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Sulfate-templated self-assembly of new M_4L_6 tetrahedral metal organic cages†

Song Yi,[a] **Valentina Brega,**[ab] **Burjor Captain**[a] **and Angel E. Kaifer***[a]

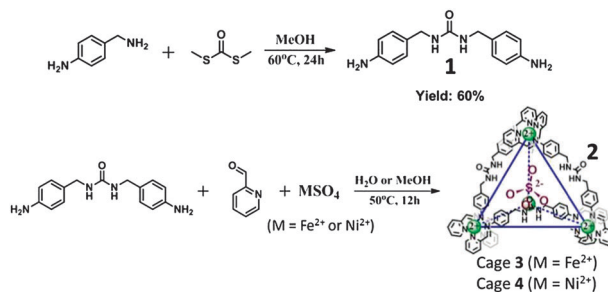**Six equivalents of N,N'-bis(4-aminobenzyl)urea, 12 equivalents of 2-formylpyridine and four equivalents of $FeSO_4$ or $NiSO_4$ undergo subcomponent self-assembly in aqueous solution to form tetrahedral cages around a single, encapsulated sulfate anion.**

The self-assembly of hollow polyhedral complexes prepared through the coordination of metal ions to suitable organic ligands has been the subject of considerable research work.[1] Raymond and co-workers have prepared M_4L_6 cages taking advantage of Fe(III) coordination to catechol-based ligands,[2] while the groups of Fujita and Stang have demonstrated a large variety of self-assembled cage structures largely based on the coordination of Pd(II) ions.[3] Among other applications the cavities of self-assembled cages can be used as containers for chemical reactions, stabilization of reactive species, and catalysis.[4]

Imine bonds are attracting increasing attention as dynamic covalent bonds in the template-directed synthesis of supramolecular species.[5] Nitschke and co-workers recently reported the highly efficient subcomponent self-assembly of a M_4L_6 tetrahedral cage, in which the ligands connecting the Fe(II) ion vertices are prepared *in situ* by the reaction of a rigid diamine with two molecules of 2-formylpyridine.[6] Here, we report the design, preparation and characterization of novel M_4L_6 metal organic cages in which the main ditopic ligand is prepared by reaction of bis(p-toluidine)urea and two molecules of 2-formylpyridine. The resulting tetrahedral cage is formed efficiently around a single sulfate anion upon mixing of the 22 other subcomponents (six ureas, 12 aldehydes, and four metal ions). Sulfate encapsulation[7] provides the key driving force for the self-assembly process (Scheme 1).

The design of our ditopic ligand (**2**) was partially based on the ligand used by Custelcean and coworkers for their tetrahedral sulfate capsule.[8] The similarities between the structures

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† Electronic supplementary information (ESI) available: Synthetic and crystallographic data for cages **3** and **4**. Additional spectroscopic data for both cage compounds as mentioned in the text. CCDC 891142 and 891143. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc35095e
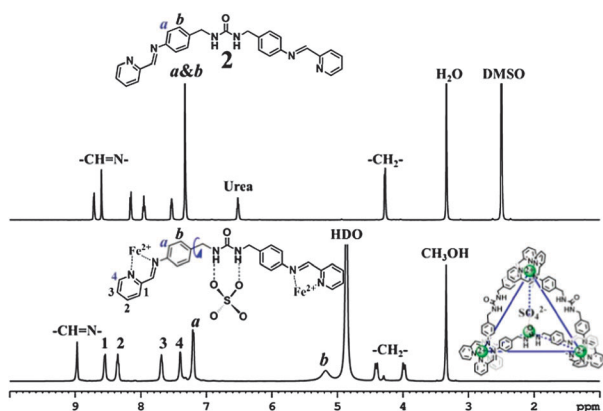

Scheme 1 Synthetic route to precursor **1** and preparation of tetrahedral cages **3** and **4** with ligand **2**.

of their ligand and our own are shown in full detail in the ESI.† We anticipated that ligand **2** would self-assemble in solution by the reaction of N,N'-bis(4-aminobenzyl)urea (**1**) with two molecules of 2-formylpyridine. In turn compound **1** can be easily prepared by reaction of two commercially available starting materials: 4-aminobenzylamine and S,S'-dimethyl dithiocarbamate (see Scheme 1 and details in the ESI†).

In aqueous solution, mixing of 6 equiv. of **1** with 12 equiv. of 2-formylpyridine and 4 equiv. of $FeSO_4$ (or $NiSO_4$) leads to the self-assembly of a tetrahedral cage containing four metal ions at the vertices (Scheme 1). The Fe(II)-based cage **3** has a well defined NMR spectrum, indicating that no oxidation to Fe(III) takes place. The purple color acquired by the solution is consistent with the intense metal-to-ligand charge transfer excitation associated with low spin Fe(II) in a hexaimine ligand environment.[9] The strong coordination and mutual stabilization[10] between the Fe(II) ions and the imine ligands play an important role in the overall stability of cage **3** in aqueous solution. Similar experiments with other metal ions [Zn(II), Co(II)] were attempted but evidence for the formation of well-defined species was obtained only for Fe(II) and Ni(II). Metallic salts containing ions such as PF_6^-, ClO_4^-, PO_4^{3-} and Cl^- also failed to produce self-assembled cages.

Due to the poor solubility of ligand **2** in water, the ^1H NMR spectrum of **2** had to be recorded in DMSO-d_6 (Fig. 1a). The ^1H NMR spectrum of cage **3** was recorded in D_2O (Fig. 1b) owing to its high aqueous solubility ($\sim$30 g L^{-1}). Both spectra show simple peaks and only one set of ligand proton resonances can be observed, indicative of the highly symmetric

Fig. 1 ¹H NMR spectra of (top) ligand **2** in DMSO-d₆ and (bottom) cage **3** in D₂O.

Fig. 2 High resolution ESI-TOF mass spectrum of cage **3**. The insert shows the experimental and calculated isotopic distribution patterns for the most intense peak (L = ligand **2**).

structure of cage **3** in solution. However, compared with the proton resonances of ligand **2**, the cage shows proton signals for the phenyl (protons **a** and **b**) and methylene groups (−CH₂− protons) that are split into two sets of peaks due to the two different orientations or spatial arrangements for these protons. Noticeably, the resonance for proton **b** in the cage is very broad and shows a very pronounced upfield shift (∼2 ppm) compared to that of proton **a**. A possible reason for this significant upfield shift is that in the structure of cage **3**, each ligand **2** is arranged in such a way that proton **b** on the phenyl group is very close (2.63 Å, *vide infra*) to the nitrogen atom in the urea group of the adjacent ligand. Therefore, the electron density around the nitrogen atom could confer a strong shielding effect to proton **b**. Since the two chemically equivalent protons **b** on each phenyl group have different magnetic environments, the rotation of the phenyl group could average these two magnetic resonances into a single broad signal. As shown in Fig. S2 (ESI†), all the proton resonances of cage **3** can be assigned correctly with the aid of 2D COSY NMR spectroscopy. On the other hand, since Ni(II) ions in octahedral fields are paramagnetic, NMR spectroscopy is not very useful to investigate the structure of the related Ni(II)-based cage **4**.

High resolution electrospray ionization (ESI) mass spectrometry provides further evidence that the self-assembled cages exist in solution. A solution obtained by dissolving cage **3** in H₂O–CH₃CN (3 : 1) gave a distinct peak with the highest intensity at $m/z = 501.6511$, corresponding to $[Fe_4(2)_6(SO_4)]^{6+}$ (expected $m/z = 501.6499$). The simulated isotopic pattern for $[Fe_4(2)_6(SO_4)]^{6+}$ matches perfectly with that of the most intense peak in the mass spectrum (Fig. 2). Similar results were obtained for cage **4**, as reported in the ESI.†

Slow vapor diffusion of dioxane into an aqueous solution of cage **3** over two weeks resulted in the growth and isolation of single crystals of **3** as its sulfate salt. X-ray crystallographic analysis clearly reveals that a metal–organic tetrahedral cage encapsulating the sulfate anion was formed (Fig. 3).[11] All four iron(II) vertices had the same chirality, which resulted in an overall homochiral cage (ΔΔΔΔ configuration in our case). As expected, the six urea groups (from the six ligands) provide a total of 12 hydrogen bonds to the encapsulated sulfate.[8]
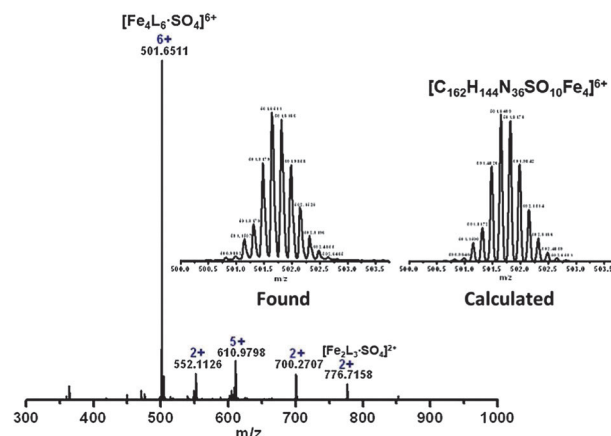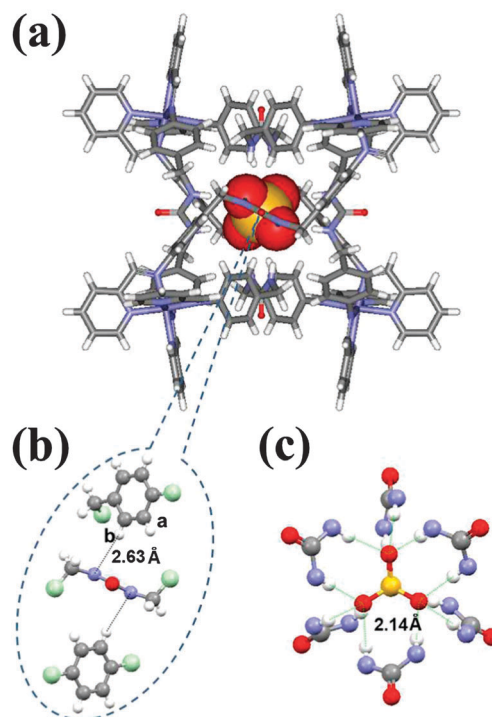

Fig. 3 (a) X-ray crystal structure of cage **3**. (b) Structural detail showing the environment of the aromatic protons. (c) Hydrogen bonding between the central sulfate and the ureas.

The measured NH–O hydrogen bond length and N–H–O angle are 2.14 Å and 177.1°, respectively.

As mentioned before, ¹H NMR shows a pronounced upfield shift for proton **b**, which could be explained by the arrangement of ligands in the structure of cage **3**. In Fig. 3b, we can see that proton **b** is close to and pointing toward the nitrogen atom of the urea group, so that the electron density around the N engenders a strong shielding effect on proton **b**. In contrast, proton **a** is farther away from the urea N, so that its magnetic environment is little affected.

Under similar conditions, we also obtained single crystals of cage **4** suitable for X-ray analysis (see ESI†).[12] The measured

Scheme 2 Reversible disassembly and reassembly of cage **3** under pH control.

NH–O hydrogen bond lengths and N–H–O angles range between 2.09 and 2.26 Å, and 152.3 and 164.9°, respectively.

A very interesting aspect of cage **3** is that it can be disrupted to release the encapsulated sulfate anion. A possible approach to do this relies on the addition of an excellent ligand for Fe(II) ions, which will remove them from the cage. An illustrative example involves the addition of tris(2-ethylamino)amine (**5**). Thus, addition of excess ligand **5** to a solution of cage **3** leads to the formation of highly stable $5 \cdot Fe^{2+}$ complexes, irreversibly disrupting cage **3** and releasing its encapsulated sulfate anion. An alternative methodology to disassemble the cage, albeit in a reversible way, takes advantage of the dynamic character of imine bond formation. Addition of HCl to a solution containing cage **3** leads to the dissociation of the imine bonds holding up ligand **2**. Protonation of the pyridine nitrogens may also play an important role on the disruption of the cage. As a result, the self-assembly of the cage is reversed, releasing the encapsulated sulfate and regenerating free **1** and 2-formylpyridine. However, this process is fully reversible and addition of NaOH regenerates the conditions for imine bond formation, allowing the self-assembly of cage **3** in the solution. This reversible process of disassembly and re-assembly of cage **3** under pH control (Scheme 2) can be verified by NMR spectroscopic measurements (see ESI†).

Finally, it is also possible to use cage **3** to transfer sulfate anions to nonaqueous solvents. The hexacationic character of cage **3** allows the manipulation of its solubility *via* counterion exchange. An aqueous solution of cage **3** (as its sulfate) can be treated with a concentrated solution of ammonium hexafluorophosphate to precipitate the hexafluorophosphate salt of **3**, which can be isolated, dried and re-dissolved in acetonitrile. The NMR spectrum of **3** in CD_3CN reveals the integrity of the cage in this nonaqueous solution (see ESI†).

Overall, we have shown that *N*,*N*′-bis(4-aminobenzyl)urea (**1**) reacts with two equiv. of 2-formylpyridine to yield the ditopic imine ligand **2**. Self-assembly of six equiv. of ligand **2** and four equiv. of Fe(II) [or Ni(II)] around a single sulfate anion leads to the formation of an hexacationic cage structure in which the sulfate ion is stabilized by 12 hydrogen bonds

to the NH urea protons on the ligands. These cages not only self-assemble from readily accessible and inexpensive components, but also cage **3** exhibits properties that allow easy control on its association/dissociation processes.

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11 Crystal data for cage **3**: $Fe_4C_{162}H_{144}N_{36}O_{22}S_4$, M_r = 3298.77, cubic, space group $I23$, a = 22.1233(8) Å, V = 10828.0(7) Å^3, Z = 2, T = 100 K, Mo K$_\alpha$ = 0.71073 Å, GOF = 1.082, no. parameters = 182, $2\Theta_{max}$ = 50.00°, Flack parameter = 0.23(4). The final $R1(F^2)$ was 0.0773 for 2985 reflections $I > 2\sigma(I)$. CCDC deposit number 891142.
12 Crystal data for cage **4**: $Ni_4C_{162}H_{144}N_{36}O_{10}S$, M_r = 3022.03, trigonal, space group $P\bar{3}$, a = b = 25.0734(12) Å, c = 19.3734(9) Å, γ = 120°, V = 10547.8(9) Å^3, Z = 2, T = 100 K, Mo K$_\alpha$ = 0.71073 Å, GOF = 1.013, no. parameters = 640, $2\Theta_{max}$ = 50.00°. The final $R1(F^2)$ was 0.0593 for 8761 reflections $I > 2\sigma(I)$. CCDC deposit number 891143.