Symmetry-Driven Rational Design of a Tetrahedral Supramolecular Ti_4L_4 Cluster**

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Nature provides examples of noncovalently linked molecular clusters of high symmetry which spontaneously self-assemble from their subunits. Examples include the 24-mer apoferritin and the 60-mer human rhinovirus protein coat, of point group symmetry O and I, respectively. Whereas the individual interactions holding the cluster building blocks together (e.g. H bonds and van der Waals interactions) are reasonably well understood, it is less clear what algorithms control the formation of single clusters of defined stoichiometry and high symmetry, rather than the construction of a variety of shapes or random polymers. Can general building principles for synthetic self-assembly structures with well-defined cavities and symmetries be deduced from the natural structures?[1]

We have answered the question affirmatively by providing a symmetry-based model of cluster formation that both explains the high symmetry clusters found in nature and provides a rational basis for predicting synthetic M_4L_6 clusters.[2a] The building principle of incommensurate coordination numbers rationalizes construction of a M_4L_6 tetrahedron by combination of a ligand of twofold symmetry (tetrahedron edges) and an octahedral metal center with threefold symmetry (tetrahedron vertices).[2]

Here we describe an alternative approach to the formation of symmetric tetrahedral clusters, in which the pseudo-octahedral metal centers (threefold axis) occupy the vertices of the tetrahedron and trigonally symmetric tris-bidentate ligands (threefold axis) occupy the faces. Consider the geometric information of a ligand–metal interaction (Figure 1a). Metals such as Ga^{III} and Ti^{IV} require three bidentate chelating groups in order to satisfy their coordination sphere. In a coordination geometry between octahedral and trigonal-prismatic, these three ligands generate a threefold axis at the metal center. While the geometry of such a complex is often described by the twist angle,[3] here it is convenient to describe this geometry with respect to the orientation of each bidentate ligand. The *approach angle* is defined as the angle between the axis determined by the two donor atoms and the threefold axis of the pseudo-octahedron. An approach angle of 0° corresponds to a trigonal prism, and an angle of 35.3° is typical of "octahedral" tris-catecholate complexes.

With these geometric considerations in mind, the problem of designing a supramolecular assembly based on metal complexes can be reduced to designing an n-fold symmetric ligand that positions its multiple chelate vectors correctly for a cluster of given symmetry, provided that the ligands also satisfy the coordination requirements of the metal of choice: The ligand must allow for the preferred coordination geometry as defined by spatial position—expressed by the approach angles—and the absolute number of the donor groups.[4] In addition, the multifunctional ligand must be designed to avoid multiple coordination to any one metal, since this could result in the formation of complexes of lower stoichiometry.

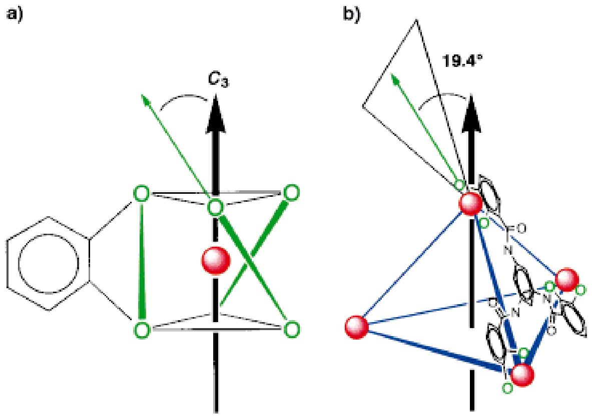

Figure 1. a) Schematic representation of the octahedral coordination environment provided by three bidentate ligands (catecholates). Illustration of the approach angle as defined by the angle between the threefold axis of the octahedron and the axis generated by the two donor atoms of each chelate. b) Identification of this approach angle in a tetrahedral M_4L_4 cluster as the result of the interaction of the planar ligand **4** and metal ions located at the vertices.

A schematic representation of a tetrahedral M_4L_4 cluster in which the faces of the tetrahedron are made up of strictly planar threefold symmetric ligands, and the vertices are made up of pseudo-octahedrally coordinated metal atoms is depicted in Figure 1b. The angle between a threefold axis and the associated faces in a tetrahedron is 19.4°. If the bound ligands are planar and coordinate as shown, this angle corresponds to the approach angle. The experimentally obtained approach angles for Ti^{IV} tris-catecholates are approximately 23.0°.[5] This, in turn, implies that the planar ligand to be used in the formation of a tetrahedral cluster is required to distort only a few degrees from planarity to comply with the ideal approach angle at the Ti^{IV} centers.

Based on the foregoing, the threefold symmetric ligand **4** was designed. The hydrogen bond formed between the amide hydrogen and the coordinating *o*-hydroxy oxygen atom imposes a coplanar arrangement of the amide bond with the catecholate unit.[6] This constraint and the favored coplanarity of the amide group with the central phenyl group produces a rigid system that predisposes the coordinating groups toward the cluster geometry.

The synthesis of **4** followed established routes (Scheme 1). 1,3,5-Triaminobenzene (**1**), derived from the reduction of 3,5-dinitroaniline,[7] was combined with 2,3-dimethoxybenzoyl chloride (**2**),[8] to produce the intermediate **3**. Deprotection of the phenolic hydroxy groups with BBr_3 provided ligand **4** in good yield (>80% over all steps).

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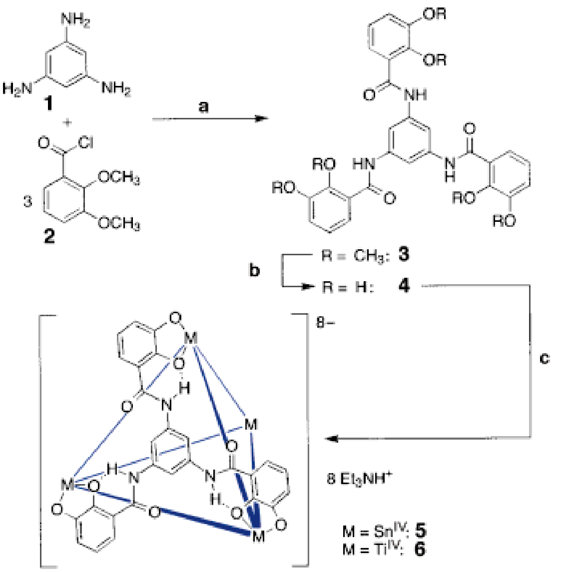

Scheme 1. Synthesis of the tetrahedral cluster. a) Et_3N/CH_2Cl_2. b) 1. BBr_3/CH_2Cl_2, 2. MeOH. c) 1 equiv [Ti(O*n*Bu)$_4$] or $SnCl_4$, Et_3N.

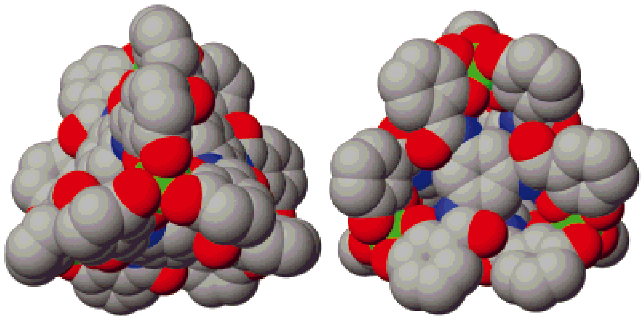

Figure 2. Space-filling model of **6** calculated from the X-ray crystal data and as viewed down the pseudo-threefold axis. Countercations and hydrogen atoms have been omitted for clarity.

Ligand **4** reacts with Al^{III}, Fe^{III}, or Ga^{III} under basic conditions to give precipitates whose ^1H NMR and mass spectra indicated the expected tetrahedral M_4L_4 species.[9] However, the high charge (12^-) of these anions apparently forestalled the formation of diffraction quality single crystals. The overall charge of the cluster is reduced with higher oxidation state metals. Pseudo-octahedral tris-catecholate complexes of both Sn^{IV} and Ti^{IV} are known;[5,10] these cations form tetrahedra **5** and **6**, respectively, but only the Ti^{IV} compound provided crystals of diffraction quality. For brevity this report will be restricted to describing the Ti^{IV} complex **6**.

A solution of [Ti(O*n*Bu)$_4$] in MeOH was combined with **4** in MeOH/Et_3N. After 12 hours, a gelatinous orange precipitation had formed. The ^1H NMR of an [D6]DMSO extract of this precipitate taken at 25 °C shows the presence of a mixture of (polymeric) compounds. Heating of the sample to 120 °C results, in the course of several hours, in a partial simplification of the spectrum. Dissolution of the precipitate in DMF under reflux for 12 hours resulted in a rearrangement of the kinetic product mixture into one thermodynamic product. Gas phase diffusion of MeOH into this DMF solution produced orange crystals of **6**.

Electrospray (ES) mass spectrometry has been useful in the characterization of the supramolecular clusters in solution.[11] Here the well resolved traces of positive ion ES mass spectrometric analysis provided proof of the existence of complex **6** in CH_3CN solution. Furthermore, the spectra showed no species of higher or lower oligomerization than Ti_4L_4. The ^1H NMR of **6** displays its high symmetry. All signals corresponding to the ligand framework are slightly shifted relative to those observed in the uncomplexed ligand.

The single crystal structure provided the ultimate proof of the proposed tetrahedral cluster;[12] a space filling representation is shown in Figure 2. The cluster lies on a crystallographic threefold axis but has molecular symmetry of the rotation group *T*, such that all the metal ions have the same chirality (all Δ or Λ). Hence, the compound crystallizes as a racemate. The eight triethylammonium counterions are highly disordered, and hydrogen-bonded to either the carbonyl or phenolic oxygens of the cluster. There is no evidence that the small cavity of the tetrahedron contains a guest, as observed in some larger M_4L_6 tetrahedra.[2d,2f,13] Despite hydrogen bonds between the amide hydrogen and the phenolic oxygens the catechol amides are more distorted from planarity than required by the design of the cluster. We attribute this to the compulsion of the system to minimize the empty volume of the cavity. This may also be the reason for the larger than expected approach angle of 28°. The distortion of the ligands is best visualized in Figure 3.

One related tetrahedral M_4L_4 cluster has appeared in the literature.[14] Although the formation of this cluster was serendipitous, its structure and formation highlights the building principles exemplified here.

In summary, the threefold axis of a pseudo-octahedral metal center coordinated by three bidentate chelates has been combined with a rigid ligand system of threefold symmetry to drive the formation of a tetrahedral cluster of the stoichiometry Ti_4L_4. This is another example showing that symmetry-driven cluster formation provides access to predesigned three-dimensional and highly symmetric clusters.

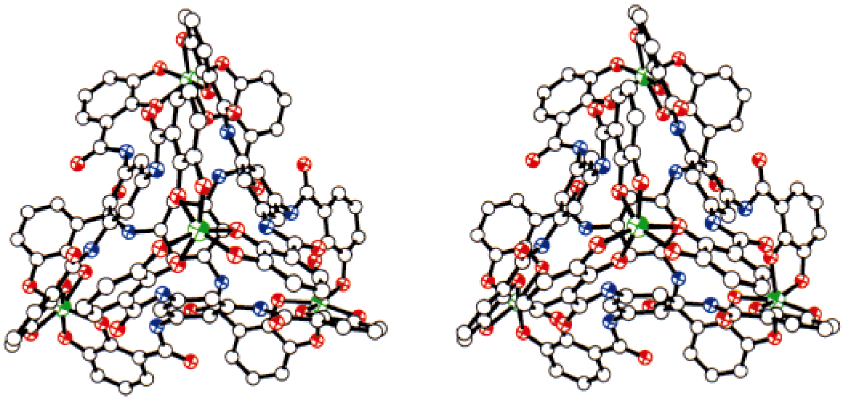

Figure 3. Stereoscopic view of the crystal structure of **6** along the crystallographically imposed threefold axis. Countercations and hydrogen atoms have been omitted for clarity.

Experimental Section

3 and **4**: The intermediate **3** was synthesized from freshly prepared **2** and **1.** Ligand **4** was prepared on a 0.1 M scale and in overall $>80\,\%$ yield by BBr_3 deprotection according to literature procedures.[7,8] Correct elemental analyses for **3** and **4** were obtained.

4: ^{1}H NMR (300 MHz, [D6]DMSO, 25°C, TMS): $\delta = 11.50$ (br. s, 1 H OH), 10.44 (s, 1 H, NH), 9.3 (s, 1 H, OH), 7.99 (s, 1 H, C*H*CN), 7.42 (d, 1 H, ^3J(H,H) = 7.8 Hz, COC*H*CH), 6.99 (d, 1 H, ^3J(H,H) = 7.8, COCHC*H*), 6.71 (t, 1 H, ^3J(H,H) = 7.8 Hz, CHC*H*CH); ^{13}C NMR (75 MHz [D6]DMSO, 25°C, TMS): $\delta = 167.7$ (C=O), 148.2, 146.3, 138.7, 119.3, 118.8, 118.6, 117.4, 110.2.

6: A freshly prepared solution of [Ti(O*n*Bu)$_4$] (107 mg, 3.1×10^{-4} mol) in MeOH (20 mL) was added to a solution of ligand **4** (165 mg, 1 equiv) in a mixture of MeOH (20 mL) and Et_3N (1 mL), and the solution was stirred for 12 h at ambient temperature. The orange gelatinous precipitate was removed by centrifugation and suspended in DMF (20 mL). The suspension was heated under N_2 to reflux for 12 h. The resulting solution was filtered through Celite and either evaporated to dryness in vacuo, to produce 190 mg of a microcrystalline solid, or MeOH vapors were allowed to diffuse into this solution at room temperature over several weeks to produce 80 mg (yield 37 %, 1st crop) of orange cuboid crystals of analytical purity. ^{1}H NMR (300 MHz, [D6]DMSO, 25°C, TMS): $\delta = 11.43$ (s, 1 H, NH), 8.2 (br s; 1 H, NH), 7.12 (d, ^3J(H,H) = 6.5 Hz, 1 H; COC*H*CH), 6.84 (s, 1 H, CHCN), 6.45 (t, 1 H, ^3J(H,H) = 7.8 Hz, CHC*H*CH), 6.21 (d, 1 H, ^3J(H,H) = 7.8, COCHC*H*); ^{13}C NMR (125 MHz, [D6]DMSO, 25°C, TMS): $\delta = 158.8$ (C=O), 140.3, 138.7, 137.5, 118.5, 116.8, 115.4, 114.5, 112.9, 43.3, 8.3; ES-MS (positive-ion detection, 100 % CH_3CN) clusters of peaks with isotope distribution patterns indicative of multiply charged ions could be assigned; a typical example is given (Na^+ is ubiquitously present; $\blacklozenge \equiv [Ti_4L_4]^{8-}$): 581 $(\blacklozenge+9Na^++4Et_3NH^+)^{5+}$; 620 $(\blacklozenge+4H^++8Na^+)^{4+}$, 681 $(\blacklozenge+10Na^++2Et_3NH^+)^{3+}$, 1162 $(\blacklozenge+9H^++1Na^+)^{2+}$, 1173 $(\blacklozenge+8H^++2Na^+)^{2+}$, 1184 $(\blacklozenge+7H^++3Na^+)^{2+}$, 1195 $(\blacklozenge+6H^++4Na^+)^{2+}$, 1206 $(\blacklozenge+5H^++5Na^+)^{2+}$, 1217 $(\blacklozenge+4H^++6Na^+)^{2+}$, 1228 $(\blacklozenge+3H^++7Na^+)^{2+}$; 2302 $(\blacklozenge+9H^+)^{+}$, 2324 $(\blacklozenge+8H^++1Na^+)^{+}$, 2346 $(\blacklozenge+7H^++2Na^+)^{+}$, 2368 $(\blacklozenge+6H^++3Na^+)^{+}$, 2390 $(\blacklozenge+5H^++4Na^+)^{+}$, 2421 $(\blacklozenge+4H^++5Na^+)^{+}$.

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[12] A red tablet crystal of $C_{156}H_{188}N_{20}O_{36}Ti_4$ of dimension $0.3 \times 0.22 \times 0.07$ mm was grown by vapor diffusion of MeOH into a DMF solution of **6**. Crystal data were collected with a Siemens SMART diffractometer equipped with a CCD area detector with $Mo_{K\alpha} = 0.71069$ nm.[15] Point group $R\bar{3}c$ (No. 167), with a = 22.6143(5), c = 106.038(2) Å, V = 46963 Å^3, Z = 12, $\rho_{calcd} = 1.32$ gcm^{-3}. Frames corresponding to an arbitrary sphere of data were collected with ω scans of 0.3° counted for a total of 30 s per frame, temperature of measurement −103(2) °C, 49921 reflections, 6019 unique ($R_{int} = 0.090$). Data in the range of $2 < 2\theta < 41.6°$ were integrated by the SAINT program.[16] An absorption correction was applied using SADABS ($T_{max} = 0.74$, $T_{min} = 0.56$).[17] The structure was solved by direct methods (SIR92) and expanded with Fourier techniques.[18] Number of observations $I > 3.00\,\sigma(I) = 1381$, 271 variables, reflection/parameter ratio = 5.1, refined against $|R|$, $R = 0.109$, $Rw = 0.120$, $R_{all} = 0.191$, min/max residual electron density = −0.40/0.51, GOF = 4.21. Oxygen and titanium atoms were refined anisotropically, all other non-hydrogen atoms were refined isotropically. Hydrogen atoms were included at calculated positions. All triethylammonium cations are disordered with respect to the conformation of their ethyl arms and their location in the crystal but could invariably be located in H-bond distance to the catecholate oxygens or the carbonyl oxygens; 8/3 Et_3NH^+ cations per asymmetric unit were distributed unequally over all four possible catecholate and all four possible carbonyl oxygen positions. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101007. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax:(+44)1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).

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