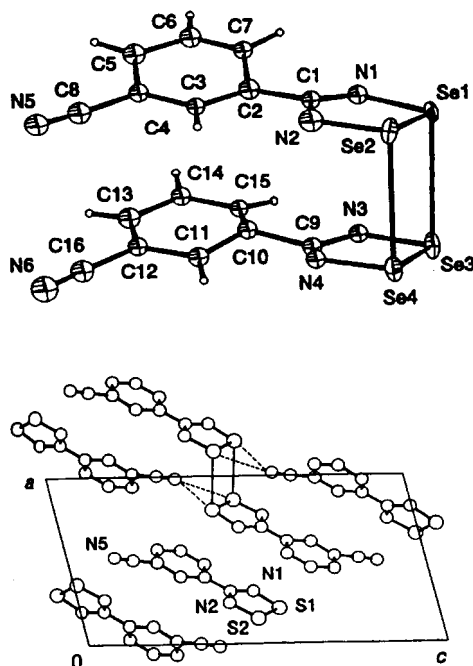
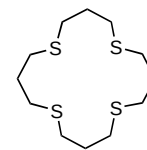


Figure 13. Molecular geometry in the two polymorphs of the dimers of **14** obtained by sublimation. Top: α phase, cofacial dimer; bottom: β phase, antarafacial dimer. (Reprinted from ref. [76] with permission.)

Another example of cosublimed phases is the compound **15** for which it appears that the sublimation conditions were systematically varied in an attempt to obtain a second polymorph.^[78] The α form was initially prepared as a single phase of golden needles by slow sublimation over several weeks at 10⁻⁶ Torr during which the sample was heated to 180°C and the cold finger was maintained at 100°C. Raising the pressure to 10⁻¹–10⁻² Torr and increasing the sample temperature to 220°C, with a cold finger in the range 120–140°C also led to the same α -phase needles, but they were accompanied by blocks of an additional β phase. The two can be separated manually. Clearly, the authors moved along the solid/vapor line of the α phase towards the intersection with the solid/vapor line of the β phase (see Figure 3).

7.8. Concomitant Crystallization by Solvent Diffusion

Concomitant crystallization has also been reported from solvent diffusion crystallization, which means that the concomitant forms have very similar solubilities in the same mixture of solvents—under the same thermodynamic and kinetic conditions. Such is the case for 1,5,9,13-tetrathiacyclohexadecane (**16**).^[79] The material is reported to be trimorphic; all three forms crystallize in polar space groups [needles, *Pbc*2₁ (α); plates, *P2*₁ (β); and twinned, apparently *Fdd*2 (γ)]. The α and β forms are obtained simultaneously at ambient temperature by diffusion of hexane into dichloromethane solutions of **16**. Lowering the temperature to –130°C for the same diffusion process leads exclusively to the γ form. The forms that crystallize concomitantly have unusual, but similar molecular conformations. Not surprising for the phenomenon observed, in particular for the α and β forms, the three melting points (59.5–60.2 (α), 57.8–59.0 (β), 60.0–60.9°C (γ)) are very similar, and the authors used the technique of mixed melting points to verify the existence of the three polymorphs.

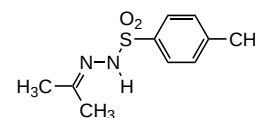


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7.9. Concomitant Crystallization of Conformational Polymorphs

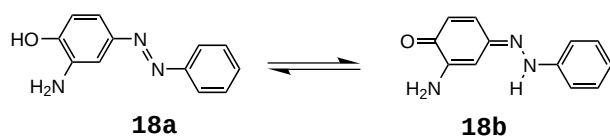
One of the definitions of polymorphism^[2, 5, 80] requires that all polymorphic structures of a material dissolve, melt, or vaporize to give the same species or equilibrium mixture of species. If this is accepted as a definition, the time necessary for equilibrium to be achieved becomes an issue, as well as the temperature of the dissolution, melting, or vaporization process. Clearly, years is too long to meet this criterion, but are hours or days too long? The question is still open. Nevertheless, a number of cases of concomitant polymorphs demonstrate the principles.

Gleason and co-workers^[81] recently reported the crystallization of two *conformational polymorphs*^[82] of acetone tosylhydrazone (**17**). A triclinic form and a monoclinic form are obtained from anhydrous ethanol, sometimes together. If the crystallizing solution is allowed to evaporate completely, only the monoclinic form is obtained, which suggests that it is the thermodynamically preferred form at room temperature. This is consistent with Ostwald's Rule of Stages^[22] and McCrone's test for relative stability of polymorphs:^[2] the more stable polymorph will grow at the expense of the less stable one. The crystal structure determination indicates that the conformations differ by $\approx 15^\circ$ about the S–C exocyclic bond. In this case, the solution has an equilibrium mixture of (at least) these two molecular conformations. Lattice energy calculations (Cerius2)^[83] are consistent with this observation, and indicate that the triclinic polymorph is more stable than the monoclinic form by about 1 kcal mol⁻¹.



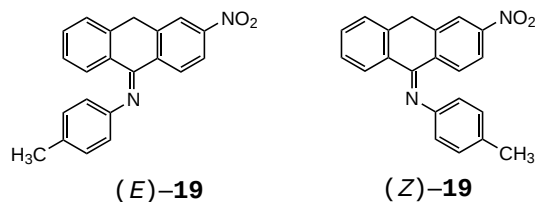
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Another issue in the definition of polymorphs is that of *tautomerism*. An example of the crystallizing tautomeric structures of 2-amino-3-hydroxy-6-phenylazopyridine (**18**) has been reported by Desiraju,^[84] **18a** being the “low temperature” form as lustrous blue needles and red **18b** being the



“high temperature” form, both with melting points of 181–182 °C. They were obtained simultaneously from recrystallization of the crude synthetic product from ethanol, but the relative amounts varied from batch to batch in subsequent crystallizations when concentration and temperature were varied. The high temperature form was always obtained; the amount of low temperature form varied with the crystallization conditions. The tautomeric separation clearly takes place upon crystallization. To complete the picture and to make this, arguably, a case of polymorphism, it must be shown that the blue and red crystals dissolve to yield the same equilibrium mixture.

A case of concomitant crystallization which involves *configurational isomerism* has been reported by Matthews et al.^[85] which again called into question the definition of polymorphism. The benzophenone anil **19** can exist in two configurational isomers, designated *E* and *Z*. The material has been shown to be trimorphic: a yellow form (triclinic, $P\bar{1}$, $Z=6$, m.p. 91 °C) and an orange form (triclinic, $P\bar{1}$, $Z=4$, m.p. 78–80 °C) often crystallizing from ethanol or benzene/diethyl ether at 0 °C. The third form (monoclinic $P2_1/c$, $Z=4$, m.p. 91 °C) is obtained from ethanol at room temperature.



In the first polymorph, all molecules exhibit the *Z* configuration. In the second, concomitant polymorph all molecules are in the *E* configuration. The third polymorph also contains molecules with *E* configuration. The conformations of the molecules in the second and third polymorphs differ slightly, which suggests that they might qualify as conformational polymorphs.^[82]

But should the first two structures be considered as properly belonging to a polymorphic system? Again, we can revert to McCrone's tests.^[2] As Matthews et al. point out, these configurational isomers can interconvert at rates which vary by up to 10^{14} . If they interconvert quickly (i.e., on the order of hours) then they will give the same equilibrium mixture and may properly be called polymorphs according to the McCrone definition.

McCrone suggests some additional tests.^[2] Two crystals of the same compound suspected of being polymorphic are

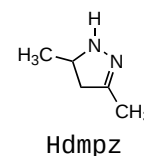
placed side by side on a microscope slide in a mutually suitable solvent. If they are polymorphs of different thermodynamic stability the more stable one will grow at the expense of the less stable one. While it is not clear how soluble the polymorphs of **19** are in Nujol, when both the *E*-containing polymorphs were allowed to stand in Nujol for a few days the result was a conversion to the *Z*-containing polymorph. On the basis of the available evidence this does seem to be a case of polymorphism, in spite of the original authors' preference to avoid the use of the term.

7.10. Concomitant Crystallization of Racemates and Enantiomers

Another issue in the definition of polymorphs deals with racemic mixtures versus enantiomerically pure crystals or conglomerates.^[2, 5, 80] In principle, enantiomerically pure crystals are different from racemic ones, but if they racemize quickly in solution and/or spontaneously resolve upon crystallization, it is still debatable whether these are to be considered polymorphic substances. Sironi and co-workers^[86] have recently characterized a concomitantly crystallized system that incorporates and illustrates many of these features, and in addition, provides an example of a substance in which the synthetic approach to the material apparently plays a role in determining which polymorph is initially obtained.

The molecule under study was $[\text{Pd}\{(\text{dmpz})_2(\text{Hdmpz})_2\}_2]$ (**20**). The material is trimorphic. The reaction mixture yields mostly (90%) the monoclinic ($C2/c$, racemic) α phase, the remainder being the triclinic ($P\bar{1}$, racemic) γ phase. The latter can be removed by recrystallization from 1,2-dichloroethane, which suggests that it is the more soluble and hence less stable polymorph in that solvent. Sironi and co-workers found that mixtures of various amounts of α and γ polymorphs could be obtained by varying the solvent and precipitation temperature (–70 °C to +50 °C), with α preferred at higher temperatures, consistent with the earlier observation of relative stabilities. Pure polymorph γ may be obtained by a different synthetic route, which, with an excess of 3,5-dimethylpyrazole, leads to an approximately 50:50 mixture of polymorphs α and γ . This system thus also represents a case in which the polymorph obtained, or the polymorphic mixture obtained, depends on the synthetic route to the desired material. It is probably more correct to state that as usual, the polymorph or polymorphic mixture depends on the crystallization conditions, and these will clearly differ in the solvent/reagent/product compositions that result from different synthetic conditions and routes.^[87]

The tetragonal ($I422$, chiral) β “polymorph” is obtained quantitatively by a solid–liquid synthesis. The product is a conglomerate of enantiomeric crystals, which the authors claim does not transform into the α phase because of the impossibility of a solid–solid transformation. Dissolution of the β phase in 1,2-dichloroethane and subsequent evaporation quantitatively restores a mixture of α and γ forms. Despite the



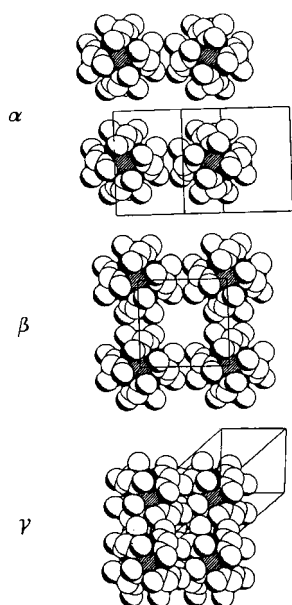
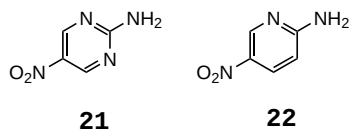


Figure 14. Packing of the $[\text{Pd}(\text{dmpz})_2(\text{Hdmpz})_2]_2$ (**20**) molecules in the three polymorphs, viewed approximately down the pseudo-fourfold axis. (Reprinted from ref. [86] with permission.)

control over the design and preparation of desired crystal structures then the phenomenon of polymorphism—and concomitantly crystallizing polymorphs—is antithetical to such an approach.^[93] One popular strategy in crystal engineering is to build up structures from systems of two molecular components between which the intermolecular interactions are well defined, usually by the potential formation of hydrogen bonds.^[94]

A recent example from this realm of chemistry, which again illustrates the role of the synthetic route in determining the generation of polymorphic structures comes from the work of Biradha and Zaworotko on **11** and **12** (see Section 7.6).

Another attempt at crystal engineering led to a remarkable number of concomitant crystallized materials. Aakeroy et al. dissolved **21** and **22** in a 1:1 ratio in butanol. Upon slow evaporation they obtained *five* crystalline materials, three polymorphs of **21** (thick, diamond-shaped plates, white needles and colorless blocks)^[95] and yellow platelike crystals of **22** along with yellow/colorless dichroic blocks of a monohydrate of **22**. Only keen observation could be responsible for the discovery and characterization of all five crystalline materials in this mixture.



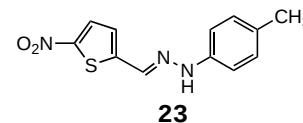
One practical mission-driven aspect of crystal engineering is the attempt to design and prepare nonlinear optical materials. This goal has led to the variation of crystallization conditions in the search for crystals of potential SHG

different space groups, the gross features of the packing modes are very similar, the molecules being arranged about a pseudo (α , γ) or real (β) fourfold axis (Figure 14). Such a view of the crystal structure is consistent with observations of Gavezzotti and Desiraju^[91] and Braga and Grepioni^[92] on the general similarities of packing features and coordination numbers of organic and organo-metallic compounds.

7.11. Concomitant Crystallization and Crystal Engineering

The growing interest in crystal engineering is certain to lead to more recognized cases of concomitant polymorphs. Indeed, if crystal engineering can be considered as

materials, and has resulted in the discovery of polymorphic systems,^[96] as well as the development of a number of strategies for obtaining structures with the required symmetry properties.^[97] Recently Pan et al. reported many crystallization studies on **23**, which is at least trimorphic, the three modifications being easily recognized by habit and color: form I, red greenish plates ($P2_1/n$); form II, red orange prisms ($Pna2_1$); form III, black needles ($P2_1/n$).



Hence only form II is SHG active. Solvent evaporation or controlled lowering of the temperature lead to form I from all solvents used, but rapid cooling of highly supersaturated solutions of protic solvents (e.g. methanol or ethanol) sometimes led to concomitant crystallization of forms II and III. The crystal structures of these three modifications could also be distinguished by the nature of the intermolecular interactions dominating them.^[98]

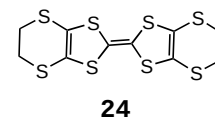
7.12. Organic Conductors and Magnets

It is not surprising that quite a few examples of concomitant polymorphs are found amongst the compounds and salts of potential use as organic conductors and magnetic materials. Considerable effort is generally expended in growing crystals and fine tuning conditions for obtaining crystals of sufficient quality for further structural and physical characterization. Thus a wide variety of crystallizing conditions are often tested and many individual crystals from a single crystallization might be subjected to structural and physical characterization.^[99] These are favorable circumstances for the preparation and recognition of polymorphism and concomitant polymorphs.

7.12.1. Organic Conductors by Electrocrystallization

Perhaps most prominent of these materials are the organic conducting and superconducting salts based on so-called ethylenedithio (“ET”) compounds, in which bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF; **24**) is the donor (cation in the salt), generally in a 2:1 ratio with the acceptor (anion in the salt).^[100a]

One of the most widely studied of these salts is $(\text{ET})_2\text{I}_3$, for which at least 14 different phases have been reported,^[100] although the α and β phases tend to dominate.^[101] Most of the 2:1 salts are obtained by electrochemical crystallization which affords additional degrees of freedom of crystallization conditions compared to “conventional” crystallization: voltage, current density, counterion (for the salt anion), supporting electrolyte, electrode materials, and so on. So, for $(\text{ET})_2\text{I}_3$ for instance, it has been shown that the α phase is the kinetically favored product (> 90 %) under conditions of high current density and a small amount of water or oxidant in the crystallization medium. Under more nearly equilibrium conditions (i.e., much lower



current density) and dry solvent (tetrahydrofuran), pure β phase can be obtained, which suggests that it is the thermodynamically preferred form. Intermediate conditions apparently lead to concomitant crystallization of the two forms.^[100]

When the crystallization is carried out as an oxidation of ET in tetrahydrofuran with a mixture of $(n\text{-C}_4\text{H}_9)_4\text{NI}_3$ and $(n\text{-C}_4\text{H}_9)_4\text{NAuI}_2$ (16/1 w/w) with an intermediate current to that described above, the α form is the main product, concomitantly crystallized with small amounts of θ and κ polymorphs.^[102] The authors note the difficulty in identifying the three forms on the basis of crystal shape alone, and the three were characterized by a combination of X-ray diffraction and other physical measurements.

Two distinct superconducting κ phases (labeled κ_{H} and κ_{L}) are obtained simultaneously in the electrocrystallization of the salt of ET with the anion $[\text{Cu}(\text{CF}_3)_4]^-$ in 1,1,2-trichloroethane.^[103] After four days black needles of the κ_{H} form appeared on the anode, and within a week black plates of the κ_{L} form appeared amongst the needles (Figure 15). Both salts

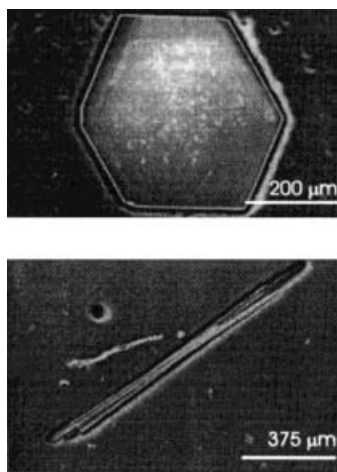
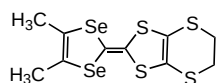


Figure 15. Photograph of the two κ phases of $(\text{ET})_2\text{Cu}(\text{CF}_3)_4$. (Reprinted from ref. [103] with permission.)

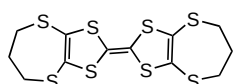
are, in fact, solvates of $(\text{ET})\text{Cu}(\text{CF}_3)_4$, with κ_{L} containing one molecule per salt formula unit, and κ_{H} containing slightly less than one molecule per salt formula unit. The authors note that the growth of the plates apparently inhibits the growth of the needles, which after 14 days amounted to approximately 5% by weight of the product. These results were reproducible. The addition of 10% ethanol to the electrolyte solution led to a slight increase in crystal quality in some experiments,

but otherwise did not alter the results. ET also forms a concomitant dimorphic salt with $\text{Pt}(\text{CN})_4$, with the stoichiometry $(\text{ET})_4\text{Pt}(\text{CN})_4$; the two forms are designated α and β .^[104, 105]

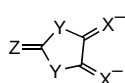
In another example that involves similar materials, the dimethyl ethylenedithio donor is DMET **25** and the acceptor is AuBr_2 to form both rhombs and platelike crystals of $(\text{DMET})_2\text{AuBr}_2$;^[106, 107] no further information on crystallization conditions, color, habit, and so on are given. The crystal



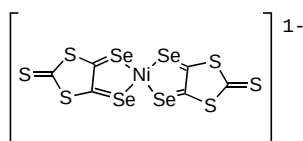
25



26



27: X, Y, Z = S, Se



28

structure and temperature-dependent resistivities differ significantly for the two polymorphs.

Montgomery et al.^[108] have shown that, in systems in which attempts were made to prepare alloys of $\beta\text{-(ET)}_2\text{I}_3$ with $\beta\text{-(PT)}_2\text{I}_3$ (PT = **26**, a propylenethio donor), they apparently obtained “single crystals” of $(\text{ET})_2\text{I}_3$ which were in fact mixtures of the α and β forms. The phenomenon in this system was initially detected and then confirmed by ESR spectroscopy, which was subsequently used to develop a quantitative procedure for the determination of the polymorphic composition of such “mixed single crystals”. There are other scattered reports in the literature of this phenomenon,^[109] which has been termed “composite crystals” and has been discussed in detail by Coppens et al.^[110]

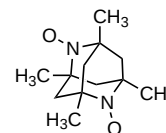
Another widely studied series of conducting organic salts is based on the ligand **27**. In the case where X = Se, Y = Z = S, known as dsit, the organometallic monovalent anion **28** can be formed with Ni^{III} to give a dimorphic salt with composition $(\text{Bu}_4\text{N})_2[\text{Ni}(\text{dsit})_2]$.^[111] Concomitant crystallization of the α and β forms was noted upon recrystallization of the crude material, the α form being chunky blocks, while the β form crystallizes as needles. Slow evaporation of a solution prepared by dissolution of both forms leads to the α form, which suggests that it is the more stable form.

7.12.2. Organic Conductors by Interdiffusion

Interdiffusion of saturated solutions (as opposed to electrocrystallization) is another method for obtaining crystals of potentially conducting salts. In most of the preparations of $\text{TTF}[\text{Pd}(\text{dmit})_2]_2$ (dmit: **27**, X = Y = Z = S) by diffusion of $(\text{TTF})_3(\text{BF}_4)_2$ and $(n\text{Bu}_4\text{N})[\text{Pd}(\text{dmit})_2]$, mainly black shiny needles of the α phase were obtained. However, some experiments yielded, in addition, a so-called α' phase (due to its structural similarity to the α phase, but different electrical behavior), and occasionally it was possible to separate a third δ phase of plate-shaped crystals from the batch.^[112–114]

7.12.3. Organic Magnetic Materials

The significant increase in interest and activity in the design, preparation, and study of organic magnetic materials has led to the discovery of a number of polymorphic systems.^[116, 117] One of the few purely organic materials shown to undergo a well-characterized ferromagnetic transition is the azaadamantane derivative **29**.^[118] The material is dimorphic, and both forms appear simultaneously by evaporation of a diethyl ether solution at room temperature. The authors note that they have not succeeded in determining the conditions for selectively crystallizing either form.



29

The structures of the α and β forms are shown in Figure 16. It can be seen that there is indeed a subtle difference in the environment of the oxygen atom on which the unpaired electrons are formally located, and in other intermolecular interactions, but the concomitant crystallization suggests that

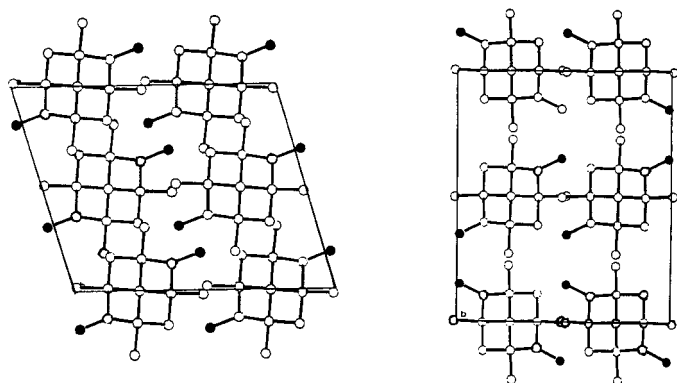
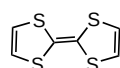


Figure 16. Representation of the packing of the two forms of **29**. Oxygen atoms are denoted by solid circles. Left: the monoclinic α form; right: the orthorhombic β form. (Reprinted from ref. [118] with permission.)

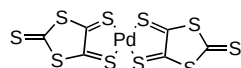
the energetic consequences of the sum of these differences are very small.

This lack of control over the polymorph obtained is in contrast to the dimorphic system HQNN **30**. Sugawara et al. reported in a preliminary communication^[119] that the bluish-purple blocks of the α phase could be obtained above 4 °C and the needle-shaped β phase can be crystallized below 0 °C. In addition, they add that “both crystals can be obtained selectively by using a seed crystal at room temperature”. In a later publication^[120] it was noted that the α phase was obtained in a refrigerator, “(≈ 4 °C) under a nitrogen atmosphere” while the β form was obtained from a solution “stored in a freezer (≈ -10 °C)”.

Legros and Valade reported the concomitant (α and γ) forms of **31** and **32**. The crystals are obtained from the slow interdiffusion of saturated solutions of (TTF)₃(BF₄)₂ and



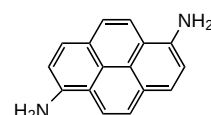
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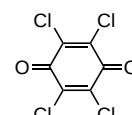
32

(*n*Bu₄N)[Pd(dmit)₂].^[112] The α form is the main product as shiny black needles, with some platelets of the γ phase usually present. Occasionally, a so-called α' phase is also obtained in this crystallization procedure. The α and γ forms have very different crystal structures and correspondingly different electrical behavior. The former are built up of segregated stacks of donor and acceptor molecules and undergoes a metal–semiconductor transition. The latter has stacks of dimers of **32**, and exhibits metallic behavior in the range 120–300 K.

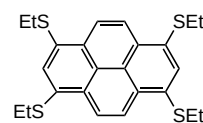
A recent study on the system of 1,6-diaminopyrene (**33**) and chloranil (**34**) is edifying with regard to the connection between structure and electrical conductivity. Compound **33** is a relatively strong donor that was an early subject of study as a component of potential electrically conducting complexes,^[121, 122] and quite a few complexes of this donor were prepared.^[123, 124] The complex of **33** with **34** was investigated in



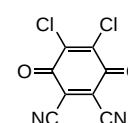
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35



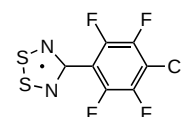
36

detail recently^[124, 125] with results that indicate both the utility and some of the limitations of studies of polymorphic systems. The 1:1 complex is polymorphic, with a dark brown α form and a green β form. Both may be obtained *simultaneously* from benzene solution by both slow cooling and “prolonged” slow evaporation.^[124] Under cooling or grinding, the resistivity of the α form is reduced by eight orders of magnitude, with no detectable structural changes by X-ray crystallography.

Modification of the substituents on the pyrene donor and the benzoquinone acceptor leads to the 1:1 complex of **35** with **36**, which was studied by Lee et al.^[126] Slow evaporation of an equimolar mixture of the compounds in dichloromethane led to a mixture of black crystals; the α phase were “branchy” microcrystals and the β phase were large platelets.

7.12.4. Free Radicals by Sublimation

The recently reported 1,2,3,5-dithiadiazolyl radical **37** is the first to retain its paramagnetic behavior in the solid state.^[127, 128] It also provides another example of concomitant crystallization by sublimation. Large black blocks of the α phase may be obtained pure by very rapid vacuum sublimation at 120 °C and 10^{−2} Torr. The long, plastically deformable needles or small red blocks of the β phase are prepared at the same pressure and 80–100 °C, with the crystals collecting just above the level of the oil bath or heating tape of the source vessel (i.e., small temperature gradient).^[129] The two phases appear simultaneously under vacuum in a sublimation tube subjected to a temperature gradient. The difference in color of the latter two types of β crystals is most likely a size effect, the larger crystals being opaque and hence reflecting.



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7.13. Concomitant Crystallization of Proteins

In view of the many experiments carried out on the crystallization of proteins and subsequently refinement of the conditions to maximize crystal size and quality for X-ray structure determination, it is not surprising that examples of concomitant crystallization are found among proteins. Wang and co-workers reported the simultaneous crystallization of three polymorphs of a m-class glutathione S-transferase from

rat liver^[130] (Figure 17). Day and McPherson reported crystallization of two crystalline forms in stages in accord with Ostwald's Rule for cytochrome c from *Valida membranaefaciens*^[131] (Figure 18). In every case of crystallization they obtained arrays of thin triclinic plates (Figure 18a), some of which grew up to 0.5 mm along the largest physical dimension (Figure 18b). In some cases, some of these dissolved (in accord with Ostwald's Rule of Stages) to give rectangular prisms (Figure 18c), which turned out to be orthorhombic.

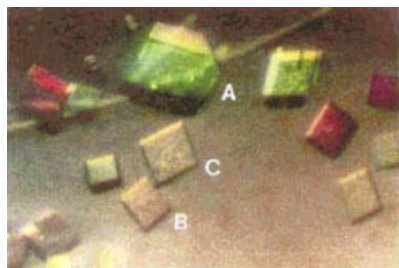


Figure 17. Photograph of cocrystallizing forms of rat liver glutathione S-transferase. The three forms are labeled. (Reprinted from ref. [130] with permission.)

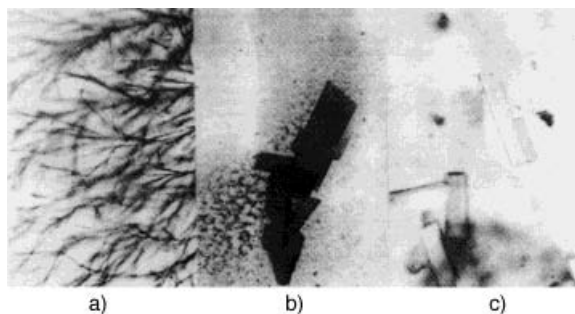


Figure 18. Example of the stagelike growth in cytochrome c from *Valida membranaefaciens*. a) Treelike arrays of small triclinic crystals. b) Triclinic crystals, which are frequently seen to dissolve at the expense of the orthorhombic prism (c). (Reprinted from ref. [131] with permission.)

8. A Structural Approach to Concomitant Crystallization

Up to this point this account of instances of concomitant polymorphs has been phenomenological. We have discussed the thermodynamic and kinetic crystallization of polymorphs. There is still the question of whether any insight can be gained from the study of the crystal structures of concomitantly crystallized polymorphs. A qualitative attempt was made to see if details of the crystal structures may provide clues to the reasons for concomitant crystallization. The squarylium dye **38** crystallizes from dichloromethane in a triclinic violet form and a monoclinic green form.^[132] The cell constants (Table 1) do not suggest any similarity of the structures. However, a projection on the molecular plane which includes two neighboring molecules (Figure 19) indicates that the stacking of the planar molecules is virtually identical in the two structures. In both cases the two molecules are related by a lattice translation: in the triclinic structure it is along the *c* axis and in the monoclinic structure along the *b* axis. Although the

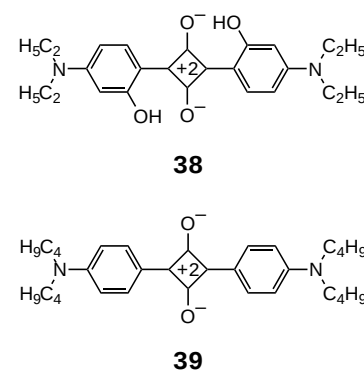


Table 1. Crystallographic cell constants for the two polymorphic forms of **38**.

	Triclinic	Monoclinic
<i>a</i> [Å]	11.911	15.72
<i>b</i> [Å]	7.401	7.283
<i>c</i> [Å]	6.501	9.591
α [°]	92.78	90
β [°]	111.9	106.11
γ [°]	98.08	90
space group	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ / <i>c</i>

views appear the same to the eye, the vertical separation between planes differs (3.40 Å vs 3.86 Å), which is a manifestation of the different axial lengths involved. The similarity of these diagrams strongly suggests that the stacking

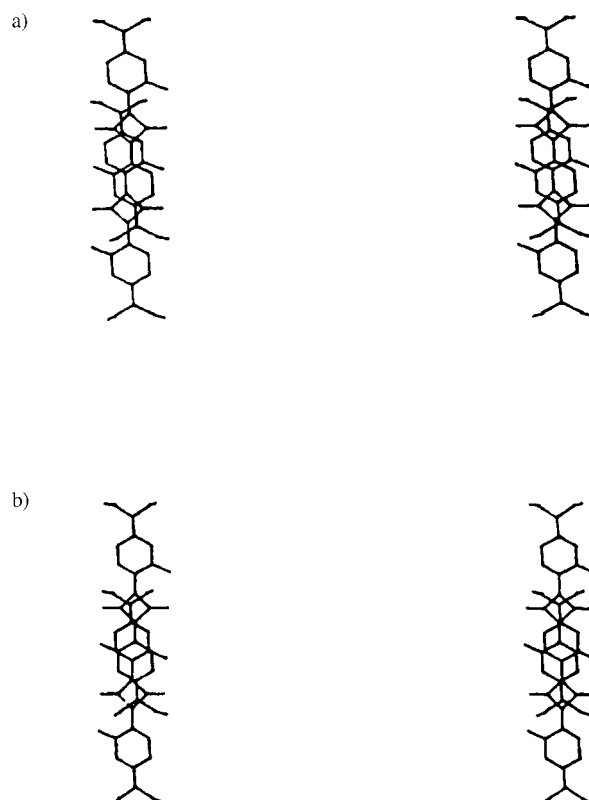


Figure 19. Stereoviews of the overlap of translationally related molecules in the two structures of **38**. In both cases the view is on the plane of the reference molecule. a) Triclinic structure, *c*-axis translation; b) monoclinic structure, *b*-axis translation. (Reprinted from ref. [132] with permission.)

is the dominant influence in the crystal growth process for both—hence the concomitant crystallization. The crystal structures differ, of course, in that stacks are related by translation in the triclinic structure and by a screw axis in the monoclinic one, as shown in Figure 20, but the fact that these phases crystallize concomitantly would be consistent with the assumption that energetically, at least, these interstack interactions contribute in a less significant way than those within the stack.

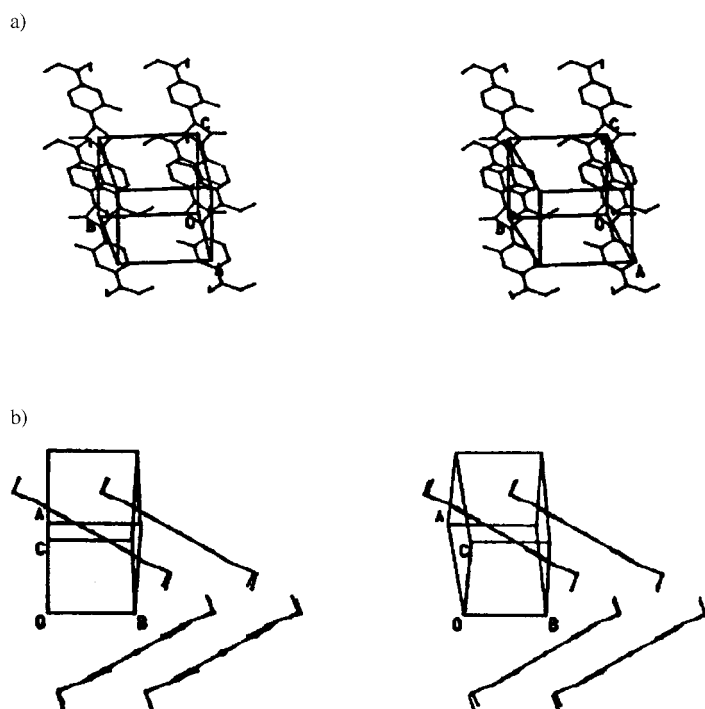


Figure 20. Stereoviews showing the relationship between the stacks shown in Figure 19 for **38**. a) Triclinic structure, translational relationship. b) Monoclinic structure, screw-axis relationship. (Reprinted from ref. [132] with permission.)

It is of interest to note that another similar squarylium dye **39** has also been shown to concomitantly crystallize in a green monoclinic phase and a purple triclinic phase.^[133] The structure has been reported for the former, but crystals of the latter were not of sufficient quality to determine the crystal structure. The monoclinic phase crystallizes in space group $P2_1/c$ with cell constants $a = 9.046$, $b = 19.615$, $c = 9.055$ Å, $\beta = 116.1^\circ$, which precludes any molecular overlap of the type seen in Figure 19 for **38**. The crystal structures of **38** and **39** are significantly different so that the similarity in the colors of the polymorphs of the two compounds appears to be entirely coincidental, albeit unusual.^[115]

9. Summary and Outlook

Sironi and co-workers have described the current situation of the discovery of polymorphs in general and of concomitantly crystallizing polymorphs in particular:^[86] “Normally, after a good-looking single crystal is randomly picked out of a

bunch of crystals, or more frequently, from a complex mixture containing also (morphologically) amorphous, microcrystalline or powdered material, no scattering measurements characterizing the nature of the bulk are routinely performed, thus overlooking the possibility of finding [the] coexistence of different crystalline phases of the same composition in the same sample.”

Sironi and co-workers advocate the use of fast (≈ 30 min) diffraction patterns as a “routine control of reaction products”. We have no argument with this: any suitable technique could and should be used. We still prefer the initial careful optical examination with the polarizing, and preferably, hot-stage microscope. Very little material is required, the method is usually non-destructive, and a great deal can be learned with a very small investment in time and money.

We have described a phenomenon that can be useful in the investigation of solid materials, and in understanding the relative crystal energetics of polymorphic materials. In general no sophisticated technique or instrumentation is required to detect concomitant polymorphs. All that is necessary is the willingness to observe crystalline samples carefully, the awareness that such samples may contain more than one polymorphic modification, and the understanding that such a situation can provide a great deal more information than one polymorphic modification can yield. We hope that this awareness will stimulate those dealing with crystallizations and with crystals to look a little closer at the batch of crystals before moving on to further study or relegating them to storage, and to describe the associated crystallizing procedures, crystal habits, color, and so on in more detail than is the common practice today.^[134]

As the awareness of polymorphism has grown, there has been increasing effort to understand the phenomenon and to gain control over the crystallization process in order to selectively obtain a desired polymorph or suppress the growth of an undesired one. Historically, this was done by a combination of trial and error, intuition, serendipity, varying solvents, temperature,^[2, 18] and occasionally additives.^[135] The availability of detailed structural data, combined with strategic design of substrates and additives, has led to significant advances in the control over the polymorphs obtained in a particular crystallization.^[136–139]

Although the phenomenon of concomitant crystallization has a long history, many of our examples have been taken from the very recent literature. This is not totally by accident. The relative ease with which crystal structures can be solved compared, say, to a generation ago has facilitated the structural investigation of crystals per se. However, a large proportion of the papers cited have been authored by what might be called practitioners of the organic solid state who, through training and experience, tend to benefit from an awareness of polymorphism and an interest in polymorphic systems. It is hoped that this review will promote that awareness throughout the general chemical community.

We are grateful to many enthusiastic colleagues who responded to our call for examples of concomitant polymorphs and to subsequent follow-ups for details. Many of the examples presented here benefited from some extra effort or assistance

from them. Helpful discussions with Dr. Nick Blagden are appreciated. Special thanks to R. Goddard for permission to describe his independent results on the preparation of the second form of tetrathiafulvalene. We also wish to thank the Alexander von Humboldt Foundation for a postdoctoral fellowship to J.-O.H., the Academic Study Group (London) for a travel grant to R.J.D. to Israel, and an Austria–Israel Cultural and Scientific Exchange Program for J.B. to travel to Innsbruck and J.-O.H. to travel to Beer Sheva. The warm hospitality and availability of resources of the Cambridge Crystallographic Data Centre during a sabbatical leave of J.B. are greatly appreciated.

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- [1] This phrase has been chosen with some consideration, and a number of other options were available. Our intention is to refer to polymorphs that are observed in the crystallization medium, usually simultaneously, although we do not rule out the possibility that they occur in stages, a later modification replacing an earlier one. This is compatible with the choice of “concomitant”, which is defined as “accompanying, or happening together”. Another possibility was “cocrystallizing”, but this term is already in use with reference to the formation of solid solutions of enantiomers and also in the formation of crystalline complexes of two or more molecules, usually as a result of hydrogen bonding. Other options (with definitions) included concurrent (happening together), concrescent (the growing together of related parts), convergent (becoming similar or identical), simultaneously crystallizing (crystallizing at the same time). None of these portrayed more aptly than “concomitant” the phenomenon we wish to describe here.
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- [35] Part of the difficulty in searching and interpreting the literature on polymorphic behavior of materials is due to the inconsistent labeling of polymorphs. In many cases, the inconsistency arises from lack of an accepted standard notation. However, often, and perhaps more important, it is due to the lack of various authors’ awareness of previous work or lack of attempts to reconcile their own work with earlier studies. While many polymorphic minerals and inorganic compounds actually have different names (e.g., calcite, aragonite, and vaterite for calcium carbonate or rutile, brookite, and anatase for titanium oxide) this has not been the practice for molecular crystals, which have been labeled with Arabic (1, 2, 3,...) or Roman (I, II, III,...) numerals, lower or upper case Latin (a, b, c,... or A, B, C,...) or lower case Greek (α , β , γ ,...) letters, or by names descriptive of properties (red form, low-temperature polymorph, metastable modification, etc.). As Threlfall has pointed out, arbitrary systems for naming polymorphs should be discouraged to avoid confusion as regards the number and identity of polymorphs for any compound.^[5] Those based on relative stability or order of melting point do not allow for the discovery of forms with intermediate values; also small differences in stability or melting point might lead to different order and different labeling by different workers. McCrone^[2] proposed the use of Roman numerals for the polymorphs in the order of their discovery, with the numeral I specifying the most stable form at room temperature. By Ostwald’s Rule^[22, 23] the order of discovery should in general follow the order of stability. McCrone also supported the suggestion by the Koflers that the Roman numeral be succeeded by the melting point in parentheses. In fact, the successors of the Koflers at the Innsbruck school have attempted to follow this practice,^[11, 30] although in general it has not been widely adopted by others. In view

of the body of literature already extant and the questions surrounding the definition of a polymorph, it is clearly not practical to define strict rules for labeling polymorphs. The Kofler method has some obvious advantages, since the melting point identifier may eliminate some questions of identity; hence its use should be encouraged. The important point for those studying polymorphic systems is to be fully aware of previous work, to try to identify the correspondence between their own polymorphic discoveries and those of earlier workers, and to avoid flippancy in the use of nomenclature in the naming of truly new polymorphs. In this review we have carried over the nomenclature adopted by the original workers.

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Into the Next Dimension: Nanometer-Sized, Oligonuclear Coordination Compounds with C_3 -Symmetric Ligands

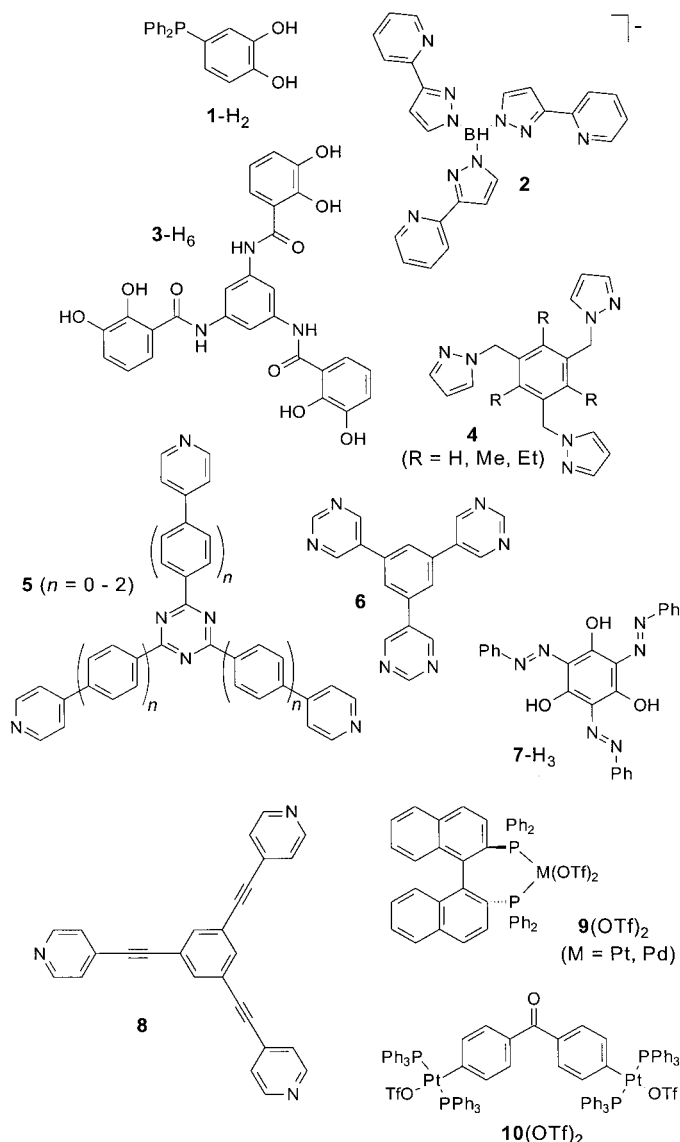
Markus Albrecht*

“Nanotechnology” is an interdisciplinary field of research which has recently inspired many researchers to transfer the function of macroscopic objects (e.g. machines) onto microscopic aggregates. Two different approaches can be discussed for this scientific challenge: The size of macroscopic objects can be reduced to a minimum, or microscopic species can be formed on a molecular basis. Examples for the latter are given by nature. For example, enzymes can act as molecular “machines” which are able to perform specific functions.^[1]

The stepwise synthesis of nanometer-sized molecules is very troublesome. Therefore, molecular self-assembly processes represent a useful alternative to “classical” strategies. Several components aggregate by noncovalent interactions to form supramolecular species. Large, highly symmetrical molecules can be formed from simple molecular building blocks which possess an appropriate symmetry. Here the assembly process is controlled by the symmetry of the components as well as thermodynamic factors (entropy, enthalpy).^[2] It is important that the noncovalent bonds can be formed and cleaved reversibly to enable the correction of errors resulting during the self-assembly process.^[3]

Studies of the self-assembly of relatively small oligonuclear units involve the formation of helicates (one-dimensional),^[4] molecular squares (two-dimensional),^[5] and tetrahedra (three-dimensional)^[6] from ligands with two (or more) binding sites for metals. The molecular cylinders described by Lehn et al. represent a class of somewhat larger complexes.^[7] However, large—nanometer-sized—coordination compounds were just recently obtained using C_3 -symmetric ligand systems with three ($[(1)_3Ti]^{2-}$, **2–6, 8**) or six binding sites for metal ions (Scheme 1). The metal complex units can possess a linear (e.g. *trans*- $Pd^{II}Br_2$) or bent structure (e.g. *cis*-(*en*) Pd^{II}).

The diphenylphosphane-substituted catechol ligand **1-H₂** forms with titanium(IV) ions the homoleptic coordination compound $[(1)_3Ti]^{2-}$. Subsequent reaction with $PdBr_2$ leads to the heteronuclear complex $[(1)_3Ti_2(PdBr_2)_3]^{4-}$.^[8] Here the $[(1)_3Ti]^{2-}$ unit acts as a C_3 -symmetric ligand bearing three

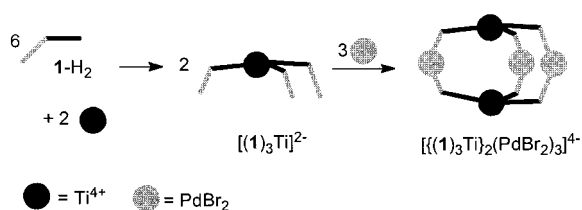


Scheme 1. Molecular building blocks discussed here for the self-assembly of nanometer-sized coordination compounds.

[*] Dr. M. Albrecht
Institut für Organische Chemie der Universität
D-76131 Karlsruhe (Germany)
Fax: (+49) 721-698529
E-mail: albrecht@ochhades.chemie.uni-karlsruhe.de

phosphorus donor atoms which can bind to the *trans*- $PdBr_2$ moiety (for a simple representation, see Scheme 2).

The C_3 symmetry of ligands **2–6** and **8** enables, upon reaction with metal ions or complex units, the formation of

Scheme 2. Formation of $[(1)_3\text{Ti}]_2(\text{PdBr}_2)_3]^{4-}$.

simple polyhedra which are built up from triangular faces (e.g. tetrahedron, hexahedron, octahedron).^[2]

Ligand **2** with manganese(II) ions^[9] as well as the deprotonated ligand **3**-H₆ with titanium(IV) ions^[10] form tetrahedral tetranuclear complexes $[(2)_4\text{Mn}_4]^{4+}$ and $[(3)_4\text{Ti}_4]^{8-}$. The metal ions are located at the corners and the ligands on the faces of the tetrahedron. The geometry corresponds to that of structure **A** in Figure 1. Figure 1a shows the spatial arrangement of the four ligands and the four metal centers. The representation in Figure 1b is reduced to the basic polyhedron (here the tetrahedron), showing only the position of one ligand and the metals bound to this ligand. Coordination of the ligands **2** and **3** to metal ions that prefer an octahedral

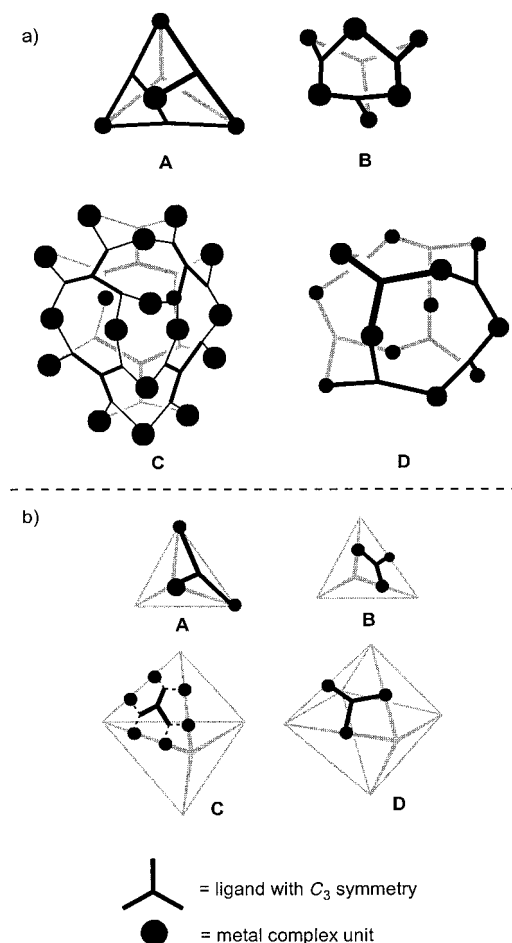


Figure 1. Types of structures of metal complexes which are formed from C_3 -symmetric ligands and appropriate metal complex units. a) Schematic representation of different structures of metal complexes; b) reduction of the structures to simple polyhedra: tetrahedron **A**, **B**, hexahedron **C**, and octahedron **D** (only one of the ligands and the metal ions which bind to this ligand are shown).

coordination geometry occurs through bidentate ligand units, resulting in a structure of type **A**.

The structure of the metal complex formed from four ligands **4** and six *trans*- PdCl_2 units also can be described as a tetrahedron.^[11] The complex $[(4)_4(\text{PdCl}_2)_6]$ represents a structure of type **B**. The ligands bridge the faces of the tetrahedron and are rotated by 30° , while the bridging metals are located at the center of the edges. Thus, the metal ions form an octahedron. In the case of $[(4)_4(\text{PdCl}_2)_6]$ the angle which connects the “trigonal faces” at the edges of the tetrahedron is given by the specific geometry of the ligands. The complex $[(5)_4(\text{en})\text{Pd}]_6^{12+}$ (*en* = ethylenediamine), which is formed by the reaction of four ligands **5** with $[(\text{en})\text{Pd}(\text{NO}_3)_2]$, is also a complex of type **B**.^[12] In contrast to $[(4)_4(\text{PdCl}_2)_6]$, which is formed from ligand **4**, in this case the *cis*-(*en*)Pd unit acts as a cornerstone to connect the triangular faces of $[(5)_4(\text{en})\text{Pd}]_6^{12+}$. Introduction of differently sized spacers (direct bond, *p*-phenylene, 4,4'-biphenyl) in ligands **5** influences the size of the self-assembled coordination compounds $[(5)_4(\text{en})\text{Pd}]_6^{12+}$. These possess internal cavities with diameters in the range of 1.9 to 4.6 nm, depending on the spacer. Guest molecules can be encapsulated in the interior of the complexes and under appropriate conditions can be exchanged against others.^[12]

Recently, a supramolecular coordination compound which possesses a hexahedral (“trigonal-bipyramidal”) structure, $[(6)_6(\text{en})\text{Pd}]_{18}^{36+}$ (Figure 2), was described by Fujita et al. This complex is formed from 24 components (6 ligands and 18 (*en*)Pd units). The structure corresponds to a type **C** geometry. Here (*en*)Pd complexes doubly connect the trigonal faces of the hexadentate C_3 -symmetric ligand **6** to neighboring ligands. The compound has a molecular mass of 7103 Da and dimensions of $3 \times 2.5 \times 2.5$ nm with an internal volume of $900 \text{ \AA}^3$. Stepwise reaction of **6** with $[(\text{en})\text{Pd}(\text{NO}_3)_2]$ allows the isolation and characterization of the intermediates $[(6)_2(\text{en})\text{Pd}]_2^{4+}$ and $[(6)_3(\text{en})\text{Pd}]_4^{8+}$, which are formed during the assembly of $[(6)_6(\text{en})\text{Pd}]_{18}^{36+}$.^[13]

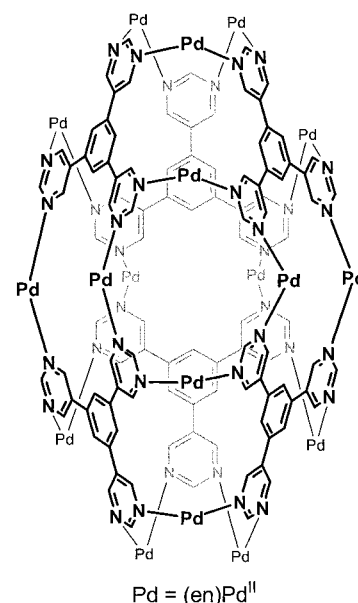


Figure 2. The structure of $[(6)_6(\text{en})\text{Pd}]_{18}^{36+}$. For clarity only the metal of the (*en*)Pd^{II}-units is shown.

Derivative **7-H₃** is deprotonated by [Me₄N]OH and forms with Cu(NO₃)₂ the neutral polynuclear copper(II) complex [(**7**)₈Cu₁₂]. Each copper(II) ion of the complex connects two ligands and shows a distorted square-planar geometry with a *trans*-N₂O₂ arrangement. The six ligands **7** form the faces of an octahedron and are connected by the metal ions which are located at the centers of the edges (see **D**, Figure 1). Here the copper ions do not act as real cornerstones, but the distortion from a square-planar geometry leads to the formation of a nearly spherical cage compound. This complex has a diameter of 1.4 nm with a volume of approximately 816 Å³. Up to six DMF molecules can be encapsulated as guests. The copper(II) ions of [(**7**)₈Cu₁₂] are located on the corners of a cube so that the geometry also can be described as cubeoctahedral.^[14]

All compounds discussed up to now could be characterized by X-ray structural analysis. In the following two coordination compounds will be described which contain the ligand **8** as organic building block. The structures of those complexes were assigned based on spectroscopic investigations and symmetry considerations.

Ligand **8** forms with the platinum(II) or palladium(II) complexes **9**(OTf)₂ (Tf = F₃CSO₂) enantiomerically pure cage compounds [(**8**)₄(**9**)₆]¹²⁺, which possess a structure of type **B**. NMR spectroscopy shows the symmetry of the complexes, while the composition is assigned by mass spectrometry (ESI-FTICR).^[15] The use of building blocks **10**, which contain two linear *trans*-platinum(II) units connected by a bent spacer, leads to the formation of the complex [(**8**)₈(**10**)₁₂]²⁴⁺. This compound possesses a cubeoctahedral geometry (**D**) and has, according to computer models, a cavity with a diameter of approximately 5 nm. A similar complex is obtained upon use of a planar C₃-symmetric trisplatinum(II) complex and bent bispyridine derivatives.^[16]

Use of the building block **10**, with a 120° angle (sp²), instead of **9**, with a 90° angle, leads upon reaction with **8** to the preferred formation of the cubeoctahedron [(**8**)₈(**10**)₁₂]²⁴⁺ (**D**) in contrast to the tetrahedral [(**8**)₄(**9**)₆]¹²⁺ (**B**). This shows that slight variations in the geometry of the supramolecular building blocks can have a big influence on the structures of the self-assembled polynuclear metal complexes.

In summary, oligonuclear coordination compounds can be formed from C₃-symmetric ligands and different metal complex fragments. The complexes obtained are nanometer-sized and possess structures which can be reduced to basic geometries (tetrahedron, hexahedron, octahedron). Which structure is obtained is influenced by the geometry of the building

blocks used. The described complexes possess cavities that allow guests to intrude. A next step will be to perform chemical reactions in the interior of the cavities and thus to imitate the function of reactive centers in enzyme pockets.

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Keywords: cage compounds • coordination chemistry • self-assembly • supramolecular chemistry

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Chemically Modified Antisense Oligonucleotides—Recent Improvements of RNA Binding and Ribonuclease H Recruitment

Oliver Seitz*

Early this year the first oligonucleotide drug, the phosphorothioate ISIS-2922 (Fomivirsen), against CMV retinitis was admitted to the market. Twenty-one years after the introduction of the antisense approach this new drug might serve as the ultimate proof of principle.^[1] In the antisense concept an exogenously added antisense oligomer selectively binds to the target mRNA and blocks the translation. A great deal of the attractiveness of this approach arises from the possibility of designing RNA binders according to the well-known Watson–Crick base-pairing rules. Thus, with such designed binders it would be feasible to virtually knock out any (pathogenic) protein at will. Phosphorothioates, the first generation of antisense oligomers, exhibit a relatively low binding affinity to the target RNA. However, the increased cellular uptake and nuclease resistance render them biological active. In addition, ribonuclease H (RNase H), an enzyme that cleaves RNA in DNA·RNA hybrids, accepts phosphorothioate·RNA hybrids and allows for the destruction of multiple copies of mRNA per antisense oligomer. Rather than providing a comprehensive overview of the progress in antisense technology, this highlight focuses on recent improvements of key elements such as RNA binding and RNase H recruitment.

Flanagan and co-workers reported on an impressive enhancement of the potency of an antisense phosphorothioate (S-AON).^[2] Their 20-mer unit with only one base modification inhibited the expression of the *c-ras* gene at nanomolar concentrations. This translated into a 25 fold increase of the antisense potency relative to a previously optimized 20-mer S-AON, which is currently being tested in phase II clinical trials for the treatment of cancer. The modified heterocycle is based on a cytosine analogue synthesized by Lin and Matteucci.^[3] A tricyclic phenoxazine **2** serves as a rigid scaffold for the attachment of groups suitable for further interactions with nucleobases (Figure 1). By appending an

aminoethoxy tether, the phenoxazine was armed with a strong hydrogen bond donor that would recognize both the Watson–Crick and the Hoogsteen sites of guanine, and was thus termed a G-clamp (**3**; Figure 2). The cytosine analogues

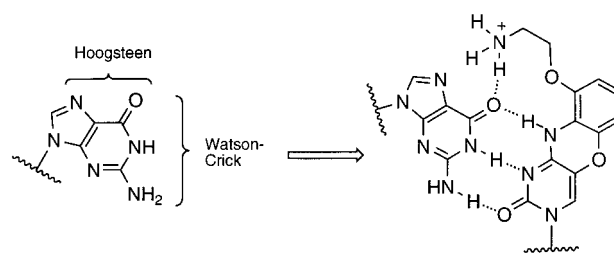


Figure 2. Proposed interaction of the G-clamp with the Watson–Crick and the Hoogsteen sites of guanine.

shown in Figure 1 were incorporated into antisense oligonucleotides (AON) and hybridized to the complementary oligodeoxynucleotide (ODN). The melting temperature T_M , a measure of the thermodynamic stability of double stranded ODNs, were determined by analysis of the temperature-dependent UV absorbance. The G-clamp-containing AON **3** displayed a dramatically enhanced stability (Table 1), while

Table 1. Analysis of the melting temperatures of different single phenoxazine-modified AONs hybridized to matched and single-mismatched ODNs.^[a]

X	Y = G ^[b]	T_M [°C] (ΔT_M [°C])		
		Y = A ^[c]	Y = T ^[c]	Y = C ^[c]
1 (5-Me-C)	50.5	32.0 (–18.5)	30.0 (–20.5)	29.0 (–21.5)
2 (phenoxazine)	57.0 (+6.5)	44.5 (–12.5)	42.0 (–15.0)	33.0 (–24.0)
3 (G-clamp)	68.5 (+18.0)	45.5 (–23.0)	41.0 (–27.5)	40.0 (–28.5)
4	51.5 (+1.0)	–	–	–

[a] Buffer: 0.14 M KCl, 5 mM Na₂HPO₄, 1 mM MgCl₂, pH 7.2. Test AON: 5'-TCTCXTCTC-3'. Target ODN: 3'-AGAGYGAGAGA-5'. [b] Matched ODNs: ΔT_M relative to **X** = **1**. [c] Mismatched ODNs: ΔT_M relative to **Y** = G.

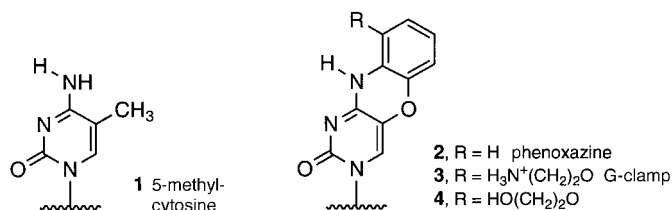


Figure 1. Cytosine analogues used in hybridization experiments (Table 1) by Lin and Matteucci.^[3]

[*] Dr. Oliver Seitz

Institut für Organische Chemie der Universität
Richard-Willstätter-Allee 2, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4825
E-mail: seitz@ochhades.chemie.uni-karlsruhe.de

the AON with the weakly hydrogen bonding hydroxyl group (phenoxazine **4**) replacing the amino group in **3** showed a very similar T_M to the parent 5-methylcytosine **1**. In order to rule out any nonspecific effects that might be caused by ionic interactions, the authors studied the dependence of the T_M on the salt concentration. Attractive Coulomb interactions would normally be weakened at high ionic strength. However, the increased affinity of the G-clamp-modified AONs relative to the 5-methylcytosine was independent of the salt concentration (ΔT_M = 16–18 °C in the range of 0.014–1.4 M KCl), which provided further support for the proposed specific hydrogen binding. Most importantly, the G-clamp AON conferred an enhanced mismatch specificity relative to

5-methylcytosine as determined by the comparison of the T_M values of matched versus mismatched hybridization (Table 1).

The greatly increased affinity and specificity of the base-modified G-clamp was confirmed in recent *in vivo* studies.^[2] African green monkey kidney cells (CV-1 cells) were transfected with a plasmid that contained the human cyclin-dependent kinase inhibitor p27^{kip1} and treated with a cytofectin and the antisense phosphorothioate (S-AON). The G-clamp (S-AON) **9** (Table 2) inhibited p27^{kip1} expression by

important role. The RNase H catalyzed cleavage assay demonstrated that the G-clamp S-AON·RNA heteroduplex was degraded 3.5 times more rapidly than the C5-propinyl substituted S-AON·RNA heteroduplex, and almost as rapidly as the unmodified duplex with **7** (Table 2). These results indicate that RNase H activation appears to be of major importance for antisense activity.

Nearly all nuclease-resistant antisense oligonucleotides currently in clinical trials contain modified phosphodiester backbones. However, the alteration of the natural D-2-deoxyribose itself can also provide AONs with increased stability against nuclease degradation. Unfortunately, none of the uniformly sugar-modified AONs were able to induce mRNA cleavage by RNase H catalysis. Damha and co-workers reported on a class of RNase H competent AONs based on arabinose, the 2-epimer of ribose.^[4] It was demonstrated that substituting the 2'-OH group of the arabinonucleic acids (ANA) with fluorine yielded 2'-deoxy-2'-fluoro-β-D-arabinonucleic acids (2'F-ANA) with a markedly enhanced affinity towards complementary RNA (Figure 4). For example, the melting temperatures of the RNA heteroduplexes with 2'F-ANA **10** and **14** were significantly increased relative

Table 2. RNase H activity of the phosphorothioates **7**, **8**, and **9**.

Compound	Sequence	Base modifications	RNase H cleavage [%] ^[a]
7	5'-TGGCTCTCCTGCGCC-3'	none	21.7
8	5'-SGG 656566566 G6G66-3'	5-propinyluracil/cytosine	4.9
9	5'-TGGCTCTC 3 TGCGCC-3'	G-clamp	17.4

[a] The % cleavage of complementary radioactively labeled RNA 5 min after treatment with nuclear extracts of HeLa cells (source of human RNase H).

96% at 30 nM, as measured by Western Blotting of cellular extracts. At this concentration the previously most potent S-AON **8**, which contains 11 C5-propinyl-modified bases (**5** and **6** in Figure 3) showed 67% inhibition of p27^{kip1} levels. A comparison of the IC_{50} values revealed that the mono substituted strand **9** was three times more potent than the

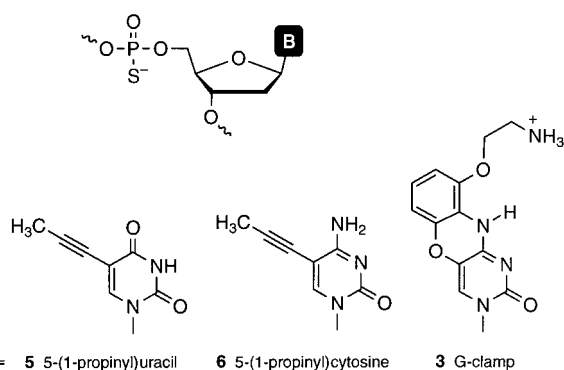


Figure 3. Nucleobase analogues incorporated in antisense agents (Table 2) by Flanagan and co-workers.^[2]

multiply substituted strand **8**. The control S-AON **7** failed to demonstrate any inhibitory activity under these conditions. The sequence specificity of the G-clamp S-AON **9** was tested by transfecting the CV-1 cells with the wild-type p27 plasmid or a single base pair mutant. This mutation changed the complementary guanine in the transcribed mRNA to a uracil group. The G-clamp S-AON **9** inhibited the expression of the single base pair mutant p27^{kip1} with a fivefold decrease in the IC_{50} value relative to the wild-type p27^{kip1}. In contrast, the inhibition of wild-type and mutant p27^{kip1} was almost identical when the C5-propinyl-substituted S-AON **8** was used. The increased antisense activity of the G-clamp S-AON **9** was even more obvious when gel-shift assays were performed. The less potent C5-propinyl-substituted S-AON **8** had an affinity for the RNA target that was almost twice as high as **9**. Thus, differential induction of RNase H was expected to play an

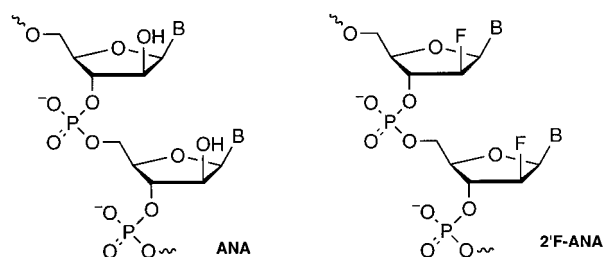


Figure 4. Chemical structure of arabinonucleic acids (ANA) and 2'-deoxy-2'-fluoroarabinonucleic acids (2'F-ANA). (B = nucleobase).

to the hybrids formed with the ANAs **11** and **15** or with the DNA strands **12** and **16** (Table 3). The higher T_M value of the 2'F-ANA·RNA heteroduplexes with **10** and **14** relative to the corresponding hybrids with the phosphorothioates (S-AON) **13** and **17** is also worth mentioning. In addition, the circular dichroism (CD) spectra of the ANA·RNA and 2'F-ANA·RNA duplexes closely resembled that of the parent DNA·RNA duplex, which suggests the common existence of an A-type helix. The specific recognition of the A-like helix of

Table 3. Analysis of the melting temperatures of the arabinonucleic acid duplexes with RNA and control DNA·RNA and S-ODN·RNA duplexes.^[a]

AON sequence	Backbone modification	T_M [°C]
5'-TTTTTTT TTTT TTTT TTTT TTTT-3'	2'F-ANA, 10	44
	ANA, 11	[b]
	DNA, 12	39
	S-DNA, 13	21
5'-TTATATTTT TCTT TCCC-3'	2'F-ANA, 14	65
	ANA, [c] 15	32
	DNA, 16	51
	S-DNA, 17	38

[a] Buffer: 0.14 M KCl, 5 mM Na₂HPO₄, 1 M MgCl₂, pH 7.2. [b] Not detectable. [c] Contained uracil instead of thymine.

DNA·RNA duplexes by RNase H is assumed to induce the selective hydrolysis of DNA·RNA duplexes even in the presence of RNA·RNA or DNA·DNA duplexes. In fact, similarly to the AON **12** and the S-AON **13**, the 2'F-ANA **10** was able to induce a RNase H catalyzed cleavage of the radioactively labeled RNA target. Neither the duplexes of the epimeric 2'-deoxy-2'-fluororibonucleic acids (2'F-RNA) nor the corresponding duplexes with RNA or RNA alone were attacked. Interestingly, ANA·RNA duplexes were poor substrates for RNase H, a result that was attributed to the low stability of the duplex. The 2'F-ANAs are the first class of uniformly sugar-modified antisense oligonucleotides that display an enhanced affinity for their RNA target and fully maintain the ability to induce RNase H. However, it has to be mentioned that this criterion is also met by antisense oligomers consisting of a non-uniform backbone. For example, chimera of DNA and peptide nucleic acids (PNA) are also substrates for RNase H.^[5]

Although the importance of RNase H induction had been emphasized, it is still a matter of debate as to whether high affinity binding to the mRNA alone might be sufficient enough to inhibit translation. A marked increase of the RNA binding affinity and the nuclease resistance would be of pivotal significance. Remarkably, stable pairing with RNA was reported for modifications with altered internucleotide linkages such as 3'-thioformacetal,^[6] methylene(methylimino) (MMI),^[7] and methylene amide spacers.^[8] Similarly, sugar-modified oligomers such as 2'-O-alkylribonucleosides,^[9] hexitolnucleosides,^[10] or α -nucleosides^[11] confer high-affinity RNA binding. Successful examples in which the entire ribose phosphate backbone has been replaced by an artificial backbone include morpholinophosphorodiamidates^[12] and peptide nucleic acids.^[13] An alternative approach, introduced by Leumann et al., makes use of rigidified ODN analogues.^[14] The restricted conformational flexibility eventually reduces the pairing entropy ΔS and this translates into a more favorable standard enthalpy ΔG of duplex formation. In this regard, several base-pairing systems were reported.^[15] The most recent example of a conformationally restricted Watson–Crick base-pairing system was published by Wengel and co-workers, who introduced the locked nucleic acids (LNA; Figure 5).^[16] The methylene bridge that connects the 2'-oxygen with the 4'-carbon atom locks the sugar in the C-3'-endo conformation typical of the A-type RNA·RNA duplex,



Figure 5. Chemical structure of locked nucleic acids (LNA) and proposed locked sugar moiety in the puckered C-3'-endo conformation.

as demonstrated by the CD spectrum of a LNA·RNA duplex.^[17] The hybridization of the mixed-sequence all-LNA nonamer **19** with the complementary DNA nonamer yielded a duplex with an unprecedented thermodynamic stability. The T_M value was increased by 36 °C relative to the corresponding

DNA·DNA duplex with **18** (Table 4).^[18] The **19**·RNA hybrid displayed an even higher increase of the thermal stability (ΔT_M of 46 °C) relative to the DNA·RNA duplex. The introduction of a single base pair mismatch resulted in a

Table 4. Analysis of the melting temperatures of LNA duplexes with DNA, RNA, and LNA as well as control DNA duplexes with DNA and RNA.^[a]

Compound	AON sequence	AON type	Complementary ODN	T_M [°C] (ΔT_M [°C])
18	5'-d(GTG ATATGC)-3'	DNA	DNA	28 (–)
			RNA	28 (–)
19	5'-GTG ATATG ^{Me} C-3'	LNA	DNA	64 (36)
			RNA	74 (46)
			LNA	93 ^[b] (> 65)

[a] Buffer: 0.1 M NaCl, 10 mM Na₂HPO₄, pH 7.0. [b] A low salt buffer (1 mM Na₂HPO₄, pH 7.0) had to be used since duplex dissociation was not detectable in the standard buffer.

decrease of the T_M value by 12–14 °C, a satisfactory selectivity that accounts for the very high binding affinity of LNA for the DNA or RNA targets. To date, LNA·LNA hybridization constitutes the most thermally stable nucleic acid type duplex system as demonstrated by the T_M of 93 °C for the duplex of **19** with its complementary LNA strand.^[17]

The examples presented above indicate that key elements of antisense technology such as RNA binding affinity and selectivity, RNase H induction as well as nuclease resistance can be improved. The employment of the various strategies in concert certainly holds much promise for the development of a new generation of antisense agents, demonstrated best by the successful combination of the phosphorothioate methodology with the modified G-clamp base.

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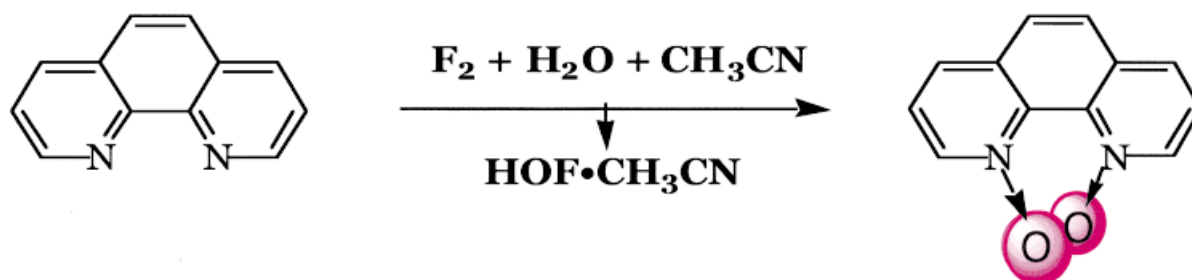
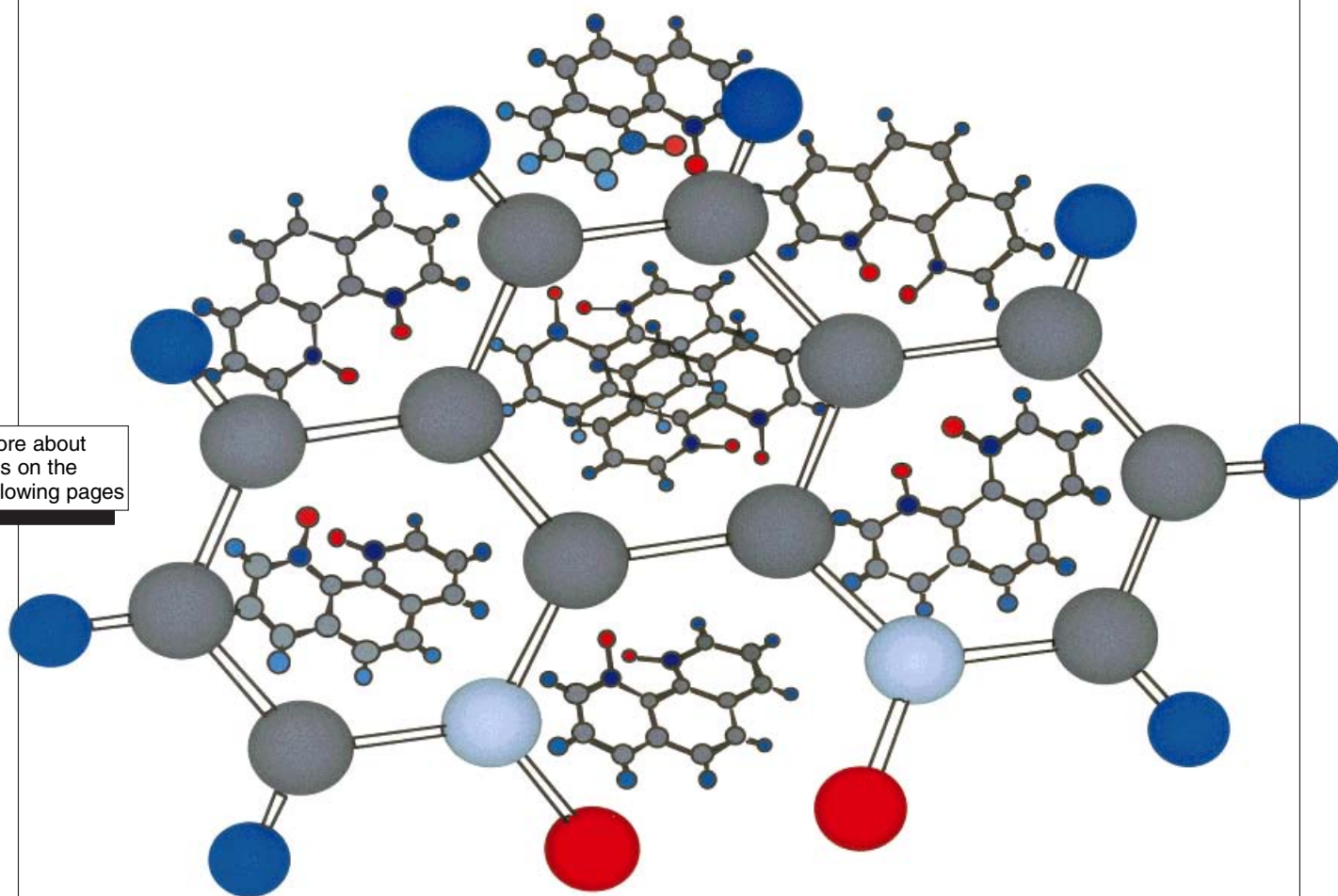
Keywords: antisense agents • nucleic acids • nucleobases • ribonucleases • translation

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*At last, 1,10-phenanthroline-*N,N'*-dioxide has been prepared with the $\text{HOF} \cdot \text{CH}_3\text{CN}$ complex—Probably the best oxygen transfer agent organic chemistry has to offer.*

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At Last, 1,10-Phenanthroline-*N,N'*-dioxide, A New Type of Helicene, has been Synthesized using HOF · CH₃CN**

Shlomo Rozen* and Sharon Dayan

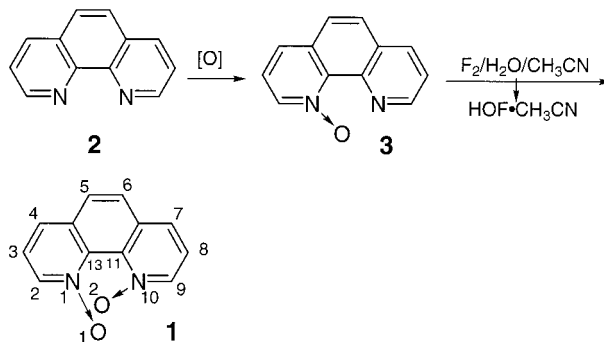
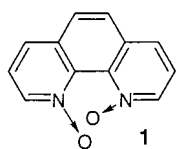
The story of 1,10-phenanthroline-*N,N'*-dioxide (**1**) starts more than 50 years ago when Linsker and Evans claimed that **1** could be prepared by simple oxidation of 1,10-phenanthroline (**2**) with hydrogen peroxide.^[1] The compound was not characterized and the only support presented was a microanalysis of the corresponding picrate. It did not take long, however, to find out that it was impossible to prepare **1** by this procedure or by any other one. In 1958 Maerker and Case reported that they were unable to prepare the *N,N'*-dioxide^[2] and a few years later Corey et al. also repeated the synthesis and were only able to get the mono *N*-oxide.^[3] Woodward and Wenkert were also interested in obtaining **1**, but they too only got the mono *N*-oxide.^[4] Several other attempts were reported^[5] which did not change the outcome.

We tried hydrogen peroxide and several peracids, but like all the others, could not get the *N,N'*-dioxide. The cumulative failures to prepare **1** convinced Gillard to publish two notes complaining about people erroneously continuing to report the existence of this molecule complexed with a variety of metal ions. He concluded that "all such (reports) are wrong"^[6] and the "claims of their existence...should be withdrawn".^[7] The reason for the failure of all these attempts is, of course, that the limited space in the bay area of the flat 1,10-phenanthroline molecule cannot accommodate two oxygen atoms. The arsenal of chemical reagents lacked the one that could force the aromatic 1,10-phenanthroline away from planarity, a precondition for a successful synthesis of **1**.

Some years ago^[8] we introduced the HOF · CH₃CN complex, which soon became probably the best oxygen-transfer agent in organic chemistry.^[9] It is easily prepared by bubbling dilute fluorine through aqueous acetonitrile (see Experimental Section) and is a versatile reagent that operates under very mild conditions. It is able to hydroxylate sp³ tertiary carbon centers, oxidize alcohols, ethers, ketones, primary aliphatic and aromatic amines, and aromatic rings, as well as epoxidize olefins.^[10] It is the only reagent able to oxidize α -amino acids to α -nitrocarboxylic acids^[11] and many thiophenes to their *S,S*-dioxide derivatives under mild conditions.^[12] It also stands alone in its ability to convert very electron-depleted C-C double bonds and sulfides directly into the corresponding

epoxides^[13] and sulfones.^[12] It has been used for the α -hydroxylation of carbonyl compounds and has helped to synthesize some previously impossible indandiones for visualization of fingerprints.^[14] Finally HOF · CH₃CN has been used successfully to convert tertiary amines into their *N*-oxides in very good yields.^[15] We therefore tried its reaction with 1,10-phenanthroline. We were not disappointed.

Treatment of a solution of 1,10-phenanthroline (**2**) in chloroform with 1.1 equivalents of HOF · CH₃CN at 0 °C for 5 minutes resulted in a good yield of the mono *N*-oxide **3** with traces of a material that was proved later to be the *N,N'*-dioxide **1** (Scheme 1). Increasing the amount of the HOF · CH₃CN to 2.2 equivalents resulted in an instantaneous yellow



Scheme 1. Synthesis of 1,10-phenanthroline-*N,N'*-dioxide with HOF · CH₃CN. [O] = *meta*-chlorobenzoic acid, H₂O₂, or HOF · CH₃CN.

coloration and again the reaction was over in 5 minutes at 0 °C. After recrystallization, the yellow solid was identified as the desired 1,10-phenanthroline-*N,N'*-dioxide (**1**). It is a stepwise process as evident from the reaction of the pure mono *N*-oxide **3** with HOF · CH₃CN. In both cases the yield of **1** was higher than 60%. Its picrate melts at 220 °C, which is much higher than that reported by Linsker and Evans (192 °C).^[1]

The microanalysis is in agreement with the structure of **1** and the ¹H NMR spectrum indicates that the two halves of the molecule are in an identical chemical environment. The signals for H2 and H9 appear at δ = 8.58 (d, ³*J*(H,H) = 6.5 Hz, 2H), a typical value for hydrogens atoms α to an aromatic N → O group. The signals for H4 and H7 are at δ = 8.11 (d, ³*J*(H,H) = 8 Hz, 2H) and the ones for H3 and H8 appear at δ = 7.74 (dd, ³*J*₁(H,H) = 6.5 Hz, ³*J*₂(H,H) = 8 Hz, 2H). The remaining two hydrogen atoms H5 and H6 appear as a singlet at δ = 7.83. The ¹³C NMR spectrum also points towards a symmetrical structure with the twelve carbon atoms in the structure giving rise to only six signals. The high-resolution mass spectrum is in excellent agreement with the structure of **1**.

The *N,N'*-dioxide **1** crystallizes in the space group *P*2₁/*c* (*Z* = 8), with two independent molecules in the asymmetric unit. Figure 1 shows that the two oxygen atoms force the whole phenanthroline skeleton away from planarity. Thus while the least squares deviation from plane for 1,10-phenanthroline is only 0.025 Å, the deviation for **1** is 0.52 Å. The torsion angle of O1-N1-C13-C11 was found to be −14.3(2)°, while that of O2-N10-C11-C13 was −14.1(2)°.^[16]

[*] Prof. S. Rozen, S. Dayan
School of Chemistry
Raymond and Beverly Sackler Faculty of Exact Sciences
Tel-Aviv University, Tel-Aviv 69978 (Israel)
Fax: (+972)3-6409293
E-mail: rozens@post.tau.ac.il

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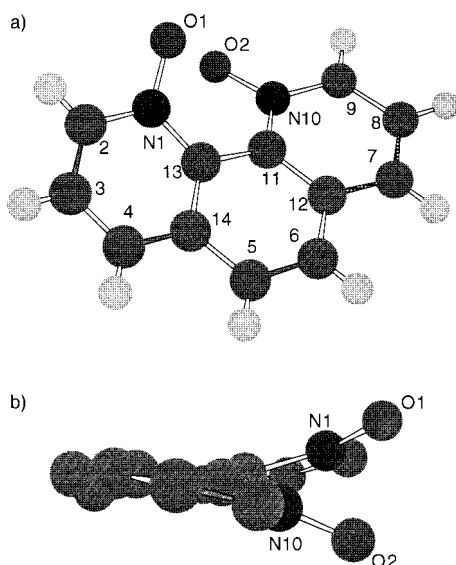


Figure 1. Structure of **1** in the solid state ($R=0.0555$, $wR2=0.1267$). a) View from above; b) side view without hydrogen atoms. Selected bond lengths [Å] and angles [°]:^[16] N1–O1 1.297(1), N10–O2 1.315(1), N1–C13 1.391(1), N10–C11 1.383(1), C2–C3 1.388(2), C8–C9 1.388(2), C3–C4 1.381(2), C7–C8 1.382(2), C4–C14 1.404(2), C7–C12 1.403(2), C13–C11 1.440(2), C5–C6 1.354(2), C13–C14 1.413(1), C11–C12 1.418(2), C5–C14 1.441(2), C6–C12 1.437(2), O1–O2 2.5; O1–N1–C2 119.07(9), O1–N1–C13 121.07(9), O2–N10–C9 119.30(9), O2–N10–C11 120.25(9), N1–C13–C14 118.26(9), C11–C13–C14 118.98(10), C5–C14–C13 118.9(10), C6–C5–C14 121.01(10).

The torsion angle of N1–C13–C11–N10 for **2** is less than -0.5° , for the monoxide **3** it is -0.9° , but for the dioxide **1** the value increases to $-31.7(2)^\circ$. These parameters are responsible for the helical character of the whole molecule (Figure 1b). The individual aromatic rings are also somewhat distorted. While the outer rings are practically identical and show only a modest distortion (the torsion angle N1–C2–C3–C4, for example, is only $2.91(2)^\circ$), the central ring is somewhat less symmetrical and has been forced considerably away from planarity (C13–C11–C12–C6 = $11.98(2)^\circ$ and N1–C13–C14–C5 = $-163.71(1)^\circ$).

The separation of the two oxygen atoms by only 2.5 Å is reflected in the UV spectrum of **1**, which shows a considerable red shift as expected from such a nonbonding interaction: Phenanthroline mono *N*-oxide (**3**) has three main absorptions at 239 nm ($\epsilon_{\max}=1.9 \times 10^4$), 268 nm ($\epsilon_{\max}=2.7 \times 10^4$), and 313 nm ($\epsilon_{\max}=4.6 \times 10^3$), while the *N,N*-dioxide **1** absorbs at 232 nm (sh, $\epsilon_{\max}=1.75 \times 10^4$), 278 nm ($\epsilon_{\max}=1.3 \times 10^4$), 335 nm ($\epsilon_{\max}=2.8 \times 10^3$), and 366 nm ($\epsilon_{\max}=2.1 \times 10^3$).

Experimental Section

¹H NMR spectra (CDCl₃ or D₂O; TMS) were recorded on a Bruker AC-200 spectrometer; the proton broad-band decoupled ¹³C NMR spectra (CDCl₃; TMS) were recorded at 90.5 MHz. High-resolution mass spectra were measured on a VG micromass 7070H instrument. IR spectra were recorded in CHCl₃ or in KBr pellets on a Bruker Vector22 FT-IR spectrophotometer. UV spectra were recorded on a Korton UVIKON 931 spectrophotometer using water as the solvent. A Nonius Kappa CCD diffractometer with MoK α radiation ($\lambda=0.7107$ Å) was used for the crystal structure elucidation.

General procedure for working with fluorine: Fluorine is a strong oxidant and a very corrosive material. It should be used only with an appropriate vacuum line such as that described in ref. [15]. For the occasional user,

however, various premixed mixtures of F₂ in inert gases are commercially available, which simplifies the process. Working with fluorine is relatively simple if elementary precautions are taken and we have had no bad experiences working with it.

General procedure for producing HOF·CH₃CN: Mixtures of 10–15 % F₂ with nitrogen were used in this work. They were passed at a rate of about 400 mL min⁻¹ through a cold (-10°C) mixture of CH₃CN (400 mL) and H₂O (40 mL). The development of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were around 0.3–0.4 M. These solutions were used as obtained with no further purification or isolation of the reagent.

1: A solution of 1,10-phenanthroline (**2**; 0.5 g) in chloroform (20 mL) at 0°C was added to 2.2 equivalents of the HOF·CH₃CN solution. After 5 min the mixture was neutralized using a saturated sodium bicarbonate solution, extracted with CHCl₃, dried over MgSO₄, filtered, and evaporated. The crude product was purified by recrystallization from EtOH/H₂O (1/3) to give 1,10-phenanthroline-*N,N*-dioxide (**1**), m.p. 200°C ; IR: $\tilde{\nu}=1221, 1211, 775, 757\text{ cm}^{-1}$; ¹³C NMR: $\delta=139.5, 133.2, 127.6, 123.1, 121.2, 98.8$; HR-MS (EI) m/z : 212.0585 [M^+], calcd for C₁₂H₈N₂O₂ 212.0586; elemental analysis calcd for C₁₂H₈N₂O₂: C 67.92, H 3.80, N 13.20; found: C 67.77, H 4.26, N 12.83. 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-132810. 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 First Enantiomerically Pure Triangulane (*M*)-Trispiro[2.0.0.2.1.1]nonane Is a σ -[4]Helicene**

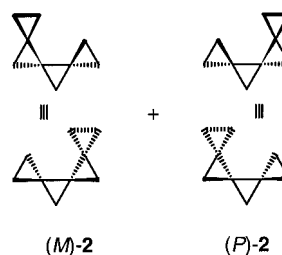
Armin de Meijere,* Alexander F. Khlebnikov,
Rafael R. Kostikov, Sergei I. Kozhushkov, Peter R.
Schreiner, Alexander Wittkopp, and Dmitrii S. Yufit

Dedicated to Professor Hans-Jürgen Quadbeck-Seeger
on the occasion of his 60th birthday

Enantiomerically pure chiral compounds that do not show any optical activity in the ordinarily accessible UV/Vis spectral range (800–200 nm) have been termed cryptochiral.^[1] As demonstrated by Wynberg et al. some 35 years ago,^[2] chiral hydrocarbons with four different alkyl groups at their centers of chirality, even in neat form, do not exhibit any optical rotation and are thus cryptochiral. This is likely to be due to the conformational mobility in such acyclic hydrocarbons. In contrast, [*n*]triangulanes **1**^[3]—that is, hydrocarbons which consist of spiro-annulated and thereby

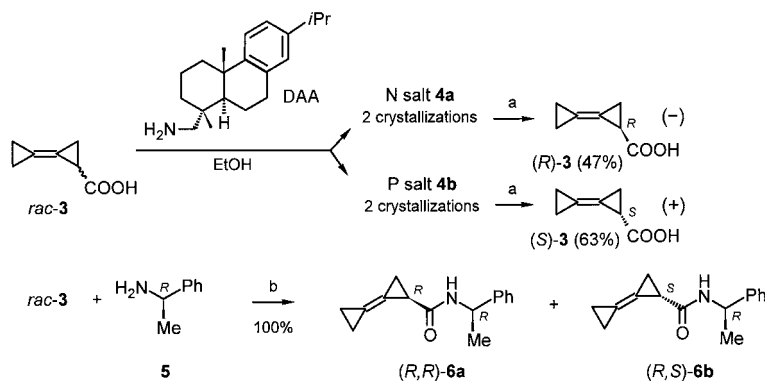
mutually orthogonal cyclopropane rings only—are completely rigid. Many of the higher [*n*]triangulanes **1** (*n* ≥ 4) not containing any centers of chirality are chiral due to their symmetry (or lack thereof),^[4] and they should not behave as cryptochiral, although they are saturated hydrocarbons.

To test this hypothesis, we have developed a synthesis of enantiomerically pure (*M*)-[4]triangulane ((*M*)-**2**), the smallest chiral [*n*]triangulane.^[4] Racemic [4]triangulane (*rac*-**2**) was first synthesized over 25 years ago,^[5] and in the meantime improved syntheses^[6] as well as spectral,^[7] structural,^[8] and thermochemical properties^[9] of *rac*-**2**



are sufficiently well documented. Essentially, the *C*₂-symmetric molecule of (*M*)-**2** is a section of a helix, so that the stereochemical descriptors for helicenes^[10] should also be applicable to (*M*)-**2** and extended unbranched triangulanes **1**.

Racemic bicyclopropylidene carboxylic acid (*rac*-**3**), which is easily available from bicyclopropylidene^[11] by deprotonation and carboxylation,^[12] was resolved by crystallization of a mixture of its diastereomeric *N* and *P*^[13] salts **4a** and **4b** with (+)-dehydroabietylamine (DAA, Scheme 1). Two crystallizations from ethanol and subsequent decomposition with



Scheme 1. Resolution of *rac*-**3** and synthesis of amides (*R,R*)-**6a** and (*R,S*)-**6b**. a) 1. aq. NaOH, 2. conc. HCl, 3. crystallization; b) Ph₂P(O)Cl, Et₃N, EtOAc, –10 °C, 1 h.

[*] Prof. Dr. A. de Meijere, Dr. S. I. Kozhushkov, Dr. P. R. Schreiner, Dipl.-Chem. A. Wittkopp
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-39-9475
E-mail: ameijer1@uni-goettingen.de
Dr. A. F. Khlebnikov, Prof. Dr. R. R. Kostikov
St. Petersburg State University, Chemical Department
St.-Petersburg (Russia)
Dr. D. S. Yufit
Department of Chemistry, University of Durham
Durham (UK)

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aqueous sodium hydroxide and acidification with concentrated hydrochloric acid furnished enantiomerically pure (*R*)-(-)-**3** ($[\alpha]_D^{20} = -183.7$, *c* = 1.00, CHCl₃; 100% *ee*) and (*S*)-(+)-**3** ($[\alpha]_D^{20} = +183.2$, *c* = 1.00, CHCl₃; 100% *ee*).

The absolute configuration of (*R*)-**3** was assigned on the basis of the relative configuration of its (*R*)-(1-phenylethyl)-amide (*R,R*)-**6a**. The amides (*R,R*)-**6a** and (*R,S*)-**6b** were prepared from the racemic acid *rac*-**3** and (*R*)-(1-phenylethyl)amine (**5**) applying a known procedure^[14] (Scheme 1) and separated by column chromatography. The configurations were assigned by comparison with authentic samples prepared from the enantiomerically pure acids (*R*)-(-)-**3** and (*S*)-(+)-**3** after the absolute configuration of (*R,R*)-**6a** had been established^[15] by an X-ray crystal structure analysis (Figure 1).^[16]

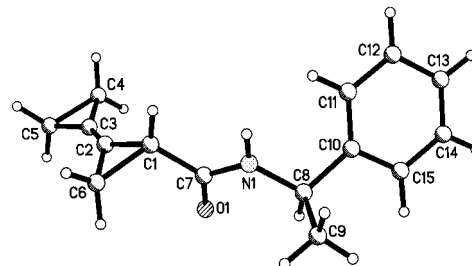
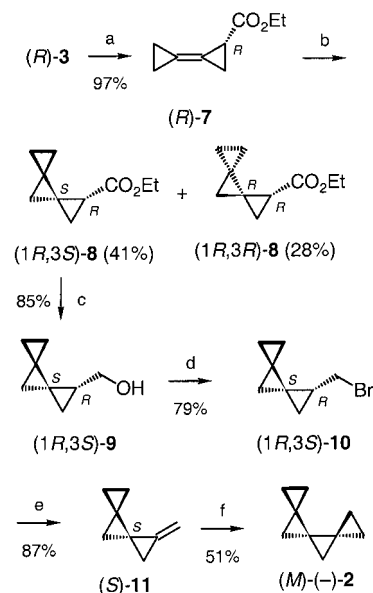


Figure 1. Structure of (*R,R*)-**6a** in the crystal.^[16]

The enantiomerically pure acid (*R*)-**3** was first transformed to its ethyl ester ((*R*)-**7**),^[12, 17] following a standard procedure,^[18] which was then cyclopropanated with the Simmons–Smith reagent (CH₂I₂/Zn)^[19] accelerated by ultrasonication^[20] to give a mixture of ethyl *endo*-(1*R*,3*R*)- and *exo*-(1*R*,3*S*)-[3]triangulane-1-carboxylates ((1*R*,3*R*)-**8** and (1*R*,3*S*)-**8**, Scheme 2).^[11a, 21] These diastereomers were easily separated by column chromatography and isolated in 28 and 41% yield, respectively. Thus, enantiomerically pure (1*R*,3*S*)-**8** was obtained in 19% yield from the racemic acid *rac*-**3**.



Scheme 2. Synthesis of (1*R*,3*S*)-**8** and (1*R*,3*R*)-**8** as well as (*M*)-(-)-**2**. a) BF₃·Et₂O, EtOH, 78 °C, 2 h; b) CH₂I₂, Zn, DME, ultrasound, 80 °C, 2 h; c) LiAlH₄, Et₂O; d) Ph₃P·Br₂, pyridine, CH₂Cl₂, –10 °C, 1.5 h, then 20 °C, 7 h; e) *t*BuOK, DMSO, 20 °C, 14 h; f) CH₂N₂, Pd(OAc)₂, Et₂O, –5 °C.

The ester (1*R*,3*S*)-**8** could be transformed to enantiomerically pure (*M*)-(-)-**2** following a sequence of routine steps established for the preparation of triangulanes.^[3] First, (1*R*,3*S*)-**8** was reduced to the alcohol (1*R*,3*S*)-**9**, which was converted into (bromomethyl)[3]triangulane ((1*R*,3*S*)-**10**) by treatment with triphenylphosphane/bromine (Scheme 2). Dehydrobromination of (1*R*,3*S*)-**10** with potassium *tert*-butoxide gave (*S*)-1-methylenedispiro[2.0.2.1]heptane ((*S*)-**11**), and cyclopropanation of (*S*)-**11** with diazomethane under Pd(OAc)₂ catalysis^[22] furnished enantiomerically pure (*M*)-(-)-**2** in 51% yield after gas-chromatographic separation in the last step. This corresponds to a 6% overall yield from *rac*-**3**, with an enantiomeric excess of 99%, as determined by gas chromatography on a chiral capillary column.^[23]

Although (*M*)-(-)-**2** does not have a chromophore that would lead to any significant absorption above 200 nm, it has a remarkably high specific rotation even at 589 nm ([α]_D²⁰ = –192.7, *c* = 1.18, CHCl₃). The specific rotation increases drastically on going to shorter wavelengths ([α]₅₇₈²⁰ = –201.3, [α]₅₄₆²⁰ = –229.7, [α]₄₃₆²⁰ = –400.2, and [α]₃₆₅²⁰ = –648.2), indicating a strongly negative Cotton effect in the optical rotatory dispersion (ORD) below 200 nm.

For a better understanding of the remarkably high rotatory strength of (*M*)-**2**, ab initio computations were carried out at a reasonably high level of theory (B3LYP/6-31G(d)),^[24–28]

Table 1. A comparison of the measured and DFT/SCI-computed specific rotations of (*M*)-(-)-**2**.

λ [nm]	measured	[α] _D ²⁰ computed
589	–192.7	–241.0
578	–201.3	–250.2
546	–229.7	–283.8
436	–400.2	–466.0
365	–648.2	–703.7

applying a full valence space single excitation configuration interaction treatment (DFT-SCI at B3LYP/TZVP) according to Grimme.^[29] Indeed, the computed specific rotations over the whole range of wavelengths are in very good agreement with the experimental values, and thus confirm the strong negative Cotton effect in the ORD going along with a large ellipticity in the circular dichroism below 200 nm (Table 1).^[30]

This good agreement between experiment and theory for (*M*)-**2** not only provides confidence in the general applicability of this computational approach to the simulation of CD spectra, but also confirms that the rotatory power of (*M*)-**2** is an outflow of its helical arrangement of σ bonds. Thus [4]triangulane is a true “σ-[4]helicene”, the first σ-bond analogue of the aromatic [*n*]helicenes, which have a helical arrangement of skeletal π bond and should therefore be termed π-[*n*]helicenes to distinguish them from these newly established σ-[*n*]helicenes.^[35]

With the same type of computations it is predicted that the rotatory strength of the next higher analogue in the series of chiral triangulanes, (*M*)-[5]triangulane ((*M*)-**12**), should be about twice as large (by a factor of 1.8) as that of (*M*)-**2**, whereas the rotatory strength of (*M*)-[6]triangulane ((*M*)-**13**) would only be slightly larger (factor of 1.1) than that of (*M*)-**12**. This may have to do with the simple fact that the sum of interplanar angles between all adjacent pairs of spiro-fused cyclopropane rings reaches 360° in (*M*)-**12**, while it is 270° in (*M*)-**2**. This is indicated in Figure 2 by the yellow spiral connecting one methylene group of each of the terminal cyclopropane rings with those of the rings in between. In (*M*)-**12**, such a spiral completes exactly one turn of a helix, while in (*M*)-**13** it simply goes 90° beyond a complete turn. To test these computational predictions, it is well worth to prepare at least the two next higher members of this family of σ-[*n*]helicenes.

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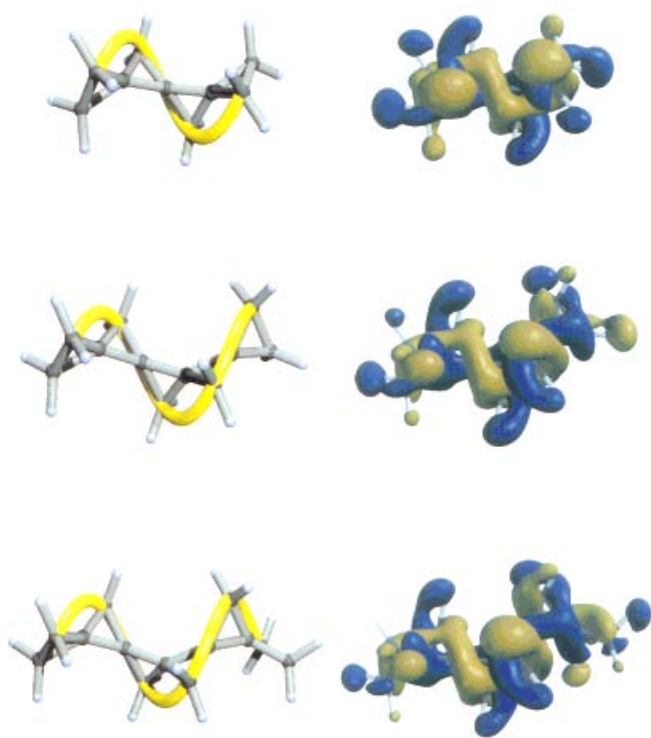


Figure 2. The helicity of (*M*)-**2** (top) and its higher analogues (*M*)-**12** (middle) and (*M*)-**13** (bottom). Left: Visualization by a spiral connecting one methylene group each of the two terminal cyclopropane rings with the methylene groups of the rings in between. Right: Lowest unoccupied orbital (LUMO) of each molecule according to DFT calculations at the B3LYP/6-31G(d) level of theory.

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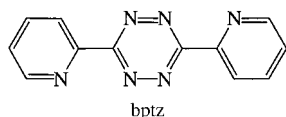
gave the specific rotations in the ORD at the recorded wavelengths (Table 1). As the calculated data are for the gas phase, whereas the experimental ones are obtained for solutions, the computed values are systematically somewhat too large. Nevertheless, the agreement between experiment and theory is remarkably good and emphasizes the quality of the theoretical approach used here.^[29]

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A One-Pot, High-Yield Synthesis of a Paramagnetic Nickel Square from Divergent Precursors by Anion Template Assembly**

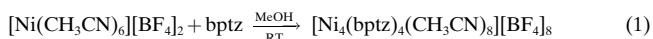
Cristian S. Campos-Fernández, Rodolphe Clérac, and Kim R. Dunbar*

Self-assembly of metal cations with nitrogen heterocyclic bridging ligands is a central theme in supramolecular chemistry aimed at developing light-harvesting assemblies of electronically coupled metal centers.^[1] The ability of these π -ligand systems to transmit electronic information between remote metal centers is well-documented,^[1–4] but much less is known about their suitability for promoting strong superexchange between paramagnetic centers. The bis-chelating α -diimine ligand 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (bptz) with its low-lying π^* orbitals is a particularly promising candidate for use as an electronic spacer,^[5] as judged by the strong coupling observed between the metal centers in $[(\text{NH}_3)_4\text{Ru}(\mu\text{-bptz})\text{Ru}(\text{NH}_3)_4]^{4+}$ which exhibits a K_c value of 10^{15} .^[5f]



Studies in our laboratories have revealed a new application for the bptz molecule, namely as a linking group in the formation of paramagnetic squares. The bptz ligand is ideally suited for this purpose for two reasons. First bptz is a rigid molecule with two bipyridine units on each end suitable for bridging two metals, and second two bptz ligands coordinated to an octahedral metal center are required to be *cis* to each other. These binding preferences are being capitalized upon in one-pot, high-yield reactions of unprotected solvated cations $[\text{M}(\text{CH}_3\text{CN})_6]^{2+}$ with bptz in the presence of tetrafluoroborate anions. In this study we report an unusual, high-yield formation of a cyclic product from

solutions of $[\text{Ni}(\text{CH}_3\text{CN})_6][\text{BF}_4]_2$ and bptz in a 1:1 molar ratio [Eq. (1)].^[6]



Regardless of the ratio of bptz and $[\text{Ni}(\text{CH}_3\text{CN})_6][\text{BF}_4]_2$, the reactions proceed at room temperature in MeOH to give a dark green solution with eventual deposition of a green solid (74% yield). Single crystals of the product are easily obtained by diffusion of toluene into a solution of the compound in acetonitrile. The reactions are quite remarkable in that there is no evidence for polymer formation in spite of the lack of protective groups and the relatively high concentrations used for the reaction. Hupp and co-workers have reported similar observations for various octahedral based squares prepared under refluxing conditions in their laboratories, and it is clear from their detailed analyses that cyclic oligomers are thermodynamic products.^[7]

An X-ray crystallographic study revealed the new compound to be the partially solvated molecular square $[\text{Ni}_4(\text{bptz})_4(\text{CH}_3\text{CN})_8][\text{BF}_4]_8 \cdot 4\text{CH}_3\text{CN}$.^[8] An ORTEP diagram is provided in Figure 1 (top) and a packing diagram is

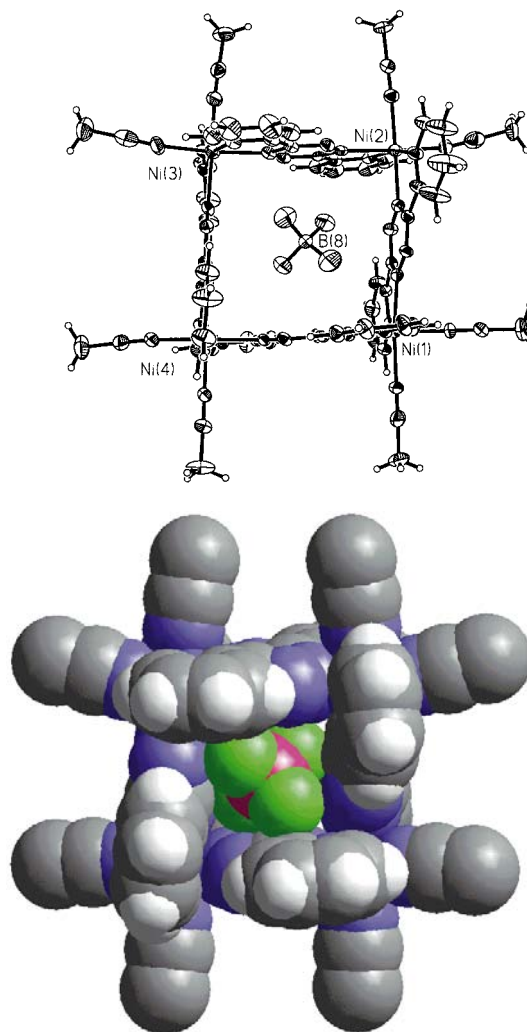


Figure 1. Top: ORTEP drawing of the molecular structure of the $[\text{Ni}_4(\text{bptz})_4(\text{CH}_3\text{CN})_8]^{8+}$ ion. Thermal ellipsoids are drawn at the 50% probability level; bottom: space-filling diagram of the molecular cation with the encapsulated $[\text{BF}_4]^-$ ion.

[*] Prof. K. R. Dunbar, C. S. Campos-Fernández, R. Clérac
Chemistry Department, Texas A&M University
P.O. Box 30012, College Station, TX 77842–3012 (USA)
Fax: (+1) 409-845-7177
E-mail: dunbar@mail.chem.tamu.edu

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provided in Figure 2. The coordination geometries of the Ni^{II} ions are octahedral as expected, with four of the coordination sites being occupied by two different bptz chelate donors and the other two positions being capped by CH_3CN molecules.

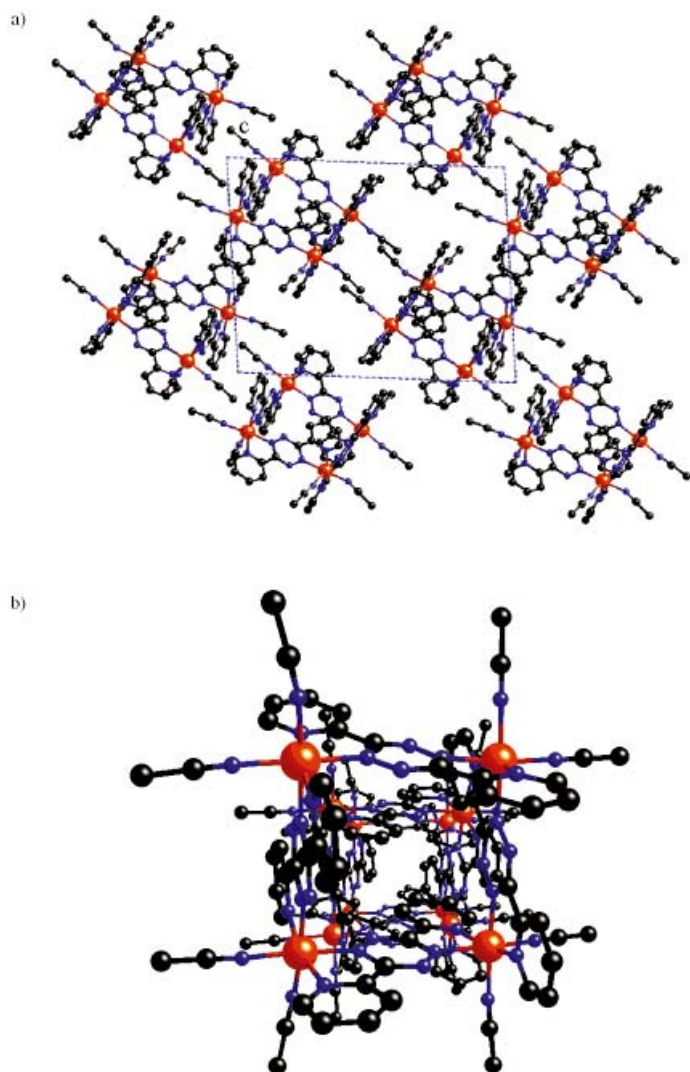


Figure 2. Packing arrangement of the Ni_4 cations emphasizing the a) and b) side views of the stacks.

The void space in the center of the square is about $4.6 \text{ \AA}$ in diameter which is an excellent size match for the $[\text{BF}_4]^-$ ion that resides in this cavity (Figure 1 bottom). The encapsulated anion appears to be central to the formation of the cyclic oligomer as evidenced by the fact that products with other anions are of a different color than the $[\text{BF}_4]^-$ salt and are noncrystalline. For example, $[\text{Ni}(\text{CH}_3\text{CN})_6][\text{PF}_6]_2$ reacts with bptz in MeOH to give dark orange-brown solutions from which only powders can be isolated. Anion template reactions are of considerable current interest in the self-assembly of supramolecular structures,^[9] but compared to cation-assisted processes, they are much less prevalent. A particularly relevant example to the present work is the report of a $[\text{BF}_4]^-$ -templated synthesis of a $[\text{Co}_4]^{8+}$ cage molecule which retains an encapsulated anion in solution.^[9b] The authors used a combination of mass spectrometry and NMR spectroscopy

to support the conclusion that the anion assists in the assembly of the tetrameric unit. These approaches were also used to lend insight into the possible role of the anion in the synthesis of $[\text{Ni}_4(\text{bptz})_4(\text{CH}_3\text{CN})_8][\text{BF}_4]_8$, but NMR spectroscopy revealed only one broad ^{11}B and ^{19}F resonance. This may be due to the paramagnetism of the molecule or to rapid exchange of the encapsulated $[\text{BF}_4]^-$ ion with the outer-sphere anions, although the latter is unlikely since low-temperature NMR measurements did not produce any changes in the spectra. The most convincing evidence for the role of the anion comes from a FAB mass spectrometric analysis of solutions of Ni ions with bptz in the presence of various anions. Solutions containing the $[\text{BF}_4]^-$ ion give a mass cluster corresponding to the square unit, but those containing $[\text{PF}_6]^-$, $[\text{SbF}_6]^-$, or $[\text{CF}_3\text{SO}_3]^-$ show only dimeric units. We take these results as a positive indication that the anion acts as a template in the self-assembly process.

The six-coordinate geometry about the metal ions is important to our goal of obtaining magnetic squares, as a square-planar geometry leads to low-spin, primarily diamagnetic ground states.^[10] Magnetic susceptibility measurements were performed on the Ni_4 compound, and, as the plot in Figure 3 indicates, μ_{eff} is constant at $5.66 \mu_{\text{B}}$ between room temperature and 50 K. These data are consistent with four high-spin Ni^{II} ($S=1$) centers. Below 50 K the moment decreases which can be attributed to a zero-field splitting effect or weak antiferromagnetic interactions ($J \approx -2 \text{ K}$).

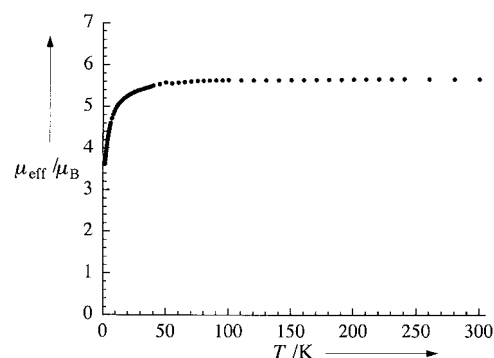


Figure 3. Thermal dependence of the effective moment at 1000 G for $[\text{Ni}_4(\text{bptz})_4(\text{CH}_3\text{CN})_8][\text{BF}_4]_8 \cdot 4 \text{ CH}_3\text{CN}$.

The new Ni_4 molecule is an unprecedented type of a partially solvated molecular square, and it is the first compound of the bptz ligand to be structurally characterized. As far as we are aware, this is the first report of a molecular square formed around an encapsulated anion, and one of the few X-ray structures obtained for a square with octahedral metal ion constituents.^[7, 11, 12] The only paramagnetic octahedral-based example of which we are aware is a Co^{II} $[2 \times 2]$ grid with bis-terpyridine type ligands.^[12a] Five-coordinate paramagnetic Cu^{II} $[2 \times 2]$ grids with bridging pyrazole ligands have also been recently reported.^[12b] The presence of the labile CH_3CN ligands in $[\text{Ni}_4(\text{bptz})_4(\text{CH}_3\text{CN})_8]^{8+}$ render these clusters ideal building blocks for the elaboration of two-dimensional square grids. In this manner a higher order supramolecular structure can easily be envisioned as resulting from connecting the squares with linear bidentate bridges

such as 4,4-bipyridine or pyrazine or even bis-chelating bidentate ligands such as bipyrimidine or oxalate. Although the unpaired electrons on the Ni^{II} ions are not magnetically communicating through the bptz ligand, this does not rule out the possibility that metal ions with different magnetic orbitals will experience superexchange. Moreover, ligand-based reduction of the π^* orbitals of the bptz ligands to produce bptz radicals, which has been achieved in other metal complexes of bptz,^[13] is expected to add an extra level of complexity to the magnetic properties.

Experimental Section

[Ni(CH₃CN)₆][BF₄]₂ (100 mg, 209 mmol) was dissolved in methanol (10 mL) and treated with bptz (47 mg, 200 mmol) under anaerobic conditions. Over the course of 5 h, the solution slowly changed color from pale red to a dark green. The solution was allowed to stir overnight during which time a green powder deposited on the bottom of the flask. The powder was dissolved in acetonitrile under anaerobic conditions and layered with toluene to give crystals of [Ni₄(C₁₂N₆H₈)₄(CH₃CN)₈][BF₄]₈ · 4CH₃CN within three days; yield: 88 mg (74%).

Magnetic susceptibility measurements were performed on a polycrystalline sample (18.8 mg) with a Quantum Design MPMS-2 SQUID magnetometer operating in the range 1.7–300 K at 1000 G.

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Amine Phosphates as Intermediates in the Formation of Open-Framework Structures

S. Neeraj, Srinivasan Natarajan, and C. N. R. Rao*

There has been intense research activity in the area of inorganic open-framework materials during this decade, partly motivated by their potential applications in catalysis and sorption and separation processes.^[1] While aluminosilicates and aluminophosphates with open architectures have been known for some time, it is only recently that diverse inorganic open-framework structures, especially phosphates, of a wide range of metals were synthesized hydrothermally in the presence of structure-directing amines.^[2] In spite of the progress made, one is not able to adequately rationalize the formation of such a variety of open-framework metal phosphate structures. In the case of aluminophosphates, it is proposed that linear chains of corner-sharing metal phosphate units are progressively transformed into ladder, layer, and three-dimensional structures.^[3] In tin phosphates, four-rings of the metal phosphate are believed to transform into larger rings and give rise to layer and other complex structures.^[4] While the variety of structures generated in a given metal phosphate system, often with the same amine, may arise because of the small energy differences amongst them or due to kinetic control of the reactions, the exact role of the amines is not fully understood, in spite of several hypotheses.^[5] We consider it of great importance to understand how the initial chain or layer structures of metal phosphates are formed, and therefore investigated whether a stable reaction intermediate, formed during hydrothermal synthesis, plays a key role, and, if so, whether this intermediate can be directly used to generate novel metal phosphates.

In the hydrothermal synthesis of open-framework metal phosphates, we isolated several amine phosphates as additional products. Initial experiments showed that the amine phosphates react with metal ions under hydrothermal conditions in the absence of additional phosphoric acid to give open-framework metal phosphates. This suggested that amine phosphates could indeed act as intermediates in the formation of open-framework structures. Although amine phosphates are known to occur as by-products in the synthesis of metal phosphates,^[6] they are not normally encountered because of their high solubility in water and the usual preoccupation with less soluble crystalline products. Amine phosphates themselves are readily prepared by the reaction of amines with phosphoric acid under normal conditions in an appropriate solvent.^[7] Here we demonstrate how the amine phosphates react with metal ions to yield various metal phosphate structures, which were characterized by X-ray crystallography on isolated products, as well as in-situ NMR and X-ray diffraction studies.

Reaction of 1,3-diaminopropane phosphate (DAPP; Figure 1a) with Zn^{II} ions under hydrothermal conditions^[8] initially gives a zinc phosphate with a ladder structure involving edge-shared four-ring metal phosphate units (Figure 1b). It is noteworthy that this ladder structure is also produced in the conventional hydrothermal synthesis with 1,3-diaminopropane (DAP) as structure-directing agent.^[9] More

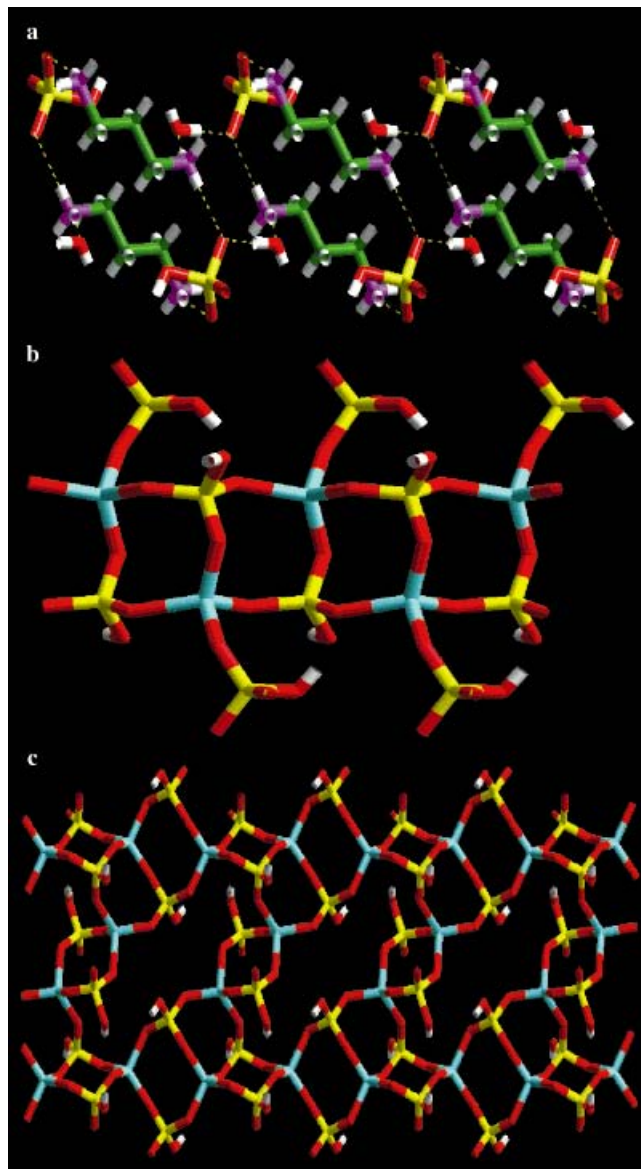


Figure 1. a) Structure of diaminopropane phosphate (DAPP) showing its hydrogen-bonded assembly (blue: Zn, yellow: P, red: O, green: C, pink: N, white: H). b) The one-dimensional zinc phosphate ladder structure. Replacement of the water molecules in (a) by Zn ions gives this structure. c) Layered zinc phosphate.

significantly, DAPP reacts with Zn^{II} to give this ladder structure at much lower temperatures (30°C for 96 h).^[8] In addition, we obtained a new layer structure (Figure 1c) when DAPP was treated with Zn^{II} for extended periods (≥ 96 h) at moderate temperatures ($\leq 85^\circ\text{C}$). This observation suggests that the layer structure may be a transformation product of the ladder structure.

[*] Prof. Dr. C. N. R. Rao, S. Neeraj, Dr. S. Natarajan
Chemistry and Physics of Materials Unit and
CSIR Centre of Excellence in Chemistry
Jawaharlal Nehru Centre for Advanced Scientific Research
Jakkur P.O., Bangalore 560 064 (India)
Fax: (+91) 80-846-2766
E-mail: cnrrao@jncasr.ac.in

Reaction of piperazine phosphate (PIPP) with Zn^{II} ions under hydrothermal conditions gave a new linear ladder structure of corner-sharing metal phosphate units, along with a new three-dimensional structure (Figure 2); two known three-dimensional structures^[10] were also obtained. Reaction

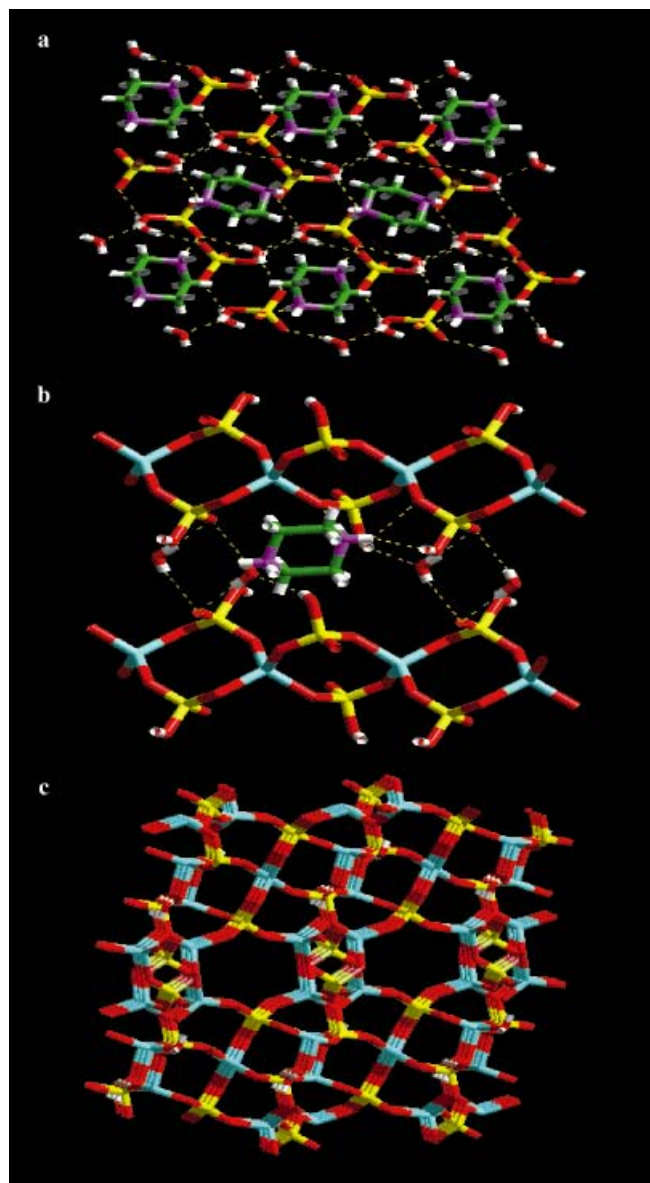


Figure 2. a) Structure of the hydrogen-bonded piperazine phosphate (PIPP) assembly. b) A new corner-shared zinc phosphate structure. This is the simplest chain structure. c) Structure of a new three-dimensional open-framework zinc phosphate. This structure can be derived from the chain structure.

of PIPP with Zn^{II} ions at 85°C also yielded the three-dimensional structures. Similarly, the phosphate of 1,4-diazabicyclo[2.2.2]octane (DABCOP) reacted with Zn^{II} ions at around room temperature to give the same three-dimensional structure that was obtained at 150°C or by direct hydrothermal synthesis.^[11] Reaction of ethylenediamine phosphate (ENP) with Zn^{II} ions at 150°C gave new ladder, layer, and three-dimensional structures. The last two were also obtained from a reaction carried out at 50°C . Table 1 lists the various

open-framework zinc phosphates obtained by the reactions of amine phosphates with Zn^{II} ions at different temperatures.

The above results suffice to indicate the key role of amine phosphates in the formation of open-framework phosphates. Furthermore there is a close similarity between the structures of DAPP (Figure 1 a) and the zinc phosphate ladder structure (Figure 1 b). The former consists of a hydrogen-bonded network with water molecules and resembles the loosely hydrogen bonded structures involved in the synthesis of aluminosilicates.^[12] The mechanism of formation of the initial ladder phosphate can be understood in terms of the displacement of the water molecules from the amine phosphate by Zn^{II} ions (Figure 3).

To further substantiate that the amine phosphates undergo facile reactions with metal ions, we monitored the reaction between DAPP and Zn^{II} ions at 85°C in an aqueous medium by in situ ^{31}P NMR spectroscopy. The intensity of the signal of

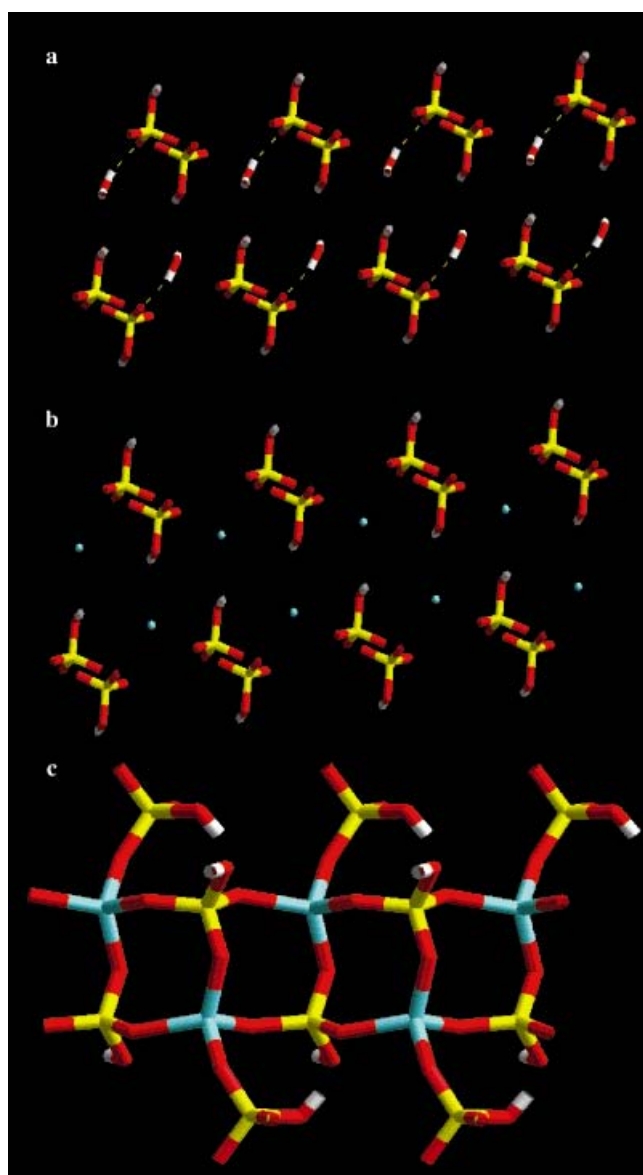


Figure 3. a) Structure of the hydrogen-bonded DAPP assembly (amine molecules omitted for clarity). b) Schematic replacement of water molecules by Zn^{II} ions. c) Edge-shared zinc phosphate ladder structure.

Table 1. Open-framework zinc phosphates obtained from amine phosphates.

Composition	T [°C] (t [h])	a [Å]	b [Å]	c [Å]	α [°]	β [°]	γ [°]	Space group	$R(F)^{[a]}$	Framework type
DAPP: [dapH ₂][HPO ₄] $\cdot$ H ₂ O ^[b]		7.009(9)	16.775(8)	7.845(9)	90.00	113.78	90.00	$P2_1/c$	7.8	(Figure 1 a)
[Zn(HPO ₄) ₂][dapH ₂]	150 (40), 95 (40), 50 (48), 30 (96)	5.222(0)	12.756(1)	15.674(1)	90.00	90.00	90.00	$P2_12_12_1$	2.2	chain ^[9]
[Zn ₂ (HPO ₄) ₃][dapH ₂]	150 (40), 85 (96)	8.614(5)	9.618(7)	17.037(8)	90.00	93.57	90.00	$P2_1/c$	4.5	layer ^[c]
[SnPO ₄] ₂ [dapH ₂]	180 (24), 85 (48), 50 (96)	18.096(7)	7.888(6)	9.150(7)	90.00	111.84	90.00	$C2/c$	2.6	layer (Figure 4)
[Al ₃ Co ₂ (OH)(HPO ₄) ₄ (PO ₄) ₂][dapH ₂]	180 (96), 110 (300) ^[d]	9.177(4)	9.250(5)	13.175(4)	93.07	92.31	112.06	$P\bar{1}$	13.0	3-D ^[c]
PIPP: [pipH ₂][HPO ₄] $\cdot$ H ₂ O ^[b]		6.425(6)	12.296(8)	11.220(8)	90.00	97.14	90.00	$P2_1/n$	6.4	Figure 2 a
[Zn(HPO ₄) ₂ (H ₂ O)][pipH ₂]	180 (36)	8.930(6)	14.025(4)	9.310(7)	90.00	95.41	90.00	$P2_1/n$	4.0	chain ^[a]
[Zn ₂ (PO ₄) ₃ (OH)][pipH ₂]	180 (36) ^[e]	16.104(8)	8.256(4)	22.997(9)	90.00	104.00	90.00	$C2/c$	2.0	(Figure 2 b)
[Zn(H ₂ O)Zn(HPO ₄)(PO ₄) ₂][pipH ₂]	180 (36), 85 (300)	12.075(5)	14.888(7)	11.835(8)	90.00	97.72	90.00	$C2/c$	3.0	3-D ^[10]
[Zn ₂ (PO ₄)(H ₂ PO ₄) ₂][pipH ₂]	180 (36), 85 (300)	13.388(3)	12.838 (6)	8.224(6)	90.00	94.77	90.00	$C2/c$	–	3-D (10)
DABCOP: [dabcoH ₂][HPO ₄] $\cdot$ H ₂ O ^[b]		6.906(2)	9.018(4)	9.271(2)	92.21	104.51	111.76	$P\bar{1}$	3.9	–
[Zn ₂ (HPO ₄) ₃][dabcoH ₂]	150 (20), 95 (20)	9.528(4)	9.948(3)	9.996(4)	107.65	98.04	114.86	$P\bar{1}$	5.5	3-D ^[11]
[Zn ₄ (PO ₄) ₂ (HPO ₄) ₂][dabcoH ₂] $\cdot$ 3 H ₂ O	150 (20), 95 (20), 50 (48), 30 (60)	9.475(1)	9.524(9)	12.312(4)	93.73	91.044	98.70	$P\bar{1}$	6.1	3-D ^[11]
ENP: [enH ₂][HPO ₄] ^[b]		7.507(1)	11.816(4)	8.055(4)	90.00	110.13	90.00	$P2_1/c$	3.0	–
[Zn(HPO ₄) ₂][enH ₂]	150 (36)	5.161(1)	15.842(2)	12.027(2)	90.00	92.36	90.00	$P2_1/c$	6.0	ladder
[Zn ₂ (HPO ₄) ₂ (H ₂ PO ₄) ₂][enH ₂]	150 (36), 50 (40)	16.420(2)	7.826(1)	14.640(1)	90.00	116.47	90.00	$P2_1/c$	5.0	layer
[Zn ₆ (PO ₄) ₄ (HPO ₄) ₂][enH ₂]	150 (36)	19.182(0)	5.036(0)	21.202(4)	90.00	103.29	90.00	$C2/c$	3.6	3-D

[a] $R(F) = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$, where $F_o > 4.0\sigma(F)$. [b] The amine phosphates were recovered initially from the hydrothermal syntheses and later synthesized by using the composition amine:1.2H₃PO₄:5H₂O at 110 °C for 12 h. [c] New structure found in this study. [d] Synthesis was carried out in ethylene glycol. [e] Different composition of the starting gel.

the amine phosphate ($\delta = 0.056$) decreases, while that of a zinc phosphate precursor^[13] at $\delta = 3.82$ increases (Figure 4). The intensity of the signal of the phosphate precursor decreases after some time due to the formation of more complex open-framework phosphates. This suggests that the unidentified intermediate reported recently^[14] in an in situ energy dispersive X-ray diffraction (EDXRD) study on the formation of the gallophosphate ULM-5 may be an amine phosphate.

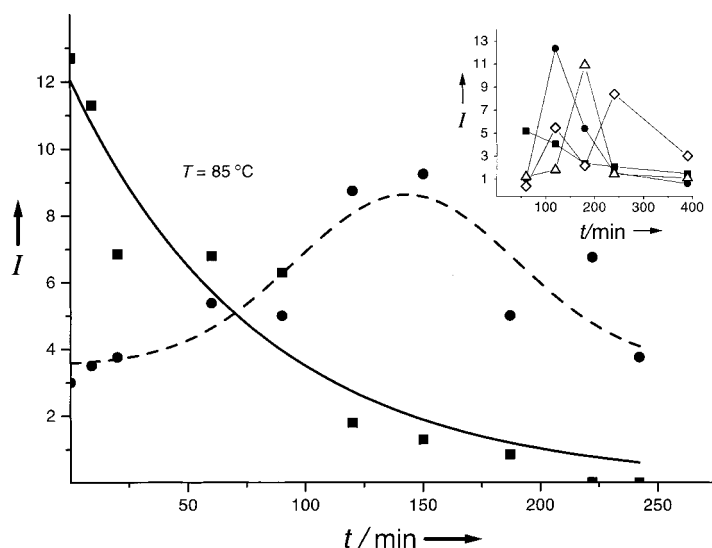


Figure 4. Plots of ³¹P NMR signal intensity I (in arbitrary units) of DAPP (—) and of the precursor zinc phosphate (---) against reaction time. The inset shows the variation in the relative intensities (arbitrary units) of the low-angle reflections in the XRD patterns of the amine phosphate and of the products of its reaction with Zn^{II} ions (■ amine phosphate, ● precursor, △ chain (edge-shared) phosphate, ◇ layer phosphate).

Heating the intermediate with gallium salts is reported to yield the gallophosphate.^[14] Our time-dependent XRD studies^[13] on the DAPP–Zn^{II} reaction lend credence to this suggestion (see inset of Figure 4).

To demonstrate the universality of the amine phosphate route to open-framework structures, we carried out the reaction of DAPP with tin(II) oxalate and obtained the layer structure shown in (Figure 5). This structure is obtained at temperatures as low as 50 °C (see Table 1). The reaction of DAPP with Co^{II} and Al^{III} ions, gave a new three-dimensional cobalt aluminum phosphate that belongs to a recently described family of materials.^[15]

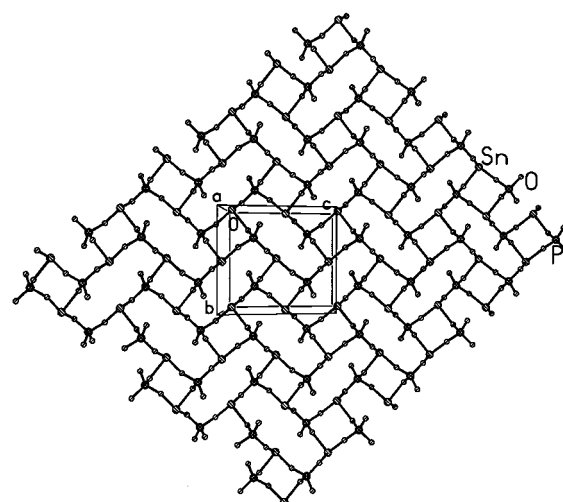


Figure 5. Layered tin(II) phosphate structure formed by the reaction of DAPP with tin(II) oxalate at around room temperature.

In conclusion, the present study demonstrates that open-framework metal phosphates can be generated under relatively mild conditions by treating amine phosphates with metal ions and that amine phosphates are intermediates in hydrothermal syntheses. The amine phosphates initially give chain or ladder structures that give rise to more complex structures, depending on time and temperature.

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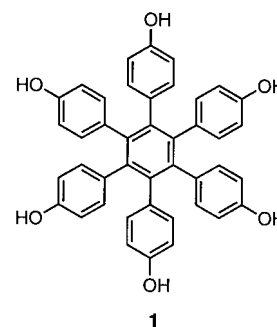
Keywords: hydrothermal syntheses • phosphorus • tin • zinc

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- [8] In a typical synthesis, 0.5 mmol of ZnO was stirred in 100 mmol of water, to which 1 mmol of HCl (35 %) was added. After stirring the mixture for a few minutes, 2.7 mmol of amine phosphate (e.g., DAPP) was added, and the mixture was stirred for 30 min. The homogenized mixture was sealed in a 23-mL teflon-lined Parr autoclave and heated at the given temperature and for the given duration (see Table 1). The product was collected by filtration, and X-ray analysis of the crystals was carried out on a Siemens SMART X-ray diffractometer with a CCD detector.
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- [13] Reaction of the amine phosphate with Zn^{II} at all temperatures first yields a fine particulate open-framework zinc phosphate with a low-angle XRD line ($d_{\text{hkl}} = 11.8 \text{ \AA}$). Time-dependent XRD studies show that the low-angle line due the precursor decreases in intensity when the characteristic reflections of the ladder, layer, and three-dimensional structures start to appear. The aqueous dispersion of the particulate material shows a ³¹P NMR signal ($\delta = 3.82$) whose intensity first increases with time and then decreases due to the formation of an edge-shared ladder or layer structures. We consider the initial phosphate material formed to be the precursor, since on further reaction or passage of time it gives the more complex ladder, layer, or three-dimensional structures. It seems likely that the precursor is a corner-shared linear ladder phosphate which we have isolated from some reactions of the amine phosphates. Accordingly, the Zn:P ratio in the precursor phosphate is 1:1 (in contrast to the edge-shared ladder phosphates, in which it is 1:2).
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Self-Assembly of a Radially Functionalized Hexagonal Molecule: Hexakis(4-hydroxyphenyl)benzene**

Kenji Kobayashi,* Toshiaki Shirasaka, Azumi Sato, Ernst Horn, and Naomichi Furukawa

Supramolecular approaches to self-assembly of molecular solids rely in a predictable manner on directional and complementary noncovalent interactions.^[1] Particular attention has recently focused on the rational design of microporous solids with specific properties such as selective adsorption^[2] and catalytic activity.^[3] However, the formation of hydrogen-bonded networks with large cavities often results in self-interpenetration to fill the voids in the initial host structure.^[4] The introduction of sterically demanding substituents into trigonal molecules^[5,6] and the use of rigid hexagonal macrocycles^[7] with multiple hydrogen-bonding sites are potential methods to prevent interpenetration of networks. Aoyama and ourselves recently prepared porous networks of bis-resorcinol orthogonal aromatic triads for the preorganization of host molecules.^[8] Hexaarylbenzene derivatives^[9] are highly symmetrical molecules that can bear diverse and multifunctional radial substituents and exhibit an orthogonal arrangement of the interactive groups with respect to the core moiety.^[10,11] Here we report on the porous two-dimensional hydrogen-bonded networks of hexakis(4-hydroxyphenyl)benzene (**1**); the topology of the network structures is flexible and guest-dependent.



Host **1** was prepared by the [Co₂(CO)₈]-catalyzed cyclotrimerization^[9] of bis(4-methoxyphenyl)acetylene (81 % yield) followed by deprotection of the resulting hexakis(4-methoxyphenyl)benzene (**2**) with BBr₃ (92 % yield). Recrystallization of **1** from various solvents afforded inclusion cocrystals, the stoichiometries of which were evaluated by ¹H NMR spectroscopy in CD₃OD: **1** · 3 C₆H₅COOCH₃ from a

[*] Dr. K. Kobayashi, T. Shirasaka, A. Sato, Prof. Dr. N. Furukawa
Department of Chemistry and
Tsukuba Advanced Research Alliance Center
University of Tsukuba, Tsukuba, Ibaraki 305–8571 (Japan)
Fax: (+81) 298-53-6503
E-mail: kenjinor@staff.chem.tsukuba.ac.jp
Prof. Dr. E. Horn
Department of Chemistry, Rikkyo University
Nishi-Ikebukuro, Toshima-ku, Tokyo 171–8501 (Japan)

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mixture of methyl benzoate and benzene; **1**·3CH₃COOEt from a mixture of ethyl acetate and hexane; **1**·4Et₂O and **1**·3CH₃COOEt in a 4:1 ratio from a mixture of diethyl ether and ethyl acetate; **1**·4DMF from a mixture of ethyl acetate, diethyl ether, and DMF (*N,N*-dimethylformamide). Thus, in the solid state, **1** prefers to include more polar guests. The crystal structures of **1**·4Et₂O (**3**) and **1**·4DMF (**4**) were determined by X-ray diffraction analysis^[12] (Figure 1).

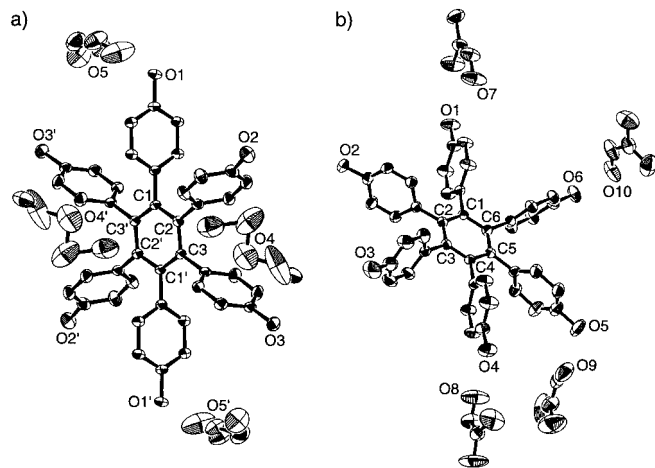


Figure 1. ORTEP plots (30% probability thermal ellipsoids) of a) **3** and b) **4**. Hydrogen atoms are omitted for clarity.

The molecular structure of **3** has a center of symmetry (Figure 1a). Two of the four included ether molecules are hydrogen-bonded to the hydroxyl groups HO1 of **1** (O1...O5 2.69 Å). The other two ether molecules interact with the aromatic core of **1**, whereby the distance between the methyl group and the face of the core is about 3.6 Å. The dihedral angles between the phenol rings and the aromatic core at C1–C3 are 102.8, 68.2, and 96.7°, respectively.

All hydroxyl groups of **1** participate in the two-dimensional hydrogen-bonded network (molecular sheet) of **3** (Figure 2a), in which the intermolecular hydrogen-bonding patterns are O2H...O3H...O1H with O...O distances of 2.81 and 2.74 Å, respectively. This network is an antiparallel assembly of one-dimensional ladder-type networks (molecular tapes). Each tape is formed by two-point O2H...O3H hydrogen bonds between adjacent molecules along the *b* axis, and the tapes are assembled into the molecular sheet in a stairlike fashion by O3H...O1H hydrogen bonds (Figures 2a and b). Hence, this molecular sheet has two types of cavities: cavities **A** (ca. 7.6 × 7.6 Å) in the tapes, and cavities **B** (ca. 6.0 × 7.6 Å) between them. One molecule of **1** constitutes one cavity **A** and two cavities **B**.^[13] The molecular sheets are layered without translation, so that two types of extended channels **A** and **B** are generated along the *a* axis (Figure 2c). The sheet–sheet (core center to core center) distance along the *a* axis is 9.87 Å.

The molecular structure of **4** has no symmetry; the dihedral angles between the phenol rings and the aromatic core at C1–C6 are 91.3, 99.6, 77.2, 83.6, 76.3, and 97.7°, respectively (Figure 1b). All DMF molecules (O7, O8, O9, and O10) are hydrogen-bonded to the hydroxyl groups HO1, HO4, HO5, and HO6 of **1** with O...O distances of 2.70, 2.69, 2.64, and 2.55 Å, respectively.

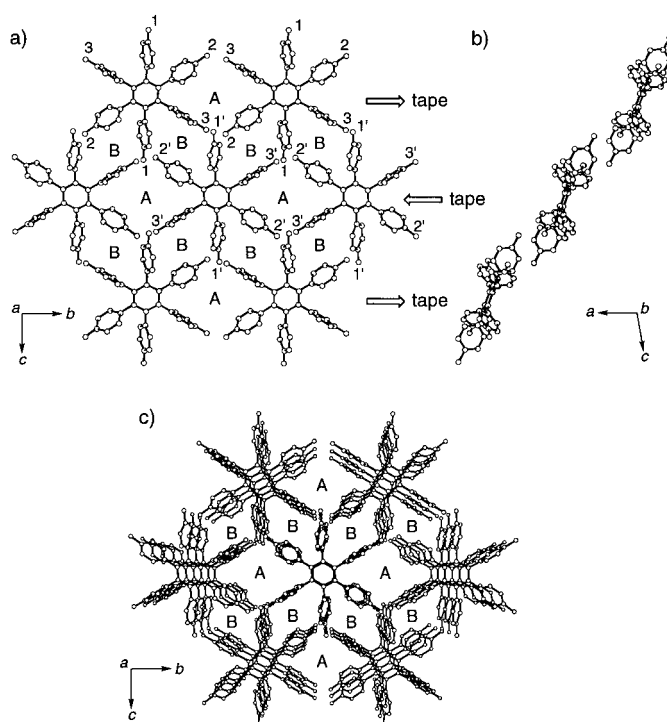


Figure 2. Views of the X-ray crystal structure of **3**: a) the two-dimensional hydrogen-bonded network (one sheet) parallel to the *a* axis, b) one sheet parallel to the *b* axis, and c) three neighboring sheets parallel to the *a* axis (perspective view). Diethyl ether molecules are omitted for clarity.

The two-dimensional hydrogen-bonded network of **4** is considerably different from that of **3**. Four hydroxyl groups of **1** are involved in the network of **4** (Figure 3a), in which the intermolecular hydrogen-bonding patterns are O2H...O6H (O...O 2.75 Å) and O3H...O5H (O...O 2.74 Å). The molecular sheet is almost flat (Figure 3b). Although the conformational asymmetry of **1** (Figure 1b) makes this host chiral, both enantiomers are alternately aligned along the hydrogen-bonded chains to give a racemic crystal of **4**. The network topology of **4** has large cavities (ca. 15.5 × 15.5 Å) which are partitioned by two phenol rings of **1**. In contrast to **3**, the adjacent sheets of **4** are laterally offset in an ABAB sequence by 11.58 Å along the *a* axis. Thus, each cavity in a sheet is sandwiched between two host molecules of adjacent sheets as ceiling and floor to form a chamber instead of a channel (Figure 3c).^[14] The sheet–sheet distance is about 5.9 Å.

The host **1** in single crystals of **3** and **4** occupies 40 and 45% of the total volume of the unit cell, respectively. The respective ratios of the volume occupied by guests in **3** and **4** are 0.51 and 0.41, which are comparable to those of 4A and 13X molecular sieves.^[8b] Single crystals of **4** are quite stable because all of the DMF molecules that are hydrogen-bonded to **1** are accommodated in the chamber.^[15] Thermogravimetric analysis (10 °C min^{−1}) of **4** showed the loss of three DMF molecules at 143–180 °C and the remaining molecule at 201–228 °C.

In summary, we have demonstrated that hexakis(4-hydroxyphenyl)benzene (**1**) as a radially functionalized hexagonal host assembles into two types of porous two-dimensional

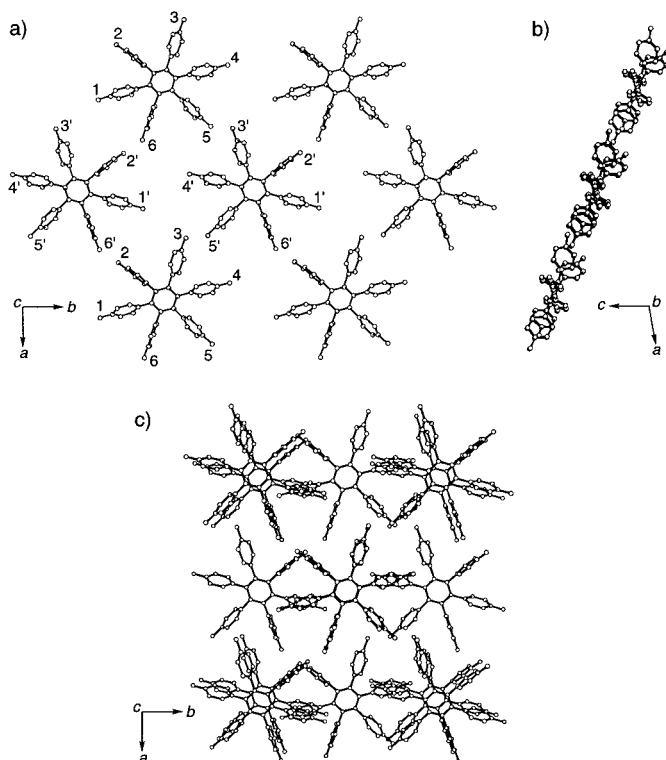


Figure 3. Views of the X-ray crystal structure of **4**: a) the two-dimensional hydrogen-bonded network (one sheet) parallel to the *c* axis, b) one sheet parallel to the *b* axis, and c) three neighboring sheets parallel to the *c* axis (perspective view). DMF molecules are omitted for clarity.

hydrogen-bonded networks without interpenetration. These are layered to form a channel or a chamber structure, depending on the nature of guest molecules. Studies on the functionalization of hexaphenylbenzene with other substituents such as carboxyl and amide groups are underway.

Experimental Section

2: A mixture of bis(4-methoxyphenyl)acetylene (480 mg, 2.01 mmol) and $[\text{Co}_2(\text{CO})_8]$ (70 mg, 0.20 mmol) in dry 1,4-dioxane (20 mL) under argon was stirred at 100 °C for 24 h. After evaporation of solvent, the residue was subjected to column chromatography on silica gel with hexane/diethyl ether (9/1) as eluent. The crude product was recrystallized from $\text{CH}_2\text{Cl}_2/\text{EtOH}$ to give **2** (388 mg, 81%). M.p. 390 °C (decomp.); ^1H NMR (270 MHz, CDCl_3): δ = 3.63 (s, 18H), 6.43 (d, J = 8.9 Hz, 12H), 6.66 (d, J = 8.9 Hz, 12H); ^{13}C NMR (67.5 MHz, CDCl_3): δ = 54.9, 112.1, 132.4, 133.6, 140.2, 156.7; EI-MS: m/z (%): 714 (96) [M^+]; elemental analysis calcd for $\text{C}_{48}\text{H}_{42}\text{O}_6 \cdot 0.5\text{H}_2\text{O}$: C 79.65, H 5.99; found: C 79.73, H 6.16.

1: A solution of BBr_3 (0.75 mL, 7.93 mmol) in dry CH_2Cl_2 (10 mL) was added to a suspension of **2** (860 mg, 1.20 mmol) in dry CH_2Cl_2 (80 mL) at –20 °C over 10 min. The mixture was allowed to warm to room temperature over 18 h and then poured into 2 M NaOH (30 mL). The aqueous layer was washed with CH_2Cl_2 , acidified with 3 M HCl, and extracted with ethyl acetate. After evaporation of the solvent, the white solid was recrystallized from ethyl acetate/diethyl ether and dried in vacuo to give **1** (696 mg, 92%). M.p. 250 °C (decomp.); ^1H NMR (270 MHz, CD_3OD): δ = 6.29 (d, J = 8.6 Hz, 12H), 6.57 (d, J = 8.6 Hz, 12H); ^{13}C NMR (67.5 MHz, CD_3OD): δ = 115.3, 134.5, 135.1, 142.5, 156.5; FAB-MS: m/z (%): 630 (35) [M^+]; elemental analysis calcd for $\text{C}_{42}\text{H}_{30}\text{O}_6 \cdot 1.5\text{H}_2\text{O}$: C 76.70, H 5.06; found: C 76.68, H 4.79.

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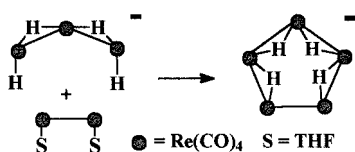
CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [13] In **3**, each cavity **A** accommodates two hydrogen-bonded ether molecules, and each cavity **B** accommodates one non-hydrogen-bonded ether molecule.
- [14] In **4**, each cavity in a sheet is filled with two molecules of DMF (O7, O8) that are hydrogen-bonded in the same sheet and two molecules of DMF (O9, O10) which are hydrogen-bonded to each of the adjacent sheets.
- [15] Single crystals of **3** quickly become opaque, probably due to loss of non-hydrogen-bonded diethyl ether.

[Re₆(μ-H)₅(CO)₂₄][−]: The First Carbonyl Cluster with a Cyclohexane-Like Structure**

Mirka Bergamo, Tiziana Beringhelli, Giuseppe D'Alfonso,* Pierluigi Mercandelli, Massimo Moret,* and Angelo Sironi

We have recently reported^[1] the synthesis of the pentametallic ring cluster [Re₅(μ-H)₄(CO)₂₀][−] through the cycloaddition of the [Re₃H₂(μ-H)₂(CO)₁₂][−] anion and the Re₂(CO)₈ fragment originated from the labile complex [Re₂(CO)₈(thf)₂]^[2] (Scheme 1). The reaction exploits the well-known σ-donor capability of M–H bonds toward coordinatively unsaturated metal centers^[3] and shows that polyhydridic



Scheme 1. Synthesis of the pentametallic ring cluster [Re₅(μ-H)₄(CO)₂₀][−].

complexes can behave as multidentate “ligands”. The Re₅ cluster anion—or, better, its neutral [Re₅(μ-H)₅(CO)₂₀] protonation derivative^[1]—were the highest members of a series of cyclic [ReH(CO)₄]_n oligomers (*n* = 3–5),^[4] which are isolobal analogues of the corresponding (CH₂)_n cycloalkanes owing to the isolobal relationship^[5] between (singlet) methylene and the ReH(CO)₄ moiety.

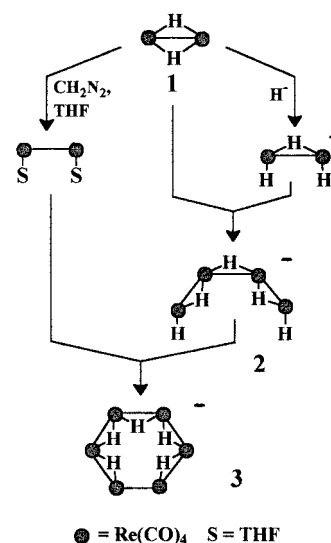
[*] Prof. G. D'Alfonso, Dr. M. Bergamo, Prof. T. Beringhelli
Dipartimento di Chimica Inorganica, Metallorganica e Analitica
Università degli Studi di Milano
Via G. Venezian 21, I-20133 Milano (Italy)
Fax: (+390) 2-2362748
E-mail: dalf@csmto.mi.cnr.it

Prof. M. Moret, Dr. P. Mercandelli, Prof. A. Sironi
Dipartimento di Chimica Strutturale e Stereochimica Inorganica
Università degli Studi di Milano
Via G. Venezian 21, I-20133 Milano (Italy)
Fax: (+390) 2-70635288
E-mail: max@csmto.mi.cnr.it

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If this approach would be used to obtain a six-membered ring cluster, a tetranuclear chain complex would be required containing two terminal hydrides, which should thus act as a bidentate bridging “ligand” toward the Re₂(CO)₈ fragment. The unsaturated complex [Re₂(μ-H)₂(CO)₈] (**1**) is known to easily add M–H[−] anions, giving L-shaped [M(μ-H)Re(CO)₄(μ-H)ReH(CO)₄][−] derivatives.^[1, 6, 7] We therefore treated **1** with one equivalent of the [NEt₄]⁺ salt of the dinuclear anion [Re₂H₂(μ-H)(CO)₈][−]^[4, 8] and obtained rapidly and with satisfactory selectivity the addition derivative [Re₄H₂(μ-H)₃(CO)₁₆][−] (**2**).

In Scheme 2 we have depicted one of the possible rotational conformers of **2**, whose fast dynamics accounts for the 2:2:1 pattern of the hydride resonances in the ¹H NMR spectrum. High conformational lability around the Re–H–Re linkages has been observed in all the other Re₄ chain clusters characterized so far.^[6, 7]



Scheme 2. Synthesis of the hexametallic ring cluster [Re₆(μ-H)₅(CO)₂₄][−].

The reaction of **2** with an equimolar amount of [Re₂(CO)₈(thf)₂] afforded a complex mixture containing several unidentified species. Monitoring by ¹H NMR spectroscopy showed that the resonance of the expected [Re₆(μ-H)₅(CO)₂₄][−] anion (**3**, Scheme 2) never exceeded 40% of the total integrated intensity of the hydride region. Crystallization of this mixture led to the isolation of orange crystals of the [NEt₄]⁺ salt of **3**.

An X-ray diffraction analysis^[9] confirmed the nature of anion **3**. Indeed, the metal centers in [Re₆(μ-H)₅(CO)₂₄][−] (96 valence electrons) exhibit a cyclohexane-like geometry (Figure 1), which is unprecedented among clusters containing only carbonyl ligands. Some metal complexes containing Ag, Ni, or Pd have metallic cores with hexagonal geometries, but the metals centers are held together by bridging sulfur ligands.^[12] The closest structural analogue of **3** is the irregular hexagon made of alternating Fe(CO)₄ and Cd(2,2'-bipyridyl) groups, which is present in [Fe(CO)₄{μ-Cd(bipy)}]₃.^[13] Therefore anion **3** represents to our knowledge the first example of a hexagonal frame of metal centers built of three-center, two-

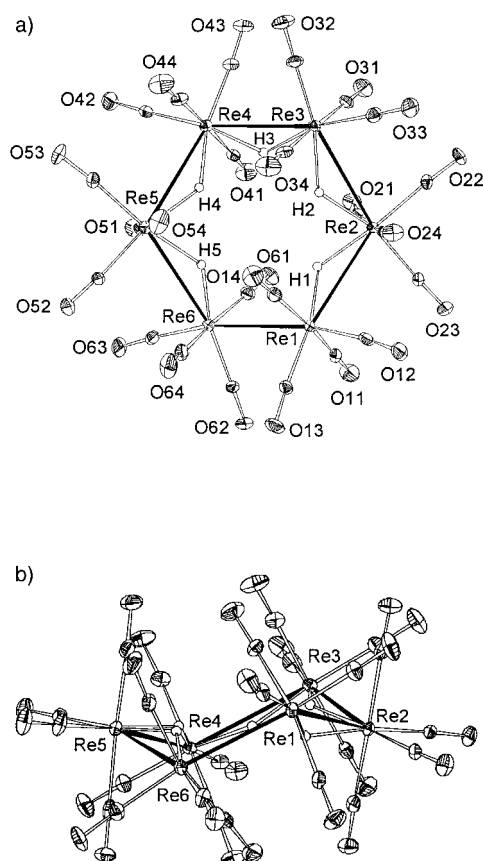


Figure 1. X-ray crystal structure of anion **3**. a) Top view and b) side view showing the cyclohexane-like geometry in a chair conformation (thermal ellipsoids with 30% probability; hydrogen atoms were given arbitrary radii). Selected bond lengths [Å]: Re1–Re2 3.3100(8), Re2–Re3 3.3148(8), Re3–Re4 3.3582(8), Re4–Re5 3.3342(8), Re5–Re6 3.2972(8), Re1–Re6 3.1109(7).

electron M–H–M bonds and two-center, two-electron M–M bonds.

Compound **3**, in fact, comprises six octahedral $\text{Re}(\text{CO})_4$ units, with local idealized C_{2v} symmetry, connected through one direct and five $\mu\text{-H}$ -bridged Re–Re interactions. In contrast to the pentanuclear analogue, which displayed an $e/s/s/e$ (s = staggered, e = eclipsed) relative conformation of the $\text{Re}(\text{CO})_4$ units,^[1] **3** exhibits an all-staggered ($s/s/s/s/s$) concatenation of these moieties. The only Re–Re bond length that is significantly different is that of the unbridged Re1–Re6 edge, which is considerably shorter (3.1109(7) Å) than the bridged ones (3.2972(8)–3.3582(8) Å), even if longer than normal unbridged Re–Re interactions.

Another striking feature of anion **3** is the conformation of the six-membered metal ring. Analyzing the ring conformation with Cremer and Pople's puckering coordinates,^[14] we found a slightly distorted chair conformation (Figure 1b; $q_2 = 0.052$ Å and $q_3 = 1.253$ Å, or, using the equivalent spherical coordinates,^[14] $Q = 1.254$ Å and $\theta = 2.4^\circ$, where $Q = (q_2^2 + q_3^2)^{1/2}$ represents the total puckering amplitude and θ is equal to 0° or 180° for a chair conformation). A comparative puckering analysis of **3**, cyclohexane,^[15] and S_6 ^[16] can be performed alternatively with Haasnoot's endocyclic torsion angles,^[17] which allows a direct comparison of molecules with different average bond lengths (3.288, 1.52, and 2.067 Å in **3**,

cyclohexane, and S_6 , respectively). Applied to the three compounds Haasnoot's formalism yields total puckering amplitudes of 56.70° , 55.07° , and 73.77° , respectively. Thus, in spite of the octahedral coordination at the Re centers, the total puckering amplitude of **3** is close to that of its hydrocarbon analogue (which is composed of tetrahedral carbon atoms), analogous to what was observed for the $[\text{Re}_5(\mu\text{-H})_4(\text{CO})_{20}]^-$ ring. It is worth noting that the Re–Re–Re endocyclic angles average to 110.8° compared to 111.4° for cyclohexane, while in S_6 , which has a significantly larger puckering amplitude, the S–S–S angles greatly deviate from the ideal tetrahedral angle (102.61°). The chair conformation adopted by **3** guarantees a good intramolecular packing of the carbonyl and hydride ligands, even if, compared to Re₃–Re₅ cycles, there are shorter intramolecular O...O contacts between axial carbonyl groups (average 3.09 Å for **3**, which is 0.2–0.4 Å shorter than those in the Re₃–Re₅ cycles).

The positions of the hydride ligands, which were located on the basis of a difference Fourier map, are in agreement with the Re–Re distances (five long H-bridged Re–Re interactions and one shorter and unbridged Re–Re interaction), the carbonyl ligands' local stereogeometry, and atom pair potential energy calculations.^[18] All these approaches strongly indicate that all the Re–H vectors are pointing inside the metal ring. Previously we reported a similar situation for the pentametallic clusters $[\text{Re}_5(\mu\text{-H})_{5-n}(\text{CO})_{20}]^{n-}$ ($n = 0, 1$)^[1] and for two of the $\text{Re}(\mu\text{-H})\text{Re}$ interactions of $[\text{Re}_4(\mu\text{-H})_4(\text{CO})_{16}]$.^[4] This feature, which seemed extravagant the first time it appeared,^[4] has now been observed in four different cyclic rhenium clusters with different nuclearities and conformations; it probably arises from the steric demands that force the less bulky ligands, in other words, the hydrides, to lie inside the “empty” metal ring.

Protonation of **3** to obtain the still-elusive neutral $[\{\text{Re}(\text{H}(\text{CO})_4\}_6]$ derivative resulted in the formation of a white precipitate, whose very low solubility has so far prevented analysis by single-crystal X-ray diffraction.

In principle, the interaction of two difunctional reactants such as **1** and **2** could result not only in cyclization, but also in polycondensation, thus providing a novel route to chain clusters. This would be an alternative to the recently reported anionic oligomerization of **1**.^[7] The probability of this second reaction path should increase with the length of the chain of the hydridic anionic reactant, making ring closure progressively more difficult. This could be the reason for the lower selectivity of the cycloaddition leading to **3**, with respect to the reaction affording the Re₅ ring.^[19]

Experimental Section

A sample of $[\text{Re}_2(\mu\text{-H})_2(\text{CO})_8]$ (60 mg, 0.10 mmol) was added to a solution of $[\text{NET}_4][\text{Re}_2\text{H}_2(\mu\text{-H})(\text{CO})_8]$ (73 mg, 0.10 mmol) in THF at 273 K. The temperature was increased to room temperature, then the solution was concentrated to dryness. NMR analysis showed that the residue consisted of almost pure (ca. 90%) $[\text{NET}_4]\text{2}$. Extraction with diethyl ether and concentration afforded a yellow precipitate, which was crystallized from $\text{CH}_2\text{Cl}_2/n\text{-hexane}$ at 253 K. IR (THF): $\tilde{\nu} = 2092\text{w}$, 2070w , 2016s , 2001sh , 1970ms , 1932m cm^{-1} (C=O); ^1H NMR (300 MHz, $[\text{D}_8]\text{THF}$, 183 K): $\delta = 3.29$ (q, 8H, CH_2), 1.71 (t, 12H, CH_3), -5.79 (s, 2H), -15.89 (s, 2H), -17.56 (s, 1H).

A solution of [NEt₄]**2** (40 mg, 0.030 mmol) in THF was treated at 273 K with one equivalent of [Re₂(CO)₈(thf)₂]. The temperature was increased to room temperature, then the solution was concentrated to dryness and the residue dissolved in CH₂Cl₂. IR and NMR spectra showed the formation of a complex mixture containing, besides anion **3**, several unidentified species. Crystals of [NEt₄]**3** were obtained by slow diffusion of *n*-hexane into a solution in CH₂Cl₂. Spectroscopic data of the anion **3** (from isolated crystals): IR (CH₂Cl₂): $\tilde{\nu}$ = 2119vw, 2100mw, 2089w, 2053w, 2031s, 2002ms, 1952ms, 1889mw cm⁻¹ (C=O); ¹H NMR (300 MHz, CD₂Cl₂, 193 K): δ = -15.42. The reaction has been repeated several times directly in CD₂Cl₂ in an NMR tube at 193 K. In all cases the resonance of **3** was the most intense, but many other unattributed resonances were also present.

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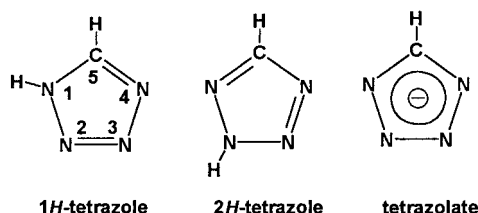
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Interpenetrated and Noninterpenetrated Three-Dimensional Networks in the Polymeric Species Ag(tta) and 2 Ag(tta) · AgNO₃ (tta = tetrazolate): The First Examples of the μ_4 - η^1 : η^1 : η^1 : η^1 Bonding Mode for Tetrazolate

Lucia Carlucci, Gianfranco Ciani,* and Davide M. Proserpio

The current interest in the self-assembly of polymeric coordination networks^[1] has afforded many noteworthy two- and three-dimensional frameworks, which are of potential interest as novel materials.^[2] Particular attention is now devoted to the use of new polyfunctional suitably tailored complex ligands that enable a certain control of the structural motifs and/or introduce peculiar features in the solid-state products. However, many interesting polymeric frameworks were also obtained in the past by using simple polydentate aromatic nitrogen heterocycles with five-membered (azoles) or six-membered (azines) rings.^[3,4] While the members of these families with two nitrogen atoms have been extensively used in the area of coordination polymers, and some examples of polymeric nets of triazoles^[5] and triazines^[6] are known, the networking ability and the full potential donor properties of species containing a higher number of nitrogen atoms, like tetrazoles and tetrazines, are almost completely unknown. Tetrazole (Htta) exists in two tautomeric forms (1*H* and 2*H*, see Scheme 1); it is an acidic species with a *pK_a* value of about 5, and the anion tetrazolate (tta) is a potentially tetradentate ligand, though in most of the reported adducts it functions as only a mono- or bidentate ligand.^[3] Substituted tetrazole derivatives have also been studied for their potential properties as explosives or detonators.

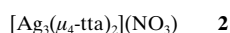
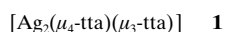
- [*] Prof. G. Ciani, Dr. D. M. Proserpio
Dipartimento di Chimica Strutturale
e Stereochimica Inorganica and Centro CNR
Via G. Venezian 21, I-20133 Milano (Italy)
Fax: (+390) 2-70-63-52-88
E-mail: davide@csmto.mi.cnr.it
- Dr. L. Carlucci
Dipartimento di Biologia Strutturale e Funzionale
Università dell'Insubria
Via J. H. Dunant 3, I-21100 Varese (Italy)



Scheme 1.

The silver salt of tetrazole has been known since 1892^[7] and many silver salts of substituted tetrazolates were prepared in the 1950s mainly for analytical purposes,^[8] but, nevertheless, the structural properties of these species, suspected to be polymeric, have until now remained unexplored.

We have reinvestigated the reactions of tetrazole (Htta) with different silver salts, and have obtained single crystals of the simple salt [Ag(tta)] suitable for an X-ray structure analysis. The structure comprises a polymeric twofold interpenetrated three-dimensional network, which is formulated as **1**. In addition, in reactions of tetrazole with AgNO₃ we have obtained the novel double salt 2Ag(tta)·AgNO₃, which consists of a three-dimensional framework with large channels and is formulated as **2**. While few cases of the $\mu_3\text{-}\eta^1\text{:}\eta^1\text{:}\eta^1$ coordination mode have been observed in tetrazolate derivatives, namely in two trinuclear organometallic rhodium(I) complexes^[9] and in the polymeric two-dimensional complex [Li($\mu_3\text{-tta}$)]·DMSO,^[10] these are the first examples of the $\mu_4\text{-}\eta^1\text{:}\eta^1\text{:}\eta^1\text{:}\eta^1$ bonding mode for this heterocycle.



The reactions of AgNO₃, AgBF₄, or Ag(CF₃SO₃) with Htta in water/ethanol at room temperature in the molar ratio 1:1 afford good yields of white polycrystalline precipitates that analyze for [Ag(tta)]. Single crystals were grown within a few days by slow evaporation of an ethanolic equimolar solution of AgBF₄ and Htta. The X-ray structure revealed that the crystals correspond to **1**.^[11] X-ray powder diffraction patterns of all the polycrystalline samples have shown the presence of pure compound **1** by comparison with the pattern calculated from the single-crystal structure. The reaction of AgNO₃ with Htta was also investigated in the presence of an excess of the salt. The polycrystalline samples obtained by using a molar ratio of 1:1.5 display a powder diffraction pattern that is completely different from that of **1**. The elemental analysis is consistent with the double salt 2Ag(tta)·AgNO₃. Single crystals were obtained in a few days by layering a solution of Htta in ethanol over a solution of AgNO₃ in water (molar ratio 1:1.5). The structure analysis revealed that they correspond to the polymeric species **2**.^[11] Also in this case, the X-ray powder diffraction pattern computed from the single-crystal data of **2** was used to assess the purity of the crude polycrystalline samples of this material.

The structure of compound **1** consists of a three-dimensional neutral network based on triconnected and tetraconnected silver centers in the ratio 1:1, which are joined through tetrazolate anions one half of which act as *exo*-tridentate

(N¹,N²,N⁴) and one half as *exo*-tetradentate ligands. The triconnected Ag^I ions display a distorted trigonal-planar coordination (Ag–N 2.197(4)–2.328(4) Å, N–Ag–N 110.2(2)–138.4(2)°), while the tetraconnected ones are distorted tetrahedral (Ag–N 2.261(4)–2.410(4) Å, N–Ag–N 94.9(2)–136.6(2)°). The framework can be rationalized by considering that it comprises one-dimensional ribbons (see Figure 1, top) all running in the [–101] direction, in which the inner tta ligands are tetradentate, while the outer ones are tridentate with two nitrogen atoms (N¹,N²) bridging metal centers inside the ribbon, and the third one (N⁴) pointing toward silver atoms of adjacent ribbons. The planes of the ribbons show two mutually perpendicular dispositions (Figure 1, bottom) and each ribbon is connected to four adjacent

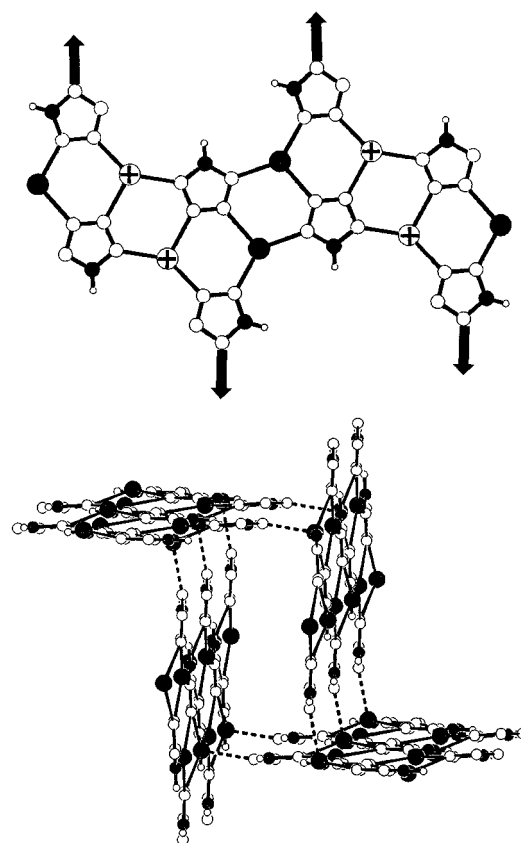


Figure 1. A view of a single ribbon (top) and of the interaction of four such ribbons (bottom) in the polymeric net of compound **1**. Big circles (filled and crossed): silver; medium filled circles: carbon; medium empty circles: nitrogen; small empty circles: hydrogen atoms. In the top view arrows depart from N-donor atoms toward adjacent ribbons, while the acceptor silver atoms (tetraconnected) are crossed. In the bottom view the dotted lines represent the N-donor→Ag-acceptor interactions and hydrogen atoms are omitted for clarity.

perpendicular ones, through N-donor (two ribbons) and Ag-acceptor (two ribbons) interactions (dotted lines in Figure 1, bottom). The resulting three-dimensional network has a novel complex (3,4)-connected topology^[12] and contains large channels (ca. 6.0 × 11.1 Å) of rectangular section. Two such identical frameworks interpenetrate in order to fill the voids within the channels (Figure 2).

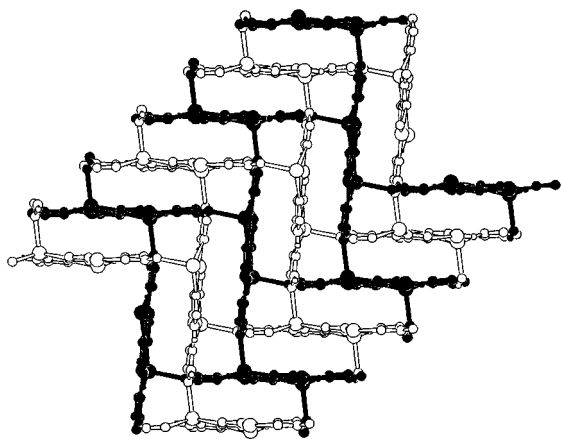


Figure 2. A view of the two interpenetrating nets of compound **1** down $[-101]$ showing the rectangular channels.

Compound **2**^[11] consists of a noninterpenetrated three-dimensional cationic framework containing triconnected and biconnected silver centers (ratio 2:1) joined by *exo*-tetradentate tta anions. The triconnected Ag^I ions show a coordination geometry intermediate between T-shaped and trigonal (Ag–N 2.239(3)–2.382(4) Å, N–Ag–N 103.9(1), 109.9(1), 145.8(1)°). These metal centers are joined by (N¹,N²,N³)-bridging tta ligands to give undulated two-dimensional layers normal to the $[100]$ direction (Figure 3 top), which comprise four-membered and eight-membered rings and are topologically equivalent to the sheets found in the two-dimensional

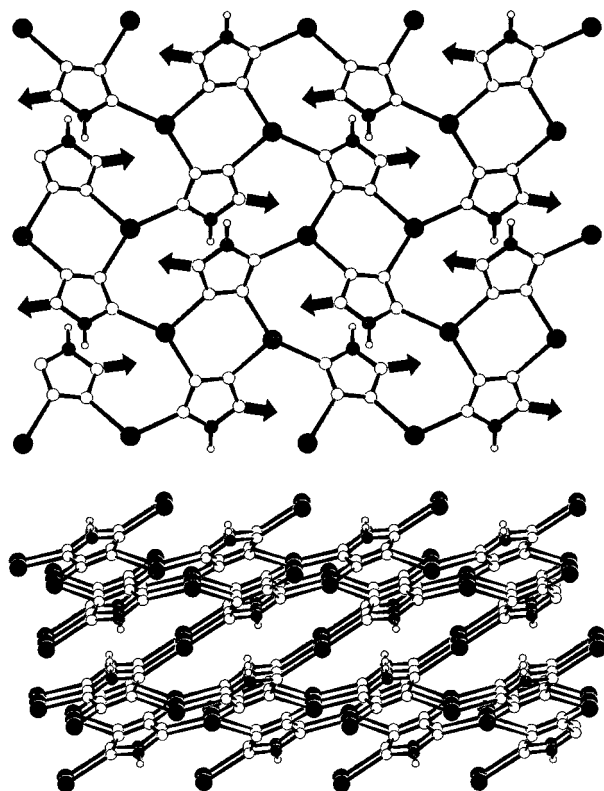


Figure 3. A single undulated layer of $(4 \cdot 8^2)$ topology, a component of the three-dimensional net in **2**, down the a axis (top). Left and right arrows indicate the directions of the N–Ag–N bridges connecting this layer with the adjacent lower and upper ones, respectively. The bottom view presents a pair of such layers linked through the biconnected Ag atoms.

polymers $[\text{Zn}(\mu_3\text{-}1,2,4\text{-triazolate})\text{Cl}]^{[5c]}$ and $[\text{Li}(\mu_3\text{-tta})] \cdot \text{DMSO}$ (in which, however, the tta ligand is (N¹,N²,N⁴)-bridging).^[10] Each layer of **2** is linked to the adjacent upper and lower layers through the fourth (N⁴) nitrogen atoms of tta, which give N–Ag–N bridges with the biconnected silver metals (Ag–N 2.161(3) Å, N–Ag–N 168.1(2)°) acting only as spacers (metal synthons, see Figure 3, bottom). The small deviation from digonal coordination of these metals arises from weak interactions with two oxygen atoms of a nitrate anion (Ag...O 2.685(4) Å). The resulting framework is illustrated in Figure 4, which also shows the anionic channels down $[001]$ containing the nitrate counterions.^[12]

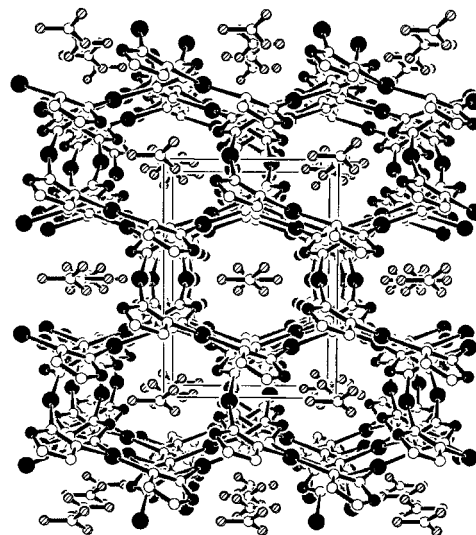


Figure 4. The three-dimensional network of **2**, down the c axis, showing the anionic channels containing the nitrates.

In both compounds the silver atoms bound to the tri- and tetradentate tta ligands show significant out-of-plane displacements with respect to the “best plane” of the heterocycle (in the ranges $-0.12/+0.70$ Å (μ^3 -tta) and $-0.36/+0.39$ Å (μ^4 -tta) for **1** and $-0.64/+0.50$ Å (μ^4 -tta) for **2**.

Tetrazolate salts and complexes of the heavy metals are known to be heat- and shock-sensitive, and several (especially 5-substituted) such complexes have found commercial use as explosives or detonators.^[3, 13–15] Tetrazole itself explodes when heated above its melting point (155–156 °C),^[13] and many silver tetrazolates decompose with a flash when heated on a spatula.^[8] Therefore, thermal analyses of these species must be carried out with caution, on small samples (<0.001 g), and only the use of a slow heating rate^[14] can avoid explosion (occurring otherwise for both **1** and **2** at $T \approx 220$ °C). Differential scanning calorimetric (DSC) and thermogravimetric (TG) analyses of compound **1** have shown that it decomposes with an exothermic peak (at 224 °C) to give a yellow solid phase, recognized as silver(I) cyanamide Ag_2CN_2 by X-ray powder diffraction and IR spectroscopy, which, on increasing T up to 600 °C, completely converts to silver metal. Compound **2** is somewhat more stable and decomposes in a complex fashion with two exothermic peaks (at 248 and 304 °C) to give a solid mixture of Ag_2CN_2 and other minor unidentified

species, which are completely converted into silver metal at 600 °C.

The results reported show that tetrazolates can employ all the available donor atoms of the aromatic ring and that they are capable of producing robust interesting polymeric networks. This confirms the potentially rich coordination chemistry of these ligands, as revealed by the recent report of another unusual ($\mu\text{-}\eta^1\text{:}\eta^2$) bonding mode of tta in some organolanthanide complexes.^[16] Another point of interest is that the existence of the double salt **2** can explain the difficulties encountered by earlier researchers in the analyses of the silver tetrazolates obtained by using an excess of silver nitrate, which were then ascribed to the fact that the precipitates appeared to “occlude or adsorb excess reagent”.^[8a]

Experimental Section

1: A solution of tetrazole (0.045 g, 0.645 mmol) in EtOH (5 mL) was added to a stirred solution of AgNO₃ (0.109 g, 0.639 mmol) in water (5 mL) at room temperature. A white precipitate was immediately formed. The reaction mixture was stirred for 2 h and the resulting precipitate was filtered, washed with ethanol, and dried in the air (yield > 90 %). Elemental analysis (%) calcd for CHAgN₄: C 6.79, H 0.570, N 31.68; found C 6.68, H 0.49, N 31.02. Product **1** was also obtained by using AgBF₄ and Ag(CF₃SO₃) under the same conditions. The polycrystalline samples obtained from the different silver salts are identical and correspond to pure **1**, as confirmed by X-ray powder diffraction data compared to the spectrum of **1** calculated from single-crystal X-ray analysis. Single crystals of **1** suitable for structural analysis were obtained by slow evaporation of an ethanolic solution of AgBF₄ and tetrazole in a molar ratio of 1:1.

2: A white powder of **2** was obtained from a solution of tetrazole (0.041 g, 0.585 mmol) in EtOH (5 mL) and a solution of AgNO₃ (0.150 g, 0.877 mmol) in water (5 mL) under the same conditions used for **1** (yield ca. 70 %). The correct tetrazole/AgNO₃ molar ratio of 1:1.5 is fundamental in order to avoid the formation of mixtures. Elemental analysis (%) calcd for C₂H₂Ag₃N₆O₃: C 4.57, H 0.385, N 24.08; found C 4.32, H 0.40, N 23.92. The purity of the samples of **2** was tested by X-ray powder diffraction.

Both compounds are air- and light-stable for long periods and insoluble in the common solvents. IR (Nujol mull): for **1**: $\tilde{\nu}$ = 3162 m, 3086 m, 1443 m, 1141 s, 1131 m, 1077 m, 1029 m, 1003 m, 930 m, 722 m, 685 m cm⁻¹; for **2**: $\tilde{\nu}$ = 3130 m, 1442 s, 1410 vs, 1354 vs, 1314 s, 1209 m, 1141 s, 1107 m, 1016 m, 911 m, 722 w, 687 m cm⁻¹. The IR pattern for **1** is consistent with that in the literature.^[17]

Thermal analyses were performed on Perkin-Elmer DSC7 and TGA7 instruments at a heating rate of 2 K min⁻¹, under a flux of nitrogen. Compound **1** decomposed exothermally at 224 °C, with a weight loss of about 25 %. The remaining yellow polycrystalline sample was characterized as silver cyanamide by its IR spectrum (IR(Nujol mull): $\tilde{\nu}$ = 2018 sh, 1969 vs, 1935 sh, 1277 m, 1190 m, 631 w cm⁻¹) by comparison with the spectrum in the literature.^[18] Moreover, the X-ray powder diffraction pattern showed broad peaks consistent with the cell parameters reported for this poorly characterized species, for which a structure model is not yet available.^[19] Silver cyanamide is known to decompose into gases (N₂ and cyanogen) and silver metal.^[20] Slow weight loss was observed in the range 250–600 °C, and the final residue was established to be silver metal by X-ray powder diffraction. Similar behavior was observed for compound **2**. After the first exothermic peak (at 248 °C, coupled with a weight loss of about 20 %) a solid mixture was obtained, whose X-ray powder diffraction pattern showed, together with the peaks attributed to Ag₂CN₂, some additional peaks which remain to be clarified. Successive slow weight loss on heating up to 600 °C again gave pure silver metal.

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Novel Ternary Alkali Metal Silver Acetylides $M^I\text{AgC}_2$ ($M^I = \text{Li, Na, K, Rb, Cs}$)**

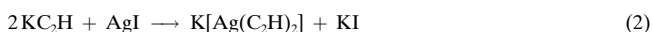
Winfried Kockelmann and Uwe Ruschewitz*

Recently we showed that Na_2PdC_2 and Na_2PtC_2 can be synthesized by the reaction of Na_2C_2 with palladium or platinum at temperatures of about 350°C under an inert atmosphere.^[1] These compounds are the first examples of ternary alkali metal transition metal acetylides. Their crystal structures are characterized by ${}^\infty[\text{M}(\text{C}_2)_{2/2}^-]$ chains ($M = \text{Pd, Pt}$) that are separated by sodium ions. In the meantime we were able to extend this synthesis to the analogous potassium, rubidium, and cesium acetylides,^[2] but attempts to synthesize ternary acetylides of transition metals other than palladium or platinum by this method were not successful up to now. In 1963 a synthesis was described by which the ternary silver acetylide KAgC_2 could be obtained.^[3] The crystal structure of this compound was not determined, but elemental analyses and IR investigations corroborated its existence. As highly explosive Ag_2C_2 was used in this synthesis [Eq. (1)], we have tried to find a different approach, which avoids this starting material.



For that purpose we treated KC_2H with AgI in liquid ammonia, which resulted in a nonexplosive complex hydrogenacetylide as intermediate [Eq. (2)], which could be trans-

formed into the ternary silver acetylide by heating under high vacuum to temperatures of about $120\text{--}130^\circ\text{C}$ [Eq. (3)].



The by-product KI [Eq. (2)] was removed by washing with liquid ammonia so that the insoluble KAgC_2 could be obtained in a pure form. It was possible to extend this synthesis to ternary silver acetylides of the other alkali metals. In a variation, the synthesis of LiAgC_2 according to Equation (3) was performed in boiling pyridine. LiI is soluble in pyridine so that the insoluble LiAgC_2 could be separated by filtration. All products are colorless, nonexplosive, and sensitive to air and moisture.

X-ray diffractometer investigations^[4] on the colorless powders of the silver acetylides resulted in the unit cells and space groups given in Table 1.^[5] It is striking that in all unit cells a lattice parameter of about $5.30\text{ \AA}$ is found. As this

Table 1. Lattice parameters of ternary silver acetylides $M^I\text{AgC}_2$ ($M^I = \text{Li, Na, K, Rb, Cs}$) at room temperature.^[4]

	<i>a</i> [pm]	<i>c</i> [pm]	Space group
LiAgC_2	379.6(1)	533.0(1)	$P\bar{6}m2$
NaAgC_2	374.7(1)	532.0(1)	$P4/mmm$
KAgC_2	424.5(1)	530.7(1)	$P4/mmm$
RbAgC_2	447.5(1)	531.0(1)	$P4/mmm$
CsAgC_2	527.7(1)	857.9(1)	$P4_2/mmc$

distance corresponds approximately to the sum of two Ag-C single bonds (2.087 and $2.108\text{ \AA}$ in $\text{Ag}_2\text{C}_2 \cdot 2\text{AgClO}_4 \cdot 2\text{H}_2\text{O}$)^[6] and one C-C triple bond ($1.206\text{ \AA}$),^[7] it was assumed that ${}^\infty[\text{Ag}(\text{C}_2)_{2/2}^-]$ chains run along this unit cell axis. However, the unit cells given in Table 1 suggest that at least three different packing variants of the silver-carbon chains must exist. With these assumptions, possible structural models were created, and the refinements of the X-ray powder diffractograms showed that NaAgC_2 , KAgC_2 , and RbAgC_2 are isotypic, but LiAgC_2 and CsAgC_2 crystallize in different structure types. To obtain precise bond lengths neutron powder diffraction experiments on a representative of each structure type (LiAgC_2 , KAgC_2 , and CsAgC_2) were performed.^[8] The resulting crystal structures are shown in Figures 1–3.^[9]

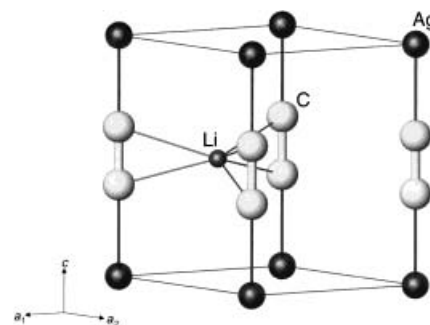


Figure 1. Crystal structure of LiAgC_2 . The unit cell, the C-C and Ag-C bonds as well as the shortest Li-C distances are emphasized. Selected interatomic distances [$\text{\AA}$]: Li-C $2.2786(9)$ ($6\times$), Ag-C $2.025(3)$ ($2\times$), C-C $1.278(6)$.

[*] Dr. U. Ruschewitz
 Institut für Anorganische Chemie der Technischen Hochschule
 Professor-Pirlet-Strasse 1, D-52056 Aachen (Germany)
 Fax: (+49) 241-8888288
 E-mail: uwe.ruschewitz@ac.rwth-aachen.de

Dr. W. Kockelmann^[+]
 Mineralogisch-petrologisches Institut der Universität
 D-53115 Bonn (Germany)

[+] Current address:
 ISIS, Rutherford Appleton Laboratory
 Chilton, OX11 0QX (UK)

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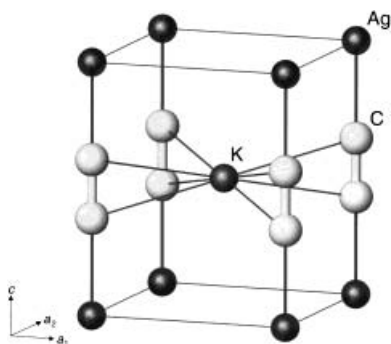


Figure 2. Crystal structure of KAgC_2 . The unit cell, the C–C and Ag–C bonds as well as the shortest K–C distances are emphasized. Selected interatomic distances [Å]: K–C 3.0506(8) ($8 \times$), Ag–C 2.032(3) ($2 \times$), C–C 1.223(6).

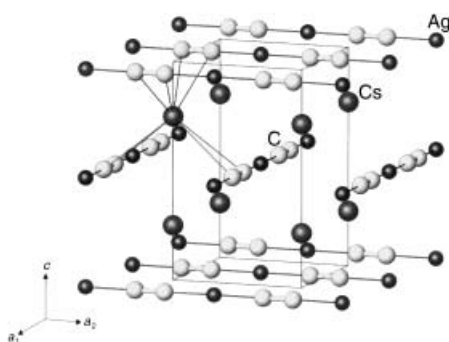


Figure 3. Crystal structure of CsAgC_2 . The unit cell, the C–C and Ag–C bonds as well as the shortest Cs–C distances around one of the cesium ions are emphasized. Selected interatomic distances [Å]: Cs–C 3.4347(7) ($8 \times$), Ag–C 2.015(4) ($2 \times$), C–C 1.217(7).

As assumed, the title compounds have $\infty[\text{Ag}(\text{C}_2)_{1/2}]$ chains as their common structural element. The C–C bond lengths in KAgC_2 and CsAgC_2 are 1.223(6) and 1.217(7) Å, respectively. This is close to the expected value for a C–C triple bond (acetylene 1.205 Å^[10]; CaC_2 1.191 Å^[11]). For LiAgC_2 a surprisingly long C–C distance of 1.278(6) Å was obtained. This distance is probably an artifact of the structural refinement, as the investigated sample contained about 13 wt % Li_2C_2 ^[12] and LiAgC_2 showed strong anisotropic reflection broadening, so that a strong overlap of reflections resulted. A C–C bond length in LiAgC_2 similar to those found in KAgC_2 and CsAgC_2 is strongly supported by the results of Raman spectroscopic investigations (see below). The determination of the lithium positions was also not clear-cut. In Figure 1 the crystal structure which gave the best R values ($P6m2$, $Z = 1$) is shown, but other structural models gave only slightly worse agreement factors.^[13]

In LiAgC_2 (Figure 1) and KAgC_2 (Figure 2) the $\infty[\text{Ag}(\text{C}_2)_{1/2}]$ chains run parallel to each other along the crystallographic c axis. In CsAgC_2 (Figure 3), however, the $\infty[\text{Ag}(\text{C}_2)_{1/2}]$ chains are aligned in layers perpendicular to the c axis, and the layers are rotated by 90° to each other. Thus the hexagonal and the two tetragonal packings of the silver–carbon chains correspond to the three simplest rod packings as described by O’Keeffe and Andersson.^[15] The alkali metal ions lie between these chains.^[16] The lithium ions in LiAgC_2 are coordinated *side-on* by three C_2 dumbbells, which sit in

distorted Li_3Ag_2 trigonal bipyramids. The Li–C distances of 2.2786(9) Å are in good agreement with the corresponding distances in Li_2C_2 (2.2122(6) and 2.4017(6) Å).^[17] The larger alkali metal ions Na^+ , K^+ , Rb^+ , and Cs^+ are coordinated *side-on* by four C_2 dumbbells, which are surrounded by distorted M_4Ag_2 octahedra. Again the agreement of the alkali metal–carbon distances in the title compounds with those in binary acetylides is very good: 3.0506(8) (KAgC_2), 3.009(3)–3.146(3) (K_2C_2),^[18] 3.4347(7) (CsAgC_2), 3.31(1)–3.83(2) Å (CsC_2H).^[19]

Neutron diffraction investigations on Na_2PdC_2 resulted in a C–C distance of 1.264(3) Å.^[2] This value is—even considering the standard deviations—distinctly larger than those found in KAgC_2 and CsAgC_2 . Therefore we have performed Raman spectroscopic investigations with a particular interest in the frequencies of the C–C stretching vibrations. The results are summarized in Table 2. It is obvious that a correlation between the C–C distance and the frequency of the C–C

Table 2. Frequencies of the C–C stretching vibrations of ternary palladium and silver acetylides.

	$\tilde{\nu}_{\text{C}\equiv\text{C}}$ [cm^{-1}]		$\tilde{\nu}_{\text{C}\equiv\text{C}}$ [cm^{-1}]
LiAgC_2 ^[14]	1962		
NaAgC_2	1965	Na_2PdC_2	1862
KAgC_2	1963	K_2PdC_2	1850
RbAgC_2	1961		
CsAgC_2	1965		

stretching vibration exists. The ternary palladium acetylides with longer C–C bond lengths have distinctly smaller frequencies, indicating weaker C–C bonding, than the silver acetylides. Moreover the Pd–C distance (2.001(1) Å) is shortened compared to the sum of the covalent radii (2.055 Å),^[20] whereas a very good agreement is found for both values in the ternary silver acetylides (KAgC_2 : Ag–C 2.032(3) Å; sum of covalent radii 2.032 Å).^[20] We think that stronger backbonding from palladium to carbon is responsible for the increase in the C–C bond length. The fact that almost the same frequencies of the C–C stretching vibration have been found for all title compounds (Table 2) supports the assumption of similar C–C distances in these compounds. Therefore the longer C–C distance in LiAgC_2 must be an artifact of the structural refinement (see above). It is unlikely that the different cation environments can account for an increase in the C–C distance by more than 5 pm.

Band-structure calculations^[21] showed that Na_2PdC_2 is a semiconductor with a very small, indirect band gap of about 0.1 eV, whereas KAgC_2 and CsAgC_2 have distinctly larger band gaps (CsAgC_2 : 2 eV). Considering that density functional calculations typically provide band gaps which are too small,^[22] these results correspond nicely to the colors of the compounds: Na_2PdC_2 is black, while the ternary silver acetylides are colorless. Measurements of the electrical conductivity (PPMS, Quantum Design, powder pellet with four silver contacts) confirmed these findings: Na_2PdC_2 showed semiconducting and CsAgC_2 insulating behavior. An analysis of the crystal orbital Hamilton population (COHP)^[23] from the band structures above confirmed the

assumption that the Pd–C backbonding in Na_2PdC_2 is stronger than the Ag–C backbonding in the ternary silver acetylides, as the integrated COHPs of the π -M–C bonding—mainly consisting of overlaps of the metal d- π orbitals with carbon p- π orbitals—are larger in Na_2PdC_2 than in KAgC_2 and CsAgC_2 .

At the moment we are investigating the analogous copper and gold compounds which can also be prepared by the synthetic route given above. They crystallize in structures analogous to those of the ternary silver acetylides.

Experimental Section

All preparations were carried out under an inert argon atmosphere using Schlenk techniques.

LiAgC₂: Lithium (69 mg, 10 mmol) was dissolved in liquid ammonia (approx. 30 mL, cooled with a CO₂/acetone bath). Acetylene was passed over the blue stirred solution until it decolorized. A surplus of acetylene must be avoided to prevent the formation of Ag₂C₂ in the next step. After addition of AgI (587 mg, 2.5 mmol)—a surplus of lithium prevents the formation of Ag₂C₂—the mixture was stirred for another hour and the solution was allowed to warm up. The white residue was dried under high vacuum at room temperature and then refluxed in pyridine overnight. After filtration the product could be obtained as a colorless residue. The sample for the neutron diffraction investigation was synthesized using enriched ⁷Li.

NaAgC₂/KAgC₂: The synthesis was analogous to the synthesis of LiAgC₂, but the residue obtained after the evaporation of ammonia was dried and then, as a solid, heated to 120–130 °C under high vacuum. Pure samples could be obtained by repeated washings with liquid ammonia.

RbAgC₂/CsAgC₂: Ammonia was condensed into a Schlenk flask loaded with the alkali metal. The further steps of the synthesis were analogous to the preparation of NaAgC₂ and KAgC₂.

Raman spectroscopic investigations: BIO-RAD-FT-Raman spectrometer, Nd-YAG-laser ($\lambda = 1064$ nm, 50 mW laser power); the samples were sealed and measured in NMR tubes ("Economy", Wilmad) under an argon atmosphere.

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scattering bank, 4 positional and thermal parameters refined, $wR_p = 0.0146/0.0211$, $R_p = 0.0111/0.0197$, $R_F = 0.0072/0.0158$; the investigated sample contained 12.8(2) wt % Li₂C₂ as an impurity. Structure refinement of KAgC₂: crystal system: tetragonal, space group $P4/mmm$ (no. 123), $a = 4.2267(8)$, $c = 5.287(2)$ Å, $\rho_{\text{calcd}} = 3.006$ g cm⁻³, $Z = 1$, Ag on 1(a), C on 2(g) with $z = 0.3843(6)$, K on 1(d), 37 reflections on the forward and 60 reflections on the back scattering bank, 4 positional and thermal parameters refined, $wR_p = 0.0183/0.0273$, $R_p = 0.0151/0.0337$, $R_F = 0.0286/0.0433$. Structure refinement of CsAgC₂: crystal system: tetragonal, space group $P4_2/mmc$ (no. 131), $a = 5.2467(6)$, $c = 8.528(1)$ Å, $\rho_{\text{calcd}} = 3.746$ g cm⁻³, $Z = 2$, Ag on 2(b), C on 4(k) with $x = 0.1159(7)$, Cs on 2(e), 110 reflections on the forward and 120 reflections on the back scattering bank, 4 positional and thermal parameters refined, $wR_p = 0.0323/0.0335$, $R_p = 0.0266/0.0368$, $R_F = 0.0461/0.0624$; the investigated sample contained 37.1(5) wt % of a second modification of CsAgC₂, which crystallizes isotypic to KAgC₂ in space group $P4/mmm$ ($a = 4.7149(8)$, $c = 5.259(3)$ Å). All refinements were carried out with the GSAS suite of programs.^[25] Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de) on quoting the depository numbers CSD-410868 (LiAgC₂), -410874 (KAgC₂), and -410873 (CsAgC₂).

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- [13] a) Space group $P6/mmm$ (no. 191), $Z = 1$ with Ag on 1(a), C on 2(e), and Li on 2(d) with an occupancy of 0.5: $wR_p = 0.0148/0.0214$ and $R_F = 0.0084/0.0170$; b) space group $P6_3/mmc$ (no. 194), $Z = 2$ (the c axis is doubled compared to the two other structural models) with Ag on 2(a), C on 4(e), and Li on 2(c): $wR_p = 0.0155/0.0214$ and $R_F = 0.0078/0.0169$.
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- [9] Structure refinement of LiAgC₂: crystal system: hexagonal, space group $P6m2$ (no. 187), $a = 3.7882(5)$, $c = 5.328(3)$ Å, $\rho_{\text{calcd}} = 3.482$ g cm⁻³, $Z = 1$, Ag on 1(a), C on 2(g) with $z = 0.3800(5)$, Li on 1(d), 22 reflections on the forward and 36 reflections on the back

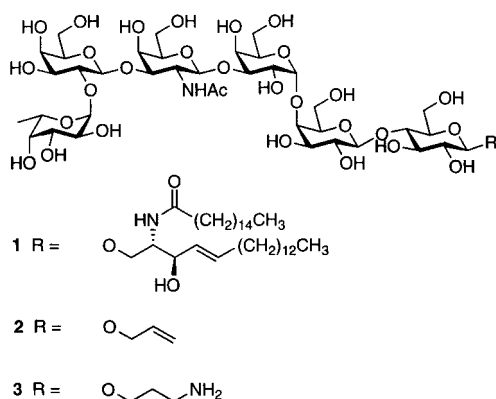
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A Two-Directional and Highly Convergent Approach for the Synthesis of the Tumor-Associated Antigen Globo-H**

Tong Zhu and Geert-Jan Boons*

Human cancer cells are often characterized by the presence of tumor-associated glycosphingolipids (GSL).^[1] Several GSL antigens have been identified as adhesion molecules that may promote tumor cell metastases. Active immunization with GSL can induce or enhance antibody titers and several studies indicate that these antibodies can suppress metastasis.^[2]

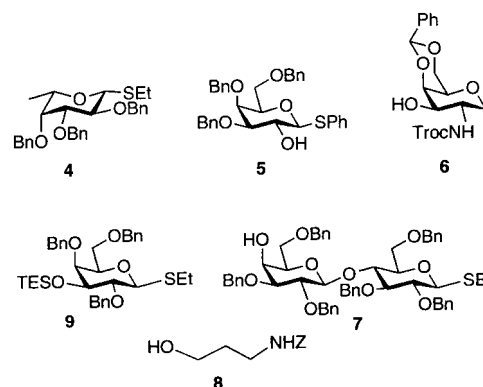
Danishefsky and co-workers synthesized the saccharide moiety of the tumor-associated antigen Globo-H^[3] (**1**) using the glycal assembly strategy. The final product was substituted with an anomeric allyl moiety ($\rightarrow$ **2**), which after oxidation to an aldehyde moiety, allowed coupling to the carrier protein



keyhole limpet hemocyanin (KLH, *Megathura crenulata*). High levels of antibodies in patients with progressive and recurrent prostate cancer could be raised by vaccination with the conjugate.^[4] Schmidt and co-workers prepared the protected Globo-H hexasaccharide by employing the trichloroacetimidate methodology.^[5]

Herein we report an alternative approach for a highly efficient synthesis of the Globo-H hexasaccharide **3**. For the

first time we demonstrate that a hexasaccharide can be assembled in five consecutive glycosylations without the need for any intermediate protecting group manipulations. The new approach gives the readily available building blocks **4**, **5**, **6**, **7**, **8**, and **9** (Scheme 1) of the protected hexasaccharide **19**, which was deprotected to yield target compound **3** (Scheme 3). The key feature of the new glycosylation



Scheme 1. Building blocks for **3**.

sequence is a combination of two-directional glycosylation approaches (see below) with chemoselective and orthogonal glycosylations.^[6] These strategies exploit both the differences in the reactivities of anomeric leaving groups and the subtle control of nucleophilicities of sugar hydroxyl groups and silyl ethers. The aminopropyl spacer was incorporated for well-defined conjugation to a carrier protein.^[7]

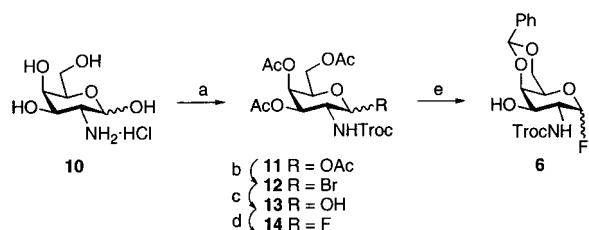
Classic strategies for oligosaccharide assembly are characterized by the manipulation of protecting groups between each glycosylation step. Such manipulations increase the linearity and decrease the efficiency of oligosaccharide assembly. Two-directional glycosylation strategies and chemoselective- or orthogonal-glycosylation approaches condense the process of oligosaccharide synthesis by removing the need for unmasking procedures. In a two-directional glycosylation strategy a saccharide derivative first acts as a glycosyl donor and the resulting product is immediately used as a glycosyl acceptor in the next coupling step.^[8] This reaction sequence can be performed with glycosyl donors and acceptors that both have a free hydroxyl group. It is critical that the hydroxyl group of the glycosyl acceptor is significantly more reactive than the hydroxyl group of the glycosyl donor to avoid self-condensation of the glycosyl donor. A complementary method exploits the finding that a thioglycoside protected as a silyl ether (for example, triethylsilyl, *tert*-butyldimethylsilyl) can act both as a glycosyl donor and acceptor. In general, silyl ethers are sufficiently stable under *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonate (NIS/TMSOTf)^[9] or iodonium dicollidine perchlorate (IDCP)^[10] mediated glycosylations. Thioglycosides of these derivatives, therefore, can act as glycosyl donors. However, the products of these coupling reactions are suitable acceptors^[11] when glycosylated with glycosyl fluorides in the presence of [Cp₂ZrCl₂]/AgOTf (Cp=cyclopentadienyl, Tf=trifluoromethanesulfonyl).^[12] Chemoselective glycosylation strategies are

[*] Prof. Dr. G.-J. Boons, Dr. T. Zhu
 Complex Carbohydrate Research Center
 220 Riverbend Road, Athens, GA 30605 (USA)
 Fax: (+1) 706-542-44-12
 E-mail: gjboons@ccrc.uga.edu

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based on the ability to control the reactivity of anomeric leaving groups in such a way that building blocks can be coupled with decreasing anomeric reactivities without the need for any protecting-group manipulations between the glycosylations. Orthogonal-glycosylation approaches use saccharide building blocks containing leaving groups with orthogonal reactivities that can therefore be activated independently.

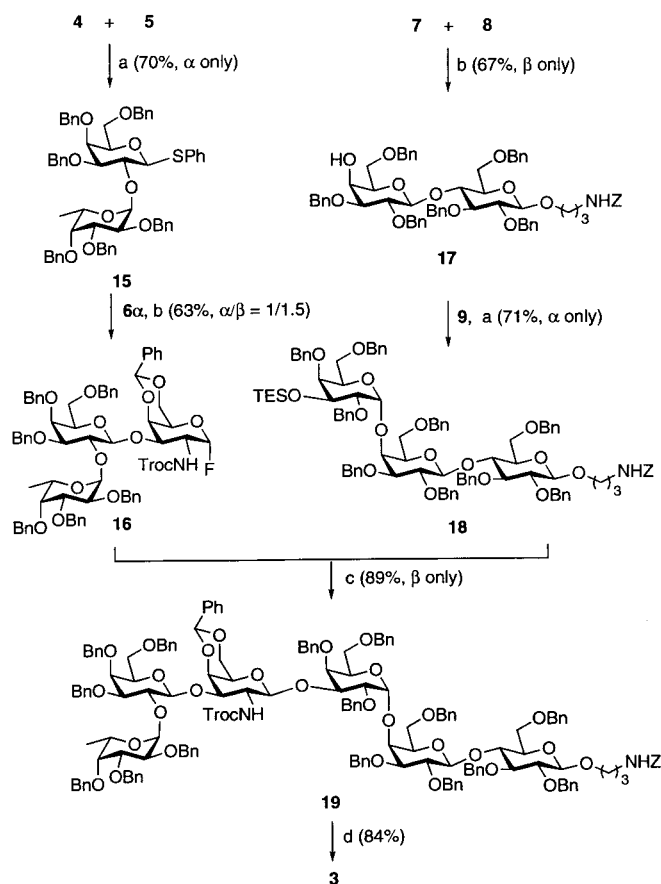
The building blocks **4**,^[13] **5**,^[14] **7**,^[15] and **9**^[16] were synthesized by standard manipulations. The preparation of glycosyl fluoride **6** was more complicated (Scheme 2). The synthesis started with the protection of the amino functionality of the



Scheme 2. Synthesis of building block **6**. a) TrocCl, NaHCO₃, H₂O then Ac₂O, pyridine (78% over two steps); b) HBr/HOAc (33%), CH₂Cl₂; c) Ag₂CO₃, acetone/water (100% over two steps); d) DAST, CH₂Cl₂, -40 °C (92%, α:β = 5:1); e) K₂CO₃, MeOH (75%) then PhCH(OMe)₂, CSA, MeCN (78%).

commercially available *N*-acetylgalactosamine hydrochloride (**10**) as a 2,2,2-trichloroethylcarbamate by reaction with 2,2,2-trichloroethyloxycarbonyl chloride (TrocCl) in aqueous sodium bicarbonate.^[17] The product obtained was acetylated with acetic anhydride in pyridine to give compound **11**^[18] in an overall yield of 78%. The anomeric acetyl moiety of **11** was replaced by a fluoride atom in a three-step procedure. Thus, treatment of **11** with HBr in acetic acid/dichloromethane gave bromide **12**,^[17] which was immediately hydrolyzed with Ag₂CO₃ in acetone/water to give lactol **13**^[19] in a quantitative overall yield. Treatment of **13** with diethylaminosulfur trifluoride (DAST)^[20] in dichloromethane gave the glycosyl fluoride **14** as a separable mixture of anomers (α:β = 5:1). The individual anomers of **14** were converted into the partially-protected derivatives **6α/β** (overall yield 78%) by removal of the *O*-acetyl protecting groups with potassium carbonate in methanol followed by treatment with benzaldehyde dimethyl-acetal in acetonitrile in the presence of a catalytic amount of camphorsulfonic acid (CSA). This reaction sequence demonstrates that glycosyl fluorides can undergo several protecting group manipulations and are stable to mildly acidic and basic reaction conditions.

With significant quantities of building blocks in hand, the assembly of fully protected hexasaccharide **19** could be performed (Scheme 3). Thus, IDCP-mediated glycosylation of the fully protected thioglycosyl donor **4** with semi-protected glycosyl acceptor **5** in dichloromethane/diethyl ether gave **15** as a single anomer in a 70% yield (Scheme 3). The observed chemoselectivity is based on the fact that 6-deoxy-sugars are more reactive glycosyl donors than their 6-hydroxy counterparts. Furthermore, thioethyl glycosides are considerably more reactive than analogous thiophenyl glyco-



Scheme 3. Synthesis of hexasaccharide **3**. a) IDCP, CH₂Cl₂/Et₂O (1/5), 4-Å molecular sieves; b) NIS/TMSOTf, 4 Å molecular sieves, MeCN, -40 °C; c) Cp₂ZrCl₂, AgOTf, CH₂Cl₂, 4-Å molecular sieves; d) 1. Zn, HOAc; 2. Ac₂O, pyridine; 3. Pd(OAc)₂, EtOH, H₂.

sides.^[21] The anomeric thiophenyl moiety of **15** could be activated with the more thiophilic reagent NIS/TMSOTf and reaction with the glycosyl fluoride **6α** gave trisaccharide **16** as a separable mixture of anomers.^[22] An intractable mixture of products was obtained when the same reaction was performed with **6β**, probably as a result of the β-fluoride being much more reactive and activated under the glycosylation conditions. The lower reactivity of the α-anomer can be rationalized on the basis of its ground state being stabilized by a strong anomeric effect. Also a low recovery of trisaccharide was obtained when a derivative of **6** was used in which the Troc protecting group was replaced by a phthalimido group. In this case the bulky phthalimido group shields the hydroxyl group at C-3 and thus reduces its nucleophilicity.

Next we focused on the assembly of trisaccharide **18**. Thus, the NIS/TMSOTf-mediated glycosylation of the partially protected lactosyl donor **7** with spacer **8** gave **17** as a pure β-anomer in a yield of 67%. Mass spectroscopic analyses of the crude reaction mixture revealed no self-condensation or oligomerization of **7**. This expected result is based on the higher reactivity of the primary hydroxyl group of **8** relative to the secondary axial hydroxyl group of **7**. The anomeric selectivity of this glycosylation is based on the formation of an intermediate α-nitrilium ion,^[21] which is substituted by the alcohol to give a β-anomer.^[23, 24] Compound **17** was immedi-

ately used in an IDCP-mediated glycosylation with **9** to give the trisaccharide **18** as the only anomer.

The fully-protected hexasaccharide **19** could be obtained by the coupling of trisaccharides **16** with **18** in the presence of $[\text{Cp}_2\text{ZrCl}_2]/\text{AgOTf}$ in dichloromethane. The reaction was almost instantaneous and the product was isolated in an 89% yield. No desilylated acceptor was observed and the reaction was significantly slower when the coupling was performed with a trisaccharide acceptor that had a free hydroxyl group. These results indicate that a triethylsilyl (TES) moiety activates the glycosyl acceptor in a $[\text{Cp}_2\text{ZrCl}_2]/\text{AgOTf}$ -mediated glycosylation. However, the same protecting group is perfectly stable in an IDCP-mediated glycosylation.

Compound **19** was deprotected in a three-step procedure. Thus, the Troc protecting group was removed by treatment with activated zinc in acetic acid and the resulting amino functionality was acetylated with acetic anhydride in pyridine. Finally, the benzyl ethers, the benzylidene acetal, and the benzyloxycarbonyl moiety were removed by catalytic hydrogenation over palladium to give the target compound **3** in a yield of 84%. Analysis of the product by 1D (^1H , gocsy; 800 MHz) and 2D NMR spectroscopy (gCOSY, HSQC, TOCSY, and gHMBC) confirmed the correct anomeric configuration of each glycosidic linkage.^[25]

In conclusion, we have described a highly convergent approach for the synthesis of a spacer-modified hexasaccharide derived from the tumor-associated antigen Globo-H. The fully-protected hexasaccharide **19** could be efficiently assembled within five glycosylation steps after the preparation of the readily available building blocks. It is to be expected that similar strategic principles can be used for the synthesis of other oligosaccharides of biological importance.

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Thermal Conversion of a Helical Coil into a Three-Dimensional Chiral Framework**

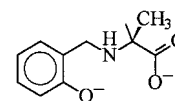
John D. Ranford,* Jagadese J. Vittal,* Daqing Wu, and Xiandong Yang

The quest to rationally design solids by the emerging principles of crystal engineering is continuing at an accelerating pace.^[1] The ultimate goal for the crystal engineers is to synthesize three-dimensional structures with desired properties for practical applications. In the newly emerging area of crystal engineering, several metal-organic compounds have been used successfully in the construction of novel architectures that are unprecedented in naturally occurring solids.^[2] We are currently interested in the synthesis of 3D open frameworks with large chiral cavities; these solids with chiral channels have potential applications, for example, in the separation of enantiomers and the purification of drugs. Such chiral coordination polymer architectures can in principle be generated by the self-assembly of chiral or achiral building blocks. Zaworotko and co-workers have recently described the formation of chiral architectures from achiral molecular components.^[3] We have reported the structures of two 3D frameworks, one held together by hydrogen bonding and the other by covalent bonding, formed from a Zn^{II} complex containing a chiral ligand.^[4] The covalently bonded network has also been obtained by the topochemical dehydration of the hydrogen-bonded network assisted by N-H...O hydrogen bonds.

Self-assembly of supramolecules with helical structures by simple mixing of ligands and metal ions has been one of the focuses in supermolecular chemistry.^[5] In most cases self-assembly of metal ions and multidentate ligands resulted in the formation of covalently bonded single-, double-, triple-, and even quadruple-stranded metal helicates.^[5, 6] However, it appears that the use of helical metal-organic polymers as building blocks for the formation of 3D networks has not been explored before.^[7] Here we report the preparation of a novel, single-stranded helical coordination polymer containing Cu^{II} from simple, chiral amino acid derivatives. These helical polymers are aligned parallel in the solid state. On heating, the single-stranded helices lose water molecules and cross-link to produce a chiral open framework. This demonstrates for the first time the conversion of 1D helical strands into a chiral framework structure. This thermal transformation is accompanied by dehydration and appears to be assisted by N-H...O hydrogen bonding.

Most metal ions, when presented with tridentate ligands, will preferentially bind two of the chelating units to form an

octahedral moiety. However, the coordination sphere around Cu^{II} is distorted and unless the ligand is unusually flexible, copper(II) will bind only one ligand. The remaining coordination site(s) are occupied by solvent, anions, or bridging ligands. We have employed the latter to prepare phenolato-bridged, dimeric copper(II) complexes of *N*-(2-hydroxybenzyl)-L-alanine (H₂sala). This ligand with Cu^{II} gives control over the axial coordination donors. Addition of cupric acetate to H₂sala affords a polymer of dimers, [[Cu(sala)]₂(H₂O)]_n (**1**), as characterized by single-crystal X-ray diffraction (Figure 1).^[8]



sala

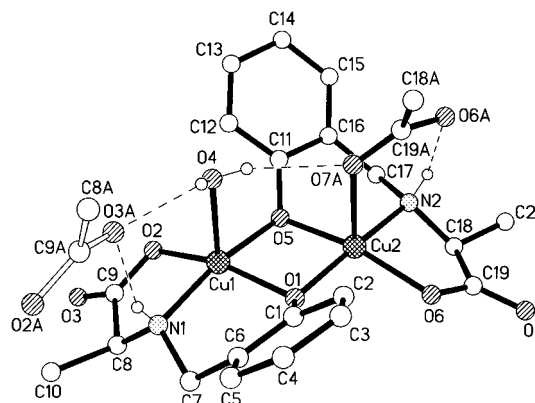


Figure 1. A perspective view showing the geometry of the dinuclear **1**, numbering scheme, and the hydrogen-bonding contacts. The hydrogen atoms attached to carbon atoms were omitted for clarity. Selected fragments of neighboring molecules involved in hydrogen bonding are shown with open bonds. Selected bond distances [Å] and angles [°]: Cu1...Cu2 2.9496(6), Cu1-O1 1.975(3), Cu1-O2 1.928(3), Cu1-O4 2.288(4), Cu1-N1 1.984(4), Cu2-O1 1.936(3), Cu2-O5 1.977(3), Cu2-O6 1.958(3), Cu2-N2 1.984(3), Cu2-O7a 2.258(3), C9-O2 1.274(5), C9-O3 1.227(5), C19-O6 1.282(5), C19-O7 1.237(5); Cu1-O1-Cu2 97.9(1), Cu1-O5-Cu2 96.7(1), O1-Cu1-O5 82.1(1), O1-Cu2-O5 82.9(1), O1-Cu1-N1 93.8(1), O5-Cu2-N2 94.5(1), O2-C9-O3 123.8(5), O6-C19-O7 124.2(4).

The ligands coordinate in the plane of the square-pyramidal Cu^{II} centers through phenolato and carboxylato O atoms and the secondary amine N atom to give a phenolato-bridged dimer. The two apical coordination sites are occupied by either water or carboxylato bridges, and it is control of these sites that determines the supramolecular architecture. Coordination of the amine N atom creates a new chiral center, which means the sala ligand, when complexed, is a diastereomer, with the hydrogen atoms on the secondary amine and *Ca* adopting a *trans* arrangement about the C-N bond axis due to steric interactions.^[9] One axial site in the dimer is occupied by a water molecule (site B), and the other (site A) forms a bridge to an adjacent dimer through a carboxylato O atom (Figure 1). The net result is a helical polymer formed from apically linked dimers.^[10] The helical strands are further sustained by O-H...O and N-H...O hydrogen bonding (Figure 2).^[11] The water molecule and the carboxylate ligand attached to the Cu^{II} centers are on the same side, supported by H-O-H...O-C hydrogen bonding. Further, the NH hydrogen atom of the ligand from site A forms a hydrogen bond to the C=O oxygen atom of the bridging carboxylate group. This

[*] Dr. J. D. Ranford, Dr. J. J. Vittal, D. Wu, X. Yang

Department of Chemistry
National University of Singapore
Lower Kent Ridge Road, 119260 Singapore
Fax: (+65) 779-1691
E-mail: chmjdr@nus.edu.sg
chmjv@nus.edu.sg

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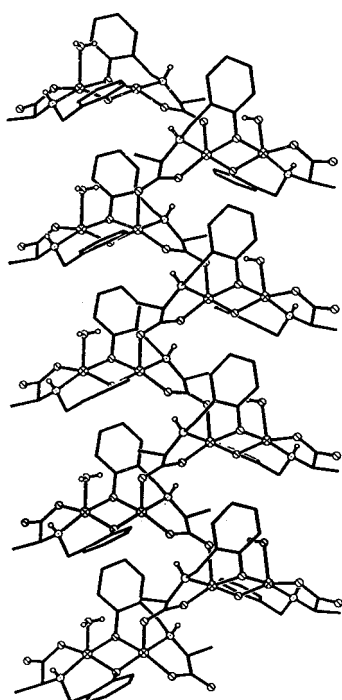
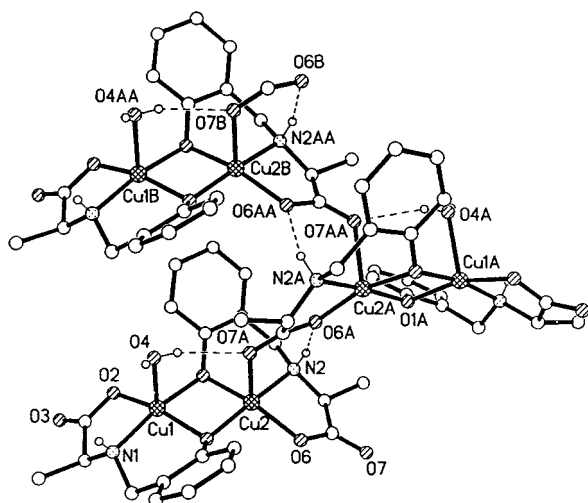


Figure 2. Top: The hydrogen-bonded pattern within the helical coordination polymer **1**. Bottom: A section of the helical coil of **1** along the *a* axis.

covalently bonded helical coordination polymer, sustained by the hydrogen bonds from the backbone of the ligands, is reminiscent of peptide α -helices.^[12]

The helical strands are arranged parallel to the *a* axis and are further hydrogen bonded to one another in the *bc* planes (Figure 3). The carbonyl oxygen atom of the ligand from site B is further intermolecularly hydrogen bonded to two hydrogen atoms, N–H and O–H. As a result, chiral channels are created along the *a* axis with approximate dimensions 4×9 Å (based on the non-hydrogen contacts). The view shown in Figure 3 is similar to the honey-combed hydrogen-bonded chiral network that we have reported for $[\{\text{Zn}(\text{sala})(\text{H}_2\text{O})\}_2] \cdot 2\text{H}_2\text{O}$ (**2**).^[4a] The channels in **1** are very narrow when compared to those in **2**, and they can still accommodate small guest molecules like water. The geometric proximity of the

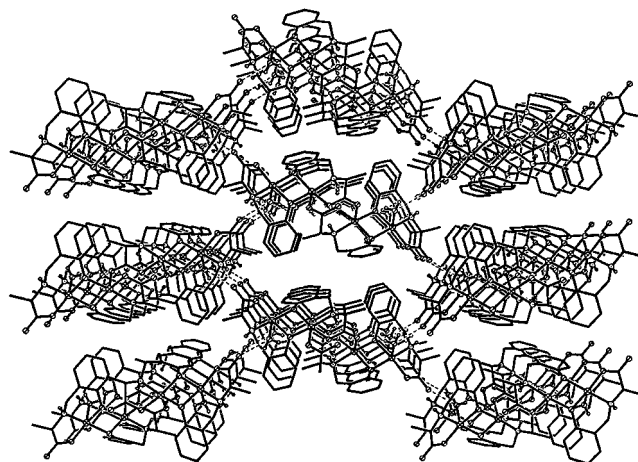
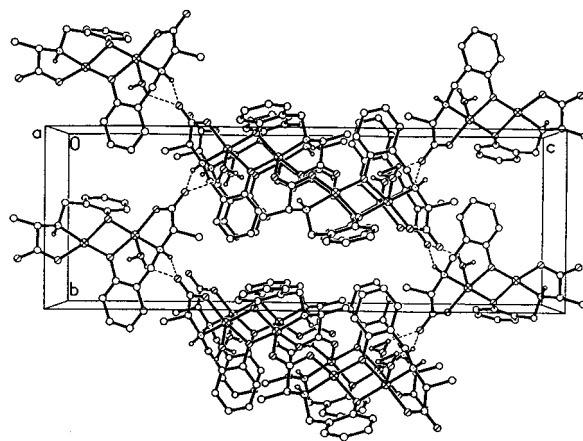
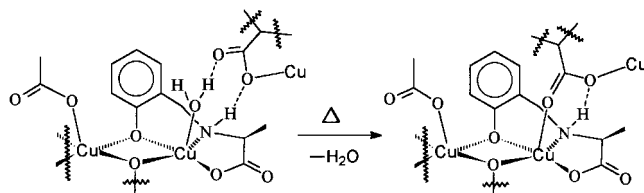


Figure 3. Top: Unit cell showing the hydrogen-bonding network in **1** in the *bc* plane. Bottom: View of **1** down the *a* axis, illustrating the channels resulting in a 3D network coordination polymer.

carboxylate groups and the Cu^{II} atoms of the B sites appears to be favorable for topochemical reactions to occur. The short $\text{Cu} \cdots \text{O}$ distance (3.70 Å) is maintained by the hydrogen-bonded network in the *bc* planes. When the water molecule on site A is removed, this carboxylate ligand is expected to bond to the copper due to this topochemical geometry.

As anticipated, removal of the water molecule in **1** by thermal dehydration^[13] yields anhydrous $[\{\text{Cu}(\text{sala})\}_n]$ (**3**; Scheme 1), where the basic dimeric structure has remained intact but now a porous, 3D network coordination polymer has been established. The X-ray structure analysis^[14] of **3** (Figure 4) reveals this architecture is isomorphous and



Scheme 1. Schematic drawings of the coordination environments and hydrogen bonding in hydrated **1** (left) and dehydrated **3** (right), illustrating the change from hydrogen bonding to covalent bonding.

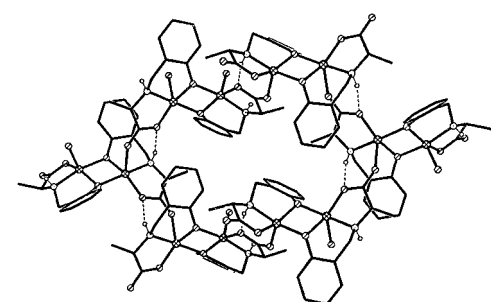
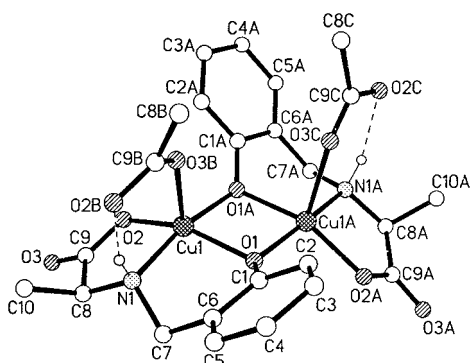


Figure 4. Top: A perspective view of **3** showing the numbering scheme, the coordination geometry around copper atoms, and the hydrogen-bonding contacts. Selected bond distances [Å] and angles [°]: Cu1...Cu1A 3.0310(5), Cu1–O1 1.948(1), Cu1–O2 1.951(1), Cu1–N1 1.986(2), Cu1–O3B 2.341(2), C9–O2 1.290(2), C9–O3 1.237(2); Cu1–O1–Cu1A 101.02(6), O1–Cu1–O1A 78.97(6), O1–Cu1–N1 94.03(6), O2–C9–O3 124.5(2). Bottom: A segment of the three-dimensional network of **3** illustrating the close resemblance to **1**.

isostructural with the analogous Zn^{II} complex $[\{\text{Zn}(\text{sala})\}_n]$ (**4**).^[4a] The arrangement of dimeric units in the solid-state structure of **3** is very similar to that of **1** as well as of **4**. The formation of **3** is accompanied by the loss of hydrogen bonds to the water molecule. However, the N–H...O hydrogen bond is preserved,^[15] as in **4**. Although minimum movement of atoms and conformational changes are enough to obtain the structure of **3** from **1**, the conversion is accompanied by a change in the crystal system and space group. Also, the single crystal of **1** became powdery when heated to 100 °C. Attempts to rehydrate **3** to give **1** have been unsuccessful, and this process appears to be irreversible, as expected. The chiral channels in **3** are just a bit smaller than those observed in **4**. However, the rehydration experiments did not yield any product that accommodates guest water molecules in these voids.

We summarize the results and implications as follows:

- 1) This is the first example for the use of a helical coordination polymer as the building block to produce a 3D coordination framework with chiral channels.
- 2) This is the second example of a solid-state conversion of one type of network into another by thermal dehydration. The presence of complementary hydrogen bonds is strategic in these transformations.
- 3) The dihydrated dimer complex $[\{\text{Cu}(\text{sala})(\text{H}_2\text{O})\}_2]$, analogous to $[\{\text{Zn}(\text{sala})(\text{H}_2\text{O})\}_2]$ has not been isolated. Al-

though the monohydrate Zn complex analogue of **1** is not known, during dehydration one would expect that the dihydrated Zn complex would go through a monohydrated intermediate similar to **1**. However, in the case of $[\{\text{Zn}(\text{sala})(\text{H}_2\text{O})\}_2]$ the thermal dehydration appears to take place in a single step (as indicated by differential thermal analysis (DTA)).^[4a]

- 4) In the Zn system, the covalent bonded network **4** was obtained from another similar hydrogen-bonded framework, **2**. In the work presented here, the same chiral network (but with Cu atoms) **3** was synthesized from different helical building blocks, **1**. This appears to be the first example of a true “solid-state supramolecular synthesis” or “crystal synthesis”, as coined by Desiraju,^[16] of an inorganic system by two different synthetic routes.

Experimental Section

H₂sala was synthesized by a procedure entirely analogous to that in ref. [9] for other ligands.

1: H₂sala (195 mg, 1.00 mmol) and LiOH (24 mg, 1.00 mmol) were stirred in water (10 mL) for 30 min, and then the reaction mixture was filtered. To the filtrate was added a solution of Cu(CH₃CO₂)₂ · H₂O (200 mg, 1.00 mmol) in water (10 mL). Dark green crystals formed in a few minutes, and were separated by decantation and dried in air. Yield: 196 mg (74 %). Elemental analysis calcd for C₂₀H₂₄Cu₂N₂O₇: C 45.2, H 4.6, N 5.3; found: C 45.0, H 4.7, N 5.2; IR (KBr): $\tilde{\nu}$ = 1624 (s, $\nu_{\text{as}}(\text{CO}_2)$), 1483 (s, $\nu_{\text{s}}(\text{CO}_2)$), 1275 cm^{−1} (s, $\nu(\text{C}=\text{O})$).

3: Compound **1** (200 mg, 0.75 mmol) was heated to 115 °C for 2 h to remove all water. The anhydrous material was recrystallized from water to give crystals suitable for X-ray structure analysis. Yield: 93 mg (48 %). Elemental analysis calcd for C₂₀H₂₂Cu₂N₂O₆: C 46.8, H 4.3, N 5.5; found: C 46.8, H 4.4, N 5.3; IR (KBr): $\tilde{\nu}$ = 1609 (s, $\nu_{\text{as}}(\text{CO}_2)$), 1477 (s, $\nu_{\text{s}}(\text{CO}_2)$), 1288 cm^{−1} (s, $\nu(\text{C}=\text{O})$). The product also forms from the filtrate of **1**. Both preparative methods suggest that **3** is the thermodynamic product of this reaction.

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- [11] Close intermolecular hydrogen-bonding contacts between two [Å] and three centers [°]: $\text{H2} \cdots \text{O6}^{\text{i}}$ 2.01(4), $\text{H4A} \cdots \text{O7}^{\text{i}}$ 2.19(3), $\text{H1} \cdots \text{O3}^{\text{ii}}$ 2.27(4), $\text{H4B} \cdots \text{O3}^{\text{ii}}$ 2.10(5), $\text{N2} \cdots \text{O6}^{\text{i}}$ 2.903(5), $\text{O4} \cdots \text{O7}^{\text{i}}$ 2.898(4), $\text{N1} \cdots \text{O3}^{\text{ii}}$ 2.98(6), $\text{O4} \cdots \text{O3}^{\text{ii}}$ 2.655(4); $\text{N2-H2-O6}^{\text{i}}$ 161(3), $\text{O4-H4A-O7}^{\text{i}}$ 161(6), $\text{N1-H1-O3}^{\text{ii}}$ 156(4), $\text{O4-H4B-O3}^{\text{ii}}$ 143(5); the N1-H1 , N2-H2 , O4-H4A , and O4-H4B distances are 0.75(4), 0.93(4), 0.74(3), and 0.74(3) Å, respectively. The H4A-O4-H4B angle is 100(6)°. Operators for generating equivalent atoms: i: $x + \frac{1}{2}$, $-y + \frac{1}{2}$, $-z + 1$; ii: $-x + 1$, $y + \frac{1}{2}$, $z + \frac{1}{2}$.
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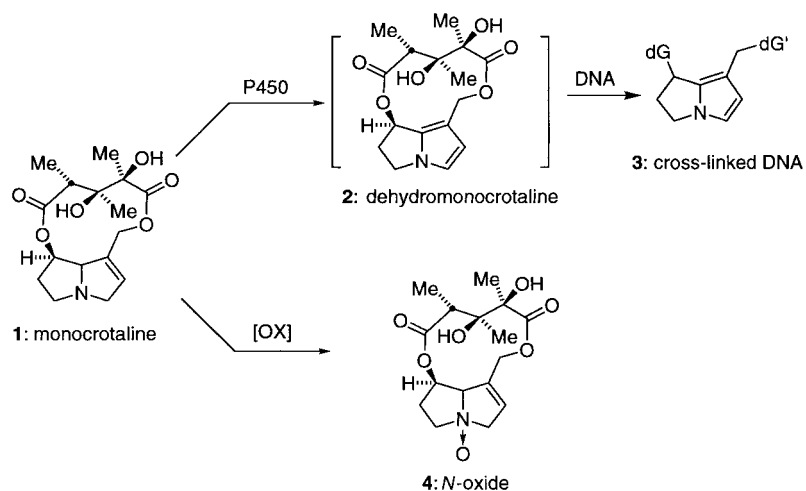
corresponding singles. Compound **3** was also prepared independently. The crystal structure was carried out on the single crystal grown during the synthesis (see the Experimental Section).

- [14] Crystal structure determination of $[[\text{Cu}(\text{sala})]_n]$ (**3**): Tetragonal, space group $P4_32_12$, $a = 8.8790(1)$, $c = 24.9879(2)$ Å, $V = 1969.96(4)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.731$ g cm⁻³. All hydrogen atoms were located successfully, and riding models were used. In the final least-squares refinement cycles on $|F|^2$, the model converged at $R_1 = 0.0226$, $wR_2 = 0.0517$, and $\text{GOF} = 1.00$ for 2371 reflections with $F_o > 4\sigma(F_o)$ and 137 parameters, and at $R_1 = 0.0257$ and $wR_2 = 0.0529$ for all 2526 data. The Flack parameter x was refined to $-0.016(13)$.^[8b]
- [15] Hydrogen-bonding parameters: $\text{H1} \cdots \text{O2}^{\text{i}}$ 2.03(2) Å, $\text{N1} \cdots \text{O2}^{\text{i}}$ 2.93(2) Å, and $\text{N1-H1} \cdots \text{O2}^{\text{i}}$ 164(2)°. Operator for generating equivalent atoms: i: $x + 0.5$, $-y + 0.5$, $-z + 0.25$.
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Reductive Activation of a Hydroxylamine Hemiacetal Derivative of Dehydromonocrotaline: The First Reductively Activated Pyrrolizidine Alkaloid Capable of Cross-Linking DNA**

Jetze J. Tepe and Robert M. Williams*

Pyrrolizidine alkaloids (PAs), such as monocrotaline (**1**, Scheme 1), are potent hepatotoxins and carcinogens isolated from a wide variety of plants.^[1, 2] Owing to their geographical



Scheme 1. Pyrrolizidine alkaloid monocrotaline (**1**) and derivatives **2–4**.

[*] Prof. Dr. R. M. Williams, J. J. Tepe
Department of Chemistry
Colorado State University
Fort Collins, CO 80523 (USA)
Fax: (+1) 970-491-5610
E-mail: rmw@chem.colostate.edu

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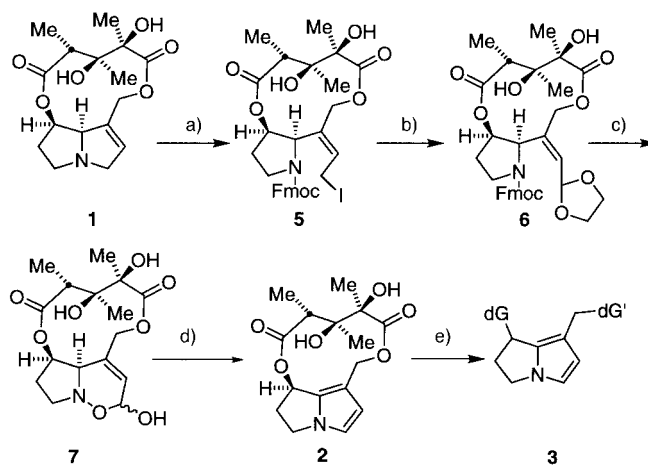
diversity and abundance, the PAs represent a serious health threat to humans and live stock.^[2, 3] The biologically active metabolites of these natural products are the corresponding dehydropyrrolizidines (for example, dehydromonocrotaline, **2**), formed upon two-electron oxidation of the 4-azabicyclo[3.3.0]octane ring system by liver cytochrome P450 mixed-function oxidases.^[4, 5] These substances have been shown to be potent agents for the interstrand cross-linking of DNA (forming adduct **3**), and it is this biochemical reactivity that is largely responsible for the cytotoxicity that this class of alkaloids displays.^[6, 7] Detoxification of the PAs occurs when an alternative N-oxidation reaction occurs ($\rightarrow$ **4**) with either cytochrome P450 or flavin-containing monooxygenases.^[4]

The oxidation of the pyrrolizidine alkaloid ring system results in the electrophilic activation of the C7 and C9 positions, by conjugation with the pyrrole nitrogen lone pair, which are prone to nucleophilic attack by the exocyclic amine group of deoxyguanosine residues in the minor groove of DNA at 5'-CpG-3' sites.^[8, 9]

The potent interstrand DNA–DNA and DNA–protein^[10] cross-linking reactions mediated by the pyrrolic PAs have made these compounds of interest as potential antitumor agents. However, the acute hepatotoxicity of these agents has obviated their clinical utility. The hepatotoxicity of these agents is a manifestation of the initial production and release of the reactive DNA-cross-linking species being generated in the liver by the mixed-function cytochrome P450 oxidases. Since the oxidative mode of activation is primarily responsible for the undesirable characteristics of these compounds, it seemed that it would be possible to improve their pharmacological profile by altering the chemical mode of activation. Based on the success of a variety of clinically significant, reductively activated DNA-cross-linking agents, such as mitomycin C, and FR900482 and congeners we anticipated that a reductive mode of activation of the PAs might not only improve the pharmacological profile of these agents, but also induce a similar tumor selectivity that many of the hypoxia-directed agents display.^[11, 12] As part of a program aimed at diversifying the chemical and biochemical repertoire of activation of a variety of clinically significant antitumor agents,^[13] we describe here the synthesis and DNA-cross-linking reactivity of the first reductively activated pyrrolizidine alkaloid, a progenitor of dehydromonocrotaline.

The synthesis of the reductively activated dehydromonocrotaline derivative **7** is shown in Scheme 2. Commercially available^[14] monocrotaline (**1**) was condensed with 9-fluorenylmethyl chloroformate (FmocCl) in the presence of KI in acetonitrile,^[15] furnishing the ring-cleaved product **5**. The allylic iodide was oxidized with DMSO and AgBF₄ to afford the unsaturated aldehyde in 95% yield. Protection of the aldehyde as the corresponding ethylene glycol acetal **6** followed by removal of the Fmoc moiety with 50% piperidine in THF provide the corresponding free amine. Compound **7**, the hydroxyl amine hemiacetal progenitor of dehydromonocrotaline, was prepared by oxidation of the free amine with *m*-CPBA in a biphasic mixture of CH₂Cl₂ and aqueous saturated NaHCO₃ followed by removal of the acetal with 1% HCl.

Similar to the well-studied mode of activation of FR900482



Scheme 2. Synthesis of **7**. a) FmocCl, KI, room temperature, MeCN, 10 h, 30%; b) 1. AgBF₄, DMSO, Et₃N, room temperature, 95%; 2. TMSCl, CH₂Cl₂, HOCH₂CH₂OH, 95%; c) 1. 50% piperidine, CH₂Cl₂, 96%; 2. *m*-CPBA, CH₂Cl₂, 61%; 3. 1% HCl (aq.), THF, room temperature, 70%; d) Fe^{II}/EDTA, –2 H₂O; e) DNA. FmocCl = 9-fluorenylmethyl chloroformate, TMS = trimethylsilyl, *m*-CPBA = 3-chloroperoxybenzoic acid, EDTA = ethylenediaminetetraacetic acid.

and congeners, **7** was reductively activated by Fe^{II}/EDTA generated in situ.^[8, 16] The HPLC analysis (reverse-phase, C-18 YMC ODS-A, 30% acetonitrile in water at 1.0 mL min^{–1}) of **7** revealed that this substance (10 μ L, 10 mM in DMSO, UV: λ_{max} = 212 nm, retention time 3.8 min) was converted into dehydromonocrotaline (**2**; UV: λ_{max} = 232 nm, retention time 11.2 min) by the addition of Fe^{II}/EDTA (20 mM, pH 8).

The results of DNA-cross-linking studies with **7** are presented in Figure 1. The DNA interstrand cross-linking ability of **7** was investigated using linear plasmid DNA by denaturing alkaline agarose gel electrophoresis according to

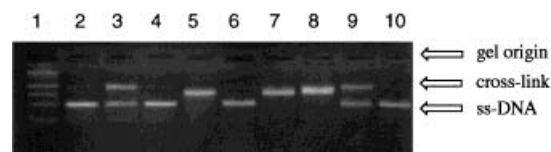


Figure 1. DNA-cross-linking studies of **7** using linear plasmid DNA by denaturing alkaline agarose gel electrophoresis. Conditions: lane 1: 0.5 μ g of Lambda Hind III (molecular weight standard); lane 2: 0.5 μ g of pBR322 (control); lane 3: 0.5 μ g of pBR322 + 10 μ M **2** (control); lane 4: 0.5 μ g of pBR322 + 1.0 mM FR900482 (control); lane 5: 0.5 μ g of pBR322 + 1.0 mM FR900482 + 100 μ M Fe^{II}/EDTA; lane 6: 0.5 μ g of pBR322 + 1.0 mM **7** (control); lane 7: 0.5 μ g of pBR322 + 1.0 mM **7** + 100 μ M Fe^{II}/EDTA; lane 8: 0.5 μ g of pBR322 + 0.5 mM **7** + 100 μ M Fe^{II}/EDTA; lane 9: 0.5 μ g of pBR322 + 100 μ M **7** + 100 μ M Fe^{II}/EDTA; lane 10: 0.5 μ g of pBR322 + 10 μ M **7** + 100 μ M Fe^{II}/EDTA. ss-DNA = single-strand DNA.

Cech.^[17] The duplex DNA substrate employed in this study was pBR322 plasmid DNA, which was linearized by restriction endonuclease digestion with EcoR1. The amount of linearized pBR322 was quantitated by UV analysis at 260 nm, as described by Borer.^[18] Compound **7** (solutions of various concentrations were prepared from a 10 mM stock solution made from 4.2 mg of **7** dissolved in 1.2 mL of DMSO) and 0.5 μ g of DNA (EcoR1 linearized pBR322) were incubated at 37 °C for 12 h with the reagents described in the legend to

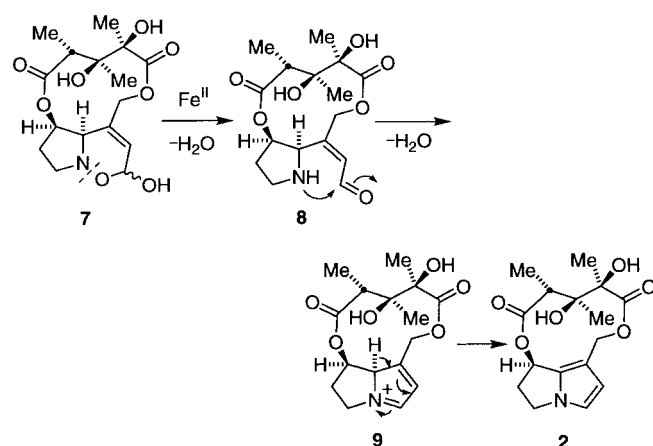
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Figure 1 (final volume 10 μ L). The Fe^{II} /EDTA was prepared by addition of an equimolar amount of FeSO_4 to a solution of EDTA (pH 8). The crude reaction mixture was loaded onto a denaturing 1.2% alkaline agarose gel,^[17] and electrophoresis was conducted at 50 V for 3 h (95 mA, 3 W). The gel was stained by the addition of 200 μ L of ethidium bromide solution (10 mg mL⁻¹, 100 mM tris(hydroxymethyl)aminomethane (Tris) at pH 7.5, 15 min) and visualized after destaining (50 mM NH_4OAc + 10 mM 2-sulfanylethanol, 1 h) on a UV transilluminator. Lambda Hind III was employed as a molecular weight standard (lane 1).

Control reactions were performed with **2** (10 μ M, lane 3) and the known reductively activated antitumor antibiotic FR900482 (1.0 mM, lane 4; and additionally with Fe^{II} /EDTA activation, lane 5).^[8, 16] The data in Figure 1 reveal that 100 μ M Fe^{II} /EDTA strongly activates compound **7** to form the interstrand-cross-linked DNA at drug concentrations of 100 μ M or more (lanes 7–9).

The mechanism of activation of **7** therefore most likely follows the known mechanism of activation of the FR900482 family of compounds: two-electron reductive cleavage of the N–O bond of **7** to form the free amine (**8**, Scheme 3), which cyclizes on the incipient aldehyde moiety and subsequently deprotonates to the highly reactive pyrrolic intermediate **2**.^[19, 20]



Scheme 3. Mechanism of reductive formation of **2** from **7**.

These preliminary studies suggest the viability of the hydroxylamine hemiacetal moiety as a potential useful functional group for applications to the reductive activation of DNA-reactive alkaloid progenitors. Since it has been demonstrated that the only other known hydroxylamine hemiacetal containing antitumor antibiotic, FR900482 and congeners, can be reductively activated by Fe^{II} salts to cross-link DNA in vitro, and because this reductive activation mechanism has also been implicated for the in vivo activation of these agents,^[8, 19, 20] the present system lends support to the notion that the reductively labile hydroxylamine hemiacetal may find other uses in prodrug activation strategies. In addition, these agents may also provide a conceptual framework upon which the design and synthesis of a wide variety of pyrrolic PA prodrugs with potential clinical applications may be examined.

Keywords: alkaloids • DNA structures • drug research • monocrotaline

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The First Catalytic Asymmetric Nitro-Mannich-Type Reaction Promoted by a New Heterobimetallic Complex**

Ken-ichi Yamada, Simon J. Harwood, Harald Gröger, and Masakatsu Shibasaki*

Catalytic enantioselective nucleophilic addition to imines is a challenging area of organic chemistry. Although numerous efficient catalytic asymmetric methods have been developed for the addition of carbon nucleophiles to carbonyl compounds,^[1] only a few examples are known for imines. To date, noteworthy and impressive developments in this field have mainly been made using organometallic reagents,^[2,3] silyl ketene acetals,^[4] or allylstannanes^[5] as nucleophiles, and recently catalytic asymmetric Strecker reactions have been reported.^[6] The catalytic asymmetric addition of nitroalkanes to imines, called the catalytic asymmetric nitro-Mannich-type reaction, provides chiral β -nitroamines. This versatile class of compounds can be easily converted into useful chiral building blocks such as α -amino acids and 1,2-diamines. To the best of our knowledge no catalytic asymmetric nitro-Mannich-type reaction has been reported to date.^[7] Herein, we report the first example.

We first examined this reaction using heterobimetallic asymmetric complexes containing both Brønsted basic and Lewis acidic functionalities. These complexes have been developed in our laboratory and have proved to be highly efficient catalysts for many types of asymmetric reactions including catalytic asymmetric nitroaldol reactions.^[8] We envisioned that development of a catalytic asymmetric nitro-Mannich-type reaction would be feasible. Unexpectedly, the use of usual imines such as *N*-benzylimines gave only unsatisfactory results.^[9] However, having discovered in previous work that P=O double bonds can coordinate to the central metal of a heterobimetallic complex,^[10] we assumed that *N*-phosphinoylimines **1** might be more suitable substrates for our target reaction. The synthesis of imine **1**, using known literature methods,^[11] proved unsatisfactory and led us to develop a modified method for imine preparation.^[12]

A screening of catalysts showed us that the complex [YbK₃(binaphthoxide)₃] (YbPB) was the best heterobimetallic catalyst for the reaction.^[13] For example, when 20 mol % of YbPB was used, the addition of nitromethane to imine **1a** afforded the nitroamine **2a** in 64 % yield and with 52 % *ee* (Table 1, entry 1). After several attempts to improve the *ee* value, we were pleased to find that reducing the amount of potassium in the Yb-containing heterobimetallic catalyst increased the *ee* value of the product (entries 2 and 3). The catalyst prepared from Yb(OiPr)₃, KOiBu, and binaphthol in

Table 1. The effects of the composition of the catalysts on the yield and *ee* value.

Entry ^[a]	Catalyst composition (Yb:K:binaphthol)	Yield [%]	<i>ee</i> [%]
1	1:3:3 (YbPB)	64	52
2	1:2:3	82	75
3	1:1:3	62	82
4	1:1:2	–	–

[a] Nitromethane was added over 14 h.

the ratio of 1:1:3 gave the best result, providing the desired product in 62 % yield and with 82 % *ee*. Importantly, it was necessary to add nitromethane slowly to obtain this result.^[14] We initially thought that the reduced amount of potassium resulted in the formation of a complex of Yb, K, and binaphthol in the ratio of 1:1:2^[15] along with a free binaphthol, and that the complex [YbK(binaphthoxide)₂] was the actual catalyst. However, this possibility was excluded because the complex prepared from Yb(OiPr)₃, KOiBu, and binaphthol in the ratio of 1:1:2 did not promote the reaction (entry 4).

The best result was obtained when the reaction was carried out at –40 °C with 20 mol % of the catalyst (Yb:K:binaphthol = 1:1:3) and slow addition (over 27 h) of nitromethane (5 equiv) to the imine **1a**. The product **2a** was formed in 79 % yield and with 91 % *ee* (Table 2, entry 1). With these optimized conditions in hand, we examined the scope

Table 2. The scope and limitations of the catalytic asymmetric nitro-Mannich-type reaction.

Entry ^[a]	Ar	Imine	Product	<i>t</i> [h]	Yield [%]	<i>ee</i> [%]
1	Ph	1a	2a	60	79	91
2	4-Cl-C ₆ H ₄	1b	2b ^[b]	60	93	87
3	<i>p</i> -tolyl	1c	2c ^[b]	168	85	89
4	2-furyl	1d	2d ^[b]	168	57	83
5	2-thiophenyl	1e	2e ^[b]	168	41	69

[a] Nitromethane was added over 27 h. [b] The absolute configuration was tentatively assigned.

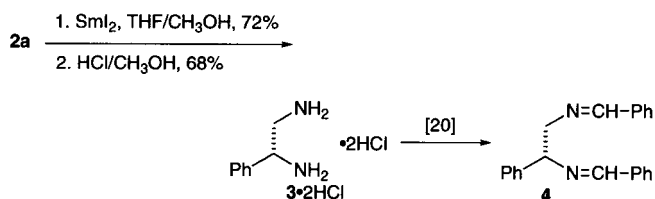
and limitations of the reaction (Table 2). As expected the reaction proceeded smoothly with the imine **1b**, which contains an electron-withdrawing substituent, giving the product **2b** in 93 % yield and with 87 % *ee* (entry 2). In the case of imine **1c**, which contains an electron-donating group, the reaction required a prolonged reaction time and gave the product **2c** in 85 % yield and with 89 % *ee* (entry 3). The reactions were rather slow with imines **1d** and **1e**, which contain electron-rich aromatic groups, and gave the products with good *ee* values but in only moderate yields^[16] (entries 4

[*] Prof. Dr. M. Shibasaki, K.-i. Yamada, Dr. S. J. Harwood, Dr. H. Gröger
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: mshibasa@mol.f.u-tokyo.ac.jp

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and 5). To date, results using imines derived from aliphatic aldehydes such as pivalaldehyde are less satisfactory.^[17]

To highlight the importance of the nitroamine products obtained from this reaction, we converted the nitroamine **2a** into the synthetically versatile diamine **3** (Scheme 1). The



Scheme 1. The transformation of the nitroamine **2a** into the dihydrochloride of diamine **3**.

nitro group was reduced to an amino group using Sm^{II} in 72 % yield,^[18] and the diphenylphosphinoyl group was cleaved under mildly acidic conditions^[19] to afford the diamine **3** in 68 % yield as the dihydrochloride. The HPLC analysis (chiral stationary phase) of the Schiff base **4**, derived from the dihydrochloride of the diamine **3**, revealed that the absolute configuration of the major enantiomer of nitroamine **2a** was *R* when the catalyst was prepared from (*R*)-binaphthol.^[20]

To determine the structure of the catalyst, we measured laser desorption/ionization time-of-flight (LDI-TOF) mass spectra of the catalyst solution. The main peaks in the positive-ion mode were at m/z 285, 1602, and 2114, corresponding to $[\text{binaphthol}]\text{H}^+$, $[\text{YbK}(\text{binaphthoxide})_2]_2\text{K}^+$, and $[\text{YbK}(\text{binaphthoxide})_2]_3\text{K}^+$, respectively. The main peaks in the negative-ion mode were m/z 286, 741, and 1519, corresponding to $[\text{H}(\text{binaphthoxide})]^-$, $[\text{Yb}(\text{binaphthoxide})_2]^-$, and $[\text{K}[\text{Yb}(\text{binaphthoxide})_2]_2]^-$, respectively. Given these observations, the structure of the catalyst could be $[\text{YbK}(\text{binaphthoxide})_2]$ (Figure 1, middle) or its aggregated complex

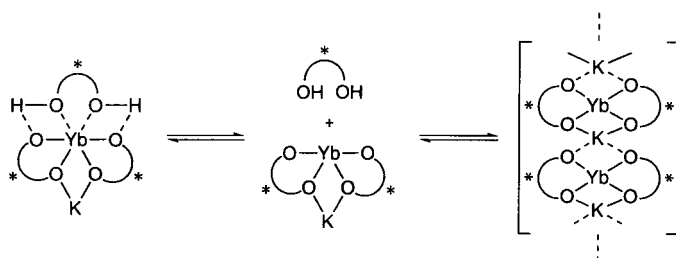


Figure 1. The proposed structure of the new heterobimetallic complex. (The semicircles represent the 1,1'-binaphthyl skeleton of binaphthol).

$[\text{YbK}(\text{binaphthoxide})_2]_n$ (Figure 1, right). However, since the 1:1:2 complex gave poor results for the nitro-Mannich reaction (Table 1, entry 4), it seems unlikely that they represent the structure of the active catalyst. Since the mass spectra reflect the structure of the catalyst in solution, we propose that the active catalyst may be a complex of $[\text{YbK}(\text{binaphthoxide})_2]$ and binaphthol, weakly associated to each other by Lewis acid–Lewis base interactions and hydrogen bonding (Figure 1, left).

In conclusion, we have developed the first enantioselective nitro-Mannich-type reaction in a catalytic manner. The best

catalyst for this reaction is a new type of heterobimetallic complex, containing Yb, K, and binaphthol in the ratio of 1:1:3, rather than the known heterobimetallic complex YbPB (1:3:3).

Experimental Section

$\text{Yb}(\text{O}i\text{Pr})_3$ was purchased from Kojundo Chemical Co., Ltd.^[21] All solvents used in the reactions were dried prior to use. All reagents were purified by standard methods. All reactions were performed under an anhydrous argon atmosphere.

Preparation of the catalyst solution: (*R*)-Binaphthol (86.5 mg, 0.30 mmol; dried at 45 °C for 4 h in vacuo) was dissolved in THF (2.8 mL), and the solution was stirred for 10 min at room temperature. $\text{Yb}(\text{O}i\text{Pr})_3$ (0.1 M solution in THF, 1.0 mL) was added to the solution, and the mixture was stirred for another 10 min. $\text{KO}t\text{Bu}$ (1.0 M solution in THF, 0.10 mL) and then after 10 min H_2O (1.0 M solution in THF, 0.10 mL) were added to the mixture. The mixture was stirred for an additional hour at room temperature before the solvent was removed in vacuo. The residual solid was dried in vacuo for a further hour, and then THF (0.50 mL) and toluene (3.5 mL) were added. The mixture was stirred for 1 h at room temperature and was then used as a 0.025 M catalyst solution (toluene/THF 7/1).

General procedure for the catalytic asymmetric nitro-Mannich-type reaction: (*R*)-*N*-(2-nitro-1-phenylethyl)-*P*,*P*-diphenylphosphinic amide (**2a**): To *N*-benzylidene-*P*,*P*-diphenylphosphinic amide (**1a**; 76 mg, 0.25 mmol) was added the freshly prepared catalyst solution (2.0 mL, 0.20 equiv), and the mixture was stirred for 10 min at room temperature. The mixture was cooled to –40 °C and stirred for 10 min before nitromethane (0.068 mL, 5.0 equiv) was added slowly over 27 h at the same temperature. After the addition of nitromethane was completed, the mixture was stirred for an additional 33 h at the same temperature, and then quenched by the addition of water (ca. 5 drops) and diluted with CH_2Cl_2 (ca. 5 mL). The mixture was allowed to warm up to room temperature, and after further dilution with CH_2Cl_2 (ca. 15 mL) the mixture was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , acetone/hexane 40/60 → 50/50) gave nitroamine **2a** (72 mg, 79 %) with 91 % *ee* as an off-white solid.^[22]

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- [14] When nitromethane was added in one portion, the result was less satisfactory (34% yield, 45% *ee*).
- [15] This is a characteristic structure for heterobimetallic complexes with a Group 13 central metal.
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Mesoporous Magnetic Materials Based on Rare Earth Oxides**

Mitsunori Yada,* Hirohumi Kitamura, Akira Ichinose, Masato Machida, and Tsuyoshi Kijima

Since the discovery of the mesoporous silicas MCM-41^[1] and FSM-16^[2] derived from their surfactant mesocomposites, increasing attention has focused on the synthesis of mesoporous materials by the template method. Mesoporous silicas with surface-modified mesopores have large internal surface areas and narrow pore size distributions, and are effective catalysts and molecular sieves.^[3] Mesoporous transition metal oxides are promising not only as catalysts and molecular sieves but also as highly functional materials with shape-specific and/or quantum effects characteristic of their ordered inorganic skeletons. Antonelli et al.^[4] and Sun et al.^[5] synthesized various micro- and mesoporous transition metal oxides such as niobium and tantalum oxides by the ligand-assisted liquid crystal template method with neutral primary amines. Layered^[6] and hexagonal^[7] mesostructured titanium oxides were found to be photocatalytically active.

Rare earth oxides and mixed oxides are useful as materials with luminescent, catalytic, electric, and magnetic properties that result from their 4f electrons. Rare earth garnets are applicable as bubble memory materials owing to their small magnetic domains with up or down spins. If such rare earth oxides were obtainable as mesoporous solids, they would be promising as adsorbents or separating agents with a combination of shape- or size-selectivity and magnetic properties. They could also act as electrically, magnetically, or optically functional host materials. We have reported the synthesis of a series of mesostructured metal oxides and demonstrated that the homogeneous precipitation method with urea is effective for the synthesis of aluminum-, gallium-, and yttrium-based dodecyl sulfate mesophases in which layered and hexagonal structures are templated by alkyl sulfate assemblies.^[8-13] The hexagonal yttrium-based mesophase was converted into a mesoporous material with a specific surface area of 545 m² g⁻¹ by anion exchange of the surfactant with acetate ions, although the Al- and Ga-based analogues collapsed on the removal of surfactants.^[13] However, the introduction of yttrium species into the inorganic framework of Al- and Ga-based mesophases yielded highly ordered mesoporous Al-Y and Ga-Y mixed oxides with specific surface areas of 798 and 714 m² g⁻¹, respectively.^[14, 15] Here we report on the first synthesis and characterization of mesoporous rare earth oxides, as well as their anomalous magnetic properties.

The X-ray diffraction (XRD) pattern of the solid erbium-based mesophase isolated after a reaction time *t* of 3 h (see

[*] M. Yada, H. Kitamura, A. Ichinose, M. Machida, T. Kijima
Department of Applied Chemistry, Faculty of Engineering
Miyazaki University
Miyazaki, 889-2192 (Japan)
Fax: (+81)985-58-2876
E-mail: t0g108u@cc.miyazaki-u.ac.jp

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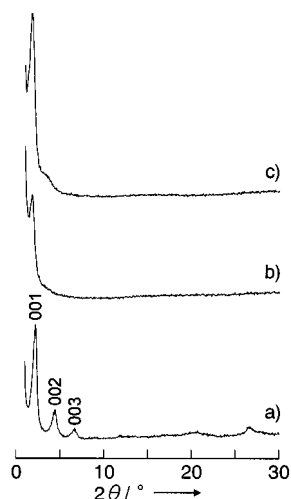


Figure 1. Powder X-ray diffraction (XRD) patterns of as-grown (a, b) and acetate-treated (c) samples of mesostructured erbium oxides isolated after reaction times of 3 (a) and 10 h (b,c).

Experimental Section) exhibited by three diffraction peaks at $2\theta = 2.2$, 4.4 , and 6.7° (Figure 1a). The peaks are attributable to the (001), (002), and (003) reflections of a layered phase with an interlayer spacing of 4.0 nm. The observed interlayer spacing can be explained by assuming that the dodecyl sulfate molecules are arranged as a bilayer between the erbium-based inorganic layers. This is consistent with the transmission electron micrograph (Figure 2a), which shows stripes based on a layered structure, which indicates the formation of lamellar particles. The curved stripes and concentric patterns are characteristic of rare earth based layered mesophases. These specific patterns are similar to those observed for the yttrium oxide/surfactant^[13] and aluminum phosphate/surfactant systems^[16] but fundamentally different from the simple straight-extended layered structure of most layered mesostructured solids, such as the silica/surfactant^[17] and zirconia/surfactant systems.^[18]

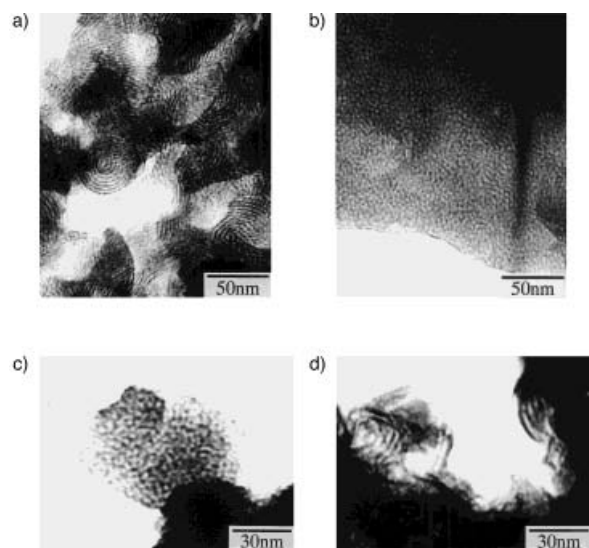


Figure 2. TEM images of the as-grown (a, b) and acetate-treated (c, d) mesostructured erbium oxides isolated after reaction times of 3 (a), 10 (b, d), and 20 h (c).

In contrast to the layered mesophase formed in the initial stage, the erbium-based mesophase obtained after a reaction time of 10 h showed a XRD pattern with one major peak at $2\theta = 1.8^\circ$ and a weak broad band at $2\theta = 2-4^\circ$ (Figure 1b). The d spacing given by the lowest angle diffraction peak increased from 4.0 nm for the initially formed layered mesophase to 4.9 nm for the mesophase formed after longer

reaction times. The XRD pattern of the product after 10 h cannot be definitely assigned to the hexagonal or cubic structure. The transmission electron micrograph of this mesophase showed a hexagonal array of channels, but with less ordering (Figure 2b) than those of MCM-41 silica^[1] and Al- and Ga-based mesophases,^[8, 12] along with a stripe image, which suggests formation of a tubular rather than a cubic structure. The appearance of the less ordered structure could be explained by the transformation of the mesophase from the curled or concentric layered structure into a hexagonal structure that is highly modulated by the strained inorganic framework. The diffraction peak corresponding to $d = 4.9$ nm can most likely be assigned to the (100) reflection of a modulated hexagonal structure with a unit cell parameter of $a = 5.6$ nm. This is consistent with the broad band observed at $2\theta = 2-4^\circ$, as expected for unresolved (110) and (200) reflections.

X-ray diffraction patterns indicative of a similar modulated hexagonal structure were observed for the Ho-, Tm-, Yb-, and Lu-based mesophases after a reaction time of 10 h. All of these XRD patterns are also similar to that of a hexagonal yttrium-based mesophase.^[13] The Tb- and Dy-based mesophases obtained at $t = 10$ h also showed a XRD peak at nearly the same angle as above ($2\theta \approx 1.8^\circ$), and the Gd-based mesophases were transformed from a layered structure ($t = 10$ h) into a modulated hexagonal form at $t = 20$ h. These three mesophases indicated a relatively weak (100) peak, together with some peaks unassignable to the hexagonal structure. The XRD data also indicated the transformation of the Eu-based mesophase from a layered structure at $t = 10$ h into a mixture of layered and hexagonal forms at $t = 20$ h. These less crystalline hexagonal forms were unstable and were finally converted into the oxide dicarbonate hydrate in the case of Eu and into amorphous or unknown phases in the case of Gd, Tb, and Dy at $t = 30$ h. This is in marked contrast to the erbium and yttrium systems, in which the hexagonal structure is retained up to $t = 40$ h. The d of 4.7–5.3 nm spacing given by the lowest-angle diffraction peak for the hexagonal Gd–Lu mesophases were obtained from their XRD patterns (Table 1). The molar ratios of surfactant to rare earth element determined by X-ray microanalysis (XMA) were in the range 0.24–0.45 for the stable and metastable hexagonal mesophases. The IR spectra of the mesophases showed a broad band in the range of $1300-1700\text{ cm}^{-1}$ attributable to CO_3^{2-} , along with some peaks assignable to dodecyl sulfate; hence, the mesophases are composed of rare earth oxide hydroxide, carbonate, and dodecyl sulfate species. The La, Ce, Pr, Nd, and Sm systems all yielded layered mesophases with an interlayer spacing of 3.6 nm as the major phase at $t = 10$ h. These layered mesophases were converted into $\text{Ce}_2\text{O}(\text{CO}_3)_2 \cdot \text{H}_2\text{O}$, PrCO_3OH , NdCO_3OH , and $\text{Sm}_2\text{O}(\text{CO}_3)_2 \cdot x\text{H}_2\text{O}$, respectively, along with residual layered phase after 30 h. In the case of La, the product was still composed mainly of the layered mesophase and only partially of $\text{La}_2\text{O}(\text{CO}_3)_2 \cdot x\text{H}_2\text{O}$ even after 30 h. These layered phases are more highly crystalline than the Er- and Y-based layered mesophases. As a typical case, the XRD patterns of the neodymium-based solids isolated from reactions at $t = 10$ h and $t = 30$ h are shown in Figure 3.

Table 1. Characterizations of the as-grown and acetate-treated mesostructured rare earth oxides.

Rare earth element	Atomic number	$d_{\max}$ [nm] ^[a]	As-grown		$d_{\max}$ [nm] ^[a]	Anion-exchanged		relative magnetic susceptibility	relative $\mu_{\text{eff}}^{\text{[c]}}$
			S/M [mol mol ⁻¹]			specific surface area [m ² g ⁻¹]	magnetic susceptibility [10 ⁻⁴ emu g ⁻¹]		
Gd	64	4.9	0.24		4.9	287	0.55	0.33	0.54
Tb	65	5.0	0.39		5.1	348	1.56	0.93	0.83
Dy	66	5.3	0.43		5.1	253	1.66	1.00	1.00
Ho	67	4.9	0.45		5.1	316	1.62	0.97	1.00
Er	68	4.9	0.44		4.9	280	1.23	0.73	0.85
Tm	69	4.9	0.37		4.9	335	0.86	0.52	0.50
Yb	70	4.9	0.32		4.9	283	0.66	0.40	0.18
Lu	71	4.7	0.32		4.7	257	0	0	0

[a] The d spacing was determined from the lowest angle diffraction peak. [b] S/M = [surfactant]/[rare earth element]. [c] μ_{eff} is the theoretical magnetic moment of the free trivalent cation.

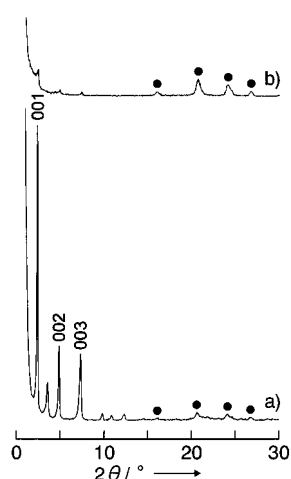


Figure 3. XRD patterns of neodymium oxides isolated after reaction times of 10 (a) and 30 h (b). •: NdCO₃OH.

a layered mesophase, whereas the medium-sized (Eu to Dy) and large (La to Sm) cations initially form a layered mesophase that finally undergoes conversion into a carbonate or other phase with and without an intermediate layer to hexagonal transition, respectively. This classification of the rare earth elements is analogous to the classification of their sesquioxides into the La₂O₃ (Type A), Sm₂O₃ (Type B), and Sc₂O₃ (Type C) crystal structures.^[19, 20]

The hexagonal mesophases were subjected to anion exchange with acetate ions^[21] to remove the incorporated surfactants. The XRD patterns of the acetate-treated mesophase all showed a single peak at $2\theta \approx 1.8^\circ$ assignable to the (100) reflection and a shoulder at $2\theta = 2-4^\circ$ associated with the (110) and (200) reflections of a hexagonal structure, as exemplified for Er in Figure 1c and for Gd–Lu in Figure 4. These patterns are similar to those of the as-grown phases, but with a more distinct shoulder. The d spacings determined for the lowest-angle diffraction peak were barely changed by treatment with acetate (Table 1). The transmission electron micrograph of the Er product showed a hexagonal array of channels, but with less ordering (Figure 2c), and a stripe image (Figure 2d) suggestive of the existence of tubular pores, similar to the as-grown mesophase. No sulfur-containing

species were detected by XMA on the acetate-treated solids. These XRD, TEM, and XMA results indicate that the dodecyl sulfate anions are completely exchanged with acetate anions and that the modulated hexagonal structure is retained. Anion exchange may be driven by the larger hydrophobic attraction between the long-chain dodecyl sulfate ions and ethanol molecules.

The N₂ adsorption isotherm of the anion-exchanged erbium mesophase showed two distinct regions (Figure 5). The N₂ adsorption in the range $P/P_0 = 0-0.2$ is due to monolayer coverage of the mesopores and the surface of the particles, whereas that in the range $P/P_0 = 0.2-0.4$ is characteristic of capillary condensation in mesopores. The desorption isotherm showed no hysteresis relative to the adsorption isotherm, and this indicates that little irreversible interaction occurs between N₂ and the mesopores. Given the ErO_{1.5} to SiO₂ mass ratio of 191.3/60.1, the mesoporous erbium oxide with a specific surface area of 280 m² g⁻¹ corresponds to a mesoporous silica with a specific surface area of 891 m² g⁻¹. This is nearly equal to that 1000 m² g⁻¹ for MCM-41 or FSM-16. A similar N₂ adsorption isotherm was observed for all other anion-exchanged mesophases. Their specific surface areas are in the range of 253–348 m² g⁻¹ (Table 1). The effective pore sizes of 2.5–3.0 nm for the anion-exchanged solids were obtained from the pore size distributions (Figure 5). On the basis of the above XRD, TEM, and N₂ adsorption data, we conclude that the anion-

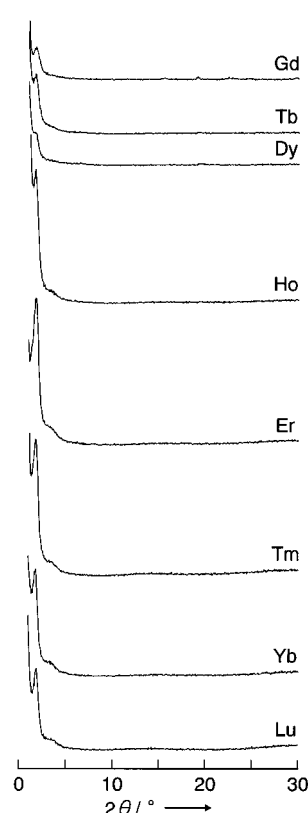


Figure 4. XRD patterns of acetate-treated rare earth oxides isolated after reaction times of 10 (Tb, Dy, Ho, Er, Tm, Yb, Lu) and 20 h (Gd, Tb).

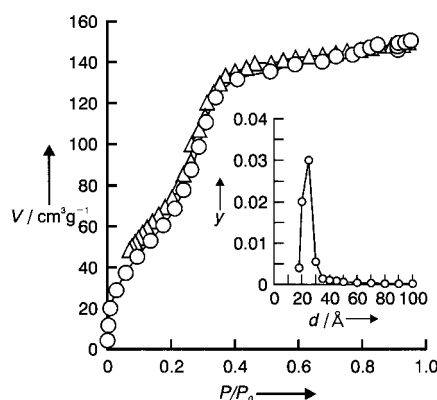


Figure 5. N_2 adsorption ($\circ$) and desorption (Δ) isotherms and pore size distribution (inset) of the acetate-treated mesostructured erbium oxide isolated after a reaction time of 10 h. $y = \Delta V / \Delta d$ [$\text{mL g}^{-1} \text{\AA}^{-1} (\text{STP})$].

exchanged products are porous materials with highly ordered mesopores.

At room temperature, the magnetic susceptibilities of the layered and modulated hexagonal erbium-based surfactant mesophases and of the acetate-exchanged mesoporous erbium oxide were 0.68×10^{-4} , 1.03×10^{-4} , and $1.23 \times 10^{-4} \text{ emu g}^{-1}$, respectively, corresponding to 35, 53, and 64 % of the value of $1.94 \times 10^{-4} \text{ emu g}^{-1}$ for reagent-grade erbium oxide. The magnetic susceptibility ratio of 0.64 for the erbium mesophase relative to bulk erbium oxide is in good agreement with its weight fraction of Er_2O_3 of 0.65, as determined by thermogravimetric analysis (TGA). The magnetic susceptibility ratios of 0.35 and 0.53 for the layered and hexagonal mesophases relative to bulk erbium oxide are less than the weight fractions of Er_2O_3 of 0.45 and 0.57, respectively. Here the dodecyl sulfate to Er molar ratios of the layered and hexagonal mesophases are 2.11 and 0.44, respectively. It is therefore most likely that the magnetic susceptibility of the mesostructured solids, layered or modulated hexagonal, is little affected by the bonding of acetate ions to the rare earth cations, but significantly decreased by the influence of the sulfate groups of incorporated surfactant. The magnetic susceptibility of the rare earth oxide based mesoporous materials is on the order of $10^{-4} \text{ emu g}^{-1}$ and ranges from $0.55 \times 10^{-4} \text{ emu g}^{-1}$ for Gd to 0 emu g^{-1} for Lu via a maximum value of $1.66 \times 10^{-4} \text{ emu g}^{-1}$ for Dy (Table 1). The relative magnetic susceptibilities for the mesoporous solids are also in agreement with the relative values of the squares of theoretical magnetic moments of the corresponding rare earth ions in their free trivalent states^[20] (Table 1). These facts suggest that the mesoporous oxides are paramagnetic materials with rare earth ions in nearly the same electron spin state as in their free trivalent ions. However, in contrast to the typical paramagnetic behavior of bulk erbium oxide, the ac magnetic susceptibility versus temperature curves of the mesostructured rare earth oxides showed a significant minimum near 23–25 K, regardless of whether their structural types is layered or hexagonal, and as-grown or acetate-exchanged (Figure 6). This magnetic anomaly resembles that of spin glasses or mictomagnetic materials and indicates that the paramagnetic ordering of spins at low temperature is

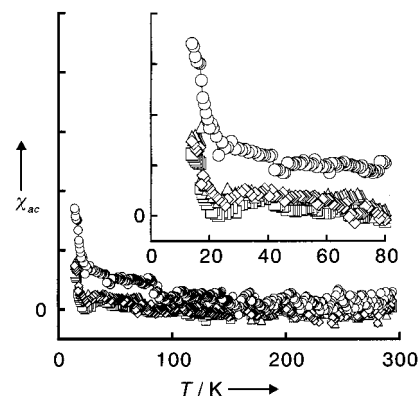
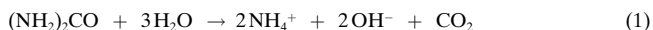


Figure 6. Plots of the ac magnetic susceptibility χ_{ac} against temperature for the bulk ($\circ$), layered ($\square$), as grown hexagonal (Δ) and acetate-treated hexagonal ($\diamond$) mesostructured erbium oxides.

decrystallized by a specific effect due to the mesostructural arrangement of rare earth ions.

Experimental Section

The mesostructured rare earth oxides were synthesized by the homogenous precipitation method with urea. Urea was used to raise the pH value of the solution, because on heating at above 60°C it undergoes hydrolysis [Eq. (1)].



Nitrates of La, Ce, Pr, Nd, Sm, Gd, Dy, Er, Yb, and Lu and chlorides of Eu, Tb, Ho, and Tm were used as rare earth element sources. The structural and morphological properties of the products were little affected by whether nitrate or chloride was the counterion.^[11] Sodium dodecyl sulfate (SDS) $\text{CH}_3(\text{CH}_2)_{11}\text{OSO}_3\text{Na}$ was used as templating agent. Rare earth metal nitrate or chloride, SDS, urea, and water were mixed in a molar ratio of 1:2:30:60 and stirred at 40°C for 1 h to yield a transparent mixed solution. The mixed solution was heated to 80°C and then kept at that temperature. The pH value of the reaction mixture increased due to the hydrolysis of urea, and precipitation occurred. After a reaction time of 3, 10, 20, and 30 h, the resulting mixture was immediately cooled to room temperature to prevent further hydrolysis of urea. After centrifugation, the solid was washed with water a few times and then dried in air.

The surfactant was removed from the mesophases by anion exchange with acetate ions.^[21] The solid (0.5 g) was mixed with a 0.05 M ethanolic solution of sodium acetate (40 mL) and stirred at 40°C for 1 h. The resulting solids were washed with ethanol and dried in air.

Powder X-ray diffraction (XRD) measurements were performed on a Simadzu XD-D1 diffractometer with $\text{CuK}\alpha$ radiation. The IR absorption spectra were measured on KBr pellets with a Nippon Bunko FT/IR-300. Transmission electron microscopy (TEM) was carried out on a Hitachi H-800MU instrument. Scanning electron microscopy (SEM) was performed on a Hitachi H-4100. X-ray micro analysis (XMA) was conducted on a HORIBA EMAX-5770 instrument. Specific surface area was measured by the BET method with N_2 .^[22] Pore size distributions was determined by the Cranston Inkley method.^[23] Thermogravimetric and differential thermal analysis (TG-DTA) was conducted with a SEIKO TG/DTA320U at $10^\circ\text{C min}^{-1}$. The dc and ac magnetic susceptibilities were measured by the field vibration method on a Rikendennshi BHV-35HT magnetometer and by the self-inductance method with a Kokuyo KC-533 LCR meter, respectively.

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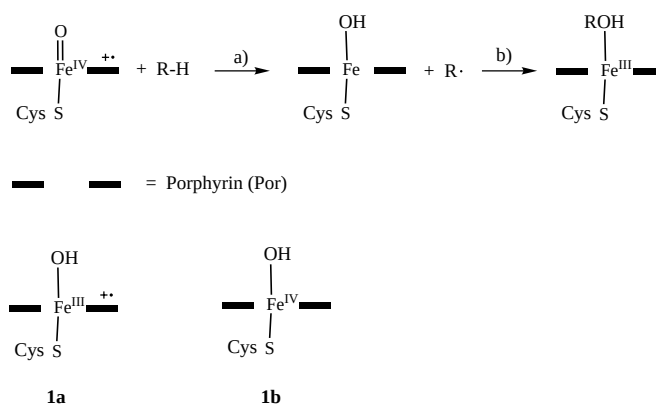
Keywords: magnetic properties • mesophases • mesoporosity • rare-earth compounds • template synthesis

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On the “Rebound” Mechanism of Alkane Hydroxylation by Cytochrome P450: Electronic Structure of the Intermediate and the Electron Transfer Character in the Rebound Step**

Michael Filatov, Nathan Harris, and Sason Shaik*

Alkane hydroxylation is a key process by which the heme enzyme cytochrome P450 metabolizes xenobiotics.^[1] The consensus mechanism (Scheme 1), called the rebound mechanism,^[2] proceeds by an initial hydrogen abstraction from the alkane (RH) by the active ferryl–oxene species (Por⁺Fe^{IV}=O), to form a radical R[•] and a hydroxo–iron complex as intermediates (step a). Subsequently the radical rebounds on the hydroxy group and generates the ferric–alcohol complex (step b). This mechanism is currently under



Scheme 1. Schematic representation of the rebound mechanism, and of the two electromeric forms (**1a** and **1b**) of the hydroxo–iron intermediate.

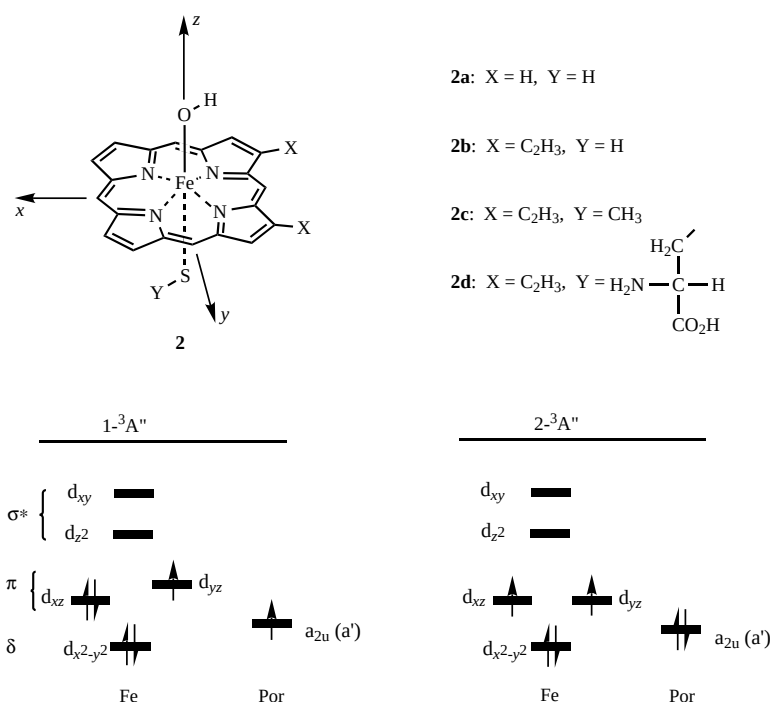
debate due to recent mechanistic studies,^[3] using ultrafast radical clocks to probe the presence of a free radical, that suggest a concerted oxene-insertion mechanism. Nevertheless, quite a few investigations do report results which are consistent with the rebound mechanism.^[2, 4] As such, the mechanism of a very important reaction in the vital system remains not fully resolved.

A great deal of mechanistic research has traditionally focused on whether the radical intermediate exists or not, while very few studies have addressed the nature of the hydroxo–iron species **1** (Scheme 1).^[5] It is important to address the electronic structure of this intermediate, since this has bearing on its reactivity in the rebound step, and hence on an eventual resolution of the mechanistic dilemma as a whole. The ferryl–hydroxo species may exist in two electromeric^[6] forms. In one (**1a**, Scheme 1) the iron appears as a Fe^{III} center to provide a cation radical porphyrin, while the other (**1b**) contains high-valent Fe^{IV} with a neutral porphyrin.^[5, 7] The spin state of the complex may be low ($S=1$), intermediate ($S=2$), or high ($S=3$).^[7c] In addition, due to available alternative occupation modes of the d-orbital block, and of the porphyrin's orbitals (the a_{1u} and a_{2u} types^[8]), there might exist a few closely lying states with different state symmetries. The present paper uses density functional and model solvent calculations to resolve this complex state situation for the hydroxo–iron species, and addresses due implications on the rebound mechanism.

All calculation were performed by use of the JAGUAR 3.5 package.^[9] Benchmark calculations showed that the pure density functional BP86^[10a] and the hybrid (HF/DFT) functional B3LYP levels^[10b] give the same stability ordering for the two electromers, and therefore the rest of the study was performed with B3LYP. Based on previous experience with the oxo iron porphyrin,^[8] reliable spin state ordering of organometallic species can be obtained with moderate basis sets, but geometry optimization is essential since different spin situations may have very different bond lengths between iron and the axial ligands. On iron we used the Los Alamos effective core potential coupled with the double zeta LACVP basis set,^[11] while for the rest of the atoms we utilized the 6-31G basis set. The latter basis set was ascertained against a calculation that used the more flexible LACV3P basis set^[11]

[*] Prof. S. Shaik, Dr. M. Filatov, Dr. N. Harris
Department of Organic Chemistry and
The Lise Meitner-Minerva Center for
Computational Quantum Chemistry
Hebrew University, 91904 Jerusalem (Israel)
Fax: (+972) 2-6585345
E-mail: sason@yfaat.ch.huji.ac.il

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Scheme 2. Model species for the hydroxo-iron intermediate, and orbital diagrams for the electromeric forms 1-³A'' and 2-³A'' (see Table 1).

on iron and 6-311G(d) basis sets on C, N, and H, and which gave the same state ordering for **2a** (Scheme 2).

Scheme 2 shows the species used to model the hydroxo-iron complex. These range from the simplest model (**2a**) to more realistic ones that involve vinyl substituents at the β -pyrrole positions (as in the native protoporphyrin IX), and a cysteinato axial ligand (**2d**). Complete geometry optimization of **2a** showed negligible energetic effects in comparison with a C_s -constrained optimization, which was then adapted wherever possible since it enables clear state assignment.

For all of the model systems we calculated the two electromers 1-³A'' and 2-³A'', where the first possesses an Fe^{III} (d^5 configuration) with a porphyrin cation radical, and the second an Fe^{IV} (d^4 configuration) with a neutral porphyrin. The d-orbital splitting is typical of six-coordination with a "three-below-two" pattern. The lowest orbital in the group of three is the δ -type orbital ($d_{x^2-y^2}$) and the higher two are π -type orbitals (d_{xz} and d_{yz}) while the group of two involves the σ -antibonding d_{z^2} and d_{xy} orbitals.^[12] In Scheme 2 the porphyrin orbital which is singly occupied in 1-³A'' is labeled with its symmetry in the free porphyrin (a_{2u}), as well as in its actual C_s

symmetry (a'). A 1-³A' state can be generated from 1-³A'' by switching the occupations of the d_{xz} and d_{yz} orbitals. In addition, high-spin situations ($S=2, 3$), analogues of 1-³A'' and 2-³A'', were generated by excitations from the π and δ d orbitals to the d_{z^2} and d_{xy} orbitals. The high-spin situations were found to be higher in energy (⁷A' by 4.1 kcal mol⁻¹, ⁵A'' by 7.9 kcal mol⁻¹, and ⁵A' by 19 kcal mol⁻¹) relative to the lowest triplet state. An alternative to 1-³A'' is the triplet state, where the singly occupied porphyrin orbital^[8] is a_{1u} -type (a''). This state was tested too and found to be 16.3 kcal mol⁻¹ higher than 1-³A''. Since all these states are significantly higher than the ones shown in Scheme 2, they are not discussed any further here.

Table 1 shows relative energies and key structural parameters for the three triplet states of the ferryl-hydroxo species. It is seen that the two electromers 1-³A'' and 2-³A'' are very close in energy to within ± 1 kcal mol⁻¹, with a small preference for one state or the other, depending on substituents, and in general agreement with a recent theoretical analysis.^[13] The small substituent effect on the relative energy of the two states is in line with the size of the a' (a_{2u}) porphyrin orbital

coefficients, which are small at the α - and β -pyrrole positions. On the other hand, the 1-³A' state (with the $d_{xz}^1 d_{yz}^2$ population) is significantly higher in energy, as might be expected from four-electron Pauli repulsion due to interaction of the sulfur and/or oxygen lone pairs with the filled d_{yz} orbital on iron. The Fe-O and Fe-S axial bond lengths in the 1-³A'' Por⁺Fe^{III}OH state are longer than in the 2-³A'' PorFe^{IV}OH state, a trend which is again expected from the higher Pauli repulsion between the lone pair electrons and the d_{yz}/d_{xz} electrons in the former state.

Mixing of the two ³A'' states is symmetry-permitted. However, since the a_{2u} (a') porphyrin orbital and the d_{yz} (a'') orbital are spatially separated and of different symmetry, the state mixing is expected to be rather small, and we may regard the two states as virtually pure ones rather than as resonance structures. To assess the barrier between the two states, which differ by single electron transfer from the iron to the porphyrin, we calculated the vertical energy separation of the two states. The vertical energy gap between 1-³A'' and 2-³A'' at the geometry of the former is 1.21 kcal mol⁻¹ for **2a**, 1.10 kcal mol⁻¹ for **2b**, and 3.48 kcal mol⁻¹ for **2c**. With such

Table 1. Bond lengths [$\text{\AA}$] and relative energies E_{rel} [kcal mol⁻¹] of the lowest states of the hydroxo-iron complex (see Scheme 2).

Species	State 1- ³ A'' (1- ³ A'), Por ⁺ Fe ^{III} OH ^[a]				State 2- ³ A'', Por Fe ^{IV} OH ^[a]			
	Fe-O	Fe-S	Fe-N ^[b]	E_{rel}	Fe-O	Fe-S	Fe-N ^[b]	E_{rel}
2a	1.829 (1.869)	2.458 (2.529)	2.017 (2.012)	0.00 (+8.67)	1.816	2.361	2.012	-0.34
2b	1.828 (1.870)	2.460 (2.526)	2.018 (2.013)	0.00 (+9.03)	1.817	2.362	2.013	-0.77
2c	1.817 (-)	2.540 (-)	2.015 (-)	0.00 (-)	1.824	2.353	2.014	+0.11
2d	1.810 (-)	2.530 (-)	2.015 (-)	0.00 (-)	1.808	2.336	2.009	+2.30
2a^[c]	1.829	2.458	2.017	0.00	1.816	2.361	2.012	+13.9

[a] Upon removal of the C_s constraints, the S-H and O-H bonds in the 2-³A'' structure assume a dihedral angle of 90° and the energy is lowered by 1.2 kcal mol⁻¹. Electromer 1-³A'' is stabilized by 0.54 kcal mol⁻¹. [b] Average value. [c] Calculated with the SCRF solvation model. Note that the bond lengths are the same as for **2a**, but the relative energies are different.

small vertical energy gaps, the two electromers are expected to be fluxional with a very small barrier for interconversion.

Since the computed dipole moment of the $1^{-3}A''$ ($\text{Por}^{+}\text{Fe}^{\text{III}}\text{OH}$) electromer (1.31 D) is larger than that of the $2^{-3}A''$ ($\text{PorFe}^{\text{IV}}\text{OH}$) electromer (1.17 D), and since the cation radical situation in the former state will endow it as well with a high polarizability, the state ordering will certainly change in the electric field environment of the protein.^[14] To mimic an environment with a dielectric, we used the SCRF solvation model (with water as solvent). While this is certainly a crude model, it is nevertheless likely to reveal the expected trend in the state ordering when the states are taken from an isolated molecular situation to an environment with a finite dielectric constant. As can be seen from the last entry in Table 1, the dielectric environment stabilizes the $1^{-3}A''$ ($\text{Por}^{+}\text{Fe}^{\text{III}}\text{OH}$) electromer relative to the $2^{-3}A''$ one, and makes it the ground state of the ferryl–hydroxo species. This result is in accord with experimental data by Groves et al.,^[5] who demonstrated that the electrochemical oxidation of $\text{PorFe}^{\text{III}}\text{OH}$ derivatives is porphyrin-centered, leading to $\text{Por}^{+}\text{Fe}^{\text{III}}\text{OH}$. In a condensed-phase environment we may also expect significant barriers for the interconversion of the two electromers. Analogous electromers ($\text{Por}^{+}\text{Fe}^{\text{III}}\text{OCH}_2\text{CHPh}$ vs. $\text{PorFe}^{\text{IV}}\text{OCH}_2\text{CHPh}$) have been discussed recently in the epoxidation of styrene by model iron porphyrin complexes.^[15]

The electronic structure of the hydroxo–ferryl complex has bearing on the reactivity of the rebound step (Scheme 1). Inspection of Scheme 2 shows that the hydroxo–iron intermediate commences with a porphyrin hole in the a_{2u} orbital. In the alcohol product, $\text{PorFe}^{\text{III}}\text{O}(\text{H})\text{R}$, the porphyrin gains an electron and its a_{2u} orbital becomes doubly occupied.^[8] This electron is lost from the alkyl radical, which acquires a positive oxidation state upon R–O bond formation.^[16] Hence, the radical coupling will be attended by an electron shift, whereby the attacking alkyl group forms an R–O bond with concomitant loss of an electron, which is shifted to fill the porphyrin hole (in $1^{-3}A''$). In the rebound step the intermediate species can couple into either a doublet ground state or a higher lying quartet state of the ferric–alcohol product (Scheme 1).^[8, 17] The barrier may occur on one of these spin surfaces, or on both; this is something which has to be deciphered in a separate study.^[17] Be this as it may, the rebound barrier is expected to depend inter alia on the oxidation potential of the alkyl group, and to increase as the alkyl group is made a poorer electron donor. Such a trend may provide a rationale for the observations that the hydroxylation of 1-alkyl-2-aryl-cyclopropane derivatives, which are radical-clock precursors, exhibits decreasing skeletal rearrangement in the alcohol product as the putative radical intermediate becomes a better electron donor.^[3]

A theoretical investigation of the entire rebound process in the electric field of the protein will be required^[18] for a more complete elucidation of the rebound mechanism. Nevertheless, with its obvious limitations, the present study provides straightforward characterization of the electronic structure of the putative intermediate in the mechanisms as well as of the electron transfer attending the rebound step, and can thereby form a basis for experimental investigation of the rebound step. Substituted iron porphyrin derivatives,^[19] different axial

ligands,^[15] medium effect, and different radical probes can provide a powerful mechanistic arsenal towards this goal.

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Experimental Evidence for the Existence of Neutral P₆: A New Allotrope of Phosphorus**

Detlef Schröder,* Helmut Schwarz,* Matthias Wulf, Heinrich Sievers, Peter Jutzi,* and Markus Reiher

Dedicated to Professor Hans-Jürgen Quadbeck-Seeger on the occasion of his 60th birthday

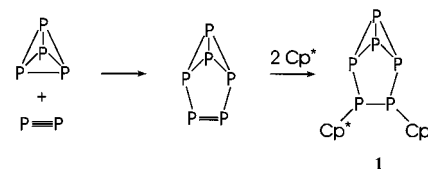
Despite the cross-relationship to carbon and the neighboring position of sulfur, experimental evidence for the existence of molecular allotropes of phosphorus P_n with *n* larger than 4 is scarce. In contrast, numerous computational studies on small phosphorus clusters such as hexaphosphabenzene and cubic P₈ have been performed since the 1980s.^[1, 2] More recent theoretical studies of phosphorus clusters^[3] also included ionic species such as cyclic P₅[−],^[4] anionic P_n[−] clusters with *n* = 1–9,^[5] P_(2*n*+1)⁺ cations with *n* = 3–5^[6] as well as multiply charged phosphorus species, for example cyclic P₇^{3−}.^[7] Far fewer experimental facts are known about phosphorus clusters larger than P₄. Positively charged P_n⁺ with *n* up to 89 and P_n[−] anions (*n* ≤ 49) have been produced by laser ablation of red phosphorus.^[8] Admixture of other elements to phosphorus in the laser-ablation process also affords the formation of heteronuclear clusters X_mP_n (X = B, C, Al, Si, Co, Ni).^[8, 9] Further, a PtP₆⁺ cation has recently been generated in the successive dehydrogenation of phosphane by bare platinum ions.^[10]

The most salient experimental information about the energetics of phosphorus clusters is so far provided by the photoelectron detachment spectra of P_n[−] anions (*n* = 1–9);^[5] for the P₆[−] species of interest here, a vertical electron binding energy of 2.22 ± 0.05 eV was determined.

While knowledge about molecular allotropes of phosphorus larger than P₄ is limited, a huge variety of polyphosphane derivatives is known, and the research conducted by Baudler and co-workers^[11] is representative in this respect.^[12] Here we report the use of such a polyphosphane derivative to probe the existence of the neutral P₆ molecule in the gas phase by means of neutralization–reionization (NR)^[13] mass spectrometry.

The synthesis of the tricyclic polyphosphane **1** was described in 1989.^[14] Compound **1** contains a P₆ unit having a benzvalene skeleton with two η¹-coordinated pentamethylcy-

clopentadienyl (Cp*) ligands. Conceptually, structure **1** can be viewed as arising from a formal [2+2] cycloaddition of a P₂ unit to a P₄ tetrahedron followed by saturation of the remaining P–P double bond in the hexaphosphabenzvalene with two Cp* ligands (Scheme 1). Conversely, **1** might serve as a precursor for the generation of P₆ due to the leaving-group character of the Cp* moiety,^[15] provided that P₆ is (at least kinetically) stable with respect to the dissociation into P₄ and P₂; the atomization energies calculated by Jones and Hohl predict the dissociation P₆ → P₄ + P₂ to be endothermic by about 1 eV.^[3a]



Scheme 1. Hypothetical cycloaddition of P₂ and P₄ to hexaphosphabenzvalene and its stabilization by two Cp* ligands resulting in **1**.

Electron ionization (EI) of gaseous **1** affords a molecular ion along with Cp*P₆⁺ and Cp*⁺ as major fragments.^[14] Not surprisingly, loss of one Cp* unit to afford Cp*P₆⁺ prevails in the unimolecular dissociation of the metastable radical cation **1**^{•+}.^[16] In the present context, the Cp*P₆⁺ cation is of particular interest. Unimolecular dissociation of the metastable ion Cp*P₆⁺ affords Cp*P₂⁺ and Cp*⁺ fragments in a ratio of about 10:1 (Figure 1 a), corresponding to formal losses of P₄ and P₆, respectively. The latter dissociation gains in importance upon collisional activation (CA) of Cp*P₆⁺ (Figure 1 b) in that the Cp*P₂⁺:Cp*⁺ ratio decreases to 1.5:1. Abundant

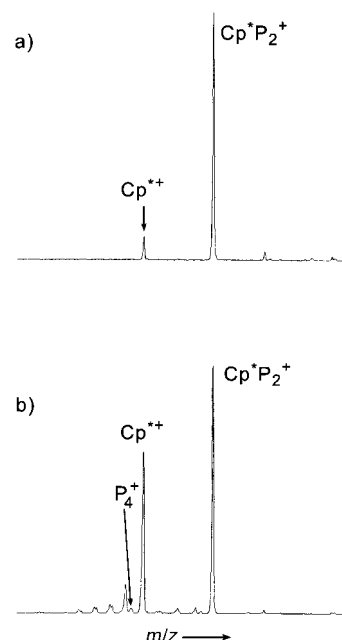


Figure 1. a) Metastable ion and b) collisional activation mass spectra (collision gas: helium) of B(1)/E(1)-mass-selected Cp*P₆⁺ generated by dissociative electron ionization of **1**. Note the characteristic series of hydrocarbon fragments C_mH_n⁺ at lower masses due to consecutive decay of ionized Cp*.

[*] Dr. D. Schröder, Prof. Dr. H. Schwarz
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-10623 Berlin (Germany)
Fax: (+49) 30-314-21102
E-mail: df@www.chem.tu-berlin.de
schw0531@www.chem.tu-berlin.de

Prof. Dr. P. Jutzi, M. Wulf, Dr. H. Sievers
Fakultät für Chemie der Universität
Universitätsstrasse 25 D-33615 Bielefeld (Germany)
Fax: (+49) 521-1066026
Dr. M. Reiher
Lehrstuhl für Theoretische Chemie der
Universität Erlangen-Nürnberg (Germany)

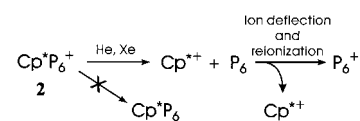
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signals corresponding to P_n^+ cations are not observed in either the CA or the EI spectra. This finding is in accordance with the assumption that the ionization energies (IEs) of phosphorus clusters are larger than that of the Cp^* radical. For example, even for the unsubstituted cyclopentadienyl radical, $IE(Cp) = 8.4$ eV is well below $IE(P_4) = 9.1$ eV^[19] and equals the computed $IE(P_6) = 8.4$ eV of the benzvalene structure;^[7b] complete methylation is safely assumed to further reduce the IE of the cyclopentadienyl unit. Formation of Cp^{*+} as a product of the unimolecular dissociation of $Cp^*P_6^+$ suggests the interesting perspective that an intact P_6 molecule is lost as a neutral species. However, sequential evaporation of P_4 and P_2 according to 1) $Cp^*P_6^+ \rightarrow Cp^*P_2^+ + P_4$ and 2) $Cp^*P_2^+ \rightarrow Cp^{*+} + P_2$ cannot be ruled out, and loss of neutral P_2 indeed constitutes a major process in the dissociation of $Cp^*P_2^+$.

The possible formation of neutral P_6 can only be monitored if a technique is used which samples the neutral species liberated upon dissociation of $Cp^*P_6^+$. The "ideal" experiment for this task is collision-induced dissociative ionization (CIDI),^[20] in which the neutral species formed upon dissociation of metastable ions are selectively ionized. Unfortunately, however, the CIDI method is not very sensitive, and no useful CIDI spectra were obtained for metastable $Cp^*P_6^+$. Instead, we examined $Cp^*P_6^+$ by means of neutralization–reionization (NR) mass spectrometry,^[13] in which two electron transfer events occur sequentially: First the ion of interest is neutralized in a high-energy collision with a suitable target gas, and the remaining ions are deflected, then the pure beam of neutral molecules is reionized in a second collision event, and the ions formed are mass-analyzed and detected; here, reionization to cations is applied.^[13]

The NR spectra of $Cp^*P_6^+$ are unexpectedly dominated by P_n^+ fragments ($n = 1–6$); hydrocarbon fragments due to the cyclopentadienyl ligand are almost absent (Figure 2). This result implies that only minor amounts of neutral C_mH_n

fragments are formed in the experiments. To achieve further insight, two different collision gases were used for neutralization, xenon (Figure 2a) and helium (Figure 2b). Xenon (IE = 12.1 eV) is known to serve as a versatile collision gas for the neutralization of cations.^[13] In the present case, neutralization of $Cp^*P_6^+$ would result in formation of neutral $Cp^*P_6^{\cdot}$ radical; whether or not this neutral is long-lived, it should inevitably give rise to $C_mH_n^+$ fragments upon reionization (c.f. the predominance of $C_mH_n^+$ over P_n^+ signals in Figure 1b). This is not observed experimentally (Figure 2a), and thus it appears as if neutralization does not take place to a major extent. According to arguments outlined by Wesdemiotis and co-workers,^[21] the use of helium in the first collision almost prevents neutralization because, even in a high-energy collision event, $IE(He) = 24.5$ eV is much too large to allow for efficient electron transfer from He to the cation under study. Instead, the high-energy collision with helium prompts dissociation of the cation, whose neutral fragments are reionized in the second step. Consequently, the resulting reionization spectrum contains information about the neutral fragments; Wesdemiotis and co-workers coined this variant of NR as neutral fragment reionization (NfR). The clean P_n^+ pattern ($n = 1–6$) observed in Figure 2b fully supports this conjecture. Accordingly, neutralization of $Cp^*P_6^+$ seems to be particularly unfavorable, and instead dissociation of the cation predominates. The distinctive P_6^+ signals in Figures 2a and 2b can thus be associated with the reionization of intact neutral P_6 , which is inter alia formed upon collision-induced dissociation of the $Cp^*P_6^+$ cation (Scheme 2). This scenario also accounts for the different signal-to-noise ratios in



Scheme 2. Competition between fragmentation and electron transfer in high-energy collisions of $Cp^*P_6^+$.

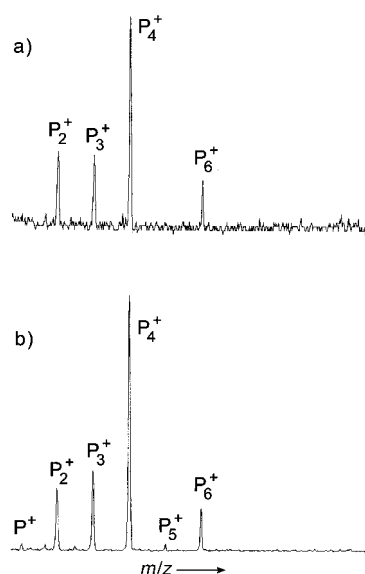


Figure 2. Neutralization–reionization mass spectra of B(1)/E(1)-mass-selected $Cp^*P_6^+$ generated by dissociative electron ionization of **1**; a) collision gases: xenon and oxygen, b) collision gases: helium and oxygen.

Figures 2a and 2b, because collision-induced dissociation of keV ions is much more effective for helium than for xenon in sector mass spectrometers. Further support for the presence of intact P_6 is provided by the fact that the P_n^+ signals for the even-numbered clusters ($n = 4$ and 6) are much more abundant than for the P_5^+ fragment, which would require loss of a phosphorus atom, even though the latter has a lower IE^[2] and prevails over P_4^+ and P_6^+ upon direct laser vaporization of phosphorus.^[22]

These experiments provide firm evidence for the existence of neutral P_6 in the gas phase with a minimal lifetime on the order of microseconds. These experiments, however, cannot provide any information concerning the structure of the neutral species. Nevertheless, the use of **1** as a precursor suggests a benzvalene skeleton. Moreover, preliminary calculations using density functional theory indicate that the benzvalene structure of the P_6 unit remains intact in the $Cp^*P_6^+$ cation.^[23] Last but not least, benzvalene structures were also predicted as the global minima in ab initio calculations of anionic,^[5] neutral,^[3, 7] and cationic hexaphos-

phorus.^[7] Consequently, it appears reasonable to assume a benzvalene structure for the neutral P_6 species formed from $Cp^*P_6^+$, which is then monitored as a cation upon vertical electron transfer in the reionization step.

Returning to the conceptual description shown in Scheme 1, the presence of a P–P double bond suggests a high reactivity of neutral P_6 , which is likely to prevent its isolation as bulk substance in the condensed phase. Besides the stabilization of the P_6 unit by covalent bonding to organic ligands, as realized in **1**, a dimerization of P_6 is also conceivable which could result in a polycyclic P_{12} allotrope which no longer possesses P–P double bonds,^[3f] and may thus be less reactive and possibly stable towards dissociation into three P_4 molecules.

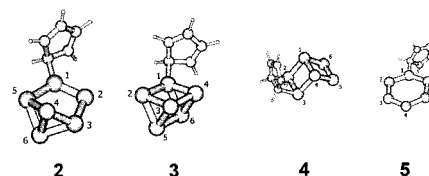
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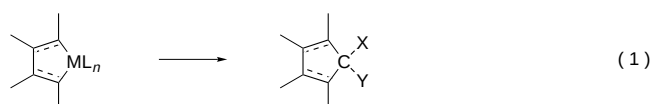


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A Titanacycle-to-Carbocycle Relay Leading to an Expedient Synthesis of Cyclopentadienols**

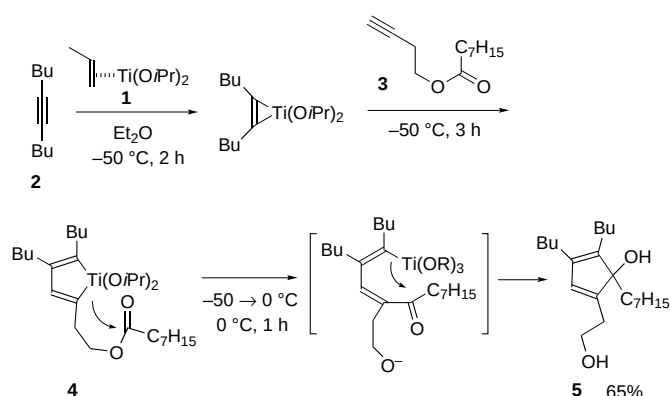
Hirokazu Urabe, Miho Narita, and Fumie Sato*

Five-membered metallacycles of a Group 4 element such as the one shown in Equation (1) ($M = \text{Ti}, \text{Zr}$) are well-known and readily accessible.^[1] Conversion of these metallacycles into carbocycles, where the metal is eventually replaced with a carbon atom, is an attractive method for the construction of five-membered carbocycles. Formation of the corresponding



carbonyl compound by treatment of the metallacycles with carbon monoxide or isocyanides^[1–3] and the equivalent reaction with triphosgene ($\text{O}=\text{C}(\text{OCCl}_3)_2$)^[4] should be the most representative and useful entry to this reaction [Eq. (1); $\text{ML}_n = \text{ZrCp}_2, \text{TiCp}_2, \text{Ti}(\text{O}i\text{Pr})_2$; $\text{CXY} = \text{CO}$]. However, other variations of the reaction are notably limited.^[5] We report here a new entry to this transformation starting with a titanacyclopentadiene.

The coupling of acetylenes **2** and **3** with $[(\eta^2\text{-propene})\text{-Ti}(\text{O}i\text{Pr})_2]$ (**1**),^[6, 7] which is readily prepared from $[\text{Ti}(\text{O}i\text{Pr})_4]$ and $i\text{PrMgCl}$ in situ,^[8] generates the titanacyclopentadiene **4** at low temperature (Scheme 1).^[7] When the reaction mixture



Scheme 1.

was simply allowed to warm up to 0°C , tandem addition of the two carbon–titanium bonds of **4** to the ester group of the same molecule^[9, 10] took place to furnish the cyclopentadienol **5** in good yield. Thus, this simple operation has achieved the aforementioned metallacycle-to-carbocycle process [Eq. (1)] without any further manipulation.

[*] Prof. Dr. F. Sato, Dr. H. Urabe, M. Narita
Department of Biomolecular Engineering
Tokyo Institute of Technology
4259 Nagatsuta-cho, Midori-ku, Yokohama
Kanagawa 226–8501 (Japan)
Fax: (+81) 45-924-5826
E-mail: fsato@bio.titech.ac.jp

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The scope of this transformation can be seen in Table 1. For a 1-silyl-1-alkyne, the product was obtained as a single regioisomer and arises from the highly regioselective cross-coupling reaction of the two different acetylenes (entries 3 and 5). Even though the reaction is conducted in the presence

Table 1. Preparation of cyclopentadienols.

Entry	Substrates	Product	Yield [%]
1			49
2			65
3			49
4			57
5			54

of a low-valent titanium reagent and/or a Grignard reagent, the iodoalkyl moiety of the starting materials was not affected; the desired (iodoalkyl)cyclopentadienols, which are useful precursors for the subsequent ring closure (see below), are obtained without decrease in yields (entries 4 and 5). In addition to the synthesis of monocyclic compounds, five- and six-membered ring-fused cyclopentadienols could be readily prepared as well from diynol esters (Table 2).

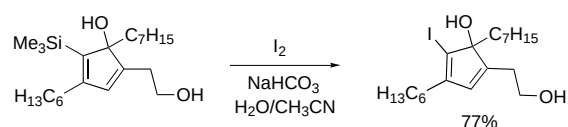
Cyclopentadienols^[11] should be interesting intermediates for further synthetic elaboration, because up to five carbon atoms can be fully functionalized. Some reactions are exemplified in the following. A silylcyclopentadienol was iodinated with I_2 in the presence of aqueous NaHCO_3 to give the corresponding iododiene (Scheme 2). Scheme 3 illustrates hydrogenation followed by ring closure, directly giving a bicyclic tetrahydrofuran.

Intramolecular carbometalation^[12] to the dienol moiety proved to be quite useful for obtaining fused ring systems, as shown in Schemes 4 and 5. Thus, the lithiation of the substrate having an iodoalkyl side chain first with $n\text{BuLi}$ ($\text{OH} \rightarrow \text{OLi}$) and then with $t\text{BuLi}$ ($\text{CH}_2\text{I} \rightarrow \text{CH}_2\text{Li}$) induced the regioselective carbolithiation of the diene together with the elimination of the hydroxy group to give the bicyclic product (Scheme 4). In the case of a bicyclic starting material, the above carbolithiation was unsatisfactory, but the addition of a catalytic amount of a copper salt permitted the reaction to proceed smoothly, again in a highly regioselective manner to give the single tricyclic compound in good yield (Scheme 5).

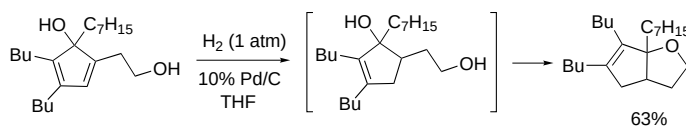
Besides the method shown in Scheme 5 for preparing tricyclic compounds, the aforementioned titanium-mediated

Table 2. Preparation of fused-ring cyclopentadienols.

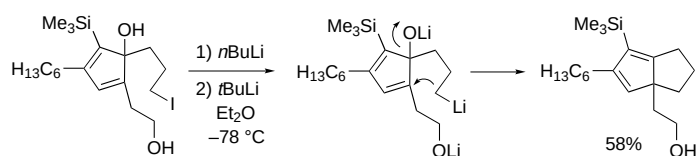
Entry	Diynol esters	Product	Yield [%]
1			70
2			56
3			51
4			76
5			85



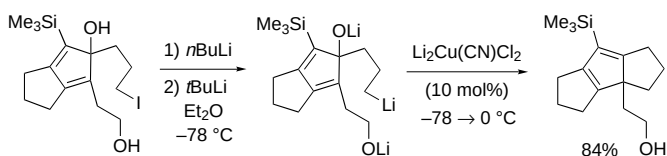
Scheme 2.



Scheme 3.

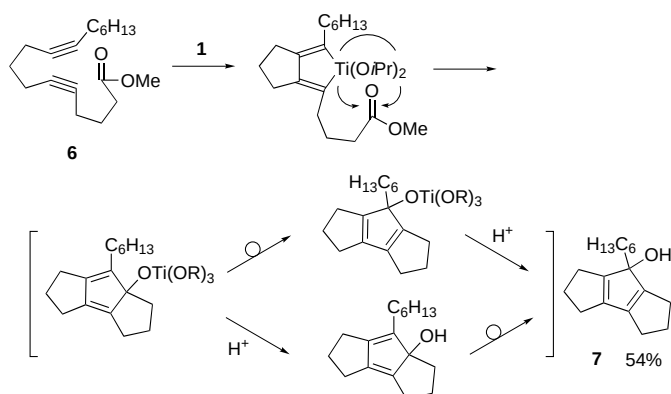


Scheme 4.



Scheme 5.

cyclization itself serves this purpose in a more straightforward manner. Thus, **1**-mediated cyclization of an open-chain precursor, diynolate **6**, afforded a tricyclic compound **7** in one step (Scheme 6). It should be noted that the positions of



Scheme 6.

the hydroxy group and the carbon–carbon double bonds in the resultant cyclopentadienol **7** are different from that expected from the results in Tables 1 and 2, most likely due to the isomerization before or during the workup.

In summary, the reaction shown here represents an example of the facile conversion of titanacyclopentadienes into cyclopentadienols, the preparation of which otherwise entails a tedious procedure. The construction of condensed bi- or tricyclic systems has been achieved by the tandem cyclization^[9] of the bis-acetylenic substrates, and it is also based on the resultant cyclopentadienols. The very low cost of the titanium reagent and the simple laboratory operation will encourage further applications of the present method in organic synthesis.^[13]

Experimental Section

Typical procedure (entry 1 in Table 2): To a stirred solution of pentadeca-3,8-diynyl propionate (30 mg, 0.109 mmol) and [Ti(OiPr)₄] (0.039 mL, 0.131 mmol) in Et₂O (1.5 mL) was added *i*PrMgCl (1.54 M in Et₂O, 0.170 mL, 0.262 mmol) at –78 °C under argon. After stirring for 30 min, the solution was allowed to warm to –50 °C over 30 min and kept at this temperature for 3 h. After the solution was allowed to reach 0 °C and then stirred at 0 °C for an additional 10 min, the reaction was terminated by the addition of aqueous 1 N HCl at 0 °C. The organic layer was separated, washed with aqueous NaHCO₃ solution, dried (Na₂SO₄), and concentrated to an oil. The crude product was purified by chromatography on silica gel (pretreated with 5% NEt₃ in hexane and then eluted with diethyl ether/hexane containing a trace amount of NEt₃) to afford 3-ethyl-2-hexyl-4-(2-hydroxyethyl)-1,4-bicyclo[3.3.0]octadien-3-ol (22 mg, 70%) as a colorless oil, which was fully characterized by IR and ¹H and ¹³C NMR spectroscopy and elemental analysis.

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Development of New Chiral P,N Ligands and Their Application in the Cu-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to Enones**

Xinquan Hu, Huilin Chen, and Xumu Zhang*

The conjugate addition of various organometallic reagents to enones is one of the most widely used synthetic methods for carbon–carbon bond formation.^[1] Many chiral auxiliaries or stoichiometric reagents have been reported for highly stereoselective 1,4-additions. Great attention has been devoted recently to developing enantioselective catalytic 1,4-addition reactions.^[2] Chiral copper, nickel, and other metal complexes have been investigated as catalysts for enantioselective additions of organolithium, Grignard, and diorganozinc reagents to enones.^[3] Most notable among these reagents are the chiral phosphorus–Cu^I complexes, for example, Feringa's chiral phosphoramidite,^[4] which have proven effective for enantioselective conjugate additions to cyclic enones. In addition, several other efficient enantioselective Michael addition reactions with cyclic enones have been described.^[5] In contrast to the cyclic enones, highly enantioselective Cu-catalyzed conjugate addition (> 95 % *ee*) to acyclic enones has not been realized (*ee* values around 90 % have been reported in several promising systems^[3d, 4a]). Because strong substrate dependence is quite common for asymmetric carbon–carbon bond forming reactions catalyzed by transition metals, the development of new chiral ligands plays a pivotal role for overcoming this substrate limitation. Herein we report the synthesis of novel chiral P,N ligands for highly enantioselective Cu-catalyzed conjugate addition of diethylzinc to acyclic enones. In addition, these P,N ligands are also very efficient for the Cu-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one.

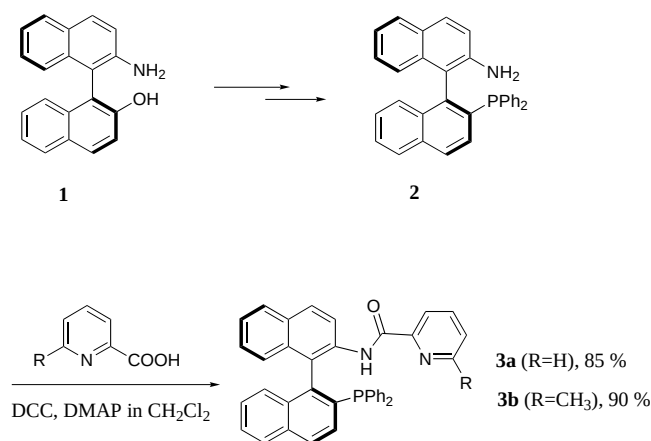
A number of chiral P,N ligands have been developed for transition metal-catalyzed asymmetric reactions.^[6] Pfaltz et al.^[4c] and Stangeland and Sammakia^[7] have applied chiral oxazoline–phosphite and oxazoline–phosphane ligands to Cu-catalyzed conjugate addition of organometallics to enones. We are particularly interested in exploring new chiral motifs to build effective P,N ligands for broad applications in asymmetric catalysis. Chiral 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN, **1**; see scheme 1) developed by Kocovsky et al. has proven to be an excellent framework for construct-

[*] Prof. X. Zhang, X. Hu
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: xumu@chem.psu.edu

Prof. H. Chen
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
Dalian, 116023 (P.R. China)

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ing chiral ligands.^[8] Several synthetic routes and resolution methods have been developed for synthesizing NOBIN in large quantity.^[8c, 9] One of the most notable applications is its use as the chiral backbone in the chiral aldol catalyst of Carreira et al.^[10] The combination of a diarylphosphane group with a substituted pyridine in a chiral binaphthyl system may lead to useful ligands, and we have derived a new family of chiral P,N ligands from **2** as shown in Scheme 1. The two chiral



Scheme 1. Synthesis of novel chiral P,N ligands.

P,N ligands (*S*)-(+)-2-(2-pyridinylcarboxamido)-2'-(diphenylphosphanyl)-1,1'-binaphthyl (**3a**) and (*S*)-(+)-2-(6-methyl-2-pyridinylcarboxamido)-2'-(diphenylphosphanyl)-1,1'-binaphthyl (**3b**) are prepared in high yields from the previously reported compound **2**.^[8c] A major difference of these chiral P,N ligands (**3**) over other chiral P,N ligands^[6] is their

relatively large bite angle when binding to transition metals. The rigid amide linker in **3** provides conformational rigidity of the biaryl ligand, which may be important for effective chiral induction.

We selected 2-cyclohexen-1-one as a typical substrate to develop optimal reaction conditions (Table 1). The enantioselective 1,4-addition of diethylzinc to 2-cyclohexen-1-one gives better conversion and enantioselectivity in nonpolar solvents than in coordinating solvents such as THF (entries 1–3 versus entry 4). Mixed solvent systems can also be used to achieve good conversion and enantioselectivity (entries 5–7). Interestingly, removal of the dissociated CH₃CN during catalyst preparation also helps to increase the conversion and enantioselectivity when [Cu(CH₃CN)₄]BF₄ is used as the catalyst precursor (entry 6 versus entry 5). By lowering the reaction temperature from 0 to –20 °C (entry 7) an 85 % *ee* could be obtained when **3a** was used as the chiral P,N ligand. Since removing CH₃CN is needed with the [Cu(CH₃CN)₄]BF₄ catalyst precursor, we chose to use Cu complexes with noncoordinating ligands such as Cu(OTf)₂ and [Cu(OTf)₂]₂·C₆H₆ (entries 9 and 10). Our results show that [Cu(OTf)₂]₂·C₆H₆ is an excellent precursor, which gives a quantitative yield of the 1,4-conjugate addition product with high enantioselectivity (entry 10). The conjugate addition can also be carried out at room temperature, albeit with a lower enantioselectivity (entry 11). The optimal reaction temperature for obtaining high enantioselectivity is –20 °C (entries 12 and 13). This enantioselective conjugate addition is apparently a ligand-accelerated process.^[11] The enantioselectivity when the ratio of **3a**:Cu = 2.5:1 is significantly higher than the result obtained with the ratio of **3a**:Cu = 1.25:1 (entry 12 versus 14). The addition of more than two equiv-

Table 1. Cu-catalyzed enantioselective 1,4-conjugate addition of Et₂Zn to 2-cyclohexen-1-one.^[a]

Entry	Cu precursor	Solvent	<i>T</i> [°C]	3a :Cu	Conv. [%] ^[b]	<i>ee</i> [%] ^[b]
1	[Cu(CH ₃ CN) ₄]BF ₄	toluene	0	2.5:1	82	82
2	[Cu(CH ₃ CN) ₄]BF ₄	Cl(CH ₂) ₂ Cl	0	2.5:1	58	78
3	[Cu(CH ₃ CN) ₄]BF ₄	CH ₂ Cl ₂	0	2.5:1	40	62
4	[Cu(CH ₃ CN) ₄]BF ₄	THF	0	2.5:1	11	56
5	[Cu(CH ₃ CN) ₄]BF ₄	toluene/Cl(CH ₂) ₂ Cl (2/1)	0	2.5:1	76	70
6 ^[c]	[Cu(CH ₃ CN) ₄]BF ₄	toluene/Cl(CH ₂) ₂ Cl (2/1)	0	2.5:1	91	76
7 ^[c]	[Cu(CH ₃ CN) ₄]BF ₄	toluene/Cl(CH ₂) ₂ Cl (2/1)	–20	2.5:1	95	85
8 ^[c]	[Cu(CH ₃ CN) ₄]BF ₄	toluene/Cl(CH ₂) ₂ Cl (2/1)	–20	3b :Cu = 2.5:1	98	92
9	Cu(OTf) ₂	toluene	0	2.5:1	100	72
10	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	0	2.5:1	100	82
11	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	25	2.5	100	65
12	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	–20	2.5:1	55	87
13	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	–40	2.5:1	41	77
14	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	–20	1.25:1	72	72
15	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	–20	5.0:1	76	91
16 ^[d]	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	–20	2.5:1	100	89
17 ^[d]	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene	–20	3b : Cu = 2.5:1	100	89
18	[Cu(OTf) ₂] ₂ ·C ₆ H ₆	toluene/Cl(CH ₂) ₂ Cl (2/1)	–20	3b :Cu = 2.5:1	100	87

[a] The reaction was carried out at 0 °C for 12 h with 1.0 mmol of the substrate and 1 mol % of Cu precursor in 3 mL of solvent. [b] The conversions were measured by GC analysis and *ee* values were determined by GC on a Cyclodextrin column with a chiral phase; the absolute configuration was determined by comparison with literature values.^[12] [c] With removal of CH₃CN under vacuum after preparation of the [Cu(**3a**)] complex. [d] The reaction was run for 48 h. – Tf = trifluoromethanesulfonyl.

Table 2. Cu-catalyzed enantioselective 1,4-conjugate addition.^[a]

$$R^1-CH=CH-C(=O)R^2 + Et_2Zn \xrightarrow[\text{solvent, } -20^\circ\text{C, 48 h}]{[Cu(OTf)]_2 \cdot C_6H_6 / \mathbf{3a} \text{ or } \mathbf{3b}} R^1-CH_2-CH(R^2)-C(=O)R^2$$

Entry	R ¹	R ²	Ligand	Solvent	Yield [%]	ee [%] ^[b]	Config. ^[c]
1	Ph	Ph	3a	toluene/Cl(CH ₂) ₂ Cl (2/1)	92	83	S
2	Ph	Ph	3b	toluene/Cl(CH ₂) ₂ Cl (2/1)	85	96	S
3	Ph	Ph	3b	toluene	72	94	S
4	Ph	4-CH ₃ O-C ₆ H ₄	3b	toluene/Cl(CH ₂) ₂ Cl (2/1)	69	97	— ^[d]
5	Ph	4-CH ₃ O-C ₆ H ₄	3b	toluene	10	90	— ^[d]
6	4-CH ₃ O-C ₆ H ₄	Ph	3b	toluene/Cl(CH ₂) ₂ Cl (2/1)	97	98	S
7	4-Cl-C ₆ H ₄	Ph	3b	toluene/Cl(CH ₂) ₂ Cl (2/1)	72	95	+ ^[d]
8	Ph	4-Cl-C ₆ H ₄	3b	toluene/Cl(CH ₂) ₂ Cl (2/1)	70	95	— ^[d]
9	Ph	CH ₃	3b	toluene/Cl(CH ₂) ₂ Cl (2/1)	70	90	S
10	iPr	CH ₃	3b	toluene	53	86	+ ^[d]

[a] The reaction was carried out at -20°C for 48 h in 1 mL of toluene and 0.5 mL of ClCH₂CH₂Cl (substrate (0.5 mmol):[Cu(OTf)]₂·C₆H₆:ligand = 1:0.01:0.05), or in 1.5 mL of toluene. [b] The ee values were determined by chiral-phase HPLC. [c] The absolute configuration was assigned by comparison of the optical rotation with reported data.^[3, 4] [d] Sign of the optical rotation.

alents of ligand has only a marginal effect on the enantioselectivity (entry 12 versus entry 15). Finally, replacing **3a** with the sterically more hindered chiral P,N ligand **3b** gives comparable or better results for enantioselective 1,4-conjugate addition to 2-cyclohexen-1-one (entries 7 and 16, entries 8 and 17, respectively). Our experiments indicate that [Cu(OTf)]₂·C₆H₆ is the best copper catalyst precursor and nonpolar solvents such as toluene or Cl(CH₂)₂Cl are desirable. This result is consistent with earlier studies conducted by several research groups.^[3, 4]

We have tried to develop effective catalytic systems for a variety of acyclic enones (Table 2). Chalcone was selected as the substrate for testing the reaction conditions. Our experimental results show that enantioselective conjugate addition of diethylzinc to chalcone (entry 2) gives better ee values when catalyzed by a [Cu(**3b**)] species than those obtained with a [Cu(**3a**)] complex (entries 1 and 2). The reaction in the mixed solvent system (toluene/Cl(CH₂)₂Cl) works better than that carried out in toluene both in terms of conversion and enantioselectivity (entry 2 versus entry 3), possibly because the substrates are more soluble in the mixed solvent system. This is especially true for a methoxy-substituted chalcone (entry 4 versus entry 5). Under the optimal conditions for enantioselective 1,4-addition of diethylzinc to chalcone (entry 2) several acyclic enones with aryl substituent groups have been successfully converted into the corresponding chiral ketones (entries 4–9, up to 98% ee). To our knowledge, the enantioselectivities achieved in this study are the best yet reported for the Cu-catalyzed enantioselective conjugate addition to acyclic enones. Furthermore, a very promising result has been obtained for an acyclic enone with only aliphatic substituents (entry 10, 86% ee).

Experimental Section

3a: 2-Pyridinecarboxylic acid (0.940 g, 7.64 mmol), 4-(dimethylamino)pyridine (DMAP, 20 mg, 0.164 mmol) and 1,3-dicyclohexylcarbodiimide (DCC, 2.06 g, 10 mmol) were added to a solution of amine **2** (0.863 g, 1.91 mmol) in CH₂Cl₂ (50 mL). The mixture was stirred overnight at RT. Water (20 mL) and AcOH (0.2 mL) were added to this mixture and stirred at RT for 2 h. The solid residue was then filtered and washed with CH₂Cl₂

(10 mL). The organic layer was separated, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was chromatographed on silica gel (80 g) eluting with hexanes/CH₂Cl₂ (1/2) to afford 906 mg (85%) of **3a** as a white solid, m.p. 185–187 °C. [α]_D²⁵ +45.6 (*c* = 1.0, CHCl₃); ¹H NMR (CD₂Cl₂): δ = 6.87 (d, *J* = 8.4 Hz, 1H), 6.93–6.98 (m, 2H), 7.03–7.35 (m, 13H), 7.49–7.53 (m, 2H), 7.76–7.81 (m, 1H), 7.91–8.09 (m, 6H), 8.87 (d, *J* = 9.0 Hz, 1H), 9.75 (s, 1H); ¹³C NMR (CD₂Cl₂): δ = 120.15, 122.70, 125.11, 125.26, 125.40, 126.54, 126.73, 126.76, 126.88, 127.05, 127.78, 127.96, 128.67, 128.76, 128.85, 128.96, 128.98, 129.04, 129.18, 129.75, 129.89, 131.13, 131.15, 131.27, 133.55, 133.65, 134.02, 134.05, 134.11, 134.16, 134.38, 134.43, 134.89, 135.50, 135.53, 137.45, 137.61, 137.65, 137.82, 138.17, 138.20, 138.37, 140.62, 141.08, 148.29, 150.49, 162.12; ³¹P NMR (CD₂Cl₂): δ = –13.71 (s); HR-MS calcd for C₃₈H₃₇N₂O₂: 559.1939; found: 559.1904.

3b: P,N ligand **3b** (747 mg, 90%) was prepared from **2** (660 mg, 1.46 mmol) according to the same procedure as used for **3a** and isolated as a white solid, m.p. 208–209 °C. [α]_D²⁵ +42.0 (*c* = 1.0, CHCl₃); ¹H NMR (CD₂Cl₂): δ = 1.98 (s, 3H), 6.82–6.87 (m, 2H), 6.99–7.30 (m, 13H), 7.30–7.40 (m, 1H), 7.48–7.57 (m, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.90–7.98 (m, 2H), 8.06 (t, *J* = 8.2 Hz, 2H), 8.95 (d, *J* = 9.0 Hz, 1H), 9.93 (s, 1H); ¹³C NMR (CD₂Cl₂): δ = 24.06, 119.40, 119.43, 124.36, 124.47, 125.21, 126.42, 126.72, 126.75, 127.10, 127.83, 128.01, 128.60, 128.70, 128.92, 128.95, 129.02, 129.03, 129.06, 129.74, 129.98, 131.08, 131.27, 131.29, 133.58, 133.67, 133.96, 134.00, 134.20, 134.26, 134.47, 135.00, 135.85, 135.88, 137.29, 137.46, 137.90, 138.07, 138.28, 138.52, 138.69, 140.65, 141.10, 149.58, 157.35, 161.95; ³¹P NMR (CD₂Cl₂): δ = –13.77 (s); HR-MS calcd for C₃₉H₂₉N₂O₂: 573.2096; found: 573.2051.

General Procedure for asymmetric 1,4-conjugate addition: A solution of [Cu(OTf)]₂·C₆H₆ (10.0 mg, 2 mmol) and **3b** (572 mg, 10 mmol) in a mixture of 1,2-dichloroethane (4 mL) and toluene (8 mL) was stirred at RT for 0.5 h in a Schlenk tube in a N₂-filled glovebox. This catalyst solution was used for four separate experiments. Enone (0.5 mmol) and then the catalyst solution (3 mL) were added to a dried Schlenk tube. The solution was stirred at RT for 10 min and then cooled to -20°C . After the solution was stirred at -20°C for 15 min, Et₂Zn (1.0 M solution in hexanes, 0.75 mL, 0.75 mmol) was added slowly. The resulting mixture was stirred at -20°C for 48 h and 5% dilute hydrochloric acid (2 mL) was added. After warming the reaction mixture to RT, Et₂O (10 mL) was added. The organic phase was washed with saturated NaHCO₃ (5 mL), dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was purified by column chromatography on silica gel and eluted with EtOAc/hexanes (1/40–1/20) to afford the addition product. All chiral 1,4-addition products are known compounds.^[3, 4]

Determination of enantiomeric excesses: racemic products were obtained by 1,4-addition of substrates with ethylmagnesium bromide (1.0 M in THF) in THF at RT. The retention times (in minutes) for the racemic products are given in minutes a) chiral capillary GC column: Supelco γ -DEX-225 (30 m $\times$ 0.25 mm (i.d.)): 3-ethylcyclohexanone: *T* = 80 °C for 40 min then 120 °C, *t*_S = 42.93, *t*_R = 43.27; 4-ethyl-5-methyl-hexan-2-one: *T* = 80 °C,

$t_1 = 23.25$, $t_2 = 23.92$, and 4-phenyl-hexan-2-one: $T = 120^\circ\text{C}$, $t_S = 32.25$, $t_R = 33.32$; b) chiral HPLC Columns: Daicel Chiralcel OD and Chiralpak AD, particle size: $5.0\ \mu\text{m}$, column dimensions: $25\ \text{cm}$ (length) $\times$ $0.46\ \text{cm}$ (i.d.), flow = $1.0\ \text{mL}\cdot\text{min}^{-1}$, 1,3-diphenyl-pentan-1-one (Chiralpak AD, 2-PrOH/hexanes = 1/99), $t_S = 20.43$, $t_R = 29.55$; 3-(4-methoxyphenyl)-1-phenyl-pentan-1-one (Chiralpak AD, 2-PrOH/hexanes = 10/90), $t_S = 12.65$, $t_R = 16.83$; 1-(4-methoxyphenyl)-3-phenyl-pentan-1-one (Chiralcel OD, 2-PrOH/hexanes = 10/90), $t_S = 19.80$, $t_R = 22.37$; 3-(4-chlorophenyl)-1-phenyl-pentan-1-one (Chiralpak AD, 2-PrOH/hexanes = 5/95), $t_S = 10.73$, $t_R = 13.87$; and 1-(3-chlorophenyl)-4-phenyl-pentan-1-one. (Chiralpak AD, 2-PrOH/hexanes = 1/99), $t_S = 25.73$, $t_R = 34.97$.

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Catalytic Aerobic Oxidation of Cycloalkanes with Nanostructured Amorphous Metals and Alloys**

Venkitasamy Kesavan, Pennadam S. Sivanand, Srinivasan Chandrasekaran,* Yuri Koltypin, and Aharon Gedanken

The functionalization of unactivated carbon–hydrogen bonds in saturated hydrocarbons has been investigated for both its synthetic and biological interest.^[1] Catalytic oxidation of alkanes has been explored using several oxidants,^[2] and those reactions with molecular oxygen under mild conditions^[3] are especially rewarding goals. The oxidation of cyclohexane turns out to be the least efficient of all major industrial processes.^[4]

Typically, cyclohexane is oxidized by air (15 atm) at 160°C in the presence of cobalt naphthenate as oxidation initiator, giving only 4% conversion with 80% selectivity for cyclohexanone and cyclohexanol.^[5] The addition of boric acid to the oxidation mixture allows approximately 10% conversion of cyclohexane with 90% selectivity for cyclohexanone and cyclohexanol.^[5] Murahashi et al. have reported the oxidation of cyclohexane with iron powder and observed 11% conversion with 95% selectivity for cyclohexanone and cyclohexanol.^[6]

Suslick and co-workers demonstrated the first sonochemical synthesis of amorphous iron particles (10–20 nm) by ultrasonic irradiation of $[\text{Fe}(\text{CO})_5]$, and the utility of these particles as an efficient catalyst in the Fischer–Tropsch process.^[7] They have extended this sonication synthesis to nanophase amorphous cobalt (20 nm) and an amorphous Co/

[*] Prof. S. Chandrasekaran, V. Kesavan, P. S. Sivanand
Department of Organic Chemistry
Indian Institute of Science
Bangalore-560012 (India)
Fax: (+91)80-334-16-83
E-mail: scn@orgchem.iisc.ernet.in
Y. Koltypin, Prof. A. Gedanken
Department of Chemistry, Bar-Ilan University
Ramat-Gan 52900 (Israel)

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Fe alloy.^[8] We have investigated the sonochemical synthesis of amorphous nickel^[9] (10 nm) from [Ni(CO)₄] and of amorphous Fe/Ni alloy^[10] (Fe₂₀Ni₈₀, 25 nm) from a solution of [Fe(CO)₅] and [Ni(CO)₄]. The amorphous nature and the particle size were established by X-ray diffraction (XRD) and transmission electron microscopy (TEM) measurements.^[11]

Here we report the oxidation of cyclohexane with up to 40 % conversion and 80 % selectivity^[12] for cyclohexanone and cyclohexanol using nanostructured amorphous metals like Fe and Co and an amorphous alloy like Fe₂₀Ni₈₀ with oxygen (40 atm) at room temperature (25–28 °C) in the absence of any solvent. In the aerobic oxidation isobutyraldehyde as coreductant and a catalytic amount of acetic acid were used. Initially the oxidations were carried out at room temperature under 1 atm of oxygen, and it was found that oxygen at 40 atm gave better conversion. The results are summarized in Table 1.

Table 1. Aerobic oxidation of cyclohexanes using amorphous metals/alloys at 28 °C.^[a]

Substrate	Nanometal/alloy	Particle size [nm]	Conversion [%] ^[b]	one:ol ^[c]
cyclohexane	Fe	20	40	1:4.5
	Co	20	41	1:5
	Fe ₂₀ Ni ₈₀	25	38	1:3.6
methylcyclohexane	Fe	20	32	1:1
	Co	20	38	1:3
	Fe ₂₀ Ni ₈₀	25	36	1:2

[a] A mixture of nanometal/alloy (0.025 g), cyclohexane (250 mmol), isobutyraldehyde (50 mmol), and acetic acid (5 mmol) was stirred in a Parr reactor with oxygen (40 atm) at room temperature for 10–15 h. [b] Conversion is defined as the percentage of the starting alkane converted into products. [c] Determined by GC analysis using starting alkane as internal standard and also by isolation of products.

For the oxidation of cyclohexane, use of amorphous cobalt gave the best result at 41 % conversion and 80 % selectivity for cyclohexanone and cyclohexanol. In a control reaction where the same cycloalkanes were treated with molecular oxygen, isobutyraldehyde, and acetic acid in the absence of amorphous Co, Fe, or alloy as catalyst, no oxidation products were obtained. The oxidation of methylcyclohexane under similar conditions occurs only at the secondary and tertiary C–H bonds; primary C–H bonds remain unaffected. In the reaction catalyzed by amorphous cobalt the product was a mixture of methylcyclohexanones and methylcyclohexanols (1:3; 2-one:3-one:4-one = 28:42:30 and 1-ol:2-ol:3-ol:4-ol = 65:9:15:11). When the oxidation of cyclohexane was carried out using nanostructured Co (20 nm) as catalyst at 70 °C under 40 atm of oxygen for 8 h, the conversion had gone up to 67 % but there was a change in the ratio of ketone to alcohol (1:2; Table 2).

Table 2. Aerobic oxidation of cyclohexane using amorphous metals/alloys at 70 °C.

Nanometal/alloy	Conversion [%]	one:ol
Fe	62	1:1.5
Co	67	1:2
Fe ₂₀ Ni ₈₀	56	1:2

The oxidation of adamantane with various nanometals/alloys was carried out under similar conditions (28 °C, 40 atm O₂), and in general the conversion was in the range of 52–57 %; adamantan-1-ol was the major product in all the reactions (Table 3). It is noteworthy that our catalytic system is quite different from the Gif^{II} system.^[13] For example, the selectivity for the tertiary or secondary C–H bond on a “per bond” basis for the oxidation of adamantane is 10 for our system and 0.25 for the Gif^{II} system. Interestingly no other oxidation products were observed in our reaction (100 % selectivity).

Table 3. Aerobic oxidation of adamantane using amorphous metals/alloys at 28 °C.

Nanometal/alloy	Conversion [%]	1-ol:2-ol:2-one
Fe	56	16:1:3
Co	57	11:1:0.5
Fe ₂₀ Ni ₈₀	52	17:2:1

Although we do not have proof for a precise mechanism at the present stage, the reaction can be rationalized by assuming the following pathway, which is similar to that suggested by Murahashi et al.^[6] The reaction of isobutyraldehyde with molecular oxygen^[14] in the presence of amorphous metal/alloy and acetic acid would give perisobutyric acid,^[15] which subsequently reacts with metal/alloy to afford a metal–oxo species^[16, 17] along with isobutyric acid. Abstraction of a hydrogen atom from cyclohexane with the oxo-metal species followed by hydroxy ligand transfer to the resulting radical would give the alcohols. Under the same reaction conditions alcohols can be converted into ketones.

The reactions presented above clearly indicate that the nanostructured amorphous metals/alloys are superior catalysts for aerobic oxidation of cycloalkanes under mild reaction conditions.

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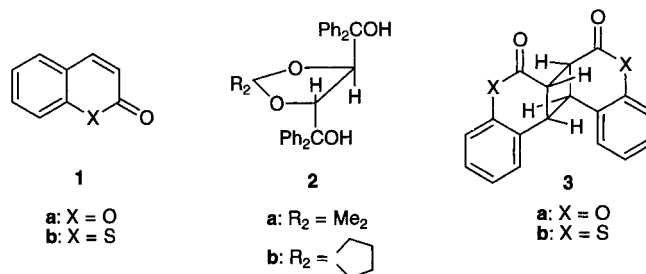
Enantioselective Single-Crystal-to-Single-Crystal Photodimerization of Coumarin and Thiocoumarin in Inclusion Complexes with Chiral Host Compounds

Koichi Tanaka, Fumio Toda,* Eiko Mochizuki, Nobuyoshi Yasui, Yasushi Kai, Ikuko Miyahara, and Ken Hirotsu

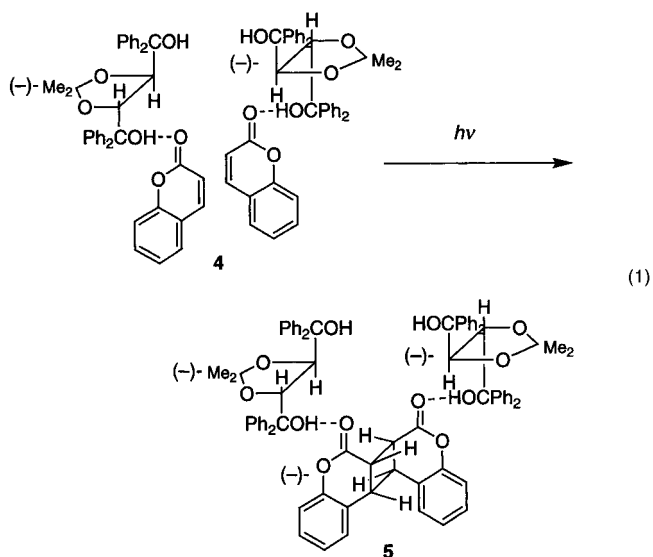
Dedicated to Professor Masazumi Nakagawa on the occasion of his 83rd birthday

Some examples of single-crystal-to-single-crystal photoreactions have been reported,^[1–5] but only a few of these involve enantioselective reactions and they are all intramolecular photocyclization reactions.^[3–5] For example, the enantioselective photocyclization of *N,N*-dibenzyl-1-cyclohexenecarbothioamide to an optically active β -thiolactam has been reported to proceed in a single-crystal-to-single-crystal man-

ner.^[4] We have now found that the single-crystal-to-single-crystal enantioselective photodimerization of coumarin (**1a**) or thiocoumarin (**1b**) proceeds efficiently in inclusion complexes with (*R,R*)-(-)-*trans*-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**2a**) or (*R,R*)-(-)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**2b**), respectively.



When a solution of a 1:1 mixture of **1a** and (-)-**2a** in a mixture of EtOAc and hexane was kept at room temperature for 3 h, a 1:1 inclusion complex (**4**) was obtained as colorless needles.^[6] Irradiation of **4** in the solid state with a 400 W high-pressure Hg lamp (Pyrex filter, room temperature, 4 h) gave a 2:1 complex (**5**)^[6] of (-)-**2a** with (-)-**3a** [Eq. (1)]. The crystals were still clear after photoirradiation and the reaction



proceeded in a single-crystal-to-single-crystal manner throughout the reaction. The (-)-*anti*-head-to-head dimer **3a** was isolated by exchange with DMF. A 1:1 complex of (-)-**2a** with DMF was obtained as colorless needles in 99 % yield after recrystallization of the 2:1 complex **5** from DMF/H₂O (5/1). Concentration of the filtrate left the optically pure (-)-*anti*-head-to-head dimer **3a**, which was isolated as colorless prisms in 89 % yield. The optical purity of (-)-**3a** was determined by comparison of its $[\alpha]_D$ value to that of enantiomerically pure **3a**.^[7] Optically pure (+)-**3a** was obtained when the host compound (+)-**2a** was used instead of (-)-**2a**.

This result shows that two molecules of **1a** are arranged in chirally related positions, which gives the optically active *anti*-head-to-head dimer **3a** by [2+2] photodimerization. This

[*] Prof. F. Toda, Dr. K. Tanaka
Department of Applied Chemistry, Faculty of Engineering
Ehime University, Matsuyama, Ehime 790–8577 (Japan)
Fax: (+81) 899-927-9923.
Dr. E. Mochizuki, Dr. N. Yasui, Prof. Y. Kai
Department of Materials Chemistry, Osaka University
Yamadaoka 2–1, Suita, Osaka 565–0871 (Japan)
Dr. I. Miyahara, Prof. K. Hirotsu
Department of Chemistry, Faculty of Science, Osaka City University
Sugimoto-cho, Sumiyoshi-ku, Osaka 558–8585 (Japan)

chiral arrangement of the achiral molecule **1a** in the inclusion complex **4** can easily be detected by measurement of the CD spectra of its Nujol mull. The 1:1 complex of **1a** with (+)- and (–)-**2a** showed CD spectra with a near mirror symmetry (Figure 1). The CD absorptions at 225, 275, 300, and 330 nm

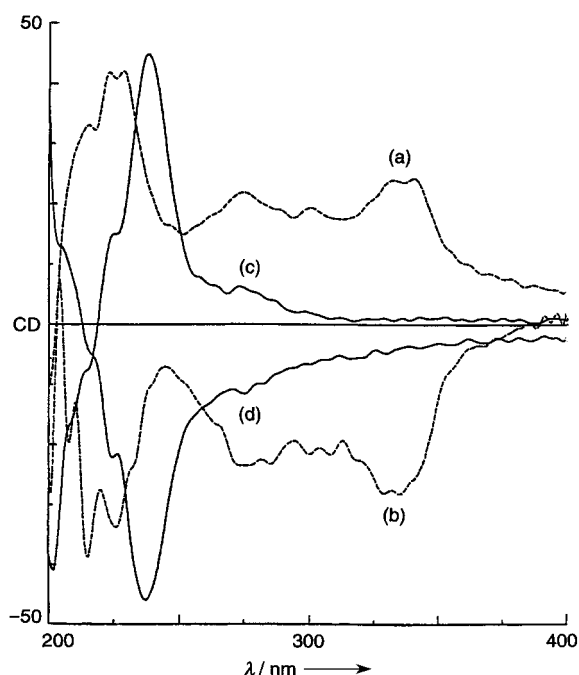


Figure 1. CD spectra in Nujol mulls: a) 1:1 complex of **1a** with (+)-**2a**; b) 1:1 complex of **1a** with (–)-**2a**; c) 2:1 complex of (+)-**2a** with (+)-**3a**; d) 2:1 complex of (–)-**2a** with (–)-**3a**.

disappeared after photoirradiation of **4**, and the new CD absorption of **5** at 240 nm appeared. The photodimerization of **4** was also monitored by measurement of the IR spectra from Nujol mulls. The ν_{CO} absorption of **1a** in **4** at 1700 cm^{-1} decreased gradually and finally disappeared after 4 h of photoirradiation and a new ν_{CO} absorption from the presence of **3a** in **5** appeared at 1740 cm^{-1} .

The single-crystal-to-single-crystal nature and the steric course of the photodimerization of coumarin (**1a**) to (–)-*anti*-head-to-head dimer **3a** in the inclusion complex **4** were investigated by X-ray crystallographic analysis and X-ray powder diffraction studies. X-ray crystallographic analysis showed that two molecules of **1a** each form a hydrogen bond between the C40=O6 atom and the H(O4) atom of a separate molecule of **2a** and are arranged in the direction that gives the *anti*-head-to-head dimer **3a** on photodimerization; the distance between the two ethylenic double bonds being short enough (3.59 and 3.42 Å) to react easily and topochemically (Figure 2).^[8] The bond distances of the cyclobutane ring connecting C38–C38* and C39–C39* atoms are 1.6 and 1.57 Å, respectively, after photoirradiation (Figure 3).^[9] According to the X-ray structure analysis of the inclusion complexes **4** and **5** the *a* axis contracts as photodimerization proceeds while the *b* and *c* axes remain virtually unchanged. The changes in lattice constants from **4** to **5** resulting from photoreaction were –2.45, –0.02, and +0.35 Å for *a*, *b*, and *c*, respectively. As

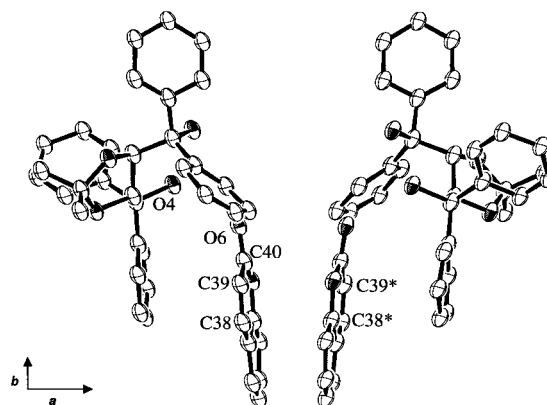


Figure 2. ORTEP drawing of the molecular structure of the 1:1 complex (**4**) of **1a** with (–)-**2a** (viewed along the *c* axis). All hydrogen atoms are omitted for clarity. The distances between C39 and C39*, and C38 and C38* are 3.59 and 3.42 Å, respectively.

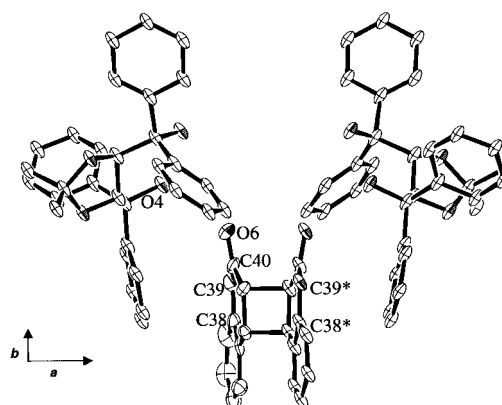
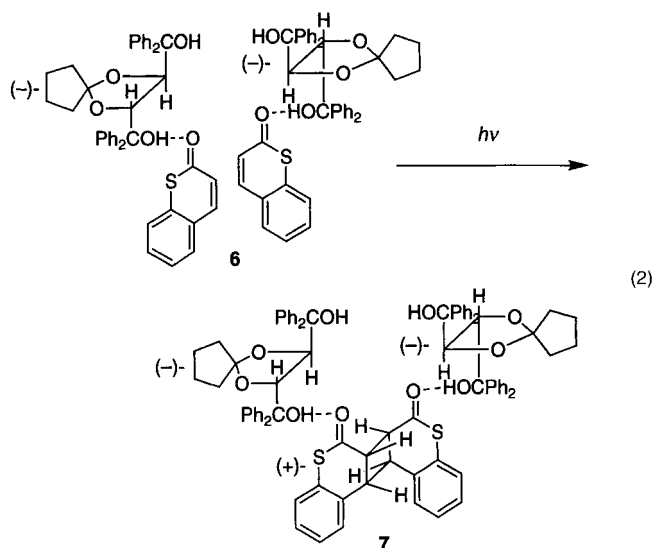


Figure 3. ORTEP drawing of the molecular structure of the 2:1 complex (**5**) of (–)-**2a** with (–)-**3a** (viewed along the *c* axis). All hydrogen atoms are omitted for clarity. The bond lengths C39–C39*, and C38–C38* are 1.57 and 1.60 Å, respectively.

seen in Figure 3 the cyclobutane ring forms approximately along the *a* axis. This corresponds well to the anisotropic changes in the lattice constants.

X-ray powder diffraction patterns were measured on a Rigaku RINT 2000 X-ray diffractometer using $\text{Cu K}\alpha$ radiation. The peaks at $2\theta = 8.90$ and 9.92 disappeared during UV irradiation and new peaks at $2\theta = 5.36$, 8.46 , and 10.78 appeared. The original crystal structure had converted almost completely into the new structure after irradiation for 4 h. Remarkably, the peak of $2\theta = 9.92$ (interplanar spacing of (400)), which corresponds to one quarter of the length of the *a* axis, had shifted to $2\theta = 10.78$. The latter peak corresponds to the interplanar spacing of (400) for the 2:1 complex **5**. From these data we conclude that the photodimerization of the 1:1 complex **4** proceeded in a single-crystal-to-single-crystal manner.

The enantioselective photodimerization of thiocoumarin (**1b**) to optically pure (+)-*anti*-head-to-head dimer (**3b**)^[10] in the 1:1 inclusion complex (**6**) of **1b** with (–)-**2b** was also found to proceed in a single-crystal-to-single-crystal manner [Eq. (2)]. Photoirradiation of **6** in the solid state (400 W high-pressure Hg lamp, Pyrex filter, room temperature, 2 h) gave a 2:1 complex (**7**) of (–)-**2b** with (+)-**3b** in quantitative



yield. Compound (+)-**3b** with 100 % ee^[11] was isolated in 73 % yield by column chromatography. The crystal-to-crystal nature of this reaction was also confirmed by X-ray powder diffraction spectroscopy.

In conclusion, the photodimerization of inclusion complexes of coumarin or thiocoumarin to the *anti*-head-to-head dimer within chiral host compounds (**2a**, **2b**) proceeded efficiently and enantioselectively. This is the first example of an enantioselective intermolecular photoreaction by a single-crystal-to-single-crystal transformation and it also provides a good example for the study of the mechanism of topochemical reactions in the crystal.

Experimental Section

4: When a solution of **1a** (3.2 g, 21.9 mmol) and (-)-**2a** (10.0 g, 21.5 mmol) in AcOEt/hexane (120 mL, 1/5) was kept at room temperature for 3 h a 1:1 inclusion complex (**4**) was obtained as colorless needles (5.7 g, 43 %, m.p. 95–98 °C).^[6] IR (Nujol): $\tilde{\nu}$: 1700 (C=O), 1607 (C=C), 3358 (OH), 3230 cm⁻¹ (OH). Elemental analysis calcd for C₄₀H₃₆O₆: C 71.37, H 3.99; found: C 71.64 H 3.82.

5: Photoirradiation of **4** (1.0 g, 1.6 mmol) in the solid state with a 400 W high-pressure Hg lamp with a Pyrex filter at room temperature for 4 h gave a 2:1 complex (**5**) of (-)-**1a** with (-)-**3a** in quantitative yield. Colorless needles (m.p. 228–232 °C). IR (Nujol): $\tilde{\nu}$: 1740 (C=O), 3433 (OH), 3262 cm⁻¹ (OH). Elemental analysis calcd for C₄₀H₃₆O₆: C 71.37, H 3.99; found: C 71.64 H 3.82.

(-)-**3a:** When the 2:1 complex **5** (1.0 g) was recrystallized from DMF/H₂O (5 mL, 5/1) a 1:1 complex of (-)-**1a** with DMF was obtained as colorless prisms (0.86 g, 99 %). Concentration of the filtrate and separation of the 1:1 DMF complex of (-)-**2a** gave optically pure (-)-*anti*-head-to-head dimer **3a** (0.17 g, m.p. 168–169 °C, [α]_D = -9.1° (c = 0.19, benzene), 100 % ee) as colorless prisms in 89 % yield after recrystallization from ethyl acetate/hexane.

6: When a solution of **1b** (0.66 g, 4.1 mmol) and (-)-**2b** (2.0 g, 4.1 mmol) in *n*-butyl ether/hexane (30 mL, 5/1) was kept at room temperature for 12 h a 1:1 inclusion complex (**6**) was obtained as colorless needles (2.1 g, 76 %, m.p. 106–108 °C). IR (Nujol): $\tilde{\nu}$: 1618 (C=O), 1582 (C=C), 3358 (OH), 3250 cm⁻¹ (OH). Elemental analysis calcd for C₄₂H₃₈O₅S: C 77.04, H 5.85; found: C 77.15, H 5.79.

7: Photoirradiation of **6** (1.0 g, 1.5 mmol) in the solid state by using a 400 W high-pressure Hg lamp with a Pyrex filter at room temperature for 2 h gave a 2:1 complex (**7**) of (-)-**2b** with (+)-**3b** in quantitative yield. Colorless needles (m.p. 190–194 °C). IR (Nujol): $\tilde{\nu}$: 1740 (C=O), 3433 (OH),

3262 cm⁻¹ (OH). Elemental analysis calcd for C₄₂H₃₈O₅S: C 77.04, H 5.85; found: C 77.12, H 5.90.

(+)-**3b:** Complex **7** (1.0 g) was dissolved in toluene (5 mL) and chromatographed on silica gel using toluene/AcOEt (4/1) to give optically pure (+)-**3b** (0.18 g, 73 % yield) as colorless prisms after recrystallization from toluene (m.p. 254–255 °C). [α]_D = +182° (c = 0.02, CHCl₃). IR (Nujol): $\tilde{\nu}$: 1681 (C=O), 1655 cm⁻¹ (C=O). Elemental analysis calcd for C₁₈H₁₂O₂S₂: C 66.64, H 3.73; found: C 66.38, H 3.60.

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- [9] Crystal structure analysis of **5**:^[12] C₄₀H₃₆O₆, *M*_r = 612.72, space group monoclinic *C*2, *a* = 32.80(3), *b* = 9.467(3), *c* = 10.360(4) Å, β = 100.27(7)°, *V* = 3164(2) Å³, *Z* = 4, ρ_{calcd} = 1.29 g cm⁻³, crystal dimensions 0.80 × 0.05 × 0.03 mm, μ = 0.86 cm⁻¹, *T* = 293 K, *R* = 0.114, *R*_w = 0.097, and *S* = 2.86 for 560 parameters and 1939 unique observed reflections with [*I* > 3σ(*I*)], $\Delta\rho_{\text{max}}$ = 0.46 e Å⁻³. Data collection and analysis were carried out in a similar way to those for **4**.
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- [11] The optical purity was determined by HPLC on a chiral stationary phase (Chiralpak AS column; Daicel Chemical Co. Ltd., Himeji (Japan)). The lactone ring of **3a** in complex **5** was opened by acid catalyzed esterification and the optical purity of the total reaction determined as 96 % ee by HPLC.
- [12] Crystallographic Data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-118773(**4**) and -118774(**5**). Copies of the data can be obtained free of charge on application to CCDC, 12 union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk)

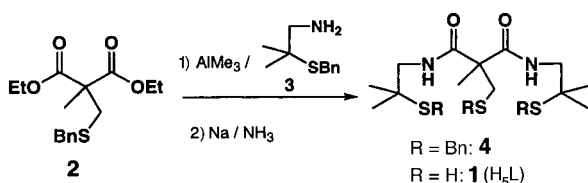
A Pentacoordinated Di-*N*-carboxamido-dithiolato-*O*-sulfinato-iron(III) Complex Related to the Metal Site of Nitrile Hydratase**

Laurent Heinrich, Yun Li, Jacqueline Vaissermann, Geneviève Chottard, and Jean-Claude Chottard*

Nitrile hydratases (NHases) are enzymes that contain non-heme iron or non-corrinoid cobalt and catalyze the hydration of nitriles to amides.^[1a] One NHase is used for industrial production of acrylamide.^[1b] A recent X-ray structure of the active form of the NHase from *Rhodococcus* sp.R312 indicated that the iron center is bound to three cystein thiolate groups and two nitrogen atoms from peptide bonds of the protein main chain.^[1c] A more precise X-ray structure of the inactive form of the NHase from *Rhodococcus* sp.N-771 provided additional information: Two of the coordinated cystein groups were posttranslationally modified to cystein sulfinic and sulfenic moieties that are both bound through sulfur, and one nitric oxide ligand occupies the sixth position.^[1a] Electron nuclear double resonance (ENDOR) measurements suggested that the sixth ligand in the active form is probably a hydroxide group that was not seen at the resolution of the first structure.^[1d]

Such an unusual Fe^{III} coordination sphere invites investigation to better understand its electronic properties and its catalytic activity in nitrile hydration. This, together with the mechanism of posttranslational oxidation of bound cysteins, can be achieved from the study of relevant mimetic complexes. A (N₂S)₂Fe^{III} complex with two aromatic thiolato, two aromatic *N*-carboxamido, and two pyridine ligands has been reported recently,^[2a] and during the writing of the current paper the same group described the bis-*S*-sulfinato derivative of this Fe^{III} complex.^[2b]

To mimic the metallic site of NHase, we need a pentacoordinated Fe^{III} complex with a free sixth coordination site. Such a complex was synthesized from **1** (H₅L; see Scheme 1), a new H₅N₂S₃ ligand containing three aliphatic thiol groups and two aliphatic amide moieties. The coupling reaction between



Scheme 1. Synthesis of ligand **1**. Bn = benzyl.

[*] Prof. Dr. J.-C. Chottard, Dr. L. Heinrich, Dr. Y. Li
Laboratoire de Chimie et Biochimie
Pharmacologiques et Toxicologiques
Université René Descartes, UMR 8601 CNRS
45, rue des Saints-Pères, F-75270 Paris Cedex 06 (France)
Fax: (+33) 1-42-86-83-87
E-mail: jean-claude.chottard@biomedicale.univ-paris5.fr
Dr. J. Vaissermann, Dr. G. Chottard
Laboratoire de Chimie des Métaux de Transition
Université Pierre et Marie Curie
ESA 7071, F-75252 Paris Cedex 05 (France)

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diethyl 2-methyl-2-benzylthiomethyl malonate (**2**)^[3a] with 2-methyl-2-(benzylthio)propylamine (**3**)^[3b] in toluene in the presence of trimethylaluminum gave diamide **4**. Upon subsequent reductive deprotection of the thiol groups with sodium in liquid ammonia, **1** was obtained in 72 % yield (Scheme 1).

Coordination of iron(III) to the deprotonated ligand L⁵⁻ gave (NEt₄)₂[Fe^{III}(L-O₂)] (**5**), whose X-ray structure shows postcoordination oxidation of the L ligand (Figure 1).^[4] The intermediate complex formed before oxidation is presumably the *tris*-thiolato complex; attempts to isolate and characterize this species under argon have failed so far.

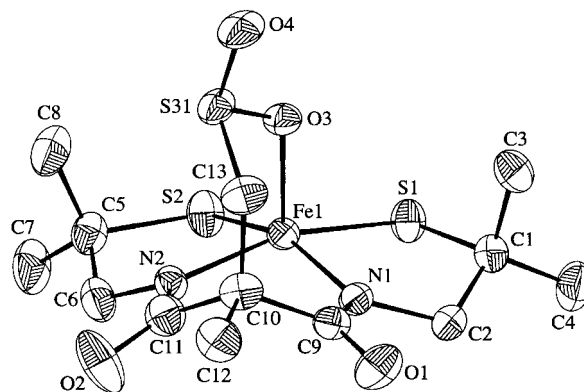


Figure 1. CAMERON representation (ellipsoid at 30% probability level) of the anion of complex **5**. The H and S3^[4] atoms are omitted for clarity. Selected bond distances [Å] and angles [°]: Fe1–S1 2.223(3), Fe1–S2 2.213(3), Fe1–O3 2.005(6), Fe1–N1 1.946(7), Fe1–N2 1.957(8); S1–Fe1–S2 87.5(1), S1–Fe1–N1 86.7(2), N1–Fe1–N2 91.5(3), S2–Fe1–N2 86.2(3), S1–Fe1–O3 102.2(2), S2–Fe1–O3 107.5(2), N1–Fe1–O3 96.6(3), N2–Fe1–O3 97.6(3).

In complex **5**, the iron center is above the plane containing the two deprotonated *N*-carboxamido and two thiolato ligands, whereas the *O*-sulfinato ligand occupies the apical position. Moreover, the presence of two NEt₄⁺ counterions per iron atom in the crystal lattice indicates that the iron is still in the +3 oxidation state. The Fe–N and Fe–S bond lengths are comparable to those reported for complexes showing *N*-carboxamido and thiolato coordination to Fe^{III}.^[2a] The Fe^{III}–O bond from the *O*-sulfinato moiety, with a length of 2.005(6) Å, has no precedent to our knowledge.

Complex **5** is soluble in polar solvents (MeCN, DMF), yielding red solutions. The EPR spectra of **5** at 10 K in MeCN (Figure 2) or DMF glasses confirm the +3 oxidation state of iron and reveal an intermediate spin state of *S* = 3/2 with axial symmetry, in agreement with the magnetic moment of 3.8 μ_B (polycrystalline sample) between 2 and 300 K. Complex **5** is stable under reductive conditions, whereas it undergoes an irreversible oxidation at *E*_{1/2} = 150 mV vs. SCE in DMF, which might correspond to a ligand oxidation or to the formation of an Fe^{IV} complex. The *N*-carboxamido ligands are known to stabilize high oxidation states of transition metal compounds,^[5] but the *cis* position of the two thiolato ligands might facilitate intramolecular disulfide formation, leading to irreversible oxidation.

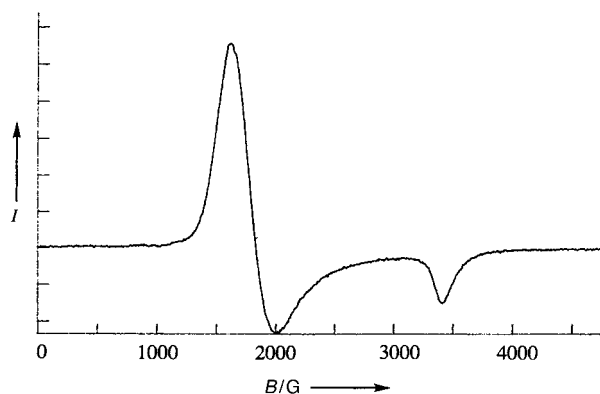


Figure 2. EPR spectrum of **5** in MeCN at 10 K ($g_{\perp} = 3.75$, $g_{\parallel} = 2.01$).

The IR spectrum (KBr pellet) of **5** shows a characteristic ν_{CO} frequency at 1575 cm^{-1} for coordinated *N*-carboxamido^[2a] and a strong band at 1040 cm^{-1} corresponding to the ν_{SO} stretching of the *O*-coordinated sulfinato.^[6] The UV/Vis spectrum of **5** in MeCN exhibits an absorption band at 475 nm ($\epsilon = 5000\text{ L mol}^{-1}\text{ cm}^{-1}$), which is responsible for the red color. The resonance Raman spectrum of **5** in MeCN with an excitation at 476.5 nm shows three bands at 604 (Fe–O stretching^[7]), 978 , and 1160 cm^{-1} (S–O stretching^[6]), which support *O*-sulfinato coordination to the iron as observed in the solid state. Moreover, the excitation profiles of the three bands in the region of $450\text{--}530\text{ nm}$ enable us to assign the band at 475 nm in the UV/Vis spectrum to a sulfinato-to-metal charge-transfer transition.

To our knowledge, complex **5** is the first example of an iron complex with such a mixed coordination sphere and the first example to result from air oxidation of an iron-coordinated thiolato ligand to an *O*-bound sulfinato ligand. Oxidation of thiolato–iron complexes by dioxygen is known to give noncoordinated disulfides or thiolato μ -oxo complexes.^[8] A few examples of sulfinato–nickel complexes have been reported that result from nucleophilic attack of bound thiolate(s) on dioxygen.^[9] We do not know yet whether the oxidation to give **5** starts by activation of dioxygen by the metal or by reaction of dioxygen with the bound thiolate. Very recently, dioxygen oxidation of a thiolato–Co^{III} complex to a *S*-sulfenato and *S*-sulfinato complexes was reported,^[10] and a *S*-sulfinato–Fe^{III} complex has been obtained by H_2O_2 oxidation of a thiolato–Fe^{III} complex.^[2b] Moreover, *O*-sulfinato complexes are known to rearrange into their more stable *S*-sulfinato form.^[11] In complex **5**, the central side chain of the polydentate ligand might be too short to allow stable coordination through *S*. This question is under examination, as is the possible oxidation of a second thiolato ligand.

Experimental Section

All operations were carried under argon, unless mentioned otherwise, with standard Schlenk techniques. Solvents were dried and distilled before use.

1: 1) A solution of **2**^[3a] (263 mg, 0.85 mmol) was added under argon at 0°C to a mixture of **3**^[3b] (500 mg, 2.56 mmol) and AlMe_3 (2 M in heptane, 1.7 mL) in toluene (8 mL). After the mixture was heated at reflux for one night, the reaction was quenched by HCl (2 M). Extraction with EtOAc gave a crude product, which was purified by chromatography over silica gel

(EtOAc/cyclohexane 1/3) to afford **4** (410 mg, 79 %). $^1\text{H NMR}$ (250 MHz, CDCl_3): $\delta = 7.31\text{--}7.19$ (m, 17 H), 3.72 (s, 2 H), 3.69 (s, 4 H), 3.25 (d, 4 H, $J = 5.7\text{ Hz}$), 2.97 (s, 2 H), 1.48 (s, 3 H), 1.26 (s, 12 H); MS (CI, NH_3): m/z : 609 (MH^+). 2) To a solution of **4** (400 mg, 0.66 mmol) in THF (4 mL) and liquid ammonia (6 mL) cooled to -45°C were added small portions of Na ($\approx 91\text{ mg}$, 4 mmol) until the blue color remained for 30 min. After addition of solid NH_4Cl (400 mg) and evaporation of ammonia, HCl (2 M) was added (pH 1). Extraction with CH_2Cl_2 followed by chromatography over silica gel (EtOAc/cyclohexane 1/4) gave ligand **1** (203 mg, 91 %). $^1\text{H NMR}$ (250 MHz, DMSO): $\delta = 7.83$ (t, 2 H), 3.25 (d, 4 H), 3.01 (d, 2 H), 2.72 (s, 2 H), 2.15 (t, 1 H), 1.42 (s, 3 H), 1.24 (s, 12 H); IR (CHCl_3): $\tilde{\nu} = 1675\text{ cm}^{-1}$ (C=O); high-resolution MS (CI, CH_4): m/z calcd for $\text{C}_{13}\text{H}_{27}\text{O}_2\text{N}_2\text{S}_3$ (MH^+): 339.1235, found: 339.1234.

5: To a solution of **1** (622 mg, 1.84 mmol) and NaH (224 mg, 9.35 mmol) in DMF (11 mL) cooled to -5°C was added a solution of FeCl_3 (296 mg, 1.83 mmol) in DMF (1.5 mL). The deep red solution was stirred at -5°C for 1 h, and then solid Et_4NCl (610 mg, 3.68 mmol) was added. After addition of EtOAc (145 mL), the solution was kept at -20°C for one night. The remaining operations were carried out in air. The red precipitate was isolated, dried under vacuum, and dissolved in CH_3CN . The solution was then filtered over celite. The solvent was evaporated to afford **5** as a highly hygroscopic, deep red solid (1.1 g, 87 %).

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The First Cyclodiastereomeric [3]Rotaxane**

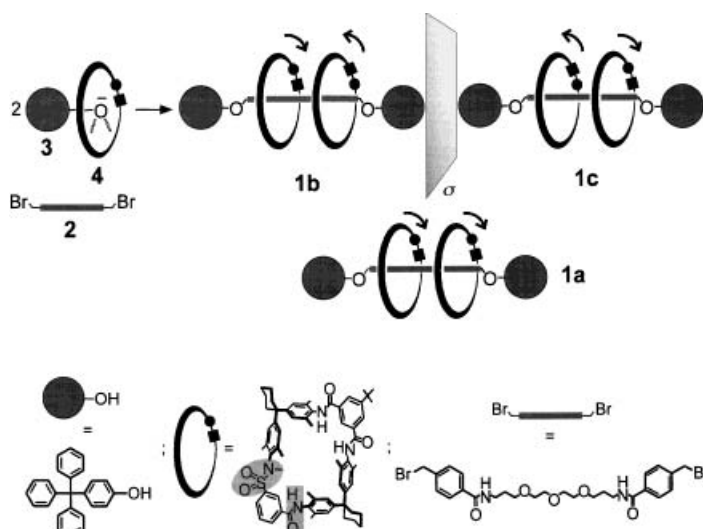
Roland Schmieder, Gosia Hübner, Christian Seel, and Fritz Vögtle*

Cycloenantiomerism in mechanically bonded molecules was first predicted by Frisch and Wassermann in 1961,^[1] and the first catenanes and molecular knots displaying this property were synthesized by Sauvage et al. almost three decades later.^[2,3] As early as 1971, Schill proposed stereoisomeric [2]rotaxanes,^[4] whose chiral information can be put down to a directed segment sequence in the macrocycle as well as in the axle. The axle and wheel are not chiral themselves; the mechanical connection, however, would yield a cycloenantiomeric rotaxane.

During the last decade several chiral [2]rotaxanes have been synthesized whose stereoisomerism is based on the central chirality.^[5,6] In 1997 we prepared the first cycloenantiomeric [2]rotaxanes and [1]rotaxanes as well as topologically chiral pretzelanes, which were separated into their enantiomers by means of chiral HPLC and chiroptically characterized.^[6e] Recently several achiral [3]rotaxanes have been reported.^[7] To our knowledge stereoisomeric [3]rotaxanes, however, have not been described yet.

We now succeeded in preparing a chiral [3]rotaxane containing two achiral wheels, which are mechanically bonded onto an achiral axle that is not directed. Analogous to the covalently linked tartaric acid, we obtained a cyclodiastereomeric compound.^[8] Applying our new efficient trapping synthesis (chemical threading) for rotaxanes with diether axles,^[9] we allowed the dibromide **2** to react with the stopper **3** in presence of the wheel **4**. Besides small amounts of the free axle and the [2]rotaxane (10%), the [3]rotaxane **1** was obtained in 29% yield (Scheme 1).^[10]

If there is only one achiral wheel on a symmetrical axle, a [2]rotaxane with no stereoisomerism results. Rotaxanes like **1** bearing two wheels, the atomic sequences of which can be arranged clockwise or counterclockwise, should occur in a



Scheme 1. Schematic representation of the synthesis of the cyclodiastereomeric [3]rotaxane as a pair of enantiomers (**1b**, **1c**) and as the *meso* form (**1a**).

meso form (**1a**) and a pair of enantiomers (**1b**, **1c**). The orientation of the macrocycles on the axle is caused by a different sequence of the three amide groups and the sulfonamide group. The two wheels **4** can have the same or opposite direction. In the case of the same orientation the *meso* compound **1a** is obtained, and the opposite direction of the wheels leads to **1b** and **1c**.

The high conformational flexibility of the molecule—in the sense of the extended translational and rotational movement of the wheels on the axle—raises the questions of whether the stereoisomers can be separated and whether chiroptical properties show significant differences. The results obtained hitherto on our separated chiral [2]- and [1]rotaxanes and catenanes indeed fueled our hopes for success. The enantiomers were successfully separated employing chiral HPLC (Chiralpak AD; Figure 1).^[11,12] First of all the (+) enantiomer was eluted in base line separation, followed by the (–) enantiomer. The retention time of the latter, however, differed only slightly from that of the *meso* form **1a** (Figure 1). Whereas the separation factor $\alpha_{(-),(+)}$ of the enan-

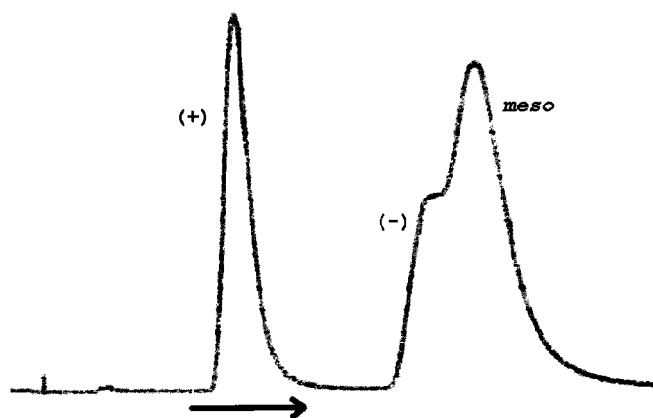


Figure 1. Chromatogram for the enantiomeric separation. Retention times: (+) enantiomer: 10.5 min, (–) enantiomer: 21.5 min, *meso* form: 23.5 min.^[12]

[*] Prof. Dr. F. Vögtle, R. Schmieder, G. M. Hübner, Dr. C. Seel
 Kekulé-Institut für Organische Chemie und
 Biochemie der Universität
 Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
 Fax: (+49)228-735-662
 E-mail: voegt@uni-bonn.de

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tiomers is 2.57, leading to a complete separation, $\alpha_{(-),meso}$ is only 1.11. Nevertheless, we were able to separate **1a** and the (–) enantiomer.

The pure enantiomer **1b** and the enriched **1c** (ca. 90%) show significant circular dichroism activity (Figure 2) as well as optical rotation at different wavelengths (Table 1).^[13] In analogy to tartaric acid, the *meso* form **1a** is not optically active.

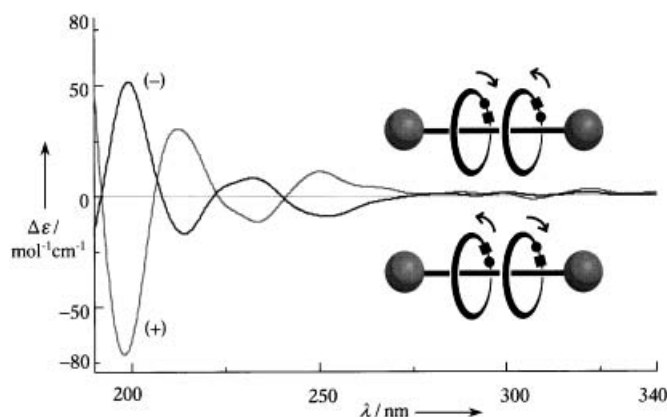


Figure 2. Circular dichroism spectra of the cycloenantiomers **1b** and **1c** in trifluoroethanol; concentration of (+) enantiomer 1.24×10^{-5} M, concentration of (–) enantiomer 3.22×10^{-5} M.

Table 1. Optical rotation ($[\alpha]^{26}$ in CHCl_3) of the cycloenantiomers **1b** and **1c** at different wavelengths; concentration of (+) enantiomer 5.82×10^{-4} M, concentration of (–) enantiomer 5.03×10^{-4} M.

λ [nm]	$\alpha(\mathbf{1b})$ [°] [a]	$\alpha(\mathbf{1c})$ [°] [a]
577	+8	–8
546	+5	–7
435	+10	–11
405	+16	–14
365	+26	–24

[a] A deviation of $\pm 1^\circ$ results from the precision of the polarimeter.

The remarkable property of this [3]rotaxane is the mechanical bonding of its achiral components, axle and wheels, which leads to a cyclodiastereomeric species. The stereoisomers are formed in statistical ratios (*meso*-**1**:(+)-**1**:(–)-**1** = 2:1:1), and can easily be separated by chromatographic methods. In this way it should be possible to form a [3]rotaxane with two different wheels, one unorientated and one orientated, as well as $[n]$ rotaxanes that also show cyclostereoisomerism.^[14] Thus, chiral rotaxanes will become more and more interesting in the future.^[15]

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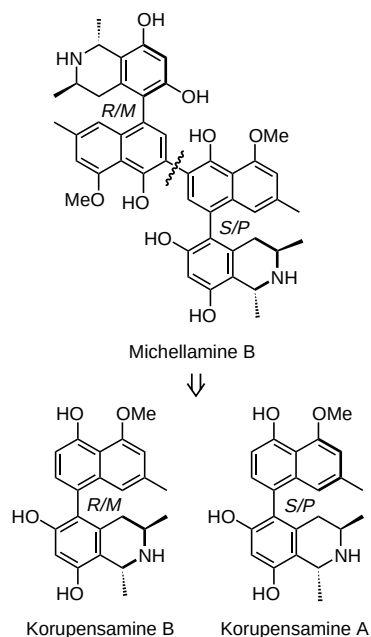
German version: *Angew. Chem.* **1999**, *111*, 3741–3743

Keywords: chirality • cycloenantiomerism • mechanical bonding • rotaxanes • supramolecular chemistry

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- [10] The workup was carried out chromatographically (SiO₂, 40–60 μ ; dichloromethane/*tert*-butyl methyl ether 12/1). The mixture of the isomers of rotaxane **1** showed the expected mass spectrum: *m/z* 3148.6 [*M*+H]⁺ (FAB, 9-nitroanthracene (9-NA)) *m/z* 3167.4 [*M*+Na]⁺ (MALDI-TOF; calcd for C₂₀₄H₂₂₀N₁₀O₁₇S₂: 3148.12). The compound has been characterized by ¹H and ¹³C NMR spectroscopy. M.p. 278 °C; elemental analysis calcd for C₂₀₄H₂₂₀N₁₀O₁₇S₂·3 CH₂Cl₂: C 73.06, H 6.69, N 4.12, S 1.88; found: C 72.98, H 6.77, N 4.13, S 2.31; the dichloromethane is detected by NMR spectroscopy.
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- [13] Optical rotation: JASCO Polarimeter P-1020, cell 100 × 3.5 mm inner diameter (CHCl₃); circular dichroism spectra: JASCO Spectropolarimeter J-720, cell 0.1 mm (trifluoroethanol).
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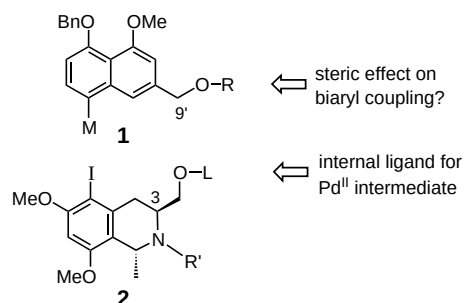
Scheme 1. Retrosynthesis of michellamine B to its components korupensamines A and B.

The guiding principles upon which our route was developed (Scheme 2) focus on the presence of a hydroxyl “handle” in each of the components. These were anticipated to afford considerable flexibility in fine-tuning the selectivity in the

A Stereospecific, Intermolecular Biaryl-Coupling Approach to Korupensamine A En Route to the Michellamines**

Bruce H. Lipshutz* and John M. Keith

The michellamines make up a rather unusual group of highly active antiviral natural products, with michellamine B receiving most of the attention as a potent anti-HIV-1 and -2 agent.^[1] The components of this alkaloid, korupensamines A and B, are related as diastereomers with respect to their axial chirality (Scheme 1).^[2] All attempts to effect a *direct*, highly stereocontrolled biaryl coupling between the naphthyl and tetrahydroisoquinoline portions have thus far met with limited success,^[3] which has encouraged a number of groups to devise clever, albeit indirect, alternatives.^[4] We now describe a novel solution to this problem that allows for *exclusive* entry to the korupensamine A series through a Pd⁰-mediated intermolecular biaryl cross-coupling reaction.



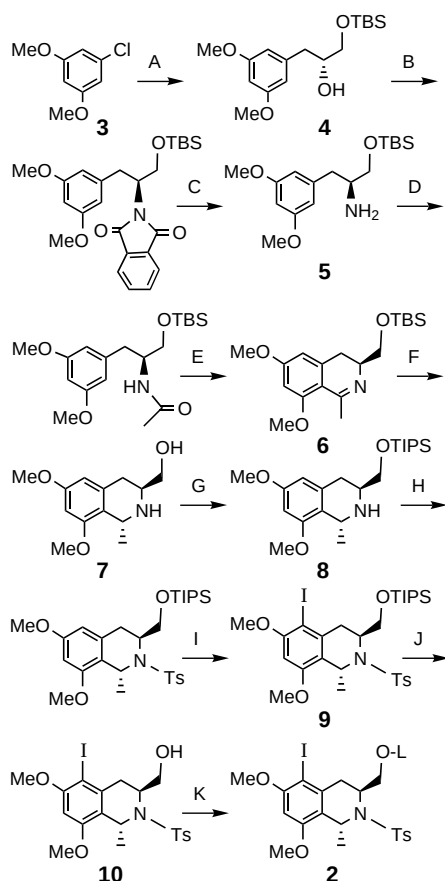
Scheme 2. Possible influence of substituents on the hydroxymethyl “handles”.

biaryl-forming step. Such a residue at C-9' in **1** might facilitate the introduction of a potentially influential steric component, while an OH function on the methyl group at C-3 in **2** would provide an opportunity for intramolecular chelation, thereby directing biaryl formation from one face of a transient polycyclic array.

Our route to nonracemic, protected hydroxymethylidod-tetrahydroisoquinoline **9** began with aryl chloride **3** (Scheme 3).^[5] A copper-catalyzed opening of commercially available (*S*)-TBS-glycidol (TBS = *tert*-butyldimethylsilyl) with the Grignard reagent derived from **3** leads to alcohol **4**, which is suitable for a Mitsunobu inversion^[6] with phthalimide followed by hydrazinolysis to give nonracemic amine **5**. Acetamide formation sets the stage for a temperature-sensitive^[7] Bischler–Napieralski cyclization to imine **6**. Careful reduction with a 1:7 mixture of Me₃Al (in heptane) and

[*] Prof. B. H. Lipshutz, Dr. J. M. Keith
Department of Chemistry
University of California
Santa Barbara, CA 93106 (USA)
Fax: (+001) 805-893-8265
E-mail: lipshutz@chem.ucsb.edu

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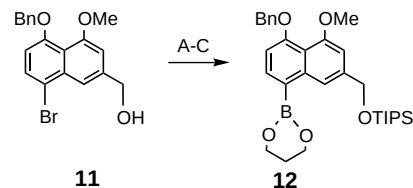
Scheme 3. A) 1) Mg, THF, BrCH₂CH₂Br Δ , 10 h; 2) (*S*)-TBS-glycidol, 10% CuBr·SMe₂, −20 °C, 4.5 h, 92%; B) phthalimide, PPh₃, DEAD, THF, 0 °C to RT, 20 h, 88%; C) H₂NNH₂, EtOH, Δ , 7 h, 89%; D) Ac₂O, Et₃N, CH₂Cl₂, RT, overnight, 99%; E) POCl₃, CH₃CN, 2,4,6-collidine, 85 °C, 3 h, 97%; F) LAH, Me₃Al, THF/hexanes, −78 °C to RT, overnight, 97% (3:1 *trans*:*cis*); G) NaH, TIPS-OTf, THF, −78 °C, 85%; H) TsCl, Et₃N, CH₂Cl₂, RT, 93%; I) PhI(O₂CCF₃)₂, I₂, CH₂Cl₂, −10 to 0 °C, 89%; J) TBAF, THF, RT, 2 h, 99%; K) NaH, THF, ClPPh₂, 0 °C to RT, 21 h, then BH₃·THF, RT, 40 min, 83%, or (2-diphenylphosphanyl)benzoic acid, DCC, CH₂Cl₂, RT, 14 h, 99%. DCC = dicyclohexylcarbodiimide; DEAD = diethyl azodicarboxylate; TBAF = tetrabutylammonium fluoride; Ts = *p*-H₃CC₆H₄SO₂.

lithiumaluminum hydride (LAH; solid)^[8] gives **7** in a 3:1 ratio of *trans*:*cis* products^[9] in excellent yield, albeit with concomitant loss of the TBS residue. To maximize the size of the L group in **2**, the triisopropylsilyl (TIPS) moiety was installed in **8** by conversion of **7** into its corresponding alkoxide followed by the low-temperature addition of TIPS-OTf (Tf = F₃CSO₂). *N*-Sulfonylation was accomplished without incident, and iodination^[10] proceeds regiospecifically at −10 to 0 °C to give the coupling partner **9**.

The halonaphthol precursor to **1**, bromide **11**, was prepared, with minor modifications, according to Bringmann,^[3a] thereby providing the hydroxymethyl “handle” required to test the effects of a bulky methyl group at this site. The nine-step sequence gave the desired derivative **11** in good overall yield (24%).

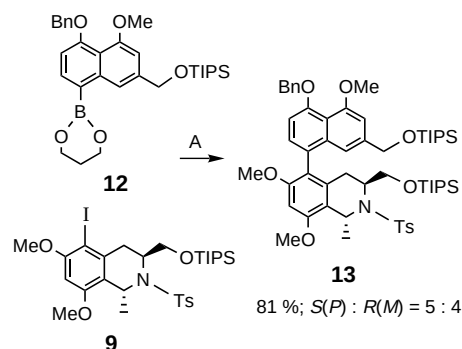
Numerous experiments designed to ascertain the most effective organometallic compound (M in **1**) for the intermolecular Pd⁰-catalyzed coupling led us to focus on Suzuki-based methodology, a conclusion also reached by Hoyer and Chen for this purpose.^[11] However, it was essential in this case

to use a boronate (**12**; Scheme 4), rather than the precursor boronic acid, which has good hydrolytic stability due to the presence of the OTIPS residue in this molecule. Initial model couplings with a simple 1-naphthalene boronate, while



Scheme 4. A) TIPS-OTf, Et₃N, CH₂Cl₂, RT, 24 h, 82%; B) *n*BuLi, −78 °C, B(OiPr)₃, RT, overnight, then NH₄Cl, 81%; C) HO(CH₂)₃OH, PhCH₃, RT, molecular sieves, 18 h, 98%.

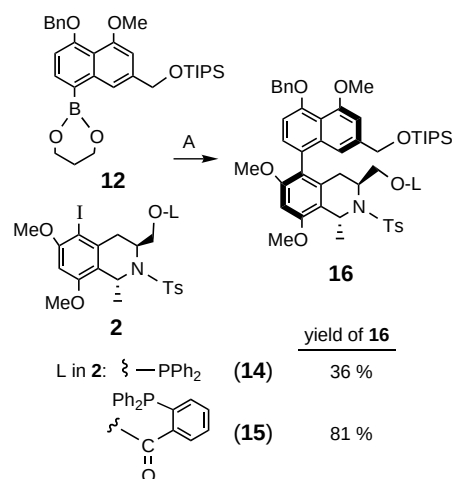
successful, did not translate to the “real” system, and revealed a critical need for 2,6-di-*tert*-butyl-4-methylphenol (BHT; 0.7 equiv)^[12] in the reaction medium (DMF). The coupling of iodide **9** with **12** occurred efficiently under these modified conditions (81%; Scheme 5), but the 5:4 ratio of *S*(*P*):*R*(*M*) atropisomers obtained indicated that steric factors alone at each hydroxymethyl site in **1** and **2** (R = L = TIPS) are not sufficient for high diastereocontrol in the biaryl forming step.



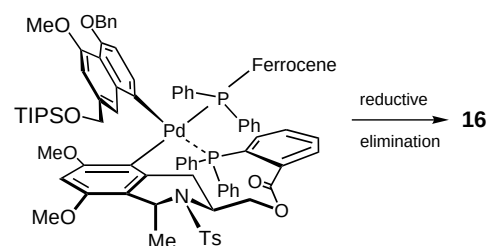
Scheme 5. A) cat. [Pd(PPh₃)₄], K₃PO₄, BHT, DMF, 96 °C.

The attachment of an internal chelating phosphane through the free hydroxyl group in **10** was far more rewarding.^[13] After conversion of **10** into the diphenylphosphane derivative **14** (Scheme 6), its Pd⁰-mediated coupling with **12** afforded a modest (36%) yield of cross-coupling product; however, a *single diastereomer* was produced. A switch to the *ortho*-diphenylphosphanylbenzoic acid ester derivative **15**^[14] was made because of the less than satisfactory level of efficiency and the tendency of **16** (L = PPh₂) to autoxidize to the corresponding phosphane oxide upon workup. The coupling of ester **15** with **12**, which was found to be better catalyzed by [Pd(dppf)Cl₂], also afforded a *single diastereomer*, now in 71% yield (dppf = 1,1'-bis(diphenylphosphanyl)ferrocenyl). Complete conversion into **16** could be accomplished by increasing the amount of catalyst and raising the temperature, thereby boosting the yield of the isolated product to 81%.

The sole formation of the *S*(*P*) atropisomer can be rationalized as viewed in Scheme 7. The PPh₂-substituted benzoate residue is best accommodated with the phosphorus



Scheme 6. A) for **12** + **14**: 10 mol % [Pd(PPh₃)₄], K₃PO₄, BHT, DMF, 99 °C; for **12** + **15**: 20 mol % [Pd(dppf)Cl₂], K₃PO₄, BHT, DMF, 117 °C.



Scheme 7. The stereochemical course of the reductive elimination.

atom ligated to the palladium atom from the bottom of the molecule relative to the plane of the tetrahydroisoquinoline moiety. Both the aryl ring of the ester, as well as the remaining two phenyl groups on phosphorus, combine to further block the back and underside. Since a dppf ligand occupies the fourth coordination site on the metal the bulky naphthylene moiety is forced to protrude forward over the aryl portion of the tetrahydroisoquinoline ring. Reductive elimination from this *cis* disposition about the palladium atom would give the observed isomer.

The assignment of the stereochemistry in **16** (L = *o*-PPh₂-C₆H₄CO) as *S*(*P*), which is associated with the korupensamine A series, could be readily made on the basis of a comparison of its CD spectrum, as well as that of its hydrolysis product **16** (L = H; NaOH, MeOH, RT, 85 %), with those of korupensamines A and B reported by Bringmann.^[1c, 2] Both derivatives of **16** (L = H, *o*-PPh₂-C₆H₄CO) display an initial positive Cotton effect in the 230–240 nm region characteristic of korupensamine A, which is strongly indicative of the chirality of the biaryl group being responsible for the observed spectra.^[15]

In summary, by virtue of a judiciously placed internal phosphane group that acts as a coordinating ligand for a Pd^{II} intermediate formed during a Suzuki biaryl coupling, the incipient axial chirality resulting from an ensuing reductive elimination can be fully controlled; in this case it leads to the korupensamine A skeleton. With this discovery, a stereo-specific route to half of the michellamine B molecule is a reasonable expectation. Moreover, by altering the residue attached to the hydroxymethyl “handles” (as in **1** and **2**),

opportunities exist for directing the orientation of the two aryl units so as to encourage formation of the *R*(*M*) atropisomer associated with korupensamine B. These and related applications to tetrahydroisoquinoline-based biaryl alkaloids, as well as to other challenging naturally occurring biaryls (for example, vancomycin) are currently under study.

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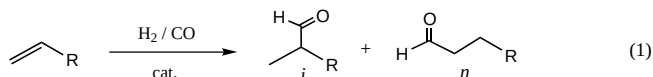
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- [15] From seminal work by Bringmann^[14] it is appreciated that structural changes with such tetrahydroisoquinolines can alter the observed CD spectra, thereby leading to erroneous assignments. In the case of derivatives **16**, it is apparent that alterations at the C-3 methyl group do not impact, let alone overshadow, the significant bias imposed in each by the axially chiral, nonracemic, biaryl nuclei.

Isomerization of Aldehydes Catalyzed by Rhodium(0) Olefin Complexes**

Christian P. Lenges and Maurice Brookhart*

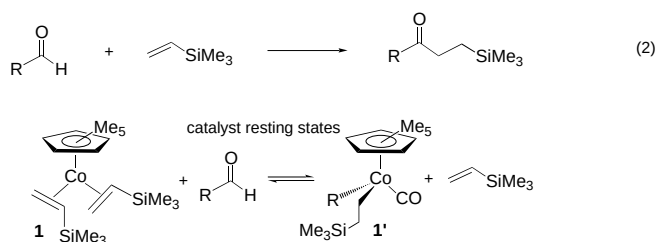
One of the earliest reported and most thoroughly investigated processes catalyzed by transition metals is the hydroformylation of olefins [Eq. (1)].^[1–8] The oxidative addition of



H₂ to a transition metal center is combined with reversible olefin and CO insertion processes to yield an acyl hydride complex. The final step in this catalytic process is generally accepted as the irreversible reductive elimination of the acyl hydride to generate the aldehyde products.^[9–11] In most applications the linear product is desired, although branched products are becoming increasingly important as indicated by recent efforts directed at the asymmetric hydroformylation of olefins.^[7b, c] An ongoing effort in this area of research is dedicated to altering the linear:branched isomer ratio by varying the ligand and catalyst structure.

We have recently reported that [C₅Me₅Co(olefin)₂] complexes can be used to carry out intermolecular hydroacylation reactions of bulky olefins such as vinyltrimethylsilane. The resting state of the catalyst was established as a mixture of the Co^I bis-olefin complex and the Co^{III} dialkyl carbonyl complex whose ratio is dependent on the substrate structures and concentrations [Eq. (2)].^[12, 13]

When *n*-butyraldehyde was used as the substrate traces of isobutyraldehyde were evident near complete conversion of aldehyde, which indicated some reversibility prior to the reductive elimination of ketone.^[12] Reductive elimination



with the second row rhodium analogues should exhibit higher energy barriers than the cobalt complexes; thus rhodium analogues may exhibit more extensive reversibility and have the potential to isomerize aldehydes prior to ketone formation.^[14, 15] Indeed, we report here that rhodium(0) olefin complexes of the type [C₅Me₅Rh(C₂H₃R)₂] catalyze the interconversion of linear and branched aldehydes as well as transfer formylation reactions.^[16]

Reduction of [(C₅Me₅RhCl₂)₂] with zinc in the presence of propene results in the formation of [C₅Me₅Rh(C₂H₃Me)₂] (**2**), which was isolated as an analytically pure yellow solid.^[17, 18] Characterization of **2** by NMR spectroscopy indicates a mixture of isomers. Recrystallization from acetone generates the single isomer **2a**, which was characterized by X-ray crystallographic analysis (Figure 1). When complex **2a** is dissolved in [D₆]acetone a mixture of isomers **2a**, **2b**, and **2c**^[19] is generated in minutes. These correspond to isomers generated by rotation around the Rh–olefin bond. Eventually a fourth isomer **2d** is observed, which is generated by olefin dissociation and rebinding (Scheme 1).

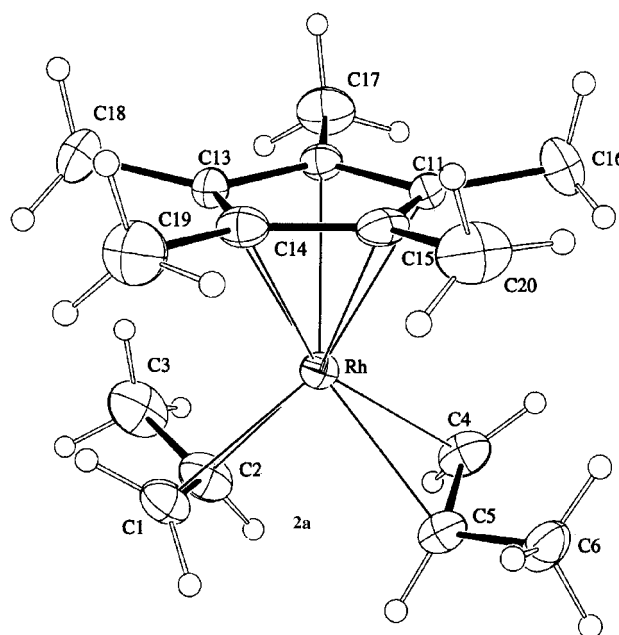
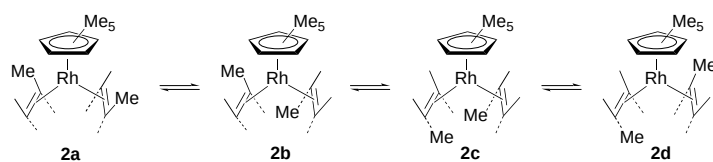


Figure 1. ORTEP diagram of complex **2a**; ellipsoids are drawn with 50% probability. Selected bond distances [Å] and angles [°]: Rh–C1 2.129(4), Rh–C2 2.129(5), Rh–C4 2.133(5), Rh–C5 2.134(4), C1–C2 1.404(6), C2–C3 1.493(7), C4–C5 1.416(6), C5–C6 1.517; C1–Rh–C2 38.51(18); C1–Rh–C4 108.61(19); C1–Rh–C5 87.38(18); C2–Rh–C4 85.15(20); C2–Rh–C5 87.00(20); C4–Rh–C5 38.77(16); C1–C2–C3 124.5(5); C4–C5–C6 120.4(4); C5–Rh–C1–C2 88.5(5); C4–Rh–C2–C1 128.4(6); C1–Rh–C4–C5 60.2(4); C2–Rh–C5–C4 86.0(5); C1–Rh–C2–C3 119.7(6); C2–Rh–C4–C5 91.2(5); C4–Rh–C5–C6 115.0(5); Rh–C1–C2–C3 110.1(7).

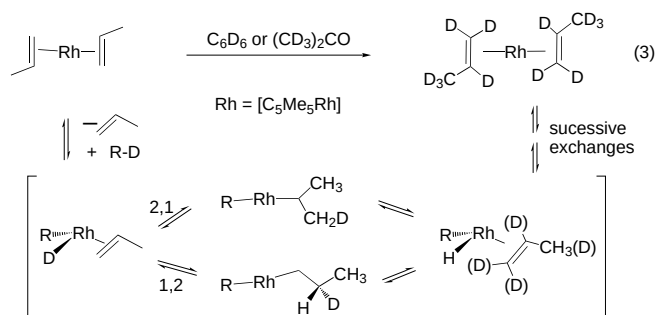
[*] Prof. Dr. M. Brookhart, Dipl. Chem. C. P. Lenges
Department of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599-3290 (USA)
Fax: (+1) 919-962-2476
E-mail: brook@net.chem.unc.edu

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Scheme 1. Isomers of **2**.

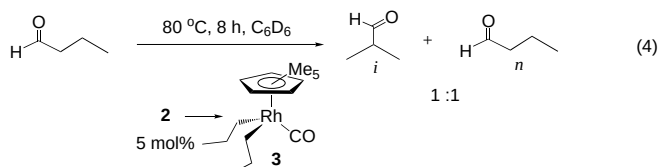
Propene readily dissociates from **2** to generate a 16-electron species of the type $[\text{C}_5\text{Me}_5\text{Rh}(\text{C}_2\text{H}_3\text{Me})]$. Thermolysis of **2** in $[\text{D}_6]$ benzene or $[\text{D}_6]$ acetone results in H/D exchange reactions of the solvent with the coordinated olefin. After C–H(D) bond activation of the solvent, reversible 1,2- and 2,1-olefin insertions can take place to exchange the deuterium label into the methine, methylene, and methyl groups. All ^1H NMR resonances for coordinated propene have vanished in the spectrum after 5 h at 55°C , with only singlets remaining in the C_5Me_5 -resonance region for the isomers of **2** [Eq. (3)].



The reaction of **2** with aliphatic aldehydes was next investigated. The *n*- and *iso*-butanals were initially examined since the largest volume hydroformylation process involves these aldehydes. The reaction of **2** with ten equivalents of *n*-butanal in $[\text{D}_6]$ benzene at 50°C results in the disappearance of the series of C_5Me_5 resonances of **2** over 30 minutes to generate a single new rhodium species **3** with a C_5Me_5 resonance at $\delta = 1.74$ in the NMR spectrum. In addition, one equivalent of free propene is observed in the reaction mixture. Removal of all volatile material at this stage leaves a yellow oil corresponding to **3** which is pure by ^1H NMR spectroscopy and exhibits a series of multiplets in the alkyl region ($\delta = 1.21$ – 1.48) that integrates to 8 protons and a triplet at $\delta = 0.89$ (t , $^3J(\text{H}, \text{H}) = 8 \text{ Hz}$, 6H; CH_3) indicating the presence of two equivalent CH_3 groups. Analysis by ^{13}C NMR spectroscopy shows, in addition to methine and methyl signals for the C_5Me_5 moiety, three resonances in the alkyl region at $\delta = 24.2$ (d, $J(\text{Rh}, \text{C}) = 25.8 \text{ Hz}$), 19.7 (d, $J(\text{Rh}, \text{C}) = 2.6 \text{ Hz}$), and 29.4 (s) and one resonance at $\delta = 196.0$ (d, $J(\text{Rh}, \text{C}) = 83.2 \text{ Hz}$), which is characteristic of a CO group coordinated to a rhodium center. Correspondingly, IR analysis of the reaction mixture shows a strong Rh–CO band at $\tilde{\nu}_{\text{CO}} = 1797 \text{ cm}^{-1}$. Complex **3** is formulated as $[\text{C}_5\text{Me}_5\text{Rh}(\text{CO})(\text{CH}_2\text{CH}_2\text{CH}_3)_2]$, which is the result of propene dissociation from **2** followed by oxidative addition of *n*-butanal, propene insertion into the Rh^{III} hydride, and CO deinsertion.^[20] Decomposition of **3** occurs over 24 h in an inert atmosphere or in solution to generate carbonylated rhodium complexes, of which the major product is the blue dimer

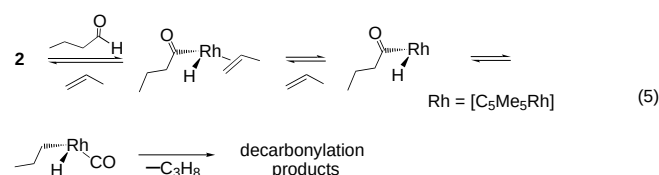
$[\{\text{C}_5\text{Me}_5\text{Rh}(\text{CO})\}_2]$ (**4**) as indicated by IR analysis ($\tilde{\nu}_{\text{CO}} = 1732 \text{ cm}^{-1}$).^[21, 22]

A reaction of **2** (0.01 g, $3.1 \times 10^{-5} \text{ mol}$) with 20 equivalents *n*-butanal at 80°C in $[\text{D}_6]$ benzene was followed by NMR spectroscopy. Complex **3** was generated in a fast, initial reaction from **2**. After 8 h, *n*-butanal was isomerized to generate a 1:1 mixture of *n*-butanal and *iso*-butanal. The only rhodium species present in solution throughout this process is **3** [Eq. (4)] in addition to small amounts of free propene. This



reaction can be performed in a variety of solvents, such as acetone, toluene, or cyclohexane with similar results. The introduction of additional *n*-butanal to a reaction mixture generated in this fashion allows further isomerization, which indicates some active catalyst was still present. Higher reaction temperatures (exceeding 100°C) favor the competing decarbonylation reaction and result in an initial fast isomerization followed by catalyst deactivation.

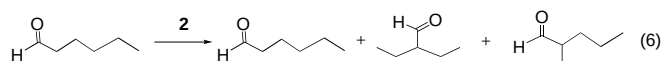
A reduced catalyst load (0.5%) still results in initial isomerization; however, catalyst deactivation to generate carbonylated rhodium complexes (mainly **4**) is observed to be competitive with aldehyde isomerization. The hydroacylation of propene under the reaction conditions does not generate significant amounts of 4-heptanone.^[23] Longer catalyst lifetimes were achieved by conducting the thermolysis of **2** in the presence of added propene (48 h at 100°C , 3 mol% **2**, *n*-butanal, 50 equiv propene generates a 3:2 mixture of *n*:*iso*-butanals). Olefin loss from a Rh^{III} acyl hydride olefin complex generated from **2** after oxidative addition of aldehyde is thought to be a major deactivation route^[12] since alkane loss from a Rh^{III} alkyl hydride carbonyl species is most likely irreversible under the reaction conditions. This pathway is minimized in the presence of excess olefin [Eq. (5)]. The formation of hexane by reductive elimination from **3** was not observed in the deactivation process.^[12, 23]



The isomerization of *iso*-butanal to *n*-butanal is also observed using **2** as a catalyst precursor (5 mol% **2**, 80°C , 24 h, 2:3 *n*:*iso*-butanals). Complex **3** is the only spectroscopically observed (^1H NMR) intermediate during this isomerization process. The possible resting state analogue $[\text{C}_5\text{Me}_5\text{Rh}(\text{CO})(n\text{Pr})(i\text{Pr})]$ (**3'**) was not observed; IR analysis of a reaction mixture generated from the reaction of *iso*-butanal with **2** showed $\tilde{\nu}_{\text{CO}} = 1980 \text{ cm}^{-1}$, which is identical to **3**. These results indicate that aldehyde isomerization is observed starting from both isomeric aldehydes, but the thermody-

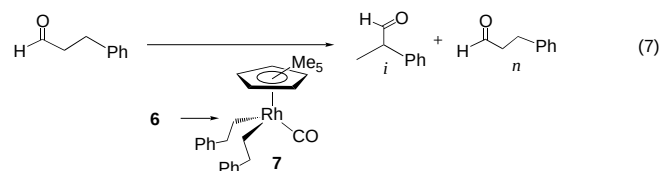
namic equilibrium for the isomeric aldehydes may not be reached in all cases because of catalyst decomposition.^[24]

n-Hexanal was investigated as substrate by using complex **2** as a catalyst precursor. Complex **2** (0.01 g, 3.1×10^{-5} mol, 5 mol %) was heated to 80 °C in the presence of *n*-hexanal (20 equiv) and five equivalents of 1-pentene in benzene. Analysis of the reaction mixture by ¹H NMR spectroscopy indicated the formation of pentene isomers and the three isomeric hexanals (9.27, t; 9.33, d; 9.51, d).^[25] Pentene isomerization is fast (30 min, 80 °C), while aldehyde isomerization occurs over 5 h. These results show that, as for butanals, aldehyde activation has occurred and is followed by insertion and deinsertion processes which distribute the formyl group throughout the pentyl chain [Eq. (6)].



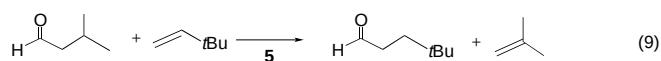
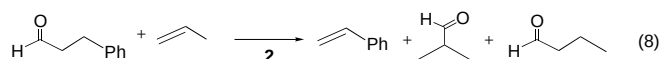
To increase the catalyst activity and to possibly extend catalysis to lower temperatures, a more electron-deficient rhodium olefin complex was investigated. The isomerization of *n*-butanal to a 1:1 mixture of *n* and *iso*-butanals with $[(C_5Me_4CF_3)Rh(C_2H_3SiMe_3)_2]$ (**5**, 0.011 g, 2.3×10^{-5} mol, 5 mol %)^[26] was observed at 55 °C over 5 h. Small amounts of an additional aldehyde, assigned as $Me_3SiCH_2CH_2C(O)H$, are also observed during this process. A resting state species analogous to **3** is proposed for this system. This is suggested by the characteristic IR band at 2000 cm^{-1} that is indicative of a significant reduction in electron density at the rhodium center, which perhaps facilitates the conversion of the Rh^{III} resting state to Rh^I intermediates.^[27]

The application of this isomerization process to substituted aldehydes was also investigated. The isomerization of 2-phenylpropanal was attempted using the bis-styrene complex $[C_5Me_5Rh(C_2H_3Ph)_2]$ (**6**) as the catalyst precursor. The rate of olefin dissociation from **6** is reduced relative to **2**. Heating a solution of **6** in $[D_6]$ benzene for 24 h at 80 °C results in complete deuteration of the olefinic sites [see Eq. (3)]. Complete ring deuteration of coordinated styrene is observed after thermolysis for one week. Heating a solution of **6** (0.01 g, 2.2×10^{-5} mol, 5 mol %) in benzene to 120 °C with 2-phenylpropanal (20 equiv) generates a mixture of the two isomeric aldehydes in a 2:1 ratio (*n*:*iso*) after 12 h. The formation of an intermediate (**7**) analogous to **3** during aldehyde isomerization was observed and is assigned as the catalyst resting state ($\delta = 1.68$, C_5Me_5 ; $\nu_{CO} = 1983\text{ cm}^{-1}$) [Eq. (7)].^[28]



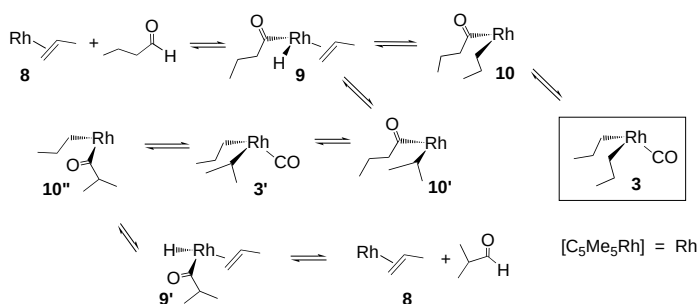
Formyl groups can be transferred between two different olefins using these rhodium catalysts. For example, thermolysis (110 °C, 24 h, $[D_8]$ toluene) of 2-phenylpropanal (6×10^{-4} mol) with catalyst **2** (0.01 g, 3.1×10^{-5} mol, 5 mol %) in the presence of excess propene results in transfer

formylation and exclusive generation of isomeric butanals and free styrene [Eq. (8)]. IR analysis of the working catalyst



system shows a band at 1980 cm^{-1} in the spectrum and suggests a Rh^{III} dialkyl carbonyl resting state; however, the nature of the alkyl groups could not be identified by ¹H NMR spectroscopy because of low catalyst loading and the presence of multiple organic species at high concentrations. Analogously, transfer formylation from isovaleraldehyde to 3,3-dimethyl-1-butene (50 equiv) using complex **5** as catalyst generates the corresponding linear aldehyde exclusively together with 2-methylpropene (2 mol % **5**, 60 °C, 24 h, 85 % conversion), [Eq. (9)].

Based on the information described herein and on prior studies detailing the reactivity of these types of rhodium complexes,^[29] a mechanism is proposed for this catalytic aldehyde isomerization process (Scheme 2). Olefin dissociation from **2** generates a reactive 16-electron species **8** which



Scheme 2. Proposed mechanism for the catalytic isomerization of aldehydes.

oxidatively adds *n*-butanal to form an intermediate rhodium(III) acyl hydride olefin complex **9**. Olefin insertion can occur with either regiochemistry to generate an acyl alkyl rhodium(III) species, either **10** or **10'**. CO-deinsertion from **10** generates the observed resting state **3**. The branched intermediate (**3'**) generated from **10'** was not observed but must be formed to account for the aldehyde isomerization. Deinsertion of **3'** to generate **10''** followed by β -elimination gives **9'**, which forms *iso*-butyraldehyde on reductive elimination. This scheme, coupled with olefin exchange, also accounts for the observed transfer formylation reactions.

In summary, the reaction of alkyl aldehydes with $[C_5Me_5Rh(olefin)_2]$ complexes results in a catalytic isomerization process that generates a mixture of isomeric aldehydes. These initial results introduce a catalytic process that offers an indirect method for influencing the *n*:*iso* ratio of aldehydes formed in hydroformylation reactions. This procedure is a conceptually different approach for the preparation of a desired linear or branched aldehyde since olefin hydroformylation can be separated from an aldehyde isomerization

process that avoids hydroformylation conditions. Catalyst deactivation pathways that result in decarbonylation products have been identified. In the presence of other olefins, transfer formylation was observed, which provides in principle a general method for the introduction of a formyl group into an olefinic substrate.

Experimental Section

All operations were carried out under an Ar atmosphere. All solvents used were degassed and purified following standard methods.

2: $[(C_5Me_5RhCl_2)_2]$ (0.2 g, 6.5×10^{-4} mol) was stirred with zinc (0.45 g, 6.5×10^{-3} mol) in THF (15 mL) for 24 h while a slow flow of propene was passed over the reaction mixture. The residual zinc was filtered from the homogeneous yellow mixture, which was evaporated, and extracted into pentane. Removal of the solvent generated a yellow solid. Recrystallization from acetone yielded complex **2a** as yellow crystalline material (one isomer) which was used for the structure determination (Figure 1). ^1H NMR (400 MHz, $[D_6]acetone$, $20^\circ C$): $\delta = 1.51, 1.56, 1.62$ (3 s, $3 \times 15H$, $3 \times C_5Me_5$), 0.95, 1.41, 1.45, 1.59 (4 d, $4 \times 3H$, Me), olefinic CH overlapping, the 4th C_5Me_5 resonance is obscured; $^{13}C\{^1H\}$ (100 MHz, $[D_6]acetone$, $20^\circ C$): **2a**: $\delta = 9.40, 97.0$ (d, 3.8 Hz, C_5Me_5), 60.0, 45.7 (d, 5.6 Hz), 21.1 (Me); **2c**: 10.1, 97.5 (d, 3.8 Hz), 52.6, 47.8 (d, 14 Hz), 21.3 (Me); **2b** and **2d**: 9.3, 96.9 (d, C_5Me_5 and 8.7, 96.5 (d, C_5Me_5), 56.0, 54.5, 54.1, 52.2, 50.1, 47.4, 46.6, 44.6 (d), 21.8, 21.4, 19.5, 17.1 (Me). Elemental analysis: calcd: C 59.63, H 8.44; found: C 59.90, H 8.62.

Structural data for **2a**: crystals obtained from acetone; $C_{16}H_{27}Rh$, $M_r = 322.29$, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 14.2482(7)$, $b = 7.1385(4)$, $c = 15.7584(8)$ Å, $\beta = 108.8420(10)^\circ$, $V = 1516.91(14)$ Å³, $\rho_{calcd} = 1.411$ g cm⁻³, $T = -110^\circ C$, $2\theta_{max} = 50^\circ$, $MoK\alpha$ radiation ($\lambda = 0.71073$ Å), 7807 reflections were measured; 2672 unique reflections were obtained, and 2100 of these with $I > 3.0\sigma(I)$ were used in the refinement, data were collected on a Siemens SMART diffractometer using the omega scan method. For significant reflections merging $R = 0.035$, residuals: $R_F = 0.044$, $R_w = 0.047$ (significant reflections), GOF: 2.54. – 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-136183. 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).

3: A solution of $[C_5Me_5Rh(C_2H_5Me)_2]$ (0.1 g, 3.1×10^{-4} mol) in benzene (10 mL) was treated with 10 equiv of *n*-butanal (0.22 g) and heated for one hour at $50^\circ C$. All volatiles were removed and complex **3** was isolated as a yellow oil. Complex **3** decomposes as the oil or in solution over several hours at $20^\circ C$; attempts to crystallize **3** from acetone were not successful. ^1H NMR (400 MHz, $[D_6]acetone$, $20^\circ C$): $\delta = 1.74$ (s, 15H, C_5Me_5), 0.89 (t, 7.8 Hz, 6H, CH_3), 1.21 (m, 4H, CH_2), 1.48 (m, 4H, CH_2); $^{13}C\{^1H\}$ NMR (100 MHz, $[D_6]acetone$, $20^\circ C$): $\delta = 9.0$ (C_5Me_5), 101.9 (C_5Me_5), 24.2 (d, 25.8 Hz, $RhCH_2$), 19.7 (d, 2.6 Hz, CH_2), 29.4 (s, CH_3), 196.0 (d, 83.2 Hz, $RhCO$); IR (toluene): $\nu_{CO} = 1979$ cm⁻¹.

6: Complex **6** was prepared in an analogous manner to complex **2** and isolated as an orange solid after recrystallization from acetone. NMR analysis shows the formation of one major isomer (70%) and two minor isomers based on olefin coordination as discussed for **2**. ^1H NMR (400 MHz, $[D_6]benzene$, $20^\circ C$): $\delta = 1.43$ (s, 15H, C_5Me_5), 2.10 (dd, 16.0, 2 Hz, 2H), 2.55 (dd, 16.0, 2 Hz, 2H), 3.83 (ddd, 16.0, 10, 2 Hz, 2H), 6.38 (m, 2H, Ar), 6.89–7.05 (m, 2H, Ar), 7.02–7.23 (m, 6H, Ar).

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Keywords: aldehydes • C–H activation • hydroformylations • isomerizations • rhodium

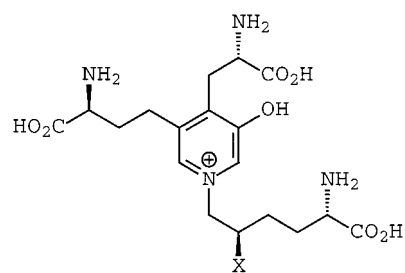
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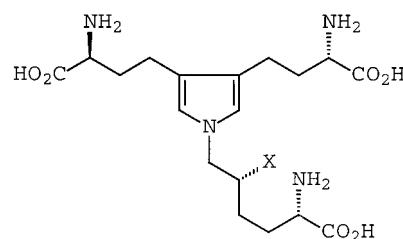
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- [28] The formation of an intermediate with the same characteristics as **7** was also observed in a reaction of 1-phenylpropanal with **6**. At this point an alternative structure for **7** can not be excluded (for example, the branched isomer as in **3'**).
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(+)-**1**: X=OH, pyridinoline
(+)-**3**: X=H, deoxypyridinoline



2: X=OH, pyrrololine
(+)-**4**: X=H, deoxypyrrololine

Total Synthesis of (+)-Deoxypyrrololine: A Potential Biochemical Marker for Diagnosis of Osteoporosis

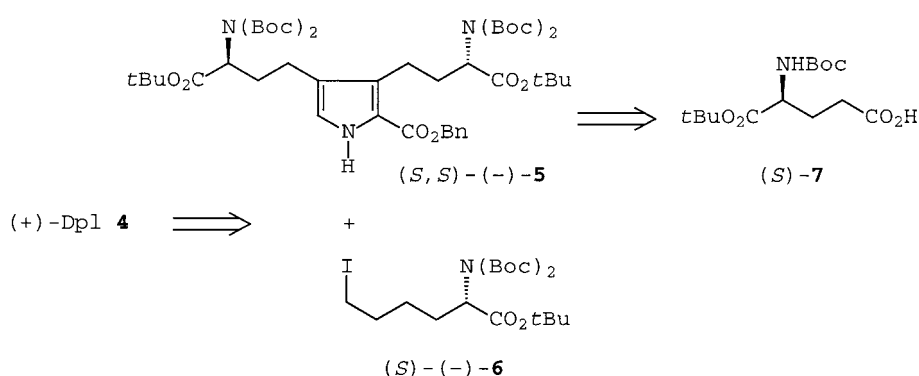
Maciej Adamczyk,* Donald D. Johnson, and
Rajarathnam E. Reddy

Osteoporosis is a crippling degenerative bone disease that affects the aged population, particularly postmenopausal women.^[1] This metabolic disease is a consequence of an imbalance in the bone renewal process, which occurs when bone resorption exceeds bone formation. The current methods for diagnosis of osteoporosis involve analysis of bone based on histomorphometry and densitometric measurements.^[2] The efforts for prevention of this bone disease, as well as to develop an effective antiresorptive therapy, have increased the search for reliable and noninvasive biochemical markers of bone resorption.^[1c, 3] The traditional markers of bone resorption, for example urinary calcium^[4] and hydroxyproline,^[5] lack clinical sensitivity and specificity for diagnosis of osteoporosis.

In recent years, the pyridinium cross-links (+)-pyridinoline (Pyl, **1**)^[6] and (+)-deoxypyridinoline (Dpd, **3**)^[7] have gained much attention owing to their potential clinical utility in the diagnosis of osteoporosis and other bone diseases.^[8–10] In 1981 Scott et al.^[11] postulated the existence of pyrrole cross-links pyrrololine (Pyl, **2**) and deoxypyrrololine (Dpl, **4**)^[12] in various tissues. Subsequent studies by several other groups have provided further convincing evidence for the existence of pyrrole cross-links.^[13, 14] Unfortunately, the attempts to isolate cross-links **2** and **4** have not been successful so far.^[3a,d] It was proposed

that **2** and **4** are formed from natural (2*S*,5*R*)-hydroxylysine and (5*S*)-lysine present in collagen by a lysyl oxidase mediated enzymatic process, in an analogous fashion to the pyridinium cross-links **1** and **3**.^[3d, 13c,d,f] Here we report the first synthesis of the pyrrole cross-link (+)-deoxypyrrololine (Dpl, **4**) from (4*S*)-5-(*tert*-butoxy)-4-[(*tert*-butoxycarbonyl)amino]-5-oxo-pentanoic acid (**7**).

The synthesis of **4** involves alkylation of the pyrrole derivative (5*S*)-(-)-**5** with iodide (5*S*)-(-)-**6**, followed by hydrolysis of the protecting groups and removal of the 2-carboxybenzyl ester moiety (Scheme 1). It was envisioned that the key intermediate (5*S*)-(-)-**5** could be prepared from the α -acetoxynitro compound **13** (see Scheme 2) and benzyl

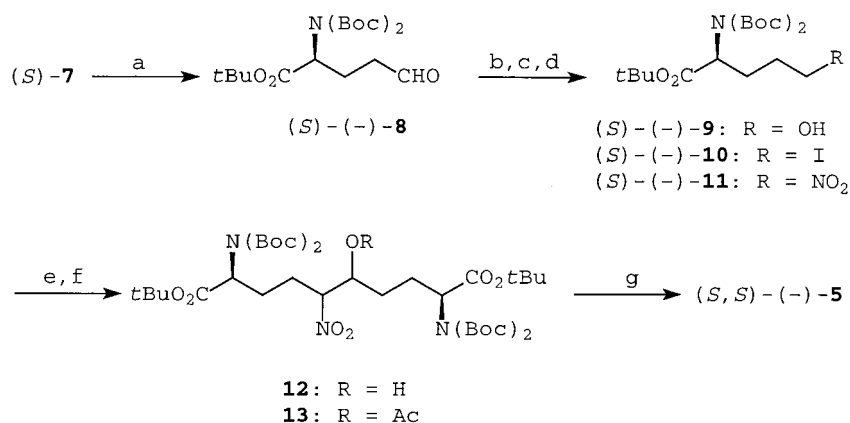


Scheme 1. Retrosynthesis of (+)-deoxypyrrololine (Dpl, **4**). Bn = benzyl, Boc = *tert*-butoxycarbonyl.

[*] Dr. M. Adamczyk, D. D. Johnson, Dr. R. E. Reddy
Division Organic Chemistry Research (9NM, AP20)
Diagnostics Division, Abbott Laboratories
100 Abbott Park Road, Abbott Park, IL 60064-6016 (USA)
Fax: (+1) 847-938-8927
E-mail: maciej.adamczyk@abbott.com

isocynoacetate (**14**)^[15, 16] by a base-promoted condensation and cyclization process. Compound **13** could be obtained from **7**.

Accordingly, the commercially available (5*S*)-**7** was converted into the aldehyde (5*S*)-(-)-**8**,^[17] which was then reduced

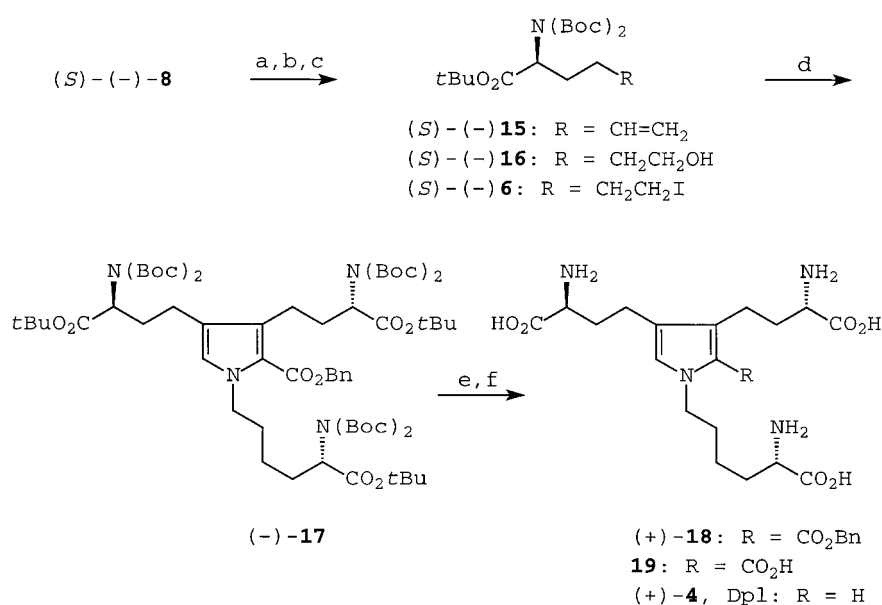


Scheme 2. Synthesis of (S,S) -(-)-**5**. Reagents and conditions: a) See ref. [17]; b) $NaBH_4$ (1.0 equiv), MeOH, 0 °C, 45 min, 95%; c) I_2 (1.5 equiv), PPh_3 (1.6 equiv), imidazole (2.0 equiv), THF, 23 °C, 1.5 h, 94%; d) $NaNO_2$ (2.0 equiv), DMF, 23 °C, 30 min, 55%; e) (S) -(-)-**8** (1.1 equiv), DMAP, (4.0 equiv), CH_2Cl_2 , 23 °C, 8 d, 91%; f) Ac_2O (1.5 equiv), DMAP (0.1 equiv), THF, 23 °C, 2 h, 96%; g) BnO_2CCH_2NC (**14**, 1.3 equiv), DBU (2.5 equiv), THF, 0–23 °C, 5 h, 57%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine.

with $NaBH_4$ in MeOH to the alcohol (S) -(-)-**9** in 95% yield (Scheme 2).^[18] The hydroxyl group in (S) -(-)-**9** was converted into the iodide to provide (S) -(-)-**10**, which was subsequently treated with sodium nitrite in DMF^[19] to afford the corresponding nitro compound (S) -(-)-**11** in 55% yield. Condensation of (S) -(-)-**11** with aldehyde (S) -(-)-**8** (Henry reaction)^[20] in the presence of 4-dimethylaminopyridine in CH_2Cl_2 gave α -hydroxynitro compound **12** in 91% yield as a mixture of diastereomers (1:1 ratio). Since the two new chiral centers (the locations of the NO_2 and OH groups) in **12** are eventually eliminated during the pyrrole ring formation, the diastereomeric mixture of **12** was converted into the corresponding acetate derivative **13** by treatment with Ac_2O in THF in almost quantitative yield (96%). Finally, condensation of the diastereomeric mixture of α -acetoxy nitro compound **13** with benzyl isocynoacetate (**14**)^[15, 16] in the presence of DBU in THF at 0 °C to room temperature, followed by column chromatography on silica gel, gave the key intermediate (S,S) -(-)-**5** in 57% yield ($[\alpha]_D^{23} = -14.9$ ($c = 1.37$, MeOH)).

The next step in the synthesis of (+)-**4** was installation of lysine chain at the pyrrole nitrogen atom in (S,S) -(-)-**5** by alkylation with **6**. The iodide (S) -(-)-**6** was prepared from aldehyde (S) -(-)-**8** in three steps (Scheme 3). First, the (S) -(-)-**8** was extended by a methylene group to the corresponding olefin (S) -(-)-**15** by Wittig reaction,^[17] which upon hydroboration afforded the alcohol (S) -(-)-**16** in excellent yield (87%). The hydroxyl group in (S) -(-)-**16** was then converted to provide the desired iodide (S) -(-)-**6** in 92%

yield using I_2 , PPh_3 , and imidazole in THF. Treatment of (S,S) -(-)-**5** with 1.0 equivalent of $tBuOK$ in THF and subsequent reaction with 2.0 equivalents of (S) -(-)-**6** in the presence of [18]crown-6^[21] at room temperature afforded the *N*-alkylated pyrrole derivative (-)-**17** in 42% yield after purification by column chromatography on silica gel.^[22] The derivative (-)-**17** has the required amino acid chains at the 1-, 3-, and 4-positions of the pyrrole ring. The synthesis of (+)-Dpl (**4**) would only require unmasking the protecting groups and removal of the benzyloxycarbonyl group at the 2-position of pyrrole ring. Thus, (-)-**17** was first treated with trifluoroacetic acid and water,^[9a] and the mixture obtained was purified by preparative reverse-phase HPLC to afford (+)-**18** in 79% yield. The



Scheme 3. Synthesis of (+)-**4**. Reagents and conditions: a) $MePPh_3Br$ (2.0 equiv), $nBuLi$ (2.0 equiv), THF 0 °C, 45 min, 61%; b) $B_2H_6 \cdot THF$ (1.3 equiv), THF, 0–23 °C, 17 h, 87%; c) I_2 (1.5 equiv), PPh_3 (1.6 equiv), imidazole (2.0 equiv), THF, 23 °C, 1 h, 92%; d) (S,S) -(-)-**5**, $tBuOK$ (1.0 equiv), [18]crown-6 (0.1 equiv), THF, 23 °C, 7 h, 42%; e) TFA/water (95/5), 23 °C, 2 h, 79%; f) 10% Pd/C, H_2 , MeOH, 23 °C, 1 h, then TFA, 23 °C, 15 min, 39%. TFA = trifluoroacetic acid.

benzyl group in (+)-**18** was removed by hydrogenation over 10% Pd/C in MeOH to give the acid **19**, which without purification was decarboxylated with trifluoroacetic acid.^[23] Concentration of the crude reaction mixture followed by purification by preparative reverse-phase HPLC and lyophilization afforded **4**^[24] in 39% yield as a pale pink powder ($[\alpha]_D^{23} = +20.6$ ($c = 0.17$, H_2O)).

In summary a general and convergent total synthesis of (+)-deoxypyrrrololine (Dpl, **4**), a pyrrole cross-link of collagen, has been achieved utilizing a commercially available chiral starting material (**7**). The method is currently being applied to the synthesis of pyrrololine (**2**) and for the preparation of

various immunocomponents (immunogens, antibodies, and probes) which are imperative for development of assays for diagnosis and treatment of bone diseases.

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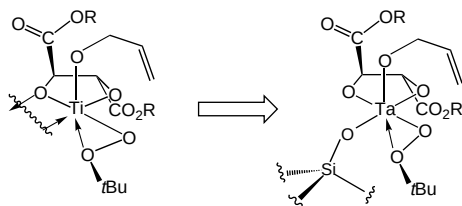
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- [22] (–)-**17**: $R_f = 0.42$ (silica gel, EtOAc/hexanes 2/8); $[\alpha]_D^{25} = -6.8$ ($c = 2.0$, MeOH); analytical reverse-phase HPLC (Waters, Rcm, μ Bondapak C18 column, 10 μ m, 8 $\times$ 10 mm; MeCN/0.1 % aq. trifluoroacetic acid 95/5, 2.0 mL min⁻¹, detection at 215 nm): $R_t = 8.7$ min (97 %); ¹H NMR (300 MHz, CDCl₃, 23 °C, TMS): $\delta = 7.43$ –7.26 (m, 5H, Ar-H), 6.58 (s, 1H, pyrrole-H), 5.26 (q, 2H, $J = 48.3$, 12.3 Hz, Ar-CH₂), 4.72–4.61 (m, 3H, 3 $\times$ N-CH-CO₂tBu), 4.11 (t, 2H, $J = 8.1$ Hz, pyrrole-N-CH₂), 2.82–2.60 (m, 2H), 2.44–1.24 (m, 12H), 1.49 (s, 18H), 1.48 (s, 18H), 1.47 (s, 18H), 1.44 (s, 9H), 1.43 (s, 9H), 1.42 (s, 9H); ¹³C NMR (75 MHz, CDCl₃, 23 °C, TMS): $\delta = 169.8$, 169.7, 169.6, 161.0, 152.5, 152.4, 136.6, 132.2, 128.5, 127.9, 126.5, 121.4, 118.2, 82.7, 82.5, 82.4, 81.1, 81.0, 77.2, 65.3, 59.3, 58.8, 58.3, 49.7, 31.7, 31.1, 29.2, 29.1, 28.0, 27.9, 23.8, 23.1, 21.3; ESI-MS (m/z %): 1319 (100) $[M+NH_4]^+$; HR-MS (FAB): calcd for C₆₈H₁₀₉N₄O₂₀: 1323.7427 $[M+Na]^+$, found: 1323.7449.
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- [24] (+)-Dpl (**4**): $[\alpha]_D^{20} = +20.6$ ($c = 0.17$, H₂O); analytical reverse-phase HPLC (Waters, Rcm, μ Bondapak C18 column, 10 μ m, 8 $\times$ 10 mm; MeCN/0.1 % aq. trifluoroacetic acid 4/96, 2.0 mL min⁻¹, detection at 215 nm): $R_t = 5.54$ min (96 %); ¹H NMR (300 MHz, CD₃OD, 23 °C, TMS): $\delta = 6.51$ (s, 2H, pyrrole-H), 3.92–3.78 (m, 5H, 3 $\times$ N-CH-CO₂H and pyrrole-N-CH₂), 2.64–2.52 (m, 4H), 2.20–1.98 (m, 4H), 1.94–1.82 (m, 2H), 1.82–1.70 (m, 2H), 1.48–1.38 (m, 2H); ¹³C NMR (75 MHz, D₂O (0.5 mL + MeCN (2.0 μ L), 23 °C): $\delta = 173.7$, 120.0, 119.7 (CN), 54.1, 54.0, 49.0, 31.6, 30.8, 30.1, 22.1, 20.7, 1.5 (CH₃); ESI-MS (m/z %): 399 (100) $[MH]^+$; HR-MS (FAB): calcd for C₁₈H₃₁N₄O₆: 399.2244 $[MH]^+$, found: 399.2253.

Silica-Supported Tantalum Catalysts for Asymmetric Epoxidations of Allyl Alcohols

Damien Meunier, Arnaud Piechaczyk, Aimerly de Mallmann,* and Jean-Marie Basset*

Asymmetric epoxidation of allyl alcohols is an important reaction in synthetic organic chemistry.^[1,2] Katsuki and Sharpless^[3] have provided a successful solution which is now used for industrial applications.^[4] Although this catalytic process seems to be well understood,^[5–8] a heterogeneous system would be advantageous.^[9] It could avoid a complicated separation of product from catalyst, which can lead to decomposition of the epoxide formed.^[6–8]

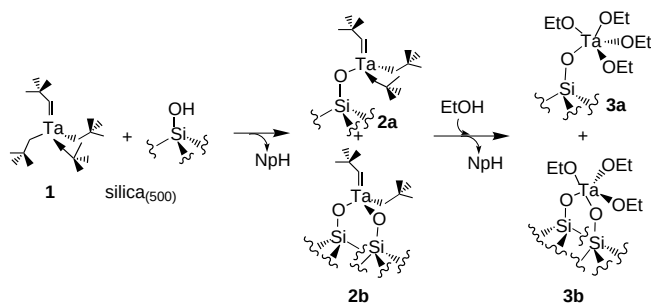
Several oxide-supported titanium compounds were prepared for catalytic epoxidations of allyl alcohols.^[10–13] However, the enantioselectivity was not reported, the metal may leach from the support, or the preparation of the solids seems to be difficult to reproduce.^[9] The choice of titanium to graft a Sharpless-type catalyst is perhaps not the right one, since the mechanism usually accepted requires a coordination sphere in which the four d electrons of Ti are involved in σ bonds with a tartrate group chelating the metal through two σ -bonded oxygen atoms, an allyl alkoxy group, and a σ/π -coordinated *tert*-butyl peroxy group (Scheme 1).^[5] If Ti^{IV} is grafted through one Si–O–Ti bond, then it cannot accommodate all these ligands. However, a Group 5 metal should be a potential active site.



Scheme 1. Left: Coordination sphere of titanium proposed by Sharpless et al.^[5] for the active sites in asymmetric epoxidations of allyl alcohols (only half of a dimer is shown). Right: Hypothetical coordination sphere of tantalum for a potential silica-supported active site.

Tantalum, which exhibits a low activity in homogeneous catalysis,^[1] could thus be a good candidate for such heterogeneous catalysis. We report here results which demonstrate that silica-supported tantalum species lead to active catalysts for these asymmetric epoxidations.

Silica-supported tantalum ethoxides were prepared in two steps (Scheme 2). The first step consists of grafting $\text{Ta}(\text{=CHCMe}_3)(\text{CH}_2\text{CMe}_3)_3$ (**1**) onto $\text{silica}_{(500)}$.^[14] Two surface tantalum species are then obtained: **2a** (ca. 50%), which is grafted to silica by one Si–O–Ta bond, and **2b** (ca. 50%), which is grafted by two such bonds.^[15] The second step consists



Scheme 2. Preparation of silica-supported tantalum alkoxides. NpH = Neopentane.

of exchanging the alkyl and alkylidene ligands of **2a** and **2b** with ethanol in order to obtain surface alkoxy–tantalum complexes **3a** and **3b**.^[16] We refer to the solids prepared in this way as [Ta]#1–[Ta]#3.^[17] A titanium catalyst, [Ti], was similarly prepared from $\text{silica}_{(500)}$ and $\text{Ti}(\text{OiPr})_4$ (1.8 wt % Ti).

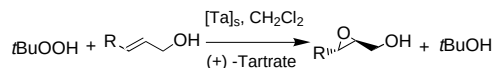
These tantalum- and titanium-containing solids were then used as catalysts for the asymmetric epoxidation of 2-propen-1-ol and *trans*-2-hexen-1-ol. The results, obtained after 48 h of reaction, are presented in Table 1. As already observed by Sharpless,^[7] when associated to (+)-diisopropyl tartrate ((+)-DIPT), $\text{Ti}(\text{OiPr})_4$ leads to an active and enantioselective catalyst for epoxidation of 2-propen-1-ol into (*S*)-glycidol (Table 1, entry 1; turnover number (TON) = 15 mol of glycidol produced per mol of titanium, 80% *ee*). The grafted titanium species in [Ti] leads to a poorly active catalyst and exhibits nearly no enantioselectivity (entry 2). Molecular $\text{Ta}(\text{OEt})_5$ does not lead to an active catalyst (entry 3), and the opposite enantiomer, (*R*)-glycidol, is obtained predominantly. Interestingly, upon use of the silica-supported tantalum species [Ta]#1–[Ta]#3, good activity and enantioselectivity are observed with molecular sieves (entry 4; TON = 28 mol of glycidol produced per mol of surface tantalum, 85% *ee*) or without molecular sieves (entry 5; TON = 15, 84% *ee*); the major enantiomer is (*S*)-glycidol. As expected, with the opposite tartrate, (–)-DIPT, the same results are obtained, but (*R*)-glycidol is the major product (compare entries 5 and 6).

The results show that the activity of silica-supported tantalum is due to surface sites and not to dissolved species since 1) molecular $\text{Ta}(\text{OEt})_5$ leads to almost inactive species with the major formation of the opposite enantiomer; 2) the chemical analysis (Ta or Ti) of the final solution and of the solids before and after reaction does not indicate any metal leaching (less than 2% of the supported metal); and 3) when the solid catalyst was isolated by filtration before the introduction of the last reactant, *tert*-butyl hydroperoxide (TBHP) or 2-propen-1-ol, as recommended by Sheldon et al.,^[18] the solutions were found to be inactive.

A precise comparison of the turnover frequencies (TOF) obtained for the molecular Ti catalyst and for the supported Ta species is not possible since we do not have enough kinetic data. Furthermore, we were not able to synthesize glycidol under experimental conditions similar to usual Sharpless conditions (0.5 M alcohol with a metal/substrate ratio of 5/100).^[7] It is difficult to work with concentrations higher than

[*] Dr. A. de Mallmann, Dr. J.-M. Basset, D. Meunier, A. Piechaczyk
Laboratoire de Chimie Organométallique de Surface, CPE-Lyon
43, Boulevard du 11 Novembre 1918
F-69616 Villeurbanne Cedex (France)
Fax: (+33) 4-72-43-17-95
E-mail: basset@coms1.cpe.fr

Table 1. Catalytic asymmetric epoxidation of allyl alcohols such as 2-propen-1-ol ($R = H$) and *trans*-2-hexen-1-ol ($R = nPr$) with solid tantalum catalysts $[Ta]_5$ or with molecular compounds, $Ti(OiPr)_4$ and $Ta(OEt)_5$.



Entry	Catalyst	R	Metal/alcohol ^[a]	Alcohol concentration	Conversion [%] ^[b]	Yield [%] ^[b]	ee [%] ^[b, c]
1	$Ti(OiPr)_4$	H	5/100	1.0 M ^[d, e]	76	72	80 (S)
2	[Ti]	H	5/100	0.4 M ^[d, e]	17	14	ca. -9 (R)
3	$Ta(OEt)_5$	H	2/100	1.0 M ^[d, f]	ca. 0.5	0.4	-45 (R)
4	[Ta]#2	H	2/100	0.1 M ^[d, f]	60	56	85 (S)
5	[Ta]#1	H	2/100	0.1 M ^[f]	31	30	84 (S)
6	[Ta]#1	H	2/100	0.1 M ^[g]	30	29	-83 (R)
7	[Ta]#3	H	2/100	0.4 M ^[f]	20	19.5	94 (S)
8	[Ta]#1	H	19/100	0.1 M ^[f]	79	77	84 (S)
9	$Ti(OiPr)_4$	<i>nPr</i>	5/100	1.0 M ^[d, h]	99	80	96 (S,S)
10	[Ta]#2	<i>nPr</i>	4/100	0.1 M ^[d, f]	48	40	90 (S,S)
11	[Ta]#2	<i>nPr</i>	4/100	0.1 M ^[h]	35	34	89 (S,S)
12	[Ta]#2	<i>nPr</i>	4/100	0.1 M ^[h, i]	35	31	93 (S,S)

[a] Molar ratio. [b] Determined after 48 h by GC (Lipodex E) with *n*-dodecane as an internal standard. [c] The major enantiomer obtained is shown in parentheses. [d] With 3-Å powdered molecular sieves previously dehydrated at 300 °C under vacuum. [e] At 0 °C; chiral inducer: (+)-DIPT; oxidant: CHP. [f] At 0 °C; chiral inducer: (+)-DIPT; oxidant: TBHP. [g] As in entry 5, but with (-)-DIPT. [h] At -20 °C; chiral inducer: (+)-DET; oxidant: TBHP. [i] As in entry 11, but with second use of the catalyst.

0.1 M while using a metal/substrate ratio of 2/100, because with the solid catalyst the reaction medium is too thick and more difficult to stir. Indeed, with a solid Ta catalyst, an increase in the alcohol concentration leads to lower alcohol conversion and yield, probably owing to the insufficient stirring, but the enantiomeric excess is better (94 % ee) and does not seem to be related to a subsequent kinetic resolution (compare entries 4 and 7). An increase in the metal/substrate ratio from 2/100 to 19/100 leads to a better yield, though the yield is not proportional to the amount of tantalum introduced (compare entries 4 and 8). The termination of the reaction may be explained by a poisoning of the catalytic sites either by water generated in side reactions or by a chelating diol produced in the ring opening of glycidol by an alcohol or water.^[6]

Silica-supported tantalum also showed good activity and enantioselectivity for the epoxidation of *trans*-2-hexen-1-ol to (2*S*,3*S*)-2-hydroxymethyl-3-propyloxirane with molecular sieves (Table 1, entry 10; TON = 10, 90 % ee) or without molecular sieves (entry 11; TON = 8.5, 89 % ee). For this substrate, homogeneous catalysis with molecular $Ti(OiPr)_4$ was very effective and enantioselective (entry 9; TON = 16, 96 % ee). The solid used in entry 11 was washed with CH_2Cl_2 after reaction and reused for a new reaction without adding tartrate. This preliminary result shows that the catalyst can be recycled and that almost the same results are obtained (entry 12; TON = 8, 93 % ee).

For these epoxidations, the surface tantalum and the Sharpless molecular titanium species both present good enantioselectivity and activity. The solid tantalum catalysts are easily separated from the reaction medium by filtration and can be recycled. The good catalytic activity observed for the solids containing tantalum and the bad performances of the silica-supported titanium catalyst are in good agreement with our conceptual approach (Scheme 1). The activity of

supported tantalum may result from the presence of well dispersed monomeric tantalum species on the silica surface, which would lead to monomeric active sites. The molecular tantalum alkoxides, $Ta(OR)_5$, which are dimers in weakly polar solvents^[19] would lead to dimers in the presence of tartrate and the reactants, as was proposed in the case of titanium.^[5] These molecular tantalum dimers would be poor active sites compared to supported monomeric species. Another important difference is the connection with the surface, which may also provide an activation of the catalytic site through the support.

Experimental Section

$Ta(=CHCMe_3)(CH_2CMe_3)_3$ (**1**) was prepared as described by Schrock et al.^[20] The silica used is an aerosil 200 from Degussa. It was activated at 500 °C under vacuum (10^{-4} mbar) and is referred to as silica₍₅₀₀₎. Diethyl (DET) and diisopropyl tartrates (DIPT) were available from Aldrich. Anhydrous *tert*-butyl hydroperoxide (TBHP) in dichloromethane was prepared by azeotropic distillation (70 % TBHP in water, Aldrich).^[7] All operations were carried out under an inert atmosphere (argon or vacuum). A solution of **1** in *n*-pentane was used to impregnate silica₍₅₀₀₎. The solid was filtered off and washed with *n*-pentane, and the amount of neopentane evolved during the grafting reaction was determined by gas chromatography (GC). Dry ethanol was condensed onto the solid, which was then thermally treated at 150 °C. The gas and liquid phases were trapped for GC analysis, and the solid was dried at 100 °C.

The epoxidation reactions were performed in a two-neck flask charged with the metal alkoxide and CH_2Cl_2 . Then DIPT or DET was introduced (usually the natural (+) tartrates; 1.2–1.5 equiv per mol of metal). The flask was cooled to the desired temperature and then the allyl alcohol and a solution of hydroperoxide (cumene hydroperoxide (CHP) or TBHP; 2 equiv per mol of alcohol) were added. The reaction was stopped by removing the catalyst from the solution by filtration. Conversions, yields, and ee values were determined by GC with a chiral γ -cyclodextrin column.

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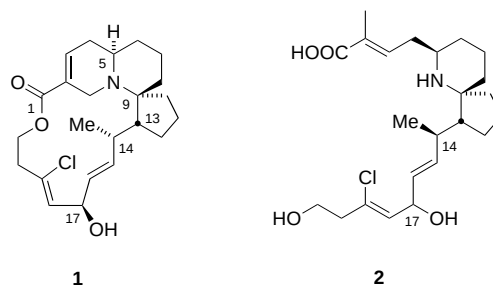
Keywords: asymmetric catalysis • epoxidations • heterogeneous catalysis • surface chemistry • tantalum

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- [15] This already known surface reaction^[14] leads to the liberation of neopentane (ca. 1.5 mol per mol of grafted Ta) with the formation of a mixture of two well-defined surface species, **2a** and **2b**.
- [16] Step 2: 2.5 mol of neopentane evolved per mol of surface tantalum.
- [17] [Ta]#1: 4.92 wt % Ta, C/Ta = 8.9; [Ta]#2: 5.40 wt % Ta, C/Ta = 7.2; [Ta]#3: 5.63 wt % Ta, C/Ta = 7.1. For a mixture of **3a** (50 %) and **3b** (50 %) a theoretical value of C/Ta = 7 should be observed; this is the case for [Ta]#2 and [Ta]#3. For [Ta]#1 the higher value may be explained by the presence of SiOEt species.
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Total Synthesis of (+)-Halichlorine: An Inhibitor of VCAM-1 Expression**

Dirk Trauner, Jacob B. Schwarz, and
Samuel J. Danishefsky*

Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin superfamily, monitors and regulates leukocyte recruitment into inflamed tissue.^[1] Since leukocyte infiltration is involved in various allergic inflammatory disorders as well as pathogenic processes such as asthma and arteriosclerosis VCAM-1 has emerged as a potential target for drug discovery. In principle, blockade or inhibition of VCAM-1 could have consequences in regulating leukocyte trafficking. Given such considerations an agent that specifically inhibits induced VCAM-1 expression could be of particular interest. While screening for active compounds from marine organisms Uemura and colleagues isolated a substance from the marine sponge *Halichondria okadai* KA-DOTA, which they named halichlorine, and identified its structure as **1**.^[2] A related structure, pinnaic acid (**2**), had been isolated from an Okinawan bivalve *Pinna muricata*.^[3]



Aside from several provocative features of halichlorine, which might pose stimulating opportunities to the organic chemist, this compound commands particular attention because it selectively inhibits the induced expression of VCAM-1 with an IC₅₀ of 7 µg mL⁻¹. Interestingly, pinnaic acid was obtained from a screen designed to identify specific inhibitors of cytosolic phospholipase A₂ (cPLA₂).

Among the challenges posed by halichlorine is that of its total synthesis.^[4] Aside from providing the setting for addressing several interesting chemical issues, its total synthesis holds the prospect of providing probe structures to document structure–activity relationships. Elsewhere we

[*] Prof. S. J. Danishefsky,^[+] Dr. D. Trauner, Dr. J. B. Schwarz
Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: s-danishefsky@ski.mskcc.org
Further address:

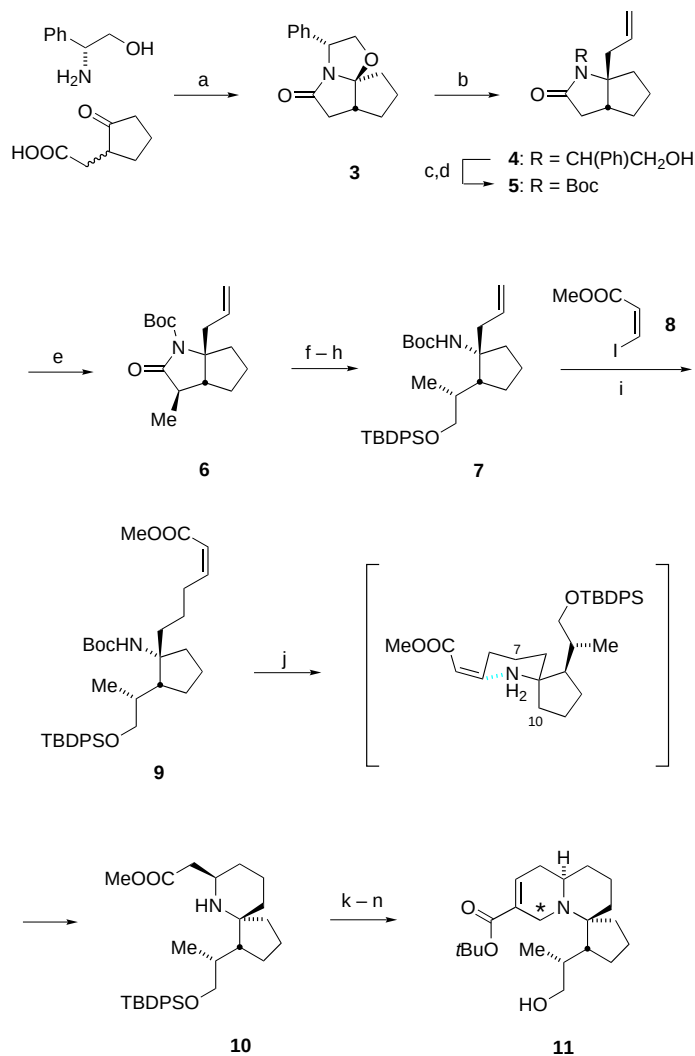
[+] Department of Chemistry
Columbia University
Havemeyer Hall, New York, NY 10027 (USA)

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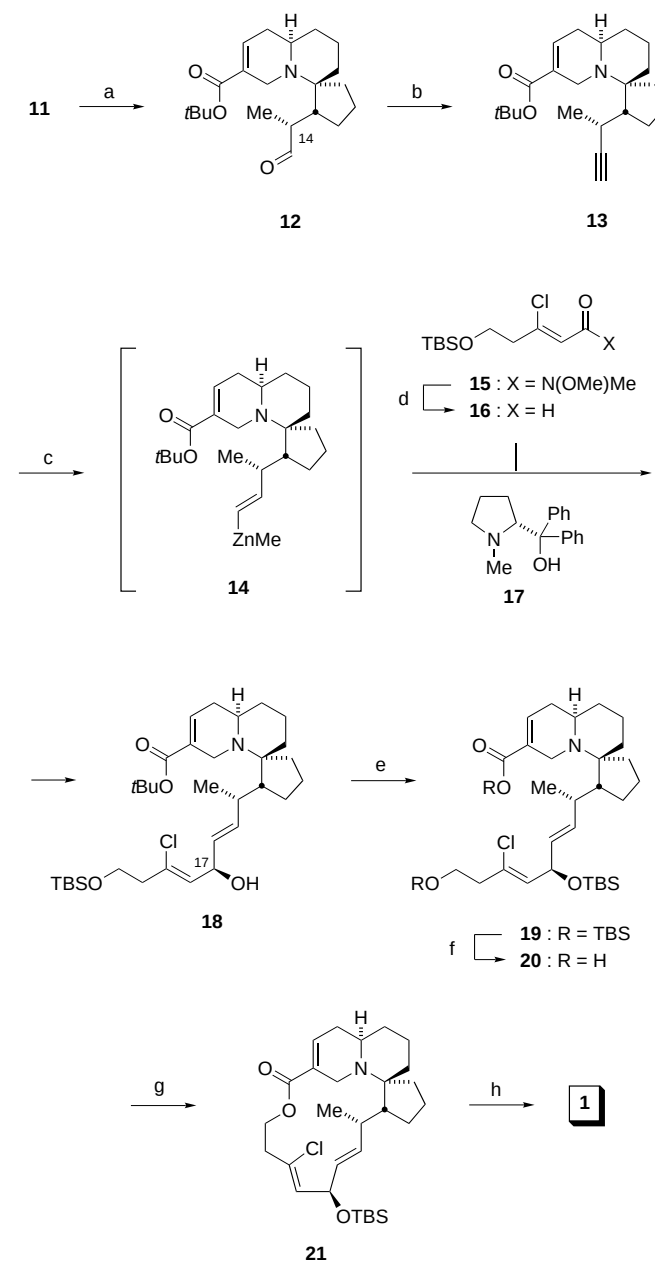
disclosed the basics of our approach to a stereocontrolled synthesis of halichlorine (Scheme 1).^[5] The readily prepared Meyers lactam **3**^[6] provides a valuable entry to **4**, and thence **5**, by Sakurai methodology. Stereoselective methylation from the convex face of the cuplike structure **5** afforded **6**. This alkylation provided the stereochemical imprint at the future

for a stereoselective Michael reaction, which resulted in the elaboration of the aza-spirobicyclic core containing the chirality imprints at C5, C9, C13, and C14 appropriate to our target (**9**→**10**). The tetrahydropyridine was constructed from a two carbon atom chain extension of **10** through a crossed Claisen condensation and a Mannich closure using formaldehyde as the linchpin (see asterisk in **11**).

Severe (and unanticipated) difficulties awaited us as we attempted to progress beyond **11** (Scheme 2). The original



C14 atom following conversion of **6** into **7** as shown. Elongation in a functionally constructive way was much simplified by application of the powerful *B*-alkyl Suzuki method ($\rightarrow$ **9**) using (*Z*)-iodoacrylate **8** as the coupling partner.^[7] The unmasking of the primary amine set the stage



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plan called for oxidation of the primary alcohol in **11** to the aldehyde (**12**), which would serve as a platform for mounting carbon atoms 16–21 into place through one of several possible convergent olefinations. Many attempted oxidations to reach **12** from **11** failed, perhaps as a consequence of the proximal tertiary amine. A further complication was the surprising vulnerability of the α -chiral center to partial epimerization. After extensive experimentation, the oxidation could be carried out with tetra-*n*-propyl ammonium perruthenate (TPAP) and excess *N*-methylmorpholine *N*-oxide (NMO) in acetonitrile.^[8] Compound **12** was used without the benefit of full purification owing to its partial epimerization during silica gel chromatography. Unfortunately, all attempts to conduct variations of the Horner-Wadsworth-Emmons methodologies with **12** were unsuccessful or led to complete racemization at C14.^[9] It is once again tempting to attribute this breakdown of seemingly straightforward conventional chemistry to the presence of the proximal tertiary amine. The only reaction conducted on crude **12** that proved to be reasonably efficient and appropriate to progression toward our goal involved the use of the Gilbert reagent^[10] to produce alkyne **13** in 57% overall yield. Less than 5% epimerization at C14 occurred under the conditions shown.

At this point we were positioned to explore significant extensions of the chemistry laid down by Wipf et al.^[11] Hydrozirconation of **13** according to the Schwartz protocol was followed by metal exchange with dimethylzinc. The resultant vinyl zinc species **14** underwent smooth coupling with aldehyde **16**, prepared from the known Weinreb amide **15**,^[4a] as shown. This key addition, when conducted in the presence of Soai's chiral amino alcohol **17**,^[12] afforded a 4:1 mixture of the desired 17*R* diastereomer **18** and its 17*S* epimer (not shown). In the absence of a chiral additive, the ratio of 17*R*:17*S* was essentially 1:1. Clearly, there is a need and room for optimization of this step. For the present, the 4:1 mixture was advanced without separation of the diastereomers.

Even with the critical coupling accomplished, serious issues remained to be overcome. Deprotection of the *tert*-butyl ester group had to be conducted with circumspection because of the acid sensitivity of the divinylcarbinol moiety. Treatment of **18** with *tert*-butyldimethylsilyl triflate (TBSOTf) generated the corresponding silyl ester of the carboxylic acid while protecting the secondary alcohol ($\rightarrow$ **19**).^[13] Exposure of **19** to ammonium fluoride in aqueous methanol^[14] cleaved the silyl groups from the carboxyl and primary alcohol functions while maintaining the valuable protection at the secondary alcohol center (**19** $\rightarrow$ **20**). Macrolactonization under Keck conditions^[15] produced 17-TBS-halichlorine (**21**) in 54% yield. It was at this stage that the separation of the 17*R* and 17*S* series (8:1 mixture) was carried out. The total synthesis was completed by deprotection at C17 with HF/pyridine to afford synthetic **1**. Comparisons of the ¹H NMR, ¹³C NMR, IR, and mass spectra as well as chromatographic profiles of fully synthetic halichlorine with the corresponding properties of a small specimen sample showed them to be identical.^[16] Comparison of the optical rotations of synthetic halichlorine ($[\alpha]_D^{25} = +234.9$, $c = 1.04$, MeOH) with that reported for the natural product ($[\alpha]_D^{25} = +240.7$, $c = 0.54$, MeOH) further supported the claim

of identity. Given the clarity of the assignment of absolute configuration of the synthetic product, the absolute configuration of the material derived from the marine sponge is further documented.

In summary, the total synthesis of (+)-halichlorine has been accomplished. Among the key reactions were the chain extension–Michael sequence (**7** $\rightarrow$ **10**), the crossed Claisen–intramolecular Mannich sequence (**10** $\rightarrow$ **11**) and the novel vinyl zirconium $\rightarrow$ vinyl zinc $\rightarrow$ allylic alcohol chemistry (**13** $\rightarrow$ **18**). The application of our strategy to the synthesis of pinnaic acid is being evaluated. However, the main focus of the halichlorine project now shifts to the exploration of important biological issues discussed at the outset using material obtained from this efficient total synthesis.

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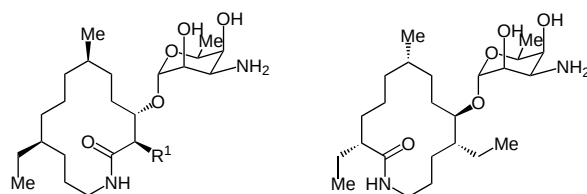
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Asymmetric Total Synthesis of Fluvirucinine A₁**

Young-Ger Suh,* Soon-Ai Kim, Jae-Kyung Jung, Dong-Yun Shin, Kyung-Hoon Min, Bon-Am Koo, and Hwa-Soon Kim

Fluvirucins, a class of macrolactam antibiotics produced by actinomycete strains, have attracted considerable attention owing to their interesting structural features and promising biological properties.^[1] Fluvirucins A₁ (**1a**) and A₂ (**1b**) are particularly attractive within the fluvirucin A series because of their low toxicity;^[2] however, they show less potent antiinfluenza virus activity than fluvirucin B₁ (**2**), a representative of the fluvirucin B series. In addition, none of the members of the fluvirucin A series has been synthesized yet, while two recent syntheses have focused on fluvirucin B₁.^[3] We herein report the first, asymmetric total synthesis of



Fluvirucin A₁ R¹ = CH₃: **1a**
A₂ R¹ = CH(OH)CH₃: **1b**

Fluvirucin B₁ **2**

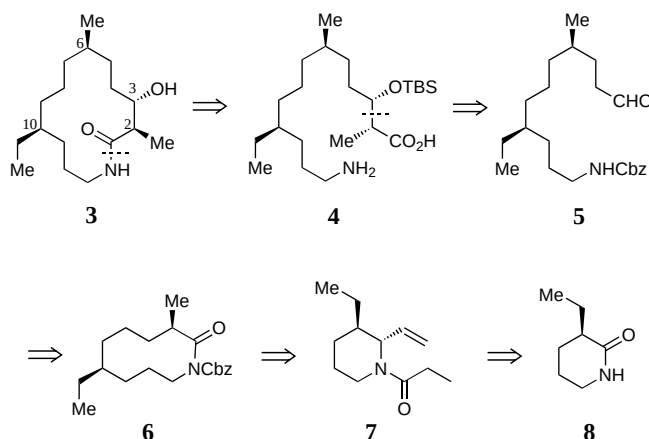
[*] Prof. Y.-G. Suh, S.-A. Kim, J.-K. Jung, D.-Y. Shin, K.-H. Min, B.-A. Koo, H.-S. Kim
College of Pharmacy
Seoul National University
San 56-1, Shinrim-Dong, Kwanak-Gu, Seoul 151-742 (Korea)
Fax: (+82)02-880-7875
E-mail: ygsuh@plaza.snu.ac.kr

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fluvirucinine A₁ (**3**; see Scheme 1), an aglycon of fluvirucin A₁, by our unique strategy, which is capable of readily introducing a variety of substituents at all chiral centers.

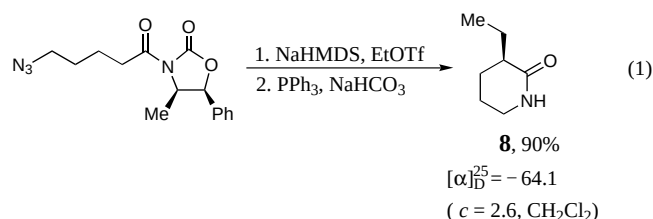
Our approach (Scheme 1) envisions efficient, remote stereocontrol of the C6 stereocenter by a key two-step sequence. The stereoselective vinyl addition to the carbonyl group of lactam **8**, possessing the initially established C10 chiral unit, and the subsequent amide enolate induced aza-Claisen rearrangement^[4] of **7** provides the ultimate 1,5-chiral



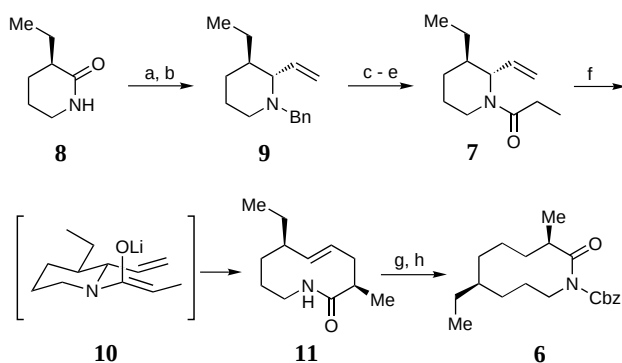
Scheme 1. Strategy for the asymmetric total synthesis of fluvirucinine A₁ (**3**). Cbz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

transfer for the C6 chiral unit. Moreover, the chiral centers C2 and C3 are efficiently introduced by the protocol of Evans et al.^[5] For the cyclization in the final stage, we employed macrolactamization, which is one of the most attractive processes for the preparation of a 14-membered lactam skeleton, from the viewpoint of synthetic versatility and generality.^[6]

Our synthesis was commenced by preparation of the optically active *trans*-2,3-disubstituted piperidine **7**, as a precursor for the aza-Claisen rearrangement, from 3-ethylvalerolactam (**8**), which is readily accessible from 3-azido-pentanoyl-4-methyl-5-phenyl-oxazolidinone by a two-step sequence [Eq. (1)].^[7] The initial stereogenic center corresponding to C10 of fluvirucinine A₁, which ultimately controls



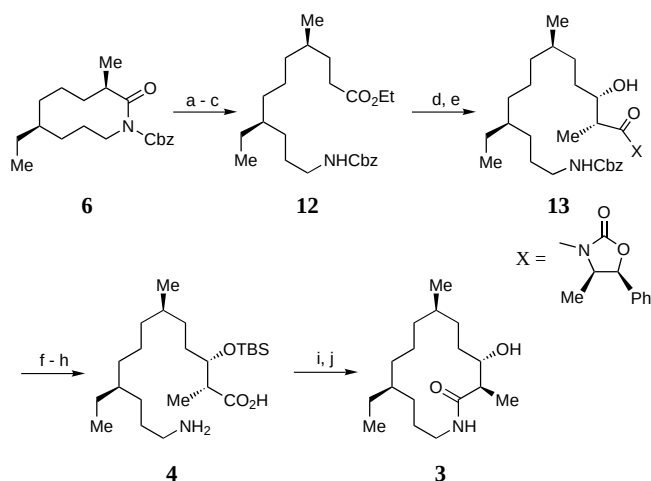
the configuration at C6, is conveniently introduced during the preparation of **8**. For the synthesis of the key lactam intermediate **6**, **8** was protected with benzyl bromide and then efficiently converted into the *trans*-disubstituted piperidine **9** (Scheme 2). After numerous attempts, we developed the direct diastereoselective vinyl addition to the lactam carbonyl group with the assistance of LiAl(OEt)₃H,^[8] which provides the desired and separable *trans* isomer **9** along with



Scheme 2. Synthesis of the key lactam intermediate **6** from **8**. a) NaH, BnBr, THF, 0 → 25 °C, 79 %; b) LiAl(OEt)₃H, Et₂O then CH₂CHMgBr, 0 °C, 70 %; c) Cl₃CCH₂OCOC₂H₅, CH₃CN, reflux, 74 %; d) Zn, AcOH; e) DMAP, (CH₃CH₂CO)₂O, Et₃N, CH₂Cl₂, 78 % over two steps; f) LHMDS, toluene, reflux, 74 %; g) H₂, Pd/C, MeOH; h) *n*BuLi, CbzCl, THF, 94 % from **11**. Bn = benzyl, DMAP = 4-(dimethylamino)pyridine, LHMDS = lithium bis(trimethylsilyl)amide.

the minor *cis* isomer in a 95:5 ratio.^[9] The aza-Claisen rearrangement precursor **7** was readily obtained by debenzyl-ation of **9** followed by propionylation of the resulting amine. Facile aza-Claisen rearrangement of **7**, induced by an amide enolate, afforded the ring-expanded lactam **11** as the sole product, which possesses the second requisite stereogenic center corresponding to C6 of the target molecule. This excellent diastereoselectivity can be understood by the combination of the favorable chair–chair-like transition state **10** with an equatorial ethyl substituent and the formation of the preferred amide (*Z*)-enolate.^[4] The lactam **6** was finally obtained by hydrogenation of the ring olefin moiety of **11** and exchange of the benzyl protecting group for the benzyloxy-carbonyl group (Scheme 2).

The lactam **6** was converted into the ester **12** by a three-step sequence (Scheme 3): Reduction with DIBAL^[10] of Cbz-



Scheme 3. Synthesis of fluvirucinine A₁ (**3**) from **6**. a) DIBAL, CH₂Cl₂, –78 °C; b) Ph₃P=CHCO₂Et, CH₂Cl₂, 70 % from **6**; c) NaBH₄, CuCl, THF/MeOH, 0 °C, 95 %; d) DIBAL, CH₂Cl₂, –78 °C; e) (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyloxazolidinone, Bu₃BOTf, Et₃N, CH₂Cl₂, –78 → 0 °C, 79 % from **12**; f) TBSOTf, 2,6-lutidine, CH₂Cl₂, –20 °C, 67 %; g) LiOH, 30 % H₂O₂, THF/H₂O, 72 %; h) H₂, Pd/C, MeOH, 100 %; i) dimethylaminopropylethyl carbodiimide, C₆F₅OH, CH₂Cl₂; j) (*n*Bu)₄N⁺F[–], THF, 62 % from **4**. DIBAL = diisobutylaluminum hydride; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

protected **6**, followed by direct Wittig olefination of the resulting aldehyde and then reduction of the olefin^[11] with NaBH₄, afforded **12**, which is extended by two carbon atoms compared to **6**. The C2 and C3 chiral units with the requisite configurations were effectively elaborated by DIBAL reduction of **12**, followed by condensation^[5] of the resulting aldehyde with the boron enolate of propionyloxazolidinone. The *ω*-amino acid intermediate **4** was straightforwardly derived from **13** by protection of the hydroxy group as *tert*-butylsilyl, removal of the oxazolidinone auxiliary,^[12] and then removal of the Cbz protecting group. For the completion of the synthesis, **4** was cyclized by treatment with pentafluorophenol^[13] in the presence of dimethylaminopropylethyl carbodiimide to furnish fluvirucinine A₁ (**3**) after desilylation. The synthetic fluvirucinine A₁ was identical in all respects to natural fluvirucinine A₁.^[2, 14]

In summary, the first, asymmetric synthesis of fluvirucinine A₁ has been accomplished, starting from the readily accessible 3-ethylvalerolactam (**8**). This unique synthetic procedure, which employs diastereoselective vinyl addition to the amide carbonyl group and amide enolate induced aza-Claisen rearrangement as the key steps, offers a concise synthetic route to this important antiviral drug prospect.

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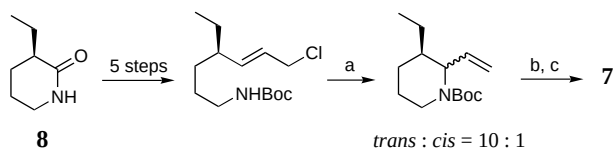
German version: *Angew. Chem.* **1999**, *111*, 3753–3755

Keywords: alkaloids • antiviral agents • natural products • rearrangements • total synthesis

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Scheme 4. Alternative synthetic route to intermediate **7**. a) $n\text{Bu}_4\text{NI}$, NaH , $[\text{Pd}(\text{Ph}_3\text{P})_4]$, THF ; b) $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 ; c) $(\text{CH}_3\text{CH}_2\text{CO})_2\text{O}$, Et_3N , CH_2Cl_2 .

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- [13] L. Kisfaludy, M. Löw, O. Nyeki, T. Szirtes, I. Schön, *Justus Liebigs Ann. Chem.* **1973**, 1421. This process was superior to other lactamizations in terms of both yield and convenience.
- [14] The structure of the synthetic fluvirucinine A_1 was also confirmed by comparison of the spectral data of the methoxy(trifluoromethyl)phenylacetic acid (MTPA) esters of synthetic and natural fluvirucinine A_1 .^[14] We thank Professor Takenori Kusumi of Tokushima University and Professor Hiroshi Kakisawa of the University of Tsukuba for kindly providing spectral data of the fluvirucins.

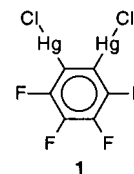
Micropore Decoration with Bidentate Lewis Acids: Spontaneous Assembly of 1,2-Bis(chloromercurio)tetrafluorobenzene**

Martin Tschinkl, Annette Schier, Jürgen Riede, and François P. Gabbaï*

Dedicated to Professor Hubert Schmidbaur on the occasion of his 65th birthday

Polydentate Lewis acids constitute a rapidly growing class of molecular compounds made up of simple bidentate

derivatives^[1–8] as well as more elaborate polydentate macrocycles.^[9–11] The importance of these derivatives is coming to light in several aspects of chemistry including activation of organic reactions,^[1] organometallic catalysis,^[2] and molecular^[3,5–10] and anion recognition.^[6–11] It occurred to us that the incorporation of polydentate Lewis acid functionalities in supramolecular nanoporous structures^[12] could also be of interest for the design of new materials with unusual guest affinity^[13] or catalytic activity.^[14] We now report that 1,2-bis(chloromercurio)tetrafluorobenzene (**1**), a rigid bifunctional Lewis acid,^[15] assembles into a microporous solid with internal Lewis acidic sites while retaining the integrity of its bidentate character. In addition, we report that guest exchange is readily observed within the host lattice. This work is part of our current interest in the chemistry of bifunctional Lewis acids as supramolecular synthons.^[16]



Slow evaporation of a solution of **1** in DMSO affords crystals of composition $\text{1} \cdot (\text{DMSO})_3$ (**2**), as determined by elemental analysis.^[17] The IR spectrum of this novel compound revealed an unresolved broad absorption in the $\text{S}=\text{O}$ stretching frequency region, suggesting the presence of chemically nonequivalent DMSO molecules.^[17] Solid-state MAS NMR spectroscopy confirmed this view, as two sets of methyl resonances could be detected in the ^{13}C NMR spectrum.^[17]

As determined by single-crystal X-ray diffraction analysis,^[18] the asymmetric unit of **2** consists of one molecule of $\text{1} \cdot (\mu_2\text{-DMSO})_2$ and one noncoordinating solvate DMSO molecule (Figure 1). Each of the coordinated DMSO molecules is chelated by the bidentate Lewis acidic pincer. The resulting $\text{Hg}-\text{O}$ bonds (av 2.70 Å) are shorter than the sum of

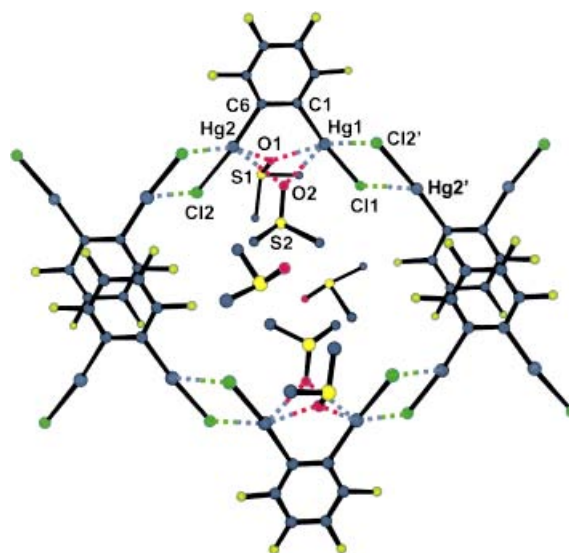


Figure 1. Ball-and-stick diagram showing the structure of **2**. The $\text{Hg} \cdots \text{Cl}$ and $\pi-\pi$ contacts are evident from this view. Selected bond lengths [Å] and angles [°]: $\text{Hg1}-\text{Cl1}$ 2.063(7), $\text{Hg1}-\text{Cl1}$ 2.315(2), $\text{Hg1}-\text{O1}$ 2.689(6), $\text{Hg1}-\text{O2}$ 2.785(5), $\text{Hg2}-\text{C6}$ 2.050(6), $\text{Hg2}-\text{Cl2}$ 2.319(2), $\text{Hg2}-\text{O1}$ 2.623(5), $\text{Hg2}-\text{O2}$ 2.686(5), $\text{S1}-\text{O1}$ 1.497(6), $\text{S2}-\text{O2}$ 1.521(2); $\text{C1}-\text{Hg1}-\text{Cl1}$ 173.6(2), $\text{C1}-\text{Hg1}-\text{O1}$ 89.9(2), $\text{Cl1}-\text{Hg1}-\text{O1}$ 94.67(13), $\text{C1}-\text{Hg1}-\text{O2}$ 87.2(2), $\text{Cl1}-\text{Hg1}-\text{O2}$ 98.28(11), $\text{O1}-\text{Hg1}-\text{O2}$ 73.6(2), $\text{C6}-\text{Hg2}-\text{Cl2}$ 174.9(2), $\text{C6}-\text{Hg2}-\text{O1}$ 91.6(2), $\text{Cl2}-\text{Hg2}-\text{O1}$ 91.10(13), $\text{C6}-\text{Hg2}-\text{O2}$ 89.3(2), $\text{Cl2}-\text{Hg2}-\text{O2}$ 95.53(11).

[*] Prof. F. P. Gabbaï, Dipl. Chem. M. Tschinkl
Department of Chemistry
Texas A&M University
College Station, Texas 77843–3255 (USA)
Fax: (+1) 409-845-4719
E-mail: gabbai@mail.chem.tamu.edu

Dr. A. Schier, J. Riede
Anorganisch-chemisches Institut der Technischen
Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)

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the van der Waals radii of oxygen (1.54 Å)^[19] and mercury (1.73–2.00 Å),^[20] and can be compared to the Hg–O distances of 2.793 and 2.804 Å in the DMSO chelate complex 1,8-bis(chloromercurio)-naphthalene · μ₂-DMSO.^[4]

Examination of the cell-packing diagram reveals the existence of infinite two-dimensional sheets. The cohesion within each sheet results from the interplay of two types of interactions. The formation of chains along the y axis can be recognized. In these chains, molecules of **1** are linked by formation of Hg₂Cl₂ bridges (Hg1–Cl2' 3.261, Hg2'–Cl1 3.555 Å; van der Waals radius of Cl: 1.58–1.78 Å,^[19] Hg: 1.73–2.00 Å),^[20] as often encountered for organomercurio halides in the solid state.^[21] These chains are parallel and interact with one another through π–π contacts of 3.54 Å involving pairs of juxtaposed phenylene rings.^[22] In this pairs, the polar molecules of **1** adopt a slightly offset^[23] and antiparallel arrangement similar to that observed for other 1,2-substituted tetrafluorobenzene derivatives.^[24, 25] In the crystal, the successive sheets are parallel to one another and form a layered structure. The shortest interlayer distance is 3.116 Å and occurs between the fluorine atoms at the 3- and 4-positions of proximate monomers belonging to different sheets. This overall arrangement leads to the formation of channels along the x axis (Figure 2). The cross-section of the channels adopts the shape of a parallelogram whose effective diagonals are 10 and 7 Å.

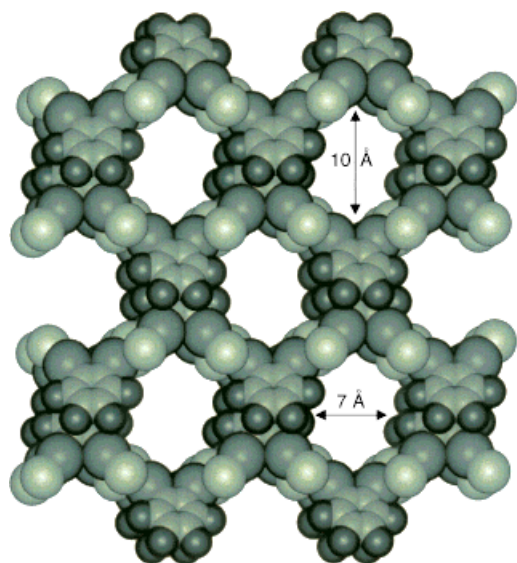
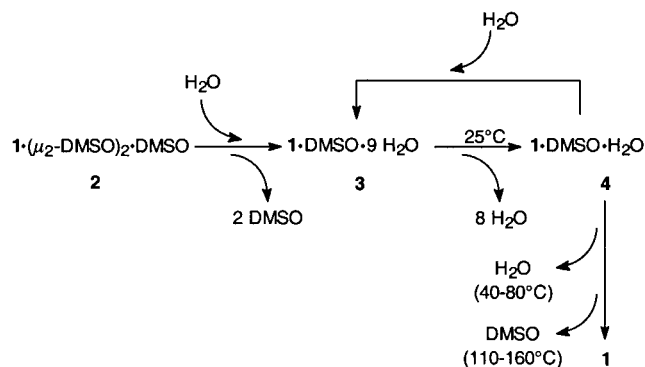


Figure 2. Space-filling model of the lattice of **2**. The DMSO molecules are omitted for clarity.

Compound **1** is insoluble in water. In water, single crystals of **2** become rapidly opaque. The opaque crystals (**3**) can be recovered and physically dried. Gravimetric analysis reveals that **3** undergoes a weight loss of 17.0(±0.5)% at room temperature to yield **4**, which was identified as **1**·DMSO·H₂O by elemental analysis as well as IR and ¹H NMR spectroscopy.^[26] When this experiment is run in D₂O, analysis of the supernatant by ¹H NMR spectroscopy indicates the presence of two equivalents of dissolved DMSO (internal standard: 3-trimethylsilyl 1-propanesulfonic acid, sodium salt

(TSP)), while ¹⁹F NMR confirms the absence of dissolved **1**. Finally, an overall weight loss of 16.5(±0.5)% is observed in going from **2** to **4**, which supports the loss of two equivalents of DMSO and addition of one equivalent of water.

These data indicate that when **2** is placed in water, displacement of two DMSO molecules by nine water molecules occurs to provide **3** (Scheme 1). When **3** is taken out of the aqueous solution, part of the water components spontaneously desorbs to yield **4**. This hydration–dehydration



Scheme 1. **2** is converted into **3** by immersion in water. In air, at 25 °C, **3** loses water to yield **4**. **4** can be converted back into **3** by addition of water or back into **1** by heating.

process is reversible, as **3** can be regenerated when **4** is immersed in water. Assuming that the pores in **3** are saturated with liquid water, the effective pore volume of **4** is 0.20 cm³ g^{−1}. The X-ray powder pattern of **4**, which indicates high crystallinity, suggests that significant structural changes occur on going from **2** to **4**.^[27] Finally, as shown by thermogravimetric analysis (TGA), **4** undergoes successive dehydration (40–80 °C) and DMSO loss (110–160 °C) accompanied by melting at 143–144 °C. We are currently investigating the structure of **4** by X-ray powder methods.

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- [18] Crystal structure data for **2**: $C_{12}H_{18}Cl_2F_4Hg_2O_3S_3$, M_r = 854.52, monoclinic, space group $P2_1/c$, a = 8.149(1), b = 14.245(1), c = 19.214(1) Å, β = 96.90(1)°, V = 2214.3(3) Å³, Z = 4, ρ_{calcd} = 2.563 g cm⁻³, $F(000)$ = 1568, Enraf-Nonius CAD4 diffractometer, Mo K_{α} radiation (λ = 0.71069 Å), T = –82 °C. Data were corrected for Lorentz, polarization, and absorption effects (DIFABS). The structure was solved by direct methods and refined by full-matrix least-square methods against F^2 (SHELXTL-PLUS, SHELXL-93). Of 4794 measured reflections, 4512 were used for refinement. The thermal motion of all non-hydrogen atoms was treated anisotropically. All hydrogen atoms were calculated in idealized geometry and allowed to ride on their corresponding carbon atom with U_{iso} = 1.5 U_{eq} of the attached carbon atom. The structure converged for 235 refined parameters to $R1$ = 0.0347 and $wR2$ = 0.0887; max./min. residual electron density +1.427/–2.291 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-124679. 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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- [27] X-ray powder diffraction (XRPD) data for **4**: d spacing [Å] (I/I_0): 10.85 (100), 6.26 (86.8), 4.57 (64.72), 4.20 (52.46), 3.91 (41.85), 3.36 (28.00), 3.27 (83.92), 3.22 (21.76), 3.16 (25.95), 2.97 (27.25), 2.93 (23.68), 2.63 (22.47), 2.57 (26.51), 2.39 (26.03). Simulated XRPD for **2** (intense peaks are given for comparison purposes): d spacing [Å] (I/I_0): 11.41 (57.48), 9.54 (92.87), 8.09 (100), 6.84 (71.73), 6.57 (15.97), 5.83 (53.45), 5.81 (44.38), 4.98 (33.54), 4.05 (22.68), 3.90 (16.25), 3.80 (17.24), 3.73 (20.69), 3.69 (33.31), 3.54 (31.58), 3.50 (19.89), 3.29 (28.99), 3.04 (20.70).

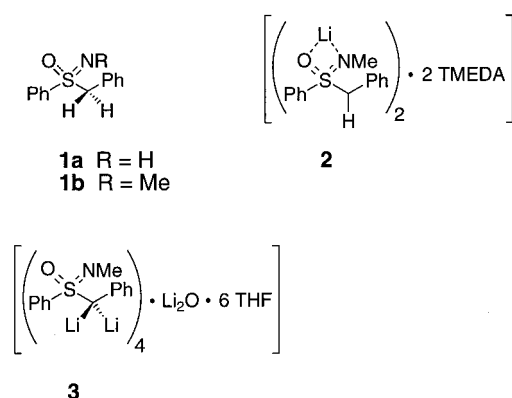
X-Ray Structure of a Heterochiral, Sulfoximine-Stabilized Dilithiomethane Derivative

Jürgen F. K. Müller,* Markus Neuburger, and Bernhard Spingler

Dilithiomethane and some of its heteroatom-stabilized analogues have been the subject of intensive research during recent years. On the one hand the elucidation of the nature and the structures of the compounds were pursued, whilst on the other hand several investigations addressed the synthetic utility of these reagents.^[1] The structure of dilithiomethane, the simplest polyolithiated compound, has been determined in the solid state by X-ray analysis and NMR spectroscopy, whereas in solution no experimental data are available.^[2] Some experimental evidence for the existence of a dimeric species in the gas phase has been reported.^[3] Computational studies suggest that dilithiomethane and its higher aggregates have tetrahedral and planar structures, respectively.^[4] The structures of heteroatom-stabilized geminal dianions, including dilithiated phosphonates,^[5] phosphinimines,^[6] sulfones, and nitriles^[7] have been determined in the solid state, in solution, and theoretically. The α,o -dilithiated intermediates known for structurally related sulfones and sulfoximines mimic the reactivity of an α,α -dianion in trapping reactions with electrophiles.^[8] This is also the case for the so called

[*] Dr. J. F. K. Müller, M. Neuburger
Institut für Anorganische Chemie der Universität
Spitalstrasse 51, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-10-18
E-mail: muellerju@ubaclu.unibas.ch
Dr. B. Spingler
Massachusetts Institute of Technology
Department of Chemistry
Cambridge, MA 02139 (USA)

quasi-dianion complexes (QUADACs) such as the complex formed between monolithiated benzonitrile and lithium diisopropylamide (LDA).^[9] Geminal dianions have been used successfully as supernucleophiles or bisnucleophiles in organic synthesis.^[11] Surprisingly, chiral substituted dilithiomethane derivatives are still unknown and since both geminal lithium atoms are in a diastereotopic environment they promise to be exciting new reagents for asymmetric synthesis.^[8, 10] Such reagents might induce two consecutive C–C bond formations in a stereoselective manner. Here we present the first experimental proof for such a chiral dilithiomethane derivative with the X-ray structure of an α,α -dilithiated sulfoximine.



The monolithiated sulfoximine **2** was obtained by treating a solution of racemic **1b** in *N,N,N',N'*-tetramethylenediamine (TMEDA) with one equivalent of *n*BuLi in hexane at -78°C . Yellow crystals suitable for X-ray analysis were grown from the resulting yellow-green solution. Figure 1 shows the molecular structure of the lithium complex **2**. For comparison the molecular structure of the starting material **1a** was also determined.^[11]

In **2**, two lithiated benzylic sulfoximine units with opposite configuration at the S atom are linked by N–Li–O bridges to give an eight membered ring with the atom sequence (Li(1)–N(1)–S(1)–O(1))₂; such a coordination mode was previously known from lithiated allyl sulfoximines and from computa-

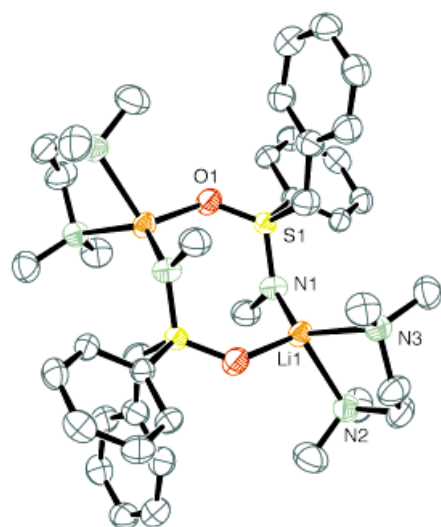


Figure 1. Molecular structure of **2** in the crystal. Hydrogen atoms are omitted for clarity.

tional investigations.^[12] Analogous arrangements have been observed in lithiosulfones.^[13] The Li–C bond found in other lithiosulfoximines is absent.^[14] The question as to whether the C(α) atom is pyramidal or not could not be answered with certainty because the benzylic proton was not located in the difference map. Lithiation of **1b** is accompanied by a shortening of the S–C(α) bond from 1.783(2) Å in **1a** to 1.66(1) Å in **2**.^[12]

Treatment of racemic **1b** with 2.5 equivalents of *n*BuLi in THF at -78°C in the presence of traces of H₂O yielded red crystals of **3**: a tetrameric heterochiral aggregate, consisting of four dilithiated sulfoximine units and a Li₆O core, which acts as a template for crystallization (Figure 2). No crystals could

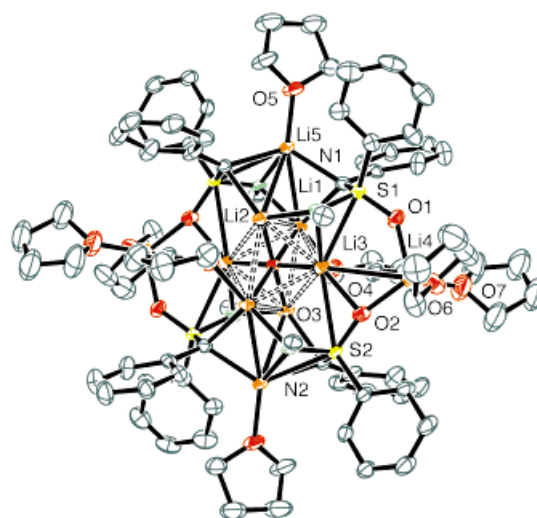


Figure 2. Molecular structure of **3** in the crystal. Hydrogen atoms and two disordered THF molecules are omitted for clarity.

be obtained without small amounts of water. Compound **3** crystallizes in the space group *P* $\bar{1}$ and the unit cell contains one cluster together with two disordered THF molecules. Since the lattice is centrosymmetric the two portions of the cluster show a reversed configuration at the S atoms. The core of the aggregate is characterized by a distorted Li₆O octahedron and contains the crystallographic inversion centre. Such a structural motif has been found to be a characteristic feature in a α,α -dilithiated sulfoximine, a dilithiated sulfone, and a dilithiated phosphane.^[7a, 8] A manifold of six-membered rings are connected to the central Li₆O core, which leads overall to a cyclic 16-membered (Li(5)–C(1)–S(1)–O(1)–Li(4)–O(2)–S(2)–C(21))₂ motif.

Two different dilithiated C atoms are in the asymmetric unit, each connected to two Li⁺ ions, and therefore distinctly pyramidalized. The two Li⁺ ions coordinated at C(21) also coordinate to a neighboring sulfoximine nitrogen atom to form either Li(5)–C(21)–S(2)–N(2) four-membered ring motifs, as known from monolithiosulfoximines, or C(21)–Li(2)–N(3)–Li(3)–O(2)–S(2) six-membered rings. The two lithium ions also differ in their further coordination sphere: Li(2) shows heteroatom coordination (N(1), O(3)), whereas Li(5) has one additional C–Li bond, by bridging two different dimetalated C atoms, and a Li–N contact. The Li(5) ion is

bound to C(1) as well as to C(21), leading to a Li(2)-C(21)-Li(5)-C(1)-S(1)-N(1) six-membered ring. An unusual three-coordination is found for Li(1), Li(2), and Li(3) of the Li_6O core.^[15] The Li-C distances (2.19(2)–2.21(2) Å) are similar to that in monolithiated sulfoximines. The Li-N bond length within the Li-C-S-N chelate (2.23(2) Å) is comparable to those from previous investigations.^[12, 14] The Li-O bond length to the sulfoximine-O atoms are significantly longer than those within the Li_6O octahedron. The extremely short S-C(α) bonds (1.61(1) and 1.64(1) Å) compared to **1a** (1.783(2) Å) and **2** (ca. 1.66(1) Å) are characteristic and typical for related dilithiated sulfoximines, sulfones, phosphonates, and nitriles.^[5–8] A comparison of **3** with **2** reveals that the atomic sequence of the eight-membered ring motif (Li-N-S-O)₂ in **2** is preserved in **3**. Insertion of the Li_6O core in this motif forms two Li(1)-N(2)-S(2)-O(2)-Li(3)-O(3) six-membered rings, which share the O(3) atom and thus lead to a spiro-type arrangement. Therefore, we conclude that the complex formed between the Li_6O core and the monolithiated sulfoximine units in **2** serves as a template for the formation of **3**. After dilithiation, the saturation of the second Li^+ ion with coordination partners from the sulfoximine group and the solvent leads to a higher aggregate than the monolithiated parent compound **2**. In addition, two C–Li bonds are formed for each sulfoximine unit, which represents a heterochiral dilithiomethane derivative with diastereotopic lithium atoms. Further studies in our group concentrate on the replacement of one of the diastereotopic lithium atoms by a transition metal, thus inducing a new stereogenic center at the C(α) atom.^[16]

Experimental Section

2: A solution of **1b** (105 mg, 0.41 mmol) in TMEDA (2 mL) was treated with $n\text{BuLi}$ in n -hexane (0.28 mL, 1.58 M, 0.45 mmol) at -78°C . After 24 h at room temperature yellow crystals of **2** were formed that were suitable for X-ray analysis (56 mg, 37%).

3: A solution of H_2O in THF (0.272 mL, 0.11 M, 0.03 mmol) was added to a solution of **1b** (54 mg, 0.22 mmol) in THF (2 mL). The resultant mixture was then treated with $n\text{BuLi}$ in hexane (0.35 mL, 1.58 M, 0.55 mmol) at -78°C . After 24 h at -78°C red crystals of **3** that were suitable for X-ray analysis had grown (15 mg, 17%).

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methods with the program SIR92.^[17] Anisotropic least squares full matrix refinement was carried out on all non-hydrogen atoms using the program CRYSTALS.^[18] The positions of the hydrogen atoms were determined geometrically. The disordered THF molecules in **3** were refined using appropriate restraints. Chebyshev polynomial weights have been used to complete the refinement.^[19] Scattering factors have been taken from the *International Tables*, Vol. IV (Ed.: T. Hahn), Kluwer Academic Publishers, London, **1995**, table 2.2B. 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-127623, 127624, and 127625. 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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Molecular Nanocapsules Based on Amphiphilic Hyperbranched Polyglycerols

Alexander Sunder, Michael Krämer, Ralf Hanselmann, Rolf Mülhaupt, and Holger Frey*

Dendrimers have been shown to exhibit unusual properties in recent years,^[1] such as the topological encapsulation of various guests,^[2] and dendrimers with amphiphilic core–shell structures have shown micelle-like properties that have led to the picture of a “unimolecular micelle”.^[3] However, most systems reported in this context show aggregation in solution as a result of their amphiphilic nature.^[4] Amphiphilic polymers with core–shell structures that are aggregation-free in solution offer the attractive potential to act as phase-transfer agents in both polar^[5,6] and apolar environments.^[7,8] To date, this solubilization effect is believed to be uniquely related to the structurally perfect, yet tedious to prepare, dendrimers. The compact dendrimer topology is promising for controlled release^[9] and confined chemical nanoreactors.^[10]

Hyperbranched polymers (prepared in a one-step reaction from AB_m-type monomers and thus randomly branched in contrast to the perfectly branched dendrimers) are generally considered to be poorly defined because of their broad polydispersity,^[11] which is a consequence of the commonly used step-growth-type of synthesis. Furthermore, hyperbranched polymers are characterized by a random distribution of functional groups throughout their globular structure. We reported recently the first controlled chain-growth-type of approach to hyperbranched polymers based on the anionic ring-opening multibranching polymerization (ROMBP) of glycidol.^[12] The polyglycerols obtained can be tailored in terms of their core functionality and molecular weight by the monomer/initiator ratio employed. As a consequence of the quasi-living nature of the polymerization these highly flexible aliphatic polyetherpolyols exhibit unprecedentedly narrow polydispersities ($M_w/M_n < 1.5$, mostly < 1.3).

Very few examples of amphiphilic hyperbranched structures have been reported.^[13,14] Herein we describe the use of hyperbranched polyglycerols for the preparation of amphiphilic “molecular nanocapsules” for hydrophilic guests. In contrast to dendrimer scaffolds where functional groups are exclusively located at the surface, polyglycerol scaffolds also contain hydroxyl groups throughout the structure. If only a certain fraction of these hydroxyl groups is modified with hydrophobic alkyl chains (43–93 %), thereby leaving residual hydroxyl moieties, the inner sphere of the molecule remains highly hydrophilic (Figure 1). The considerable flexibility of the polyether structure should permit the hydroxyl groups to arrange in a manner that represents a solvating environment for polar guest molecules in apolar solvents.

[*] Priv.-Doz. Dr. H. Frey, Dipl.-Chem. A. Sunder, M. Krämer, Dr. R. Hanselmann, Prof. Dr. R. Mülhaupt
Institut für Makromolekulare Chemie
Hermann-Staudinger-Haus und
Freiburger Materialforschungszentrum (FMF) der Universität
Stefan-Meier-Strasse 21/31, D-79104 Freiburg (Germany)
Fax: (+49) 761-203-4709
E-mail: holfrey@fmf.uni-freiburg.de

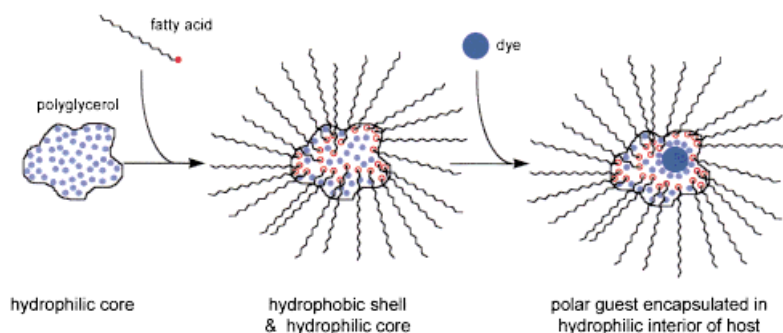
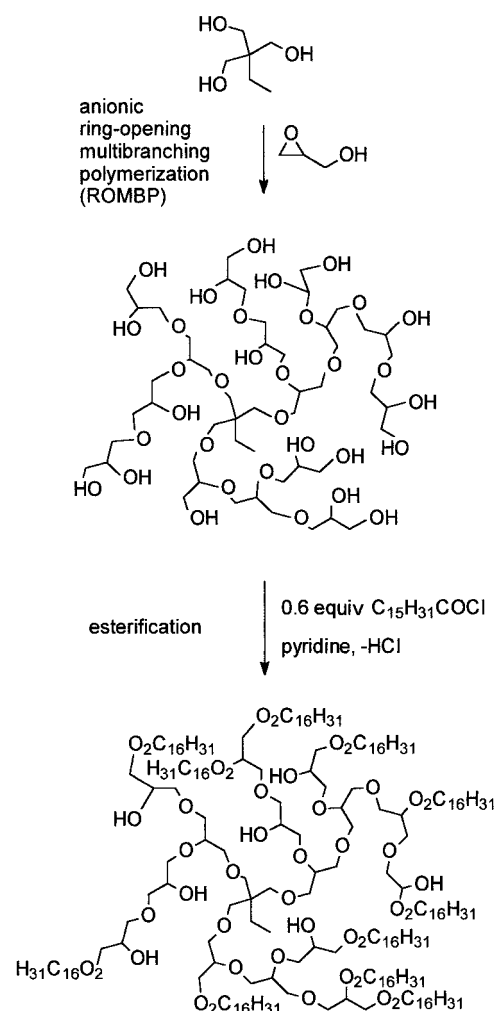


Figure 1. Synthesis of an inverted unimolecular micelle from a hyperbranched polyol by partial hydrophobization of the end groups and subsequent take-up of a water-soluble guest-molecule (small blue circles: free hydroxyl groups, small red rings: hydroxyl groups esterified with alkyl chains).

The polyglycerols with nonpolar shells were prepared by a straightforward two-step approach. In the first step we polymerized glycidol anionically by the method described previously using trimethylolpropane as the trifunctional initiator.^[12] In the second step the polyetherpolyols were partially esterified using various fatty acid chlorides (Scheme 1).^[15]



Scheme 1. Synthesis of partially esterified polyglycerols: step 1: controlled base-catalyzed ring-opening multibranching polymerization (ROMBP) of glycidol; step 2: partial esterification of the hyperbranched polyglycerol with a fatty acid chloride (for example, palmitoyl chloride).

Two polyglycerols with molecular weights of 1800 and 6300 with molecular weight distributions (M_w/M_n) of 1.2 and 1.5, respectively, were employed for this study. Four partially esterified polyols varying both in the degree of alkyl substitution (α) and the length of the alkyl chains were prepared from these two polymers. Palmitoyl (C16) and caprylic acid (C8) chlorides were used and between 43 % and 93 % of the hydroxyl groups were esterified. All products exhibited narrow polydispersities comparable to that of the substrates (Table 1).

The esterified polyglycerols are soluble in a large variety of nonpolar organic solvents (for example, toluene, chloroform, and hexane) in

Table 1. Analytical data for the partially esterified polyglycerol samples from NMR, GPC, and UV/Vis measurements.

sample ^[c]	Polyglycerol core		Partially esterified polyglycerol			
	NMR $\bar{M}_n$	GPC ^[a] M_w/M_n	NMR α [%] ^[d]	NMR $\bar{M}_n$	GPC ^[b] M_w/M_n	UV/Vis (Load)
P(G ₂₃ C16 _{0.6})	1800	1.2	60 %	5300	1.3	0.8
P(G ₂₃ C16 _{0.9})	1800	1.2	93 %	7300	1.2	0.7
P(G ₈₄ C16 _{0.6})	6300	1.5	55 %	17500	1.3	2.7
P(G ₈₄ C8 _{0.4})	6300	1.5	43 %	10800	1.5	1.3

[a] Performed in DMF at 45 °C with poly(propylene glycol) standards. [b] Performed in CHCl₃ at 30 °C with polystyrene standards. [c] Nomenclature P(G_xCY _{α}): $x = DP_n$ of polyglycerol, Y: length of alkyl chain as measured by the number of carbon atoms. [d] α : degree of alkyl substitution per hydroxyl group.

contrast to polyglycerol that is soluble only in extremely polar media, such as water or methanol. We chose Congo red as a representative anionic, water-soluble dye and chloroform as the apolar phase, in which this dye is not soluble (Figure 2, left sample tube) to investigate the phase-transfer properties of the esterified polyglycerols).

As a consequence of the spatially confined amphiphilic topology we expected to observe a point of saturation at which the maximum load of dye molecules per polymer



Figure 2. Demonstration of the solubilization effect (bottom layer: chloroform, upper layer: water). From left to right: 1) no polymer in organic layer; 2) molar ratio P(G₂₃C16_{0.6}):Congo red 1:4; 3) molar ratio P(G₂₃C16_{0.6}):Congo red 1:0.4; 4) organic layer from (3) transferred into a tube containing hydrochloric acid (pH 2).

molecule is reached. Therefore we prepared chloroform solutions of the polymers and agitated them briefly with different concentrations of dye dissolved in the aqueous phase.^[16] The organic phase was investigated, after phase separation, by UV/Vis spectroscopy as well as dynamic light scattering (DLS). In all cases a linear increase in the color intensity of the organic phase was observed below the saturation point. Once the saturation concentration of the dye in the organic phase was reached the absorption did not change with further increase of the dye concentration (Figure 2, second sample tube from left). The defined number of guests encapsulated is clearly supported by the results of the UV/Vis measurements shown in Figure 3 for three of the

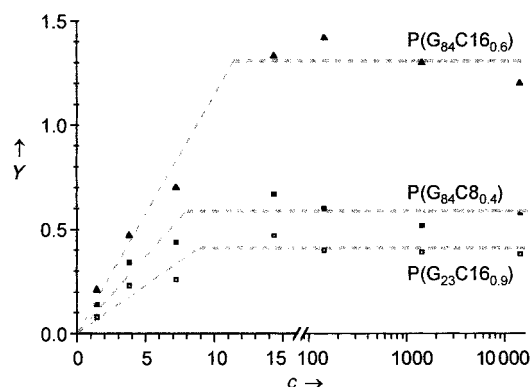


Figure 3. Determination of the average load of dye molecules per polymer from the absorption in the UV/Vis spectra (polymer concentration 0.01 wt % in chloroform). c : dye concentration (10^{-6} M in aqueous phase); Y : average loading of dye molecules per polymer.

samples studied. Remarkably, Congo red was quantitatively extracted from the aqueous layer into CHCl_3 at dye concentrations below the saturation concentration (Figure 2, third sample tube from left). The average maximum load (that is, the saturation concentration) of dye molecules per polymer can be calculated from UV/Vis experiments by assuming the same absorption coefficient for the dye in water and in the amphiphilic structure. Calculation of the load from the determination of the saturation point gives similar values.

As shown in Table 1 the average maximum load depends on two factors: 1) the molecular weight of the polyglycerol used, and thus, the size of the hydrophilic hyperbranched topology and the related number of free hydroxyl groups (compare loadings of 0.7 and 2.7 for $\text{P}(\text{G}_{23}\text{C}_{16}_{0.6})$ and $\text{P}(\text{G}_{84}\text{C}_{16}_{0.6})$, respectively) and 2) on the length of the alkyl chains attached to the polyglycerol scaffold (compare loadings of 2.7 and 1.3 for $\text{P}(\text{G}_{84}\text{C}_{16}_{0.6})$ and $\text{P}(\text{G}_{84}\text{C}_{8}_{0.4})$, respectively). The degree of substitution α seems to play a minor role (compare loadings of 0.8 and 0.7 for $\text{P}(\text{G}_{23}\text{C}_{16}_{0.6})$ and $\text{P}(\text{G}_{23}\text{C}_{16}_{0.9})$, respectively).

Various light-scattering experiments with dye-loaded samples obtained from the solubilization procedure described above were carried out to clarify whether the host molecules are present as unimolecular species in the organic phase, that is, whether the solubilization observed is actually a consequence of the presence of an inverted unimolecular micelle type of structure (Figure 1). Static light-scattering experiments with the samples $\text{P}(\text{G}_{23}\text{C}_{16}_{0.6})$ and $\text{P}(\text{G}_{23}\text{C}_{16}_{0.9})$ at a

concentration of 10^{-3} wt % showed no scattering intensity at any angle, which showed that no uncontrolled aggregation took place at the investigated concentration. Dynamic light-scattering measurements were performed with the sample $\text{P}(\text{G}_{23}\text{C}_{16}_{0.9})$ at concentrations of 0.05 and 0.025 wt % at an angle of 90° . The hydrodynamic radius distribution was obtained by CONTIN analysis. In both cases an extremely weak scattering intensity was found below an average hydrodynamic radius of 100 nm. Thus, our experimental results point to a unimolecular nature of the solvating species. This is supported by the stability of the solutions of the dye-loaded polymers over extended periods that exceeded several months. It should be noted that our data cannot completely exclude the formation of small aggregates.

The solubilization described for Congo red appears to be general, namely similar behavior is observed with other water-soluble dyes (for example, bromophenol blue, rose Bengal) and other organic solvents (for example, toluene, *n*-hexane). For instance, when using *n*-hexane as the apolar solvent and rose Bengal as the hydrophilic dye, we observed an average load of 1.4 molecules of rose Bengal per polymer $\text{P}(\text{G}_{23}\text{C}_{16}_{0.6})$. This slightly enhanced value relative to Congo red appears to be related to the somewhat more compact structure of rose Bengal in comparison to the extended rodlike structure of Congo red.

Two fundamental issues need clarifying: 1) whether the dye encapsulation is reversible and 2) whether chemical reactions of the solubilized species that take place in a polar environment can also be realized in the organic phase. Since Congo red is a pH-sensitive dye ($\text{pH} > 3$: red, $\text{pH} < 3$: blue), the most simple experiment concerning a chemical reaction in the molecular nanocapsule is the effect of a pH change in the aqueous phase on the dye solubilized in the chloroform phase. Therefore, we transferred the organic phase of a sample prepared as described above (neutral pH) into a new tube and added fresh water on top. Remarkably, after agitation and even ultrasonication no coloration of the aqueous phase was observed, which indicates irreversible encapsulation of the dye. The pH of the aqueous layer was lowered to a value of 2 by subsequent addition of hydrochloric acid and the sample agitated again. Interestingly, the color of the organic phase changed from red to blue, demonstrating that the dye solubilized in the hosting polymer is still accessible by protons and thus sensitive to pH changes (Figure 2, right sample tube). Release of the encapsulated dyes could only be observed after cleavage of the hydrophobic alkyl chains by ester hydrolysis. Since the presence of hydroxyl and ether groups in the core is a prime requirement for achieving irreversible encapsulation this unusual behavior can best be accounted for by hydrogen-bond formation.

In conclusion, the construction of molecular nanocapsules with hydrophilic interiors from hyperbranched polymers has been achieved for the first time using narrow polydispersity polyglycerols and simple esterification with fatty acids. Synthesis of these inverted micelle-type architectures requires only two synthetic steps and can conveniently be carried out on a multi-gram scale. The hyperbranched molecular nanocapsules are capable of solubilizing a distinct average number of polar molecules in their interior, depending on the core size

and substituents. This encapsulation based only on a hydrophobically shielded, hydrophilic solvating microenvironment represents a different principle in comparison to the topological entrapment observed for some dendrimer-based structures.^[2] From light scattering measurements it was tentatively concluded that the solvating species are present in a unimolecular form in organic solvents, thus, representing "inverted unimolecular micelles". Since there appears to be no measurable release of encapsulated guests, the term "micelle" is slightly misleading; we favor the term "molecular nanocapsules". Release of the encapsulated dyes is achieved by means of cleaving the ester bond, thus, removing the hydrophobic molecular shield of the nanocapsules.

Molecular nanocapsules and their corresponding host/guest compounds offer an attractive potential for use in a wide variety of applications ranging from controlled drug release, solubilization of inorganic compounds in organic media, dispersion of polar dyes in hydrophobic polymers, preparation of inorganic/organic hybrid nanoparticles, to the design of microreactors and catalysts.^[17]

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- [16] In a typical experiment the respective aqueous dye solution (4 mL) was manually shaken for some seconds with 0.01 wt % solution (4 mL) of the partially esterified polyglycerol in chloroform. After phase separation (two experiments after 3 h and 24 h), an aliquot of the organic layer (2 mL) was transferred into a UV/Vis cuvette and its absorption spectrum measured. No difference between the 3 h and 24 h measurements was observed. The solutions remained unchanged for several months.
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Biomimetic Explorations Towards the Bisorbicillinoids: Total Synthesis of Bisorbicillinol, Bisorbibutenolide, and Trichodimerol**

K. C. Nicolaou*, Klaus B. Simonsen, Georgios Vassilikogiannakis, Phil S. Baran, Veroniki P. Vidali, Emmanuel N. Pitsinos, and Elias A. Couladouros

Dedicated to Professor Gerasimos J. Karabatsos on the occasion of his 67th birthday

The bisorbicillinoids^[1] are a growing family of novel natural products with interesting and diverse biological activities. Included within this class are bisorbicillinol (**1**),^[2] bisorbibutenolide (**2**),^[3] trichodimerol (**4**),^[4] bisorbicillinolide (**5**),^[3] and

[*] Prof. Dr. K. C. Nicolaou, Dr. K. B. Simonsen, Dr. G. Vassilikogiannakis, P. S. Baran
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)
V. P. Vidali,^[+] Dr. E. N. Pitsinos, Prof. Dr. E. A. Couladouros^[+]
Organic and Bioorganic Chemistry Laboratories
NCRS Demokritos
153 10 Agia Paraskevi, Attikis, POB 60228, Athens (Greece)

[+] Further address:
Department of Sciences, Chemistry Laboratory
Agricultural University of Athens
Iera Odos, Athens 11855 (Greece)

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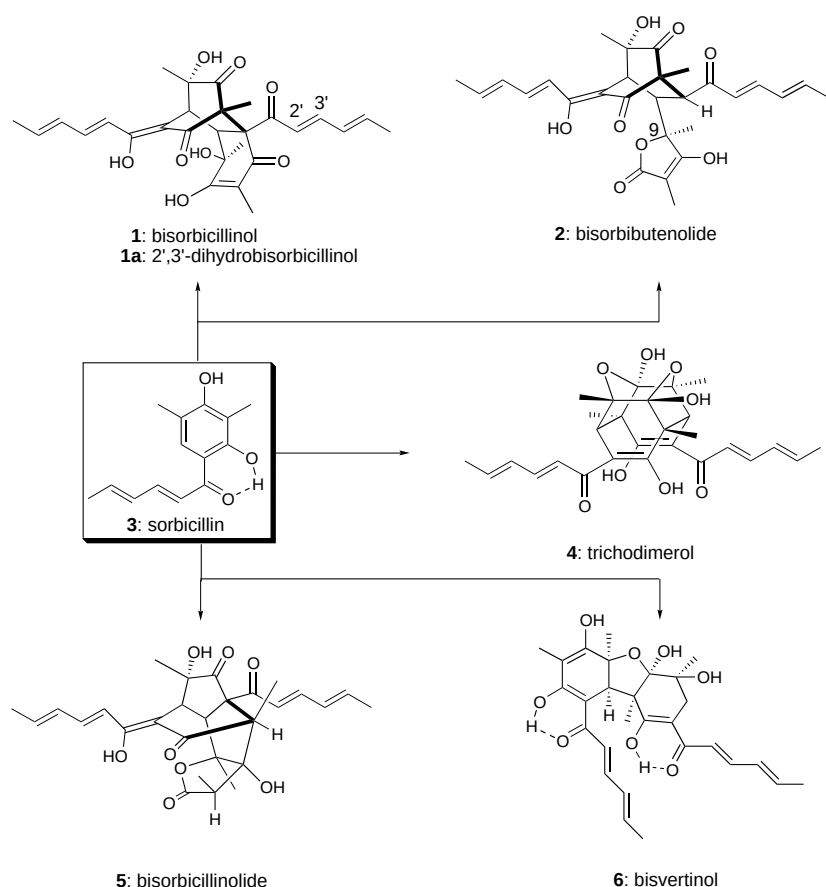


Figure 1. Structures of selected bisorbicillinoids and their postulated biosynthetic precursor sorbicillin (3).

bisvertinol (6),^[5] all of which are thought to be biosynthetically derived from sorbicillin (3), itself a naturally occurring substance (Figure 1).^[6]

Isolated from various species of fungi, bisorbicillinol (1), bisorbibutenolide (2), and bisorbicillinolide (5) exhibit antioxidant properties,^[2, 3] while an oxidized form of bisvertinol (6) represents the first inhibitor of β -6-glucan biosynthesis, and is, therefore, considered as a potential antifungal agent.^[5b] Trichodimerol (4), on the other hand, originally isolated from the genus *Trichoderma*, showed inhibitory activity against lipopolysaccharide-induced production of tumor necrosis factor α (TNF- α) in human monocytes and, consequently, is considered to be a potential lead for the treatment of septic shock.^[4b] The novel and complex molecular architectures of these molecules coupled with their intriguing biological properties and unusual biosynthetic pathways prompted us to initiate a

program directed towards their biomimetic total synthesis. Here we report the total syntheses of three members of this class of natural products, namely, bisorbicillinol (1), bisorbibutenolide (2) and trichodimerol (4).

The unifying feature of these structurally connected dodecaketides resides in the mechanistically related proposals regarding their biosynthetic origin from sorbicillin (3; Figures 1 and 2). Thus, the first member of this family, bisvertinoquinol (1a), reported by Dreiding et al. in 1983, was postulated to arise from a Diels–Alder reaction between two different quinols derived from 3 and 2',3'-dihydrosorbicillin by enantioselective oxidation.^[7] A similar hypothesis was advanced by Abe et al. to explain the biosynthesis of the newly isolated bisorbicillinol (1) (Figure 1).^[2] The same group also proposed the biosynthesis of the soon thereafter isolated bisorbibutenolide (2) and bisorbicillinolide (5) by anionic rearrangement of 1.^[3a] We have recently proposed a possible biosynthetic pathway for trichodimerol (4) involving a two-step Michael addition–ketalization sequence from an oxidized form of 3.^[1] We now suggest that the bisvertinols (e.g. 6), representing the largest group of the bisorbicillinoids, are biosynthesized by a similar mechanism involving a Michael addition followed by ketalization and finally reduction (see Figure 2).^[8]

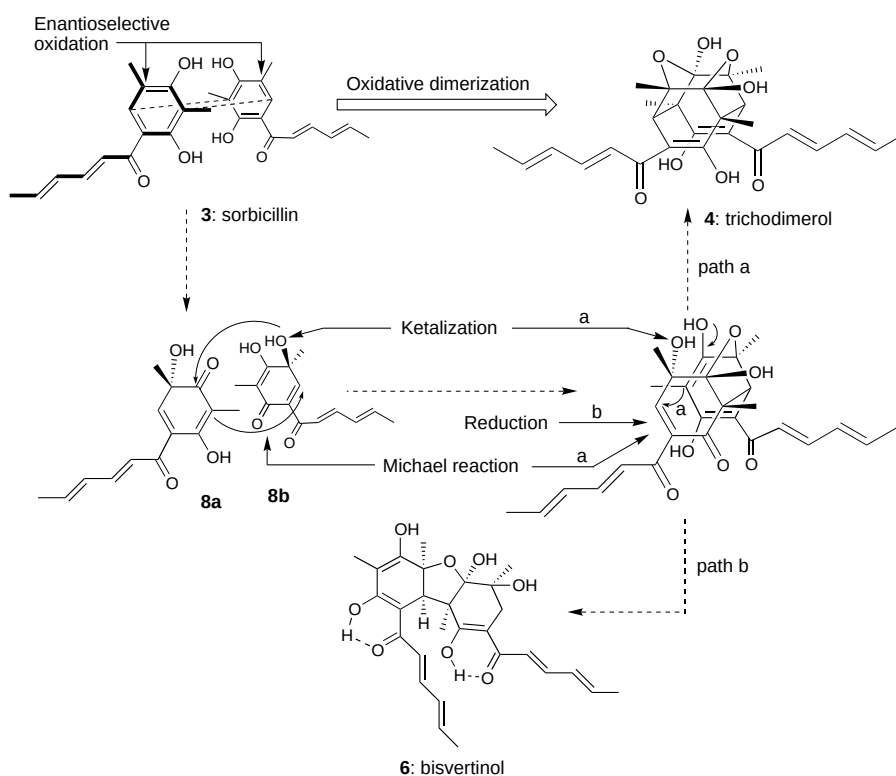
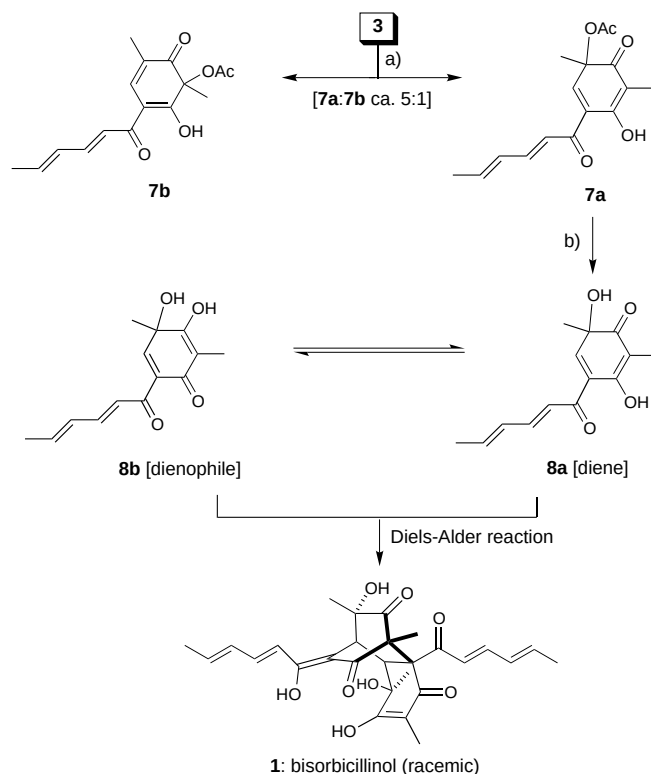


Figure 2. Proposed biosynthetic pathways from sorbicillin (3) to trichodimerol (4) and bisvertinol (6).

Inspired by biosynthetic considerations, we began our synthetic studies towards the bisorbicillinoids with sorbicillin (**3**) and had acetate **7a** (Scheme 1) as the first objective. Thus, **3**, obtained by the boron trifluoride catalyzed acylation of 2,4-dimethylresorcinol^[9] with sorbic acid,^[10] was subjected to



Scheme 1. Biomimetic total synthesis of bisorbicillinol (**1**) from sorbicillin (**3**). a) $\text{Pb}(\text{OAc})_4$ (1.2 equiv), AcOH , 25°C , 2 h, 40% **7a** and 10% **7b**; b) KOH (10 equiv), $\text{THF}/\text{H}_2\text{O}$ (9/1), 0°C , 2 h; then 1 N aq. HCl , 40%; or $\text{THF}/\text{conc. HCl}$ (9/1), 25°C , 2 h, 43%.

oxidation with lead tetraacetate in acetic acid to afford the desired α -hydroxydienone **7a** as the major product together with its regioisomer **7b** (ca. 5:1 ratio, Scheme 1). Flash column chromatography (silica, dichloromethane/acetone 9/1) followed by recrystallization furnished **7a** in 40% yield (Table 1).

When acetate **7a** was treated with solid KOH (10 equiv) in $\text{THF}/\text{H}_2\text{O}$ (9/1; 0.05 M) at 0°C for 1 h followed by quenching with 1 N aq. HCl , the Diels–Alder adduct bisorbicillinol (**1**) was isolated in 40% yield. The spectral properties of synthetic **1** were identical to those reported by Abe et al.^[2, 11] Generating four stereogenic centers, two of which are quaternary, this reaction proceeds with remarkable regio- and diastereocontrol (*endo* selectivity).^[12]

It is postulated that the first stages of this sequence (**7a** $\rightarrow$ **1**) involve deacetylation followed by scrambling of the resulting dianion to a mixture of diquinolates (derived from **8a** and **8b**, Scheme 1). Acidification of the reaction mixture presumably results in the formation of quinols **8a** and **8b**, which readily combine in a Diels–Alder reaction to generate **1**. A similar dimerization was observed by Barton et al. when they generated *ortho*-quinols by allowing phenols to react with

Table 1. Selected physical properties of compounds **7a**, **12**, and **13**.

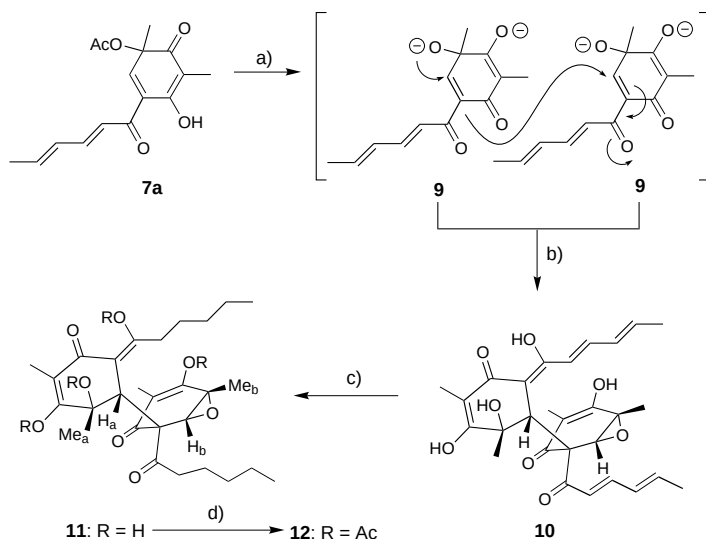
7a: $R_f = 0.41$ (silica gel, dichloromethane/acetone 9/1); m.p. $149\text{--}150^\circ\text{C}$ (diethyl ether/*n*-hexane); IR (film): $\tilde{\nu}_{\text{max}} = 2930, 1737, 1650, 1644, 1612, 1555, 1215, 1245, 1070, 1018\text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 11.90$ (s, 1H), 7.46 (dd, $J = 14.8, 10.8\text{ Hz}$, 1H), 7.25 (s, 1H), 6.66 (d, $J = 14.8\text{ Hz}$, 1H), 6.38 (m, 1H), 6.31 (m, 1H), 2.15 (s, 3H), 1.93 (d, $J = 6.6\text{ Hz}$, 3H), 1.86 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 195.4, 193.7, 170.4, 162.9, 152.3, 148.7, 145.3, 130.5, 125.9, 120.6, 112.1, 78.6, 24.5, 21.0, 19.6, 7.6$; HR-MS (MALDI): calcd for $\text{C}_{16}\text{H}_{18}\text{O}_5\text{Na}$ [$M + \text{Na}^+$]: 313.1052, found: 313.1055

12: $R_f = 0.40$ (silica gel, ethyl acetate/hexane 2/3); IR (film): $\tilde{\nu}_{\text{max}} = 2931, 1769, 1710, 1671, 1370, 1242, 1185, 1071\text{ cm}^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 5.90$ (s, 1H), 4.08 (s, 1H), 3.51 (ddd, $J = 13.8, 10.0, 5.5\text{ Hz}$, 1H), 2.87 (dt, $J = 19.3, 7.3\text{ Hz}$, 1H), 2.63 (ddd, $J = 13.7, 10.1, 5.5\text{ Hz}$, 1H), 2.19 (dt, $J = 19.3, 7.3\text{ Hz}$, 1H), 1.96 (s, 3H), 1.92–1.86 (m, 1H), 1.86 (s, 3H), 1.78 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.68–1.61 (m, 1H), 1.59 (s, 3H), 1.58–1.52 (m, 2H), 1.50 (s, 3H), 1.41–1.34 (m, 2H), 1.33–1.26 (m, 2H), 1.25–1.16 (m, 2H), 1.15–1.07 (m, 2H), 0.88 (t, $J = 7.4\text{ Hz}$, 3H), 0.81 (t, $J = 7.3\text{ Hz}$, 3H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 205.2, 194.5, 184.9, 168.6, 167.7, 166.2, 165.4, 163.4, 157.8, 157.7, 127.3, 127.0, 119.7, 82.7, 79.6, 79.2, 71.5, 59.7, 44.0, 33.0, 32.0, 31.2, 27.7, 25.4, 23.4, 23.0, 22.9, 22.9, 21.6, 20.7, 20.0, 19.9, 14.3, 14.1, 10.7, 10.6$; HR-MS (MALDI): calcd for $\text{C}_{36}\text{H}_{48}\text{O}_{12}\text{Na}$ [$M + \text{Na}^+$]: 695.3038, found: 695.3013

13: $R_f = 0.38$ (silica gel, dichloromethane/methanol 9/1); IR (film): $\tilde{\nu}_{\text{max}} = 2933, 1790, 1619, 1558, 1415, 1349, 1224, 1095, 948\text{ cm}^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 16.95$ (s, 1H), 7.48 (dd, $J = 14.5, 10.9\text{ Hz}$, 1H), 6.19–6.11 (m, 1H), 5.74 (d, $J = 14.4\text{ Hz}$, 1H), 5.72–5.64 (m, 1H), 2.77 (dd, $J = 12.2, 8.3\text{ Hz}$, 1H), 2.08 (dd, $J = 17.5, 8.3\text{ Hz}$, 1H), 2.05 (s, 3H), 1.90 (dd, $J = 17.5, 12.2\text{ Hz}$, 1H), 1.53 (d, $J = 7.0\text{ Hz}$, 3H), 1.11 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 189.9, 175.2, 168.7, 163.9, 140.2, 137.7, 131.1, 119.4, 110.9, 101.7, 84.0, 41.5, 36.4, 23.9, 18.6, 7.8$; HR-MS (MALDI): calcd for $\text{C}_{16}\text{H}_{18}\text{O}_5\text{Na}$ [$M + \text{Na}^+$]: 313.1052, found: 313.1063

diphenylseleninic acid anhydride.^[13] The proposed pathway from **7a** to **1** was supported by NMR studies. Thus, when the above experiment was carried out in an NMR tube using $[\text{D}_8]\text{THF}$ and D_2O , the ^1H NMR signals of the rapidly formed deep orange solution revealed the presence of two distinct quinolates and the absence of **1** until acidification, whereupon the resonances corresponding to **1** appeared. These observations suggested the possibility of converting **7a** into **1** directly by acid hydrolysis of the acetate group. Indeed this was proven to be the case, whereby treatment of **7a** with concentrated HCl in THF produced **1** in 43% yield. Again a ^1H NMR experiment proved the fleeting nature of quinols **8a** and **8b**, while it nicely allowed the monitoring of the appearance of **1** at the expense of **7a** during the course of two hours.

Interestingly, when the saponification of **7a** was carried out with KOH (10 equiv) in a minimum amount of $\text{THF}/\text{H}_2\text{O}$ (10/1), a different product was formed, together with only a small amount of the previously obtained **1** (Scheme 2). Although the major product according to thin-layer chromatography (TLC, ca. 65% crude yield), the new compound proved labile on silica gel and could only be isolated in pure form by flash column or preparative thin layer chromatography, and the yield was much lower. The physical properties of the new compound were suggestive of the dimeric structure **10**. Further support for this structure was obtained by hydrogenation of the side chains (H_2 , 10% Pd/C , EtOAc , 81%) and acetylation of the resulting compound (**11**; Ac_2O , 4-DMAP, 80%) to furnish tetraacetate **12**, whose structure was fully established by ^1H , ^{13}C , ^1H – ^1H COSY, HMQC, and



Scheme 2. Synthesis of sorbicillin dimer **10** from acetate **7a**. a) KOH (10 equiv), THF/H₂O (10/1), 0 °C, 2 h; b) 1N aq. HCl, 65 % (crude yield); c) H₂, 10 % Pd/C, EtOAc, 25 °C, 2 h, 81 %; d) Ac₂O (10 equiv), 4-DMAP (0.1 equiv), EtOAc, 25 °C, 2 h, 80 %. nOes observed for **12**: Me_a/H_a (4.5 %), H_a/H_b (3.9 %), and H_b/Me_b (3.0 %). 4-DMAP = 4-(dimethylamino)pyridine.

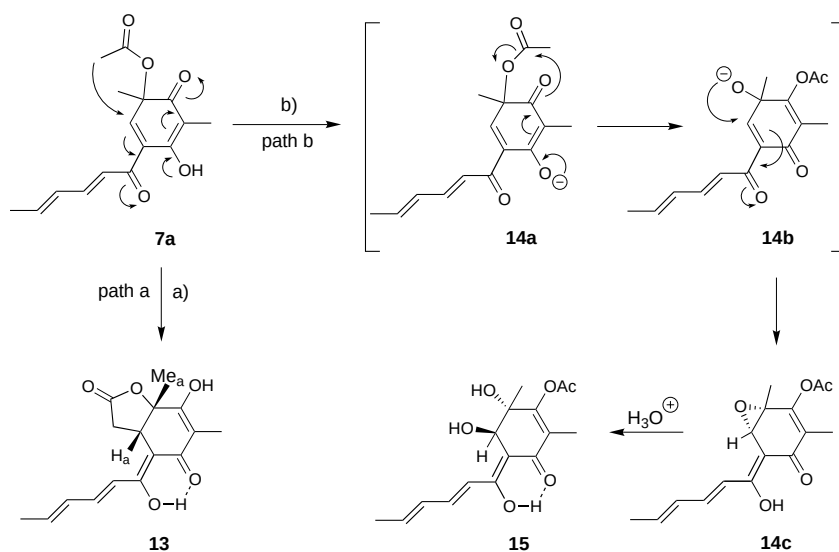
HMBC NMR spectroscopic techniques. Particularly useful in defining the configuration of **12** were the nOes observed, in a 1D nOe experiment, for the following protons: Me_a/H_a (4.5 %); H_a/H_b (3.9 %); H_b/Me_b (3.0 %). A mechanistic rationale for the formation of **10** from **7a** is presented in Scheme 2. Thus, it is reasoned that the initially formed dianion **9** rearranges by an intramolecular Michael reaction to an epoxy dianion (not shown), which attacks a second molecule of **9** in an intermolecular Michael reaction, generating in the process a quaternary center; the observed product **10** is formed upon acidification.

In another series of experiments, we attempted to force acetate **7a** into entering pathways that may lead to other bisorbicillinoids. Thus, while reaction of **7a** with LiHMDS at $-78 \rightarrow 25^\circ\text{C}$ produced only the orange lithium enolate, treatment of **7a** with excess KHMDS (3.0 equiv) in anhydrous THF at -78°C produced first a red solution and subsequently, upon acidification, the yellow γ -lactone **13** (60 % yield, Scheme 3). When the same reaction was performed with 0.9 equiv of KHMDS at -78°C , a yellow solution (presumably of the enolate anion) was initially formed, and after stirring at 25°C for 12 h followed by aqueous workup, the yellow and rather labile *trans*-diol **15** was isolated. Mechanistically, these events can be rationalized by assuming enolate-induced cascade reactions. Thus, for the formation of **13**, acetate **7a** is required to undergo rearrangement of its quinol moiety to form its acetate enolate before collapsing, by an intramolecular Michael addition, on its enone system

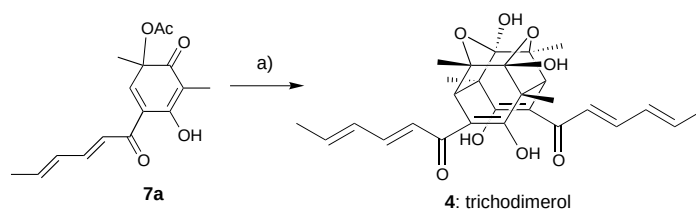
(Scheme 3, path a). With less than one equivalent of base, **7a** follows a different pathway (path b) initiated by the formation of its quinolate **14a**. Thus, rearrangement of quinolate **14a** followed by acetate migration leads to alkoxy anion **14b**, which undergoes an intramolecular Michael addition to the enone system to form epoxide **14c**. Stereoselective epoxide opening by a molecule of water furnishes diol **15**.^[14]

The prospect of generating trichodimerol (**4**) from acetate **7a** was finally realized when we altered the method of quenching the corresponding monomeric diquinolate (Scheme 4). Thus, treatment of **7a** with CsOH · H₂O for 7 h followed by addition of powdered NaH₂PO₄ · H₂O and stirring at 25°C for 12 h furnished **4**, which was isolated in 16 % yield after column chromatography together with **3** (12 %) and **1** (22 %). Synthetic **4** (racemic) exhibited identical spectroscopic properties to that reported by Ayer et al.^[4a, 15] The very slow neutralization of this reaction is crucial for the extraordinary dimerization of acetate **7a**.^[16]

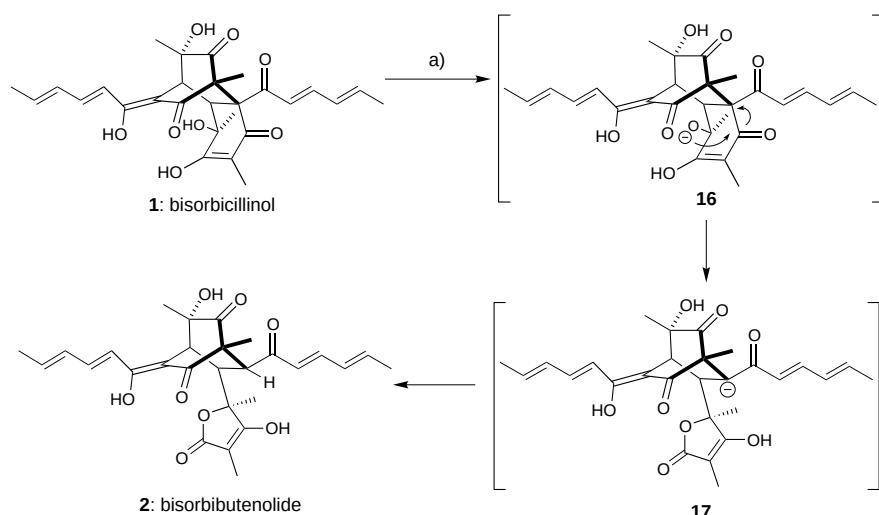
Finally, the hypothesis put forward by Abe et al.^[3] for the biosynthesis of bisorbibutenolide (**2**) and bisorbicillinolide (**5**) from bisorbicillinol (**1**) was investigated. Indeed, when a solution of **1** in THF was treated with one equivalent of KHMDS at ambient temperature, a more polar compound was formed (80 % yield) whose structure was established to be that of bisorbibutenolide (**2**) by spectroscopic means and



Scheme 3. Transformations of acetate **7a**. a) KHMDS (3.0 equiv), THF, -78°C , 2 h, 60 %; b) KHMDS (0.9 equiv), THF, $-78 \rightarrow 25^\circ\text{C}$, 2 h; then 25°C , 12 h, 35 %. nOes observed for **13**: Me_a/H_a (1.8 %). KHMDS = potassium salt of 1,1,1,3,3,3-hexamethyldisilazane.



Scheme 4. Biomimetic total synthesis of trichodimerol (**4**) from acetate **7a**. a) CsOH · H₂O (10 equiv), MeOH, 25°C , 7 h; then NaH₂PO₄ · H₂O, 25°C , 12 h, 16 % **4**, 12 % sorbicillin (**3**) and 22 % bisorbicillinol (**1**).



Scheme 5. Biomimetic synthesis of bisorbibutenolide (**2**) from bisorbicillinol (**1**). a) KHMDS (1.1 equiv), THF, 25 °C, 24 h; then 1N aq. HCl, 80%.

comparison of its ^1H and ^{13}C NMR spectra with those of the naturally occurring compound (Scheme 5).^[11] Interestingly, bisorbicillinolide (**5**) was not observed in this reaction.

The findings described herein—including the total synthesis of bisorbicillinol (**1**), bisorbibutenolide (**2**), and trichodimerol (**4**)—shine light on the chemistry of the bisorbicillinoids and confirm a number of hypothetical proposals regarding their biosynthesis. Furthermore, the novel synthetic pathways elucidated during this study add to the repertoire of cascade reactions as an enabling technology for complex molecule construction, while the unusual molecular frameworks produced enrich our pool of advanced synthetic intermediates and building blocks.

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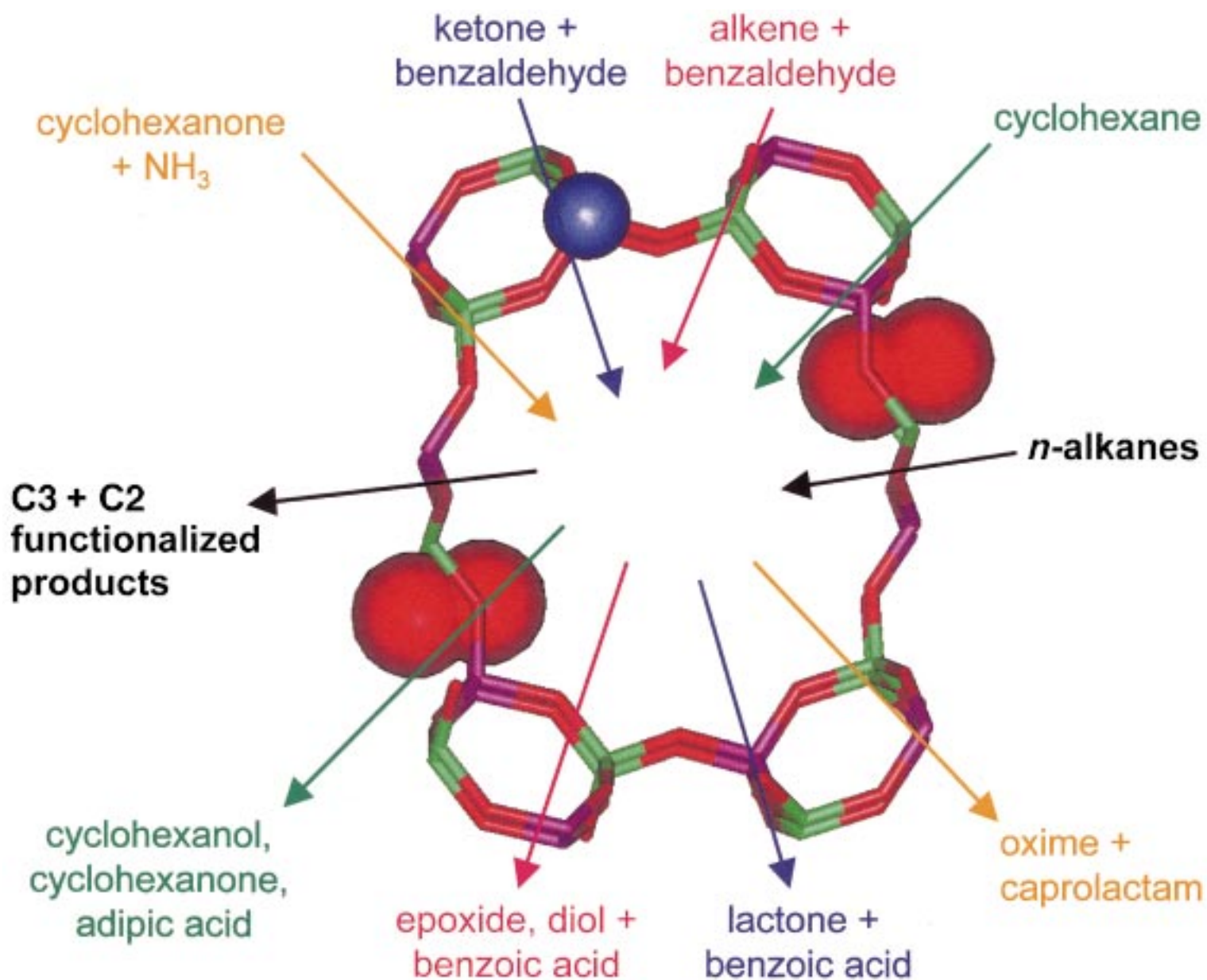
Keywords: biomimetic synthesis • bisorbicillinols • dimerizations • natural products • trichodimerol

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- [14] Attempts to induce **7a** to react under Lewis acid catalysis conditions were also made. Interestingly, when **7a** was exposed to TBSOTf or TMSOTf, **3** was the major product formed together with small amounts of **1**. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.
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The molecular sieves CoAIPO-36 and MnAIPO-36 are extremely versatile catalysts.



Design, Synthesis, and In Situ Characterization of New Solid Catalysts**

John Meurig Thomas*

Two distinct strategies exist for the design of solid catalysts. One adopts the reductionist approach, whereby the individual steps involved in overall catalytic conversion—the processes of adsorption, surface rearrangement, desorption, and transport of reactants and products to or from exterior surfaces—are analyzed in great detail so that the resulting information may be used to interpret the behavior of existing catalysts with a view to generating superior ones. The other focuses on the precise atomic architecture of the catalytically active site—its determination under operating conditions, its assembly and scope for its modification, the subtleties of its mode of action—which leads to the design of new catalysts capable of facilitating conversions that have hitherto proved either impossible or very difficult to effect. The present

article deals exclusively with the second strategy, which is an integrated one. It seeks to demonstrate that, by adopting the principles and practices of solid-state chemistry (augmented by lessons derived from enzymology, and computational and organometallic chemistry) a wide range of new catalysts may be designed that, *inter alia*, effect regioselective, shape-selective, and enantioselective conversions, as well as producing high-performance catalysts for the isomerization and hydrogenation of alkenes. All the new catalysts described herein are either microporous or mesoporous solids. These have the dual advantages of possessing large surface areas and being amenable to delicate structural and compositional variation either during preparation or subsequently by anchoring on to their inner walls well-

defined, isolated, and accessible molecular units that are heterogenized versions of homogeneous catalysts. The specific catalysts described are those designed for the following low-temperature reactions: the aerobic oxyfunctionalization of terminal groups in linear alkanes; low-temperature selective aerobic oxidation of cyclohexane; the radical-free (as well as free-radical) epoxidations of alkenes; Baeyer–Villiger oxidations of ketones to lactones; the preferential dehydrations of methanol to yield ethene and propene; and enantioselective allylic amination.

Keywords: catalysts • heterogeneous catalysis • microporosity • solid-state chemistry • synthetic methods

1. Introduction

It is clear that Karl Ziegler changed the world into which he was born. Polymers, in all their rich diversity of forms, nowadays profoundly influence our daily lives. But his scientific legacy in fields other than those of Ziegler catalysts and Ziegler–Natta polymers is also of high significance. For example, his “Aufbau method” of producing detergents, his

demonstration of the reality of free-radical autoxidation reactions, as well as the elegance of his use of radical scavengers to terminate chain processes are all facets of his intellectual percipience and the penetrating power of his scientific work.

Listening to and reading the accounts of the early life, temperament, and religious conviction of Karl Ziegler, and recognizing the oft-repeated assertion that he viewed pure and applied research as a continuum, and that he also had unquenchable intellectual curiosity and an omnivorous scientific appetite, comparisons can be drawn between him and one of my scientific heroes, Michael Faraday—who, like Ziegler, was of puritanical disposition. This is not the place to expatiate upon the admirable qualities of Faraday^[1]—held by many to be one of the greatest ever Englishmen—except to note that, like Ziegler, he left the world a very different place from that which he himself had inherited. Political theorists and philosophers sometimes argue—and how right they are—that “interpreting the world” is secondary to the much more demanding task of changing it.^[2]

[*] Prof. Dr. Sir J. M. Thomas
Davy–Faraday Research Laboratory
Royal Institution of Great Britain
London W1X 4BS (UK)
Fax: (+44) 171-629-3569
E-mail: dawn@ri.ac.uk
and

Department of Materials Science, University of Cambridge
Cambridge CB2 3QY (UK)

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2. The World Of Catalysis

Although the word catalysis was not coined until 1835 (by Berzelius)^[6] the phenomenon itself was known to the ancients. Aristotle describes it in his treatise on meteorology, the Arab alchemist, Jabir, in the eighth century A.D., demonstrated how a mineral acid could catalyze the conversion of alcohol to ether, and it has been the backbone of the chemical industry for nearly two hundred years.

In designing and synthesizing new solid inorganic catalysts the aims are to maximize surface area, activity, selectivity, longevity, and durability. Unfortunately, few if any of the marvellous new tools, techniques, and avenues that are available to the organic chemist and molecular biologist—namely site-directed mutagenesis,^[7, 8] chemically modified mutant enzymes,^[9] the exploitation of non-natural amino acids in an expanded genetic code,^[10] catalytic antibodies^[11] (which turn to advantage the teeming multiplicity and subtleties of the immune system), design by directed (Darwinian) evolution^[12, 13]—will ever be capable of being incorporated directly into the inorganic world, which is destined, almost by definition, to be impervious to the charms and advantages of animate life.

All is not lost, however, for there are real prospects, adumbrated in this review, that the technical virtuosity inherent in the development of a vast range of inorganic homogeneous catalysts, especially organometallic ones,^[14, 15] may be simulated and extended by adroit design, synthesis, and manipulation of new inorganic solids. The key lies in producing materials with large surface areas, the surface composition, structure, and atomic architecture of which are incontrovertably characterized under operating conditions. Before we proceed to describe how this is done, it is first instructive to enumerate what the desiderata of these new, engineered heterogeneous catalysts are. These desiderata are

shown in Table 1, the format of which owes much to the elegant animadversions of Cornils and Herrmann^[15] on the “two cultures” that are so conspicuously ingrained in the minds of those who dwell on the strengths and weaknesses of homogeneous and heterogeneous catalysis.

Table 1. Desiderata for new engineered heterogeneous catalysts.

Apart from possessing high activity, high selectivity, long lifetimes, and durability, other desiderata are:

- the capability of operating under mild conditions that are environmentally and economically efficient
- freedom from restrictions imposed by diffusional considerations
- possession of isolated, well-defined (single site) active centers, the atomic architecture of which may be delicately modified
- capability of yielding a detailed mechanistic understanding of catalytic action (for example, by strategies such as that summarized in Figure 4).

Microporous and mesoporous solid catalysts are potentially, and in very many cases (as described in this article), capable of achieving all these desiderata.

At first sight, it would appear that, in seeking to create new, solids with large surface areas that are to be endowed with marked catalytic activity, the most propitious path to take is that which leads to the production of monodisperse particles of colloidal dimension. The dispersion D , defined as the fraction of the total number n of atoms in a particle that are at the surface (Figure 1), is clearly higher the smaller the value of n . Is it not sensible, therefore, if our aim is to maximize activity—given that we have chosen the right material for its intrinsic activity in the first instance—to work towards convenient, easy methods of producing highly comminuted solids, the diameter of the individual particles of which should be in the 10–20 Å diameter range? The answer is not a simple yes, because small particles have melting points that are far below those of their bulk analogues. This result is because the amplitudes of the motion of atoms at a surface far exceed

*John Meurig Thomas is Professor of Chemistry and Former Director of the Davy Faraday Research Laboratory, The Royal Institution of Great Britain, London, and Master of Peterhouse and Honorary Research Fellow, Department of Materials Science, University of Cambridge. For nine years he was Head of the Department of Physical Chemistry, University of Cambridge and for twenty years prior to that he was at the University of Wales (Bangor and Aberystwyth), where he graduated (Swansea) in 1954. He is one of the founders of modern solid-state chemistry; and for his contributions to it, to surface and materials chemistry, and to heterogeneous catalysis he has received numerous national and international awards. These include the Davy Medal of the Royal Society, the Faraday Medal of the Royal Society of Chemistry, the Willard Gibbs Gold Medal of the American Chemical Society, the Messel Gold Medal of the Society of Chemical Industry, and the Semenov Centenary Medal of the Russian Academy of Sciences. Earlier this year he became the first recipient of the American Chemical Society Award for Creative Research in Homogeneous and Heterogeneous Catalysts for his development of in situ methods in catalysis and for laying the foundations of the molecular design of catalytically active centers. He is the author of over 850 publications, ten patents, and many books including (together with W. J. Thomas) *Heterogeneous Catalyses: Principles and Practice*, Wiley-VCH, Weinheim, 1997, and *Michael Faraday and The Royal Institution: The Genius of Man and Place*, Institute of Physics, Bristol, 1991. His 1987 series of Royal Institution Christmas Lectures on Crystals was broadcast nationally by the BBC. He is the founding co-editor-in-chief of *Catalysis Letters*, *Topics in Catalysis*, and *Current Opinion in Solid State and Materials Science*. He was knighted in 1991 for his services to chemistry and the popularization of science.*



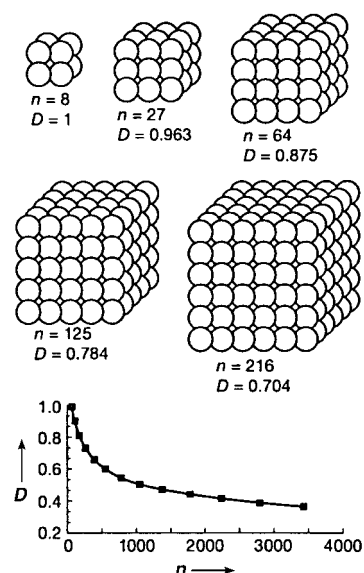


Figure 1. One way to increase the fraction D of surface-situated atoms in a crystal is to prepare it in nanoparticulate form. The smaller the particle size, the larger is this fraction (n = total number of atoms in the crystal).^[16] Another method (see Figure 2) is by producing the crystal in such a porous state that D is close to unity even for micron-sized or even larger crystals.

those of atoms in the bulk.^[17] The mobility of small particles is therefore large; consequently they are prone to coalesce and sinter, thereby greatly decreasing the total surface area. If, however, nanoparticles of diameter 10–20 Å can, by appropriate chemical strategies (see Figures 46 and 48), be securely anchored to the atoms of the substratum upon which they have been laid down, then indeed the answer to the question posed earlier is a resounding yes for so-called structure-insensitive reactions.

Although there are certain, high-performance inorganic catalysts (such as the bimetallic ones described in Section 7.6) that are good examples of nanocrystals, the way towards creating a versatile and large family of large-area, high-performance inorganic catalysts lies elsewhere, namely by harnessing the advantages of microporous and mesoporous solids.

3. Solids With Three-Dimensional Surfaces: The Expanding Realm Of The Microporous And Mesoporous

Highly microporous or mesoporous solids such as those that possess channels, cavities, or cages with diameters in the range of 4 to 14 Å (micro) and 15 to 150 Å (meso) offer the best means for designing or modifying new inorganic heterogeneous catalysts (Figure 2). As operating catalysts it is to be noted that they:

- permit free ingress of reactant and egress of product species that have cross-sections smaller than the diameter of the pores
- offer greater scope (especially mesoporous solids) for the grafting of organometallic moieties^[18–23] on to the inner surfaces of the pores. This opens ready routes for the

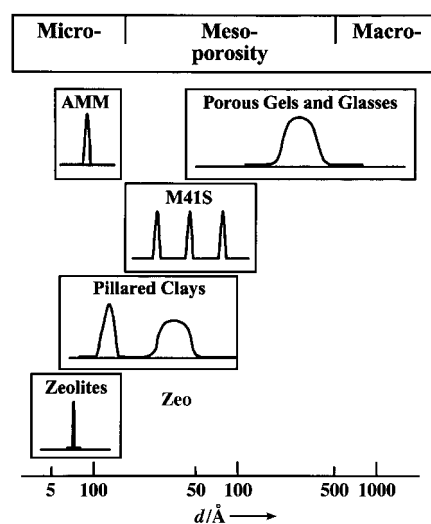


Figure 2. Solids may nowadays be routinely produced with (largely internal) surface areas that exceed 1000 m² g^{−1}. Some of these are microporous (aperture diameters from ca. 3 to 14 Å), some mesoporous (ca. 15 to 150 Å), and some macroporous. It is occasionally possible to produce solids with a bimodal pore-size distribution (of micro- and mesopores). AMM = amorphous microporous metallosilicate (W. F. Maier, I.-C. Tilgner, M. Wiedorn, H.-C. Ko, *Adv. Mater.* **1993**, *5*, 726; W. F. Maier, J. A. Martens, S. Klein, J. Heilmann, R. Parton, K. Vercruysse, P. A. Jacobs, *Angew. Chem.* **1996**, *108*, 222; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 180); for M41S are MCM-41, MCM-48, and MCM-50 included (C. T. Kresge et al.;^[52] J. C. Vartuli, J. S. Beck;^[56] for pillared clays see J. M. Thomas in *Intercalation Chemistry* (Eds.: M. S. Whittingham, E. J. Jacobson), Academic Press, New York, **1982**, p. 56. (After Behrens^[51])

heterogenization of homogeneous catalysts, thus capitalizing on the advantages of high activity and single-site active centers of the homogeneous category, and the robustness and ease of separation that is a feature of the heterogeneous catalysts

- open up many new strategies for shape-selective, enantio-selective, and regioselective conversions

Moreover, because they are, in essence, solids with three-dimensional surfaces, they greatly facilitate experimental procedures for their characterization. Thus, the full panoply of spectroscopic and diffraction (or other scattering) tools may be deployed^[24, 25] to determine, often under in situ conditions, either the local or average structure of the solid catalyst itself, or the nature of the species undergoing conversion at its (three-dimensional) surface (Figure 3).

What is particularly convenient here is that, with this category of solid, the distinction between the model catalyst (tailored so as to facilitate retrieval, usually by the academically oriented researcher, of structural and compositional information) merges with the operational (real life) catalyst, engineered by the applied scientist so as to exhibit the best possible chemical performance.

Because of their relative ease of production and the wide range of compositional variation that they exhibit, it is possible to realize most of the catalytic desiderata enumerated in Table 1. Moreover, because the engineered catalysts described in this review have such well-defined, single-site active centers, it is also possible to synthesize soluble “fragments” of the catalysts in which the active site is placed in a

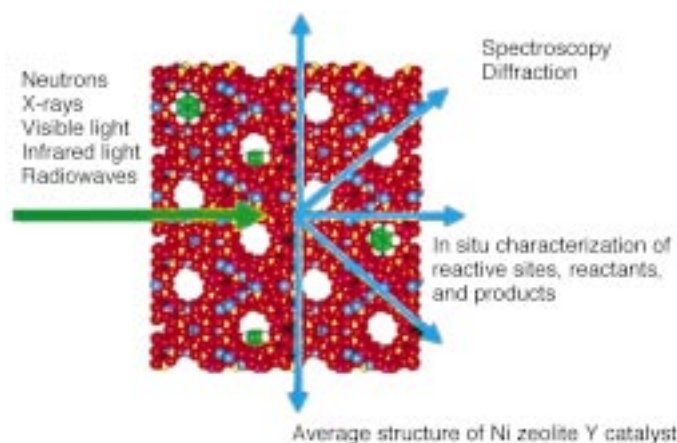


Figure 3. The detailed atomic structure of this rather complicated Ni^{2+} -ion-exchanged zeolite Y catalyst may be determined under operating conditions from a Rietveld refinement procedure of either the X-ray or neutron powder diffraction pattern. The precise atomic environment of the Ni^{2+} ions (that are the active sites for the catalytic conversion of acetylene to benzene)^[26] may also be determined in situ by X-ray absorption spectroscopy. With catalysts such as this, which have three-dimensional surfaces, a wide range of both spectroscopic and diffraction methods may be used to retrieve structural and mechanistic information pertaining to the catalyst itself and the reactants that are catalytically converted at their (interior) surfaces. Specific examples are described later in the text. Red: oxygen; yellow: silicon; blue: nickel. For clarity, sodium ions are not shown.

well-defined, and controllable, atomic environment (Figure 4). This makes it possible to achieve an understanding of the factors that govern catalytic performance to a degree previously unequalled. It also paves the way to a deeper understanding of the determinants of catalytic promotion, poisoning, and inhibition.^[28]

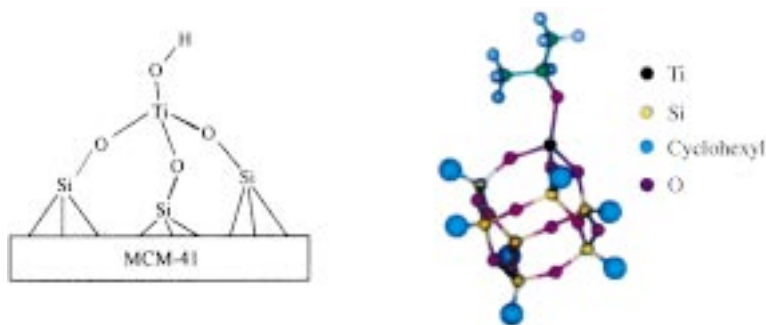


Figure 4. The in situ techniques described in this article and in ref. [27] yield the atomic architecture of active sites in heterogeneous catalysts, such as in the epoxidation of alkenes. The Ti^{IV} ions, with their pendant OH groups, are tripodally attached to the silica (or silica-germania) support (left). Titanosilsesquioxanes, such as that shown on the right, are soluble analogues of the active sites and are amenable to structural and mechanistic studies by the classical tools (NMR spectroscopy, spectrophotometry, etc.) used in studies of homogeneous catalysts.^[28]

4. Rational Design Or Blind Chance: Is The Combinatorial Approach Destined To Be Invincible?

Any discussion of engineered catalysts, like any discussion of new generations of pharmaceutical or agrochemical products, nowadays tends to be dominated by the compelling

immediacy of combinatorial methods^[29] (first introduced by Hungarian workers in the early 1970s). The laborious methods of trial-and-error—which have served catalysis and many other fields of science so well over the last two centuries—must, it is argued, give way to more streamlined combinatorial methods of discovery. These new methods, which are an inherent feature in biological nature^[30] especially in the immune system, and are used increasingly in drug design, consist essentially of three main components: 1) automated library syntheses of new candidate catalysts (using robots, for example) that are readily amenable, 2) miniaturization or microminiaturization, 3) high-throughput screening of catalytic performance. Taken altogether, these three features then lead to an ultra-rapid production of databases from which numerous key items of catalytic information pertaining, for example, to the best combination of elemental composition and atomic structure or architectures (for a given desired catalyst) may be extracted.

The first example of combinatorially prepared inorganic catalysts was reported by Hill and Gall,^[31] who synthesized a library of various polyoxometalates for the aerobic oxidation of the mustard gas analogue tetrahydrothiophene from stock solutions that contained precursors such as Na_2WO_4 , Na_2MoO_4 , and Na_2HPO_4 . Central to the combinatorial methodology is the development of an effective algorithm for the discovery of a new catalyst. This, in turn, requires a rapid and reliable method of screening (that is, of quantitatively recording the performance) of the library of assembled candidate catalysts.

It is timely to quote two highly relevant examples (highlighted on the front cover of *Angewandte Chemie*, Figure 5) of work done at Ziegler's laboratory in Mülheim. In both of these studies the enthalpy changes associated with the chemical reactions under investigation were used as a quantitative measure of catalytic activity for the purposes of rapid screening.

Maier and co-workers showed that thermal imaging is a very sensitive means of detecting activity in positional catalytic libraries that contain only about 200 μg of catalyst at each addressable position in the library.^[32] Minute wells sunk into a slab of slate (chosen because of its low thermal reflectivity so as to minimize interference) were filled with sol-gel precursor solutions for so-called^[33] amorphous mixed-metal oxides of different compositions, which were processed to yield an array of candidate catalysts (Figure 6). A thermal image of the whole array without substrate was stored and subsequently subtracted from the images of the array under operation. This procedure permitted Maier et al. to minimize the effect of different thermal emissivities of the catalyst wells, so that they could detect very small temperature differences associated with catalytic activity. This technique offers a fast, convenient parallel assay of quite a sizeable library of catalysts for the hydrogenation of 1-hexyne at 100 °C and for the oxidation of isooctane and toluene at 350 °C.

Reetz and co-workers^[34] also demonstrated the power and utility of sensitive thermal imaging (infrared cameras and

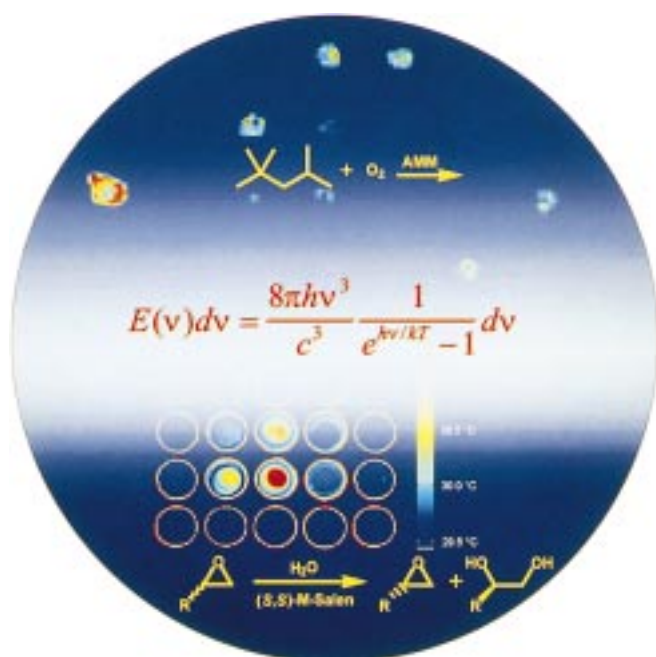


Figure 5. Visual portrayal of the combinatorial approach to the screening of a library of amorphous mixed-metal (AMM) oxides for the catalytic oxidation of isooctane^[32] (top) and of enantioselective transition metal catalysts for the ring-opening hydrolysis of epoxides^[34] (bottom) on the cover picture of Issue 19 of *Angewandte Chemie* in 1998. In each case, thermal imaging (implied here by the central equation) is used as a very sensitive means of detecting activity in addressable catalytic libraries.

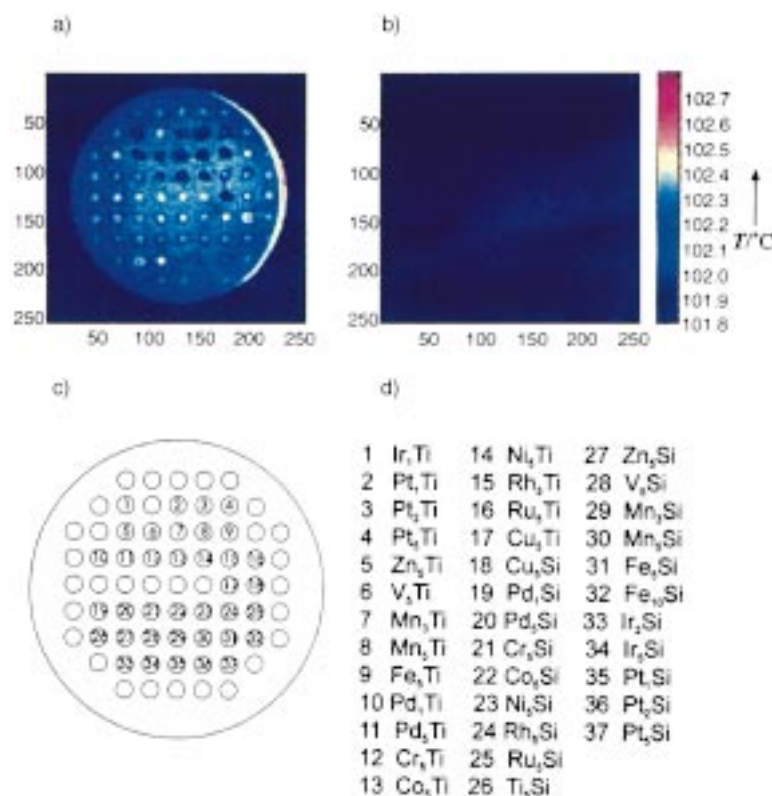


Figure 6. a) IR image of the library of catalysts without correction for emissivity; b) emissivity-corrected IR-thermographic image of the library of catalysts prior to the start of reaction (bar on right is the temperature key); c) deposition pattern of the library;^[32] d) composition of the oxide catalyst spots of the library according to the AMM notation, which give the molar percentages of active metal and base metal oxides.

array detectors) to explore a library of homogeneous catalysts for the enantioselective acylation of a chiral alcohol (1-phenylethanol) that was catalyzed by immobilized lipase. They also demonstrated this approach in the enantioselective ring-opening of chiral epoxides with transition metal–salen catalysts. The array of reactants included the two different enantiomers of the substrate, for which the catalysts showed drastically different activities.

It is a relatively simple matter to devise high-throughput methods to probe catalytic selectivities as well as activities. Mallouk et al.^[35] have done this in their quest for optimized alloy electrocatalysts for the electrochemical oxidation of methanol in a fuel cell; Senken^[36] has done it for an array of solid catalysts on a porous support; and Weinberg et al.^[37] in their high-throughput screening (and synthesis) of a combinatorial library of 120 different heterogeneous ternary alloy catalysts (based either on Rh–Pt–Cu, Rh–Pd–Cu, or Rh–Pd–Pt thin films) in the oxidation of CO by either O₂ or NO.

For solids, in which the performance (catalytic or otherwise) of the prepared composition and structure more-or-less instantaneously reaches their steady-state value at the instant of preparation, the combinatorial (blind chance) approach is a reliable means of making rapid progress in the quest for new materials. But when the catalytic performance (or other measured property) takes a substantial time before achieving its optimal value, or when it is a critical

function of a time-dependent (crystallographic) structure, the combinatorial approach can be misleading at best, and unhelpful at worst (see Thomas^[25] and Schlögl^[38] for a selection of such examples). These deficiencies can be compounded if the solid catalysts prepared in the library of candidates exhibit varying degrees of structural abnormalities such as nonstoichiometry, antiphase boundaries, or crystallographic shear planes.^[23]

In summary, therefore, it is assuredly the case that the combinatorial approach is here to stay. It will undoubtedly grow in importance, if only because it shortens the length of the cycle from synthesis to testing or re-designing and formulation. But it is not invincible. There remains immense scope for the traditional approaches that combine insight, inspiration, know-how, and various kinds of technical virtuosity.^[39, 40] One only has to recall the emergence of the seminal developments of asymmetric catalysts (by Sharpless et al.^[41] and others) using procedures based on straightforward and novel ligand variation around a transition metal ion center, to appreciate the power of conventional methods in homogeneous catalysis. The same can be said of numerous other designed catalysts such as the β -cyclodextrin-modified diphosphanes as ligands for supramolecular rhodium catalysts^[42] and of the many examples cited by Cornils and Herrmann.^[14] Likewise, in heterogeneous catalysis an eloquent illustration of the role of flair and imagination is seen in the

design^[43–46] of powerful microporous catalysts (see Figures 7 and 8). Even in the field of designing new synthetic enzymes, it is not essential to opt only for biological routes such as mutagenesis. Dutton et al.^[47] demonstrate the importance of flair coupled to rational design in their elegant work on so-called “maquette catalysts”.

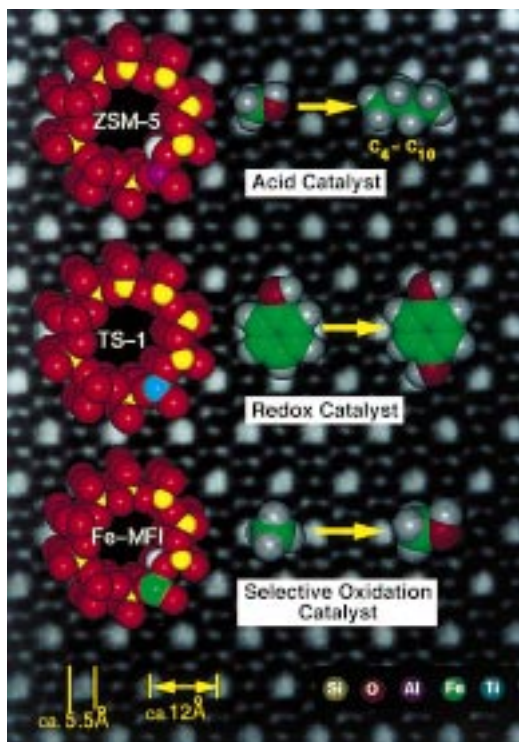


Figure 7. Superimposed on a high-resolution electron micrograph of silicalite, which has pores of diameter 5.5 Å, are computer graphic, scalar models of the pore openings of the catalysts ZSM-5^[44] (top), TS-1^[45] (middle), and Fe-MFI^[25] (bottom) where, respectively, framework Si⁴⁺ ions have been isomorphously replaced by Al³⁺ (to produce a solid acid catalyst), Ti^{IV}, to produce a so-called “redox” catalyst (but which is better described, see Section 7.4.2, as a selective oxidation catalyst) and Fe³⁺, which is promising as a catalyst for the conversion of methane into methanol.

The phenomenally successful, shape-selective, solid acid catalyst ZSM-5 arose largely from the work of Weisz and his co-workers, who were initially concerned with academic considerations relating to the acid-catalyzed dehydration of linear and branched alkanols inside the pores of model acid catalysts such as Ca²⁺ ion-exchanged zeolite A.^[43, 44] It was premeditated action by researchers in the ENI Chem company,^[45, 46] who focused on the aim of combining the inherent shape-selectivity of a pentasil structure (such as silicalite I, which is the pure siliceous end member of the aluminosilicate ZSM-5) and the well-known propensity of Ti^{IV} ions as an active center for selective oxidation (in the presence of H₂O₂), that led to the design of the versatile TS-1 catalyst for many commercially important selective oxidations. The same is essentially true of my own group’s work described herein, and represented in part by the structures shown in Figure 8.^[48]

5. Engineering Microporous And Mesoporous Catalysts

About one third of all the commonly encountered elements of the Periodic Table are nowadays capable of being incorporated into the framework structures (almost invariably in tetrahedral coordination) of the ever-growing families of micro- and mesoporous solids. In the case of microporous solids, also known as zeotypes or molecular sieves, the largest two sub-families are the aluminosilicates and aluminophosphates (known as AIPOs). These may be viewed as three-dimensional networks of corner-sharing SiO₄ and AlO₄ tetrahedra and of AlO₄ and PO₄ tetrahedra, respectively. Hetero atoms, which could be any of a wide range of di-, tri-, tetravalent, or higher value ions (typically Co²⁺, Mg²⁺, Mn²⁺, B³⁺, Ga³⁺, Fe³⁺, Ge⁴⁺, Ti⁴⁺, P⁵⁺...), may be incorporated substitutionally at regular framework sites. And it is generally possible (indeed often it is the only satisfactory means) to incorporate these ions during the synthesis of the zeotype. Mesoporous solids, on the other hand, are generally easier to prepare in their pristine state (as SiO₂, TiO₂, Al₂O₃, GeO₂, SnO₂, ZrO₂, Nb₂O₅, and, quite recently, metal sulfides), and the heteroatoms which serve as the loci of catalytic action are grafted onto the inner surfaces of the mesopores after synthesis. For a summary of the various kinds of materials that fall into one of other (or both) of these two categories see refs. [25, 27, 49–58]. It is, however, not difficult to synthesize mesoporous solids, especially silica, with one of very many different types of heteroatom in the framework.^[55, 58]

An indication of the burgeoning field of microporous solids (most of which display special catalytic activity and selectivity) may be gauged from the gallery of new materials^[59–66] portrayed in Figure 8. Many of these are high-performance catalysts for such processes as skeletal isomerization of butenes^[60] and the conversion of methanol to olefins.^[62, 65]

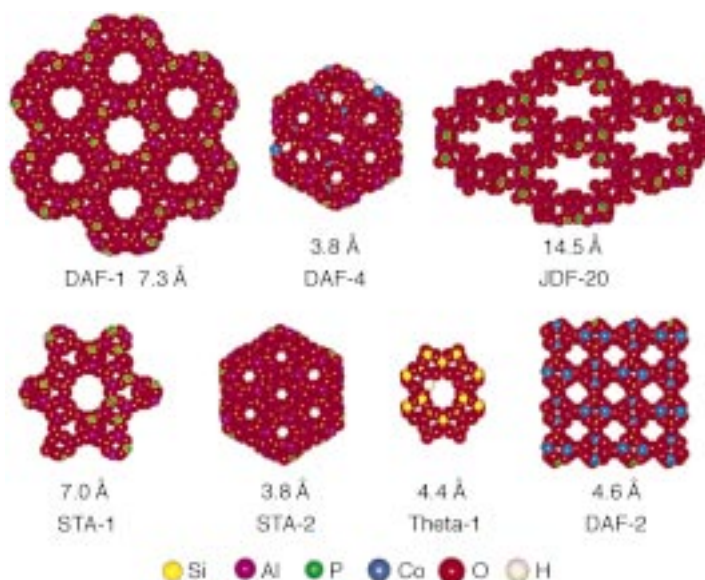


Figure 8. Projection models, to scale, of a selection of new microporous solids synthesized in recent years, usually with the aid of structure-directing templates (see Section 5). With the exception of DAF-2 and JDF-20, which tend to collapse when the template is driven away by calcining in air, all these new microporous solids are thermally robust solid catalysts.

Some, however, notably JDF-20 (Jilin-Davy-Faraday No. 20), which has the largest aperture so far recorded for a synthesized microcrystalline solid, is not particularly thermally stable. The structure collapses when the organic template used for its synthesis is driven off by thermal treatment.

In the family of mesoporous materials labeled M41S by their discoverers at the Mobil Oil Company,^[52, 56] of which MCM-41 is a hexagonal mesoporous phase (and MCM-48 is a cubic phase^[67]), experiment shows that, although there is good ordering of the hexagonal (or cubic) stacking of the channels themselves, comparatively little crystallographic order exists in the walls of the pores. Graphic representations of the nature of these mesoporous materials (which are also termed supramolecular-templated structures) are shown in Figure 9, and some typical high-resolution electron micrographs^[68, 69] of such material are reproduced in Figure 10.

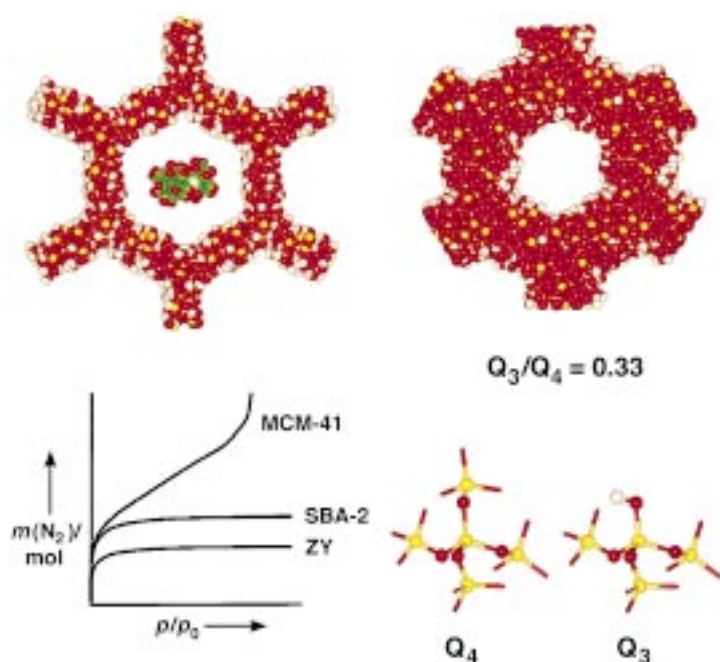


Figure 9. The MCM-41 mesoporous silicas depicted here have pore diameters of ca. 30 Å, and are easily capable of incorporating large organometallic species, such as multinuclear metal carbonylates, typically $[Ru_6C(CO)_{16}]$. Adsorption isotherms (of N_2 at 78 K) take up the shape shown in the top of the three plots (bottom left). For comparison adsorption isotherms for a zeolite Y (bottom of the three) and for SBA-2 (Santa Barbara No. 2), middle, are also shown. The top two structures are the energy-minimized ones computed by atom–atom procedures combined with molecular dynamics. (The computed ratio of Q_3/Q_4 of 0.33 for the structure at the top right is close to the value (0.40) determined from ^{29}Si MAS NMR spectroscopy). Q_3 and Q_4 are defined at the bottom right.

In meeting the challenge of how to synthesize new microporous crystalline solids, two interrelated approaches may be pursued: 1) design by experiment based on intuition and accumulated chemical experience, and 2) design by computer modeling. Success in synthesizing new microporous catalysts using the first approach comes from an appropriate choice of constituents of the nutrient gel from which the templated solid crystallizes during hydrothermal treatment. Twenty years ago it became apparent that quaternized ammonium salts were

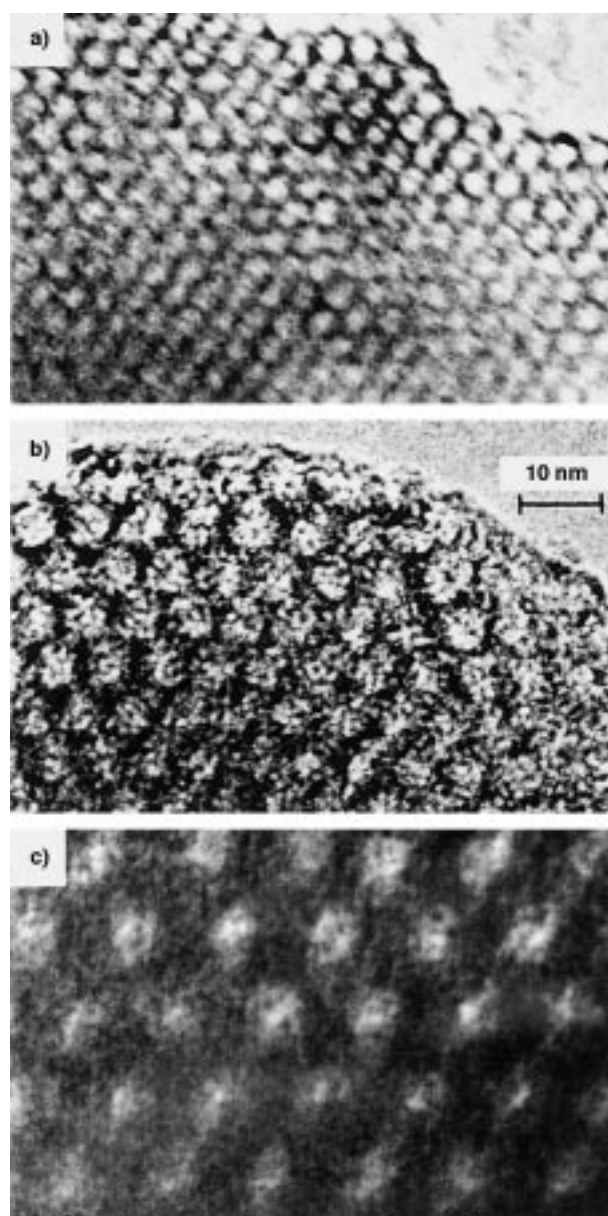


Figure 10. Depending upon the templates used, and the precise conditions of preparation, mesoporous silica belonging to the M41S family may exhibit pore diameters in excess of 100 Å and different thicknesses of pore walls.^[68, 69] The inter-pore distances (center-to-center) shown here are 42, 68, and 122 Å. Well-defined cubic–hexagonal (ABC-AB), polytypic intergrowths are also frequently observed in certain types of mesoporous silica.^[68]

ideal structure-directing template ions that favored production of the pentasil catalysts ZSM-5 and ZSM-11. In an extension of this strategy diisopropylamine was used^[70, 71] to yield MAIPO-18 ($M = Co, Mn, Zn, Mg, Mn...$) when the acetate of the divalent ion was added to mixtures of $Al(OH)_3$ and H_3PO_4 . Cyclohexylamine is the template of choice to produce MAIPO-44, and decamethonium ions for DAF-1, and so on. In the second approach a new procedure, of growing power and potential has evolved from the use of energy minimization methods^[72–74]—to investigate the packing energies of organic amines (such as triethylammonium ions) within distinct AlPO structures—to one in which, for a given

target solid, an appropriate algorithm is used to build up, within the desired cavity of the target microporous catalyst, the template molecule to be used in its chemical synthesis (see Section 5.1).

We focus first on the design based on accumulated chemical intuition. To make explicit our aim we are setting out to “find” the most appropriate template that will yield a microporous acid catalyst such as CoAlPO (or SAPO), which, after driving away the template by calcination leaves active sites of the type that we can establish in quantitative terms, using *in situ* characterization by X-ray absorption, X-ray diffraction, and FT-IR spectroscopy. This Brønsted acid site is, in effect, a detachable proton bound to the framework oxygen atom that is adjacent to a Co^{II} ion that has isomorphously replaced Al^{III} in the framework. In effect, our aim is to synthesize both cobalt- and silicon-containing solid acids based on AlPO, in which the cavities are somewhat different from those in CoAlPO-18^[70] and SAPO-18^[75]. (In a SAPO catalyst the detachable proton is bound to an oxygen atom which is next to the framework Si^{IV} center which has isomorphously replaced the P^V center).

More will be said later (Section 7.5) about microporous solid acid catalysts, derived by replacing Al^{III} ions in the framework of a “targeted” AlPO with divalent ions such as Co^{II} or Mn^{II}. We shall also have more to say (see Section 7.1) about the microporous oxidation catalyst analogues that are produced by calcining the parent solid acid in O₂ so as to yield a neutral framework in which up to about 4 atoms per cent of the Al^{III} ions are isomorphously replaced by Co^{III}, Mn^{III}, or Fe^{III} ions.

5.1. Designing Templates for the Synthesis of Microporous Solids Using a De Novo Computer-Modeling Technique

De novo ligand design has been applied for some time in the search for biologically active materials—see refs. [76–82] for further details and applications. These techniques allow a molecule to be “grown” so as to fit accurately into a targeted space. The molecule is grown, in a computational sense, to promote favorable interactions between the substrate and the target cavity. But owing to the complex, and frequently ill-defined nature of biological active sites, a number of approximations are often made, for example, restricting the growth to linking units^[79–81] and annealing dense arrangements of atoms into suitable molecules.^[83] Template molecules required for the production of microporous inorganic solids are usually much simpler and smaller than those required in biological contexts. Furthermore, the target host (the microporous material) has many advantages over the organic cavity. Firstly, it is crystalline, and can therefore be readily described atomistically; even hypothetical structures can be defined in this way. Secondly, the frameworks possess reasonable rigidity so that conformational changes in the pore need not in general be considered. Finally, the interactions present in the templating of microporous materials are dominated by van der Waals interactions.^[76, 84] Interactions involving charge and hydrogen bonding are less important in determining the final structure formed, although they are significant in the gel

chemistry that is an essential precursor of the crystalline product.

We have recently developed a new code, ZEBEDDE^[74] (zeolites by evolutionary *de novo* design), to investigate the application of *de novo* techniques to designing templates for microporous materials. The target space (the framework) in which a molecule (the template) is to be grown is supplied by the user, along with a library of fragments from which the template is to be constructed. The template then grows by a number of randomly selected actions until a cost function, which measures the effective fit of the molecule in the framework, is satisfied. We exploit the crystalline nature of the framework, by allowing the symmetry of the template to be defined and for the growth to occur under periodic boundary conditions. The actions available allow 1) the addition of new atoms, by selecting molecular fragments from a library and bonding them to the existing template, 2) rotation of single or multiple fragments around the new bonds formed, 3) the displacement and rotation of the growing molecule within the framework, 4) the formation of rings from chains, 5) the optimization of the molecule using energy minimization, either in isolation or within the reference framework. Throughout these actions, the growth is controlled by the cost function and additional van der Waals overlap functions. Further details are given elsewhere.^[74]

Our initial applications of this new methodology have proven to be fruitful, firstly in demonstrating the effectiveness of the method for generating previously identified templates and also in predicting a new template that has been shown independently to be an effective template for the targeted levyne framework.^[62] We have considered a number of frameworks, which exhibit different topological features—cages, intersecting channels, pockets—in our evaluation of the method and we highlight a number of these applications here.

In our study of the levyne structure we first attempted to “reproduce” the relatively complex cyclic templates 1-amino-adamantane and *N*-methylquinuclidium used experimentally, to form the synthetic zeolite NU-3,^[85] which is isotypic with levyne.^[86] This was accomplished in two ways. First, by including adamantane and quinuclidine in the fragment library we could test whether our algorithms could successfully insert such large fragments into a confined region. Secondly, we wished to see if such complex fragments could be formed by our ring-formation strategy which converts chain molecules into rings, by bonding *n*th order neighbors if they are within a suitable distance (*n* = 5 forms 6-membered rings). Each of these approaches proved successful and close analogues of both experimental templates were generated (Figure 11). In addition a number of other cyclic templates were generated, of which 1,2-dimethylcyclohexane was considered to be an excellent candidate given its high binding energy.^[72] Independent experimental work in this laboratory led us to use an amino analogue, 2-methylcyclohexylamine, to form a CoAlPO, designated DAF-4, which possesses the levyne structure (see below). Figure 12 illustrates how this template was generated by our code.

To test further the trustworthiness of our methodology, we attempted to grow templates for ZSM-5, which has a three-dimensional intersecting channel system. Again, the method



Figure 11. An overlay of the predicted position of the ZEBEDDE-constructed aminoquinuclidine analogue and the experimental (red)^[87] position of the *N*-methylquinuclidinium template in the levyne cage. The cage is represented by the positions of the tetrahedral cations (Al, P, Co) of the framework. The oxygen atoms, which lie approximately midway between the vertices, are omitted for clarity. (From J. M. Thomas, D. W. Lewis, *Z. Phys. Chemie* **1996**, 197, 537).

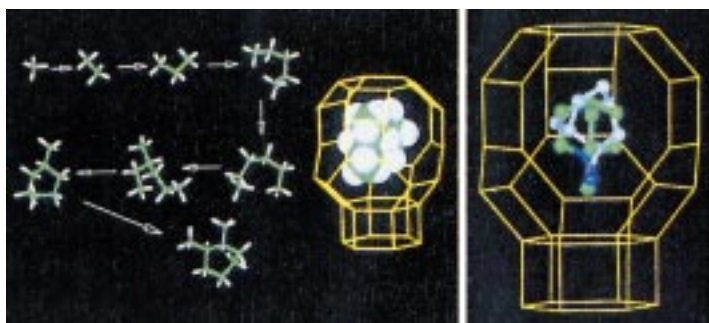


Figure 12. The growth process involved (in ZEBEDDE) in the formation of the 1,2-dimethylcyclohexane in the levyne structure. Starting from the methane seed, the alkyl chain grows inside the restricted void of the levyne structure. When an atom with a 5th order neighbor within a distance of 3 Å is selected (along with the ring formation action), methylcyclohexane is formed and further substitutions of this ring then occurs. The predicted position of the template in the levyne unit cell is shown on the right.

proved successful and generated a number of the variety of templates known to form this. Simulations of templating in this structure allowed us to validate the importance of specifying template symmetry within the host. Large templates, such as tetrapropylammonium, tend to be located at the channel intersections, and specifying the growth of one template at each intersection encouraged the formation of quaternary ammonium ions and similar templates (for example, tripropylamine). Similarly, if the symmetry were specified so as to favor a higher template concentration, then smaller, linear templates (such as *n*-diamines), are formed in the channels. Further details of these simulations are given elsewhere.^[74]

We have recently^[88] been guided in the synthesis of a small-pore microporous material (known as DAF-5^[89]) using the computationally designed template ZEBEDDE. Our aim was to synthesize an aluminophosphate-based material processing a chabazite structure (CHA) that would crystallize out of a nutrient phase containing an appropriate template (structure-

directing) organic cation. We judged^[88] that the following features would be crucial in our strategy: a) the selected template would form a CHA framework quickly and in a phase-pure form; b) the template would be present at a concentration of one molecule per unit cell and must fully occupy the CHA cage; c) the charge on the template could be varied to accommodate a range of metal ion (for example, Co^{II}) concentrations in the framework and thus allow a degree of control over the catalytic behavior arising from the presence of these constituents.

We performed a number of simulations using seeds from C₁ (methane) to C₄ (*n*-butane).^[89, 90] Bicyclohexane, another molecule generated by our code, was more rigid. Pursuing our principles of rational design (described in detail in ref. [89]), we identified 4-piperidinopiperidine as a suitable candidate for initial evaluation of templates based on the cyclohexane motif; the commercial availability of this material is also important. The generation of 4-piperidinopiperidine from an ethane seed within the CHA structure^[91] is illustrated in Figure 13 a, and Figure 13 b depicts the energy-minimized geometry of the molecule in a siliceous unit cell of chabazite.

Preparations with a typical gel composition of 0.2 CoO:0.9 Al₂O₃:15 P₂O₅:30 H₂O:2.0 C₁₀H₂₀N₂ yielded a single blue crystalline phase, designated DAF-5. Its X-ray powder diffraction pattern could be readily indexed with the auto-indexing program TREOR^[92] to a hexagonal unit

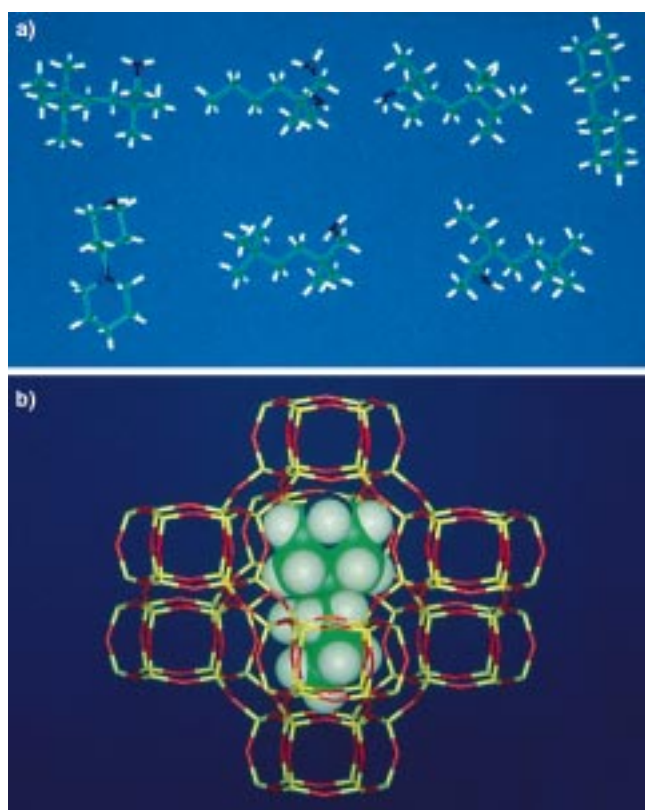


Figure 13. a) Generation of the 4-piperidinopiperidine template molecule (starting from a substituted ethane seed) with the ZEBEDDE code to yield a new chabazite CoAlPO structure known as DAF-5; b) energy-minimized position of the 4-piperidinopiperidine inside the chabazitic cage (From D. W. Lewis, G. Sankar, J. M. Thomas, C. R. A. Catlow, J. K. Wyles, D. J. Willock, *Angew. Chem.* **1997**, 109, 2791; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2675).

cell, very similar to that of the mineral chabazite. Although high-resolution X-ray (synchrotron-based) powder diffractograms proved invaluable in refining the positions of atoms in the AlPO-framework of DAF-5, only micro-single crystal ($30 \times 30 \times 30 \mu\text{m}$ specimen size) diffraction, again using synchrotron radiation,^[93, 94] was sufficiently powerful to determine the structure of the disordered template (4-piperidinopiperidine) within the individual chabazite cages (Figure 14). More details pertaining to the application of computer modeling to the mechanisms of synthesis of microporous catalytic materials have been published elsewhere.^[95]

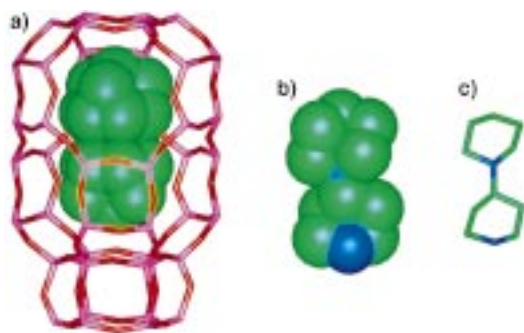


Figure 14. a) Graphical representation of the structure of DAF-5 derived from a single crystal diffraction study. For clarity only one of the cages is shown that contains all possible conformations of the occluded template molecule, 4-piperidinopiperidine. One of the possible conformations of the latter is also shown using ball (b) and stick (c) representations, the carbon atoms being green, the nitrogen atoms blue.

6. Characterizing The Architecture Of Engineered Catalysts

Ultimate success in the design of solid oxide catalysts as well as other covalently bonded or heterogenized organo-metallic catalysts predicates knowledge of precisely what structure or architecture it is that has to be targeted. This, in turn, demands the greatest possible precision in determining, under operating conditions, the structure of the catalyst in general and of that of the active site in particular. It follows ineluctably that there is an exigent need for in situ methods of characterizing solid catalysts if one is to succeed in engineering desired, well-defined active sites at the surfaces of large-area (porous) solids.

Demonstrably, only those interrogating probes, such as high energy photons or neutrons that are capable of penetrating through the walls of a catalytic reactor and into the cavernous recesses of the interior of micro- and mesoporous catalysts, will, in the final analysis, prove adequate to meet the demanding needs of in situ characterization of commercially viable reactors. In laboratory studies of model catalysts considerable insights may be gained through the use of noninvasive techniques such as infra-red and (laser) Raman spectroscopy, not least because such techniques, such as those described in Section 6.2, may be deployed under in situ conditions. This does not, however, mean that all ex situ methods are secondary (at best) or worthless (at worst). On the contrary, there are a number of ex situ methods, especially

those based on electron beams, which are invaluable for the elucidation of the structure of catalysts. We, therefore, illustrate in the next section the principles and merits of such methods, before focusing on in situ methods.

6.1. Ex Situ Methods

6.1.1. Electron Microscopy

The single most remarkable attribute of the electron microscope is its versatility.^[96] It can identify new (or hitherto established) phases by diffraction or from high-resolution electron microscopic (that is real-space) images, and simultaneously yield X-ray emission or electron-energy loss spectroscopy (EELS).^[97, 98] Information pertaining to chemical bonding and oxidation states in a spatially resolved fashion^[99] may also be retrieved through its agency.

The characterization of the ultrastructure of zeolitic and related (catalytically significant) solids by electron microscopy was pioneered in the early 1980s at the University of Cambridge^[100–105] and subsequently extended by the research groups of Terasaki,^[106, 107] Treacy,^[108] Bovin,^[109] and others.^[110] A measure of the power of the high-resolution (transmission) electron microscopic (HR(T)EM) images for microporous and mesoporous siliceous catalysts is seen in Figures 7 and 10. Images of this quality, such as that shown in Figure 15, permit precise details of surface structure, of crystallographic (polytypic and other) intergrowths, to be determined.^[107, 111] New types of structures and correctivities among mesoporous variants (such as SB-2 and STAC-1) have been identified by HREM by Zhou and his co-workers.^[68, 112]

Recent advances in detector technology (of charge-coupled devices (CCD) and image plates in particular) permit the recording of HREM images with far lower electron dose than

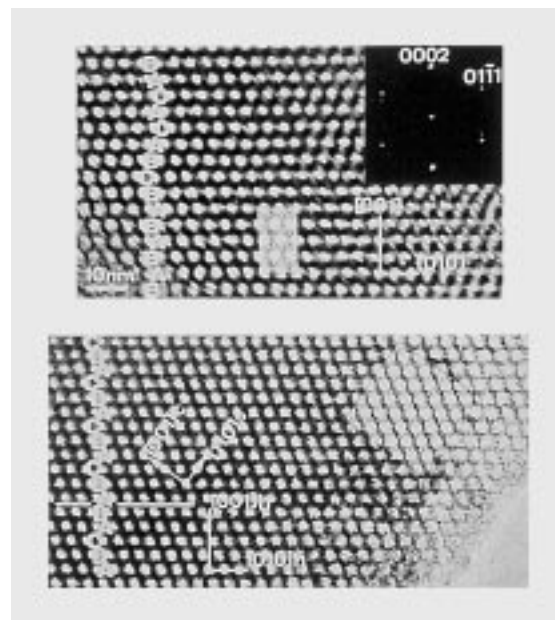


Figure 15. High-resolution electron micrographs with accompanying diffraction pattern (top right) and computed images of the new mesoporous silica known as STAC-1 (St. Andrews and Cambridge). Well-defined cubic (ABC stacking) and hexagonal (AB) polytypic intergrowths are frequently present in such preparations.^[68]

for film recording.^[113, 114] This means that it is much easier to treat the digital data of electron-diffraction patterns and HREM images (in the manner pioneered by Klug^[115] and Henderson^[116]) quantitatively. Indeed, the era of electron crystallography, which has been so conspicuously successful in virus research,^[115, 117] is now a demonstrated success in the determination of the structure of zeolitic solids, thanks to the work of Gonzalez-Calbet and Vallet-Regi.^[118] Figure 16 illustrates the kind of information that may be obtained.

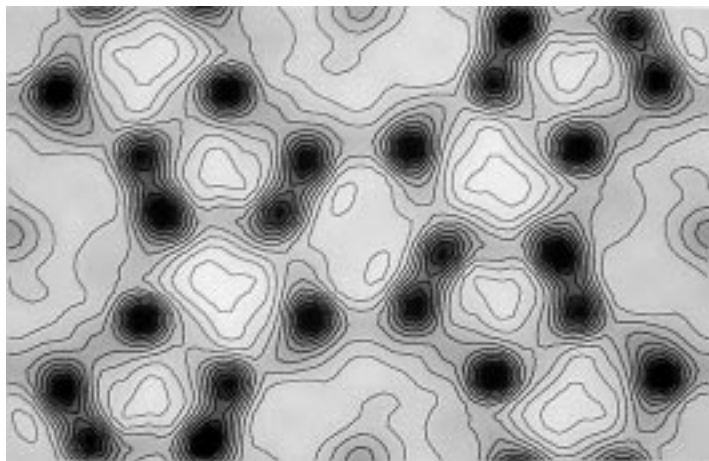


Figure 16. Typical illustration of the quality of the electron-density map for a zeolitic solid that may be derived by the application of electron crystallography.^[118, 119]

Very recently, Wagner, Terasaki, and Davis^[119] at Tohoku University, Japan, used electron crystallography to obtain the three-dimensional structure (and to refine it) of a new large-pore, high-silica molecular sieve that contains an occluded organic structure-directing agent. Alas, such is the exceptionally rapid beam damage suffered by AIPO-based molecular sieves (see refs. [120, 121]) during electron microscopic examination that it is not yet possible to solve their structures even with electron crystallography aided by the most sensitive detector system. But this situation will soon change. Those microporous solids that are sufficiently beam-stable, such as SSZ-48,^[119] have their structures solved by applying direct methods to a three-dimensional electron diffraction data set collected from submicron-sized crystals that are too small for single crystal X-ray analysis.

Recently, largely through the pioneering work of structural biologists such as Baumeister and colleagues, information about the three-dimensional spatial organization (for example, minute metallic particles interspersed within a supporting matrix) has been obtained by electron tomography, which is a general method for 3D reconstruction of a specimen from a series of projection images, that is, from a tilt series. A powerful feature of electron tomography is that individual objects may be investigated in situ to reveal structural detail in three dimensions. The resolution finally achieved is, of course, governed by the number of images recorded and is, typically, about 200 for a specimen of 1000 Å thickness to achieve a spatial resolution of 15 Å.

6.1.2. Scanning Transmission Electron Microscopy (STEM) and the use of Rutherford Scattering for Z-Contrast Imaging

Images in the scanning transmission electron microscope are formed by rastering a focused probe over the specimen and at each point in the raster detecting either transmitted electrons to form a bright-field (BF) image or scattered electrons to form a dark-field (DF) image. The simple diagram of Figure 17 illustrates^[110] the detector geometry

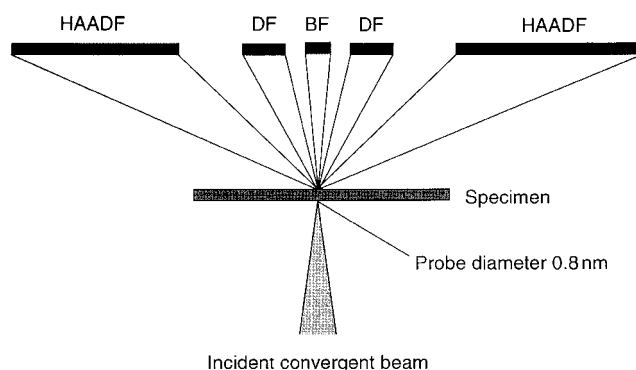


Figure 17. Schematic diagram illustrating the geometry of the detectors in a STEM. Typical values for the detector collection angles are BF picture 0–19 mrad, DF picture 10–50 mrad, HAADF picture 80–200 mrad.^[69]

found in the STEM. Conventional DF images are recorded using an annular detector placed around the BF detector. Such images are formed from electrons that have been scattered to relatively small angles. Electrons scattered to low angles are predominantly coherent and thus both BF and DF images will show phase contrast (diffraction contrast) and are thus prone to contrast reversals with changes in specimen thickness or defocus. Electrons scattered to high angles are predominantly incoherent and images formed using a high-angle annular dark field (HAADF) detector^[122] do not show the contrast changes associated with coherent scattering. Further, electrons scattered at such high angles must have been scattered from close to the nucleus of the atom and thus the cross-section for HAADF scattering approaches the unscreened Rutherford cross-section which is strongly dependent on the atomic number Z : in fact it is proportional to Z^2 .^[123, 124] Thus an image formed with a HAADF detector is very sensitive to changes in specimen composition and is thus an ideal way to image small nanoparticles with moderate or high atomic number on a support with a low atomic number. The power of the STEM is that BF and HAADF images can be acquired concurrently with other chemically sensitive signals such as X-ray emission, as shown below.

Figure 18 shows images recorded in the BF and HAADF modes of a mesoporous (MCM-41) silica that encapsulates catalytically active bimetallic particles of composition Pd_6Ru_6 (prepared^[69, 125] from the mixed metal cluster carbonylate $[\text{Ru}_6\text{Pd}_6(\text{CO})_{24}]^{2-}$). The nanoparticles stand out (by Z -contrast) very clear on the siliceous (low Z) background. From the “element maps”, recorded from the X-ray (K-emission) images of Pd and Ru, it seems that the bimetallic nanoparticles retain their 1:1 stoichiometry.

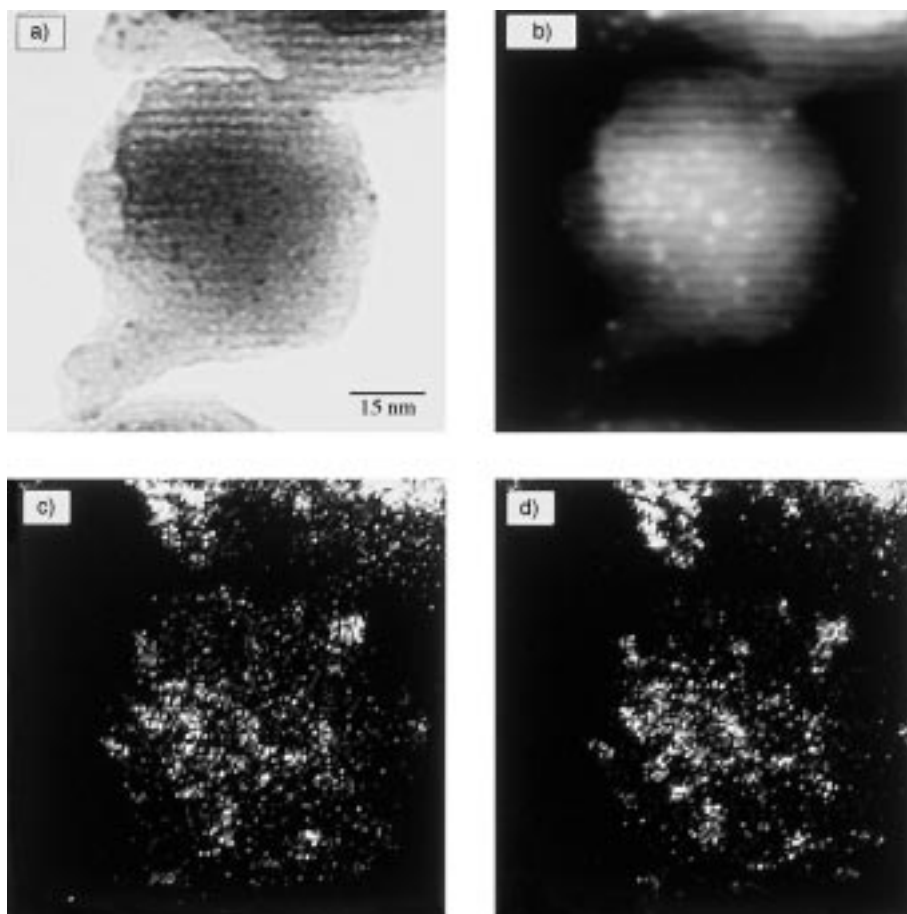


Figure 18. a) BF and b) HAADF images of mesoporous MCM-41 silica in which particles of Pd_6Ru_6 are encapsulated (top). The corresponding electron-stimulated X-ray emission images below show the spatial distribution of the Pd (c) and Ru (d).^[69]

6.1.3. Environmental Cells in an Electron Microscope

In certain circumstances gas–solid reactions (both catalytic and stoichiometric) may be probed directly on the atomic scale using an appropriate chemical microreactor (environmental cell, ECELL) attached to the column of a high-resolution transmission electron microscope. Many designs for achieving this end have been described, but few can surpass the system evolved by Gai and Boyes.^[126–128] The ECELL is fully integrated and permanently mounted inside the EHREM. A variety of accessories are added to aid simultaneous structural and compositional analyses of the reactor contents. In the EHREM, structures and chemistries of unknown phases are revealed by imaging, electron diffraction, and chemical analyses (with a sensitivity of $\leq 10^{-20}$ g of sample) whilst the sample is immersed in gas atmospheres at elevated temperatures (but still maintaining structural and compositional capabilities of a normal HREM operating in a vacuum). Detection of characteristic X-rays emitted by the interactions between the electron beam and the sample (namely, electron-stimulated X-ray spectroscopy) provides compositional information about the sample. The short wavelength of electrons (for example, 0.00251 nm at 200 keV) permits atomic-scale resolution. A conventional chemical reactor-type gas manifold system enables the inlet of gas mixtures into the reactor so that the flow rates and

exchange gases can be controlled. The gas manifold system permits operation under vacuum as well as under gas environments. A heat source (furnace) and temperature control system allow the sample to be heated. With this method one may study reactions at elevated gas pressures and at temperatures between -196°C and $+1000^\circ\text{C}$. A low light-level television camera and a video recorder system connected to the EHREM allow real-time (time-resolved) dynamic events to be recorded. Low-dose imaging techniques minimize any invasive beam damage and none is detected in Gai's experiments. Blank experiments (without the beam) are also performed to confirm in situ data (with the beam switched on for a few seconds only to record the final state of the material).

The development of in situ electron microscopy provides direct and unparalleled insights into the dynamic evolution of structural changes. The ECELL has proved invaluable in elucidating the nature of the vanadyl pyrophosphate-catalyzed conversion of butane to maleic anhydride. As yet no microporous or mesoporous catalyst has proved amenable to study by this method, primarily because of the sensitivity of the beam.

6.1.4. High-Resolution Solid-State NMR Spectroscopy

It has long been appreciated^[129–131] that magic-angle-spinning (MAS) NMR spectroscopy and many other variants of the resonance technique are ideally suited for the determination of crucial structural details pertaining to active sites in siliceous solids, aluminosilicates, and aluminophosphates. The convenient values of the relative isotopic abundances and magnetogyric ratios of ^{29}Si , ^{27}Al , ^{31}P , and ^{17}O make NMR spectroscopy an ideal technique to probe the architecture of a wide range of porous catalysts, and the corresponding properties of ^{13}C , ^{15}N , ^1H , and ^2H isotopes offer great scope for probing the nature of bound and catalytically implicated guest organic species undergoing conversion at the internal surfaces of the porous catalyst. Multiple-quantum solid-state NMR spectroscopy is an especially powerful means of locating cation locations inside solid catalysts.

When a new microporous solid is prepared, one of the best procedures for establishing its structure (after certifying by X-ray powder diffractometry that it is structurally unique) is to record the high-resolution MAS NMR spectrum in its pure siliceous form. It was shown^[132] early on that the number of discrete ^{29}Si peaks in the spectrum is exactly the same as the number of crystallographically distinct sites occupied by

silicon in the structure. Moreover, the precise magnitude of the ^{29}Si chemical shift yields (by an equation established by Thomas et al.^[133]) the value of the so-called T-O-T angle, where T is the tetrahedral site occupied by one silicon atom and joined, through an oxygen atom, to another. This approach has been put to good effect by the group of the Spanish worker Cambor^[134] to establish the structure of several new microporous silicas in a family designated ITQ.

Lippmaa, a pioneer^[135] of solid-state NMR spectroscopy, and his co-workers, have recently shown^[136] how great insight into the acid strengths of these important microporous catalysts may be gained by monitoring the changes in “spinning side-band” intensities and shape (for the ^1H nucleus) as a function of temperature for a series of acid zeolites (H-Y, H-Mordenite, and H-ZSM-5). There is a clear difference in behavior between a proton attached to a surface oxygen atom that bridges tetrahedrally coordinated Si^{4+} and Al^{3+} ions and that which is attached to a Si^{4+} ion (Figure 19). Dipolar interaction is prominent in the latter case, and this is what gives rise to the changing profiles of the spinning side

bands, attributable to bridging (acidic) hydroxyl groups, as a function of temperature.

Although solid-state NMR spectroscopy is not ideally suited as an in situ technique for commercial-scale catalysts (operating at extremes of pressure and temperature) several successful attempts have been made, especially by Haw and co-workers,^[138] to probe quantitatively the acidity (and alleged degree of superacidity) of zeolitic catalysts.

6.2. In Situ Methods

Insofar as retrieval of quantitative values of bond distances and angles are concerned, there are only three truly viable ways of attacking the structure of a solid catalyst operating under the severest commercial conditions—pressure as high as 100 bar, temperatures close to 700°C —and they involve either neutrons or X-rays as the primary probing radiation (see Figure 3).^[**]

Such are the fundamental aspects of the physics of neutron scattering that it is quite feasible to employ a beam of neutrons that can penetrate container walls or reaction cells made of stainless steel and yet be sensitive to very light atoms (^1H , ^2H , ^{12}C , etc.) at the site of catalytic reaction. High-energy (and high-flux) X-ray beams, such as those in a synchrotron radiation source, are likewise capable of reaching the solid catalyst inside a high-pressure, high-temperature cell, even when there are sturdy walls to the container. But with X-rays, in contrast to the situation that applies to neutrons, the walls of a metallic container have to be rather thin to avoid serious attenuation of the primary beam intensity.

6.2.1. Neutron Scattering

The availability of powerful sources of neutrons (either from a nuclear reactor or from a spallation proton source) makes it possible to conduct both spectroscopic (inelastic) and diffraction (elastic) measurements to high precision on catalysts undergoing chemical conversions. So far, however, very few genuine in situ measurements of operating catalysts have been completed. (One of these used^[139] inelastic neutron scattering to determine the nature of hydrogen bound to a large-area MoS_2 hydrosulfurization catalyst). But neutron diffraction studies of zeolitic solids at low and room temperatures have opened the way to important future possibilities.

Provided a catalyst is monophasic and well ordered, its atomic structure can be determined by neutron diffraction, even if it exists as a microcrystalline powder. This situation exists for many catalysts, especially zeolitic ones, and consid-

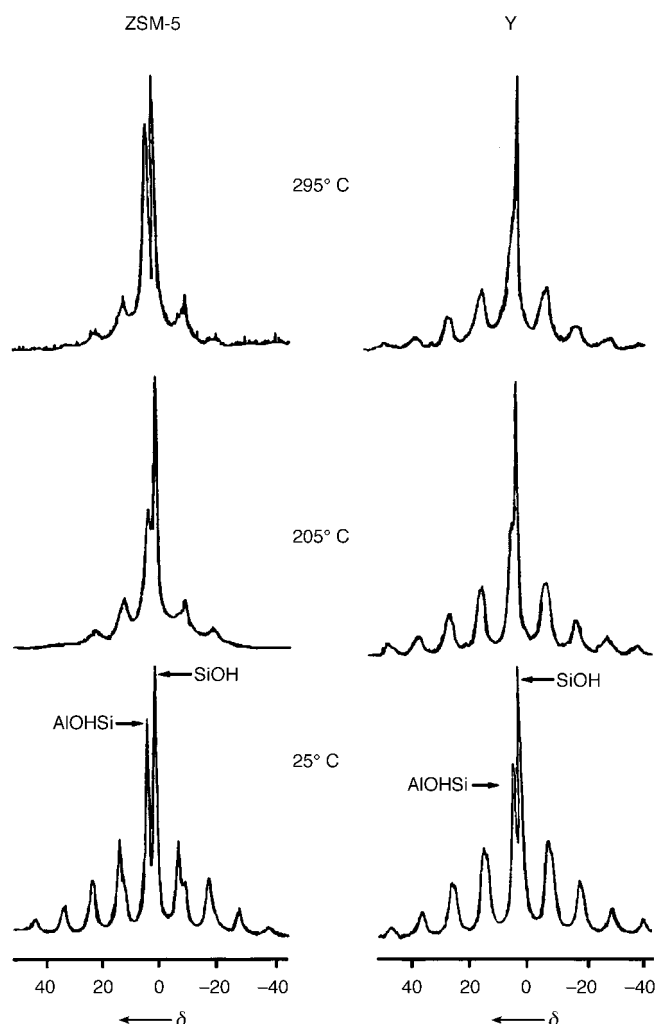


Figure 19. Insights into the acid strengths of a zeolitic catalyst ZSM-5 (left) and Y (right) may be gleaned by monitoring changes in intensities and shape of “spinning side bands” (for the ^1H nucleus) as a function of temperature.^[137]

[**] There are a number of other powerful techniques, notably IR and Raman spectroscopy, Mössbauer and positron emission spectroscopy, ellipsometry, nuclear reactions, temporal analysis of products and luminescence life times, that can yield valuable information about catalysts operating close to industrially relevant conditions, but none of these enable the atomic architecture of active sites to be determined. For fuller discussions of many of these techniques, see ref. [23], pp. 232–241, and the special issue on in situ characterization of catalysts, in *Topics in Catalysis* **1999**, 8. See in particular the paper by H. Knözinger and G. Mestl on Raman-based methods (p. 45).

erable progress has been made recently in arriving at the details of framework structure and location of exchangeable cations, and of model catalytic reactants sorbed within intrazeolite cavities. The method used for this purpose is the Rietveld neutron powder profile procedure. It was devised for analyzing complex diffraction patterns by curve-fitting techniques in which the least-squares refinement minimizes the difference between the observed and calculated profiles, rather than individual reflections. For neutron diffraction patterns, it can normally be assumed that the reflections have a Gaussian distribution, and that the calculated intensity at each point on the profile is obtained by summing the contribution from the Gaussian functions that overlap at that point. Besides the conventional parameters in the least-squares refinement (atomic coordinates and temperature factors of the individual atoms), additional parameters are required: the lattice parameters, which determine the positions of the reflections, a correction factor for setting the zero point of the detector, and three parameters that describe the variation of the half-width of the Gaussian distribution with scattering angle. Rietveld refinement procedures have been used to great effect in the study of uniform heterogeneous catalysts. Figure 20 illustrates^[140] the kind of information that

can be derived by Rietveld analysis. No less an achievement than determining the precise structural detail of the active site in La^{3+} -ion-exchanged zeolite Y (an important cracking catalyst) is seen here. Here is the direct proof (previously only inferred) that La^{3+} ions in zeolite Y polarize their hydration shells so much that $(\text{LaOH})^{2+}$ ions together with “free” protons, loosely attached to a framework oxygen atom are formed.^[141, 142]

In a collaboration with W. I. F. David and his associates at the Rutherford–Appleton Laboratory, Dr. John Turner, Richard Catlow, and members of my group at the Royal Institution have made significant progress in reaching the goal of following the course of the cyclotrimerization^[26] of acetylene at a Ni^{2+} -ion-exchanged Y catalyst surface.

6.2.2. Partial Radial Distribution Functions and the Isotopic Substitution Method

Consider an atom designated α at the origin and ask what is the average number of β -type atoms that occupy a spherical shell of radius r and thickness dr at an instant of time. That number is given by Equation (1). Here $\rho_\beta = N_\beta/V$, and N_β is the number of β species contained in the sample of volume V . It follows from the definition of $g_{\alpha\beta}(\mathbf{r})$, the partial radial distribution function in Equation (1), that the value of the integral [Eq. (2)] is the so-called running coordination number, that is, the average number of β atoms within a sphere or radius r_s for the chosen α atom.

$$dn_\alpha^\beta = 4\pi\rho_\beta g_{\alpha\beta}(\mathbf{r}) r^2 dr \quad (1)$$

$$4\pi\rho_\beta \int_0^{r_s} g_{\alpha\beta}(\mathbf{r}) r^2 dr \quad (2)$$

If neutrons are incident on a solid containing several nuclear species the intensity of the scattered neutrons, $I(\mathbf{k})$ is given by Equation (3) with $C_\alpha = N_\alpha/N$. Here $\mathbf{r}_i(\alpha)$ denotes the position of the i th nucleus of α -type characterized by a neutron scattering length b_α and $\mathbf{k}$ is the scattering vector whose modulus k for elastic scattering (that is, $|\mathbf{k}_0| = |\mathbf{k}_1|$) is given by Equation (4), where θ is half the scattering angle and

$$I(\mathbf{k}) = \sum_\alpha \sum_\beta b_\alpha b_\beta \left(\sum_{i(\alpha)} \sum_{j(\beta)} e^{i\mathbf{k}(\mathbf{r}_i(\beta) - \mathbf{r}_j(\alpha))} \right) \\ = N \left[\sum_\alpha c_\alpha b_\alpha^2 + \sum_\beta c_\alpha c_\beta b_\alpha b_\beta [S_{\alpha\beta}(\mathbf{k}) - 1] \right] \quad (3)$$

$$k = 4\pi \sin\theta/\lambda_0 \quad (4)$$

λ_0 is the wavelength of the incident neutrons. The angular brackets show that an ensemble average has been taken, and $S_{\alpha\beta}(\mathbf{k})$ are the partial structure factors. Each $S_{\alpha\beta}(\mathbf{k})$ can be inverted to yield $g_{\alpha\beta}(\mathbf{r})$ through a Fourier transformation [Eq. (5)].

$$g_{\alpha\beta}(\mathbf{r}) = 1 + \frac{V}{2\pi^2 N r} \int dk (S_{\alpha\beta}(\mathbf{k}) - 1) k \sin kr \quad (5)$$

Aided by the above background theory we now turn to the supreme advantages of replacing natural nickel ($^{\text{nat}}\text{Ni}$) atoms by the isotope ^{62}Ni . There is an enormous difference in neutron scattering lengths between these two species. In going

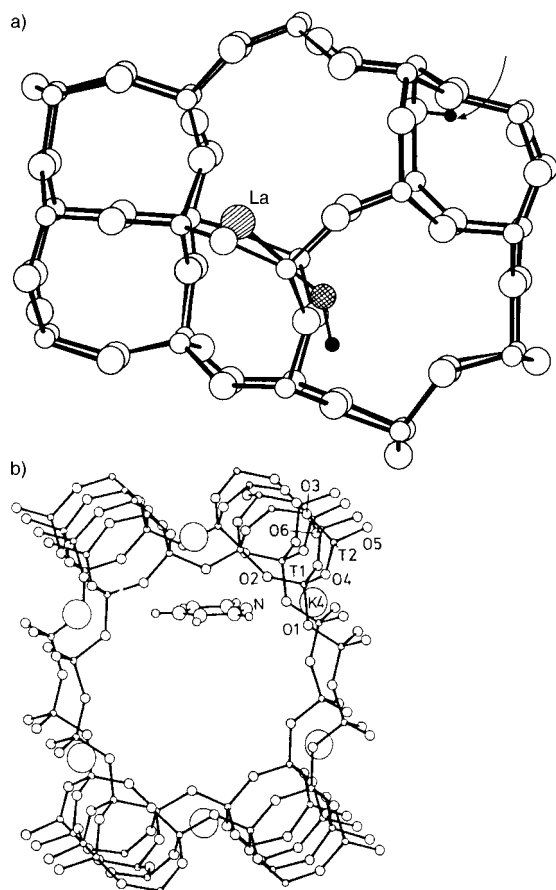


Figure 20. a) This picture of the catalytically active site, known in atomic detail, of La^{3+} exchanged zeolite Y was derived by Rietveld profile analysis of the neutron powder diffractogram.^[141] b) The location of the pyridine in the catalyst potassium zeolite-L, as determined by neutron diffraction. The nitrogen atom of the pyridine forms a Lewis acid–base complex with the potassium ion, whilst the aromatic ring experiences short-range interaction with the aluminosilicate framework.^[142]

from $^{\text{nat}}\text{Ni}$ to ^{62}Ni the change (Δb) in scattering length is 18.9 fm, even larger than the substantial change (10.4 fm) in going from ^1H to ^2H .^[143] Enderby has shown (Figure 21) that great insight into the nature of the hydration of

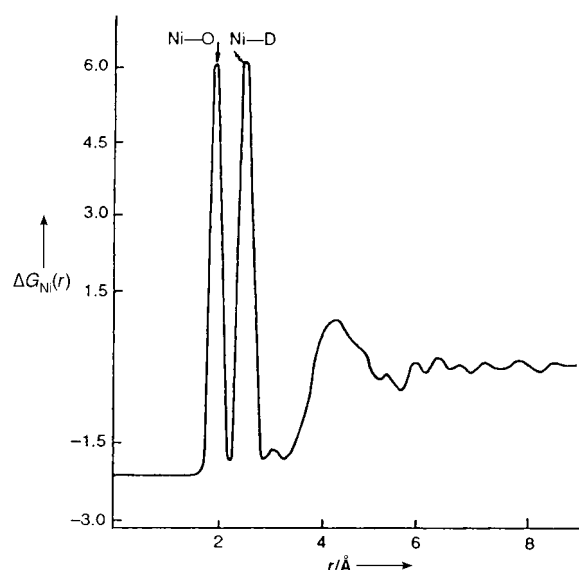


Figure 21. The hydration of Ni^{2+} ions may be studied precisely by neutron scattering as demonstrated by Enderby^[143] if ^{62}Ni isotopes are used in place of natural Ni, and if D_2O is employed in place of H_2O . Here the first-order difference function $\Delta G_{\text{Ni}}(r)$ (in 10^{-2} barns str^{-1}) for a 1.46 molal solution of $^{62}\text{NiCl}_2$ in D_2O is shown (see text).

Ni^{2+} ions in water (D_2O) is achieved in this way (see also Figure 22 and Table 2).^[143] One sees that the geometry of the complex formed between the Ni^{2+} ions and water may be

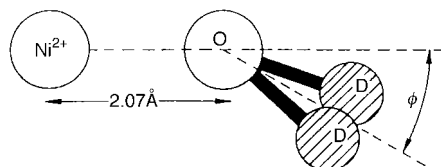


Figure 22. Neutron scattering also permits the determination of the instantaneous angle ϕ defined here, and also yields hydration numbers as a function of concentration (see Table 2).^[143]

Table 2. Illustrative values of hydration numbers n_{Ni} of Ni^{2+} ions in D_2O (from Enderby^[143]).

Electrolyte	Molality	n_{Ni}
NiCl_2	4.41	5.82
	3.05	5.82
	0.50	5.92
$\text{Ni}(\text{ClO}_4)_2$	3.80	5.82

accurately worked out. Proceeding in a rather similar fashion, Turner et al.^[144] have achieved initial success in their ultimate goal to follow the course of cyclotrimerization in atomic detail, by assembling the appropriate partial structure factors around the ionic active sites in NiNaY catalysts. Figure 23 shows the results obtained for the bond distances in the

complex formed between C_2D_2 and the active site, the first step in the catalytic process. With a special cell already assembled and tested^[145] for operation in a pressure range of 10^{-6} mbar to 12 bar and temperatures from the cryogenic extreme up to 700 (with gold seals) or up to 1000°C (with platinum seals), much can be expected from this powerful in situ technique in the future.

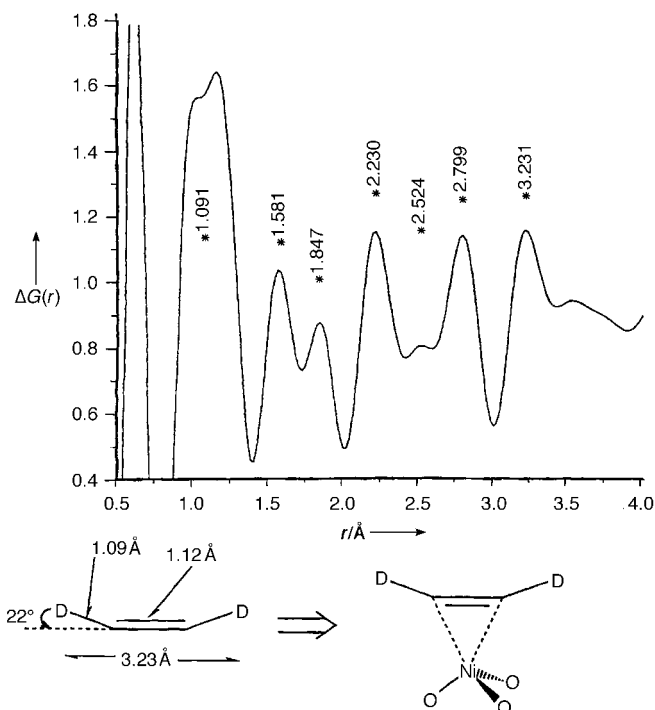


Figure 23. $\Delta G(r)$ plotted versus distance for the Na^{62}NiY zeolite + C_2D_2 system. Bottom left is an interpretative drawing showing the distortion of the acetylene molecule when bound to the active site. Bottom right, the classical Dewar-Chatt-Duncanson picture of bound acetylene.

6.2.3. Combined X-Ray Absorption Spectroscopy and X-Ray Diffraction

There are numerous techniques now available for in situ studies of solid catalysts. They have been discussed at length in a recent monograph^[23] and updated in a recent review.^[146] We shall concentrate here only on those in situ techniques that utilize synchrotron radiation. A particularly powerful combination of techniques for micro- and mesoporous catalysts is that of X-ray absorption spectroscopy (XRA) and X-ray diffraction (XRD).^[147–150] From the former, information pertaining to the immediate atomic environment of the absorbing atom (which is selected to be at, or close to, the active site) is extracted from the pre-edge, near-edge, and extended-edge fine structure (respectively abbreviated as PEXRA, XANES, and EXAFS). From the latter (XRD), information about the overall structural integrity and other aspects of long-range order within the phase in question is obtained. Between them, therefore, we achieve insights into the architecture of both the active site itself and the average picture of the solid in which the active site is situated.

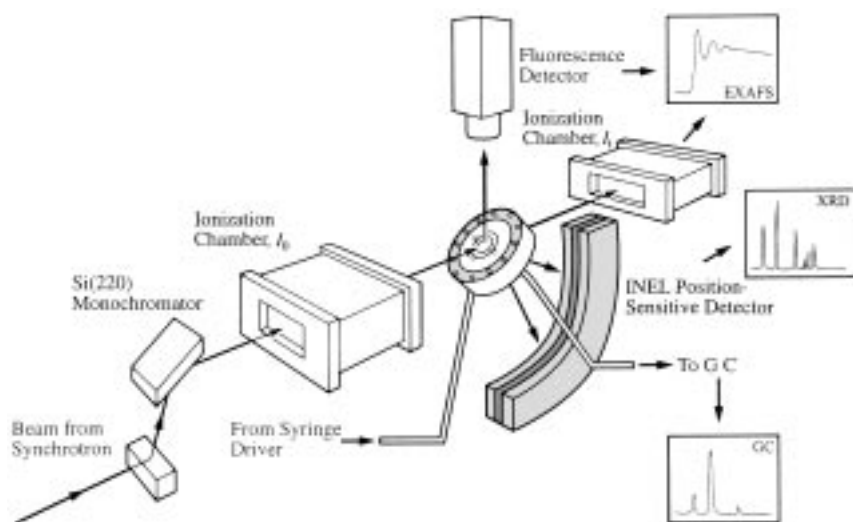


Figure 24. Schematic representation of the set-up used for the in situ parallel recording of X-ray absorption (XRA) spectra and X-ray diffraction (XRD) of solid catalysts in contact with either liquid or gaseous reactants. The fluorescence detector makes it possible to probe absorption edges of elements present at the ppm level in the catalyst (see also refs. [146, 151]).

Figure 24 shows the deployment of the XRA/XRD combination for in situ studies of either solid–liquid or solid–gas heterogeneous catalytic systems.^[25, 151] The GC/MS analytical facility ensures that measurements of catalytic performance are conducted strictly in parallel with those of the nature of the active site.

6.2.4. X-Ray-Based in situ Studies of the Crystallization of Microporous Catalysts

Combined XRA-XRD measurements may be made in a time-resolved fashion using the set-up shown in Figure 25 to chart the growth of framework-substituted microporous AlPO catalysts such as CoAlPO-5 and CoAlPO-18. With a capillary reaction vessel housed in an appropriately designed furnace, both XRD patterns as well as richly detailed X-ray absorption spectra are obtainable (see Figure 7 of ref. [149]). The pre-edge X-ray absorption spectra,

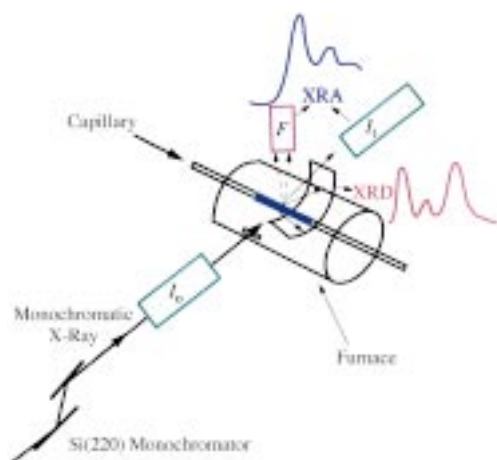


Figure 25. Schematic representation of the set-up used by Sankar et al.^[149] for the combined XRD/XAS in situ measurements used to follow crystallization of molecular sieve catalysts from liquids and gels.

and also the XANES and EXAFS information (taken in conjunction with the XRD results), unmistakably reveal^[149] that, prior to the onset of crystallization, octahedral Co^{II} ions in the precursor (templated) gel become tetrahedrally coordinated. With this technique one may record the appearance and disappearance of transitory phases during the course of the crystal growth in the phase that ultimately predominates.

Energy-dispersive X-ray diffraction techniques (EDXRD, Table 3) may be readily applied to study the development of crystalline phases during the synthesis of microporous material. One convenient arrangement, which uses three separate detectors set at different values of θ so as to cover a wide range of d -spacings is shown in Figure 26a. The time-resolved diffractograms in Figure 26b shows the

Table 3. The rudiments of energy dispersive X-ray diffraction (see Figure 26).^[149]

$$\lambda = hc/E$$

$$n\lambda = 2d \sin \theta$$

$$E/n = hc/(2d \sin \theta)$$

- The detector angle 2θ was kept fixed at typically 1.5° ; calibrated with a radioactive source and a silicon standard; the wavelength is varied as opposed to conventional XRD where wavelength is fixed and 2θ varied.
- White radiation permits simultaneous measurement over a wide range of energies (or d -spacing); the measurement range is dependent on the detector angle.
- The high intensity of X-rays allows the beam to pass through the stainless steel in situ hydrothermal cell, PTFE liner, and sample.
- The time-resolved technique typically used 1–2 min per scan.
- Poor resolution and intensity variation contribute towards the ED-XRD data being unsuitable for Rietveld refinement since structure factors are currently unobtainable.

sudden transition (at ca. 100 min) from an amorphous precursor gel to a crystalline zeolite (type A).

Normalized sigmoidal plots for the development of crystalline zeolite A at a series of fixed temperatures (Figure 27) all obey Avrami–Erofeev kinetics in which α (the fraction of crystalline product) is given by Equation (6), which, in turn, yields Equation (7). A plot of $-\ln(1-\alpha)^{1/n}$ versus $(t-t_0)$, where t is the time at which the data were collected after the

$$\alpha = 1 - e^{(-kt)^n} \quad (6)$$

$$-\ln(1-\alpha)^{1/n} = kt \quad (7)$$

start of the measurement procedure and t_0 is the induction period (see Figure 27), that is, the time at which the X-ray reflections begin to appear, is indeed linear for $n=4$. The gradient of the linear plot yields the rate coefficient k , which was determined over a range of temperatures. The resulting Arrhenius plot gave an activation energy of approximately $58 \pm 3 \text{ kJ mol}^{-1}$, a value that accords well with the 60 kJ mol^{-1} computed for condensation reactions for Si–O–Si linkages in silicate systems.

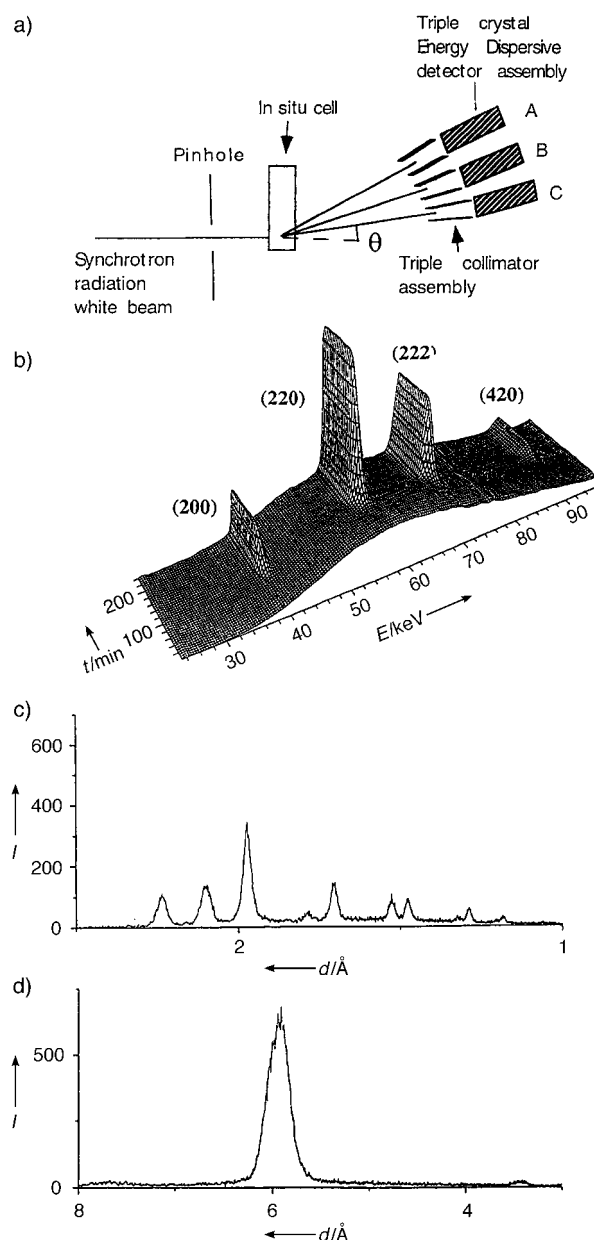


Figure 26. a) Set-up used for energy-dispersive X-ray diffraction (EDXRD) in situ measurements of the kinetics of crystallization of microporous materials. A bank of three detectors, each at fixed values of θ , ensures that a wide range of d-spacings is explored (c and d). b) A typical stacked, time-resolved EDXRD plot for zeolite A synthesized at 367 K.^[149]

7. Selected Case Histories

Equipped with all the information outlined above, we are now well placed to describe the atomic architecture of porous catalysts that have been engineered by my colleagues and me for the following types of reaction:

- selective oxidation of linear alkanes by molecular oxygen
- selective oxidation of cyclohexane (to cyclohexanone and cyclohexanol) using molecular oxygen or sacrificial oxidants
- Baeyer–Villiger conversions of ketones to lactones

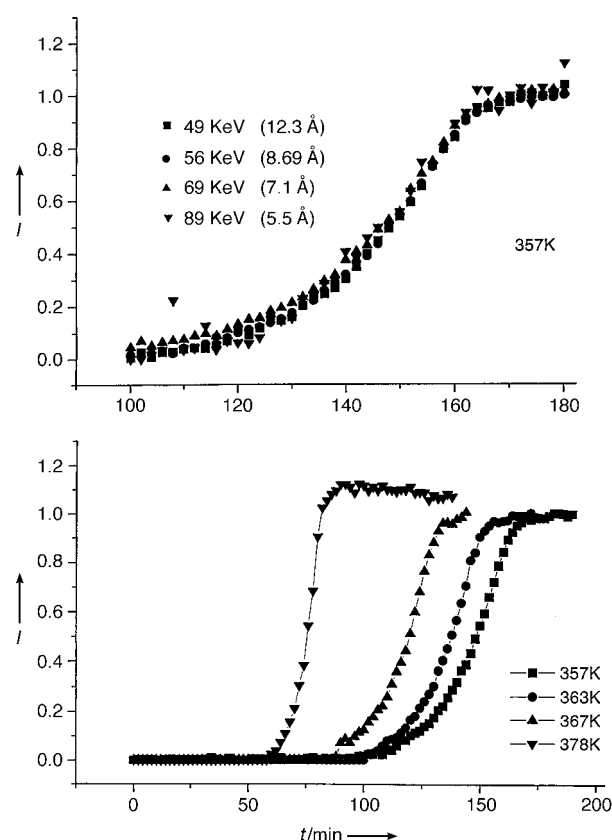


Figure 27. (Top) Normalized (against the intensity of the final data point) sigmoidal curves for zeolites synthesized at 357 K. Four strong reflections (at 12.3, 8.7, 7.1, and 5.5 Å) at four temperatures (bottom) were chosen so as to compare the rate at which the crystalline phase is formed. Since all four curves superimpose, we infer that the crystal growth is uniform.^[149] In the bottom graph the temperature-dependence of the induction period t_0 can be seen.

- epoxidation of alkenes using either alkylhydroperoxides or molecular oxygen
- methanol to light-olefin conversion (preferentially to ethene and propene)
- hydrogenation of alkenes
- regioselective and enantioselective allylic amination.

All the catalysts that we have designed for these reactions are either microporous or mesoporous. Moreover the nature of the active site for each category of catalyst has been incontrovertibly established by the techniques described in Section 6.

7.1. Molecular-Sieve Catalysts for the Selective Oxidation of Linear Alkanes by Molecular Oxygen^[152–154]

Terminally oxidized hydrocarbons are of considerable interest as potential feedstocks for the chemical and pharmaceutical industry, but selective oxidation of only the terminal methyl groups in alkanes remains a challenging task. It is accomplished with high efficiency and selectivity by some enzymes, but inorganic catalysts, while inferior in overall performance under benign conditions, offer significant advantages from a processing standpoint.^[154] Controlled partial

oxidation is easier to achieve with “sacrificial” oxidants, such as hydrogen peroxide,^[155] alkyl hydroperoxides, or iodosylbenzene,^[156] than with molecular oxygen or air. These sacrificial oxidants, themselves the product of oxidation reactions, have been used in catalytic systems involving tailored transition metal complexes in either a homogeneous state,^[157–159] encapsulated in molecular sieves,^[160–162] or anchored to the inner surfaces of porous siliceous supports.^[163] Here we report the design and performance of two aluminophosphate molecular sieves containing isolated, four-coordinated Co^{II} or Mn^{II} ions that are substituted into the framework and act, in concert with the surrounding framework structure, as regioselective catalysts for the oxidation of linear alkanes by molecular oxygen. The catalysts operate at temperatures between 373 and 403 K through a classical free-radical chain-oxidation mechanism. They are thus able to use molecular oxygen as an oxidant, which, in combination with their good overall performance, raises the prospect of using this type of selective inorganic catalyst for industrial oxidation processes.

Cobalt(II) is one of the transition metal ions that, when occupying a small percentage of the framework (tetrahedral) sites in a molecular sieve, may be raised^[164–166] to a higher oxidation state (Co^{III}) while remaining within the framework and act as active sites for the catalytic oxidation of cyclohexane^[167] and other alkanes in air.^[168] By taking advantage of this fact and choosing a molecular sieve that allows only end-on entry of the linear alkanes into the cavities containing the active sites (compare ref. [169]) we have been able to design effective catalysts that favor functionalization by oxygen at the terminal CH_3 and penultimate CH_2 groups and operate with air as the oxidant. (In conventional autoxidation of *n*-alkanes under homogeneous conditions and in the absence of steric constraints the regioselectivity is governed by the relative bond-dissociation energies. That is, whereas the bond-dissociation energies decrease from primary to secondary to tertiary carbon atoms, the corresponding selectivities increase).

We selected the molecular sieve known as aluminophosphate (AIPO) number 18 (idealized formula $\text{Al}_{24}\text{P}_{24}\text{O}_{96}$), which has pores similar to the zeotypic analogue of the aluminosilicate mineral chabazite. A few atom per cent of various divalent metal ions may be readily accommodated into the tetrahedral sites of this material's framework as isomorphous replacements for Al^{III} ions. This is done by templated hydrothermal syntheses as outlined in Section 5.

In this process the redox ions (Co^{II} or Mn^{II}) are raised to their triply charged states during calcination in O_2 . In the course of the partial oxidations the transition metal ions, which replace some 4 atom % of the Al^{III} ions, eventually return to their 2+ states, and the catalyst changes color from green to blue (for $\text{Co}^{\text{III}} \rightarrow \text{Co}^{\text{II}}$) and blue $\rightarrow$ white (for $\text{Mn}^{\text{III}} \rightarrow \text{Mn}^{\text{II}}$). Combined in situ extended X-ray absorption spectroscopy and X-ray powder diffraction (Figure 28) show that the oxidation of the ion during calcination is accompanied by only minor structural changes, and these measurements yield quantitative structural information about the environment of the active Co^{III} - and Mn^{III} -centers.

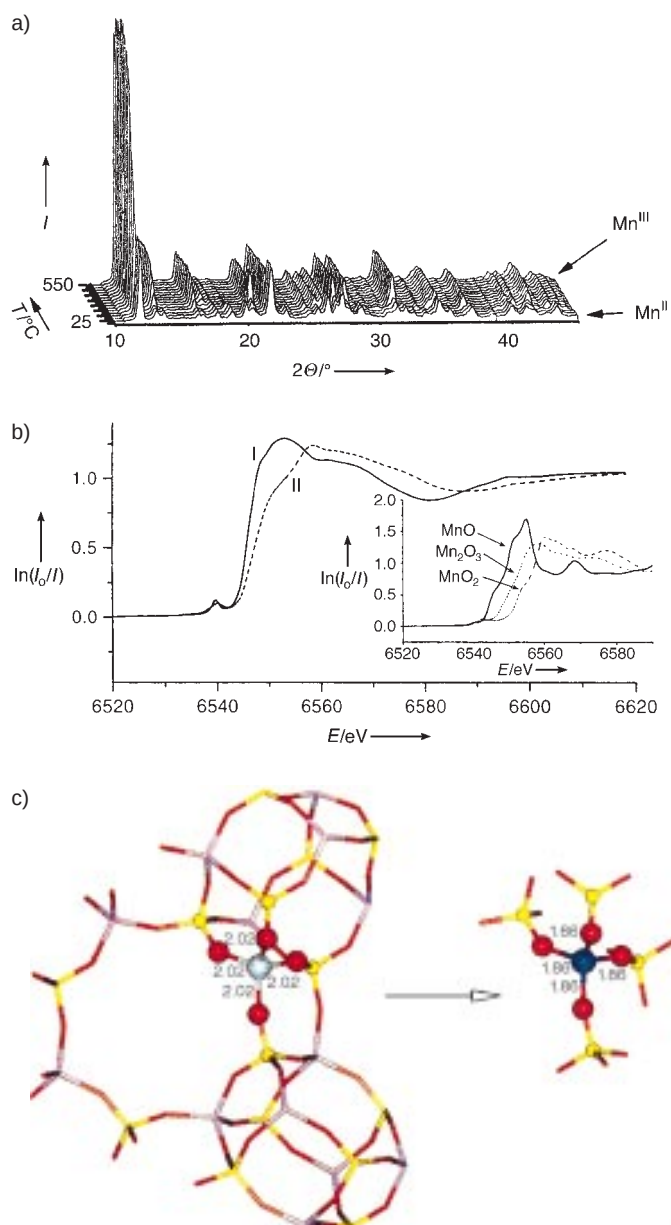


Figure 28. a) Stacked plots of X-ray diffractograms (recorded during calcination), showing that the integrity of the framework structure remains intact when Mn^{II} framework ions are oxidized to their Mn^{III} state. No exsolution occurs even after several oxidation–reduction cycles. b) X-ray absorption near-edge spectra of the Mn K-edge for MnAlPO-18 samples. The solid line (I) represents the as-prepared state, the dashed curve (II) the calcined state. For comparison the inset shows the corresponding information for three (model) oxides of manganese. c) The spatially-averaged EXAFS-derived structure around Mn^{II} (left) and Mn^{III} ions (right) in the AIPO-18 framework. (red: oxygen; yellow: aluminium; purple: phosphorous; gray: Mn^{II} ; and blue: Mn^{III} ; distances in Å).^[153]

Measurements of the shifts in the K-edges and of the extended X-ray absorption fine structure of the Co and Mn ions show that these ions in the as-prepared (templated) form of CoAlPO-18 and MnAlPO-18 may be completely converted in dry air or O_2 into the Co^{III} or Mn^{III} states, respectively. For reasons that are not yet clearly understood, only a fraction of the Co^{II} or Mn^{II} ions isomorphously incorporated into the AIPO-36, AIPO-11 and AIPO-5 structures are convertible

into the +3 oxidation state by similar treatment in O₂ or dry air.^[165] (In MAIPO-36 the fraction is ≈ 0.45 , in MAIPO-11, ≈ 0.30 , and in MAIPO-5, ≈ 0.20 , where M = Co or Mn, all these values being deduced from changes in Co-O and Mn-O distances.)

The catalytic performance of the CoAlPO-18, MnAlPO-18, MgAlPO-18, CoAlPO-36, MnAlPO-36, MgAlPO-36, CoAlPO-11, and CoAlPO-5 molecular sieves was tested for the selective oxidation of *n*-pentane, *n*-hexane, and *n*-octane. Full details are described elsewhere, but the salient results are shown (for *n*-octane) in Figure 29. The overall performance of CoAlPO-18 and MnAlPO-18 is superior to that of all previously reported inorganic catalysts for the regioselective oxidation of linear alkanes, even though the latter use sacrificial oxidants, not air or O₂. An exception is the catalyst developed by Tolman et al.,^[169] which uses a gas mixture of H₂ and O₂ to generate H₂O₂ in situ over finely divided Pd/Fe bimetallic particles.

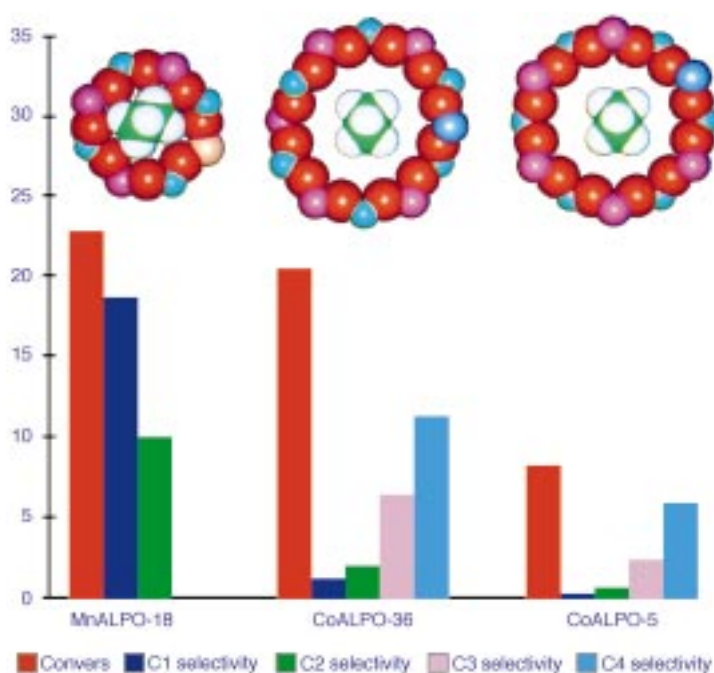


Figure 29. In the aerobic oxidation of *n*-octane (and other linear alkanes), terminal attack leading to oxyfunctionalization is much more favored in Mn (of Co) AlPO-18, than in Mn/CoAlPO-36, or in Mn/CoAlPO-5.^[152, 153] The vertical axis shows the product quantities in mmol.

Given the pore dimensions and the fact that, under reaction conditions, the framework transition metal ions are all in their +3 state, it is unsurprising that CoAlPO-18 and MnAlPO-18 show the greatest activity—twice as active (in both *n*-hexane and *n*-octane oxidation) as a CoAlPO-11 catalyst. Our catalysts also show a high degree of regioselectivity: about 65.5 % of the oxidation products of *n*-hexane after 24 h are the result of oxyfunctionalization at the terminal methyl group for MnAlPO-18 (61.5 % for CoAlPO-18). As much as 31.7 % (36.1 % for CoAlPO-18) consist of 2-hexanol and 2-hexanone; there is no sign of attack at C₃ in hexane or at C₄ in the oxidation of *n*-octane.

It is well known^[170] that the oxidation of alkanes by transition metals generally involves the participation of free

radicals. We believe, for three reasons, that the overall selective oxidations of all the alkanes reported here, including that of cyclohexane, are no exceptions. Because of the small aperture of the AlPO-18 structure, it is easier to test the role of free radicals using the AlPO-36 structure, which has apertures large enough to allow alkylhydroperoxide radicals and radical scavengers to enter their interior surfaces (see Figure 33). First there is an induction period in the yield versus time plots (typified by that for *n*-hexane, using CoAlPO-36 as the catalyst, Figure 30), and this period is

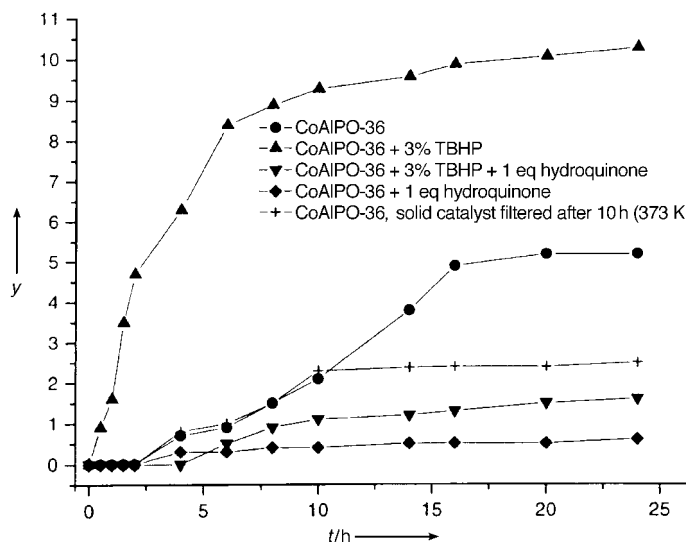


Figure 30. Kinetics of oxidation of *n*-hexane (conversion *y* in mol %) in air using CoAlPO-36 in the presence (▲) and absence (●) of a radical initiator. The addition of the free-radical initiator greatly reduces the initial induction period, accelerates the rate of the catalytic reaction, and gives rise to enhanced activity (the product selectivity is not affected). Addition of small amounts of hydroquinone (free-radical scavenger) completely suppresses the reaction (▼, ◆), which suggests the participation of free radicals in the catalytic process. In an identical experiment, the solid catalyst was filtered off from the reaction mixture (when hot) after 10 h, and the reaction was continued for a further period of 14 h (+). No increase in conversion was observed, indicating that the leached out metal ions (if any) are not responsible for the observed activity. In addition this experiment rules out the possibility of any gas-phase radical reactions. The resulting filtrate was independently analyzed for free or dissolved metal ions and only traces (<3ppb) were detected.^[153]

greatly diminished by the prior addition of traces of free-radical initiators such as *tert*-butylhydroperoxide (TBHP). Second, addition of small quantities of hydroquinone, a free-radical scavenger, greatly hinders the oxidation (see curves plotted with ▼ and ◆ in Figure 30). Third, in the oxidation of cyclohexane (the peroxide of which is easier to analyze than that of *n*-alkanes) under identical conditions over a range of Co^{III}- and Mn^{III}AlPO catalysts, the presence of cyclohexyl peroxide (which subsequently decomposes to cyclohexanol and cyclohexanone) has been directly detected^[171].

Although the precise mechanism of the oxidation of the alkanes involving CoAlPO and MnAlPO catalysts and dioxygen is not clear—as in the case of cytochrome P450^[172] and other enzymatic reactions—there is little doubt that catalytic autoxidation dominates here. It is certain that framework-isolated Co^{II} or Mn^{II} ions present initially in the

freshly prepared sieve are vital for catalysis when converted into the Co^{III} or Mn^{III} state. It is likely that scope for expansion of the coordination shell of the transition metal ion (as with the Mn^{III} ion in the superoxide dismutase^[173]) is a significant factor in facilitating the reaction. Divalent ions that cannot be raised to higher oxidation states, such as Mg^{II} , are totally inactive as oxidation catalysts. Experiments using MgAlPO-18 and MgAlPO-36 as catalysts (for the oxidation of *n*-octane under the conditions of Figure 29 at 373 K) showed no activity. This fact also rules out the possibility that free radicals produced solely in the gas phase are significant in the autoxidation. Moreover, introduction of acetonitrile (known to coordinate Co^{II} ions) before the admission of air poisons the CoAlPO-18 catalyst.

Overall conversions in the oxidations reported here have to be kept to a low level ($\approx 7\%$) to avoid leaching of the transition metals by polar products (that is, carboxylic acids). However, they are comparable^[161] to those in industrially significant oxidations of cyclohexane, and superior to what has been achieved to date using other inorganic catalysts.^[153] The rates of reaction are rather slow, which reflects the diffusional requirements that have to be overcome when liquid reactants and products compete with one another and with solvated molecular oxygen for access to the sub-surface active site. It is possible that further enhancement of the catalytic performance may be achieved by optimizing such variables as the concentrations of Co^{III} or Mn^{III} ions substituted into the chabazite cages, the crystallite size, and the surface area. Moreover, by using a high-pressure flow system optimized with respect to contact time and oxygen pressure a higher yield of desirable products should be facilitated. It is also likely that other transition metal ions may serve equally well or better as selective oxidation catalysts. The regioselectivity of the oxidation is already remarkable, and may be understood from a computer simulation that determines the lowest energy state adopted by the alkane inside the chabazite cavity of the AlPO-18 framework (Figure 31).^[174] A bound

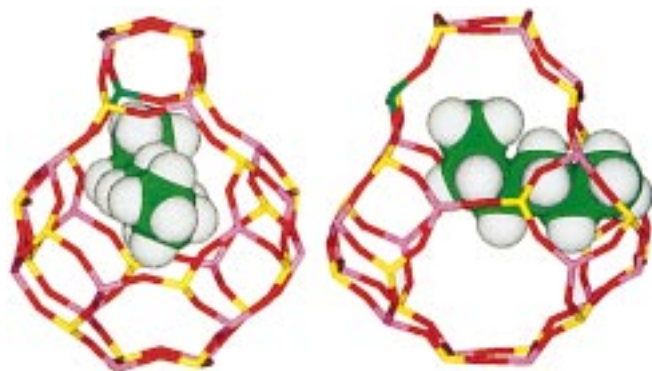


Figure 31. Energy-minimized configuration (two views) adopted by *n*-hexane at 0 K inside an AlPO-18 framework. This configuration was derived from a calculation that combines Monte Carlo molecular dynamics and docking procedures.^[153] The framework composition was assumed to be SiO_2 , for which more reliable potentials are available than for AlPO_4 . Note that the terminal methyl group is significantly closer to a tetrahedral framework site than either C_2 or C_3 , the respective distances being 3.53 Å (C_1), 3.75 Å (C_2), and 4.03 Å (C_3). The implication here is that Co^{III} (or Mn^{III}) ions in the framework of the AlPO-18 cage, along with intracage O_2 , exert a greater influence on C_1 than on other carbon atoms in the hexane backbone.^[153]

hexane (or any other linear alkane) molecule, gains easy access to the active sites and its end becomes slightly bent (shown by molecular dynamics calculations). This selectivity favors oxidation at the terminal and penultimate carbon atoms.

7.2. Designing Catalysts for the Selective Oxidation of Cyclohexane

The conversion of cyclohexane into cyclohexanol is one of the principal target reactions in the broad field of selective oxidation of alkanes since the latter compound is used as a feedstock in several industrial processes including the production of nylon from ϵ -caprolactam and adipic acid. Cyclohexane is expected to retain its dominant position as the feedstock of choice for adipic acid manufacture in the coming decade.

The conventional process is a thermal one, taking place at 125 to 165 °C and at pressures from 8 to 15 bar. It is accepted that the oxidation involves free radicals (facilitated by catalysts of Mn or Co salts) and intermediates such as cyclohexylhydroperoxide, which is selectively (and catalytically) decomposed to yield the alcohol and the ketone. It is prudent to limit the conversion to a maximum of about 10 %, to avoid build-up of other, unwanted products. Homogeneous catalytic oxidation of cyclohexane with cobalt acetate—the most popular industrial catalyst—suffers from the generation of by-products such as alkyl acetates, other ketones, cyclohexanediyl diacetate, and alkyl chlorides. (The precise structure of the active cobalt acetate catalyst remains unclear.) To confer greater stability upon the homogeneous Co^{III} acetate catalyst it is also necessary to employ, for reasons that are not entirely understood, either acetic acid or trifluoroacetic acid (or trichloroacetic acid) as solvent for the reactant mixture. Bromides are also often used as promoters.

With the aim of arriving at a cleaner, more efficient catalytic system for the production of cyclohexanone from cyclohexane, and also of gaining deeper insights into the nature of the catalytically active centers by in situ EXAFS studies, we designed^[175] a new catalyst that entails harnessing the advantages of homogeneous organometallic catalysis on the one hand and of a large-area, well-defined (MCM-41) mesoporous silica support on the other.

Although there is still considerable debate^[14,20,176,257] about the mechanism of the oxidation of cyclohexane in the presence of Co^{III} , Mn^{III} , and Ce^{IV} salts in acetic acid, our point of departure in this work is the earlier observation that several oxo-centered trimeric cobalt(III) acetates (coordinated with pyridine)^[177] exhibit much greater activity in selectively oxidizing the tertiary C-H bond in adamantane than their dimeric analogues.

The apertures of the MCM-41 samples prepared by us are close to 30 Å and readily permit ingress of the monohydroxy-cobalt complexes $[\text{Co}_3(\mu_3\text{-O})(\text{OAc})_3(\mu_2\text{-OH})(\text{py})_3]\text{PF}_6$ to substitute the hydroxyl group for other ligands,^[178] which we selected for immobilization inside the channels of the

MCM-41 mesoporous silica. It is possible to employ various routes to effect immobilization: anchoring to the surface directly or using surfaces functionalized with, for example, alkylcarboxylic acids. Each of these routes yields a catalyst for the selective oxidation of cyclohexane to cyclohexanone. However, distinct differences are observed in their respective turnover frequencies (TOFs), life times, and selectivities (see Table 4). The catalysis was effected in an essentially solvent-free fashion: the sacrificial oxidant *tert*-butylhydroperoxide (TBHP) and the reactant cyclohexane form a miscible liquid and each is consumed to yield cyclohexanone, cyclohexanol, other minor amounts of by-products (dicyclohexyl ether, dicyclohexylperoxide, and *tert*-butylcyclohexylperoxide), and *tert*-butyl alcohol (from TBHP).

In our first attempt at immobilization we reacted the monohydroxy cobalt complex with partially dehydrated siliceous MCM-41. The EXAFS spectrum after immobilization showed that there was virtually no change in the structure of the complex, which indicated either substitution of the bridging hydroxide ligand by a surface silanol group or physisorption brought about by interaction of the surface with the cationic cluster. Catalytic tests (Table 4) showed that 7.6% of the available cyclohexane was converted with a selectivity of about 89% into cyclohexanol and cyclohexanone after 24 h. The catalyst life time, however, was less than 48 h. This limited life time is most likely a result of the mobility of the cobalt clusters on the surface, giving rise to cluster–cluster and other unfavorable interactions at the interior surface, as well as some leaching indicated by slight discoloration of the solution.

Working on the principle that immobilization at a carboxyl-functionalized surface (that is envisaging the replacement of the bridging hydroxyl ligand by a carboxyl group) may produce a potentially more-stable catalyst, we proceeded to functionalize the MCM-41 surfaces with a 3-bromopropyltrichlorosilane tether, which we then derivatized by reaction with glycine. The virtual lack of solubility of glycine in solvents other than water means that the efficiency of the reaction between the amine part of the glycine and the bromoalkyl group could be expected to be low owing to the interaction of water with the amine. However, this would as a side-effect provide a means to ensure a high dispersion of the cobalt complex, which might aid stability (and, hence, longevity) by reducing possible interactions between cobalt clusters. Additionally, the nonderivatized bromoalkyl groups might act as a potential promoter echoing the use of bromide in commercial processes.

Catalytic tests established that after an initial TOF of around 352 mol cyclohexane per mol of catalyst per hour, a steady TOF of around 216 could be sustained for at least four days. The true heterogeneity of the catalyst was also examined by separating it by filtration and establishing that the filtrate displayed no further activity under the same reaction conditions. Additionally, no leaching could be detected (within experimental error) when comparing the elemental analysis results of the catalyst before and after reaction. No induction period could be observed (at a time resolution of 5 min); after an initial exponential behavior, the catalyst continued to produce cyclohexanone essentially in a linear fashion. At the outset more cyclohexanol than cyclohexanone is produced, but after about six hours cyclohexanone production is predominant, an equilibrium between cyclohexanol generation and consumption to form the ketone being reached after about 12 h (Figure 32).

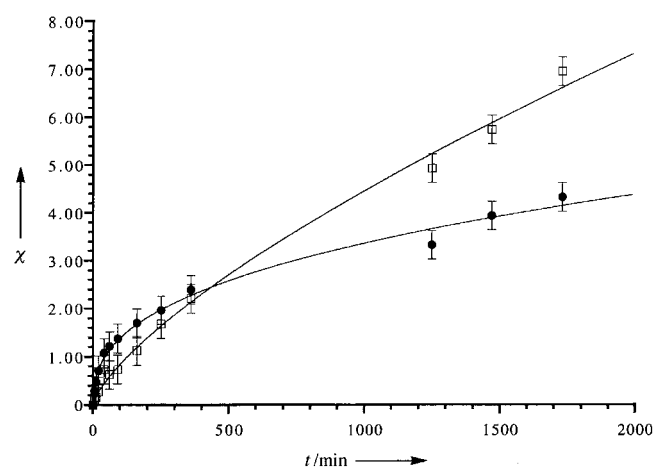


Figure 32. Plot of the of formation of cyclohexanol (●) and cyclohexanone (□) from cyclohexane against time with 150 mg of catalyst.^[175] *x* is the percentage conversion.

Additionally, in situ X-ray absorption spectroscopy using synchrotron radiation enabled the detailed atomic environment of the active cobalt complex to be determined both prior to and during the course of the solid–liquid heterogeneous catalysis at realistic temperatures under continuous flow using a novel liquid/solid cell. A combination of in situ X-ray absorption spectroscopy and ex situ ²⁹Si MAS NMR spectroscopy yielded precise quantitative information of the heterogenized trimeric oxo-centered cobalt catalyst (see Figure 3 of ref. [175]).

The recent isolation^[179–181] and characterization of a new series of multinuclear cobalt acetates provides further oppor-

Table 4. Catalytic performance in cyclohexane oxidation of the [Co₃(μ₃-O)(OAc)₅(μ₂-OH)(py)₃]PF₆ complex (see text) anchored to MCM-41 silica.^[175]

Catalyst support	Co [wt %]	Si:Co	<i>t</i> [h]	Conversion [%] ^[a]	TOF ^[b]	Selectivity [%] ^[c]	Cyclohexanone: Cyclohexanol	Lifetime [h]
nonderivatized	0.376	210	4	3.7	89	85	0.6	< 48
MCM-41, glycine-functionalized through bromoalkyl tethers	0.201	300	24	11.9	230	89	1.5	
	0.201	300	96	38.1	216	95	3.3	

[a] 9.5 mL cyclohexane, 10 mL TBHP, and 0.5 mL mesitylene (internal standard) at 70 °C are required for 150 mg of catalyst. [b] In mol cyclohexane per mol catalyst per hour (Note: mol of catalyst refers to moles of the complex). [c] Based on cyclohexanone and cyclohexanol. [d] The experiment was stopped after four days.

tunities of improving anchored, heterogeneous, selective-oxidation catalysts for the conversion of cyclohexane into the corresponding alcohol and ketone.

7.2.1. From Sacrificial Oxidants to Selective Oxidation by Molecular Oxygen

As useful as alkylhydroperoxides are for the selective oxidation of cyclohexane (and for the conversions of alkenes into epoxides—see Section 7.4.2), it would be so much better if a solid catalyst were developed that effected such conversions using molecular oxygen or dry air. Such catalysts have been developed both in these laboratories and also at the National Chemical Laboratory in Pune (India).

Raja and Ratnasamy^[182] showed how a solid catalyst comprising of transition metal complexes of a phthalocyanine or porphyrin (where some of the peripheral hydrogen atoms were replaced by electron-withdrawing groups) exhibited high stability and activity in the conversion of cyclohexane into the ketone and alcohol in the temperature range of 20 to 80 °C and a pressure of up to 60 bar. The performance of the catalyst is greatly improved if it is encapsulated in an aluminosilicate molecular sieve. Similar catalysts were developed^[183] by them for the preparation of adipic acid from cyclohexane.

We have taken advantage in our studies of the convenient fact that a certain aluminophosphate (AIPO) molecular sieve containing isolated, four-coordinated Co^{III} or Mn^{III} ions that are substituted into the framework acts, in concert with the surrounding framework structure, as highly selective catalysts for the oxidation of cyclohexane to (predominantly) cyclohexanone and cyclohexanol in O₂ or air (see Section 7.1). One of the best AIPO molecular sieve catalysts to use for this purpose is CoAIPO-36 (the structure of which was determined^[184] by stochastic methods). The results,^[185] summarized in Figures 33 and 34, are compared with those for other (previously reported) CoAIPO structures.

Very recently^[186] we prepared a very powerful selective oxidation catalyst for cyclohexane, again based on an AIPO structure, but this time with Fe^{III} ions (replacing Al^{III}) in four-coordinated sites in the framework. The conditions under which the oxidation ensues are benign: 403 K and 15 bar of dry air. The results (Figure 35) are vastly superior to those obtained with the cobalt-substituted analogue. (It is believed that, in this particular molecular-sieve structure, very few Co^{II} sites in the framework can be oxidized to the Co^{III} state, in marked contrast to the situation with Fe^{II} and Fe^{III} states). Incontrovertible evidence has been cited earlier for the free-radical (autoxidation) nature of the catalyzed selective oxidation of cyclohexane (see Figure 30 and the discussion of regioselective oxidations of alkanes in molecular-sieve catalysts in Section 7.1).

7.3. Baeyer–Villiger Oxidations with a Difference: The Facile Conversion of Ketones into Lactones

A century ago Baeyer and Villiger^[187] reported the conversion of cyclic ketones into lactones using a peroxyacid as

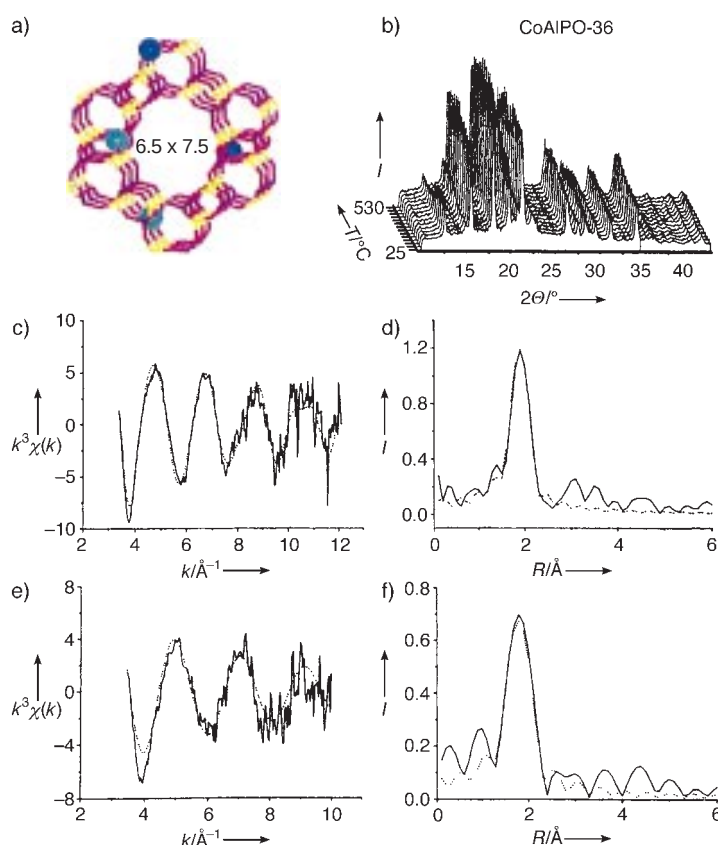


Figure 33. a) Computer graphic representation of the AIPO-36 structure in which cobalt ions have replaced some of the Al^{III} framework sites. After calcination in O₂, about 50% remain in the Co^{II} state (blue). b) XRD patterns of CoAIPO-36 catalysts recorded in situ during calcination in O₂ using combined XRD/XAS. The corresponding Co K-edge EXAFS data, recorded at room temperature and after calcination at 550 °C are shown in (c) and (e), respectively. The associated Fourier transforms (FT) are shown in (d) and (f). Solid line: experimental; dashed line: calculated.^[185]

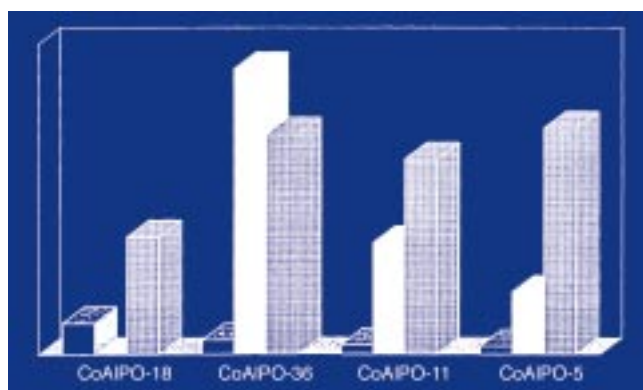


Figure 34. Bar-chart representation of the fraction of oxidized cobalt (dark), pore dimension (hatched), and catalytic activity (as % conversion; white) of CoAIPO-5, CoAIPO-11, CoAIPO-36, and CoAIPO-18 catalysts in the oxidation of cyclohexane in air (1.5 MPa) at 373 K.^[185]

oxidant. For this purpose they used the most powerful oxidant then known, peroxomonosulfuric acid H₂SO₅, otherwise known as Caro's acid. As has been explained in a recent admirable review,^[188] Baeyer–Villiger oxidations are of major

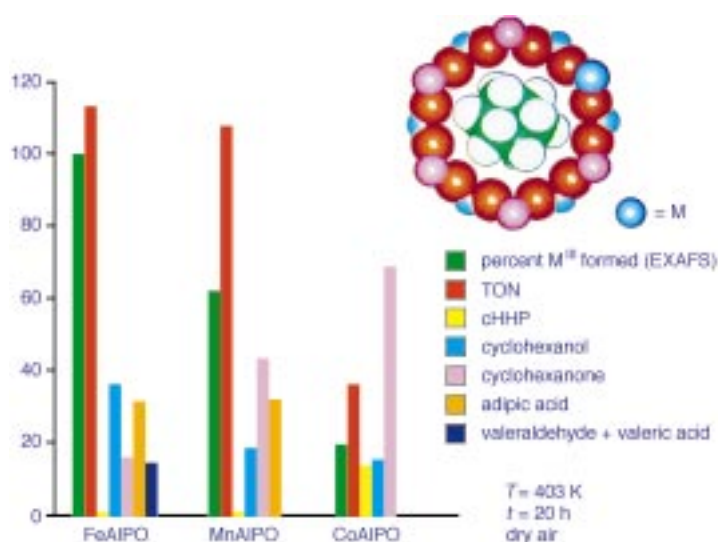


Figure 35. In the aerobic oxidation of cyclohexane, framework-substituted Fe^{III} ions yield more effective catalysts than Mn^{III} or Co^{III} ions for the same (AlPO-5) structure. TON = turnover number and cHHP = cyclohexylhydroperoxide.

synthetic interest in organic chemistry, with applications spanning such diverse areas as antibiotics, steroids, and many aspects of agrochemistry.

The peracids used for the first half-century or so of Baeyer–Villiger oxidations are now increasingly frowned upon (when not banned) because of environmental and other reasons, notably safety. The withdrawal from the market of 90 % H_2O_2 (which was the replacement for the original Caro's acid)—because of its highly explosive properties—has prompted greater use of lower grade peracids, and stimulated the search for effective catalysts (including enzymatic ones)

that would enable Baeyer–Villiger reactions to be carried out with molecular oxygen.

Several heterogeneous catalytic systems based on hydro-talcites^[189] or heteropolyoxometalates^[190] have been used to effect Baeyer–Villiger oxidations. We argued, taking into account the redox properties^[191] and pore dimensions of a range of metal ion substituted AlPOs, that Mn^{III} and Co^{III} -substituted AlPO-36, as well as CoAlPO-18 and MnAlPO-18 (for smaller reactants), would be prime candidates as new Baeyer–Villiger catalysts. This is indeed the case; but these catalysts work under the so-called Mukaiyama conditions^[192], whereby aldehydes are used sacrificially to create the desired peracid in situ (within the pores of the molecular sieve). This active peroxyacid then converts the cyclic ketone into the lactone outside the catalyst (Table 5).

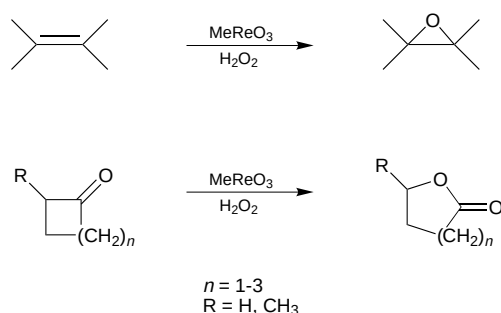
The Mukaiyama conditions used by us and others are of considerable interest in that they offer attractive alternatives to the use of environmentally less acceptable oxidants such as CrO_3 , KMnO_4 , $\text{Pb}(\text{OAc})_4$, RuO_4 , Ag_2O , and $\text{Co}(\text{acac})_3$ (many of which function stoichiometrically, at least in partial oxidations of alkenes, rather than catalytically).^[193] H_2O_2 in the presence of an appropriate catalyst (for example, methyltrioxorhenium^[194]) is also a good oxidant for the conversion of olefins into epoxides and cyclic ketones into lactones (Scheme 1^[188]).

We have identified three different structures of potential catalysts that contain small amounts (up to 4 atom %) of either manganese or cobalt redox cations. The catalysts we have used are CoAlPO-36 , MnAlPO-36 , CoAlPO-5 , MnAlPO-5 , CoAlPO-18 , and MnAlPO-18 . The structure^[195] of aluminum phosphate no. 36 (IZA structure code ATS) has well-defined, oval shaped channels ($6.5 \times 7.5 \text{ \AA}$; see Figure 33), which, by appropriate preparative means (as descri-

Table 5. Baeyer–Villiger oxidation of ketones (Mukaiyama's conditions).^[a]

Entry	Substrate	Catalyst	Pore size [$\text{\AA}$]	T [K]	t [h]	TOF [h^{-1}] ^[b]	Conv. [%]	Lactone selectivity [%]
1	cyclohexanone	CoAlPO-36	6.5×7.5	323	6	250	71	98 ^[a]
2	cyclohexanone	CoAlPO-5	7.3×7.3	323	6	204	60	80 ^[a]
3	cyclohexanone	$\text{MnAlPO-36}^{[c]}$	6.5×7.5	323	6	257	78	98 ^[a]
4	cyclohexanone	MnAlPO-5	7.3×7.3	323	6	207	64	82 ^[a]
5	cyclohexanone	MgAlPO-36	6.5×7.5	323	6	[d]	20	64 ^[a]
6	cyclohexanone	CoAlPO-18	3.8×3.8	323	6	[d]	22	62 ^[a]
7	cyclohexanone	No catalyst	—	323	6	—	20	65 ^[a]
8	cyclohexanone	$\text{CoAlPO-18}^{[c]}$	3.8×3.8	323	6	166	48	72 ^[a]
9	cyclopentanone	CoAlPO-36	6.5×7.5	323	6	238	58	92 ^[b]
10	cyclopentanone	CoAlPO-5	7.3×7.3	323	6	185	46	76 ^[b]
11	cyclopentanone	MnAlPO-36	6.5×7.5	323	6	246	61	94 ^[b]
12	cyclopentanone	MnAlPO-5	7.3×7.3	323	6	187	50	77 ^[b]
13	adamantan-2-one	CoAlPO-36	6.5×7.5	353	5	220	80	99
14	adamantan-2-one	MnAlPO-36	6.5×7.5	353	5	224	87	99
15	2-methylcyclohexanone	CoAlPO-36	6.5×7.5	323	6	201	65	86
16	2-methylcyclohexanone	MnAlPO-36	6.5×7.5	323	6	208	72	89

[a] Reaction conditions: substrate ca. 20 g; catalyst ca. 0.15 g; substrate:benzaldehyde = 1:3 (molar); O_2 (air) = 30 bar; Products: ϵ -caprolactone from cyclohexanone; δ -valerolactone from cyclopentanone. [b] TOF = moles of ketone converted per hour per mole of metal (Co, Mn) in the catalyst. [c] After the reaction the catalyst was filtered off, washed thoroughly with methanol, and calcined at 550°C for 12 h. It was then re-used twice without significant loss of catalytic activity. The reaction mixture (after 6 h) was also analyzed by ICP (and AAS) and only trace amounts (< 2 ppb) of metal were detected. In a separate experiment, the solid catalyst (entry 3) was filtered off from the reaction mixture (at 323 K) after 2 h (conv. = 29 %) and the reaction was continued for a further 4 h (conv. after 6 h = 33 %) with the resulting filtrate (which also had trace amounts (< 2 ppb) of metal). No substantial increase in conversion was observed, clearly showing that the reactions are heterogeneously catalyzed. [d] The TOF have not been calculated in these cases, as the conversions obtained here are noncatalytic. [e] Hexanal was used instead of benzaldehyde.



Scheme 1. Example of oxidation with $\text{H}_2\text{O}_2/\text{MeReO}_3$.

bed in Section 5), may be lined with a substantial number of either cobalt or manganese ions substituted in the framework in place of Al^{III} ions. Similarly, two other types of materials, AIPO-5 (AFI) and AIPO-18 (AEI) with pore dimensions of 7.3 and 3.8 Å, respectively, were synthesized with specific metal ions having identical concentrations. By calcining the freshly prepared MAIPOs samples ($M = \text{Co}$ or Mn) in oxygen at 550 °C, the substituted ions may be converted^[195] into their +3 oxidation states, to a degree that is dependent on the structure: the trend in the concentration of the +3 state in the three structures is AIPO-18 > AIPO-36 > AIPO-5.

Although the mechanistic details of the aerobic oxidation of ketones to lactones reported here still require elucidation, preliminary studies point to the fact that the active centers in the redox catalysts are the Co^{III} (or Mn^{III}) ions that line the micropores. We know for several reasons that the higher conversions are effected by the higher valence framework-substituted ions in the molecular sieve catalysts. Firstly, AIPO-36 analogues substituted with divalent ions, such as Mg^{2+} (or Zn^{2+}), that are not raised to higher oxidation states upon calcination in O_2 yield conversions not significantly different from those of the Mukaiyama sacrificial oxidations with benzaldehyde alone (see Table 5, entries 5 and 7). Secondly, in a parallel experiment using the smaller pore CoAIPO-18 (or MnAIPO-18), where all the transition metal ions are in the +3 oxidation state, and the diameter of micropores is 3.8 Å, no catalytic conversion of cyclohexanone into ϵ -caprolactone occurs when benzaldehyde is used as a sacrificial oxidant (Table 5, entry 6) because the latter is too large to gain access to the active site. (In addition, this clearly rules out the possibility of autoxidation by surface or transition metal impurities. It also constitutes proof that we are not dealing with homogeneous catalysis.) To substantiate that the autoxidation of the aldehyde is shape-selective, we used the straight chain *n*-hexanal, which is small enough to enter the 3.8 Å cages of the CoAIPO-18 catalyst as a sacrificial oxidant. The Baeyer–Villiger conversion of cyclohexanone into ϵ -caprolactone (Table 5, entry 8) freely ensues because the hexanal gains ready access to the framework active sites and forms the peroxyacid. Thus, large-pore CoAIPO-36 (or MnAIPO-36) and CoAIPO-5 (or MnAIPO-5) catalysts offer easy access to bulky sacrificial oxidants (such as benzaldehyde), and oxidize a number of ketones, including adamantane-2-one, to their corresponding lactones with very high selectivity.

The implications are clear: the aldehyde is first converted by O_2 at the active sites into the corresponding peroxyacid

inside the micropores, and this peroxy acid, in the manner first outlined by Criegee^[188, 196]—involving its initial nucleophilic attack at the carbonyl carbon atom—leads to the production of the lactone.^[**] In addition, as in our study of the selective oxidation of cyclohexane,^[167] there appears to be a clear trend in the dependence of catalytic activity on the combination of the pore-dimension of the molecular sieve and the framework-substituted ion: the ATS structure shows higher conversion and selectivity compared to AFI, and Mn^{III} -containing catalysts are slightly more active than their Co^{III} analogues. This agrees well with our estimation of the fraction of the metal ions that undergoes redox reaction.^[191]

7.4. Epoxidation of Alkenes

The liquid-phase epoxidation of alkenes proceeds in the presence of hydroperoxides with catalytic systems that contain titanium(IV) ions (heterogeneously) or molybdenum(VI) ions (homogeneously). Thus the Shell process using Ti/SiO_2 and ethylbenzene hydroperoxide produces propylene oxide on an annual scale of more than one million tons of propylene oxide worldwide from propylene.^[197] The ARCO HALCON process, on the other hand,^[198] is carried out homogeneously using complexes of Mo or W.

Whereas the use of alkylhydroperoxides (in association with an appropriate catalyst) currently dominates the industrial scene, there have recently been attempts made to epoxidize alkenes using molecular oxygen. We begin this section, therefore, with a summarized account of our successful use of molecular-sieve catalysts for doing just that.

7.4.1. Epoxidation using Molecular Oxygen

As with the Baeyer–Villiger reactions described in Section 7.3, the center-piece of our heterogeneous catalyst is the aluminum phosphate molecular sieve AIPO-36, in which, as before, up to 4 atom % of Al^{III} sites have been isomorphously replaced by either Co^{III} or Mn^{III} ions. Again, as with the Baeyer–Villiger–Mukaiyama conditions outlined above, we exploit the easy autoxidation of aldehydes to promote the *in situ* formation of peroxy acids.^[199]

By extending our earlier work on the design of redox molecular sieve catalysts for the aerobic terminal oxidation of linear alkanes (Section 7.1 above), for the selective oxidation of cyclohexane (Section 7.2), and for the Baeyer–Villiger oxidation of ketones to lactones (Section 7.3), we have achieved good conversions and selectivities for the epoxidation of cyclohexene and other alkenes using framework-substituted metal ions (M) in microporous alumina phosphate MAIPO-36 ($M = \text{Mn}$ or Co) catalysts.^[200]

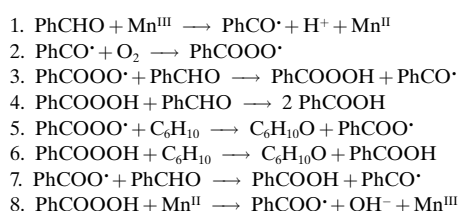
[**] For the sake of completeness, it ought to be mentioned that the transition metal in the framework may itself be directly implicated in the Baeyer–Villiger reaction by, for example, catalyzing the addition of the peroxy species to the $\text{C}=\text{O}$ group or by the formation of metal–peroxy species. In addition, the transition metal could also influence the second step of the Criegee mechanism.^[196] I am grateful to Dr. Markus Dugal for drawing my attention to these possibilities.

Details of the synthesis (and structure) of the Mn^{II} - and Co^{II} -containing AIPO-36 molecular sieves have been given earlier (ref. [185]). Briefly, the Mn^{II} (or Co^{II}) ion is introduced to the template-containing precursor gel from which small crystals of phase-pure product appear. Upon calcination in O_2 at about 550°C , the organic template (tetrapropylammonium hydroxide) is entirely gasified, leaving the oval-shaped cages ($6.5 \times 7.5 \text{ \AA}$) of the resulting catalyst empty. X-ray absorption spectroscopy shows that, after calcination in O_2 , some fifty per cent of the Mn^{II} (or Co^{II}) originally present (isomorphously substituting for Al^{III}) are converted into the Mn^{III} (Co^{III}) oxidation state, but that all these transition metal ions remain securely in tetrahedral coordination within the microporous AIPO framework. Others have also shown that Co^{II} ions in framework sites may be raised to the Co^{III} state without loss of structural integrity of the AIPO framework.^[201–203]

In a typical experiment, 0.25 g of catalyst, 20 g of the alkene, and an alkene:benzaldehyde (mole) ratio of 1:3 are used. The reaction mixture is loaded into a stainless steel, high-pressure catalytic reactor (Cambridge Reactor Design) lined with polyethyl ether ketone (PEEK) and equipped with a mechanical stirrer and liquid-sampling valve. Dry air is pressurized into the reaction vessel (30 bar), and the reactor heated typically for 8 h at a temperature of 323 K. The results are summarized in Table 6. Results obtained with comparable, larger-pore (MAIPO-5) and smaller-pore (MAIPO-18) redox molecular sieve catalysts, the shapes of which are $7.3 \times 7.3 \text{ \AA}$ and $3.8 \times 3.8 \text{ \AA}$, respectively, are also tabulated. It is noteworthy that conversions are consistently higher for both the MnAlPO-36 and CoAlPO-36 catalysts than with those of their larger-pore (AIPO-5) analogues. Almost certainly, the reasons for the superior performance of the MAIPO-36 catalyst is because a greater fraction (ca. 0.5 compared with 0.25) of the

Mn or Co can be raised to the +3 oxidation state, which is the root cause of the catalytic activity. Significantly MgAlPO-36 is totally inactive; there is no redox ion in the framework of the micropores in this case, and hence no means of initiating the free-radical reactions that lead to epoxidation.

Benzaldehyde molecules may freely enter the large (ca. $650 \text{ m}^2 \text{ g}^{-1}$) internal surfaces of both MAIPO-36 and MAIPO-5 catalysts, thereby generating^[203, 204] first $\text{PhCO}^\bullet$ and then the $\text{PhCOOO}^\bullet$ radicals, which, from the sequence of steps shown in Scheme 2, lead to the formation of benzoic acid and cyclohexene oxide. In this sequence, reaction 5 is known^[205, 206] to proceed much faster than 6. This free-radical based epoxidation of cyclohexene (and the other alkenes listed in Table 6) is mechanistically quite distinct from the radical-free epoxidation of alkenes using alkylhydroperoxides and titanate catalysts (which is discussed in Section 7.4.2).



Scheme 2. Probable mechanism of the transformations summarized in Table 6.

Other aldehydes may also be used as sacrificial oxidants provided they are small enough to gain access to the active sites situated at the inner surface of the molecular-sieve catalyst. Benzaldehyde is itself too large to enter Mn - or CoAlPO-18 , but hexanal is not. Although it diffuses less rapidly into the MAIPO-18 structure than benzaldehyde does in AIPO-36, it nevertheless functions efficiently in epoxidizing hex-1-ene (Table 6).

Figure 36 is a composite representation of the versatility of a CoAlPO-36 (and MnAlPO-36) molecular-sieve catalyst in the aerobic oxidation of cyclohexane and in the aerobic (Baeyer–Villiger) lactonization of ketones (Mukaiyama

Table 6. Catalytic aerobic partial oxidation of alkenes.^[a]

Substrate	Catalyst	t [h]	Conv. [%]	Product selectivity [%]		
				epoxide	diol	others ^[b]
cyclohexene	CoAIPO-36	8	54	69	27	4
	Co-AIPO-5	8	47	74	15	11
	MnAIPO-36	8	62	77	19	5
	MnAIPO-5	8	44	77	13	10
	MgAIPO-36	8		No reaction		
α (+)-pinene	CoAIPO-36	8	54	84	–	16 ^[c]
	CoAIPO-5	8	32	55	–	46
	MnAIPO-36	8	59	91	–	9
	MnAIPO-5	8	42	66	–	34
<i>R</i> (+)-limonene	CoAIPO-36	8	46	78	–	23
	CoAIPO-5	8	28	39	–	61
	MnAIPO-36	8	51	87	–	13
	MnAIPO-5	8	30	51	–	49
styrol	CoAIPO-36	4	46	34	58.6	8
	MnAIPO-36	4	55	27	61.3	12
	MnAIPO-5	4	32	49	50.0	1
1-hexene ^[c]	CoAIPO-18	24	37	87	–	13
	MnAIPO-18	24	43	91	–	9

[a] Reaction Conditions: $T = 323 \text{ K}$; 30 bar dry air; 35 g substrate; substrate: benzaldehyde mole ratio 1:3; solid catalyst 0.25 g. [b] These other products were mainly 2-cyclohexen-1-ol and 2-cyclohexen-1-one from cyclohexene; verbenol and verbenone from α (+)-pinene; carveol, carvone and *trans*-carveyl acetate from (*R*)(+)-limonene; and 1-phenyl-1,2-ethanediol from styrol. [c] hexanal was used instead of benzaldehyde.

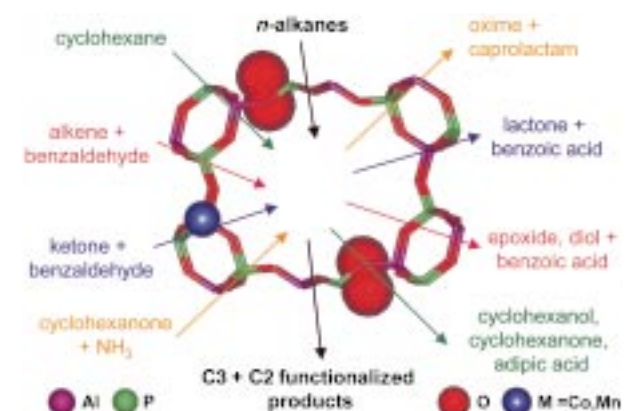


Figure 36. The AIPO-36 microporous structure with either Mn^{III} or Co^{III} ions at framework sites gives rise to excellent catalysts for the various processes.

conditions). For completeness, the ability of this engineered catalyst to effect ammoximation of cyclohexanone to yield the corresponding oxime and caprolactam, is also included.

7.4.2. Epoxidation using Alkylhydroperoxides

Epoxidation using a sacrificial oxidant, especially alkylhydroperoxides (such as tertiary butylhydroperoxide TBHP, cumene hydroperoxide CuHP, 2-methyl-1-phenyl-2-propyl hydroperoxide MPPH,^[207] or ethylbenzene hydroperoxide EBHP, the latter being the reagent of choice in the Shell process for the epoxidation of propylene), is much easier to effect (in the presence of an appropriate catalyst) than doing so with molecular oxygen.^[197, 198] One of the most widely used catalysts, certainly on a commercial scale, for the epoxidation of propylene with alkylhydroperoxides is the $\text{Ti}^{\text{IV}}/\text{SiO}_2$ heterogeneous catalyst that is utilized in the Shell process.^[208]

With the arrival of the M41S family of mesoporous silicas, Corma et al.^[209] were quick to realize that the larger pores of these mesoporous silicas opened up new possibilities for the epoxidation of larger alkenes, provided Ti^{IV} ions could be satisfactorily “placed” at the walls of the silica. In 1995 my colleagues and I embarked^[210] on an extensive study of the preparation with a titanocene precursor of a uniquely powerful alkene epoxidation catalyst by using Ti^{IV} ions grafted on to MCM-41 mesoporous silica. By using the preparative and in situ characterizing techniques described earlier in this review, we established the following facts:

- all the Ti^{IV} centers are isolated (single site) surface species, spatially well-separated (when the Ti loading of the catalyst is low) from one another
- the atomic architecture of these Ti^{IV} -centered catalytically active sites is quantitatively defined
- effectively they are titanol groups tripodally linked through Ti-O-Si bonds to the surfaces of the mesoporous silica support
- numerous additional spectroscopic studies (in addition to X-ray absorption spectroscopy,^[25, 210] including diffuse reflectance,^[211] and UV/Vis photoluminescence^[212] measurements) leave^[146] no doubt concerning the precise structure of the $\text{Ti}(\text{IV})$ centered active site, which is shown, along with its mode of creation, in Figure 37.

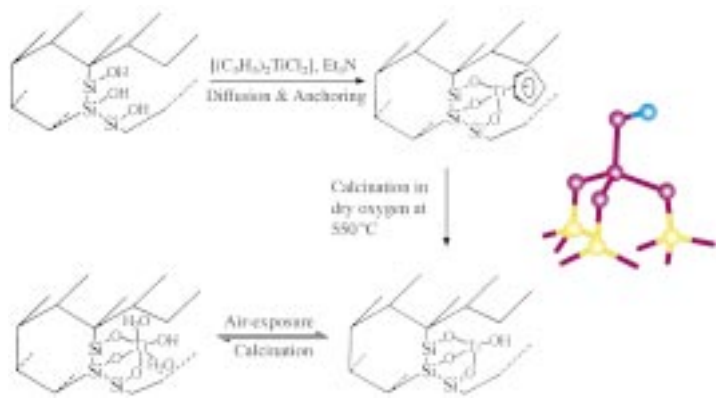


Figure 37. In situ X-ray absorption (XRA) measurements reveal that both the half-sandwich and calcined materials (derived from anchoring titanocene to the inner walls of MCM-41^[210]) are tripodally attached to the silica.^[146]

Combined in situ XRA and XRD investigations (as outlined in Section 6.3 and Figure 25) reveal how, from the changes in the X-ray absorption spectra in proceeding from the calcined state to the catalytically active form of the catalyst, the O-Ti bond lengths and the coordination number of the titanium active site is determined (Figure 38). We see clear evidence of the expansion of the coordination sphere of the active site during catalysis.

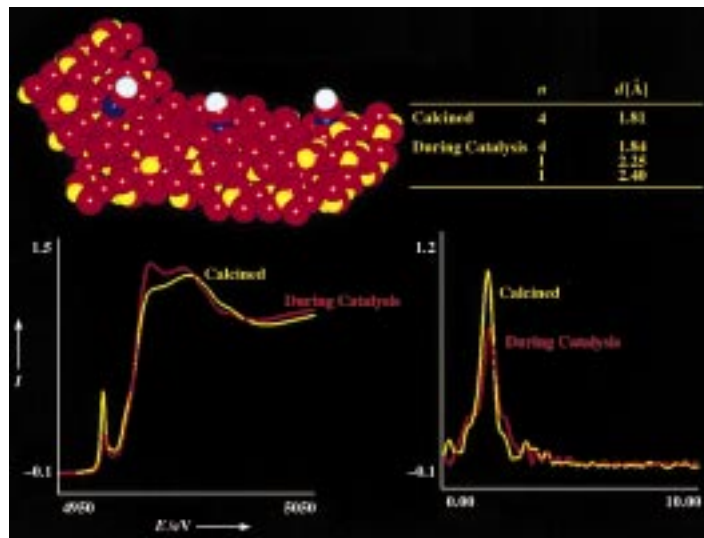
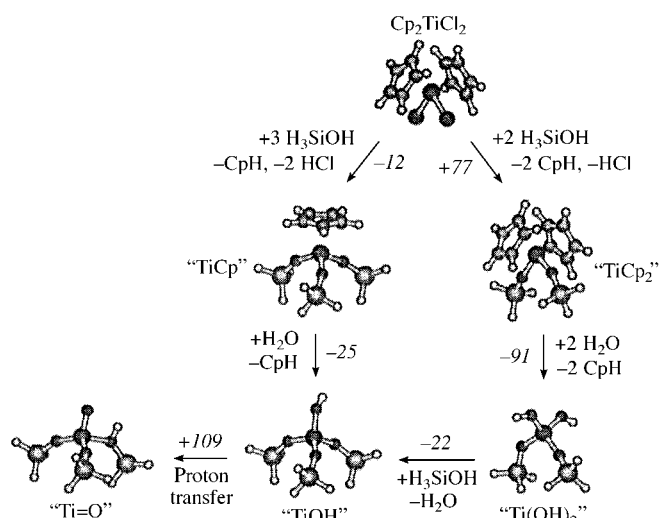
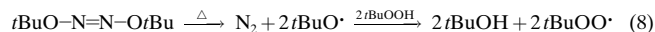


Figure 38. In situ XRA spectra of reacting epoxidation catalysts $\text{Ti}^{\text{IV}}/\text{MCM-41}$ (where the pendant OH groups attached to tripodally bound Ti^{IV} ions stand proud of the surface) reveal an expansion of the Ti coordination number from four to six.^[25] EXAFS analysis corroborated by the observed changes in pre-edge absorption intensities, yield quantitative data pertaining to the reaction sphere of the active site. (The XRA evidence shows no change in valence of the Ti^{IV} ion. Cyclic-voltammetry studies with titanosilsesquioxane analogues (which are soluble) also show no sign of valence change of the Ti^{IV} during the course of catalytic epoxidation). The spectra here (bottom left) were obtained by in-situ X-ray measurements.

Computational studies,^[213] using nonlocal density functional theory, reveal two interesting insights (Figure 39).



Another compelling argument for a radical-free mechanism comes from our oxidation studies of *cis*-stilbene with *tert*-butyl peroxy radicals, generated by the thermal decomposition of di-*tert*-butyl hyponitrite in the presence of TBHP. Here, because of Reaction (8): we expect, and do indeed find,

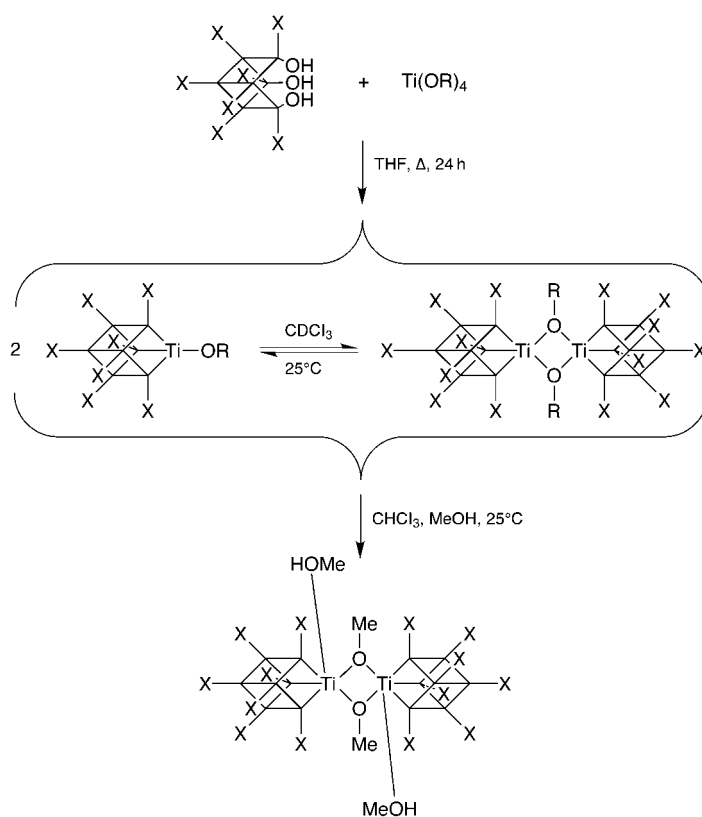


benzaldehyde and *trans*-stilbene oxide in approximately equal amounts, together with a small quantity of *trans*-stilbene. However, reaction of *cis*-stilbene with TBHP or MPPH in the presence of our Ti^{IV}-centered epoxidation catalyst, gives *cis*-stilbene oxide as the only oxidation product. It is therefore clear that epoxidation proceeds by non-radical chemistry, and our experiments indicate that the alkene and the peroxide must both be coordinated to the Ti^{IV} center for reaction to ensue. This is borne out by the increased coordination number measurable from in situ EXAFS studies (see Figure 38).

7.4.2.3. Exploring the Influence of Steric Congestion on the Catalytic Performance of Ti^{IV} Active Centers using Soluble Titanosilsequioxane Analogues

The remarkable similarity in the local structures of the established active site in our Ti/silica epoxidation catalysts and that of the heteroatom vertex in a titanosilsequioxane such as R₇Si₇O₁₂TiOX (see Figure 4), studied earlier by Feher,^[225] Roesky,^[197] and others^[226, 227] offers abundant scope for detailed investigations into the mode of operation of our (single-site) heterogeneous catalyst through the agency of a large range of soluble, strictly comparable, model compounds. Take, for example, the incompletely condensed silsesquioxane [(*cis*-C₅H₉)₇Si₇O₉(OH)₃] with titanium isopropoxide Ti(O*i*Pr)₄. Three of the four Ti(O*i*Pr) ligands will substitute for the three pendant OH groups on the incomplete silsesquioxane box (Scheme 4).^[230] There is a tendency for the resulting (C₅H₉)₇Si₇O₉TiO*i*Pr to dimerize. When the same incompletely condensed silsesquioxane is treated with another titanium tetraalkoxide (Ti(OR)₄), the corresponding titanosilsequioxane complexes [(*cis*-C₅H₉)₇Si₇O₁₂TiOR]_{*n*} (*n* = 1, 2) are also formed (Scheme 4). The dimeric titanosilsequioxanes (*n* = 2) may form yielding a situation in which the tripodally bound (to -O-Si) titanium atom becomes five-coordinated, one of the Ti-O links being (determined from X-ray crystallographic studies)^[228] so long (ca. 2.25 Å) as to indicate the presence of a dative bond (compare with results shown in Figure 38). Detailed catalytic studies^[229, 230] of the epoxidation of cyclohexene in CDCl₃ solution at 45 °C in the presence of each of the titanosilsequioxanes enumerated above leave no doubt that steric accessibility to the Ti^{IV} active site is the principal determinant of catalytic performance.

Titanosilsequioxanes also offer further scope to explore the relative importance in catalysts (through their Ti^{IV} active centers) of ions that are bipodally or monopodally attached, through an oxygen atom, to a tetrahedrally coordinated silicon atom. There is no doubt that, so far as durability and sustained activity of such catalysts go, a tripodally bound



Scheme 4. Synthetic scheme and proposed structures for titanosilsequioxane; the unlabeled corners are Si atoms, the edges O bridges. X = cyclopentyl, cyclohexyl; R = Me, Et, *n*Pr, *i*Pr, *n*Bu, *t*Bu, Me₂CH₂CH₂CH₂.

Ti^{IV} center is superior. Preliminary experiments^[231] using silsesquioxanes in which the titano-vertex is as shown in Figure 4 (right), show that a Ti^{IV} ion juxtaposed to Ge (through oxygen) is, as seen in the case of the heterogeneous catalysts,^[219] the most powerful epoxidation catalyst.

7.4.2.4. Converting an Inactive Four-Coordinated Ti^{IV} Compound into an Active Epoxidation Catalyst by Grafting it to a Silica Surface

Deeper insights into the supreme importance of steric accessibility of the reactants to a central, potentially catalytically active four-coordinated titanium atom are well illustrated by the comparative behavior of the two entities schematized in Figure 41. The molecule on the left displays zero catalytic activity in the epoxidation of cyclohexene (under the same conditions as employed for the titanosilsequioxanes described above). When, however, three of the OSiPh₃ groups are removed (by refluxing in THF) so as to yield the species on the right, this now exhibits catalytic activity some eighty per cent of that of the Ti↑MCM-41 catalyst in ref. [210]). Indeed, upon calcining this material so as to generate a tripodally bound titanol group, as in Figure 4 (left), the material has an activity as good as that of the titanocene-derived analogue.^[231] Molecular dynamics calculations help to understand how an increase in the accessibility to the central titanium engenders catalytic activity (Figure 42).

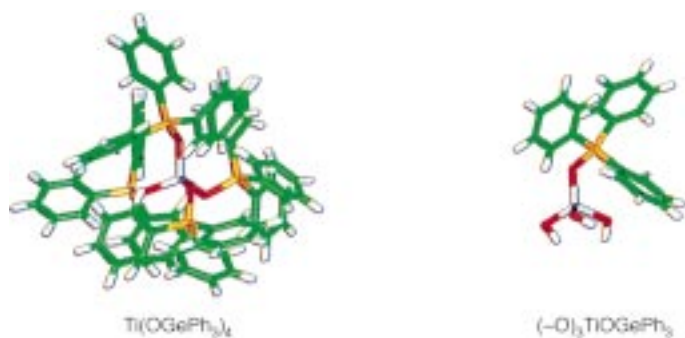


Figure 41. The tetrahedrally bonded Ti^{IV} center in the molecule on the left and also in its silico analogue $\text{Ti}(\text{OSiPh}_3)_4$ is inactive as a catalyst in cyclohexene epoxidation with alkyl hydroperoxides (such as THBP).^[231] When, however, either of these is tripodally anchored to mesoporous silica so as to leave only one pendant OGePh_3 (or OSiPh_3) group (right) the Ti^{IV} ion becomes catalytically active (see Figure 42).

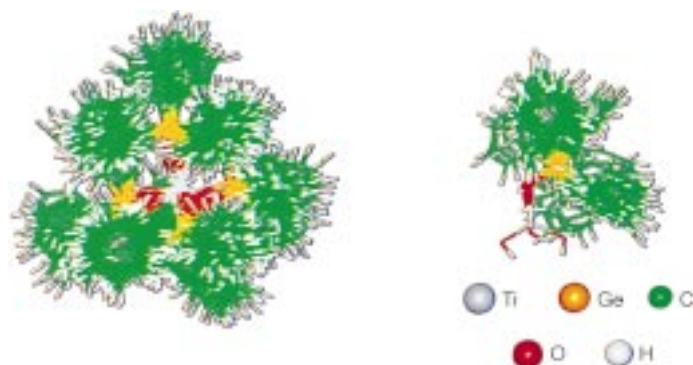


Figure 42. The molecular dynamic simulations for each of the clusters in Figure 41 were carried out at 500 K for a duration of 5 ps, using a 1 fs timestep. The Ti atom and the three anchoring oxygen atoms were kept fixed during the simulation for the surface-anchored cluster. These representations consist of superposition of frames from the simulation taken at 200 fs intervals. By comparing these two views it is clear that the access of the reactants is far greater for the right than for the left entity. The latter shows how effectively the four triphenyl groups shroud the central potentially catalytically active (and coordinatively unsaturated) Ti^{IV} ion.

7.5. Engineered, High-Area, Shape-Selective Solid Acid Catalysts

Ever since Weisz et al.^[43, 44] demonstrated the power and widespread utility of ZSM-5 as a solid acid catalyst for the shape-selective dehydration of methanol to useful hydrocarbons, there have been intense research efforts on two fronts. First, the quest for new microporous solids that are engineered so as to limit (shape-selectively) the process of dehydration of methanol so as to favor the production of only light olefins (ethene, propene, and butene) rather than of benzene, toluene, and xylene. Second, the preoccupation with the mechanism of the dehydration, and, in particular, with the precise steps that lead to the formation of C-C bonds. Greater progress has been achieved in the first than in the second of these two efforts.

Considerable efforts have also been made to generate new, solid acid catalysts that favor the skeletal isomerization of 1-butene or 1-pentene into their branched chain analogues. For example, conversion of 1-butene into 2-methylpropene is of great value as a stepping stone towards the production of *tert*-butyl methyl ether (MTBE), a valuable (high-octane) constituent of petrol (gasoline).

In collaboration with K. I. Zamaraev and his associates, my colleagues and I established^[232, 233] that the catalytic dehydration of all alcohols takes place over strong Brønsted acid sites, rather than over Lewis acid ones. Several different HZSM-5 catalysts (some of small, some of large crystallite size, and some partially ion-exchanged such as NaHZSM-5) were investigated and all compared with amorphous aluminosilicate specimens with larger pore diameters but with comparable acid strength. Detailed investigations of the catalytic dehydration of all four isomeric butanols were made and yielded an unambiguous answer (Figure 43). The catalytic activity of all the catalysts is directly proportional to the concentration of the bridging hydroxyl Al-O(H)-Si groupings (that is, the Brønsted acid sites) and does not correlate with the concentration of strong (or weak) Lewis acid sites. Further proof that Lewis acid sites are not catalytically active, whereas Brønsted ones are, comes from the fact that preadsorbed acetonitrile (which affects Lewis but not Brønsted sites) has no effect on the rate of dehydration, whereas increasing

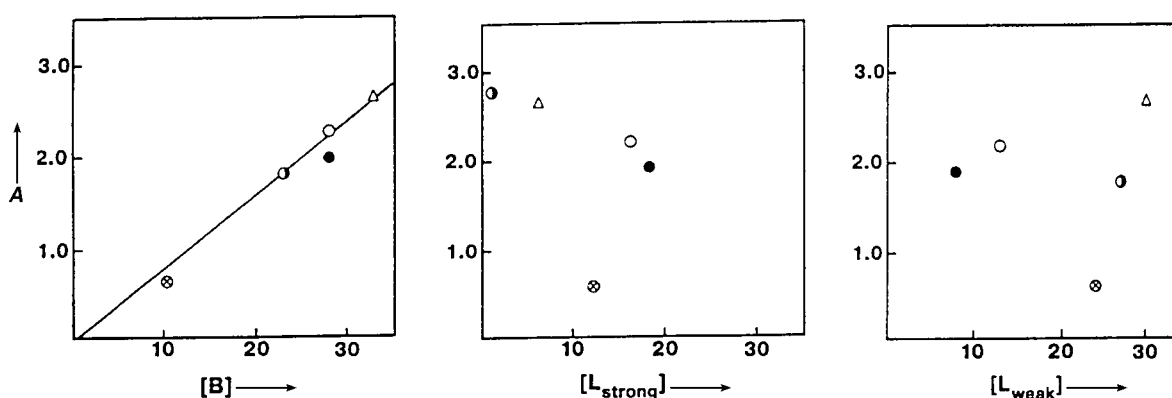


Figure 43. Observed^[233] relation between the acid catalytic activity A (in 10^{17} molecules per second and per gram of catalyst) of a series of ZSM-5 samples (Δ (NaHZSM-5, sample 2), $\circ$ (HZSM-5, sample 3), $\bullet$ (HZSM-5, sample 4)) and an amorphous aluminosilicate ($\otimes$) in the dehydration of 2-butanol to butene and the concentration of Brønsted (B) and Lewis acid (L) sites.

amounts of preadsorbed pyridine (which becomes attached to Brønsted sites) progressively decreases the rate of dehydration of 2-butanol. (The concentration of the Brønsted Al-O(H)-Si sites was measured by four distinct methods: ^1H NMR spectroscopy, (quantitative) IR spectroscopy, by “poisoning” titration with pyridine, and from direct analysis of the Al content).

7.5.1. DAF-4 and STA-2: Catalysts that Generate Light Olefins in the Dehydration of Methanol

Success on this front consists of designing a microporous solid, the pore apertures and diameters of which function as constraints for the production of bulky hydrocarbons, but still favor the generation of the light olefins mentioned above. Much interest has been shown both academically and industrially in developing appropriate catalysts for such purposes.^[234–236]

By careful choice of an organic template (as the structure-directing agent, see Section 5), my colleagues and I prepared a new shape-selective microporous solid acid catalyst that has a structure akin to that of the naturally occurring, zeolitic (aluminosilicate) mineral levyne^[237] (idealized formula: $\text{Ca}_9[\text{Al}_{18}\text{Si}_{36}\text{O}_{108}] \cdot 50\text{H}_2\text{O}$), which is isotypic with the previously reported synthetic material ZK-20.^[238] This new, designed catalyst, known as DAF-4,^[62] is an aluminophosphate in which up to 20 % of the Al^{III} framework ions is replaced by Co^{II} (or other divalent) ones. Our aim in designing it was to arrive at a microporous solid acid catalyst in which the cavities were somewhat different from those in CoAlPO-18 and SAPO-18 (see Section 5).

We judged it desirable to “create” cavities that were slightly smaller in one direction than they are in CoAlPO-18, and larger in the other so as to secure the shape selectivity that would prevent the methanol yielding heavier alkenes upon dehydration. With the knowledge that a 1,4-diaminocyclohexane template gives rise to a porous layered AlPO_4 structure^[239] we reasoned that 1,2-diaminocyclohexane would favor the formation of a microporous solid with 8-ring windows (that is, with eight oxygen atoms lining the window), as in the chabazitic materials SAPO-34, CoAlPO-18, and CoAlPO-44, but significantly different in its cavity shape. However, because 1,2-diaminocyclohexane was found to be unstable under the hydrothermal conditions of synthesis, we chose instead the more stable 2-methylcyclohexylamine as the template (these templates are spatially similar because the CH_3 group occupies almost the same space as a protonated NH_2 group). Crystallization

from a gel of composition $x\text{CoO}_n : (1-x/2)\text{Al}_2\text{O}_3 : y\text{SiO}_2 : (1-y/2)\text{P}_2\text{O}_5 : 25\text{H}_2\text{O} : 1.0\text{C}_7\text{H}_{15}\text{N}$, where $x = 0-0.4$ and $y = 0-0.2$, under autogenous pressure for 7 d at 200°C resulted in the production of the desired solid. In its Co^{II} substituted form, DAF-4 transforms methanol with greater than 75 per cent conversion at 350°C into ethene and propene, with a selectivity of about 60 % and about 20 % for the two alkenes, respectively.

Wright and his colleagues^[64] have succeeded in producing another, well-defined microporous solid acid (AlPO) catalyst known as STA-2 (see Figure 8). In its Mg^{II} -substituted form this catalyst also converts methanol with high efficiency into ethene and propene. The similarity in cage dimensions and disposition of (protonic) acid sites in these two catalysts is illustrated in Figure 44. So far as the mechanistic details of methanol dehydration (leading to alkenes) is concerned, ingenious proposals have been made by van Santen et al.,^[240] by Catlow et al.,^[241] as well as by others.^[242–244] One plausible explanation, which is backed up by reliable computational evidence, is shown in Scheme 5.

7.5.2. Skeletal Isomerization of 1-Butene: The Merits of Boron-Substituted Zeolite β

Here, the aim is to arrive at maximal amounts of 2-methylpropene (Figure 45). Previous work (see for example refs. [245, 246]) has shown that both aluminosilicate and aluminophosphate microporous acid catalysts are viable catalysts for this conversion. Recent work^[247] has shown that, contrary to expectation, certain borosilicate microporous materials are very good catalysts for this isomerization. This fact again highlights how subtle is the dependence of Brønsted

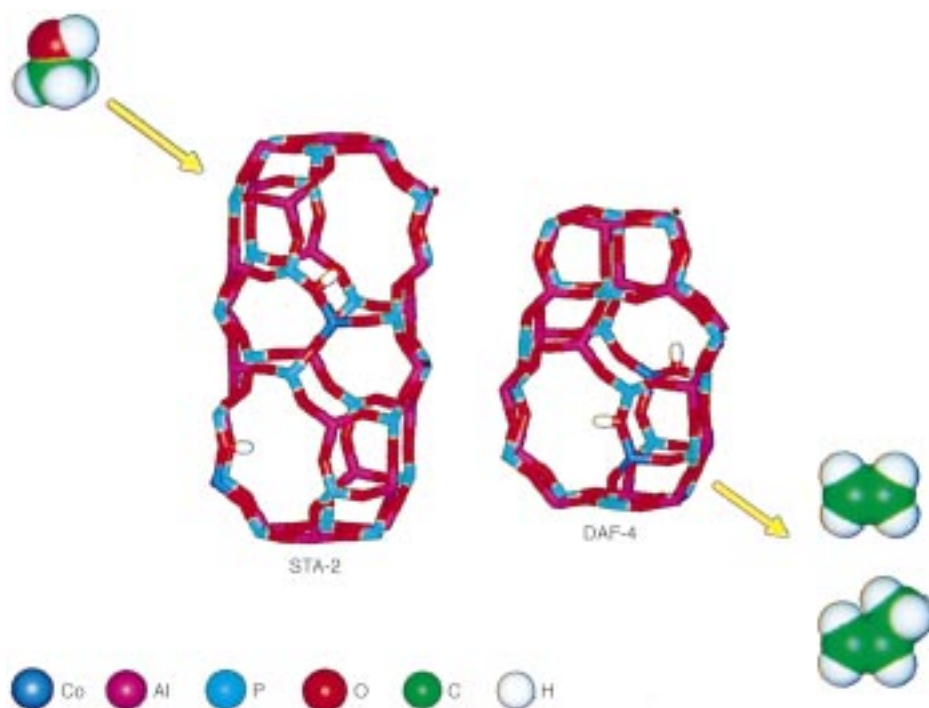
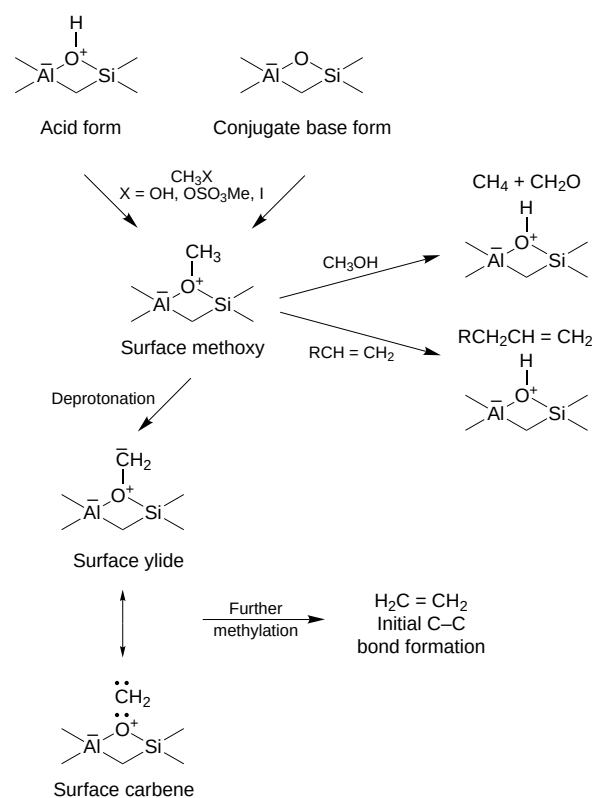


Figure 44. The solid acid, molecular sieve catalysts St. Andrews No. 2 (STA-2)^[64] and Davy-Faraday No. 4 (DAF-4),^[62] each with a cage diameter of ca. 3.8 Å function as excellent shape-selective catalysts in the preferential conversion of methanol into the light olefins ethene and propene.



Scheme 5. Methyloxonium mechanism for the dehydration of methanol.^[241]

7.6. Designing Durable, High-Performance Bimetallic Catalysts for the Hydrogenation of Alkenes

Bimetallic nanoparticles possess catalytic properties that differ sharply from those of solid solutions of the bulk metals. This was one of the key conclusions to emerge from the early work of Sinfelt,^[248] and its veracity has been multiply attested. Among the many studies of bimetallic catalysts, some are of great technological importance (for example, Pt-Re, Pt-Ir, and Pt-Rh) in processes such as the reforming of naphtha and, to a lesser degree, in the control of autoemissions.^[249] The current interest in the use of bimetallic catalysts is largely a consequence of the enhanced activity and selectivity that may be achieved by two metals working synergistically. However, despite considerable effort, the preparation of these systems by metal-salt deposition and subsequent calcination followed by reduction to the active, low-valent species is not always reliable and has many drawbacks, the greatest of which is the lack of control over size, morphology, and homogeneity of the resulting bimetallic nanoparticles. Preformed colloids however offer useful scope in these contexts. But there is a crucial practical factor: nanoparticles tend to migrate, coalesce, and sinter, thereby leading to drastic loss of active surface and hence of catalytic performance.

All these disadvantages are overcome if mixed carbonylmetalate clusters are used as the precursors of the dimetal nanocatalysts. Moreover, if one of the metals in the cluster is oxophilic, it will tend to be anchored securely to a siliceous (large-area) support. In our group^[250–252] we have taken steps to circumvent all the above-mentioned disadvantages, and have indeed used a number of mixed carbonylmetalates as a means of producing well-dispersed, dimetal nanoparticles of composition $\text{Ag}_3\text{Ru}_{10}$,^[250] $\text{Cu}_4\text{C}_2\text{Ru}_{12}$,^[251] and Pd_6Ru_6 .^[252] The strategy employed is schematized in Figure 46.

In situ X-ray absorption and FTIR spectroscopies as well as ex situ high-resolution electron microscopy (see Section 6) were used to chart the progressive conversion, by gentle thermolysis of the parent carbonylates into the derived, dimetal nanoparticle catalysts. Thus, for the anionic cluster carbonyl species $[\text{Ru}_6\text{C}(\text{CO})_{16}\text{Cu}_2\text{Cl}]_2[\text{PPN}]_2$ —where PPN = bis(triphenylphosphane)iminium—separate recorded copper and ruthenium K-edge X-ray absorption spectra yield a detailed structural picture (Figure 47) of the active, approximately 15 Å diameter catalyst. It is a rosette-shaped entity (Figure 48) in which twelve exposed Ru atoms are connected to a square base composed of relatively oxygen concealed Cu atoms. These, in turn, are anchored by four oxygen bridges to four Si atoms of the mesopore lining.

The dimetal catalysts prepared in this way exhibit no tendency to sinter, aggregate, or fragment into their component metals during use. The nanoparticles perform well in the catalytic hydrogenation of 1-hexene—a detailed kinetic study^[251] at 373 K and 20 bar H_2 shows the maximum turnover frequency (TOF) [(mol_{substr}) per (mol_{cluster}) per hour] to be 51200, with an average value of 22400—and also in the hydrogenations at 65 bar H_2 and 373 K of diphenylacetylene, phenylacetylene, stilbene, *cis*-cyclooctene, and α -limonene, the average TOF being 17610, 70, 150, and 360, respectively.

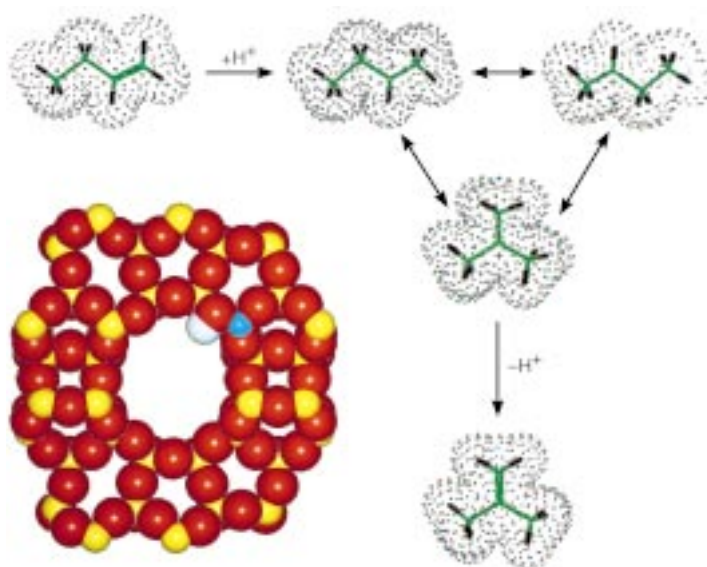


Figure 45. The acid-catalyzed isomerization of 1-butene (top left) to 2-methylpropene (bottom right) occurs rapidly on the inner walls (which provide protons) of microporous catalysts such as DAF-1^[60] (see Figure 8) and boron-substituted zeolite β (shown schematically).^[247]

acid strength (and hence catalytic performance) upon the precise structure of the microporous silicate into which the boron is incorporated (tetrahedrally). Work done jointly with P. A. Wright on a series of boro- and aluminosilicate structures (such as ZSM-12, ZSM-48, and zeolite β) with comparable values of Si/Al and Si/B ratios, strongly imply that long-range electrostatic effects profoundly influence the Brønsted activity of certain sites.

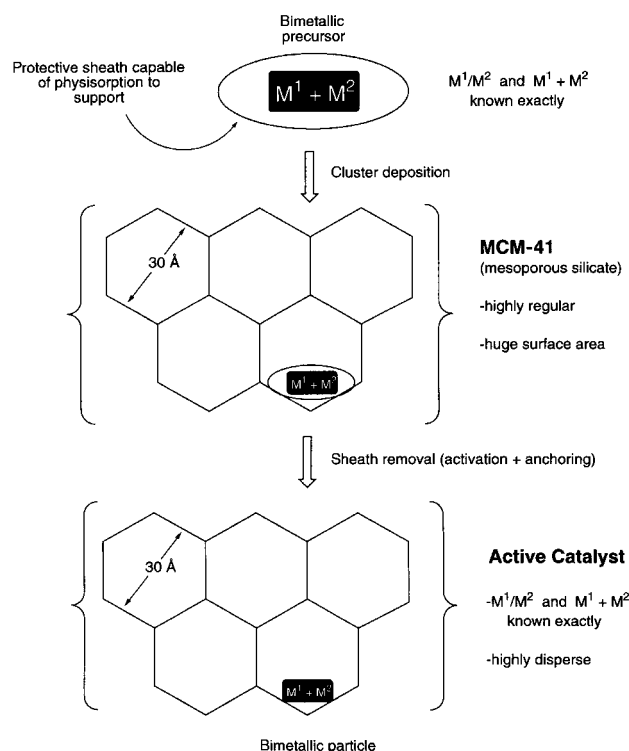


Figure 46. The strategic principles employed^[250–252] to prepare high-performance, dimetal nanoparticle catalysts encapsulated within mesoporous silica (MCM-41).

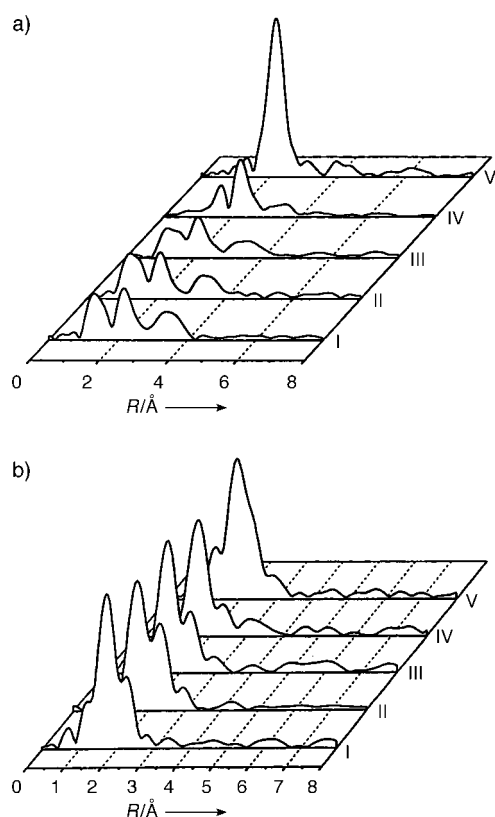


Figure 47. Fourier transforms of the EXAFS data taken during the gentle thermolysis of the mixed carbonylmetallate precursor $[\text{Ru}_6\text{C}(\text{CO})_{16}\text{Cu}_2\text{Cl}]_2^{2-}$ (I) from its original state (II), through to the encapsulated and heat-treated product (III 80 °C, IV 130 °C) to yield the active $\text{Cu}_4\text{C}_2\text{Ru}_{12}$ nanocatalyst (V 180 °C).^[251] a) Ru K-edge, b) Cu K-edge.

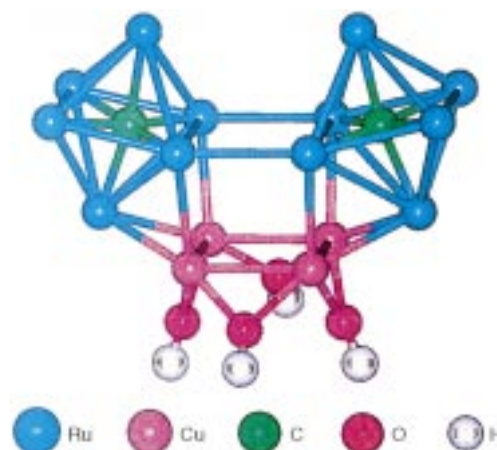


Figure 48. The EXAFS results lead to a picture of the active catalyst, which is ca. 15 Å in diameter, and which is rosette-shaped; for further information, see the text and Figure 49.

We now return to the structure shown in Figure 48. Bromley et al.^[253] have recently used this as a starting model for various computational techniques to determine the energy-minimized structure. By applying molecular dynamics methods based on interatomic potentials to this “precursor” mixed-metal carbide nanocatalyst, the structure was optimized to find low-energy configurations. This procedure was carried out for both the cluster in free space, and for a number of silica-cluster bonding scenarios. Fully quantum mechanical ab initio density functional theory (DFT) was applied to each of a number of possible cluster structures, optimized by the molecular dynamics calculations. DFT single-point calculations were performed on each cluster so as to compare their total energies. With preference given to the lowest energy clusters, but also guided by our experimental EXAFS results, candidate clusters were chosen. These were then further energy-minimized and geometry optimized using DFT.^[254] The resulting geometry of the cluster, especially when it is bound to a silica surface, agrees well with our EXAFS data (Figure 49). Significantly, it is seen that the carbon atoms,

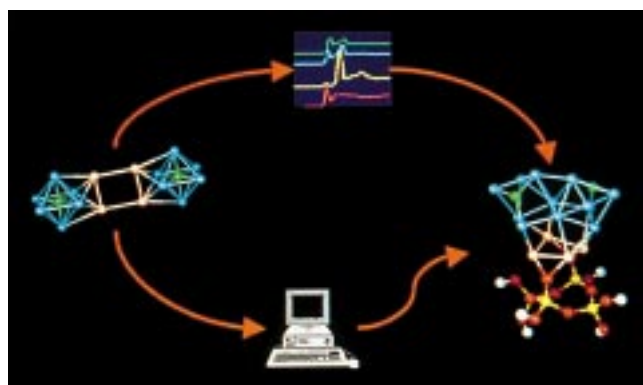


Figure 49. A combination of molecular dynamics energy minimization and density functional computations (shown here as a computer) on the “initial” $\text{Cu}_4\text{C}_2\text{Ru}_{12}$ cluster (left) leads to a new structure (right) in which the carbon atoms are situated at the surface of the silicon-anchored cluster.^[253] The structure is in good agreement with that determined by experimental EXAFS data (top).

initially located at the centers of Ru_6 octahedra in the parent mixed carbonylmetalate tend to take up positions at the surface of the catalytically active nanoparticle catalyst. The precise significance of this fact, which would have been almost impossible to establish by any other technique, remains to be discovered.

7.7. Designing Constrained Chiral Catalysts: Heterogeneous Organometallics For A Range of Organic Reactions

In the pharmaceutical and agrochemical industries, as well as in the expanding fields of fragrances and flavors, there is a growing demand for enantiomerically pure products. Not surprisingly, therefore, increased attention is now being given to the design of powerful enantioselective catalysts. After all, only a relatively minute amount of the requisite chiral catalyst is needed to generate large amounts of the targeted chiral product. But how does one set about designing the requisite catalyst? Leaving aside engineered enzymes and other biological, macromolecular chiral catalysts, the most popular procedure to date has been to “construct” the right homogeneous transition metal-based complex, which generally operates at low temperatures and at moderately high pressures.^[14, 255–257]

To date homogeneous catalysts in which metal ion complexes are attached to carefully designed chiral ligands are still the most effective enantioselective catalysts. But it has been appreciated for some time—see, for example, the early review by Burwell^[258]—that heterogeneous catalysts would be preferable owing to a variety of intrinsic practical advantages that are directly connected to such factors as ease of separation, handling, and recovery, not to mention their higher potential for regeneration and re-use. Awareness of such advantages prompted Schwab^[259] several decades ago to modify metal surfaces such as Raney nickel with certain stereospecific adsorbents so as to confer enantioselectivity on the resulting catalyst. Much later, Akabori and co-workers^[260] in Japan reported the first reasonably reliable metal-catalyzed asymmetric hydrogenation. Their preparation consisted of metallic Pd supported on silk and this was successful in the hydrogenations of oximes and ketones.

As Swiss workers have recently emphasized,^[261, 262] there are only a limited number of possible approaches to the design of enantioselective heterogeneous catalysts. One of these seeks to find (or prepare) solids in which the active sites are located in a chirally discriminating environment. To be precise, this approach encompasses (but is not restricted to) the use of chiral solids (that is those that exhibit a chiral space group, such as $P2_12_12_1$, so that an active site in any one of the three mutually perpendicular crystallographic screw axes is intrinsically prochiral). Stratagems of this kind were used in early work on photoactive prochiral molecular crystals.^[263, 264]

Another approach entails the phenomenon of chiral leaching, in which a cavity may be created in a solid by a stereospecific etchant (such as that which occurs when D- or L-tartaric acid attacks the sites of screw dislocations at the cleavage surfaces of calcite^[265]). Related to this is the recent

ingenious achievement of Gellman et al.^[266] in creating chiral kinks (produced when monatomic terraces interact) on single crystal faces of metallic Ag. However, neither of these two approaches seem particularly well-suited for routine use or scale-up. Chiral imprinting, which involves the interaction of a chiral template with a solid such that, upon removal of the template, a chiral imprint or “footprint” is left, might prove to be a powerful technique for the preparation of enantiomerically discriminating catalysts, but is still in its very early stages.

In contrast, the last family of approaches to be considered here, namely the *creation of a chiral environment for the active sites* has already been shown to be viable for a range of reactions. One way forward, therefore, is to graft a chiral ligand/modifier (which exerts stereochemical control) to a catalytically active (but not itself stereoselective) solid, a classic example being the use of adsorbed cinchona alkaloid on a Pt surface for hydrogenation. Another is to graft an “ordinary” active site to a chiral solid support. Yet another entails the heterogenization (or immobilization) of chiral homogeneous transition metal complexes on a large-area solid support. We have focused on the last of these three options.

7.7.1. The strategy

As mentioned earlier, the availability of a large range of materials in well-defined, mesoporous forms unlocks new possibilities in solid-state catalysis as they provide uniquely advantageous supports for the development of new chiral catalysts. Indeed, the large diameter channels (see Figures 9 and 10) of the MCM-41 family of mesoporous silica permit the direct grafting of complete chiral metal complexes and organometallic moieties on to the inner walls of these large surface solids by a variety of ways that include functionalizing the pendant surface silanol with organic groups such as alkyl halides, amines, carboxylates, and phosphanes. This opens routes to the preparation of novel catalysts consisting of quite large concentrations of accessible, well-spaced, and structurally well-defined active sites. One may, therefore, expect, and we do indeed find (as shown below), that such heterogeneous solids catalysts behave at least as efficiently as their homogeneous counterparts and sometimes with far superior enantio- or regioselectivity.

Various kinds of organometallic, chiral catalysts may be tethered to the inner walls of a mesoporous host employing the strategy adumbrated in Figure 50. The key features here

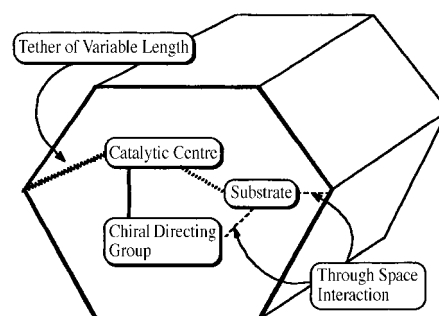


Figure 50. Schematic representation of the confinement concept in which the substrate is incarcerated in the cavity of a chiral modified mesoporous host and leads to chiral heterogeneous catalysis.^[269]

are the reactant's (substrate's) interaction with both the pore wall and the chiral directing group. The confinement of the reactant (substrate) within the mesoporous channel should lead to a larger influence of the chiral directing group on the orientation of the substrate (reactant) relative to the reactive catalytic center when compared to the situation in solution. (This is not only the case for enantioselective reactions but also for regioselective ones).

The chiral chelate ligands based on 1,1'-bis(diphenylphosphanyl)ferrocene (dppf) are particularly attractive for tethering into MCM-41 for several reasons: first, their planar chirality never undergoes racemization; second, they are synthetically very accessible;^[267] and third, they possess functionalities suitable for reaction with pore-bound tethers. The opportunities for variations of the groups attached to an adjacent nitrogen atom and hence the steric/electronic characteristics for both metal complexation and tailoring of the chiral environment, chiral catalysts offer great scope for the designer of constrained chiral catalysts.

The homogeneous transition metal complexes of dppf derivatives are active for a large variety of stereoselective reactions, such as cross-coupling of organometallic reagents with alkenyl or aryl halides, aldol-type reactions, substitutions of allylic substrates with nucleophiles, hydrogenation and hydrosilylation of olefins and ketones, and hydroboration. Thus, with the chiral MCM-41 derivatives, catalytic regio- and enantioselective syntheses (that is, the altered selectivity of the chiral complexes tethered in siliceous MCM-41 versus that of their homogeneous analogues) might, for example, be explored in the fashion typified by Corma et al.^[268] in the rhodium/USY system, where an increase in the enantiomeric selectivity from 75 to 95% could be achieved. (This is thought to have been caused by the additional substrate-pore wall interaction as shown above.)

7.7.2. Designing a Chiral Catalyst Confined Within Mesoporous Silica: Its Superior Performance Relative to its Homogeneous Analogue in Allylic Amination

We have demonstrated^[269, 270] that a chiral ligand derived from dppf bonded to an active metal center (in this case Pd^{II}) and tethered, through a molecular link of appropriate length, to the inner walls of a mesoporous support (MCM-41, ca. 30 Å diameter) yields a degree of catalytic regioselectivity as well as enantiomeric

excess that is far superior to either the homogeneous counterpart or the Cabosil-bound catalyst (Cabosil is a nonporous, large-area siliceous material).

Our conceptual methodology was to take a homogeneous system of known catalytic behavior and perform suitable modifications prior to tethering this catalyst within the mesopore. Care is taken to ensure that all activity is confined to the internal surface of the MCM-41 channels. This is achieved by selectively deactivating the external surface of the support. (We have shown previously by electron microscopy on functionalized mesopores stained with Ru₆-based clusters that this is a reliable and satisfactory method).

Our approach to the preparation of our catalytic system is shown schematically in Figure 51. The mesoporous framework was first treated with Ph₂SiCl₂ under nondiffusive conditions to deactivate the exterior walls of the material. The interior walls of this same material were then derivatized with 3-bromopropyltrichlorosilane to give the activated MCM-41 (**1**). The ferrocenyl-based ligand **2** was prepared from ferrocene by literature methods.^[271] Treatment of the activated MCM-41 (**1**) with an excess of **2** yields the chiral catalytic precursor **4**, which, on reaction with PdCl₂/MeCN, gives the required catalyst **6**. In a separate experiment the closely

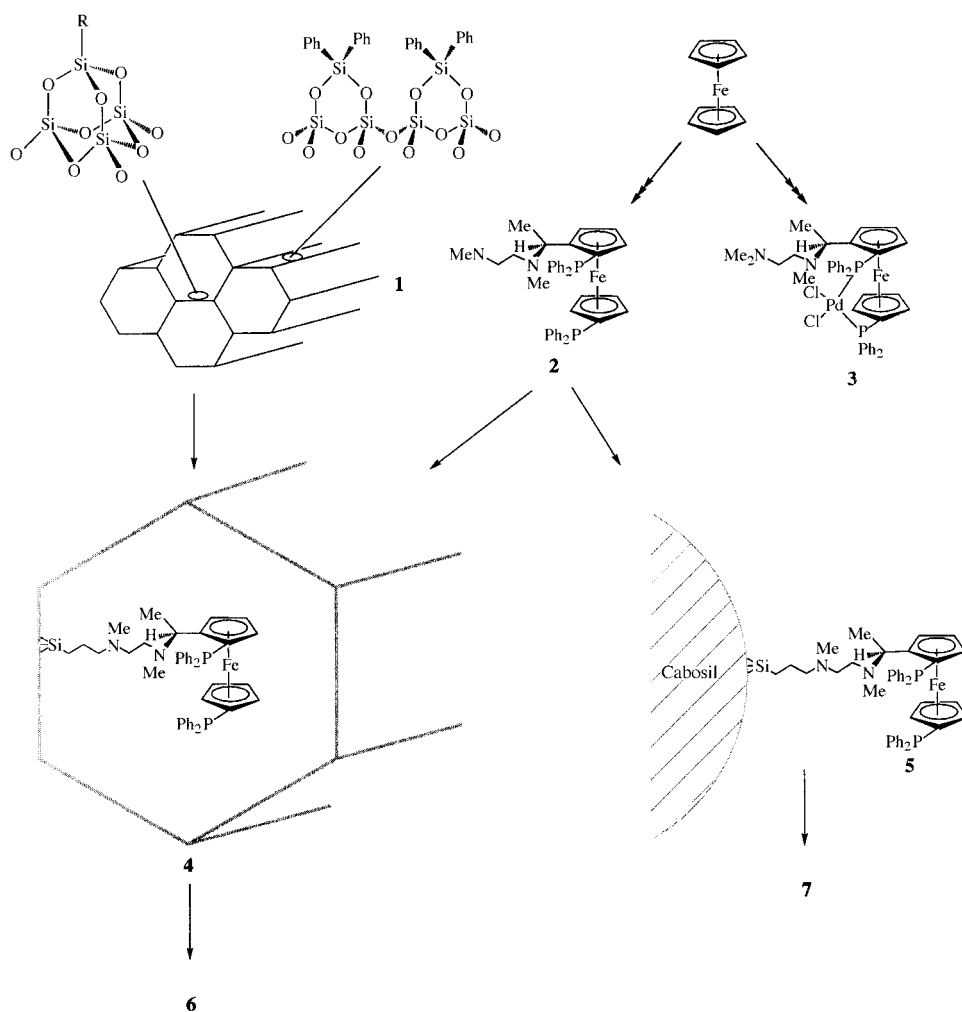


Figure 51. Sequence of steps showing the immobilization of *N*-[1',2-bis(diphenylphosphanyl)ferrocenyl]-ethyl-*N,N'*-dimethylethylenediamine (**2**) in its chirally constrained and unconstrained (**5**) states.^[270] R = (CH₂)₃Br.

related cabosil-supported catalyst **7** was prepared in a similar manner from surface-activated Cabosil and **2** followed by addition of the required Pd^{II} salt.

The catalyst **6** was fully characterized by a range of techniques. First, the structural integrity of the MCM-41 catalytic precursor **4** was established by MAS NMR and EXAFS spectroscopy. The presence of the tethered ferrocenyl catalysts was confirmed by comparison of the ¹³C MAS NMR spectrum of **4** with that of the unattached precursor **2**. Apart from the additional signals arising from the propyl tethering unit, the spectra were essentially the same. Examination of the ³¹P MAS NMR spectra of **2** and **4** showed identical chemical shift values. Significant changes in the aliphatic region of the ¹³C MAS NMR and in the ³¹P MAS NMR spectra were noted on incorporation of the Pd^{II} ion to yield the active catalyst **6**. Two ³¹P resonances at $\delta = 15.9$ and 34.4 were recorded, which clearly indicates two different phosphorous environments, these have been assigned as one being *trans* to a nitrogen atom and the other being *trans* to a chloride ion.^[272] The change in the aliphatic region of the ¹³C MAS NMR spectrum corresponds to changes in the methyl resonances of the amines, further corroborating the assignment of the ³¹P spectrum. This entire arrangement was borne out by a detailed EXAFS analysis of **6**. The coordination environment of the cationic species within the mesopore is depicted in Figure 52.

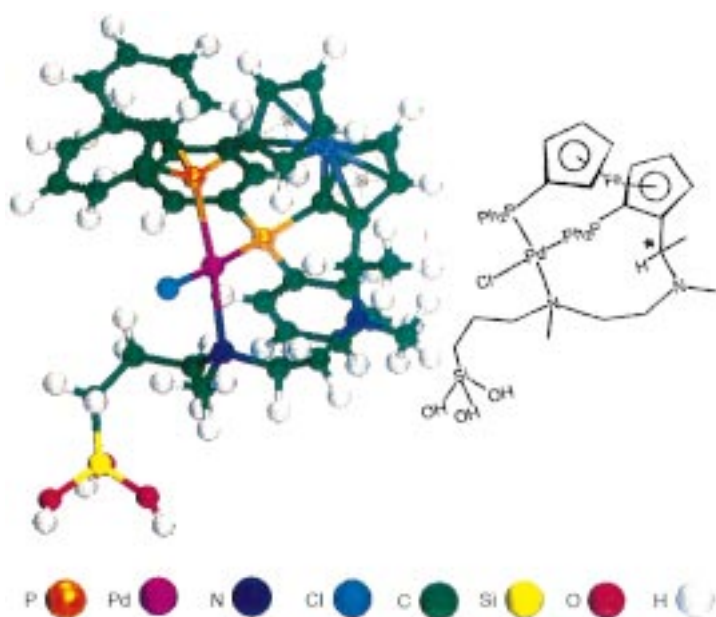


Figure 52. The structure of the organometallic “dppf”-Pd^{II} entity (labeled A in Figure 53) used for the allylic amination of cinnamyl acetate described in the text.

To test our catalysts we used an allylic amination (Tsuji–Trost) reaction between cinnamyl acetate and benzylamine. This reaction has two possible products: a straight-chained product (which is favored as a result of the retention of the delocalized π system) and a chiral-branched product (Figure 53). The aim of the reaction is to produce the greatest possible yield of the branched product with the highest possible enantiomeric excess (*ee*). Three catalysts were

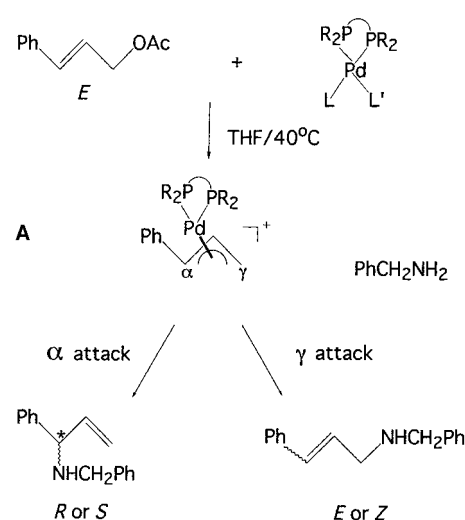


Figure 53. The allylic amination of cinnamyl acetate with benzylamine in the presence of a Pd^{II} complex as a catalyst. See also Table 7.

examined: the homogeneous **3** (see Figure 51), the Cabosil-supported one **7**, and that attached within the mesoporous material **6**. Preliminary results of the studies are listed in Table 7. With the homogeneous catalyst **3** the reaction is directed solely towards the straight-chain product whereas

Table 7. Catalytic performance of entities **3**, **6**, and **7**—see ref. [270], and Figures 51 and 53—in the allylic amination of cinnamyl acetate.

Catalyst ^[a]	Conversion [%] ^[b]	Straight chain product [%] ^[c]	Branched [%]	% <i>ee</i>
3 (<i>S</i>)	76	99 +	—	—
7 (<i>S</i>)	98	98	2	43
6 (<i>S</i>)	99 +	49	51	> 99
6 (<i>R</i>)	99 +	50	50	93

[a] Symbols in brackets denote the chirality of the directing group. [b] Conversion is stated relative to the use of benzylamine. [c] Regioselectivity and enantiomeric excess determined by chiral GC-MS.

catalyst **7** showed some of the desired regioselectivity by producing 2% of the branched product. However, the enantioselectivity of the reaction is relatively low being 43% *ee*. But the use of the mesopore-confined catalyst **6** promotes a dramatic change in the regioselectivity of the reaction, producing 51% of the branched product. The enantioselectivity of the confined catalyst (compare Figures 51, 52, and 54) is also greatly improved relative to the Cabosil-bound catalyst, with the *ee* value now approaching 100%. These results indicate that the control exercised by the MCM-41 on the activity of the palladium–ferrocenyl catalyst is considerable. The profound changes in the regio- and enantioselectivity are clearly apparent from the data listed in Table 7.

It requires little imagination to see that, in addition to Pd, a range of other platinum group metals (Ru, Rh, Os, Ir, Pt), placed strategically within appropriate chiral organic drapery on the inner walls of mesoporous silica (and other oxides), may be used to design a rich variety of other chirally constrained catalysts. Rhodium, platinum, and other ions,

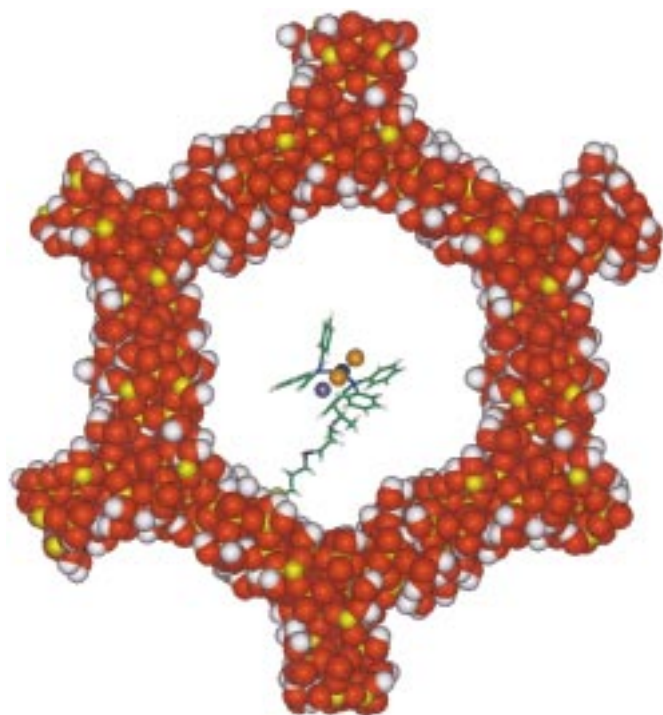


Figure 54. Scalar model of the “dppf”-Pd^{II} chiral catalyst that exhibits superior performance both in regard to regioselectivity and enantiomeric excess in the allylic amination of cinnamyl acetate. Color scheme as in Figure 55.

including those like gold outside the platinum group offer the possibility of enabling the strategy established above to be harnessed in such processes as aldol cyclizations and hydroformylations. There is also abundant scope, not only systematically to modify the ferrocenylphosphane ligand, but also to utilize quite distinctly different kinds of ligands such as those derived from semicorrine and bisoxazoline (as utilized so effectively in other contexts by Pfaltz et al.^[273] and Evans et al.,^[274] respectively).

7.7.3. Quantitative Comparisons of Heterogeneous and Homogeneous Catalysts

The fact that we may now routinely design (using the strategies described above) soluble homogeneous, catalytic single-site, entities that are strictly comparable to designed, single-site, insoluble heterogeneous catalysts, places us in a uniquely powerful position to compare the catalytic performance of the same engineered active site in the homogeneous (freely dispersed, unconstrained, and accessible) state with that of the heterogeneous, spatially constrained state. Figures 54 and 55 summarize in a visual fashion how this comparison is made in the case of the dppf-based catalyst used for the allylic amination process described in the preceding section.

The stage is set to enable many other strictly comparable homogeneous and heterogeneous catalysts to be investigated, the targets being: to assemble and to modify desired catalytically active sites, to explore the subtleties in their mode of

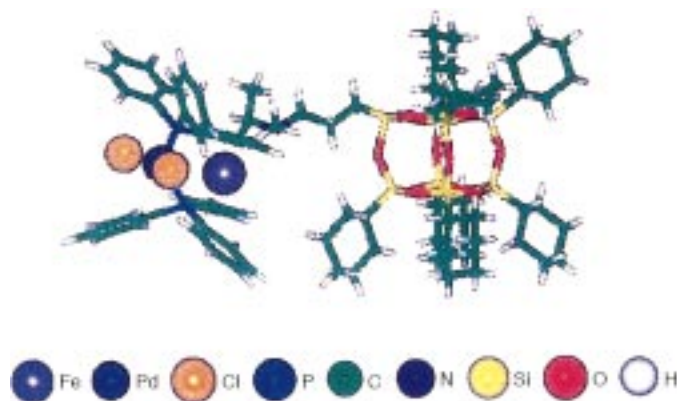


Figure 55. The soluble, unconstrained, cyclohexylsilsesquioxane analogue of the chiral “dppf”-Pd^{II} catalyst shown in Figure 54.

action, and to determine the precise atomic architecture of the sites under operating conditions.^[*]

7.8. Concluding Remarks: Biomimetic Catalysts and Beyond

Our aim, which in some measure has been achieved, is to make those attributes of catalysis that are important measurable, rather than be tempted to make those that are readily measurable important. The deliberate choice of microporous and mesoporous solids facilitates the successful design, synthesis, and detailed characterization of many new catalysts covering a wide range of important organic reactions. All the catalysts described here have the active sites located at, or tethered to, the inner surfaces of these large-area solids. There is abundant scope, however, to construct yet a further kind of catalyst also using porous solids. The diameter of the cages of the pores must be so designed as to facilitate the in situ assembly (and testing) of well-defined “homogeneous” organometallic catalysts locked (or rattling) inside the inorganic container. These are akin to the “tea bag”^[24] or “ship-in-bottle”^[169] catalysts described previously.

An important example of “ship-in-bottle” catalysts is the one consisting of dimeric copper oxyalts so constrained within an appropriate zeolitic cage as to alter significantly the electronic properties of bound dioxygen molecules. The bound oxygen molecule is known^[275] to be perpendicular to the Cu-Cu axis. It is also known^[276] from incarceration, in a judicious matter, of the dimeric copper compounds inside the “right” inorganic cage, that scission of the O-O bond is facilitated, thereby yielding catalysts that mimic enzymes such as tyrosinase, which converts L-tyrosine to L-DOPA. The challenges here are obvious: to achieve the best synthesis of the “ship-in-bottle” catalyst, and to monitor, by in situ techniques the precise changes in catalytic performance consequent upon incarceration. Computational work, incorporating density functional and molecular dynamics procedure of the kind described above, will have an increasingly im-

[*] Note added in proof (November 18, 1999): Our comparison of the catalytic performance of homogeneous engineered Ti^{IV}-centered active sites in [(*c*-C₅H₉)₇Si₇O₁₂TiOXPh₃], where X = Si, Ge, or Sn with their heterogeneous analogues (see ref. [220]) has now been published (ref. [231]).

portant interpretative and predictive role to play. In addition, there is a considerable range of possibilities emerging from the chiral confinement concept summarized in Figure 51.

The term inorganic enzyme has been used^[277] to describe the kind of catalyst that has been discussed here. This term seems justified, since our catalysts exhibit several of the cardinal features of enzymes: a well-defined catalytic site (or pocket), and the element of molecular selectivity (shape-, regio- or enantioselectivity). And just as the assembly and modification of active sites in mutant^[8, 9, 278] and maquette^[47] enzymes play key roles in protein engineering, so likewise does the fashioning and functioning of active sites in engineering their inorganic analogues. Time-resolved structural studies are indispensable techniques for both.

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How Do Charges Travel through DNA?—An Update on a Current Debate**

Mark W. Grinstaff*

The biological role of deoxyribonucleic acid (DNA) is to store and code genetic information. This unique biopolymer consists of a double helix with major and minor grooves. An aromatic π -stack core runs throughout the structure where the bases of the pyrimidine deoxynucleotides (thymidine, T; cytidine, C) and purine deoxynucleotides (adenosine, A; guanosine, G) participate in Watson–Crick base pairing (A:T; C:G). Although first posed in the 1960s,^[1, 2] the question of how charged species can be transported over short or long distance in DNA is still debated.^[3–8] An intense worldwide research effort is underway to explain the large variations in observed electron transfer rates (microsecond to picosecond) and to develop well-defined chemical systems for further study.

Radiation, carcinogens, and metabolic waste products can damage DNA, and, if left unrepaired by the normal cellular machinery, these damages can lead to mutations and carcinogenesis with grave health consequences.^[9–17] Further analysis reveals many of these damages to be a result of selective radical reactions with guanine bases, consistent with the relative ease with which guanine is oxidized compared to adenine, cytosine, and thymine.^[18–23] A study of electron transfer and radical-cation migration in DNA as well as identification of the factors that control the rates of these processes will provide valuable information for understanding DNA damage in vivo and insight into the mechanism of charge transfer through different media. A greater understanding of DNA-mediated electron transfer may have an additional clinical impact through the development of novel diagnostic tools for screening nucleic acids, proteins, or carcinogens.

Although significant advances in the study of charge transport in DNA have been reported within the last five years,^[7, 24–26] a number of issues remain unresolved. Current studies address multiple factors affecting this process such as oligonucleotide sequence, base pairing, π stacking, and duplex structure as well as the donor–acceptor distance, the labeling site, and the dynamics. In contrast to electron transfer

through proteins, where the factors controlling electron-transfer rates are more clearly recognized,^[27–30] our understanding of charge transport through DNA is limited owing to fewer experimental and theoretical studies. Yet many of the experimental techniques developed for investigating protein-mediated electron transfer and concepts understood with regard to this process can be used to study electron transfer in DNA. A three-pronged approach used to investigate charge transfer in DNA includes 1) labeling DNA with redox probes through intercalation and/or covalent linkages, 2) initiating charge transport by photochemical or electrochemical techniques, and 3) detecting the transfer events by spectroscopic, electrochemical, or biochemical methods. With these tools in hand, experiments are ongoing to further understand the dynamics of DNA-mediated electron transfer and the role of charge-transfer reactions in DNA damage and repair.^[31]

Diederichsen's 1997 highlight "Charge Transfer in DNA: A Controversy" describes the limitations and advantages of the first DNA electron-transfer experiments.^[3] Electron transfer data from these experiments are summarized in Table 1. Organic and inorganic intercalators were first reported for studying electron transfer in DNA.^[32–35] These experiments provide only limited information on electron transfer, given the lack of an accurate measurement of the distance between the donor and acceptor as well as concern for pairing of the donor–acceptor complexes.^[36–39] The next advance came with covalently linked donor and acceptor intercalators. Rapid electron transfer between two tethered ruthenium and rhodium intercalators ($[\text{Ru}(\text{phen})_2(\text{dppz})]^{2+}$ and $[\text{Rh}(\text{phen})-(\text{phi})_2]^{3+}$; phen = 1,10-phenanthroline, dppz = dipyrro[2,3- α :2',3'-c]phenazine, phi = 9,10-diimine phenanthrenequinone) separated by more than 40 Å in DNA is observed; the lower limit of this electron transfer rate is 10^9 s^{-1} . The effect of the medium on this electron transfer is small, since β , which represents the ability of the intervening medium to facilitate electron transfer, is 0.2 Å^{-1} .^[40] Investigations with the fluorophore stilbene incorporated in a DNA hairpin yield distance-dependent electron-transfer rates spanning from 10^8 to 10^{12} s^{-1} ($\beta = 0.64 \text{ Å}^{-1}$).^[41] Similarly, distance-dependent electron transfer is reported between an intercalated acridine and guanine at rates that range from 10^5 to 10^{10} s^{-1} ($\beta = 1.4 \text{ Å}^{-1}$).^[42] A relatively slow electron-transfer (10^6 s^{-1}) is measured between two ruthenium complexes that modify the ribose moiety of a DNA duplex.^[43] For additional information on these electron-transfer experiments, the reader is referred to

[*] Prof. M. W. Grinstaff
Department of Chemistry, Paul M. Gross Chemical Laboratory
Duke University, Durham, NC 27708 (USA)
Fax: (+1) 919-660-1605
E-mail: mwg@chem.duke.edu

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Table 1. The results of studies on DNA-mediated electron transfer.

Donor and acceptor	Covalently attached	d [Å] ^[a]	β	k_{ET} [s ⁻¹]	Research group	Year
tethered Ru ^{II} and Rh ^{III} intercalators	yes	> 40	0.2	10 ⁹	Barton ^[40]	1993
Ru ^{II} and Rh ^{III} intercalators	no	–	0.2	10 ¹⁰	Barton ^[35]	1996
tethered E and Rh ^{III} intercalators	yes	17–36	–	10 ¹⁰	Barton ^[52]	1997
A ₂ , A _e and G, Z	yes	3.4–10.2	0.1–1.0	10 ⁹ –10 ¹⁰	Barton ^[54]	1999
daunomycin and Au electrode	yes	10–35	–	10 ²	Barton/Hill ^[57]	1999
E intercalator and Z	yes	10–17	–	10 ¹²	Barton/Zewail ^[53]	1999
E and MV ²⁺	no	–	–	10 ⁵	Fromherz ^[32]	1986
E and MV ²⁺ , AO and DAP ²⁺	no	10–17	1.0	10 ⁸	Harriman ^[34, 51]	1992, 1999
stilbenedicarboxamide and guanine	yes	4–18	0.64	10 ⁸ –10 ¹²	Lewis ^[41]	1997
naphthalene and A	yes	–	–	10 ⁹	Lewis ^[56]	1999
Ru ^{II} and Ru ^{III} ribose complexes	yes	27	1.0–1.5	10 ⁶	Meade ^[43]	1995
intercalated acridine and guanine	yes	3–10	1.4	10 ⁵ –10 ¹⁰	Tanaka ^[42, 55]	1998

[a] d = distance between donor and acceptor.

the original articles cited as well as several commentaries^[5, 6, 8, 26, 44–47] and theoretical studies.^[48, 49]

A theoretical analysis^[50] of recently published DNA-mediated charge-transfer reactions provides both insight into the charge-transfer mechanisms (hopping versus superexchange)^[49, 50] and a template from which to discuss the reactions summarized below (Tables 1–4). A key point in

tailed steady-state and time-resolved fluorescence studies of ethidium quenching as a function of MV²⁺ concentration and reaction temperature yields a reorganization energy λ of 0.66 eV and β value of 1.0 Å⁻¹ ($k_{ET} = 10^6$ – 10^9 s⁻¹). The electron transfer rates also decrease dramatically with distance for both quenchers examined (MV²⁺ and *N,N'*-dimethyl-2,9-diazapyrenium (DAP²⁺)). The values of λ and β are similar to those previously determined for protein-mediated electron transfer and electron tunneling. This is the first determination of λ for a DNA-mediated electron-transfer reaction and emphasizes the need for additional studies of tethered intercalators and covalently linked donor–acceptor systems.

When a tethered and intercalated donor and acceptor are at each end of a DNA duplex, the rates and distance dependence of electron transfer are dramatically different. In this next study of DNA-mediated electron transfer, the ethidium donor transfers an electron to the [Rh(phi)₂(bpy)]³⁺ (bpy = 2,2'-bipyridyl) acceptor upon photoexcitation (Table 4, entry 1; $k_{ET} = 10^{10}$ s⁻¹).^[52] Systematic variations of the ethidium–Rh^{III} distance from 17 to 36 Å do not substantially alter the quenching of the ethidium fluorescence; however, changes in the sequence do. For example, introduction of a cytosine–adenine mismatch in the modified duplex dramatically reduces the ability of the Rh^{III} center to quench the ethidium fluorescence. These results stress the importance of a well-defined duplex structure for facile electron transfer.

A recent report describes the femtosecond electron transfer between an intercalated and tethered acceptor and a nucleobase donor.^[53] The acceptor, ethidium, is at the 5'-end of a DNA duplex, while the electron donor, deazaguanine (Z), is at various oligonucleotide positions 10 to 17 Å from the ethidium (Table 3, entry 2). In this investigation, transient absorption and fluorescence upconversion experiments were used to directly measure ultrafast electron transfer in DNA. Quenching of the photoexcited intercalated ethidium by Z occurs within about 5 ps. This fast electron transfer is the first step to the DNA bridge in a hopping mechanism. A second slower component is also present and attributed to movement of the intercalated ethidium in DNA. This molecular motion reflects the need for the ethidium to preorganize in order to participate in the electron transfer

Table 2. Results of studies on DNA radical-cation migration.

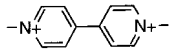
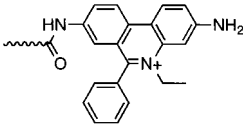
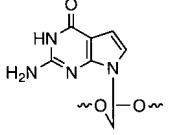
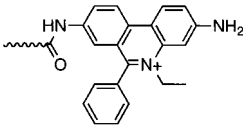
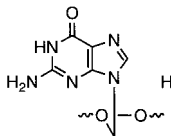
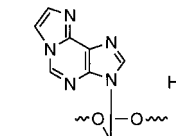
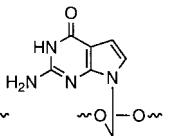
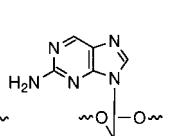
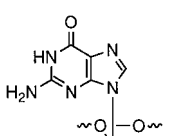
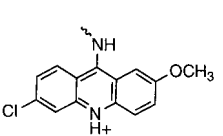
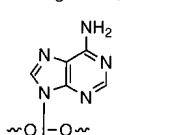
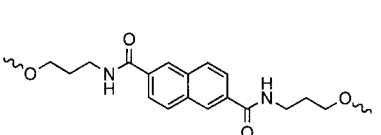
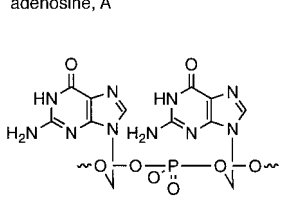
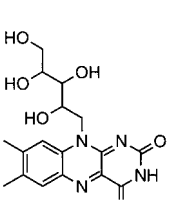
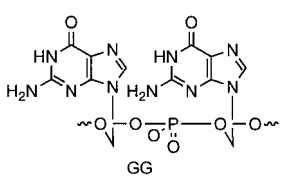
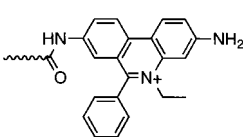
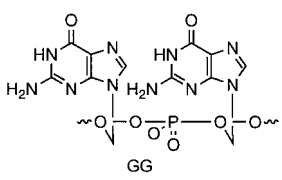
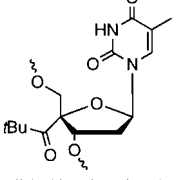
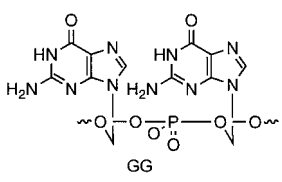
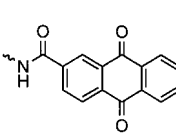
Donor and acceptor	d [Å] ^[a]	Research group
Rh and Ru tethered intercalators and GG	10–200	Barton ^[65–68]
E and GG	17, 44	Barton ^[69]
acylated A or G and GGG	7–54	Giese ^[59, 71, 72]
riboflavin and GG, GGG	–	Saito ^[64]
tethered anthraquinone and GG	10–200	Schuster ^[60, 61, 73, 74]

[a] d = distance between donor and acceptor.

the article concerns charge-transfer donors and acceptors possessing different energetics and thus participating in different mechanisms.^[50] The relative energetics of the donor and acceptor with respect to the DNA bridge determine if 1) a one-step superexchange mechanism occurs (characterized by an exponential decay of the charge-transfer rate with distance) or 2) a hopping mechanism occurs (characterized by a weak dependence of the charge-transfer rate on distance). Superexchange occurs when a positive energy gap exists between the lowest electronic state of the excited donor (D*) and the vibronic manifold of the DNA bridge. The hole hopping mechanism, however, occurs when the lowest vibronic state of electronic origin of D* is in resonance with the highly degenerate DNA vibronic manifold. The rate of hopping is controlled by the energetics of the ion-pair states in the DNA manifold.

Measurements of electron transfer in DNA between discrete donors and acceptors are described first in this highlight, followed by a discussion of photoinduced guanine oxidation and radical-cation transport. The first case study focuses on the DNA-mediated electron transfer between intercalated ethidium (E) and methyl viologen (MV²⁺; Table 3, entry 1), electrostatically bound to the DNA.^[51] In this system MV²⁺ quenches the photoexcited ethidium. De-

Table 3. Recently studied organic donors and acceptors.

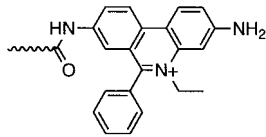
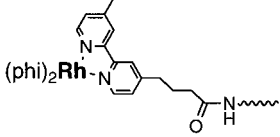
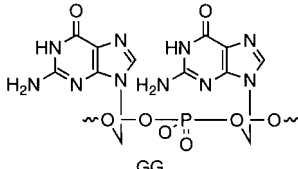
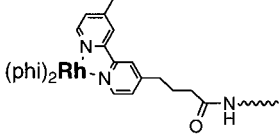
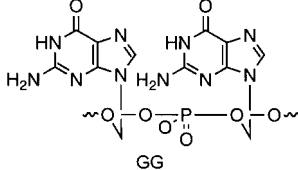
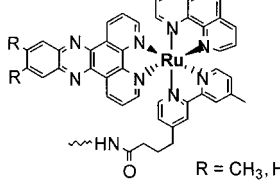
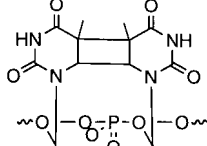
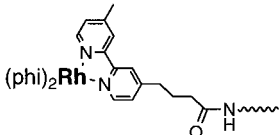
Entry	Donor	Acceptor	Ref.
1	 methyl viologen, MV ²⁺	 ethidium, E	[34, 51]
2	 deazaguanine, Z	 ethidium, E	[53]
3	 guanine, G	 1,N6-ethenoadenine, A _ε	[54]
	 deazaguanine, Z	 2-aminopurine, A ₂	
4	 guanine, G	 acridine	[42, 55]
5	 adenosine, A	 naphthalenedicarboxamide	[56]
6	 GG	 riboflavin	[64]
7	 GG	 ethidium, E	[69]
8	 GG	 4'-tert-butyl-acylated thymidine	[71, 72]
9	 GG	 anthraquinone, AQ	[73, 74]

reaction. The electron-transfer rate does not vary significantly with distance; only the yield of quenched ethidium varies. The implications of these results are significant since DNA base dynamics may control the electron-transfer, suggesting that β may not be the best parameter to describe DNA-mediated electron transfer.

The results described above are strikingly different between the tethered and nontethered ethidium electron-transfer systems. In the first system described (intercalated ethidium and surface-bound MV²⁺; Table 3, entry 1) the electron-transfer rate shows a significant distance dependence over short distances (3–17 Å). Yet fast electron-transfer occurs over longer distances between the covalently tethered ethidium and rhodium(III) complex (Table 4, entry 1). The electron-transfer rates are relatively insensitive to distance (17–36 Å) but sensitive to oligonucleotide sequence. Is this discrepancy a result of different electron-transfer dynamics, the locations of donor and acceptor, or oligonucleotide sequences/structures? Future experiments are needed to explain this apparent discrepancy, and to assess which factors control the electron-transfer rate.

Measurements between fluorescent analogues of adenine (2-aminopurine (A₂) and 1,N6-ethenoadenine (A_ε)) and guanine (G) and deazaguanine (Z; Table 3, entry 3) further explore the effect of oligonucleotide structure on the electron-transfer rate.^[54] In this system, one oligonucleotide strand of the duplex contains both the donor (G or Z) and acceptor (A₂ or A_ε), which are separated by 3.4, 6.8, and 10.2 Å. Steady-state emission and time-correlated single-photon counting experiments show that quenching of G by A_ε occurs on the time scale of 10⁹ s⁻¹ (β = 1.0 Å⁻¹). In contrast, quenching of G by A₂ occurs even faster (>10¹⁰ s⁻¹) and β is closer to 0.1 Å⁻¹. Even though the energetics of both these electron-transfer reactions are similar, the electron-transfer rates and β values are different. Structural studies on oligonucleotides containing A₂ and A_ε show that A₂ participates in normal Watson–Crick base pairing, while the bulky A_ε adopts a poorly stacked conformation. These data reveal that structural changes in the base stack influence electron-transfer rates.

Table 4. Recently studied inorganic donors and acceptors.

Entry	Donor	Acceptor	Ref.
1	 ethidium, E	 $[\text{Rh}(\text{phi})_2(\text{bpy})]^{3+}$	[52]
2	 GG	 $[\text{Rh}(\text{phi})_2(\text{bpy})]^{3+}$	[65–68]
3	 GG	 $[\text{Ru}(\text{bpy})(\text{phen})(\text{dppz})]^{3+}$ R = CH ₃ , H	[65–68]
4	 thymine dimer	 $[\text{Rh}(\text{phi})_2(\text{bpy})]^{3+}$	[31]

A recent report describes the distance-dependent electron transfer between a photoexcited acridine and guanine (Table 3, entry 4).^[55] In this study, a derivatized 2-methoxyacridine substitutes a nucleobase position in an oligonucleotide. Quenching of the acridine excited state occurs by an adjacent guanine. Rate constants for the forward electron transfer vary from 10^5 to 10^{10} s^{-1} as the distance increases from 3 to 10 Å. The β value of 1.47 Å^{-1} is in agreement with an earlier value reported from static fluorescence measurements.^[42] There is no directional anisotropy for DNA-mediated electron transfer, since the electron transfer rates are similar in both the 5' and 3' directions. These data are also consistent with a superexchange mechanism occurring between acridine and guanine.

Similar to earlier work reported on stilbenedicarboxamide hairpins,^[41] where superexchange is likely the electron transfer mechanism, an incorporated naphthalene can be used to probe DNA-mediated electron transfer in several novel DNA-hairpin structures.^[56] The naphthalene serves as a bridgehead unit in these hairpins, which are synthesized with an automated DNA synthesizer. Quenching of the naphthalene-excited state in the hairpin by an adjacent adenosine (A) occurs swiftly with a rate constant of 10^9 s^{-1} (Table 3, entry 5).

To characterize ground-state electron transfer in DNA, as opposed to photoinitiated electron transfer, a recent report

describes electron transfer in well-defined DNA duplex assemblies bound to gold electrodes.^[57] The DNA duplexes modified at a specific guanine base with daunomycin are used to probe this ground-state electron-transfer reaction between the redox-active quinone of daunomycin to the gold electrode. The relatively slow electron-transfer rate (10^2 s^{-1}) estimated from the electrochemical data is insensitive to the distance between the redox partners. However, the electron-transfer rate is sensitive to an intervening single base mismatch, which “shuts off” the electron transfer to the gold electrode. The sensitivity of the reaction to base stacking but not to distance suggests that the rate-determining step is not electron transfer through the π stack, but instead electron tunneling through the σ linker to the gold electrode.

A new experimental approach to measure the electrical conducting properties of DNA uses a low-energy electron point source (LEEPS) microscope.^[58] Under ultrahigh vacuum conditions, the electrical current of the DNA fibers are directly measured as a function of applied potential. Resistivity values calculated from these measurements are comparable to those of conducting polymers. Excitingly, these measurements are made over very large distances (600 nm or more); photoinduced experiments typically measure electron-transfer rates over distances of less than 5 nm. These results further support the hypothesis that charges can propagate over large distances in DNA.

The measured rates of electron transfer in DNA are remarkably different as summarized above and described in earlier reports (see Table 1). Do non-intercalator donors and acceptors access the DNA π stack? Does the linker from the donor or acceptor to DNA control the rate? Are the rate differences a consequence of different reaction mechanisms? To what degree do different local duplex microstructures (sequences) modulate electron-transfer rates? Is the strong distance dependence previously observed in some systems a consequence of duplex structure or energetics? Additional studies are needed to discern the effect of donor and acceptor site and DNA microstructures on electron-transfer rates. The ability of DNA to facilitate or inhibit long-range electron transfer is significant with regard to the mechanism of oxidative DNA damage.

Oxidative damage in DNA is of utmost importance, and a means to study this biologically relevant process may lead to a better understanding of DNA damage in vivo. Characterizing guanine oxidation in DNA is possible, since photoinduced triggers can initiate this charge-transfer reaction. In these experiments a hole-hopping (or phonon-assisted polaron) mechanism is proposed whereby the photoinduced radical cation (i.e., the hole) moves in a stepwise fashion from one low-energy site in DNA to another.^[4, 50, 59–63] This mechanism is consistent with the energies of the donor and acceptor being comparable to the energy levels of the intervening DNA bridge. Since the energy of the radical cation is lowest on G (compared to A, C, and T), the radical cation will localize on

G as it traverses the DNA from one G to another. This radical cation does not possess sufficient energy to reside on the other bases; therefore it must jump to the next G in one complete step (a coherent superexchange transfer). The intervening sequence and distance between the guanine bases affects the electron-transfer rate. In this scenario, a radical cation migrates over large distances in DNA. Recent *ab initio* calculations of ionization potentials of guanine in B-DNA duplexes reveal that sequences adjacent to guanine affect the ionization potential of guanine.^[64] Thus, some local regions of DNA are more likely than others to facilitate radical-cation migration.

Experimental conformation of long-range oxidative damage in DNA requires the use of site specifically labeled probes with well-defined photochemical reactivity. For example, both $\text{Rh}^{\text{III}}(*\text{Rh}^{\text{III}})$ and Ru^{III} metallointercalators oxidize guanine over extended distances of 60 base pairs (200 Å).^[65–68] After irradiation of the intercalated metal complex, gel electrophoresis identifies the oxidized guanine at a 5'-GG-3' site (Table 4, entries 2 and 3). The yield of oxidized guanine varies slightly with distance for both tethered metallointercalators. In addition, the efficiency of this guanine oxidation is sensitive to sequence. For example, sequences composed of 5'-TA-3' regions are particularly poor conduits compared to 5'-AA-3' regions. The ability of a DNA–protein assembly to alter the local microstructure of DNA also affects guanine oxidation by the $*\text{Rh}^{\text{III}}$ complex.^[69] Additionally, a tethered ethidium intercalator yields similar results, indicating that guanine oxidation is not particular to metallointercalators.^[70] The lack of an apparent strong dependence on distance in these oxidation reactions, combined with the observation that these charge-transfer reactions are dependent on sequence as well as sensitive to the integrity of the π stack, mirrors the results of previous electron-transfer reactions between metallointercalator complexes.

Photoinitiated radical-cation migration in DNA with subsequent guanine oxidation can also occur using an incorporated 4'-*tert*-butyl-acylated thymidine (Table 3, entry 8) or guanine.^[4, 59, 71, 72] A Norrish type I cleavage occurs upon photolysis, generating a radical cation on the ribose of a DNA duplex. This radical cation then migrates to the guanine on the complimentary strands, where DNA strand scission occurs as a result of G^{++} formation. The radical cation is transported over both short (7–17 Å) and long distances (54 Å), and the efficiency of charge transfer over 54 Å is similar to that over 10 Å. The relative intensity ratios of the cleaved sequences (GGG/ G^{++}) yield the relative rate constant data. The calculated value for β is 0.7 Å^{-1} for this biologically relevant charge-transfer reaction. The intervening sequence between the radical cation and the GGG units influences this process substantially, and a simple change from 5'-AT-3' to 5'-GC-3' increases the cleavage yield by two orders of magnitude. These results confirm that long-range radical-cation transport can occur by a multistep hopping process.^[71]

A recent report describes the influence of nucleotides adjacent to guanine to modulate its reactivity towards oxidative damage.^[64] In this study of photoinduced one-electron guanine oxidation, a nontethered riboflavin accepts an electron from duplexes containing the 5'-XGY-3' sequence

(X, Y = A, C, G, and T; see, for example, Table 3, entry 6). The efficiency of GG cleavage occurs in the following order: GGG > CGG > AGG = TGG > TGT, with pyrimidine-G-pyrimidine being the least reactive. Calculations on the same sequences support this experimental result since the ionization potentials are lower (highest oxidative reactivity) for purine-G-purine sequences than for pyrimidine-G-pyrimidine sequences.

Long-distance (200 Å) radical-cation transport also occurs in an AQ-linked DNA duplex (AQ = anthraquinone; Table 3, entry 9) containing four separate GG blocks.^[73] Irradiation of the tethered anthraquinone leads to electron transfer and formation of the anthraquinone radical anion and guanine radical cation.^[20, 73, 74] Photoinduced radical-cation cleavage of DNA occurs at GG steps adjacent to and remote from the tethered AQ. The distance dependence for guanine oxidation between AQ and the GG steps is minimal. A linear relationship between the log of the GG-cleavage efficiency and the distance between the AQ and the radical cation indicates that the intervening sequence does not significantly influence radical-cation migration.

Radical-cation migration to guanine occurs over long distances with intercalator, 5'-terminal phosphate, and 4'-ribose probes. Yet the efficiency of oxidized guanine is not the same in all cases. Additional experiments need to account for these differences and identify the factors that govern this reaction. Moreover, the data are seemingly contradictory on the effect of sequence on the charge-transfer rate. Future studies must address this issue and quantify the effects of different sequences and mismatches on radical-cation transport. The biological implications of this long-range charge transfer are significant with regard to the extent that a radical cation can propagate in DNA and induce oxidative damage.

The current electron transfer and radical-cation migration systems differ in a number of ways: the specific donors and acceptors, the driving force (ΔG^0) of the electron-transfer reaction, the energetics of donor and acceptor relative to the DNA bridge, the distances between the donor and acceptor, the manner in which the donor and acceptor are covalently linked to (or intercalated in) the oligonucleotide duplex, the sequences, and the local duplex microstructures. Many of these critical issues are highlighted throughout the text; however, additional key points remain at large or unanswered. First, the number of new spectroscopic or electrochemical probes reported in the literature is small. The current repertoire of probes available for study must be expanded to include those that can further explore the dynamics and energetics of charge transfer in DNA.^[75–77] Second, the need for NMR studies of solutions or X-ray crystal structures of oligonucleotide duplexes labeled with the donor and acceptor is strikingly evident. Recent NMR solution structure studies on an intercalated Rh–oligonucleotide model system provide the first structural information.^[78] Third, the dependence of ΔG^0 on the DNA-mediated charge transfer is unknown. Fourth, the electronic coupling and reorganization energy for tethered intercalators and covalently bound donors and acceptors remains elusive. As was done previously for protein-mediated electron transfer,^[28]

these data can be experimentally determined by measuring the rate of charge transfer between the donors and acceptors as a function of driving force and temperature, when the thermodynamic data (ΔG^0 , ΔS^0 , and ΔH^0) for the charge-transfer reaction are known. Fifth, understanding the dynamics of charge transfer is critical, and additional femtosecond experiments on site specifically labeled DNA are needed to explore the first event(s) in DNA-mediated charge transfer. Finally, the number of theoretical studies reported is limited. New DNA-mediated charge-transfer systems need to be proposed and experimentally tested.

This highlight is intended to briefly summarize new results, stimulate critical discussions, and pique scientific interest. Moreover, it is an invitation to the general scientific community to examine this exciting area of DNA-mediated charge transfer.

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Tyrosyl-tRNA Synthetase: A Housekeeping Protein and an Attractive Harbinger of Cellular Death

Hermann Schluesener*

Apoptosis, or programmed cell death, is a physiological process that occurs during tissue reorganization in embryonic development and pathological conditions. During execution of this cellular suicide program, nucleases fragment chromosomal DNA and activated proteases dismantle the cell by cleaving multiple substrates, including cytoskeletal proteins and enzymes that are essential for normal cellular function and cell repair.

Cells undergoing apoptosis are usually swiftly ingested by macrophages and this phagocytic clearance of intact apoptotic cells is a safe disposal route since local inflammatory reactions that result from a massive release of cellular debris are avoided. Furthermore, the ingestion of apoptotic cells by phagocytes may actively down-regulate local inflammatory and immune responses.^[1]

Surprisingly, two novel signaling molecules of the apoptotic cascade have been described recently by Wakasuki and Schimmel.^[2] These cytokines are fragments of tyrosyl-tRNA synthetase, an unsuspicious enzyme that is essential in protein synthesis (and consequently belongs to the housekeeping proteins). Cellular protein synthesis relies on a supramolecular organization of the mammalian translation system.^[3] This protein-synthesizing machinery is a complex, but highly organized apparatus and the macromolecular components are not freely diffusible in mammalian cells. In particular, aminoacyl-tRNA appears to be channeled within the cell, that is, directly transferred from the aminoacyl-tRNA synthetases to the elongation factor, and then to the ribosomes, without dissociation into the cellular fluid.^[4]

Functionally, human tyrosyl-tRNA synthetase is composed of a catalytic terminal amino domain and a terminal carboxy sequence. Approximately 50% of the terminal carboxy sequence is identical to the terminal carboxy region of the p43 protein, an auxiliary RNA binding factor of the mammalian multi-synthetase complex.^[5]

During apoptosis, the translational apparatus is systematically destroyed. Interestingly, tyrosyl-tRNA synthetase is secreted from cells undergoing apoptosis. After cleavage by elastase or related proteases, two fragments with surprisingly novel bioactivities are generated (Figure 1). Both fragments

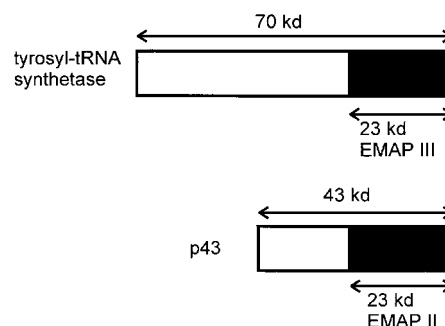


Figure 1. Tyrosyl-tRNA synthetase and the auxiliary p43 protein are cleaved by elastase or related proteases (such as caspases or multicatalytic protease) into two fragments. The terminal carboxy fragments EMAP II and III are homologous modulators of leukocyte migration and activation.

appear to act as local signaling molecules (cytokines) that orchestrate the tissue response and culminate in the safe removal of apoptotic cells.

Tyrosyl-tRNA Synthetase: Surprising Bioactivities of Cleavage Products

Full-length tyrosyl-tRNA synthetase has no effect on leukocytes, but both fragments are potent leukocytic activators with different spectra of bioactivities.^[2] The catalytic aminoterminal domain contains an Glu-Ag-Leu (ERL) sequence motif, which is characteristic of certain chemokines, a family of chemoattractant cytokines. It has been shown that the aminoterminal peptide of tyrosyl-tRNA synthetase binds to the interleukin-8 (IL-8) receptor type A (also known as CXCR1). Subsequent bioassays showed that this peptide has IL-8 activity, predominantly by activating and inducing migration of neutrophilic granulocytes.^[2]

[*] Prof. Dr. H. Schluesener
Institut für Hirnforschung der Universität
Calwer Strasse 3, D-72076 Tübingen (Germany)
Fax: (+49) 7071-29-5456
E-mail: hirnforschung@uni-tuebingen.de

The carboxyterminal sequence is homologous to the carboxyterminal region of the protein p43. This fragment of p43 is likewise liberated during apoptosis and has cytokine-like properties. The cytokine is termed endothelial-monocyte-activating polypeptide II (EMAP II).^[6] EMAP II and the terminal carboxy fragment of tyrosyl-tRNA synthetase, consequently designated EMAP III, have similar effects on leukocytes, but the receptors are not known and a comparative analysis of these two cytokines have not so far been performed.^[7]

EMAP II and III activate resting monocytes by elevating the free Ca^{2+} concentration in the cytosol, thereby stimulating chemotaxis.^[6] In contrast to the terminal amino fragments, the EMAPs stimulate the production of tumor necrosis factor α (TNF- α) and tissue factor (thromboplastin) by macrophages and release of myeloperoxidase from neutrophilic granulocytes. Furthermore, EMAP II activates endothelial cells by elevation of the concentration of free calcium in the cytosol, release of von Willebrand factor, induction of tissue factor, and expression of the adhesion molecules E-selectin and P-selectin. EMAP II induces endothelial cell apoptosis, which results in the hemorrhage of blood vessels of certain experimental tumors, such as fibrosarcoma, melanoma, and adenocarcinoma, thereby inducing tumor regression. It is so far unknown, whether the terminal carboxy fragment of EMAP III has similar effects on endothelial cells.

Tyrosyl-tRNA Synthetase: A Novel Regulator of Tissue Homeostasis?

EMAP II is produced in tumors, neuroautoimmune and other inflammatory lesions, and during tissue reorganization in embryology.^[8] In all of these conditions a disturbance in tissue homeostasis is associated with apoptosis and expression of EMAPs. Thus, a global regulatory mechanism is emerging, which links the degradation of the cellular translational machinery with homeostasis of the entire surrounding tissue elements. The process is summarized in Figure 2: tyrosyl-tRNA synthetase can be secreted by cells undergoing apoptosis and the secretion of an essential component of the translational apparatus might accelerate the cellular suicide program. Outside of the cell, the synthetase is split into two distinct signaling molecules. These cytokines are chemoattractants, which recruit neutrophilic granulocytes and phagocytes into the lesions. Furthermore, these activated leukocytes secrete proteases, which induces further generation of cytokines from tyrosyl-tRNA synthetase and invasion by leukocytes. Finally, this recursive cycle leads to removal of the apoptotic cells.

Outlook

The characterization of the exceptional organization of human tyrosyl-tRNA synthetase opens a variety of possibilities for further research. In addition to many basic aspects of phylogenetic development and function of these modules in other organisms, applied pharmacological research appears to be rewarding. Most prominently, the two cytokines with profound function on neutrophils and monocytes might be

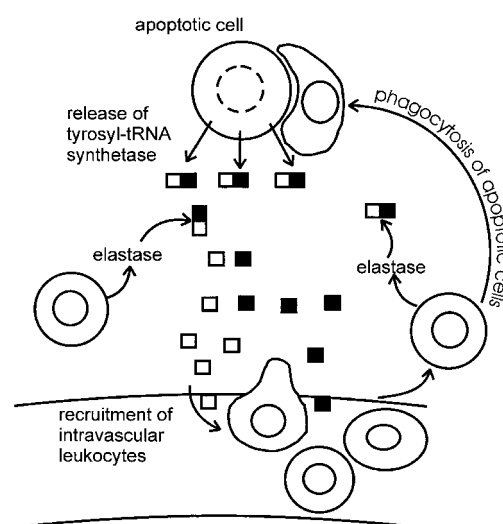


Figure 2. Tyrosyl-tRNA synthetase is secreted by apoptotic cells and split by elastase into two chemoattractant fragments, which recruit leukocytes from the vascular lumen into the tissue. The migrating leukocytes release further elastase, thus amplifying the proteolytic cleavage of tyrosyl-tRNA synthetase and the generation of chemoattractants. Finally, this self-amplifying, recursive cycle is terminated by safe removal of the apoptotic cells by invading macrophages.

used as immunomodulators. In comparison to EMAP II, the terminal carboxy fragment of tyrosyl-tRNA synthetase might have effects on endothelial cells. EMAP II expression has been repeatedly linked with tumors: Mouse EMAP II has been cloned from fibrosarcoma and human EMAP II from histiocytoma cells. EMAP II appears to be identical to other previously described mediators of tumor cells, such as the cytokine J82 derived from bladder carcinoma (BCDC), or FO-1 and HS-1 produced by melanomas.^[9] Thus, the terminal carboxy fragments of tyrosyl-tRNA synthetase and EMAP II have potential as anti-angiogenesis agents in tumor therapy, whereby they inhibit pathological tumor endothelial cell function and thereby promote thrombohemorrhage of tumor blood vessels associated with tumor regression. As a mediator associated with tumor angiogenesis, these peptides are highly interesting candidates of antiangiogenic drug development and might complement current strategies to abrogate tumor growth and metastasis by interfering with pathological endothelial cell function in neoangiogenesis.^[10]

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Dynamics of Ligands and Water Molecules in Trinuclear Carboxylate Complexes

Heinz Dieter Lutz*

Trinuclear transition metal complexes of the general formula $[M_3O(L)_6(L_t)_3]$ (M = transition metal, L = bidentate bridging ligand, L_t = terminal ligand) with central oxygen atoms have proven to be important model compounds for studying basic chemical and physical phenomena.^[1] In order to study the dynamics of ligands and water molecules in such trinuclear carboxylate complexes, Stride et al.^[2] performed incoherent inelastic neutron scattering (IINS) experiments on the chromium acetate complex $[Cr_3O(CH_3CO_2)_6(H_2O)_3]Cl \cdot 5H_2O$ (CRAC, CRACHH) as well as on partially deuterated ($[Cr_3O(CH_3CO_2)_6(D_2O)_3]Cl \cdot 5D_2O$ (CRACHD), $[Cr_3O(CD_3CO_2)_6(H_2O)_3]Cl \cdot 5H_2O$ (CRACDH)) and isotopically diluted species (about 5% H; $[Cr_3O(CD_3CO_2)_6(D_2O)_3]Cl \cdot 5D_2O$ (CRACDD)). Because of the large scattering cross-section of hydrogen atoms the observed IINS signals were assigned to vibrations of the acetate methyl groups and especially to the vibrations of the ligands and hydrate H_2O molecules, that is, the bending mode ($\delta(HOH)$), the rocking ($\rho(H_2O)$ or $r(H_2O)$), wagging ($\omega(H_2O)$ or $\gamma(H_2O)$), and twisting libration ($\tau(H_2O)$ or $t(H_2O)$) as well as the $Cr-OH_2$ translational mode ($\nu(CrOH_2)$).^[3]

In the case of HDO molecules, which are present in partially deuterated and isotopically diluted species (in addition to H_2O and D_2O molecules), intramolecular coupling of the OH and OD stretching vibrations as in the case of H_2O and D_2O is no longer possible. This is claimed correctly by Stride et al.^[2] The frequency of the observed OH stretching vibration of HDO then resembles the mean value of the

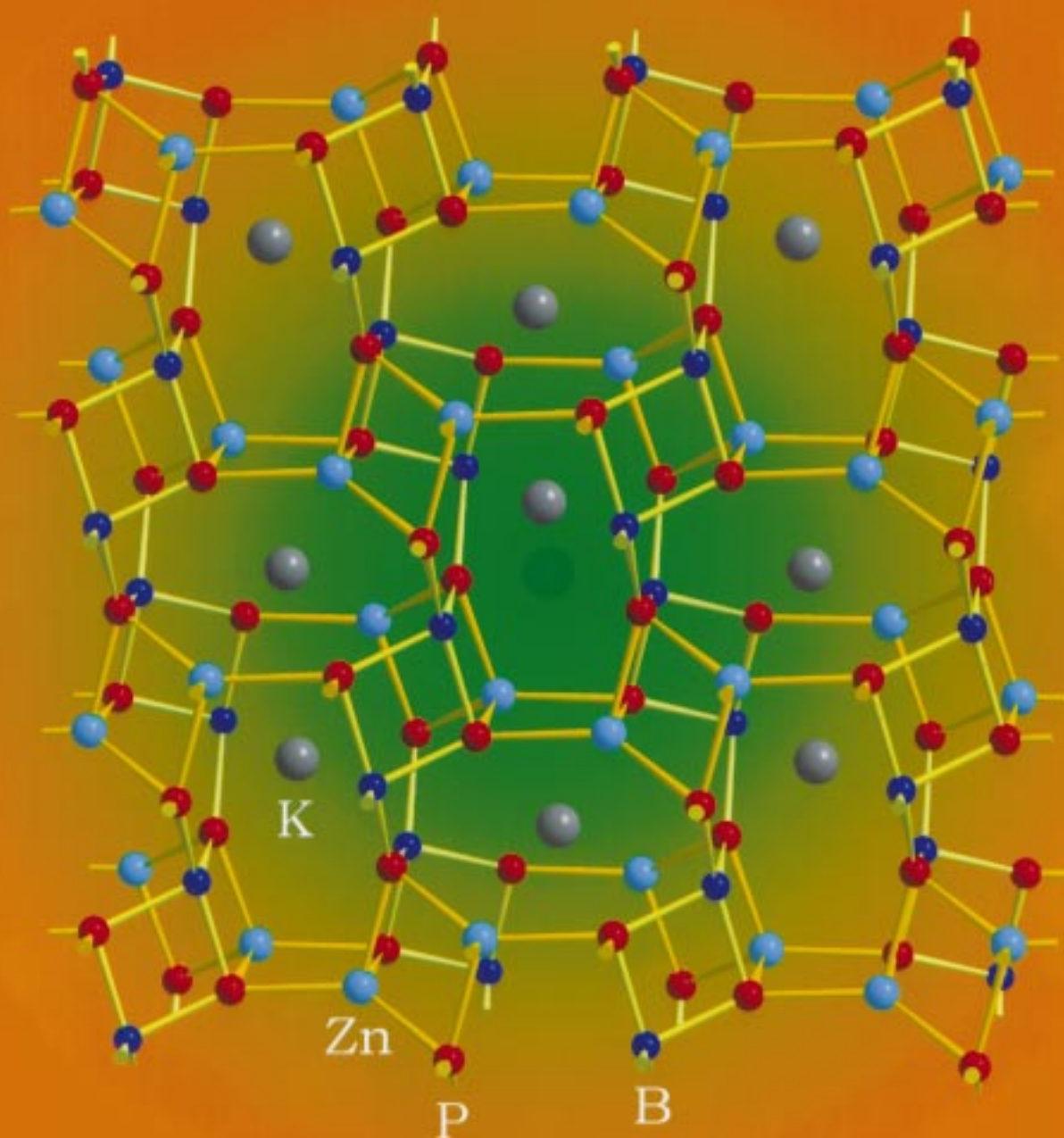
frequencies of the symmetric (ν_{sym}) and the antisymmetric OH stretching mode (ν_{asym}) of the H_2O molecule. Analogous considerations can be made for out-of-plane librations ($\gamma(H_2O)$ and $t(H_2O)$),^[4, 5] as was likewise undertaken by Stride et al.^[2] In the case of the in-plane vibrations ($\delta(HOH)$ and $r(H_2O)$), however, this is not possible. Since $\delta(HOH)$ is an internal mode, predominantly covalent bonds within the H_2O , HDO, and D_2O molecules are strained. The rocking vibration ($r(H_2O)$), however, is an external vibration, and the molecules vibrate more or less as rigid units. The rocking vibration is primarily controlled by lattice forces. The assumption discussed by Stride et al.—namely, that the frequency of the in-plane OH and the OD bending vibrations of HDO molecules resembles the mean value of the frequencies of $\delta(HOH)$ and $r(H_2O)$ or $\delta(DOD)$ and $r(D_2O)$ ^[2]—is completely unfounded. Therefore, the bending mode of HDO molecules ($\delta(HDO)$) in solid hydrates and aqua complexes is observed in the range from 1400 to 1460 cm^{-1} ,^[5] and not at about 970 cm^{-1} as assumed by the authors. At least in this respect, the paper by Stride et al.^[2] has to be corrected.

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[*] Prof. Dr. H. D. Lutz
Anorganische Chemie I
Universität-Gesamthochschule Siegen
D-57068 Siegen (Germany)
Fax: (+49) 271-740-2555
E-mail: lutz@chemie.uni-siegen.de

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Metalloborophosphates provide access to new systems with microporous structures. The tetrahedral framework structures of zincoborophosphates display a close relationship to topologies of the anionic partial structures in feldspars and gismondine. Find out more on the following pages.

K[ZnBP₂O₈] and A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺): Zincoborophosphates as a New Class of Compounds with Tetrahedral Framework Structures**

Rüdiger Kniep,* Gerd Schäfer, Holger Engelhardt, and Insan Boy

Materials based on aluminosilicate cage structures (e. g. the zeolite family) have been studied for some time from various standpoints in view of their potential applications as catalysts, molecular sieves, and ion exchangers.^[1] In the last few years the interest in microporous and zeolite-analogous systems has focused primarily on aluminum phosphates^[2] and substituted variants^[3] as well as on zinc-,^[4] beryll-,^[5] gallium/gallo-,^[6] and zincogallophosphates.^[7] A microporous zincoborate^[8] is also known. In contrast, borophosphates have only recently been studied systematically.^[9] This is remarkable, since the effect of the substitution of aluminum and/or silicon by boron in zeolitic molecular sieves, such as in the boron/MFI-zeolite, has long been known in technical processes.^[10]

Our studies aimed at the systematic development of the structural chemistry of the borophosphates^[11] have led to a broad spectrum of new compounds with quite different anionic partial structures, such as oligomeric units,^[12] chains,^[9, 13] ribbons,^[14] layers,^[15] and three-dimensional frameworks.^[16] In water-containing borophosphates with chain structures and molar B:P ratios of >1, boron is both tetrahedrally and trigonal-planar coordinated by oxygen.^[11, 13] With the synthesis of K[ZnBP₂O₈] and A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺)^[17] we have now succeeded in extending the chemical diversity of compounds with tetrahedral framework structures. The zincoborophosphates presented here contain tetrahedral nets, whose topologies display a close relationship to tecto-aluminosilicates (feldspar family and gismondine).

The characteristic basic units in the crystal structures of K[ZnBP₂O₈] and A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺)^[18] are based on four-rings, which contain corner-sharing borate, phosphate, and zincate tetrahedra. These occur in three ordered variants (Figure 1, right): four-rings from two borate and two phosphate tetrahedra, from two phosphate and two zincate tetrahedra, or from one borate, one zincate, and two phosphate tetrahedra; a linkage of borate and zincate tetrahedra is avoided. All four-ring systems display, with

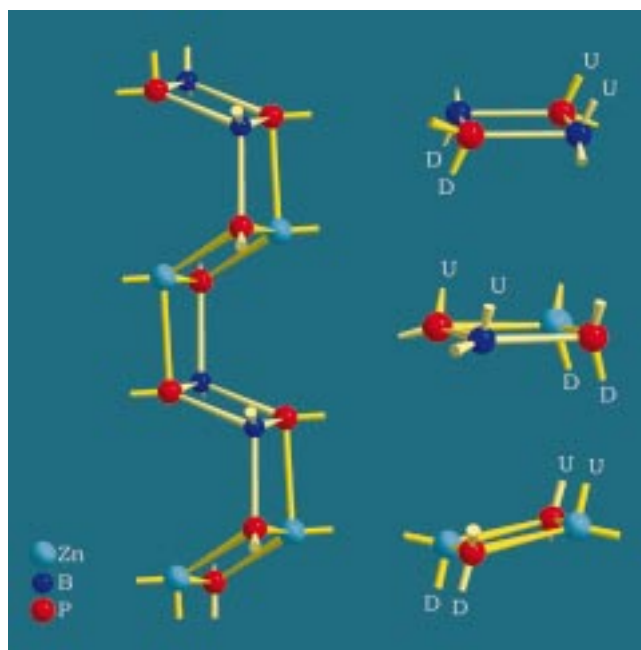


Figure 1. Topology, conformation, and linkage of tetrahedral four-ring centers in zincoborophosphates. Right: Four-rings in the crystal structures of K[ZnBP₂O₈] and A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺). Left: Crankshaft-like four-ring ribbons that occur in both crystal structures. See text for further details.

respect to the alignment of the vertices, the conformation UDD (up-up-down-down). Four-ring building blocks of this general type are denoted as secondary building units (SBU) and form the basis of the structural chemistry of a large group of tecto-aluminosilicates, among which are the feldspars.^[19] Bond lengths and angles of the BO₄, PO₄, and ZnO₄ groups in the title compounds are similar to known values in zincophosphates^[4] and borophosphates.^[20]

The linkage of the four-ring systems with each other leads in an initial formal step to 4.8² nets,^[21] from which the topology of the networks can be derived. The complex framework in the crystal structures of the isotypic compounds A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺) contains a conformation pattern of the 4.8² nets, which is also present in gismondine (Ca[Al₂Si₂O₈] · 4H₂O).^[22] Here, only the four-rings $\overline{\text{Zn-P-Zn-P}}$ and $\overline{\text{P-B-P-B}}$ participate in the formation of the nets, which are then linked through zincate with phosphate and through borate with phosphate tetrahedra, respectively. Four-rings with three different tetrahedral centers $\overline{\text{Zn-P-B-P}}$ result from the linkage of the nets with each other. Additional building units resulting from this mode of linkage are crankshaft-like four-ring ribbons, which run along [101] (Figure 1, left). Figure 2 shows the three-dimensional structural framework as exemplified by NH₄[ZnBP₂O₈] as well as the characteristic 4.8² nets with gismondine topology (IZA structure designation GIS).^[23] Along [101] the nets are linked with each other in an ABAB sequence. The resulting network is evidently very flexible and is realized in a large number of different compounds, such as SAPO-43,^[24] NaP-^[25] and CaP-zeolites,^[26] and zincogallophosphates (T)[ZnGaP₂O₈] (T = CN₃H₅ and C₄NH₉).^[27] The minimum/maximum opening areas of the eight-rings (distances O...O) are 351/896 (NH₄ phase), 308/885 (Rb phase), and

[*] Prof. Dr. R. Kniep, Dipl.-Ing. I. Boy
Eduard-Zintl-Institut der Technischen Universität
D-64289 Darmstadt (Germany)
Fax: (+49) 6151-166029
E-mail: boy@ac.chemie.tu-darmstadt.de
kniep/zuecker@cpfs.mpg.de

Dipl.-Ing. G. Schäfer, Dipl.-Ing. H. Engelhardt
Max-Planck-Institut für Chemische Physik fester Stoffe
im VEM Sachsenwerk
D-01257 Dresden (Germany)
Fax: (+49) 351-208-4502
E-mail: engelhar@cpfs.mpg.de
schaefer@cpfs.mpg.de

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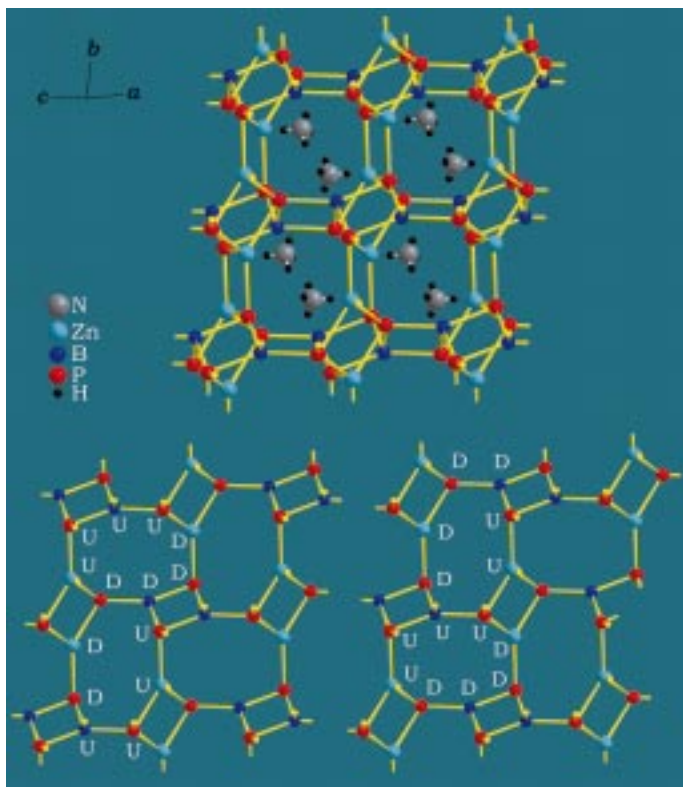


Figure 2. Gismondine-analogous linkage of tetrahedral centers in the crystal structure of $\text{NH}_4[\text{ZnBP}_2\text{O}_8]$. Top: Topology of the framework structure (view approximately along [101]). Bottom: 4.8^2 nets. See text for further details.

313/891 pm (Cs phase). Rb^+ and Cs^+ ions in the cavities are surrounded by seven oxygen atoms, giving rise to irregular polyhedra. In the crystal structure of the ammonium compound hydrogen bonds $\text{N}-\text{H}\cdots\text{O}$ ($\text{N}\cdots\text{O}$ 288–307 pm) fix the complex cation to the oxygen sites of adjacent tetrahedra. The tetrahedral network density (framework density (FD): number of tetrahedrally coordinated atoms in a volume of $1000 \text{ \AA}^3$)^[28] of the isotypic compounds lies in the range between 21.4 and 22.8, and thus resembles the framework density of cristobalite (23.0).^[29] Difference thermoanalytical/thermogravimetric studies (Netzsch STA 409EP, heating rate 5 K min^{-1} , open system in air) indicate a remarkable thermal stability of the compounds: 480°C ($\text{NH}_4[\text{ZnBP}_2\text{O}_8]$), 850°C ($\text{Rb}[\text{ZnBP}_2\text{O}_8]$), and 940°C ($\text{Cs}[\text{ZnBP}_2\text{O}_8]$).

The crystal structure of $\text{K}[\text{ZnBP}_2\text{O}_8]$ can be described starting from 4.8^2 nets with feldspar topology. As in the previously discussed compounds these nets from four-rings $\overline{\text{Zn-P-Zn-P}}$ and $\overline{\text{P-B-P-B}}$ are formally used for the framework construction. Figure 3 shows the three-dimensional framework of $\text{K}[\text{ZnBP}_2\text{O}_8]$ as well as the characteristic 4.8^2 nets with feldspar topology, whose elliptical eight-ring systems are built from four phosphate, two borate, and two zincate tetrahedra. The linkage of the nets along [001] corresponds to the sequence $\text{A}\bar{\text{A}}\bar{\text{A}}\bar{\text{A}}$, where $\bar{\text{A}}$ is the symbol for an inverted net. The special nature of the linkage leads to eight-ring channels, in which the potassium ions are irregularly surrounded by eight or ten oxygen neighbors. Also in this case crankshaft-like four-ring ribbons result, which run along [001] (Figure 1,

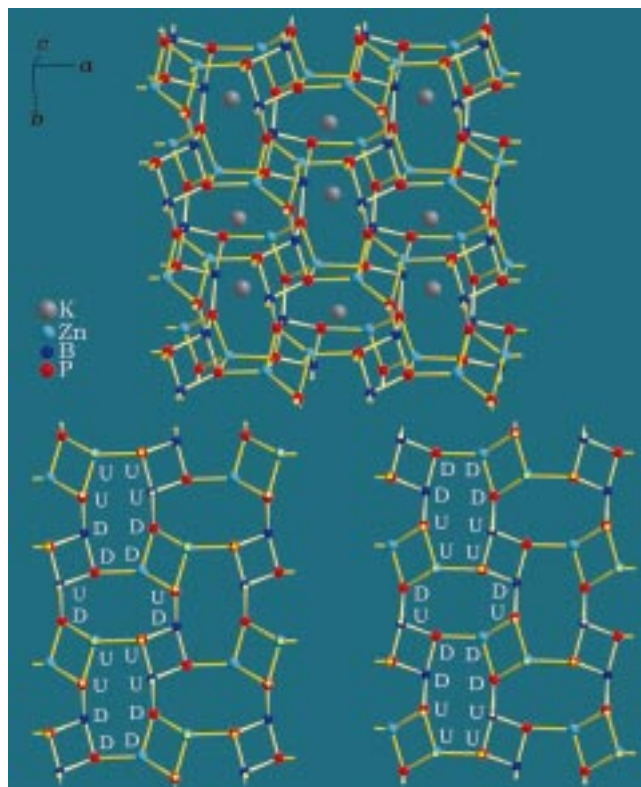


Figure 3. The crystal structure of $\text{K}[\text{ZnBP}_2\text{O}_8]$. Top: Topology of the framework structure (linkage of the tetrahedral centers). Bottom: feldspar-analogous 4.8^2 nets. See text for further details.

left). The network linkage $\text{A}\bar{\text{A}}\bar{\text{A}}\bar{\text{A}}$ is new. In the feldspar family (e.g. anorthite ($\text{Ca}[\text{Al}_2\text{Si}_2\text{O}_8]$))^[30] the 4.8^2 nets are linked according to an ABAB pattern. The minimum/maximum opening area of the elliptical eight-rings of $\text{K}[\text{ZnBP}_2\text{O}_8]$ (distances $\text{O}\cdots\text{O}$) is 296/930 pm. The tetrahedral network density (see above) of $\text{K}[\text{ZnBP}_2\text{O}_8]$ is 23.6. The compound is thermally stable up to 822°C .

Based on the compounds presented it becomes clear that with metalloborophosphates anionic partial structures can be realized, which open the door to real microporous systems. Also of significance is that the elements participating in the anionic structures are distributed in an ordered fashion. The next generations of this class of compounds will probably contain redox-active transition metals. In addition the possibility of integrating three-coordinate boron in the anionic partial structures should be kept in mind.

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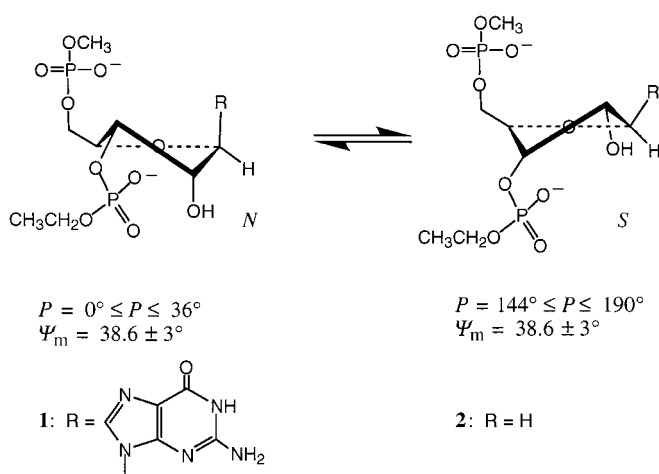
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- [17] The title compounds K[ZnBP₂O₈] and A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺) were prepared under mild hydrothermal conditions in teflon autoclaves (internal volume 20 mL). For this the starting materials (see below) were heated to about 80 °C in demineralized water (10 mL) and treated under stirring with 85 % H₃PO₄, until the components had dissolved completely. The clear solutions were concentrated to about 15–20 mL to give a highly viscous gel. The pH values were between 1 and 1.5. The highly viscous gels were transferred to the teflon autoclaves (degree of filling about 60–80 %) and stored for three to four days at about 170 °C. The crystalline reaction products were filtered off in vacuo, washed with demineralized water, and dried at 60 °C. Single crystals with an approximate monoclinic habit grow to a length of about 0.8 mm under these conditions. Starting materials used for the syntheses: a) K[ZnBP₂O₈]: 0.65 g ZnO, 2.44 g K₂B₄O₇ · 4H₂O, 2.2 g K₂HPO₄ (molar ratio 1:1:2), 5.5 mL 85 % H₃PO₄, degree of filling 60 %; b) NH₄[ZnBP₂O₈]: 2.33 g ZnO, 0.99 g B₂O₃, 7.55 g (NH₄)₂HPO₄ (molar ratio 2:1:4), 6 mL 85 % H₃PO₄, degree of filling 70 %; c) Rb[ZnBP₂O₈]: 7.62 g RbOH, 3.02 g ZnO, 1.29 g B₂O₃ (molar ratio 2:2:1), 9 mL 85 % H₃PO₄, degree of filling 65 %; d) Cs[ZnBP₂O₈]: 8.6 g CsOH, 2.33 g ZnO, 0.99 g B₂O₃, (molar ratio 2:2:1), 7.1 mL 85 % H₃PO₄, degree of filling 90 %.
- [18] a) Crystal structure determinations: Diffractometer: Philips PW 1100 (modernized by Stoe) for K[ZnBP₂O₈], Siemens P4 for A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺); MoK_α radiation; graphite monochromator; measurement range 5 ≤ 2θ ≤ 60; Lorentzian, polarization, and absorption (Ψ scan) corrections; structures solved by direct methods and refined by full-matrix least-squares methods by using the SHELX-97 program (G. M. Sheldrick, SHELX-97, Universität Göttingen, **1997**); anisotropic displacement parameters (except for N and H). The positions of the H atoms in NH₄[ZnBP₂O₈] were obtained from difference-Fourier syntheses, refinement with restraints (N–H distances to 0.86 Å, H–N–H angle approximately the tetrahedral angle and U_{iso}(H) = 1.2 U_{iso}(N)). b) Crystal structure data: 1) K[ZnBP₂O₈]: monoclinic, space group C2/c (no. 15), a = 1261.7(5), b = 1277.3(6), c = 841.5(3) pm, β = 91.25(3)°, V = 1355.8(1) Å³, Z = 8, ρ_{calcd} = 2.991 g cm^{−3}; μ(MoK_α) = 4.72 mm^{−1}; 4110 measured reflections, 1978 independent reflections, 1586 with F_o > 4σ(F_o); 119 free parameters; GOF = 0.954; R values for F_o > 4σ(F_o): R1 = 0.0273, wR2 = 0.0630; max./min. residual electron density: 0.519/−0.554 × 10^{−6} e pm^{−3}. 2) A[ZnBP₂O₈] (A = NH₄⁺, Rb⁺, Cs⁺): triclinic, space group P1̄ (no. 2); NH₄[ZnBP₂O₈]: a = 743.7(1), b = 761.2(1), c = 785.0(1) pm, α = 119.05(2), β = 101.59(1), γ = 103.43(1)°, V = 351.18(9) Å³, Z = 2, ρ_{calcd} = 2.687 g cm^{−3}; μ(MoK_α) = 3.969 mm^{−1}; 4758 measured reflections, 1968 independent reflections, 1892 with F_o > 4σ(F_o); 121 free parameters; GOF = 1.162; R values for F_o > 4σ(F_o): R1 = 0.0224, wR2 = 0.0628; max./min. residual electron density: 0.801/−0.720 × 10^{−6} e pm^{−3}. Rb[ZnBP₂O₈]: a = 743.9(2), b = 763.9(2), c = 786.1(2) pm, α = 118.82(2), β = 101.73(2), γ = 103.51(2)°, V = 353.4(2) Å³, Z = 2, ρ_{calcd} = 3.304 g cm^{−3}; μ(MoK_α) = 10.779 mm^{−1}; 3752 measured reflections, 1878 independent reflections, 1616 with F_o > 4σ(F_o); 118 free parameters; GOF = 1.073; R values for F_o > 4σ(F_o): R1 = 0.0283, wR2 = 0.0674; max./min. residual electron density: 1.63/−1.04 × 10^{−6} e pm^{−3}. Cs[ZnBP₂O₈]: a = 750.6(2), b = 791.4(2), c = 803.8(2) pm, α = 118.05(2), β = 102.96(2), γ = 104.50(2)°, V = 373.9(2) Å³, Z = 2, ρ_{calcd} = 3.545 g cm^{−3}; μ(MoK_α) = 8.520 mm^{−1}; 4022 measured reflections, 2010 independent reflections, 1457 with F_o > 4σ(F_o); 118 free parameters; GOF = 1.057; R values for F_o > 4σ(F_o): R1 = 0.0488, wR2 = 0.1084; max./min. residual electron density: 1.47/−1.55 × 10^{−6} e pm^{−3}. Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depositary numbers CSD-410869, CSD-410870, CSD-410871, and CSD-410872.
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The Transmission of the Electronic Character of Guanin-9-yl Drives the Sugar–Phosphate Backbone Torsions in Guanosine 3',5'-Bisphosphate**

Parag Acharya, Anna Trifonova, Christophe Thibaudeau, Andr  s F  ldesi, and Jyoti Chattopadhyaya*

The intrinsic dynamics and architectural flexibility of nucleic acids,^[1a] manifesting into specific biological function, are the result of cooperativity of its three essential components: the pentofuranose, the nucleobase, and the phosphodiester. We have earlier shown that the interplay and balance of stereoelectronic *gauche*^[2a–c, g, h] and anomeric effects^[2g, h, j] energetically drive the two-state pseudorotational equilibrium between north-type (*N*, C2'-*exo*-C3'-*endo*) and south-type (*S*, C3'-*exo*-C2'-*endo*)^[1a, 2b, g, 3] ($N \rightleftharpoons S$, Scheme 1). These works have subsequently led to a detailed dissection^[2] of various



Scheme 1. Schematic representation of the dynamic two-state $N \rightleftharpoons S$ pseudorotational equilibrium^[1a, 2b, g, 3] of the β -D-pentofuranose moiety, which is influenced by the nature and relative orientation of the substituents through the *gauche* and anomeric effects.^[2, 3a] P = phase angle, Ψ_m = puckering amplitude.

gauche and anomeric forces which are dictated by the electronic nature of various pentose sugar substituents. The chemical nature of many of these sugar substituents (especially aglycone and the phosphate) can be altered and

tuned by the pH of the medium as well by the complexes formed between the nucleotide and the ligand present in the solution.

We herein report our studies on the pD-dependent conformational analysis of guanosine 3',5'-bisphosphate (EtpGpMe, **1**) as a model mimicking the central nucleotide moiety in a trinucleoside diphosphate in a single-stranded RNA. A complete interdependency with respect to conformational preference has been found for the sugar $N \rightleftharpoons S$ pseudorotational^[1a, 2] and phosphate $\epsilon^+ \rightleftharpoons \epsilon^-$ equilibria^[1a, 2j] in **1**, as the protonation $\rightleftharpoons$ deprotonation equilibrium at the N7 basic site^[2j] of guanin-9-yl in **1** changes as a function of pH; such an effect is completely absent in the apurinic counterpart [Etp(AP)pMe] (**2**). It has been demonstrated that as the electronic character of the guanine moiety in **1** changes with the protonation $\rightleftharpoons$ deprotonation equilibrium,^[2j] the strength of the anomeric effect ($n_{O4'} \rightarrow \sigma_{C1'-N9}^*$ orbital mixing^[2g, h, j, 3a, 4]) is continuously modulated to induce a change in the electron-density potential of O4' (tunable $n_{O4'} \rightarrow \sigma_{C1'-N9}^*$ orbital mixing). This, in turn, dictates the nature of the orbital overlap of $\sigma_{C3'-H3'}$ with $\sigma_{C4'-O4'}^*$ as well as the stabilization energy of the newly formed hybrid orbitals (the 3'-*gauche* effect: $\sigma_{C3'-H3'} \rightarrow \sigma_{C4'-O4'}^*$ orbital mixing^[2g, 3a, 5]). As the 3'-*gauche* effect becomes effective, the charge density at C3' changes, which further influences the electron-density potential of O3' and consequently the ability of its lone pair orbital to overlap with the antibonding orbital of P3'-O(ester) (a tunable anomeric transmission of $n_{O3'} \rightarrow \sigma_{P3'-O(ester)}^*$). This tunable transmission of the charge density from the aglycone, turning the conformational wheel across the sugar–phosphate backbone, is influenced by the relative donor–acceptor capabilities of bonding, nonbonding, and antibonding orbitals of various sugar atoms and substituents. This is conceptually very similar to the through-space transport of charge or electrons by stacked nucleic acid aglycones in conventional nucleic acid molecular wires,^[1b, c] except for the fact that the nucleic acid chain is damaged in the latter upon transport of electrons through the stacked nucleobases in a distance-dependent manner. In contrast, in the former the conformational wheel is turned by tunable change of the electron-density potential of various donor and acceptor orbitals by both through-space and through-bond effects.

The basis of our analysis is as follows: The mole fractions of *N*- and *S*-type conformers from pD 1.0–6.7 have been extracted by pseudorotational analysis^[2, 3a, 6–8] of temperature-dependent $^3J_{H,H}$ coupling constants with the PSEUROT program (version 5.4)^[7] using a generalized Karplus-type equation.^[8a, b] The values for ΔG^0 of the two-state $N \rightleftharpoons S$ pseudorotational equilibrium at seven pD levels between 6.7 and 1.0 were obtained (Table 1). As the medium becomes more acidic, N7 of the guanin-9-yl group becomes protonated^[2j] and the electron density at N9 is reduced, causing an increase in the strength of the anomeric effect ($n_{O4'} \rightarrow \sigma_{C1'-N9}^*$ orbital mixing).^[2g, h, j] The conformational outcome of this is that the aglycone takes up the pseudoaxial orientation and the $N \rightleftharpoons S$ pseudorotational equilibrium for **1** is gradually shifted towards *N*-type (78% *S* at pD 6.7 to 53% *S* at pD 1.6), which is reflected by a change in ΔG^0 (at 298 K) from -3.2 kJ mol^{-1} at pD 6.7 to 0.0 kJ mol^{-1} at pD 1.0 (Table 1).

[*] Prof. J. Chattopadhyaya, P. Acharya, A. Trifonova, C. Thibaudeau, A. F  ldesi
 Department of Bioorganic Chemistry, Box 581, Biomedical Centre
 University of Uppsala
 S-751 23 Uppsala (Sweden)
 Fax: (+46) 185-54-495
 E-mail: jyoti@bioorgchem.uu.se

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Table 1. Determination of ΔG^0 values (at 298 K) of two-state $N \rightleftharpoons S$ and $\epsilon^t \rightleftharpoons \epsilon^-$ equilibria at different pD values from pseudorotational analyses and EPSILON calculations, respectively, as well as the percentage population of γ^+ and β^t conformers at 298 K for EtpGpMe (**1**)^[a].

pD	$N \rightleftharpoons S$		$\epsilon^t \rightleftharpoons \epsilon^-$		β^t [%]	γ^+ [%] ^[c]
	ΔG^{298} (°) ^[b]	S [%]	ΔG^{298} (°) ^[b]	ϵ^- [%]		
1.0 ^[d]	−0.0 (0.1)	—	0.3 (0.2)	—	—	—
1.6	−0.3 (0.2)	53	0.2 (0.2)	48	78	77
2.0	−0.7 (0.2)	58	0.0 (0.5)	50	79	78
2.4	−1.4 (0.2)	64	−1.2 (0.2)	62	79	74
2.7	−2.3 (0.2)	72	−1.7 (0.2)	66	80	73
3.0	−2.4 (0.2)	72	−1.8 (0.2)	67	80	71
6.7	−3.2 (0.2)	78	−2.0 (0.2)	69	81	72

[a] For the experimental procedure used to calculate the values, see the Supporting Information. [b] Values for ΔG^{298} (in kJ mol^{−1}) of the $N \rightleftharpoons S$ and $\epsilon^t \rightleftharpoons \epsilon^-$ equilibria were calculated directly from the average logarithm $\ln_{av}(x_a/(1-x_a))$ by using the Gibbs equation $\Delta G^T = -(RT/1000)\ln_{av}(x_a/(1-x_a))$ with $1-x_a=x_b$, where $x_a=x_S$ or $x_a=x_{\epsilon^-}$ and $x_b=x_N$ or $x_b=x_{\epsilon^t}$; R is the gas constant, and T is the temperature. The standard deviations (°) are given in parentheses. [c] Calculated from the sum of $^3J_{H5',P5'}$ and $^3J_{H5'',P5'}$; the proton signals are assigned as downfield shift of $\delta(H5')$ and upfield shift of $\delta(H5'')$. [d] Due to the overlapping of the H3' peak with the signal for residual water (298 K, pD 1.0), the coupling constants could not be used for conformational analyses. To calculate ΔG^{298} the value of $\ln_{av}(x_a/(1-x_a))$ at pD 1.0 has been extrapolated from the values at $T=288$ K and $T=303$ K.

The plot of $\Delta G^{0[2g, i-k]}$ for the $N \rightleftharpoons S$ equilibrium in **1** as a function of pD (Figure 1 A) has the typical sigmoidal shape with an inflection point at 2.4, which is identical to the pK_a of the constituent guanine-9-yl, determined independently from the plot of $\delta(H8)$ as a function of pD (Figure 1 B). Noteworthy is that such sigmoidal plots have been found earlier for β -D-2',3'-dideoxynucleosides,^[2i] 2'-deoxynucleosides,^[2i] and ribo N - or C -nucleosides^[2k] as well as some α -D-2',3'-dideoxynucleosides^[2i] and 2'-deoxynucleosides.^[2i] The pK_a value for **1** was confirmed by the Hill plot^[2g, i-k] (Figure S1 in the Supporting Information), which was characteristic of a single protonation site. In a control experiment, the difference in $^3J_{H,H}$ at neutral and acidic pD values at 298 K (Table S4 in the Supporting Information) was found to be negligible (± 0.1 Hz over the pD range studied) for **2**, showing that in the absence of the aglycone, the $N \rightleftharpoons S$ equilibrium is unbiased and remains unchanged at all pD values.

Since the ϵ^+ conformer with respect to the C3'–O3' bond is energetically forbidden,^[9a] and is not found in the crystal structure,^[9b] the temperature-dependent $^3J_{C4',P3'}$, $^3J_{C2',P3'}$, and $^3J_{H3',P3'}$ experimental coupling constants for **1** have been interpreted in terms of a two-state $\epsilon^t \rightleftharpoons \epsilon^-$ equilibrium; this gives the temperature-dependent mole fractions upon use of the program EPSILON^[2c, f, 9, 10] (see the Supporting Information). The logarithm of the ratio of the resulting mole fractions of ϵ^- and ϵ^t gave ΔG^0 at 298 K for the $\epsilon^t \rightleftharpoons \epsilon^-$ equilibrium in **1** at seven pD values between 6.7 and 1.0; ΔG^{298} varied from -2.0 to $+0.3$ kJ mol^{−1} (Table 1) for the population of ϵ^- , decreasing from 69 % at pH 6.7 for neutral guanine to 48 % at pH 1.6 for N7-protonated guanine. In the case of our reference compound **2** no change in $^3J_{H,P}$ and $^3J_{C,P}$ was observed (Table S4 in the Supporting Information), thereby allowing us to conclude that the conformational changes observed with respect to C3'–O3' in **1** over the pD range studied is a result of a modulation of the electronic

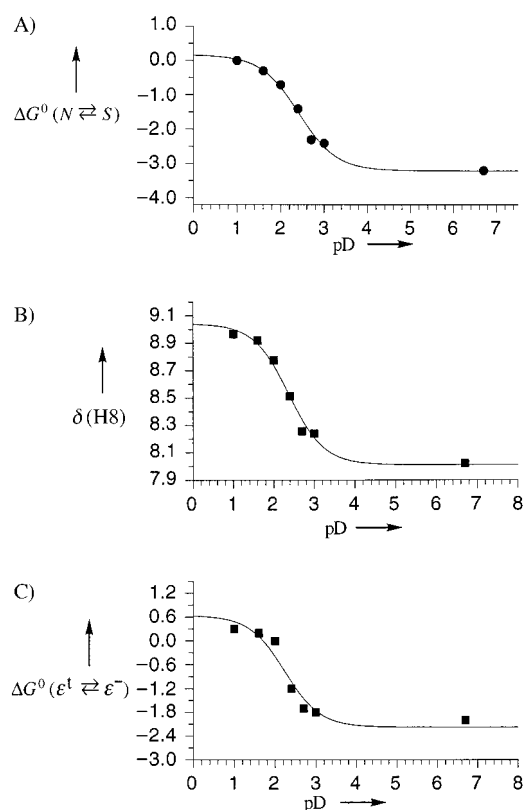


Figure 1. Plots of ΔG^0 [kJ mol^{−1}] for the $N \rightleftharpoons S$ pseudorotational equilibrium of the pentofuranose moiety (A), the chemical shift of H8 of the guanine-9-yl nucleobase (B), and ΔG^0 [kJ mol^{−1}] of the $\epsilon^t \rightleftharpoons \epsilon^-$ equilibrium of the 3'-ethylphosphate group in **1** (C) as a function of pD at 298 K. The sigmoidal curves result from the best iterative least-square fit of $\Delta G^0(N \rightleftharpoons S)$, $\delta(H8)$, and $\Delta G^0(\epsilon^t \rightleftharpoons \epsilon^-)$ values to the Henderson–Hasselbalch equation (see the Supporting Information); pD at the inflection point: A) 2.4, B) 2.4, C) 2.3. See text for further details.

character of the neutral guanine moiety upon protonation to guanine-N7H⁺. Interestingly, the plot of ΔG^0 as a function of pD for the $\epsilon^t \rightleftharpoons \epsilon^-$ equilibrium for **1** also gives a sigmoidal curve (Figure 1 C). The pD value of 2.3 at the inflection point is nearly identical (i.e., within the accuracy of the measurements) to the pK_a value of 2.4 for the guanine-9-yl group in **1**; this was also confirmed by the Hill plot analysis^[2g, i-k] (Figure S1 in the Supporting Information). Thus, the pD-dependent conformational reorientation of the C3'–O3' bond (reflected by ΔG^0 values for the $\epsilon^t \rightleftharpoons \epsilon^-$ equilibrium) is directly dictated by the pK_a of the constituent C1'-aglycone in **1**.

The correlation plot of ΔG^0 for the $N \rightleftharpoons S$ equilibrium of the pentofuranose sugar as a function of ΔG^0 for the $\epsilon^t \rightleftharpoons \epsilon^-$ equilibrium of the 3'-phosphate moiety in **1** gives a straight line with a high Pearson correlation coefficient ($R=0.97$, Figure 2 A). This means that as the guanine-9-yl nucleobase in **1** is gradually protonated in the acidic medium, and the modulation of the strength of the anomeric effect shifts the $N \rightleftharpoons S$ equilibrium toward N , which in turn dynamically shifts the $\epsilon^t \rightleftharpoons \epsilon^-$ equilibrium towards ϵ^t relative to the situation at neutral pD. Additional evidence that the transmission of the free energy of the protonation/deprotonation equilibrium steers the phosphate conformation by changing the conformation of the sugar moiety is that the plots of $\Delta G^0(N \rightleftharpoons S)$

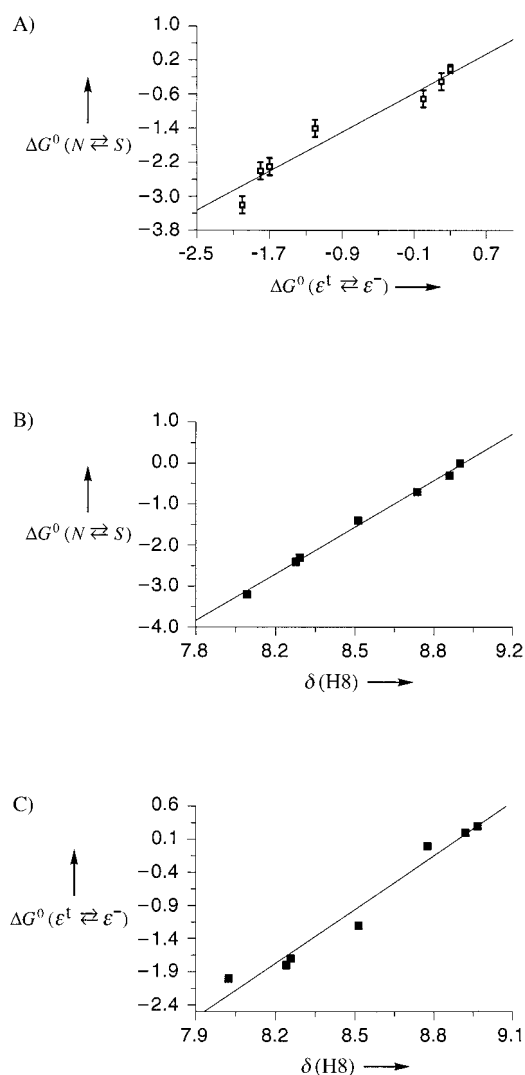


Figure 2. A) The plot of ΔG^0 [kJ mol⁻¹] for the $N \rightleftharpoons S$ pseudorotational equilibrium at 298 K for **1** as a function of ΔG^0 [kJ mol⁻¹] for the $\epsilon^1 \rightleftharpoons \epsilon^-$ equilibrium; $R = 0.97$, slope 1.15 ($\sigma = 0.08$), intercept -0.45 ($\sigma = 0.10$). The vertical bars show the standard deviations at each pD value. B) The plot of ΔG^0 [kJ mol⁻¹] for the $N \rightleftharpoons S$ pseudorotational equilibrium for **1** as a function of $\delta(\text{H8})$ at 298 K; $R = 1.00$, slope 3.25 ($\sigma = 0.06$), intercept -29.16 ($\sigma = 0.50$). C) The plot of ΔG^0 [kJ mol⁻¹] for the $\epsilon^1 \rightleftharpoons \epsilon^-$ equilibrium for **1** as a function of $\delta(\text{H8})$ at 298 K; $R = 0.98$, slope 2.70 ($\sigma = 0.14$), intercept -23.96 ($\sigma = 1.16$). In each case the data points are given for the seven pD values investigated.

(Figure 2B) or of $\Delta G^0(\epsilon^1 \rightleftharpoons \epsilon^-)$ (Figure 2C) in **1** as a function of $\delta(\text{H8})$ give straight lines with high correlation coefficients ($R \geq 0.97$).

Consistent with our earlier observation on ribonucleoside 3'-ethylphosphates^[2f] at neutral pH and room temperature, we found that the methylene protons of the 3'-ethylphosphate moiety in **1** are nonequivalent owing to the 2'-OH-promoted hydrogen bonding with the vicinal O3' atom. Hence all our ΔG^0 measurements were performed well below the hydrogen-bond melting temperature for **1** (298 K). This means that all changes of free-energy observed at 298 K for **1** (Table 1) as the pH value is changed are attributed to the free-energy changes of the protonation $\rightleftharpoons$ deprotonation equilibrium of the aglycone to drive the sugar-phosphate backbone in a concerted manner.

As the pD-tunable change of the electronic character of the nucleobase tunes the strength of the anomeric effect, an increased preference for the *N*-type sugar conformation is imposed because of enhanced $n_{\text{O4}'} \rightarrow \sigma_{\text{C1}'-\text{N9}}^*$ orbital interaction.^[2g, h, j, 3a, 4] This in turn affects the strength of the O3'-C3'-C4'-O4' *gauche* effect by retuning the energy levels of the donor and acceptor orbitals in the $\sigma_{\text{C3}'-\text{H3}'} \rightarrow \sigma_{\text{C4}'-\text{O4}'}^*$ interaction.^[2g, 3a, 5] The extent of $\sigma_{\text{C3}'-\text{H3}'} \rightarrow \sigma_{\text{C4}'-\text{O4}'}^*$ participation influences the electron density at O3', which in turn modulates the O3'-P3'-O anomeric effect^[3a, 11] (a tunable transmission of the $n_{\text{O3}'} \rightarrow \sigma_{\text{P3}'-\text{O(ester)}}^*$ orbital interaction, Figure 3, next page).^[12] It is noteworthy that the stereoelectronic transmission takes place from the aglycone to the sugar to the phosphate, and not in the reverse direction. The proof of this one-way transmission of stereoelectronic information in **1** is two-fold: 1) The $\text{p}K_{\text{a}}$ value of the guanine-9-yl aglycone remains around 2.4, and is independent of any OH or phosphate substituents in the sugar moiety. Thus the $\text{p}K_{\text{a}}$ values of N7 are as follows for a series of guanine nucleosides (within the error limits of our NMR experiments):^[2] 2',3'-dideoxyguanosine ($\text{p}K_{\text{a}}$ 2.5), 2'-deoxyguanosine ($\text{p}K_{\text{a}}$ 2.3), guanosine ($\text{p}K_{\text{a}}$ 2.1), and **1** ($\text{p}K_{\text{a}}$ 2.4). 2) When the 3'-phosphate ($\text{p}K_{\text{a}} \approx 1.5$) in **2** is partially protonated at pD 1.6 under our experimental condition, the coupling constant $^3J_{\text{H,H}}$ for the endocyclic sugar moiety remains unaltered, which is in contrast to the situation for **1**. This suggests that the change in the electronic character of the phosphate does not influence the structural and dynamic character of the sugar moiety.

The conformational equilibrium across the γ^+ torsion^[13a] (at 298 K) changes from 72% at pD 6.7 to 77% at pD 1.6, which is correlated with $\delta(\text{H8})$ for **1** (Figure 4A) as a manifestation of the O4'-C4'-C5'-O5' *gauche* effect. There is, however, no propagation of this transmission further along the $\beta(\text{C4}'-\text{C5}'-\text{O5}'-\text{P5}')$ torsion. Similarly the ratio of *syn* and *anti* conformers^[13b] does not change as a function of pH, suggesting that

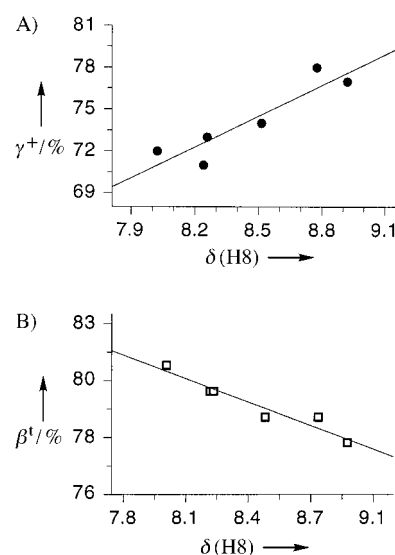


Figure 4. A) The plot of percentage population of γ^+ conformer in **1** (taking H5' downfield and H5' upfield) as a function of $\delta(\text{H8})$ at different pD values; $R = 0.91$, slope 7.37 ($\sigma = 0.99$), intercept 11.88 ($\sigma = 8.37$). B) The plot of percentage population of β^+ conformer in **1** as a function of $\delta(\text{H8})$ at different pD values; $R = 0.96$, slope -2.93 ($\sigma = 0.25$), intercept 104.25 ($\sigma = 2.07$).

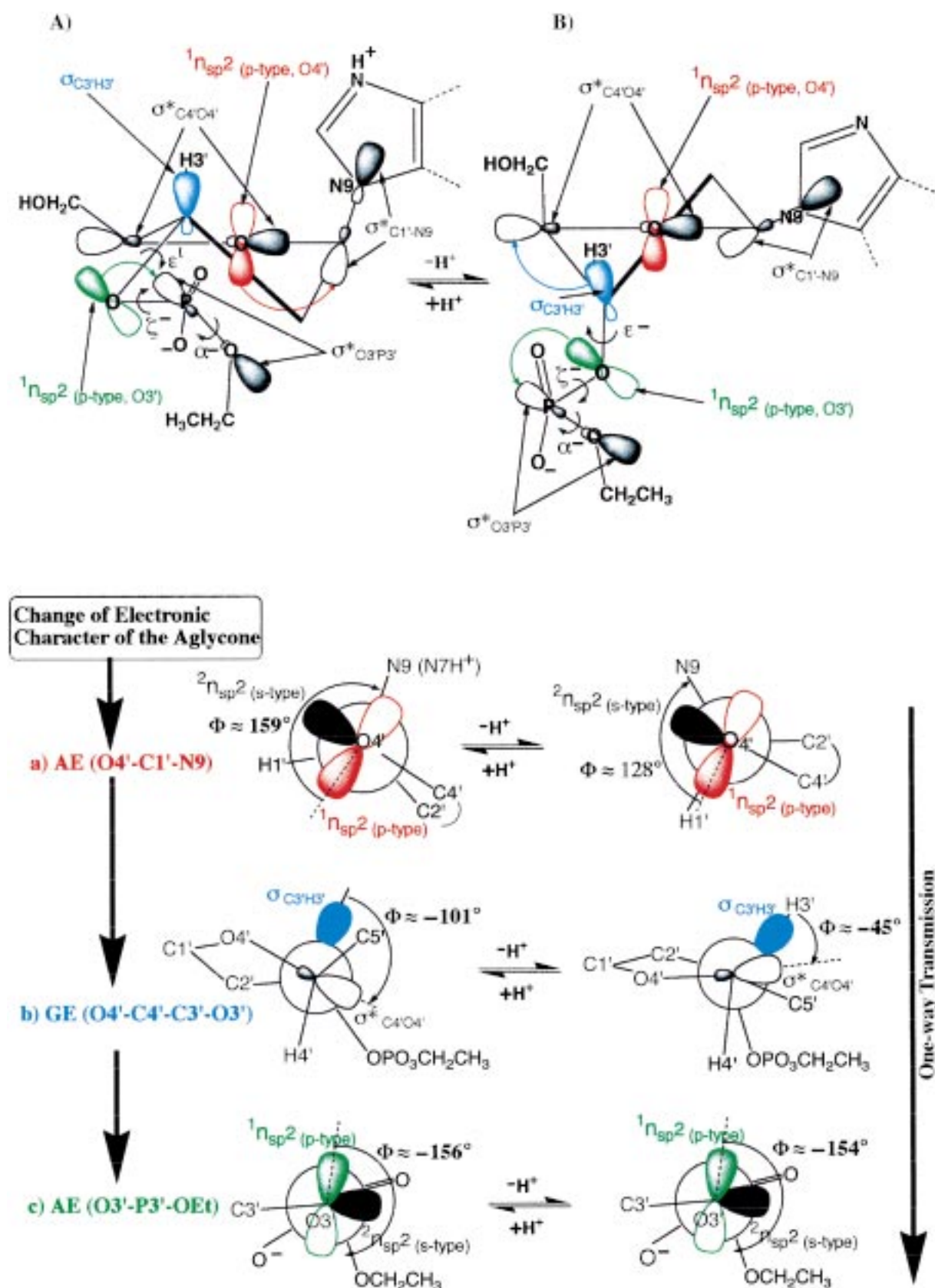


Figure 3. The demonstration of RNA molecular wires using the model EtpGpMe (**1**). Transmission of the free energy of the protonation $\rightleftharpoons$ deprotonation equilibrium of the guanine-9-yl group in **1** drives the sugar–phosphate conformations through three consecutive stereoelectronic tunings (a–c; AE = anomeric effect, GE = *gauche* effect). Appropriate orbital overlap and the energy difference between the donor and acceptor orbitals, dictated by various sugar atoms and substituents, drive the sugar–phosphate conformation through the interplay of *gauche* and anomeric effects. All orbitals are shown by straight arrows. Smaller curved arrows show the preferred torsional orientation, whereas the larger curved arrows indicate the mixing of donor and acceptor orbitals. See reference [12] for further details.

protonation of the aglycone has no measurable effect on the orientation of the glycosyl torsion. On the other hand, plots of the pH-dependent ^{31}P chemical shift of the 3'-phosphate moiety in **1** as function of ΔG^0 for the $N \rightleftharpoons S$ or $\epsilon^+ \rightleftharpoons \epsilon^-$ equilibria give straight lines ($R \geq 0.94$, Figure 5 A, B), which

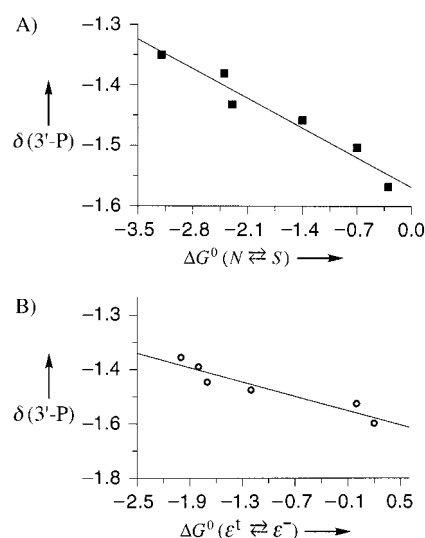


Figure 5. Plots of the ^{31}P chemical shift of the 3'-phosphate moiety ($\delta(3'\text{-P})$) in **1** as function of ΔG^0 [kJ mol $^{-1}$] of the $N \rightleftharpoons S$ pseudorotational equilibrium (A; $R = 0.97$, slope -0.07 ($\sigma = 0.01$), intercept -1.62 ($\sigma = 0.01$)) and of ΔG^0 [kJ mol $^{-1}$] of the $\epsilon^+ \rightleftharpoons \epsilon^-$ equilibrium (B; $R = 0.94$, slope -0.08 ($\sigma = 0.01$), intercept -1.58 ($\sigma = 0.01$)) at different pD values.

is not the case with the 5'-phosphate group (see the Supporting Information). This shows that the stereoelectronic transmission is more effective at the 3' end than at the 5' end.

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not fully operational in the *N*-type sugar conformation, the charge density at the O3' lone pair ($n_{\text{sp}^2(\text{p-type})}$, O3') is fully available to act as a donor and interact through the anomeric effect with the antibonding $\sigma_{\text{P3'-O(ester)}}^*$ orbital ($\text{AE}(\text{O3'-P3'-OCH}_2\text{CH}_3)^{[3a, 11]}$), when C3'-O3' is in ϵ^t , O3'-P3' in ζ^- , and P3'-O5' in α^- conformations. The Newman projection (Figure 3c) shows that the overlap between the O3' lone pair orbitals and the $\sigma_{\text{P3'-O(ester)}}^*$ orbital ($n_{\text{O3'}} \rightarrow \sigma_{\text{P3'-O(ester)}}^*$ orbital mixing) stabilizes ϵ^t over ϵ^- . This is not only due to an antiperiplanar orientation of $n_{\text{sp}^2(\text{p-type})}$ with respect to the P3'-O(ester) bond, as $\phi(n_{\text{sp}^2(\text{p-type})}\text{-O3'-P3'-OCH}_2\text{CH}_3)$ is nearly the same for the two cases, but largely owing to the greater electron density available at $n_{\text{O3'}}$, arising from the absence of 3'-GE in the *N*-type sugar. The conformational parameters used to build up the model structure of *N*, ϵ^t , ζ^- , α^- , and *S*, ϵ^- , ζ^- , α^- conformations of **1** to draw the Newman projections are provided in Table S6 in the Supporting Information.

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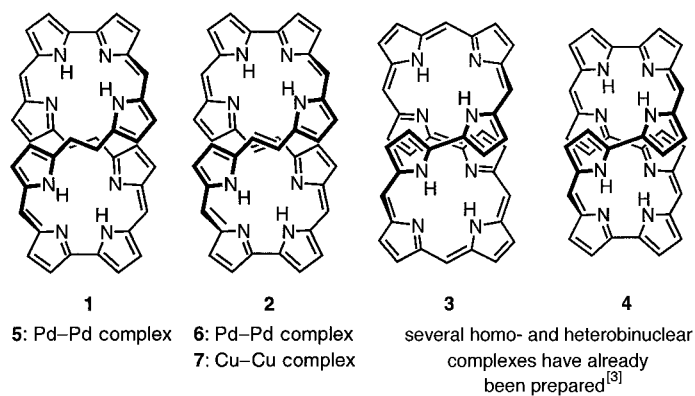
“Figure Eight” Cyclooctapyrroles: Enantiomeric Separation and Determination of the Absolute Configuration of a Binuclear Metal Complex**

Andreas Werner*, Martin Michels, Lars Zander, Johann Lex, and Emanuel Vogel*

Dedicated to Professor Karl Schlögl on the occasion of his 75th birthday

Cyclooctapyrroles (octaphyrins), of which compounds **1–4** (in each case as the hexadecaethyl derivative, Scheme 1) are representatives, have developed as an unexpected sideline of our research into porphyrin and corrole isomers.^[1] It was during studies on the synthesis of the still hypothetical *trans*-corrphycene that a versatile route to such polypyrrole macrocycles and potential ligands unfolded. We found that cyclooctapyrroles are formed as—in many cases dominating—competing products to cyclotetrapyrroles (porphyrin isomers, corroles, porphyrins-(1.0.1.0), and others) when two suitably functionalized dipyrrole components, of which at least one must be a bipyrrole derivative, are subject to an acid-catalyzed MacDonald condensation.^[2]

Although **1**, **3**, and **4** (**2** is derived from **1** by dehydrogenation) were originally formed in only minor quantities, these



Scheme 1. The figure eight ligands **1–4**.

macrocycles are now obtainable in yields of 40, 42, and 25 %, respectively (i.e., on a preparative scale), when acid catalysis is replaced by BF_3 catalysis^[4] (cyclotetrapyrrole formation is completely suppressed with **1**, **3**, and **4**).

A geometric feature of all previously known cyclooctapyrroles is that—in analogy to Sessler’s cyclodecapyrrole turcasarin^[5]—both in solution and (where structural analysis is available) in the crystal they exist in a chiral, figure eight conformation of two equidirectional helices (*P,P* or *M,M*),^[6] which, assuming sufficiently restricted mobility, is expected to allow enantiomeric separation. Both **2** and its (according to molecular models) less rigid tetrahydro derivative **1** as well as **3** are highly promising candidates for enantiomeric separation: Based on the observation that the diastereotopicity of the ethyl CH_2 protons remains intact, also in ^1H NMR spectra measured at elevated temperature, the inversion barrier of the figure eight loop is expected to be at least 85 kJ mol^{-1} .^[1a] In contrast, the NMR study and theoretical calculations^[7] show **4** to be a dynamic molecule, even at room temperature, so there is not much chance that stable enantiomers can be obtained.

The cyclooctapyrroles **1–4** appear predestined to form binuclear metal complexes since the loop-shaped conformation of these macrocycles exhibits two structurally identical, helical N_4 cavities. Enantiomers of such complexes, which are presumably generally very stable towards racemization owing to the rigidity of the molecule imposed by the incorporation of the metal, are of interest as possible models for binuclear metalloenzymes^[8] and as potential catalysts in asymmetric synthesis.^[9] In this study, therefore, compounds **1** and **2** as well as their recently obtained palladium and copper complexes **5–7** were investigated as examples to effect enantiomeric separation. The success of these efforts is reported here. However, before the separations as such are described in detail, the hitherto still outstanding X-ray structural analyses^[10] of **1** and **2** are included and the aforementioned metal complexes of these ligands are described.

According to the analysis, the molecular frameworks of the cyclooctapyrroles **1** and **2** show the figure eight conformation previously derived from the NMR studies (Figure 1 a and 1 b). As can be seen from the side view of **2** (Figure 1 c), the four dipyrrole units are in each case almost planar, so that the helical conformation of the two tetrapyrrole substructures is

[*] Prof. Dr. A. Werner^[†]

Institut für Organische Chemie der Universität
Währinger Strasse 38, A-1090 Wien (Austria)

Prof. Dr. E. Vogel, Dr. M. Michels, Dr. L. Zander, Dr. J. Lex
Institut für Organische Chemie der Universität
Greinstrasse 4, D-50939 Köln (Germany)
Fax: (+49) 221-470-5057
E-mail: emanuel.vogel@uni-koeln.de

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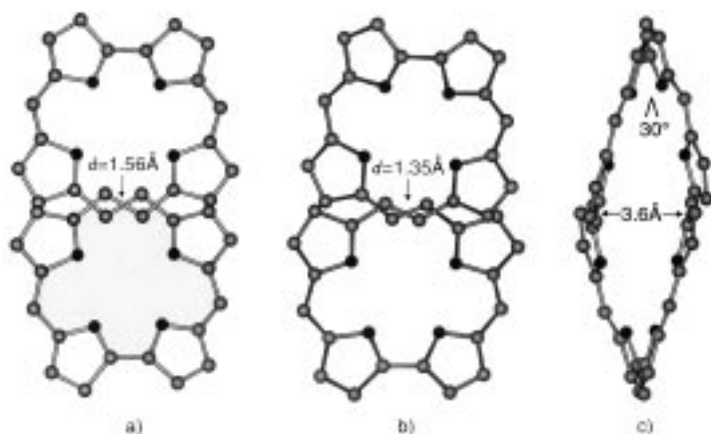


Figure 1. Structures **1** and **2** in the crystal of the racemate: a) plan view of **1**; b) plan view and c) side view of **2**. The ethyl groups are omitted for clarity.

mainly attributable to the torsions of the bipyrrrole C–C single bonds (N–C–C'–N' torsion angle: $\Phi = 30^\circ$).

The ability of the cyclooctapyrroles **1** and **2** to form binuclear chelates was confirmed by the preparation of the homobinuclear palladium(II) complexes **5** and **6** as well as the copper(II) complex **7**^[11] (see the Experimental Section and Table 1). X-ray structure analysis^[10] of complexes **6** and **7**

Table 1. Selected physical data of the metal complexes **5**–**7**. ¹H NMR: 300 MHz; ¹³C NMR: 75.5 MHz; IR: CsI; UV/Vis: CH₂Cl₂.

5: ¹H NMR (CDCl₃, 298 K): $\delta = 6.24$ (s, 4H, H-9,20,29,40), 3.83/3.72 (AA'BB' system, 8H, H-14,15,34,35), ABX₃ systems: 2.43/2.36/1.09 (20H, H-2a,b,7a,b,22a,b,27a,b), 2.41/2.39/1.03 (20H, H-3a,b,6a,b,23a,b,26a,b), 2.35/2.26/1.01 (20H, H-11a,b,18a,b,31a,b,38a,b), 2.16/2.01/0.96 (20H, H-12a,b,17a,b,32a,b,37a,b); ¹³C NMR (CDCl₃, 298 K): $\delta = 165.86$, 149.95, 149.19, 138.61, 135.36, 131.52, 131.25, 128.25, 120.05, 29.30, 18.39, 17.90, 17.68, 17.39, 17.39, 17.21, 16.74, 15.21; IR: $\tilde{\nu} = 2963$, 2929, 2869, 1587, 1302, 1196, 1107, 1012, 997, 952, 871 cm⁻¹; UV/Vis: λ_{max} (ϵ) = 441 (72200), 543 (57400), 652 (19100); MS (FAB): m/z (%): 1282 (100) [M^+]

6: ¹H NMR (CDCl₃/thiophenol, 298 K): $\delta = 6.99$ (s, 4H, H-9,20,29,40), 6.88 (s, 4H, H-14,15,34,35), ABX₃ systems: 2.70/1.22 (20H, H-2a,b,7a,b,22a,b,27a,b), 2.70/1.28 (20H, H-11a,b,18a,b,31a,b,38a,b), 2.66/1.18 (20H, H-3a,b,6a,b,23a,b,26a,b), 2.38/0.91 (20H, H-12a,b, 17a,b,32a,b,37a,b); ¹³C NMR (CDCl₃/thiophenol, 298 K): $\delta = 162.06$, 150.30, 145.11, 140.10, 139.65, 135.27, 134.18, 130.80, 130.00, 118.97, 11.84, 11.68, 17.98, 17.91, 17.63, 17.35, 17.00, 14.28; IR: $\tilde{\nu} = 2961$, 2929, 2868, 1587, 1279, 1195, 1012, 955, 876, cm⁻¹; UV/Vis: λ_{max} (ϵ) = 281 (27000), 355 (37700), 396 (32500), 559 (60000), 654 (166000); MS (FAB): m/z (%): 1278 (100) [M^+]

7: IR: $\tilde{\nu} = 2962$, 2928, 2868, 1587, 1387, 1287, 1188, 1012, 955, 876 cm⁻¹; UV/Vis: λ_{max} (ϵ) = 359 (47000), 594 (70000), 638 (246000); MS (FAB): m/z (%): 1192 (100) [M^+]

Correct C, H, N analytical data are available for **5**–**7**.

show that on incorporation of two Pd^{II} or Cu^{II} ions into the two N₄ cavities of **2** the molecular symmetry remains unaffected, but there are marked conformational changes in the ligand framework (Figure 2 for the palladium complex **6**; the same applies for **7**). The intramolecular separations of the metal centers of **6** (7.70 Å) and **7** (7.48 Å) are not conducive to significant intermetal interactions. Accordingly, a temperature-independent effective magnetic moment, the value of which can be accommodated by a model in which the two

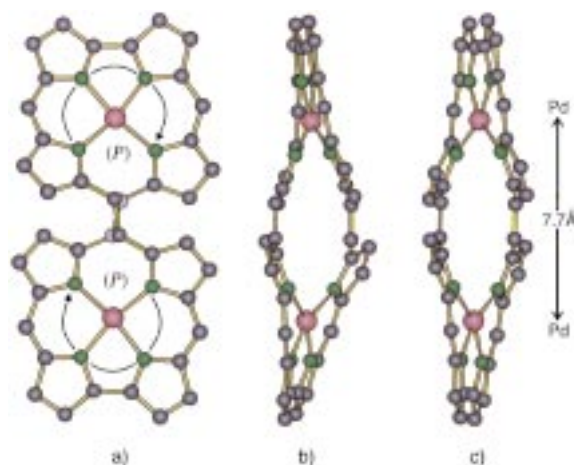


Figure 2. Structure of the (*P,P*)-configured enantiomer of the palladium complex **6** (first eluate) in the crystal of the enantiomer: a) plan view and b) side view. Structure of the (*P,P*)-configured enantiomer of **6** in the crystal of the racemate: c) side view. The ethyl groups are omitted for clarity.

copper(II) centers are practically uncoupled, can be derived from the magnetic susceptibility of **7**.^[12]

The enantiomeric separation of cyclooctapyrrole ligand **2** tried first was carried out on an analytical HPLC column (4.6 × 250 mm) with commercially available Chiralcel OD (silica gel coated with cellulose tris(3,5-dimethylphenyl carbamate) (CDMPC)) from the company DAICEL.^[13] The samples used for the measurement of the circular dichroism (CD) spectra of the enantiomers of **2** were separated by applying 200-μL volumes of a saturated solution of the racemate in eluent to the analytical column (separation factor $\alpha = 2.28$; Table 2). The mirror-image CD spectra show that

Table 2. Chromatographic data of the analytical and preparative enantiomeric separation of the cyclooctapyrroles **1** and **2** and the metal complexes **5**–**7**.^[a]

Compd.	Analytical (HPLC, Chiralcel OD)				Preparative (CDMPC-C ₁₈)			
	<i>k</i> ₁	<i>k</i> ₂	α	<i>R</i> _S	<i>k</i> ₁	<i>k</i> ₂	α	<i>R</i> _S
1	0.15	0.35	2.37	2.87	–	–	–	–
2	0.18	0.41	2.28	3.10	0.1	0.21	2.16	1.33
5	0.25	0.32	1.28	0.96	0.19	1.2	6.3	4.9
6	0.55	1.05	1.91	3.43	0.15	8.51	56.7	27
7	0.36	0.36	1	0	0.15	1.53	10	8.1

[a] Eluent: *n*-Hexane with addition of 2-propanol (0.25 %) and diethylamine (0.1–0.2 %); room temperature (at 15 °C for **1** because of the tendency to racemize); equilibration time: 3 h; *k*₁, *k*₂: capacity factors of the enantiomers; α : separation factor; *R*_S: resolution.

the racemate separation had been successful (Figure 3). Owing to the intense color of the solution it was not possible to measure the optical rotation with any reliability (this applies to all the compounds investigated here). The enantiomers of **2** are optically stable, as their solutions in *n*-hexane can be warmed at 60 °C for several hours without measurable racemization occurring.

The tetrahydro derivative **1** of **2** can also be separated into the enantiomers on the above HPLC column. Since the enantiomers of **1** racemize even at room temperature, the

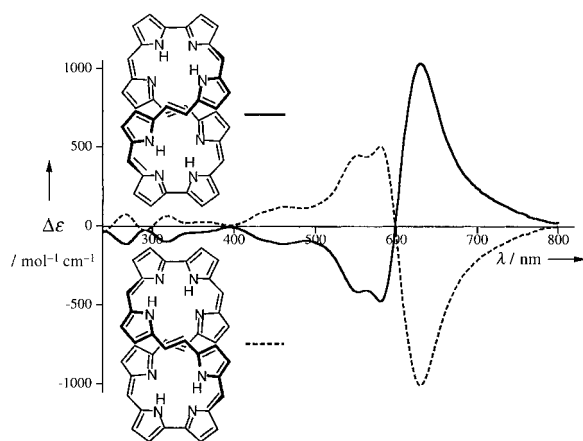


Figure 3. CD spectra (CH_2Cl_2) of the enantiomers of **2**; first eluate: (*M,M*) enantiomer (—); second eluate: (*P,P*) enantiomer (---).^[17]

separation was carried out at 15 °C ($\alpha = 2.37$; Table 2) under otherwise identical conditions as with **2**. The two enantiomer fractions were kept in an ice bath and then freed of solvent under high vacuum (ice cooling), and the enantiomers remaining were dried at 0.001 Torr. This separation procedure was repeated with the already highly enriched samples (70–80% *ee*), with the effect that the enantiomeric purity was increased to over 95% *ee*.

The kinetics of racemization in *n*-hexane of the enantiomers of **1** thus obtained were determined by CD spectroscopy on the basis of the changes in circular dichroism with time. The measurements were carried out at three temperatures (299 K: $k = 7.2 \times 10^{-5} \text{ s}^{-1}$; 312 K: $k = 2.3 \times 10^{-4} \text{ s}^{-1}$, and 321 K: $k = 4.7 \times 10^{-4} \text{ s}^{-1}$) and at $\lambda = 396 \text{ nm}$, the most intense band in the UV/Vis spectrum of **1**. The rate constants k of the racemization were determined from a logarithmic plot of the change in extinction against time t . A value of $96.5 (\pm 0.5) \text{ kJ mol}^{-1}$ was thus derived for the free activation enthalpy $\Delta G_{298}^\ddagger$ of racemization. The prognosis, based upon NMR results,^[1a] that the inversion barrier, not only for **2** but also for the less rigid **1**, is greater than 85 kJ mol^{-1} is thus confirmed.

The enantiomeric separation of **2** on a preparative scale, which is of interest for the synthesis of enantiomeric metal complexes, required the preparation of an appropriate chiral stationary phase. Based upon the investigations of Matlin et al.^[14] spherical silica gel with a pore diameter of 120 Å and a particle size of 30 μm (Hyperprep) was used; after successive treatment with dimethyloctylchlorosilane and trimethylchlorosilane^[15] (formation of “octyl silica gel”) the gel was coated with 10 wt% of the chiral selector CDMPC. This stationary phase (CDMPC- C_8), packed in a thermostated glass column (25 × 300 mm), enabled 15 mg of racemic **2** to be separated into the enantiomers by cyclic medium pressure chromatography (closed loop technique) with the eluent proven from the analytical method (separation factor $\alpha = 2.16$, Table 2). The fractions thus obtained with an enantiomeric excess of over 97% *ee* were brought to a purity of greater than 99.8% *ee* by repeated chromatography on this phase.

Most notably, the metal complexes **5–7** could be separated into the enantiomers particularly efficiently on the prepara-

tive phase CDMPC- C_8 , whereas on the analytical HPLC column a base-line separation was obtained only with **6** (Table 2). In accord with the increase in the rigidity of the ring framework associated with the metallation of **1** and **2**, not only did the enantiomers of **6** and **7** prove to be optically fully stable, but so did those of **5**, which were derived from the readily racemizable tetrahydrooctaphyrin **1**.^[17]

The remarkably high enantioselectivity of the chiral cellulose phase CDMPC- C_8 towards the palladium complex **6** (separation factor $\alpha = 56.7$!, Table 2) allowed racemate separation on a 100-mg scale without undue effort. This made possible the growth of single crystals of the two enantiomers of **6** for the determination of their absolute configuration—and consequently that of the enantiomers of **2**—by X-ray structural analysis.^[10] The analysis, which was carried out with use of the anomalous scatter contribution of the two heavy atoms, showed that in the case of the first eluted enantiomer of **6** the four pyrrole units of a coordination sphere are each arranged equidirectionally in a right-handed (*P*)-helix around the palladium atom (Figure 2a).^[6] A comparison of the side views of the structures of the (*P,P*)-configured enantiomer and the racemate of **6** (Figures 2b and c) shows that the structure of the single enantiomer exhibits a distinctive curvature as a result of different packing effects in the crystal lattice. Whereas the crystals of the enantiomers of **6** belong to the noncentrosymmetric, monoclinic $P2_1$ space group, the crystals of the racemate form a lattice of the triclinic $P\bar{1}$ space group with an inversion center.

This study confirms the expectation that figure eight cyclooctapyrroles and—presumably in general—their binuclear metal complexes are amenable to preparative enantiomeric separation by chromatography on suitable phases (here a CDMCP coated silica gel proved suitable). With a view to potential applications, particularly in asymmetric catalysis, it is intended to subject a selection of the fairly large number of homo- and heterobinuclear metal complexes of ligands **3** and **4** already synthesized to racemate separation.^[18,19]

Experimental Section

Cyclooctapyrrole 1: Bis(5-benzyloxycarbonyl-3,4-diethyl-2-pyrrolyl)ethane^[1a] (540 mg, 1 mmol) and 3,3',4,4'-tetraethyl-5,5'-diformyl-2,2'-bipyrrrole (300 mg, 1 mmol) are dissolved in tetrahydrofuran/methanol (3/2, 300 mL). Boron trifluoride ethyl etherate (15 mL) is added with vigorous stirring to this solution over 30 min at –10 °C, and the mixture is allowed to stand at room temperature for 15 h. The reaction mixture is then neutralized with 2M sodium hydroxide and extracted with toluene (3 × 250 mL). The organic phase is washed several times with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. On chromatography of the residue on basic aluminum oxide (activity II–III, Merck AG, Darmstadt; column 50 × 300 mm) with *n*-hexane/toluene (2/1) **1** elutes as the first, red-brown fraction. Compound **1** is obtained as violet needles (decomp. 250 °C) by crystallization from *n*-hexane/dichloromethane (4/1); yield: 215 mg (40%).

Standard synthetic method for the metal complexes 5–7: The hexadecaethylcyclooctapyrroles **1** or **2** (53 mg, 0.05 mmol) are dissolved in chloroform (40 mL) and triethylamine (2 mL), and after the addition of a solution of the respective metal diacetate (0.25 mmol) in methanol (20 mL) the solution is allowed to stand at room temperature under an inert atmosphere (**5** and **6**: $\text{Pd}(\text{OAc})_2$, 16 h; **7**: $\text{Cu}(\text{OAc})_2$, 1 h). The reaction mixture is then treated with more chloroform (50 mL). The organic phase is washed several times with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. On chromatography of the residue on

basic alumina (activity II–III, column: 20 × 120 mm) with *n*-hexane/toluene (1/1) the binuclear metal complexes are eluted first as intensely colored fractions (**5**: blood red; **6**: blue; **7**: blue-green); **5**: violet crystals (from methanol/dichloromethane), decomp. 280 °C, yield: 45 mg (70 %); **6**: golden crystals (from methanol/dichloromethane), decomp. > 310 °C, yield: 50 mg (78 %); **7**: dark green crystals (from acetonitrile/dichloromethane), decomp. > 310 °C, yield: 48 % (80 %).

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Tightening the Belt on Polymerases: Evaluating the Physical Constraints on Enzyme Substrate Size**

Miriam Frieden, Enrique Pedrosa,* and Eric T. Kool*

Recent X-ray crystal structures have shown that the active site cleft of DNA polymerases holds approximately five base pairs of double-stranded DNA in a linear A-like conformation.^[1] Polymerases are relatively large proteins consisting of about 600–1000 amino acids, and have dimensions of 50–100 Å on a side. Despite the large size of the proteins and the generally rigid, linear conformation of DNA substrates for these enzymes, recent studies have shown that DNA and RNA polymerases can be active on quite small, constrained templates.

For example, synthetic circular single-stranded (ss) oligodeoxynucleotides have been tested as substrates for polymerases.^[2, 3] Interestingly, evidence suggests that DNA circles as small as 26 nucleotides can be active as templates for DNA polymerases.^[2b] Similarly, studies with RNA polymerases (RNAPs) have shown that ssDNA circles as small as 34, or even 28, nucleotides (nt) may be active substrates for transcription.^[3a, 4] Those surprising results raise an interesting question: How small can a circular DNA be and still act as a template for these enzymes? Here we show that polymerases can utilize circular templates that are remarkably small, which lends insight into the geometric constraints of these important enzymes, and also has practical implications in methods for the amplified synthesis of DNA and RNA.

To test this question, we prepared cyclic DNAs of 28, 23, 18, and 13 nucleotides (**1–4**, Figure 1) using recently developed methods.^[5] We chose 28 nt as the upper limit because previous studies suggested that this largest circular DNA might be a substrate for both classes of enzymes.^[2b, 4] The sequences were taken from the HIV-1 *gag* gene; if copied by polymerases, the resulting repeating DNA or RNA strands would be complementary (antisense) to the gene. The sequences are nested, in that the smaller circles are subsets of the larger ones. Also included is a recognition site (T•CGA) for *Taq* Ia restriction endonuclease.

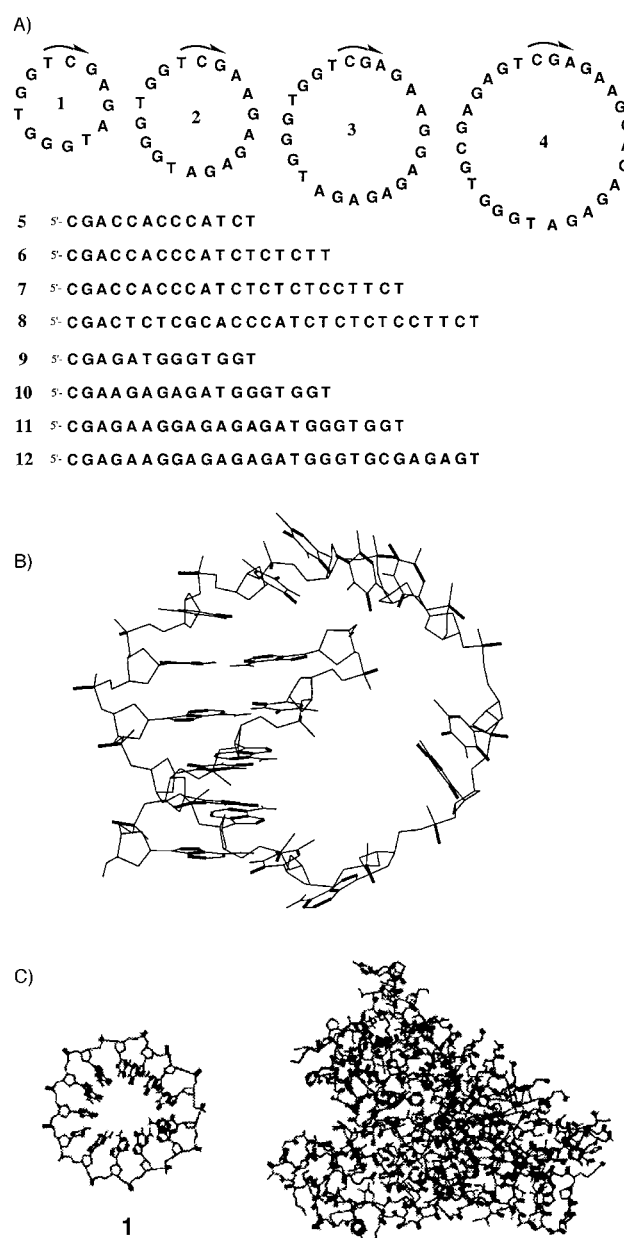


Figure 1. Sequences and structures used in this study. A) Sequences of circular DNA oligonucleotides **1–4**, complementary primers **5–8**, and linear controls **9–12**. Curved arrow denotes 5'→3' strand orientation. B) Molecular model showing how a circular 13-mer might conceivably form four base pairs of duplex (as in a template–primer complex in a polymerase active site) without strongly distorting it. C) Models showing relative sizes of circle **1** and KF polymerase.

We then examined whether these could be enzyme substrates by incubating them with DNA polymerases, a complementary primer (**5–8**, Figure 1), and deoxynucleoside triphosphates, or with RNA polymerases and ribonucleoside triphosphates. We also tested the linear versions of the circular DNAs as controls (**9–12**, Figure 1). Three DNA polymerases were examined: The Klenow fragment of *E. coli* DNA polymerase I (KF), T4 DNA polymerase, and Sequenase 2.0 (a T7 DNA polymerase mutant). The results show that the T4 and Sequenase enzymes apparently do not accept any of the four circular DNAs as templates (data not shown). However, the KF enzyme gave relatively long products (ca.

[*] Prof. E. Pedrosa, M. Frieden
 Departament de Química Orgànica
 Facultat de Química, Universitat de Barcelona
 Barcelona, E-08028 (Spain)
 Fax: (+34) 93-33-97-878
 E-mail: pedrosa@admin.qo.ub.es
 Prof. E. T. Kool^[+]
 Department of Chemistry, University of Rochester
 Rochester, NY 14627 (USA)

[+] Current address:
 Department of Chemistry, Stanford University
 Stanford, CA 94305-5080 (USA)
 Fax: (+1) 650-725-0259
 E-mail: kool@chem.stanford.edu

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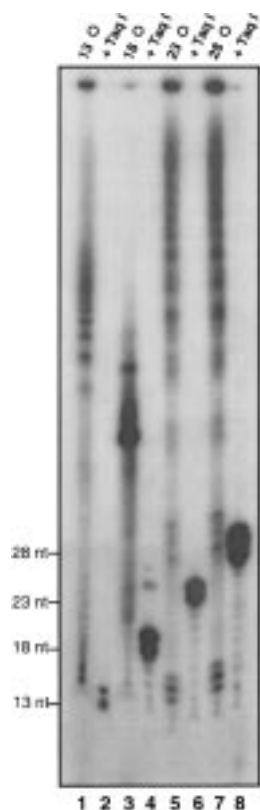


Figure 2. Products of DNA polymerase reactions on distorted circular templates **1**–**4**. The enzyme in these experiments is the Klenow fragment of *E. coli* DNA Polymerase I. Presented is an autoradiogram of a denaturing polyacrylamide gel, showing long DNA products synthesized on circular templates (lanes **1**, **3**, **5**, **7**) and the products of cleavage of these long DNAs with *Taq Ia* restriction enzyme (lanes **2**, **4**, **6**, **8**). Doubling of bands in the even lanes is expected because of the labeling method used.^[6]

synthesis on such repetitive polydisperse products, or possibly to a decreased level of fidelity on these unusual templates.

We then tested two different RNA polymerases, T7 RNA Polymerase and *E. coli* RNA polymerase, with these four very small circular templates. The data show that with the linear templates only very short RNAs are produced (Figure 4). However, cyclization of the DNAs results in the synthesis of quite long RNAs. For *E. coli* RNAP, the results show that this polymerase is active on the 28nt circle, producing RNAs longer than 1000nt. This same polymerase also utilizes the 23nt circular template, although to a lesser extent. This appears to be the size limit for this enzyme, as the shorter 18nt and 13nt DNAs are apparently not transcribed.

Interestingly, the results for the smaller T7 RNA polymerase are quite different. This enzyme appears to actively synthesize long RNAs on all four templates (Figure 4). The

300 to greater than 1000nt) with three of the four circles, including the smallest one (**1**), which is only 13 nt (Figure 2). By contrast, the linear controls gave no long DNA products, supporting the idea that circular structure is required for this activity (data not shown). The products of the 18nt circle were shorter; it is as yet unclear why this is the case, but it is possible that this sequence adopts a secondary structure which disfavors primer binding. A regular banding pattern is visible for three of the cases; this we ascribe to pausing once per turn around the circle prior to incorporation of radiolabeled dGTP, which is kept at low concentrations. The expected products are single-stranded DNAs of a repeating sequence (complementary to the circle), and the regular banding pattern provides evidence that the products are indeed faithful copies of the circular templates.

Cleavage of the products with *Taq Ia* resolved them into the predicted short products (Figure 2),^[6] serving as a second confirmation of accurate polymerase copying. Finally, dye-terminator sequencing of the products shows that all four cases give evidence of the expected repeating sequences (see Figure 3 for results with the 13-mer circle). Perhaps significantly, there are a number of errors observed in these sequences; this is likely due to standard sequencing errors and to artifacts such as fold-back and slipped

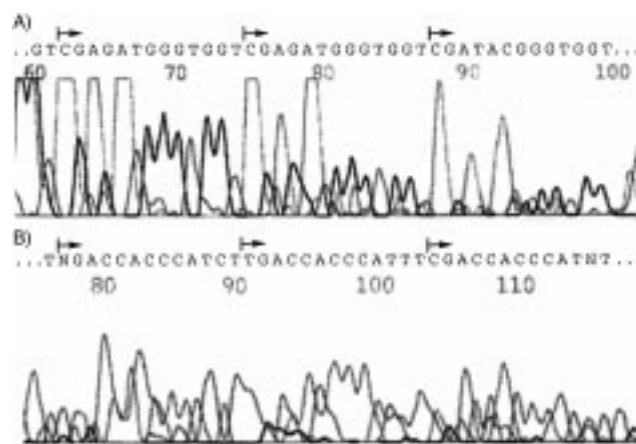


Figure 3. Dye-terminator sequencing results for repeating nucleic acids produced on 13-mer circular template **1**. Arrows denote the observed repeats encoded by the circle. A) Sequencing of DNA produced with the *KF* DNA polymerase. B) Sequencing of RNA produced with T7 RNA polymerase. Note that only short reads can be obtained because the primer can bind anywhere in the body of the repeating sequence.

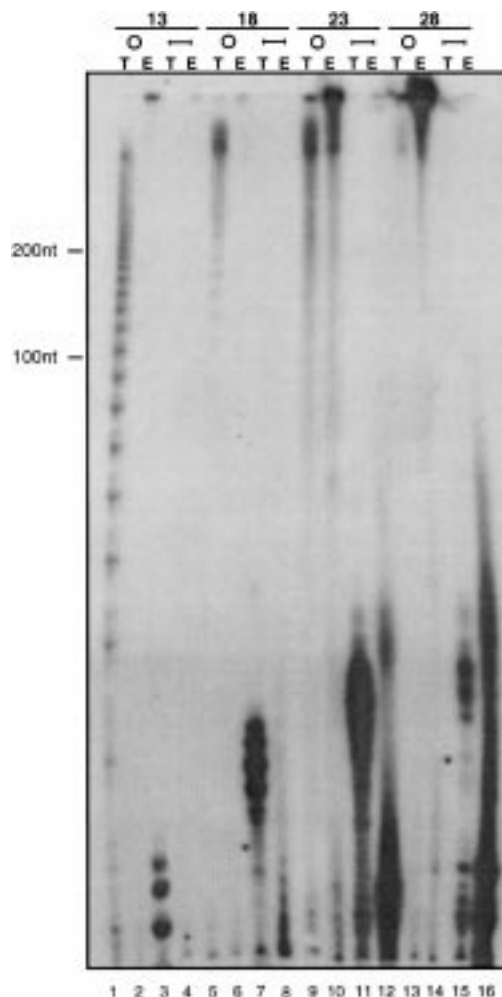


Figure 4. Products of RNA polymerase reactions on circular templates **1**–**4**. The enzyme used is denoted by E (*E. coli* RNAP) or T (T7 RNAP); the template topology (circular or linear) is denoted by circles and lines.

RNA products are shorter on the 13-mer template than on the longest two; this may reflect some inefficiency with utilization of this most distorted template. Once again, a regular banding

pattern is observed; this we ascribe to preferential initiation with GTP at the single C in the sequence combined with partial termination at each round of synthesis.^[4] Again, these regular banding patterns serve as evidence that the polymerase is indeed utilizing these very small circles as viable templates. Further, sequencing of the RNAs shows in general that the chief identifiable sequences are indeed the predicted repeating sequences encoded by these circles. Even the 13 nt circle shows evidence for at least eleven repeats (implying eleven trips around the circular template). This is consistent with the gel evidence (Figure 4), which shows that at least 15 repeats can be synthesized with this smallest circle.

Such small constrained DNAs put significant topological constraints on polymerase activity. For DNA polymerases, a primer oligonucleotide must bind for several adjacent nucleotides, which in itself may be problematic with a circle only 13 nt in size. The polymerase must then bind this complex before nucleoside triphosphates are added to the primer end. X-ray crystal structures of DNA polymerases bound to double-stranded DNAs show that in the enzyme the DNA is straight and in an A-like conformation for roughly five base pairs.^[1] If one assumes that five base pairs of duplex are formed in the active site, this causes additional topological difficulties for a circular 13-mer. Half a helical turn (5 bp) of DNA forces the two ends of one strand to be oriented nearly on opposite faces of the duplex. Models suggest (Figure 1B) that the remaining eight nucleotides could conceivably bridge this distance; however, it is possible that fewer base pairs (perhaps two to four) are formed in the active site at one time with these constrained templates. It is worth noting that since the 13-mer circle is active as a template, the actual size limit may be even smaller than this for the KF and T7 RNAP enzymes, although our models suggest that this may be unlikely.

Although there are fewer crystal structures of RNA polymerases for comparison,^[7a] RNA polymerases likely face many of the same issues.^[7b] One significant difference is that RNA polymerases do not require a primer for initiation; rather, they initiate immediately downstream of a conserved double-stranded promoter sequence. Thus the present results are unusual both because these templates are strongly structurally distorted and because they contain no promoters.

Replication and transcription of naturally occurring DNAs often requires processing of topologically closed (i.e., circular) templates, such as those from bacteria and viruses. On a local scale, however, bacterial and viral genomes are essentially linear, as they are quite large. For example, the genome of *E. coli* has 4.6 million base pairs,^[8] and even the much smaller circular genome of the T7 bacteriophage has 40 000 base pairs.^[9] We find it remarkable that polymerases from these organisms can process a circular 13-mer.

Finally, small synthetic circular DNAs have been investigated in several laboratories recently for their unusual ability to act as templates for amplified DNA and RNA synthesis.^[2–4] These rolling circle replication (RCR) and rolling circle transcription (RCT) reactions have utility in detection of nucleic acids and for in vitro synthesis of amplified quantities of DNAs and RNAs. The current results indicate that even very short DNAs could in principle be

synthesized enzymatically on a monomer-length circular template. For example, restriction cleavage of the products from the present 23-mer template (Figure 2) produces a linear DNA very close in sequence to an oligonucleotide which has undergone clinical trials for treatment of HIV infection.^[10]

Experimental Section

Cyclic oligodeoxynucleotides: The 28-, 23-, 18-, and 13-mer cyclic oligodeoxynucleotides **1–4** were synthesized as reported elsewhere^[5] on a 2- μ mol scale. The crude products were obtained in 7, 9, 8, and 7% yields, respectively. The 13-mer was purified by semipreparative HPLC, and the rest by preparative denaturing 20% polyacrylamide gel electrophoresis (PAGE). The product band was isolated by excision, crushing, and elution into 2 M ammonium acetate. Salts were removed with a Sep Pak C18 cartridge (Waters), and the DNA was quantitated by absorbance at 260 nm. The circular structures were confirmed by their altered size dependence of gel mobility, by their partial chemical and/or enzymatic (S1 nuclease) degradation (which produced bands migrating as expected for linear products of nicking),^[11] and by MALDI-TOF mass spectrometry, (showing in all cases the expected mass). Linear DNA controls and primers were synthesized on an ABI 392 DNA synthesizer using the standard DNA cycle. Deprotection in concentrated ammonia was carried out at 55 °C for 12 h. After lyophilization, the DNAs were purified by preparative denaturing PAGE and quantitated by UV absorbance at 260 nm.

DNA polymerase reactions: Conditions for DNA synthesis using the Klenow fragment (KF) of DNA polymerase I (Pharmacia) were as follows: 1 μ M circle or linear control, 1 μ M primer, 3 U enzyme, 0.5 mM each of dATP, dTTP, and dCTP, 60 μ M dGTP (Boehringer Mannheim), 0.30 μ Ci [α -³²P]dGTP in a buffer (pH 7.5) containing 50 mM Tris·HCl, 10 mM MgCl₂, 1 mM dithiothreitol (DTT), and 50 μ g mL⁻¹ acetylated bovine serum albumin (BSA), in 15 μ L total volume. – Conditions for T4 DNA polymerase (Gibco BRL) were: 1 μ M circle or linear control, 1 μ M primer, 3.75 U enzyme, 0.5 mM each of dATP, dTTP, and dCTP, 60 μ M dGTP (Boehringer Mannheim), 0.30 μ Ci [α -³²P]dGTP in a buffer (pH 7.9) containing 33 mM Tris·acetate, 66 mM NaOAc, 10 mM Mg(OAc)₂, 100 μ g mL⁻¹ acetylated BSA, and 0.5 mM DTT, in a volume of 15 μ L. – Conditions with T7 Sequenase version 2.0 (Pharmacia) were: 1 μ M circle or linear control, 1 μ M primer, 4.5 U enzyme, 0.5 mM each of dATP, dTTP, and dCTP, 60 μ M dGTP (Boehringer Mannheim), 0.30 μ Ci [α -³²P]dGTP in a buffer (pH 7.5) containing 40 mM Tris·HCl, 20 mM MgCl₂, and 50 mM NaCl, in a total volume of 15 μ L. – Reaction mixtures were incubated at 37 °C for 1.5 h and stopped by addition of one volume of stop solution (30 mM EDTA, 8 M urea). Reaction mixtures were heated to 90 °C for 2 min, and then chilled on ice before being loaded on a 10% polyacrylamide denaturing gel (0.4 mm thick).

RNA polymerase reactions: Conditions for an internally labeled rolling circle transcription reaction were: 1 μ M circle or linear control, 3 U *E. coli* RNA polymerase holoenzyme (Boehringer Mannheim) or 25 U T7 RNA polymerase (New England Biolabs), 0.5 mM ATP, GTP, and CTP (Pharmacia Biotech), 60 μ M UTP (Boehringer Mannheim), 0.30 μ Ci [α -³²P]UTP in a buffer (pH 8.1) containing 25 mM Tris·HCl, 20 mM NaCl, 12 mM MgCl₂, 0.4 mM spermine·HCl (Sigma), 100 μ g mL⁻¹ acetylated BSA (New England Biolabs), 10 mM DTT, and 12.5 U mL⁻¹ RNase inhibitor (Promega), in a total reaction volume of 15 μ L. Reaction mixtures were incubated at 37 °C for 1.5 h and stopped by addition of one volume of stop solution. They were then analyzed by PAGE as above.

Cleavage of DNA Multimers: Rolling circle reactions were carried out with internal labeling so that cleaved products would retain their labels. The reaction mixture was the same as described above for DNA synthesis. DNA products after 1.5 h were precipitated with 2.5 volumes of cold ethanol and 0.2 volumes of NaOAc (3 M, pH 5.2) and resuspended in a buffer (pH 8.4) containing 100 U of restriction enzyme *Taq* I α (20 U μ L⁻¹) (New England Biolabs), 100 μ g mL⁻¹ BSA, 100 mM NaCl, 10 mM Tris·HCl, and 10 mM MgCl₂ in a total volume of 20 μ L. After 12 h incubation at 65 °C, the products were extracted with phenol/chloroform (1/1) and separated from dNTPs and other small molecules with Micro Bio-Spin 6 column (Bio-Rad). Products were analyzed by denaturing PAGE.

Sequencing of Products: Unlabeled DNA was prepared from rolling circle replication reaction as above but with all four dNTPs at 0.5 mM. After 1.5 h incubation at 37 °C, the mixture was heated to 90 °C for 5 min and partially purified with Micro Bio-Spin 30 columns (Bio-Rad). Sequencing was carried out using a BigDye Terminator Cycle Sequencing Kit (Applied Biosystems) following the recommended procedure. The linear controls **9**–**12** were used as sequencing primers. Unlabeled RNA was prepared from rolling circle transcription reactions as above but with all four rNTPs at 0.5 mM. After 1.5 h incubation at 37 °C, the mixture was heated to 90 °C for 5 min and the repetitive RNA products were partially purified by size exclusion as above. The complementary DNA was obtained by using these conditions: partially purified RNA, 50 pmol linear primer DNA (either **9**, **10**, **11**, or **12**), 50 U AMV Reverse Transcriptase (Pharmacia), 10 mM dATP, dGTP, dCTP and dTTP, 20 U RNase inhibitor (Promega) in a buffer (pH 8.3) containing 100 mM Tris·HCl, 10 mM MgCl₂, 10 mM DTT, and 50 mM KCl, in a total volume of 20 µL. After 1 h incubation at 42 °C, the reaction mixture was heated to 90 °C for 5 min and cleaned up with a Micro Bio-Spin 30 column. The complementary DNA was then sequenced as above, using primers **5**–**8**.

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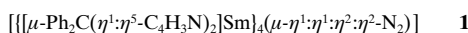
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Tetrametallic Reduction of Dinitrogen: Formation of a Tetranuclear Samarium Dinitrogen Complex**

Tiffany Dubé, Sabrina Conoci, Sandro Gambarotta,* Glenn P. A. Yap, and Giuseppe Vasapollo

Examples of dinitrogen complexes are rare in lanthanide chemistry and have been documented for only four cases.^[1, 2] In the case of samarium in particular, the two existing complexes display a completely different extent of dinitrogen reduction.^[1] Thus, in an attempt to evaluate the role played by the nature of the ligand in promoting dinitrogen reduction, we have now prepared a novel diphenylmethyldipyrrolide dianion and investigated its ability to stabilize Sm^{II} complexes.^[3] Herein we describe the first example in which a four-electron dinitrogen reduction is achieved through the cooperative one-electron oxidation of four metal centers. To the best of our knowledge this type of process has been observed only in the nitrogenase enzyme.^[4]

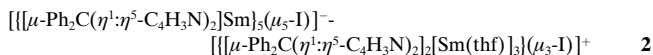
The reaction of [SmI₂(thf)₂] with one equivalent of diphenylmethyldipyrrolide dianion (dipyr²⁻; either as disodium or dipotassium salt) at room temperature under N₂ yielded a dark purple-brown solution from which dark brown crystals of **1** (Figure 1) were isolated in an analytically pure form in good



yield on a reproducible basis. Unlike [[N(CH₂CH₂NSi^tBuMe₂)₃U]₂(μ-η²-η²-N₂)]^[5] or [(η⁵-C₅Me₅)₂Sm]₂(μ-η²-η²-N₂)]^[1a] and similar to the case of the calix-tetrapyrrole derivative,^[1b] complex **1** showed no sign of reversible coordination of dinitrogen and remained unchanged upon prolonged exposure to heat or vacuum.

The presence of a molecule of coordinated dinitrogen in the molecular structure was demonstrated by an X-ray crystal structure analysis. The complex is composed of four [[Ph₂C(C₄H₃N)₂]Sm] units; the four metal atoms arrange to form a slightly distorted lozenge, in the center of which is located a dinitrogen molecule that is coordinated *side-on* to two metal atoms and *end-on* to the other two metal atoms. The N–N distance and the fact that degradation with anhydrous HCl did not release N₂ indicates that the Sm atoms are present in the formal trivalent state.^[6]

The same reaction carried out under an argon atmosphere afforded dark red crystals of a new ionic compound formulated as **2** (Figure 1). The ionic structure is formed by a



[*] Prof. S. Gambarotta, T. Dubé, Dr. G. P. A. Yap
Department of Chemistry, University of Ottawa
Ottawa, ON, K1N 6N5 (Canada)
Fax: (+1) 613-562-5170
E-mail: sgambaro@oreo.chem.uottawa.ca

Dr. S. Conoci, Prof. G. Vasapollo
Department of Material Science, Faculty of Engineering
University of Lecce (Italy)

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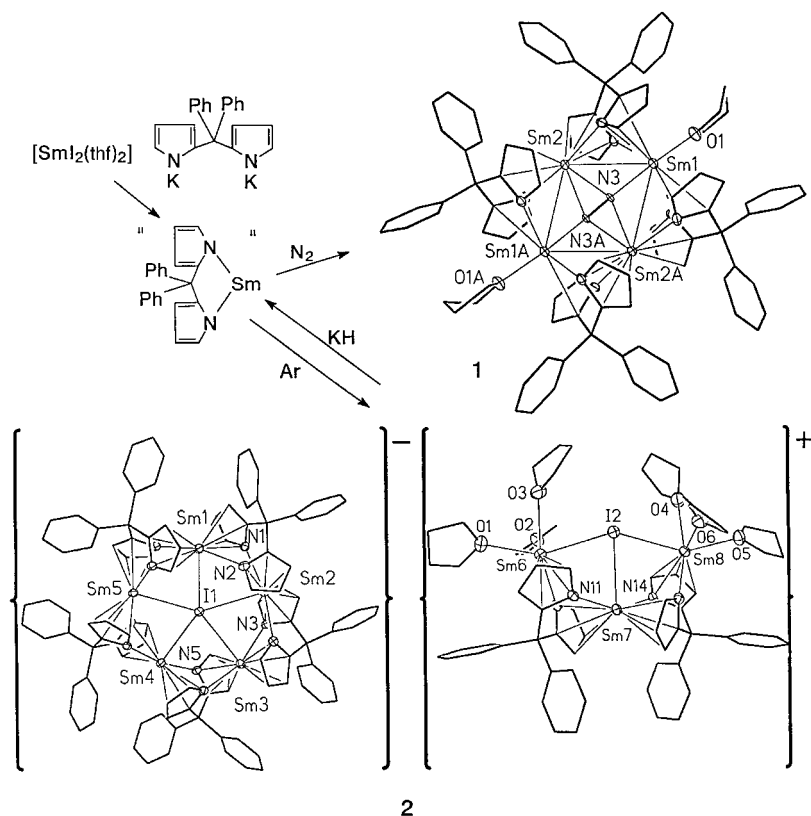
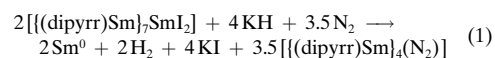


Figure 1. Synthesis and structures of **1** and **2**. Bond lengths [Å] and angles [°]: for complex **1**: N3–N3A 1.412(17), Sm1–N3 2.177(8), Sm2–N3 2.327(3), Sm2–N3A 2.327(3), Sm1...Sm2 3.602(9), Sm2...Sm2A 4.434(9), Sm1...Sm1A 5.678(9), Sm1–N1 2.701(8), Sm1–N2 2.736(8), Sm2–N1 2.574(8), Sm2–N2 2.697(7); Sm1–N3–N3A 156.6(11), O1–Sm1–N3 150.5(4); for complex **2**: Sm1–I1 3.434(1), Sm2–I1 3.480(1), Sm3–I1 3.634(1), Sm4–I1 3.455(1), Sm5–I1 3.520(1), Sm1–N1 2.810(7), Sm1–N2 2.670(7), Sm1–N9 2.664(7), Sm1–N10 2.768(7), Sm6–I2 3.3168(8), Sm7–I2 3.369(1), Sm8–I2 3.3047(9), Sm1...Sm2 4.123(1), Sm1...Sm5 4.101(1), Sm7...Sm6 4.028(1), Sm7...Sm8 4.038(1), Sm1–I1–Sm2 73.211(18), Sm1–I1–Sm5 72.260(16), Sm7–I2–Sm6 74.090(18), Sm7–I2–Sm8 74.468(18), Sm6–I2–Sm8 148.35(2).

trinuclear cation and a pentanuclear anion. The cation consists of three samarium atoms bridged by one nearly coplanar iodine atom which adopts a distorted “T-shape” geometry. The three samarium atoms are also bridged by two diphenylmethyldipyrrolium dianions, which adopt the same bonding mode observed in complex **1**. The counteranion is a pentanuclear samarium complex with five samarium atoms pentagonally arranged around a central, and coplanar iodine atom. The five diphenylmethyldipyrrolium dianions adopt the usual π - and σ -bonding modes with each ligand bridging two samarium centers.

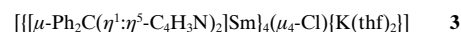
Complex **2** does not show any appreciable sign of reaction with nitrogen gas even after long periods and upon heating. Thus questions arise about the striking diversity of behavior resulting in the formations of **1** and **2**. Complex **2** exclusively contains divalent samarium atoms. The unit formula formally consists of seven $[\text{Ph}_2\text{C}(\text{C}_4\text{H}_3\text{N}_2)]\text{Sm}$ units and one SmI_2 organized in stable cluster structures around the two halogen atoms. The presence of the two iodine atoms is likely to be the factor responsible for the lack of reactivity with dinitrogen. Attempts to avoid their presence, by carrying out the prepara-

tion of **2** with excess ligand, did not modify the result. The elimination of the formal SmI_2 unit was achieved by reaction of **2** with KH and resulted in an immediate color change and concomitant release of H_2 according to the Equation (1).



The fact that this reaction afforded **1** in good yield suggests that halogen elimination from **2** dissociates the cluster structures leading to the release of “ $[\text{Ph}_2\text{C}(\text{C}_4\text{H}_3\text{N}_2)]\text{Sm}$ ” fragments which are then free to react with dinitrogen.

In an effort to further clarify the role of the halogen atom, attempts were made to generate the “ $[\text{Ph}_2\text{C}(\text{C}_4\text{H}_3\text{N}_2)]\text{Sm}$ ” unit by reduction of a “ $[(\text{Ph}_2\text{C}(\text{C}_4\text{H}_3\text{N}_2)]\text{Sm}]\text{Cl}$ ” precursor with potassium under nitrogen and in THF (Figure 2). The reaction yielded a new Sm^{II} compound formulated as **3**. Similar to the case of **2**, **3** showed no signs of reactivity towards



dinitrogen despite the striking structural similarity of its tetrametallic core with that of **1**. A chlorine atom is present instead of N_2 in the center of the square plane defined by the four samarium atoms, while one potassium is π -bonded to one of the pyrrole rings already

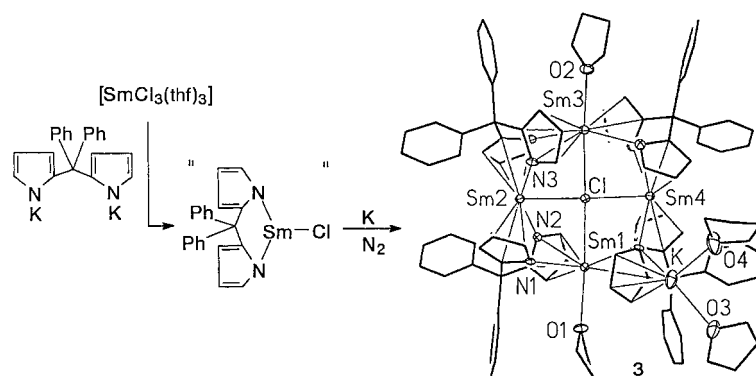


Figure 2. Synthesis and structure of **3**. Bond lengths [Å] and angles [°]: Sm1–Cl 3.045(2), Sm2–Cl 2.847(2), Sm3–Cl 3.042(2), Sm4–Cl 2.845(2), Sm1–N1 2.726(6), Sm1–N2 2.849(6), Sm1–N7 3.040(8), Sm1–N8 2.712(7), Sm1...Sm2 4.136(2), Sm1...Sm4 4.240(2), Sm1...Sm3 6.087(2), Sm2...Sm4 5.689(2); Sm1–Cl–Sm2 89.10(6), Sm1–Cl–Sm3 178.30(8), Sm1–Cl–Sm4 92.03(6), Sm2–Cl–Sm4 176.69(9), O1–Sm1–Cl 168.53(13).

engaged in σ - and π -bridging interactions with two samarium centers. This result confirms that the halogen has indeed an inhibitory effect on the ability of the samarium diphenylmethyldipyrrolium system to interact with dinitrogen. Notably, in spite of the oxophilicity of samarium, the presence of THF does not prevent dinitrogen fixation.

Experimental Section

1: Method A: A solution of potassium diphenylmethyldipyrrolide (1.3 g, 3.4 mmol) in THF (100 mL) was treated under N₂ with [SmI₂(thf)₂] (1.8 g, 3.4 mmol). The color immediately changed to dark purple-brown. Stirring was continued for 12 h after which the solution was filtered to eliminate a small amount of insoluble material. The filtrate was concentrated to 50 mL and layered with toluene (50 mL). After the mixture had been left to stand at room temperature for 24 h, large, red-brown crystals of **1** (1.3 g, 0.66 mmol, 78%) were obtained. Elemental analysis (%) calcd for Sm₄C₉₂H₈₀O₂N₁₀: C 56.40, H 4.12, N 7.15; found: C 56.35, H 4.08, N 7.09; IR (Nujol mull): $\tilde{\nu}$ = 3048 w, 1597 w, 1491 m, 1464 s, 1417 w, 1377 s, 1261 w, 1182 w, 1147 m, 1078 w, 1043 s, 985 w, 874 w, 798 m, 785 m, 756 s, 740 s, 696 s, 658 w, 640 cm⁻¹. μ_{eff} = 6.55 μ_{B} per formula unit.

Method B: A solution of **2** (0.7 g, 0.25 mmol) in THF (50 mL) under N₂ was treated with KH (0.050 g, 1.2 mmol). A vigorous reaction with effervescence and a color change to purple-brown was immediately observed. The solution was allowed to stir for 30 min, followed by filtration to remove a small amount of insoluble material. After the mixture had been layered with toluene and left to stand at room temperature for three days, crystals of **1** were obtained (Yield 76%).

2: A solution of diphenylmethyldipyrrolide (1.0 g, 3.4 mmol) in THF (100 mL) was stirred with KH (0.3 g, 6.7 mmol) for 30 min at room temperature under argon. Subsequent addition of [SmI₂(thf)₂] (1.8 g, 3.4 mmol) resulted in an immediate color change to dark brown. After stirring overnight the solution was filtered to eliminate a small amount of dark insoluble material, concentrated to 50 mL, and layered with toluene (25 mL). The mixture was allowed to stand for 24 h at room temperature, which resulted in the precipitation of large, dark red crystals of **2** (1.0 g, 0.22 mmol, 53% calculated relative to Sm). Elemental analysis (%) calcd for Sm₃N₁₄O₇C_{206.5}H_{205.5}: C 59.07, H 4.93, N 4.67; found: C 58.88, H 4.81, N 4.59; IR (Nujol mull): $\tilde{\nu}$ = 3049 w, 1595 w, 1489 m, 1464 s, 1419 w, 1377 s, 1263 w, 1234 w, 1184 w, 1151 m, 1076 m, 1038 s, 980 w, 964 w, 926 w, 891 m, 848 m, 789 m, 748 s, 704 s, 658 w, 634 m cm⁻¹. μ_{eff} = 9.14 μ_{B} per formula unit.

3: A solution of diphenylmethyldipyrrolide (1.1 g, 3.7 mmol) in THF (100 mL) was treated with KH (0.3 g, 7.5 mmol). Stirring was continued at room temperature for 30 min until all of the KH had been consumed. Subsequent addition of [SmCl₃(thf)₃] (1.7 g, 3.7 mmol) resulted in the formation of a yellow suspension which was stirred for 1 h. Potassium metal (0.15 g, 3.8 mmol) was then added to the reaction mixture together with a catalytic amount of naphthalene (0.01 g, 78 μ mol). Within minutes the color began to deepen to reddish-brown. After 4 h all the potassium had been consumed. The solution was filtered to remove a small amount of insoluble material. The dark brown filtrate was concentrated to 50 mL and layered with toluene (30 mL). After the mixture had been left to stand at room temperature for two days, large, dark brown crystals of **3** were obtained (1.2 g, 0.5 mmol, 58%). Elemental analysis (%) calcd for C₁₀₄H₁₀₄N₈O₅KClSm₄: C 56.21, H 4.72, N 5.04; found: C 56.11, H 4.66, N 4.97; IR (Nujol mull): $\tilde{\nu}$ = 3050 w, 1597 w, 1493 m, 1464 s, 1415 w, 1377 s, 1261 m, 1236 w, 1182 w, 1151 m, 1091 m, 1078 m, 1039 s, 980 w, 924 w, 879 w, 849 m, 795 m, 760 s, 700 s, 660 m, 636 m cm⁻¹. μ_{eff} = 7.02 μ_{B} per tetramer.

Crystal data for **1**: Sm₄C₉₂H₈₀O₂N₁₀, M_r = 1059.32, monoclinic, $C2/m$, a = 21.542(6), b = 19.232(6), c = 12.437(3) Å, β = 116.96(3)°, V = 4593(2) Å³, Z = 2, ρ_{calcd} = 1.405 Mg m⁻³; absorption coefficient 2.567 mm⁻¹, $F(000)$ = 1900, reflections collected 17557, independent reflections 5668, GOF = 1.007, R = 0.0546, wR^2 = 0.1696.

Crystal data for **2**: Sm₃N₁₄O₇C_{206.5}H_{205.5}, M_r = 4451.95, monoclinic, $P2(1)/c$, a = 18.186(2), b = 23.349(2), c = 43.492(4) Å, β = 90.169(2)°, V = 18467(3) Å³, Z = 4, ρ_{calcd} = 1.601 Mg m⁻³; absorption coefficient 2.895 mm⁻¹, $F(000)$ = 8802, reflections collected 145877, independent reflections 44562, GOF = 1.018, R = 0.0553, wR^2 = 0.1086.

Crystal data for **3**: C₁₀₄H₁₀₄N₈O₅KClSm₄, M_r = 2221.90, triclinic, $P\bar{1}$, a = 13.462(1), b = 17.534(2), c = 20.970(2) Å, α = 110.006(1), β = 100.343(2), γ = 90.421(1)°, V = 4562.8(7) Å³, Z = 2, ρ_{calcd} = 1.617 Mg m⁻³; absorption coefficient 2.670 mm⁻¹, $F(000)$ = 2216, reflections collected 35786, independent reflections 11862, GOF = 1.047, R = 0.0385, wR^2 = 0.1010.

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-117425 (**1**),

CCDC-117426 (**2**), CCDC-117427 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A Paramagnetic Diniobium Complex with a Very Short Nb–Nb Distance: Evidence for a Pseudo Nb–Nb Triple Bond?*

Maryam Tayebani, Khalil Feghali, Sandro Gambarotta,* Glenn P. A. Yap, and Laurence K. Thompson*

Low-valent second- and third-row transition metals typically form significant and robust M–M bonds.^[1, 2] Divalent Group 5 metals provide a puzzling exception. In principle, the d³ electronic configuration makes them good candidates for the formation of triple bonds. Exceedingly short V≡V triple bonds were indeed observed in a few dinuclear V^{II} complexes,^[3] although these bonds seem to display the same paradoxical weakness^[4] that was previously observed for quadruply bonded dichromium compounds.^[5] Conversely, for the heavier Nb and Ta homologues no such information is

[*] Prof. S. Gambarotta, M. Tayebani, K. Feghali, Dr. G. P. A. Yap
Department of Chemistry
University of Ottawa
ON, K1N6N5 (Canada)
Fax: (+1) 613-562-5170
E-mail: sgambaro@oreo.chem.uottawa.ca
Prof. L. K. Thompson
Department of Chemistry, Memorial University
St. John's, NF, A1B 3X7 (Canada)

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available, since the few known di- and polynuclear M^{II} compounds are para- or diamagnetic and have long M–M distances.^[6–8] An Nb^{II} complex of a three-center chelating pyrimidinate ligand^[9] has a characteristic paddle-wheel shape and the shortest Nb–Nb distance (2.2035(9) Å). On the basis of its diamagnetism, the existence of an “intrinsically stable” Nb≡Nb bond was proposed.^[10h] In an attempt to probe the strength of the Nb–Nb interaction, we attempted the preparation of another paddle-wheel dinuclear complex. However, we selected the 7-azaindoyl anion as a ligand whose bite usually accommodates long intermetallic distances.^[10]

Reaction of $[Nb_2Cl_5Li(tmeda)_3]$ (*tmeda* = *N,N,N',N'*-tetramethylethylenediamine) with four equivalents of 7-azaindoyllithium in THF afforded a deep blue solution, from which dark blue crystals of $[(7\text{-azaindoyl})_4Nb_2(\mu\text{-Cl})Li(thf)_3] \cdot 2THF$ (**1**) were isolated in good yield. The complex is dinuclear, and the two Nb atoms are bridged by four 7-azaindoyl anions, which together with the Nb_2 unit, adopt the characteristic paddle-wheel configuration (Figure 1). However, in contrast to the previously reported pyrimidinate complex,^[9] **1** bears two terminally bound LiCl units on the intermetallic axis, which provide the niobium atoms with a formal pyramidal coordination geometry. The Nb–Nb distance is only 0.065 Å longer than that of the pyrimidinate complex. The long Nb–Cl distance suggests that the coordination of the axial $(thf)_3LiCl$ moiety is rather weak.

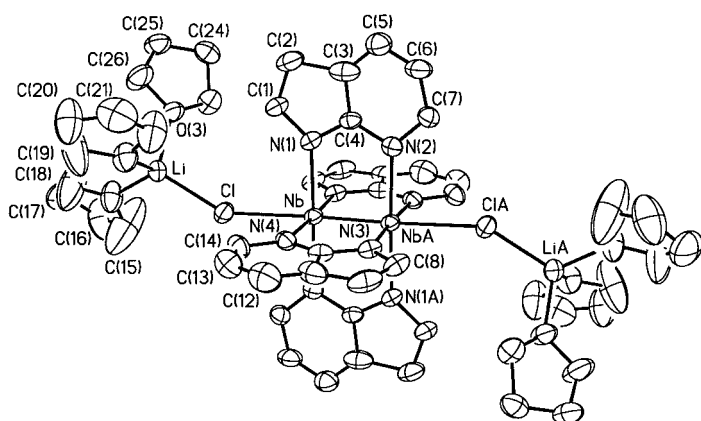


Figure 1. ORTEP drawing of **1** (30% probability thermal ellipsoids). Selected bond lengths [Å] and angles [°]: Nb–NbA 2.2683(13), Nb–Cl 2.733(2), Nb–N(1) 2.247(6), Nb–N(4) 2.266(6), Li–Cl 2.279(15); N(1)–Nb–N(4) 90.9(2), N(1)–Nb–N(3a) 88.3(2), N(1)–Nb–N(2a) 177.6(2), N(4)–Nb–N(3a) 177.4(2), N(1)–Nb–Cl 91.04(17), N(4)–Nb–Cl 88.37(18), Nb–Cl–Li 142.2(4), Nb(a)–Nb–Cl 177.56(6).

While this work was in progress, an Nb^{II} complex of the same ligand was reported.^[10h] In spite of the close similarity of the Nb_2 cores, the two compounds display remarkable structural differences. Complex **1** is composed of discrete dimeric units, while the other is a linear polymer. On the basis of the sharpness of the NMR signals in acetone solution, it was concluded that the polymeric complex was diamagnetic, in line with the alleged existence of an “intrinsically stable” Nb–Nb triple bond.^[10h] To our surprise, **1** is paramagnetic in the solid state and, to a small extent, in solution, in spite of having an Nb–Nb distance that is even slightly shorter than that of the linear polymeric complex. Measurement of the

magnetic moment (SQUID magnetometer) as a function of temperature on a sample in a sealed quartz tube showed the presence of residual paramagnetism at 4.5 K ($0.6 \mu_B \text{ mol}^{-1}$; Figure 2). The magnetic moment increases sharply with

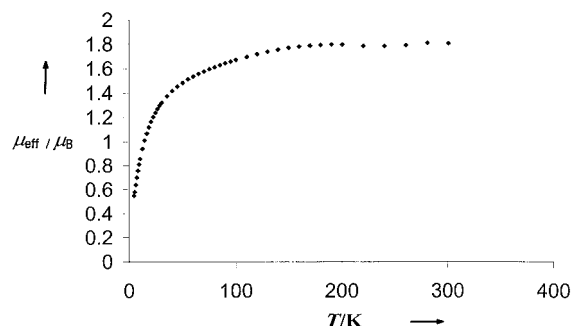


Figure 2. Magnetic moment of **1** as a function of temperature.

increasing temperature, reaches a maximum of $1.8 \mu_B$ at 200 K, and then remains roughly constant up to 300 K. This behavior is most unusual and could imply the presence of an antiferromagnetically coupled dinuclear system. However, the behavior does not conform to that expected for a d^3 – d^3 , d^2 – d^2 , or a d^1 – d^1 antiferromagnetic system. A magnetization study at 3.0 K as a function of field strength (0–5.0 T) gave a linear response, and this suggests the absence of any ferromagnetic coupling. Even though a complete interpretation of the magnetic behavior is not possible at this stage, we can confidently conclude that **1** is paramagnetic and tends towards an $S = 0$ ground state at low temperature. In THF solution, the NMR spectrum showed rather broad lines. A well-resolved spectrum was obtained only in acetone solution, in which, however, the color of the complex changed to dark orange-brown.

The paramagnetism of **1** may be inconsistent with the presence of a significant Nb≡Nb bond and is in sharp contrast to the short Nb–Nb distance. However, a geometry optimization calculation, starting with the atomic coordinates of both **1** and the pyrimidinate complex^[9] and using a force field without electrostatic interactions, predicted Nb–Nb distances of 2.7 and 2.5 Å, respectively. The value calculated for the 7-azaindoyl complex is in good agreement with that observed for the “superlong” quadruple bond of the dichromium complex and other derivatives of the same ligand^[10a] once the different dimensions of the metal atoms are taken into consideration. Hence the presence in both complexes of Nb–Nb distances in the range of 2.2 Å clearly indicates a substantial attractive force between the two metal centers. However, the complex nature of the paramagnetism of **1** indicates that other factors in addition to a Nb–Nb bond may contribute to the nature of the metal–metal interaction.

The density functional calculations (DFT) calculations on the singlet and triplet states yielded consistent results. The singlet state has a total energy value of which is only 1.8 kcal mol^{−1} smaller than that of the triplet state. This small difference, together with the small HOMO–LUMO gap in the singlet state (0.19 eV), accounts for the paramagnetism in terms of a low-lying and thermally accessible triplet state. Both HOMO and LUMO are mainly lithium-centered

molecular orbitals (Figure 3). The LUMO (−2.69 eV) is almost exclusively formed by an out-of-phase combination of one lithium 2s (87 %) and one chlorine 3p_z (10 %) atomic orbital. A similar situation was observed for the HOMO (−2.88 eV), which has large contributions from the other

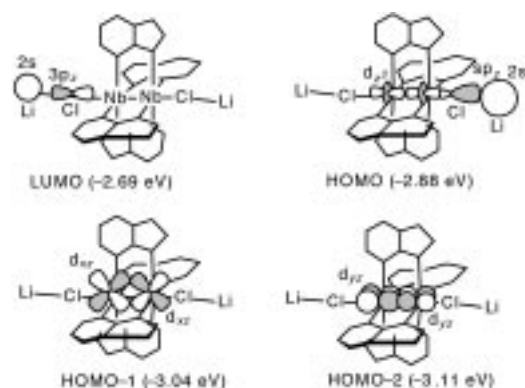


Figure 3. Molecular orbitals of **1** (DFT calculations).

lithium 2s orbital (68 %) and a second chlorine 3s/3p_z hybrid (21 %). However, the two niobium d_{z2} atomic orbitals also participate in this orbital with an in-phase combination that provides an almost negligible Nb–Nb σ-bond character (10 %). The next frontier orbitals HOMO – 1 (−3.04 eV) and HOMO – 2 (−3.11 eV) are nearly degenerate Nb–Nb-centered π orbitals and are respectively formed by the overlap of the d_{xz} and d_{yz} orbitals. The overall calculated Mulliken Nb–Nb bond order is 2.17. The fact that the HOMO and LUMO orbitals are mainly Li-centered suggests that the presence of LiCl on the intermetallic axis is responsible for the destabilization and virtual disappearance of the Nb–Nb σ bond and, ultimately, for the observed paramagnetism. The pyrimidine complex with no LiCl on the axis is indeed diamagnetic.^[9] The question arises whether the small variation in intermetallic distance between the two complexes is sufficient to cause such a remarkable difference in magnetic properties. Calculations on the same model compound of **1** but without LiCl and with Nb–Nb distances of 2.268 and 2.203 Å gave increased Nb–Nb bond orders of 2.97 and 3.02, respectively, and showed the presence of an MO with a clear Nb–Nb σ-bond character. This confirms that the presence of LiCl on the intermetallic axis is indeed the factor responsible for decreasing the formal Nb–Nb bond order and implies that the presumably weak coordination of LiCl is preferred to the formation of a presumably strong Nb–Nb σ bond. These observations remind us of the oddities and intricacies in metal–metal bonding, and on the basis of these findings, the alleged stability of Nb≡Nb bonds should perhaps be reconsidered.

Experimental Section

A solution of 7-azaindole (1.3 g, 11.1 mmol) in diethyl ether (70 mL) was treated with a solution of methyllithium (8 mL, 1.4 M) at 0 °C. The mixture was stirred for 20 min. The solvent was removed in vacuo and replaced by THF (70 mL). [Nb₂Cl₃Li(tmeda)₃] (2.0 g, 2.8 mmol)^[7a] was added, and the mixture stirred for 12 h. After filtration and allowing the resulting solution to stand at −30 °C, blue crystals of **1** separated (1.4 g, 1.1 mmol, 39 %).

Elemental analysis calcd (found) for C₆₀H₈₄O₈N₈Nb₂Li₂Cl₂: C 54.76 (54.33), H 6.43 (6.28), N 8.52 (8.45); IR (Nujol, NaCl) [cm^{−1}]: $\tilde{\nu}$ = 1591(s), 1556(s), 1417(m), 1334(s), 1199(s), 1147(s), 1113(s), 933(s), 912(s), 889(s), 798(s), 783(s), 757(s); ¹H NMR ([D₆]THF, 500 MHz, 23 °C): δ = 8.40 (brs, 1H), 7.93 (brm, 2H), 6.75 (brt, 1H), 6.11 (brs, 1H); ¹H NMR ([D₆]acetone, 500 MHz, 23 °C): δ = 8.20 (d), 7.93 (dd), 7.44 (d), 7.00 (dd), 6.45 (d).

Crystal data for **1** (C₆₀H₈₄O₈N₈Nb₂Li₂Cl₂): *M*_r = 1315.95, monoclinic, space group *P*2₁/*n*, *a* = 14.280(1), *b* = 12.9435(9), *c* = 18.307(1) Å, β = 108.264(1)°, *V* = 3213.4(4) Å³, *Z* = 2, ρ_{calcd} = 1.360 g cm^{−3}, absorption coefficient 0.497 mm^{−1}, *F*(000) = 1372, reflections collected 25 347, independent reflections 4187, GOF = 1.028, *R* = 0.0572, *wR*₂ = 0.1730. The molecule was located on an inversion center. One of the two 7-azaindoly ligands was “end-over-end” disordered. The disorder was modeled by refining the C(5) atom over the two disordered positions with a 60/40 site occupancy. The other disordered ring atoms could not be located, presumably because of close proximity to the primary contributing atom positions. All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were treated as idealized contributions. 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-118120. 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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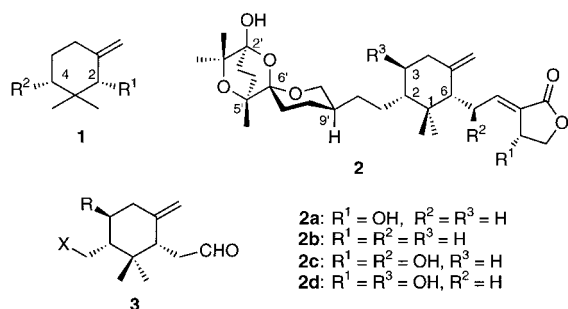
Keywords: magnetic properties • metal–metal interactions • niobium

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Towards the Total Synthesis of Saponaceolides: Synthesis of *cis*-2,4-Disubstituted 3,3-Dimethylmethylenecyclohexanes**

Barry M. Trost,* James R. Corte, and Mark S. Gudiksen

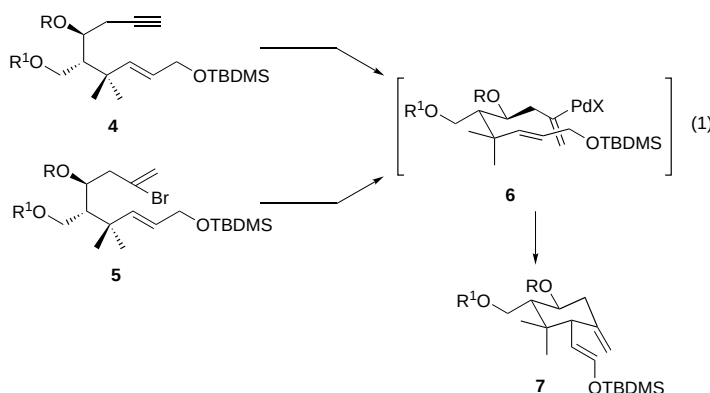
A variety of natural products are characterized by the cyclohexane structural unit **1**. For example, the cycloiridals are prized for their fragrance, and they show interesting activities such as potent piscicidal activity.^[1] Carotenoids such as sarcinaxanthin also have this core unit.^[2] The high cytotoxicity of saponaceolides A–D (**2a–d**) towards a large number of



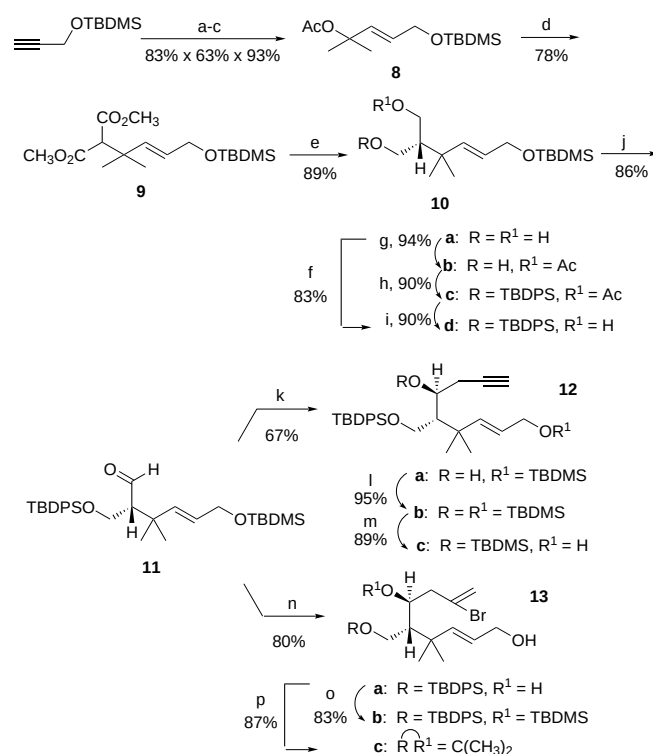
tumors focused our interest on the core unit of this family of compounds.^[3, 4] While natural products have both *cis* and *trans* 2,4-substitution in **1**, all of the above-mentioned compounds show *cis* substitution. The fact that the *cis* isomer is the thermodynamically less stable isomer has hampered its access.^[5] A recent report of the synthesis of 2-*epi*-saponaceolide B highlights this issue^[6] and stimulated us to report our studies directed at this unit in the context of a total synthesis of the saponaceolides.

For a synthesis of the saponaceolides, the cyclohexyl system **3** serves as our target. Traditional strategies to structures like **1** based upon carbonyl chemistry that set the relative stereochemistry by base-catalyzed epimerization invariably led to the *trans* isomer.^[5] Our interest in palladium-catalyzed cycloisomerizations of enynes^[7, 8] led us to consider an alternative strategy to methylenecyclohexanes and raised the question of the geometrical constraints imposed by an intramolecular carbametalation. Simple modeling suggested that the intra-

molecular carbametalation via conformer **6** [Eq. (1); TBDMS = *tert*-butyldimethylsilyl] is 2.8 kcal mol⁻¹ lower in energy than the alternative reaction leading to the *trans* product. In principal, this intermediate can be accessed by a cycloisomerization of enyne **4** or a Heck-type process with vinyl bromide **5**.



Scheme 1 outlines the synthesis of the cyclization precursors **4** (i.e., **12**) and **5** (i.e., **13**) in racemic form (the latter was



Scheme 1. a) *n*-C₄H₉Li, THF, –78 °C then CH₃COCH₃; b) Red-Al, Et₂O, 0 °C; c) Ac₂O, 5% DMAP, (C₂H₅)₃N, RT; d) CH₂(CO₂CH₃)₂, BSA, 5% [Mo(CO)₆], PhCH₃, reflux; e) LAH, THF, 0 °C; f) NaH, THF, 55 °C then TBDPSCI, RT; g) PCL (Amano), CH₂=CHOAc, THF, RT; h) TBDPSCI, imidazole, DMF, 0 °C; i) Ba(OH)₂, CH₃OH, RT; j) 5% TPAP, NMO, 3-Å MS, CH₂Cl₂, 0 °C; k) CH₂=C=CHMgBr, Et₂O, –78 °C; l) TBDMSO-SO₂CF₃, 2,6-lutidine, CH₂Cl₂, 0 °C; m) C₂H₅OH, PPTS, 50 °C; n) CH₂=C(Br)CH₂Br, Sn, HBr, Et₂O, H₂O, RT; o) same as (l) then C₂H₅OH, PPTS, 55 °C; p) TBAF, THF, RT, then CH₃COCH₃, amberlyst 15-H⁺, RT. DMAP = 4-dimethylaminopyridine, BSA = *N,O*-bis(trimethylsilyl)acetamide, TBDPS = *tert*-butyldiphenylsilyl, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholin-*N*-oxide, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetrabutylammonium fluoride.

[*] Prof. B. M. Trost, Dr. J. R. Corte, M. S. Gudiksen
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@leland.stanford.edu

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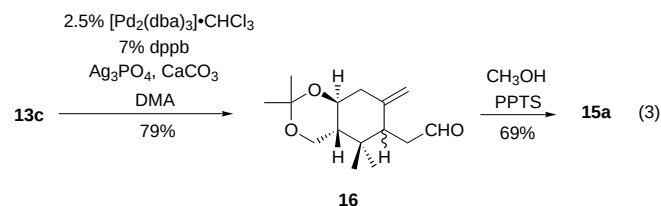
obtained in enantiomerically enriched form as well). Introduction of the malonate moiety regioselectively by allylic alkylation with acetate **8** takes advantage of the bias of molybdenum catalysts to direct nucleophilic attack towards the more highly substituted allyl terminus; regioisomer **9** is the exclusive product.^[9]

The racemic silyl ether **10d** is available directly from the diol **10a** by the method of McDougal et al.^[10] Enantiomerically enriched monoacetate **10b** is obtained by enzymatic transesterification with 86% ee (45% yield, 91% yield based on recovered starting material) with *Pseudomonas fluorescens* lipase (PFL).^[11] With *Pseudomonas cepacia* lipase (PCL)^[12] higher conversions (68% yield, 94% yield based on recovered starting material) are obtained, but with a slightly lower ee value (81% ee). The absolute configuration was established by the known stereochemical preferences of the enzymes employed and verified by correlation with a known compound.^[13] Interestingly, organometallic additions to aldehyde **11** proceeded completely diastereoselectively with allenyl-magnesium bromide^[14] to give **12** and with tin and 2,3-dibromopropene^[15] under Barbier conditions to give **13**. The relative configuration in both cases was established by converting the 1,3-diol units into cyclic acetonides (**13c** in the latter case), and NMR spectroscopy verifies the *trans* relationship of the two methine hydrogen atoms (for **13c**, $J = 9.2$ Hz). This stereochemistry corresponds to a Felkin–Anh mode of addition.^[16]

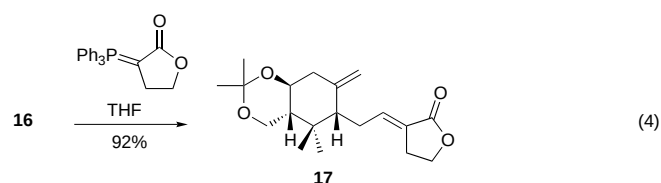
Previous work suggests that the cycloisomerization of substrates like **12** should produce 1,3- rather than 1,4-dienes.^[7, 17] In contrast to this expectation, palladium-catalyzed cycloisomerization of **12b** proceeded to form exclusively the 1,4-diene product, an enol silyl ether, which is directly hydrolyzed to the aldehyde **14** [Eq. (2)]; dba = dibenzylideneacetone. Alternatively, cycloisomerization of **12c** provides the aldehyde **14** directly as the sole product. In both cases, the product is isolated as a 2:1 mixture in which the major isomer indeed has the desired *cis* configuration (see below).

To compare the two processes, the corresponding Heck reactions of vinyl bromides **13b** and **13c** were examined. Cyclization of **13b** to **14** proceeded smoothly to generate a poorer 1:1 ratio of the *cis:trans* products **14** [Eq. (2)].^[18] On the other hand, the rigid acetonide **13c** leads to the cyclization product **16** in a *cis:trans* ratio as high as 2.4:1. Efforts to further increase this ratio failed. Preparatively, the highest yield (53%) of the *cis* isomer stemmed from the conditions^[19]

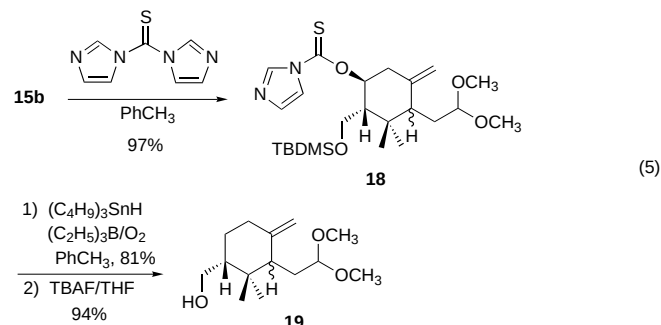
illustrated in Equation (3) in which a *cis:trans* ratio of 2:1 was observed (dppb = 1,4-bis(diphenylphosphanyl)butane, DMA = *N,N*-dimethylacetamide). Methanolysis of **16** resulted in conversion into **15a**.



To establish the relative configuration, the aldehyde **16** was converted into **17** [Eq. (4)], which corresponds to the right-hand portion of deoxysaponaceolide D. X-ray crystallography established the full stereochemistry as depicted. The diol **15a** may serve as a general intermediate for the synthesis of

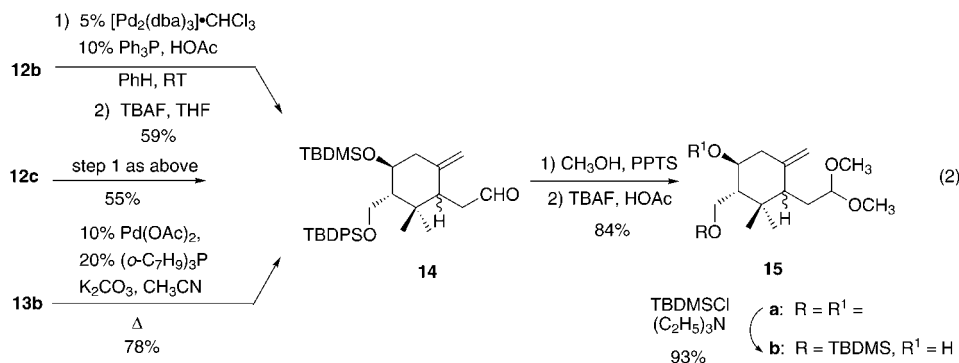


saponaceolides. While saponaceolide D requires retention of both hydroxyl groups, the syntheses of saponaceolides A–C require the removal of the free hydroxyl group from the monosilyl ether **15b**. For this purpose, we turned to free radical chemistry [Eq. (5)]. The reaction proceeded unevent-



fully via thionocarbamate **18** to give the saponaceolide intermediate **19**.^[20] The pure *cis* isomer can be isolated at the stage of the diol **15a**, its monosilyl ether **15b**, or the monoalcohol **19**. Practically, the separation was best done with alcohol **19**.

The palladium-catalyzed cycloisomerization and Heck reactions described here provide the best route to date for the formation of the requisite *cis*-3,3-dimethyl-2,4-disubstituted methylencyclohexyl unit **1** common to many natural products. The unusual nature of this core unit is further illustrated by the com-



pletely different regioselectivity, wherein a 1,4- rather than a 1,3-diene was obtained in the cycloisomerization and in the silver-promoted Heck cyclization. The route constitutes a reasonable strategy for the synthesis of cyclohexyl cores that can provide access to all the currently known saponaceolides. Its practicality is highlighted by its use in a successful synthesis of saponaceolide B.^[21]

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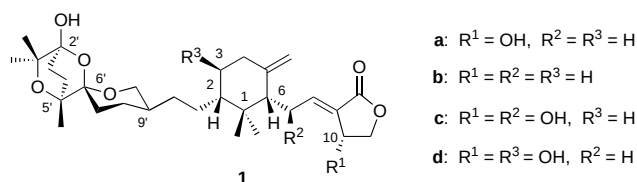
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Total Synthesis of (+)-Saponaceolide B**

Barry M. Trost* and James R. Corte

The saponaceolides A–D (**1a–d**), discovered by Vidari and co-workers from the northern Italian mushroom *Tricholoma saponaceum*,^[1] possess antitumor activity in 60 human cancer cell lines.^[2] They possess several challenging structural



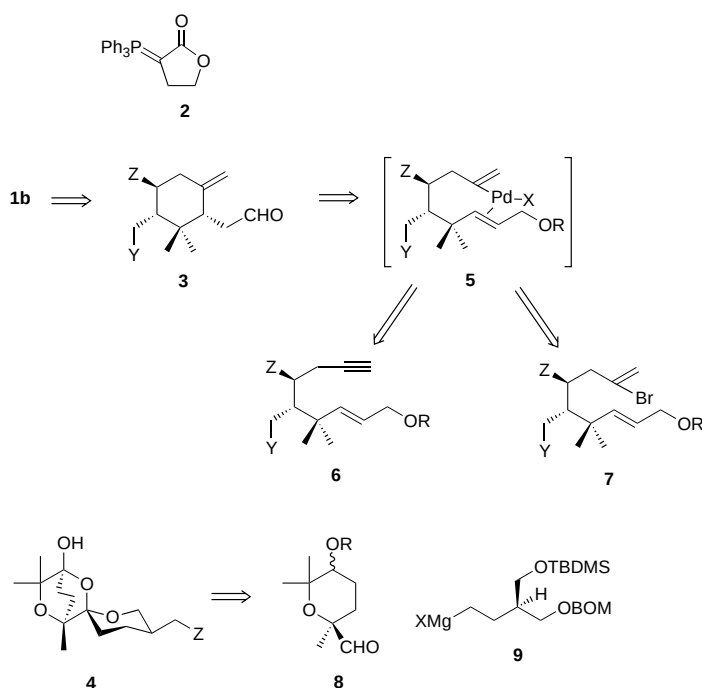
elements including the unique tricyclic trioxaspiroketal and a *cis* 2,6-disubstituted 1-methylene-3,3-dimethylcyclohexane ring. While a number of synthetic efforts have targeted portions of these structures,^[2, 3] until recently only a synthesis of 2-*epi*-saponaceolide B has appeared, where the difficulties of controlling the ring configuration were highlighted.^[4] We report here our efforts that have culminated in a synthesis of (+)-saponaceolide B (**1b**), a member that exhibits significant activity in four human cancer cell lines—leukemia K-562, nonsmall cell lung NCI-H23, melanoma LOX-IMVI, and SK-MEL-5.^[2]

Scheme 1 illustrates the retrosynthetic analysis into the three subunits **2–4**. The central core unit **3** represents a significant challenge since the *cis* configuration at C2 and C6, which is thermodynamically less stable than the *trans* configuration, has proven difficult to access—a fact emphasized by the reported synthesis of only the 2-*epi* isomer.^[4] The accompanying paper describes a synthesis of this unit.^[13]

[*] Prof. B. M. Trost, Dr. J. R. Corte
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@leland.stanford.edu

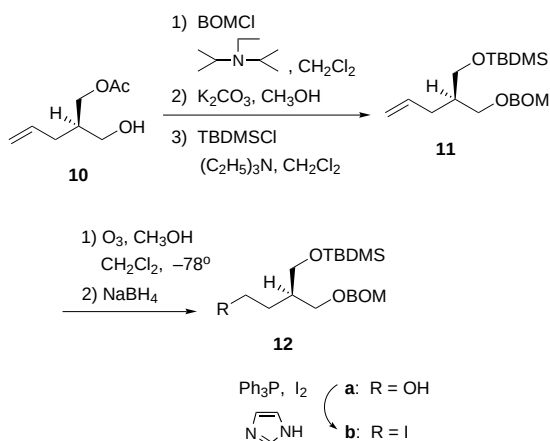
[**] We thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs. J.R.C. held a NSF predoctoral Fellowship and a Veatch Fellowship. Mass spectra were provided by the Mass Spectrometry Facility of the University of California-San Francisco, supported by the NIH Division of Research Resources. We are grateful to Prof. Dr. G. Vidari for copies of spectra of the natural product.

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Here we record a synthesis of the spiroketal unit and the assemblage of the three fragments **2–4** to complete an asymmetric synthesis of (+)-saponaceolide B.

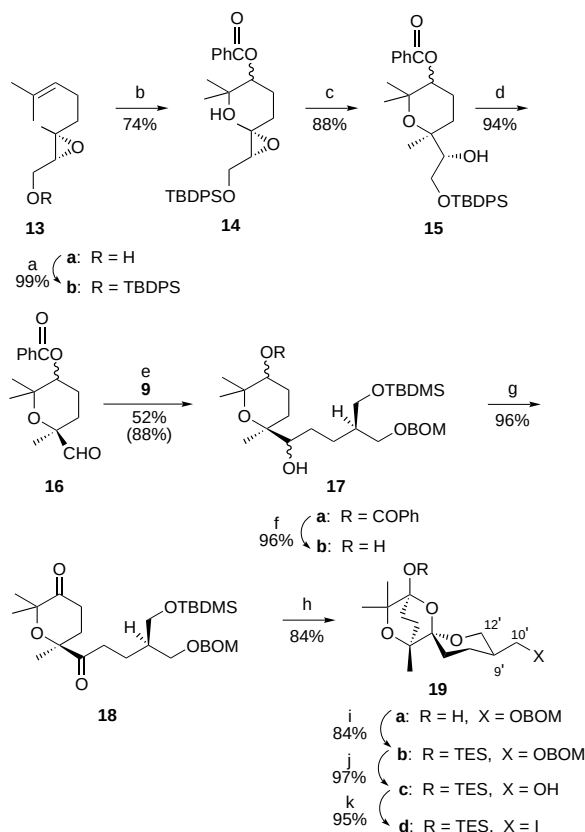
Schemes 2 and 3 outline the synthesis of the spiroketal portion starting from the known (*R*)-acetate **10**^[5] and known geraniol epoxide **13a**.^[6] The iodide precursor **12b** of the Grignard reagent **9** was derived from acetate **10** in straight-forward fashion (Scheme 2). Protecting groups were incorporated in hydroxyacetate **10** by conversion into **11** (91 % overall



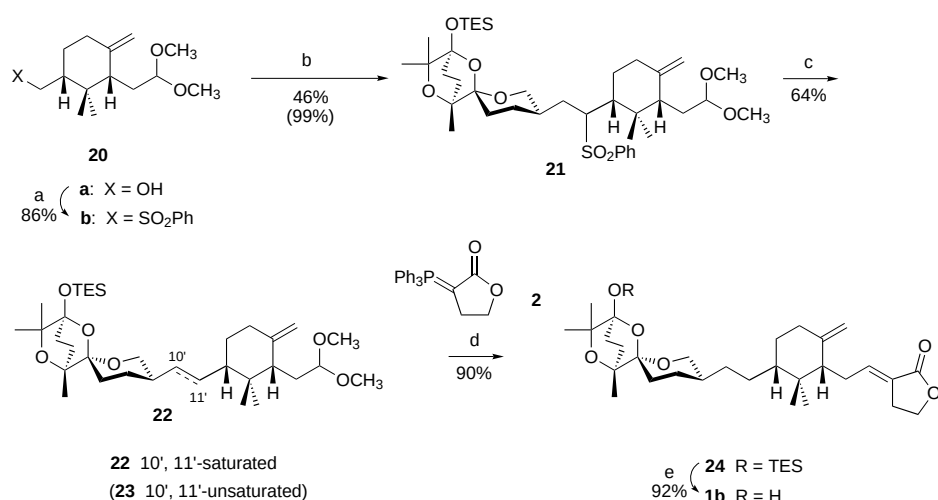
yield) to make the compound compatible for formation of an organomagnesium reagent. Oxidative cleavage with ozone and workup with borohydride furnished **12a** (83 % yield); subsequent iodination of **12a** to form **12b** (98 % yield) completes the synthesis of the iodide precursor of the

Grignard reagent. The latter was generated by iodide–lithium exchange (2 equiv of *tert*-C₄H₉Li) followed by addition of magnesium bromide.

The aldehyde **16**, easily accessed from **14** via **15** as described by Vidari et al.^[3a] followed by oxidative cleavage, proved to be the best intermediate for forming the entire carbon skeleton of the spiroketal unit (Scheme 3). While the lithium reagent derived from iodide **12b** added to **16**, better yields



were obtained with the organomagnesium reagent to give **17a**. Hydrolysis to diol **17b** followed by double oxidation with tetrapropylammonium perruthenate (TPAP)^[7] produces the diketone **18**. The acyclic stereochemistry of diketone **18** directs the folding to place the alkoxyethyl group in an equatorial position. The correctness of this assertion is verified by the coupling constants between the proton on C9' and the two protons on C12' (saponaceolide numbering), which are consistent with an axial–axial (*J* = 11 Hz) and equatorial–axial coupling (*J* = 5.0 Hz). Functional-group manipulation by conversion of **19a** into the iodide **19d** sets the stage for the coupling.



Scheme 4. a) (C₄H₉)₃P, PhSSPh, PhH, RT then TPAP, NMO, 4-Å MS, CH₃CN, 0 °C; b) *n*-C₄H₉Li, THF, HMPA, **19d**, -55 → -30 °C; c) 5% Na(Hg), NaH₂PO₄, CH₃OH, -15 °C; d) CF₃CO₂H, THF, H₂O, RT, then **2** CH₂Cl₂, RT; e) TBAF, HOAc, THF, RT. HMPA = hexamethyl phosphoramide. Yields in parentheses are based upon recovered starting material.

Alkylation of a sulfone-stabilized anion was chosen for the coupling of fragments **3** and **4**. The sulfone **20b** was prepared from the corresponding alcohol **20a** in 86% yield by sulfide displacement followed by oxidation^[8] (Scheme 4). The alkylation of sulfone **20b** with iodide **19d** proceeded nearly quantitatively at 50% conversion.

Reductive desulfonation of **21** with sodium amalgam^[9] gave **22** accompanied, surprisingly, by some elimination product **23**. That the alkene **23** did not form by base-catalyzed elimination is suggested by the absence of any dependence on the amount of added buffer nor on varying the reductant to samarium diiodide.^[10, 11] The completion of the synthesis proceeded straightforwardly as outlined (Scheme 4). Olefination of the aldehyde liberated from the acetal **22** with the stabilized Wittig reagent **2**^[12] gave a 13:1 ratio of the *E*:*Z* alkenes. The lower field shift ($\delta = 6.70$) of the new olefinic hydrogen of the major isomer compared to the minor one ($\delta = 6.19$) establishes the former as the *E* alkene. Desilylation then delivers synthetic saponaceolide B (**1b**, [α]_D²² = +14.4, *c* = 1.54 in CH₂Cl₂), whose spectral data agrees well with those recorded for the natural product.^[1] The success of this synthesis derived from its access to a stereodefined cyclohexyl unit, which in turn is prepared by the palladium-catalyzed cycloisomerization of enynes or the Heck protocol.^[13] The convergent strategy should also provide access to other members of the saponaceolide family as well their analogues. The strategy outlined also provides opportunities to provide other natural products emanating from the cyclohexyl core **3**.

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Teaching Old Indicators New Tricks: A Colorimetric Chemosensing Ensemble for Tartrate/Malate in Beverages**

John J. Lavigne and Eric V. Anslyn*

The development of general methods for the colorimetric analysis of small and medium-sized analytes in solution is highly desirable since visual inspection yields immediate qualitative information, while absorption spectroscopy gives quantitative information. Many colorimetric assays exist, but most often they deal with the analysis of pH,^[1] simple cations^[2] and anions,^[3] and radicals.^[4] The majority of these sensors have the chromophore covalently attached to the recognition element. Upon binding of the analyte the electronic transitions of the chromophore are perturbed. In contrast, many colorimetric assays for large biological mole-

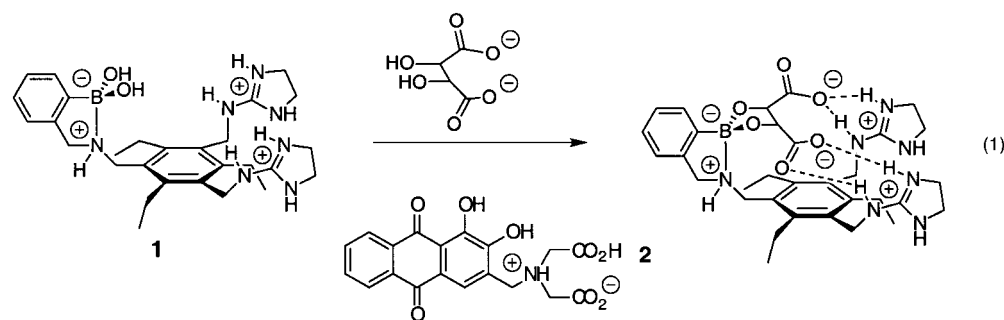
[*] Dr. E. V. Anslyn, J. J. Lavigne
Department of Chemistry and Biochemistry
The University of Texas at Austin, Austin, TX 78712 (USA)
Fax: (+1) 512-471-8696
E-mail: anslyn@ccwf.cc.utexas.edu

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cules are known. These screens most often employ antibodies, as in common pregnancy tests,^[5] or biotin–avidin-based sandwich assays. However, another alternative that is amenable to the creation of a colorimetric method, and still used almost exclusively in biological systems, involves the competition of an indicator with the desired analyte.^[6] For example, upon exposure of an immobilized antibody saturated with a tagged antigen to analyte, a competition for the antibody binding site takes place between the tagged antigen and the target analyte, which results in a signal modulation.

We have recently been exploring fluorescence competition assays employing synthetic receptors.^[7] Fluorescence is useful for the analysis of analytes that are present at very low concentrations. However, the concentrations of many common analytes in beverages, bodily fluids, and environmental samples are quite amenable to analysis by absorption spectroscopy. Hence, given the advantage of having a colorimetric assay we set out to develop a general method for creating colorimetric assays from synthetic receptors. Herein we report a specific example: the analysis of tartrate in beverages.

Tartrate is a common natural product present in wines and other grape-derived beverages. The structure of tartrate makes it quite attractive for complexation by a synthetic receptor since it is relatively small, while still possessing several functional groups (alcohols and carboxyl groups) for binding interactions. On the basis of the previous use of boronic acids to bind 1,2- and 1,3-diols,^[8] and guanidinium groups imbedded in aminoimidazoline groups for binding carboxylates,^[9] we designed synthetic receptor **1** for tartrate [Eq. (1)].^[10] Compound **1** features a single boronic acid and



two guanidinium groups preorganized to converge and create a cavity of the correct dimensions for tartrate. The preorganization comes from the use of a hexasubstituted benzene ring, where it has been shown that the steric bulk forces the alternating substituents to opposite sides of the benzene spacer.^[11]

There is a significant amount of prior precedence for the use of an aminomethyl moiety in the position *ortho* to a boronic acid in a sensor. All of these use a tertiary amine that is involved in the signal transduction mechanism, usually by quenching of the signal by photoinduced electron transfer (PET)^[12] or internal charge transfer (ICT).^[13] The current system utilizes a secondary amine solely for linking and restricting the degrees of freedom of the boronic acid

group.^[14] Studies of other secondary amines coordinated to boronic acids suggest a zwitterionic complex containing tetracoordinate boron and nitrogen atoms.^[15] The strength of the N–B interaction is approximately 19 kcal mol^{−1}.^[15a] The geometry of the boron atom was determined from a ¹¹B NMR spectrum of **1**. Under the assay conditions (see Experimental Section), the spectrum shows one peak at $\delta = 12.8$ (referenced to BF₃Et₂O in toluene at $\delta = 0$), which is indicative of a tetrahedral boron atom.^[16]

A pH indicator with a chromophore possessing the same functionalities as tartrate was chosen for use in a competition assay. Importantly, the choice of indicator was guided by the expectation that complexation by the receptor would result in a color change of the indicator. This effect is afforded by a change in the “protonation state” (for this analysis we consider the boron atom to be acting like a proton) when the indicator is either bound to the receptor or free in solution at a constant pH. We chose alizarin complexone (**2**) for the analysis of tartrate [Eq. (1)] since it also possesses a 1,2-diol and two carboxylate groups. This indicator has been previously used to signal a change in pH^[17] as well as the presence of lanthanide,^[17] and fluoride ions.^[18] The functional groups are not arranged in the same manner as with tartrate, and hence a lower affinity between **1** and **2** was anticipated. We predicted that the binding between **1** and **2** would significantly shift the “protonation state” of the phenols as a result of the formation of a boronate ester as a result of reaction with the boronic acid. Indeed, the color changed from burgundy to yellow/orange (Figure 1A) upon addition of **1** to a solution of **2** (0.1 mM) in a water/methanol mixture (25 vol% water; pH 7.3, buffered with 10 mM HEPES). By following the absorption at 450 nm and fitting the data to a 1:1 binding algorithm^[19] a binding constant of $2.7 \times 10^4 \text{ M}^{-1}$ was obtained.

As expected, the addition of stock solutions of L-tartrate to an ensemble of **1** and **2** (see Experimental section; this solution is referred to as the sensing ensemble) resulted in a change from yellow/orange back to burgundy (Figure 1B). We analyzed for tartrate as well as several

other possible competing analytes with structures similar to tartrate, including: ascorbate, L-malate, succinate, lactate, and sugars, using this colorimetric assay (Figure 2). A binding constant of $5.5 \times 10^4 \text{ M}^{-1}$ was calculated for **1** and tartrate using algorithms for competitive equilibria.^[19] In comparison, a binding constant of 150 M^{-1} between **1** and glucose was measured by UV/Vis spectroscopy; this value is in the range found for a single boronic acid and a sugar.^[12b] We also found that succinate binds to **1** with a binding constant of 350 M^{-1} . Furthermore, a monohydroxy carboxylate such as lactic acid only had a binding constant of 500 M^{-1} with **1**. With the exception of malate (K_a with **1** is $4.8 \times 10^4 \text{ M}^{-1}$) we find excellent selectivity for tartrate. Hence, good cooperativity exists between the boronic acid and the two guanidinium

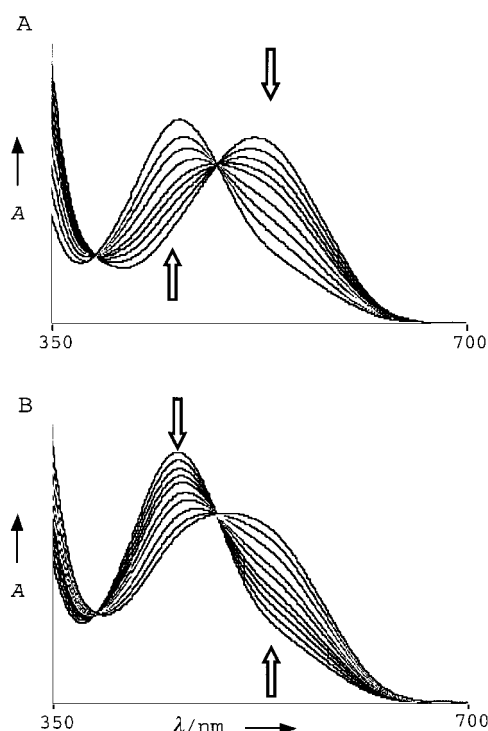


Figure 1. UV/Vis spectra of **2**. A) Addition of **1** to a constant concentration of **2** (180 μM) results in an increase in the absorbance at 450 nm with a decrease in absorbance at 525 nm. B) Addition of tartrate to a solution containing both **1** and **2** (180 μM each) at a constant concentration causes a decrease in the absorbance at 450 nm and an increase in the absorbance at 525 nm.

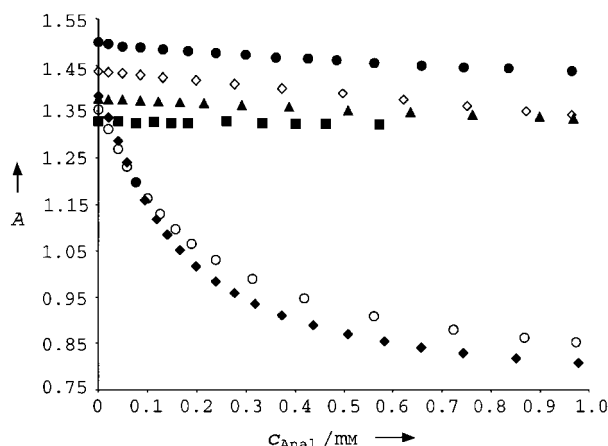


Figure 2. Calibration curves at 450 nm used for the sensor assay. Addition of tartrate (♦), malate (○), ascorbate (◇), lactate (◆), succinate (▲), and glucose (■). $c_{\text{Anal.}}$ = concentration of the analyte.

groups of **1** for the complexation of the hydroxyl and carboxylate moieties of tartrate.

For final proof of principle the calibration curves generated for tartrate and malate (Figure 2) were used to evaluate various solutions. The addition of microliter quantities of several grape-derived beverages to the sensing ensemble gave the concentrations of tartrate/malate present (Table 1). An NMR assay for the total tartrate/malate concentration was used as a control. In all cases very good agreement (less than 10% difference) between the two methods was obtained. This suggests that the sensing ensemble is able to quantitate

Table 1. Concentration of tartaric and malic acids [mM] in different solutions as determined by different methods.

	Gravimetric	NMR	UV/Vis (1 + 2)
tartaric acid model solution	50	51.2	50.2
calibration solution	50	–	47.9
Ernest & Julio Gallo Sauvignon Blanc	–	35.6	32.9
Ste. Genevieve Chardonnay	–	34.1	36.3
Henri Marchant Spumante	–	26.5	24.9
Talus Merlot	–	19.5	20.3
Santa Cruz organic white grape juice	–	43.6	42.3
Welch's grape juice	–	69.4	71.3

tartrate/malate in the presence of large concentrations of sugars, electrolytes, pectins, and tannins.

In summary, a colorimetric assay for tartrate using a synthetic receptor has been created. In this assay a common pH indicator that has the same or similar functionalities to that of the analyte of interest has been used. Since the receptor is most complementary to the analyte there is a lower relative affinity for the indicator, which leads to the facile displacement of the indicator from the receptor upon addition of the analyte and a color change of the indicator occurs. We are currently exploring this approach for the analysis of many other analytes in liquids.

Experimental Section

1: 1-aminomethyl-2,4,6-triethyl-3,5-(*N*-(imidazoline-2-yl-aminomethyl)benzene (300 mg, 0.53 mmol)^[20] was mixed with (2-formylphenyl)boronic acid (87.6 mg, 0.58 mmol) in anhydrous methanol to which was added distilled triethylamine (360 μL, 2.65 mmol) and activated 3-Å molecular sieves. The solution was stirred at 25 °C for 3 h. Sodium borohydride (20.2 mg, 0.53 mmol) was then added to the solution and stirred for an additional hour. The solution was filtered through a pad of celite to remove the sieves and the solvent removed by rotary evaporation. The resulting residue was placed under reduced pressure (6 Torr) for two days to remove the trimethylborate. This residue was then dissolved in water and filtered through a pad of celite to remove the reduced aldehyde. The water was lyophilized to yield a fluffy white solid (366 mg, 99%). M.p. 197 °C (decomp); ¹H NMR (300 MHz, CD₃OD, 25 °C): δ = 1.12 (t, 6H; CH₃), 1.23 (t, 3H; CH₃), 1.81 (s, 9H; CH₃), 2.74 (q, 2H; CH₂), 2.82 (q, 4H; CH₂), 3.75 (s, 8H; CH₂), 3.97 (s, 2H; CH₂), 4.11 (s, 2H; CH₂), 4.43 (s, 4H; CH₂), 7.11 (d, 1H; Ph), 7.15–7.23 (m, 2H; Ph), 7.49 (d, 1H; Ph); ¹³C NMR (75 MHz, CD₃OD, 25 °C): δ = 16.4, 16.6, 23.1, 24.1, 42.0, 44.1, 53.5, 116.2, 127.9, 128.4, 130.8, 131.4, 146.7, 161.2, 162.8, 163.2, 178.8; ¹⁵B NMR (160 MHz, CD₃OD, 25 °C): δ = 8.2; HR-MS (FAB (gly), as the glycerol boronate ester): *m/z*: found: 576.3839; calcd for C₃₁H₄₇BN₂O₃: 576.3833 [*M*⁺+1].

UV/Vis determination of tartrate/malate: HEPES buffer (10 mM) at pH 7.35, **1** (180 μM), alizarin complexone (180 μM) in 25% water in methanol. Sample preparation involved adjusting the pH of beverage (5 mL) with aqueous sodium hydroxide and diluting to 10 mL with water. An aliquot of this dilute wine solution (40 μL) was added to the sensing ensemble (960 μL; to maintain a constant indicator and host concentration). A portion of this solution (5–50 μL) was then added to the sensing ensemble (1 mL). The average of four scans was used to determine one value.

NMR determination of tartrate/malate: Beverage (50 mL) was adjusted to pH 7.35 with aqueous sodium hydroxide and the water removed by lyophilization. The residue was then dissolved in D₂O (5 mL) and the volume brought to 10 mL with D₂O. The internal reference solution was made by dissolving dichloroacetic acid (0.5 mL) in D₂O, the pH brought to 7.35 with sodium deuterioxide, and the volume brought to 10 mL. D₂O (800 μL) was combined with dichloroacetic acid solution (100 μL) in an

NMR tube and wine solution (100 and 300 µL) added. The area of the integral for dichloroacetic acid was normalized to the areas from malate and tartrate and the concentrations calculated.

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New Efficient Multicomponent Reactions with C–C Coupling for Combinatorial Application in Liquid and on Solid Phase**

Armin de Meijere,* Hanno Nüske, Mazen Es-Sayed, Thomas Labahn, Maarten Schroen, and Stefan Bräse*

*Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday*

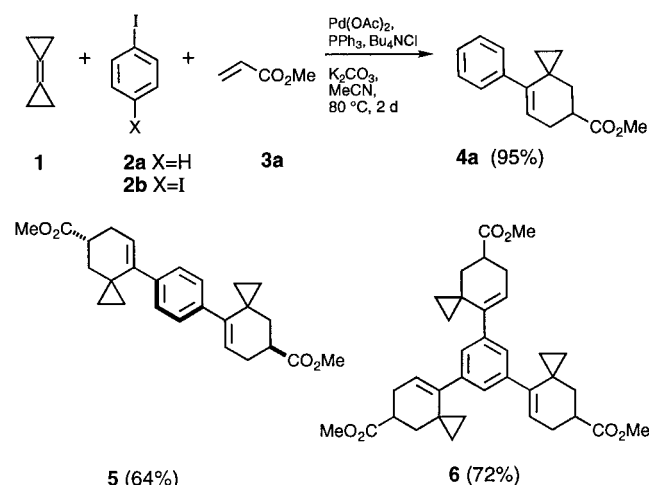
Elegance in chemical synthesis is reflected in the art of finding simple ways to construct complex structures.^[1] In the age of combinatorial chemistry,^[2] multicomponent and domino reactions^[3] are of special importance. This is especially true for liquid-phase combinatorial chemistry,^[4] in which the usually required and always relatively time-consuming purification often limits the practical sequences to a few steps.^[5] In the continuing development of classic multicomponent reactions, for example those developed by Ugi,^[6a] Biginelli,^[6b] and Mannich,^[6c] the preferential formation of heteroatom–carbon bonds is prominent. We were recently able to extend the repertoire of less common cascade reactions solely leading to

- [*] Prof. Dr. A. de Meijere, Dipl.-Chem. H. Nüske, Dipl.-Chem. T. Labahn
Institute für Organische und Anorganische Chemie der Universität D-37077 Göttingen (Germany)
Fax: (+49) 551-393231
E-mail: ameijer1@uni-goettingen.de
- Dr. S. Bräse, M. Schroen
Institut für Organische Chemie der Technischen Hochschule D-52074 Aachen (Germany)
Fax: (+49) 241-8888127
E-mail: Braese@oc.RWTH-Aachen.de
- Dr. M. Es-Sayed
Bayer AG, GB Pflanzenschutz
D-40789 Monheim (Germany)
Fax: (+49) 2173-383342
E-mail: Mazen.Es-Sayed.ME@Bayer-ag.de

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carbon–carbon bonds, for example those developed by Robinson,^[6d] Baylis–Hillman,^[6e] and Grieco,^[6f] by a genuine three-component reaction. A highly reactive alkene, an alkenyl or aryl halide and a dienophile react with each other in a domino Heck–Diels–Alder reaction to give spiro[2.5]octene derivatives, in the course of which three C–C bonds are formed with high regioselectivity.^[7]

In the meantime the yield of the reaction of bicyclopropylidene (**1**) with iodobenzene (**2a**) and methyl acrylate (**3a**) has been improved to 95 % by working at higher concentration levels (Scheme 1). Under the optimized reaction conditions,^[8] the even more complex symmetrical system **5** was obtained



Scheme 1. Three- and five-component reactions for the synthesis of spiro[2.5]octene derivatives.

from 1,4-diiodobenzene (**2b**) in 64 % yield, and after 48 h at 80 °C and a pressure of 10 kbar the product **5** of double coupling and double [4+2] cycloaddition was isolated in 87 % yield. Therefore even this formal five-component reaction proceeds completely unambiguously with the formation of six C–C bonds.^[9] The reaction product is obtained as a single diastereomer and was characterized as the *meso* form by crystal structure analysis; the D,L-enantiomer pair could not be detected by ¹H NMR spectroscopy (500 MHz) or HPLC-MS, even in the crude product (Figure 1).^[10] A further improvement was achieved by using 1,3,5-triiodobenzene, whose reaction with **1** and methyl acrylate furnished the triple coupling triple cycloadduct **6** in 72 % yield.

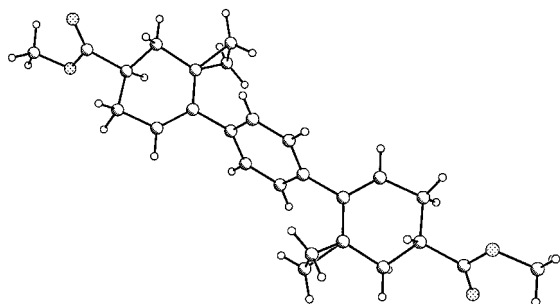
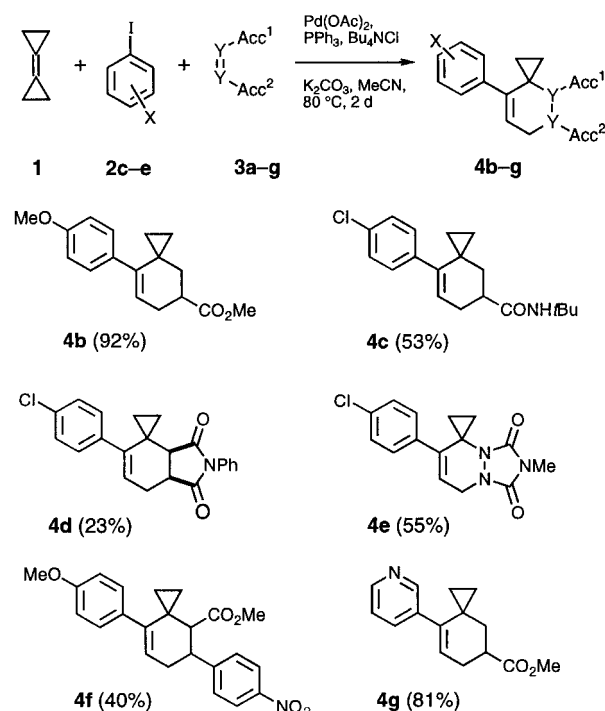


Figure 1. Structure of the double coupling double cycloadduct **5** from 1,4-diiodobenzene, bicyclopropylidene (**1**), and methyl acrylate (**3a**).

The potential of this multicomponent reaction in liquid phase combinatorial chemistry is demonstrated by the broad variability of both the iodoarene and the dienophile component (Scheme 2).^[11] In the process, N-substituted maleimides and triazoline diones do not constitute a fundamental



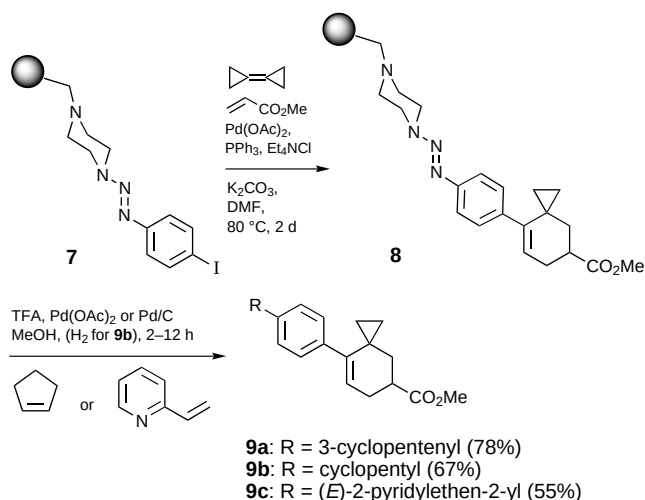
Scheme 2. Liquid-phase three-component combinatorial chemistry (examples).

problem, whereas 3-substituted acrylates are only of limited suitability. Thus, hardly any cycloadducts were obtained with crotonic acid, cinnamic acid, or methyl *p*-chlorocinnamate, other than with methyl *p*-nitrocinnamate. The constitution of the coupling cycloadduct **4f** isolated in 40 % yield, which was formed with inverted regioselectivity compared with acrylates, was verified by X-ray structure analysis.^[10]

When carried out on the solid phase, this unusual three-component reaction can be extended by a further dimension. The iodoarenyltriazenyl-substituted Merrifield resin **7**,^[12] already used successfully for Heck reactions, was allowed to react with bicyclopropylidene (**1**) and methyl acrylate (**3a**) to yield the coupling cycloadduct **8** under standard conditions. In solid-phase reactions, the dimerization of the iodoarene component, a possible side reaction, is suppressed per se, and side products from the dimerization of bicyclopropylidene are easy to remove.

Reaction of the resin-bound triazenylphenyl-substituted spiro[2.5]octene **8** with trifluoroacetic acid generates the corresponding aryl diazonium salt under cleavage from the resin. This salt immediately reacts with cyclopentene or 2-ethenylpyridine in a Heck reaction in the presence of palladium acetate. After filtration from the resin, the products of the four-component reaction **9a** (as a mixture of two diastereomers in a 1:1 ratio) and **9c** were obtained in 78 and 55 % yield, respectively, and with a purity > 95 %. The

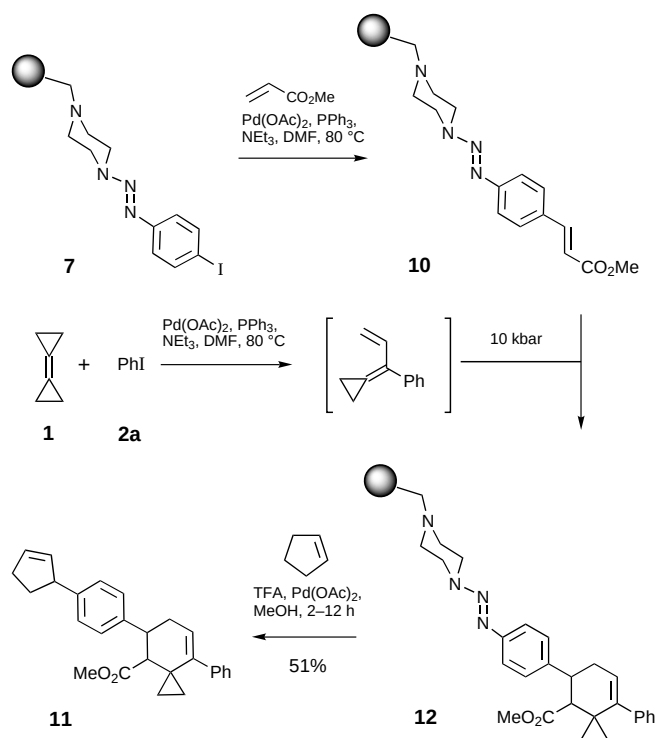
palladium-catalyzed hydrogenation of **9a** furnished the cyclopentyl derivative **9b** in 67% yield. Potential variations of this novel sequence of Heck, Diels–Alder, and a renewed Heck reaction^[13] (Scheme 3) should be readily available by using a variety of alkenes in the last step.



Scheme 3. Solid-phase cleavage–cross-coupling reactions on the aryltriazenyl-substituted resin **7**. TFA = Trifluoroacetic acid.

A further permutation is offered by the possibility of first coupling resin-bound triazenylphenyl iodide **7** with an acceptor-substituted alkene in a Heck reaction and then introducing the product in the domino Heck–Diels–Alder reaction with bicyclopropylidene (**1**) and iodoarenes. In fact, in analogy to the *p*-nitrocinnamate, the resin-bound, electron-deficient cinnamic acid derivative **10** obtained from **7** and methyl acrylate (**3a**) reacts under palladium catalysis with **1** and iodobenzene to give the coupling cycloadduct **12**, at least under high pressure.^[14] In a subsequent Heck reaction of the diazonium ion obtained from **12** under cleavage from the resin, the novel spiro[2.5]octene **11** is obtained in 51% yield together with the side product (35%) methyl *p*-(3-cyclopentyl)cinnamate formed by Heck coupling of the diazonium ion directly formed from **10**. The success of this reaction sequence proves that the triazenyl group in **10** activates the cinnamic ester in a similarly strong way as a nitro group. This novel five-component reaction carried out in two steps, a Heck–Heck–Diels–Alder–Heck reaction sequence, also combines the simplest building blocks to form a complex molecule (Scheme 4).

With the help of these new C–C linking multicomponent reactions, relatively simple molecules can be coupled very efficiently and variably to give considerably more complex spirocyclopropane-annelated carbon skeletons. Thus, up to nine new C–C bonds are formed in a single operation.^[15] The combinatorial potential of these sequences does not, however, lie solely in the variability of the starting material, but also in the diversity of combinations of different Heck variants with the Diels–Alder reaction: From the three-component reaction in the Heck–Diels–Alder sequence to the four-component reaction in the Heck–Diels–Alder–Heck sequence to



Scheme 4. Heck–Heck–Diels–Alder–Heck reaction.

the five-component reaction in the Heck–Heck–Diels–Alder–Heck sequence, the method provides true combinatorial chemistry.

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Incorporation of Magnetic Nanoparticles in New Hybrid Networks Based on Heteropolyanions and Polyacrylamide**

Cédric R. Mayer, Valérie Cabuil,* Thierry Lalot, and René Thouvenot

Hybrid organic–inorganic materials have received increasing attention over the last few years^[1] as a result of the specific properties. This is due to a synergy between both organic and inorganic parts. Functionalized polyanions are good candidates for the elaboration of such materials.^[2]

Herein we present a magnetic hybrid hydrogel that results from the incorporation of a magnetic particle from an aqueous dispersion into a polymeric network cross-linked by an organometallic species. The cross-linker is a new water-soluble molecular precursor in the form of a tetra-functionalized polyoxometalate (POM) of formula [γ -SiW₁₀O₃₆(RSiO)₄]⁴⁻ (R = C₃H₆OC(O)C(Me)=CH₂).^[3] This hybrid consists of a divacant polyanion [γ -SiW₁₀O₃₆]⁸⁻ unit, in

[*] Dr. V. Cabuil

UMR 7612, Laboratoire des Liquides Ioniques et Interfaces Chargées
équipe Colloïdes Magnétiques
Université Pierre et Marie Curie, Case 63
4 Place Jussieu, F-75252 Paris Cedex 05 (France)
Fax: (+33) 1-44-27-36-75
E-mail: cabuil@ccr.jussieu.fr

Dr. C. R. Mayer, Dr. R. Thouvenot
ESA 7071, Laboratoire de Chimie Inorganique et
Matériaux Moléculaires
Université Pierre et Marie Curie, Case 42
4 Place Jussieu, F-75252 Paris Cedex 05 (France)

Dr. T. Lalot
UMR 7610, Laboratoire de Synthèse Macromoléculaire
Université Pierre et Marie Curie, Case 184
4 Place Jussieu, F-75252 Paris Cedex 05, France

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which a cyclic tetrasiloxane ($\text{RSiO})_4$ is grafted onto the polyoxometalate surface through four Si-O-W bridges (Figure 1).

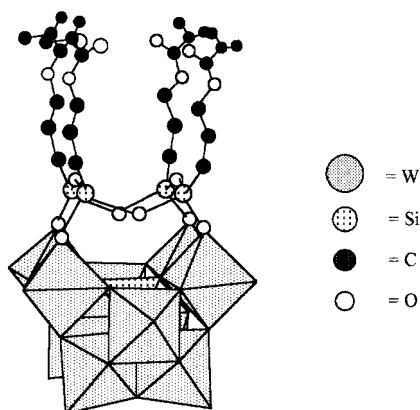


Figure 1. Polyhedral representation of the functionalized polyanion $[\gamma\text{-SiW}_{10}\text{O}_{36}(\text{RSiO})_4]^{4-}$ ($\text{R} = \text{C}_3\text{H}_6\text{OC}(\text{O})\text{C}(\text{Me})=\text{CH}_2$).

This polyanion behaves as a surfactant in water: its surface tension is 43.5 mN m^{-1} , its critical aggregation concentration (CAC) in water is $4.32 \times 10^{-4} \text{ M}$, and the surface area (σ) of its polar head is estimated to be $140 \text{ \AA}^2$. It also acts as a cross-linker towards monomers such as acrylamide, and allows the production of gels by usual radical copolymerization. The potassium persulfate initiator is thermally activated in the reaction mixture (see Experimental Section). The propagating polyacrylamide chains are cross-linked by the polyanions during the polymerization and a hybrid network is obtained. The amount of POM in the polymerization mixture controls the density of reticulation. The concentration of the functionalized polyanion in the syntheses is higher than the CAC; thus it forms aggregates in the aqueous polymerization mixture. Analysis by transmission electron microscopy (Figure 2a) confirms the presence of polyanionic aggregates inside the

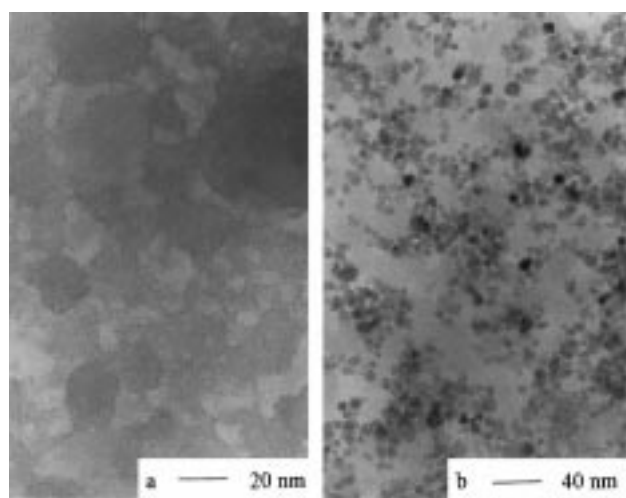


Figure 2. Transmission electron micrographs of the hybrid materials. a) View of a 5% POM gel without magnetic nanoparticles; b) view of the same gel containing maghemite nanoparticles of diameter 7.5 nm (1.4 vol % $\gamma\text{-Fe}_2\text{O}_3$ particles).

gel. We investigated the effect of three POM/monomer molar ratios (2, 5, and 10%), denoted 2% POM, 5% POM, and 10% POM. Since the polyanionic aggregates are negatively charged, the networks have the ability to be superabsorbent materials. This polyelectrolyte effect^[4,5] allows a swelling ratio (defined as being the ratio m/m_0 , where m is the mass of the gel sample swollen in aqueous solution and m_0 the mass of the dry gel) as high as 137.5 for 2% POM gels.

In addition to the potential properties of these new materials such as electrochromism, photochromism, conductivity, electrochemistry, or catalysis, these hybrid materials behave as promising superabsorbents. Unlike polyelectrolytes, the electric charges are located on the polyanionic cross-linkers, and it is possible to incorporate hydrophilic nano-objects with electrostatic charges inside the swelled network. Here we introduce negatively charged magnetic nanoparticles and take advantage of the magnetic properties of the particles to test the characteristics of the network. Some other ferrogels were produced a few years ago for applications in the field of magnetorheology^[6] and magnetostriction.^[7] These new hybrid hydroferrogels are expected to have applications, for example, in the areas of biomaterials and optics.

The magnetic particles are made of maghemite ($\gamma\text{-Fe}_2\text{O}_3$). They are polydisperse with an average diameter that can be controlled of between 6 and 14 nm.^[8] They are coated by citrate molecules so that they are negatively charged at pH values higher than 4, and can be thus dispersed at pH 7 in water as individual grains as a consequence of electrostatic repulsions. To maintain this stability during the copolymerization process, the polyanions used are obtained at pH 5.4. The copolymerization of acrylamide and the polyanion cross-linker is performed in the dispersion of magnetic particles for different volume fractions of particles. In this way, it is possible to trap large amounts of particles.

Figure 3 shows the magnetization curve of a ferrogel cross-linked by a polyanion (2% POM) with as much as 18 vol % magnetic oxide. It has the same shape as the magnetization

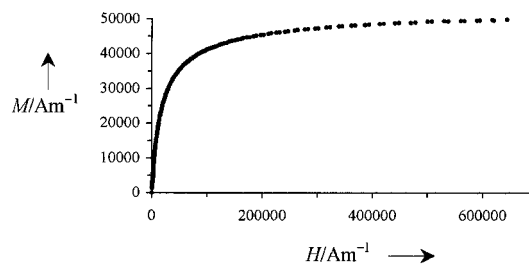


Figure 3. Magnetization curve of a 2% POM ferrogel (18% vol % $\gamma\text{-Fe}_2\text{O}_3$ particles).

curve of the corresponding aqueous dispersion of particles (characteristic of superparamagnetic behavior),^[9] which indicates that particles in the gel remain well dispersed. On the other hand, the presence of particles does not seem to modify the structure of the gel. Indeed, the IR spectrum presents the same bands with the same ratio of intensity as a hydrogel formed from the same ratio of reagents but without particles. In the region where the $\nu_{\text{asym}}(\text{C}=\text{O})$ stretching vibrational bands ($1600\text{--}1730 \text{ cm}^{-1}$) occur, one can observe a shift of the

bands arising from POM from 1713 to 1725 cm^{-1} , and the presence of two bands at 1615 and 1670 cm^{-1} characteristic of polyacrylamide, which attest to the loss of conjugation. The large band at 1119 cm^{-1} supports the formation of polyacrylamide chains. Moreover, the conservation of the polyanionic framework is confirmed by the presence of the same stretching vibrational bands ($\nu_{\text{asym}}(\text{W}=\text{O}_{\text{ter}})$ and $\nu_{\text{asym}}(\text{W}-\text{O}_b-\text{W})$) as those of the polyanion before polymerization.^[3] On the other hand, the stretching vibrational bands at 627 and 561 cm^{-1} ($\nu(\text{FeO})$) of maghemite particles are apparent.^[10] Figure 2b shows the transmission electron micrograph of a 5% POM gel, which contains 1.4 vol% maghemite particles (approximately 7.5 nm in diameter). This picture confirms the presence of polyanionic aggregates inside the gel and the presence of $\gamma\text{-Fe}_2\text{O}_3$ particles between the aggregates.

Figure 4 shows a ferrogel after the synthesis and the same ferrogel swelled in an aqueous solution for four days, which corresponds to the equilibrium degree of swelling. The



Figure 4. A hybrid 2% POM ferrogel a) after synthesis; b) swelled in an aqueous solution during four days (5.5 vol% $\gamma\text{-Fe}_2\text{O}_3$ particles).

polyelectrolyte effect of the polyanionic aggregates stays efficient in the ferrogels. It is controlled by the amount of POM, and not by the number of particles in the network. When the amount of POM is increased, the mesh of the polymeric network becomes smaller and the degree of swelling decreases. For example, for a ferrogel with 1.4 vol% particles, the degree of swelling drops from 60-fold for a 2% POM gel, to 24-fold for a 5% POM gel, and to 9-fold for a 10% POM gel.

The mobility of the nanoparticles in the network can be estimated by taking advantage of their magnetic properties. When a magnetic field is applied to a dispersion of maghemite nanoparticles this dispersion becomes birefringent as a result of the alignment of the particles in the field direction.^[11] The value of the birefringence, which reflects the number of particles aligned, allows the estimation of whether particles are immobilized or not in the network. When the field is cut off the birefringence vanishes as these unblocked particles return to random positions at a characteristic rate that is a function of the particle size and of the local viscosity around them (Figure 5). In the case of 8-nm particles (polydisperse system), 5% POM gels are able to block more particles than 2% POM gels, and at the same time, the relaxation time is smaller in the first case, which indicates that the unblocked particles are smaller than in the second gel. Since the system is polydisperse, these results lead to the conclusion that the colloidal particles can be either immobilized in the network, or free to rotate, depending on their size and the amount of POM used as cross-linking agent.

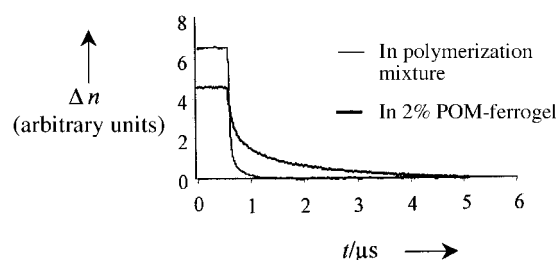


Figure 5. Relaxation of the birefringence signal for the polymerization mixture and for the corresponding ferrogel (molar fraction of POM (0.017 M) with respect to acrylamide (0.84 M): 0.02; 0.25 vol% $\gamma\text{-Fe}_2\text{O}_3$ particles).

This result is also related to the fact that, depending on the size of the particles, a release of particles during the swelling of the hydrogel can be observed. For example, when mono-sized particles are introduced into 2% POM gels, no particles are released if the particle diameter is larger than 9 nm; only 1% of the magnetic materials is released for 7.5-nm particles and about 5% is released for 6.1-nm particles. Results of this type have been reported for polymeric gels containing homopolymers of varying mass.^[12]

We have presented a hybrid absorbent material based on polyanions covalently linked to a polymeric network with included magnetic nano-sized objects. Two properties are particularly worthy of mention and are important for future applications: the rotational mobility of the particles in the network and their release during the swelling process. For both properties, the relevant parameters are the volume of the mesh of the network, and therefore the ratio of cross-linker, and the diameter of the particles. Indeed, for a given gel at a given degree of swelling, a critical diameter can be defined over which all particles are trapped in the gel. Likewise, this hybrid material is potentially promising for the sorting of nanometric objects on the basis of size. Two areas of application expected for these materials are biomaterials and optics.

Experimental Section

Sample preparation: Magnetite nanoparticles were synthesized according to Massart's method.^[13] The mean diameter of the particles was controlled by the experimental conditions used.^[14, 15] They were further oxidized to maghemite and then coated by citrate molecules according to reference [8]. Then they were dispersed in water. The ionic strength arose from unadsorbed trisodium citrate and was deduced from conductivity measurements and adjusted to a given value by dialysis of the colloidal solution against a reservoir containing a 8×10^{-3} M solution of trisodium citrate.

$[\gamma\text{-SiW}_{10}\text{O}_{36}(\text{RSiO})_4]^{4-}$ ($\text{R} = \text{C}_3\text{H}_6\text{OC}(\text{O})\text{C}(\text{Me})=\text{CH}_2$) was synthesized following the procedure already described:^[3] $\text{H}_2\text{C}=\text{C}(\text{Me})\text{C}(\text{O})\text{O}-\text{C}(\text{C}_3\text{H}_6)\text{Si}(\text{OMe})_3$ (0.94 mL, 4 mmol) was added to a solution of $\text{K}_8[\gamma\text{-SiW}_{10}\text{O}_{36}] \cdot 12\text{H}_2\text{O}$ ^[16] (3 g, 1 mmol) in a mixture of CH_3CN (30 mL) and H_2O (20 mL). The mixture was then acidified with 12 M HCl (0.4 mL) and the solution stirred for 4 h. The hygroscopic crude compound (ca. 3 g) was obtained after evaporation of the mixed solution. The product was then dissolved in deionized water and the pH of the solution raised to 5.4 by an aqueous solution of NaOH. The product was obtained after evaporation of the solution and washing with EtOH (30 mL) and acetone (20 mL), followed by drying under vacuum, and was kept under argon; yield 2.9 g (90.7%). Elemental analysis (%) calcd for $\text{C}_{28}\text{H}_{45.1}\text{Na}_{2.9}\text{Si}_5\text{W}_{10}\text{O}_{48}$ (3195.0): C 10.52, H 1.43, Na 2.09, Si 4.39, W 57.54; found: C 11.04, H 1.48, Na 2.07, Si 4.42, W 57.88. IR (KBr): $\tilde{\nu} = 1714 \text{ cm}^{-1}$ (vs, $\nu(\text{CO})$), 1636 (m, $\nu(\text{C}=\text{C})$), 1324 (m, $\delta(\text{CH})$), 1300 (m, $\delta(\text{COR})$), 1200 (vs, $\delta(\text{CO})$), 1170 (s, $\nu(\text{SiC})$), 1108 (vs,

$\nu(\text{SiO})$ from $\{\text{RSiO}_3\}$, 1081 (vs, $\nu(\text{SiO})$ from $\{\text{RSiO}_3\}$), 1058 (vs, $\nu(\text{SiO})$ from $\{\text{RSiO}_3\}$), 989 (vw, $\nu(\text{SiO})$ from $\{\text{SiO}_4\}$), 963 (vs, $\nu(\text{WO}^{\text{ter}})$), 925 (vs, $\nu(\text{WO})$), 902 (vs, $\nu(\text{WO})$), 868 (vs, $\nu(\text{WO})$), 820 (vs, $\nu(\text{WO})$), 748 (vs, $\nu(\text{WO})$), 562 (vw, $\delta(\text{SiO})$), 538 (vw, $\delta(\text{SiO})$), 412 (vw, $\delta(\text{WO})$), 368 (vw, $\delta(\text{WO})$).

The POM-ferrogels were prepared by the radical copolymerization of acrylamide (0.84 M) in an aqueous dispersion (pH 7) of $\gamma\text{-Fe}_2\text{O}_3$ particles (volume fraction of particles: 0.25, 0.7, 1.4, 2.75, 7, 12, 18%), POM (0.017, 0.042, and 0.084 M) as the cross-linker, and potassium peroxodisulfate (2.2×10^{-3} M) as the radical initiator. The polymerization mixture was then heated at 70 °C for 1 h. IR data for a POM ferrogel with $[\text{POM}] = 0.042$ M and a volume fraction of $\gamma\text{-Fe}_2\text{O}_3$ of 11%, IR (KBr): $\bar{\nu} = 1725$ cm^{-1} (m, $\nu(\text{CO}_2)$ from $\{\text{RSiO}\}$), 1670 (s, $\nu(\text{CO})$ from polyacrylamide), 1615 (m, $\delta(\text{NH})$), 1456 (w, $\delta(\text{CH}_2)$), 1414 (w, $\delta(\text{CH})$), 1349 (vw, $\nu(\text{CN})$), 1322 (vw, $\delta(\text{CH})$), 1298 (vw, $\delta(\text{C}-\text{O}-\text{CH}_2)$ from $\{\text{RSiO}\}$), 1196 (w, $\delta(\text{CO})$), 1119 (m, $\nu(\text{C}-\text{C}-\text{O})$ from $\{\text{RSiO}\}$), 1053 (w, $\nu(\text{SiO})$), 962 (w, $\nu(\text{WO}^{\text{ter}})$), 926 (w, $\nu(\text{WO})$), 902 (w, $\nu(\text{WO})$), 866 (w, $\nu(\text{WO})$), 820 (w, $\nu(\text{WO})$), 749 (w, $\nu(\text{WO})$), 627 (vs, $\nu(\text{FeO})$), 561 (vs, $\nu(\text{FeO})$).

Physical measurements: The compound $\gamma\text{-K}_8[\text{SiW}_{10}\text{O}_{36}] \cdot 8\text{H}_2\text{O}$ was prepared according to the literature.^[16] Other reagents, $\text{RSi}(\text{OMe})_3$, and solvents were purchased from Aldrich and used as received. Elemental analyses were performed by the Service Central de Microanalyses du CNRS, Vernaison, France. The IR spectra (4000–250 cm^{-1} ; KBr) of the compounds and dried hydroferrogels were recorded on a Bio-Rad FTS 165 FT-IR spectrometer. The magnetic measurements were performed by using a classical Foner device.^[17] They allow the volume fraction of magnetic particles to be deduced from the saturation magnetization, and the particles size from the shape of the magnetization curve.^[9] The apparatus used for the birefringence experiment is described elsewhere.^[9] Visualization of POM aggregates and of magnetic particles in the hydroferrogels were performed with a transmission electron microscope (JEOL 100 CX2) on microcoats of hydroferrogel deposited on a carbon-coated copper grid after microtomy at the Centre Régional de Mesures Physiques, Paris. The pictures of the gels were obtained with a charge-coupled device (CDD) color camera (Vista, VPC 4130, UK). Surface tension measurements were obtained at 25 °C on a Krun KT10 tensiometer.

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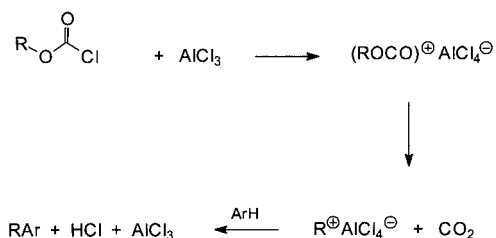
Friedel–Crafts Alkylation of Alkenes: Ethylaluminum Sesquichloride Induced Alkylations with Alkyl Chloroformates**

Ursula Biermann and Jürgen O. Metzger*

*Dedicated to Professor Hansjörg Sinn
on the occasion of his 70th birthday*

The alkylation of alkenes is of considerable importance.^[1] Our interest lies in the alkylation of long-chain unsaturated fatty compounds such as oleic acid (**1a**) since they are renewable raw materials of increasing significance^[2, 3] and alkyl-branched fatty compounds have interesting properties.^[4] However, there are no methods for the direct alkylation of nonactivated C–C double bonds with simple alkyl residues such as the isopropyl group. Thermal radical addition of alkanes is applicable to terminal double bonds only, not to internal double bonds.^[5] Friedel–Crafts alkylations of alkenes, which have been thoroughly investigated by Mayr et al., lead to 1:1 adducts only under certain restricted conditions.^[6–9] Thus, ZnCl_2 -induced reactions of isopropyl chloride with propene or isobutene gave no monoalkylation products, but exclusively oligomers.^[6] Cationic additions of alkanes are restricted to tertiary alkanes, for example the formation of isooctane by the reaction of isobutene and isobutane in the presence of concentrated acids.^[1, 10]

Friedel and Crafts^[11] as well as Rennie^[12] showed that benzene is ethylated with ethyl chloroformate in the presence of AlCl_3 (Scheme 1).^[13] Chloroformates fragment in the presence of Lewis acids with the formation of carbenium



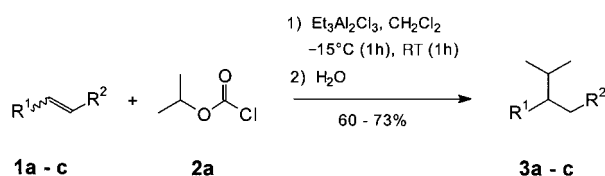
Scheme 1. Friedel–Crafts alkylation of arenes by AlCl_3 -induced formation of carbenium ions from chloroformates.^[13] Ar = Aryl, R = Alkyl.

[*] Prof. Dr. J. O. Metzger, Dr. U. Biermann
Fachbereich Chemie der Universität
Postfach 2503, D-26111 Oldenburg (Germany)
Fax: (+49) 441-798-3329
E-mail: juergen.metzger@uni-oldenburg.de

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ions.^[13, 14] We now report for the first time the alkylation of alkenes with alkyl chloroformates.

The reaction of oleic acid (**1a**) with isopropyl chloroformate (**2a**) in the presence of ethylaluminum sesquichloride ($\text{Et}_3\text{Al}_2\text{Cl}_3$) gave after 2 h a 1:1 regioisomeric mixture of 9- and 10-isopropyloctadecanoic acid (**3a**) in 73 % yield (Scheme 2). The analogous reaction with *trans*-4-octene (**1b**) gave 4-isopropyloctane (**3b**) in 67 % yield; small

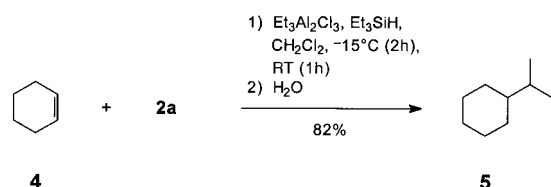


1, 3	R ¹	R ²
a	(CH ₂) ₇ CH ₃	(CH ₂) ₇ COOH
b	(CH ₂) ₃ CH ₃	(CH ₂) ₂ CH ₃
c	(CH ₂)CHOH(CH ₂) ₅ CH ₃	(CH ₂) ₇ COOCH ₃

Scheme 2. $\text{Et}_3\text{Al}_2\text{Cl}_3$ -induced reaction of oleic acid (**1a**), *trans*-4-octene (**1b**), and methyl ricinoleate (**1c**) with isopropyl chloroformate (**2a**). Compound **3a** was obtained as a regioisomeric mixture (ca. 1:1), **3c** as a regioisomeric and diastereomeric mixture.

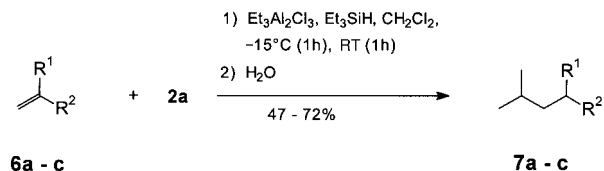
amounts (ca. 10%) of the regioisomeric addition products and the regioisomeric ethylisopropyloctanes were also formed. In the reaction of methyl ricinoleate (**1c**) the alkylation product **3c** was obtained in 60 % yield as a mixture of regio- and diastereoisomers. Clearly the isopropyl cation formed from the chloroformate **2a** with $\text{Et}_3\text{Al}_2\text{Cl}_3$ adds to the C–C double bond of the alkenes **1a–c** and the subsequent transfer of a hydride ion from $\text{Et}_3\text{Al}_2\text{Cl}_3$ to the adduct carbenium ion leads to the saturated addition products **3a–c**. It is known that ethylaluminum compounds can transfer hydride ions as well as ethyl groups;^[15] notably, in this case the hydride ion is transferred significantly more rapidly than the ethyl group, as is demonstrated by the small amount of ethylated product in all reactions.

The alkylation of cyclic alkenes such as cyclohexene (**4**) under the reactions conditions described for the alkenes **1a–c** occurred with only moderate yields. A product mixture was formed which consisted mainly of oligomers. However, the addition of a more effective hydride donor, for example triethylsilane^[9] considerably suppressed oligomerization, and isopropylcyclohexane (**5**) was isolated in 82 % yield (Scheme 3).



Scheme 3. Alkylation of cyclohexene (**4**) with isopropyl chloroformate (**2a**).

The reactions of 1,1-dialkylethenes, such as 2-methyl-1-undecene (**6a**), and 1-alkenes, such as 1-octene (**6b**) and methyl 10-undecenoate (**6c**), with **2a** also proceeded predominantly with oligomerization; alkylation products **7a–c** were not formed or only in poor yields. The addition of an equimolar amount of triethylsilane, on the other hand, gave **7a–c** in 47–72 % yield (Scheme 4).

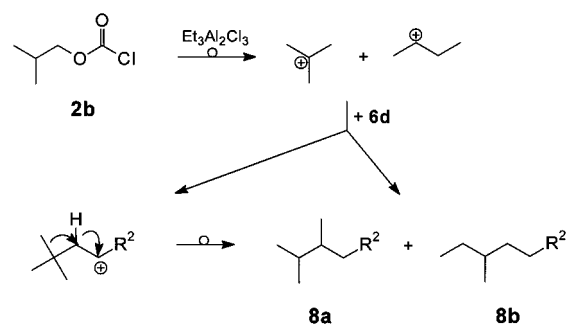


6, 7	R ¹	R ²
a	CH ₃	(CH ₂) ₈ CH ₃
b	H	(CH ₂) ₅ CH ₃
c	H	(CH ₂) ₈ COOCH ₃
d	H	(CH ₂) ₈ COOH

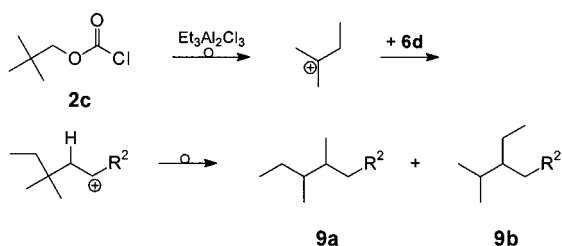
Scheme 4. Alkylation of 2-methyl-1-undecene (**6a**), 1-octene (**6b**), and methyl 10-undecenoate (**6c**) with isopropyl chloroformate (**2a**).

We have described a new method for the isopropylation of alkenes in which in an $\text{Et}_3\text{Al}_2\text{Cl}_3$ -induced reaction an isopropyl cation is formed from the respective chloroformate and is added to the C–C double bond with subsequent hydride transfer. This addition can be applied to alkenes with a 1,2-dialkyl-substituted double bond and—with the addition of triethylsilane—also to 1-alkenes, 1,1-dialkylethenes, and cyclic alkenes. On the basis of these results the alkylation of alkenes should be possible with other alkyl chloroformates.

We have therefore treated 10-undecenoic acid (**6d**) in the presence of $\text{Et}_3\text{Al}_2\text{Cl}_3$ with the isobutyl (**2b**) and neopentyl (**2c**) esters of chloroformic acid, expecting interesting rearrangements. In both cases we obtained two constitutional isomeric addition products **8a/b** and **9a/b**, respectively, in a straightforward reaction (Schemes 5 and 6); after the rearrangement of the primary alkyl groups^[16] and the addition, rearrangement of the carbenium ion adduct occurs. It is notable that as with the cationic addition of isobutane to 1-alkenes^[10] no addition products with quaternary carbon atoms were found. Similar results were also



Scheme 5. Reaction of isobutyl chloroformate (**2b**) with 10-undecenoic acid (**6d**). The addition products **8a** and **8b** were formed in the ratio 2.2:1. $\text{R}^2 = (\text{CH}_2)_8\text{COOH}$.



Scheme 6. Reaction of neopentyl chloroformate (**2c**) with 10-undecenoic acid (**6d**). The addition products **9a** and **9b** were formed in the ratio 2.2:1. $\text{R}^2 = (\text{CH}_2)_8\text{COOH}$.

obtained with 2-ethylhexyl chloroformate. In contrast, reactions with ethyl chloroformate led to oligomeric products.

Experimental Section

General method for the synthesis of **3a–c**: A mixture of the respective alkene **1a** (1.42 g, 4.2 mmol), **1b** (0.56 g, 5 mmol), or **1c** (1.56 g, 4.2 mmol) and isopropyl chloroformate (**2a**) (0.7 g, 5 mmol) in CH_2Cl_2 (10 mL) was stirred in a N_2 atmosphere (1 bar) for 5 min at -15°C . Then $\text{Et}_3\text{Al}_2\text{Cl}_3$ (1.86 g, 7.5 mmol for **1a**, 1.24 g, 5 mmol for **1b**, and 2.47 g, 10 mmol for **1c**) was added dropwise over 1 h at -15°C and the solution was stirred at room temperature for a further 1 h. Diethyl ether (100 mL), H_2O (40 mL), and 10% HCl to dissolve precipitated aluminum salts were then added. The organic phase was separated and washed with H_2O (3×30 mL). After the combined extracts had been dried over Na_2SO_4 the solvent was removed in vacuum. Purification of **3a** was achieved by column chromatography (silica gel 60, 70–230 mesh, 1.7×33 cm) with petroleum ether/ethyl acetate (7/3, 300 mL) to yield 0.99 g **3a** (73%). Pure **3b** (0.52 g, 67%) and **3c** (0.90 g, 60%) were obtained by kugelrohr distillation.

General method for the synthesis of **5** and **7a–c**: A mixture of the respective alkene **4**, **6a–c** (5 mmol), and **2a** (0.7 g, 5 mmol) in CH_2Cl_2 (10 mL) was stirred in a N_2 atmosphere (1 bar) for 5 min at -15°C . A mixture of triethylsilane (0.58 g, 5 mmol) and $\text{Et}_3\text{Al}_2\text{Cl}_3$ (1.24 g, 5 mmol) was then added dropwise over 1 h (2 h for **5**) at -15°C and the mixture was stirred for a further 1 h at room temperature. Diethyl ether (100 mL), H_2O (40 mL), and 10% HCl to dissolve precipitated aluminum salts were then added. The organic phase was separated and washed with H_2O (3×30 mL). After the combined extracts had been dried over Na_2SO_4 , the solvent was removed in vacuo, and the residues eluted over silica gel 60 with pentane. Evaporation of the pentane followed by kugelrohr distillation gave **5** (0.52 g, 82%), **7a** (0.50 g, 47%), **7b** (0.43 g, 55%), or **7c** (0.86 g, 72%).

General method for the synthesis of **8a/b** and **9a/b**: A mixture of **6d** (0.92 g, 5 mmol) and **2b** (0.68 g, 5 mmol) or **2c** (0.75 g, 5 mmol) in CH_2Cl_2 was stirred in a N_2 atmosphere (1 bar) for 5 min at -15°C . Then $\text{Et}_3\text{Al}_2\text{Cl}_3$ (1.24 g, 5 mmol) was added as described for **3a–c**. The reaction mixtures were worked up as described and purified by column chromatography to give **8a/b**: (0.79 g, 65%) and **9a/b**: (0.89 g, 70%), respectively.

The products were identified by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

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van't Hoff–Le Bel Stranger: Formation of a Phosphonium Cation with a Planar Tetracoordinate Phosphorus Atom**

Matthias Driess,* Joachim Aust, Klaus Merz, and Christoph van Wüllen

Dedicated to Professor Gerhard Fritz on the occasion of his 80th birthday

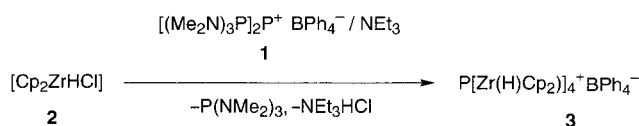
Molecular differentiation in nature would be strongly limited with respect to stereochemistry if a tetracoordinate carbon atom did not prefer a tetrahedral geometry.^[1] It was the fundamental contribution of van't Hoff and Le Bel, in the final quarter of the nineteenth century, which predicted that the phenomenon of stereochemistry for tetracoordinated

[*] Prof. Dr. M. Driess, Dipl.-Chem. J. Aust, Dr. K. Merz
Lehrstuhl für Anorganische Chemie I der Universität
Fakultät für Chemie
Universitätsstrasse 150, D-44801 Bochum (Germany)
Fax: (+49)234-709-4378
E-mail: matthias.driess@ac1.ruhr-uni-bochum.de
Priv.-Doz. Dr. C. van Wüllen
Lehrstuhl für Theoretische Chemie der Universität
Fakultät für Chemie
Universitätsstrasse 150, D-44801 Bochum (Germany)

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carbon compounds is based on the tetrahedron model of methane.^[2] Nowadays this geometry is well known in molecular science. Moreover, isoelectronic molecules and ions usually adopt classical tetrahedral structures too. This can be rationalized by employing the far-reaching Lewis-bonding concept ("octet rule") and classical molecular orbital theory.^[3] However, about 100 years after the finding of van't Hoff and Le Bel it was suggested that the seemingly impossible goal of stabilizing an "anti-van't Hoff–Le Bel" configuration of an eight valence electron molecule ER_4 (for example, planar methane, $E = C$, or silane derivatives, $E = Si$) or isoelectronic ions (for example, quarternary ammonium, NR_4^+ , or phosphonium ions, PR_4^+ ; R = organic or organometallic substituent) may not be out of reach.^[4–7] While recent reports have shown that compounds with planar tetracoordinate carbon centers can be synthesized by employing organometallic substituents,^[8–9] attempts to prepare planar isoelectronic ER_4 compounds with other main-group elements failed. Herein we describe the synthesis and structure of the first phosphonium cation, PR_4^+ , which has exclusively electropositive organometallic zirconocene substituents R ($R = (C_5H_5)_2ZrH$, zirconocenyl hydride) and an "anti-van't Hoff–Le Bel" configuration. Furthermore we report the results of ab initio calculations on a series of isoelectronic model ER_4 compounds ($E = B^-, C, N^+, Al^-, Si, \text{ and } P^+$), which show that this organometallic substituent R represents a facile and, at the same time, universal ligand for the stabilization of elusive "anti-van't Hoff–Le Bel" configurations of various main-group elements.

On the basis of the MO model of planar methane^[4, 5] it is not difficult to understand why it is possible to stabilize planar tetracoordinate carbon atoms in methane derivatives: The mainly electronic trick to reduce and possibly reverse the energy gap between tetrahedral and planar configurations is to coordinate at least two electropositive metal centers at the four-coordinate carbon atom. At the same time these metal centers serve as strong σ -donor and π -acceptor ligands.^[6–9] This enables delocalization of the unfavorable π electrons in the hypothetical planar CH_4 molecule and leads, therefore, to a substantial change in the energy difference between tetrahedral and planar geometry. Thus, one expects that strongly electropositive metal ligands with π -acceptor functions should support "anti-van't Hoff–Le Bel" structures of the isoelectronic ions NR_4^+ (ammonium), PR_4^+ (phosphonium), and AsR_4^+ (arsonium cation).^[7] So far, only some gold(I) complexes $E(AuL)_4^+$ with $E = N$ and As (L = neutral donor ligand such as $P(C_6H_5)_3$) have been isolated, of which the NR_4^+ ion possesses the classical tetrahedral structure, while the AsR_4^+ ion adopts a tetragonal pyramidal structure, with the arsenic atom sitting above the Au_4 square, as a result of its relatively large atom size and favorable Au–Au interactions.^[10] The analogous PR_4^+ ion has not yet been prepared, but ab initio calculations predict the same tetragonal pyramidal geometry as observed for AsR_4^+ .^[11] In our search for a stable tetrametalated phosphonium salt ($PR_4^+X^-$, R = metal ligand, X = any counterion), we found that the tetrametalation of the triphosphenium salt **1**^[12] with the Schwartz reagent $[(C_5H_5)_2ZrHCl]$ (**2**)^[13, 14] in the molar ratio of 1:9 in THF and in the presence of triethylamine as an auxiliary base



surprisingly leads to the tetrazirconio-substituted phosphonium cation in **3**, which adopts an "anti-van't Hoff–Le Bel" configuration. Compound **3** is diamagnetic, sparingly soluble in aromatic solvents, THF, and CH_2Cl_2 , but soluble in DMF (but slow decomposition occurs), and has been isolated in an analytically pure state (correct C,H combustion analysis) in the form of green crystals in 11 % yield.

The mechanism for the formation of **3** is not yet known, but paramagnetic reactive intermediates have been observed, but which could not be characterized. Apparently, **1** is a source of phosphorus cations in this reaction, since the only detectable phosphorus-containing product in the ^{31}P NMR spectrum of the reaction mixture, besides **3**, is merely the "free" triamino-phosphane $P(NMe_2)_3$ ($\delta(^{31}P) = 123.9$). The latter is liberated from **1** through a ligand substitution reaction (metathesis). The ^{31}P NMR spectrum of solutions of **3** in $[D_6]DMF$ shows a quintet resonance signal at relatively low field ($\delta = 254.2$) as a result of $^2J(P, H)$ couplings with four chemically equivalent ZrH protons ($J = 29.5$ Hz), and a singlet in the $^{31}P\{^1H\}$ spectrum. The expected sets of phenyl, C_5H_5 , and ZrH proton resonances are observed in the ^1H NMR spectrum, with the characteristic high-field resonance of the ZrH protons ($\delta = -3.8$ ($^2J(H, P) = 29.5$ Hz)) clearly indicating the presence of $Zr-H-Zr$ bridges. This has been confirmed by a single-crystal X-ray diffraction analysis of **3**.^[15] It crystallizes in the monoclinic space group $C2/c$ with four ion pairs in the unit cell and the phosphorus atoms as symmetry centers in the cations. The most striking feature of the structure is the planar tetracoordinate phosphorus atom in the cation (Figures 1 and 2) along with its isoelectronic, classical tetraphenylborate counterion. The $Zr-P$ (2.616(1) and 2.610(2) Å) and $Zr-H$ bond lengths (1.93, 2.07, and 2.12 Å) are unremarkable and resemble those values reported for zirconium phosphanides^[16] and μ -hydrido zirconium hydrides.^[14, 17] The $Zr1a-P-Zr2$ and $Zr1a-P-Zr2$ angles of 89.84(4) and 90.16(4)°, respectively, are almost ideal for such a coordination mode. The bridging

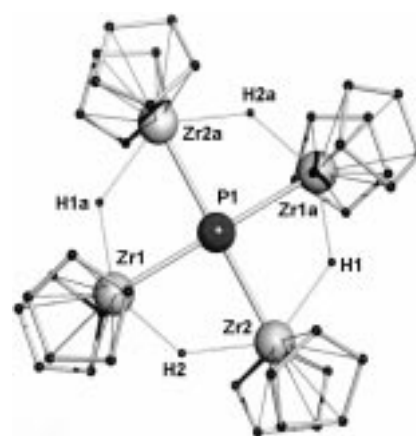


Figure 1. Molecular structure of the phosphonium cation $P[Zr(H)(C_5H_5)_2]_4^+$ in the tetraphenylborate salt **3**; the hydrogen atoms of the C_5H_5 groups are omitted for clarity.



Figure 2. van der Waals model of the phosphonium cation in **3** (see also Figure 1).

hydride centers facilitate the formation of an almost planar eight-membered Zr_4H_4 cycle, which can be regarded as an “anti crown ether” ligand^[18] for the phosphorus cation. The endocyclic H-Zr-H angles of 132 – 138° reflect the almost equidistant bridging mode of the hydride centers.

What are the reasons for the unprecedented geometry of the phosphonium cation? Apparently, steric congestion by the C_5H_5 groups of the zirconocene moieties plays a role in the energy gap between the planar and tetrahedral form. However, *ab initio* calculations^[19] of the model cation $P[Zr(H)Cl_2]_4^+$, in which the C_5H_5 groups have been fully replaced by chlorine atoms, clearly show that the planar (“anti-van’t Hoff–Le Bel”) structure (D_{4h} symmetry) is still favored by 74 kcal mol^{-1} (!) with respect to the classical tetrahedral one (S_4 symmetry). Interestingly, the Zr-H hydride atoms in the optimized S_4 structure prefer terminal coordination sites. Apparently, the Zr-H-Zr hydrogen bridges contribute to the energy gap, but they probably do not make a substantial contribution. It seems crucial, as in the case of stable, planar methane derivatives, that the p_z lone-pair electrons of phosphorus in the HOMO (Highest Occupied Molecular Orbital) can be delocalized by π -backbonding to symmetry-adopted empty d orbitals of the four metal centers (Figure 3). According to its MO model the planar cation

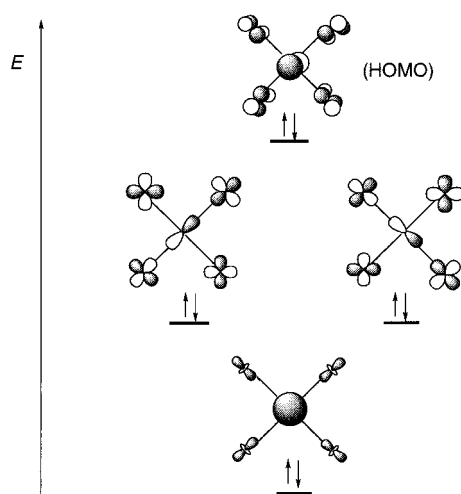


Figure 3. Molecular orbital representation of the σ and π interactions between zirconium and phosphorus atoms in the PZr_4^+ core of the cation in **3**.

possesses Zr,P,Zr-three-center σ -bonds in the molecular plane (Figure 3), which are mostly responsible for the unusual low-field chemical shift of the ^{31}P nucleus. It should be mentioned that previous calculations of the very unfavorable planar PH_4^+ form (energy gap between tetrahedral and planar configuration (D_{4h}) $276 \text{ kcal mol}^{-1}$ (!)) revealed its spontaneous distortion to an tetragonal pyramidal structure (C_{4v}), which is still $163 \text{ kcal mol}^{-1}$ less stable with respect to the tetrahedral form.^[7] This result underlines the remarkable incommensurability of the phosphonium cation in **3** versus PH_4^+ . Furthermore, our calculations of the hypothetical silane SiR_4 and of the corresponding alanate AlR_4^- with $R = Zr(H)Cl_2$ revealed that the planar configuration is, in analogy to the PR_4^+ analogue, 66 and 60 kcal mol^{-1} more stable, respectively, than the tetrahedral geometry. This large energy gap is intriguing, since the structural preference of such planar entities is almost independent of the electronegativities of the central main-group atoms. It is therefore very surprising, that the isoelectronic species of elements of the second period (ER_4 , $E = B^-, C, N^+$) prefer a strongly distorted tetrahedral geometry with one large Zr-E-Zr angle of about 140° and Zr-H-Zr hydride bridging.

These structures are 6 – 13 kcal mol^{-1} more stable than their planar D_{4h} forms. The energy gap is probably reduced or even reversed as a result of steric influence if C_5H_5 ligands instead of chlorine substituents are bonded to the metal. Apparently, the different behavior of second versus third period elements is a consequence of the smaller size of boron, carbon, and nitrogen atoms and reflects their preference to undergo sp hybridization in contrast to aluminum, silicon, and phosphorus atoms.^[20] Compound **3** is clearly important as a starting material for studies of structure–reactivity relationships of this rare class of compounds. The simple and, at the same time, universal organometallic ligand R in **3** offers tremendous advantages for the preparation of other “anti-van’t Hoff–Le Bel”-configured eight valence electron ER_4 molecules and ions.

Experimental Section

A slurry of **2** (2.56 g, 9.93 mmol) in THF (40 mL) and NEt_3 (10 mL) at $-70^\circ C$ was treated with **1** (0.73 g, 1.08 mmol). The reaction mixture was then slowly warmed up to room temperature whereby the red suspension was stirred for four days. Filtration and subsequent evaporation of solvents left a solid residue, which was dissolved in CH_2Cl_2 (30 mL). This solution was then layered with hexane (10 mL), whereby the product precipitated in the form of analytically pure green crystals (yield: 0.14 g, 0.12 mmol; 11 %); m.p. $178^\circ C$ (decomp). ^1H NMR (250 MHz, $[D_6]DMF$, 300 K): $\delta = -3.80$ (d, 4H, Zr-H, $^2J(H,P) = 29.5 \text{ Hz}$), 6.31 (s, 40H, C_5H_5), 7.00 (m, 4H, p - C_6H_5), 7.10 (m, 8H, m - C_6H_5), 7.50 (m, 8H, o - C_6H_5); ^{31}P NMR (101 MHz, $[D_6]DMF$, 300 K): $\delta = 254.2$ (quint., $^2J(P,H) = 29.5 \text{ Hz}$).

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- [15] Crystal structure data: monoclinic, space group $C2/c$, $a = 25.484(18)$, $b = 13.219(8)$, $c = 18.109(11)$ Å, $\beta = 120.400(17)^\circ$, $V = 5262(6)$ Å³, $Z = 4$, $\rho = 1.565$ g cm⁻³, $\mu = 0.842$ mm⁻¹, $F(000) = 2512$, crystal size = $0.2 \times 0.2 \times 0.1$ mm. Crystals were mounted on a glass capillary with perfluorinated hydrocarbons and immediately chilled to 203 K. Data collection was performed with a Bruker axis SMART diffractometer (MoK α graphite monochromator). A total of 11 158 reflections ($1.80 < \theta \leq 25.37^\circ$) were collected, of which 4690 unique reflections ($R_{\text{int}} = 0.100$) were used. The structure was solved using the program SHELXS-97 and refined (326 parameter) using the program SHELXL-97 to $R1 = 0.0525$, $wR2 = 0.1137$ (all data) ($I > 2\sigma(I)$); both programs from G. M. Sheldrick, Universität Göttingen, 1997). The positions of the Zr-H hydrogen atoms were localized in the difference Fourier map and refined; non-hydrogen atoms were anisotropically refined. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. CCDC-116996. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Lectin-Mediated Drug Targeting: Discrimination of Carbohydrate-Mediated Cellular Uptake between Tumor and Liver Cells with Neoglycoconjugates Carrying Fucose Epitopes Regioselectively Modified in the 3-Position**

Hans-Georg Lerchen,* Joerg Baumgarten, Norbert Piel, and Victoria Kolb-Bachofen

Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday

The specific interaction between carbohydrate epitopes and corresponding endogenous cell-surface lectins plays a fundamental role in a variety of intercellular recognition processes such as sperm–egg adhesion, leucocyte adhesion to platelets and endothelium, cancer metastasis, and microorganism adhesion to host cells.^[1] Various lectins have been identified and characterized with respect to carbohydrate specificity on rat, mice, and mammalian tissues, particularly on the liver.^[2] The utility of these carbohydrate–lectin interactions for receptor-mediated drug targeting has already been explored mainly focussing on liver targeting.^[3] Also tumor cells express a distinct lectin pattern on their surfaces.^[4] However, to our knowledge, so far no tumor-specific lectins have been described, and a lectin-mediated drug targeting to tumor cells is extremely challenging.^[5] Prerequisites are the discrimination of the targeting moiety between tumor cells and healthy tissue and the circumvention of an efficient scavenging of glycoconjugates by liver cells as described for Kupffer cells and hepatocytes.^[6]

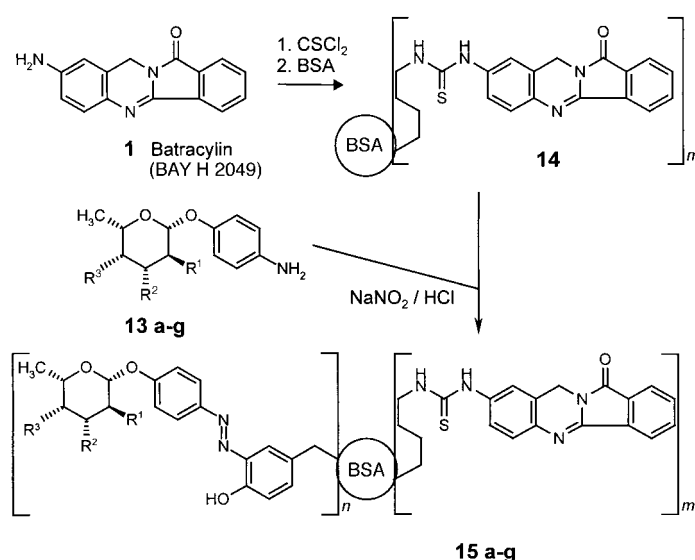
The goal of this work was the identification of carbohydrate residues appropriate for tumor targeting. A fucose-binding receptor has been identified on colon cancer cells such as SW480 and was considered to be an appropriate target mediating tumor cell binding and uptake.^[7] However, fucose also efficiently binds to lectins in the liver, particularly on Kupffer cells.^[2] Therefore a discrimination between the recognition of tumor and liver cell had to be achieved. Neoglycoconjugates such as glycoconjugates of bovine serum albumin (BSA) are appropriate tools for studying lectin–carbohydrate interactions and carbohydrate-mediated cellu-

[*] Dr. H.-G. Lerchen
Bayer AG, Zentrale Forschung, Wirkstoff-Forschung
Gebäude, D-51368 Leverkusen (Germany)
Fax: (+49) 214-3050070
E-mail: hans-georg.lerchen.hl@bayer-ag.de
Dr. J. Baumgarten
Bayer AG, Zentrale Forschung, Biotechnologie
Gebäude, D-51368 Leverkusen (Germany)
Dr. N. Piel
Bayer Corp., Business Group Diagnostics
511 Benedict Avenue, Tarrytown NY 10591-5097 (USA)
Prof. Dr. V. Kolb-Bachofen
Forschungsgruppe für Immunbiologie
Heinrich-Heine-Universität Düsseldorf
Moorenstrasse 5, D-40001 Düsseldorf (Germany)

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lar uptake.^[4a] A couple of methods have been described for the attachment of carbohydrate residues to different amino acid side chains of the protein.^[4a, 8] The clustered carbohydrate epitopes on the BSA molecule effect a multivalent and efficient binding to corresponding receptors on cellular membranes.^[8, 9] To investigate potential differences of cellular uptake of tumor and liver cells, we designed novel BSA conjugates with modified fucose epitopes which were subsequently labeled with colloidal gold particles for electron microscopic detection of cellular uptake. This functional endocytosis assay rather than studies at isolated lectins was considered to be most significant in exploring the targeting potential of these carbohydrate residues, because of the expression of a variety of lectins on cellular membranes with overlapping carbohydrate specificities. BSA conjugates carrying unmodified fucose residues are expected to be endocytosed by both tumor and liver cells. Previous studies from other groups with distinct lectins have demonstrated a strong impact of chemical modifications of the carbohydrate hydroxyl functionalities on lectin binding.^[10] Therefore, the rationale of this work was a systematic investigation of BSA conjugates carrying regioselectively modified fucose residues to identify a particular modification of the carbohydrate epitope that is tolerated by receptors on tumor cells and at the same time decreases receptor mediated uptake into liver cells. For this purpose a straightforward synthesis of regioselectively modified *p*-aminophenyl β -L-fucoside derivatives starting from readily available *p*-nitrophenyl β -L-fucoside has been developed. These modified fucose derivatives were attached to the tyrosine side chains of BSA, and the uptake of these neoglycoconjugates into the tumor cell line SW480 and into different liver cells was investigated. Furthermore, an additional attachment of a toxophore moiety to the lysine side chains allowed the measurement of cytotoxic activity of these BSA conjugates against the tumor cell line SW480.

As a toxophore moiety the fluorescent cytostatic agent batracylin (BAY H 2049; **1**) was selected.^[11] The anilinic amino group of **1** was activated with thiophosgene to provide the corresponding isothiocyanate, which in a second step reacted with the lysine side chains of BSA to give the conjugate **14** (Scheme 1). Appropriate carbohydrate moieties for attachment to BSA are *p*-aminophenyl glycosides such as the *p*-aminophenyl β -L-fucoside (**13a**) and its modified derivatives



Scheme 1. Synthesis of BSA conjugates with batracylin and modified fucose residues.

13b–g. They were diazotated with sodium nitrite and subsequently attached to the tyrosine side chains that show the highest reactivity under these acidic reaction conditions.^[4a, 8] In the obtained BSA conjugates **15a–g** about 15–30 lysine side chains are linked to the toxophore moiety and 10–22 tyrosines are modified with carbohydrate residues (Table 1).

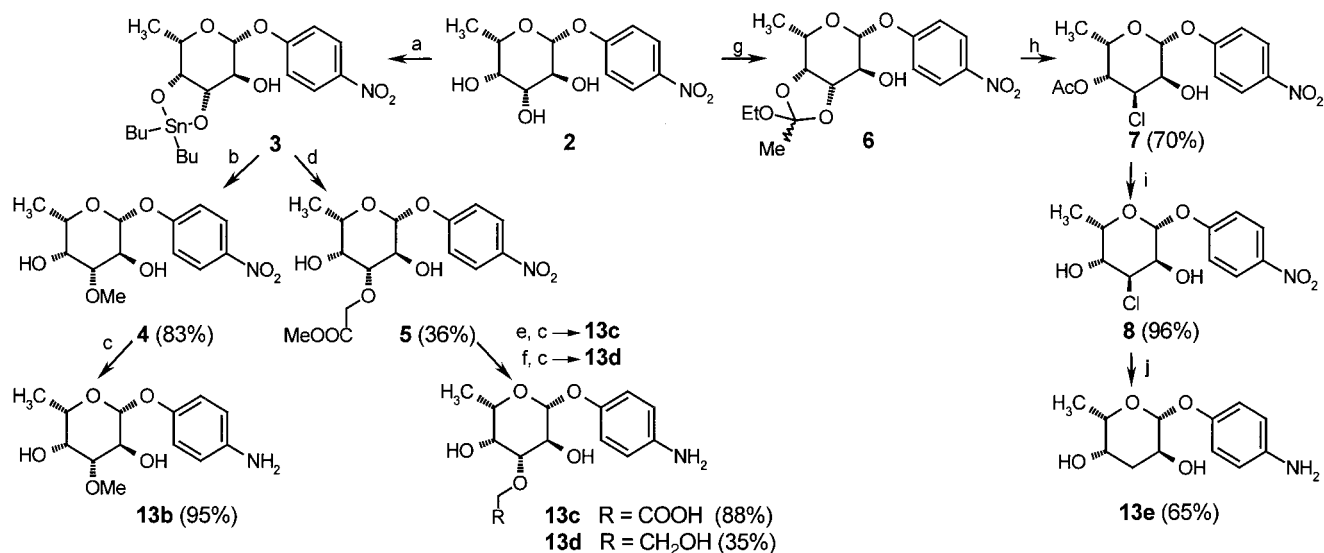
For the synthesis of regioselectively modified *p*-aminophenyl β -L-fucosides **13b–g** readily available *p*-nitrophenyl β -L-fucoside **2** was used as a convenient starting material. Conversions of the hydroxyl groups without the placement of protecting groups at the anomeric center are possible. Furthermore, after completion of the conversions hydrogenolytic reduction of the nitro group quickly generates the *p*-aminophenyl fucosides **13b–g** suitable for attachment to BSA.

An efficient access to a series of 3-O-modified *p*-aminophenyl β -L-fucosides is shown in Scheme 2 utilizing tin chemistry.^[12] The *cis* hydroxyl groups **2** were converted into the tin acetal **3** with dibutyltin oxide in methanol. After evaporation of methanol the addition of alkylating agents such as methyl iodide or methyl bromoacetate in DMF or

Table 1. Substitution pattern of *p*-aminophenyl fucosides **13a–g** as well as the constitution and biological data (cellular uptake and cytotoxic activity) of BSA conjugates **15a–g**.

Entry	compd	modified fucoside residue	R ¹	R ²	R ³	BSA conjugate compd	<i>n</i>	Kupffer cells	Uptake ^[a] into hepatocytes	SW480 cells	Cytotoxicity against SW480 cells [μM] ^[b]
1	13a	OH	OH	OH	OH	15a	9	+++	++	+	7
2	13b	OH	OMe	OH	OH	15b	20	(+)/++ ^[c]	+	++	12
3	13c	OH	OCH ₂ -COOH	OH	OH	15c	22	–	(+)	++	7
4	13d	OH	OCH ₂ -CH ₂ OH	OH	OH	15d	21	(+)	+	n.d.	15
5	13e	OH	H	OH	OH	15e	14	(+)/++ ^[c]	n.d.	n.d.	25
6	13f	OMe	OH	OH	OH	15f	15	+++	n.d.	n.d.	> 60
7	13g	OH	OH	H	H	15g	4	+++	(+)	n.d.	25

[a] Uptake was assessed against the uptake of gold-adsorbed asialofetuin, which was defined as highly efficient (+++) in all three cell types. +++ = highly efficient uptake, similar to that of the control; ++ = good uptake; + = weak uptake; (+) = uptake in a few events; – = no uptake; n.d. = not determined. [b] Assay detecting cellular growth using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT assay). Concentrations for 50% growth inhibition. [c] Heterogeneous uptake repeatedly seen with a smaller subpopulation demonstrating good uptake.



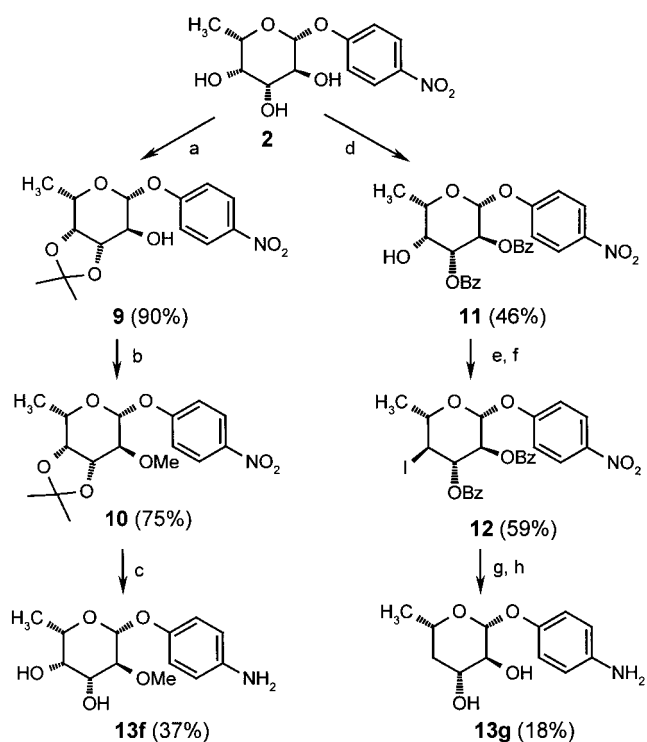
Scheme 2. Synthesis of 3-O-modified *p*-aminophenyl fucosides. a) $\text{Bu}_3\text{SnO}/\text{MeOH}$; b) MeI/DMF ; c) $\text{H}_2/\text{Pd-C}$, MeOH ; d) $\text{BrCH}_2\text{COOMe}/\text{Bu}_4\text{NI}$ in dioxane; e) LiOH , MeOH , then Lewatit SC108; f) NaBH_4 , $\text{THF}/\text{H}_2\text{O}$ 40°C ; g) triethyl orthoacetate, *p*-TosOH, THF ; h) $\text{HCl}/\text{CH}_2\text{Cl}_2$; i) MeOH/NaOMe ; j) $\text{H}_2/\text{Pd-C}$, MeOH , NEt_3 . Tos = toluene-4-sulfonyl.

dioxane resulted in an opening of the tin acetal and an alkylation of the more reactive equatorial position with high regioselectivity. Particularly the 3-O-methylated derivative **4** was obtained in 83 % yield and was subsequently reduced with hydrogen on palladium/charcoal to yield *p*-aminophenyl 3-O-methyl- β -L-fucoside (**13b**).

The alkylation of **3** with methyl bromoacetate proceeded most efficiently at 100°C in dioxane in the presence of catalytic amounts of tetrabutylammonium iodide. The intermediate methyl ester **5** was cleaved with lithium hydroxide in methanol. The carboxylate was acidified with the ion-exchange resin Lewatit SC108 [H^+] and subsequently reduced to give *p*-aminophenyl 3-O-carboxymethyl- β -L-fucoside (**13c**). Alternatively, **5** could be transformed in two reduction steps with sodium boranate in THF/water at 40°C and subsequent hydrogenolysis to *p*-aminophenyl 3-O-hydroxyethyl- β -L-fucoside (**13d**).

Ortho esters of *cis* hydroxyl groups in carbohydrates have been shown to open preferentially to the axially acylated derivatives.^[13] Compound **2** was converted into a mixture of diastereomeric ortho esters **6** (Scheme 2). During the efforts to convert the 2-hydroxyl group of **6** with benzoic acid chloride into the benzoate, a side reaction of an opening of the ortho ester with chloride ions was observed. Upon treatment of **6** with hydrogen chloride in dichloromethane this reaction was the main reaction, giving the 3,6-dideoxy-3-chloro-L-gulose derivative **7** in 70 % yield. This reaction should open an efficient access to *p*-aminophenyl 3-deoxy- β -L-fucoside (**13e**). The acetyl group was removed with catalytic amounts of sodium methoxide in methanol under Zemplén conditions to avoid epoxide formation and to give the gulose derivative **8**. Hydrogenolysis of **8** in methanol in the presence of triethylamine as acid scavenger gave **13e** in one step.

Selected procedures for a regioselective modification of the 2- and 4-hydroxyl groups of *p*-nitrophenyl β -L-fucoside are exemplified in Scheme 3: For access to the 2-hydroxyl group the *cis*-configured 3- and 4-hydroxyl groups were protected as



Scheme 3. Synthesis of 2- and 4-O-modified *p*-aminophenyl fucosides. a) 2-methoxypropene, *p*-TosOH in dioxane/DMF; b) MeI (5 equiv) in THF , then NaH (1.5 equiv); c) 80 % AcOH , H_2/PtO_2 ; d) BzCl (2 equiv), CH_2Cl_2 , pyridine, -35°C ; e) $(\text{CF}_3\text{SO}_2)_2\text{O}$, CH_2Cl_2 ; f) NaI , DMF ; g) H_2/PtO_2 , MeOH , NEt_3 ; h) NaOMe , MeOH . Bz = benzoyl.

isopropylidene acetal ($\rightarrow$ **9**) with methoxypropene in dioxane/DMF in the presence of *p*-toluenesulfonic acid. Subsequently the 2-hydroxyl group was deprotonated with 1.5 equivalents of sodium hydride in the presence of a fivefold excess of methyl iodide, giving the 2-alkylated derivative **10** in 75 % yield. Hydrogenolysis with hydrogen on platinum oxide in 80 % acetic acid gave *p*-aminophenyl 2-O-methyl- β -L-fucoside (**13f**) in one step in 37 % yield.

The axial 4-hydroxyl group in the fucose moiety is the least reactive with respect to acylations.^[14] It was possible to acylate selectively the 2- and 3-hydroxyl groups of **2** with benzoic acid chloride in dichloromethane in the presence of pyridine at low temperatures (−35 °C). The 4-hydroxyl group of **11** was allowed to react with trifluoromethanesulfonic acid anhydride, and the corresponding triflate was substituted by iodide. Hydrogenolysis in the presence of triethylamine followed by alcoholysis of the benzoates with sodium methoxide in methanol gave *p*-aminophenyl 4-deoxy- β -L-fucoside (**13g**).

Each of the modified *p*-aminophenyl β -L-fucoside derivatives **13b–g** was treated, in analogy to **13a**, with the batracylin–BSA conjugate **14** to give the conjugates **15b–g** (Scheme 1). Subsequently, these conjugates were adsorbed onto colloidal gold particles of 5 or 17 nm in diameter for electron microscopic detection of cellular uptake.^[15] Gold sols were prepared by reduction of a chloroauric acid solution with phosphoric acid (for 5-nm particles) or sodium citrate (for 17-nm particles). These gold sols were mixed with conjugate solutions at a final concentration of 10 μ g of protein per mL of gold sol, stabilized with addition of polyethylene glycol, and washed by centrifugation to remove excess protein. Saturation of the adsorption was monitored by color changes after addition of excess NaCl. Freshly isolated or cultured cells were incubated with the coated gold particles at 4 °C for monitoring the binding or at 37 °C for studying uptake, and processed for electron microscopy after removal of unbound ligands. The uptake into the tumor cell line SW480 and into liver cells such as Kupffer cells and hepatocytes was semi-quantitatively assessed in comparison to the endocytosis of gold-adsorbed asialofetuin as a control. Furthermore, cytotoxic activity of the conjugates **15a–g** against SW480 tumor cells has been measured using the MTT assay (Table 1).

The BSA glycoconjugate **15a** carrying unmodified β -L-fucose epitopes was endocytosed by SW480-tumor cells, but even more efficiently by Kupffer cells and hepatocytes (Table 1, entry 1). The analogues BSA glycoconjugates with 2-*O*-methyl- and 4-desoxyfucose epitopes (**15f** and **15g**) did not show any decrease of cellular uptake into Kupffer cells compared to **15a** (Table 1, entries 6 and 7). In contrast, BSA conjugates with various fucose epitopes modified in the 3-position, **15b–e** (Table 1, entries 2–5), exhibited a marked decrease of liver cell endocytosis compared to **15a**.

Furthermore, as shown for **15b** and **15c**, the tumor cell line SW480 apparently tolerated a modification of the fucose epitopes in this particular position and exhibited an efficient endocytosis of those glycoconjugates. The desired discrimination between tumor and liver cells was most pronounced with the BSA conjugate **15c**, carrying 3-*O*-carboxymethylfucose epitopes.

Owing to the attached batracycline residues the neoglycoconjugates with fucose residues which are unsubstituted or modified in the 3- or 4-position also demonstrated a significant cytotoxic activity. Concentrations for 50% growth inhibition were in the range of 7–25 μ M, which is expected in the case of cellular uptake (Table 1). In contrast, the carbohydrate-free batracycline–BSA conjugate **14** did not show any cytotoxic activity at SW480, and also the cytotoxic activity of **15f** was markedly decreased, indicating a carbohy-

drate-mediated uptake and cytotoxicity of the glycoconjugates **15a–e** and **15g**.

These results indicate that in particular the modification of the 3-position of fucose residues leads to the desired discrimination of cellular uptake between tumor and liver cells. Furthermore, the detected uptake into tumor cells correlates with a cytotoxic activity of these neoglycoconjugates.

Thus, BSA neoglycoconjugates have proven to be powerful tools for identifying carbohydrate residues which might be suitable for tumor targeting. However, its use in vivo might be limited because of the immunogenic potential. Therefore, the investigation of the tumor targeting potential of the identified carbohydrate residues using low molecular weight glycoconjugates of cytotoxic agents is ongoing.

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Rolling Loop Scan: An Approach Featuring Ring-Closing Metathesis for Generating Libraries of Peptides with Molecular Shapes Mimicking Bioactive Conformations or Local Folding of Peptides and Proteins**

John F. Reichwein, Bas Wels, John A. W. Kruijtzter, Cees Versluis, and Rob M. J. Liskamp*

Nature has found many intriguing and elegant ways to reduce the flexibility of peptides and proteins in order to increase both affinity and selectivity with an interacting partner molecule. Apart from the size of a peptide or protein, reduction of the flexibility by disulfide bridges is probably the most well known way to control shape.^[1] Even more sophisticated modes for reducing the flexibility include sulfide bridges, zinc fingers, and multiple side chain knotting.^[2–4] Often the affinity and/or biological activity is lost or at least significantly reduced upon breakage or absence of these conformational constraints. The principle of reducing flexibility—thereby increasing the affinity for a receptor by limiting the unfavorable entropy loss upon binding—is one of the most widely applied principles in drug development.

It is quite a challenge to reduce flexibility or to mimic local folding of peptides or (part of) proteins. Often the biologically active conformation of a peptide is not known or no longer present if only a small part of the protein—that is, a peptide—is studied. Clearly, ways for “probing” the biologically active conformation, approaches for creating alternative bioactive conformations, and possibilities for mimicking the spatial structure of parts of proteins could well lead to new insights into structure–biological activity relationships of peptides and proteins. Furthermore, this could also lead to new biologically interesting peptidomimetics to be used, for example, for interference with undesired disease-causing peptide–protein or protein–protein interactions.

We are therefore interested in developing general approaches for the introduction of conformational constraints into peptides without compromising the side chains of the amino acid residues, since these are often important for interaction with, for example, a receptor. In addition, we want to be able to introduce a conformational constraint, in principle, at any desired position of a peptide and of any desired size. The resulting procedure is therefore amenable to combinatorial approaches.

The approach is schematically depicted in Figure 1. The important characteristics are immediately apparent: 1) The loops connect two peptide–amide moieties, and thus do not compromise the α -carbon side chains; 2) loops can be formed by connecting any two desired peptide–amide bonds, thereby forming loops of any desired size; and 3) the loops “roll” over

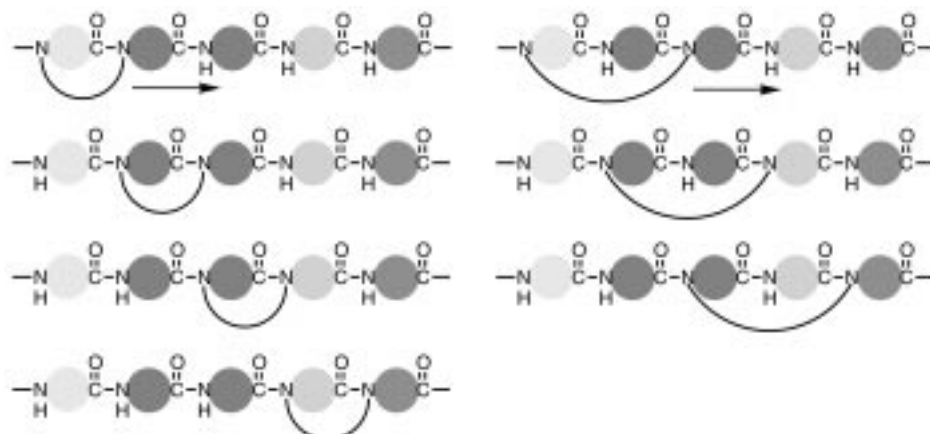
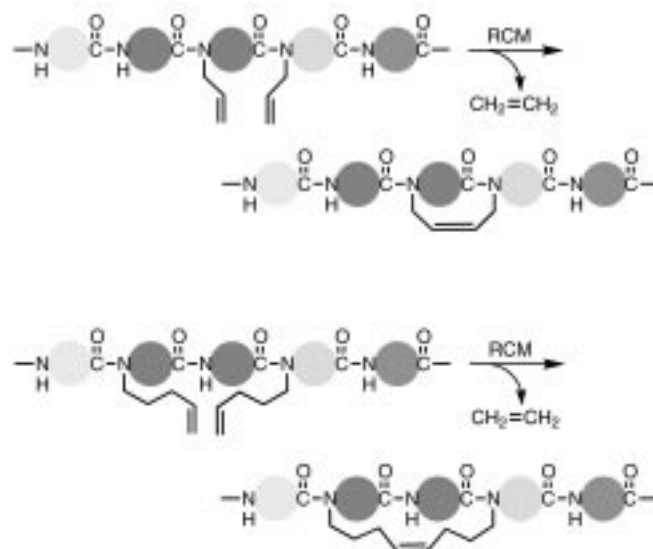


Figure 1. Schematic representation of the “rolling loop scan”.

a peptide sequence, thereby “scanning” local conformations. We have therefore coined this approach the “rolling loop scan”.

In this approach the loops were prepared by ring-closing metathesis (RCM, Scheme 1).^[5] This is a particularly attrac-



Scheme 1. Connecting the side chains of N-alkylated peptides by ring-closing metathesis (RCM).

[*] Prof. Dr. R. M. J. Liskamp, J. F. Reichwein, B. Wels, Dr. Ir. J. A. W. Kruijtzter
Department of Medicinal Chemistry
Utrecht Institute for Pharmaceutical Sciences
Utrecht University
P. O. Box 80082, NL-3508 TB Utrecht (The Netherlands)
Fax: (+31)30-2536655
E-mail: r.m.j.liskamp@pharm.uu.nl

C. Versluis
Department of Biomolecular Mass Spectrometry
Bijvoet Center for Biomolecular Research, Utrecht University

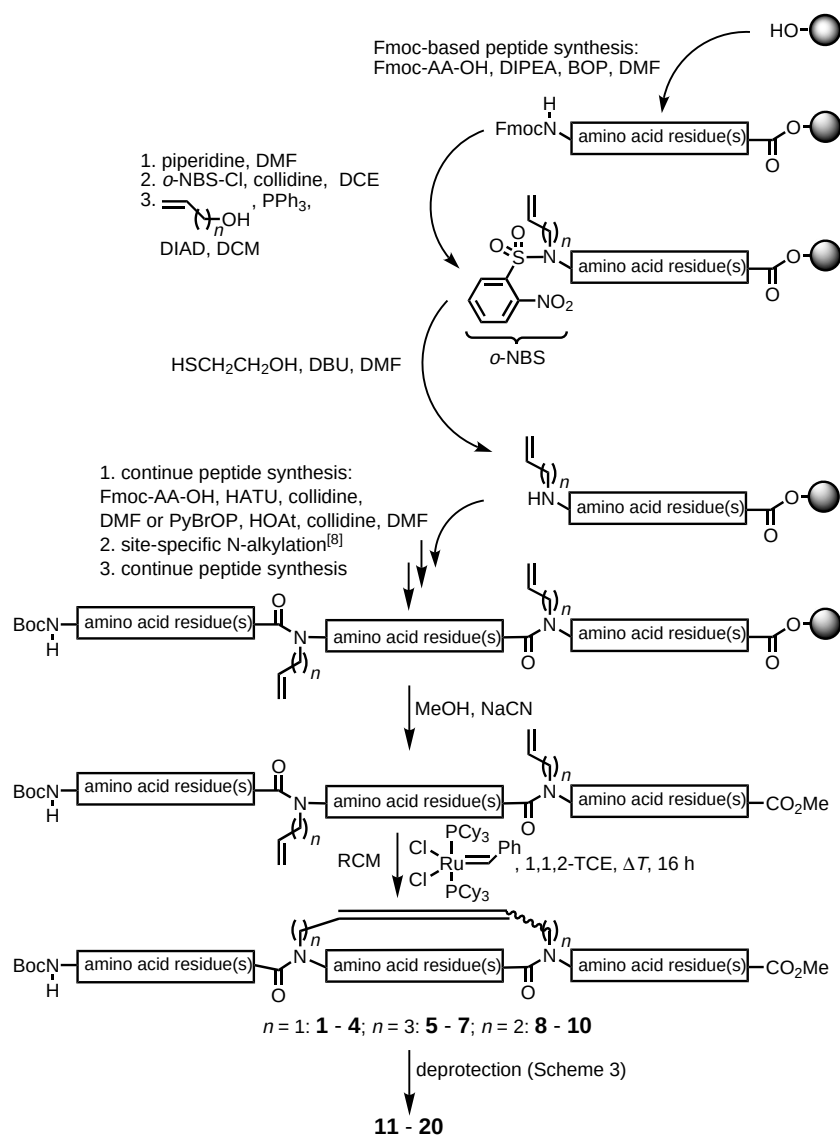
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tive method, since the yields of RCM are usually high and no protection of the connecting side chains is required.^[6, 7]

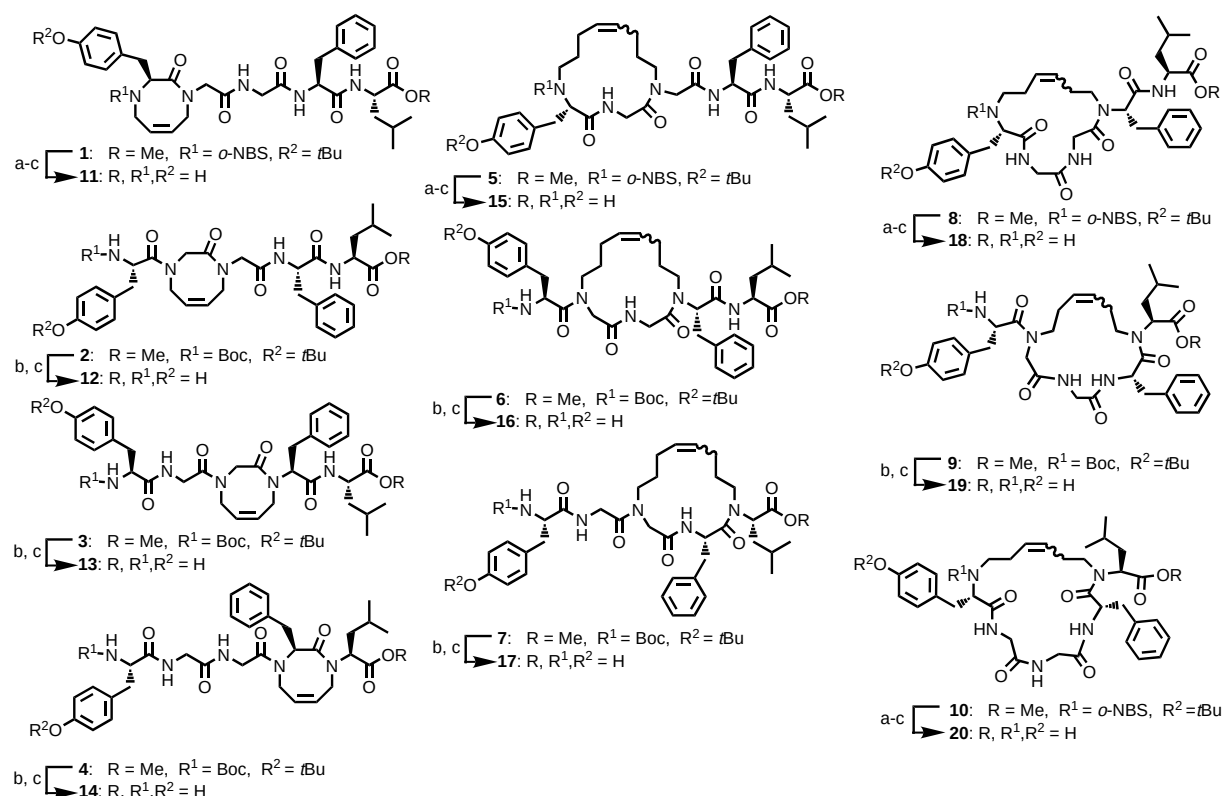
For the preparation of the bis-*N*-alkylated peptides—containing alkene side chains on the *N*-atoms of peptide–amide bonds—required for RCM a versatile solid-phase procedure was developed based on our site-specific *N*-alkylation of peptides, which enabled introduction of a side chain at any desired peptide–amide bond (Scheme 2).^[8] First, a peptide was synthesized by the Fmoc strategy until the position was reached where the loop had to start. Then, the Fmoc group was removed and substituted by an *o*-nitrobenzenesulfonyl (*o*-NBS) group, which increases the acidity of the NH proton so that the amide became susceptible for a Mitsunobu reaction with an appropriate unsaturated alcohol. After removal of the *o*-NBS group, peptide synthesis was continued until the other end of the loop was reached. The second alkene side chain was introduced as described, and peptide synthesis was continued until the end of the peptide was reached. Ring-closing metathesis was carried out after cleavage from the resin, leading to the cyclized peptide.^[9]

To demonstrate the principle of the rolling loop scan Leu-enkephalin was chosen. However, before applying this procedure one major hurdle had to be overcome. It was found that, depending on the number of amide bonds involved in the preparation of the loop, certain rules concerning the length of the alkene substituent had to be obeyed for RCM to take place:^[10] 1) If two amide bonds are involved in the loop *N*-allylamides can be used in the starting bis-alkylated peptide ($n = 1$); 2) if three amides are involved in the loop *N*-pentenylamides have to be used ($n = 3$); 3) if four or more amide bonds are involved in the loop, *N*-homoallylamides will work ($n = 2$).

Obeying these rules a rolling loop scan of Leu-enkephalin was now carried out. All possible loops of Leu-enkephalin were prepared by RCM of the appropriate bis-*N*-alkylated amides according to the general procedure depicted in Scheme 2. The thus synthesized loop-containing Leu-enkephalin derivatives **1–10** were deprotected to give **11–20**, which were purified by preparative HPLC (Scheme 3). From these structures the “rolling” of the loops is evident (for example going from structures **11** to **14** and from structures **15**



Scheme 2. General solid-phase procedure for preparation of the cyclization precursors for the loop synthesis by RCM. AA = amino acid, Boc = *tert*-butoxycarbonyl, BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, DCE = 1,2-dichloroethane, DCM = dichloromethane, DIAD = diisopropyl azodicarboxylate, DIPEA = ethyldiisopropylamine, DMF = dimethylformamide, Fmoc = 9-fluorenylmethoxycarbonyl, HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole, *o*-NBS = *o*-nitrobenzenesulfonyl, PyBrOP = bromotripyrrolidinophosphonium hexafluorophosphate, 1,1,2-TCE = 1,1,2-trichloroethane.



Scheme 3. All possible loop-containing Leu-enkephalin derivatives obtained by RCM. a) PhSH, K₂CO₃, MeCN; b) Tesser's base;^[11] c) trifluoroacetic acid.

to **17**). The solid-phase synthesis was extremely efficient as is apparent from the overall yields and the calculated yield per step (in most cases > 90 %, Table 1). The yields of the RCM were more variable, but were quite satisfactory ($\approx$ 50 %) to good (> 70 %) and in some cases very good (> 80 %). The final deprotection was somewhat disappointing, but still the yields were quite satisfactory after preparative HPLC (Table 1).^[11, 12]

An important aspect is the characterization and structural studies of these compounds. The use of mass spectrometry was quite essential. With ESI-MS the expected molecular ions were observed in all cases. The use of FAB-MS-MS was especially fruitful. It provided additional proof for the presence as well as the position of the loop (Figure 2). It was observed that the loop-containing enkephalin derivatives

gave rise to ions which resulted in most cases from successive loss of C-terminal residues. However, this fragmentation occurred until the loop was reached, providing unequivocal proof for the position of the loop in the peptide. In general both ¹H (300 and 600 MHz) and ¹³C NMR spectra of the loop-containing Leu-enkephalin derivatives were very complicated due to the presence of several conformers. In addition to peptide–amide rotamers other conformers were present which—probably because of the presence of the loop—were sufficiently stable at room temperature to be observed on the NMR time scale.

In conclusion, we have developed a general and versatile procedure for the synthesis of bis-N-alkylated peptides, from which loops can be formed by ring-closing metathesis. We think that this procedure is generally applicable to any

Table 1. Yields of the Leu-enkephalin derivatives **1**–**20** as well as exact masses of Leu-enkephalin derivatives **11**–**20**.

	overall ^[a]	Yield [%]			overall ^[d]	Yield [%]		Exact mass	
		per step ^[b]	RCM ^[c]			per step ^[b]	found	calcd	
1	56	96	49	11	5.1	86	608.3069	608.3084	
2	40	94	54	12	2.4	82	608.3058	608.3084	
3	68	97	98	13	2.6	82	608.3094	608.3084	
4	25	91	48	14	2.8	83	608.3064	608.3084	
5	54	96	72	15	6.5	87	664.3723	664.3710	
6	43	95	87	16	2.6	83	664.3718	664.3710	
7	43	94	77	17	3.6	84	664.3733	664.3710	
8	28	92	46	18	2.3	82	636.3403	636.3397	
9	32	93	91	19	3.0	83	636.3416	636.3397	
10	16	89	41	20	1.1	79	636.3422	636.3397	

[a] The overall yield of the solid-phase synthesis. These yields may appear low, but are in fact quite high in view of the number of reactions (15) in this multistep synthesis. [b] Average yield per step. [c] Yield of the ring-closing metathesis. [d] Determined after purification by preparative HPLC.

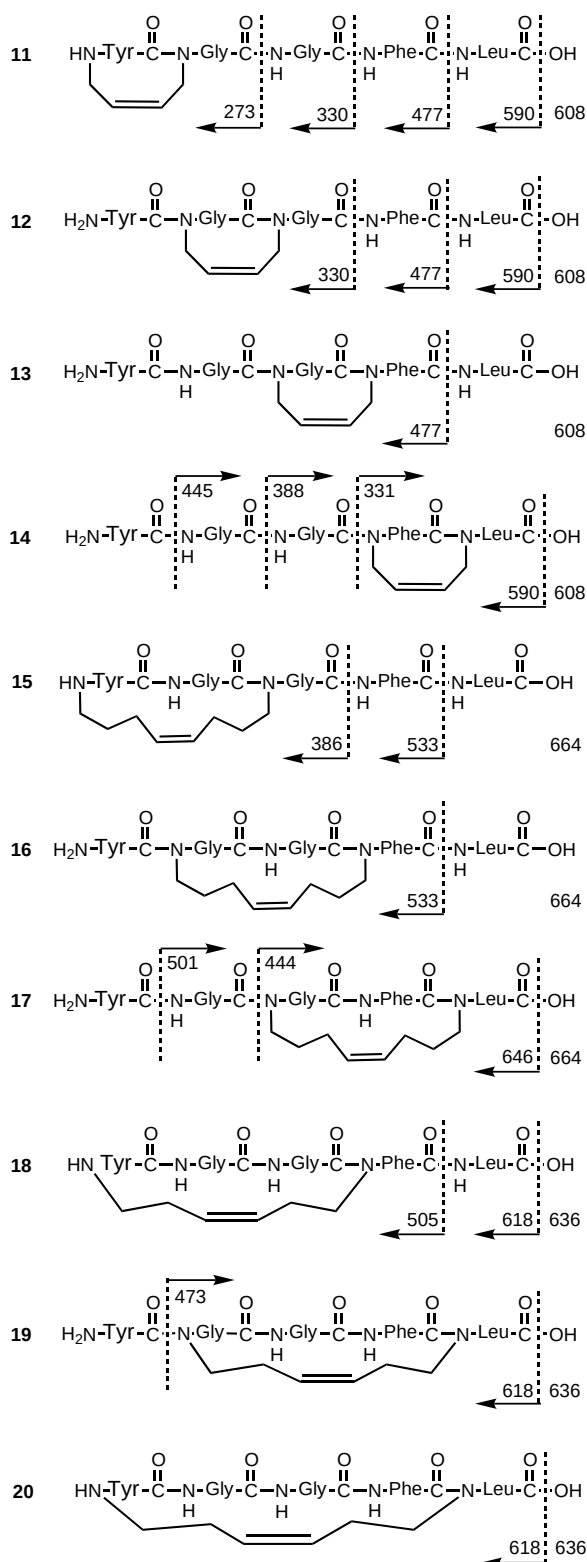


Figure 2. FAB-MS-MS fragments of Leu-enkephalin derivatives **11–20**.

peptide. Since all possible loops of a particular peptide can be formed, this rolling loop scan can be considered as a combinatorial approach towards generating libraries of (bio-active) conformers.

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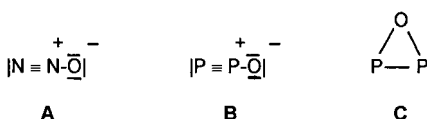
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- [10] The studies which led to these rules will be published elsewhere. Not all sizes of loops are allowed, since in addition to steric factors imposed by the side chains, a peptide–amide bond usually assumes a *trans*-like conformation: J. F. Reichwein, C. Versluis, R. M. J. Liskamp, unpublished results.
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P₂O, the Phosphorus Analogue of N₂O, as a Ligand in a Tetranuclear Cluster**

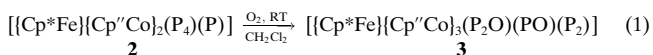
Otto J. Scherer,* Sascha Weigel, and
Gotthelf Wolmershäuser

*Dedicated to Professor Gerhard Fritz
on the occasion of his 80th birthday*

After the synthesis of $[(\text{Cp}^{\text{R}}\text{Ni})_2\{\text{W}(\text{CO})_4\}(\mu_3\text{-PO})_2]$ (**1**, $\text{Cp}^{\text{R}} = \text{C}_5\text{H}_5\text{Pr}_4$), in which it was possible to coordinatively stabilize PO, the group homologue of NO, for the first time,^[1] the next worthwhile objective was to attempt to bind further phosphorus analogues of the type N_xO_y within the coordination sphere of transition metal complex fragments. The 16-valence-electron (VE) molecule diphosphorus monoxide P₂O (**B**), which is isoelectronic with N₂O (**A**), appeared to be a particularly promising candidate.



The cluster skeleton of $[(\text{Cp}^*\text{Fe})\{\text{Cp}''\text{Co}\}_2(\text{P}_4)(\text{P})]$ (**2**, $\text{Cp}^* = \text{C}_5\text{Me}_5$; $\text{Cp}'' = 1,3\text{-}i\text{Bu}_2\text{C}_5\text{H}_3$), which is formed, amongst other products, by the cothermolysis of $[\text{Cp}^*\text{FeP}_3]$ and $[\text{Cp}''\text{Co}(\text{CO})_2]$,^[2] can be extended by oxidation at room temperature with atmospheric oxygen to form the tetranuclear complex **3**, which contains a PO ligand in addition to a P₂O ligand [Eq. (1)].



Cluster **3** forms brown crystals that can be handled for a short time in air. The crystals are barely soluble in nonpolar solvents but are well soluble in toluene and dichloromethane. In the ³¹P NMR spectrum of **3** (ABMXY spin system),^[3] the largest low-field shift of $\delta = 558.8$ is found for P_A (P1 in Figure 1) which is connected to three L_nM fragments. The chemical shifts and coupling constants of P_M (P2) and P_B (P3)^[3] support the idea that the P₂O ligand is not “separated” into a $\mu_3\text{-PO}$ and a $\mu_3\text{-P}$ ligand.

The Co₃FeP₅ framework of **3** (Figure 1)^[4] can be described as a boatlike six-membered ring (Co1,P3,P2,Co2,P5,P4) bridged by the P1O1 ligand. This results in two five-membered rings, P1,Co1,P4,P5,Co2 and P1,Co1,P3,P2,Co2: the latter is capped by the 13VE fragment Cp*Fe1, while the phosphorus atoms of the P2,P3,P4,P5 part of the six-membered ring are coordinatively bound to the 14VE fragment of Cp''Co3 (Figure 1).

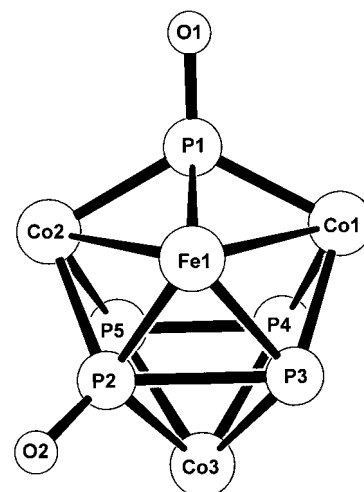


Figure 1. Structure of **3** in the crystal. The Cp* and Cp'' ligands have been omitted for clarity. Selected distances [Å] and angles [°]: P1–O1 1.496(6), P2–O2 1.509(6), P2–P3 2.456(3), P4–P5 2.151(4), P2...P5 2.574(3), P3...P4 2.560(4), Co1–P1 2.190(3), Co1–P3 2.247(3), Co1–P4 2.232(3), Co2–P1 2.206(3), Co2–P2 2.248(3), Co2–P5 2.245(3), Co3–P2 2.242(3), Co3–P3 2.302(3), Co3–P4 2.280(3), Co3–P5 2.310(3), Fe1–P1 2.161(3), Fe1–P2 2.227(3), Fe1–P3 2.271(3), Co1–Fe1 2.7164(17), Co2–Fe1 2.7215(17), Co3...Fe1 3.74, Co1...Co2 3.81, Co1...Co3 3.71, Co2...Co3 3.70; P3–P2–P5 88.34(11), P2–P3–P4 84.84(11), P3–P4–P5 95.78(13), P2–P5–P4 91.04(12), P3–P2–O2 127.2 (3).

The most remarkable structural part of **3** is the P₂O ligand. In contrast to $[(\text{OC})_{13}\text{Ru}_4\text{P}_2\text{O}]$ (**4**),^[5] in which the P₂O ligand forms a $\mu_6\text{-POP}$ bridge, here it was possible to coordinatively stabilize the N₂O-analogue P₂O for the first time. Free P₂O (**B**), which can be produced from P₂ (P₄) and ozone, has been characterized in a matrix by IR and UV/Vis spectroscopy.^[6] Ab initio calculations^[7a,b] showed that for P₂O the linear form **B** is somewhat more stable than the three-membered ring structure **C**.

The P2–O2 bond length of 1.509(6) Å in **3** as part of the $\mu_4\text{-}\eta^1\text{:}\eta^2\text{:}\eta^2\text{:}\eta^1\text{-P}_2\text{O}$ ligand (Figure 1) is only slightly longer than the calculated value of 1.446 Å for uncomplexed P₂O in form **B**,^[7a] while the P–P bond is stretched (1.852 Å in **B**^[7a]) by the twofold *side-on* and terminal coordination ($\sigma,\sigma,\pi,\pi\text{-P}_2\text{O}$) to 2.456(3) Å; a bond length that has been found for the intact P–P edge of the P₄ tetrahedron in the complex $[\text{Cl}(\text{Ph}_3\text{P})_2\text{Rh}(\eta^2\text{-P}_4)]$ (**5**, 2.46 Å).^[8] A P–P bond length of 2.118 Å was calculated for the energetically unfavorable bent form of P₂O.^[7a] Both the $\mu_3\text{-PO}$ ligand (P1O1 in Figure 1) and the $\mu_3\text{-}\eta^1\text{:}\eta^2\text{:}\eta^1\text{-P}_2$ ligand contain bond lengths within the expected range (P1–O1 1.496(6) Å^[1, 9] and P4–P5 2.151(4) Å; compare with the compounds **1** and **6**).^[10, 11] The P2...P5 and P3...P4 distances of 2.574(3) and 2.560(4) Å, respectively, are on the borderline,^[2, 11] which may also be a result of the cluster geometry. The clear differences in the P–P bond lengths within the P2–P5 quadrangle (Figure 1) and in the chemical shifts and coupling constants,^[3] as well as the comparison with **6** ($3 \times \text{P}_2$ ligands)^[11a] do not support the existence of a *cyclo*-P₄O ligand in **3**. Ab initio studies show that a planar five-membered ring is the most stable conformation for P₄O.^[12] The following arguments support the idea that P₂O is not “separated” into a $\mu_3\text{-PO}$ and a $\mu_3\text{-P}$ ligand: the ³¹P NMR chemical shifts (in this case $\delta = 558.8$ (P1) and 265.1 (P2))

[*] Prof. Dr. O. J. Scherer, Dr. S. Weigel, Dr. G. Wolmershäuser^[+]
Fachbereich Chemie der Universität
Erwin-Schrödinger-Strasse, D-67663 Kaiserslautern (Germany)
Fax: (+49) 631-205-2187
E-mail: oscherer@rhrk.uni-kl.de

[+] Crystal structure analysis

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should then only differ slightly. For P3 as a "separated" μ_3 -P ligand, a much stronger low-field shift would be expected than the observed value of $\delta = 501.6$.^[2] The coupling constant of -190.7 Hz must also be considered as further support for a P2–P3 bond (2.456(3) Å in the σ, σ, π, π ligand P₂O); this value is comparable to that found in **5** (ca. 180 Hz)^[8] as well as in compounds in which the *cyclo*-P₃ ligand is additionally *side-on* coordinated ($d(\text{P}–\text{P}) \approx 2.35$ Å, $J(\text{P}, \text{P}) \approx -200$ Hz).^[2]

The Co₃FeP₅ framework can also be formally derived from the molecular structure of the complex $[\{\text{Cp}^*\text{Co}\}_3(\mu_3\text{-}\eta^2\text{-}\eta^2\text{-}\text{P}_2)(\mu_3\text{-}\eta^1\text{-}\eta^2\text{-}\eta^1\text{-}\text{P}_2)_2]$ (**6**).^[11a] by replacement of the $\mu_3\text{-}\eta^2\text{-}\eta^2\text{-}\text{P}_2$ ligand by a $\{\text{Cp}^*\text{FeP}(\text{O})\}$ fragment and by oxidation of one of the $\mu_3\text{-}\eta^1\text{-}\eta^2\text{-}\eta^1\text{-}\text{P}_2$ ligands to P₂O. This could then form the $\mu_4\text{-}\eta^1\text{-}\eta^2\text{-}\eta^2\text{-}\eta^1\text{-}\text{P}_2\text{O}$ ligand of **3** by additional *side-on* coordination of the Cp*Fe fragment.

Stable N₂O complexes are rare. A linear, terminal N₂O ligand has been proposed in complexes of the type $[\text{Ru}(\text{NH}_3)_5(\text{N}_2\text{O})]\text{X}_2$ (X = Br, I, BF₄, PF₆), which can be stored at -5°C .^[13] No details can be given as yet about the formation of **3** from **2** by the extension of the cluster skeleton by a Cp*Co fragment.

Experimental Section

3: $[\{\text{Cp}^*\text{Fe}\}[\text{Cp}^*\text{Co}]_2(\text{P}_4)(\text{P})]$ (**2**)^[2] (180 mg, 0.22 mmol) was dissolved in dichloromethane (40 mL) and stirred for 1 min at room temperature in air (open reaction vessel) (longer exposure to air results in complete decomposition) and then stirred in a closed reaction vessel for 18 h (monitored by ³¹P NMR spectroscopy). After removal of the solvent, the brown residue was dissolved in dichloromethane (ca. 5 mL), treated with silylated silica gel (ca. 2 g) and dried under an oil pump vacuum until a pouring consistency was obtained. Column chromatography (column: 8 × 1.0 cm, silylated silica gel, petroleum ether, water cooled; petroleum ether/diethyl ether (2/1)) yielded **3** (52 mg; 22% relative to **2**) as a dark brown fraction. The large amount of brown residue retained on the column material could not be eluted by any common solvent.

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- [4] Crystal structure data for **3**: C₄₀H₇₈Co₃FeO₂P₅, $M_r = 1086.60$, monoclinic, space group $P2_1/n$, $a = 10.5809(16)$, $b = 21.0882(17)$, $c = 24.391(4)$ Å, $\beta = 101.825(18)^\circ$, $V = 5326.8(12)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.355$ Mg m⁻³, $T = 293(2)$ K, θ range: $1.96\text{--}23.95^\circ$, measured reflections: 51 646, independent reflections: 8096 ($R_{\text{int}} = 0.1456$), R values: final R value ($I > 2\sigma(I)$): $R1 = 0.0639$, $wR2 = 0.1289$, all data: $R1 = 0.1549$, $wR2 = 0.1481$. Diffractometer: Stoe IPDS, structure solution:

direct methods, program: SHELXS-97, refinement: full-matrix least-squares against F^2 . Program for refinement: SHELXL-97, data/parameters: 8096/688. One of the Cp* ligands is rotationally disordered. Crystallographic data (excluding structure factors) for the structure reported in this publication have been deposited as supplementary publication no. CCDC-120672 with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge from: CCDC, 12 Union Road, Cambridge CB21EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Rhodium-Induced Selective B(3)/B(6)-Disubstitution of *ortho*-Carborane-1,2-dithiolate**

Max Herberhold,* Hong Yan, Wolfgang Milius, and Bernd Wrackmeyer*

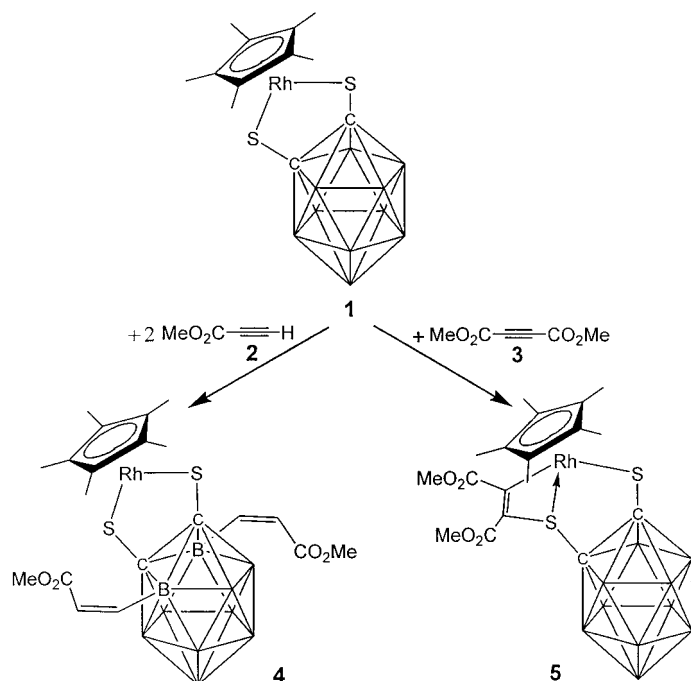
Dedicated to Professor Hubert Schmidbaur on the occasion of his 65th birthday

Ever since the discovery of 1,2-dicarba-*closo*-dodecaborane(12), the chemistry of this exceptionally stable carborane and its 1,7- and 1,12-isomers has aroused considerable interest. Although C-functionalization had readily been accomplished from the beginning,^[1] and more recently the complete substitution at all boron positions has been achieved,^[2] the selective synthesis of B-substituted derivatives proved to be rather difficult.^[3] We have recently reported on the synthesis of the 16e rhodium complex $[\text{Cp}^*\text{Rh}[\text{S}_2\text{C}_2(\text{B}_{10}\text{H}_{10})]]$ (**1**).^[4] and suggested that this species may be promising for further transformations owing to its electron deficiency at the rhodium center, the reactivity of the rhodium–sulfur bonds, and the potential activation of B–H

[*] Prof. Dr. M. Herberhold, Dr. H. Yan, Dr. W. Milius, Prof. Dr. B. Wrackmeyer
Laboratorium für Anorganische Chemie der Universität, D-95440 Bayreuth (Germany)
Fax: (+49) 921-552157
E-mail: max.herberhold@uni-bayreuth.de
E-mail: b.wrack@uni-bayreuth.de

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bonds of the carborane cage^[5] at sites close to the rhodium atom. In this context, we have studied the reaction of **1** with acetylene methyl carboxylate **2** and acetylene dimethyl dicarboxylate **3** (Scheme 1).



Scheme 1. Reaction of **1** to give **4** and **5**.

In the case of **2**, the B(3)/(6)-disubstituted 16e complex **4** was isolated and characterized.^[6] In contrast, the reaction of **1** with **3** gave the 18e complex **5** as the sole product.^[7] In a rhodium-catalyzed reaction, a CpRh-dithiolene complex, formed as an intermediate, also reacts with **3**, to give the adduct analogous to **5**.^[8] Recently, the 16e complex [CpCo{S₂C₂(B₁₀H₁₀)}], comparable with **1**, has been reported.^[9] The reactions of this CpCo complex with **3** and terminal alkynes have afforded adducts (with molecular structures similar to **5**), which—like **5**—do not undergo further rearrangements. Thus, the molecular structure of **5** is suggested to be typical of an intermediate which remained undetected in the reaction of **1** with the monosubstituted acetylene **2**.

The molecular structures of **4**^[10] and **5**^[10] are shown in Figure 1 and Figure 2, respectively. A planar rhodadithiolene five-membered ring is present in **4**, as expected for a 16e species.^[9, 11, 12] This electron count is also in agreement with the magnetic deshielding of the ¹⁰³Rh nucleus ($\delta(^{103}\text{Rh}) = +1210 \pm 5$, close to that of **1** with $\delta(^{103}\text{Rh}) = +1165 \pm 5$).^[4] The structure of **5** indicates that an addition of **3** to one of the Rh–S bonds has taken place to give a four-membered ring containing a C=C bond, a Rh–C σ bond, and a coordinative S→Rh bond.

The *Z* configuration at the C=C bonds in **4** rules out the possibility that **4** has been formed by way of direct 1,2-hydroboration. We therefore suggest an alternative mechanism briefly outlined in Scheme 2. Complex **5** (Scheme 1) is apparently a type of 18e complex which is frequently formed when an alkyne is added to a M–S bond in metalladithio-

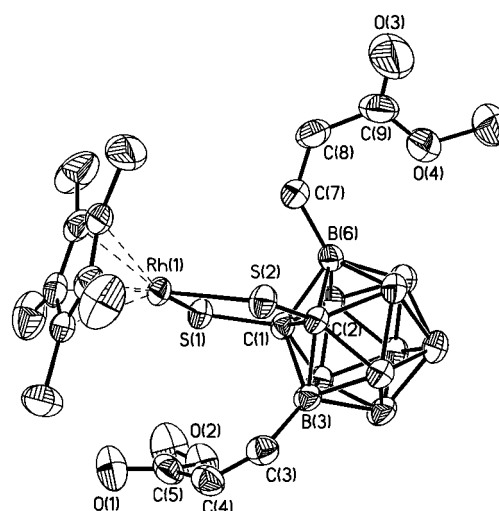


Figure 1. ORTEP plot of the molecular structure of **4**. Selected bond lengths [pm] and angles [°]: Rh(1)–Z 178.2, Rh(1)–S(1) 227.94(10), Rh(1)–S(2) 227.31(10), S(1)–C(1) 178.3(4), S(2)–C(1) 178.2(4), C(1)–C(2) 164.3(5), B(3)–C(3) 157.1(6), B(6)–C(7) 155.8(6), C(3)–C(4) 131.7(5), C(7)–C(8) 133.8(6); S(1)Rh(1)S(2) 92.42(4), S(1)Rh(1)S(2)/S(1)C(1)C(2)S(2) 179.1, B(3)C(3)C(4)/C(3)C(4)C(5) 5.2, B(6)C(7)C(8)/C(7)C(8)C(9) 1.6.

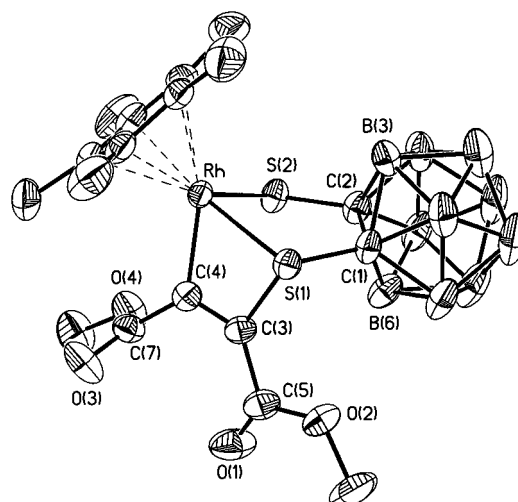
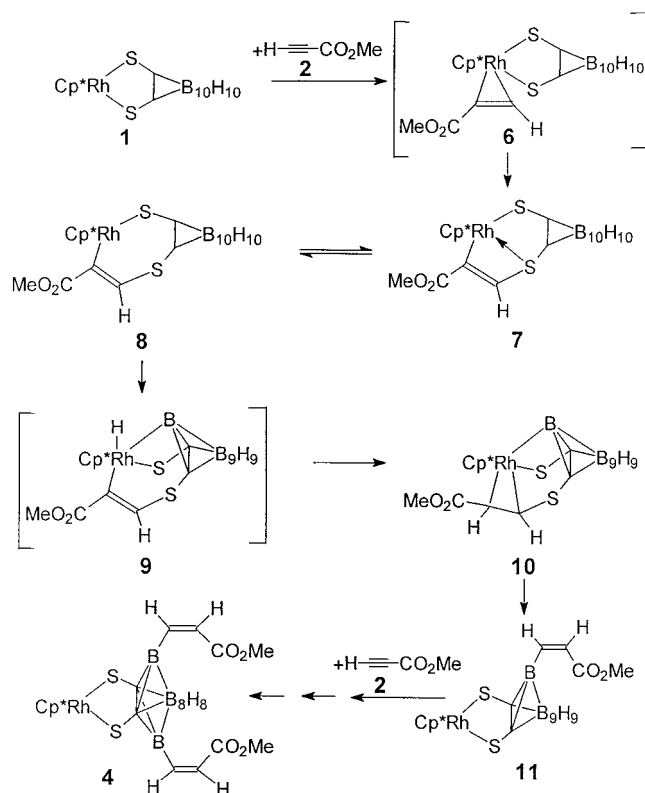


Figure 2. ORTEP plot of the molecular structure of **5**. Selected bond lengths [pm] and angles [°]: Rh–Z 183.8, Rh–S(1) 239.66(9), Rh–S(2) 238.04(9), Rh–C(4) 202.2(4), S(1)–C(1) 180.6(3), S(2)–C(2) 177.7(4), S(1)–C(3) 178.8(3), C(1)–C(2) 167.8(5), C(3)–C(4) 133.5(5); S(1)RhS(2) 87.88(3); S(1)RhC(4) 67.93(10), S(1)C(3)C(4) 104.8(2), S(1)RhS(2)/S(1)C(1)C(2) 154.3, S(1)RhC(4)/S(1)C(3)C(4) 170.5

lenes.^[8, 9] Therefore, it can be safely assumed that complex **7** (analogous to **5** in Scheme 1), generated by rearrangement of the η^2 -alkyne complex **6**, is an intermediate in the reaction of **1** with **2** (Scheme 2). An equilibrium between the 18e complex **7** and its 16e isomer **8** (formed by opening of the coordinative S→Rh bond), enables the rhodium atom to approach the sites of either B(3)–H or B(6)–H with the result of B–H activation.^[5] These agostic interactions are the prerequisite for hydride transfer from the boron atom to the rhodium atom accompanied by formation of a Rh–B bond in **9**.^[5, 13] and further transfer of the hydride from rhodium to the adjacent olefinic carbon atom in **10**.^[13] The next step includes cleavage of the Rh–B bond and formation of the boron-substituted



Scheme 2. Proposed mechanism for the reaction of **1** with **2** to give **4**.

carborane **11** as a 16e complex. Repetition of the whole sequence starting from **11** leads to the B(3)/B(6)-disubstituted final product **4**.

In conclusion, addition of an alkyne to a 16e rhodium complex, followed by insertion into the flexible Rh–S bond, starts a fascinating interplay between 16e and 18e complexes and makes use of all reactive sites. In the present example this provides a straightforward route to a selectively B(3)/B(6)-disubstituted *ortho*-carborane.

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elemental analysis; yield 80%; m. p. 202 °C (decomp). ¹H NMR (250 MHz, CDCl₃, 25 °C, TMS): δ = 1.83 (s, 15H; Cp*), 3.73 (s, 6H; MeO), 5.80 (d, ³J(H,H) = 15.2 Hz, 2H; =CH–B), 6.27 (d, ³J(H,H) = 15.2 Hz, 2H; =CH–C(O)); ¹³C NMR (62.9 MHz, CDCl₃, 25 °C, TMS): δ = 10.3 (Cp*), 51.0 (MeO), 94.4 (S₂C₂B₁₀H₁₀), 99.5 (¹J(¹⁰³Rh, ¹³C) = 7.4 Hz), 132.6 (=CH), 138.2 (b, =CH–B), 167.1 (CO); ¹¹B NMR (160.5 MHz; CD₂Cl₂, 25 °C, Et₂O–BF₃): δ = –6.5 (3,6), –8.0, –8.5, –11.0 (in the ratio 2:2:4:2); ¹⁰³Rh NMR (15.8 MHz, CDCl₃, 20 °C, Ξ(¹⁰³Rh) = 3.16 MHz): δ = 1210 ± 5; EI MS (70 eV): *m/z*: 612 (100) [*M*⁺].

- [7] Preparation of **5**: The reaction of **1** with **3** was carried out in the same way as described in reference [6]. The color turned red immediately after addition of **3**. Evaporation of the solvent left a red residue which gave pure **5** after recrystallization from CH₂Cl₂/hexane [80%; red needles; m. p. 187 °C (decomp)]. ¹H NMR (250 MHz, CD₂Cl₂, 25 °C): δ = 1.68 (s, 15H; Cp*), 3.75 (s, 3H; MeO), 3.78 (s, 3H; MeO); ¹³C NMR (62.9 MHz; CD₂Cl₂, 25 °C, TMS): δ = 9.3 (Cp*), 52.0 and 52.7 (MeO), 77.7 and 97.2 (C₂B₁₀H₁₀), 100.3 (¹J(¹⁰³Rh, ¹³C) = 5.8 Hz; Cp*), 123.0 (¹J(¹⁰³Rh, ¹³C) = 5.9 Hz; SC=), 158.5 (¹J(¹⁰³Rh, ¹³C) = 2.0 Hz), 168.5 (¹J(¹⁰³Rh, ¹³C) < 2 Hz; CO), 182.2 (¹J(¹⁰³Rh, ¹³C) = 28.4 Hz; Rh–C=); ¹¹B NMR (160.5 MHz; CD₂Cl₂, 25 °C, Et₂O–BF₃): δ = –4.0, –5.3, –5.8, –7.8, –9.2, –11.0 (signals overlap); ¹⁰³Rh NMR (15.8 MHz, CD₂Cl₂, 20 °C, Ξ(¹⁰³Rh) = 3.16 MHz): δ = 1049 ± 2.
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- [6] Preparation of **4**: To the green solution of **1** (0.2 g, 0.45 mmol) in CHCl₃ (30 mL) **2** (0.38 mL; 4.5 mmol) was added in one portion. The mixture was heated at reflux for three days; the color changed first to red and then gradually to green. After removal of the solvent, the residue was chromatographed on silica gel (Merck, Kieselgel 60). Elution with CH₂Cl₂ gave **4** as a deep green zone. Recrystallization from CH₂Cl₂/hexane afforded air-stable dark red crystals. Correct

Synthesis and Characterization of InAs/InP and InAs/CdSe Core/Shell Nanocrystals**

Yun-Wei Cao and Uri Banin*

Semiconductor nanocrystals have unique size-dependent optical properties governed by the quantum confinement effect.^[1,2] The optical and electronic properties can also be controlled by fabricating advanced core/shell nanocrystal structures, where a shell of a higher band gap semiconductor is grown on the core, yielding superior surface passivation.^[3–5] Previous work has primarily focused on II–VI semiconductor core/shell nanocrystals, for example CdSe/CdS and CdSe/ZnS.^[4,5] Significant enhancement of the emission quantum yield, and increased stability against oxidation compared to the cores, were observed. These improved nanocrystals have been used as a novel type of fluorescence markers in biological applications, with marked advantages over the traditional fluorescent dyes.^[6] Here we report on the synthesis and properties of novel core/shell nanocrystals with InAs cores. The band gap of InAs nanocrystals is size tunable through the near IR spectral region, where the selection of dyes is poor and their stability is low. These core/shell nanocrystals may be useful in future applications as biological fluorescent markers in the near IR spectral region.

The enhancement of the fluorescence quantum yield in core/shell nanocrystals is based on confinement of the carrier wavefunctions to the core region. In bulk InAs, the electron effective mass is substantially smaller than in CdSe (0.024 m_e versus 0.11 m_e , where m_e = mass electron). As a result, the confinement of the electron wavefunction to the core region can be expected to be more problematic in InAs cores. Therefore, in this core/shell system, the quality of the outer surface may play an important role in determining the fluorescence quantum yield. We examine this issue by growing two types of shells on InAs cores: InP and CdSe. The conduction band offset between InAs and these two shell materials is nearly identical,^[7] making the comparison of their properties particularly interesting.

We developed a high-temperature route to grow core/shell nanocrystals with InAs cores. Previously, a low-temperature route was used to prepare InAs/CdS core/shells in pyridine and benzylamine.^[8] The high-temperature route (260 °C) is necessary here to overcome the large reaction barriers for the decomposition of InP and CdSe precursors, and is also advantageous in achieving higher crystallinity of the core/

shell nanocrystals. The difficulty in using high temperature in the shell growth lies in Ostwald ripening of the nanocrystals, which leads to broadening of the size distribution.^[1] For CdSe cores, ripening is fast and this limits the usable growth temperature of the shells in this case.^[5] In contrast, we found that for the InAs cores, the rate of ripening is slow even at high temperature. Ripening should also be avoided during shell growth. For this we need to use high concentration of shell precursors. On the other hand, we need to prevent new nucleation of nanocrystals of the shell material, which is favorable at high concentration. By exploring the effects of core concentration, shell precursors concentration, and rate of precursor addition, we optimized the conditions for shell growth which do not yield substantial nucleation of nanocrystals of the shell semiconductor, while still minimizing the Ostwald ripening process.

Figure 1 presents the evolution of the absorption spectrum upon growth of an InP shell on InAs cores with radius of 17 Å. The shell growth is accompanied by a red shift of the spectrum, while its overall shape is nearly maintained

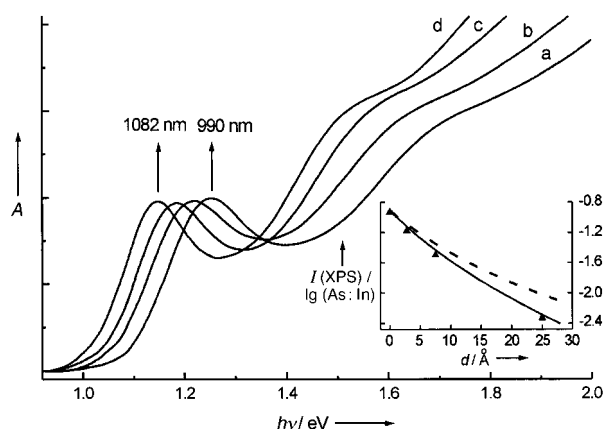


Figure 1. Absorption spectra of InAs core and InAs/InP core/shell nanocrystals during shell growth. The spectra were obtained for aliquots extracted 2 min after the injections of the InP stock solution. a) core with 17 Å in radius, core/shells with shell thickness in number of monolayers: b) 0.7, c) 1.4, d) 2.2. Insert: XPS intensity ratio of peak As_{3d} to $In_{3d5/2}$ peak (logarithmic scale), versus shell thickness d . Note the good agreement between the experimental data points (triangles), and a simulation of the expected ratio for a spherical core/shell structure (solid line). Also shown, is the simulated ratio for a spherical alloy structure (dashed line). The following photoelectron escape depths (λ) under $Al_{K\alpha}$ radiation (1486.6 eV) were used in the simulations: For InAs core: As_{3d} : 24.8 Å, $In_{3d5/2}$: 19.2 Å, for InP shell, As_{3d} : 24 Å, $In_{3d5/2}$: 18.6 Å.^[9]

[*] Dr. U. Banin, Dr. Y. W. Cao
Department of Physical Chemistry
and The Farkas Center for Light-Induced Processes
The Hebrew University of Jerusalem, Jerusalem 91904 (Israel).
Fax: (972) 2-561-8033
E-mail: Banin@chem.ch.huji.ac.il

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indicating that the good size distribution is preserved. Compared to the original cores, the fluorescence quantum yield in this case is substantially lowered, by a factor of 8. The systematic red shift of the band gap with the shell growth results from the extension of the carrier wavefunction into the shell region. In the case of alloy formation, a blue shift is expected.^[4] Additional direct proof for the growth of the shells was provided by X-ray photoelectron spectroscopy (XPS). In the insert of Figure 1, we present the ratio of the measured intensity of the $In_{3d5/2}$ to As_{3d} peaks versus shell thickness (triangles). Upon shell growth, the photoelectron signal of As is substantially quenched because of the reduced

escape probability through the InP shells. Due to the similarity between the size of the nanocrystals and the photoelectron escape depths (λ , values given in caption of Figure 1), we use the integral $\int e^{-z/\lambda} dz$ to correct the sensitivity factors of XPS peaks.^[9, 10] The solid line is the calculated intensity ratio under the assumption of a core/shell spherical structure, and good agreement with the experimental data is observed.

Figure 2 presents the evolution of the absorption and emission spectra upon growth of a CdSe shell on another fraction of the same InAs cores. As in the InP case, we observe a red

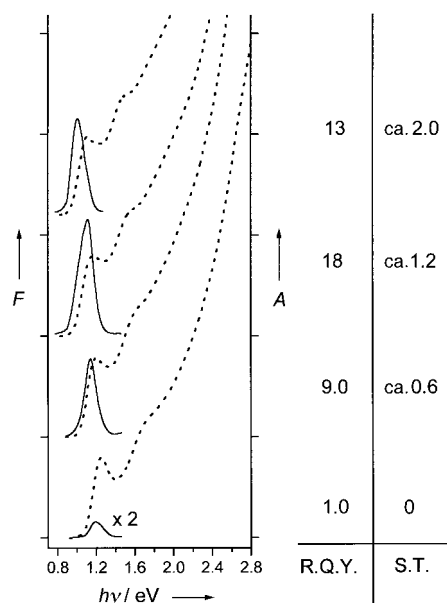


Figure 2. Absorption (dotted lines) and fluorescence (solid lines) spectra of InAs/CdSe core/shell nanocrystals. The core radius is 17 Å. The shell thickness (ST), and the relative fluorescence quantum yield (R.Q.Y.), are indicated on the right side.

shift of the band gap with shell growth. But in this case, as can be seen in the figure, the fluorescence quantum yield is substantially enhanced as compared to the fresh core, up to a maximum of an 18-fold increase. The quantum yield of these InAs/CdSe core/shells was directly compared with the yield of the laser dye IR140,^[11] using 826 nm excitation, and was found to be two times larger (absolute yield of 20%). To study the growth of the core/shell nanocrystals, we also used high-resolution transmission electron microscopy (HRTEM). Figure 3 shows HRTEM images of a single InAs core nanocrystal (18 Å radius, frame A), and of an InAs/CdSe core/shell nanocrystal (33 Å radius, frame B). In both nanocrystals, the zinc blende structure is observed as viewed along the [110] zone axis.

To further characterize the core/shell structures, we used powder X-ray diffraction (XRD). Figure 4 compares the diffraction patterns of InAs cores with InAs/InP and InAs/CdSe core/shells. The positions of the peaks of the InAs cores (dotted line) match those of the bulk InAs zinc blende peaks, consistent with the HRTEM images. The peaks are broadened because of the finite size of the nanocrystals. Upon the growth of the InP shell (dashed line), peak positions shift to higher angles, towards the positions of the bulk InP zinc blende

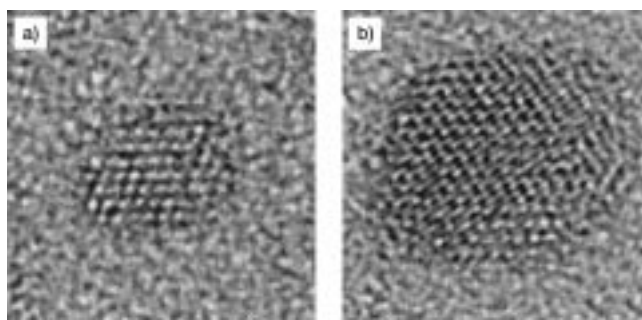


Figure 3. HRTEM images (8 × 8 nm) of a single InAs core nanocrystal (A), and an InAs/CdSe core/shell nanocrystal (B). Both nanocrystals are viewed in the [110] projection of the zinc blende structure.

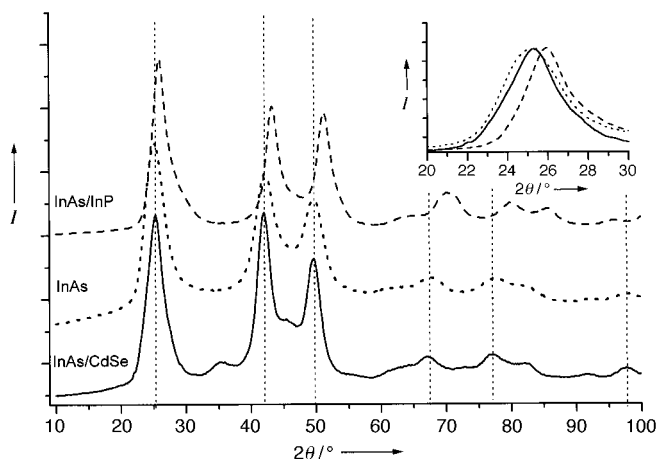


Figure 4. XRD patterns of InAs cores, 17 Å in radius (dotted line); InAs/InP core/shell with 25 Å shell thickness (dashed line); and InAs/CdSe core/shell with 14 Å shell thickness (solid line). The insert shows a zoom-in of the zinc blende (111) peak for the three samples, demonstrating the narrowing of the peaks upon shell growth.

peaks. In addition, substantial narrowing of the diffraction peaks is observed as demonstrated for the (111) peak shown in the insert of Figure 4. The narrowing results from an increase of the crystalline domain size, indicating that shell growth is epitaxial. For the CdSe shells (solid line), the peak positions do not shift as compared with the InAs core. This is consistent with the nearly zero lattice mismatch of InAs and zinc blende CdSe, indicating epitaxial growth for this case as well. The diffraction peaks also narrow upon shell growth for the same reason as in the case of the InP shell.

InAs/InP and InAs/CdSe core/shell nanocrystals are similar in many respects including the basic synthetic route for their preparation, the epitaxial growth mode as evidenced by the XRD patterns, and the red shift of the absorption spectra upon shell growth. Moreover, the conduction band offsets between the InAs core and these two shell materials, and thus the radial electron potentials, are similar.^[7] However, the fluorescence quantum yield of these two core/shell nanocrystals is completely different. Upon growth of the InP shells the quantum yield is quenched, while upon growth of the CdSe shells it is substantially increased. To explain this marked difference, we calculated the energy of the lowest electron state for both core/shells using a model of a particle in a spherical potential well.^[12] We found that the energy of this state in both cases is higher than the core/shell conduction

band offset, and as a result, the electron wavefunction has substantial probability of presence at the outer surface. Thus, the quality of the outer surface in the core/shell nanocrystals, may have a profound effect on the quantum yield.

To test this hypothesis, we carried out two experiments that directly affect the outer surface. In Figure 5a, we present the fluorescence spectra of fresh and oxidized InAs/InP core/shells. After oxidation, the absorption of the core/shells hardly

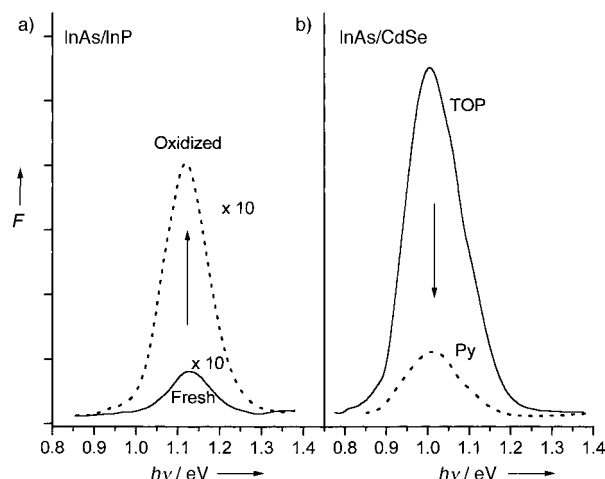


Figure 5. Outer surface effect in InAs/InP and in InAs/CdSe core/shell nanocrystals (core radius 17 Å, shell thickness 2 monolayers), detected by the fluorescence spectra. a) InAs/InP core/shells fresh (solid line), and oxidized (dotted line) in O_2 -saturated toluene for four days. b) Fluorescence for InAs/CdSe core/shells capped by TOP (solid line), and by pyridine (dotted line). All the spectra were taken in the same conditions, and presented in the same fluorescence intensity scale, with the InAs/InP spectra multiplied by 10.

changed, but the fluorescence quantum yield increased by a factor of 6, up to the level of the fresh core. This directly demonstrates the importance of the outer surface for the InAs/InP core/shell fluorescence. A similar behavior was observed previously upon oxidation of InP nanocrystals.^[13] In Figure 5b, we compare the fluorescence spectra of InAs/CdSe core/shells coated by trioctylphosphine (TOP), with another fraction of the same core/shells coated by pyridine. The quantum yield of the pyridine-coated nanocrystals is substantially quenched compared to the TOP-coated nanocrystals. The absorption of these samples was similar, and the quenching of the fluorescence can be directly assigned to the change of the outer surface.^[4] The two experiments provide direct evidence for the importance of the outer surface in determining the fluorescence QY of these core/shell nanocrystals. For the InAs/CdSe core/shells, where the outer surface quality is high, we obtained a substantial enhancement of the fluorescence QY up to levels better than traditional organic IR dyes, and with improved photostability.

Experimental Section

A two-step synthesis route was used to prepare the core/shell nanocrystals. In the first step, InAs nanocrystals with controlled sizes between 10–40 Å in radius were synthesized by using a pyrolytic reaction of organometallic precursors, Tris(trimethylsilyl)arsenide and indium(III) chloride, in a liquid surfactant, trioctylphosphine (TOP).^[14,15] The width of the size distribution

of cores after this synthesis was on the order of 15%. Before shell growth, we improved the size distribution of the cores to 10%, using size-selective precipitation. In the second step, the shell was grown. InAs cores were dissolved in TOP (3–6 g) in a three-necked flask. Under a flow of argon on a Schlenk line, the nanocrystal solution was heated to 260 °C, and the InP shell precursor solution (indium(III)chloride and tris(trimethylsilyl)phosphane TOP solution), or CdSe shell precursor solution (dimethylcadmium and tributylphosphane selenide TOP solution) were introduced into the hot solution by dropwise addition. After addition was complete, the reaction mixture was cooled to room temperature. InAs/InP or InAs/CdSe core/shell nanocrystals passivated by TOP were obtained by precipitation using a mixture of methanol and toluene. The growth of cores and core/shells was monitored by UV/Vis spectroscopy of aliquots taken from the reaction flask.

UV/Vis absorption spectra were measured by using a Shimadzu UV-1601 or UV-3101pc spectrophotometer. Photoluminescence experiments were performed using a He-Ne laser (632 nm, output power: 3 mW, spot size: 3 mm) as the excitation source. The emission was collected at a right angle configuration, dispersed by a monochromator and detected by a liquid nitrogen cooled InGaAs diode with lock-in amplification. Relative quantum yield measurements were carried out by using solutions with identical optical densities at the excitation wavelength. X-ray photoelectron spectroscopy (XPS) were performed by using a Perkin-Elmer PHI-5600 ESCA system under $Al_{K\alpha}$ radiation at 200 W. High-resolution spectra of As_{3d} and In_{3d} were obtained at a pass energy of 11.74 eV with a resolution of 0.025 eV per step interval. Transmission electron microscopy (TEM) to determine the shell thickness was conducted by using a Philips CM-120 microscope or a JEOL-100CX microscope. HRTEM images were obtained by using a JEOL-JEM-2010 electron microscope operated at 200 kV. Powder X-ray diffraction (XRD) patterns were obtained on a Philips PW-1830/40 X-ray diffractometer with $Cu_{K\alpha}$ radiation.

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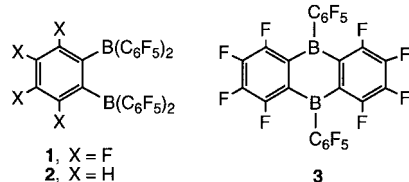
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Activation of $[\text{Cp}_2\text{ZrMe}_2]$ with New Perfluoroaryl Diboranes: Solution Chemistry and Ethylene Polymerization Behavior in the Presence of $\text{MeAl}(\text{BHT})_2$ **

V. Clifford Williams, Chaoyang Dai, Zengmin Li, Scott Collins,* Warren E. Piers,* William Clegg, Mark R. J. Elsegood, and Todd B. Marder

Perfluoroaryl-substituted boranes^[1] and alanes^[2] are potent Lewis acids which are able to abstract alkylidene groups (e.g. CH_3^- , methide) from organotransition metal complexes, forming highly reactive cationic complexes.^[3] This is done most often within the context of olefin polymerization catalysis and perfluoroaryl-substituted boranes $\text{B}(\text{Ar}_\text{F})_3$ have become important as cocatalysts in commercial processes. Effects of counterions on the activity and thermal stability of the catalysts are profound and depend to a large degree on the nature and strength of the ion–ion interaction in solution.^[4]

Marks et al. have suggested that one way to ameliorate these interactions is to distribute the negative charge of the anion over more atoms through the use of bifunctional Lewis acids.^[5] To this end, we have recently reported the synthesis of the novel diboranes **1** and **2**.^[6] While developing the synthetic route to **1**, we prepared the 9,10-boraanthracene compound 9,10- $\text{Cl}_2\text{C}_{12}\text{B}_2\text{F}_8$, which can be converted smoothly into the perfluorophenyl substituted analogue **3** by use of $\text{Zn}(\text{C}_6\text{F}_5)_2$ ^[7] as a C_6F_5 transfer agent. Diboraanthracene **3** has been prepared and disclosed independently by Marks et al.^[8]



[*] Prof. S. Collins, Dr. C. Dai, Dr. Z. Li
Department of Chemistry, University of Waterloo
Waterloo, ON, N2L3G1 (Canada)
Fax: (+1) 519-746-0435
E-mail: scollins@uwaterloo.ca

Prof. W. E. Piers, Dr. V. C. Williams
Department of Chemistry, University of Calgary
2500 University Drive NW
Calgary, AB, T2N 1N4 (Canada)
Fax: (+1) 403-289-9488
E-mail: wpiers@ucalgary.ca

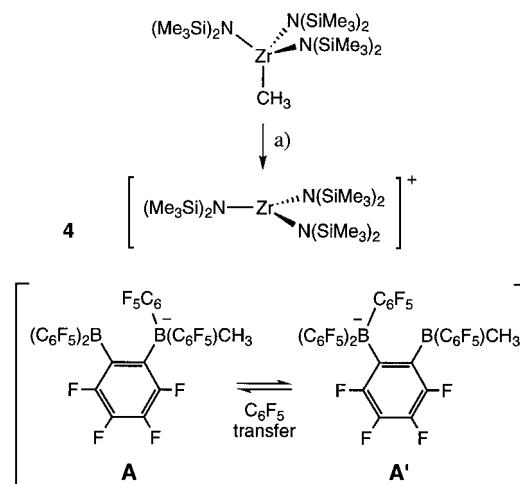
Prof. W. Clegg, Dr. M. R. J. Elsegood
Department of Chemistry, University of Newcastle
Newcastle upon Tyne, NE1 7RU (England)

Prof. T. B. Marder
Department of Chemistry, University of Durham
Durham, DH1 3LE (England)

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Herein we report the methide abstraction reactions of **1** with organozirconium compounds and a comparative assessment of $\text{B}(\text{C}_6\text{F}_5)_3$ and diboranes **1–3** as olefin polymerization initiators. In addition, we describe the behavior of these various activators in the presence of $\text{MeAl}(\text{BHT})_2$ (MAD; BHT = 2,6-di-*tert*-butyl-4-methylphenoxide), a monomeric alkylaluminum compound^[9] which appears to be an example of a “noninteracting” scrubbing agent of use in olefin polymerization.^[10]

To assess the solution and solid-state structure of the anion formed upon methide abstraction by **1**, we employed the tris-amido zirconium complex $[\text{MeZr}\{\text{N}(\text{SiMe}_3)_2\}_3]$ ^[11] as a CH_3^- source. In $\text{C}_6\text{D}_5\text{Br}$, reaction of **1** and $[\text{MeZr}\{\text{N}(\text{SiMe}_3)_2\}_3]$ in a 1:1 ratio cleanly formed a stable ion pair (**4**, Scheme 1).



Scheme 1. Synthesis of the stable ion pair **4**. a) **1** (1 equiv), $\text{C}_6\text{D}_5\text{Br}$.

The solution structure of the anionic portion of **4** was investigated by 1D and 2D ^{19}F NMR experiments. The ^{19}F NMR spectrum (282.4 MHz) collected at room temperature is shown in Figure 1. The anion comprises two species as indicated by the two signals at $\delta = -146.9$ (major) and

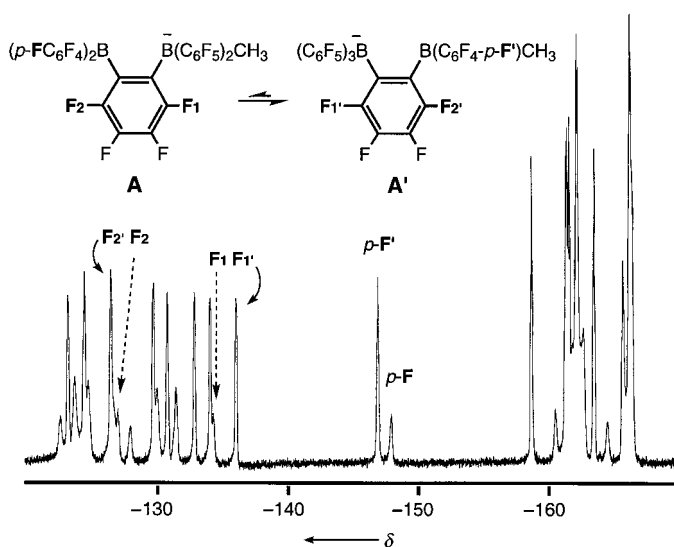


Figure 1. ^{19}F NMR spectrum (282.4 MHz) of **4** recorded in CD_2Cl_2 at room temperature.

–147.9 (minor), which are characteristic of *para*-fluorine atoms on a C₆F₅ ring bound to a neutral borane center (*p*-F' and *p*-F, respectively).^[12] The presence of the two resonances suggests that there are two different neutral borane centers in the anion, related by reversible C₆F₅ transfer (Scheme 1). ¹⁹F COSY 45 experiments allow for assignment of the *ortho*-fluorine atoms of the central ring; the resonances at $\delta = -136.0$ and -126.5 are ascribed to the fluorine atoms *ortho* to the borate and borane centers, respectively, of the major species (**F1'** and **F2'**); the less intense resonances at $\delta = -134.3$ and -127.1 are the analogous peaks for the minor species (**F1** and **F2**). Since the signals at $\delta = -136.0$ (major species, *ortho*-borate fluorine) and $\delta = -146.9$ (major species, *para*-C₆F₅) integrate in a 1:1 ratio, we assign the major solution species the structure **A'**, formed by C₆F₅ transfer from the (presumably) kinetically formed minor species **A** (see Scheme 1). Comparison of the two distinct *para*-fluorine resonances suggests that **A'** predominates over **A** in approximately a 6:1 ratio.

The ¹⁹F EXSY experiments show that exchange of the C₆F₅ groups in the anion is extensive. Particularly informative is the EXSY map of the well-resolved *ortho* region of the spectrum, which indicates that at least two processes are operative. The first, manifested by exchange between *ortho* fluorine atoms of the major species, can be explained on the basis of rotation about the B–C₆F₅ and C₆F₄–B axes, which is restricted at room temperature in this sterically crowded system. Cross-peaks in the EXSY map between peaks ascribed to the *ortho*-fluorine atoms of **A** and the *ortho*-fluorine atoms of **A'** can only arise by transfer of a C₆F₅ ring between boron centers; in this fashion, all the C₆F₅ rings are scrambled. A correlation between the peaks ascribed to the *para*-fluorine atoms of the C₆F₅ rings bound to neutral three-coordinate borane centers is also consistent with this process.

Layering a solution of **4** in CH₂Cl₂ with hexanes produced crystals suitable for X-ray analysis.^[13] The cationic portion of the molecule is nearly identical to that reported by Green and co-workers;^[14] the structure of the anion in **4** is given in Figure 2. The anion's solid-state structure corresponds to that of the major isomer in solution, that is, **A'**. While the B1–C1–C6–B2 dihedral angle is 19.9(2)° in free borane **1**,^[6] these

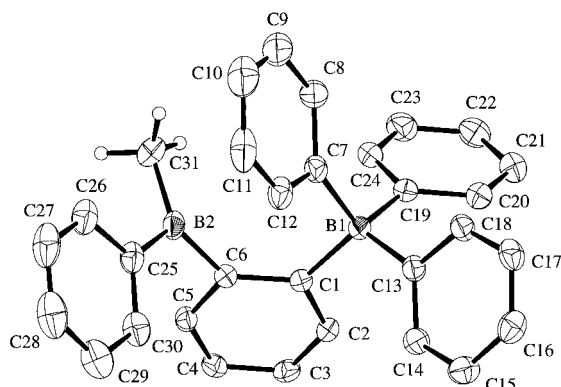
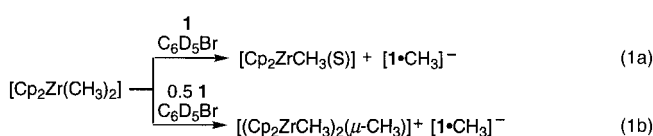


Figure 2. Molecular structure of the anion in **4**. Selected bond distances [Å] and angles [°]: B1–C1 1.650(4), B1–C7 1.662(4), B1–C13 1.657(4), B1–C19 1.674(4), B2–C6 1.601(4), B2–C25 1.590(5), B2–C31 1.565(5); B1–C1–C6 127.2(2), B1–C1–C2 117.3(2), B2–C6–C1 131.5(2), B2–C6–C5 110.1(2), C1–B1–C7 109.2(2), C1–B1–C13 115.6(2), C1–B1–C19 104.2(2), C6–B2–C25 119.4(3), C6–B2–C31 117.3(3), C25–B2–C31 121.5(3).

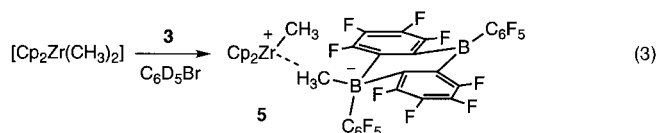
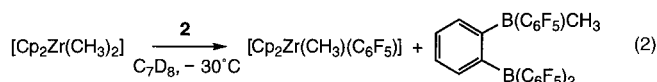
atoms are essentially coplanar in the anion of **4**, suggesting an alignment of the borate negative charge with the neutral borane center at B2. Steric tension is evident, however, in the large B2–C6–C1 and B1–C1–C6 angles of 131.5(2)° and 127.2(2)°, respectively.

Diborane **1** readily abstracts a methide group from [Cp₂ZrMe₂]. Reactions in toluene yield immiscible oils; in C₆D₅Br, however, the products are soluble and stable for several hours. In the 1:1 (**1**:Zr) reaction the major species ($\approx 90\%$) is a monomeric, solvent-separated ion pair [Eq. (1a); S = solvent] that slowly ($t_{1/2} \approx 2$ d) decomposes to an unknown product. The 1:2 reaction produces a μ -methyl zirconium dimer^[3a, 15] [Eq. (1b)], as indicated by the appearance of signals at $\delta = 0.07$ and -1.05 in a 2:1 ratio, assigned to



the terminal and bridging methyl groups, respectively. The ¹H, ¹¹B, and ¹⁹F NMR data for the monomeric and dimeric compounds indicate that the structure of the counteranion in these systems is the same as that found in **4**. In the ¹H NMR spectra of these complexes, broad signals at $\delta = 1.19$ and 1.67 ($\approx 5:1$) are a consistent feature and are assigned to B_{neutral}CH₃ of **A'** and B_{borate}CH₃ of **A**, respectively.

Diborane **2** appears to react with [Cp₂ZrMe₂] in an analogous fashion [Eq. (2)], although the ion pair is thermally unstable, even at -30°C in [D₈]toluene; the major products observed result from C₆F₅ transfer^[15d] from the counterion to Zr. In contrast, diboraanthracene **3** reacts with [Cp₂ZrMe₂] to furnish the stable ion pair **5** [Eq. (3)], in which there is



restricted rotation about both exocyclic B–C₆F₅ bonds. The ¹H chemical shift of BCH₃ ($\delta = 0.12$) is consistent with a contact ion pair structure.^[3a] Interestingly, further addition of one equivalent of [Cp₂ZrMe₂] to solutions of **5** led to the formation of a precipitate, with complete disappearance of all NMR signals due to **5** (and [Cp₂ZrMe₂]). The precipitate is insoluble/unstable in common NMR solvents, and may be a diboraanthracene species such as [Cp₂ZrMe]₂[9,10-Me₂C₁₂B₂F₈].^[8]

To assess the suitability of these diboranes as cocatalysts, ethylene polymerizations were conducted in toluene slurry using [Cp₂ZrMe₂] and each of the cocatalysts B(C₆F₅)₃ and **1–3**. Initially, experiments were conducted by mixing [Cp₂ZrMe₂] (1.0 equiv) with the cocatalyst (1.2 equiv) in a small volume of toluene just prior (i.e., contact time < 1 min)

to delivery to the reactor, which was presaturated with ethylene and contained AlMe_3 as a scrubbing agent ($\approx 30 \mu\text{M}$).

As shown in Table 1 (entries 1–3) the order of polymerization activity under these conditions is $\text{B}(\text{C}_6\text{F}_5)_3 > \mathbf{1} > \mathbf{2}$. The lower activity of the ion pair derived from $\mathbf{2}$ and $[\text{Cp}_2\text{ZrMe}_2]$ may be a reflection of the limited stability of this species at room temperature (or even at low temperature, see above); we have noted elsewhere that even ion pairs with limited

Table 1. Ethylene polymerization using $[\text{Cp}_2\text{ZrMe}_2]$ and various cocatalysts.^[a]

Entry	Cocatalyst	AlR_3 (conc. [μM])	Act. ^[b]	M_w	M_w/M_n
1	$\text{B}(\text{C}_6\text{F}_5)_3$	AlMe_3 (30)	4.4	340	2.17
2	$\mathbf{1}$	AlMe_3 (30)	3.3	290	2.08
3	$\mathbf{2}$	AlMe_3 (30)	2.8	370	1.83
4	$\text{B}(\text{C}_6\text{F}_5)_3$	MAD (50)	1.5	–	–
5	$\text{B}(\text{C}_6\text{F}_5)_3$	MAD (100)	1.6	–	–
6	$\text{B}(\text{C}_6\text{F}_5)_3$	MAD (200)	13.9	270	2.18
7 ^[c]	$\text{B}(\text{C}_6\text{F}_5)_3$	MAD (300)	13.4	260	2.00
8 ^[c,d]	$[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$	MAD (300)	48.9	240	2.06
9 ^[c,e]	$[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$	MAD (300)	30.1	340	2.24
10 ^[c,d,f]	$[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$	MAD (300)	10.8	250	2.18
11	$\mathbf{1}$	MAD (300)	5.0	260	1.98
12	$\mathbf{2}$	MAD (300)	3.8	200	2.04
13 ^[g]	$\mathbf{2}$	MAD (300)	0.39	–	–
14 ^[c]	$\mathbf{3}$	MAD (300)	1.5	280	2.23
15 ^[h]	$\mathbf{3}$	MAD (300)	1.8	260	1.98

[a] Conditions: 500 mL of toluene, 30 °C, 20 psi (1.38 bar) C_2H_4 , 1000 rpm with $c([\text{Cp}_2\text{ZrMe}_2]) = 10 \mu\text{M}$ and $c(\text{cocatalyst}) = 12 \mu\text{M}$, except where noted. The cocatalyst was added to the reactor, presaturated with monomer and containing scrubbing agent, followed immediately by the addition of $[\text{Cp}_2\text{ZrMe}_2]$ except where noted. [b] Activity in 10^6 g of polyethylene per mol Zr per hour. [c] $c([\text{Cp}_2\text{ZrMe}_2]) = 2.0 \mu\text{M}$, $c(\text{cocatalyst}) = 2.2 \mu\text{M}$. [d] 30 psi (2.07 bar) C_2H_4 . [e] $[\text{Cp}_2\text{ZrMe}_2]$ was added 5 min after the cocatalyst. [f] $[\text{Cp}_2\text{ZrMe}_2]$ was added 10 min after the cocatalyst. [g] $[\text{Cp}_2\text{ZrMe}_2]$ and $\mathbf{2}$ were premixed in toluene (20 mL) for 5 min at 25 °C. [h] $c([\text{Cp}_2\text{ZrMe}_2]) = 4.0 \mu\text{M}$, $c(\text{cocatalyst}) = 2.0 \mu\text{M}$

thermal stability can be competent polymerization catalysts when generated in situ.^[15d] The lower polymerization activity of the ion pair derived from $\mathbf{1}$, compared to that formed from $\text{B}(\text{C}_6\text{F}_5)_3$, is surprising in view of both the thermal stability of the ion pair derived from $\mathbf{1}$ and $[\text{Cp}_2\text{ZrMe}_2]$ in bromobenzene and the fact that the major species appears to be a solvent-separated ion pair

It is known that simple scrubbing agents such as AlMe_3 or $\text{Al}i\text{Bu}_3$ can be incompatible with neutral boranes, such as $\text{B}(\text{C}_6\text{F}_5)_3$,^[16] or other common cocatalysts, such as $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$.^[12b] This complexity makes interpretation of polymerization experiments conducted under conditions such as those reported here (i.e., continuous in monomer and with effective stirring) difficult, as the different activities observed using the different activators might be entirely due to differences in the concentration of activator (or even the nature of the activator) and thus ultimately the catalytically active species $[\text{Zr}^*]$.

We have discovered that MAD appears to be an example of a “noninteracting” scrubbing agent, at least with $\text{B}(\text{C}_6\text{F}_5)_3$. This compound is unreactive towards $[\text{Cp}_2\text{ZrMe}_2]$, $\text{B}(\text{C}_6\text{F}_5)_3$, or the ion pair derived from these compounds in toluene at room temperature, as revealed by ^1H and ^{19}F NMR spectroscopy.^[17]

As shown in Table 1, substitution of AlMe_3 by MAD leads to pronounced improvements in catalytic activity of $[\text{Cp}_2\text{ZrMe}_2]$ and $\text{B}(\text{C}_6\text{F}_5)_3$ (entries 4–7). Having said that, MAD appears to be a less effective scrubbing agent than AlMe_3 in the sense that higher concentrations (and longer contact times) are required to effectively remove impurities from solvent and monomer. However, unlike the situation with AlMe_3 , which can have an inhibitory effect at high concentrations,^[15a] MAD is much more convenient to use as a scrubbing agent as the amount employed (above the threshold value required to remove impurities) does not seem to influence polymerization activity.

While MAD is unreactive towards $\text{B}(\text{C}_6\text{F}_5)_3$, it does react slowly with $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$ at room temperature in $[\text{D}_5]\text{chlorobenzene}$ ($t_{1/2} \approx 1$ h with $c(\text{MAD}) = c([\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]) \approx 0.05$ M). The principal reaction appears to involve hydride (rather than CH_3^-)^[12b] abstraction from MAD, as revealed by the formation of Ph_3CH . The nature of the aluminum-containing products has not yet been determined, but the AlMe moiety appears to remain intact. As the polymerization results using $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$ demonstrate (Table 1, entries 8–10), incompatibility of the cocatalyst and the scrubbing agent can have definite consequences on polymerization activity when $[\text{Cp}_2\text{ZrMe}_2]$ introduction is delayed.

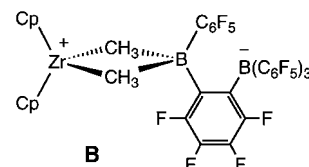
Even with MAD, the same activity order is observed using these diborane cocatalysts. Indeed, the activity of $\mathbf{1}/[\text{Cp}_2\text{ZrMe}_2]$ is not as dramatically improved compared with the use of $\text{B}(\text{C}_6\text{F}_5)_3/[\text{Cp}_2\text{ZrMe}_2]$ in the presence of MAD. These results suggest that the lower activity of the ion pair resulting from $\mathbf{1}/[\text{Cp}_2\text{ZrMe}_2]$ may be intrinsic, despite the apparent lower coordinating ability of the counteranion in bromobenzene. One possible explanation is that the counterion does coordinate to Zr in toluene, but the interaction involves the borane moiety, rather than the perfluoroarylborate portion of the molecule (e.g. **B**).^[18] The resulting adduct would be analogous to those formed from metallocenium ions and AlMe_3 ^[15a] and would be expected to have lower activity.

As might be expected, premixing $\mathbf{2}$ and $[\text{Cp}_2\text{ZrMe}_2]$ in toluene, prior to polymerization, leads to a tenfold decrease in activity compared to in situ generation (Table 1, entry 13 versus 12), demonstrating that ion pair stability effects [Eq. (2)] are important. Interestingly, $\mathbf{3}$ is an effective cocatalyst, even when the Zr:B ratio is 1:1 instead of 1:2 (entry 15 versus 14).^[8] In light of the solution chemistry reported for $\mathbf{3}/[\text{Cp}_2\text{ZrMe}_2]$ (see above), in the latter case (Zr:B = 1:2) the likely species present is the ion pair **5**.

Experimental Section

General techniques have been described in detail elsewhere.^[15d] ^1H NMR spectra acquired in $\text{C}_6\text{D}_5\text{Br}$ were referenced to the residual *meta*-protons at $\delta = 6.90$.

Synthesis of **4**: Hexane (20 mL) was condensed into a flask containing $[\text{MeZr}\{\text{N}(\text{SiMe}_3)_2\}_3]$ (0.12 g, 0.21 mmol) and diborane **1** (0.18 g, 0.21 mmol) at -78°C . The solids slowly dissolved as the sample was warmed to room



temperature, forming a colorless oil. Trituration afforded a white powder, which was isolated by filtration and dried in vacuo (0.35 g, 95%). ^1H NMR (200 MHz, CD_2Cl_2 , 25 °C, TMS): δ = 0.17 (s, SiCH_3); ^{11}B NMR (96.29 MHz, CD_2Cl_2): δ = -15 (borane signal not observed); see Figure 1 for the ^{19}F NMR spectrum; elemental analysis calcd for $\text{C}_{49}\text{H}_{57}\text{B}_2\text{F}_{24}\text{N}_3\text{Si}_6\text{Zr}$: C 41.3, H 4.0, N 2.9; found: C 41.2, H 3.9, N 2.8.

Generation of metallocenium cations from $[\text{Cp}_2\text{ZrMe}_2]$ and **1**: Monomeric and dimeric metallocenium cations were generated in situ by adding a solution of **1** in $\text{C}_6\text{D}_5\text{Br}$ to a solution of $[\text{Cp}_2\text{ZrMe}_2]$ in a 1:1 or a 1:2 (**1**:Zr) stoichiometry. The solutions were then assayed by ^1H , ^{11}B , and ^{19}F NMR spectroscopy; the results of the latter two were essentially identical to that found for **4**. ^1H NMR for $[\text{Cp}_2\text{ZrCH}_3(\text{S})]^+[\text{A}'/\text{A}]^-$ (S = solvent; 200 MHz, $\text{C}_6\text{D}_5\text{Br}$, 25 °C): δ = 5.83 (s, C_5H_5), 1.67 (brs, $\text{B}_{\text{borate}}\text{CH}_3$), 1.19 (brs, $\text{B}_{\text{borane}}\text{CH}_3$), 0.48 (s, ZrCH_3); ^{13}C NMR (100.61 MHz, $\text{C}_6\text{D}_5\text{Br}$): δ = 115.3 (C_5H_5), 53.8 (ZrCH_3), 17.3 ($\text{B}_{\text{borate}}\text{CH}_3$), 15.0 ($\text{B}_{\text{borane}}\text{CH}_3$). ^1H NMR for $[(\text{Cp}_2\text{ZrCH}_3)_2(\mu\text{-CH}_3)]^+[\text{A}'/\text{A}]^-$ (200 MHz, $\text{C}_6\text{D}_5\text{Br}$, 25 °C): δ = 5.89 (s, 20H, C_5H_5), 1.67 (brs, $\text{B}_{\text{borate}}\text{CH}_3$ of A), 1.19 (brs, $\text{B}_{\text{borane}}\text{CH}_3$ of A'), 0.07 (s, 6H, ZrCH_3), -1.05 (s, 3H, ZrCH_3Zr).

Generation of metallocenium cations from $[\text{Cp}_2\text{ZrMe}_2]$ and **3**: Ion pair **5** was generated in situ by mixing $[\text{Cp}_2\text{ZrMe}_2]$ and diborane **3** in $\text{C}_6\text{D}_5\text{Br}$. ^1H NMR (200 MHz, $\text{C}_6\text{D}_5\text{Br}$, 25 °C): δ = 5.74 (s, 10H, C_5H_5), 0.36 (s, 3H, ZrCH_3), 0.12 (brs, 3H, $\text{B}_{\text{borate}}\text{CH}_3$); $^{19}\text{F}\{^1\text{H}\}$ NMR ($\text{C}_6\text{D}_5\text{Br}$, 25 °C): δ = -124.74 (brm, 2F), -133.8 and -136.8 (2 $\times$ brm, total 2F, o-F), -134.4 (m, 2F), -135.8 (brm, 2F, o-F), -146.6 (brm, 2F), -156.4 (t, J(F,F) = 20.7 Hz, p-F), -159.8 (brm, 2F, m-F), -160.9 (brm, 1F, p-F), -163.2 and -163.8 (2 $\times$ brm, total 2F, m-F), -165.2 (brm, 2F).

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Titanium–Thiolate–Aluminum–Carbide Complexes by Multiple C–H Bond Activation**

Frédéric Guérin and Douglas W. Stephan*

Much of early transition metal thiolate chemistry is based on metallocene derivatives.^[1] More recently, interest has focused on related monocyclopentadienyl analogues as such systems have proved to be more reactive, often affording novel reactivity and products.^[2–13] For example, we have observed that CpTi–thiolate species undergo either β -C–H or C–S bond activation of the thiolate ligands depending on the reaction conditions.^[3–7] An interesting aspect of early transition metal chemistry in general involves the perturba-

[*] Prof. D. W. Stephan, Dr. F. Guérin
School of Physical Sciences, Chemistry and Biochemistry
University of Windsor
Ontario, N9P 3P4 (Canada)
Fax: (+1) 519-973-7098
E-mail: stephan@uwindsor.ca

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tion of reactivity precipitated by judicious choice of ancillary ligands. In this regard, we have recently applied the notion of a steric and electronic analogy between cyclopentadienyl and phosphinimide ligands^[14, 15] to develop effective ethylene polymerization catalysts.^[16, 17] We have now combined these two approaches in the quest for unique reactivity of CpTi–thiolate complexes. Herein we describe the reactions of [Cp(*i*Pr₃PN)Ti(SR)₂] with AlMe₃. The result is an unprecedented triple C–H bond activation of a methyl group to yield Ti–Al–carbide clusters.

The red compounds [Cp(*i*Pr₃PN)Ti(SR)₂] (**1**: R = Ph, **2**: R = CH₂Ph) are readily prepared by reaction of [Cp(*i*Pr₃PN)–TiCl₂]^[16] with the lithium thiolates LiSPh or LiSCH₂Ph. These species are isolated in 64 and 75 % yields, respectively. The ³¹P{¹H} NMR spectra for **1** and **2** reveal single resonances at δ = 34.94 and 31.55, respectively. The ¹H and ¹³C{¹H} NMR data are unexceptional and are consistent with the formulations.

Compounds **1** and **2** react with excess AlMe₃. Monitoring of these reactions by ³¹P{¹H} NMR spectroscopy shortly after mixing reveals the presence of three new resonances in addition to a signal from the starting material. When the reaction mixtures were left standing for 24 h at 25 °C, these signals were replaced by single resonances at δ = 54.09 and 52.87, respectively, inferring the quantitative formation of new species **3** and **4**. These species were isolated in 83 and 74 % yield, respectively. The ¹H NMR spectra of **3** and **4** reveal resonances attributable to two inequivalent thiolate ligands, a cyclopentadienyl and phosphinimide ligands. In addition, **3** and **4** exhibit five resonances between δ = 0.30 and –0.32 attributable to methyl groups. The corresponding ¹³C resonances for the ligand fragments are observed, whereas the signals for the methyl groups are extremely weak. This latter observation is consistent with aluminum-bound methyl groups.

On the basis of these NMR data, formulations incorporating a Ti and three Al atoms could be proposed, although the precise nature of the molecular structure remained unclear. For this reason, crystallographic studies of **3** and **4** were undertaken.^[18] Despite repeated attempts to obtain suitable crystals of **3**, the structure solved for **3** was of less than desirable quality. Nonetheless, the data did permit the establishment of the molecular connectivity of **3**.

In contrast, high-quality crystals of **4** were obtained by recrystallization from benzene. The X-ray structural data for **3** and **4** confirmed that they are analogous and can be formulated as [CpTi(μ -SR)(μ -NPiPr₃)(C)(AlMe₂)₂(μ -SR)-AlMe] (**3**: R = Ph, **4**: R = CH₂Ph; Figures 1 and 2). In both of these molecules, the pseudo-“three-legged piano stool” coordination sphere of Ti comprises a cyclopentadienyl ring, a thiolate sulfur, a phosphinimide nitrogen, and a carbide carbon. Three aluminum atoms complete the bonding sphere of the carbide carbon atom. Bridging the titanium-bound thiolate and the carbide is an AlMe₂ moiety; a second AlMe₂ fragment on the carbide is coordinated to a second thiolate group, which also bridges to a third aluminum center. This last AlMe moiety is also bonded to the titanium-bound phosphinimide nitrogen atom. The majority of the metric parameters are unexceptional. The most interesting feature is the

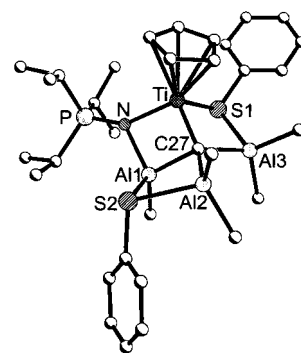


Figure 1. Molecular structure of **3**; hydrogen atoms have been omitted for clarity.

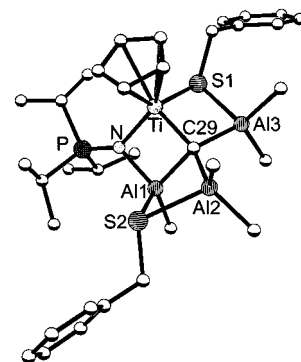
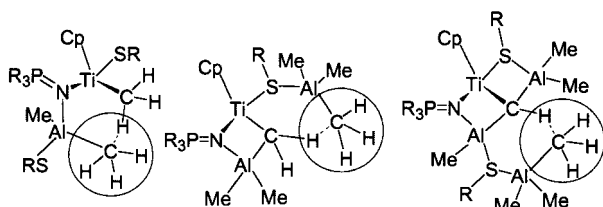


Figure 2. Molecular structure of **4**; hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Ti–C2) 1.900(3), Ti–N 2.005(2), Ti–S1 2.4588(10), Al1–N 1.883(2), Al1–C29 2.002(3), Al1–S2 2.3599(12), Al2–C29 1.991(3), Al2–S2 2.4564(13), Al3–C29 2.001(3), Al3–S1 2.4103(12), P–N 1.604(2); C29–Ti–N 92.82(10), C29–Ti–S1 93.17(8), N–Ti–S1 104.53(6), N–Al1–S2 113.31(7), C29–Al1–S2 90.20(8), C29–Al1–Ti 45.07(8), P–N–Al1 131.25(13), P–N–Ti 141.24(13), Al1–N–Ti 87.07(9), Ti–C29–Al2 141.36(14), Ti–C29–Al3 96.68(12), Al2–C29–Al3 114.10(13), Ti–C29–Al1 86.69(10), Al2–C29–Al1 94.75(11), Al3–C29–Al1 123.08(13).

geometry about the carbide carbon atom. The Ti–carbide distance in **4** is 1.900(3) Å, which is significantly shorter than the terminal Ti–CH₃ distance in [Cp(*t*Bu₃PN)TiMe{ μ -CH₃B(C₆F₅)₃}] (2.123(5) Å).^[16] This is attributed to the relative increase in the Lewis acidity of the Ti center as a result of the interaction of the S and N donors with Al. The geometry about the carbide is severely distorted tetrahedral. The Ti–C–Al2 and Al1–C–Al3 angles are 141.36(14)° and 123.08(13)°, respectively, in **4**. These distortions are consistent with the carbide being central to three fused four-membered rings, where the corresponding Ti–C–Al and Al–C–Al angles range from 86.6(7) to 97.0(6)°.

The mechanism of formation of **3** and **4** is unknown, although it is clear that there are several key steps involved. The observation of intermediate species upon addition of AlMe₃ to **1** or **2** suggests binding of the Lewis acid to the thiolate and/or phosphinimide ligands. Clearly, such adducts could lead to facile methyl-for-thiolate exchange, which is ultimately inferred by the nature of the product. Ligand-for-methyl exchange has been observed previously as in reactions of [CpTi(OAr')₂Cl] with AlMe₃.^[19] Subsequent C–H bond activating steps liberating methane are thought to result from the proximity of the ligand-bound AlMe fragments and the intermediate Ti-bound methyl group (Scheme 1).



Scheme 1. Possible geometries of intermediates affording C–H bond activation and methane elimination.

Despite the importance of alkylaluminum reagents as activators for early transition metal catalyst precursors, there is a paucity of well-defined products resulting from stoichiometric reactions of early transition metal compounds and Al reagents.^[20] Of those known, perhaps the most familiar is the Tebbe reagent, $[\text{Cp}_2\text{Ti}(\mu\text{-CH}_2)(\mu\text{-Cl})\text{AlMe}_2]$, obtained from the reaction of titanocene dichloride with AlMe_3 .^[21] Roesky et al. have described Zr–Al and Hf–Al clusters of the general formulae $[(\text{Cp}^*\text{MMe})(\mu\text{-F})_3\text{AlMe}_2]_2$ and $[(\text{Cp}^*\text{M})_3\text{Al}_6\text{Me}_8(\mu_3\text{-CH}_2)_2(\mu_4\text{-CH})_4(\mu_3\text{-CH})]$ derived from the reactions of Cp^*MF_3 with one and five equivalents of AlMe_3 , respectively ($\text{Cp}^* = \text{C}_5\text{Me}_5$).^[22, 23] Complexes **3** and **4** represent unique contributions to this class of compounds as they are rare examples in which a methyl carbon atom undergoes complete C–H bond activation.^[24] This observation infers that transient Ti–methyl, Ti–methylene, and Ti–methine fragments remain accessible and yet the steric demands of the ancillary phosphinimide preclude oligomerization.

Experimental Section

1, 2: These compounds were prepared in a similar fashion, thus only the preparation of **1** is detailed: To a solution of $[\text{Cp}(\text{iPr}_3\text{PN})\text{TiCl}_2]$ (0.250 g, 0.698 mmol) in THF (10 mL) was added solid LiSPh (0.180 g, 1.550 mmol) at room temperature. The yellow solution turned dark red within 30 min. The solution was stirred for 12 h. The solvent was removed under vacuum, and the solid extracted with benzene (3×10 mL). The volume of the solution was reduced to 5 mL. A red microcrystalline solid was formed upon addition of hexanes (20 mL). Red solid **1** was isolated by filtration and dried under vacuum (0.225 g, 0.445 mmol, 64 %).

1: ^1H NMR (C_6D_6 , 25 °C): δ = 8.04 (d, 4H, SPh), 7.13 (t, 4H, SPh), 6.97 (t, 2H, SPh), 6.16 (s, 5H, Cp), 1.50 (d of sept, $^3J_{\text{PH}} = 11.6$ Hz, 3H, PCHMe_2), 0.81 (dd, $^3J_{\text{PH}} = 15.3$ Hz, 18H, PCHMe_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 34.94; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 147.74, 133.12, 124.26, 112.01, 25.84 (d, $^1J_{\text{PC}} = 55.5$ Hz, PCHMe_2), 16.65.

2: Yield 75 %. ^1H NMR (C_6D_6 , 25 °C): δ = 7.57 (d, 4H, SCH_2Ph), 7.20 (t, 4H, SCH_2Ph), 7.06 (t, 2H, SCH_2Ph), 6.27 (s, 5H, Cp), 4.70 (AB quart, 4H, $^3J_{\text{HH}} = 13.2$ Hz, SCH_2Ph), 1.62 (d of sept, $^2J_{\text{PH}} = 11.2$ Hz, 3H, PCHMe_2), 0.91 (dd, $^3J_{\text{PH}} = 15.1$ Hz, 18H, PCHMe_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 31.55; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 144.87, 129.00, 126.10, 110.86, 43.43, 26.10 (d, $^1J_{\text{PC}} = 56.4$ Hz, PCHMe_2), 16.83.

3, 4: These compounds were prepared in a similar fashion, thus only the preparation of **3** is detailed. To a solution of **1** (0.200 g, 0.396 mmol) in hexane (10 mL) was added a solution of AlMe_3 in toluene (0.75 mL, 2.0 M, 1.500 mmol). A dark red solid precipitated over 24 h at room temperature. The solid was isolated by filtration and washed with hexane (3×15 mL). Recrystallization from benzene afforded dark red, crystalline **3** (0.220 g; 0.327 mol; 83 %).

3: ^1H NMR (C_6D_6 , 25 °C): δ = 7.58 (d, 2H, SPh), 7.55 (d, 2H, SPh), 7.05 (m, 4H, SPh), 6.95 (m, 2H, SPh), 6.18 (s, 5H, Cp), 1.80 (d of sept, $^2J_{\text{PH}} = 12.8$ Hz, 3H, PCHMe_2), 0.88 (dd, $^3J_{\text{PH}} = 13.7$ Hz, 9H, PCHMe_2), 0.85 (dd, $^3J_{\text{PH}} = 14.0$ Hz, 9H, PCHMe_2), 0.30 (s, 3H, AlMe_3), 0.17 (s, 3H, AlMe_3), 0.06 (s, 3H, AlMe_3), 0.04 (s, 3H, AlMe_3), –0.32 (s, 3H, AlMe_3); $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 54.09; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 140.02, 133.78,

132.75, 131.70, 126.49, 126.13, 111.28, 26.67 (d, $^1J_{\text{PC}} = 56.4$ Hz, PCHMe_2), 16.72, –4.43, –5.76, –7.07.

4: Yield 74 %. ^1H NMR (C_6D_6 , 25 °C): δ = 7.27 (d, 4H, SCH_2Ph), 7.13 (t, 4H, SCH_2Ph), 7.03 (t, 2H, SCH_2Ph), 6.26 (s, 5H, Cp), 3.85 (AB quart, $^2J_{\text{HH}} = 12.8$ Hz, 2H, SCH_2Ph), 3.75 (AB quart, $^2J_{\text{HH}} = 13.1$ Hz, 2H, SCH_2Ph), 1.64 (d of sept, $^2J_{\text{PH}} = 13.0$ Hz, 3H, PCHMe_2), 0.74 (dd, $^3J_{\text{PH}} = 14.8$ Hz, 9H, PCHMe_2), 0.57 (dd, $^3J_{\text{PH}} = 15.1$ Hz, 9H, PCHMe_2), 0.27 (s, 3H, AlMe_3), 0.11 (s, 3H, AlMe_3), –0.01 (s, 3H, AlMe_3), –0.07 (s, 3H, AlMe_3), –0.29 (s, 3H, AlMe_3); $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 52.87; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 25 °C): δ = 141.16, 129.02, 128.97, 127.04, 126.77, 110.123, 38.25, 32.61, 26.49 (d, $^1J_{\text{PC}} = 56.4$ Hz, PCHMe_2), 16.36 (d, $^2J_{\text{PC}} = 34.0$ Hz, PCHMe_2), 14.26, –4.75, –6.87, –7.15, –7.79.

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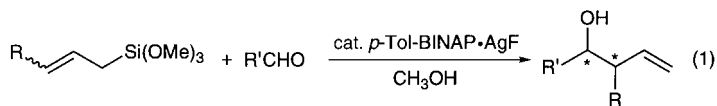
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- [18] Diffraction experiments were performed on a Siemens SMART System CCD diffractometer, and structures were solved employing the SHELX-TL software package. Crystal data for **3** ($\text{C}_{38}\text{H}_{57}\text{Al}_3\text{NP}_2\text{S}_2\text{Ti}$): $M_r = 751.8$, space group $P2_1/n$, $a = 12.100(3)$, $b = 23.018(7)$, $c = 15.648(3)$ Å, $\beta = 90.75(2)^\circ$, $V = 4357.8(19)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.146$ g cm^{–3}, $\mu = 0.414$ cm^{–1}, 3859 data, 395 parameters, GOF = 1.798, $R_1 = 0.1326$, $R_w = 0.3052$. Crystal data for **4** ($\text{C}_{34}\text{H}_{55}\text{Al}_3\text{NPS}_2\text{Ti}$): $M_r = 701.7$, space group $P2_1/n$, $a = 10.065(2)$, $b = 15.340(3)$, $c = 26.120(7)$ Å, $\beta = 93.24(2)^\circ$, $V = 4027(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.158$ g cm^{–3}, $\mu = 0.444$ cm^{–1}, 7031 data, 379 parameters, GOF = 0.884, $R_1 = 0.0406$, $R_w = 0.1158$. 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-127820 (**3**) and CCDC-127821 (**4**). 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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Enantioselective Addition of Allylic Trimethoxysilanes to Aldehydes Catalyzed by *p*-Tol-BINAP · AgF**

Akira Yanagisawa, Hiromi Kageyama, Yoshinari Nakatsuka, Kenichi Asakawa, Yukari Matsumoto, and Hisashi Yamamoto*

Allylic trialkoxysilanes are known as reactive allylic silanes since they form pentacoordinate silicates by reaction with nucleophiles.^[1] These allylic silicates are sometimes utilized for allylation of carbonyl compounds under basic conditions,^[2] but as far as we know there are no reports on asymmetric reactions of these reagents. We report here the first example of asymmetric addition of allylic trimethoxysilanes to aldehydes catalyzed by the *p*-Tol-BINAP · AgF complex [Eq. (1); BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl; *p*-Tol-BINAP = 2,2'-bis(di-*p*-tolylphosphanyl)-1,1'-binaphthyl].^[3]



We initially adopted the complex (*R*)-BINAP · AgF^[4] as a chiral catalyst for asymmetric allylation, anticipating that the fluoride ion would activate the trialkoxysilanes.^[5] In fact, treatment of benzaldehyde (1 equiv) with allyltrimethoxysilane (1 equiv) in MeOH in the presence of (*R*)-BINAP · AgF (10 mol %) at –20 °C for 4 h gave the corresponding *R*-enriched homoallylic alcohol in 72 % yield and with 91 % *ee*. In contrast, when (*R*)-BINAP · AgOTf (Tf = F₃CSO₂) was used as catalyst, the racemic homoallylic alcohol was obtained in only 5 % yield. Results of the (*R*)-BINAP · AgF-catalyzed asymmetric allylation with various solvents and optimization of the reaction conditions are listed in Table 1. Among the solvents tested, alcohols proved to be effective for the

Table 1. Enantioselective allylation of benzaldehyde with allyltrimethoxysilane and BINAP · AgF as catalyst.^[a]

Entry	Solvent	[(<i>R</i>)-BINAP] [mol %]	[AgF] [mol %]	<i>T</i> [°C]	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	MeOH	10	10	–20	72	91
2	EtOH	10	10	–20	86	82
3	<i>i</i> PrOH	10	10	–20	64	39
4	HOCH ₂ CH ₂ OH	10	10	0	33	60
5	THF ^[d]	10	10	–20	<1	–
6	CH ₃ CN	10	10	–20	5	<1
7	MeOH	10	10	–40	37	93
8	MeOH	10	10	0	75	86
9 ^[e]	MeOH	10	10	–20	77	90
10 ^[f]	MeOH	10	10	–20	82	93
11 ^[f]	MeOH	6	10	–20	92	94
12 ^[f]	MeOH	3	5	–20	84	93
13 ^[f,g]	MeOH	3	5	–20	80	94

[a] Unless otherwise noted, the reaction was carried out with (*R*)-BINAP · AgF as catalyst, allyltrimethoxysilane (1 equiv), and benzaldehyde (1 equiv) in the specified solvent at temperature *T* for 4 h. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [d] AgF did not dissolve in THF. [e] 1.2 equivalents of allyltrimethoxysilane were used. [f] 1.5 equivalents of allyltrimethoxysilane were used. [g] (*R*)-*p*-Tol-BINAP was used.

reaction, and MeOH provided the best result (entries 1–6), while no reaction occurred in THF because AgF is insoluble in this solvent (entry 5). It is noteworthy that as the alcohol becomes bulkier, the enantioselectivity gradually decreases (entries 1–3). Several reaction temperatures were examined, and allylation at –20 °C gave a satisfactory result with respect to both chemical yield and the *ee* of the product (entries 1, 7, and 8). Further improvement in the yield and enantioselectivity was achieved when 1.5 equivalents of allyltrimethoxysilane were introduced (entries 1, 9, and 10). We also attempted to decrease the amount of catalyst and found that the reaction proceeded in high yield without any loss of enantioselectivity when only 3 mol % of (*R*)-BINAP was present (entries 10–12).^[6] Employment of (*R*)-*p*-Tol-BINAP^[7] furnished *ee* values similar to those obtained with (*R*)-BINAP (compare entries 12 and 13).

Optimal conditions were established for MeOH as solvent at –20 °C, and we then employed these conditions in catalytic enantioselective addition of allyltrimethoxysilane to typical aromatic and α,β -unsaturated aldehydes (Table 2). All reac-

Table 2. Enantioselective allylations of various aldehydes with (*R*)-*p*-Tol-BINAP · AgF as catalyst.^[a]

Entry	Aldehyde	Yield ^[b] [%]	<i>ee</i> [%] ^[c] (config.)
1 ^[d]	PhCHO	80	94 (<i>R</i>)
2	(<i>E</i>)-PhCH=CHCHO	93	78 (<i>R</i>)
3	2-furyl-CHO	70	83 (<i>R</i>)
4	1-naphthyl-CHO	81	92 (<i>R</i>)
5	4-MeOC ₆ H ₄ CHO	67	93 (<i>R</i>)
6	4-BrC ₆ H ₄ CHO	90	93 ^[e]

[a] Unless otherwise specified, the reaction was carried out with allyltrimethoxysilane (1.5 equiv) and aldehyde (1 equiv) in the presence of a chiral silver(i) catalyst prepared from (*R*)-*p*-Tol-BINAP (6 mol %) and AgF (10 mol %) in MeOH at –20 °C for 4 h. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralcel OD-H or OJ, Daicel Chemical Industries, Ltd.). [d] 3 mol % of (*R*)-*p*-Tol-BINAP and 5 mol % of AgF were used. [e] The absolute configuration is unknown.

[*] Prof. Dr. H. Yamamoto, Dr. A. Yanagisawa, H. Kageyama, Y. Nakatsuka, K. Asakawa, Y. Matsumoto
 Graduate School of Engineering
 Nagoya University, CREST
 Japan Science and Technology Corporation (JST)
 Chikusa, Nagoya 464–8603 (Japan)
 Fax: (+81) 52-789-3222
 E-mail: j45988a@nucc.cc.nagoya-u.ac.jp

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tions furnished satisfactory yields in the presence of a chiral silver(I) catalyst prepared from (*R*)-*p*-Tol-BINAP (6 mol %) and AgF (10 mol %) at -20°C for 4 h;^[8] with the α,β -unsaturated aldehyde, 1,2-addition took place exclusively (entry 2).

Condensation of γ -substituted allylmetal reagents with carbonyl compounds is a fascinating problem with regard to regioselectivity (α/γ) and stereoselectivity (*E/Z* or *anti/syn*).^[3a-e, 9, 10] We examined the BINAP·AgF-catalyzed reaction of (*E*)- and (*Z*)-crotyltrimethoxysilane [Eq. (2)]. Addition of *E*-enriched crotyltrimethoxysilane (*E/Z* = 83/17) to

96% *ee*); 2) remarkable γ and *anti* selectivities are observed for the reaction with crotylsilanes, irrespective of the configuration at the double bond; 3) the allylation can be performed exclusively by using commercially available chemicals; 4) environmentally friendlier MeOH is used as a solvent; 5) low reaction temperatures (e.g., -78°C or lower) are not required. Hence, this catalytic procedure should be broadly applicable in organic synthesis.

Experimental Section

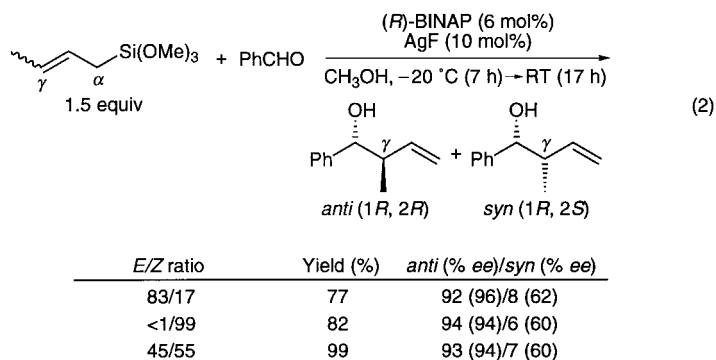
Typical procedure for asymmetric allylation of aldehydes with allylic trimethoxysilanes with (*R*)-*p*-Tol-BINAP·AgF as catalyst: Synthesis of (*R*)-1-phenyl-3-buten-1-ol (in Table 1, entry 13; Table 2, entry 1): A mixture of AgF (13.0 mg, 0.102 mmol) and (*R*)-*p*-Tol-BINAP (40.9 mg, 0.0603 mmol) was dissolved in dry MeOH (12 mL) under argon atmosphere with exclusion of direct light, and the reaction mixture stirred at 20°C for 10 min. To the resulting solution were added dropwise benzaldehyde (200 μL , 1.97 mmol) and allyltrimethoxysilane (500 μL , 2.97 mmol) successively at -20°C . The mixture was stirred for 4 h at this temperature and treated with a mixture of 1 N HCl (10 mL) and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting precipitate was filtered off by a glass filter funnel filled with Celite and silica gel. The filtrate was dried over Na_2SO_4 and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel with ethyl acetate/hexane (1/15 $\rightarrow$ 1/3) as eluant to afford the homoallylic alcohol (232.9 mg, 80% yield) as a colorless oil. The enantioselectivity was determined to be 94% *ee* by HPLC analysis on a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd., hexane/*i*PrOH 40/1, flow rate 0.5 mL min⁻¹): $t_{\text{major}} = 25.6$ min (*R*), $t_{\text{minor}} = 29.8$ min (*S*); ¹³C NMR (75 MHz, CDCl_3): $\delta = 43.5, 73.2, 117.8, 125.7$ (2C), 127.2, 128.1 (2C), 134.3, 143.8; $[\alpha]_D^{25} = +47.6$ ($c = 1.0$, benzene); elemental analysis calcd for $\text{C}_{10}\text{H}_{12}\text{O}$: C 81.04, H 8.16; found: C 81.02, H 8.25. Other physical and spectroscopic data (TLC, IR, and ¹H NMR) were identical with those in the literature.^[3k, 4, 12] Other homoallylic alcohols (Table 2, entries 2–6) were prepared and purified according to similar procedures. The absolute configurations of these compounds were determined by comparison of the $[\alpha]_D$ values with published data.

(*R*)-(*E*)-1-Phenyl-1,5-hexadien-3-ol (Table 2, entry 2): ¹³C NMR (75 MHz, CDCl_3): $\delta = 41.9, 71.7, 118.4, 126.4$ (2C), 127.6, 128.5 (2C), 130.3, 131.5, 134.0, 136.6; $[\alpha]_D^{25} = -12.6$ ($c = 1.0$, Et_2O); elemental analysis calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: C 82.72, H 8.10; found: C 82.63, H 8.35. Other physical and spectroscopic data (TLC, IR, and ¹H NMR) were identical with those in the literature.^[3k, 4, 12] The enantioselectivity was determined to be 78% *ee* by HPLC analysis on a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd., hexane/*i*PrOH 20/1, flow rate 0.5 mL min⁻¹): $t_{\text{major}} = 14.3$ min (*R*), $t_{\text{minor}} = 26.4$ min (*S*).

(*R*)-1-(2-Furyl)-3-buten-1-ol (Table 2, entry 3): ¹³C NMR (75 MHz, CDCl_3): $\delta = 40.0, 66.8, 106.0, 110.0, 118.4, 133.6, 141.9, 155.9$; $[\alpha]_D^{25} = +24.9$ ($c = 1.0$, CHCl_3); elemental analysis calcd for $\text{C}_9\text{H}_{10}\text{O}_2$: C 69.54, H 7.30; found: C 69.37, H 7.62. Other physical and spectroscopic data (TLC, IR, and ¹H NMR) were identical with those in the literature.^[4, 13] The enantioselectivity was determined to be 83% *ee* by HPLC analysis on a chiral column (Chiralcel OJ, Daicel Chemical Industries, Ltd., hexane/*i*PrOH 40/1, flow rate 0.5 mL min⁻¹): $t_{\text{minor}} = 33.5$ min (*S*), $t_{\text{major}} = 36.4$ min (*R*).

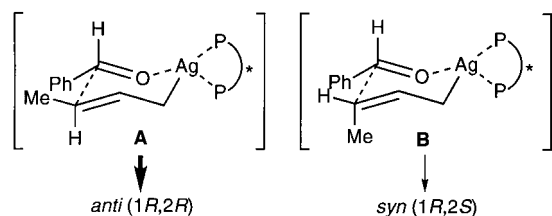
(*R*)-1-(1-Naphthyl)-3-buten-1-ol (Table 2, entry 4): IR (neat): $\tilde{\nu} = 3650 - 3120, 3071, 2979, 2940, 2908, 1640, 1597, 1510, 1433, 1395, 1167, 1055, 916, 801, 777$ cm⁻¹; ¹³C NMR (75 MHz, CDCl_3): $\delta = 42.7, 69.8, 118.0, 122.7, 122.9, 125.3$ (2C), 125.9, 127.8, 128.8, 130.1, 133.6, 134.7, 139.4; $[\alpha]_D^{25} = +97.3$ ($c = 1.0$, benzene); elemental analysis calcd for $\text{C}_{14}\text{H}_{14}\text{O}$: C 84.81, H 7.12; found: C 84.71, H 7.31. Other physical and spectroscopic data (TLC and ¹H NMR) were identical with those in the literature.^[4, 14] The enantioselectivity was determined to be 92% *ee* by HPLC analysis on a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd., hexane/*i*PrOH 9/1, flow rate 1.0 mL min⁻¹): $t_{\text{minor}} = 7.8$ min (*S*), $t_{\text{major}} = 12.8$ min (*R*).

(*R*)-1-(*p*-Methoxyphenyl)-3-buten-1-ol (Table 2, entry 5): ¹³C NMR (75 MHz, CDCl_3): $\delta = 43.7, 55.2, 72.9, 113.7$ (2C), 118.1, 127.0 (2C), 134.6,



benzaldehyde in the presence of (*R*)-BINAP·AgF in MeOH at -20 to 25°C afforded exclusively the γ adduct with an *anti/syn* ratio of 92/8. The *anti* isomer had 96% *ee* and the 1*R*,2*R* configuration. Employment of (*Z*)-crotyltrimethoxysilane (*E/Z* < 1/99) or an almost 1/1 mixture of (*E*)- and (*Z*)-crotyltrimethoxysilane gave similar results.

The reason why high *anti* selectivity is obtained regardless of the configuration of the crotylsilane is not clear. The (*R*)-BINAP·AgF-catalyzed reaction is believed to proceed via a six-membered cyclic transition state **A** or **B** (Scheme 1) with a



Scheme 1. Probable cyclic transition-state structures.

BINAP-coordinated silver atom on the basis of NMR spectroscopic results. When crotyltrimethoxysilane was treated with a 1/1 mixture of (*R*)-BINAP·AgF and DMF in CH_3OD at room temperature, no peaks of the crotylsilane were observed in the ¹³C NMR spectra.^[11] This result implies the occurrence of transmetalation to give a crotylsilver species, and if the subsequent isomerization of the (*Z*)-crotylsilver moiety to the *E* isomer takes place more rapidly than the reaction with aldehyde, the *anti*-homoallylic alcohol can be obtained as a major product both from the (*E*)- and (*Z*)-crotylsilanes via the cyclic transition state **A**.

The main features of our new reaction are as follows: 1) the procedure is straightforward and can provide various optically active homoallylic alcohols with high enantioselectivity (up to

136.0, 158.9; $[\alpha]_D^{25} = +41.1$ ($c = 1.0$, benzene); elemental analysis calcd for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found: C 74.13, H 8.07. Other physical and spectroscopic data (TLC, IR, and ^1H NMR) were identical with those in the literature.^[3k, 4, 14b] The enantioselectivity was determined to be 93% *ee* by HPLC analysis on a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd., hexane/*i*PrOH 20/1, flow rate 1.0 mL min⁻¹): $t_{major} = 10.1$ min (*R*), $t_{minor} = 11.8$ min (*S*).

1-(*p*-Bromophenyl)-3-buten-1-ol (Table 2, entry 6): ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.6, 72.5, 118.6, 121.1, 127.5$ (2C), 131.3 (2C), 133.9, 142.7; $[\alpha]_D^{25} = +47.0$ ($c = 1.0$, benzene); elemental analysis calcd for $C_{10}H_{11}OBr$: C 52.89, H 4.88; found: C 52.90, H 5.12. Other physical and spectroscopic data (TLC, IR, and ^1H NMR) were identical with those in the literature.^[4, 15] The enantioselectivity was determined to be 93% *ee* by HPLC analysis on a chiral column (Chiralcel OJ, Daicel Chemical Industries, Ltd., hexane/*i*PrOH 9/1, flow rate 0.5 mL min⁻¹): $t_{minor} = 16.0$ min, $t_{major} = 17.3$ min. The absolute configuration is unknown.

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Membrane Anchoring and Intervesicle Transfer of a Derivative of the Antibiotic Moenomycin A**

Alexej Anikin, Andrij Buchynskyy, Uwe Kempin, Katka Stembera, Peter Welzel,* and Gabriela Lantzsch*

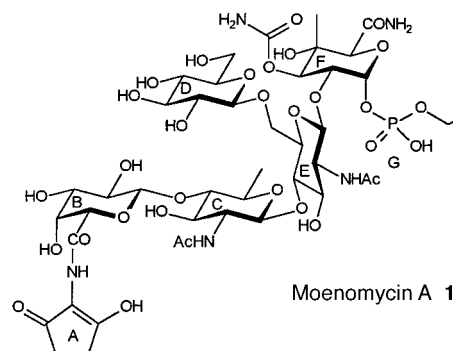
The glycopeptide antibiotics, which have vancomycin as a prominent example, are of increasing importance in the treatment of bacterial infections because of the problem of resistance.^[1] They function by binding (as dimers or using a

[*] Prof. Dr. P. Welzel, Dr. A. Anikin, Dipl.-Chem. A. Buchynskyy, Dr. U. Kempin, Dipl.-Biochem. K. Stembera
Institut für Organische Chemie der Universität
Talstrasse 25, D-04103 Leipzig (Germany)
Fax: (+49) 341-973-6599
E-mail: welzel@organik.orgchem.uni-leipzig.de

Dr. G. Lantzsch
Institut für Experimentelle Physik I der Universität
Vor dem Hospitltore 1, D-04103 Leipzig (Germany)
Fax: (+49) 341-973-2599
E-mail: lantzsch@rz.uni-leipzig.de

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membrane anchor) to the membrane-anchored peptidoglycan precursors terminating in D-Ala–D-Ala and thus prevent transglycosylation (and/or transpeptidation^[2]) in the final phase of peptidoglycan biosynthesis of the bacterial cell wall. There is another class of compounds that interfere with the transglycosylation reaction, namely the moenomycins (for example, moenomycin A (**1**)). However, their mode of action



is completely different. They have been shown to bind reversibly to the enzyme and thus inhibit growing of the peptidoglycan polysaccharide strands.^[3] The moenomycins are, therefore, unique tools for elucidating the structure of the enzyme and the detailed mechanism of the transglycosylation reaction.

The structure–activity relationships of the moenomycins have been studied extensively^[4] and a mechanism of their mode of action has been proposed.^[5] It is assumed that they compete with the substrate(s) of the transglycosylation reaction for a binding site at the enzyme, most probably for the binding site of the growing peptidoglycan chain (the glycosyl donor).^[5] The oligosaccharide part of the moenomycin-type transglycosylase inhibitors is recognized with high selectivity by the enzyme.^[4] However, there is another prerequisite for antibiotic activity: membrane anchoring of the antibiotic through its lipid part. Thus, removal of the C₂₅ lipid from moenomycin^[6] or introduction of one or several OH groups into the lipid chain^[7] causes complete loss of antibiotic activity.

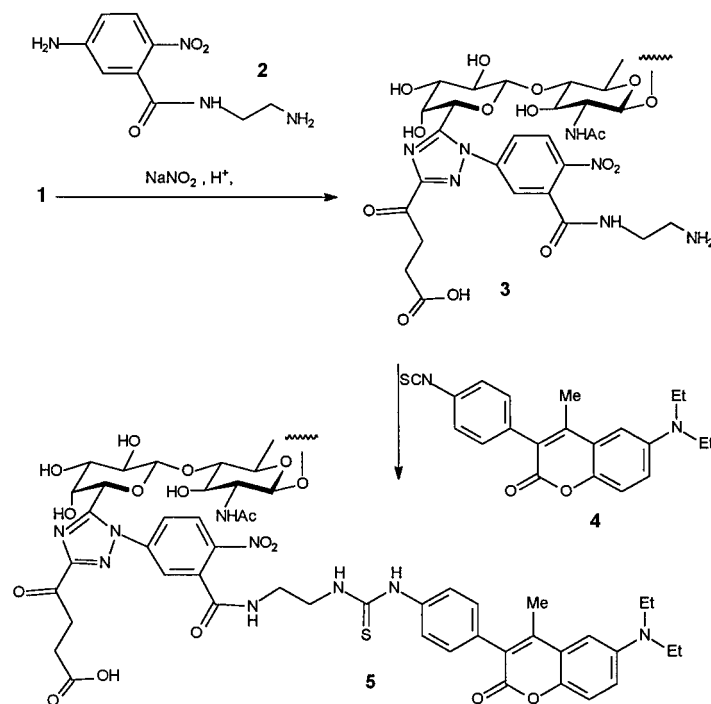
Whereas the structure–activity relationships in the oligosaccharide part of the moenomycins are fairly well understood the role of the lipid moiety has remained elusive. Attempts to study the interaction of the lipid part of moenomycin with artificial membranes (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) vesicles) by isothermal titration calorimetry at concentrations in the range of the minimal inhibitory concentration (MIC, see below) failed since the method was not sensitive enough.^[8]

We describe herein successful experiments that allowed the quantitation of the interaction of moenomycin with artificial membranes by means of fluorescence methods. These experiments give information for the first time on the extent of the anchoring of moenomycin to membranes, as expressed by a partition coefficient, and of the transfer of moenomycin from one vesicle to another, as expressed by a rate constant. The former information is important for developing an understanding of the contribution of moenomycin membrane anchoring for the interaction with the enzyme (and to its

antibiotic activity). The latter is important in the context of pharmacokinetics, since unfavorable transport properties of the moenomycins have until now precluded their use in human medicine.

Units C and E–I of **1** are indispensable for antibiotic activity.^[4] We wanted, therefore, to attach the fluorescent label to unit A. A sequence of a) reaction of the enolized β -diketone unit of moenomycin A with the diazonium salt obtained from **2**, b) Japp–Klingemann ring cleavage of the thus formed azo com-

pound, and c) triazol formation of the intermediate amidrazone was used to prepare compound **3** (Scheme 1).^[9] Most notably, **2** could be selectively converted into the aromatic diazonium salt since the aliphatic amino group was protected by protonation under the conditions of diazonium salt formation. Compound **3** was then coupled to the 7-diethylamino-4-methylcoumarin chromophore by reaction with isothiocyanate **4**^[10] to provide thiourea **5**. The compound was purified by careful chromatographic separations and was characterized by electrospray ion cyclotron resonance mass spectrometry (ESI-ICR-MS) and by its fluorescence spectra (λ_{ex} : 396 nm, λ_{em} : 477 nm,^[11] in methanol). The MIC values against seven different *Staphylococcus aureus* strains were determined by a microdilution method on microtiter plates. Under these conditions moenomycin A turned out to be more active by a factor of 10 (MIC in the range of $6.9 \times 10^{-9} \text{ mol L}^{-1}$) than previously assumed.^[4] A MIC of $1.7 \times 10^{-7} \text{ mol L}^{-1}$ was determined for **3** and $1.2 \times 10^{-6} \text{ mol L}^{-1}$ for **5**. The reason for the difference in antibiotic activity is not understood at present, but both **3** and **5** appear to be well suited for future binding studies with the enzyme (work is in progress).



Scheme 1. Synthesis of **5**.

Moenomycin A is known to form micelles in aqueous solution above a definite concentration (the critical micelle concentration, cmc). The cmc has been shown to depend on the pH and the ion strength (about $5 \times 10^{-4} \text{ mol L}^{-1}$ at pH 6.8).^[12] At concentrations of $50\text{--}200 \times 10^{-9} \text{ mol L}^{-1}$ the coumarin-labeled moenomycin derivative **5** gave clear dispersions in water, which indicates the existence of monomers and/or micelles. The fluorescence intensity increased to a new stable value upon addition of unilamellar POPC vesicles to the aqueous dispersion of **5** (Figure 1). This effect reflects the

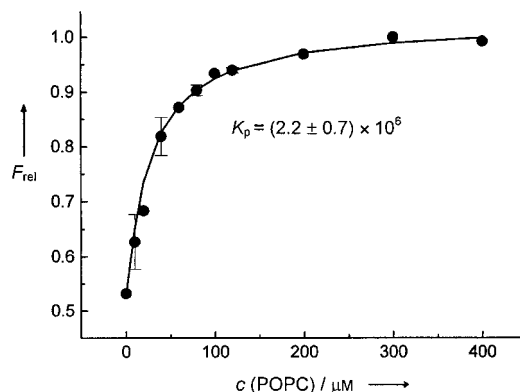


Figure 1. Fluorescence intensity of **5** as a function of the lipid concentration. The experimental data represent the average of three measurements with different concentrations of **5** (50, 100, and 200 nM).

insertion of **5** into the vesicles. The partition coefficient K_p was obtained from the dependence of the fluorescence intensity on the POPC concentration and K_p is defined as X^m/X^w , where X^m and X^w are the molar fractions of **5** incorporated into the membranes and in the water phase, respectively. The current fluorescence intensity is then described by Equation (1). The

$$F = (K_p F_\infty + W F_0 / C_L) / (W / C_L + K_p) \quad (1)$$

fluorescence intensities F_0 and F_∞ are the fluorescence intensities if all molecules of **5** are dissolved in water and incorporated into the membrane, respectively. W is the concentration of water (55 mol L^{-1}) and C_L is the lipid concentration in the sample. Using this formalism K_p was determined to be $(2.2 \pm 0.7) \times 10^6$ (see Figure 1).

The transfer of **5** between POPC vesicles has been investigated by fluorescence resonance energy transfer (FRET), a powerful tool for studying interbilayer transfer of membrane-anchored molecules. An especially useful donor/acceptor pair has been described by Silvius et al. who reported that the fluorescence of 7-diethylamino-4-methylcoumarin (see above) is efficiently quenched by the (4-dimethylamino)azobenzene chromophore (DABS, λ_{abs} : 447 nm).^[11] For this investigation we used **5** and the DABS-labeled phospholipid **6**, which was prepared essentially as published by Silvius et al.^[11] Figure 2 illustrates the results of quenching experiments. POPC vesicles containing different amounts of the quencher lipid **6** were asymmetrically loaded with appropriate amounts of donor **5**. The fluorescence intensity of **5** decreases as increasing molar percentages of **6** are incorporated in the vesicles. When compared with the results reported by Silvius et al. it is clear that a somewhat higher percentage of **6**

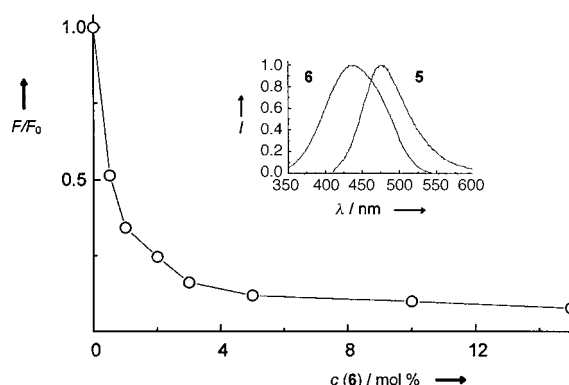
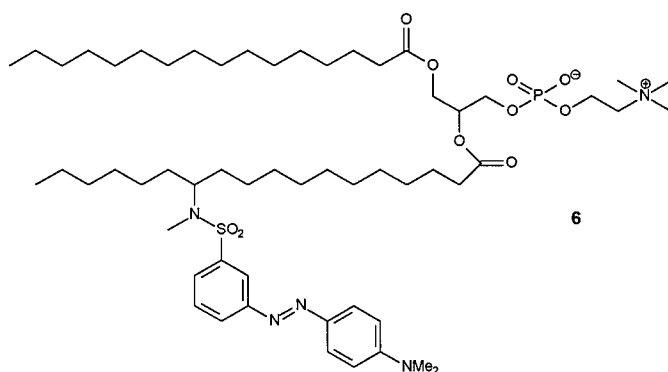


Figure 2. Quenching of the coumarin fluorescence of **5** incorporated into POPC vesicles for increasing concentrations of **6**. The inset shows the overlap of the absorption spectrum of **6** with the fluorescence spectrum of **5**.

(0.57 mol %) is needed to achieve the half-maximal energy transfer. This is most probably a consequence of differences in the location of the donor group in the two systems. The interbilayer transfer experiments were performed as indicated in Figure 3. Addition of POPC vesicles to vesicles containing donor **5** and acceptor lipid **6** resulted in an increase of



fluorescence intensity (see Figure 4), whereas the mixing of vesicles loaded with the donor with vesicles containing only the acceptor led to a decrease in the fluorescence intensity. The opposite effects observed in the two approaches demonstrates the intervesicle transfer of **5**. In the first case the number of quenched donor molecules diminishes on transfer

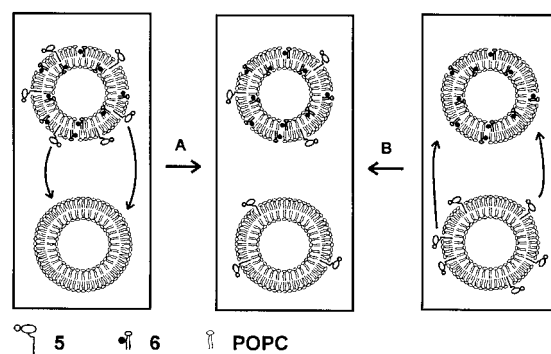


Figure 3. Principle of the interbilayer transfer experiments. A) "Empty" vesicles are added to donor- and acceptor-labeled vesicles, and B) donor-labeled vesicles are added to acceptor-labeled vesicles.

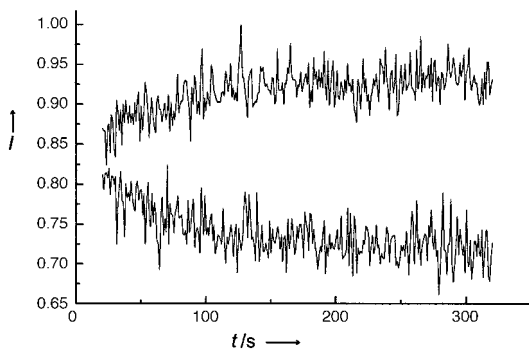


Figure 4. Plot of the fluorescence intensity for the two interbilayer transfer experiments A and B (see Figure 3).

into the acceptor-free vesicles, while in the second case it increases as they transfer into the acceptor-filled vesicle. The fraction of transferred molecules of **5**, $X = n_D/(n_D + n_{DQ})$, can be estimated from Equation (2), where n_D , n_{DQ} , and F_{TX} denote the number of donor molecules not quenched and

$$X = (F_{\infty} - F_0)/(F_{TX} - F_0) \quad (2)$$

quenched and the fluorescence intensity after addition of Triton X-100 (1%), respectively. Three experiments using different amounts of acceptor lipid **6** (0.5, 1, and 2%) yielded $X = 0.4-0.5$, which is reasonable for mixing equal amounts of lipid.

The transfer of **5** is a fast process and $t_{1/2}$ can be roughly estimated to be in the range of seconds (see Figure 4). Subsequent stopped-flow experiments (Figure 5) yielded

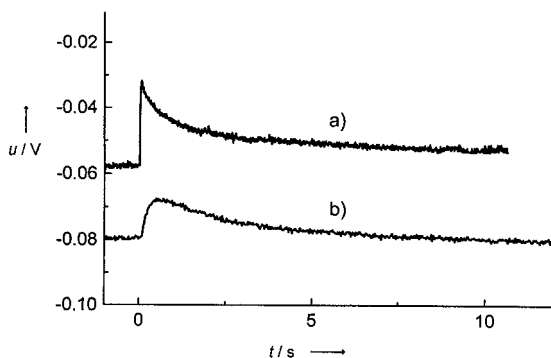


Figure 5. Plot of the voltage in the stopped-flow experiments a) upon addition of POPC vesicles to an aqueous solution of **5** (insertion) and b) on mixing of vesicles labeled with **5** and **6** with "empty" vesicles (transfer). A decrease in the voltage indicates an increase in the fluorescence.

$k_t = 0.25 \pm 0.05 \text{ s}^{-1}$ from Equation (3), which is obtained by integration of Equation (4). V_0 and V_{∞} are the read voltages

$$V(t) = -k_t |V_0 - V_{\infty}| t \quad (3)$$

$$k_t = [(dV(t)/dt)_{t=0}]/(V_{\infty} - V_0) \quad (4)$$

(inversely proportional to the fluorescence intensity) immediately after combining the POPC vesicles and the aqueous solutions of **5** in the cell and after equilibration, respectively.

The initial rate constant $k_t = 0.25 \text{ s}^{-1} = 15 \text{ min}^{-1}$ is comparable to values found for short chain phospholipid conjugates (C_{11} or C_{12} unbranched alkyl chains).^[13]

The insertion of **5** into the lipid vesicles was also observed by stopped flow experiments. The initial rate of this process, $k_i = 0.8 \text{ s}^{-1}$, was found to be comparable to the intervesicle transfer rate.

In conclusion, we have set up an experimental system that has allowed the investigation of the interaction of moenomycin-type compounds with artificial membranes for the first time. These results can be used in competition experiments to study new moenomycin analogues and, thus, are expected to form the basis for the rational design of transglycosylase inhibitors with improved transport properties. Work along these lines is in progress.

Experimental Section

3 was prepared essentially as described for a thiol analogue.^[9] It was purified by ultrafiltration (Amicon INC, YM3) and the subsequent chromatographic purifications: a) flash chromatography (FC; silica gel, 1-propanol/2 mol L⁻¹ ammonia 7/3), b) medium pressure chromatography (MPLC; RP₁₈, methanol/water 1/1). The yield was 38%. The ¹³C NMR spectrum was fully in accord with the structure. $C_{78}H_{117}N_{10}O_{37}P$ (1817.80, 1817.73), FAB-MS (matrix: nitrobenzyl alcohol): m/z 1817.3 ($[M+H]^+$), 1839.6 ($[M+Na]^+$).

5 was prepared by reaction of **3** with **4** in a pyridine/DMF (1/10) solution at 20°C. After 48 h the solvents were evaporated and the residue purified by chromatography a) FC (silica gel, chloroform/methanol 20/12 → chloroform/methanol/water 20/12/2, 2 ×), b) MPLC (RP₁₈, acetonitrile/water 1/1, 3 ×). The yield was 25%. $C_{99}H_{137}N_{12}O_{39}PS$ (2182.26, 2180.86), ESI-ICR-MS: m/z : 2181.8685 ($[M+H]^+$, calcd: 2181.8642), 2203.7990 ($[M+Na]^+$, calcd: 2203.8462).

MIC values were determined by a serial twofold microdilution method (Iso-Sensitest medium, Oxoid). A series of decreasing concentrations of the compound under investigation was prepared in the medium. For inoculations $1 \times 10^5 \text{ cfu mL}^{-1}$ were used. The MICs were determined (absence of visible turbidity) after 24 h at 37°C.

Unilamellar POPC vesicles containing **6** and loaded with **5** (1.5 mL of 300 μM) were mixed with an equal volume of an equal amount of empty POPC vesicles by stirring. In an analogous series of experiments vesicles with only **6** were mixed with vesicles loaded with **5**. The probe content of the samples was determined by the fluorescence intensity in the presence of 1% Triton X-100, which eliminates the energy transfer. All fluorescence values were corrected for the background using the appropriate blank values as well as for inner filter effects using fluorescence values determined in the presence of Triton X-100. The influence of Triton X-100 on the quantum yield of **5** was also accounted for. All measurements were carried out at room temperature on a CD900 spectrofluorometer (Edinburgh Instruments) using 1 nm slits for excitation and 1.5 nm for emission monochromators. The stopped-flow-instrument Hi-Tech Scientific SF51 was used for fast kinetic measurements.

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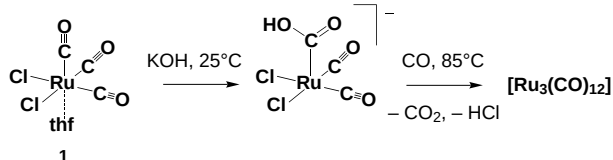
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Novel Polymeric Carbonylhaloruthenium(II) Polyanions: Rational Design and Self-Reorganization in the Presence of CO₂ and H₂O**

Luc Maurette, Bruno Donnadieu, and Guy Lavigne*

Dedicated to Professor René Poilblanc
on the occasion of his 65th birthday

We recently reported that Ru^{II} is readily reduced to Ru⁰ by simple treatment of [Ru(CO)₃Cl₂(thf)] (**1**) with KOH followed by thermally induced decarboxylation of the incipient hydroxy-carbonyl adduct at 85 °C under CO (1 atm) to produce [Ru₃(CO)₁₂] (Scheme 1).^[1] The reaction is understood in terms of a reductive elimination of HCl^[2,3] from an



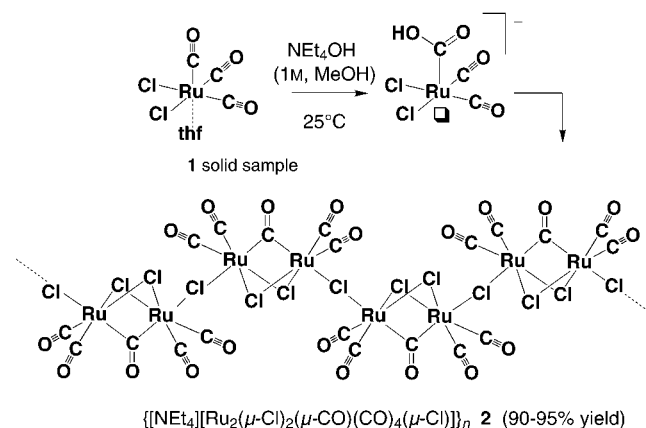
Scheme 1. Reaction of **1** with KOH.

[*] Dr. G. Lavigne, Dipl.-Chem. L. Maurette, Dr. B. Donnadieu
Laboratoire de Chimie de Coordination du CNRS
205 route de Narbonne, F-31077 Toulouse, Cedex 4 (France)
Fax: (+33) 5-61-55-30-03
E-mail: lavigne@lcc-toulouse.fr

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unstable “acid”^[4] hydrido intermediate. Though elusive, the latter is prone to insertion reactions in the presence of olefins or alkynes.^[1,5,6] Upon simply replacing KOH by [NEt₄][OH] with the aim to obtain highly concentrated solutions of the hydroxy-carbonyl adduct for a ¹³C NMR investigation, we were surprised to observe that CO₂ evolution was becoming significant at room temperature, and occurred at rates apparently depending both on the nature of the counterion and the concentration.

Typically, when one equivalent of a concentrated methanolic solution of [NEt₄][OH] (1 mL, 1.5 M) was added to a solid sample of **1** (500 mg, 1.5 mmol) at 25 °C, rapid dissolution of the complex was observed within seconds along with gas evolution (strong ν(CO₂) IR absorption at 2338 cm⁻¹) and development of an intense red color. This was rapidly followed by nearly quantitative precipitation of a red-orange microcrystalline product. High-quality homogeneous single crystals of this product were obtained from slightly modified experiments where **1** was dissolved in a minimum amount of ethanol or methanol (1–2 mL) prior to the addition of the hydroxide. This complex, recovered in 90–95 % yield, was formulated as **2** (Scheme 2) on the basis of an X-ray structure analysis revealing its polymeric nature (Figure 1).^[7]



Scheme 2. Synthesis of the polymeric polyanion **2**. The square represents a vacant coordination site.

The structure of **2** is based on the discrete association of identical monoanionic dimeric units. The basic motive is a face-sharing bioctahedron in which two ruthenium centers are connected through two bridging halides and one bridging carbonyl group. Each ruthenium atom bears two terminal carbonyl groups in a *fac* arrangement with the bridging one. The third halide (*trans* to the bridging CO) serves as a symmetric bridge between neighboring units of the polymeric chain. Though the metal–metal separation within the dimer is 2.964(1) Å, an electron count reveals that, formally, there is no metal–metal bond.

Complex **2** appears to be the first representative of the family of binary halo-carbonyl Ru^I species. Indeed, the relevant edge double-bridged Ru^I prototype [Ru₂X₂(CO)₆] recently identified by Fachinetti, Funaioli et al.^[8] for X = trifluoroacetate, is still unknown for X = halide,^[9] though a number of phosphane-substituted derivatives have been prepared from other precursors.^[10,11]

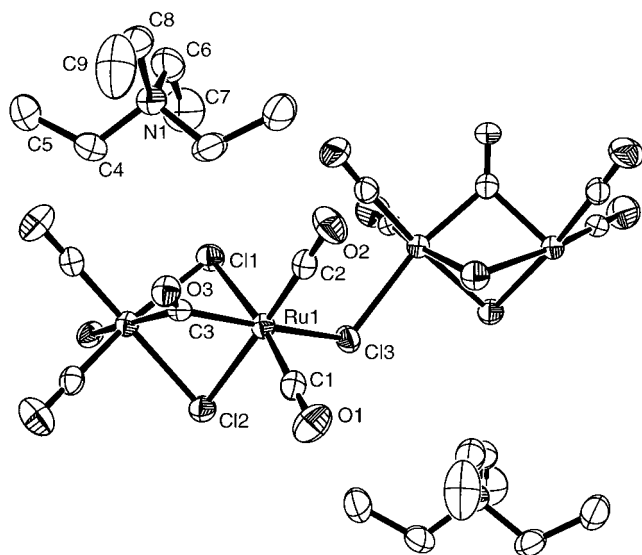
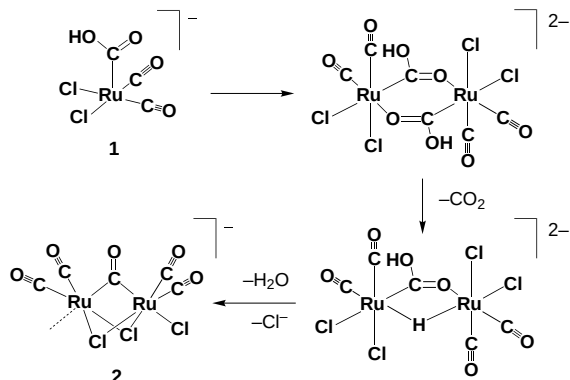


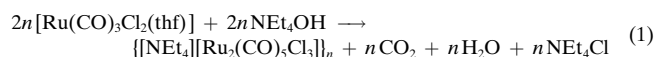
Figure 1. Perspective view of two consecutive units of the polymeric polyanion **2**. Selected interatomic distances [Å] and angles [°]: Ru1–Ru1* 2.964(1), Ru1–C1 1.842(6), Ru1–C2 1.838(6), Ru1–C3 2.031(6), Ru1–Cl1 2.499(2), Ru1–Cl2 2.489(2), Ru1–Cl3 2.614(2); Ru1–Cl3–Ru1* 113.24(8), Cl1–Ru1–Cl2 84.81(6), Cl1–Ru1–Cl3 88.64(6), Cl2–Ru1–Cl3 87.30(4), C1–Ru1–C2 87.9(2), C1–Ru1–C3 93.5(3), C2–Ru1–C3 90.7(2).

Why do we get Ru^I here? Indeed, reductive elimination of HCl from a Ru^I precursor should normally give Ru⁰, as previously observed^[1] when the decarboxylation of K[Ru{C(O)OH}Cl₂(CO)₂] is thermally induced under CO atmosphere (Scheme 1). We propose that both the high concentration and the absence of a strongly coordinating solvent favor intermolecular association of the incipient unsaturated mononuclear hydroxy-carbonyl adduct as a dimer involving either bridging hydroxy-carbonyl groups^[12] or bridging halides (Scheme 3).

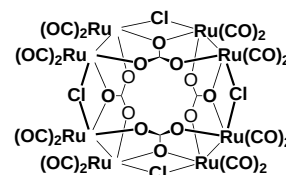
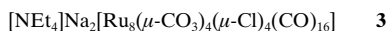


Scheme 3. Proposed mechanism for the formation of **2**.

At room temperature, the molecule loses only one CO₂ per dimeric unit to form a transient bimetallic hydrido-hydroxy-carbonyl complex. Intramolecular neutralization between the “acid” hydride and the OH[−] of the remaining hydroxy-carbonyl group will lead directly to the unsaturated building block of the polymer [Eq. (1)].



On several occasions, beautiful yellow crystals of a minor species exhibiting an IR absorption at 1532 cm^{−1} were obtained from the filtrate of the reaction in Equation (1) after a few days. Their electrospray mass spectrum revealed a puzzling pattern, consisting of three multiplets at high *m/z*, namely, 1816.3, 1757.4, and 1651.1. A single-crystal X-ray analysis provided the clue to this phenomenon (see the Experimental Section) and allowed unambiguous formulation of the compound as the tetraanionic cluster **3** containing carbonate ligands (Scheme 4, Figure 2).^[7b, 13]



Scheme 4. The tetraanionic unit of the carbonate cluster **3**.

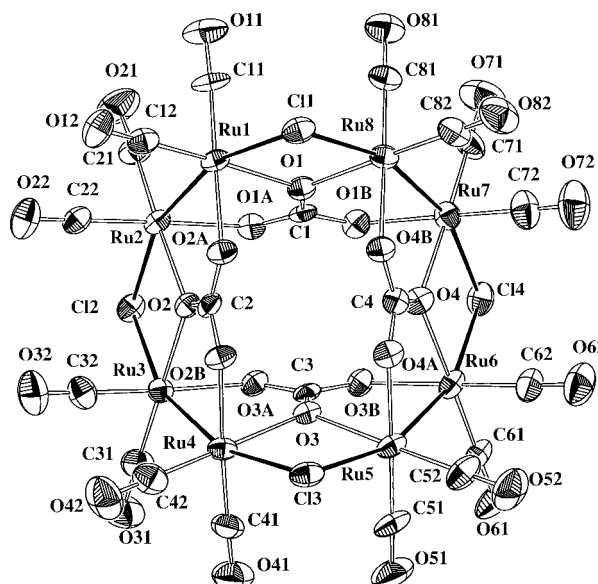


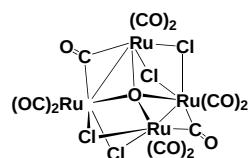
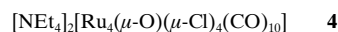
Figure 2. Perspective view of one of the two identical independent tetraanionic units of the carbonate cluster complex **3**. Selected interatomic distances [Å]: Ru1–Ru2 2.648(1), Ru3–Ru4 2.645(1), Ru5–Ru6 2.637(1), Ru7–Ru8 2.639(1), Ru1–O1 2.138(5), Ru8–O1 2.130(5), Ru1–Cl1 2.552(2), Ru8–Cl1 2.526(2), Ru1–O2A 2.108(5), Ru8–O4B 2.120(5), Cl1–O1 1.32(1), Cl1–O1A 1.26(1), Cl1–O1B 1.262(9), Ru1–Cl1 1.811(8), Ru1–Cl2 1.804(9), C11–O11 1.16(1), C12–O12 1.16(1).

The tetraanionic ensemble is based on the fusion of four identical metal–metal-bonded dimeric units “Ru₂(CO)₄” assembled together into a ring by four bridging halides and four bridging carbonate moieties. The carbonate groups are the principal building blocks responsible for the observed annulation: Each one holds two consecutive Ru dimers by acting 1) as a bridging ligand connecting these dimers through a μ₂-oxygen atom spanning the same open Ru···Ru edge as the μ-halide, and 2) as a doubly chelating ligand supporting the two Ru–Ru-bonded edges. Though carbonate ligands are rarely seen in ruthenium carbonyl complexes, there is some precedent with other metals.^[14] A close examination of the

packing^[7b] reveals that the sodium cations are located on both sides of the crown, along its virtual fourfold symmetry axis, and in close contact with the carbonate oxygen atoms.

Let us confess that the source of sodium ions in the original preparation giving the first crystals of **3** was incidental: We believe they came from our glassware which had been cleaned by immersion into an ethanolic NaOH bath and might have been insufficiently rinsed. It is amazing that such traces of sodium ions were selectively removed from the solution by the multiply charged anion just acting as a crown ether.

Of course, the carbonate ligand originates from the reaction products, namely, CO₂ and H₂O. Evidence for this dual origin could be obtained by simple modifications of the experimental conditions: First, when the released CO₂ was evacuated under reduced pressure, the minor product obtained in addition to **2** was no longer **3**, but the known oxo species **4** (Scheme 5),^[15, 16] the oxygen atom of which comes from the water released in the reaction [see Eq. (1)]. The oxo compound even became the major product when more water was added. Second, we found that improved yields of **3** can be obtained when the reaction is carried out in the presence of NaHCO₃ (see the Experimental Section).



Scheme 5. The dianionic unit of the oxo cluster **4**.

Thus, the addition of [NEt₄][OH] to **1** at 25 °C in concentrated solution appears to be a simple, rapid, and mild procedure to generate unsaturated ruthenium carbonyl halide fragments in a low oxidation state. Such fragments are prone to either polymerization in the absence of donor ligand or capturing any potentially coordinating molecule (including those produced in situ, as observed here). Consequently, we should be able to quench the polymerization process by any incoming donor ligand.^[17] Effectively, if we saturate the solution and the atmosphere of the Schlenk flask with CO prior to the addition of [NEt₄][OH] to **1** at 25 °C, we do not generate the polymer **2**. Instead, a 1/1 mixture of [Ru₃(CO)₁₂] and [NEt₄][Ru(CO)₃Cl₃] is recovered after a few hours. A glance at the basic unit of **2** allows an understanding of this phenomenon: The relative oxidation states of the two metal centers within the dimeric unit depend formally on how the bridging halides share their three electrons. Thus, the Ru^I–Ru^I dimer can be alternatively viewed as a Ru⁰–Ru^{II} dimer in which we can even visualize the preformed ligand environment of the Ru^{II} center, “[Ru(CO)₃Cl₃][–]”. Disruption of the chain by CO leads to a net differentiation between Ru⁰ and Ru^{II} centers.

The present observation is reminiscent of the CO-induced disproportionation of [Ru₂X₂(CO)₆] (X = CF₃COO) in the presence of an excess of X[–].^[8] Our concordant findings, probably generalizable to a range of other anionic nucleo-

philes, demonstrate the ability of halides or pseudohalides to mediate an interplay between low oxidation states of ruthenium, with possible relevance for their role as promoters in many catalytic systems.^[6, 18]

We have recently observed that treatment of **1** with [NEt₄][OH] at 25 °C in the presence of various unsaturated incoming substrates (e.g., olefins, alkynes, formate esters) does not yield the polymer **2**, but new trappable adducts between these substrates and the unsaturated fragments thus generated.

Experimental Section

2: A solid sample of **1**^[11] (500 mg, 1.5 mmol) was dissolved in ethanol (ca. 1–2 mL) and stirred in a small Schlenk flask under nitrogen. A 1.5 M solution of NEt₄OH in methanol (1 mL) was added dropwise. Magnetic stirring was stopped after 2 min. Homogeneous large crystals of **2** suitable for X-ray diffraction were obtained within 2 h. The mother liquor was then cannulated into another tube and kept separately. Slower crystallization of the minor product **3** was then observed after a few days; a direct synthesis of **3** was also devised (see below). Crystals of **2** were washed with dichloromethane and alcohol, and isolated (420 mg, 95% yield). IR (KBr pellets from single crystals): $\tilde{\nu}$ = 2052(s), 2043(s), 2021(s), 1984(s), 1962(s), 1944(sh), 1928(sh), 1728(s), 1723(s) cm^{–1} (ν (CO)). The crystals are only soluble in CH₃CN, which, however, causes disruption of the polymer as indicated by 1) the disappearance of the absorption for the bridging CO group (IR (CH₃CN): $\tilde{\nu}$ = 2047(s), 2021(s), 1982(s), 1964(s) cm) and 2) the detection of the ion [Ru₂(CO)₄Cl₃][–] (*m/z* 422.6) in the electrospray mass spectrum.

3: Complex **1** (500 mg, 1.5 mmol) and NaHCO₃ (126 mg, 1.5 mmol) were dissolved in ethanol (10 mL). After addition of a 1.5 M solution of NEt₄OH in methanol (1 mL), the solution was heated at 85 °C for 5 min, during which the orange color intensified. After addition of acetone (2 mL), the solution was allowed to crystallize at room temperature.^[13] Crystals of **3** suitable for X-ray diffraction appeared on the walls of the glassware over a period of 5 d. They were isolated by filtration and washed with ethanol (70 mg, 19% yield). IR (KBr pellets from single crystals): $\tilde{\nu}$ = 2028(vs), 1953(m), 2021(s), 1948(s, br), 1910(m) (ν (CO)), 1532(s) cm^{–1} (ν (OCO)). ¹³C{¹H} NMR (100 MHz, CD₃CN) δ = 204.8, 204.6 (CO), 169.5 (CO₃), 52.5 (N(CH₂CH₃)₄⁺), 14 (N(CH₂CH₃)₄⁺); ES-MS (CH₃CN): *m/z*: 843 ([Na₂(Ru₈(CO₃)₄Cl₄(CO)₁₆)^{2–}], 1816 ([Na₂(NEt₄)(Ru₈(CO₃)₄Cl₄(CO)₁₆)[–]], 1758 ([Na(NEt₄)(Ru₈(CO₃)₄Cl₃(CO)₁₆)[–]], 1651 ([Na₂(Ru₈(CO₃)₄Cl₃(CO)₁₆)[–]]).

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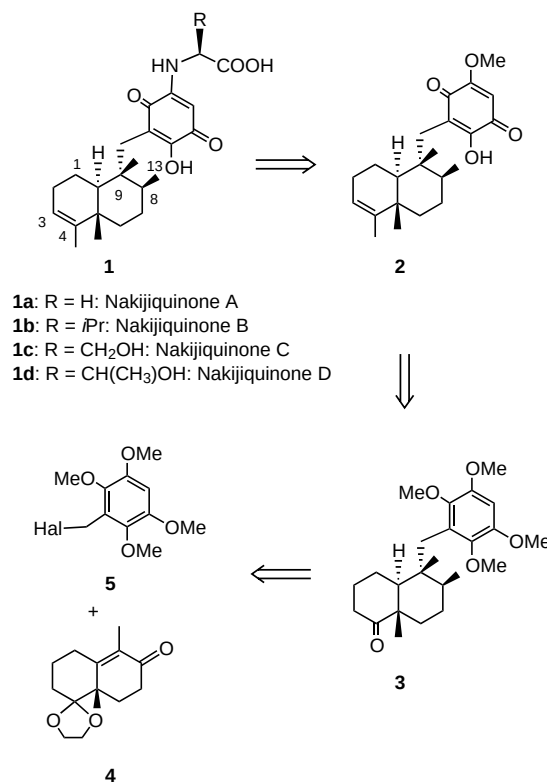
Asymmetric Synthesis of the Nakijiquinones—Selective Inhibitors of the Her-2/Neu Protooncogene**

Petra Stahl and Herbert Waldmann*

Extracellular growth-promoting signals are recognized in many cases by transmembrane receptors with tyrosine kinase activity. These proteins trigger numerous intracellular signaling cascades by which cell growth, proliferation, and other genetic programs are regulated.^[1] Dysregulation of these signal sequences may contribute to or cause many diseases. For instance, enhanced activity of receptor tyrosine kinases can promote tumor growth and has been implicated in carcinogenesis.^[2] A particularly relevant example is the Her-

2/Neu-protooncogene (also called erbB-2). This receptor is vastly overexpressed in about 30% of primary breast, ovary, and gastric carcinomas.^[1, 3, 4] Amplification is closely correlated with the clinical behavior of these neoplasms, such that tumors with Her-2 amplification are more aggressive and associated with reduced patient survival. Therefore, compounds that can selectively block Her-2 activity are of paramount importance for the development of new anti-cancer drugs.^[1, 2, 5] A monoclonal antibody against Her-2 has already been introduced by Genentech into the clinic as a new revolutionary treatment for breast cancer. In addition, such drugs are likely to be useful in dissecting signalling pathways.^[2, 6, 7] Until today only a few natural products with intrinsic tyrosine kinase inhibiting activity per se were isolated and, in particular, a natural product that inhibits Her-2 has not been synthesized.^[2, 6] Recently, however, the nakijiquinones **1a–d** (see Scheme 1) were identified as selective inhibitors of the Her-2/Neu kinase, displaying pronounced cytotoxicity against L 1210 murine leukemia cells and KB human epidermoid carcinoma cells.^[8] We now disclose the first enantioselective total synthesis of the nakijiquinones.

The nakijiquinones embody three basic structural elements, an amino acid, a central *p*-quinoid unit, and a diterpenoid system. To reach a high degree of convergency, the nakijiquinones were first, dissected in a retrosynthetic sense into isospongiaquinone (**2**), an interesting natural product in its own right^[9] and an amino acid that can be introduced in the last step by conjugate addition to the vinylogous methyl ester present^[8] (Scheme 1). It was further planned to generate the selectively functionalized quinoid system by oxidation of a tetramethoxy-substituted aromatic precursor **3** to a 1,4-dicarbonyl compound and subsequent selective saponification



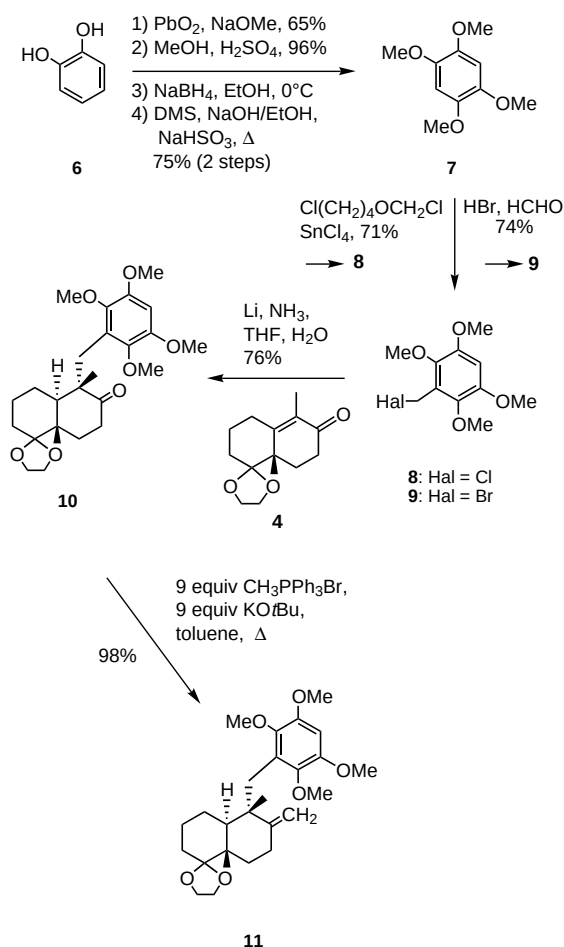
Scheme 1. Retrosynthetic analysis of the nakijiquinones **1**.

[*] Prof. H. Waldmann, Dipl.-Chem. P. Stahl
 Max-Planck-Institut für molekulare Physiologie
 Otto-Hahn-Strasse 11, D-44227 Dortmund (Germany)
 Fax: (+49) 231-133-2499
 E-mail: herbert.waldmann@mpi-dortmund.mpg.de

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of one of the two vinylogous methyl esters generated thereby. For the synthesis of the diterpene structure and its coupling with the alkoxy-substituted aromatic compound, we resorted to the reductive alkylation of α,β -unsaturated Wieland–Miescher type enone **4** with a benzyl halide **5**. This strategy had already proven to be useful in the construction of related natural products.^[10] Finally, we envisaged generating the endocyclic 3,4-alkene by olefination of a ketone at C-4 and subsequent isomerization of the generated exocyclic double bond. It was also planned to introduce the C-13 methyl group by an olefination/reduction sequence of an intermediary generated ketone.

Benzyl halides **8** and **9** were prepared from catechol (**6**) in five-step sequences as shown in Scheme 2. To this end, **6** was oxidized to the corresponding *ortho*-quinone, which rapidly added NaOMe. Subsequent reoxidation led once again to an



Scheme 2. Synthesis of tetramethoxyaryl intermediates **8** and **9**.

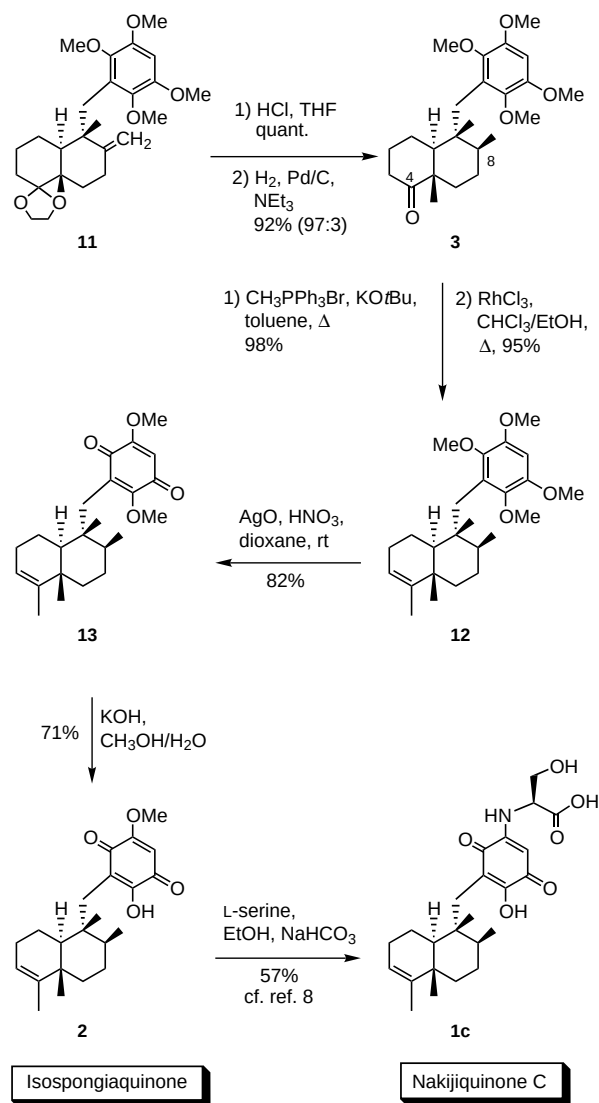
ortho-quinone that was rearranged under acidic conditions to the corresponding *para*-quinoid compound.^[11] The keto groups were then reduced, and the resulting 1,4-diphenol was O-methylated to give tetramethoxybenzene **7**. Compound **7** was converted efficiently in one-step reactions into benzyl halides **8** and **9**. Wieland–Miescher type ketone **4** required for the critical reductive coupling step was synthesized by Robinson-annulation and subsequent selective monoprotection by transacetalization.^[12] In the decisive coupling of benzyl

halides **8** and **9** and enone **4** the reaction conditions reported for related structures could not be employed successfully. Benzyl chloride **8** did not react at all with the radical anion generated from enone **4** by treatment with lithium in ammonia. However, a yield of 76% was obtained reproducibly if a solution of twelve equivalents of benzyl bromide **9** in THF was added rapidly at -78°C to a preformed solution of the radical anion in NH_3/THF (final ratio $\text{NH}_3:\text{THF} = 1.0:0.7$) and subsequent refluxing at -33°C for 2 h. The radical anion was generated by adding a solution of enone **4** in THF/water (1:0.018) at -78°C to 30 equivalents of Li/NH_3 followed by refluxing for 45 min and recooling to -78°C .

The conversion of the keto group present in **10** into the corresponding *exo*-methylene compound **11** was unexpectedly difficult. Several established methylenation reagents such as the Tebbe reagent^[13] and $[\text{Cp}_2\text{TiMe}_2]$ ^[14] failed completely, and under various conditions the Wittig reaction either yielded no product at all or only an unsatisfactory low amount of the desired olefin. Finally, the use of nine equivalents of $\text{H}_3\text{CPh}_3\text{PBr}$ together with nine equivalents of KOtBu in refluxing toluene^[15] turned out to be the method of choice, yielding the exocyclic olefin **11** in nearly quantitative yield. Disappointingly, reduction of the olefin **11** with PtO_2 proceeded without recordable stereoselectivity. We felt that this might be due to an unfavourable conformation of the bicyclic system and envisaged that removal of the acetal protecting group might improve the situation. This turned out to be the case. After cleavage of the acetal, the stereoselectivity of the reduction with PtO_2 in CH_2Cl_2 was raised to 80:20, and use of Pd/C as catalyst in NEt_3 as solvent yielded ketone **3** in 92% as a 97:3 mixture of epimers at C-8 (Scheme 3). As planned, the ketone at C-4 was converted in very high overall yield to endocyclic alkene **12** by olefination (for which the conditions described above once more proved to be very efficient), and subsequent rhodium-catalyzed isomerization of the exocyclic to the endocyclic double bond.

The next two steps in the synthetic sequence, that is the oxidation of the tetramethoxyphenyl ring to the *para*-quinoid system and the subsequent selective removal of the correct *O*-methyl group posed major problems. Oxidation of the aromatic system was initially attempted by applying CrO_3 or cerium ammonium nitrate which had proven to be useful reagents in related studies.^[10c,d,16] However, oxidized intermediate **13** was formed only in low yield or not at all. After substantial variation of the reaction conditions, finally the use of AgO and catalytic amounts of HNO_3 at room temperature in dioxane as solvent evolved as the method of choice.^[17] Under these conditions *p*-diketone **13** and the regioisomeric *o*-diketone were obtained in a total yield of 82% as an isomeric mixture. The undesired *o*-diketone was readily rearranged to **13** by treatment with acid.

Selective removal of the correct *O*-methyl group was attempted by a variety of methods. In particular, the use of various different Lewis acids (BCl_3 , BBr_3 , AlCl_3 , $\text{BF}_3 \cdot \text{OEt}_2$, EtSH , HClO_4 and trimethylsilyl iodide) was unsuccessful and led to decomposition of the starting material. Also, attempts to cleave a methyl ether before the oxidation did not succeed and resulted exclusively in Lewis acid mediated rearrangements of the terpene backbone. Finally, treatment of vinyl-



Scheme 3. Synthesis of isospongiaquinone (**2**) and nakijiquinone C (**1c**).

ogous diester **13** with KOH in aqueous methanol led to saponification of the correct methoxy group and gave rise to the desired product **2** in 71 % yield. Presumably, the reaction proceeds by conjugate addition of hydroxide to one of the vinylogous esters and elimination of methanol. Compound **2** is identical with isospongiaquinone, a natural product isolated from *Stelospongia conulata*.^[9] Specific rotation, IR and NMR spectroscopic data of synthetic **2** were in full accord with the data reported for the natural product, thereby proving the absolute configuration of the synthesized compound.^[18]

Isospongiaquinone (**2**) may be employed as a central intermediate for the synthesis of all nakijiquinones. Treatment of this compound with amino acids in ethanol in the presence of NaHCO₃ results in the conversion of the remaining vinylogous ester in **2** into the corresponding vinylogous amide.^[8] We have verified this finding and converted isospongiaquinone (**2**) into nakijiquinone C (**1c**) by treatment with L-serine (Scheme 3). The IR and NMR spectroscopic data recorded for the synthetic sample completely matched the data published for the natural product.^[19] Unexpectedly, however, synthetic nakijiquinone **1c** displayed a positive

specific rotation, whereas for the compound isolated from natural sources a negative rotation was reported.^[8] But as described above, the IR and NMR data of **1c** are in full accord with the published values for natural nakijiquinone C, and the diastereomer formed from isospongiaquinone and D-serine shows a markedly different specific rotation.^[8] Thus, in the conversion of intermediate **2** to target compound **1c** an undesired diastereomer cannot have been formed. In addition, all data (including the specific rotation) recorded for isospongiaquinone synthesized as shown in Scheme 3, are in full accord with the values published for this natural product. Thus, if the absolute configuration of synthetic **2** is correct, nakijiquinone C (**1c**) must have been formed with the correct absolute configuration, as well.^[20]

In conclusion we have developed the first enantioselective access to the nakijiquinones, the only natural products known to selectively inhibit the Her-2/Neu protooncogene. This synthetic route should give access to various analogues of these interesting and biologically relevant kinase inhibitors. Thereby new opportunities for the development of selective inhibitors of the Her-2/Neu receptor tyrosine kinase and for the study of the signaling pathways influenced by this enzyme may be opened up.

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- [18] Analytical data for **2**: M.p. 1359 °C (hexene) [ref. [9]: m.p. 135.5–1369 °C (hexene)]; IR (KBr): $\tilde{\nu}$ = 3337, 1645, 1609, 1460, 1380, 1320, 1234, 1209, 1043 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.48 (br.s, 1H), 5.85 (s, 1H), 5.12 (br.s, 1H), 3.84 (s, 3H), 2.63 (d, 1H, *J* = 13.7 Hz), 2.49 (d, 1H, *J* = 13.7 Hz), 2.06–1.97 (m, 1H), 1.92–1.83 (m, 1H), 1.63 (dt, 1H, *J* = 12.7, 3.3 Hz), 1.54 (s, 3H), 1.47–1.04 (m, 6H), 1.00 (s, 3H), 0.97 (d, 3H, *J* = 6.1 Hz), 0.92–0.88 (m, 1H), 0.84 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃): δ = 182.4, 182.1, 161.8, 153.2, 144.0, 120.9, 117.6, 102.0, 56.8, 47.8, 43.1, 38.5, 37.8, 36.0, 32.3, 27.9, 27.0, 20.2, 19.8, 18.2, 17.7, 17.4; MS: (EI, 70 eV, 858 C): *m/z*: 358 [*M*⁺], 281, 236, 191, 168; HRMS (EI) calcd for C₂₂H₃₀O₄ 358.2144, found 358.2131; [α]_D²⁰ = +62.4 (*c* = 0.25, CHCl₃) [ref. [9]] [α]_D²⁰ = +64.8 (*c* = 1, CHCl₃).
- [19] Analytical data for **1c**: IR (KBr): $\tilde{\nu}$ = 3417, 1679, 1650, 1597, 1556, 1391, 1209 cm⁻¹; ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.16 (d, 1H, *J* = 7.3 Hz), 5.34 (s, 1H), 5.06 (s, 1H), 4.21 (m, 1H), 3.82 (m, 1H), 3.78 (m, 1H), 2.43 (d, 1H, *J* = 13.5 Hz), 2.32 (d, 1H, *J* = 13.5 Hz), 2.01–1.89 (m, 3H), 1.54 (m, 1H), 1.47 (s, 3H), 1.39–1.15 (m, 4H), 1.03–0.98 (m, 2H), 0.93 (s, 3H), 0.89 (d, 3H, *J* = 7.3), 0.77 (s, 3H); MS: (–FAB, diethanolamine matrix): *m/z*: 432 [*M*+H], [α]_D²⁰ = +62 (*c* = 0.13, EtOH) [ref. [8]] [α]_D²⁰ = –73° (*c* = 0.03, EtOH)].
- [20] The direction of the specific rotation reported for nakijiquinone C isolated from natural sources is indeed incorrect. Reexamination of the original sample yielded a value of [α]_D²⁰ = +138° (*c* = 0.1, EtOH): Prof. Jun'ichi Kobayashi, Hokkaido University, Sapporo; personal communication.

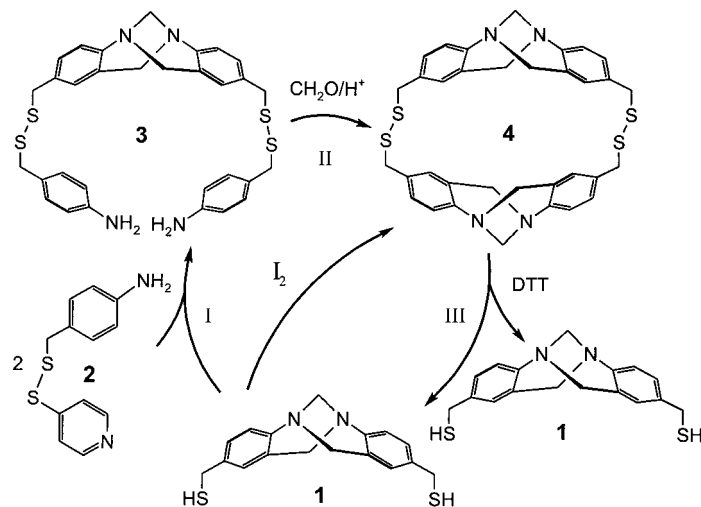
Stepwise Replication of a Tröger's Base Analogue**

Braja G. Bag and Günter von Kiedrowski*

Molecular replication lies in the heart of biological systems. In its minimal representation, molecular replication is the ability of a molecule to form a copy of itself with transfer of

constitutional information. In recent years, the phenomenon has been studied with various chemical model systems based on oligonucleotides,^[1] peptides,^[2] and other synthetic supramolecular systems,^[3] aiming to gain an improved understanding of prebiotic replication.^[4] A common problem of these template-mediated catalytic systems, regardless of whether they are autocatalytic or cross-catalytic, is product inhibition leading to parabolic amplification. Recently, an exponential amplification procedure based on oligonucleotides immobilized on a solid support was reported by Luther et al.^[5] Here we report a new scheme for stepwise replication that is based on a Tröger's base analogue and utilizes macrocyclization and covalent templating.

Tröger's base with its rigid V-shaped geometry has become attractive in recent years in the general area of supramolecular chemistry.^[6] For the design of a novel replicating system based on a Tröger's base analogue, we realized that a thiol–disulfide exchange reaction^[7] could be integrated with the formation of Tröger's base.^[6b] Molecular modeling using the PCMODEL^[8] program supported the geometric feasibility of the “dimeric” macrocyclic structure **4** (see Scheme 1). We chose compound **1**, which has two appended thiol groups at the 2- and 8-methyl groups of Tröger's base, as a template. It occurred to us that reaction of **1** with **2** will produce **3** by a thiol–disulfide exchange reaction (Scheme 1). Intramolecular condensation of the two aniline units of **3** will produce **4**. Reductive cleavage of the disulfide linkages of **4** will generate a replica of **1** along with the parent template.



Scheme 1. Stepwise replication of Tröger's base analogue **1** by macrocyclization and covalent templating.

We have previously reported the synthesis of compound **1**.^[9] Indirect evidence for the practicability of the replication Scheme came from the fact that oxidation of **1** with iodine^[10] under high dilution conditions in THF afforded **4** as the major product detectable by HPLC (Table 1). Treatment of a solution of **1** in chloroform with **2** in the presence of *p*-toluenesulfonic acid afforded **3** in quantitative yield. The insoluble byproduct 4-thiopyridone was separated by filtration and the bis-amine **3** was directly used for the macrocyclization. Condensation of **3** with formalin in chloroform/

[*] Prof. Dr. G. von Kiedrowski, Dr. B. G. Bag
Lehrstuhl für Organische Chemie I – Bioorganische Chemie
der Universität
Universitätsstrasse 150, D 44780 Bochum (Germany)
Fax: (+49) 234-32-14355
E-mail: kiedro@ernie.orch.ruhr-uni-bochum.de

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Table 1. Selected data for compounds 2–4.

2: M.p. 129–131 °C; ¹H NMR (200 MHz, CDCl₃): δ = 8.40 (d, *J* = 6.3 Hz, 2H), 7.32 (d, *J* = 6.3 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 2H), 3.88 (s; CH₂), 3.67 (brs, 2H; NH₂); ¹³C NMR (50 MHz, CDCl₃): δ = 147.8, 145.3, 129.4, 124.3, 119.1, 114.0, 42.2; MS: *m/z* (%): 248 (*M*⁺, 1.5), 138 (3), 106 (100); HR-MS: calcd for C₁₂H₁₂N₂S₂: 248.0442, found: 248.0432

3: ¹H NMR (200 MHz, CDCl₃): δ = 7.05 (s, 4H), 6.96 (d, *J* = 8.4 Hz, 4H), 6.73 (s, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 4.66 (d, *J* = 16.3 Hz, 2H), 4.29 (s, 2H), 4.11 (d, *J* = 16.3 Hz, 2H), 3.49 (s, 4H), 3.47 (s, 4H); ¹³C NMR (50 MHz, CDCl₃): δ = 146.7, 144.3, 132.7, 130.0, 128.2, 127.4, 127.3, 124.6, 115.4, 66.6, 58.3, 42.5, 39.8; FAB-MS (positive ion): calcd for C₃₁H₃₃N₄S₄ (*M*⁺+H): 589.8, found: 589.2

4: ¹H NMR (400 MHz, CDCl₃, for the mixture of diastereomers): δ = 7.07–7.01 (m, 4H), 6.81–6.75 (m, 4H), 6.49 (brs, 4H), 6.39 (brs, 4H); the integration ratio of the peaks at 6.49 and 6.39 is 1:1.8; 4.67 (d, *J* = 16.1 Hz, 4H), 4.64 (d, *J* = 16.6 Hz, 4H), 4.38 (s, 4H), 4.37 (s, 4H), 4.06 (d, *J* = 16.6 Hz, 4H), 4.05 (d, *J* = 16.1 Hz, 4H), 2.91 (d, *J* = 12.6 Hz, 4H), 2.85 (d, *J* = 12.3 Hz, 4H), 2.75 (d, *J* = 12.3 Hz, 4H), 2.69 (d, *J* = 12.6 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃, for the mixture of diastereomers): δ = 146.9, 146.7, 133.4, 133.1, 129.1, 128.9, 127.8, 124.5, 124.4, 67.7, 67.5, 59.9, 59.7, 42.8, 41.9; FAB-MS (positive ion): calcd for C₃₄H₃₃N₄S₄ (*M*⁺+H): 625.2, found: 625.2

ethanol (3/1) under high dilution conditions in the presence of hydrochloric acid produced **4** as a 1:1.8 mixture of diastereomers. The crude reaction mixture was directly used for the reduction step after neutralization with ammonia and equilibration with water. Reduction with dithiothreitol (DTT)^[11] in the presence of triethylamine afforded compound **1**. The progress of the individual reaction steps was monitored by HPLC, and the yield of the final product was determined from the area of the HPLC peak. After a complete replication cycle the amount of compound **1** increased by 40%. A control experiment with the amine **2** at twice the initial concentration with respect to macrocyclization yielded only traces of the desired Tröger's base derivative, and most of the starting material was recovered. This supported the template-mediated pathway shown in Scheme 1.

The presence of an excess of the reducing agent DTT and traces of triethylamine gave anomalous results in recycling the material. However, the use of a controlled amount of DTT during reduction (Scheme 1, step III) followed by thorough removal of triethylamine under reduced pressure and the use of an acidic catalyst (*p*-toluenesulfonic acid) in the following step (step I) gave satisfactory results up to three generations with about 35–40% yield per cycle (Figure 1).^[12]

The stepwise replication procedure described here represents a new way for exponential amplification during chemical self-replication and can be further extended to other classes of coupling reactions. Current efforts in our laboratory address the question of chirality transfer during stepwise replication. Also, studies of similar cou-

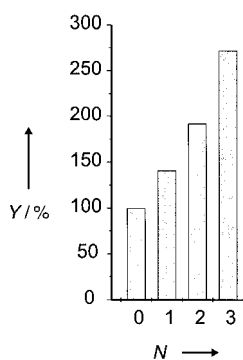


Figure 1. Plot of total yield *Y* of compound **1** versus the number of replication cycles *N*. When the reaction is initiated with 0.75 g of **1**, the total yields were 141, 192, and 272% for first, second, and third replication cycles, respectively, affording 2.04 g of **1** in the end.^[12]

pling reactions to generate a chiral center^[13] might prove useful for the design of new chiral amplification strategies.^[14]

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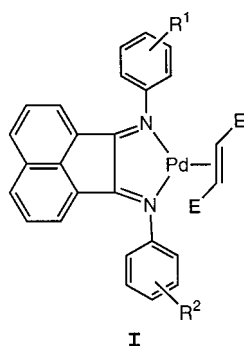
Selective Homogeneous Palladium(0)-Catalyzed Hydrogenation of Alkynes to (Z)-Alkenes**

Martijn W. van Laren and Cornelis J. Elsevier*

The selective semihydrogenation of alkynes to (Z)-alkenes seems to be a simple reaction, yet this type of conversion remains a desirable synthetic tool. A variety of catalysts is available for the conversion of alkynes into (Z)-alkenes; the best known and most efficient ones are heterogeneous catalysts such as the Lindlar catalyst,^[1] nickel boride,^[2] the "P2Ni" catalyst,^[3] and palladium immobilized on a clay.^[4] Especially the Lindlar catalyst suffers from a number of major problems in the selective *cis*-hydrogenation of alkynes, notably, partial isomerization of the (Z)-alkene product to the (E)-alkene, shift of the double bond, overreduction to the alkane, and problems with reproducibility. Only a few examples are known of homogeneous catalyst systems that show good selectivity for a wider range of substrates, for example, rhodium-^[5] and Cr(CO)₃-catalyzed hydrogenation.^[6] For palladium, however, few homogeneous catalyst systems are known, and these involve palladium(II) complexes.^[7, 8] The only homogeneous palladium(0) catalyst is the complex [Pd₂(dppm)₃], which shows low activity in the hydrogenation of propyne and 2-butyne.^[9]

Here we report the first example of a homogeneous palladium(0) catalyst bearing a bidentate nitrogen ligand that is able to homogeneously hydrogenate a wide variety of alkynes to the corresponding (Z)-alkenes with very high selectivity. Additionally, enynes are selectively converted into dienes.

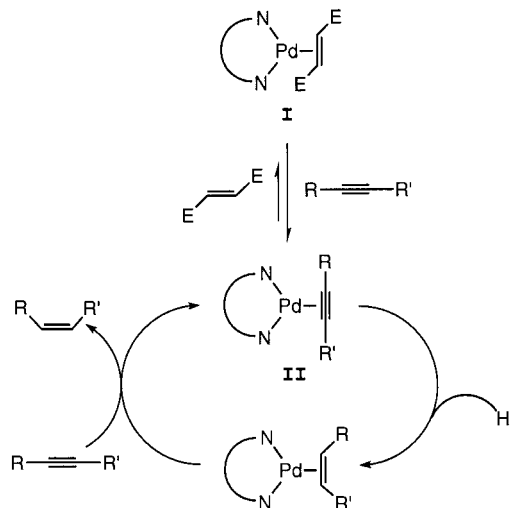
As part of our continuing interest in carbon–element (e.g., C–C, C–H, C–N, C–X) bond-forming reactions,^[10] we employed zerovalent palladium precatalysts **I**, which contain the rigid bidentate nitrogen ligand bis(arylimino)acenaphthene (bian). These have previously been isolated with an electron-



E = CO₂Me

- a: R¹ = R² = 4-OCH₃
 b: R¹ = 4-OCH₃; R² = 4-CH₃
 c: R¹ = R² = 4-CH₃
 d: R¹ = R² = 2,6-(CH₃)₂

deficient alkene as the ancillary ligand;^[11] however, analogues of **I** with electron-rich alkenes are not stable. We reasoned that since simple alkenes are expected to be readily substituted by alkynes, if alkynes were hydrogenated in the presence of molecular hydrogen, subsequent fast substitution by excess alkyne could give rise to a viable catalytic cycle (Scheme 1).



Scheme 1. Proposed catalytic cycle for hydrogenation of alkynes.

We conducted hydrogenation reactions of alkynes at 20 °C and 1 bar hydrogen pressure with initial sample concentrations of about 0.5 M in THF and 1 mol % of **1a** as precatalyst. With 3-hexyne (**1**) and 4-octyne (**3**), high stereoselectivity (>99.5%) for the formation of (Z)-3-hexene and (Z)-4-octyne was observed, and hydrogenation proceeded with excellent yield. Various other alkynes were then subjected to these hydrogenation conditions (Table 1).

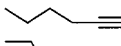
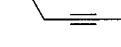
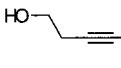
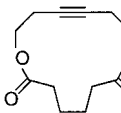
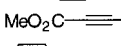
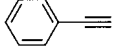
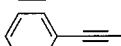
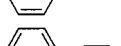
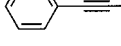
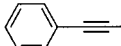
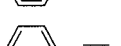
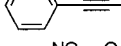
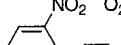
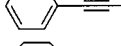
The stereoselectivity for the formation of the (Z)-alkene is generally excellent and in many cases superior to that obtained with Lindlar^[1] or P2Ni catalysts^[3] and comparable to or in several cases better than those of known homogeneous systems.^[5–7] Generally, quantitative conversion of the alkyne to the desired (Z)-alkene takes place, without concomitant alkane formation. The selectivity is highest (Z/E > 99/1) for simple alkynes such as **1** and **3**. The Lindlar catalyst gives 95/5 and 94/6 mixtures of Z/E alkenes, respectively, and only partial conversion in these cases.^[1c, d] Excellent results were also obtained for the homopropargylic alcohol **4**, alkynes with aryl- and/or electron-withdrawing substituents (**5–7**, **10**, **12**), and cyclooctyne (**13**). For **7** the stereoselectivity was determined by reaction with D₂. Semihydrogenation of **7** usually results in the formation of ethylbenzene; an 89/11 mixture of styrene/ethylbenzene was obtained at full conversion of **7**.^[1e]

Phenylacetylenes show somewhat lower but still very good selectivities, comparable to conversions with Lindlar or P2Ni catalysts, and for **8** and **9** only a small amount of alkane is formed. In several cases (**5**, **9**, **10**, **12**, **13**) some Z–E isomerization occurs, but only to a minor extent. Remarkably, no isomerization to (E)-stilbene was observed with **11**, whereas the amount of 1,2-diphenylethane is somewhat

[*] Prof. Dr. C. J. Elsevier, M.Sc. M. W. van Laren
 Institute of Molecular Chemistry, Inorganic Chemistry
 Universiteit van Amsterdam, Nieuwe Achtergracht 166
 NL-1018 WV Amsterdam (The Netherlands)
 Fax: (+31)20-525-6456
 E-mail: else4@anorg.chem.uva.nl

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Table 1. Product distribution in the hydrogenation of alkynes with **1a** as precatalyst.^[a]

Substrate	Product distribution [%] ^[b]		
	(Z)-alkene	(E)-alkene	alkane
1 ^[c] 	> 99	–	–
2 ^[c] 	1-hexene exclusively		
3 	> 99	–	–
4 	> 99	–	–
5 	95	5	–
6 	> 98	< 1	< 1
7 	> 99 ^[d]	–	–
8 	92	2	6
9 	91	6	3
10 	95	5	–
11 	87	–	13
12 	97	3	–
13 	96	4	–
14 	ethenylcyclohexene exclusively		
15 	ethenylcyclooctene exclusively		

[a] Reaction conditions: 80 mm substrate and 0.8 mm precatalyst **1a** in THF at 20 °C and 1 bar H₂ pressure. [b] The reaction was monitored by GC analysis. The product distribution was determined by GC and ¹H NMR analysis at > 99.5% conversion of alkyne. [c] Hydrogenated with **1c** as precatalyst. [d] Determined by reaction with D₂.

higher than is obtained with Lindlar procedures; a 93/2/5 mixture of (Z)-alkene/(E)-alkene/alkane was reported.^[1f]

In the case of **1–6**, **10**, and **12** very little or no alkane is formed. The high selectivity in the case of dimethyl butyryl diolate (**6**) is noteworthy, as it indicates that hydrogenation of the Pd alkyne complex is faster than formation of the palladacycle with a second molecule of butyryl diolate, which is known to be a fast reaction.^[10b, 12] A Pd–alkyne complex similar to **II** was observed as an intermediate in the formation of such a palladacycle.^[10a, b]

Evidently, the hydrogenation of alkynes takes place with high chemoselectivity towards the triple bond. No hydrogenation of functional groups such as ester, carboxylic acid or nitro substituents has been observed, but **I** is capable of hydrogenating the carbon–carbon double bond in several cases. It was previously known that electron-deficient alkenes

can be hydrogenated with **I** as a precatalyst,^[13] but styrene and stilbene reacted sluggishly. In this context it is noteworthy that conjugated enynes such as **14** and **15** are cleanly (though in the case of **14** sluggishly) converted into the corresponding dienes by hydrogenation with **1a**, with no trace of hydrogenation of the double bond(s); hydrogen uptake stops completely after hydrogenation of the triple bond, without any decomposition of the catalyst. Employing a Lindlar catalyst with **14** led to significant overreduction (86/8/6 mixture of diene/ethylnylcyclohexene/ethynylcyclohexene) after uptake of one equivalent of H₂.^[14]

The effect of the substituents on the *N*-Ar moieties of **1a** on the selectivity was briefly addressed for the hydrogenation of 1-phenyl-1-propyne (**8**; Table 2). The selectivity for (Z)-1-phenyl-1-propene decreases markedly with decreasing electron-donor character of the substituents on the *N*-aryl groups. For entries 1–3, the Z/E ratio decreases from 46 to 11, with a

Table 2. Product distribution in the hydrogenation of 1-phenyl-1-propyne to 1-phenyl-1-propene and 1-phenylpropane.

Entry	Precatalyst	Product distribution [%]		
		(Z)-alkene	(E)-alkene	alkane
1	1a	92	2	6
2	1b	85	5	10
3	1c	80	7	13
4	1d	62	3	35

concomitant increase of the amount of alkane formed. Especially the sterically congested complex **1d** (entry 4) exhibits a rather low selectivity and leads to formation of larger amounts of alkane. The latter result may be due to steric crowding, since **1d** may form a more stable complex with the (Z)-alkene than with the alkyne.

Use of zero-valent palladium catalyst precursors with other ligands—such as [Pd(dba)₂], [Pd(bpy)(alkene)], and [Pd(dab)-(alkene)] (Table 3)—leads to unstable complexes and/or

Table 3. Product distribution in the hydrogenation of 1-phenyl-1-propyne.

Entry	Precatalyst ^[a]	Product distribution (%)		
		(Z)-alkene	(E)-alkene	alkane
1	[Pd(dba) ₂]	70	8	22
2	[Pd(bpy)(dmfu)]	73	6	21
3	[Pd(dab)(dmfu)] ^[b]	–	–	–
4	[Pd(dppe)(dmfu)]	80	2	18
5	[Pd(bian)(dmfu)]	92	2	6

[a] bpy = bipyridyl, dab = *p*-anisyl diazabutadiene, dba = dibenzylideneacetone, dmfu = dimethyl fumarate, dppe = bis(diphenylphosphanyl)ethane. [b] The precatalyst decomposed almost immediately.

serious decomposition under the conditions employed. As a result, in these cases heterogeneous hydrogenation of **8** with low selectivity and a high degree of overreduction to *n*-propylbenzene was observed. The use of a complex containing a chelating biphosphane ligand such as dppe gives very stable alkyne and alkene complexes, and no decomposition is observed, but hydrogenation is very slow, and larger amounts of *n*-propylbenzene are formed. Thus, the selectivity of the Pd(bian) complexes **I** for hydrogenation of alkynes is much higher than those of the other precatalysts in Table 3.

The homogeneity of the hydrogenation was monitored by the addition of a tenfold excess of cyclohexene to the reaction mixture in several cases. Cyclohexene is not or only very slowly hydrogenated by homogeneous Pd species, but is readily hydrogenated by colloidal or heterogeneous Pd. As we did not observe the formation of any cyclohexane during the hydrogenation of the alkynes, it can be concluded that the Pd(bian)-catalyzed hydrogenation reaction is homogeneous.^[15]

The mechanism of this selective hydrogenation of alkynes is as yet unclear. The complexes **I** should be considered precatalysts, and the actual catalyst is probably a [Pd(bian)(alkyne)] complex **II** (Scheme 1). The stability of **II** relative to the corresponding alkene complex **I** is probably important for the observed chemoselectivity of hydrogenation. For most or all alkynes a high ratio **II/I** would be expected. Hydrogenation could readily take place by addition of hydrogen to **II** and subsequent insertion/elimination or by a pairwise transfer of hydrogen atoms. The latter was substantiated in similar hydrogenations by means of the *para*-hydrogen-induced polarization in ¹H and ²H NMR spectroscopy during hydrogenation.^[16] Currently, we are trying to extend the scope and to elucidate the mechanism of the reaction.

Experimental Section

Typical procedure for the catalytic hydrogenation of alkynes: **1a**^[11b] (25 mg, 0.04 mmol) and the alkyne (4.0 mmol) were added to 50 mL of dry THF in a Schlenk tube under nitrogen atmosphere. The solution was then subjected to a hydrogen atmosphere of 1 bar by first flushing with hydrogen and then slowly blowing hydrogen over the surface while the solution was vigorously stirred at 20 °C. The reaction was monitored by GC (Varian 3300; DB-5 column) and stopped when all alkyne had been consumed (conversion 99.5–100 %). The composition of the reaction mixture was determined by GC and ¹H NMR spectroscopic analysis.

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Self- and Directed Assembly of Hexaruthenium Macrocycles**

George R. Newkome,* Tae Joon Cho, Charles N. Moorefield, Gregory R. Baker, Randy Cush, and Paul S. Russo

Elegant work in the area of self-assembly by Stang,^[1] Lehn et al.,^[2] and many others^[3–7] has prompted our investigation of the potential to spontaneously construct Ru-based (macro)-molecules. More specifically, our goal involved the design and preparation of polyterpyridyl ligands that would form the basis of a “modular building block set”^[8] capable of being used to access “higher order” (fractal) architectures. Herein we report the construction of a bis(terpyridyl) monomer that facilitates the preparation of hexaruthenium macrocycles.

Linear bis(terpyridyl) monomers have been employed for the formation of layered polyelectrolyte films,^[9] Ru^{II}-based dendrimers,^[10] helical ligands,^[11] grids,^[12] racks,^[13] and photoactive molecular-scale wires,^[14] to mention but a few. Whereas progress in directed synthesis of cyclic rigid structures^[15] can be found in “shape-persistent” phenylacetylenes,^[16–18] diethynylbenzene macrocycles,^[19] and a hexagon containing 24 phenylene units,^[20] advances in self-assembly have yielded, for example, chiral^[21] and achiral circular

[*] Prof. Dr. G. R. Newkome, Dr. T. J. Cho, Prof. Dr. C. N. Moorefield, Prof. Dr. G. R. Baker
Center for Molecular Design and Recognition
University of South Florida
Tampa, FL 33620 (USA)
Fax: (+1) 813-974-6564
E-mail: gnewkome@research.usf.edu

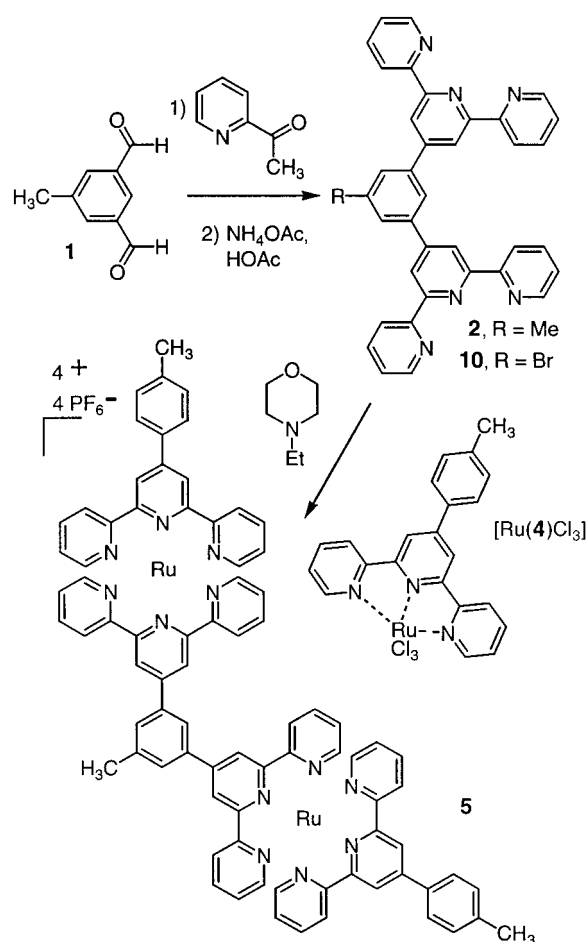
R. Cush, Prof. Dr. P. S. Russo
Department of Chemistry, Louisiana State University
Baton Rouge, LA 70803 (USA)

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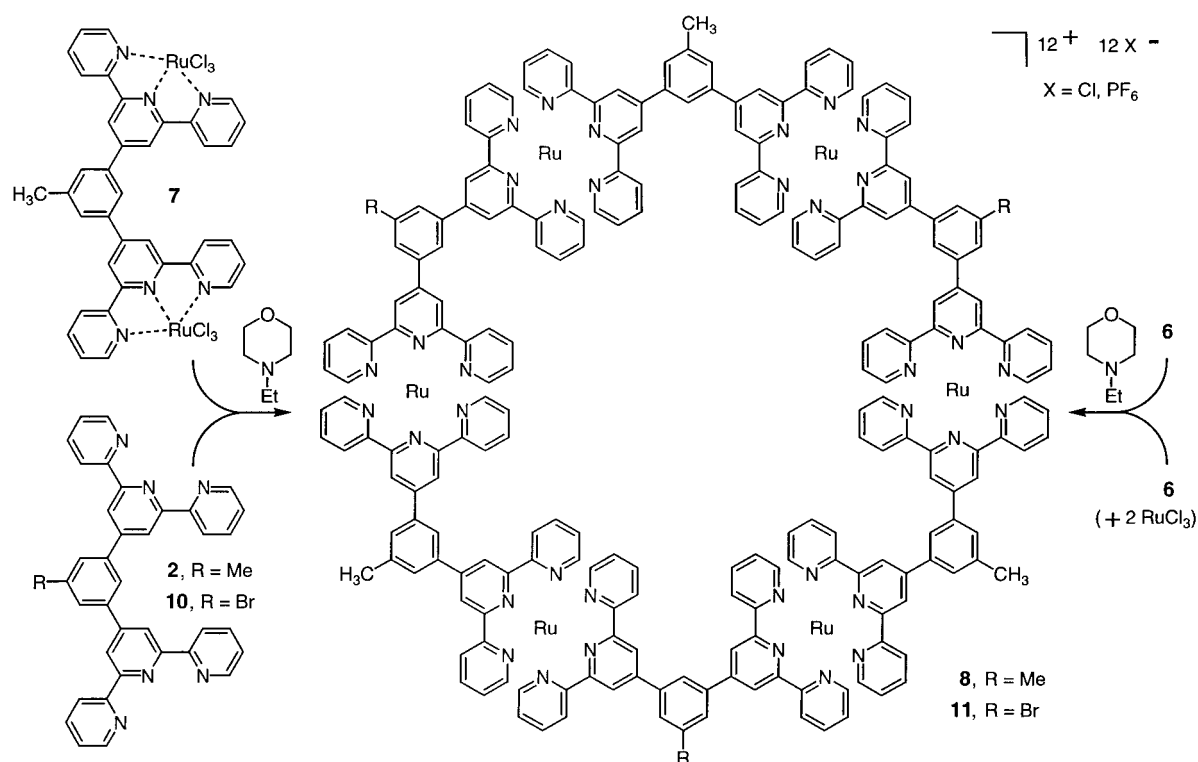
helicates,^[22] cylindrical cage structures,^[23] Pt-coordinated bipyridyl squares,^[24] metal-templated [2]catenanes,^[25, 26] and cyclic porphyrin trimers.^[27]

Our strategy involved the preparation of a bis(terpyridyl) monomer possessing a 60° angle with respect to the two ligating moieties. This would facilitate the assembly of six building blocks with six connecting metals in the ubiquitous benzenoid architecture. The potential to synthesize such constructs, with little equilibration (metal–ligand exchange) under mild physicochemical conditions, is predicated on the unique strength of the terpyridine–Ru coordination.^[28]

Synthesis of the requisite building block began with treatment of the known dialdehyde^[29] **1** with excess 2-acetylpyridine^[30] and base (1N NaOH followed by NH₄OAc and acetic acid) to afford the desired angular bis(terpyridine) **2** (66% yield; Scheme 1). Confirmation of this structure included the diagnostic ¹H NMR signals at δ = 7.38 (dd; 5,5''-H), 7.82 (s; 4,6-Ar), and 8.83 (s; 3',5'-H). Reaction of hexagon precursor **2** with two equivalents of RuCl₃·*n*H₂O produced the minimally soluble, paramagnetic bis-Ru^{III} adduct **7** (Scheme 2), which was treated without further purification with one equivalent of monomer **2** under reducing conditions (*N*-ethylmorpholine) to yield the self-assembled, diamagnetic, hexameric Ru^{II} complex **8** (40% yield; Table 1). The ¹H NMR spectrum (Figure 1b) of the purified material revealed a single aliphatic resonance at δ = 2.93 (CH₃), which suggested the presence of only one type of monomeric unit, which is not the expected case for a linear oligomer. Other diagnostic spectral attributes (¹H NMR) included upfield and downfield shifts, respectively, of the 6,6''-H signals (δ = 7.62; $\Delta\delta$ = –1.15) and the 3',5'-H signals (δ =



Scheme 1. Synthesis of the key monomer **2** and the Ru^{II} complex **5** that aided in structural elucidation of the metallamacrocycles.



Scheme 2. Self- and directed-assembly of macrocycles **8** and **11**.

Table 1. Selected data for compounds **2**, **3**, **5**, **6**, **8**, **10**, and **11**.

2: ^1H NMR (CDCl_3): δ = 2.59 (s, 3 H, CH_3), 7.38 (dd, J = 6 Hz, 4 H, $\text{H}^{5,5'}$), 7.82 (s, 2 H, $\text{H}^{4,6}$), 7.91 (dd, J = 8 Hz, 4 H, $\text{H}^{4,4'}$), 8.22 (s, 1 H, $\text{H}^{2,6}$), 8.71 (d, J = 8 Hz, 4 H, $\text{H}^{3,3'}$), 8.77 (d, J = 4 Hz, 4 H, $\text{H}^{6,6'}$), 8.83 (s, 4 H, $\text{H}^{3,5}$); ^{13}C NMR (CDCl_3): δ = 21.60 (CH_3), 119.24 (C^3), 121.50 ($\text{C}^{5,5'}$), 121.71 (C^3), 123.53 ($\text{C}^{2,6}$), 123.94 (C^3), 128.94 ($\text{C}^{6,6'}$), 136.97 (C^4), 139.48 ($\text{C}^{4,4'}$), 149.20 (C^6), 150.31 (C^4), 155.97 (C^2), 156.20 (C^2); ESI-MS: m/z : 555 [$M + \text{H}^+$]; m.p. 187–188 °C (decomp); elemental analysis calcd for $\text{C}_{37}\text{H}_{26}\text{N}_6$: C 80.14, H 4.69, N 15.16; found: C 79.34, H 4.84, N 18.9

3: ^1H NMR (CD_3CN): δ = 2.74 (s, 3 H, CH_3), 7.37 (dd, 2 H, $\text{H}^{5,5'}$), 7.62 (d, 2 H, $\text{H}^{6,6'}$), 7.78 (d, 2 H, $\text{H}^{3,5}$), 8.14 (dd, 2 H, $\text{H}^{4,4'}$), 8.31 (d, 2 H, $\text{H}^{2,6}$), 8.83 (d, 2 H, $\text{H}^{3,3'}$), 9.19 (s, 2 H, $\text{H}^{3,5}$); ^{13}C NMR (CD_3CN): δ = 21.91 (CH_3), 122.83 (C^3), 125.94 (C^3), 128.89 (C^5), 129.14 ($\text{C}^{2,6}$), 131.77 ($\text{C}^{3,5}$), 135.39 ($\text{C}^{4,4'}$), 139.47 (C^4), 142.52 ($\text{C}^{4,4'}$), 149.75 (C^6), 153.91 (C^6), 156.88 (C^2), 159.74 (C^2); MALDI-TOF-MS: m/z : 892 [$M - \text{PF}_6$], 747 [$M - 2\text{PF}_6$]

5: ^1H NMR (CD_3CN): δ = 2.68 (s, 6 H, CH_3 (**4**)), 2.96 (s, 3 H, CH_3 (**2**)), 7.35 (dd, 8 H, $\text{H}^{5,5'}$ (**4** + **2**)), 7.62 (m, 8 H, $\text{H}^{6,6'}$ (**4** + **2**)), 7.74 (d, 4 H, $\text{H}^{3,5}$ (**4**)), 8.12 (m, 8 H, $\text{H}^{4,4'}$ (**4** + **2**)), 8.28 (d, 4 H, $\text{H}^{2,6}$ (**4**)), 8.49 (s, 2 H, $\text{H}^{4,6}$ (**2**)), 8.82 (d, 4 H, $\text{H}^{3,3'}$ (**4**)), 8.92 (d + s, 5 H, $\text{H}^{3,3'}$ + $\text{H}^{2,6}$ (**2**)), 9.17 (s, 4 H, $\text{H}^{3,5}$ (**4**)), 9.40 (s, 4 H, $\text{H}^{3,5}$ (**2**)); ^{13}C NMR (CD_3CN): δ = 20.41, 20.77 (CH_3 (**4** + **2**)), 121.35, 121.83 (C^3 (**4** + **2**)), 124.30, 124.51 (C^3 (**4** + **2**)), 127.50 (C^5 (**4** + **2**)), 127.70 ($\text{C}^{2,6}$ (**4** + **2**)), 130.26 ($\text{C}^{4,4'}$ (**4**) + $\text{C}^{6,6'}$ (**2**)), 133.89 ($\text{C}^{4,4'}$ (**4**) + $\text{C}^{6,6'}$ (**2**)), 138.03 (C^4 (**4** + **2**)), 141.02 ($\text{C}^{4,4'}$ (**4** + **2**)), 147.55, 148.39 (C^4 (**4** + **2**)), 152.46 (C^6 (**4** + **2**)), 155.34, 155.60 (C^2 (**4** + **2**)), 158.23 (C^2 (**4** + **2**)); MALDI-TOF-MS: m/z : 1837 [$M - \text{PF}_6$], 1692 [$M - 2\text{PF}_6$], 1547 [$M - 3\text{PF}_6$]

6: ^1H NMR (CD_3OD): δ = 2.79 (s, 3 H, CH_3), 2.94 (s, 6 H, CH_3), 7.40–9.76 (m, aromatics and terpyridines, 69 H); ^{13}C NMR (CD_3OD): δ = 20.89, 122.01, 122.60, 125.19, 125.69, 128.01, 130.54, 136.84, 138.51, 141.32, 148.76, 149.25, 152.40, 156.12, 158.97; MALDI-TOF-MS: m/z : 1864 [$M - 4\text{Cl}$]

8: ^1H NMR (CD_3CN): δ = 2.93 (s, 3 H, CH_3), 7.31 (dd, 4 H, $\text{H}^{5,5'}$), 7.62 (d, 4 H, $\text{H}^{6,6'}$), 8.06 (dd, 4 H, $\text{H}^{4,4'}$), 8.41 (s, 2 H, $\text{H}^{4,6}$), 8.87 (d + s, 5 H, $\text{H}^{3,3'}$ + $\text{H}^{2,6}$), 9.37 (brs, $\text{H}^{3,5}$, 4 H); ^{13}C NMR ($[\text{D}_6]\text{DMSO}$): δ = 21.54 (CH_3), 121.83 (C^3), 124.62 ($\text{C}^{4,4'}$), 125.09 (C^3), 127.96 ($\text{C}^{4,4'}$), 130.32 (C^5), 137.60 ($\text{C}^{4,4'}$), 138.24 (C^4), 140.10 ($\text{C}^{4,4'}$), 146.86 (C^4), 152.24 (C^6), 155.25 (C^2), 158.14 (C^2); elemental analysis calcd for $\text{C}_{222}\text{H}_{156}\text{N}_{36}\text{Ru}_6\text{P}_{12}\text{F}_{72} \cdot 8\text{H}_2\text{O}$: C 45.82, H 2.96, N 8.67; found: C 45.86, H 2.98, N 8.68; MALDI-TOF-MS: m/z : 5544 [$M - \text{PF}_5$], 5400 [$M - \text{PF}_6 - \text{PF}_5$], 5292 [$M - 3\text{PF}_5$], 5166 [$M - 4\text{PF}_5$], 5020 [$M - 4\text{PF}_5 - \text{PF}_6$] (results were interpreted as the loss of either PF_5 alone or as both PF_5 and PF_6 together)^[34]

10: ^1H NMR (CDCl_3): δ = 7.41 (dd, J = 6 Hz, 4 H, $\text{H}^{5,5'}$), 7.94 (dd, J = 8 Hz, 4 H, $\text{H}^{4,4'}$), 8.15 (s, 2 H, $\text{H}^{2,6}$), 8.30 (s, 1 H, $\text{H}^{4,6}$), 8.73 (d, J = 8 Hz, 4 H, $\text{H}^{3,3'}$), 8.78 (d, J = 5 Hz, 4 H, $\text{H}^{6,6'}$), 8.81 (s, 4 H, $\text{H}^{3,5}$); ^{13}C NMR (CDCl_3): δ = 119.23 (C^3), 121.62 (C^3), 123.90 ($\text{C}^{4,4'}$), 124.18 (C^5), 125.23 ($\text{C}^{4,4'}$), 130.96 ($\text{C}^{2,6}$), 137.12 (C^4), 141.63 ($\text{C}^{4,4'}$), 148.88 (C^4), 149.33 (C^6), 156.10 (C^2), 156.33 (C^2); ESI-MS: m/z : 620 [$M + \text{H}^+$]; m.p. 308–309 °C

11: ^1H NMR (CD_3CN): δ = 2.90 (s, 3 H, CH_3 (**2**)), 7.30 (m, 8 H, $\text{H}^{5,5'}$ (**2** + **10**)), 7.60 (d, 8 H, $\text{H}^{6,6'}$ (**2** + **10**)), 8.05 (dd, 8 H, $\text{H}^{4,4'}$ (**2** + **10**)), 8.41 (s, 2 H, $\text{H}^{4,6}$ (**2**)), 8.75 (s, 2 H, $\text{H}^{2,6}$ (**10**)), 8.85 (d + s, 9 H, $\text{H}^{3,3'}$ (**10** + **2**) + $\text{H}^{3,5}$ (**2**)), 9.18 (s, 1 H, $\text{H}^{4,6}$ (**10**)), 9.43 (s, 8 H, $\text{H}^{3,5}$ (**2** + **10**)); ^{13}C NMR ($[\text{D}_6]\text{DMSO}$): δ = 22.01 (CH_3 (**2**)), 122.79 (C^3 (**2** + **10**)), 124.84 ($\text{C}^{4,4'}$ (**2**)), 125.88 (C^3 (**2** + **10**)), 127.11 ($\text{C}^{4,4'}$ (**10**)), 128.50 (C^5 (**2** + **10**) + $\text{C}^{4,4'}$ (**2**)), 131.05, ($\text{C}^{6,6'}$ (**2**)), 132.10 ($\text{C}^{4,4'}$ (**10**)), 132.66 ($\text{C}^{4,4'}$ (**10**)), 138.47 ($\text{C}^{4,4'}$ (**10**)), 138.84 (C^4 (**2** + **10**)), 140.49 ($\text{C}^{4,4'}$ (**2**)), 146.15 (C^4 (**10**)), 147.99 (C^4 (**2**)), 153.00 (C^6 (**2** + **10**)), 156.04 (C^2 (**2** + **10**)), 158.89 (C^2 (**2** + **10**))

9.37; $\Delta\delta$ = +0.54) relative to the corresponding signals in the uncomplexed ligand (Figure 1a). COSY and HETCOR spectra of the biscoordinating ligand **2** and the self-assembled macrocycle **8** verified the peak assignments and coupling patterns. Hexamer **8**, isolated as the 12Cl^- salt, was soluble in MeOH and hot H_2O , while conversion into the 12PF_6^- salt facilitated solubilization in MeCN, acetone, and DMSO.

Initially, further characterization of the key monomer **2**, as well as the bis(terpyridyl)– Ru^{II} connective moieties, was provided by the formation of the mono- and di- Ru^{II} com-

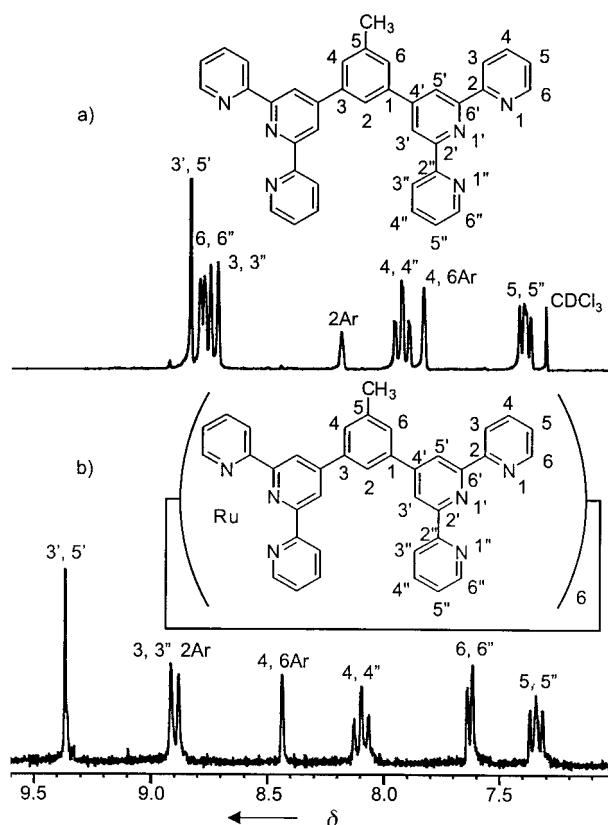
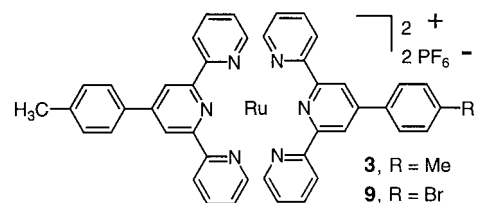


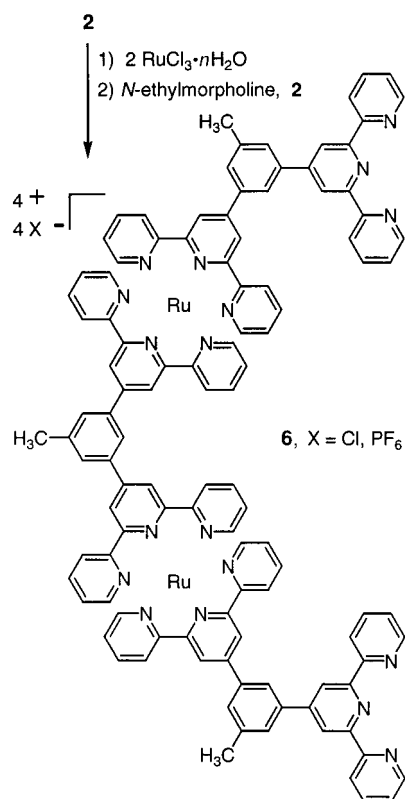
Figure 1. ^1H NMR spectra of the bis(terpyridyl) ligand **2** (a) and the self-assembled hexa- Ru^{II} complex **8** (b).

plexes **3** and **5** (Scheme 1). Reaction of 4'-(4-methylphenyl)-2,2':6',2''-terpyridine (**4**)^[31] with $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ ($\rightarrow [\text{Ru}(\text{4})\text{Cl}_3]$; Scheme 1) followed by addition of the unmetalated mono- and



bis-terpyridyl ligands (**4** and **2**) afforded the desired complexes (**3** and **5**, respectively). As in the case of hexamer **8**, complexes **3** and **5** exhibited a downfield shift (^1H NMR) of the 3',5'-H resonances (**3**, δ = 9.19, $\Delta\delta$ = +0.36; **5**, δ = 9.17, $\Delta\delta$ = +0.34) and an upfield shift of the 6,6''-H signals (**3** and **5**, δ = 7.62; $\Delta\delta$ = –1.15). Bisruthenium complex **5** was also prepared employing ligand **7** followed by capping with the free monoterpyridine **4**.

In order to ensure structural verification of macrocycle **8**, a stepwise, directed route to the material was devised. Subsequently, the diamagnetic tris-oligomer **6** was prepared from building block **2** by sequential treatment with two equivalents of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ and then unmetalated monomer **2** (Scheme 3). The ^1H NMR spectrum of trimer **6** showed a complex pattern of broadened absorptions in the aromatic region (δ = 9.76–7.40) as well as the two anticipated singlets arising from the nonequivalent methyl groups (δ = 2.79 (3 H);



Scheme 3. Construction of bis-Ru^{II} trimer **6** used in the directed synthesis of macrocycle **8**.

2.94 (6H)). Finally, reaction of the oligomer **6** with one equivalent of **7** (Scheme 2) yielded a material possessing identical spectral and physical characteristics to that of the self-assembled hexamer **8**. Notably, TLC on silica gel of the macrocycle **8** prepared by both procedures, eluting with a mixture of CH₃CN and aqueous KNO₃, exhibited identical *R_f* values (0.55), while the UV extinction coefficients (ϵ) exhibited a 5.1, 5.5, and 5.8 fold increase for λ_{max} at 290, 312, and 496 nm, respectively (Table 2), relative to the analogously measured coefficients for the mono-Ru^{II} complex **3**. Molec-

Table 2. UV absorption data of complexes **3** and **8**.

Complex	λ_{max} [nm]	ϵ
3	284	58 900
	310	66 100
	486	24 800
8	290	322 900
	312	336 800
	496	143 400

ular modeling of macrocycle **8** revealed a diameter of 37.5 Å, a minimum inner void distance of 17.5 Å, and a distance between adjacent Ru metals of 13.5 Å.

Figure 2 shows analytical ultracentrifugation absorption profiles at equilibrium^[32] for hexamer **8** (obtained from the reaction mixture derived from the self assembly of **7** and **2**) at a concentration of 0.5 % in acetonitrile. The data can be fitted equally well with a floating baseline term and a single exponential (Figure 2b), which indicates an average molec-

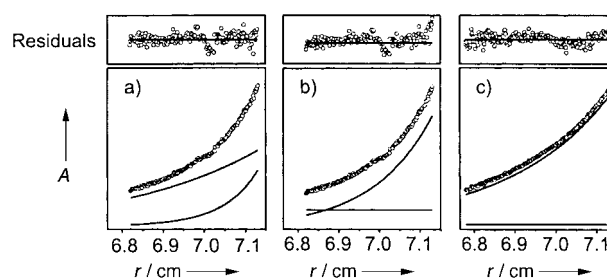


Figure 2. a) Concentration profile (A = absorbance, r = radius) for 0.5 wt % of **8** showing individual fits corresponding to two species; b) profile for 0.5 wt % and the fit to one species and a single baseline term; c) profile for 0.006 wt % and the fit to one species with a single baseline term.

ular weight of $M = 3250 \pm 100$, or with a two-exponential term and no floating baseline (Figure 2a), which yields $M = 1340 \pm 200$ (78 % of chromophores) and $M = 5600 \pm 900$ (22 % of chromophores). We assume that both species have the same partial specific volume. Figure 2 also shows the fitted profiles in both cases. The baseline is strikingly large for the single exponential fit with a floating baseline. This result suggests a nonsedimenting component (perhaps small, chromophoric ions) along with structures whose average mass falls only slightly short of the expectation for **8** ($M = 5670$ or 3930 without counterions). The two-exponential fit without floating baseline (Figure 2a) suggests an alternate viewpoint, in which significant amounts of fully formed **8** (22 % by chromophoric response) coexist with a mixture of low molecular mass species comparable in mass to either **7** or **2**. This very high concentration was chosen to facilitate comparison with the NMR results (typically 0.5 % for ¹H and 2.5 % for ¹³C) and requires investigation at wavelengths away from the maximum absorptions in the spectrum. By using more normal concentrations (0.006–0.02 %) in the analytical ultracentrifuge the data are fitted well by a single exponential with a small floating baseline (Figure 2c) and molecular weights of $M \approx 2600 \pm 200$, approximately half that expected for **8**. These solutions are sufficiently dilute to yield molecular parameters without undue influence from thermodynamic nonideality.

In an effort to modify the generally poor solubility of macrocycle **8**, as well as provide organizational scaffolding for the formation of a noncovalently-bonded network, the counter ions in **8**¹²⁺(12Cl[−]) were exchanged with a dodecacarboxylate-terminated dendrimer^[33] to give **8**¹²⁺[C(CH₂OCH₂CH₂CONHC(CH₂CH₂CO₂[−])₃)₄], which is an extremely insoluble assembly. However, a 1:1 mixture of hexamer **8** and a third generation carboxylate-terminated dendrimer gave **8**¹²⁺(G3-108-CO₂[−]), which produced a deep red solution in D₂O (25 °C), allowing verification of its structure by ¹H NMR spectroscopy. The use of compact, charge concentrated, (pseudo)spherical dendrimers possessing uniquely positioned anionic counterion character affords a convenient circumvention of the spatial randomness of traditional simple counterions in such complexes.

These results prompted the construction of heteroleptic macrocycles. Bromo analogues of **2** and **4** were prepared starting with 5-bromo-*m*-xylene or 4-bromobenzaldehyde, respectively. Reaction of the bromomonoterpyridyl ligand

(not depicted) with Ru^{III} adduct [Ru(4)Cl₃] gave the anticipated Ru^{II} complex **9**, which exhibited nearly identical ¹H and ¹³C NMR spectra to that of complex **3**. Thus, addition of the bromo building block **10** to the bis-Ru^{III} adduct **7** afforded the anticipated mixed monomer macrocycle **11** (Scheme 2). Evidence for its formation includes a symmetrically similar yet expectedly broadened ¹H NMR spectrum corresponding exactly to that of the hexamethyl analogue **8**; HETCOR experiments further support the structure. These experiments suggest the potential to access larger and more complex macrocycles as well as other architectures.

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$$A(r) = A(a) e^{\omega^2 M(1-\rho\nu)(r^2-a^2)/2RT} \quad (1)$$

frequency [rad s⁻¹], *M* the molar mass, ρ the solvent density, ν the solute partial specific volume, *r* the radius from the center of the rotor, *a* the radius at the meniscus, *R* the gas constant, and *T* the temperature in Kelvin. The absorbance profile of a multicomponent system has additional exponential growth terms. A Parr DMA58 precision densitometer was used to determine the partial specific volume.

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Synthesis of the First [3₄]Allenophane: 1,3,10,12,19,21,28,30-Octamethyl- [3.3.3]paracyclophan-1,2,10,11,19,20,28,29- octaene**

Stephan Thorand, Fritz Vögtle, and Norbert Krause*

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

Allenes belong to the most interesting target molecules of organic chemistry because of their axial chirality and their high reactivity. Although numerous achiral and chiral allenes with different substitution patterns have been synthesized,^[1] several types of allenes with unusual topologies and properties are still unknown. Among these are oligomeric cyclic arylallenes which represent a new class of cyclophanes^[2]

[*] Prof. Dr. N. Krause,^[+] Dr. S. Thorand, Prof. Dr. F. Vögtle
Institut für Organische Chemie und Biochemie der Universität
Gerhard-Domagk Strasse 1, D-53121 Bonn (Germany)

[+] New address: Lehrstuhl für Organische
Chemie II der Universität
D-44221 Dortmund (Germany)
Fax: (+49) 231-755-3884
E-mail: nkrause@pop.uni-dortmund.de

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(“allenophanes”) and which should possess interesting properties as chiral ligands/hosts for metal ions and small guest molecules,^[3, 4] also because they are axially and planar chiral when substituted suitably. Additionally, investigations of ring strain and circular dichroism^[5] should provide information about the interaction between the π -electron systems of the aromatic rings and the allenic bridges. The few allenophanes reported until now are either ansa compounds, that is, cyclophanes with only one bridged arene ring,^[6] or macrocycles with only one allene bridge.^[7] We now report the first synthesis of a “true” allenophane bearing several aromatic rings and allenic bridges, that is, of the [3₄]allenophane 1,3,10,12,19,21,28,30-octamethyl[3.3.3.3]paracyclophan-1,2,10,11,19,20,28,29-octaene (**1**). This hydrocarbon exists as four diastereomers with different topologies (Figure 1)^[8] which should show an individual complexing ability.

Our synthesis starts with the aromatic building blocks 4-trimethylsilyl ethynylbenzaldehyde and -acetophenone (**3**), which were prepared in high yield by using a new variant of the Sonogashira-coupling procedure developed by us

(Scheme 1).^[9] The former compound was acetalized with 1,3-propanediol and desilylated to **2** with K₂CO₃/methanol. Attempts to add the lithium acetylide of **2** to **3** gave the desired product **4** only in about 45% yield; it seems that enolization of the ketone by the strongly basic acetylide prevails. This problem could be solved by transmetalation to the less basic titanium acetylide^[10] which provided **4** in 89% yield. Acylation of **4** was followed by introduction of the first allene moiety, making use of an S_N2' substitution with methylmagnesium bromide in the presence of copper(I) iodide and lithium bromide.^[11] Diaryllallene **6** was obtained with 88% yield and deprotected chemoselectively to **7** or **8** with standard methods. Lithiation of **7** and addition to **8** then gave the propargylic alcohol **9**. The alcohol **9** was transformed into the tertiary acetate **12** by oxidation with activated manganese dioxide, followed by addition of methyllithium and acylation. Another S_N2' substitution gave trisallene **13** with good yield (85%) which was then deprotected at both termini to provide **14** (Scheme 2).

In the key step of the synthesis, this had to be cyclized to the 28-membered macrocycle **15**. Among different procedures which were tested for this purpose, addition of **14** to a diluted solution of potassium hexamethyldisilazide in THF at –80 °C gave the best results (see Experimental Section). The macrocycle **15** was thus obtained in 52% yield and transformed into the propargylic acetate **18** with the usual sequence of oxidation, addition of MeLi, and acylation; finally, the fourth allenic bridge was introduced by another S_N2' substitution with MeMgBr. Allenophane **1** was thus synthesized over 16 steps in 5.0% overall yield.

The synthesis of **1** presented here is not stereoselective; therefore, trisallene **13** was obtained as a mixture of four diastereomers, resulting in very complex NMR spectra of this compound and of the subsequent products **14–18**. In contrast, only one set of signals was observed for allenophane **1** in the ¹H (δ = 7.33, 2.26) and ¹³C NMR spectrum (δ = 207.0, 134.8, 125.5, 102.5, 15.8); even addition of the shift reagents [Eu(fod)₃]/[Ag(fod)]^[12] did not result in a splitting of the resonances (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione). Attempts to prove the existence of the four diastereomers shown in Figure 1 by HPLC failed due to the low solubility of the compound. We are currently working on the diastereo- and enantioselective synthesis of the isomers of **1**, making use of the high *anti*-stereoselectivity of the S_N2' substitution of derivatives of chiral propargylic alcohols.^[1, 13] Additionally, we intend to study the use of the acyclic oligomeric arylallenes of the type **13/14** as precursors for helically chiral polymers which are of high current interest as model compounds for biologically relevant receptors and catalysts.^[14] Also, macrocyclic hydrocarbons such as **1** may be useful as wheels for rotaxanes.

Experimental Section

Cyclization of **14**: Potassium hexamethyldisilazide (50 mg, 0.25 mmol) was dissolved in THF (40 mL), and the resulting solution was cooled to –80 °C. A solution of **14** (70 mg, 0.125 mmol) in THF (10 mL) was then added within 20 min. Stirring at –80 °C was continued for 40 min; hydrolysis with saturated NH₄Cl solution was followed by extraction with diethyl ether (three times). The combined organic layers were washed once with brine

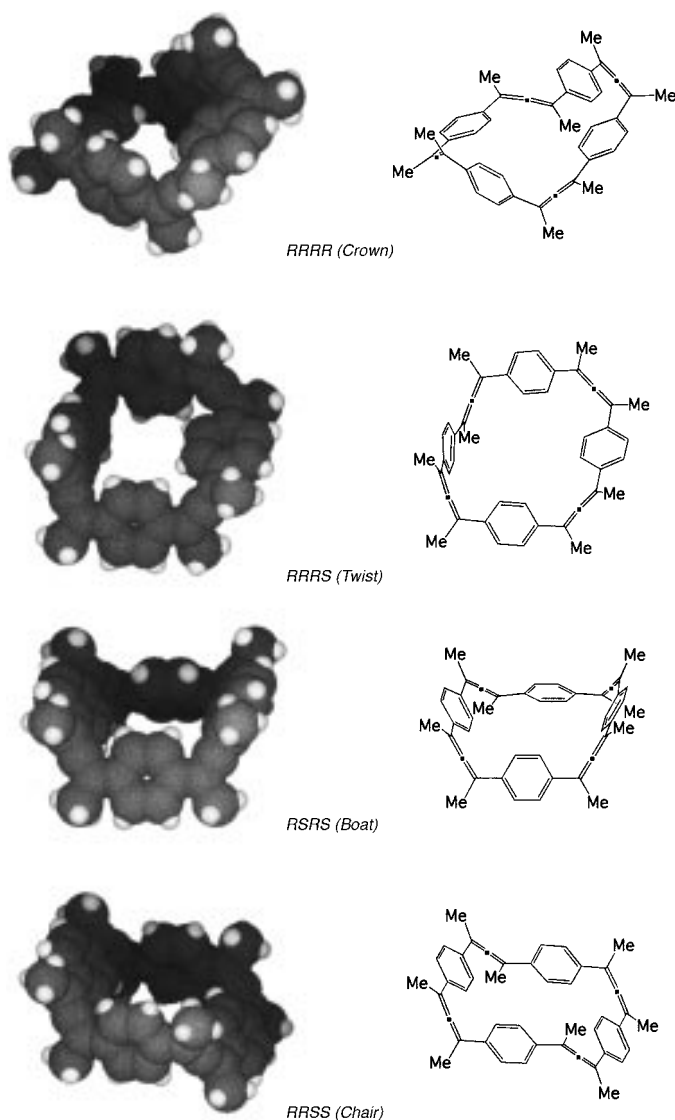
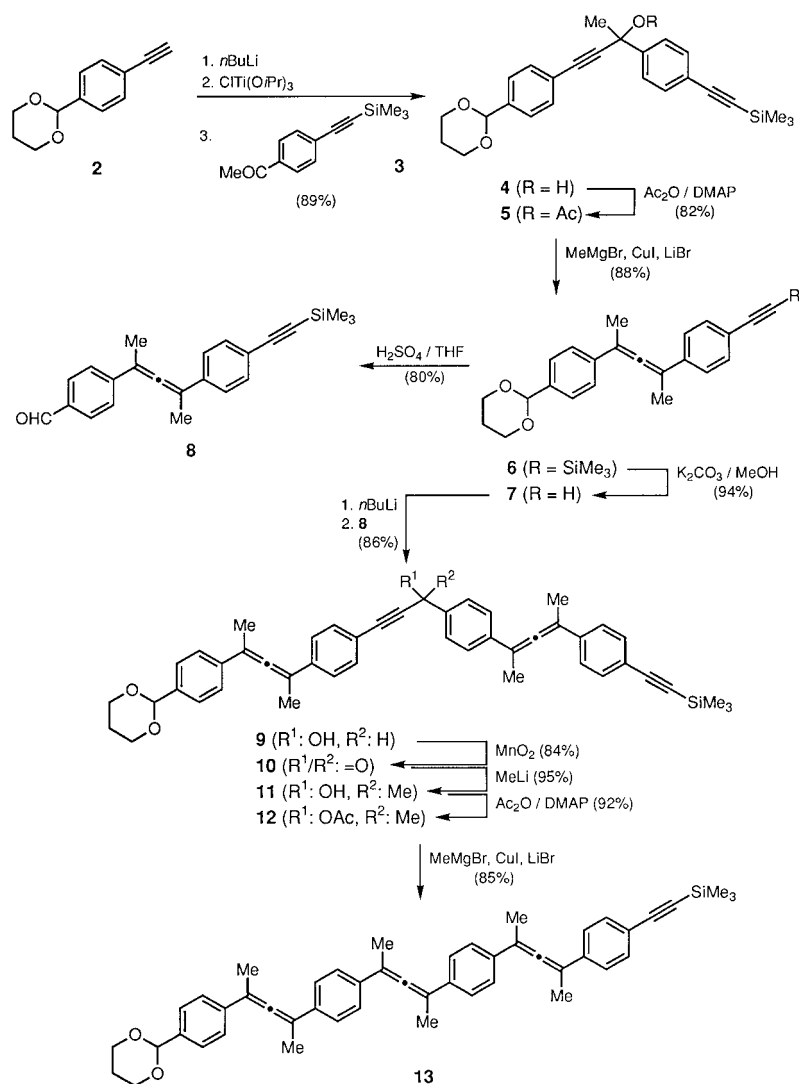
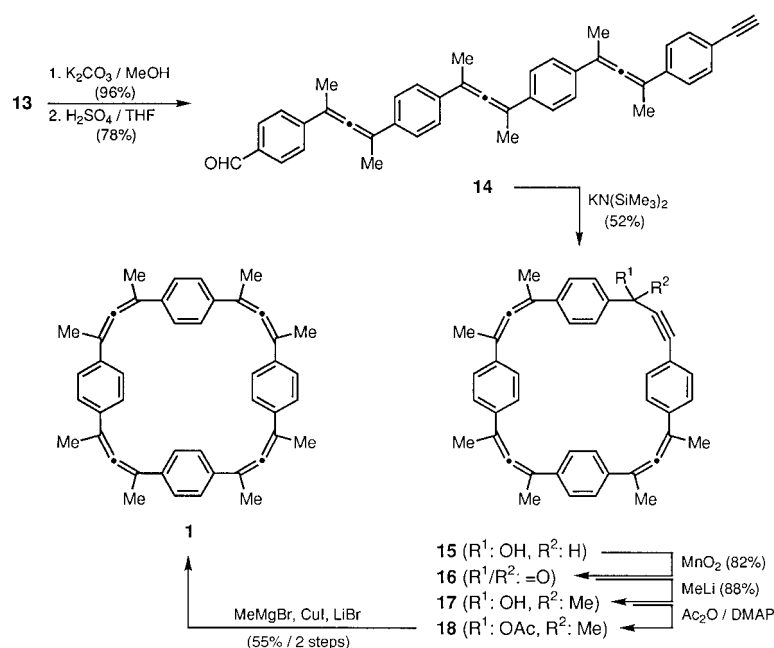


Figure 1. Diastereomers of allenophane **1**.



Scheme 1. Synthesis of the trisallene **13**. DMAP = 4-dimethylaminopyridine.



Scheme 2. Conclusion of the synthesis of **1**: Cyclization and final reactions on the macrocyclic framework.

and dried with MgSO₄; the solvent was distilled off in vacuo. Purification of the crude product by chromatography (SiO₂, toluene) gave **15** (36 mg, 52%) as a colorless solid. Spectroscopic data of 1,3,10,12,19,21,28,30-octamethyl-[3.3.3.3]paracyclophane-1,2,10,11,19,20,28,29-octaene (**1**): ¹H NMR (500 MHz, CD₂Cl₂): δ = 7.33 (s, 16H, Aryl-H), 2.26 (s, 24H, CH₃); ¹³C NMR (125 MHz, CD₂Cl₂): δ = 207.0 (×), 134.8 (×), 125.5 (+), 102.5 (×), 15.8 (+); IR (KBr): ν̄ = 2982–2852, 1928, 1602, 1502, 833 cm⁻¹; MS (EI, 70 eV): *m/z* (%): 568 (100, [M]⁺), 553 (50); high-resolution MS: calcd: 568.3129, found: 568.3123. ((×) and (+) denote the phases in the DEPT spectrum.)

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[Pt₁₉(CO)₂₁(NO)]³⁻ and [Pt₃₈(CO)₄₄]²⁻: Nitrosyl Bending through Intramolecular Electron Transfer as an Intermediate Step in the Nucleation Process from Polydecker to *ccp* Platinum Carbonyl Clusters**

Alessandro Ceriotti,* Norberto Masciocchi,*
Piero Macchi, and Giuliano Longoni

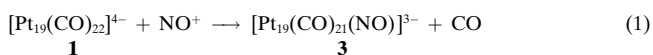
In memory of Paolo Chini

High-nuclearity carbonyl metal clusters (HNCCs) are often considered to be excellent model systems for studying important events concerning small metal particles, for example chemisorption and catalytic activity, which are highly dependent on the local structure of the active sites (exposed faces, surface defects, kinks, steps).^[1] Several different metal packings have been found in HNCCs, but still little information is available about skeletal transformations, nucleation processes, and ligand activation.^[2, 3] Several years ago we reported the synthesis and the crystal structure determination of [Pt₁₉(CO)₂₂]⁴⁻ (**1**), which contains a principal axis of idealized fivefold symmetry.^[4] At that time [Pt₃₈(CO)₄₄]²⁻ (**2**) was also isolated from the reaction of **1** with protic acids; however, the poor quality of the miscellaneous crystals of **2** obtained over the years defeated all attempts to fully elucidate its structure and only disclosed a *ccp* Pt₃₈ cluster core.^[5] Consequently, the number of cations and carbonyl ligands could only be inferred from elemental analyses^[5] and theoretical expectations.^[6]

The exceptional redox propensity of **1** and **2** pointed out by electrochemical and spectroelectrochemical studies^[5b, 7] prompted us to reinvestigate the chemistry of **1** with the aim to explore the effect of its electron-sponge behavior toward coordinated ligands other than CO. A further objective was to gain better understanding of the nucleation process leading from the fivefold symmetry core of **1** to the *ccp* core of **2**. We report here the synthesis and molecular structure of the unprecedented nitrosyl HNCC [Pt₁₉(CO)₂₁(NO)]³⁻ (**3**). As a part of these studies, a new synthesis and the full structural

characterization of **2**, which disclosed the exact stereochemistry of all carbonyl ligands, is also reported.

Compound **3** has been obtained by controlled addition of one equivalent of NOBF₄ to a solution of **1** in acetonitrile at room temperature and under nitrogen atmosphere [Eq. (1)]. Apparently, Equation (1) represents the plain sub-



stitution of a carbonyl with a nitrosyl ligand. However, as we will show, **1** and **3** cannot be considered isoelectronic, and the latter has two cluster valence electrons (CVEs) less than the former. The IR spectrum of **3** in acetonitrile shows absorption bands assigned to terminal (2025s, 1965w cm⁻¹) and edge-bridging carbonyl groups (1817 cm⁻¹) and bent nitrosyl ligands (1617w cm⁻¹); the latter absorption is clearly observed also when crystals of [PPh₄]₃·**3** are dissolved in THF.

Further gradual addition of two equivalents of NOBF₄ to **3** in acetonitrile leads to different products as a function of the reaction atmosphere. Thus, under a carbon monoxide atmosphere, the reaction of **3** with NO⁺ selectively leads to **2**, which separates out as a sparingly soluble quaternary ammonium or phosphonium salt [Eq. (2)].



According to the sum of Equations (1) and (2), the direct transformation of **1** into **2** can be conveniently carried out by adding three equivalents of NOBF₄ to **1** under a carbon monoxide atmosphere. Compound **2** shows two sharp IR absorptions (2056s, 1807m cm⁻¹) in THF. In contrast, under a nitrogen atmosphere, monitoring by IR spectroscopy suggests the additional formation of yet uncharacterized oxidized species not containing metal-bound nitrosyl groups.

The molecular structure of **3** has been determined by X-ray diffraction on a single crystal of its PPh₄⁺ salt. The asymmetric unit contains two crystallographically independent (but very similar) anions.^[8] As in the parent species **1**, each anion contains a Pt₁₉ metal core derived from the fusion of three pentagonal bipyramids along a common axis, resulting in a Pt-Pt₅-Pt-Pt₅-Pt-Pt₅-Pt array of idealized D_{5h} symmetry (Figure 1). Eleven terminal and ten edge-bridging carbonyl groups and one terminally bonded nitrosyl group surround the metal core and, if the differences in the C/N labels are neglected, the connectivity pattern of **1** is fully maintained. Since the metal core and ligand geometries of the two independent moieties of **3** are strictly comparable and match (to within 0.03 Å) the average values for the eight chemically distinct sets of intermetallic distances of the parent species **1** (see legend to Figure 1), the original detailed discussion on the nature of the different metal–metal interactions in **1** holds also for **3**.

The coordination of the NO fragment, which occurs selectively on one apical Pt atom, can be easily evinced by the bent Pt–N–O angles (142(2) and 150(2)°); all other terminal ligands show M–C–O values in the 172(2)–179(2)° range.^[9] Bent σ-bonded nitrosyl ligands typically show M–N–O angles between 120 and 160°.^[10] Such observed bending points

[*] Prof. A. Ceriotti
Dipartimento di Chimica Inorganica
Metallorganica e Analitica e Centro CNR
Università di Milano, via G. Venezian 21, I-20133 Milano (Italy)
Fax: (+39)02-23-62-748
E-mail: ceriotti@csmtbo.mi.cnr.it

Prof. N. Masciocchi
Dipartimento di Scienze Chimiche Fisiche e Matematiche Università
dell'Insubria sede di Como, via Lucini 3, I-22100 Como (Italy)
Fax: (+39)02-70-63-52-88
E-mail: norbert@csmtbo.mi.cnr.it

Dr. P. Macchi
Dipartimento di Chimica Strutturale e Stereochimica
Inorganica, Metallorganica e Analitica e Centro CNR
Università di Milano, Milano (Italy)

Prof. G. Longoni
Dipartimento di Chimica Fisica e Inorganica
Università di Bologna (Italy)

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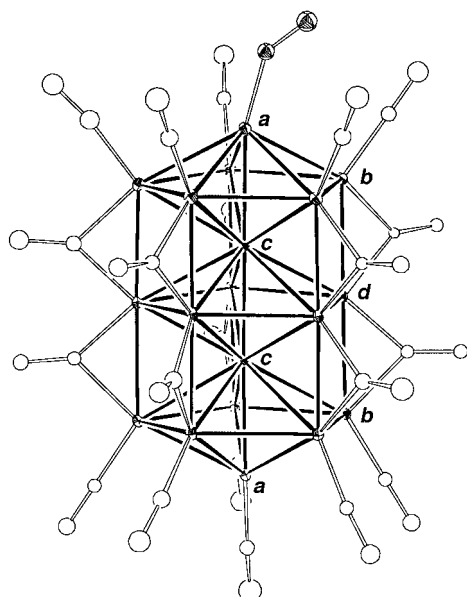


Figure 1. ORTEP drawing of **3** showing the unique nitrosyl ligand on one apical Pt atom. Thermal ellipsoids are drawn at the 50% probability level. Average Pt...Pt distances [Å] (values for **1** in parentheses): $a-b$ ($20 \times$) 2.74 (2.75), $a-c$ ($4 \times$) 2.66 (2.68), $b-c$ ($20 \times$) 2.79 (2.81), $b-d$ ($20 \times$) 2.72 (2.72), $c-d$ ($20 \times$) 2.79 (2.80), $c-c$ ($2 \times$) 2.64 (2.64), $b-b$ ($20 \times$) 2.86 (2.87), $d-d$ ($10 \times$) 2.87 (2.90); additional bond distances [Å] and angles [°]: Pt-N 1.79(2)–1.82(2), N-O 1.14(2)–1.15(2), av C–O_{terminal} 1.16, av C–O_{bridging} 1.21; Pt-N-O 142(1)–150(2).

out that the nitrosyl group of **3** is σ -bonded and formally behaves as a one-electron donor. Evidently, a redistribution of CVEs (from 238 in **1** to 236 in **3**) has occurred by means of an intramolecular redox reaction, which localizes onto the NO ligand two electrons formerly delocalized over the metal cluster. Therefore, it appears that the versatile NO fragment, in its linear or bent mode, could stabilize isostructural clusters with different numbers of CVEs, like those observed in the electrochemical oxidation of **1**.^[7]

The intramolecular redox reaction leading to **3** has been rationalized by semiempirical extended Hückel (EH) molecular orbital computations with CACAO^[11] on a [Pt₁₉(CO)₂₁]³⁻ fragment of idealized C_{5v} symmetry interacting with a terminally bonded NO ligand. These point out that the stabilization deriving from the $\pi^*(NO)-d_{xz}, d_{z^2}$ interaction in the bent mode overwhelms the destabilizing $\sigma(NO)-d_{z^2}$ overlap.^[12] Furthermore, a Walsh diagram reveals a minimum of the EH total orbital energy for Pt-N-O bending close to 140°, which is in agreement with the experimental value. That this rationalization is at least qualitatively reliable has been shown by computing also the corresponding diagrams of the mononuclear species [M(S₂CNR₂)₂(NO)] (M = Fe, R = Et^[13] and M = Co, R = Me^[14]) bearing a linear and bent nitrosyl ligand, respectively, and the most relevant [Pt₁₉(CO)₂₁(CO)]⁴⁻ anion (**1**, for which the linear geometry of the apical carbonyl is correctly predicted).

Coordination of bent NO on electron-rich metal centers is well documented; bending of linear metal-bound NO has been suggested to occur upon reduction or photochemical excitation on the basis of spectroscopic studies and is thought to prelude NO activation in a number of reactions.^[15] To our

knowledge **3** is the first structurally characterized carbonyl cluster bearing a bent nitrosyl group.

The structure of **2**, as derived from its [N(PPh₃)₂]⁺ salt,^[8] is based on the previously ascertained *ccp* metal core of idealized O_h symmetry (Figure 2). The 38 platinum atoms

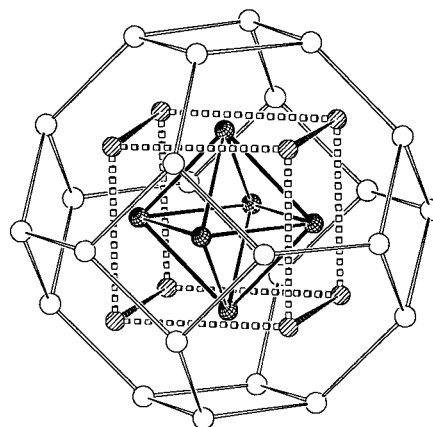


Figure 2. Perspective drawing of the Pt₃₈ metal cage of **2** showing the Pt₆ octahedron encapsulated in a shell of 32 Pt atoms with O_h symmetry. Empty circle: Wyckoff d position, hatched circle: Wyckoff b position, cross-hatched circle: Wyckoff a position. Average Pt...Pt distances [Å]: $a-a$ ($12 \times$) 2.881(5), $a-b$ ($24 \times$) 2.784(28), $a-d$ ($24 \times$) 2.859(37), $b-b$ ($48 \times$) 2.848(31), $d-d$ ($24 \times$) 2.844(23). Mean values and estimated standard deviations (in parentheses) of chemically equivalent interactions computed as $x_{av} = 1/n \sum x_i$ and $\sigma_{n-1}^2 = 1/(n-1) \sum (x_i - x_{av})^2$.

constitute a truncated ν_3 octahedron with only three chemically distinct types of metal atoms: 6 in a , 8 in b , and 24 in d (Wyckoff positions of the O_h point group). In addition, this cluster bears 32 terminal carbonyl groups (one on each surface atom (b and d)) and 12 edge-bridging CO ligands (two on opposite sides of the six square faces made by d atoms); the overall idealized symmetry is thus lowered to D_{2d} (Figure 3).

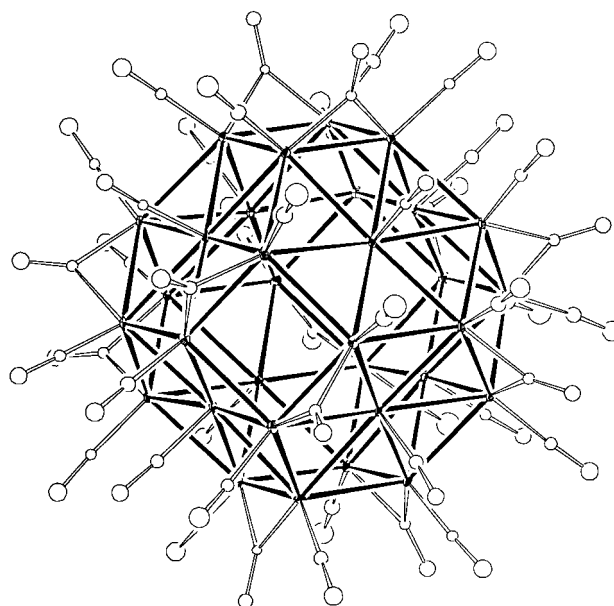


Figure 3. ORTEP drawing of **2**. For simplicity the inner Pt₆ octahedron has been removed. Thermal ellipsoids are drawn at the 50% probability level; av C–O_{terminal} 1.15, av C–O_{bridging} 1.22 Å.

While the Pt...Pt distances lie in the 2.749(1)–2.919(1) Å range, a much more uniform distribution is observed for the fully encapsulated Pt₆ octahedron (2.803(1)–2.818(1) Å), which does not suffer from the less symmetric environment sustained by the surface platinum atoms. These can be divided in two distinct sets: 1) the six centers of slightly concave (average displacement ca. 0.07 Å) hexagons, and 2) the 24 peripheral *d* atoms, showing shorter Pt...Pt distances (av 2.814 Å) for carbonyl-bridged edges than for unsupported ones (av 2.859 Å). The analysis of the bond lengths and carbonyl geometry, as well as the adopted synthesis, does not support the presence of hydrides within the cluster or close to its surface.

Yet a limited number of close-packed HNCC containing fully encapsulated groups of metal atoms are known, for example [Pt₂₆(CO)₃₂]²⁻,^[5a,b] [H_{6-n}Ni₃₈Pt₆(CO)₄₈]ⁿ⁻ (*n* = 4–6),^[16] [Ni_{36+x}Pt₄(CO)_{45+x}]⁶⁻ (*x* = 0, 1),^[17] [H_xRh₂₈N₄(CO)₄₁]⁴⁻ (*x* = 0 or 2),^[18] and [H₁₂Pd₂₈Pt₁₃(CO)₂₇(PMe₃)(PPh₃)₁₂]^{19]}. Due to interest in them also as electron-sink compounds,^[16b] it is hoped that the recent availability of CCD area detectors could rapidly increase this number. Within this class, compound **2** features the largest homometallic core exclusively stabilized by carbonyl ligands and the smallest polyhedron for which an inner octahedron is fully surrounded by a second shell of metal atoms. In this respect, it is comparable to the well-known species [H_xRh₁₃(CO)₂₄]^{(5-x)-} (*x* = 1–3)^[20] and **1**, which encapsulate one and two metal atoms, respectively.^[21]

Efforts to clarify the condensation process from **1** to **2**, the reactivity of the bent NO ligand and the redox behavior of **3** are underway.

Experimental Section

[PPh₄]₃-**3**: A solution of NOBF₄ (10 mg, 0.086 mmol) in acetonitrile (5 mL) was added in small portions to a solution of [NBu₄]₄-**1** (460 mg, 0.087 mmol) in acetonitrile (15 mL). The resulting mixture was stirred for about 1 h while the reaction was monitored by IR spectroscopy. The solid product was precipitated and recovered by addition of a solution of PPh₄Cl (500 mg) in isopropanol (40 mL). The resulting solid was filtered, washed with isopropanol (20 mL), and crystallized from acetonitrile (20 mL) and diisopropyl ether (50 mL) to yield 230 mg of [PPh₄]₃-**3** (48 % yield based on Pt). Elemental analysis: calcd: C 20.90, H 1.13, N 0.26; found: C 21.00, H 1.05, N 0.20.

[N(PPh₃)₂]₂-**2**: [N(PPh₃)₂]₄-**1** (1.94 g, 0.3 mmol) was dissolved in acetonitrile (40 mL) under a CO atmosphere. A solution of NOBF₄ (105 mg, 0.9 mmol) in acetonitrile (5 mL) was slowly added, and the mixture was stirred for 4 h. The resulting black precipitate was filtered, washed with acetonitrile (10 mL), and crystallized from THF (20 mL) and cyclohexane (60 mL) to yield 580 mg of [N(PPh₃)₂]₂-**2** (40 % yield based on Pt). Elemental analysis: calcd: C 14.32, H 0.62, N 0.29; found: C 14.10, H 0.75, N 0.25.

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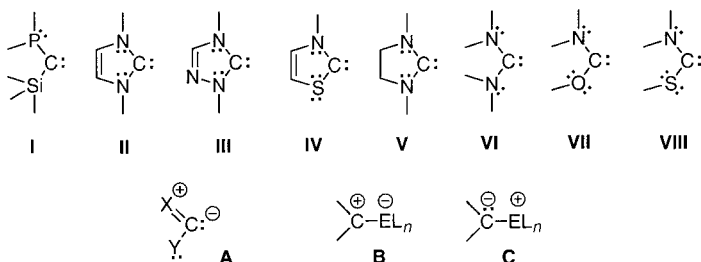
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- [8] a) Crystal data for [PPh₄]₃[Pt₁₉(CO)₂₁(NO)] ([PPh₄]₃-**3**): triclinic, space group *P* $\bar{1}$, *a* = 19.928(3), *b* = 23.685(4), *c* = 24.058(4) Å, *a* = 113.63(1), *β* = 90.21(1), *γ* = 102.78(1)°, *V* = 10.091(3) Å³, *Z* = 4, *ρ*_{calcd} = 3.517 g cm⁻³, *μ*(Mo_{Kα}) = 263.3 cm⁻¹;^[8c] b) Crystal data for [N(PPh₃)₂]₂[Pt₃₈(CO)₄₄] ([N(PPh₃)₂]₂-**2**): monoclinic, space group *C*2/*c*, *a* = 32.768(2), *b* = 14.110(2), *c* = 36.459(2) Å, *β* = 105.80(1)°, *V* = 16,220(3) Å³, *Z* = 4, *ρ*_{calcd} = 3.98 g cm⁻³, *μ*(Mo_{Kα}) = 327.2 cm⁻¹;^[8c] c) Graphite-monochromated Mo_{Kα} radiation (*λ* = 0.71073 Å). Experimental procedure (values for [N(PPh₃)₂]₂-**2** in parentheses): 140 702 (37 301) reflections with *θ* < 30.5 (26.0)° were measured at 193 K (173 K) on a Bruker SMART diffractometer equipped with a CCD area detector, on a crystal of approximate dimensions 0.10 × 0.15 × 0.25 mm (0.05 × 0.10 × 0.15 mm), mounted in air but protected by a cooling N₂ stream during the data collection. Data were corrected for Lorentz, polarization, and absorption effects (empirical absorption corrections by SADABS: G. M. Sheldrick, unpublished). The structures were solved by direct methods (A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115), and refined with full-matrix least squares (G. M. Sheldrick, *SHELXL97, Program for Structure Refinement*, Universität Göttingen, Germany, **1997**) using 53 926 (14 000) independent reflections. Anisotropic displacement parameters were assigned to Pt and P atoms. The final agreement factors were *R* = 0.050 (0.056) and *R*_w = 0.086 (0.163); maximum *Δρ* = 3.0 (4.3) e⁻ Å⁻³, close to the Pt atoms. 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-127446 (**3**) and CCDC-127447 (**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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 [21] However, the Pt₁₉ metal atom cage is not compatible with translational symmetry.

The Electrophilic Behavior of Stable Phosphanylcarbenes Towards Phosphorus Lone Pairs**

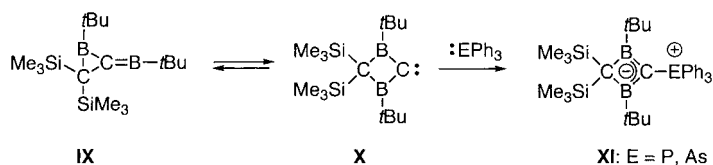
St phanie Goumri-Magnet, Orest Polishchuk, Heinz Gornitzka, Colin J. Marsden, Antoine Baceiredo, and Guy Bertrand*

All the known stable carbenes **I–VIII**^[1,2] feature two heteroatom substituents. According to calculations,^[3] all these carbenes are strongly stabilized by electron donation from the



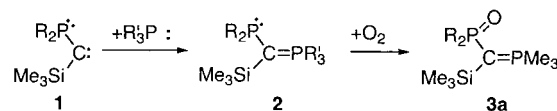
nitrogen or phosphorus lone pair into the formally “empty” p_π orbital. In other words, the peculiar stability of these compounds is due to the crucial contribution of the ylide form **A**. Therefore, carbenes **I–VIII** show strong nucleophilic character and readily react with Lewis acids to give reverse ylides **B**.^[1,4] On the other hand, transient electrophilic carbenes are known to react with Lewis bases to give normal ylides **C**. For example, carbene–pyridine adducts have been spectroscopically characterized and used as a proof for the formation of carbenes.^[5] The reaction of transient dihalocarbenes with phosphanes is even a preparative method for *C*-dihalo phosphorus ylides.^[6] Lastly, addition of triphenylphosphane and triphenylarsane to the borandiylborirane **IX**, the

hidden form of the electrophilic carbene **X**, led to the corresponding ylides **XI**.^[7] These reactions which involve the vacant orbital of singlet carbenes have not yet been observed with the stable carbenes **I–VIII**.



Moss et al. have shown that in contrast to dialkoxycarbenes, carbenes featuring only a weak π -donor substituent, such as acetoxyphenylcarbene, give carbene–Lewis base adducts.^[8] Among the stable carbenes **I–VIII**, only the phosphanyl-silylcarbene **I** has a single π -donor substituent. Moreover, it has been theoretically^[9] and experimentally^[10] demonstrated that phosphorus is a weaker π donor than nitrogen. Here we report that the stable carbene **1** indeed reacts with phosphanes to give the corresponding phosphorus ylides; the extension of this reaction to a bimetallic complex containing a side-on-coordinated $\text{:P}\equiv\text{P}$ moiety is also presented.

Instantaneous and quantitative formation of phosphorus ylides **2** occurred when one equivalent of phosphane was added at 0 °C to a solution of carbene **1** in pentane (Scheme 1).^[11] The coupling of the phosphane with the



Scheme 1. Synthesis of *C*-phosphanyl phosphorus ylides **2** and oxidation of **2a** to **3a**. R = *c*Hex₂N; R₁ = Me₃P (**a**), Et₃P (**b**), Me₂PhP (**c**), MePh₂P (**d**), Ph₃P (**e**).

carbene center was indicated by AX systems in the ³¹P NMR spectra. Ylides **2** are highly sensitive to oxygen. Attempted recrystallizations of **2a** led to the corresponding phosphane oxide **3a**, which was isolated in 90 % yield, as colorless crystals suitable for an X-ray diffraction study (Figure 1).^[12] The formation of **2** clearly demonstrates that the derivative **1** possesses an available vacant orbital at the carbene center, as

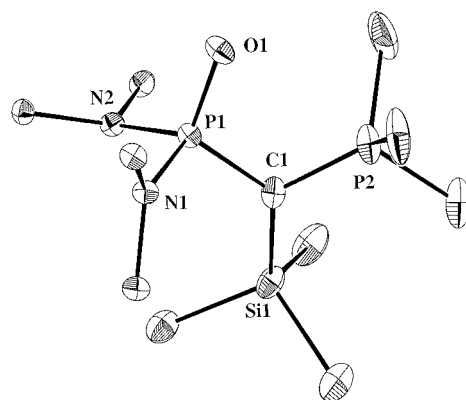


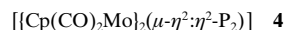
Figure 1. Crystal structure of **3a** (a part of the cyclohexyl groups and the hydrogen atoms have been omitted for clarity). Selected bond lengths [ ] and angles [ ]: P1–C1 1.755(2), P1–O1 1.4867(16), P2–C1 1.707(2), C1–Si1 1.849(2); P1–C1–P2 110.58(13), P1–C1–Si1 130.04(13), P2–C1–Si1 118.69(12).

[*] Dr. G. Bertrand, Dr. S. Goumri-Magnet, Dr. O. Polishchuk, Dr. H. Gornitzka, Dr. A. Baceiredo
 Laboratoire d’H t rochimie Fondamentale et Appliqu e
 Universit  Paul Sabatier
 118, route de Narbonne, F-31062 Toulouse cedex 04 (France)
 Fax: (+33) 5-61-55-82-04
 E-mail: gbertran@ramses.ups-tlse.fr
 Prof. C. J. Marsden
 Laboratoire de Physique Quantique, IRSAMC, UMR 5626-CNRS
 Universit  Paul Sabatier, Toulouse (France)

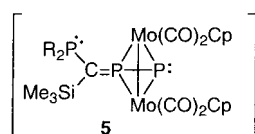
[**] Thanks are due to the CNRS for financial support of this work, and to the “Minist re de l’Education Nationale, de l’Enseignement Sup rieur et de la Recherche” for a postdoctoral fellowship (O.P.).

expected for a genuine singlet carbene. In contrast, it has been shown that the free electron of the radical anion formed by reduction of a carbene of type **III** is not located in the area of the carbenic center but on the NBO-LUMO of the C=N bond.^[13] This might explain the absence of reactivity of N-heterocyclic carbenes with Lewis bases.

The lone pairs of the :P=P: fragment in complexes such as **4**^[14] are available for further complexation reactions.^[15] Therefore, in the hope of synthesizing the hitherto unknown



phosphorus analogue **5** of a diazo compound, complex **4** was added at 0 °C to a solution of carbene **1** in toluene. After workup, a new complex was isolated as dark yellow crystals in



69% yield. Here also, the coupling of the carbene center with the phosphorus complex was clearly indicated by an AMX system in the ³¹P NMR spectrum (see the Experimental Section).

A single-crystal X-ray diffraction study^[12] revealed, instead of the desired product **5**, the heterocyclic structure **6** [Eq. (1), R = cHex₂N; Figure 2].

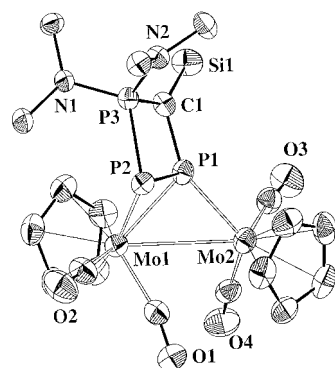
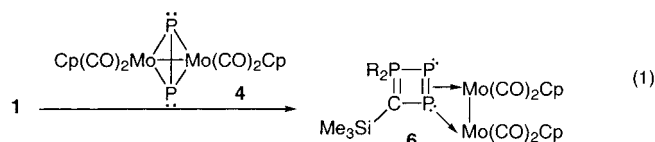
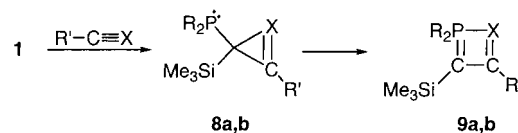


Figure 2. Crystal structure of **6** (a part of the cyclohexyl groups and the hydrogen atoms have been omitted for clarity). Selected bond lengths [Å] and angles [°]: P1–P2 2.152(3), P2–P3 2.220(3), P3–C1 1.733(6), P1–C1 1.754(7), P1–Mo2 2.340(2), P1–Mo1 2.492(2), P2–Mo1 2.636(2), Mo1–Mo2 3.279(1); C1–P1–P2 97.0(2), P1–P2–P3 72.33(9), P2–P3–C1 95.2(3), P1–C1–P3 95.5(3).

The symmetrical tetrahedrane structure of the starting P₂Mo₂ complex is no longer present, the two Mo atoms now showing different coordination geometries: Mo1 is linked to phosphorus atoms P1 and P2 (2.492(2) and 2.636(2) Å), while Mo2 is only bonded to P1 (Mo2...P1 2.340(2), Mo2...P2 3.765(2) Å). Both the four-membered P–P–P–C ring (maximum deviation 0.008(3) Å) and the ring carbon atom (sum of angles 359.8°) are planar. Together, these geometric parameters along with the P1–P2 bond length (2.152(3) Å) describe

what can be regarded as an ylidic four π electron four-membered heterocycle^[16] featuring a μ-η¹:η²-diphosphene fragment.^[17] The ligand in complex **6** is the first example of a 1λ³,2λ³,3λ⁵-triphosphete.^[18]

We have already shown that carbene **1** reacts with benzonitrile^[19a, b] and *tert*-butylphosphaalkyne^[19c, d] to give the corresponding three-membered heterocycles **8a, b**, which readily rearrange to afford the four-π-electron four-membered heterocycles **9a, b** (Scheme 2). Therefore the transient



Scheme 2. Synthesis of **8a, b** and subsequent rearrangement to **9a, b**. R = cHex₂N; X = N, R' = Ph (**a**); X = P, R' = *t*Bu (**b**).

formation of the 3*H*-diphosphirene complex **7**, which could undergo a ring expansion reaction to give **6** is quite likely. By analogy with the results observed by addition of phosphanes to **1**, the formation of the P-analogue **7** of a 3*H*-diazirine could result from the cycloisomerization of the initial P-analogue **5** of a diazoalkane.^[20, 21]

The reactivity of stable phosphanylcarbenes with various Lewis bases, and of the P₂-complex **4** towards various transient carbenes, is currently being investigated.

Experimental Section

All operations were carried out under argon using Schlenk techniques. In a typical experiment, to a solution of **1**^[11] (0.1 g, 0.2 mmol) in pentane (1 mL) was added at 0 °C a stoichiometric amount of phosphane or complex **4**.^[14] According to ³¹P NMR spectroscopy, in all cases the reaction was quantitative.

2a: ³¹P{¹H} NMR (C₆D₆): δ = 4.1 (σ⁴-P), 97.2 (σ³-P), ²J(P,P) = 218 Hz; ¹H NMR(C₆D₆): δ = 0.40 (s, 9H, CH₃Si), 1.24 (dd, 9H, ²J(P,H) = 11.6, ⁴J(P,H) = 2.4 Hz, PCH₃); ¹³C{¹H} NMR (C₆D₆): δ = 7.7 (d, ³J(P,C) = 3.1 Hz, CH₃Si), 19.8 (dd, ¹J(P,C) = 57.9, ³J(P,C) = 17.6 Hz, PCH₃). **2b**: ³¹P{¹H} NMR (C₆D₆): δ = 25.2 (σ⁴-P), 101.7 (σ³-P), ²J(P,P) = 192 Hz. **2c**: ³¹P{¹H} NMR (C₆D₆): δ = 7.1 (σ⁴-P), 98.1 (σ³-P), ²J(P,P) = 224 Hz. **2d**: ³¹P{¹H} NMR (C₆D₆): δ = 13.4 (σ⁴-P), 100.4 (σ³-P), ²J(P,P) = 229 Hz. **2e**: ³¹P{¹H} NMR (C₆D₆): δ = 24.6 (σ⁴-P), 108.4 (σ³-P), ²J(P,P) = 265 Hz.

3a: Attempted recrystallization of **2a** in pentane at –20 °C gave colorless crystals of **3a** (0.10 g, 90%). ³¹P{¹H} NMR (C₆D₆): δ = 8.5 (PCH₃), 46.2 ((cHex₂N)₂PO), ²J(P,P) = 16.0 Hz; ¹H NMR (C₆D₆): δ = 0.40 (s, 9H, CH₃Si), 1.36 (d, 9H, ²J(P,H) = 12.3 Hz, PCH₃); ¹³C{¹H} NMR (C₆D₆): δ = 7.1 (s, CH₃Si), 19.5 (dd, ¹J(P,C) = 56.7, ³J(P,C) = 16.0 Hz, PCH₃); MS (DCI, NH₃): *m/z*: 569 ([M+1]); m.p. > 250 °C.

6: Recrystallization from heptane/toluene at –20 °C gave dark yellow crystals of **6** (0.13 g, 69%). ³¹P{¹H} NMR (C₆D₆): δ = 250.3 (P1), –47.3 (P2), 63.8 (P3), *J*(P1,P3) = 15, *J*(P1,P2) = 285, *J*(P2,P3) = 256 Hz; ¹H NMR (C₆D₆): δ = 0.20 (s, 9H, CH₃Si), 5.05 (s, 10H, C₅H₅); ¹³C{¹H} NMR (C₆D₆): δ = 4.1 (dd, ³J(P,C) = 2.5, 1.0 Hz, CH₃Si), 58.2 (d, ²J(P,C) = 5.6 Hz, P–NCH), 58.5 (d, ²J(P,C) = 5.0 Hz, P–NCH), 91.9 and 93.3 (2 × s, C₅H₅); m.p. 155–157 °C (decomp.); elemental analysis calcd for C₄₂H₆₃Mo₂N₂O₄P₃Si: C 51.85, H 6.53, N 2.88; found: C 52.27, H 6.63, N 3.00.

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A Copper(II) Bis-phenanthroline Complex Buried in Fullerene-Functionalized Dendritic Black Boxes**

Nicola Armaroli,* Corinne Boudon, Delphine Felder, Jean-Paul Gisselbrecht, Maurice Gross,* Giancarlo Marconi, Jean-François Nicoud, Jean-François Nierengarten,* and Veronica Vicinelli

Dedicated to Prof. Guy Solladié on the occasion of his 60th birthday

On account of their fascinating structures and properties, dendrimers have attracted increasing attention in the past few years.^[1] In the development of procedures to synthesize monodispersed dendrimers,^[1, 2] increasing emphasis is being placed on the design and study of functionalized dendrimers.^[3–5] For example, because the dendrimer surface may contain multiple copies of a given chromophore, it can be used as an antenna for light harvesting.^[4] It is conceivable that a large number of peripheral chromophores could prevent direct photoexcitation at the central core. Whereas dendrimers containing various electro- and photoactive chromophores have been prepared in order to explore the influence of the microenvironment inside the macromolecule on the properties of the functional core,^[5] very large surrounding dendritic branches may be able to isolate a central functional core and thus prevent any external contact.

Here we report on the electrochemical and photophysical behavior of dendrimers with a bis(1,10-phenanthroline)copper(II) ([Cu(phen)₂]²⁺) core and peripheral fullerene π chromophores^[6] and show how the surrounding fullerene-functionalized dendritic branches are able to isolate the central Cu^I complex. The dendrimers and the parent compounds are depicted in Figure 1.

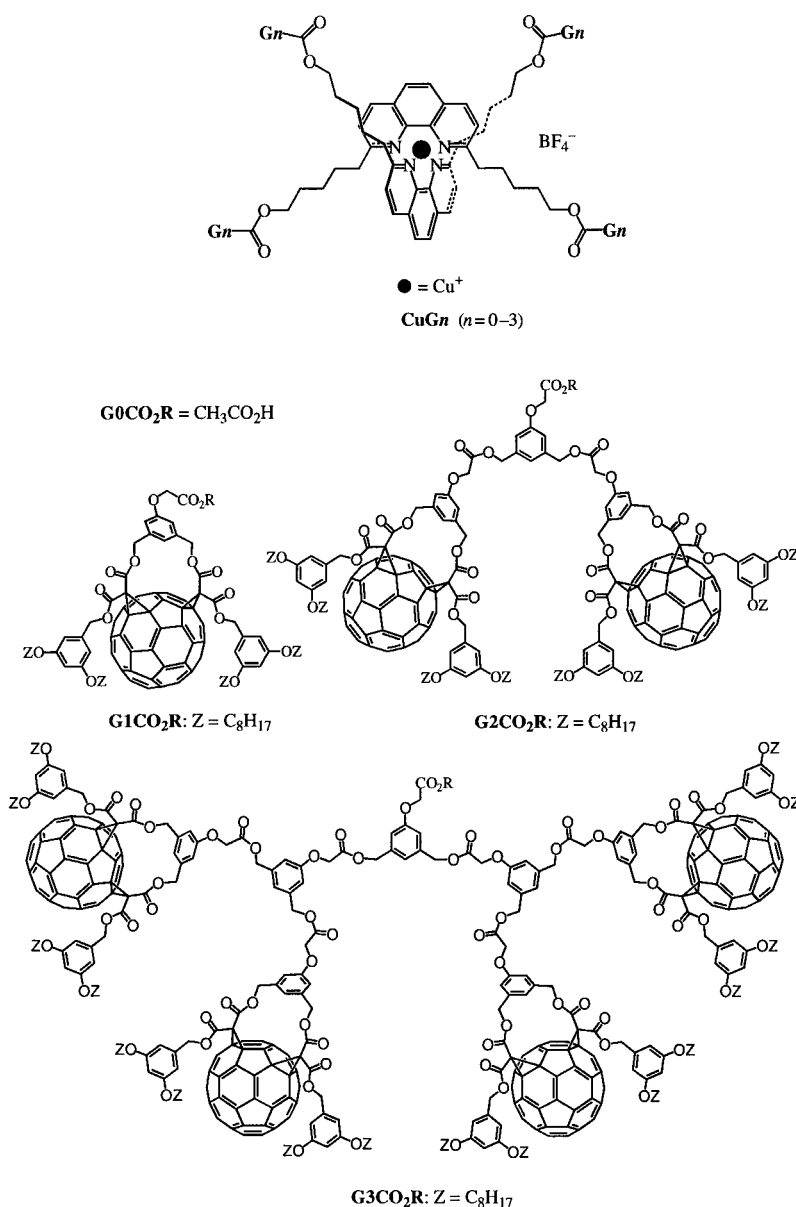


Figure 1. Schematic representation of the investigated dendrimers.

[*] Dr. N. Armaroli, Dr. G. Marconi, Dr. V. Vicinelli
Istituto di Fotochimica e Radiazioni d'Alta Energia del CNR
via Gobetti 101, I-40129 Bologna (Italy)
Fax: (+39)051-6399844
E-mail: armaroli@frae.bo.cnr.it
Prof. M. Gross, Dr. C. Boudon, Dr. J.-P. Gisselbrecht
Laboratoire d'Electrochimie et de Chimie Physique du Corps Solide
Université Louis Pasteur and CNRS
UMR no. 7512, 4 rue Blaise Pascal, F67008 Strasbourg (France)
Fax: (+33)3-88-61-15-53
E-mail: gross@chimie.u-strasbg.fr
Dr. J.-F. Nierengarten, D. Felder, Prof. J.-F. Nicoud
Groupe des Matériaux Organiques
Institut de Physique et Chimie des Matériaux de Strasbourg
Université Louis Pasteur and CNRS
23 rue du Loess, F-67037 Strasbourg (France)
Fax: (+33)3-8810-7246
E-mail: niereng@michelangelo.u-strasbg.fr

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The electrochemical investigations on **GnCO₂tBu** and **CuGn** were carried out by steady-state voltammetry (SSV) on a rotating-disk electrode and cyclic voltammetry (CV) in CH₂Cl₂/0.1M Bu₄NPF₆ on a glassy carbon electrode.^[7a] Both SSV and CV gave identical redox potentials (Table 1). Compound **G1CO₂tBu** showed the characteristic behavior previously reported for fullerene *cis*-2 bis-adducts.^[7] Whereas the first reduction at –1.07 V versus ferrocene/ferrocenyl cation (Fc/Fc⁺) is reversible, the second reduction at about –1.4 V is irreversible. It was shown that the second electron transfer in *cis*-2 derivatives is followed by a chemical reaction.^[7] The similar results that were obtained for reductions of the dendrimers of higher generations **G2CO₂tBu**, **G3CO₂tBu**, and **CuG1–CuG3** show that the peripheral fullerene subunits behave as independent redox centers in all compounds. The Cu^I/Cu^{II} oxidation potential of **CuG1** remains unchanged relative to the parent compound **CuG0**, and this indicates the absence of intramolecular electronic

Table 1. Data on the reduction and oxidation of **G1CO₂tBu**–**G3CO₂tBu** and **CuG0**–**CuG3** determined by CV on a glassy carbon electrode in CH₂Cl₂/0.1M Bu₄NPF₆.^[a]

Compound	Reduction		Oxidation
	<i>E</i> ₁	<i>E</i> ₂	<i>E</i> ₁
G1CO₂tBu	−1.07 (75)	−1.45 ^[b]	+1.2 ^[b]
G2CO₂tBu	−1.07 (75)	−1.45 ^[b]	+1.1 ^[b]
G3CO₂tBu	−1.08 (80)	−1.45 ^[b]	+1.1 ^[b]
CuG0	−2.20 ^[b, c]	–	+0.60 (70)
CuG1	−1.08 (80)	−1.39 ^[b]	+0.60 ^[d, e]
CuG2	−1.08 (80)	−1.43 ^[b]	n.o. ^[f]
CuG3	−1.07 (70)	−1.40 ^[b]	n.o. ^[f]

[a] Values for (*E*_{pa} + *E*_{pc})/2 [V] vs Fc/Fc⁺ and Δ*E*_{pc} [mV] (in parenthesis) at a scan rate of 0.1 V s^{−1}. [b] Peak potential values at a scan rate *v* of 0.1 V s^{−1}; irreversible process. [c] Reversible for *v* > 0.5 V s^{−1}. [d] Poorly resolved signal of small amplitude, irreversible process. [e] The slope observed in SSV for this oxidation is ca. 200 mV per log unit, which also indicates an irreversible oxidation process. [f] n.o. = not observed.

communication between the central copper(II) complex and the four surrounding fullerene units in **CuG1**. The amplitude of the fullerene-centered reduction wave is expected to be four times larger than that of the Cu-centered oxidation. Surprisingly, however, the amplitude of the oxidation peak of **CuG1** is smaller than expected.^[8] In addition, the metal-centered oxidation became irreversible, which indicates a decrease in the electron-transfer rate, as was previously observed for other electroactive cores in dendrimers.^[3] This suggests that the bulky fullerene units around the Cu center partially prevent its approach to the electrode surface and, as a result, oxidation at the central core could not be completed on the timescale of the CV measurement. Consistent with this, the electrochemical oxidation of the Cu site could no longer be observed with dendrimers of the highest generations **CuG2** and **CuG3**. The central electroactive site appears to be totally inaccessible owing to isolation by the bulkier surrounding dendrimer structures. This observation is in full agreement with molecular modeling studies, which show that the interior of the dendrimer in **CuG2** and **CuG3** is virtually inaccessible to external contacts.^[9]

The absorption and luminescence spectra of **CuG0**, **G1CO₂tBu**, and **CuG1** in CH₂Cl₂ are shown in Figure 2. The absorption spectrum of **CuG0** in CH₂Cl₂ exhibits the typical intense π–π* ligand-centered bands in the UV and the much weaker metal-to-ligand charge-transfer (MLCT) bands in the visible region, typical of the [Cu(phen)₂]⁺-type chromophore.^[11] In CH₂Cl₂, **CuG0** displays luminescence from the lowest MLCT excited state^[12] both at room temperature (*λ*_{max} = 718 nm, Φ = 0.0011, τ = 163 ns, deaerated solution) and at 77 K (*λ*_{max} = 670 nm, τ = 3.2 μs). The absorption spectrum of the dimethanofullerene **G1CO₂tBu** is less resolved than those of methanofullerenes and plain C₆₀.^[13] In the UV region, only one distinct band is present (*λ*_{max} = 258 nm, ε = 107 000 M^{−1} cm^{−1}) with two shoulders above 300 nm, in contrast to the two distinct bands observed for the parent compounds in the same spectral region.^[13] In the visible region the spectrum is very broad, and the band corresponding to the lowest allowed singlet transition, which is typically very sharp and distinguishable for C₆₀,^[13] is barely detectable (*λ*_{max} = 433 nm, ε = 3300 M^{−1} cm^{−1}).

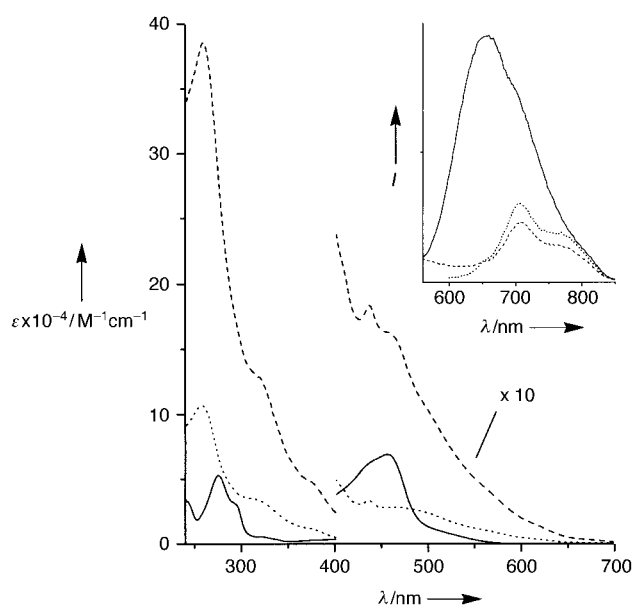


Figure 2. Absorption spectra of **CuG0** (solid line), **G1CO₂tBu** (dotted line), and **CuG1** (dashed line). Inset: emission spectra of the same compounds at *λ*_{exc} = 456 nm, *A* = 0.150 (CH₂Cl₂, 298 K).

The compound **G1CO₂tBu** displays fluorescence at room temperature (*λ*_{max} = 706 nm, Φ_{em} = 0.0003, τ = 1.5 ns, CH₂Cl₂) and 77 K (*λ*_{max} = 704 nm, τ = 2.0 ns, methylcyclohexane glass). The picosecond time-resolved absorption spectrum of **G1CO₂tBu** (Figure 3) shows singlet–singlet (*λ*_{max} = 560 and

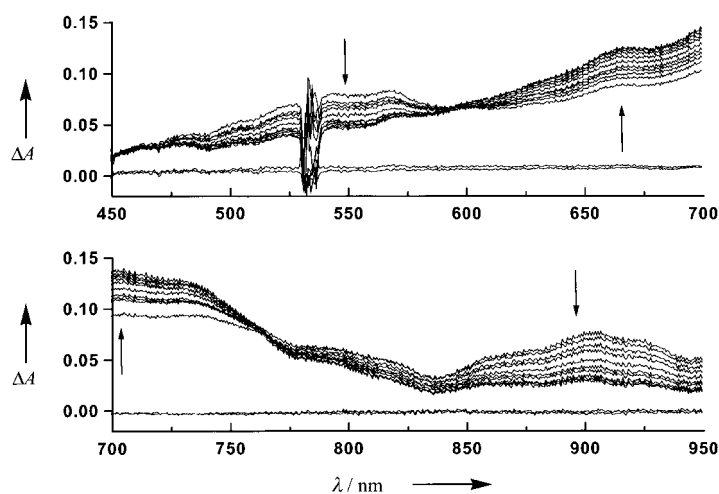


Figure 3. Picosecond transient absorption spectrum of **G1CO₂tBu** (CH₂Cl₂; *λ*_{exc} = 532 nm; energy: 5 mJ per pulse; *A* = 0.220; time intervals 330 ps).

900 nm) and triplet–triplet (*λ*_{max} = 705 nm) absorption features. On a longer timescale the decay of the triplet state can be determined (18 μs, deaerated solution) and is shorter than that of C₆₀ (60 μs),^[13] as is typical for substituted fullerenes.^[14] The absorption spectra of **G2CO₂tBu** and **G3CO₂tBu** have the same shape as that of **G1CO₂tBu**, but the molar extinction coefficients are respectively two and four times larger than those of **G1CO₂tBu**. They also exhibit the same luminescence properties.

In an attempt to rationalize the spectroscopic features of the fullerene dendrons, quantum mechanical calculations were performed on **G1CO₂tBu** with the ZINDO/S program,^[15] with a CI limited to 196 singly excited configurations after optimization of the geometry by the MM+ molecular mechanics procedure. The results of the calculation are in good agreement with the energy of the main peaks in the absorption spectrum. In particular, the lowest singlet transition is calculated to be at 647 nm, with a small oscillator strength ($f=0.004$) owing to the disruption of the high symmetry of C₆₀ (I_h) upon substitution (C_s). The lowest triplet transition is located at 882 nm, that is, a large red shift with respect to the unsubstituted compound ($\lambda(T_1)=758$ nm for C₆₀). The first allowed singlet transition (T_{1u}) is split into three components at 453, 449 and 445 nm, with a total f value of 0.024, while at higher energies, relevant bands are found at 390 ($f=0.113$), 308 ($f=0.083$), and 252 nm ($f=0.229$), in good agreement with the peaks detected at 372, 312, and 259 nm. The most notable peaks of the transient spectrum (Figure 3) are calculated to lie at 1083, 994, 920, 580 and 526 nm for the singlet manifold ($S_1 \rightarrow S_n$), and at 1263 and 658 nm for the triplet-triplet transitions.

The absorption spectra of the dendrimers **CuG1–CuG3** correspond to the sum of the corresponding component units, without appreciable ground-state electronic interactions among them. The increasing number of fullerene units around the Cu^I complex core implies increased shielding of the central core from incident light, especially in the UV region. In this regard, it is noteworthy that the molar extinction coefficient of **CuG3** at 258 nm reaches a value of $1.5 \times 10^6 \text{ M}^{-1} \text{ cm}^{-1}$, probably one of the highest ever found for soluble supermolecules, and thus allows a limit of detection below 1 ppm in CH₂Cl₂.

Upon selective excitation of the peripheral units at 600 nm, fullerene fluorescence is observed for all dendrimers **CuGn**; the corresponding emission quantum yield and excited state lifetimes are identical, within experimental error, to those of the corresponding dendronic subunits **Gn**. Despite the fact that selective excitation of the [Cu(phen)₂]⁺ central core is not possible, clear evidence for the quenching of the luminescence of such a moiety can be obtained. For instance, by exciting **CuG1** at 456 nm, although the light partition is about 40% (core) and 60% (fullerenes), the MLCT emission of the central core is dramatically quenched in a steady-state experiment (Figure 2). Analogous patterns are shown by **CuG2** and **CuG3**, although the light partition is less favorable for the central core because of the above-mentioned shielding effect. In a time-resolved experiment we did not observe any residual luminescence decay for **CuG1** within the time resolution (20 ns); hence, a rate constant of $k_q > 5 \times 10^7 \text{ s}^{-1}$ can be estimated for the quenching of the luminescence of the central core by the peripheral units.

The photophysics of the dendrimers can be rationalized by means of an energy level diagram with all low-lying electronic levels (Figure 4), that is, the lowest singlet (¹Gn) and triplet (³Gn) levels centered on the peripheral fullerene fragments and the lowest MLCT excited state of the Cu^I-complexed central core (^{MLCT}Cu). The energy values were obtained from corrected luminescence band maxima at 77 K or, where these

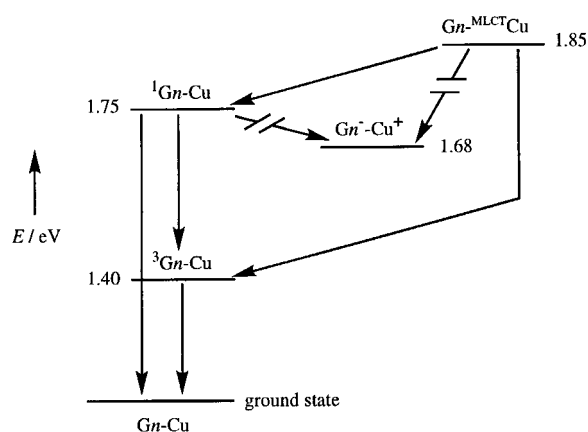


Figure 4. Energy-level diagram describing the excited state deactivation pathways and the intercomponent energy transfer processes of the dendrimers in CH₂Cl₂. On the left are the lowest electronic levels centered on the peripheral fullerene units, and on the right the lowest MLCT level centered on the [Cu(phen)₂]⁺ core. Gn[−]–Cu⁺ represents the charge-separated state formed upon electron transfer from the electron-donating central core to an electron-accepting fullerene peripheral fragment.

were unavailable, as in the case of ³Gn,^[16] from theoretical calculations. It is noteworthy that a new low-energy electronic level is made available in the supramolecular array, namely, the charge-separated state Cu⁺–Gn[−] at 1.68 eV, as deduced from the electrochemical data. In principle, the quenching of the MLCT excited state (positioned at 1.85 eV) can occur by three pathways:^[17]

- 1) Energy transfer to the fullerene centered singlet ¹Gn ($\Delta G = -0.10$ eV)
- 2) Energy transfer to the fullerene centered triplet ³Gn ($\Delta G = -0.45$ eV)
- 3) Electron transfer to the charge separated state ($\Delta G = -0.17$ eV).

We believe that electron transfer (process 3) is not the prevailing phenomenon for at least two reasons: 1) it does not take place from ¹Gn (no quenching of the fluorescence of the fullerene moiety is observed), although a similar thermodynamic driving force ($\Delta G = -0.07$ eV) would be involved, and

2) the quenching of the central core also occurs at 77 K, but electron-transfer in a rigid matrix is usually blocked unless it is exothermic by at least 0.6–0.7 eV^[18] (in our case $\Delta G = -0.17$ eV; Figure 4). A straightforward discussion of the energy transfer mechanism involved, that is, dipole–dipole (Förster-type) or exchange (Dexter-type), is made difficult by the fact that the two partners are linked by flexible connections. We calculated the rate of energy transfer according to a Förster mechanism using spectroscopic quantities^[13] on the order of $7 \times 10^7 \text{ s}^{-1}$ for components separated by only 5 Å, a distance at which the exchange mechanism can also play a role. The determination of the experimental rate constants by ultrafast luminescence spectroscopy will probably give a better insight into this issue.

Experimental section

All photophysical investigations were carried out in CH₂Cl₂ (Carlo Erba, spectrofluorimetric grade). Absorption spectra were recorded with a Perkin-Elmer $\lambda 5$ spectrophotometer. Emission spectra were obtained with

a Spex Fluorolog II spectrofluorimeter. Details of the correction of emission spectra and the determination of luminescence quantum yields were as reported previously.^[14] Luminescence lifetimes on the nanosecond timescale were determined with an IBH single photon counting apparatus ($\lambda_{\text{exc}} = 337 \text{ nm}$) or a single-shot Nd:YAG laser apparatus ($\lambda_{\text{exc}} = 532 \text{ nm}$). Transient absorption spectra and lifetimes with picosecond and nanosecond resolution were obtained with two pump and probe systems based on Nd:YAG lasers; excitation with the second (532 nm) or third harmonic (355 nm) was used. Details of this time-resolved spectroscopy equipment were reported earlier.^[14] Experimental uncertainties were estimated to be $\pm 8\%$ for lifetime determination, $\pm 20\%$ for quantum yields, and $\pm 3 \text{ nm}$ for emission and absorption peaks.

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2-Phenylquinoline – Carbohydrate Hybrids: Molecular Design, Chemical Synthesis, and Evaluation of a New Family of Light-Activatable DNA-Cleaving Agents**

Kazunobu Toshima,* Ryusuke Takano, Yutaka Maeda, Masataka Suzuki, Akira Asai, and Shuichi Matsumura

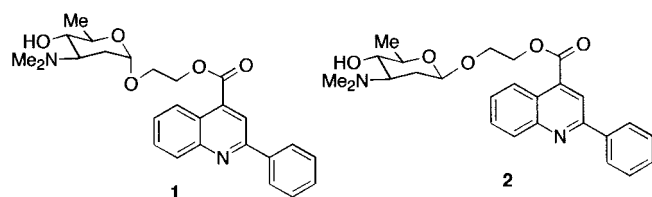
The development of photochemical DNA-cleaving agents, which selectively cleave DNA by irradiation with light with a specific wavelength under mild conditions and without any additives such as metals and reducing agents, is very interest-

[*] Prof. Dr. K. Toshima, R. Takano, Y. Maeda, M. Suzuki, Prof. Dr. S. Matsumura
Department of Applied Chemistry, Faculty of Science and Technology
Keio University, 3-14-1 Hiyoshi
Kohoku-ku, Yokohama 223-8522 (Japan)
Fax: (+81)45-563-0446
E-mail: toshima@apple.keio.ac.jp

Dr. A. Asai
Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd.
3-6-6 Asahi-machi, Machida-shi, Tokyo 194-8533 (Japan)

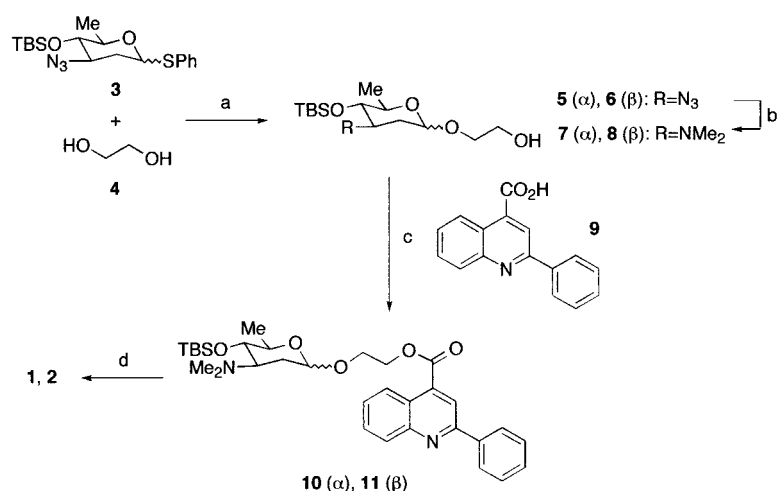
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ing from both chemical and biological standpoints and offers considerable potential in medicine.^[1] Here, we discuss the molecular design, chemical synthesis, DNA-photocleaving properties, and cytotoxicity of two novel and artificial light-activatable DNA-cleaving agents, namely, the 2-phenylquinoline-carbohydrate hybrids **1** and **2**.



In our approach to create novel DNA-cleaving molecules, we designed artificial intercalator-carbohydrate hybrid systems,^[2–4] because many clinically useful antitumor antibiotics such as anthracyclines^[5] and aureolic acids,^[6] which interact with DNA, were commonly found to contain both aromatic and carbohydrate domains. Since Denny et al.^[7] demonstrated the efficacy of 2+1 unfused tricyclic aromatic systems such as phenylquinolines as “minimal intercalators”, 2-phenylquinoline^[8, 9] was selected as the DNA intercalator. The conjugated C=N bond in the 2-phenylquinoline unit was also expected to generate the photoexcited $^3(n \rightarrow \pi^*)$ state upon photoirradiation, which may have a radical character and could be capable of cleaving DNA. On the other hand, certain 2,6-dideoxy amino sugars seemed appropriate as the carbohydrate source, since they are DNA groove binders in some DNA-binding antitumor antibiotics^[10] and our previously reported artificial DNA-interactive intercalator-carbohydrate molecules.^[4] Therefore, we designed novel, artificial intercalator-carbohydrate hybrids that consist of 2-phenylquinoline and a 2,6-dideoxy amino sugar, which are connected by an ethylene glycol linker.

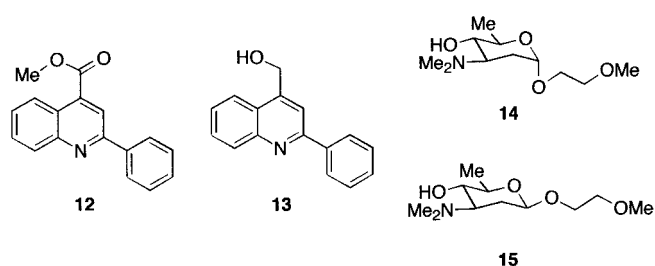
The designed 2-phenylquinoline-carbohydrate hybrids **1** and **2** were synthesized by a short reaction sequence (Scheme 1). Thus, the glycosidation of the phenylthio sugar **3**^[11] (1.0 equiv) with ethylene glycol (**4**, 5.0 equiv) using *N*-



Scheme 1. Synthesis of **1** and **2**. a) NBS (1.5 equiv with respect to **3**), 4-Å molecular sieves, MeCN, 0 °C, 1 h, 79%, **5:6** = 1.4:1; b) H₂, cat. Pd/C, 35% HCHO (aq), MeOH, 25 °C, 18 h, 81%; c) **9**, DCC (1.0 equiv), cat. 4-DMAP, CH₂Cl₂, 0 °C, 4.5 h, 93% for **10**, 90% for **11**; d) HF/Py, Py, 25 °C, 15 h, 99% for **1**, 94% for **2**. TBS = *tert*-butyldimethylsilyl.

bromosuccinimide (NBS)^[12] in MeCN gave a mixture of the α -glycoside **5** and the β -glycoside **6** in 79% yield in a ratio of 1.4:1. The azide groups in **5** and **6** were next converted into *N,N*-dimethylamino groups by treatment with 35% HCHO (aq) and a catalytic amount of Pd/C in MeOH under a hydrogen atmosphere to afford **7** and **8** in 81% yield. After their separation by column chromatography, **7** (1.0 equiv) and **8** (1.0 equiv) were esterified with 2-phenylquinoline-4-carboxylic acid (**9**, 1.5 equiv) by using *N,N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (4-DMAP) in CH₂Cl₂ to give the hybrids **10** and **11** in 93 and 90% yields, respectively. Finally, removal of the silyl groups in **10** and **11** with HF/pyridine (Py) furnished the desired 2-phenylquinoline-carbohydrate hybrids **1** and **2**, respectively, in high yields.

The photoinduced DNA-cleaving activities of the hybrids **1** and **2** along with the components of these hybrids, **12–15**,^[11] were assayed with supercoiled Φ X174 DNA. As apparent



from Figure 1, the 2-phenylquinoline-carbohydrate hybrids **1** (500 μ M) and **2** (500 μ M) caused significant cleavage of DNA, leading to small fragments upon photoirradiation with long-wavelength UV light (365 nm), while **12–15** did not show



Figure 1. Photocleavage of supercoiled Φ X174DNA. Φ X174DNA (50 μ M per base pair) was incubated with various compounds in 20% acetonitrile in Tris-HCl buffer (Tris = tris(hydroxymethyl)aminomethane, pH 7.5, 50 mM) at 25 °C for 1 h under UV irradiation (365 nm, 15 W) from a lamp placed 10 cm from the mixture, and analyzed by gel electrophoresis (0.9% agarose gel, ethidium bromide stain). Lane 1: DNA alone; lane 2: DNA with irradiation; lanes 3–8: compounds **1**, **2**, **12**, **13**, **14**, and **15** (500 μ M), respectively. Form I = covalently closed supercoiled DNA, Form II = open circular DNA, and Form III = linear DNA.

DNA-cleaving activity under the same conditions. These results clearly indicate the importance of the hybrid structure for DNA cleaving. These results also strongly suggest that the 2,6-dideoxy amino sugar works as the DNA groove binder and significantly enhances the intercalating ability of the 2-phenylquinoline. In the absence of light no DNA cleavage by **1** and **2** was observed. Furthermore, the DNA-cleaving ability of the β -anomer hybrid **2** was found to be stronger than that of the α -anomer hybrid **1** (Figure 2). This result demon-

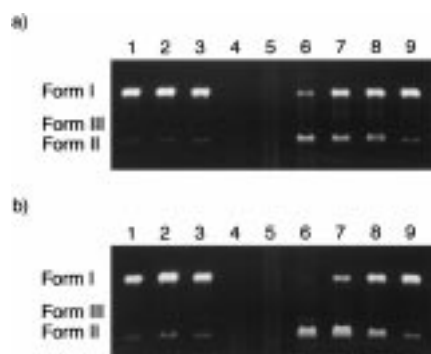


Figure 2. Photocleavage of supercoiled Φ X174DNA. Φ X174DNA (50 μ M per base pair) was incubated with the hybrid in 20% acetonitrile in Tris–HCl buffer (pH 7.5, 50 mM) at 25 °C for 1 h under UV irradiation (365 nm, 15 W) from a lamp placed 10 cm from the mixture, and analyzed by gel electrophoresis (0.9% agarose gel, ethidium bromide stain). a) Lane 1: DNA alone; lane 2: DNA with irradiation; lane 3: DNA + **1** without irradiation; lanes 4–9: **1** (1000), **1** (500), **1** (300), **1** (100), **1** (30), and **1** (10 μ M), respectively. b) Lane 1: DNA alone; lane 2: DNA with irradiation; lane 3: DNA + **2** without irradiation; lanes 4–9: **2** (1000), **2** (500), **2** (300), **2** (100), **2** (30), and **2** (10 μ M), respectively.

strates that the DNA-cleaving activity is definitely dependent on the configuration of the sugar moiety in the hybrid. Since the DNA-cleaving activity of **1** and **2** significantly decreased in the presence of a radical scavenger, dimethyl sulfoxide, the DNA cleavage must arise from the photoexcited 2-phenylquinoline radical. The DNA-cleaving site specificity of the hybrids **1** and **2** was also analyzed according to the Sanger protocol.^[13] The results in Figure 3 clearly show the identical high guanine selectivity.

The cytotoxicity of the DNA-cleaving hybrids **1** and **2** was next examined using HeLaS3 cells exposed to each agent for 72 h with or without 1 h of photoirradiation.^[14] The IC₅₀ values of **1** and **2** without photoirradiation were 12 and 18 μ M, respectively, and those with photoirradiation were 0.44 and 0.25 μ M, respectively. These results indicate that the cytotoxic

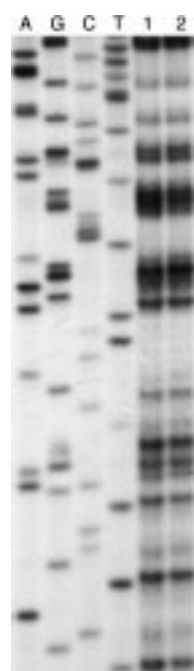


Figure 3. Autoradiogram of slab gel electrophoresis with 12% polyacrylamide/8M urea for sequence analysis. The 5'-end-labeled M13mp18 DNA was cleaved by the hybrids at pH 7.5 and 25 °C for 1 h under UV irradiation (365 nm, 15 W) from a lamp placed 10 cm from the mixture (bases 49–105 are shown). Lanes A, G, C, and T: Sanger A, G, C, and T reactions, respectively; lanes 1 and 2: **1** and **2** (1000 μ M), respectively.

activities of **1** and **2** with photoirradiation were much higher than those without, and correlated with their capacity to cleave DNA. Furthermore, we found that when the HeLaS3 cells were exposed to 1 μ M of hybrid **1** or **2** without photoirradiation, practically all of the cells survived, while similar treatment combined with photoirradiation wiped out the cells. These results clearly show that the DNA-cleaving activity induced by photoirradiation significantly affects the cytotoxicity of the hybrids, and the life of the cancer cells can be controlled by treatment with an appropriate amount of the 2-phenylquinoline–carbohydrate hybrid with or without the photoirradiation.

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Novel, Spongelike Ruthenium Particles of Controllable Size Stabilized Only by Organic Solvents**

Olivia Vidoni, Karine Philippot, Catherine Amiens, Bruno Chaudret,* Olivier Balmes, Jan-Olle Malm, Jan-Olov Bovin, François Senocq, and Marie-José Casanove

In materials science there is considerable current interest in controlling the structure of a material at both the microscopic and mesoscopic levels and thus to influence its physical properties and reactivity. A recent method involves transferring the structure of surfactant aggregates to inorganic solids by calcination to give materials of controlled porosity.^[1] Similarly, metal nanoparticles are attracting increasing interest because of the novel physical properties displayed by nanosized objects and the chemical properties exhibited by colloidal particles in solution.^[2] In this case, the structure of surfactant aggregates is transferred by synthesizing ordered nanoparticles of metals, metal oxides, or metal sulfides in “nanoreactors” such as inverse micelles.^[3] A drawback of this method is the presence of surface contaminants resulting from the reaction conditions, such as water, salts, organic residues, or even an oxide shell. This problem can be solved by decomposing an organometallic precursor under mild conditions in a polymer.^[4] The physical properties of the resulting nanoparticles resemble those of free clusters in the gas phase (e.g., lattice-parameter contraction^[4a] and enhanced magnetization^[4d,e]). The disadvantage here is the presence of the polymer, which makes the material unsuitable, for example, for applications involving electron transfer and catalysis. Ligands have been used to stabilize metal particles,^[4a,c] but they strongly modify their physical and chemical properties.^[4e] However, we have shown that a combination of CO and THF, both weakly coordinated, allows the synthesis of monodisperse platinum particles.^[4c] Similar titanium particles, weakly protected by THF, were recently reported by Bönnemann et al.^[5]

We looked for similar effects, avoiding CO, which modifies the electronic configuration of the surface, by employing weakly coordinating polar solvents. The stabilization of the

particles could then result from coordination or from the electrostatic repulsion that results from solvent-induced polarization of the surface. As the metal precursor, we chose [Ru(cod)(cot)]^[6] (**1**; cod = 1,5-cyclooctadiene, cot = 1,3,5-cyclooctatriene), which is readily decomposed by dihydrogen at or below room temperature and which leads to well-defined nanoparticles in polymer matrices.^[7] Here we report on the synthesis of spongelike ruthenium nanoparticles of adjustable uniform size which are soluble in organic solvents and protected only by weakly coordinating solvents.

The reactions of **1** (50 mg, 1.54×10^{-4} mol) dissolved in 50 mL of various solvents with 3 bar of H₂ were carried out at 21 °C in a closed pressure bottle for 45 min (standard conditions). In THF, a black precipitate formed almost immediately. However, in pure methanol or THF/methanol (90/10, 95/5, or 99/1), the initial yellow solution rapidly became dark brown, after which it remained unchanged and stable for at least several days. Addition of pentane gave a black precipitate consisting of particles, the size of which depends upon the methanol content of the reaction mixture (Table 1). The isolated particles cannot be redissolved; they are very air sensitive and burn in the open air. However, an oxide passivation layer can be formed by bubbling a few milliliters of air through the reaction solution.

Table 1. Mean particle size as a function of reaction conditions.

THF/MeOH	[1] [mol L ⁻¹]	T [°C]	Mean size [nm]
0/100	3.53×10^{-3}	21	70
90/10	3.65×10^{-3}	21	16
95/5	3.8×10^{-3}	21	24
99/1	3.67×10^{-3}	21	80–100
—[a]	3.65×10^{-3}	21	> 500
90/10	3.2×10^{-2}	21	54
90/10	1.6×10^{-1}	21	40–70; 230–280
90/10	3.2×10^{-3}	0	35–45
90/10	3.2×10^{-3}	41	12
90/10[b]	3.2×10^{-3}	21	24
90/10[c]	3.2×10^{-3}	21	35

[a] A stoichiometric quantity of methanol was used. [b] With addition of 2 equiv of cyclooctane. [c] With addition of 20 equiv of cyclooctane.

The products were analyzed by microanalysis, transmission electron microscopy (TEM), high-resolution electron microscopy (HR-EM), X-ray diffraction (XRD), and X-ray photoelectron spectroscopy (XPS). Preliminary wide-angle X-ray scattering (WAXS) and atomic force microscopy (AFM) studies were also performed.

Under standard conditions, the mean size of the particles varies from 16 nm (10 vol% methanol) to 24 nm (5 vol% methanol) and 80–100 nm (1 vol% methanol; Figure 1). Addition of one molar equivalent of methanol with respect to ruthenium leads to the precipitation of unorganized material, whereas in pure methanol a mean particle size of 70 nm was obtained (Figure 2). Other parameters that influence the size of the particles are the temperature (for MeOH/THF 10/90: ca. 40 nm at 0 °C and 12 nm at 41 °C), the precursor concentration (for MeOH/THF 10/90: [Ru] = 3.2×10^{-2} , 54 nm; [Ru] = 1.6×10^{-1} , bimodal, ca. 50 and ca. 250 nm), and the presence of an excess of cyclooctane (for

[*] Dr. B. Chaudret, O. Vidoni, Dr. K. Philippot, Dr. C. Amiens
Laboratoire de Chimie de Coordination du CNRS
205, Route de Narbonne, F-31077 Toulouse Cedex 04 (France)
Fax: (+33) 5-61553003
E-mail: chaudret@lcc-toulouse.fr
O. Balmes, Dr. J.-O. Malm, J.-O. Bovin
Lund University, Inorganic Chemistry 2
PO Box 124, S-22100 Lund (Sweden)
Dr. F. Senocq
Laboratoire Interfaces et Matériaux
Ecole Nationale Supérieure de Chimie
118, Route de Narbonne, F-31077 Toulouse Cedex 04 (France)
Dr. M.-J. Casanove
CEMES-CNRS, 29, Rue Jeanne Marvig
BP 4347, F-31055 Toulouse Cedex (France)

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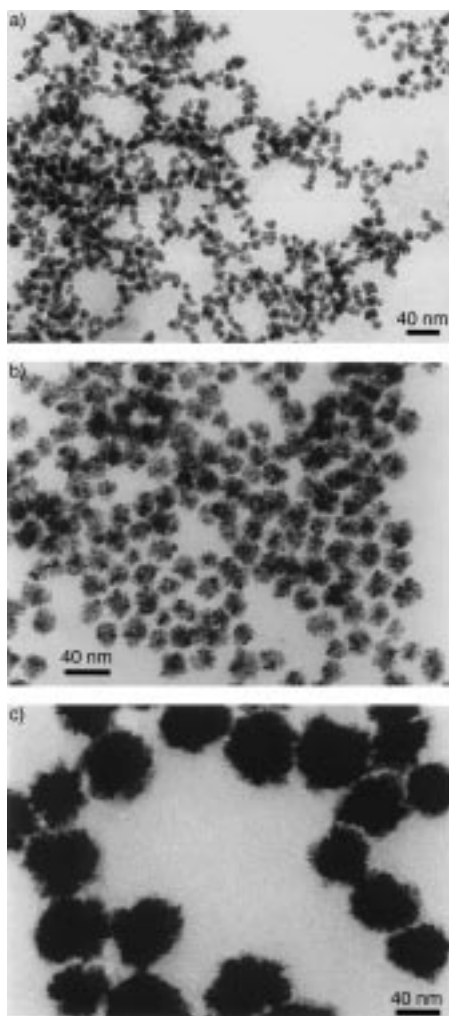


Figure 1. Micrographs of ruthenium particles prepared at room temperature in mixtures of methanol/THF: a) 10/90, b) 5/95, c) 1/99.

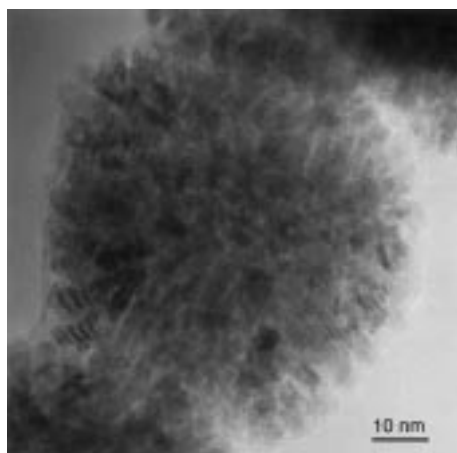


Figure 2. High-resolution micrograph of a ruthenium particle prepared at room temperature in pure methanol.

MeOH/THF 10/90: $[C_8H_{16}]/[Ru] = 2$, 24 nm; $[C_8H_{16}]/[Ru] = 20$, 35 nm).

For each preparation, the particles have a narrow size distribution and a porous, polycrystalline aspect. The XRD experiments on passivated particles showed that they consist of hexagonal close packed (hcp) ruthenium. A very weak peak

was attributed to the passivating RuO_2 layer, no evidence of which was obtained in WAXS experiments in an air-free Lindemann capillary. Only peaks corresponding to well-crystallized hcp ruthenium particles were observed. These results are also confirmed by XPS on a passivated sample; the spectrum displays peaks due to oxidized ruthenium and oxygen. However, the disappearance of almost all oxygen peaks after argon bombardment to remove the external layers of the material shows that only a thin external passivation layer is present.

The polycrystallinity of the particles was deduced from HR-EM studies; the size of the individual crystallites is on the order of a few nanometers. The fact that the particles consist of a uniform spongelike structure rather than an agglomerate of small crystallites was indicated by application of the Scherrer equation to the XRD data (using the (101) diffraction line for particles prepared at 10 vol% MeOH in THF gave a calculated size of 16–18 nm); by preliminary AFM experiments, which showed that 16-nm particles keep their integrity when moved by the tip; and by reactivity studies (see below). Precedents for such porous structures are known and have been discussed by Antonietti and Göltner.^[8] The particle morphology is referred as “raspberry” or “cauliflower” according to the growth mechanism of the particles, that is, whether individual particles aggregate in a single micelle or form in a micelle and aggregate after their formation because of a lack of stabilization by the block copolymer. However, such structures were always obtained in the presence of a protective layer (block copolymers that form micelles).

The particles display interesting reactivity. For example, a solution prepared at 10 vol% MeOH in THF catalyzed the complete reduction of benzene to cyclohexane under mild conditions (20 bar, 80 °C, 15 h, 1000 equiv). A black precipitate was observed at the end of the reaction but could be redispersed in solution, and micrographs of the particles before and after catalysis were essentially identical.

Since the solubility of these particles was astonishing, we observed their organization in solution by cryomicroscopy (Figure 3). The cryomicroscopy experiments were performed on a Philips CM-120 bioTWIN Cryo, which is equipped with a specially designed objective lens to enhance image contrast relative to a normal 120-kV microscope. The specimens were first frozen by fast immersion in liquid ethane. This freezes the solvent to amorphous ice fast enough to prevent any rearrangement of the particles in the solution. The sample was then transferred to a cryo-holder (Oxford CT-3500) cooled with liquid nitrogen to below –180 °C. Microscopy was performed under low-dose conditions to prevent beam damage (especially transformation of the amorphous ice into crystalline ice). This type of sample preparation is particularly relevant for particles synthesized in solution, because it shows whether structural features observed after drying were already present in the liquid phase. We observed individual spongelike^[8] particles, agglomerated in some cases, in complete agreement with the data obtained from samples deposited on a grid.

The intriguing properties of these particles—that is, 1) their solubility in organic solvents, 2) the size control induced by

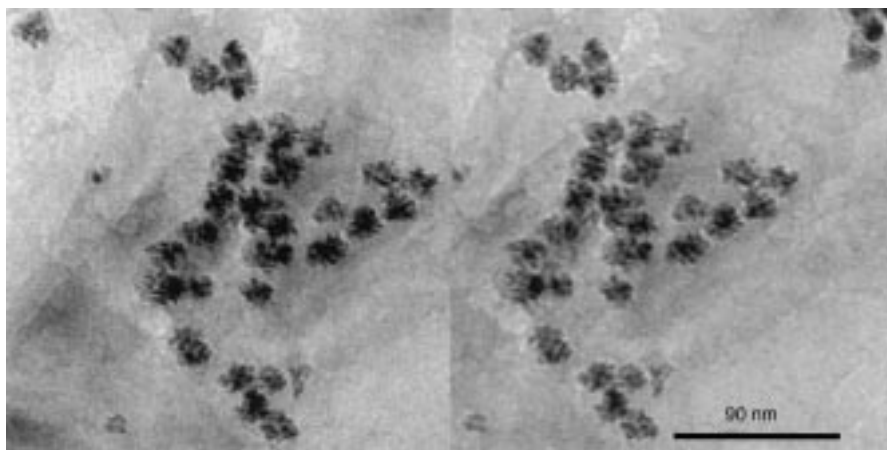


Figure 3. Stereoview of a TEM micrograph of ruthenium particles in a frozen solution of methanol/THF (10/90; cryomicroscopy technique).

the solvent composition, and 3) the influence of concentration, temperature, and excess cyclooctane—can be understood if one imagines the formation of a nanosized emulsion whose droplets act as nanoreactors. Methanol could be ordered around the particles by forming hydrogen-bonded networks with THF. These structures would be more stable when both solvents are present, since methanol is a good hydrogen-bond donor, and THF a good hydrogen-bond acceptor. The core of the droplets would be lipophilic, as can be deduced from the influence of as little as two equivalents of cyclooctane relative to ruthenium.

In conclusion, we have prepared novel ruthenium nanoparticles that are free of protective oxide or polymer layers, uncontaminated by ligands or impurities from the synthesis other than the solvent mixture, soluble in organic solvents, and controllable in size by means of the solvent composition. These highly porous particles are catalytically active and remain unchanged by the catalytic process.

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Broadening the Aldolase Catalytic Antibody Repertoire by Combining Reactive Immunization and Transition State Theory: New Enantio- and Diastereoselectivities**

Guofu Zhong, Richard A. Lerner,* and Carlos F. Barbas III*

The aldol reaction is a C–C bond forming reaction that is key to the practice of synthetic organic chemistry.^[1] As a result of its utility intensive effort has been applied to the development of catalytic enantioselective variants of this reaction. Catalytic enantioselective aldol reactions are typically accomplished with preformed enolates and chiral transition metal catalysts^[2a–e] or with natural aldolase enzymes.^[2f–h] The enantioselectivity of transition metal catalyzed aldol reactions is readily reversed by exchange of the chiral ligand that directs the stereochemical course of the reaction. However, a general approach to the reversal of enantioselectivity is not available with enzymes. To address the problem of the de novo

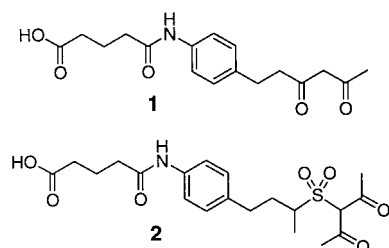
[*] Prof. Dr. C. F. Barbas III, Prof. Dr. R. A. Lerner, Prof. Dr. G. Zhong
The Skaggs Institute for Chemical Biology and
The Department of Molecular Biology
The Scripps Research Institute
10550, North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-9098
E-mail: carlos@scripps.edu

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

generation of aldolase enzymes, we developed the strategy of reactive immunization using β -diketone haptens to program into antibodies a chemical mechanism analogous to that used by nature's Class I aldolase enzymes.^[3a] The chemistry of this class of enzymes is based on a unique chemically reactive lysine residue that is essential to the covalent mechanism of these catalysts.

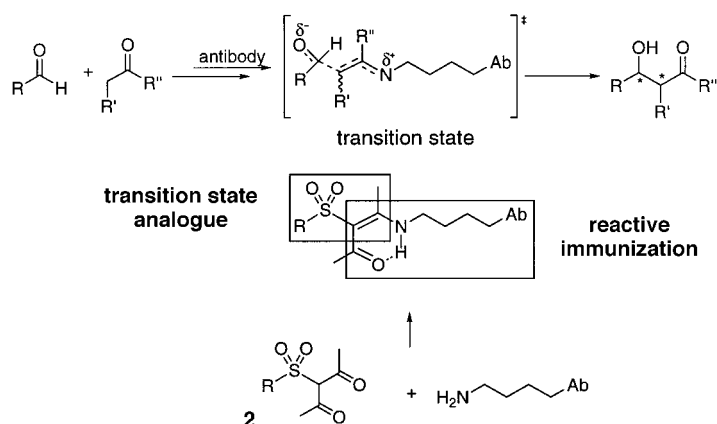
In our original design the β -diketone functionality of hapten **1** was used as a reactive immunogen to trap a chemically reactive lysine residue in the active site of an



antibody. Covalent trapping was facilitated by intramolecular hydrogen bonding that stabilizes an enaminone in the active site of the antibody. The chemical mechanism leading up to the stabilized enaminone should match that of Class I aldolases over this portion of the reaction coordinate. Given the mechanistic symmetry around the transition state in which the C–C bond is formed, this approach allowed for the programming of this multi-step reaction mechanism into antibodies.^[3a,d] The resulting efficient antibody catalysts ab38C2 (Aldrich) and ab33F12 have been shown to catalyze a broad array of enantioselective aldol and retro-aldol reactions.^[3] Herein we present our efforts to increase the repertoire of catalysts for this reaction, in particular to search for antibodies with antipodal reactivity. In this search we tested the potential of a new hapten design concept to provide more efficient reaction programming.

Towards these goals, the β -diketo sulfone hapten **2** was designed and synthesized. A perceived limitation of our original hapten design (**1**) is that it does not address the tetrahedral geometry of the rate-determining transition state of the C–C bond forming step.^[3a,4] Hapten **2** addresses this limitation and contains features common to the transition state analogue approach that has been successful for so many reactions^[5] and the β -diketone functionality key to the reactive immunization strategy. The tetrahedral geometry of the sulfone moiety in hapten **2** mimics the tetrahedral transition state of the C–C bond forming step and therefore should facilitate nucleophilic attack of the enaminone intermediate on the acceptor aldehyde (Scheme 1).

Mice were immunized with hapten **2** coupled to the carrier protein keyhole limpet hemocyanin (KLH) and 17 monoclonal antibodies were prepared and purified.^[3a] All antibodies were first screened for their ability to covalently react with 2,4-pentanedione to form a stable enaminone.^[3a] Nine antibodies, 85A2, 85C7, 92F9, 93F3, 84G3, 84G11, 84H9, 85H6, and 90G8, showed the characteristic enaminone absorption maximum at 316 nm after incubation with 2,4-pentanedione. All antibodies were then assayed with fluorescent and UV-active retro-aldol substrates ($\pm$)-**3**^[6] and ($\pm$)-**4**,^[3f] respective-



Scheme 1. Mechanism of the antibody-catalyzed aldol reaction and reactive immunization with **2** for the generation of new aldolase antibodies.

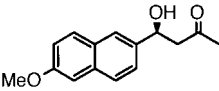
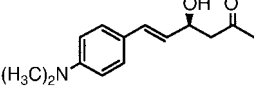
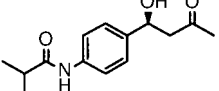
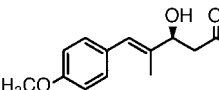
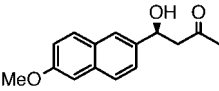
ly. Catalysis was observed only with antibodies that had demonstrated enaminone formation with 2,4-pentanedione. A study of the ability of the antibodies to catalyze the aldol addition of acetone to 3-(4-acetamidophenyl)propanal (**12**) and 4-isobutyramidobenzaldehyde (**13**) identified the same catalysts. All antibody-catalyzed aldol and retro-aldol reactions followed Michaelis–Menten kinetics and were inhibited by the addition of a stoichiometric amount of 2,4-pentanedione. These results are consistent with a covalent catalytic mechanism in which a reactive amine is programmed in these antibodies.^[3] The number of catalysts prepared using this hapten, 9 of 17, is significantly greater than our previous studies with hapten **1**, where only 2 of 20 antibodies were catalysts.^[3a]

In order to compare these antibodies with the commercially available aldolase antibody 38C2, several aldol and retro-aldol reactions were chosen for study. Antibodies 93F3 and 84G3 were characterized in detail in these studies.

Scope and synthetic utility: To begin to probe the synthetic scope and enantioselectivity of these antibodies, we studied their utility in the kinetic resolutions of β -hydroxyketones. Racemic aldols **3–7** were treated with ab93F3 or ab84G3 (0.2–0.4 mol %) in aqueous buffer as previously described for ab38C2.^[3f] Analysis by high-performance liquid chromatography (HPLC) indicated that in each case the retro-aldolization reactions halted at approximately 50 % conversion, which showed that the antibody was highly enantioselective. The unconverted aldols were recovered and studied using chiral-phase HPLC. Comparison of the results with those of enantiomerically enriched standards^[7] indicated that the catalyst was highly enantioselective and provided the recovered *S* aldols with *ee* values typically greater than 96 % (Table 1). Antibody 38C2 provides the corresponding *R* aldols by kinetic resolution, thus ab93F3 is its antipodal complement. The study with ab84G3 revealed an enantioselectivity similar to ab93F3.^[8]

We then studied the catalysis of the synthetic reaction of acetone with four different aldehydes, **12**, **13**, 4-nitrobenzaldehyde (**14**), and 4-nitrocinnamaldehyde (**15**), to aldols **5** and **8–10** (Table 2). Chiral-phase HPLC analysis demonstrated that the enantioselectivities of ab93F3- and ab84G3-catalyzed aldol addition reactions are substrate dependant.

Table 1. Antibody-catalyzed kinetic resolutions by retro-aldolization.

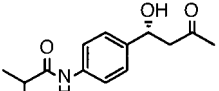
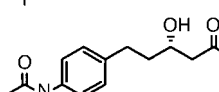
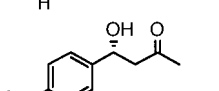
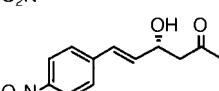
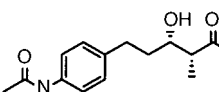
Product ^[a]	Conversion [%]	<i>ee</i> [%]
 (S)- 3	50	99 ^[a]
 (S)- 4	50	97 ^[a]
 (S)- 5	52	> 99 ^[a,b]
 (S)- 6	50	96 ^[a]
 (S)- 7	50	> 99 ^[b]

[a] Antibody 93F3 was used. Absolute configurations were assigned by comparing aldol products with those obtained from ab38C2 catalyzed reactions. [b] Antibody 84G3.

Aldols (*R*)-**5**, (*R*)-**9**, and (*R*)-**10** are provided in essentially enantiomerically pure form with either catalyst, while a moderate enantioselectivity is obtained in the synthesis of (*S*)-**8** (69% *ee* with ab93F3 (Table 2) or 54% with ab84G3). The *ee* values obtained with these catalysts are quite similar to those obtained with ab38C2, however, the enantioselectivity is reversed.

To examine the diastereoselectivity of ab93F3, we studied the reaction of 3-pentanone to give aldol **11**. In this case ab93F3 provided *syn*-**11** as the major product. The antibody 93F3 exhibited diastereo- and enantioselectivities that differ from that obtained with ab38C2. Antibody 93F3 provides **11**

Table 2. Antibody 93F3 catalyzed aldol reactions.

Product ^[a]	<i>ee</i> [%]
 (<i>R</i>)- 5	> 99%
 (<i>S</i>)- 8	69%
 (<i>R</i>)- 9	95%
 (<i>R</i>)- 10	98%
 (<i>S,R</i>)- 11	90% (<i>syn:anti</i> = 95:5)

[a] Absolute configurations assigned by asymmetric synthesis of the aldols.^[7]

with 90% *de* (*syn-α*-isomer) and 90% *ee*, while ab38C2 provides **11** with 62% *de* (*anti*-isomer) and 59% *ee*.

To further characterize the scope of reactions catalyzed by these antibodies, we have studied a variety of ketones as aldol donor substrates in the reaction with aldehyde **14**. Preliminary results indicate that in addition to acetone and 3-pentanone, seven ketones: 2-butanone, 3-methyl-2-butanone, 2-pentanone, cyclopentanone, cyclohexanone, hydroxyacetone, and fluoroacetone, are substrates. Thus these antibodies share the characteristic broad scope we observed previously with ab38C2.

Kinetic studies: The results of kinetic studies of three retro-aldol reactions and one aldol addition reaction are provided (Table 3). The catalytic proficiency^[9] of ab93F3 and ab84G3 exceeds that of ab38C2 in most of the cases studied (see Supporting Information for more examples). A threefold increase in the catalytic proficiency is observed in the aldol reaction of 3-pentanone with **12** that provides (*S,R*)-**11**. The overall trend towards increased efficiency is consistent with the notion that the inclusion of transition state analogy into

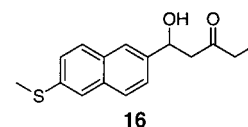
Table 3. Kinetic parameters for antibody-catalyzed aldol and retro-aldol reactions.

Substrate	Antibody	$k_{\text{cat}}^{\text{[a,b]}}$ [min ⁻¹]	$K_{\text{m}}^{\text{[a,b]}}$ [μM]	$k_{\text{cat}}/k_{\text{uncat}}^{\text{[c]}}$	$(k_{\text{cat}}/K_{\text{m}})/k_{\text{uncat}}^{\text{[d]}}$
(±)- 3	93F3	2.65	15	2.7×10^6	1.8×10^{11}
	84G3	3.5	23	3.6×10^6	1.6×10^{11}
	38C2 ^[6]	1.0	14	1.0×10^6	7.1×10^{10}
(±)- 7	93F3	43.3	6.5	4.9×10^7	7.4×10^{12}
	84G3	46.8	10.3	5.2×10^7	5.0×10^{12}
	38C2	0.053	29.5	5.8×10^4	2.0×10^9
(R)- 16	93F3	69.6	2.6	1.9×10^8	7.4×10^{13}
	84G3	81.4	4.2	2.3×10^8	5.4×10^{13}
12 & acetone	93F3	33×10^{-3}	34	1.5×10^5	4.4×10^9
	84G3	27×10^{-3}	29	1.2×10^5	4.1×10^9
	38C2 ^[3a]	6.7×10^{-3}	17	2.9×10^4	1.7×10^9

[a] Conditions: The data for (±)-**7** and (*R*)-**16** were collected using phosphate buffer at pH 7.7, others were studied in phosphate buffered saline (PBS) at pH 7.4. [b] Per antibody active site. k_{cat} and K_{m} were obtained by fitting experimental data to nonlinear regression analysis using Grafit software. [c] Aldol reaction rate constants in units of M. [d] Retro-aldol reaction rate constants in units of M⁻¹.

the hapten design results in increased catalytic efficiency. This effect is particularly evident with substrate **7** where a 10³-fold increase in proficiency over ab38C2 is observed. On the basis of the success of this substrate we synthesized analogue **16**.

Since in antibody-based resolutions of aldols the unprocessed enantiomer can be inhibitory to the processing of the enantiomer that is the substrate for the antibody^[3b], we isolated (*R*)-**16** using chiral-phase HPLC. A study of the kinetics of retro-aldolization of (*R*)-**16** by ab84G3 revealed that it was processed by the antibody extremely rapidly with a $k_{\text{cat}} = 1.4 \text{ s}^{-1}$. A study of the uncatalyzed reaction revealed that (*R*)-**16** was not more chemically reactive than the corresponding methoxy derivative **7**, and that the antibody provides a rate enhancement $k_{\text{cat}}/k_{\text{uncat}}$ of 2.3×10^8 . The catalytic proficiency^[9] of ab84G3 for the retro-aldolization of aldol (*R*)-**16** is



approximately 1000-fold higher than that reported for any other catalytic antibody.^[3f, 10] The catalytic efficiency of the antibody for this substrate, $3.3 \times 10^5 \text{ s}^{-1} \text{ M}^{-1}$, compares favorably with the efficiency of natural muscle aldolase, $4.9 \times 10^4 \text{ s}^{-1} \text{ M}^{-1}$, in the retro-aldolization of its substrate fructose-1,6-bisphosphate.^[11]

In conclusion, we have demonstrated that combining transition state analogy and reactive immunization design into a single hapten can result in increases both in the output of catalysts from the immune system as well as their efficiency. This strategy resulted in the characterization of the most proficient antibody catalysts prepared to date. Antibodies 93F3 and 84G3 catalyze a wide array of aldol reactions with *ee* values exceeding 95% in most of the cases studied. A new stereogenic center is formed when acetone is the aldol donor substrate by attack on the *re*-face of the aldehyde, which provides the antipodal complement of ab38C2 in aldol reactions. Both aldol enantiomers may be accessed through aldol and retro-aldol reactions. These catalysts should provide access to a wide variety of enantiomerically enriched synthons with application to natural product syntheses.

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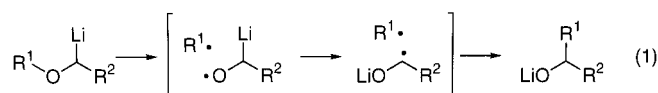
Keywords: aldol reactions • asymmetric synthesis • catalytic antibodies • enantiomeric resolution • retro reactions

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Enantioselective [1,2] Wittig Rearrangement Using an External Chiral Ligand**

Katsuhiko Tomooka,* Kyoko Yamamoto, and Takeshi Nakai*

Since its discovery by Wittig and Löhmann in 1942,^[1] the reaction of α -lithiated ethers, now known as the [1,2] Wittig rearrangement, has attracted much interest from both mechanistic and synthetic points of view.^[2] This type of carbanion rearrangement is recognized to proceed by means of the radical dissociation–recombination mechanism [Eq. (1)].^[2, 3]

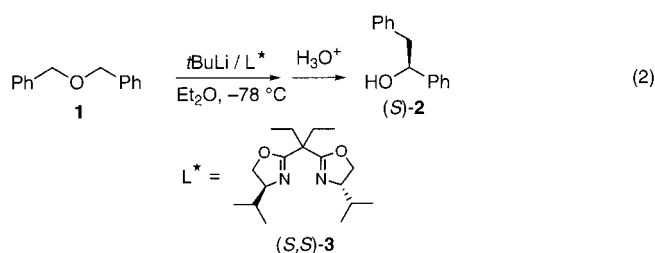


Despite its long history, however, no enantioselective versions of the Wittig rearrangement have been developed yet. Clearly, the radical character provides a great challenge. We now disclose the first enantioselective Wittig rearrangement which relies upon an asymmetric lithiation protocol^[4] in which (*S,S*)-bis(dihydrooxazol) **3** serves as an external chiral ligand^[5, 6] [Eq. (2)]. The most striking feature is that the

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[*] Prof. Dr. K. Tomooka, K. Yamamoto, Prof. Dr. T. Nakai
Department of Applied Chemistry
Graduate School of Science and Engineering
Tokyo Institute of Technology
Meguro-ku, Tokyo 152-8552 (Japan)
Fax: (+81)3-5734-3931
E-mail: ktomooka@o.cc.titech.ac.jp
takeshi@o.cc.titech.ac.jp

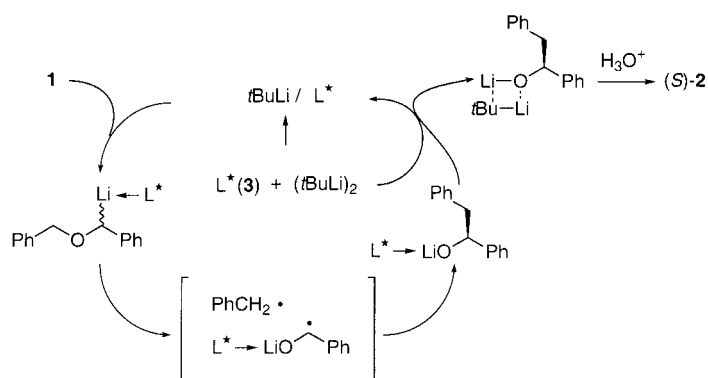
[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and by the Research for the Future Program, administered by the Japan Society of the Promotion of Science.



rearrangement proceeds with essentially the same enantioselectivity even when only a catalytic amount of chiral ligand **3** is used.

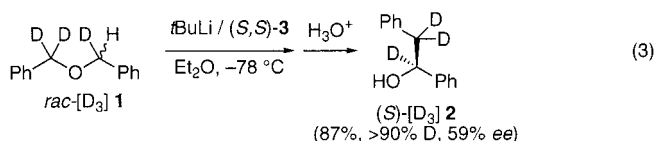
We found that the rearrangement of dibenzyl ether (**1**), a historic Wittig substrate,^[1] when induced with the premixed complex *t*BuLi/**3** (1.0 equiv each) in diethyl ether at -78°C , afforded alcohol (*S*)-**2** in 55% yield and with 60% *ee*, along with recovered **1** in 43% yield.^[7, 8] This is the first example of an enantioselective Wittig rearrangement, though the enantioselectivity is moderate.^[9] Significantly enough, when either one more equivalent of *t*BuLi was added after the reaction or the complex *t*BuLi/**3** (2.0/1.0) was initially used, the yield of **2** increased to 90–94% while the same level of enantioselectivity (62% *ee*) was maintained. This means that two equivalents of *t*BuLi are required for the complete reaction. At this point we made two suppositions: 1) The initial lithiation would be effected almost exclusively by the *t*BuLi/**3** complex; *t*BuLi itself, which is known to exist as a dimer in diethyl ether,^[10] could not function as an efficient lithiating agent under these conditions.^[11] 2) The *t*BuLi dimer could participate in complexing with the resulting **3**-bound lithium alkoxide, thereby taking half out of action to form the *t*BuLi/alkoxide complex^[12, 13] while regenerating the active complex *t*BuLi/**3**. These arguments explain how the enantioselective version could proceed even with a catalytic amount of the chiral ligand **3**.

Therefore, the rearrangement of **1** was carried out using 10 mol% of **3** and two equivalents of *t*BuLi under the same conditions. As anticipated, alcohol (*S*)-**2** was obtained in equally high enantioselectivity and chemical yield (60% *ee*, 86%). A similar use of 5 mol% of **3** resulted in 54% *ee* and 81% chemical yield. Scheme 1 depicts a plausible asymmetric catalytic cycle in which the enantioselectivity might be determined at the radical-recombination step involving the chiral ligand-bound anion radical. Indeed, a similar rearrange-



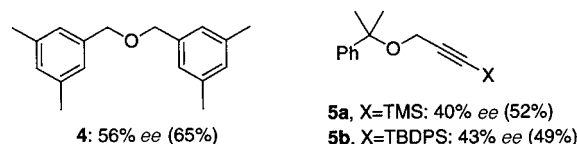
Scheme 1. Plausible catalytic cycle of the enantioselective [1,2] Wittig rearrangement.

ment of $[\text{D}_3]$ **1** (racemate) afforded (*S*)- $[\text{D}_3]$ **2** (>90% D content) in 87% yield and with essentially the same enantiomeric excess as previously observed for **1** [Eq. (3)], indicating

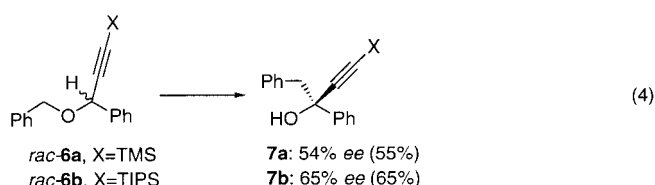


that the lithiation stereochemistry has nothing to do with the product stereochemistry. The most striking feature of this asymmetric catalysis is that during the course of reaction the chiral ligand **3** switches the lithium species partner at each stage, thereby playing the dual role as a catalyst for the lithiation step and a chiral auxiliary for the rearrangement step. The exact mechanism of the asymmetric induction at the rearrangement step is unclear at present; more detailed work is needed.

Encouraged by this success, we also examined the enantioselective rearrangement of ethers **4–6** (TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl) using *t*BuLi/**3** (2.0 equiv each). The results thus obtained are



shown below the formula drawings.^[14, 15] Of particular interest is the rearrangement of *rac*-**6**, which provides the tertiary alcohol **7** with a relatively high enantioselectivity [Eq. (4)].



We have described the first example of an enantioselective [1,2] Wittig rearrangement which can proceed even in an asymmetric, catalytic fashion. This is also the first example of an enantioselective, catalytic carbanion-radical rearrangement. Thus, this work opens a new chapter for classic Wittig chemistry as well as for asymmetric reactions of radicals and organolithium species.

Experimental Section

To a solution of (*S,S*)-**3** (11.2 mg, 0.038 mmol) in diethyl ether (6 mL) at -78°C was added a commercial solution of *t*BuLi in pentane (0.48 mL of a 1.57 M solution, 0.75 mmol) by means of a syringe, and the mixture was stirred for 15 min. The mixture was maintained at -78°C , and a solution of **1** (75.9 mg, 0.38 mmol) in diethyl ether was added dropwise by means of a syringe. The reaction mixture was stirred at -78°C for 2 h and then treated with a saturated aqueous solution of ammonium chloride. The resulting mixture was extracted with diethyl ether three times, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by

chromatography on silica gel (hexane/diethyl ether 10/1) to give 65.4 mg of (S)-alcohol **2** (86% yield, 60% ee).

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- [15] The enantiomeric excesses were determined by ¹H NMR analysis of the (S)-MTPA esters. The absolute configurations of the major enantiomers obtained from **4** and **5** were not determined. The (R) configuration of **7a** was assigned by conversion into the known (R)-methyl α-benzylmandelate: [α]_D²³ = –13.5 (c = 1.20 in CHCl₃) (65% ee); value of [α]_D²⁵ = –32.4 (c = 3.4 in CHCl₃) in the literature: H. R. Sullivan, J. R. Beck, A. Pohland, *J. Org. Chem.* **1963**, 28, 2381–2385.

The Design of Leadlike Combinatorial Libraries

Simon J. Teague,* Andrew M. Davis, Paul D. Leeson, and Tudor Oprea

Combinatorial chemistry is now widely applied in the drug-discovery process, for both the identification and optimization of lead compounds (chemical starting points). Initially the key factors in the design of libraries intended for finding lead compounds were considered to be library size and diversity.^[1] More recently consideration has been given to designing libraries in which the members have druglike physicochemical properties.^[2] Druglike properties are most commonly defined using the “rules of 5”: *M_r* is smaller than 500, the calculated logarithm of the octanol–water partition coefficient (clg *P*) is less than 5, there are less than five hydrogen-bond donor atoms, and the sum of the number of nitrogen and oxygen atoms is less than 10.^[3] These guidelines have achieved widespread acceptance as defining the limiting properties of most orally active drugs which are able to be absorbed by passive mechanisms. However, it should be borne in mind that these are empirical rules derived by examination of the properties of existing drugs. Herein we propose that the properties required of library compounds intended to provide leads suitable for further optimization may be rather different.

Our analysis starts from consideration of the common sources of leads for drug discovery (Figure 1). These have been divided broadly into three types. The first are leadlike,

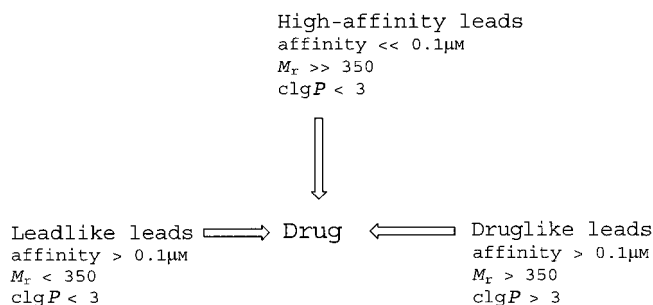


Figure 1. Classification of leads by binding affinity. Lower potency leads are subdivided into leadlike and druglike by reference to their *M_r* and clg *P* values.

low-affinity (>0.1 μM)^[4] compounds which have low molecular weight and clg *P*, typified by some endogenous molecules, for example histamine and GABA. These have been converted into drugs, through the optimization of potency and pharmacokinetic profile, by increasing molecular weight and lipophilicity (Table 1, entries 1–8). The second major source of leads is typified by high affinity and molecular weight. It

[*] Dr. S. J. Teague, A. M. Davis, P. D. Leeson, T. Oprea
Department of Medicinal Chemistry
AstraZeneca R&D Charnwood
Bakewell Road
Loughborough, Leicestershire LE11 5RH (UK)
Fax: (+44) 1509-645-571
E-mail: simon.teague@charnwood.gb.astra.com

Table 1. Examples of low-affinity leads which have been converted into drugs.^[a]

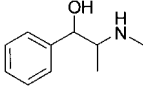
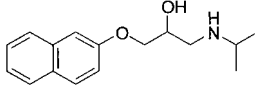
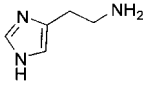
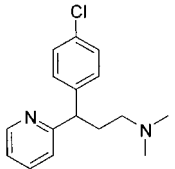
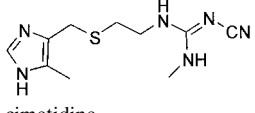
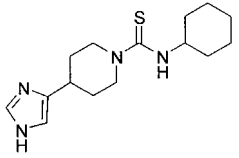
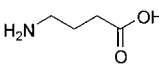
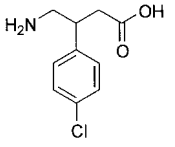
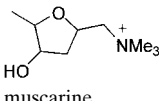
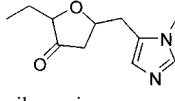
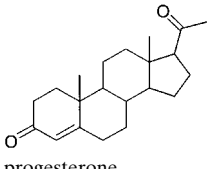
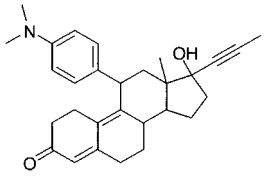
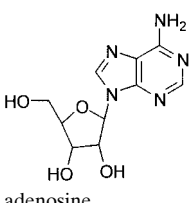
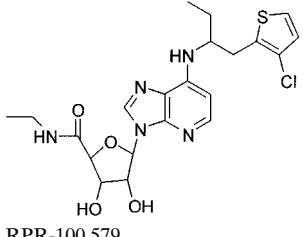
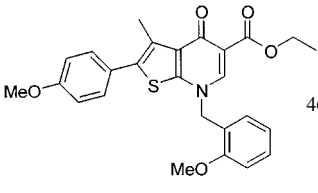
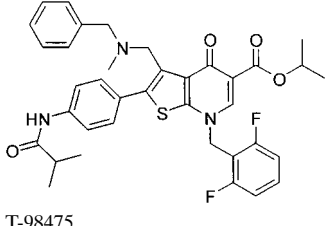
Entry	Receptor	Lead ^[b]		Drug		ΔM_r	$\Delta \text{clg } P$	Ref.
			M_r $\text{clg } P$		M_r $\text{clg } P_d$			
1	$\beta 1$	norepinephrine	165 1.05	propranolol	259 3.1	94	2.05	[8]
2	H1		111 -0.84		274 3.39	163	4.23	[9]
3	H2	histamine	111 -0.84		252 0.36	141	1.2	[10]
4	H3	histamine	111 -0.84		292 1.73	181	2.57	[11]
5	GABA		103 -0.64		213 1.56	110	2.2	[12]
6	muscarinic		147 -[c]		208 -0.1	61	-[c]	[13]
7	steroid		314 4.04		429 4.91	115	0.87	[14]
8	adenosine		267 -1.26		477 3.05	210	4.31	[15]
9 ^[d]	LHRH		463 5.09		657 7.04	194	1.95	[16]

Table 1. (Continued)

Entry	Receptor	Lead ^[b]		Drug		ΔM_r	$\Delta \text{clg } P$	Ref.
			M_r $\text{clg } P$		M_r $\text{clg } P_d$			
10	MAO	 isoniazid	137 −0.89	 iproniazide	179 0.55	42	1.44	[17]
11	Cl channel	 sulfanilamide	172 −0.72	 chlorothiazide	295 −0.03	123	0.69	[18]
12	Cl channel	 chlorothiazide	295 −0.03	 furosemide	330 2.92	35	2.95	[19]
13	Ang II	 Takeda lead	351 3.18	 losartan	422 3.5	71	0.32	[20]
14	Ang II	 Takeda lead	351 3.18	 eprosartan	448 6.75	97	3.57	[21]
15	endothelin	 sulfathiazole	255 0.33	 BMS-182874	345 3.72	90	3.39	[22]
16	dopamine	 L-745,870	229 3.52	 SDZPGU 693	326 4.08	97	0.56	[23]
17	AGT	 clavamycin D	315 −2.3	 L-366,509	411 3.78	96	6.08	[24]
18	oxytocin	 L-366,509	339 4.83	 L-366,509	459 3.03	120	−1.8	[25]

[a] An increase in M_r (ΔM_r) of 100–200 and in $\text{clg } P$ ($\Delta \text{clg } P$) of 0.5–4 is typically observed. [b] Unless indicated otherwise, the leads are leadlike (see Figure 1). [c] $\text{clg } P$ is not definable for a permanently charged compound. [d] The lead is druglike (see Figure 1).

encompasses many peptidic materials and certain potent natural products. This type of lead has provided a number of drugs, for example indinavir from HIV protease substrate^[5] and trimethoprim from dihydrofolate.^[6] Here the issue is usually one of retaining sufficient potency whilst improving pharmacokinetic profile. This is often achieved by reducing molecular weight and increasing lipophilicity. However, the increasing dependency upon screening historical compound collections and combinatorial libraries in order to obtain leads often results in a third type of lead. These have low affinity and druglike molecular weight (350–500) and lipophilicity (3–5). This is borne out by examination of the results obtained from our own high-throughput screens. The distribution of IC_{50} values for approximately 3000 compounds identified in 10^6 high-throughput screens at AstraZeneca R&D Charnwood is plotted in Figure 2 together with the corresponding distribution of M_r and $clgP$ values.

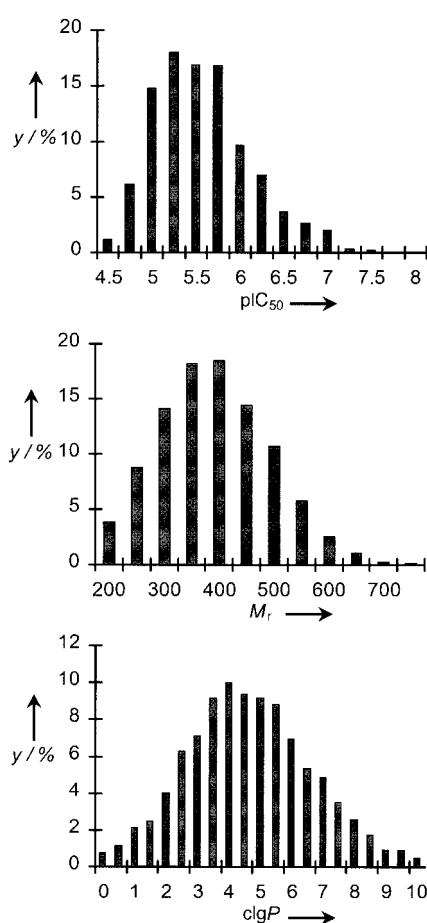


Figure 2. Distributions of pIC_{50} values (top) for approximately 3000 compounds identified in 10^6 high-throughput screening tests and the corresponding distributions of M_r (middle) and $clgP$ values (bottom). The ordinate (y) represents percentages of the total sample set in each abscissa bin.

We find that potent ligands ($IC_{50} < 0.1 \mu M$) are rarely found directly from screening druglike libraries. To achieve high potency, a specific, tight fit between the ligand and the receptor binding pocket is needed, requiring the correct placement of hydrogen bonds as well as charged and hydrophobic groups. The data suggests that the probability of this

occurring is small ($< 1:10^6$). The usual result is the discovery of a number of ligands with IC_{50} values of 1–10 μM (83% with $> 1 \mu M$) with M_r values of 350–450 (54% with > 350) and $clgP$ of 3–4.5 (75% with > 3). Optimization of these molecules with druglike properties and leadlike affinity is difficult. Precedent from small, polar leads (Table 1, entries 1–8) suggests that an increase in M_r of 1–200 and in $clgP$ of 0.5–4 often results, as a consequence of affinity enhancement, during the optimization of a low-potency lead into a drug. However, both of these changes are likely to move a druglike lead out from under the envelope of druglike property distributions into regions where poor bioavailability would be predicted (Table 1, entry 9).

Druglike leads probably achieve μM affinity using many poorly optimised interactions. This is demonstrated by using Andrews' equation.^[7] Although this analysis is only a crude estimation of binding affinity, large positive and negative deviations of potency from that predicted by Andrews' analysis are indicative of the complementarity of the drug–receptor interaction. As the original paper states, “the primary use of the *average* binding energies is to deduce whether a particular drug represents a good or bad match to its receptor”. The predicted and observed binding affinities for our 3000 active compounds are compared on the same scales in Figure 3. A large percentage of the druglike leads have much less affinity than would be expected for molecules with this number of molecular features. In 10^6 screening determinations no compounds produced an IC_{50} of less than 10 nM. From Andrews' analysis 22% of compounds of this complexity would have been expected to have an AVERAGE pK_i of less than 10 nM.

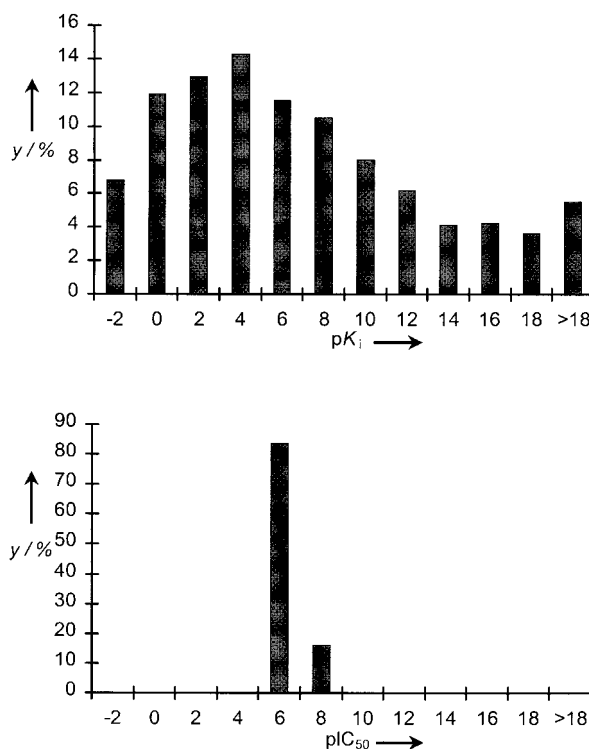


Figure 3. Comparison of pK_i values calculated by Andrews et al.^[7] and observed IC_{50} values of active compounds from 10^6 high-throughput screening determinations. The ordinate (y) represents percentages of the total sample set in each abscissa bin.

Another source of leads which are not very potent at the required receptor are those that are obtained by observing side effects in existing drugs (Table 1, entries 10–12). Here the same pattern of increasing molecular weight and lipophilicity is observed. Finally there are many recent examples where the lead originating from high-throughput screening of historical collections is elaborated by exploiting additional lipophilic interactions to produce molecules with druglike physicochemical properties and high affinity (Table 1, entries 13–18). Thus if it is anticipated that both molecular weight and lipophilicity will increase during the process of lead-to-drug optimization, and that orally active compounds are eventually required, there are clear implications for the design of libraries intended for lead discovery.

We propose that there is a great deal of precedent to suggest that libraries consisting of molecules with $M_r = 100$ –350 and $\text{clog } P = 1$ –3.0 are greatly superior to those comprising druglike compounds. These libraries are intended to provide leads with μM affinity in high-throughput screens, but also to allow for the discovery and exploitation of additional interactions in the lead-optimization phase. This is illustrated graphically in Figure 4, where the molecular weight distributions of a library of leadlike molecules, all oral drugs from the Physicians Desk Reference (PDR),^[26] and a typical combinatorial chemistry library are represented. Optimization of affinity for leadlike molecules produces a rightward shift into the druglike region.

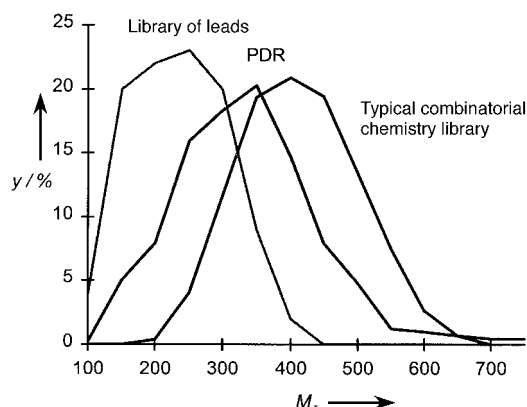


Figure 4. Distributions of M_r for a leadlike library, oral drugs (Physicians Desk Reference (PDR), 1994), and a typical combinatorial chemistry library.

Molecules with leadlike molecular weight and lipophilicity must still interact with a receptor to produce an IC_{50} in the 1–10 μM range if they are to be detected in a high-throughput screening determinations. This may account for the preponderance of leadlike molecules bearing a single charge at physiological pH values, since this provides for the possibility of a large binding affinity with little molecular weight penalty.

It is clear that small, polar molecules can also display sufficient selectivity in receptor binding assays. Thus, norepinephrine, dopamine, and histamine, for instance, display selectivity for their respective receptors, even though these receptors all belong to the G-protein-coupled receptor (GPCR) superfamily. Often receptor subtype selectivity, starting from one endogenous agonist, is obtained by the

introduction of potency-enhancing, specific, lipophilic interactions. Small leadlike molecules have a better chance of binding to a receptor, because they can more easily find a binding mode than larger druglike molecules. Once a small polar molecule with affinity at μM levels has been found, more focused libraries can be rapidly improve upon it. This is often achieved by the introduction of lipophilic groups which simultaneously improve affinity and the pharmacokinetic properties of these molecules. However, if libraries of molecules of druglike size are used at the outset, this opportunity is lost.

An emphasis upon generating libraries consisting of low molecular weight, polar molecules, with the aim of obtaining leads with affinity at μM levels may justify a reexamination of the role of some combinatorial technologies. Large libraries generated by concatenating several monomers using multi-component reactions or using several steps incorporating split-and-mix protocols may not be the most effective approach. Relatively simple one- or two-step elaboration of a wide variety of small templates is more useful in providing libraries of this type. The leads discovered are more easily elaborated into drugs with the required physical properties. In our experience the relative values of active compounds emerging from a high-throughput screen can usefully be assessed on the basis of biological activity per unit of molecular weight and lipophilicity. The selection of leadlike compounds for further optimization eases the pressure on subsequent and more labor-intensive parts of the drug-discovery process, such as obtaining suitable bulk properties together with an acceptable metabolic and pharmacokinetic profile.

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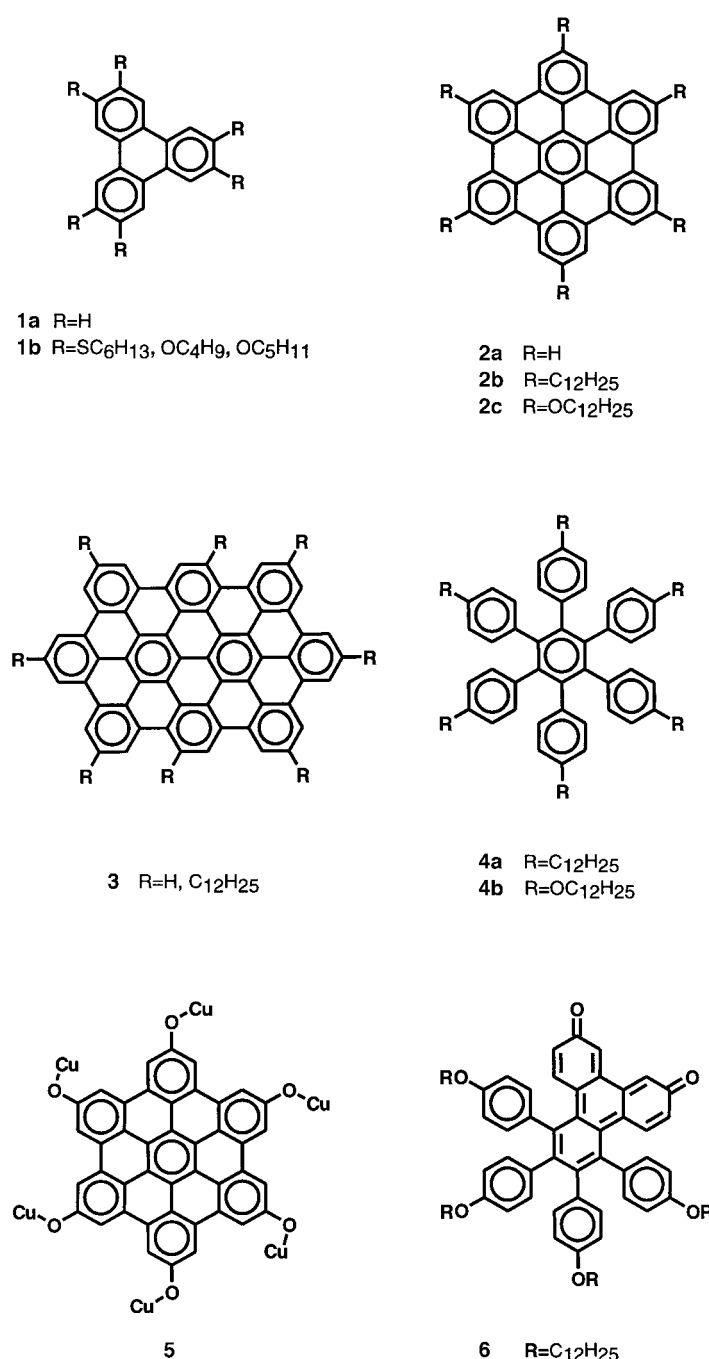
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Template-Mediated Synthesis of Polycyclic Aromatic Hydrocarbons: Cyclodehydrogenation and Planarization of a Hexaphenylbenzene Derivative at a Copper Surface**

Klaus Weiss, Gunda Beernink, Florian Dötz, Alexander Birkner, Klaus Müllen, and Christof H. Wöll*

Polycyclic aromatic hydrocarbons (PAHs) such as triphenylene (**1a**), hexa-*peri*-hexabenzocoronene (HBC, **2a**), and its higher homologue **3** (Scheme 1) form two- and three-



Scheme 1. Polycyclic aromatic hydrocarbons 1–6.

dimensional superstructures that are attracting considerable attention in the field of charge transfer processes.^[1–4] The deposition of monomolecular layers, a central step for using such disklike molecules in nanoelectronic devices, can be performed by evaporating PAHs in ultrahigh vacuum (UHV) and, in case of alkyl-substituted soluble derivatives, also by deposition from solution. However, both preparation procedures cannot be applied to larger PAHs which have recently been synthesized.^[5–8] We therefore present a method to produce PAHs, for example, hexabenzocoronene, directly by a thermally induced cyclodehydrogenation route starting from a precursor molecule adsorbed on a Cu(111) surface. This new synthetic route is based on the following concept:

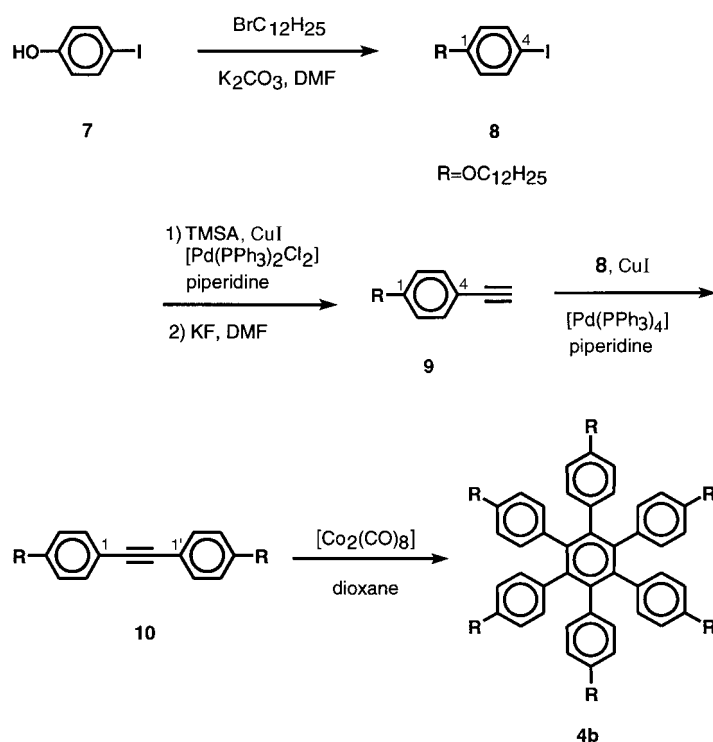
[*] Prof. Dr. C. H. Wöll, Dr. K. Weiss, G. Beernink, Dr. A. Birkner
Lehrstuhl für Physikalische Chemie I der Universität
Universitätsstrasse 150, D-44780 Bochum (Germany)
Fax: (+49) 234-3214182
E-mail: woell@pc.ruhr-uni-bochum.de
F. Dötz, Prof. Dr. K. Müllen
Max-Planck-Institut für Polymerforschung
Ackermannweg 10, D-55127 Mainz (Germany)

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First a precursor **4b** of the target compound **5** is synthesized and deposited in monolayers on a Cu surface. On heating this adsorbate layer, **4b** is completely dealkylated and converted by cyclodehydrogenation into the planar product **5**. The PAH **5** does not exist in solution, but is stabilized through the interaction of the oxygen atoms with the Cu surface, which also hinders its desorption.

We used near edge X-ray absorption fine structure (NEXAFS) spectroscopy for the characterization of molecules adsorbed on metal surfaces and for the analysis of products formed by chemical modifications. This method allows a determination of the molecular orientation and provides detailed information on the electronic structure of the molecules. Scanning tunneling microscopy (STM) provides additional information on the lateral order of the molecular adsorbate.

The synthetic route to hexaether **4b** is shown in Scheme 2. Starting from commercially available 4-iodophenol (**7**), etherification with 1-bromodecane affords 4-(dodecyloxy)iodobenzene (**8**), which is then coupled to (trimethylsilyl)acetylene



Scheme 2. Synthesis of the precursor molecule **4b**. R = OC₁₂H₂₅.

(TMSA) by using the method developed by Hagihara, Sonogashira et al.^[9] Deprotection of the trimethylsilyl group with KF in DMF afforded the acetylene **9**, which, after renewed Hagihara–Sonogashira coupling with **8** was converted into 4,4'-di(dodecyloxy)diphenylacetylene (**10**). The cyclotrimerization of **10** with [Co₂(CO)₈] in dioxane finally gives the precursor **4b**.^[10] The key step on the path to the PAH **2c** is the oxidative cyclodehydrogenation of the oligophenylene precursors. Optimization of the appropriate cyclization conditions finally proved FeCl₃ to be superior to all other Lewis acids on the way to hexaalkyl-substituted HBCs. In a

typical cyclization experiment the precursor **4a** is dissolved in dichloromethane, and a solution of FeCl₃ in nitromethane is added dropwise at room temperature. After the starting material had disappeared (TLC) the mixture was precipitated in methanol, and purified by column chromatography or recrystallization. However, in the case of **4b** this synthetic protocol did not give the desired compound **2c** but the quinone **6** (Scheme 1) in 96% yield. Oxidative dealkylation and dehydrogenation leads to an extended quinonoid system which also incorporates the central aromatic ring. It is well known that compounds such as **4b** undergo reactions in the presence of Lewis acids which involve both ether cleavage and oxidation to quinonoid aromatic structures as well as formation of new carbon–carbon bonds between adjacent phenyl rings.^[11, 12] Which of the two reactions occurs first depends on the system.^[12]

The thermogravimetric analysis of **4b** shows that this substance is stable up to temperatures of 490 K; in the temperature range between 490 K and 570 K about 1% loss in weight can be observed. Monolayers of **4b** with a film thickness of about 3 Å were deposited at a temperature of *T* = 540 K from a stainless steel Knudsen cell onto a clean, structurally well-defined Cu(111) surface. The deposition rate of 3 Å min^{−1} was controlled by a quartz crystal microbalance. The samples were heated for 5–10 min to different temperatures and subsequently investigated by NEXAFS spectroscopy. For each temperature the layer thickness was determined by relating the height of the edge jump to the signal intensity at 280 eV.^[13] The results reveal that the amount of molecules present on the surface is essentially unchanged.

Figure 1 shows a series of NEXAFS spectra recorded at the C(1s) absorption edge at normal and grazing photon inci-

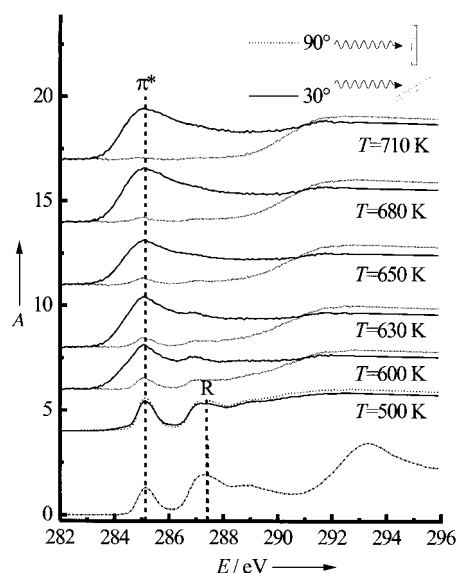


Figure 1. C(1s) NEXAFS spectra of **4b** monolayers adsorbed on Cu(111) and heated for 5–10 min to different temperatures. The spectra were recorded for normal and grazing photon incidence, where the angle between the electric field vector of the linearly polarized synchrotron light and the surface normal is 90° and 30°, respectively. The spectra are normalized to the absorption step at 325 eV and focus on the NEXAFS spectral features in close proximity to the absorption edge which is located at around 291 eV. The bottom spectrum was recorded for **4b** deposited from solution.

dence. The spectra recorded for **4b** heated to 500 K reveal a well-defined resonance at 285.1 eV, which is assigned to an excitation of C(1s) core level electrons into the lowest unoccupied π^* orbital of the phenyl subunits. Following previous studies on linear saturated hydrocarbons^[14] an additional weak resonance R at 287.4 eV is attributed to excitations of C(1s) electrons into Rydberg(R) orbitals of the alkyl chains. The comparison with spectra recorded for **4b** deposited from solution shows that most of the alkyl chains were removed during evaporation. For the sample heated to temperatures above 500 K the spectra of **4b** recorded at normal and grazing incidence are virtually identical. This absence of dichroism is consistent with a wide distribution of phenyl orientation angles as expected from the nonplanar structure of the molecules. In contrast, spectra recorded for the surface heated to higher temperatures reveal an increasing amount of dichroism, which provides direct evidence for a thermally induced planarization of the molecule **4b**.^[15] Since such a planarization is—because of steric constraints—not possible for the unmodified molecule, this observation provides strong evidence for the onset of dehydrogenation. This effective planarization is completed after heating the sample to 710 K, at which temperature essentially all molecules are oriented coplanar with the surface.

A more detailed investigation of the NEXAFS spectra reveals that the occurrence of the dichroism is accompanied by two thermally induced effects. The significant broadening of the phenylene π^* -resonance is attributed to the interaction of the phenyl groups with the Cu(111) surface and indicates a direct interaction of all ring systems with the surface. This is a general feature in NEXAFS spectra of π -electron systems in direct contact with metal surfaces and has previously been seen for benzene adsorbed on Cu substrates.^[16, 17] The disappearance of the resonance at 287.4 eV at temperatures above 570 K supports the complete dealkylation of the hexaether on the Cu surface. This finding is supported by the results of a detailed X-ray photoelectron spectroscopy (XPS) study, where in addition—due to the formation of a O—Cu bond—a significant O(1s) binding energy shift has been observed.^[18]

To obtain independent information on the products of this temperature-induced reaction we have carried out STM measurements on submonolayers of **4b** using a UHV-based instrument. No stable imaging was observed directly after deposition of the molecule. This behavior is expected since the as-deposited molecules are bound to the surface only through weak van der Waals forces and the molecules should thus be very mobile. Reproducible STM results were only obtained after heating the samples above 500 K; typical STM topographs are presented in Figure 2. After the samples had been heated to 570 K, the STM data reveal the formation of well-ordered islands of adsorbed molecules. The diameter of the spherical objects within these islands (bright areas) amounts to 17 ± 1 Å, which within the error bars agrees with the diameter of a single hexaphenylbenzene unit. At this stage the height of the islands amounts to 2.1 Å (see Figure 2). When the samples were heated further, the STM images reveal a substantial reduction in contrast and a significant decrease of the island heights from 1.8 Å (after heating to

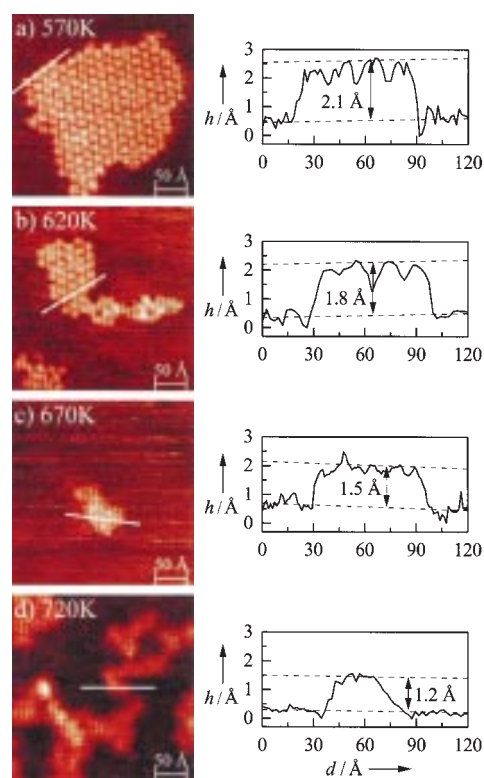


Figure 2. STM images ($300 \text{ Å} \times 300 \text{ Å}$) of **4b** submonolayers adsorbed on Cu(111) and heated for 10–15 min to different temperatures. Right: Line profiles which were taken along the white lines indicated in the images. All images were recorded in the constant current mode. No filtering procedures were used. The images (a)–(c) were recorded with a tip bias voltage of -0.3 V and a tunneling current of 0.03 nA . Image (d) was recorded with a tip bias voltage of -1.0 V and a tunneling current of 0.5 nA .

620 K) to 1.5 Å (after heating to 670 K) and then to 1.2 Å (after heating to 720 K).

The results of our NEXAFS and STM studies provide very strong evidence for the reaction scenario depicted in Figure 3.

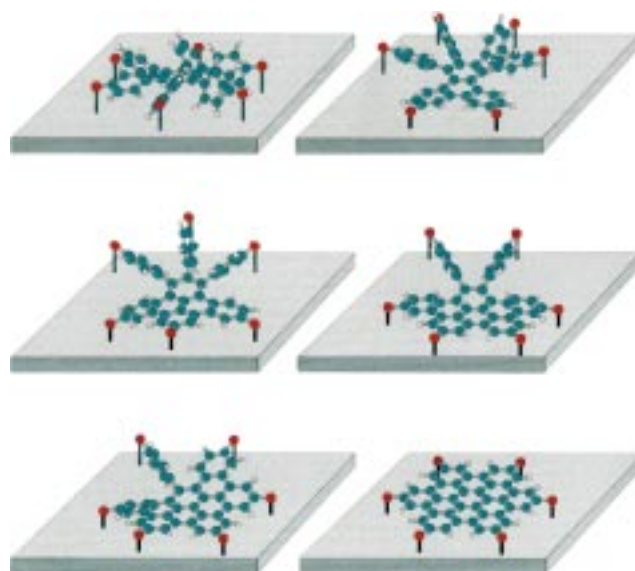


Figure 3. Schematic representation of the stepwise planarization of the hexaphenylbenzene unit of **4b** by thermally induced cyclodehydrogenation. The molecule is anchored through the oxygen atoms to the Cu(111) surface. The formation of hexabenzocoronene unit **5** (shown at the bottom, right) is completed at 710 K.

Heating **4b** to a temperature of 470 K leads to sublimation accompanied by substantial dealkylation, and a physisorbed film is deposited on the substrate at room temperature. Heating the substrate to temperatures above 570 K leads to complete dealkylation followed by the formation of an O–Cu bond. A very similar reaction mechanism has been found in a recent study on the temperature-induced reaction of hexabutyloxytriphenylene with a Cu(111) surface.^[19] In this case the cleavage of the alkyl–O bond and the formation of a O–Cu bond was also found to occur at 570 K. At this temperature the height of the islands is 2.1 Å, which is consistent with the presence of the unmodified hexaphenylbenzene unit. The NEXAFS data demonstrate that the structure of the phenyl rings is unmodified at this temperature.

Although the lateral mobility of the molecules is expected to decrease significantly as a result of the formation of covalent O–Cu bonds, the high degree of lateral order seen in the STM topographs demonstrates the presence of a mobility which is sufficiently high to allow the formation of well-ordered islands. The NEXAFS data (shape and polarization dependence of the π^* -resonance) as well as the STM measurements (height of the islands) reveal that the dehydrogenation/planarization process is completed at 710–720 K. The substrate is covered with hexabenzocoronene units, which are bound (as shown in **5**) through oxygen atoms to the surface. The importance of graphite segments and molecularly defined graphitic structures suggests the transfer of this novel strategy, namely the surface-induced PAH synthesis, to considerably larger oligophenylenes.^[6, 8]

Experimental Section

The NEXAFS measurements were recorded at the synchrotron radiation facility BESSY I (Berlin) using beamline HE-TGM2^[20] and a multi-chamber UHV system operated in the low 10^{-10} mbar pressure range. The spectra were recorded in partial electron yield (PEY) detection mode by using a channeltron with a retarding voltage of –150 V. After calibrating the photon energy scale with respect to the NEXAFS data for highly oriented pyrolytic graphite and correcting the spectra for the monochromator transmission function by division through the spectrum of the clean Cu(111) surface, the spectra were normalized to the edge jump at 325 eV.^[21] The STM data were recorded at room temperature with a UHV Omicron Micro STM (base pressure lower than 1×10^{-11} mbar) in the constant current mode with tip bias voltages of –0.3–1.0 V and tunneling currents of 0.03–0.5 nA. Imaging was performed with a scanning speed of 900 Å s^{–1}. In both UHV systems the Cu(111) surface was cleaned by extensive Ar⁺ sputtering (ion energy 1 keV) and annealing cycles prior to the experiments. Measurements using thermogravimetry were carried out using a Mettler TG 50 thermobalance.

8: 4-Iodophenol (**7**) (100.01 g, 454.59 mmol), 1-bromododecane (226.82 g, 910.08 mmol), and potassium carbonate (125.72 g, 911.01 mmol) were dissolved in dimethylformamide (DMF) (500 mL) and refluxed for 3 h. The solution was then diluted with water, hydrochloric acid (2 N), and extracted with dichloromethane. The combined extracts were washed with aqueous sodium bicarbonate, sodium chloride, and dried (MgSO₄). Evaporation of the solvent in vacuo and column chromatography (petroleum ether/dichloromethane) of the crude product yielded a colorless solid (149.56 g, 85 %). M.p. 37 °C; ¹H NMR (200 MHz, CDCl₃): δ = 7.56 (d, ³J(H,H) = 8.0 Hz, 2H; 3-H, 5-H), 6.68 (d, ³J(H,H) = 8.0 Hz, 2H; 2-H, 6-H), 3.39 (t, ³J(H,H) = 7.0 Hz, 2H; OCH₂), 1.90–1.70 (m, 2H; OCH₂CH₂), 1.60–1.10 (m, 18H; H_{alkyl}), 0.91 (t, ³J(H,H) = 7.9 Hz, 3H; CH₃); ¹³C NMR (50 MHz, CDCl₃): δ = 159.56 (C-1), 138.64, 117.47 (C_{arene}), 82.88 (C-4), 68.65 (OCH₂), 32.43, 30.15, 30.09, 29.87, 29.68, 26.51, 23.20 (all C_{alkyl}), 14.61 (CH₃); MS (FD, 8 kV): m/z (%): 388.3 (100) [M^+] (calcd for C₁₈H₂₀OI = 388.3).

4-Dodecyloxy(trimethylsilyl)ethynylbenzene: 4-(Dodecyloxy)iodobenzene (**8**) (70.02 g, 180.31 mmol), triphenylphosphane (2.36 g, 9.03 mmol), copper(I) iodide (1.71 g, 8.98 mmol), and *trans*-[Pd(PPh₃)₂Cl₂] (1.90 g, 2.71 mmol) were dissolved in piperidine (700 mL) under an argon atmosphere. TMSA (19.51 g, 197.92 mmol) was added dropwise, and the mixture stirred for 6 h and then cooled to room temperature. The mixture was then washed with aqueous ammonium chloride, extracted with dichloromethane, and the combined extracts were washed again with aqueous ammonium chloride and water, and dried over MgSO₄. After removal of the solvent in vacuo, the crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give a colorless oil (58.76 g, 92 %). ¹H NMR (300 MHz, CDCl₃): δ = 7.43 (d, ³J(H,H) = 8.5 Hz, 2H; 3-H, 5-H), 6.82 (d, ³J(H,H) = 8.5 Hz, 2H; 2-H, 6-H), 3.94 (t, ³J(H,H) = 6.4 Hz, 2H; OCH₂), 1.80 (m, 2H; OCH₂CH₂), 1.33–1.21 (m, 18H; H_{alkyl}), 0.96 (t, 3H, ³J(H,H) = 6.3 Hz; CH₃), 0.23 (s, 9H; SiCH₃); ¹³C NMR (50 MHz, CDCl₃): δ = 159.90 (C-1), 133.84, 115.69 (C-2), 114.84, 105.97 (Ar–C≡C), 92.60 (Ar–C≡C), 68.47 (OCH₂), 32.48, 30.20, 30.15, 29.93, 29.75, 26.56, 23.23, (all C_{alkyl}), 14.62 (CH₃), 0.61 (SiCH₃); MS (FD, 8 kV): m/z (%): 358.2 (100) [M^+] (calcd for C₂₃H₃₈O_{Si} = 358.6).

9: 4-Dodecyloxy(trimethylsilyl)ethynylbenzene (37.83 g, 105.48 mmol) was dissolved in DMF (450 mL), and a solution of potassium fluoride (18.61 g, 321 mmol) in water (65 mL) was added. The solution was stirred for 3 h, diluted with water, and extracted with toluene. The combined extracts were washed with water, dried over MgSO₄, and the solvent evaporated in vacuo. Column chromatography (petroleum ether/ethyl acetate) afforded **9** as a colorless oil (30.06 g, 98 %). ¹H NMR (200 MHz, CDCl₃): δ = 7.46 (d, ³J(H,H) = 9.0 Hz, 2H; 3-H, 5-H), 6.85 (d, ³J(H,H) = 9.0 Hz, 2H; 2-H, 6-H), 4.95 (t, ³J(H,H) = 7.4 Hz, 2H; OCH₂), 3.01 (s, 1H; ≡CH), 1.81 (m, 2H; OCH₂CH₂), 1.34–1.21 (m, 18H; H_{alkyl}), 0.98 (t, 3H, ³J(H,H) = 7.1 Hz; CH₃); ¹³C NMR (50 MHz, CDCl₃): δ = 160.09 (C-1), 134.01, 114.95 (C-4), 114.66, 84.30 (Ar–C≡C), 76.21 (Ar–C≡C), 68.51 (OCH₂), 32.55, 30.28, 30.02, 29.81, 26.63, 23.29 (all C_{alkyl}), 14.65 (CH₃); MS (FD, 8 kV): m/z (%): 286.1 (100) [M^+] (calcd for C₂₀H₃₀O = 286.5).

10: 4-(Dodecyloxy)iodobenzene (**8**) (33.55 g, 86.40 mmol), copper(I) iodide (1.64 g, 8.63 mmol), and [Pd(PPh₃)₄] (1.36 g, 1.72 mmol) were dissolved in piperidine (350 mL) under an argon atmosphere. 4-(Dodecyloxy)ethynylbenzene **9** was also dissolved in piperidine (100 mL), added, and the mixture was stirred for 3 h. The resulting mixture was diluted with water (300 mL), extracted with dichloromethane, and dried over Na₂SO₄. The organic solvent was removed in vacuo and the residue was purified by chromatography with petroleum ether to yield a colorless solid (46.12 g, 97 %). M.p. 97 °C; ¹H NMR (300 MHz, CDCl₃): δ = 7.42 (d, ³J(H,H) = 8.4 Hz, 4H; 2-H, 2'-H, 6-H, 6'-H), 6.85 (d, ³J(H,H) = 8.4 Hz, 4H; 3-H, 3'-H, 6-H, 6'-H), 4.98 (t, ³J(H,H) = 6.2 Hz, 4H; OCH₂), 1.80 (m, 4H; OCH₂CH₂), 1.60–1.20 (m, 36H; H_{alkyl}), 0.92 (m, 6H; CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 159.09 (C-4, C-4'), 133.03, 116.08 (C-1, C-1'), 115.02, 84.00 (C≡C), 68.58 (OCH₂), 32.41, 30.13, 29.88, 29.73, 26.52, 23.17 (all C_{alkyl}), 14.57 (CH₃); MS (FD, 8 kV): m/z (%): 547.1 (100) [M^+] (calcd for C₃₈H₅₈O₂ = 546.9).

4b: 4,4'-(Dodecyloxy)diphenylacetylene (**10**) (30.50 g, 54.95 mmol) and [Co₂(CO)₈] (0.51 mg, 1.49×10^{-3} mmol) were dissolved in 1,4-dioxane (600 mL) under an argon atmosphere and refluxed for 4 h. Solvent was removed in vacuo and the brown residue purified by column chromatography (petroleum ether/dichloromethane) to give a yellowish solid (26.72 g, 89 %). M.p. 52 °C; ¹H NMR (250 MHz, CD₂Cl₂): δ = 6.68 (d, ³J(H,H) = 8.5 Hz, 12H; H *meta* to O), 6.40 (d, ³J(H,H) = 8.5 Hz, 12H; H *ortho* to O), 4.74 (t, ³J(H,H) = 6.6 Hz, 12H; OCH₂), 1.64 (m, 12H; OCH₂CH₂), 1.45–1.15 (m, 108H; H_{alkyl}), 0.87 (m, 18H; CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 156.80 (C_{arene}–O), 140.75, 134.05, 132.95, 113.38 (all C_{arene}), 68.24 (OCH₂), 32.45, 30.09, 29.96, 29.82, 26.53, 23.16 (all C_{alkyl}), 14.57 (CH₃); MS (FD, 8 kV): m/z (%): 1639.5 (100) [M^+] (calcd for C₁₁₄H₁₇₄O₆ = 1639.3).

6: Hexaphenylbenzene (**4b**) (1.01 g, 0.62 mmol) was dissolved in dichloromethane (150 mL) in a Schlenk flask under an argon atmosphere. Throughout the whole reaction a constant stream of argon was bubbled through the mixture to remove HCl formed in situ. A solution of FeCl₃ (1.80 g, 11.10 mmol) in nitromethane was added dropwise and the mixture stirred for 30 min at room temperature. Methanol (100 mL) was added and a beige solid precipitated which was filtered and dried in vacuo (768 mg, 96 %). M.p. 178 °C; ¹H NMR (500 MHz, [D₆]DMSO, 393 K): δ = 7.32 (d, ³J(H,H) = 8.4 Hz, 4H; H_{arene}), 7.04 (d, ³J(H,H) = 8.4 Hz, 4H; H_{arene}), 6.75 (dd, ³J(H,H) = 4.4 Hz, ⁴J(H,H) = 1.0 Hz, 2H; *ortho*-H_{quinone}), 6.70 (d,

$J(\text{H,H}) = 9.8 \text{ Hz}$, 4H; H_{arene}), 6.60 (d, $^4J(\text{H,H}) = 1.0 \text{ Hz}$, 2H; *ortho*- $\text{H}_{\text{quinone}}$), 6.37 (d, $^3J(\text{H,H}) = 4.4 \text{ Hz}$, 2H; *meta*- $\text{H}_{\text{quinone}}$), 6.14 (d, $^3J(\text{H,H}) = 9.8 \text{ Hz}$, 4H; H_{arene}), 1.91 (m, 4H; OCH_2), 1.75 (m, 4H; OCH_2CH_2), 1.62 (m, 4H; $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.58–1.32 (m, 68H; H_{alkyl}), 1.04–0.94 (m, 12H; CH_3); ^{13}C NMR (125 MHz, $[\text{D}_8]\text{THF}$): $\delta = 185.98$ ($\text{C}_{\text{quinone}}$), 161.75 ($\text{C}_{\text{arene}}-\text{O}$), 161.36 ($\text{C}_{\text{arene}}-\text{O}$), 147.32, 145.05, 140.90, 137.00, 135.94, 130.60 (all C_{arene}), 58.57 (OCH_2), 34.08, 31.82, 31.45, 28.25, 24.75 (all C_{alkyl}), 15.63 (CH_3); MS (FD, 8 kV): m/z (%): 1300.4 (100) [M^+] (calcd for $\text{C}_{90}\text{H}_{122}\text{O}_6 = 1300.0$); IR (KBr pellet): $\tilde{\nu}$ [cm^{-1}] = 3062(w), 3041(w), 2918(s), 2847(s), 1663 [(CO) $_{\text{stretch}}$], 1603(m), 1495(m) [$\nu(\text{C}=\text{C})_{\text{arene}}$], 1244(s) [(Ar–O–R)], 1170(m), 825(m); UV/Vis (CHCl_3): λ [nm] (lg ϵ [$\text{L mol}^{-1}\text{cm}^{-1}$]): 314 (sh, 4.52), 330 (4.69), 347 (4.74).

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Fluorescence Detection from Single Dendrimers with Multiple Chromophores**

Thomas Gensch, Johan Hofkens, Andreas Heirmann, Kenji Tsuda, Wendy Verheijen, Tom Vosch, Thomas Christ, Thomas Basché, Klaus Müllen,* and Frans C. De Schryver*

Following the pioneering studies of Moerner and Kador as well as Orrit and Bernard^[1] a wealth of experiments have been performed using high-resolution single-molecule spectroscopy (SMS) at low temperature.^[2] Single molecules that are immobilized on and in thin polymer films and gels, as well as on glass, have been investigated at room temperature with various types of optical microscopies.^[3, 4] The spectroscopic study of single molecules in solution has attracted substantial attention and is currently being developed as a new tool in analytical chemistry.^[5]

In the majority of the SMS studies the single molecules are investigated through their fluorescence properties. One of the most prominent observations in SMS studies is the occurrence of sudden changes in fluorescence intensity, often called the on–off behavior of a single molecule. This is in contrast to bulk measurements where the fluorescence intensity decreases exponentially with irradiation time as a result of photobleaching. Herein we investigate the difference between SMS of a single chromophore and of multichromophoric systems with the emphasis on the passage from the typical on–off behavior of a single molecule to the behavior of the ensemble. To this end a system has to be synthesized in which chromophores can be placed at a specific distance without being coupled through bonds. One way to obtain multiple chromophores in a well arranged environment is based on dendrimer synthesis.

We have recently introduced a new type of dendrimers and hyperbranched 3-dimensional polyphenylenes consisting of penta- or hexaphenylbenzene building blocks with strongly twisted benzene units.^[6, 7] The polyphenylene dendrimers are synthesized by repetitive Diels–Alder reactions using ethynyl-substituted aromatic cores such as 3,3',5,5'-tetraethynylbiphenyl (**1**) and the cyclopentadienone derivative **2** as the branching (A_2B -type) reagent. The stepwise approach to

[*] Prof. Dr. K. Müllen, A. Heirmann
Max-Planck-Institut für Polymerforschung
Ackermannweg 10, D-55128 Mainz (Germany)
Fax: (+49) 6131-379350
E-mail: muellen@mpip-mainz.mpg.de

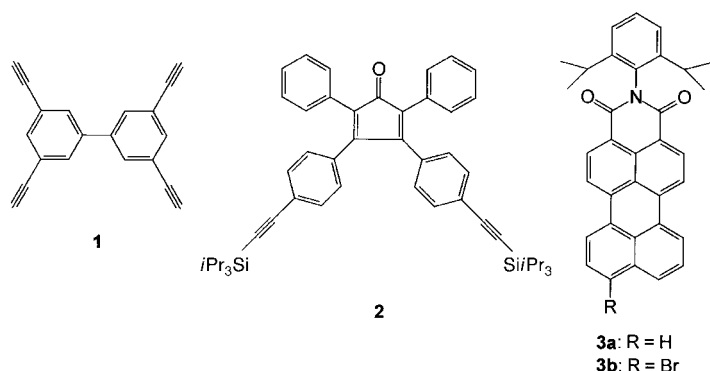
Prof. Dr. F. C. De Schryver, T. Gensch, J. Hofkens, K. Tsuda,
W. Verheijen, T. Vosch
Department of Chemistry
Katholieke Universiteit Leuven
Celestijnenlaan 200F, B-3001 Heverlee (Belgium)
Fax: (+32) 16-327989
E-mail: frans.deschryver@chem.kuleuven.ac.be

T. Christ, T. Basché
Fakultät für Chemie der Universität
Welderweg 11, D-55099 (Germany)

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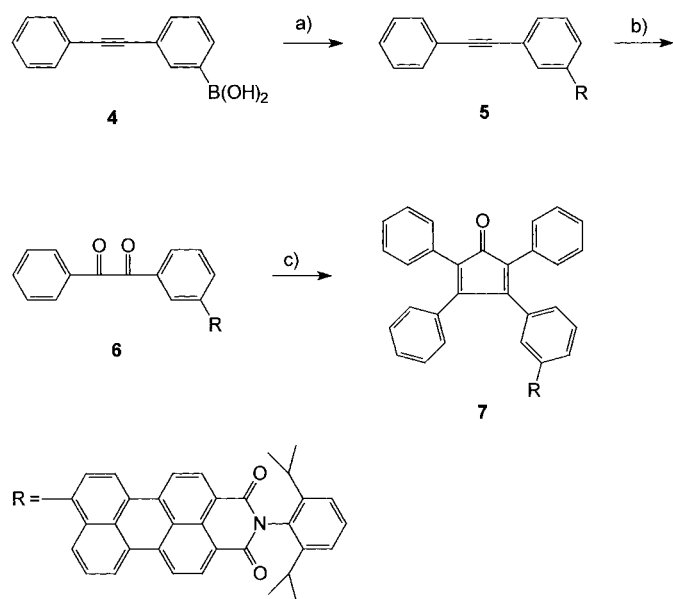
building successive generations of dendrimer rests upon the following: in the reaction of **1** with **2** the latter acts only as diene if its ethynyl functions are sterically blocked by triisopropylsilyl groups, but the dienophile functions can be "activated" by removal of the silyl groups with tetrabutylammonium fluoride. The final Diels–Alder reaction can be used to attach functional groups to the surface of the dendrimer. Although the polyphenylene framework does not serve as a chromophore in its own right at our excitation wavelength, a defined number of chromophore molecules can be attached to the outer rim of the dendrimer to form unique nanoemitters. We have chosen the perylenedicarboximide **3a** as the

troscopy measurements will be reported elsewhere. The analogous Diels–Alder reaction of **7** with dendrimer **8** produces the higher homologue **9**, that is, the second generation dendrimer with eight fluorophores covalently bound to the dendrimer rim (Scheme 2). The two possible

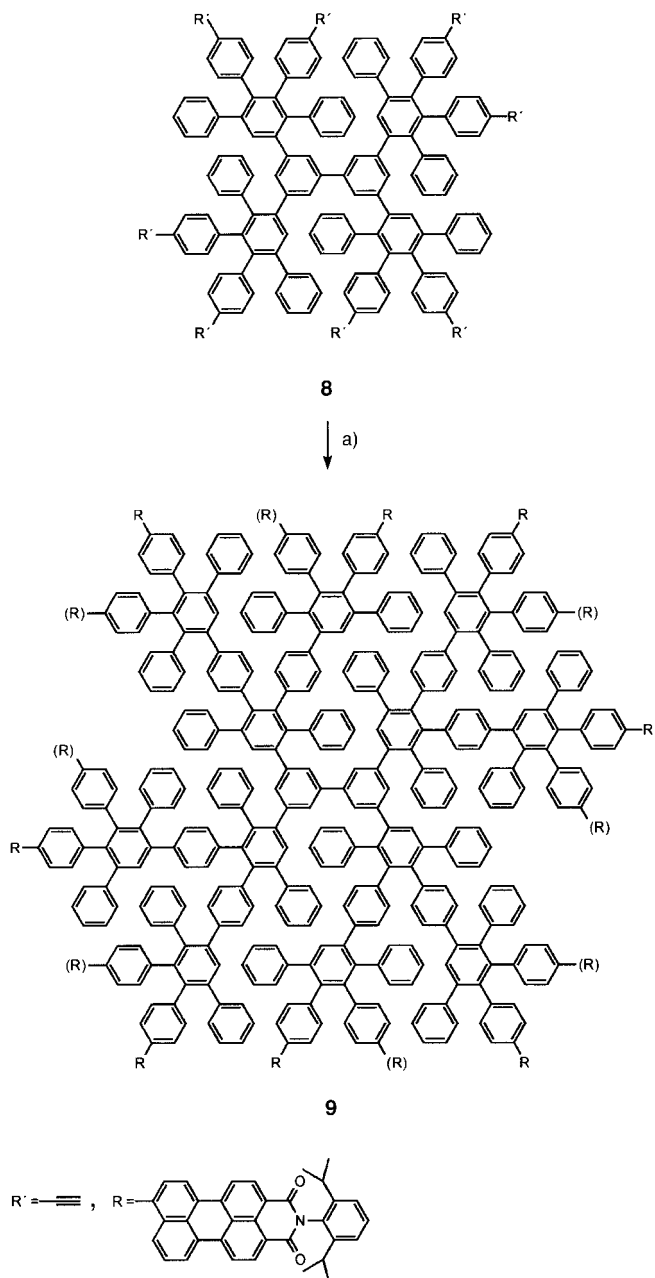


chromophore because of its photostability, its absorption wavelength (around 500 nm), its high absorption coefficient, and its high fluorescence quantum yield ($\Phi_F = 0.90$). Its bromoderivative **3b** is coupled to **4** in a Suzuki^[8] reaction and the resulting diarylacetylene **5** transformed into the corresponding α -diketone **6**, which then affords the functionalized cyclopentadienone **7** (Scheme 1).

The Diels–Alder cycloaddition of **7** with the core molecule **1** leads to the first generation of a polyphenylene dendrimer carrying four fluorophores, for which single molecule spec-



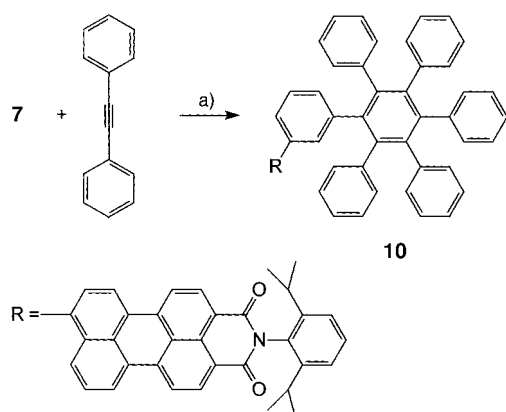
Scheme 1. a) **3b**, 5 mol % $[\text{Pd}(\text{PPh}_3)_4]$, toluene, 2 M K_2CO_3 , ethanol, 120 °C, 12 h, 72%; b) I_2 , DMSO, 150 °C, 12 h, 85%; c) diphenylacetone, *n*-tetrabutylammonium hydroxide 0.8 M, toluene, 90 °C, 1 h, 68%.



Scheme 2. a) 12 equiv **7**, diphenyl ether, tetraethyleneglycol, 195 °C, 82%. (R) = alternative positions of substituents R.

regiochemically different courses of the Diels–Alder reaction of **7** means there is some structural ambiguity in **9**. This, however, does not hamper the photophysical characterization given below since the photophysical study in solution leads to averaged information and does not affect the analysis at the single-molecule level. The structural proof of **9** came from the MALDI-TOF mass spectrometric analysis which supports the existence of the defect-free transition from the first to the second generation dendrimer.^[9] As a model compound for **9**

we have also synthesized the hexaphenylbenzene **10** in which only one peryleneimide chromophore is attached (Scheme 3).^[9]



Scheme 3. a) Diphenyl ether, 260 °C, 85%.

The determination of the absorption and fluorescence spectra of **10** and **9** by SMS allows the comparison of the fluorescence behavior of a single chromophore and eight chromophores in a single molecule. (Figure 1). The absorption spectrum of compound **9** is slightly broadened at the red edge of the spectrum (width at half peak height = 3100 cm⁻¹ for **10** and 3300 cm⁻¹ for **9**) and has less fine structure around 515 nm compared to that of **10**. The fluorescence properties of

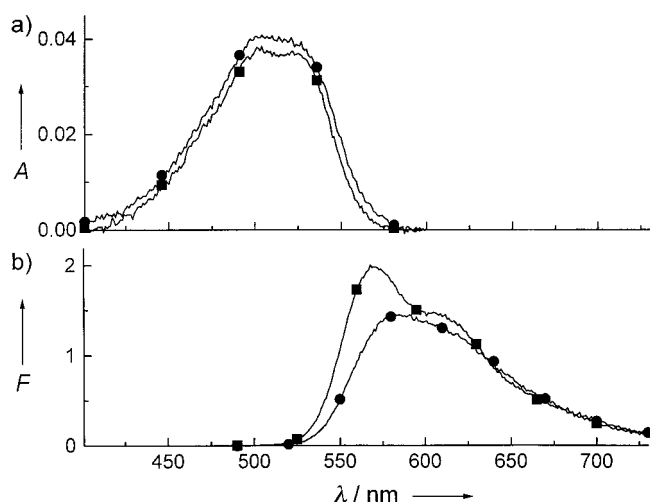


Figure 1. Absorption (a) and fluorescence spectra (b, excitation at 508 nm) of **10** (■) and **9** (●) in chloroform.

9 are also distinctively different: the spectrum shows less structure (see Figure 1), the quantum yield is lower, and the fluorescence decay is multiexponential, with a decay time equal to that of **10** as a major component and at least two additional components (Table 1). The differences between the absorption spectrum of **9** and **10** in solution indicate an interaction of some of the eight peryleneimide chromophores already occurring in the ground state. In a recent study devoted to the dynamic behavior of **9** and **10** in solution several processes were identified for **9** which were absent for **10**. These processes, with characteristic times ranging from several picoseconds up to nanoseconds, were attributed to

Table 1. Fluorescence properties of **10** and **9** in bulk solutions and as single molecules.

Compound	Φ_F	τ_F [ns] ^[a]	N_{sm}	$t_{survival}$ [s] ^[b]	n [s ⁻¹] ^[b,d]	ϵ [mol ⁻¹ cm ⁻¹] ^[c]
10	0.80	4.2 (100 %)	81	70	1 200	35 000
9	0.65	0.25 (25 %)	74	250	3 500	240 000
		4.2 (60 %)				
		7.5 (15 %)				

[a] Measured at 570 nm, $\chi^2 < 1.1$; the normalized relative amplitudes are given in parentheses. [b] Average value for all single molecules N_{sm} . [c] Measured at 495 nm. [d] Maximum dwelling rate.

excitation transfer processes between two or more of the eight chromophores and interactions between excited states.^[10]

The confocal fluorescence microscopy images of polymer films produced from dilute solutions of **10** and **9** in polyvinylbutyral (PVB) typically show 10 to 25 spots corresponding to single molecules of **10** and **9** on a 5 × 5 μm² area. The images of **9** are three-to-fourfold as intense and exhibit a clear on–off behavior (“blinking”) relative to **10**, which displays almost uniform spots exclusively (Figure 2 and Table 1). The

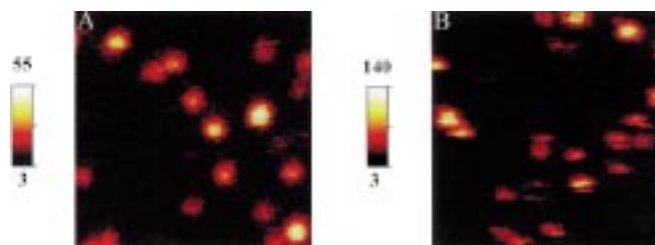


Figure 2. Confocal fluorescence images (5 × 5 μm², scale in counts per 10 ms; λ_{exc} = 543.5 nm, linear polarized light, P = 200 W cm⁻², 10 ms dwell time per pixel) of single molecules of compound **10** (A) and compound **9** (B) in a PVB film.

fluorescence transients, that is, the fluorescence intensity of a single molecule as a function of time, are obtained by positioning the excitation beam on a fluorescent spot in the images of single molecules of either **10** or **9**. The number of single molecules thus studied is 81 for **10** and 74 for **9**. Typical transients are investigated by visual inspection as well as by a histogram analysis (Figure 3). On–off behavior as well as jumps between different emissive levels are detected for both molecules. The observations are, however, very different for **10** and **9**. Transients of single molecules of **9** show more levels, more jumps, and longer survival times compared to those of **10** (see Table 1 and Figure 3). If the eight chromophores of **9** absorbed and emitted independently from each other one would expect mainly jumps between neighboring intensity levels. For many of the fluorescence transients of **9**, however, jumps from levels of high to low fluorescence intensity (including the zero level) and vice versa are observed. These jumps suggest the existence of strong electronic interactions between several peryleneimide chromophores within one dendrimer and supports the interpretation of the bulk solution studies.^[10]

The different fluorescence levels could result from different processes: rotational and spectral diffusion, electronic coupling or decoupling of the single chromophores (only for **9**), a changed population of the short-living off-states (relative to the dwelling time of 10 to 50 ms) such as triplets or

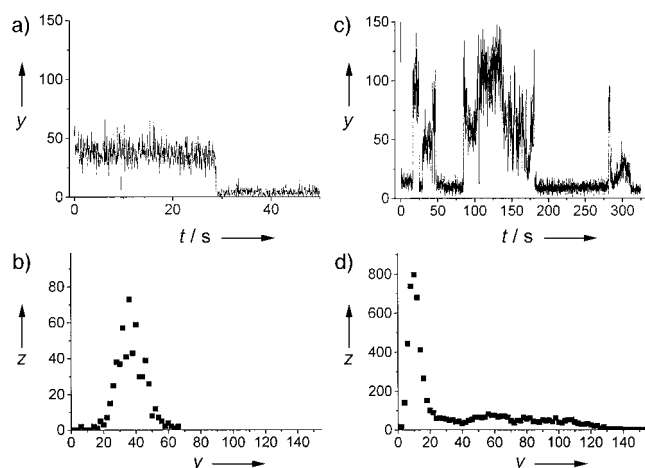


Figure 3. Fluorescence intensity transient (y, 50 ms dwell time) of compound a) **10** and c) **9** as well as the corresponding histograms (z = frequency of occurrence of a certain count rate) of the transient of b) **10** and d) **9**.

reversible photochemical reactions. Spectral jumps are a likely source of dynamics in the fluorescence transient since the excitation is performed in the red edge of the absorption spectrum of **10** and **9**. Therefore for a detailed investigation series of spectra of single molecules (30 for each compound) were recorded (Figure 4). A comparison of the spectra showed that there was a shorter survival time of **10**, but most of the spectra of **10** showed a uniform spectral shape with a vibrational fine structure similar to the solution spectra and only small differences in the emission maximum. However, the spectra of **9** are distinctively different for individual molecules, with the spectral shape ranging from broad, unstructured bands similar to the solution spectrum of **9** to spectra with vibrational fine structure similar to **10** in solution. Additionally, large differences in the wavelength of maximum fluorescence (from 560 nm to 595 nm) were observed.

It is rather exceptional to observe these various spectral types and spectral shifts within the life time of individual molecules. The spectra reported in Figure 4b for a molecule of **9** starts with a broad, unstructured red-shifted spectrum, which is followed by a large blue shift within 40 s and accompanied with the development of a spectrum with fine structure. After another 30 s it adopts a broad spectral band shape with a blue-shifted maximum relative to the first spectrum. Within the next 90 s some minor spectral changes occur with only small changes in intensity, and at 160 s an irreversible photoreaction leads to a nonemitting photoproduct of **9**. This nonemission could be the result of the photoproduct having a low fluorescence quantum yield as well as a large shift of the absorbance spectrum, which prevents excitation at 543 nm. The fact that single dendrimers of **9** show fluorescence spectra similar to those of **10** can be explained by a loss of the electronic interactions between the perylene-imide chromophores within one dendrimer. This situation can be either static, in which molecules of **9** show only the structured spectrum, or dynamic, in which molecules of **9** switch back and forth between the two spectral shapes. Finally, the measurement of the series of fluorescence spectra explains at least partially the larger dynamics in the fluorescence intensity transients of **9** relative to **10**.

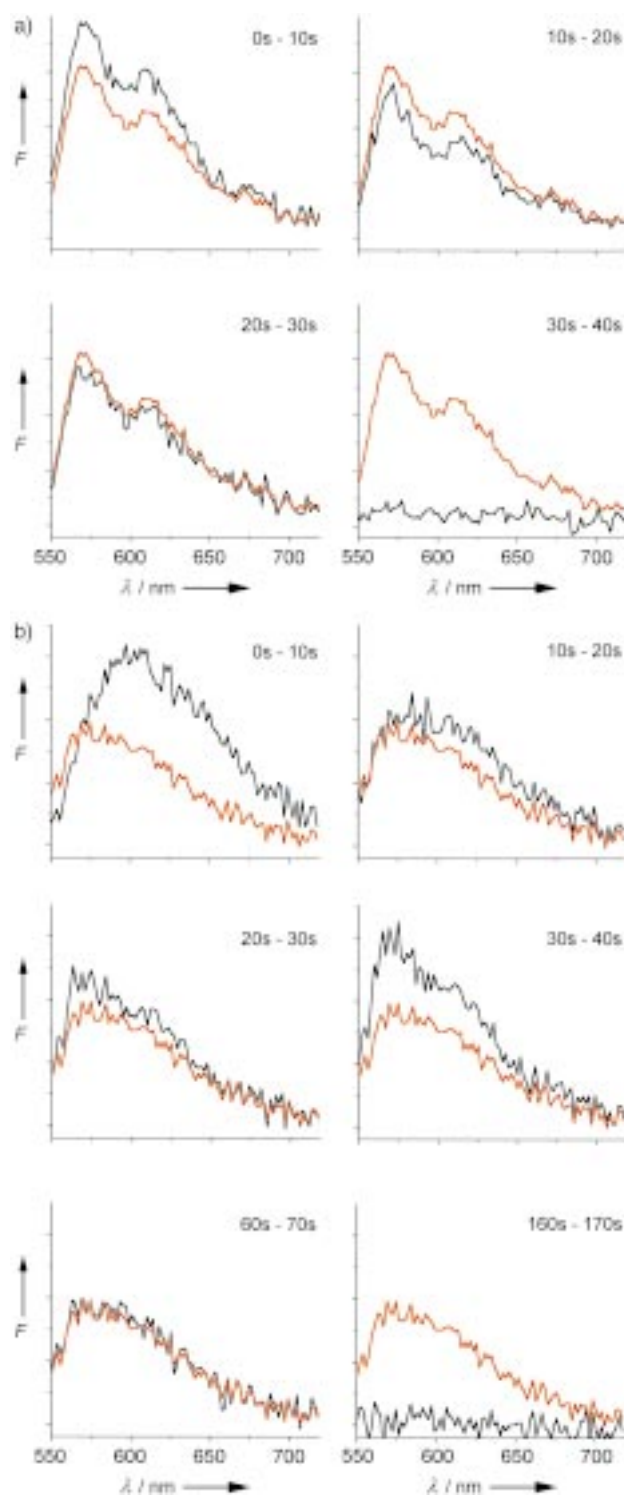


Figure 4. Sequence of fluorescence spectra (10 s integration times) for a single molecule of a) **9** and b) **10**. The red line represents the average fluorescence spectrum integrated over the analysis time of the investigated single molecule.

Compounds **10** and **9** together with other generations of this and similar dendritic structures with multiple chromophores are currently under investigation, both in bulk solutions and on the single-molecule level, using different fluorescence and absorption spectroscopic techniques. These studies offer the possibility of closing the gap between single-molecule studies on single chromophores^[11] and multichromophoric systems

such as fluorescent polymers, phycoerythrocyanin, and light-harvesting protein complexes from the photosynthetic apparatus.^[12] The synthetic approach chosen here offers ease of variation and control of the number of chromophores as well as their interactions and therefore the possibility of tailoring molecules for single-molecule spectroscopy.

Experimental Section

Preparation of the PVB films: Solutions of **10** or **9** (10^{-9} M) in chloroform were mixed with a solution of polyvinylbutyral (3 mg mL⁻¹) in chloroform. These mixtures were spin-coated on a cover glass at 4000 rpm to yield 10 nm thick polymer films. The sample preparation included a careful cleaning of all glassware used for the sample and polymer solutions and the cover glasses by sonication in acetone, sodium hydroxide (10%), and milliQ water.

The absorption spectra were measured on a Perkin-Elmer Lambda-6 and fluorescence spectra on a SPEX Fluorolog 1680. The time-resolved fluorescence SPT apparatus with 10 ps time resolution has been described elsewhere.^[13]

The fluorescence of single molecules was detected using a confocal microscope (Diaphot 200, Nikon) with an immersion oil, high-numerical aperture (NA = 1.4) lens using an avalanche photodiode in the single photon counting mode (SPCM AQ151, EG&G) with suitable filters (Notch Plus 543.5, Kaiser Optics) as the detector. The fluorescence intensity transients were measured with dwell times of 10 to 50 ms. The fluorescence spectra were measured with a liquid-nitrogen cooled, back-illuminated CCD camera (LN/CCD-512SB, Princeton Instruments) coupled to a 150 mm polychromator (SpectraPro 150, Acton Research Cooperation) using 5 or 10 s integration times. The excitation source was a green continuous wave HeNe laser (543.5 nm, Melles Griot). Its randomized output was linearly polarized by using a Glan-Thomson polarizer. The excitation power density at the sample was between 100 and 500 W cm⁻².

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