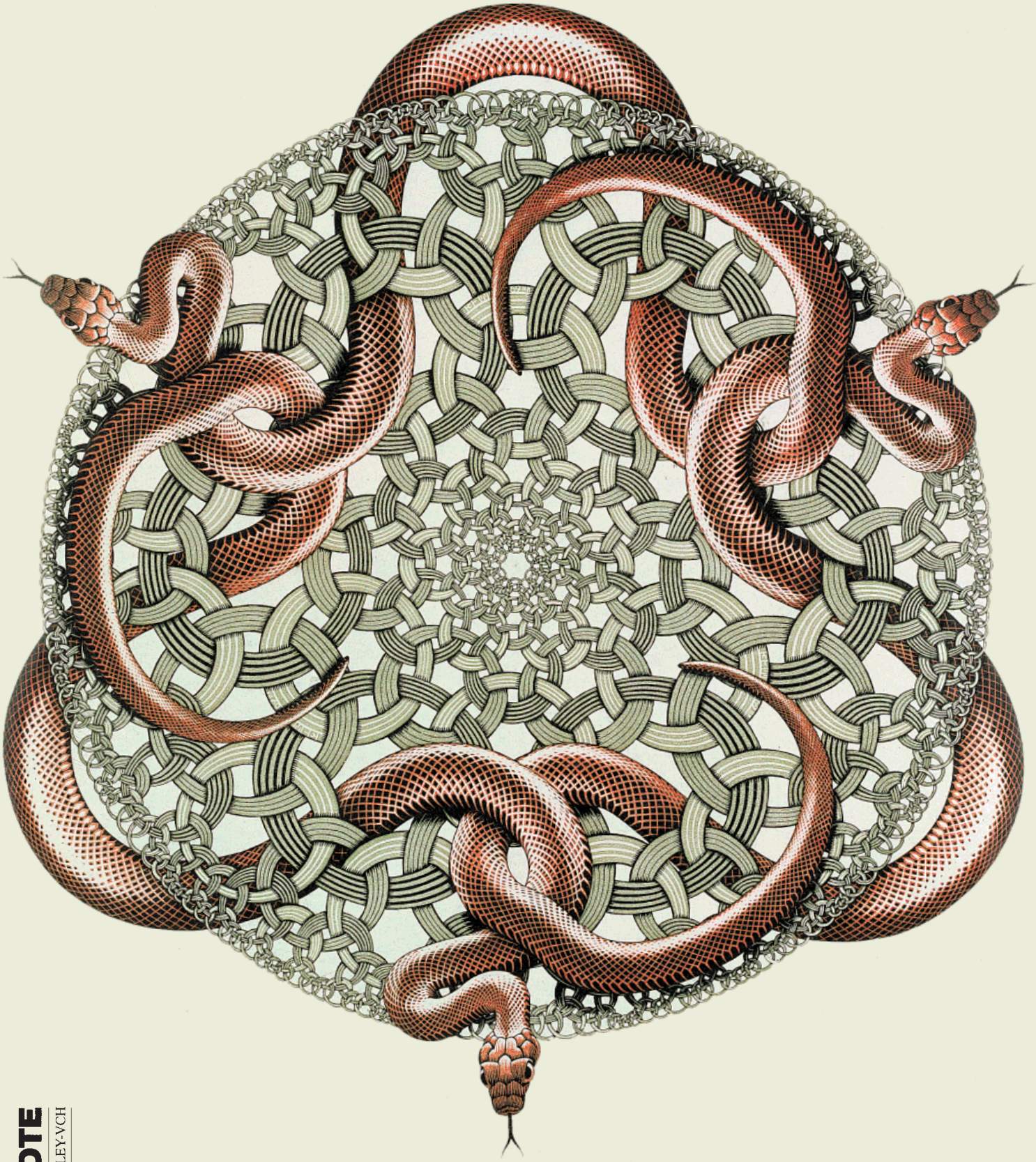

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C_3 Symmetry is fascinating not only in the visual arts, as this picture by M. C. Escher demonstrates (Copyright © Cordon Art, Baarn, The Netherlands, 1997), but also in chemistry. Of particular interest are the potential advantages of chiral compounds of higher symmetry as ligands and catalysts.

C_3 Symmetry in Asymmetric Catalysis and Chiral Recognition

Christina Moberg*

Chiral recognition is a key process in all efforts aimed at obtaining enantiomerically pure chiral compounds, whether by synthetic procedures or by separation techniques. Several cooperating factors contribute to achieving high selectivity in the processes involving chiral recognition. A complete understanding of these factors is beyond the scope of today's knowledge. It is a great challenge, however, to gain a deeper understanding of the factors responsible for chiral discrimination by taking into account the important characteristics of the interacting species. These include primarily their steric and electronic properties, the various attractive intermolecular interactions, and the dynamics of the recognition process. A further factor that may be important is the symmetry properties of the interacting entities. This review highlights the role of rotational symmetry, with an emphasis on C_3 symmetry, in asymmetric catalysis and chiral recognition. The situations in which rotational symmetry is important are considered, methods for the preparation of molecules with threefold rotational symmetry are discussed, and the various types of compounds with threefold rotational symmetry and their applications in asymmetric catalysis and chiral recognition are surveyed.

Keywords: asymmetric catalysis · chirality · rotational symmetry

1. Introduction

Symmetry is a property of objects, systems, and states that is closely connected with beauty and the harmony of proportions. Symmetrical objects are often considered to be aesthetically appealing. Symmetry plays a fundamental role in such diverse disciplines as art, music, architecture, philosophy, mathematics, physics, and chemistry.[1] In problem solving the consideration of symmetry may help to simplify and systematize.[2] In chemistry molecules with symmetry exert a special attraction due to their beauty. In addition, symmetry may be advantageous in synthesis design,[3] in supramolecular self-assembly,[4] and for chemical selectivity.[5]

Chiral molecules containing symmetry elements are of special interest.[6] Among the symmetry elements, only proper rotational axes are compatible with chirality. In contrast to molecules that contain no element of symmetry and are therefore truly asymmetric (C_1-symmetric), molecules with rotational axes—and rotational axes *only*—are dissymmetric and belong to either the point groups C_n or D_n ($n>1$) or to one of the less common groups *T*, *I*, and *O*. Molecules with twofold rotational symmetry have been the subject of wide recent interest. Extensive original literature dealing with this topic and a review covering the subject have appeared.[7] The extension to threefold and higher rotational symmetries has been less noticed, although a few reviews covering the preparation of chiral molecules with high symmetry exist.[8, 9]

This survey deals with molecules having rotational symmetry and their role in asymmetric synthesis and in other processes involving chiral recognition. It mainly covers threefold symmetry, with emphasis on chiral molecules belonging to point groups C_3 and D_3. Selected compounds and their applications which have appeared in the literature or have been studied by our own group serve as examples. Some achiral ligands with threefold rotational axes that can be potentially transformed into C_3-symmetric compounds are included. Most of the results covered by previous reviews[8, 9] are not repeated here. Compounds with chiral conformations having low barriers of inversion and achiral compounds that crystallize in chiral space groups are not covered by this survey.

2. Topology

Topology, also known as "rubber band geometry", is a branch of modern mathematics that can be used for the description of molecules, conformational changes, and chemical reactions. It deals with the continuity of functions, with the connectivity of objects, and with shape, in other words, with those properties of objects that remain unchanged upon

[*] Prof. C. Moberg
Department of Chemistry, Organic Chemistry
Royal Institute of Technology
SE-10044 Stockholm (Sweden)
Fax: Int. code + (46) 8-791 2333
e-mail: kimo@kth.se

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stretching, twisting etc.[10] An object that does not have a precisely defined geometry but preserves some topological features is classified as a topological object. Molecules should thus not be considered as geometrical but as topological objects.

A tridentate ligand or a trifunctional molecule with C_3 symmetry can have four principally different topologies (Figure 1). It may be acyclic (a), "exocyclic" (b), macrocyclic

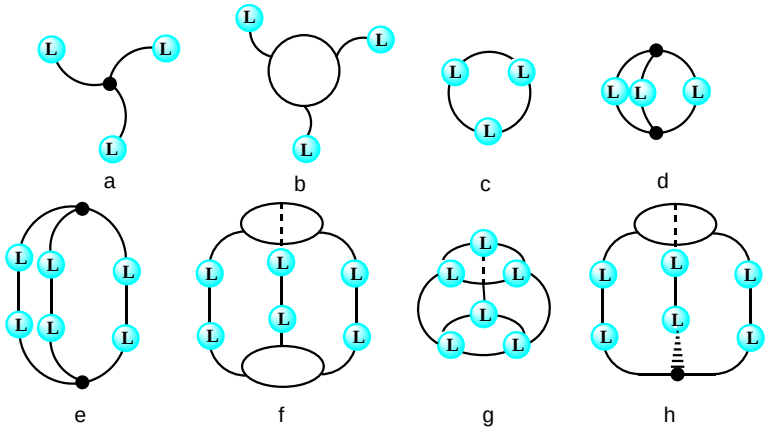


Figure 1. Topologies of structures with C_3 and D_3 symmetry.

(c), or bicyclic (d). If two twofold rotational axes perpendicular to the main axis are present, the molecule belongs to a point group of higher symmetry, D_3. Several examples of molecules are known for all of these forms. In addition, dimeric arrangements may be formed by combining any two of the structures a–d. When two equal halves are combined, the result is a species with D_3 symmetry (Figure 1e–g), whereas the combination of two unequal parts gives a molecule with C_3 symmetry (Figure 1h).

In all of these types of molecules the presence of a center of chirality (as in Figure 2a) is commonly a requirement for dissymmetry, although molecules are known in which axes of chirality cause dissymmetry. These include cyclic compounds in which the chirality originates from the direction of the array of substituents on the ring (Figure 2b).

Conformational preferences may also result in chiral species. Occasionally the barriers of inversion are sufficiently high to permit the isolation of nonsymmetric species. A

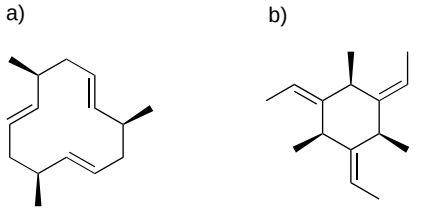


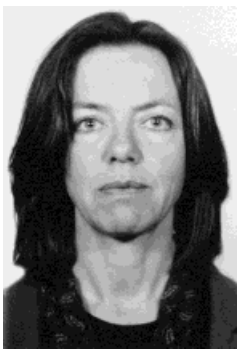
Figure 2. C_3-symmetric molecules with stereogenic centers (a) and axes (b).

further possible arrangement possessing C_3 symmetry is a triple helix.[11] Here the chirality is based on an axis of chirality. The asymmetric folding of the strands may be induced by stereogenic centers in the strands.[12]

3. Synthetic Routes: The Desymmetrization of Molecules with Higher Symmetry

Molecules belonging to point group C_3 or to a chiral group of higher order containing threefold axes can be obtained in two ways: by the proper assembly of homochiral or occasionally even achiral entities, and by the desymmetrization of molecules having improper rotational axes or mirror planes in addition to the C_3 axis. Such molecules belong to one of the following point groups: I_h, O_h, T_h, T_d, S_6, D_{6d}, D_{6h}, C_{6h}, C_{6v}, D_{3d}, D_{3h}, C_{3h}, C_{3v}.[13] The desired desymmetrization is brought about by destruction of all symmetry elements of the second kind (s, i, S_n), while symmetry elements of the first kind (C_n), at least one threefold axis, are maintained. The desymmetrization can be a change in conformation, but more important situations, in which configurationally stable species are formed, will be discussed here.

A simple illustration is given by methane (point group T_d), which, at least theoretically, can be desymmetrized in various ways. Substitution of three of the four hydrogen atoms by homochiral groups (of identical constitution) yields C_3-symmetric compounds (Figure 3a), whereas substitution of all four hydrogen atoms normally destroys the threefold rotational axes, leading to three different possible cases



Christina Moberg was born in 1947 in Gävle, Sweden and studied chemistry at the University of Stockholm (B.Sc. 1970). She then moved to the Royal Institute of Technology in Stockholm, where she earned her doctorate under the direction of Professor M. Nilsson. After a postdoctoral stay with Professor J. Normant at the Université Paris 6, she worked in the group led by Professor Åkermark at the Royal Institute of Technology before starting independent research. In 1989 she was granted a research position in organometallic chemistry by the Swedish Scientific Research Council, and she became a full professor in 1994.

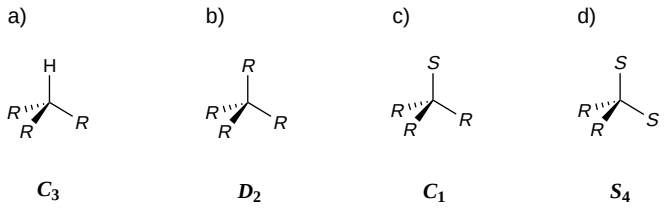


Figure 3. Symmetry of substituted methanes. *R* and *S* indicate the absolute configurations of isometric asymmetric ligands.

(Figure 3b–d). Complete substitution by homochiral groups with identical constitution yields a D_2-symmetric species; with one heterochiral substituent an asymmetric (C_1) species is obtained; and the third product is achiral since it has an S_4 symmetry axis. This topic was discussed by Mohr already at the beginning of this century,[14] and was experimentally verified half a century later by studies of esters prepared from pentaerythritol and chiral acids.[15]

The situation is different, though, when the desymmetrization is brought about by substituents with inherent C_3 symmetry. This operation is expected to yield a compound with *T* symmetry containing no less than four C_3 axes (in addition to two C_2 axes). This kind of operation has indeed been accomplished experimentally, not with methane[16] but instead with adamantane, which like methane has T_d symmetry (Figure 4).[17]

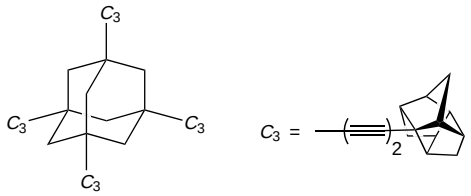


Figure 4. A *T*-symmetric adamantane derivative with four identical, C_3-symmetric substituents.

In regular polyhedra, symmetry elements of the second kind are generally destroyed while symmetry elements of the first kind are preserved by the attachment to each vertex of a chiral group having a rotational axis of the same order as and coinciding with that passing through the vertex.[9] In this manner, a chiral species having the same symmetry number as the regular polyhedron is obtained. Thus, when C_3-symmetric substituents are attached to each of the eight carbon atoms of cubane, [18] its symmetry is reduced from O_h to pure rotational *O* (with three C_4 axes and six C_2 axes in addition to the four C_3 axes). The analogous desymmetrization of an octahedral arrangement of atoms requires substituents with local C_4 symmetry, since fourfold instead of threefold axes pass through the atoms at the corners of a regular octahedron. The desymmetrization of molecules with I_h symmetry can also be achieved by a proper choice of substituents. For an icosahedral arrangement of atoms, substituents with a fivefold rotational axis at each of the twelve vertices result in *I* symmetry (with six C_5 axes and fifteen C_2 axes in addition to the ten C_3 axes). In dodecahedrane,[19] however, desymmetrization is achieved by twenty substituents with inherent threefold rotational symmetry. Since only C_1 axes pass through the vertices of a truncated icosahedron, any chiral substituent attached to each vertex would reduce its symmetry from I_h to *I*. Thus, if it were possible to add chiral groups to all of the 60 carbon atoms of buckminsterfullerene,[20] a species with *I* symmetry would be obtained.

The desymmetrization of molecules with polyhedral symmetry can also be achieved by introducing chiral groups at axes passing through the edges or faces of the polyhedra. The requirement is that the local symmetry of the group is equal to the order of the axis. C_2-Symmetric bridges would thus serve to reduce the T_d symmetry of methane to *T*.[21] Since twofold axes bisect the sides of the other regular polyhedra as well, the desymmetrization of molecules with cubic and icosahedric symmetries can be brought about analogously.

Experimentally, the simplest and probably the most common route to chiral molecules containing a threefold rotational axis is the desymmetrization of molecules containing mirror planes, inversion centers, and/or improper axes in addition to the threefold axis, but having lower symmetry than the special groups *T*, *I*, and *O*. Molecules of this type have C_{3v}, C_{3h}, D_{3h}, D_{3d} symmetry (or those having sixfold instead of threefold axes) or S_6 symmetry. A variety of simple starting materials that can serve as excellent precursors for C_3- and D_3-symmetric molecules are commercially available.

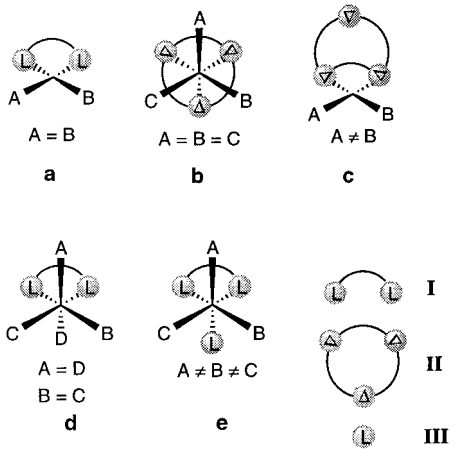
A desymmetrization procedure may also involve some asymmetric modification of a compound with higher symmetry leading to the formation of several diastereomers, which must be separated subsequently. The assembly of prochiral entities or of components in a racemic mixture is also expected to lead to a mixture of stereoisomers. This type of procedure as well as reactions performed on a prochiral, trifunctional compound with a threefold rotational axis should statistically lead to a 1:3:3:1 mixture of the *RRR*, *RRS*, *RSS*, and *SSS* isomers, although deviations may arise due to cooperative effects.

4. Metal-Binding Ligands

4.1. Metal Complexes: Molecular Equivalence Caused by Rotational Axes

The consideration of molecular symmetry is sometimes important, since symmetry can reduce the number of possible intermediates/transition states, thus increasing the probability of success in asymmetric reactions and other chiral recognition processes. By definition, C_2 symmetry is characterized by the fact that an identical situation is obtained upon rotation of the C_2-symmetric species 180° about the rotation axis. In an event involving chiral recognition this implies that two complexes that are identical in the C_2 case would be diastereomeric in the C_1 case. With threefold symmetry each rotation of 120° yields an identical situation, thereby reducing the number of different complexes. Examples of these situations will be given and analyzed.[22]

Let us consider a square-planar metal complex containing a bidentate, C_2-symmetric ligand (Scheme 1, **a**). This is a favorable situation, since the two remaining coordination



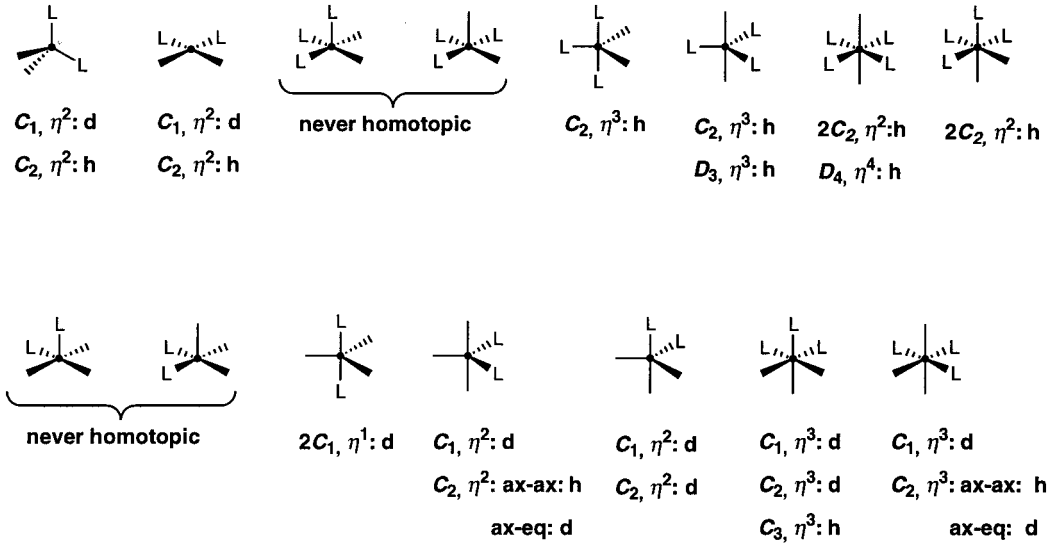
Scheme 1. Relationships between empty coordination sites (A – D) in complexes with C_2-symmetric, bidentate (**I**) and C_3-symmetric, tridentate ligands (**II**). **III**: achiral, monodentate ligand; h = homotopic, d = diastereotopic.

sites (A and B) are homotopic, in other words, identical. Another favorable situation is created by a tridentate, C_3-symmetric ligand in an octahedral environment (**b**), where the three remaining positions (A, B, and C) are identical (homotopic). On the other hand, this kind of ligand may yield an unfavorable situation in a square-planar arrangement where the ligand occupies two sites (**c**). Here the two remaining positions (A and B) are different (this may not be valid if the complex is dynamic and the positions are identical with time). In an octahedral environment the introduction of a bidentate, C_2-symmetric ligand results in a complex (**d**) with two sets of coordination sites, which are pairwise homotopic (A/D, B/C) but mutually diastereotopic (e.g. A/C). Addition of a monodentate ligand results in a complex with three different (diastereotopic) coordination sites (**e**). Thus, the conclusion is that C_2-symmetric ligands have favorable properties in square-planar geometries, whereas C_3-symmetric ligands are versatile in octahedral complexes.

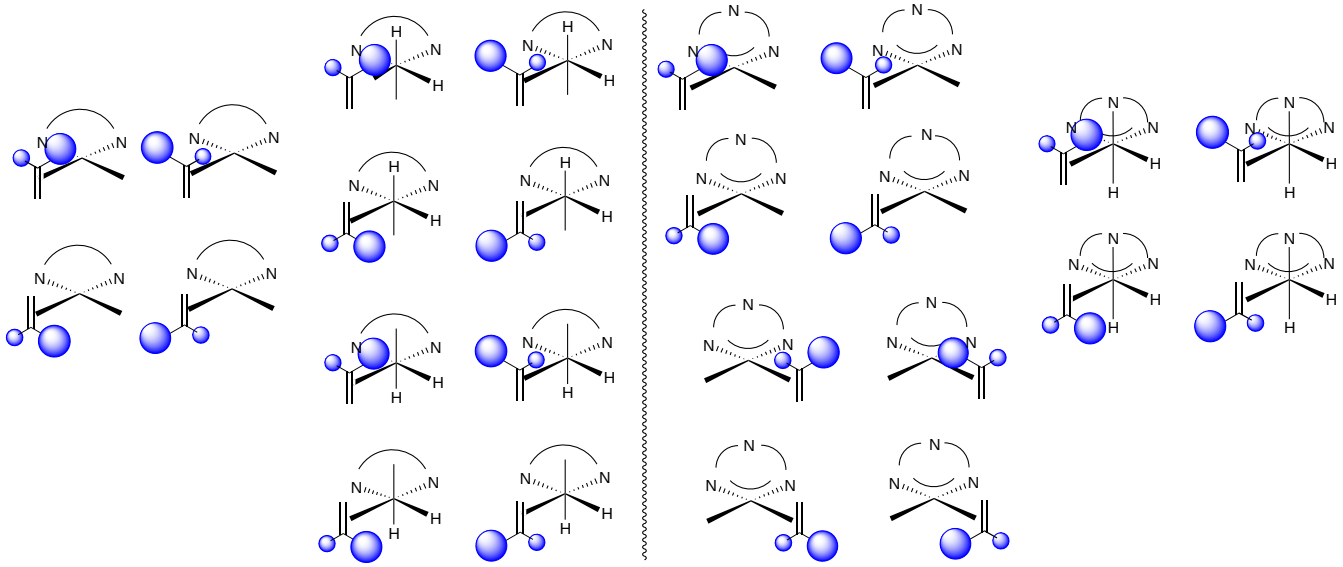
Scheme 2 shows a more complete analysis of situations arising from the coordination of mono-, bi-, and tridentate ligands with C_1, C_2, and C_3 symmetry, respectively, in their most common coordination geometries. Homotopic coordination sites are encountered with C_2-symmetric ligands under several conditions, whereas homotopicity with C_3-symmetric ligands is restricted to a few types of complexes. The following is evident in Scheme 2: 1) Two identical coordination sites remain in tetrahedral and square-planar environments upon coordination of one bidentate ligand with C_2 symmetry and in octahedral geometry upon coordination of two such ligands. 2) Homotopic sites also result from coordination of a tridentate, C_2-symmetric ligand in trigonal-bipyramidal complexes. 3) In the presence of a C_2-symmetric ligand three sites are never homotopic in any of the coordination environments shown in Scheme 2. 4) The only situation in which homotopic coordination sites are observed with a C_3-symmetric ligand is in octahedral geometry. 5) Ligands with threefold and fourfold dihedral symmetry result in homotopic sites in trigonal-pyramidal and octahedral complexes, respectively.

Let us analyze the special case that arises when a prochiral olefin is coordinated to a complex containing either a bidentate ligand with a twofold rotational axis or a tridentate ligand with a threefold rotational axis. These situations are encountered in common catalytic processes such as hydrogenations, hydroformylations, and hydrosilylations.[23] The specific example illustrated in Scheme 3 is a catalytic hydrogenation, where the coordination of the olefin is assumed to occur before the oxidative addition of hydrogen. This is the mechanism known for catalysts prepared from noncharged rhodium(I) complexes.[23]

With two homotopic sites in the square-planar complex containing a bidentate, C_2-symmetric ligand, four possibilities exist for the coordination of the prochiral olefin (provided that the presence of only two rotamers is considered likely),



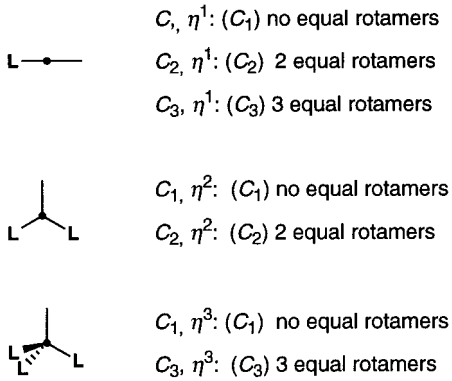
Scheme 2. Relationships between coordination sites in chiral complexes containing ligands of different denticities (η^n) and symmetries (C_n); h = homotopic, d = diastereotopic. Top: two free coordination sites; bottom: three free coordination sites; ax-ax describes the relationship between two axial coordiation sites, ax-eq that between an axial and an equatorial site.



Scheme 3. Square-planar metal–olefin complexes containing a bidentate, C_2-symmetric (left) or a tridentate, C_3-symmetric ligand (right), and isomeric complexes obtained through oxidative addition of H_2 to these complexes.

since coordination to the second site would yield a set of identical complexes due to the C_2 symmetry of the ligand. After addition of H_2 and formation of an octahedral complex, the two sites left for coordination of the olefin are no longer homotopic. Consequently, eight diastereomeric complexes are possible. In contrast, with a tridentate, C_3-symmetric ligand, only four different octahedral complexes arise due to the equivalence of the three sites. (If the olefin is equipped with an additional coordinating group, the number of isomeric complexes may be further reduced by a factor of two.) The conclusion from this analysis is that a C_2-symmetric ligand should be chosen if the selectivity is determined in a square-planar complex, whereas a C_3-symmetric ligand is the choice when the selectivity-determining step involves an octahedral complex. (If the square-planar complexes with C_3 symmetry equilibrate to render the two sites homotopic with time, a situation equivalent to that of a complex with a C_2-symmetric ligand may obviously be obtained.) As yet, this conclusion has not been unambiguously verified in practice, and it cannot be excluded that the mechanism of a particular reaction may change when a C_2-symmetric ligand is replaced by one having C_3 symmetry.

The olefin complexes in Scheme 3 are pairwise diastereomeric due to restricted rotation around the metal–olefin bond. In principle an infinite number of rotamers are possible, but only a limited number are usually observed. The symmetry properties of ligands can be exploited to reduce the number of structurally different rotamers in complexes having a single free coordination site. This is reflected by the site symmetry of that free site, as shown in Scheme 4.



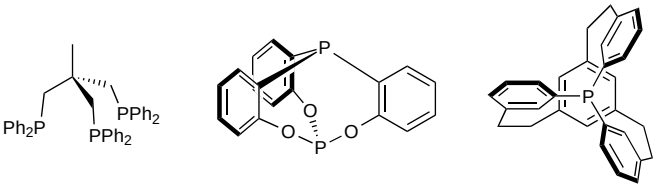
Scheme 4. The influence of the symmetry (C_n) and hapticity (η^n) of a ligand L in linear, trigonal, and tetrahedral complexes on the symmetry (C_n in parentheses) of the remaining free coordination site and the number of identical rotamers.

4.1.1. *Phosphanes and Phosphites with C_3* Symmetry

The most common method for preparing chiral metal complexes is the coordination of chiral ligands to the metal ion. A large variety of such ligands are known today and their metal complexes have proven highly useful in asymmetric synthesis.[24]

Phosphane ligands have been the most commonly studied ligands for application in homogeneous catalysis. A wide range of monodentate and bidentate phosphane ligands, chiral as well as achiral, are known and some of them are applied even in industrial processes.[25]

Achiral tripodal phosphanes with threefold rotational axes have been studied extensively over the last three decades mainly by the groups of Sacconi,[26] Meek,[27] Venanzi,[28] and Bianchini.[29] The most frequently studied ligands of this type are triphos (**1**) and analogues in which the central carbon



1 **2** **3**

atom has been replaced by a heteroatom (nitrogen or phosphorus). Such compounds have proven to be versatile ligands in coordination and organometallic chemistry. They have excellent bonding properties and form complexes with metal ions in various oxidation states.

It is not surprising, therefore, that the preparation of chiral analogues was soon attempted. C_3-Symmetric monophosphanes carrying three identical chiral groups on phosphorus were used in early investigations of enantioselective, nickel-catalyzed oligomerizations.[30] In contrast, monophosphanes **2** and **3**, in which the threefold rotational axis is a chirality axis, could not be resolved due to rapid racemization.[31]

More recently, a few enantiomerically pure tripodal phosphanes with C_3 symmetry have been reported. The first examples, **4** and **5**, were prepared from cyclic lithiophosphanes and the appropriate trichloro compounds.[32] Cationic rhodium(I) complexes of **4** and **5** were both shown by X-ray structural investigations to have trigonal-bipyramidal geometry. The use of the former as a catalyst precursor for the hydrogenation of methyl acetamidocinnamate resulted in 89% enantiomeric excess, a selectivity similar to that observed when the corresponding bidentate, C_2-symmetric ligand is used (85% *ee*). In the hydrogenation of dimethyl itachonate with **4**, 94% *ee* was obtained (90% with the C_2-symmetric ligand).[33] The tridentate ligand **4** was less reactive, however, requiring higher reaction temperature and longer reaction time. This was suggested to be due to the required dissociation of one ligand arm from a stable five-coordinate intermediate. Compound **6**, another C_3-symmetric, tripodal phosphane, has centers of asymmetry on phosphorus instead of carbon (as in **4** and **5**). This tridentate ligand was prepared by Venanzi and co-workers from (*R*)-(*tert*-butyl)(methyl)(phenyl)phosphane–borane by deprotonation, reaction with trichloromethylsilane, and finally deprotection.[34] The structure of the cationic Rh^I complex of **6** was determined and shown to have a distorted square-pyramidal geometry. No reports on its ability to induce chirality in asymmetric synthesis have appeared as yet.

The tripodal, tetradentate, C_3-symmetric ligand **7** was described in 1993.[35] With Pt^0 this ligand formed a tetrahedral complex, which could be protonated and methylated to yield trigonal-bipyramidal complexes, all with C_3 symmetry. A monodentate phosphite containing three identical sugar residues, tris(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosido)phosphite, was also prepared recently and shown to form a tetrameric Cu^I complex with a cubane structure.[36]

4.1.2. C_3-Symmetric Compounds Containing Pyridine Rings

In recent years nitrogen-based ligands such as pyridine derivatives[37] have replaced those containing phosphorus in many reactions mainly due to their ease of preparation and their often higher stability.[38] However, since pyridine ligands do not exert the strong *trans* effect characteristic of phosphorus ligands,[22] they sometimes have different applications.

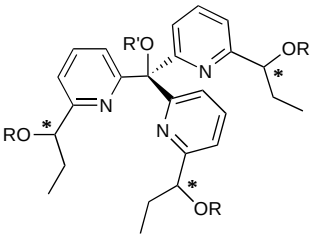
Three pyridine rings can be connected to form either acyclic, macrocyclic, or bicyclic arrangements. The first case is represented by tri(2-pyridyl)methane and derivatives such as **8**, R = H, Et, OAc.[39] This ligand was known already in the 1950s.[40] This type of compound has since been extensively studied because it can serve as a symmetric, tridentate ligand. It has thus been used to mimic the tetrahedral transition state in the reaction of carbonic anhydrase, the enzyme responsible for the fixation of carbon dioxide and its physiologically important reversible hydration to bicarbonate.[41] The active site in the enzyme is composed of a zinc ion coordinated to the imidazole side chains of three histidine residues and either a water molecule or a hydroxide ion. Mimicking this structure

with synthetic ligands is one way to gain knowledge about the mechanism of the enzymatic processes.[42]

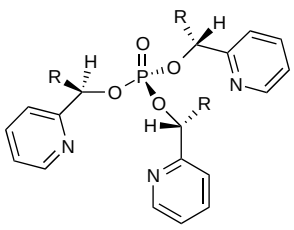
Tripyridylmethanol **8**, R = H, can give complexes with metal ions by either N,N,N-coordination or N,N,O-coordination, whereas O-alkylated derivatives undergo symmetric N,N,N-coordination only. Transition metal complexes of this type of ligand have also proven to be important in synthetic applications, for example for use as transition metal Lewis acids.[43, 44]

A macrocyclic arrangement of pyridine units is found in cyclophane **9**, which was prepared in four steps starting from 2,6-bis(6-bromopyridinoyl)pyridine.[45] Finally, the macrobicyclic pyridine derivative **10** was prepared by reaction of 2,6-dichloropyridine with the anion of triethanolamine.[46] Several cage compounds of this type with bipyridine incorporated in the chains have also been described.[47]

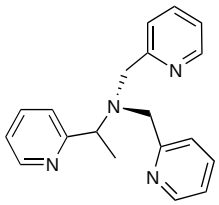
Chiral analogues, compounds lacking the vertical and/or horizontal mirror plane present in these symmetric parent compounds, can be constructed in a variety of ways. This has been realized for tripyridylmethanol **8**, R = H, by the introduction of keto substituents in the 6-positions of the pyridine nuclei and subsequent reduction of the keto groups using a chiral reagent to give compounds such as **11**.[48]



R = H, Me
R' = H, Me
11



R = Me, *t*-Bu, 2-neomenthyl
12



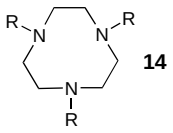
13

Although the chiral reagent was shown to afford roughly 90% *ee* upon reduction of an analogous monomer, essentially complete selectivity was observed with the trifunctional compound (instead of the expected 85.74:13.54:0.71:0.01 mixture). Another experimentally facile method is the reaction of phosphorus oxychloride with 2-(1-hydroxyalkyl)-pyridine to yield compounds of type **12**.[49] The reaction of racemic 2-(1-hydroxyethyl)pyridine with phosphorus oxychloride gave the expected 1:3 mixture of homochiral and heterochiral isomers. In contrast, reaction of the sterically more hindered 2-(1-hydroxy-2,2-dimethylpropyl)pyridine afforded a 1:1 mixture of isomers; in other words, the reaction proceeded in favor of the homochiral compound. Since enantiomerically pure 2-(1-hydroxyethyl)pyridines are available by a variety of procedures, enantiopure compounds with the structure **12** are easily accessible. Methods have also been developed that permit the grafting of the tripyridyl ligands onto various types of polystyrenes, thus allowing convenient handling.[44]

Tris[(2-pyridyl)methyl]amine adopts a helical conformation upon complexation to metal ions. The α-methyl-substituted analogue **13** was prepared in order to favor one enantiomeric conformation.[50] Although this compound has C_1 symmetry, metal complexes of the ligand probably fold in a manner similar to that expected with a trisubstituted C_3-symmetric ligand.

4.1.3. Aliphatic Amines

Several simple starting materials suitable for the preparation of amines with acyclic and cyclic topologies are commercially available. Numerous achiral 1,4,7-triazacyclononanes **14**[51] have been prepared and investigated, in particular in



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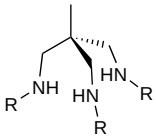

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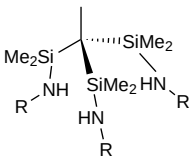

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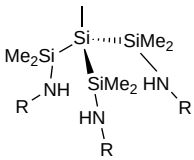

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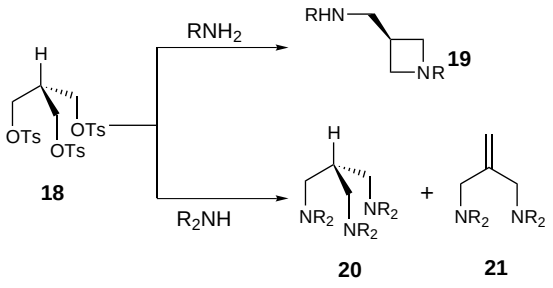
connection with studies of carbonic anhydrase mimics.[52] Compounds with three identical chiral R groups, thus with C_3 symmetry, have also been prepared.[53]

A variety of tridentate, acyclic, C_3-symmetric amines having a central carbon skeleton (**15**) or a skeleton containing silicon (**16**, **17**) have also been prepared, and some of their metal complexes have been studied.[54] The ligands with silicon atoms in their skeleton allow the complexation of larger metal ions than the ligands based on carbon only. The synthetic method used for preparing ligands **16** and **17**, the reaction of an alkylsilicon bromide with a primary amine, gives easy access to chiral analogues when a chiral primary amine is employed. A chiral analogue of **16** (R = (*S*)-CH(CH$_3$)Ph) was prepared with (*S*)-1-phenethylamine.[55]

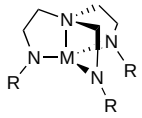
In the triamidostannate obtained by reaction of compound **16** (R = (*S*)-CH(CH$_3$)Ph) with butyllithium followed by $SnCl_2$ the metal ion was shown to bind to the three nitrogen atoms; however, the symmetry was reduced by a lithium ion bridging two nitrogen atoms. This bridging was dynamic and resulted in time-averaged threefold symmetry.[56] The complex served as a metal-centered nucleophile and reacted with some electrophiles to yield C_3-symmetric complexes. Ti^{IV},[57] Y^{III},[57] Zr^{IV},[58] Sn^{II},[58] and Pb^{II} complexes[59] with achiral analogues of ligand **16** have also been prepared and characterized.

Attempts to prepare ligands analogous to **15** starting from **18**, the tritosylate of 2-hydroxymethyl-1,3-propanediol, were

less successful. Reactions with primary amines resulted in the exclusive formation of 3-(aminomethyl)azetidines **19**. Secondary amines afforded the desired triamines **20**, but the



elimination of one ligand to form C_2-symmetric unsaturated amines **21** was a serious side reaction in that case (C_2:$C_3 \approx$ 1:4.4 when prolinol was used as the amine component).[60] The tritosylate of 2-hydroxymethyl-2-methyl-1,3-propanediol did not react with either primary or secondary amines.



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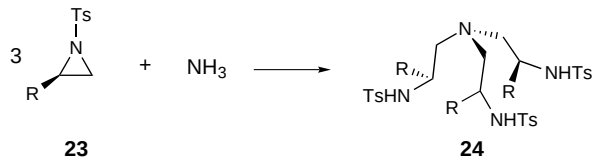
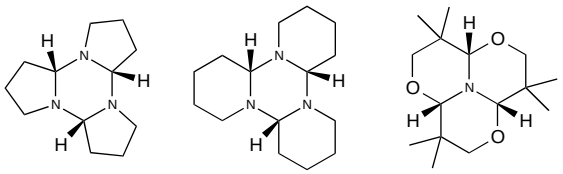
Tetradentate trisaminoamine ligands like that in **22** have been the subject of extensive studies.[61] The properties of these complexes are dependent on the nature of the substituents R, and on the extent to which the bridgehead nitrogen atom takes part in the complexation.[62] Several complexes with early transition metals were recently prepared.[63] Monomeric trigonal bipyramidal complexes with vacant apical positions were obtained with Ti^{III}, V^{III}, Cr^{III}, Mn^{III}, Fe^{III} and R = *tert*-butyldimethylsilyl,[64] with M = B and R = methyl, and with M = Al and R = trimethylsilyl.[65] The boron compound was shown to adopt a chiral conformation; interconversion between the enantiomers was slow on the NMR time scale at room temperature.

Tetradentate, tripodal, C_3-symmetric amines analogous to the ligand in **22** can probably be prepared easily by N-alkylation with chiral electrophiles. However, such ligands are expected to exert insufficient stereocontrol in catalytic reactions, since their conformation is most likely flexible. It would probably be more efficient to have the stereogenic center residing in the chelate framework. Chiral analogues such as **24** were, in fact, conveniently obtained in high yields by nucleophilic ring-opening of chiral aziridines **23** (in turn



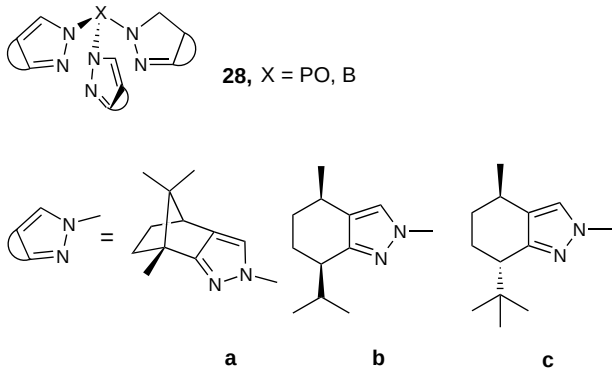
obtained from readily available chiral aminoalcohols[66]) using ammonia as the nucleophile.[67] The aziridines have to be activated by an electron-withdrawing substituent (for example a tosyl or mesityl group) attached to the nitrogen atom in order for ring-opening to occur.

Some C_3-symmetric amines with interesting structures have been known for a long time, although no applications to catalytic reactions have been reported. 1,2-Didehydropyrrolidine[68] and Δ^1-piperideine (3,4,5,6-tetrahydropyridine)[69] trimerize spontaneously to yield **25** and **26**, respectively. C_3-Symmetric, racemic monoamines like **27** have been prepared by some different methods.[70]



4.1.4. Dihydroborazoles and -oxazoles and Related Compounds

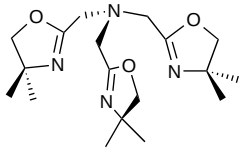
Like tripyridylmethane derivatives, tris(pyrazolyl)hydroborates have been employed in organometallic chemistry and in studies aimed at mimicking biological processes.[71] They are used as terminal ligands in the study of iron binding in proteins,[72] they are used to approximate the binding site typically found or suggested for copper(I) ions in metalloproteins, and they serve as models of carbonic anhydrase.[41] Successful results were obtained with 3-substituted tris(pyrazolyl)hydroborates, in that the desired monomeric complexes with threefold rotational axes were observed.[73] The logical extension, the preparation of C_3-symmetric chiral analogues such as **28a–c** (X = B), was readily achieved by



reaction of chiral pyrazoles with potassium tetrahydroborate.[74] Analogous ligands with a phosphorus atom joining the three heterocyclic moieties were obtained by reaction of the pyrazoles with phosphorus oxychloride. A Cu^I complex of one of these ligands was shown to catalyze the cyclopropanation of styrene with diazoesters with up to 60% *ee*.[75] The geometry around the metal ion heavily depends on the structure of the ligand: in the Tl^I complex of the tris(pyrazolyl)hydroborate prepared from **28b** the torsion angles Tl-N-N-C are close to 180°, and the Tl^I complex prepared from **28c** (X = B) has a distorted propellerlike structure.[76]

A little later three types of borate–[Rh^{I}LL] complexes (LL = 2 CO, norbornadiene, cyclooctadiene) were identified. In one type of complex the tris(pyrazolyl)borate ligand serves as an η^3 ligand, and in two other forms the ligand occupies only two coordination sites.[77] Upon irradiation the Rh^{I} carbonyl complexes of **28b** (X = B) underwent stereo- and regioselective C–H bond activation to give alkyl(hydrido)-rhodium complexes resulting from insertion of the metal in a C–H bond of a methyl substituent in the ligand isopropyl group.[78] No intermolecular C–H bond activation was observed; such processes are probably prevented by the steric bulk of the ligand.

In contrast to the trispyrazolyl ligands **28**, the C_3-symmetric, tripodal trisdihydrooxazole ligand **29** forms a dimeric Cu^{I} complex, in which the metal ion is surrounded by two oxazolyl nitrogen atoms from one ligand and one from the second ligand.[79] Cu^{I} and Cu^{II} complexes of chiral analogues of **29** were shown to catalyze the oxidation of cyclopentene with *tert*-butyl perbenzoate in up to 84% *ee* (somewhat higher under conditions that gave low yields of products).[80] Tris(imidazolyl)phosphane ligands and their metal complexes have been prepared, although no chiral analogues have been reported.[81] In our group we have attempted to prepare chiral tris(dihydrooxazolyl)methanes without success.



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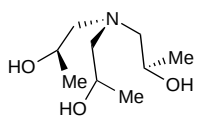
4.1.5. Alcohols

Atranes, triethanolamine derivatives in which silicon, phosphorus, tin, or other metal ions are bound to the three deprotonated hydroxy groups, have been extensively studied.[54] Examples are titanatranes, complexes with Ti^{IV}, which are monomers or dimers depending on the nature of the ligand occupying the fifth coordination site of the metal.[82] Analogous chiral metal complexes were obtained when triethanolamine was replaced by C_3-symmetric tris(2-hydroxypropyl)amine (**30**).[83] This ligand and its complexes have also been employed in asymmetric synthesis. Triol **30** has been used as a chiral auxiliary in reductions with lithium aluminum hydride,[84] and a boron compound having the same ligand has been prepared.[85] The Zr^{IV} complex of the chiral ligand has a complicated oligomeric structure but has proved to be an efficient catalyst for the ring-opening of *meso* epoxides under certain conditions; ring-opened products are obtained with high selectivity (up to 93% *ee*).[86] Mechanistic studies indicate that a dimer is the catalytically active species, and that the catalytic activity requires the cooperative action of two Zr^{IV} centers.[87] Interestingly, no stereoselectivity was observed when the *R*,*R*,*S* isomer was employed in the catalytic reaction. In contrast, the Ti^{IV} complex of **30** turned out to be a poor catalyst for this same reaction,[88] but was used for the enantioselective oxidation of sulfides to sulfoxides (up to 66% *ee*).[89] The C_3-symmetric, tridentate triol **31** has also been prepared,[90] but no reports of its use in asymmetric synthesis have appeared.



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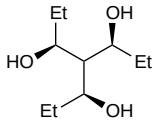

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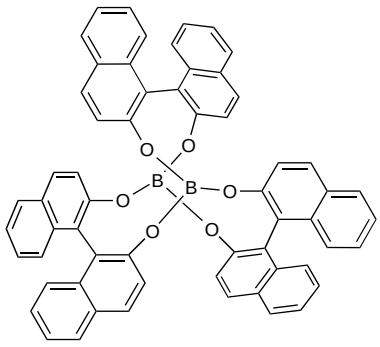
The C_3-symmetric diborate **32** was obtained from the reaction of (*S*)-(−)-1,1′-bi-2-naphthol with monobromoborane/dimethyl sulfide. This compound catalyzed the Diels–Alder reaction of cyclopentadiene and methacrolein in a highly enantioselective manner (90% *ee*, 97.4% *exo* selectivity).[91]



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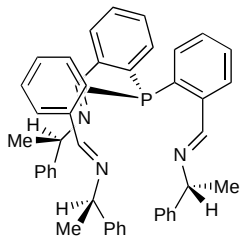
4.1.6. Other Ligands

The use of the Schiff's base **33**, obtained by condensation of tris(2-formylphenyl)phosphane with (*R*)-(+)-1-phenylethylamine, as a ligand in rhodium-catalyzed reductions was investigated.[92] A complex prepared in situ from **33** and [Rh(cod)Cl]$_2$ did not catalyze the hydrogenation of (*Z*)-α-(acetylamino)cinnamic acid at 50°C and 1 bar. Although a complex prepared in the same manner did catalyze the hydrosilylation of acetophenone, no enantioselectivity was observed. This disappointing result does not seem to be attributable to the threefold symmetry of the ligand, since an asymmetric, monodentate ligand, in which two of the chiral groups on phosphorus (in **33**) were replaced by phenyl rings, also showed poor selectivity under the same conditions.



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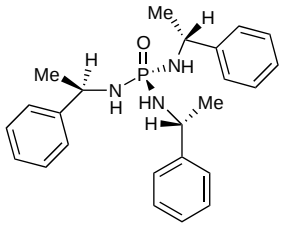
The reduction of acetophenone was also performed using **34** as a chiral catalyst, but with borane/dimethyl sulfide as the reducing agent instead of a hydrosilane.[93] The results were slightly inferior to those obtained when asymmetric analogues were employed in which one or two of the chiral substituents on phosphorus (in **34**) were replaced by phenyl groups (70% yield of (*S*)-1-phenylethanol with 20% *ee*).



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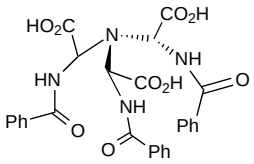

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The synthetic pseudotripeptide **35**, which is of potential interest both as an asymmetric ligand in catalytic applications and as a model for studies of metalloenzymes (vide infra), was described in 1995.[94] In the complex obtained from **35** and [$CpTiCl_3$] the C_3 symmetry was lost because one carbonyl group is also coordinated to the metal ion. This was evident in the ^1H NMR spectrum, in which separate signals were observed for the three amide chains. The advantage of a ligand with threefold symmetry is that only one complex is formed, no matter which of the three equivalent carbonyl groups takes part in the complexation.

4.2. Lack of Rotational Symmetry May Be Advantageous

It should be noted that the benefits achieved by using reagents with rotational symmetry may also be obtained by other means, which may occasionally even be more efficient. Consider, for example, a macrocyclic metal complex that in a particular reaction coordinates a substrate in one of the two axial positions, a situation encountered, for instance, in oxidative processes.[95] The approach of a C_2-symmetric reagent from below is identical to approach from above, and the number of different reaction paths is thus reduced by a factor of two. Alternatively, only one kind of approach is also possible if one face is blocked by a pendent arm of the ligand (Figure 5).[96]

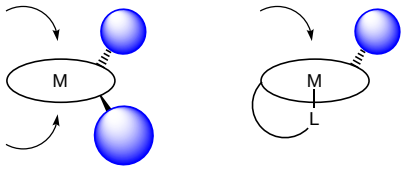


Figure 5. The approach of a substrate to macrocyclic complexes. Left: the complex is C_2-symmetric; right: the complex is C_1-symmetric and bears a blocking group. See text for details.

In certain situations truly asymmetric reagents offer clear advantages over reagents with rotational symmetry. In reactions where the asymmetric induction relies on the regiodifferentiating ability of the reagent, for example, the absence of rotational symmetry may likely be beneficial in given situations. Consider the attack of a nucleophile on a π-allylpalladium complex containing a prochiral (*meso*) allyl group derived, for example, from *rac*-1,3-diphenyl-2-propenyl acetate.[97] With an asymmetric ligand, two diastereomeric complexes (**A** and **B**, Figure 6) may form and both are usually

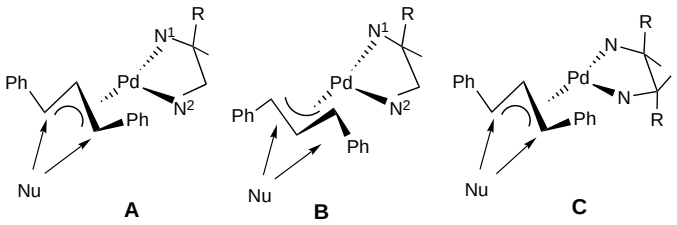
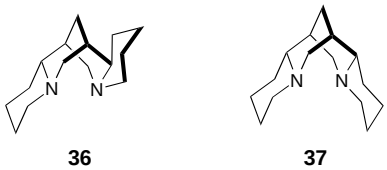


Figure 6. π-Allylpalladium complexes with C_1- (**A** and **B**) and C_2-symmetric ligands (**C**).

also obtained. The enantioselectivity in this case arises from regioselective attack on one of the complexes. The most abundant complex is usually the one being attacked, since the reactions are exothermic and therefore the transition states and the intermediates are close in energy.[98] With a C_2-symmetric ligand, only one complex (**C**) is obtained (rotation of the π-allyl ligand 180° yields an identical complex), and the selectivity depends on the regiodifferentiation of the reagent alone.

It is probably easier to achieve high regioselectivity when the complexing atoms in the ligand are different. Their *trans* effects are different and thus the reactivities at the two sites are different. When the coordinating atoms are different, the ligand is by definition C_1-symmetric. These arguments imply that regiodifferentiation could be an easier task in **A** and **B** (C_1-symmetric ligand) than in **C** (C_2-symmetric ligand). What is crucial in reactions employing C_1-symmetric ligands is that the diastereomeric complexes **A** and **B** have different reactivities. The advantage of using a ligand with C_2 symmetry is thus that only one complex is formed and the selectivity is determined solely by the regioselectivity. When the ligand has C_1 symmetry, however, regiodistinction may be a much simpler matter. As soon as the two complexes **A** and **B** have different properties, and one of them leads preferentially to product, the asymmetric ligand may be the more successful one.

Several ligands, C_1- as well as C_2-symmetric, are known for high asymmetric induction (>99% *ee*) in the palladium-catalyzed allylation.[97, 99] It is not possible to find two ligands that differ *only* in their symmetry properties, and thus to compare the efficiencies of the different types of ligands. It is interesting, however, to compare sparteine (**36**)[100] and α-isosparteine (**37**).[101] With 1,3-diphenyl-2-propenyl acetate as

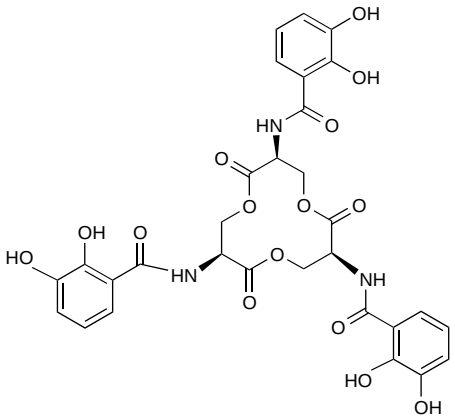


36 37

a substrate, higher selectivity was observed when the asymmetric ligand **36** was employed (92% *ee* vs 70% *ee* with **37**; both reactions in refluxing THF).[101] However, with aliphatic substrates, the C_2-symmetric ligand led to higher stereoselectivity and also turned out to be more reactive. This shows that ligands with rotational symmetry are not necessarily superior.

4.3. Natural Siderophores and Other Ionophores

In nature strong complexing agents are required to keep trivalent iron ions in solution and to enable transport.[102] This is accomplished by siderophores, a class of compounds that transport cations and promote bacterial growth. Several compounds of this type have been found in nature, for example enterobactin (**38**), which was first described in



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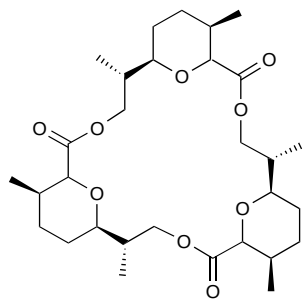
1970.[103] The molecule, the cyclic triester of 2,3-dihydroxybenzoyl-L-serine, possesses C_3 symmetry. This geometry is highly advantageous, since it allows extremely efficient binding to Fe^{III} ions in an octahedral arrangement, as shown by the resistance of its iron complex towards ligand exchange with EDTA.

A variety of C_3-symmetric molecules have been prepared in attempts to mimic the properties of the natural siderophores.[104] The synthetic models typically have catecholate or hydroxamate units as ligating groups in open or bicyclic arrangements, with six oxygen atoms serving as donors.[105] Most of the models are achiral, although they contain a threefold rotational axis.[106] Ionophores aimed at complexation with metals other than iron, some of them possessing C_3 symmetry, have also been prepared. Recent examples include ionophore **39**, whose binding to alkali metal ions has been examined,[107] and similar compounds studied in the context of transmembrane ion channels.[108]



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4.4. Octahedral Metal Complexes

Metal complexes can be chiral and belong to point group C_n or D_n even when they contain only achiral ligands.[109] The simplest example is a tetrahedral complex with four different ligands, which like the analogous carbon-based compound has C_1 symmetry. Octahedral metal complexes may be chiral as a result of the arrangement of achiral ligands around the metal ion. Frequently encountered examples are complexes in which the metal ion is coordinated to three identical bidentate ligands (Figure 7).[110] The first thoroughly

Figure 7. Enantiomeric octahedral complexes with Λ and Δ configurations.

studied examples were complexes containing a metal ion surrounded by three 1,2-diaminoethane molecules. The ligands can arrange themselves in two different ways with a mirror image relationship, and thus with different absolute configurations (Λ and Δ). Such complexes have D_3 symmetry.[111]

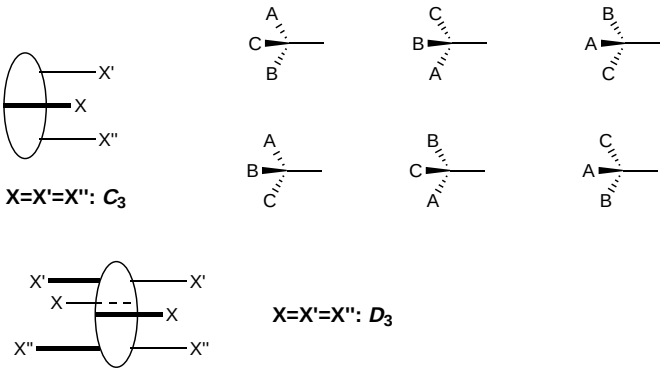
5. Receptors for Organic Molecules and Ions

5.1. Molecular Recognition

A common requirement for a chiral receptor is that it differentiate between the two enantiomers of a substrate. If the substrate is endowed with three sites that can interact with a receptor, the receptor should in turn contain three complementary groups for efficient complexation. Obviously, a receptor with threefold rotational symmetry should be advantageous for the complexation of a substrate with the same symmetry. This has also been unambiguously demonstrated in two sets of complexation reactions: 1) an alkylammonium ion was more strongly bound to calix[6]arenes than to calix[4]arenes (the latter lacks threefold symmetry),[112] and 2) the same ion formed a stronger complex with a hexahomotrioxacalix[3]arene having a C_3-symmetric conformation than with conformers lacking that symmetry.[113]

With this kind of three-point interaction, chiral discrimination is, in principle, possible. The situation is complicated by the fact that six different complexes may be formed by the interaction of the racemic substrate with the receptor (Scheme 5). With a C_3-symmetric receptor ($X = X' = X''$), each enantiomer gives rise to only one complex; in other words, there are only two possible modes of coordination, one for each enantiomer. The situation is thus simplified and the probability of chiral discrimination is increased.

If the substrate can approach the receptor from both faces, it is desirable that these faces be identical. This is the key to the favorable properties observed with many C_2-symmetric



Scheme 5. The six possible modes of binding a racemic substrate to a trifunctional receptor are reduced to only two when the receptor has C_3 symmetry. This is because for each enantiomer (top and bottom rows) the three possible binding modes lead to identical results.

compounds. If the threefold symmetry is to be kept, a receptor with D_3 symmetry, which by definition has two equal faces, is required. The general conclusion from these arguments is that when the substrate can be approached both from the front and from the back, D_3 symmetry is most efficient for decreasing the number of interactions, whereas with a bowl-shaped receptor, in which the interacting sites reside inside the cavity, C_3 symmetry is desirable.

A different solution to making the faces of a receptor homotopic was presented in 1996.[114] In this example a calixarene was trialkylated with two different electrophiles. The one used for monoalkylation was small enough to slip through the cavity, and the resulting methyl ether unit was thus able to take part in the binding at both faces (Figure 8).

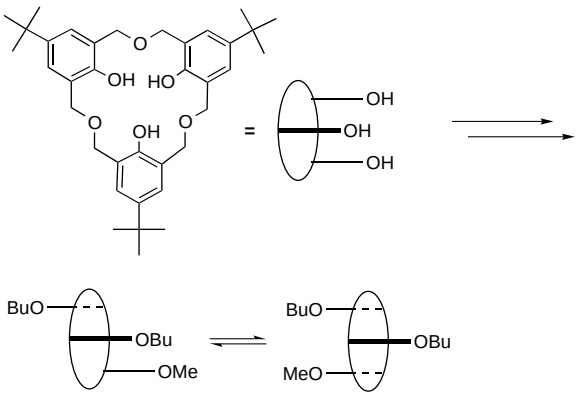


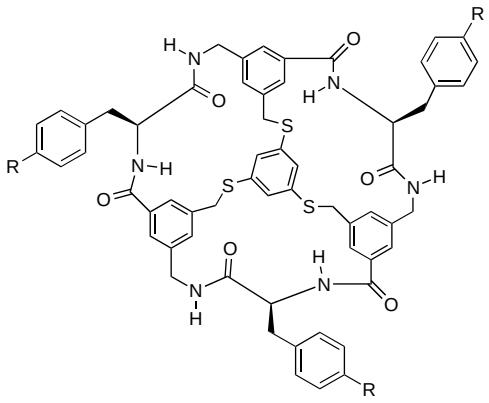
Figure 8. Alkylation transforms a C_{3v}-symmetric calixarene into a C_2-symmetric receptor, which exposes two identical faces to a reagent.

The result was that two equal faces were exposed by the receptor to an incoming substrate, and that the substrate could still be bound to three oxygen donors, two alkoxy oxygens, and one ether oxygen. A trivial case is provided by a substrate capable of being bound through a single one-point interaction. Obviously, the higher the order of the rotational axis, the higher the number of equal interactions.

The next sections provide a survey of receptors that can bind organic molecules and ions. Several of the receptors may also form complexes with metal ions and may thus serve as ionophores as well.

5.1.1. Peptides and Pseudopeptides

In the design of synthetic model receptors, symmetric host molecules have the advantage of more selective binding because several modes of binding are equivalent. Numerous synthetic receptors that take advantage of this feature have been described.[115] High selectivity was reported by Still for the reversible binding of peptides to some C_3-symmetric, tricyclic receptors.[116] Receptor **40** (R = H, $OCH_2CH{=}CH_2$)



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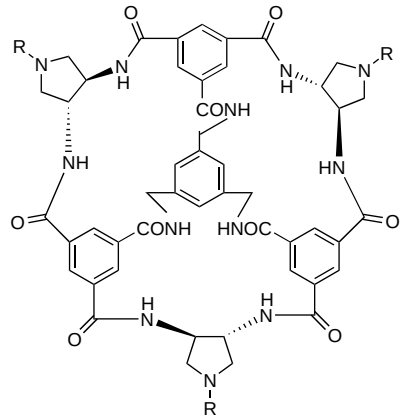
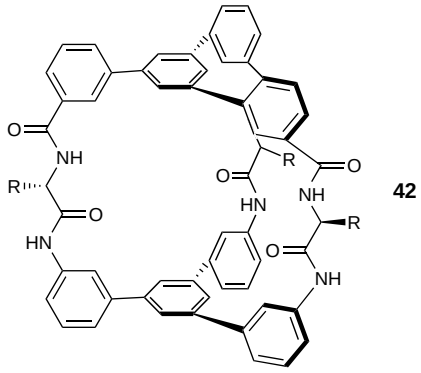


41

showed a high enantioselectivity in the complexation of amino acids.[117] Its potential as a resolving agent was elucidated by covalent attachment of the ligand to silica gel. Separation factors up to 21 were observed for neutral tripeptides.[118] The binding properties of an analogous receptor, **41**, in which the pyrrolidine units were linked to a dye (R = $CO(CH_2)_2CO_2$-dye), were established with a polymer-supported library of about 50 000 acylated tripeptides, where each polymer bead was coated with *one* of the tripeptides.[119]

Macrocyclic C_3-symmetric amides with structures resembling that of receptor **40** were also prepared. Hexacarboxylic acids were transformed into macrolactams by reaction with (*R*,*R*)-1,2-diaminocyclohexane. No binding studies with these new receptors were reported.[120]

The cage compound **42** (R = CH_2CHMe_2, CH_2Ph), in which short peptide chains join two triarylbenzene residues, was shown to bind N-protected amino acids.[121] Chiral recognition was demonstrated upon complexation of the enantiomers of N-Z-protected glutamic acid: the complex of **42** (CH_2Ph) with the L enantiomer was 1.0 kcal mol^{-1} more stable than that with the D enantiomer. The discrimination of enantiomers having a



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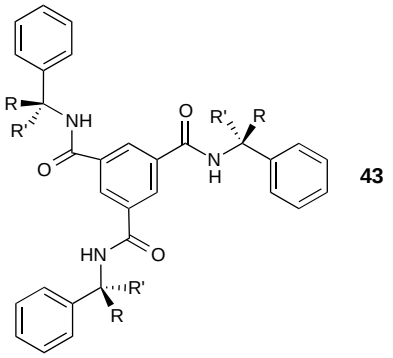
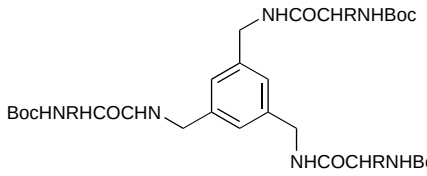


43

chiral center directly attached to an electron-rich aromatic ring was studied using **43**.[122]

C_3-Symmetric pseudopeptides containing three parallel peptide chains were also prepared by using the triacid **35** as a reactive template.[94, 123] $CpTi^{IV}$ complexes of pseudononapeptides were shown to have C_3 symmetry based on their NMR spectra, which exhibited only one set of signals for each peptide chain. This arrangement is stabilized by hydrogen bonds. The cavity formed by the cyclic arrangement in the metal complex was believed to be too small for a hypothetical guest molecule. Some pseudopentadecapeptides were prepared with the same template. An interesting pattern of interstrand hydrogen bonding, the nature of which was shown to depend on the structure of the amino acid incorporated in the peptide and on the solvent, was found during studies of tripeptides **44** and **45**.[124] Leucine-derived **44** (R = *i*Bu) was found to have a propellerlike conformation. Studies of the ability of metal ions to serve as regulatory elements in C_3-symmetric, tripodal tripeptides showed that Li^+ generates a chiral helical conformation in **46** ($n = 1$), whereas Ca^{2+} does so in the larger analogue ($n = 2$).[125]

Some naturally occurring, C_3-symmetric or pseudo-C_3-symmetric, cyclic hexapeptides with cytotoxic activity were recently isolated. Compounds **47**[126] and **48**[127] were found in a



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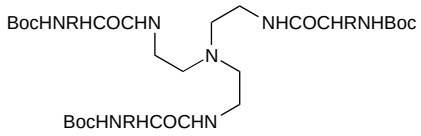

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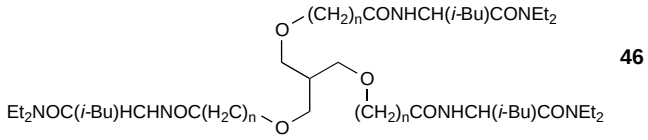

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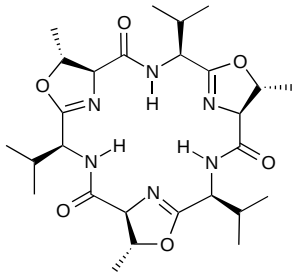

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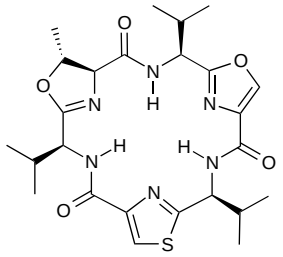

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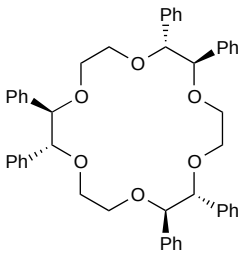
marine alga, and **47** also in a terrestrial cyanophyte.[128] The total synthesis of **47** relied on a cyclotrimerization, in which the desired trimer was formed along with a C_4-symmetric tetramer.[129]

5.1.2. Crown Ethers and Podands

The D_3-symmetric [18]crown-6 ether **49** was used as a catalyst in the Michael addition of methyl phenylacetate to methyl acrylate with potassium *tert*-butoxide as base.[130] The yield was low and the enantioselectivity moderate. Similar selectivity but considerably higher yields were obtained with tetraphenyl-substituted, D_2-symmetric analogues. The best results were obtained when a C_2-symmetric, dimethyl-substituted [18]crown-6 ether was used.



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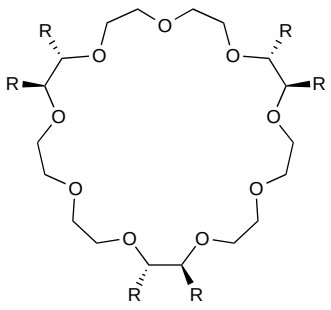

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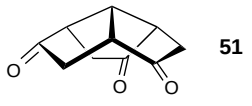
The larger [27]crown-9 ion **50** ($R = CO_2^-$) forms more stable complexes with guanidinium ion than with ammonium ion, while the reverse was found for a D_2-symmetric [18]crown-6 analogue.[131] The symmetric, uncomplexed, (*R*,*R*,*R*)*-trisbinaphthyl[18]crown-6 ether was shown to be slightly destabilized in relation to the (*R*,*R*,*S*)* diastereomer.[132] The reaction of D-diisopropylidenemannitol with diethylene glycol tosylate afforded a C_3-symmetric [27]crown-9 ether as a by-product.[133]

5.1.3. Cyclotriveratrylenes

The C_3-symmetric perhydrotriquinacene ketone **51** serves as a useful precursor for the preparation of C_3-symmetric podands.[134] Catalytic hydrogenation afforded the tris(*endo* alcohol) **52**, which, however, turned out to be quite unreactive towards alkylation reagents. Instead, direct reductive amination of **51** with 1-aminooligoethers afforded aminopodands such as **53**.[135] Triketone **51** could also be used for the synthesis of cage compound **54** ($n = 2$, 3) and analogues.[136] Compound



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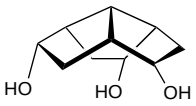

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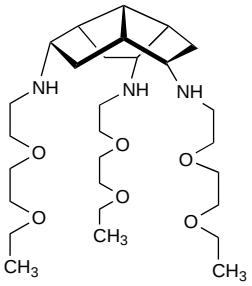

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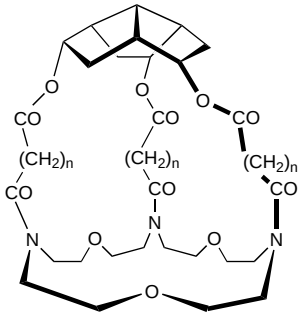

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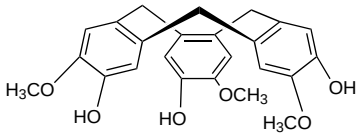
54 was shown to complex the methylammonium ion efficiently, although possibly to the external face of the polar subunit. No attempts to achieve chiral induction were reported.

Ring inversion in cyclotriveratrylene takes place only around 200°C, and compounds of this type with two different substituents are therefore chiral under ordinary conditions. The C_3-symmetric cyclotriveratrylene **55** was described early on by Collet and Jacques.[137] The enantiomerically pure cryptophane **56** based on the same compound was shown to give an inclusion complex with racemic bromochlorofluoromethane.[138] Different ^{1}H NMR signals were observed for the guest molecules in the diastereomeric complexes formed. Interestingly, chiral recognition was achieved: one complex was favored over the other by about 1.1 kJ mol^{-1}. Analogous, D_3-symmetric compounds **57**[139] afford inclusion complexes with a variety of guest compounds such as methane ($n = 2$, R = Me),[140] isobutane ($n = 3$, R = Me),[141] tetramethylammonium ion ($n = 3$, R = Me, K = 225 000 M^{-1}), and acetylcholine ($n = 5$, $R = CH_2CO_2H$).[142] For larger members of this family of compounds ($n \geq 6$), equilibrating in–out and out–out topoisomers were observed.[143] Self-assembled, hetero-



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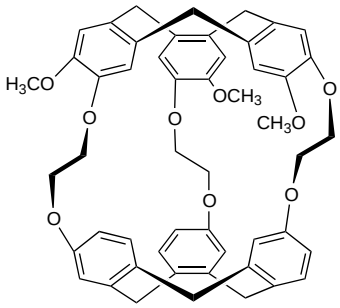

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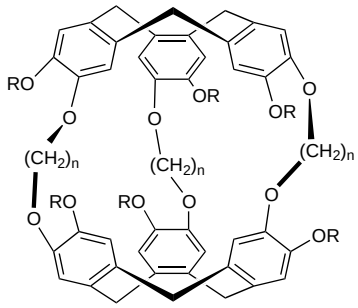


57

dimeric cyclotriveratrylenes, in which the two units are held together by hydrogen bonds, were also prepared and shown to form inclusion complexes.[144] Some new cyclotriveratrylenes bearing iodine substituents on the benzene rings are expected to serve as useful precursors for a variety of derivatives.[145]

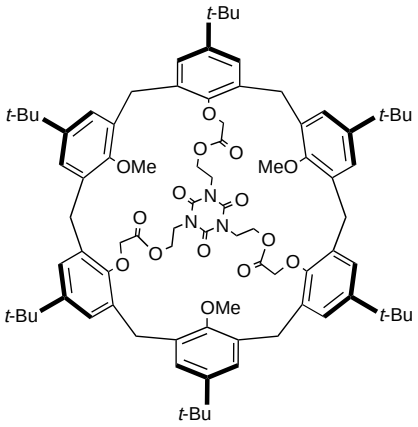
Cyclotriveratrylenes equipped with substituents suitable for complexation to metal ions have been prepared.[146] Studies of octahedral Fe^{II} complexes revealed that when complexed with a racemic host containing three bipyridine units, the absolute configuration at the metal center was determined by the absolute configuration at the cyclotriveratrylene unit: only the enantiomeric pair $M\Delta/P\Lambda$ was observed.[147]

5.1.4. Calixarenes

A variety of achiral calixarenes with threefold symmetry (C_{3v}-symmetric) have been prepared by proper substitution of calix[6]arenes.[148] To avoid conformational changes destroying the threefold symmetry and favorable complexing ability, the conformationally immobilized calix[6]arenes **58**[149] and **59**,[150] capped on the lower[151] and upper rim, respectively, were synthesized.

Some chiral, although not enantiomerically pure, calix[3]indols have been described.[152] Compound **60** (Ar = C_6H_5, *p*-BrC_6H_4, *p*-$MeOC_6H_4$) is achiral, however, as indicated by its ^{1}H NMR spectrum, which exhibits a singlet for the methylene protons. This is consistent with either a rapidly inverting *cone* conformer or a fluxional, flattened *partial cone* conformer. On the other hand, compound **61** (Ar = *p*-ClC_6H_4, R = Me, *t*Bu), which has substituents on the bridging methylene groups, is chiral. It was isolated as a mixture of two conformers, which could be separated for R = *tert*-butyl, Ar = *p*-ClC_6H_4.[153] The C_3-symmetric compound was obtained in 17% yield, and the stereoisomer in 45% yield.

Calixarenes containing three dihydroxybiphenyl residues have been prepared.[154] Alkylation of the hydroxyl groups resulted in restricted rotation around the Ar–Ar bonds. The isomer with D_3 symmetry was, however, not observed among the atropisomers obtained.



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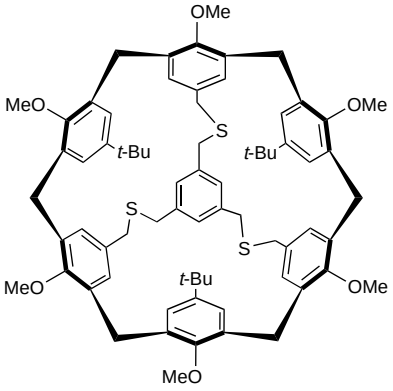

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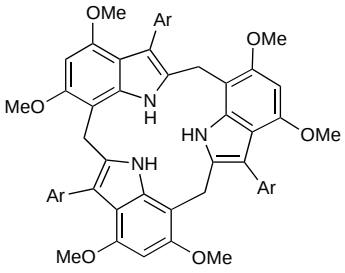

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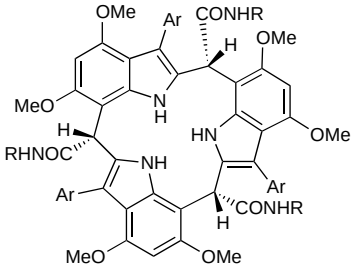

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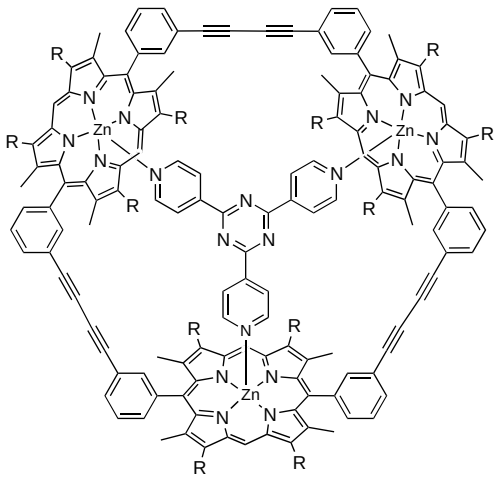

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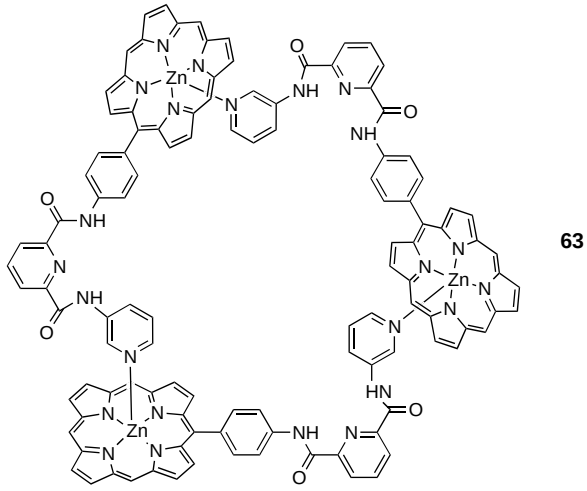

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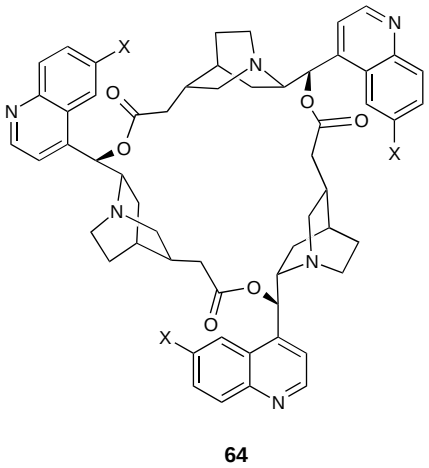

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5.1.5. Porphyrins

The cyclic zinc porphyrin trimer **62** ($R = CH_2CH_2CO_2Me$), which has a cavity suitable for complexation of tris(4-pyridyl)-triazine, was obtained when this guest was used as a template.[155] By proper adjustment of the angle between the plane of the porphyrin ring and the pyridine ligand in the monomer, self-assembled trimers such as **63** were obtained.[156] Although the compounds described were achiral, desymmetrization to achieve C_3 symmetry can easily be imagined.

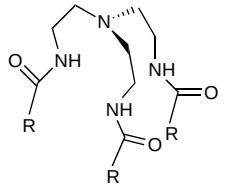
5.1.6. Other Receptors

Macrocyclic trimers of derivatives of the cinchona alkaloids quinine (**64**, X = OMe) and cinchonidine (**64**, X = H) were obtained in high yield from monomeric derivatives of the alkaloids.[157] The trimers were shown to be the thermodynamic products formed in a reversible process. A thermodynamic mixture of products consisting of dimers, trimers, and higher oligomers was also obtained by macrolactonization of cholic acid derivatives.[158]

Cyclodextrins are cyclic oligomers consisting of six, seven, or eight glycose units. The smallest member of the series, α-cyclodextrin, has been substituted symmetrically with three substituents to give C_3-symmetric receptors.[159] A trisammo-

nium derivative of α-cyclodextrin was used as a host for benzyl phosphate.[160] Recently, C_3- and C_4-symmetric cyclodextrin analogues were described which were made up of L-rhamnose and D-mannose units.[161]

Interesting, although achiral amides **65** ($R = CH_2Cl$, $(CH_2)_4CH_3$, C_6H_5, 4-$MeOC_6H_4$), obtained from tris(2-aminoethyl)amine, were shown to serve as phosphate or sulfate receptors. The properties of the receptors depend on the structure and the substituents.[162] Examples of other achiral compounds serving as receptors for small organic molecules include macrocyclic cage compounds containing phosphane oxide units,[163] bowl-shaped or capped aryl thioethers,[164] macrocyclophanes,[165] and bridged triarylmethanes.[166] Some receptors with threefold symmetry were also included in recent reviews.[167]



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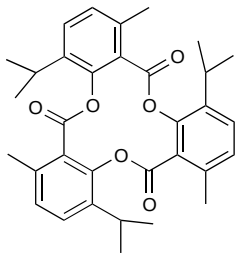
5.1.7. Clathrands

Several important clathrands (compounds acting as hosts in the solid state) possess threefold symmetry.[8,9] Although many of the hosts are achiral, propellerlike conformations have been observed for the hosts as well as for their complexes.[168] Common examples are perhydrotriphenylene (C_3 symmetry), triphenylmethane, and tri-*o*-thymotide (**66**),[169] the last two of which adopt chiral conformations.



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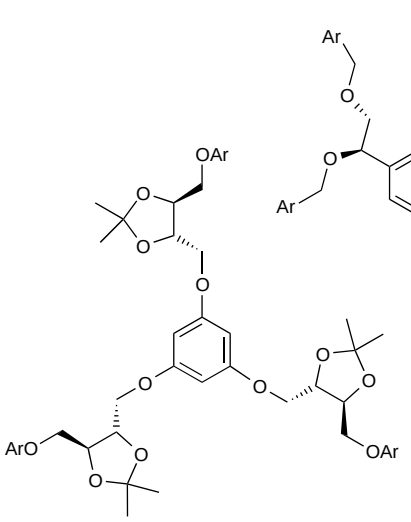
6. Other Compounds

A variety of other compounds possessing threefold symmetry, hydrocarbons as well as compounds containing functional groups, have been prepared. Surveys of such compounds are given in the reviews by Nakazaki[9] and by Farina and Morandi.[8] Only a few recent examples will be given here.

Dendrimers are three-dimensional, branched, highly ordered macromolecules.[170] Although such compounds have been known for several decades, the first syntheses of chiral dendrimers have been undertaken only recently.[171] The chirality of dendrimers may be due either to a chiral nucleus, to which achiral building blocks are attached, or to the attachment of chiral substituents to the core, or, finally, to the use of chiral building blocks, resulting in a chiral interior domain. These kinds of chiral macromolecules are expected to become useful in chemical operations including asymmetric catalysis, chiral recognition, and resolution.

A few dendrimers with overall C_3 symmetry are known. Such dendrimers have been synthesized from 1,3,5-substituted benzene derivatives and tartaric acid derivatives (**67**; only the first generation of the dendrimers is shown)[172] or 3-hydroxybutanoic acid[173] as chiral units and by asymmetric synthesis, using the Sharpless dihydroxylation reaction (**68**).[174] It is doubtful, however, whether the overall C_3 symmetry of the macromolecule is of any importance in the microenvironment of a guest molecule or of a substrate bound to a catalytically active site.



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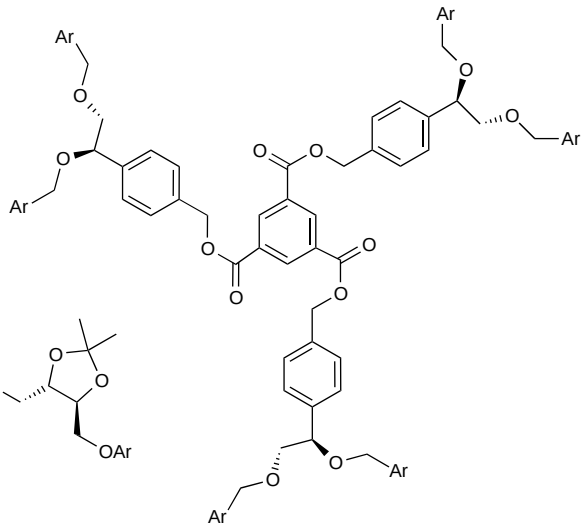

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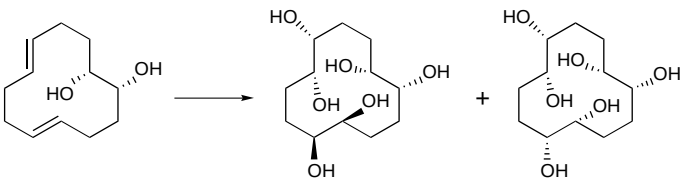
Fullerenes are carbon clusters having symmetries ranging from I_h to C_1. It is interesting to note that one of the C_{78} isomers possesses D_3 symmetry.[175]

It seems appropriate to close this survey of chiral compounds having threefold rotational symmetry with an example of a compound whose preparation relies on one of today's most potent asymmetric reactions, the Sharpless dihydroxylation.[176] Dihydroxylation of the three olefinic bonds of all-*trans*-1,5,9-cyclododecatriene is expected to yield a mixture of two compounds, **69** and **70**, which have C_2 and D_3 symmetry, respectively. Enantiomerically pure (*R*,*R*)-diol **71** afforded only small amounts of the hexol with threefold symmetry when quinuclidine or 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinyl)pyrimidine, $(DHQ)_2$-PYR, was employed as the ligand in the reaction. 2,5-Diphenyl-4,6-bis(9-*O*-dihydroquinidyl)-pyrimidine, $(DHQD)_2$-PYR, gave the two compounds in a ratio of 2:1; the total yield of the D_3-symmetric compound **70** was as high as 32%.[177]



71 *(R,R)* **69** *(R,R,R,R,S,S)* **70** *(R,R,R,R,R,R)*

7. Molecules with Higher Symmetry

Some chiral compounds analogous to those described above but with higher symmetry have been reported. Examples of compounds with a single fourfold axis include some calixarenes,[178] a tetraphenylporphyrin capped with a calix[4]amide,[179] and a C_4-symmetric dendrimer.[180] C_5 through C_7 symmetries are represented by the cyclodextrins. Examples of high-symmetry compounds belonging to a dihedral group are a D_4-symmetric metallotetraphenylporphyrin,[181] a D_4-symmetric amine,[182] and a hexaamine with D_6 symmetry.[182] This last compound has symmetry number 12 and is, together with the *T*-symmetric adamantane shown in Figure 4,[17] the most symmetric chiral compound synthesized to date. Nature, however, has provided us with supramolecular assemblies of proteins[183] and viruses[184] having *O* and *I* symmetry, in other words, with symmetry numbers as high as 24 and 60, respectively.

8. Summary and Outlook

The justification for using rotational symmetry to achieve high symmetry has been discussed repeatedly, and symmetry is sometimes considered to be a more or less magic property. Symmetry is advantageous when it improves the selectivity by decreasing the number of different reaction paths and thereby the number of intermediates; what is achieved by symmetry is simply the reduction of competing alternatives. This may have a profound effect on the selectivity, as has been demonstrated repeatedly in recent years. Symmetry may also be helpful for the monofunctionalization of a compound containing several reactive sites; if the reactive groups are symmetry-related, the compound desired is obtained by functionalization at any site. Furthermore, the analysis of the observed enantioselectivity and thus the mechanistic interpretation may be simplified.

Rotational symmetry is often but not always the key to high stereoselectivity. What is always important is a thorough analysis of the symmetry and the number of possible intermediates in the reaction under study. The purpose of this survey was to present the known compounds with C_3 symmetry, which have been used or which may be useful in asymmetric synthesis or chiral recognition, and to show under which circumstances these compounds may be advantageous. Another purpose was to demonstrate that the key to high stereoselectivity is often found within the larger family of reagents with various types of rotational symmetry.

I am grateful to Professor Jean-Claude Fiaud and Professor John Osborn for encouraging me to write this review and to Dr. Hans Adolfsson, Dr. Gunhild Aulin-Erdtman, Professor Carsten Bolm, Professor Jan-Erling Bäckvall, Professor Torbjörn Norin, Dr. Tobias Rein, Professor Olof Wennerström, and Dr. Paul Wyatt for valuable criticism and comments on the manuscript. I would also like to thank one of the referees for many valuable suggestions.

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