Host–Guest Systems

DOI: 10.1002/anie.200803066

An Unlockable–Relockable Iron Cage by Subcomponent Self-Assembly**

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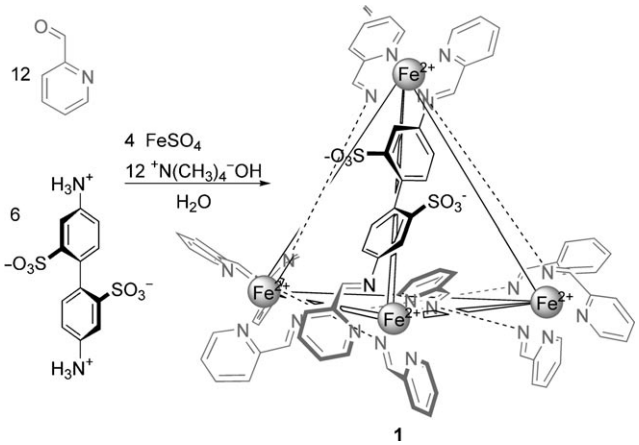
The study of hollow polyhedra prepared through metal–organic self-assembly,[1–3] within the wider context of container molecules,[4–6] has been a topic of great interest in recent years. These structures provide an inner phase[5] of well-defined void space, within which the chemical reactivity[7,8] and dynamics[9] of guest molecules have been altered and studied in novel ways.

Herein we describe a new metal–organic cage complex that is capable of tightly binding a hydrophobic guest molecule in aqueous solution and in the solid state. Our anionic cage exhibited high selectivity for appropriately sized hydrocarbon guests (no affinity was detected for similarly sized alcohols or organic cations), and the constrictive nature of guest binding allowed a smaller guest to be selectively removed from the cage in vacuo while a larger one remained bound. A novel and potentially useful aspect of the cage's behavior is that it could be readily opened through the application of either one of two chemical signals, releasing the trapped guest molecule. One of these opening methods proved reversible, allowing guest exchange through the application of chemical signals.

Tetrahedral cage **1** was the unique product observed from the aqueous reaction of the 4,4′-diaminobiphenyl-2,2′-disulfonic acid and 2-formylpyridine subcomponents shown in Scheme 1 with iron(II) and base. Cage **1** contains exclusively iron(II) in the low-spin state, as indicated by its sharp, diamagnetic NMR spectra and dark purple coloration, indicative of the intense metal-to-ligand charge-transfer excitations associated with low-spin iron(II) in a hexaimine ligand environment.[10] The strong binding and mutual stabilization[11] between iron(II) and imine ligands[10] appear to play an important role in the stability of **1**. Neither cobalt(II) nor zinc(II) produced well-defined products when employed in place of iron(II). In keeping with the elegant chiral M_4L_6 cage motif discovered by Saalfrank and coworkers[2] and explored by several other groups,[3,8,12] **1** displays tetrahedral symmetry in solution as detected by NMR spectroscopy; only one set of ligand proton resonances are observed.



Scheme 1. Preparation of tetrahedral cage **1** salt by aqueous subcomponent self-assembly;[14] the structure of only one edge is fully shown for clarity.

Slow evaporation of a water/acetone (1:1 v:v) solution permitted the isolation of single crystals of **1** as the tetramethylammonium salt. In spite of the moderate quality of the crystals, the crystal structure of **1** could be determined by X-ray diffraction (Figure 1). This structure is consistent with NMR spectra and revealed an internal cavity of 141 Å^3, as calculated using PLATON VOIDS.[13] The sulfonate groups of **1** are symmetrically arrayed towards the exterior. We infer that their presence and orientation contribute to the high observed aqueous solubility of **1** (34 g L^{-1}).

When cage **1** was prepared in the presence of cyclohexane, a new resonance attributed to cyclohexane within the cage was observed at $\delta = 0.37$ ppm, that is, 1.03 ppm upfield of free cyclohexane. Resonances corresponding to the cage were also shifted upon guest complexation, and a strong nuclear Overhauser effect[15] was observed between the resonance corresponding to encapsulated cyclohexane and inward-pointing H5 of the benzidinedisulfonate residues of the cage. Integration of the ^{1}H NMR spectrum indicated the formation of a 1:1 complex. The cyclohexane guest proved to be very tightly bound; in the solid state, finely powdered

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[**] This work was supported by the Walters–Kundert Charitable Trust, the Royal Society, the Swiss National Science Foundation, and the Academy of Finland (122350), the Graduate School of Organic Chemistry and Chemical Biology (K.B.) and the Marie Curie IIF Scheme of the 7th EU Framework Program (P.M.).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803066.

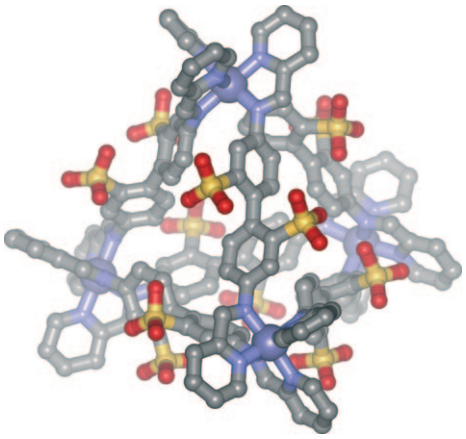
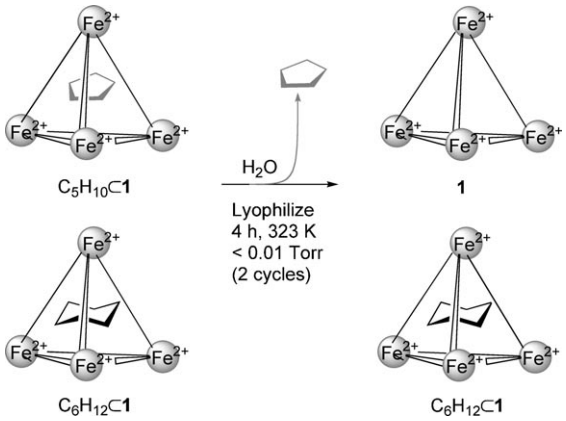


Figure 1. View of the crystal structure of **1**; cations, hydrogen atoms, and solvent of crystallization are not shown for clarity. Fe violet-gray, N blue, S yellow, O red, C gray.



Scheme 2. Selective removal of smaller cyclopentane guests from cages in vacuuo.

$C_6H_{12}\subset$**1** complex could be heated at 323 K for 24 h under dynamic vacuum (less than 0.01 Torr) without any appreciable degree of guest loss, as measured by subsequent solution NMR spectroscopy.

When excess cyclohexane was added to an aqueous solution of preformed **1**, the half-life for guest incorporation was approximately 18 h at 298 K or 2 h at 323 K. We attribute this slow guest exchange, in spite of high guest affinity, to the rigidity of **1** together with the small size of the portals in the faces of the cage: the largest sphere able to pass freely through these apertures in the crystal structure, just in van der Waals contact, would have a diameter of 2.04 Å. Although some degree of cage deformation[16] would be possible without great energetic cost, the deformation required to pass cyclohexane (approximate narrowest van der Waals cross section of 6 Å) through a portal of cage **1** is likely to be extensive. Guest binding is thus constrictive in nature.[17]

Cyclopentane also served as a guest, forming a 1:1 complex with **1** more rapidly ($t_{1/2} \approx 1.5$ h at 323 K) than cyclohexane, owing to its smaller size. When a competition experiment was carried out in an aqueous solution saturated in both cyclopentane and cyclohexane, an equilibrium mixture of 1.40:1 $C_5H_{10}\subset$**1**:$C_6H_{12}\subset$**1** was formed. This finding suggests that cyclohexane is slightly favored over cyclopentane, since cyclopentane is 3.4 times more soluble in water than cyclohexane.[18]

A cyclohexane guest molecule fills 61 % of the available space within the central cavity of **1**, suggesting that this guest is a good one following the Rebek rule that 55 % occupation is optimal.[19] Cyclopentane occupies 51 % of the cavity volume; the near-equal deviation of these two guests from 55 % occupation may explain the lack of selectivity between them displayed by **1**.

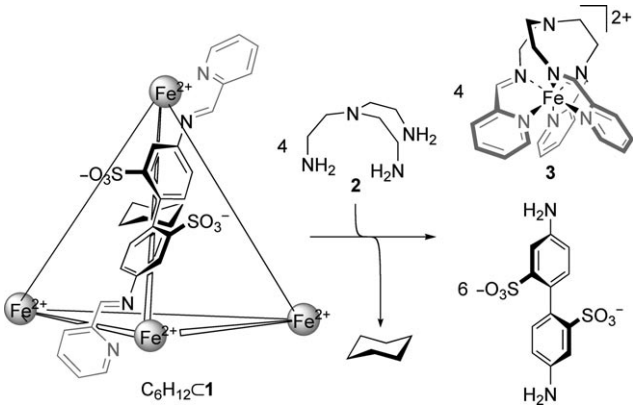
The differing sizes of cyclohexane and cyclopentane molecules led, however, to differing degrees of ease in passing through the portals of **1**, as reflected in the more rapid formation of $C_5H_{10}\subset$**1** than $C_6H_{12}\subset$**1**. This difference was used as the basis of a novel separation of these two very similar hydrocarbons (Scheme 2).

Following lyophilization of an aqueous 1.40:1 mixture of $C_5H_{10}\subset$**1** and $C_6H_{12}\subset$**1** (see the Supporting Information), integration of the ^{1}H NMR spectrum indicated a 1.35:0.07:1 mixture of free **1**:$C_5H_{10}\subset$**1**:$C_6H_{12}\subset$**1**. Of the initial cyclopentane, just 5 % thus remained encapsulated, whereas less than 2 % of the cyclohexane had escaped. The cyclohexane could then readily be liberated from the cage (see below).

Neither $[NMe_4]^+$ nor *t*BuOH was observed to bind within **1** in solution or the solid state, despite their tetrahedral geometries and 55 % and 50.6 % fill ratios. This high degree of selectivity for neutral, hydrophobic guests may be attributed to the hydrophobic effect.[20] This effect has been observed to drive aqueous alkane binding by container molecules in the groups of Raymond,[18] Gibb,[21] and Rebek.[22] The complete lack of affinity of anionic **1** for tetraalkylammonium ions ($[NMe_3Et]^+$, $[NMeEt_3]^+$, and $[NEt_4]^+$ cations were screened in addition to $[NMe_4]^+$), which contrasts with their binding within Raymond's anionic tetrahedra,[3] may be a consequence of the lesser overall charge of **1** and the guest's greater screening from the externally directed sulfonates and the apical Fe^{II} ions of **1.** We thus attribute the selectivity observed to the rigid and hydrophobic nature of the cavity of **1**, which is surrounded entirely by hydrophobic aryl rings.

Both dynamic covalent[23] (C=N) and coordinative (N→Fe) bonds hold **1** together; **1** thus shares features with two distinct classes of container molecules: metal–organic polyhedra[1–3,7–9,12] and dynamic-covalent cages.[6,24] A feature of the subcomponent self-assembly[14] approach used to prepare **1** is that both coordinative and covalent linkages may be independently addressed, providing two distinct means of opening **1**, thus allowing for the liberation of the more tightly bound cyclohexane guest. These methods are described below.

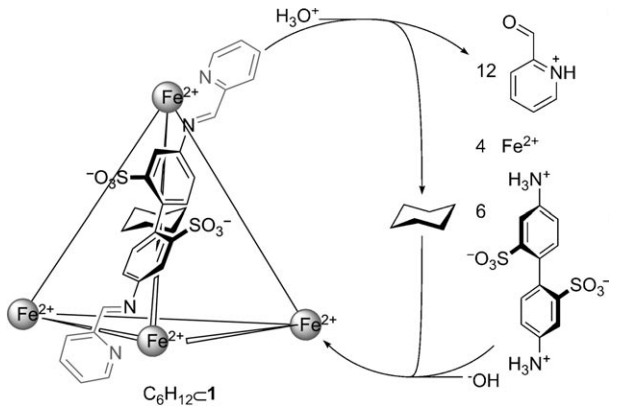
First, tris(2-ethylamino)amine **2** readily underwent imine exchange with **1**, resulting in the formation of mononuclear Fe^{II} complex **3** and the liberation of the cyclohexane (or cyclopentane) guest (Scheme 3). This imine exchange[25] reaction appears to have been driven to completion by both enthalpic (electron-rich alkylamine replacing electron-poor arylamine)[26] and entropic (increase in the number of particles)[27] factors. It was not possible to regenerate **1**



Scheme 3. Liberation of the cyclohexane guest within **1** by the addition of chelating amine **2**.

through the addition of acid to the mixture of **3** and diamine;[28] cage **1** appeared not to be stable under the acidic conditions required to induce the dissociation of **3**. The reaction of Scheme 3 might thus be considered as irreversibly breaking open cage **1**.

Second, variation of the solution pH could also be used to reversibly open the cage. The addition of *p*-toluenesulfonic (tosylic) acid (10.0 equiv) to an aqueous solution of the $C_6H_{12}\subset$**1** complex induced the cage to come apart, with liberation of the cyclohexane guest (Scheme 4). In this case,



Scheme 4. "Unlocking" of cage **1** through the addition of acid and subsequent base-driven "relocking" of cyclohexane within **1**.

however, the dissociation of the cage was reversible. The addition of sodium bicarbonate (15.0 equiv) induced $C_6H_{12}\subset$**1** to re-form. Although the structural change involved in the pH-driven "unlocking" of **1** is more radical than the portal-opening organic system described by Diederich and co-workers,[29] the pH-dependent behavior of **1** may similarly be considered as switching.

The "payload" of **1** may thus be released in a desired environment through opening with amine **2** or acid. If the acid-opened cage is then closed with base, a different guest molecule may be recovered from the environment.

Figure 2 documents this "capture-and-release" behavior by ^{1}H NMR spectroscopy. After the addition of excess acid

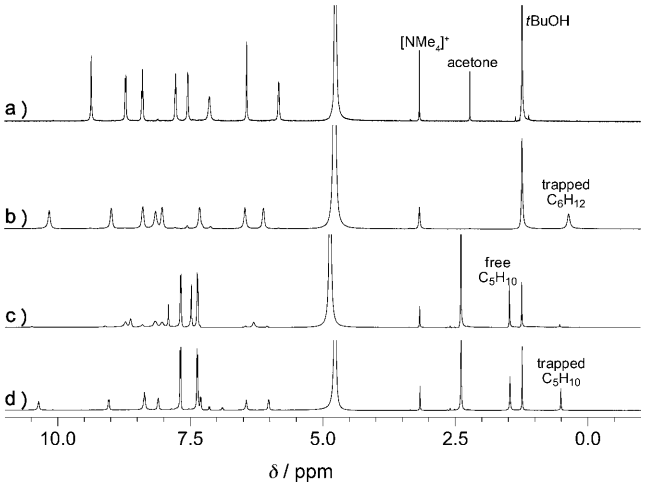


Figure 2. ^{1}H NMR spectra of a) cage **1**, b) $C_6H_{12}\subset$**1**, c) $C_6H_{12}\subset$**1** after reaction with tosylic acid (10 equiv) and in presence of excess cyclopentane, d) generation of complex $C_5H_{10}\subset$**1** after the addition of sodium bicarbonate (15 equiv).

and cyclopentane, the cyclohexane guest was observed to have been released (Figure 2c) and had presumably partitioned into the cyclopentane layer present in the NMR tube.[30] Following the addition of base, **1** was observed to re-form as the cyclopentane adduct (Figure 2d).

The tight, reversible, and selective encapsulation of hydrophobic guest molecules within **1** might be exploited to allow drug delivery uniquely to the vicinity of a target area, where "opener" molecules would be selectively placed. Conversely, potentially harmful hydrophobic molecules might be safely sequestered within **1** after the addition of base to the precursor subcomponents. A major practical advantage of **1** is its low cost—its precursors are commercially available and inexpensive. Current efforts are focusing on investigating the reactivity of trapped guests and on the preparation of longer linear diamines to allow for the encapsulation of larger guests or multiple guest molecules within more voluminous analogs of **1**.

Experimental Section

1: 4,4′-diaminobiphenyl-2,2′-disulfonic acid (purity 70%, balance water, 1.0 g, 2.03 mmol), 2-formylpyridine (0.435 g, 4.06 mmol), tetramethylammonium hydroxide pentahydrate (0.737 g, 4.06 mmol), and iron(II) sulfate heptahydrate (0.376 g, 1.35 mmol) were added to a 100 mL Schlenk flask containing degassed water (25 mL) and a stir-bar. All starting materials dissolved, giving a dark purple solution. The flask was sealed, and the atmosphere was purified of dioxygen by three evacuation/argon fill cycles. The reaction was stirred for 20 h at 50 °C. The product was then isolated as dark purple crystals by slow vapor diffusion of acetone into the aqueous solution of **1**; yield of isolated product 0.734 g (83%); ^{1}H NMR (400 MHz, 300 K, D_2O, referenced to 2-methyl-2-propanol at 1.24 ppm as internal standard): $\delta = 9.29$ (s, 12H, imine), 8.68 (d, $J =$ 7.6 Hz, 12H, 3-pyridine), 8.39 (t, $J = 7.6$ Hz, 12H, 4-pyridine), 7.75 (t, $J = 6.5$ Hz, 12H, 5-pyridine), 7.50 (d, $J = 7.6$ Hz, 12H, 6-pyridine), 7.12 (d, $J = 7.0$ Hz, 12H, 6,6′-benzidine), 6.43 (s, 12H, 3,3′-benzidine), 5.82 (d, $J = 7.0$ Hz, 12H, 5,5′-benzidine), 3.18 ppm (s, $[NMe_4]^+$); ^{13}C NMR (100.61 MHz, 300 K, D_2O, referenced to 2-methyl-2-prop-

anol at 30.29 ppm as internal standard): $\delta = 176.9, 158.7, 156.6, 150.8, 143.7, 140.5, 136.7, 132.7, 132.6, 130.5, 122.4, 121.6$ ppm; ESI-MS: m/z: −548.0 ($[L_2Fe]^{2-}$), −835.9 ($[\mathbf{1}]^{4-} \equiv [L_6Fe_4]^{4-}$), −1124.4 ($[L_4Fe_3]^{2-}$), −1412.8 ($[L_5Fe_4]^{2-}$).

Violet crystals of $(NMe_4)_4$**1** were obtained for X-ray structure analysis by slow evaporation of an acetone/H_2O solution. Analysis was performed using a Bruker Kappa Apex II diffractometer with graphite-monochromated $Mo_{K\alpha}$ ($\lambda = 0.71073$ Å) radiation. Collect software[31] was used for the data measurement and DENZO-SMN[32] for the processing. The structure was solved by direct methods with SIR97[33] and refined by full-matrix least-squares methods in three blocks using the WinGX-software,[34] which utilizes the SHELXL-97 module.[35] No absoption correction was applied. All CH hydrogen positions were calculated using a riding atom model with $U_H = 1.5\,U_O$ or $1.2\,U_C$. The NMe_4 cations are badly disordered; only the N atoms (one disordered over two sites with occupancy of 0.5) could be assigned. The residual electron density was modeled as disordered water molecules (H atoms could not be located) until a plateau of approximately 1 e Å^3 was reached. Crystal data: $M_r = 3923.6$, violet prism, $0.25 \times 0.25 \times 0.25$ mm^3, trigonal, space group $R\bar{3}$, $a = 34.8364(3)$, $c = 101.073(1)$ Å, $V = 106226(2)$ Å^3, $Z = 18$, $\rho_{calcd} = 1.104$ g cm^{-3}, $F000 = 36008$, $\mu = 0.419$ mm^{-1}, $T = 153.0(1)$ K, $2\theta_{max} = 46.5°$, 33862 reflections used, 18679 with $I_o > 2\sigma(I_o)$, $R_{int} = 0.0784$, 2608 parameters, 426 restraints, GoF = 1.454, $R = 0.150$ [$I_o > 2\sigma(I_o)$], w$R = 0.433$ (all reflections), $1.08 < \Delta\rho < -0.57$ e Å^3. CCDC-688687 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.

Detailed methods for the other procedures described herein are given in the Supporting Information.

Received: June 25, 2008
Published online: August 26, 2008

Keywords: coordination chemistry · dynamic covalent chemistry · host–guest systems · iron · self-assembly

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[30] When the acid-driven opening of $C_6H_{12}\subset$**1** was carried out in the absence of cyclopentane (shown in Figure S3 of the Supporting Information), free cyclohexane was observed in aqueous solution along with the protonated subcomponents of **1**.

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