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Container Molecules

A Self-Assembled M_8L_6 Cubic Cage that Selectively Encapsulates Large Aromatic Guests**

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Biological encapsulants such as ferritin,[1] lumazine synthase,[2] and viral capsids[3] achieve their selective separation and sequestration of substrates by providing: 1) a guest microenvironment isolated from the surroundings, 2) favorable interactions complementing a size and shape match with the encapsulated guests, and 3) sufficient flexibility to allow guests to be incorporated and released.[4] These biological hosts self-assemble from multiple copies of identical protein subunits, the symmetries and connection properties[5] of which dictate the hollow polyhedral structures of the encapsulant. In order to create abiological molecular systems that are capable of expressing functions of similar complexity to biological systems and to explore new applications of synthetic hosts,[6] there is a need to create synthetic capsules capable of tightly and selectively binding large substrates.

Taking inspiration from natural systems[1–3] and from other previously reported metal–organic capsules,[7] we report the design and synthesis of a series of metallo-supramolecular cage molecules capable of selectively encapsulating large aromatic guests. The necessary features to achieve this function are: 1) small pore sizes to isolate guests from the environment,[8] 2) large cavity sizes to ensure sufficient volume for the guests of interest, 3) enough flexibility and lability to allow guests to enter and exit the host, and 4) regions of the cage walls rich in π-electron density to provide favorable interactions with targeted guests.[9] The selective encapsulation of large aromatic molecules is an attractive goal since their physicochemical properties are similar, which can render their separation difficult. The higher fullerenes represent particularly attractive targets because their potential applications[10] remain difficult to explore because of the challenges associated with their separation, despite recent advances.[11]

Employing principles of geometric analysis,[5] we determined that combination of the C_4-symmetric tetrakis-bidentate ligand shown in Figure 1 with the C_3-symmetric iron(II) tris(pyridylimine) center would result in the formation of an *O*-symmetric cubic structure of general formula M_8L_6, in which the corners of the cube are defined by the metal centers and the faces by the ligands (Figure 1). This cage represents the first example of a new class of closed-face metallo-supramolecular cubic hosts to be synthesized. In order to provide favorable binding sites for our target guests we incorporated porphyrin moieties, which have previously been demonstrated to interact with large aromatic molecules,[11a–c,12] into our design. This design also provides for small pore sizes and the potential to create new chemical functionality through the introduction of different metal ions into the centers of the N_4 macrocycle and by substituting these metals' axial ligands. We chose to employ labile iron(II) centers with pyridylimine ligands as chelating agents to allow for the formation of the ligand in situ through the subcomponent self-assembly approach.[13]

The reaction between tetrakis(4-aminophenyl)porphyrin (H_2-tapp), 2-formylpyridine, and iron(II) trifluoromethanesulfonate (triflate, OTf^-) in DMF produced cage [H_2-**1**]·16 OTf (Figure 1) as the uniquely observed product, as verified by NMR spectroscopy (Figure 3 b), electrospray mass spectrometry (ESI-MS), and elemental analysis. Substitution of nickel(II) tetrakis(4-aminophenyl)porphyrin (Ni-tapp) or zinc(II) tetrakis(4-aminophenyl)porphyrin (Zn-tapp) for H_2-tapp under identical conditions yielded the nickel-containing (Ni-**1**) and zinc-containing (Zn-**1**) congeners of H_2-**1** (Figures S2a and S3a in the Supporting Information), respectively, suggesting the formation of such capsules to be a general feature of tetrakis(4-aminophenyl) porphyrins (Figure 1).

Vapor diffusion of diethyl ether into a DMF/acetonitrile solution of Ni-**1** resulted in the isolation of block-shaped dark purple crystals. Single-crystal X-ray diffraction revealed a solid-state structure (Figure 2) consistent with the *O*-symmetric NMR spectra recorded in solution.

Each face of Ni-**1** is covered by one porphyrin ligand and each corner is defined by a six-coordinate low-spin Fe^{II} ion. All of the Fe^{II} centers within each cage adopt the same Λ or Δ configuration; both enantiomers of Ni-**1** are present in the crystal lattice. The Ni–Ni distance between opposite faces is 15 Å, and the internal cavity volume is 1340 Å^3 (Figure S2e).

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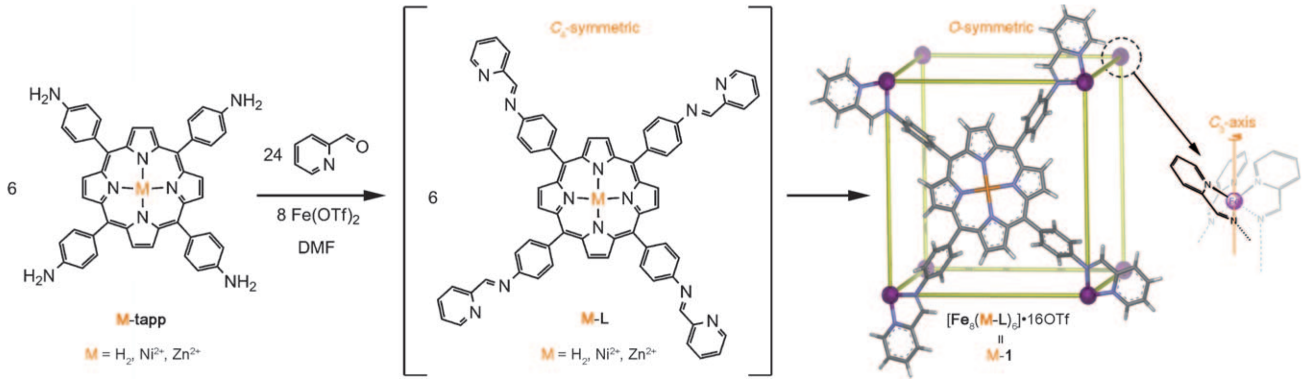

Figure 1. Design and synthesis of cubic cages M-**1** (where M = H_2, Ni^{2+}, Zn^{2+}) through subcomponent self-assembly.[13] The combination of C_4-symmetric tetrakis-bidentate ligands with C_3-symmetric iron(II) tris(pyridylimine) centers resulted in the formation of a cube having O (chiral octahedral) point symmetry, where eight octahedral metal ions occupy the corners and six ligands form the faces.

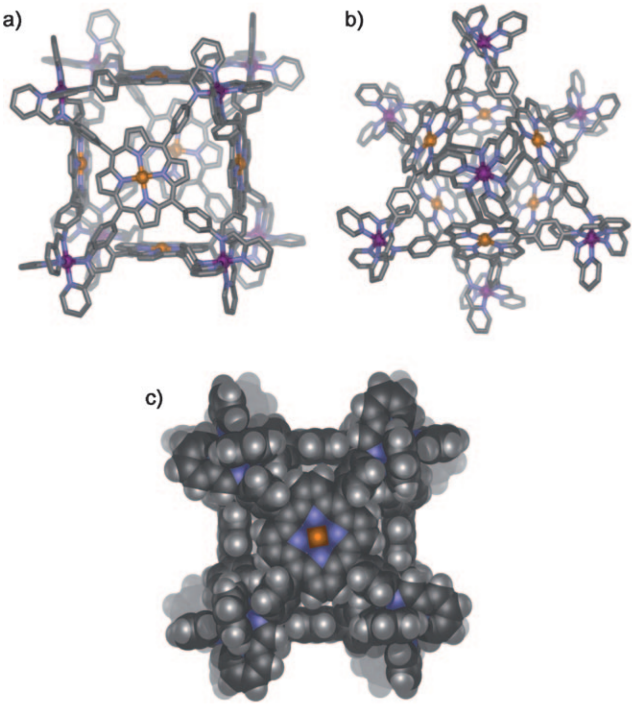

Figure 2. The X-ray structure of Ni-**1**·16 OTf·26 Et_2O·28 DMF·30 H_2O. All views omit molecules of solvent and anions for clarity; views (a) and (b) also omit hydrogen atoms. a) Perspective view emphasizing one of the C_4 symmetry axes; b) view down one of the C_3 axes; c) a space-filling representation of the structure illustrating the small sizes of the pores.

This large volume is well isolated from its surroundings; the largest sphere that could enter or exit the cavity of Ni-**1** through a pore without distorting the host framework has a radius of only 1 Å.

Initial binding studies of large aromatic guest molecules were carried out using coronene, $C_{18}H_{12}$ (Figure 3a). The addition of excess coronene to H_2-**1** or Ni-**1** in DMF produced host–guest complexes in which exactly three equivalents of this flat, aromatic guest were encapsulated per host, as confirmed by NMR spectroscopy, ESI-MS, and microanalysis. The encapsulated coronenes gave rise to two ^{1}H NMR signals (integrating in a 2:1 ratio), which are shifted significantly upfield relative to those of free coronene (Figure 3). This suggests a persistently-ordered "sandwich" stacking of the three guest molecules. The ^{1}H NMR spectrum of [coronene$_3$⊂H_2-**1**] also shows two distinct sets of signals attributable to the phenyl protons of the ligand, which correspond to those that are *endo* (H^{8}* and H^{9}*) and those that are *exo* (H^8 and H^9) to the wall of the cage. The NOESY spectrum of [coronene$_3$⊂H_2-**1**] also confirmed encapsulation of the three coronenes with through-space magnetization transfer observed between the inner and outer stacked coronenes as well as between the coronene guests and the *endo* phenylene protons of the host, but not its *exo* protons (Figure S6c).

Cooling [coronene$_3$⊂H_2-**1**] in DMF solution to 248 K led to a loss of observed symmetry in the ^{1}H NMR spectrum, which suggested that the tumbling of the guests within the host had become slow on the NMR timescale. In contrast, the ^{1}H NMR spectrum of [coronene$_3$⊂Ni-**1**] displays a similar lack of symmetry at 298 K; only upon heating the solution to 328 K is a spectrum obtained consistent with guests' tumbling at a higher rate. The greater mobility of the stack of three coronene guests within H_2-**1** when compared to those within Ni-**1** may be attributed to the greater rigidity of the metalated porphyrin walls of Ni-**1** or more favorable interactions of the coronenes with Ni-porphyrins.

Ni-**1** was then investigated as a fullerene receptor. Both C_{60} and C_{70} were observed to form 1:1 host–guest complexes with capsule Ni-**1** in DMF. The reaction between C_{60} (5 equiv) and Ni-**1** resulted in 35% conversion to the host–guest complex [C_{60}⊂Ni-**1**] after 5 days equilibration at 343 K, consistent with a binding constant of $5.5 \times 10^3\,\mathrm{L\,mol^{-1}}$ (derivation provided in the Supporting Information). Through encapsulation the maximum concentration of C_{60} in DMF solution can thus be increased six-fold. The addition of C_{70} (2 equiv) to Ni-**1** resulted in its complete conversion to [C_{70}⊂Ni-**1**] within 3 h at 343 K, indicating a higher affinity of Ni-**1** for C_{70} than C_{60}; C_{70}'s greater deviation from a spherical shape may allow it to benefit from a larger number of stabilizing π–π interactions than C_{60} within Ni-**1**.

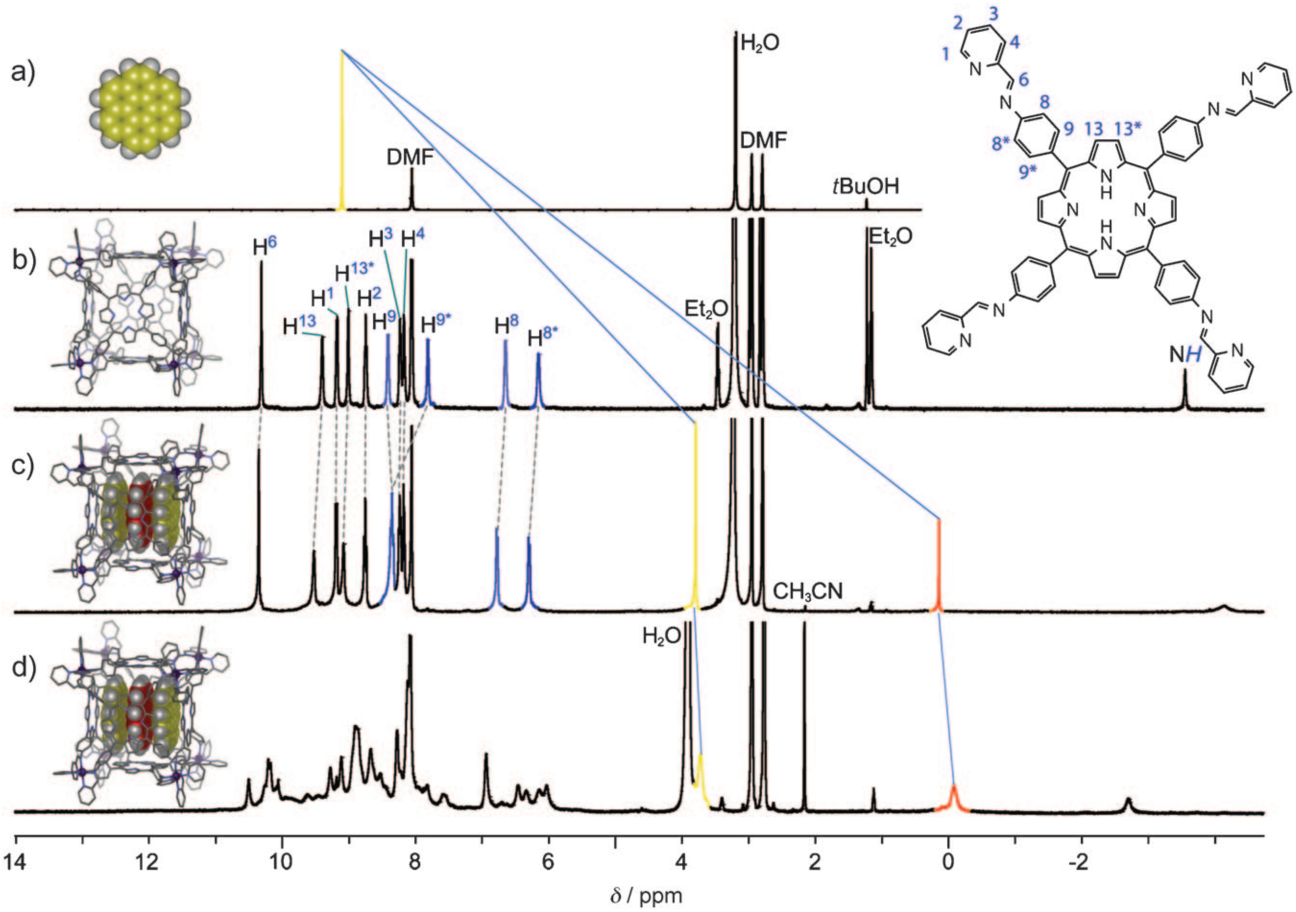

Figure 3. ^{1}H NMR spectra for a) coronene (recorded at 298 K), b) H_2-**1** (343 K), c) [coronene$_3$⊂H_2-**1**] (343 K), and d) [coronene$_3$⊂H_2-**1**] (248 K). The yellow and orange peaks come from coronenes. The dark blue peaks correspond to the *endo* phenyl protons (H^{8*} and H^{9*}) in the ligand, while the lighter blue peaks correspond to the *exo* phenyl protons (H^8 and H^9).

As shown in Figure 4, the stronger binding of both coronene and C_{70} compared to C_{60} allowed us to establish a host–guest hierarchy for Ni-**1**. The addition of a slight excess of coronene (3.5 equiv) to a DMF solution of C_{60}-saturated Ni-**1** resulted in complete displacement of C_{60} in favor of coronene: [coronene$_3$⊂Ni-**1**] was the only product observed by ^{1}H NMR spectroscopy and ESI-MS following 12 h at 343 K. Likewise, the addition of excess C_{70} (2 equiv) to a similar C_{60}-saturated Ni-**1** solution resulted in complete conversion to [C_{70}⊂Ni-**1**]. No guest substitution, however, was observed when excess C_{70} was added to a solution of [coronene$_3$⊂Ni-**1**] or vice versa following 12 h at 343 K, possibly due to low release rates of C_{70} and coronene as compared to C_{60}.

The hierarchical binding preference of Ni-**1** for C_{70} over C_{60} encouraged us to consider the discrimination between other fullerenes[11d–i] using fullerene soot as a mixed source. When Ni-**1** (10 % by weight) was mixed with commercially available fullerene soot in DMF for 12 h at 343 K, neither empty Ni-**1** nor [C_{60}⊂Ni-**1**] were observed in ESI-MS spectrum (Figure 5); instead, host–guest complexes of [C_{70}⊂Ni-**1**], [C_{76}⊂Ni-**1**], [C_{78}⊂Ni-**1**], [C_{82}⊂Ni-**1**], and [C_{84}⊂Ni-**1**] were observed (Figure 5).

Although mass spectra do not directly provide quantitative information as to the proportions of different species present in a mixture without careful calibration,[9] we note that the ratios of [C_{60}⊂Ni-**1**] and empty Ni-**1** measured by both NMR spectroscopy and ESI-MS were in close agreement (Figures S7a and S7b), indicating comparable MS ionization behavior of host–guest complex and free host. The absence of peaks corresponding to free Ni-**1** or [C_{60}⊂Ni-**1**] in the mass spectrum (Figure 5) are thus consistent with selective encapsulation of the higher fullerenes C_{76}, C_{78}, and C_{82} from fullerene soot, although relative affinities may not be extracted from the data. In the case of C_{82}, the mass spectrum could reflect near-quantitative extraction, given the low (0.7 %) reported abundance of C_{82} in the commercial product.[11c] As with tetrahedral hosts[14] prepared using subcomponent self-assembly,[13] capsules M-**1** could be opened through treatment with acid or tris(2-aminoethyl)-amine, taking advantage of the cube's lability towards acid and by substituting the tapp-based amino groups by more electron-rich amines following methods that we have established. Encouraged by the results of these initial competition studies, we are currently carrying out further quantification of the binding constants as well as investigations of the mechanisms of guest binding and release. Given the small sizes of the hosts' pores as compared to the guests investigated herein, we hypothesize guest exchange to require deligation of at least one pyridyl(imine) ligand "arm" from a Fe^{II} center. This hypothesis is being tested.

A new class of porphyrin-faced M_8L_6 hollow cubic architectures has thus been designed and prepared through subcomponent self-assembly. The inner voids of these cubes are large (> 1300 Å^3), well isolated from bulk media due to small pore size, and bounded by ligands rich in π-electron density. These properties enable extensive host–guest chemistry that is of demonstrated use in selectively encapsulating higher fullerenes from fullerene soot. Such guest sequestration may be of use in keeping reactive molecules away from others until an appropriate signal opens a capsule,[15] or in keeping toxic drug molecules away from sensitive tissues pending their delivery.[16] These hosts are chiral; efforts are currently underway to separate their enantiomers in order to carry out chiral guest discrimination.[17] Different metalloporphyrin faces could also lend functionality to new cubic hosts in this series, reflecting the wide range of uses that metalloporphyrins have found in nature.

CCDC 780771 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

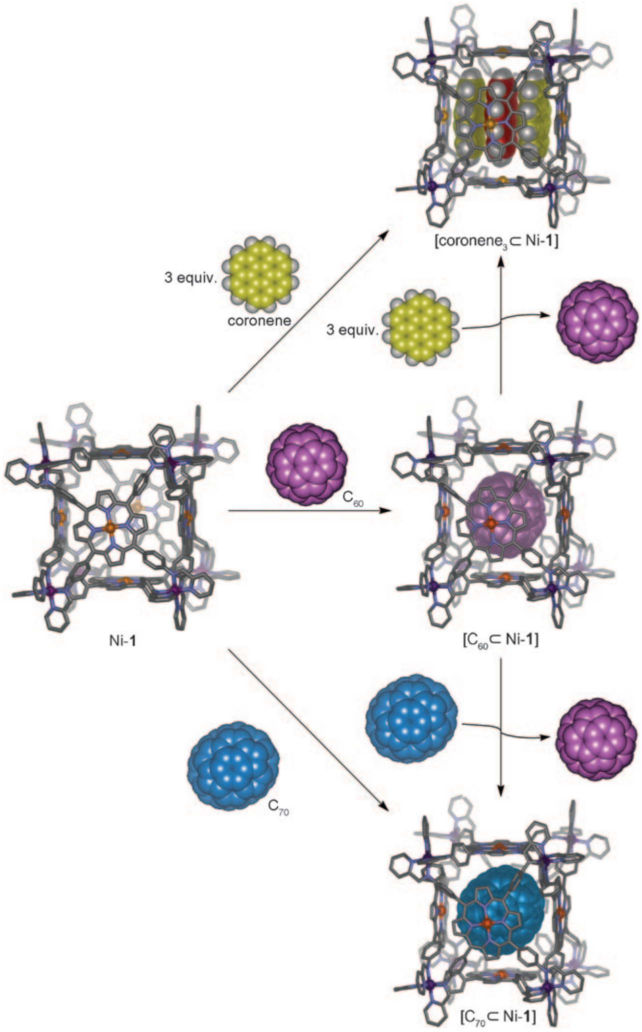

Figure 4. Hierarchies of host–guest inclusion of coronene, C$_{60}$, and C$_{70}$ within host Ni-**1**. C$_{60}$ was observed to bind within the cavity of Ni-**1**. C$_{70}$ and coronene guests were observed to bind more strongly than C$_{60}$.

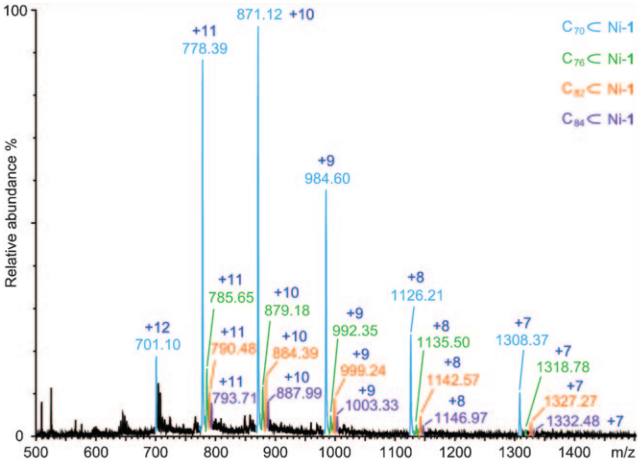

Figure 5. Electrospray mass spectrum for the reaction mixture of fullerene soot and Ni-**1** (10% by weight of fullerene soot used).

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