

Self-Assembly

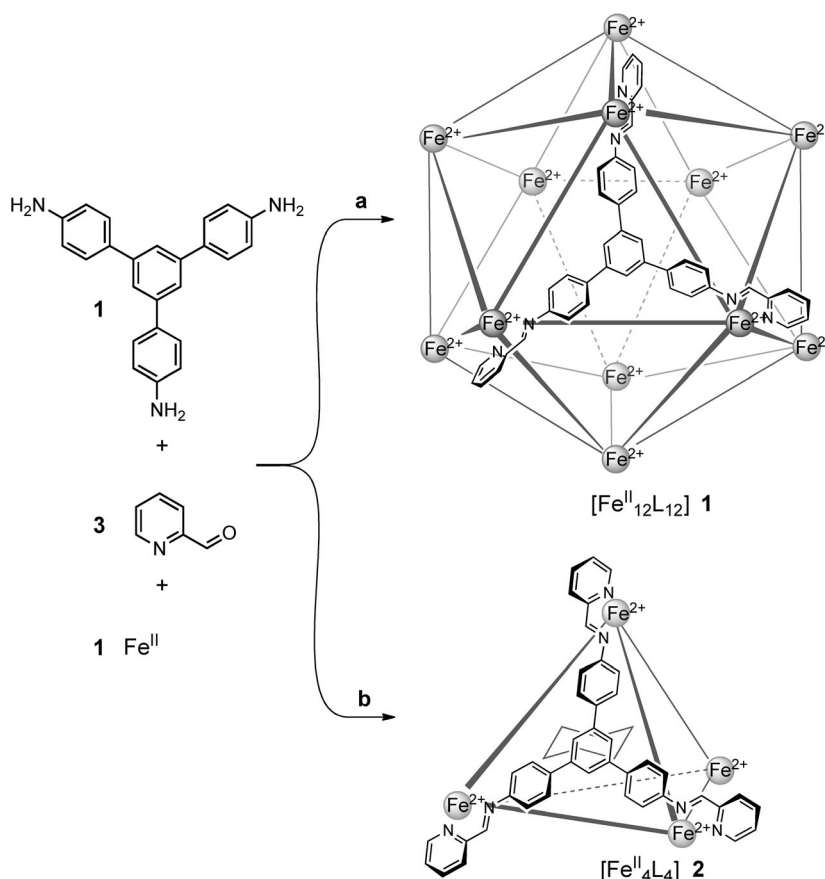
A Self-Assembled $[\text{Fe}^{\text{II}}_{12}\text{L}_{12}]$ Capsule with an Icosahedral Framework**

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Viruses are effective encapsulants for the same reasons that make them feared as pathogens—the dynamic nature and plasticity of their capsids in assembling and disassembling under controlled conditions allow the site-specific delivery of molecular payloads.^[1] The interior cavities of viral capsids, which serve to host viral genetic material in nature, have been co-opted for the encapsulation and controlled synthesis of organic, inorganic,^[2] and polymeric^[3] materials.

For reasons of genetic economy,^[4] many icosahedral viral capsids assemble from multiple copies of a single asymmetric protein subunit. Binding sites on these subunits link together in such a way as to generate the curvature and symmetry of the closed polyhedral capsid. In similar fashion, the principles of chemical self-assembly have allowed the formation of complex polyhedral assemblies from simpler precursors, built through DNA nanofabrication,^[5] hydrogen bonding,^[6] and metal–ligand interactions.^[7]

The field of metal–organic capsule design, in particular, has seen rapid growth in recent years, as understanding has been gained as to the relevant architectural principles.^[8] These concepts allow outcomes to be controlled by the stoichiometry, symmetry and geometry of the components employed.^[9] Various high-symmetry metal–organic capsules based on Platonic (faces consisting of one regular polygon) and Archimedean (faces consisting of two or more regular polygons) solids have been successfully prepared. Explora-



Scheme 1. Subcomponent self-assembly of **1** and **2**. a) Capsule **1** was preferentially formed from $\text{Fe}(\text{OTf})_2$ in a 50:50 (v/v) methanol/acetonitrile solution at 343 K. b) Capsule **2** was preferentially formed from $\text{Fe}(\text{NTf}_2)_2$ in acetonitrile at 323 K in the presence of cyclohexane as a template.

tion of the chemistry of these capsules has been driven by their applications in reactivity modulation of bound guests, molecular recognition, and catalysis.^[7f,e,10]

Herein we report the synthesis of new metal–organic capsule **1** (Scheme 1) based on an icosahedral array of metal ions. Whereas metal–organic capsules are most frequently constructed using metal centers and ligands to define the symmetry axes of Platonic polyhedra,^[7f] including tetrahedral,^[10] cubic,^[11] octahedral^[12] and dodecahedral^[13] assemblies, the symmetry axes of capsule **1** are coincident neither with its ligands nor its metal centers. This arrangement is reminiscent of the structures of icosahedral viral capsids, wherein the protein subunits are asymmetric, and symmetry axes are defined by linkages between capsid-forming proteins.

Capsule **1** was obtained through subcomponent self-assembly, in which coordinative ($\text{N} \rightarrow \text{Fe}$) and dynamic-

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covalent^[14] (C=N) bonds are formed during the same overall reaction. This method has proven a fruitful technique for the synthesis of metal–organic capsules.^[15]

We have previously reported the synthesis of tetrahedral face-capped [Fe^{II}₄L₄] capsule **2**^[16] from the tritopic triamine 1,3,5-tri(4-aminophenyl)benzene (4 equiv), 2-formylpyridine (12 equiv), and iron(II) triflimide (4 equiv) in the presence of a template (a small organic compound, e.g. cyclohexane). In the absence of a template, the same stoichiometry of starting materials yielded a mixture of products in solution at 323 K. In addition to capsule **2** and a [Fe^{II}₂L₃] triple helicate **3**,^[16] the mixture was found to contain a new product **1**, which gave rise to a set of NMR resonances that reflected a lower-symmetry ligand environment than that of capsule **2**.

The yield of **1** could be maximized to 88% by using the more polar solvent system of 50:50 (v/v) methanol:acetonitrile at 343 K, by employing iron(II) triflate in place of the triflimide and by increasing the concentration of Fe^{II} from 25.4 mM to 46.5 mM (Figure S10, Supporting Information). We infer that more polar solvent mixtures are better able to stabilize the more highly -charged framework of **1**, favoring its formation.

Vapor diffusion of diethyl ether into an acetonitrile solution of a mixture of both capsules resulted in the formation of crystals of **1** suitable for X-ray structure determination using synchrotron radiation at Diamond Light Source.^[17] The crystal structure revealed **1** to be an [Fe^{II}₁₂L₁₂] capsule (Figure 1). The twelve iron(II) centers form

an approximately icosahedral framework, with the tris-bidentate ligands capping twelve of the twenty faces of an icosahedron. All Fe^{II} centers have the same Δ or Λ stereochemistry within each capsule and both enantiomers are present in the unit cell. All the iron(II) centers in **1** display lower-symmetry meridional (*mer*) coordination around the metal centers, in contrast to the facial (*fac*) coordination required to define the C₃ axes of the smaller tetrahedral capsule **2**.^[16] Only three of the five faces that meet at each vertex are occupied by a ligand, resulting in loss of the C₃ symmetry axes present at the vertices of a regular icosahedron; consequently the structure has overall *T* symmetry.

The longest Fe–Fe separation between antipodal vertices of **1** is 2.7 nm and the overall diameter of the assembly is approximately 3.6 nm, as measured by the longest distance between the outermost hydrogen atoms of the farthest-spaced ligands. The Fe–Fe distances along the edges of the icosahedral framework are in the range 13.134(3)–15.510(3) Å with an average distance of 14.3 Å. Capsule **1** is thus the largest architecture prepared to date using subcomponent self-assembly,^[15a] approaching the scale of the largest synthetic discrete metal–organic assemblies.^[18]

The surface of **1** is not fully enclosed; it contains three types of pores (**A**, **B**, and **C**, shown in Figure 1 c). The two types of larger pores (**A** and **B**) surround C₃ symmetry axes, and correspond to icosahedral faces that are not occupied by ligands. The smaller pores (**C**) surround C₂ axes and are located between pairs of adjacent faces that are occupied by ligands. The largest spheres that could pass through pores **A**, **B**, and **C** without steric hindrance would have diameters of 6.8 Å, 3.4 Å, and 1.1 Å, respectively.

In analogous fashion to the proteins that form icosahedral virus capsids, in **1** identical copies of a single subunit occupy symmetry-non-equivalent positions. This allows, in both cases, for a large void volume to be enclosed by a set of relatively small subunits.

The crystal structure of capsule **2**, which had not been obtained during the course of our previous study,^[16] was also obtained as part of this work. Single crystals were grown through vapor diffusion of diethyl ether into an acetonitrile solution containing bicyclo[2.2.1]heptane-**2** in the presence of excess KBF₄. The four facially coordinated Fe^{II} centers are bridged by the four C₃-symmetric ligands resulting in a face-capped tetrahedral arrangement with crystallographic *T* symmetry.

The metal-to-metal distance of **2**, 14.408(1) Å, falls within the range observed in **1**. Capsule **2** crystallized in the chiral cubic space group *I*23 with all Fe^{II} centers in the tetrahedron adopting the same Δ configuration; we anticipate that there were also crystals of the all- Λ isomer within the sample. The ligands on the faces of **2** adopt a C₃ symmetric propeller-like configuration, in which the handedness of the propeller is the same as the handedness of the metal centers that they bridge, as has been observed for similar cage molecules.^[16,19] This conformation contrasts with the lower symmetry orientation of the ligands in **1**, whereby two arms extend above the triangular face and the third arm drops under the face to achieve *mer* configuration at the Fe^{II} centers.

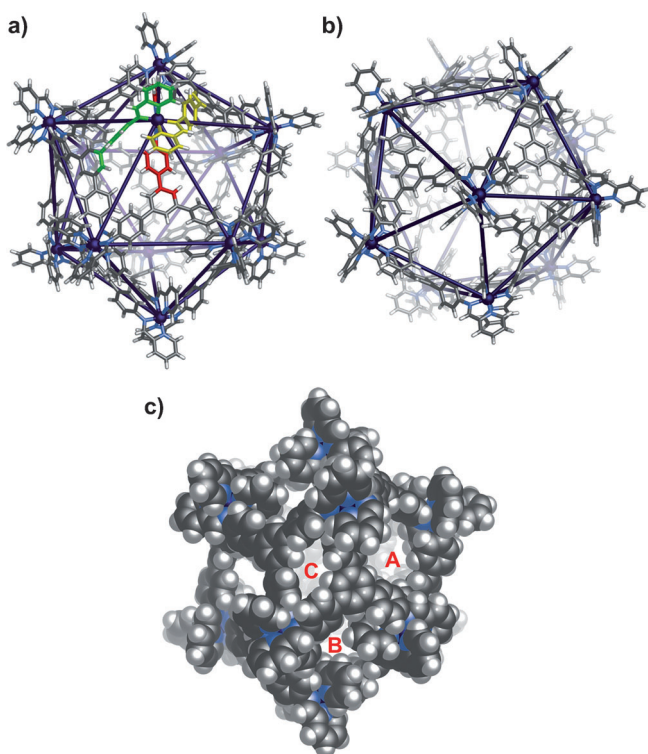


Figure 1. Crystal structure of **1**,^[25] 24NtF₂; anions are omitted for clarity. a) View down one of the faces of **1**, highlighting the three different environments adopted by the ligands (indicated in green, red, yellow). b) View down one of the vertices of **1**. c) Space filling representation of **1** showing pore types **A**, **B**, and **C**.

The simple change from *fac* to *mer* geometry around the metal centers in the formation of **1** resulted in an increase in structural complexity, overall charge and cavity volume compared to **2**. The unprecedented formation of **1** forms part of a broader trend where the incorporation of *mer* centers into a structure gives rise to architectures that are difficult to predict using geometric analysis.^[20]

NMR spectroscopic analyses in acetonitrile solution were in agreement with the solid-state data, confirming that the symmetry and stereochemistry of **1** and **2** are retained in solution. In contrast with tetrahedron **2**, for which a single set of resonances was observed for each ligand proton, in the case of **1** three sets of resonances in a 1:1:1 ratio were observed; this is attributed to the *fac* and *mer* arrangements of the ligands around the metal ions in each capsule respectively. The persistence of these complexes in solution was further confirmed by high-resolution ESI mass spectrometry; experimentally observed isotope patterns were in good agreement with theoretically predicted patterns (Figure S5).

The size difference between the capsules in solution was confirmed by diffusion ordered ¹H NMR spectroscopy (DOSY) in 50:50 (v/v) methanol/acetonitrile, in which the diffusion coefficients of **1** and **2** were found to be 2.8×10^{-10} and $4.3 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, respectively (Figure S6).

Capsules **1** and **2** each enclose a void cavity capable of encapsulating guest molecules (Figure 2). The guest binding properties of **2** were investigated previously;^[16] its well-enclosed cavity is sufficiently large ($177 \text{ \AA}^3$ as determined by VOIDOO based on the crystal structure)^[21] to enable the binding of a wide range of neutral guest species, such as cyclohexane and carbon tetrachloride. Anionic species were

not observed to bind to **2** in solution. Capsule **1** encloses a much larger cavity volume of $2768 \text{ \AA}^3$ as determined by VOIDOO calculation^[21] potentially allowing larger guests to be encapsulated.

The guest binding properties of **1** were investigated by screening a range of neutral and anionic prospective guest molecules (Table S1 in the Supporting Information). Capsule **1** was found to bind only dodecafluoro-*closo*-dodecaborate ($[\text{B}_{12}\text{F}_{12}]^{2-}$); no evidence was observed for binding neutral molecules of similar size, or for other large anions, such as tetraphenylborate and tetrakis(pentafluorophenyl)borate. The poorly coordinating^[22] $[\text{B}_{12}\text{F}_{12}]^{2-}$ was observed to undergo fast exchange between solution and the cavity of **1** as observed by ¹H and ¹⁹F NMR spectroscopy. The binding process was followed by ¹H NMR titration; the phenyl protons of **1** closest to the metal center (H_t) were observed to undergo the largest downfield shift, from $\delta = 6.15 \text{ ppm}$ before the addition of the dianion to $\delta = 6.60 \text{ ppm}$ upon saturating the solution with the guest (Figure S12). The imine peaks of the host also underwent spectral shifts consistent with guest binding. The guest binding strength was thus found to be $3.8 \pm 0.7 \times 10^2 \text{ M}^{-1}$ in acetonitrile. The approximate diameter (longest F–F distance) of $[\text{B}_{12}\text{F}_{12}]^{2-}$ is $6.13 \text{ \AA}$,^[23] permitting it to diffuse into the cavity of the capsule through the largest apertures (pore **A**). We infer its binding to occur through electrostatic attractions and van der Waals forces; we attribute the failure of **1** to bind other guests to the large sizes of its pores and the consequently low degree of cavity enclosure.

The system shown in Scheme 1 can thus be induced to express either capsule from the same set of subcomponents, larger **1** or smaller **2**, depending on the reaction conditions. Despite their incorporation of the same building blocks in the same ratios, differing metal stereochemistry between these two structures leads to drastic differences in cavity volumes, shapes, and sizes, leading to the encapsulation of different guests. Future investigations will probe the generality of the cage-forming reaction that leads to the formation of **1**—whether, for example, the introduction of bulky substituents in specific places upon subcomponents can direct a self-assembling system^[24] away from structures like **2** and towards analogues of **1**. Such substituents might also enhance solubility in desired solvents, and occlude pores, thus increasing the degree of cavity enclosure. Both of these effects could be used to tune guest selectivity, with the aim of developing new functions based upon the structure of **1**.

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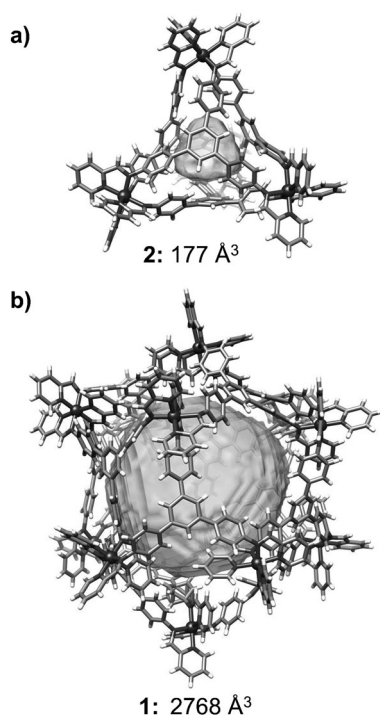


Figure 2. The crystal structures of capsules **1** and **2**;^[25] void spaces are indicated in each case by a surface. Cavity volumes were calculated using the crystal structure of the corresponding capsule.

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