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The Role of Guest Molecules in the Self-assembly of Metal–ligand Clusters*

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Understanding the self-assembly of nanoscale metal–ligand clusters is an important research area in supramolecular chemistry, especially, if one wishes to develop a truly predictive design strategy for synthesizing these nanoscale clusters. As the building blocks for forming these clusters have become larger and more complex, spacious clusters have been synthesized which often contain large cavities. These assemblies can house guest molecules which play a previously uncharacterized role in the self-assembly processes. We seek to analyze this role: do these guest molecules act as templates? Are the guest molecules necessary for cluster formation? Does the guest drive cluster assemble by forming a stable host–guest complex with the cluster? Must a truly *rational* design strategy for forming metal–ligand clusters incorporate the use of templates? The role of guest molecules in the self-assembly of nanoscale coordination clusters is reviewed in this article.

Keywords: Metal–ligand clusters; Host–guest complex; Nanoscale

INTRODUCTION

Several predictive design strategies for the self-assembly of metal–ligand clusters recently have been advanced [1–11]. These have resulted in a plethora of aesthetically pleasing supermolecules that show promise in areas as diverse as molecular recognition, host–guest chemistry [12–16], catalysis [17,18] and molecular magnetism [19–22]. Included among the various self-assembled clusters are two-dimensional topologies such as triangles, squares [3,23–27], rings [21,28,29], metallacrowns [8,30–34], circular helicates [35–37], helicates [7,11,38,39] and their *meso* counterparts [40–44]; and three-dimensional structures [1,5,8,45] such as tetrahedra [19,46–55], adamantanoids [56–58], cylinders

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*A review in the series "Coordination Number Incommensurate Cluster Formation." For a recent paper in this series, see Sun, X., Johnson, D.W., Raymond, K.N. and Wong, E.H. (2001), *Inorg. Chem.* 40, 4504–4506.

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[59,60], hexahedra [61], octahedra [62,63], cubes [64–68], cages [69–72], dodecahedra [73] and coordination nanotubes [13]. In many instances, these supermolecules have cavities capable of binding guest molecules. What is the role of these guest molecules in the self-assembly reactions, and must host–guest interactions be included in a *rational* design strategy for these clusters?

This article seeks to explore the roles these guest molecules play in the self-assembly of both two- and three-dimensional metal–ligand clusters. We consider three cases for the role of the guest molecules: (i) the cluster is capable of binding a guest molecule but the guest is not vital for cluster formation; (ii) the guest molecule templates the reaction, forming a cluster that maintains its integrity even when the guest molecule is removed; (iii) the guest molecule forms a constituent component of the assembly wherein removal of the guest destroys the cluster or allows formation of a different cluster topology.

The case in which an innocent guest is present (i) is fairly straightforward, although solvent may play an unseen role in these self-assembly reactions. Is the presence of solvent molecules within clusters merely a solvation effect, or are these "guests" vital to cluster formation [74]?[¶] The role of the guest molecules in cases (ii) and (iii) above is even more confused in the relevant literature. Guest molecules have been described as templates in the course of a chemical reaction. However, the use of templates in chemical synthesis has been systematically studied by Busch [75]. He has described the template effect as either a kinetic or a thermodynamic phenomenon, where "the chemical template organizes an assembly of atoms...in order to achieve a particular linking of atoms." In addition, Busch suggests that a template should not be thought of as part of a lock-and-key interaction, because in this case, the key is a constituent part of the assembly [76]. Rather, a template more resembles a platform, consistent with the general definition of a template as "a pattern, mold, or the like, usually consisting of a thin plate of wood or metal, serving as a gauge or guide in mechanical work [77]." This implies that the process is repeatable, i.e. catalytic, as opposed to a stoichiometric reaction. That is, can we consider a guest molecule really a template when it forms an *essential* component of the cluster [36]?[§] We answer that this should really be thought of as a *host–guest complex* where the two components are inseparable, barring complete destruction of the host.[‖] Guest molecules acting as either templates or as constituent components of assemblies are discussed in this paper with particular attention paid to the role the guest plays in the self-assembly of the cluster.

To limit the scope of this review, only self-assembled supramolecular metal–ligand clusters will be discussed. Therefore, many elegant cavity-containing molecules such as hydrogen-bonded assemblies [78–81], zeolites [82,83],

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[¶] Often in these host–guest complexes, the guest molecule can be exchanged for other suitable guests. Presumably, in this case either the cluster is broken apart and rebuilt around the new guest, or the cluster partially disassembles to allow guest exchange via solvation of the cavity followed by guest replacement. The mechanism for this guest exchange in metal–ligand clusters requiring a guest in order to form is not well understood. Rebek and coworkers have studied the kinetics of guest exchange in a hydrogen-bonded "softball".

[§] Lehn has used the term "virtual combinatorial library (VCL)" for describing the type of system where different guests are able to drive formation of a specific cluster out of a "virtual combinatorial library" of structures. By using this type of terminology, the guest molecules are not thought of as templates. Rather, the guests select, out of a dynamic combinatorial library, the host best suited for that particular guest. As the interactions holding together these metal–ligand clusters are labile, any one component of the library represents the entire library. This forms the basis for a dynamic combinatorial library.

[‖] This is reminiscent to the case of a simple ML_3 coordination complex; it would be inappropriate to call the metal ion a template that brings three ligands in close proximity. Rather, the new species formed from a combination of three ligands and one metal is more accurately and reasonably given a new name—a coordination complex.

metal-oxo clusters [84–86], organic cryptates, macrocycles and catenanes (including those formed via metal template reactions) [11,87–89], micelles [90–92], vesicles [93], clathrates [94] and metallacarborands, among others are not discussed. In particular, only those metal–ligand clusters where host–guest chemistry *may* play a role in cluster formation will be included (i.e. cases (ii) and (iii) above).

TWO-DIMENSIONAL CLUSTERS

This section will focus on metal–ligand clusters in which the metal ions lie in roughly the same plane. Within the geometry outlined by the metal ions, these topologies (e.g. squares, rings, etc.) have cavities capable of guest binding. The role these guest molecules play in the self-assembly of two-dimensional clusters is examined.

Triangles and Squares

Early examples of cyanometal compounds were characterized as M_4L_4 stoichiometry molecular squares as early as 1935 and more recently cyanorhodium molecular triangles were reported [95–99]. A contemporary example of an M_4L_4 molecular square (**1**) using a two-fold symmetric ligand was reported by Fujita and coworkers [100] in 1990 (Fig. 1) and was shortly succeeded by numerous other reports of molecular squares by Stang [27,101], Lehn [102], Hupp [103], Lippert [104] and Hong [105], among others. All these squares possess cavities capable of guest inclusion, but only in the case of Hong's square (**3**) is a dependence on the guest molecule noted in the self-assembly.

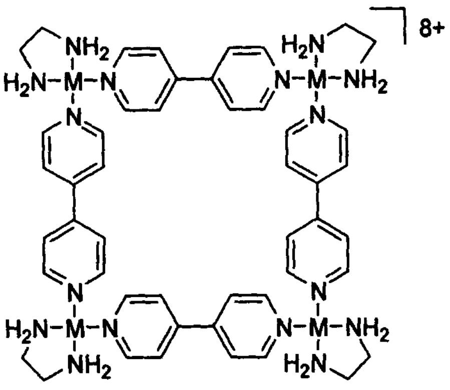

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FIGURE 1 A contemporary molecular square, reported by Fujita *et al.* The square is comprised of either square planar Pd(II) or Pt(II) at the corners with nitrate counterions.

Figure 2 depicts the molecular square of Hong and coworkers (**3**) self-assembled when the bipyridyl ligand is treated with $Pd(en)(NO_3)_2$ to form a mixture of Pd_3L_3 (**2**) and Pd_4L_4 (**3**) clusters. These assemblies exist in a concentration dependent equilibrium, with the smaller stoichiometry triangle favored at lower concentrations, as evidenced by NMR spectroscopy, vapor pressure osmometry and mass spectrometry. Remarkably, this equilibrium can be influenced by the presence of suitable guest molecules. The binding of small guests such as *p*-dimethoxybenzene or the sodium salt of cholic acid (depicted as small spheres in the figure) drives this equilibrium to the triangle. Similarly, the addition of larger guests such as 18-crown-6 or adamantanedicarboxylate to the equilibrium mixture of triangles and squares pulls the equilibrium to the larger square.

The authors describe this as an "induced-fit molecular recognition" in which the binding of small guests directs the equilibrium of the system to the more favorable host structure. Presumably, since the slightly flexible ligand is not designed to perfectly form a rigid square [5], the system is able to access both geometries with the guest molecules providing a thermodynamic driving force between the two nearly energetically equivalent assemblies. Fujita and coworkers [106] have also noted a similar concentration-dependent equilibrium between molecular squares and triangles with slightly flexible ligands; however, no mention of guest

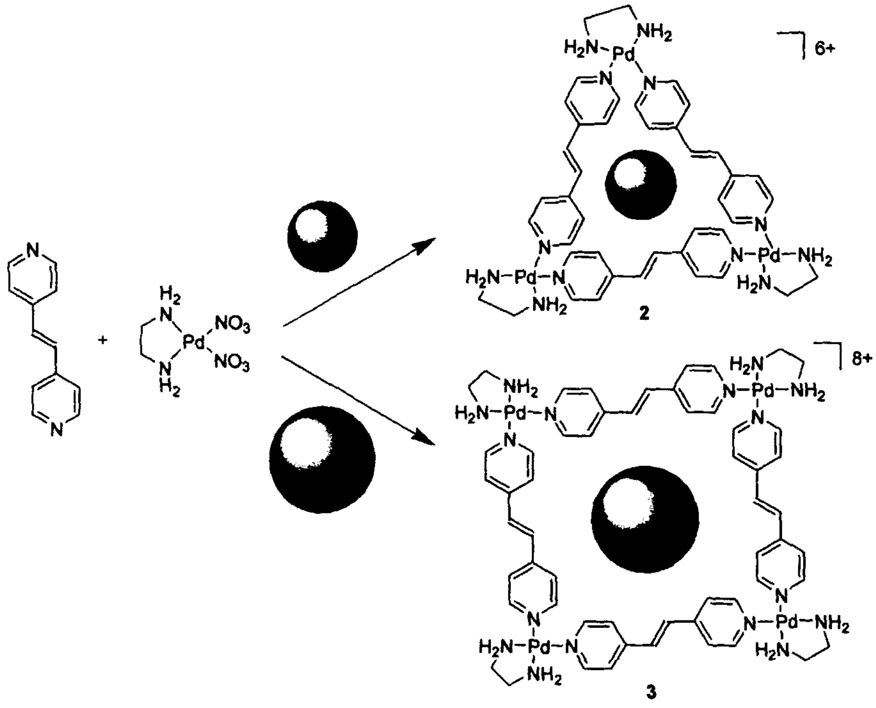
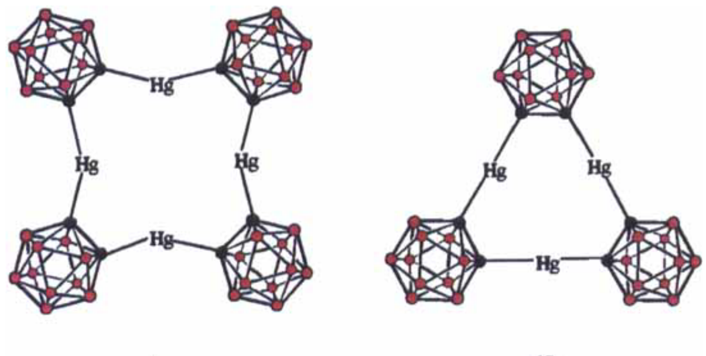


FIGURE 2 The binding of smaller guest molecules (e.g. *p*-dimethoxy benzene or cholic acid sodium salt, small red spheres) induces formation of the smaller triangle-shaped guest receptor **2**. Binding of large guest molecules such as 18-crown-6 or adamantane dicarboxylate (large blue spheres) favors formation of the larger square-shaped host.

molecules influencing the self-assembly process was made.

M_nL_n two-dimensional assemblies have also been synthesized using a carborand ligand to coordinate mercuric ions (Fig. 3). The mercury ions form a square array [107] (**4a**) with a halide ion bound in the cavity when mercuric halide salts are used as starting materials and a triangle [108] (**4b**) when mercuric acetate is used. Both the square and triangle bind chloride ions in the solid state and solution as determined by ^{199}Hg NMR spectroscopy [26]. Perhaps, this suggests



4a **4b**

FIGURE 3 Hawthorne and coworkers have prepared a square (**4a**) and a triangle (**4b**) from mercuric acid and a carborand ligand. The triangle self-assembles in the absence of a guest, but if the reaction is performed in the presence of a templating anion, the square forms. Red spheres are boron atoms, black spheres are carbon (adapted from Ref. [26]).

that the smaller triangular structure is thermodynamically preferred in the absence of a templating halide ion. This structure, once formed, appears to be kinetically inert and able to bind chloride ions in its cavity rather than reassembling into the square array, which was formed as the thermodynamic product in the presence of halides.

Helicates, Circular Helicates and Rings

In general, simple dinuclear helicates (and their *meso* analogues, referred to as mesocates for the remainder of this review) are not spacious enough to house guest molecules. However, in some cases, helicates and mesocates have been shown to bind small guests such as solvent molecules or alkali metal cations along the helical axis or within clefts of the clusters [39,40,43,109–112].

An early $[Ti_2L_3]^{4-}$ mesocate is capable of binding alkali metal cations between the two titanium centers coordinated by catecholate ligands [112]. A similar Ti_2L_3 mesocate (**5**), shown in Fig. 4, only forms in the presence of small alkali metal cations such as Li^+ or Na^+, as reported by Albrecht [110]. In the absence of such guest molecules, an oligomeric mixture (or "dynamic combinatorial library") [45] forms. Addition of $LiClO_4$ or $NaClO_4$ to the potassium salt of the oligomeric mixture effected transformation to the mesocate in a matter of hours, as confirmed by NMR spectroscopy. Albrecht and coworkers again observed similar results with a di(8-hydroxyquinoline) ligand, where an oligomeric mixture is present unless a suitable guest cation is used to drive assembly of the desired M_2L_3 species [113].

An appropriate choice of counterion was again vital in the assembly of the heterometallic mesocate system of Wong and coworkers [40,114]. The $M_2M'_3L_6$ mesocate (**6**) shown in Fig. 5 was formed in a stepwise manner if Cs^+ was employed as the counterion. The first step involved synthesizing the Cs^+ salt of the M(IV)-triscatecholate complex. Treatment of this with *cis*-$PdBr_2(PhCN)_2$ resulted in formation of the desired mesocate. In the solid state, this large cesium cation occupies the three molecular clefts and binds to the *endo*-catecholate oxygens of the cluster. Remarkably, the use of diazobicyclooctane (DABCO) or ammonia as the base effected *self-assembly* of the entire cluster from all 15 components. Again the ammonium or DABCO-H^+ counterions (the conjugate acid of the base used) occupy the clefts of the molecule in the solid state. In solution, the exchange of these cluster-bound guests with free counterions is fast on the NMR timescale.

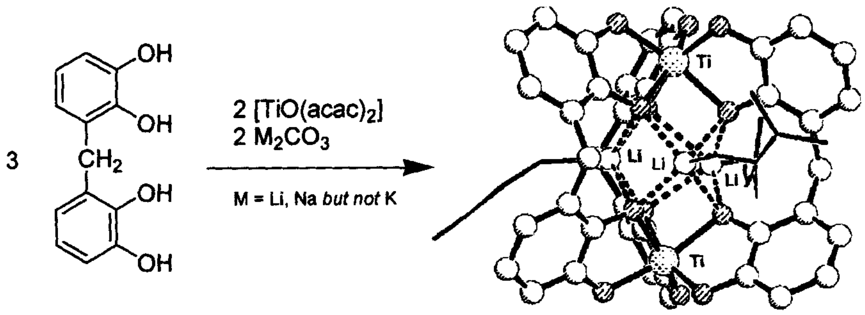


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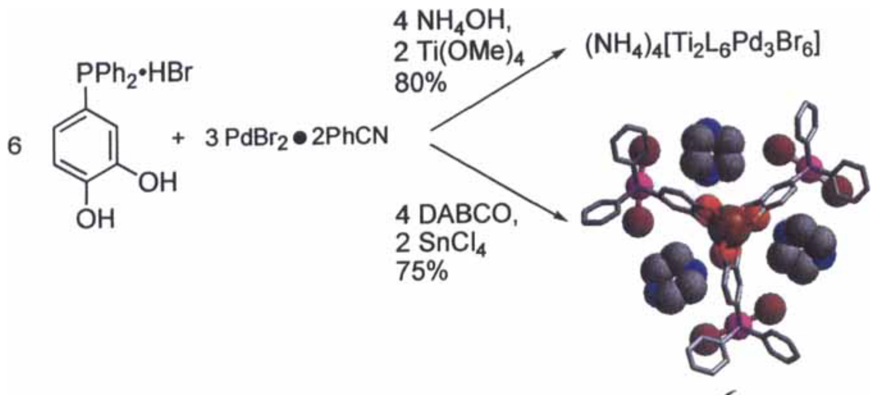
FIGURE 4 Countercation-dependent synthesis of a Ti_2L_3 (**5**) mesocate reported by Albrecht [110]. In the absence of a suitable cationic alkali metal guest molecule, an oligomeric mixture is formed (adapted from Ref. [108]).



6

FIGURE 5 The *self-asssembly* of the pictured mixed-metal mesocates (e.g. **6**) is only possible with an appropriate counterion present. DABCO-H and ammonium (the conjugate acid of the base used) allow for self-assembly of the entire mesocate whereas the use of Cs^+ as a counterion necessitates formation of the structure in a step-wise fashion.

In the aforementioned mesocates, the guest drives formation of the cluster and forms an integral part of the assembly. Raymond and coworkers reported a very early example of a helical M_2L_3 supramolecular cluster which traps a water molecule within its small cavity during crystallization [39]. This solvent species appears to be innocent during the self-assembly processes. In order to further probe the role of the guest in the formation of helicates and mesocates, Raymond and coworkers [43] explored the system shown in Fig. 6 in which a ligand is able to assemble *both* structure types with a guest dependent equilibrium between the two isomers.

To determine if a helicate to mesocate equilibrium could be observed in solution, the di(2-hydroxy-3-pyrdinone)-based ligand in Fig. 6 was synthesized [43]. First, the flexible three-carbon chain backbone contained in the ligand allows for structural changes in the resulting complexes. Secondly, the ligand has two methyl groups on the middle carbon of the backbone. These two methyl groups were designed as stereotopic probes and allow for facile determination between a D_3 symmetry helicate and a C_{3h} mesocate in solution by ^{1}H NMR spectroscopy. In the former case, the methyl groups are related by a two-fold axis, in the latter case, the methyl groups are inequivalent, residing on the mirror plane of the cluster.

Treatment of this ligand with $Ga(acac)_3$ in refluxing methanol generated the mesocate **7** pictured in Fig. 6. Remarkably, this species exists in a guest-dependent equilibrium with the helicate **8** in DMSO solution. DMSO is too large to be a favorable guest for the helicate and thus the mesocate is greatly favored. However, addition of water (a good-sized guest for the helicate) to this DMSO solution shifted the equilibrium towards the helicate. This process is entropy driven, presumably the result of solvent liberation upon desolvation of the guest. The single crystal X-ray structure of the Ga_2L_3 mesocate (**7**) and a related Al_2L_3 helicate shed light on this phenomenon. It was determined that the metal–metal separation in the mesocate is over 2.5 Å larger than in the guest-bound helicate. This shortening of the metal–metal distance creates a pocket inside the helicate as the ligands bow out away from the guest to allow for hydrogen bonding between the endohedral catecholate oxygens and the bound water molecule.

To increase cavity sizes in these two-dimensional clusters, rings and circular helicates of higher nuclearity have been prepared, which

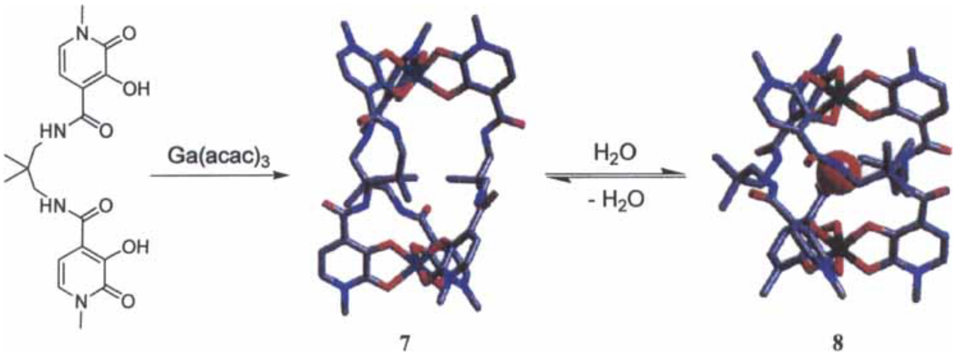
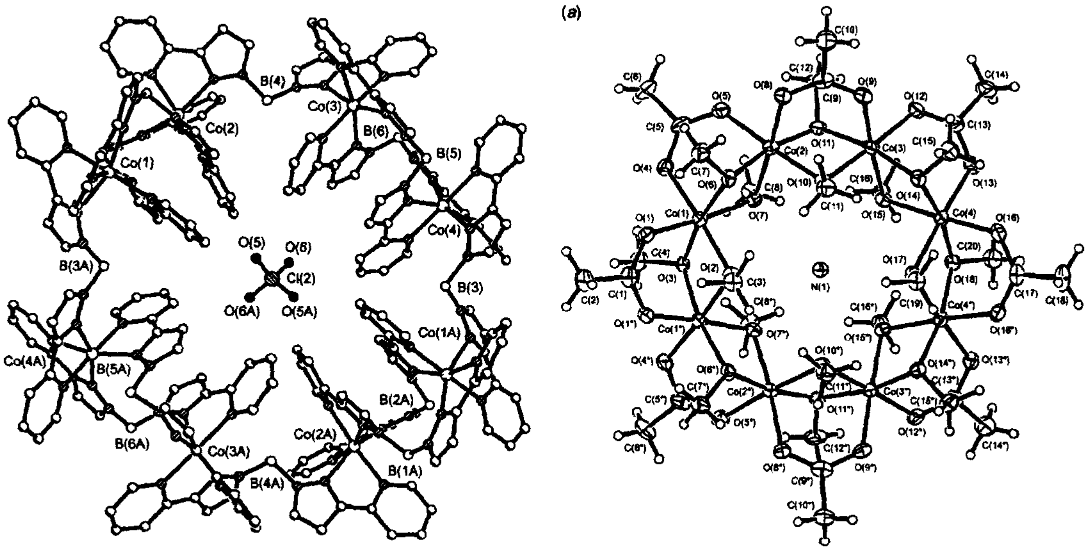


FIGURE 6 The ligand pictured at left self-assembles with Ga(III) to form a *meso*-Ga_2L_3 complex (**7**). In the presence of a small guest molecule, such as water (red spere), the mesocate exists in equilibrium with a helical Ga_2L_3 (**8**) complex. The helicate has a shorter Ga–Ga distance, thus the ligand buckles out to allow for guest encapsulation.



9 **10**

FIGURE 7 The circular helicate of McCleverty, Ward and coworkers (**9**) binds small anions such as perchlorate and hexafluorophosphate. The ring of Masters and coworkers (**10**) binds ammonium cations in the solid state. The role of these guest molecules in the self-assembly process is not clear, but the guests were necessary for single crystal growth (reproduced from Refs. [29 (**9**),28 (**10**)] with permission from The Royal Society of Chemistry).

often bind small guest molecules within the circular host. An octanuclear circular helicate (**9**) binds small anions such as perchlorate [29] and a toroidal inclusion complex (**10**) [28] binds ammonium cations in the solid state (Fig. 7). In both of the preliminary reports on these clusters, the authors remark that the central guest molecules may act as templates in these self-assembly reactions. In the case of **9**, no evidence of anion binding in solution was presented, and the authors suggested that perhaps the ring forms during crystallization. The toroidal complex **10**, however, binds the ammonium cations in solution, as determined by the downfield shift of the hydrogen resonances in the ^1H NMR spectrum. At the very least, these clusters seem able to encapsulate a counterion, and this guest facilitates crystal growth.

Lehn and coworkers [35,36,115] have prepared a variety of tetra-, penta- and hexa-nuclear

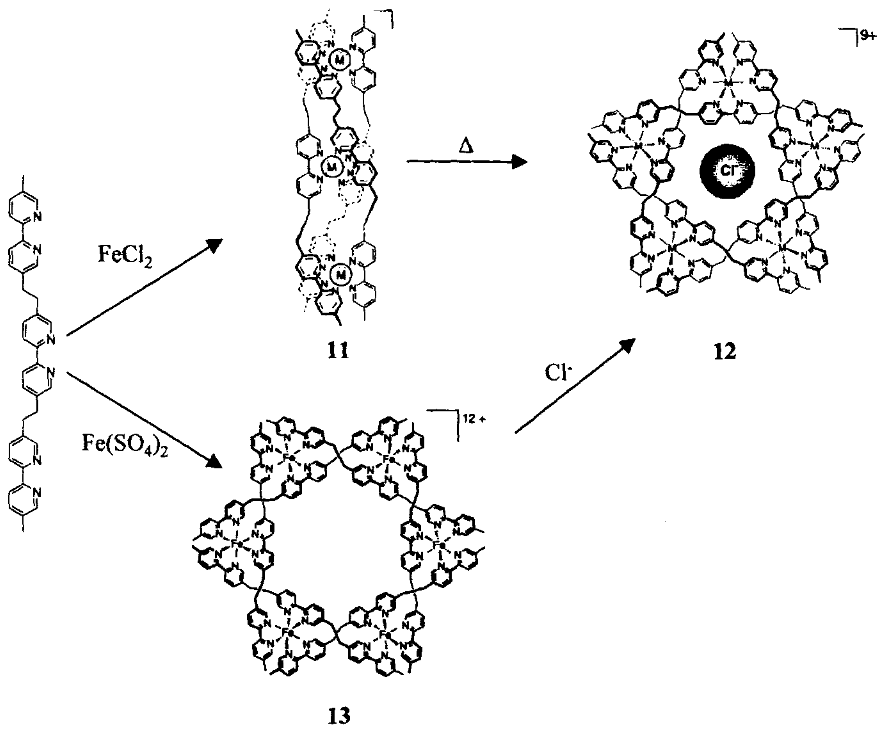


FIGURE 8 With FeCl$_2$, the pictured ligand forms a trinuclear triple helicate (**11**) as a kinetic product. Prolonged heating effects transformation to the thermodynamic product, pentanuclear circular helicate **12**. Additionally, the same ligand self-assembles hexanuclear circular helicates (**13**) with Fe(SO$_4$)$_2$. This species can be quantitatively converted to **12** upon anion exchange with chloride (adapted from Refs. [113 (**11** and **12**),35 (**13**)]).

circular helicates. In particular, Fig. 8 depicts a ligand system that is capable of forming *both* penta- and hexa-nuclear helicates, as well as a trinuclear triple helicate. The tris(bipyridyl) ligand pictured in Fig. 8 formed a trinuclear triple helicate (**11**) with FeCl$_2$ as a kinetic product after about 50 min. Prolonged heating of this solution effected complete transformation to the thermodynamically favored pentanuclear circular helicate **12** in 24 h. The authors were careful to point out that the linear helicate is not necessarily a mechanistic intermediate in this pathway. Furthermore, the smaller helicate **11** should be entropically favored over the circular helicate **12**, therefore some other factor, e.g. guest binding, is responsible for the thermodynamic stability of the circular helicate [115].

Further investigations into the self-assembly of the ligand pictured in Fig. 8 with various ferrous salts have revealed even more intriguing results. In particular, treatment of the ligand with Fe(SO$_4$)$_2$, Fe(SiF$_6$)$_2$ and Fe(BF$_4$)$_2$ lead to formation of a hexanuclear circular helicate. Use of FeBr$_2$ lead to a mixture of penta- and hexa-nuclear helicates. The authors suggest that the anion is capable of selecting the most stable host structure from a "virtual combinatorial library" of hosts [35]. Each member of this library thus represents the entire library itself, since each cluster is labile and exists in a dynamic equilibrium. To verify this hypothesis, the sulfate anion of **13** was exchanged with chloride to effect complete conversion back to the pentanuclear helicate **12**.

Metallacrowns

Pecoraro and coworkers prepared the first examples of the compounds they termed

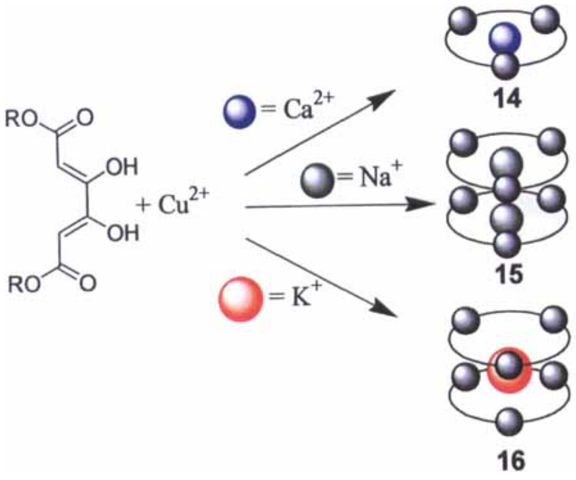


FIGURE 9 Depending on the size of the cationic guest molecule employed, Saalfrank and coworkers formed metallacoronate **14**, double-decker metallacrown **15** or metallacryptate **16**.

metallacrowns, inorganic analogues of the crown ethers [32]. These inorganic macrocycles have internal cavities similar to the ring topologies discussed above that are capable of guest biding. In one case, a [9]-metallacrown-3 is capable of forming a sandwich compound, a metallacryptate (e.g. **16**), around a sodium ion. This cation is presumably necessary for the formation of the structure; however, four bridging hydroxyl groups between the faces of the metallacrowns also hold the cluster together. Pictured in Fig. 9 is an example in which a bis(bidentate) ligand forms three different structure types depending on the guest molecule [116]. Metallacoronate **14** self-assembled when Ca^{2+} was used as the counterion. When the larger Na^+ was used, triple-decker metallacrown **15** assembled. The use of K^+ as counterion resulted in the assembly of the metallacryptate **16**—presumably the large size of the potassium cation prevents a 1:1 metallacrown to cation complex from forming.

For even larger metallacrowns, the guest molecule dictates the size of the ring formed [30]. Depicted in Fig. 10 is a schematic representation of the self-assembly of trisethanolamine with ferric chloride reported by Saalfrank and coworkers. In the presence of small guest cations such as sodium, $Na^+\subset$[12]-metallcrown-6 systems are formed (**17**). The sodium ion is able to select from all the possible iron-trisethanolatoamine oligimers the thermodynamically preferred [12]-metallacrown-6 host–guest complex. The authors therefore predicted that larger guest cations would assemble even larger rings. Gratifyingly, treatment of the ligand with ferric chloride in the presence of cesium cations generates $Cs^+\subset$[16]-metallacrown-8 (**18**). This is another striking example of the guest molecule selecting the most stable host from a dynamic equilibrium between the labile metal and ligand components.

THREE-DIMENSIONAL CLUSTERS

We have seen previously that guest molecules often dictate the geometries of two-dimensional metal–ligand clusters either by allowing access to multiple topologies or by allowing self-assembly of clusters previously unattainable. In this section, the role the guest molecule plays in the self-assembly of three-dimensional clusters is discussed. This includes cases in which three-dimensional and two-dimensional clusters exist in equilibrium.

Coordination Nanotubes

This section will begin with the work of Fujita and coworkers, who have produced many of the most elegant examples of *guest molecules* which truly control the topologies of *three-dimensional* metal–ligand clusters. To begin with, Fig. 11 depicts the only structurally characterized "coordination nanotube" synthesized in their laboratories (**19**). Fujita and coworkers have also reported the synthesis of larger nanotubes from tetra- and penta- pyridyl analogues of this ligand [117]. In all cases, the presence of the rodlike guest molecule 4,4′-biphenylenedicarboxylate was necessary to effect nanotube formation. In

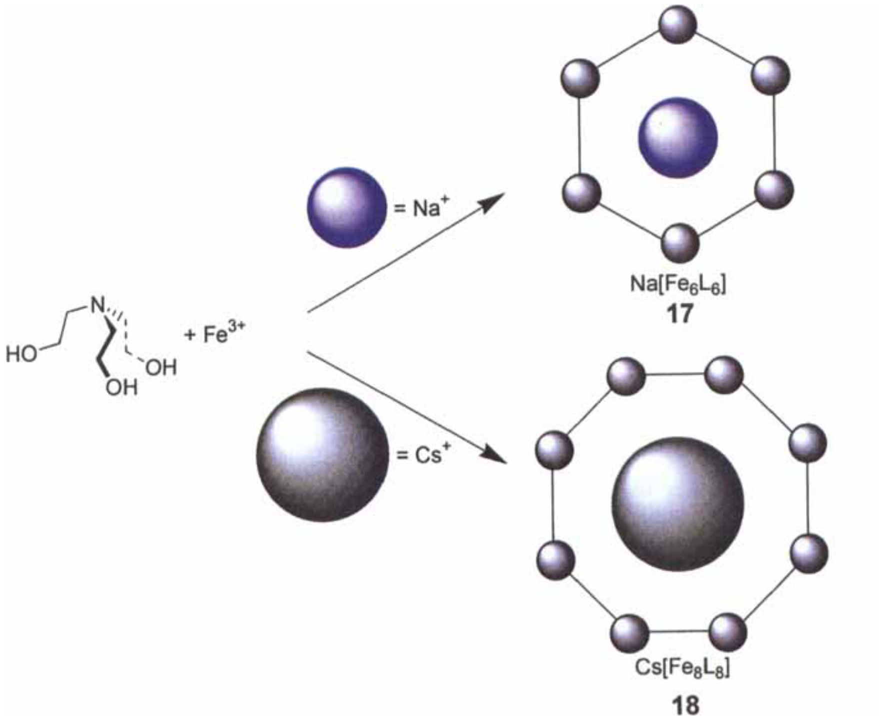


FIGURE 10 Saalfrank and coworkers found that trisethanolamine is able to assemble hexanuclear metallacrowns using sodium cation as the guest molecule. In the presence of Cs cations, the more spacious octanuclear cluster is formed to accommodate the larger guest ion.

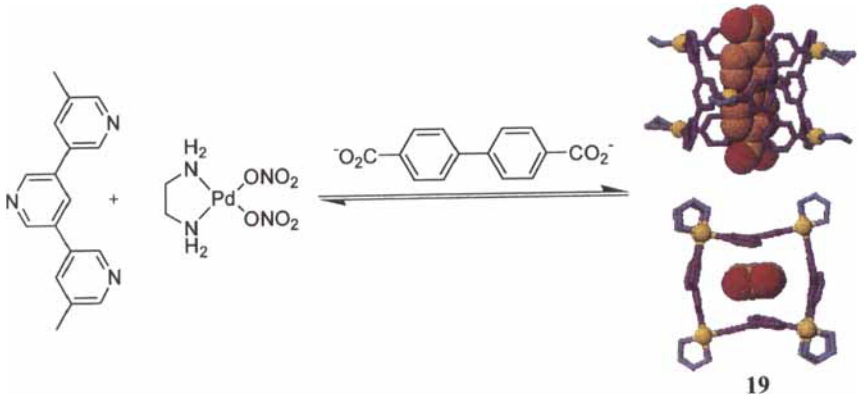
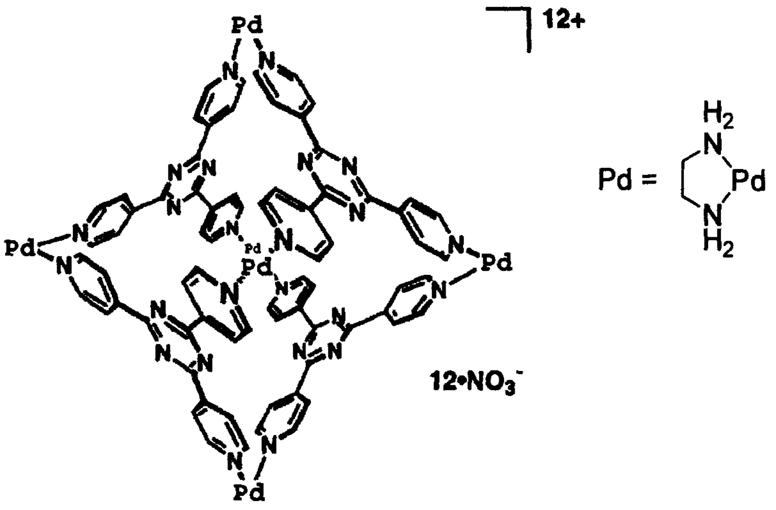


FIGURE 11 The coordination nanotube **19** only forms in the presence of a suitable rodlike guest molecule. In the absence of the guest molecule, an oligomeric mixture is present, which can be converted to the nanotube upon formation of the host–guest complex (adapted from Ref. [115]).

the absence of the guest molecule, an oligomeric mixture results even upon using reaction times of one week at elevated temperatures. Addition of the guest molecule transforms the oligomeric mixture into the corresponding nanotubes within 1 h. Remarkably, the guest molecule can be extracted from the host resulting in destruction of the nanotube. Upon the addition of a guest molecule, the nanotube is regenerated, showing formation of the host–guest complex is



20

FIGURE 12 In the M_6L_4 tetrahedron from Fujita and coworkers (**20**) the metals reside on the edges of a tetrahedron and the three-fold symmetric ligands comprise its faces. Four molecules of adamantyl dicarboxylate were found embedded in holes at the corners of the tetrahedron, and their presence was necessary for single crystal growth (adapted from Ref. [17]).

a completely reversible process. This is another elegant example of a guest molecule allowing formation of an intricate metal–ligand cluster through formation of a host–guest complex.

Tetrahedra and Adamantanoids

Saalfrank and coworkers [58] synthesized the first tetrahedral metal–ligand cluster, an adamantanoid M_4L_6 structure with molecular *T*-symmetry. This molecule forms in high yield from very simple starting materials and its self-assembly does not rely on a guest molecule. Fujita and coworkers [46] then reported the next *T*-symmetry metal–ligand cluster (**20**) with their system shown in Fig. 12. Again, the synthesis of this molecule does not rely on a guest molecule (according to NMR spectral data); however, the single crystal X-ray structure of the cluster reveals four guest molecules filling the large void volume of the cluster. Raymond and coworkers [52,118] have also shown that single crystal growth necessitates the use of a guest in two of their systems in which the guest molecule is not vital for cluster formation in solution. These findings have paved the way for exploring a variety of guest-assisted self-assembly reactions to form tetrahedral clusters.

Cationic M_4L_6 tetrahedral clusters (Fig. 13) have been assembled around tetrafluoroborate anions by McCleverty, Ward and coworkers [48] and Huttner *et al.* [47] In the case of **21**, Huttner and coworkers state "for cages of an appropriate size, counterions of matching symmetry could be incorporated into the framework of the host molecule." Indeed, a tetrahedral anion is encapsulated within their host molecule, according to NMR spectroscopic data and X-ray crystallographic data, but it is unclear whether this guest molecule is vital for cluster formation. In the tetrahedron **22**, the tetrafluoroborate anion comprises an essential component of the cluster. In the absence of this templating anion, an M_2L_3 species forms, suggesting that the tetrahedron may exist in equilibrium with the smaller, entropically favored dinuclear complex. However, no evidence for this equilibrium has been observed to date. A similar M_4L_6 tetrahedron with a cavity larger than that of **22** has recently been reported by McCleverty, Ward and coworkers [119]. However, no guest molecules were found inside this large tetrahedron in the

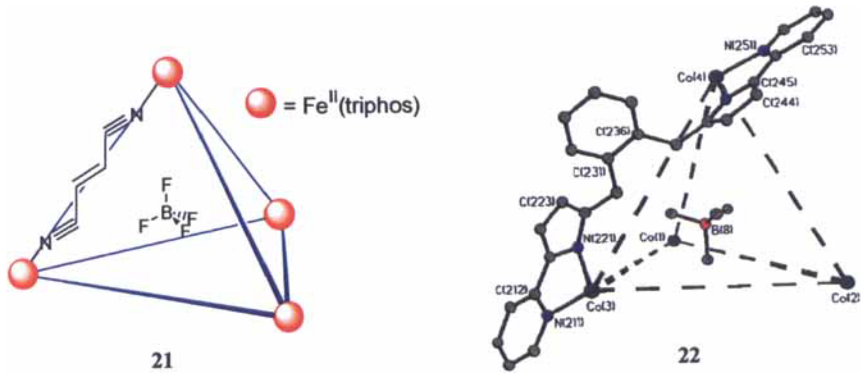


FIGURE 13 The tetrahedron synthesized by Huttner and coworkers (**21**) self-assembles around a BF_4^- counteranion. This guest molecule may be necessary for cluster formation. The tetrahedron at right, **22**, synthesized by Ward, McCleverty, *et al.* also forms around a BF_4^- anion. Here a host–guest complex is formed, where in the absence of the guest molecule, a dinuclear M_2L_3 structure presides (the figure for **22** was adapted from Ref. [46]).

solid-state structure, nor has any evidence of guest inclusion been reported in solution. (The abundance of diffuse electron density inside the cavity in the Fourier difference map suggests the presence of severely disordered solvent within the cluster in the solid state.)

Truncated tetrahedra that encapsulate small solvent molecules have been synthesized from metal-assisted self-assembly reactions (Fig. 14). The M_6L_4 stoichiometry cluster **23** reported by Steel and Hartshorn [120] is derived from a three-fold symmetric ligand comprising the faces of a tetrahedron. The solid-state structure revealed a disordered DMSO molecule within the cavity of the cluster. Presumably, the solvent molecule merely occupies void volume inside the cluster without actually driving the self-assembly. The tetrahedron of Cotton and coworkers [72] (**24**) also has a severely disordered solvent molecule within its cavity. These authors are careful to note that the use of a template or guest molecule is *not* necessary for cluster formation, although they are mindful of this possibility in their systems. However, would the use of a solvent that is too large to fit within the cluster still allow for cluster formation under similar reaction conditions?

In the preceding examples, the self-assembled tetrahedra contained guests, but either the guest molecule was not vital for cluster formation or its role in the self-assembly process was not clear [121,122].[#] It is interesting to note at this point, however, that solvent molecules are often found to occupy the space within these large cavities. Presumably, this is just a result of solvation and the size and shape of the solvent is not very important to cluster formation. Rather, the solvent is just filling a vacuum and solvating the interior of the cluster. More systematic studies on the role of solvent, as well as guests, are needed to fully understand these self-assembly processes and to elaborate further the design strategies for these clusters. In the remainder of this section, systems are discussed in which the guest molecules clearly play a role in the self-assembly of metal–ligand clusters.

A naphthyl-dicatecholamide ligand that was used to assemble early examples of M_4L_6

[#] Mingos, James and coworkers and Saalfrank *et al.* have described adamantanoid structures in which counterions on the outside of the cluster seem to assist the self-assembly of the clusters. In particular, Mingos, James *et al.* have explored the use of a variety of weakly coordinating anions in assisting their reaction and determined that only triflate effectively suits this purpose. Saalfrank *et al.* have synthesized adamantanoid tetrahemispheraplexes capable of binding ammonium on the periphery of the tetrahedral cluster. These external cations can then be exchanged with alkylammonium cations.

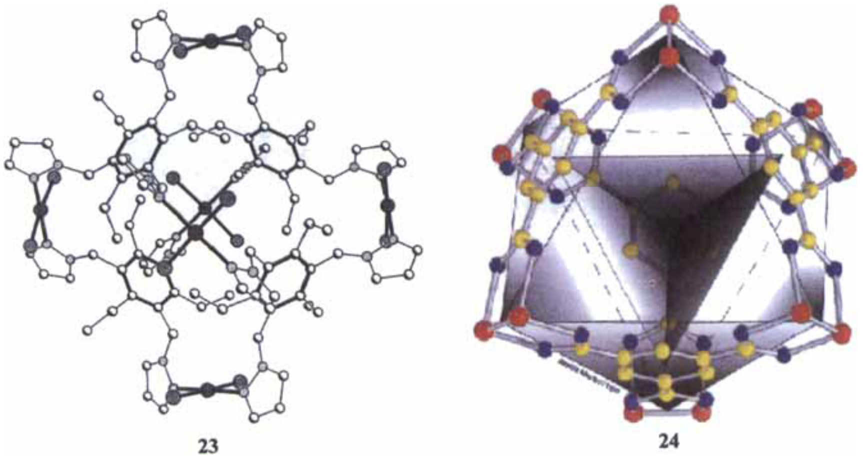


FIGURE 14 The tetrahedron of Steel and Hartshorn (**23**) assembles with a molecule of DMSO encapsulated in the cluster cavity. The solid state structure of the cluster of Cotton, Murillo and coworkers (**24**) contains a disordered CH_2Cl_2 molecule in its cavity. Presumably, these solvent guest molecules do not play a role as templates in these self-assembly processes (figures reproduced from Refs. [118 (**23**),70 (**24**)] with permission from The Royal Society of Chemistry).

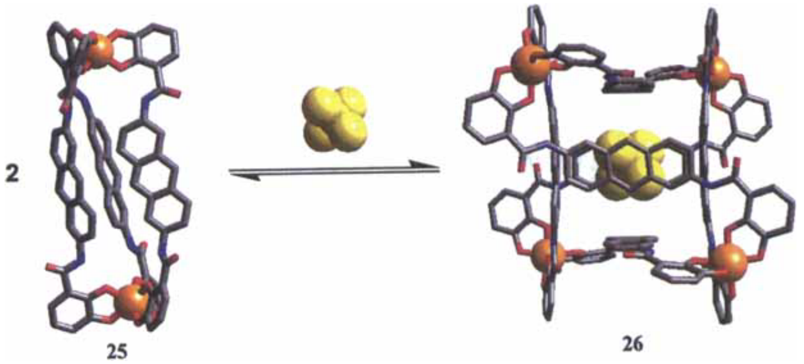


FIGURE 15 The anthracenyl dicatecholamide ligand of Raymond and coworkers assembles with tri- and tetra-valent metals to form an M_2L_3 helicate (**25**). The binding of a small cationic guest molecule completely transforms the helicate into an M_4L_6 tetrahedral host–guest complex (**26**). The yellow space-filling model represents tetramethylammonium.

tetrahedral clusters with trivalent metal ions was reported by Raymond and coworkers [52]. This tetrahedron has a cavity of *ca.* 300 $Å^3$ and forms in solution in the absence of suitable guest molecules. To enlarge the cavity of this cluster an anthracene spacer was employed between the two catecholamide binding units using the same ligand design [51]. Remarkably, this tetrahedron (**26**) only forms in the presence of suitable cationic guest molecules (Fig. 15). In the absence of such a guest molecule, the entropically favored M_2L_3 helicate (**25**) forms. Figure 15 depicts the solid state structures of these clusters. NMR and UV/vis spectroscopic data have been used to confirm this equilibrium in solution. The binding of a guest molecule to form a host–guest complex is sufficient to force the equilibrium to the tetrahedral cluster, as determined by ^1H NMR spectroscopy.

Expanding on this biscatecholamide design strategy, a similar system using pyrene as the ligand backbone was examined [123]. In this case, the bulky pyrene ligand prevents helicate formation according to molecular models (MM3) [124]. Indeed, this ligand self-assembles with Ga(III) and Fe(III) to form M_4L_6 tetrahedra (**27**) but

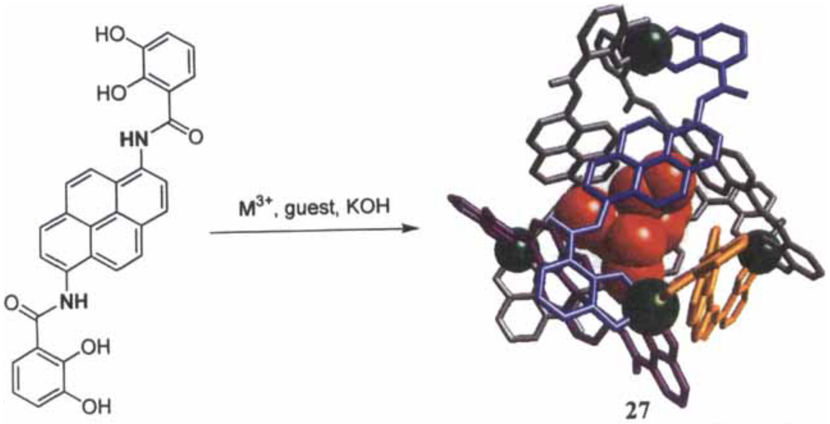


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FIGURE 16 The pictured pyrene biscatecholamide ligand of Raymond and coworkers assembles to form a tetrahedral M_4L_6 host–guest complex (**27**) with small cationic guests. Tetraethylammonium is the guest in the solid-state structure above, represented as a red space-filling model.

only if a suitable cationic guest is present (Fig. 16). The guest (tetraethylammonium is pictured in Fig. 16) comprises an integral component of this host–guest complex, and formation of this host–guest complex is the thermodynamic driving force for cluster formation.

Cavity-containing clusters using combinations of these biscatecholamide ligands have also been reported by Raymond and coworkers [125]. By combining several different M_4L_6 tetrahedral clusters with $M_2L'_3$ helical clusters in the presence of excess guest molecules, libraries of supramolecular $M_4L_nL'_{6-n}$ tetranuclear clusters form. These were characterized by high-resolution electrospray mass spectrometry and NMR spectroscopy. For every characterized member of the library, a guest molecule was encapsulated within the cluster cavity. In fact, tetranuclear clusters were formed which incorporated ligands that do not themselves form tetrahedral $M_4L'_6$ structures. Apparently, the strong thermodynamic driving force provided by the assembly of a stable host–guest complex is enough to drive formation of clusters that do not otherwise form in the absence of a guest.

An alternative approach to synthesize molecular tetrahedral clusters by using three-fold ligands to comprise the face of the tetrahedron has been developed by Fujita and coworkers [46]. More recently, they have synthesized a ligand, which does not fit the strict geometric requirements for tetrahedral cluster formation. Rather than using a flexible ligand backbone to suit this purpose, they have broken the C_3 symmetry of the triangular ligand to allow the ligand "faces" to assemble in multiple ways when forming clusters (Fig. 17) [126]. Remarkably, the self-assembly of several different clusters with the ligand is driven by host–guest interactions.

Figure 17 depicts the single crystal X-ray structure of the pseudo-tetrahedron (**28**) that results from the self-assembly of the C_2 symmetry triangular-shaped ligand with Pd(II) in the presence of CBr_4. This cluster does not have tetrahedral symmetry, but topologically, it is equivalent to a tetrahedron with four triangular ligands comprising the cluster faces. In this structure, the authors note that the ligands self-assemble in an "antiparallel" arrangement with the pyrimidine ligands *cis* to a pyridine ligand coordinated to Pd(II). This cluster forms a closed shell capable of encapsulating small tetrahedral guests such as CBr_4. Alternately, the triangular ligands can self-assemble in a "parallel" fashion. Indeed, when dibenzoyl is used as a guest in the self-assembly reaction, an open cone square pyramidal structure is formed, **29**. In this M_8L_4

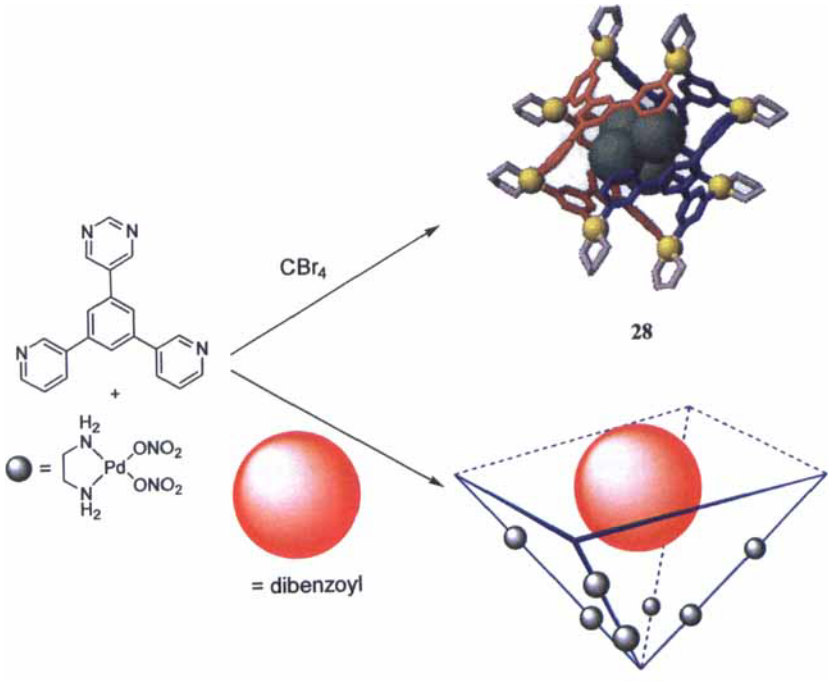

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FIGURE 17 The triangular ligand of Fujita and coworkers forms a tetrahedral-shaped (**28**) cluster when CBr_4 is used as a guest. Alternately, the use of a larger guest like dibenzoyl effects formation of the open cone square pyramid **29**. In the absence of a guest, **29** exists in equilibrium with a trigonal pyramidal open cone (adapted from Ref. [124]).

structure, all four pyrimidine moieties are located at the apex of a square pyramid and are coordinated in a *cis* geometry to each of the three Pd(II) cations (bottom right, Fig. 17). The authors also observed a smaller open cone *trigonal* pyramidal M_6L_3 structure at high concentrations in the absence of a guest molecule. This trigonal pyramidal cluster can be converted to the square pyramid **29** upon addition of a guest such as dibenzoyl. This cluster can then in turn be converted to the tetrahedral cluster **28** upon addition of excess CBr_4.

Cages, Hexahedra and Cubes

This section will begin with the smallest examples of three-dimensional cages formed through "induced fit molecular recognition," another elegant system developed by Fujita and coworkers [71,127,128]. Although, not a three-dimensional structure in the strict sense of the definition provided earlier, the authors describe these clusters as cages and their inclusion here is thus more appropriate. Figure 18 depicts the synthesis of four different Pd_3LL' clusters, all of which form as the result of an "induced fit molecular recognition." In other words, the formation of the most stable host–guest complex from a mixture of **30**, **31**, the Pd(II) source and a guest drives these self-assembly reactions to one of the four structures.

The treatment of only **31** with palladium(ethylenediamine)dinitrate resulted in the formation of homodimeric cluster **31**·**31**, which exists as two structural isomers (**a** and **b**), a result of the dissymmetry in ligand **31** [71]. These two homodimers exist in a guest-driven equilibrium. Treatment of **31** with palladium(ethylenediamine)-dinitrate resulted in an oligomeric mixture. This mixture is converted to homodimer (**31**·**31**)**a** upon addition of spherical guests such as CBr_4 or $CBrCl_3$. Addition of the flatter guests

1,3,5-benzenetricarboxylic acid or *p*-xylene to the oligomeric mixture effected transformation to the homodimer (**31**·**31**)**b**. Hence, these two homodimers can be interconverted if a solution of the host–guest complex is flooded with a guest better suited for the other cluster. This demonstrates the induced fit molecular recognition of substrates by assembly interconversion put forward by these authors and others [105,127].

Fujita and coworkers have also reported that **30** assembles homodimers in high yields only in the presence of suitable guest molecules [127]. Furthermore, this dimer maintains its integrity even upon removal of the guest, demonstrating an example of the classical template effect outlined by Busch [76]. With these results in hand, Fujita and coworkers utilized both **30** and **31** in the same self-assembly reaction in an effort to generate an even larger library of assemblies. Indeed, these two ligands are capable of making homo- and hetero-dimers when self-assembled with appropriate guest molecules and Pd(ethylenediamine)$(NO_3)_2$ (Fig. 18) [128]. As expected from molecular models, spherical guests are preferentially encapsulated in the more spherical cavities of the heterodimer **30**·**31** and homodimer (**31**·**31**)**a**, although all four species are present to some extent depending on the guest present. The shapes of the cavities were inferred from molecular modeling studies, and the guest binding preferences were determined by NMR spectroscopy.

In addition to studying the role of anions in the self-assembly of tetrahedra, Mingos and coworkers [70] have also explored the role anions play in the self-assembly of larger coordination clusters. A Ni_6L_8 cage complex was synthesized using a thiourea ligand coordinated to nickel. The solid-state structure of this complex reveals a chloride anion completely sequestered within the cage architecture. Interestingly, the use of other anions to promote the self-assembly results in the formation of only simple salts of NiL_2. Treatment of these salts with stoichiometric amounts of chloride or bromide effected transformation to the cage compound. The authors do not report whether the anion can be removed from the cage or whether the cage exists in equilibrium with the simple monomer, although the latter seems likely.

Two cage systems in which alkali metal cations play a role similar to that of the chloride anion discussed above were presented by Rauchfuss and coworkers [64,69]. When the molybdenum tricarbonyl starting material shown in Fig. 19 reacts with stoichiometric amounts of cyanide ions and potassium cations, a trigonal prismatic cage species assembles (**32** in Fig. 19). This structure is only formed in the presence of a potassium cation source and the potassium ion is encapsulated in the final structure. In the absence of this guest molecule, a square forms (**33**) if only one equivalent of CN^- is used. (In the presence of an excess of CN^- a "corner" of the prism is formed.) The authors do not mention if the trigonal prism remains intact if the potassium ion is removed from the structure.

Early examples of molecular cubes from cyanometallate fragments have been reported by Rauchfuss *et al.* [129] and Long and coworkers [65]. Neither of these early examples exhibited host–guest chemistry inside the cationic clusters. To facilitate cation binding within the cubes, Rauchfuss and coworkers [64] have synthesized an anionic analogue of their earlier structure. Surprisingly, not only is cation binding facilitated within the cavity of this cube, it is necessary for cluster formation. In the absence of an alkali metal guest, such as K^+ or Cs^+, a mixture of species forms. Furthermore, the cube has a cavity slightly too large to accommodate a potassium cation, thus cesium is bound much more strongly than potassium and is capable of displacing bound K^+ from the cluster cavity.

An analogue to their earlier cyanometallate cube structure was reported by Long and coworkers in which $Ni(CN)_4$ moieties make up the faces of an enlarged molecular cube (**35** in

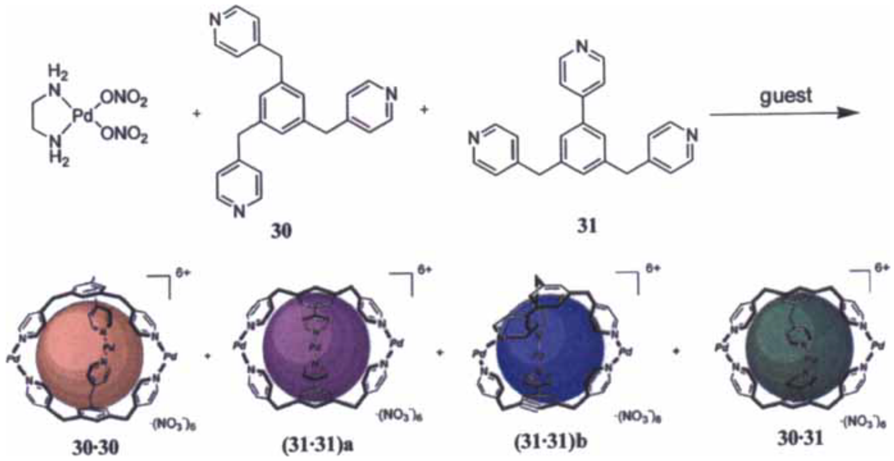

FIGURE 18 The treatment of ligands **30** and **31** with various guests in the presence of a suitable Pd(II) source results in a library of various homo- and hetero-dimeric assemblies. The relative abundance of the various clusters is driven by host–guest interactions; the host with the best-fit cavity for a given guest is favored (adapted from Ref. [126]).

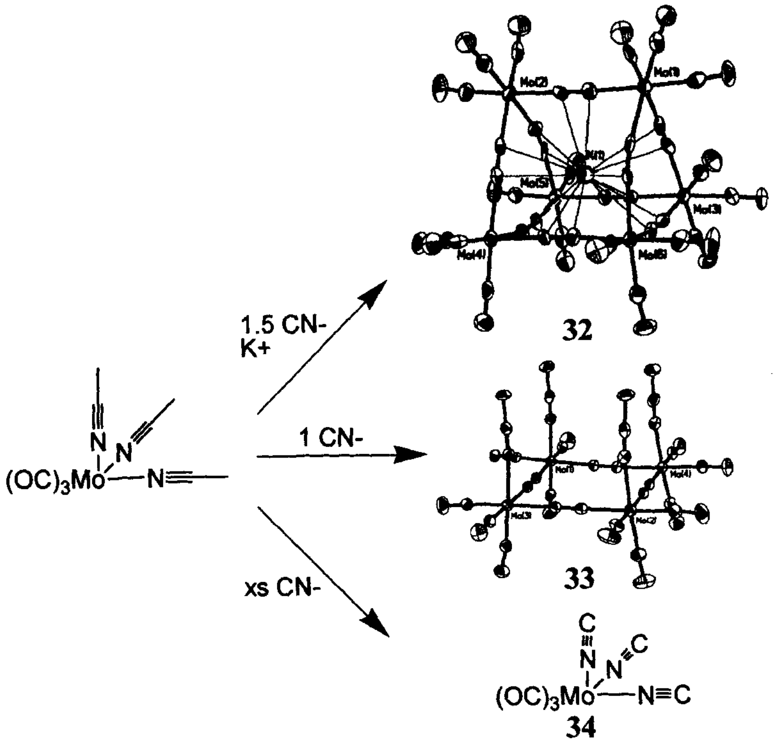

FIGURE 19 Rauchfuss and coworkers have reported that the trigonal prismatic structure **32** only forms in the presence of potassium cations. In the absence of this guest either the square **33** or the monomeric complex **34** forms (adapted from Ref. [67]).

Fig. 20) [130]. Interestingly, one face of the cationic cube is missing which makes the structure resemble more of a barrel with an opening of 0.6 Å. The inside of this "barrel" houses one iodide counteranion arising from the NiI_2 starting material. It appears likely that this counterion comprises part of a host–guest complex and is necessary for cluster formation;

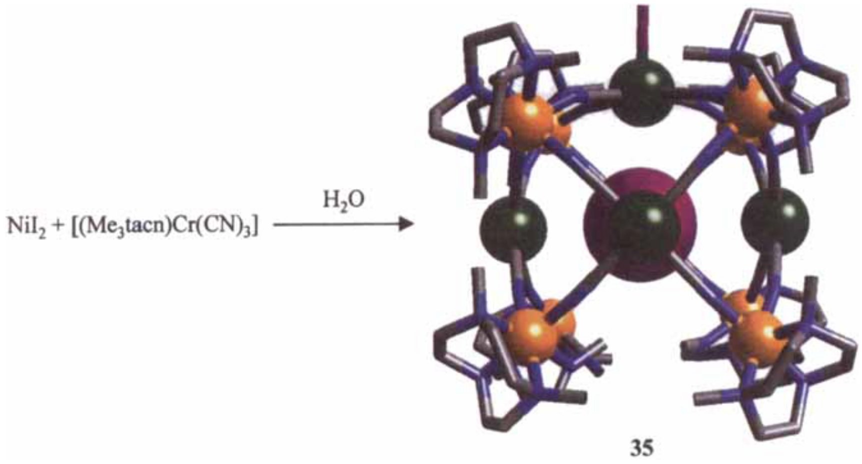

FIGURE 20 Long and coworkers reported a large cube-shaped cluster formed with Cr atoms at the corners (orange spheres) and Ni atoms comprising five of the six faces of the cluster (green spheres). An iodide anion (purple sphere) is trapped inside the cube during cluster synthesis. The ligands are represented as wireframes with carbon grey and nitrogen blue.

efforts to form this structure with other Ni(II) starting materials have failed [131].

Although they fall outside the scope of this review, several related large clusters are worth mentioning. Fujita and coworkers [132] have reported a "molecular nanobowl" possessing a hydrophobic pocket. This bowl-shaped molecule homodimerizes around organic guest molecules. This dimer does not self-assemble as the result of metal–ligand interactions. Nanoscale molecular dodecahedra [73] and cuboctahedra [63] have been reported by Stang and coworkers. These molecules lack solid state structural characterization and no solution data have been reported discussing host–guest chemistry. Thus, the contents of the large cavities in these molecules are unknown. In solution, these large molecules presumably encapsulate many solvent molecules, however, the role of these guests is not well understood in the self-assembly process [133]. Robson and coworkers [62] and Hong *et al.* [68] have reported single crystal X-ray structures of octahedra generated from three-fold symmetric ligands. These assemblies both house DMF solvent molecules, but their self-assembly appears to proceed without guest assistance.

SUMMARY

We have seen in this review that many wonderful supramolecular metal–ligand clusters form in which guest molecules either thermodynamically drive cluster formation, allow for induced-fit molecular recognition from a multitude of possible hosts, or play the role of a template in the synthesis. When guest molecules play no role in the self-assembly, even the presence of solvent molecules within the cavities of these clusters indicates that solvation effects within the cluster may contribute to cluster formation. The frequency with which solvent molecules are seen in the cavity of metal–ligand clusters begs an in-depth study of solvent effects in supramolecular self-assembly reactions. Do the electronic and/or steric effects of solvent molecules facilitate/inhibit cluster formation? In one case discussed in this review, Raymond and Parac [43] actually reported a solvent molecule playing a role much more involved than just solvation. Adventitious water molecules present in the DMSO solution were able to act as guest molecules to induce helicate formation over mesocate formation. In fact, as the concentration of water was increased, this equilibrium shifted dramatically to the helicate. In this system, the use of different sized *solvents* actually results in the formation of different cluster topologies. Similar to the solvent effects, characterized in classical physical organic chemistry, can a similar coherent theory be developed for cavity-containing supramolecular systems?

The possibility of forming different structures from metal and ligand components by finding guests that drive formation of either larger or smaller clusters (through induced-fit molecular recognition) remains intriguing. It is becoming increasingly clear that guest molecules, and perhaps solvent molecules, play a powerful role in the self-assembly of metal–ligand clusters. In very few cases discussed in this review are these guest molecules able to be removed from the host, as in the case of classical template reactions. Rather, the guest becomes a part of a new supramolecule, the *host–guest complex*. In many other cases, no attempts were made at removing the guests from the cluster cavity. The clusters were found to contain guests and these assemblies were reported without further details on the host–guest chemistry. A detailed understanding of the role played by these guests in the self-assembly of large clusters will require careful observation and controls.

As clusters become larger, with more spacious cavities, host–guest interactions will be increasingly important in predictive design strategies for forming supramolecular nanoclusters. Relying on serendipity will become obsolete as the size and complexity of these container-type molecules grow. Retrosynthetic analysis of large metal–ligand clusters will mandate starting from the stabilized host–guest complex, analogous to the design of specific ligands wherein the final coordination complex is the starting point in the retrosynthetic analysis. Already metal–ligand nanoclusters have been reported which stabilize reactive species or allow otherwise unlikely reactions to occur within the cluster cavities [17,18,66]. Increasingly, one can envision tailor-made host–guest complexes, formed using a specific guest molecule, targeted to accomplish a specific catalytic or chiral induction function.

Acknowledgements

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