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Selective Encapsulation and Sequential Release of Guests Within a Self-Sorting Mixture of Three Tetrahedral Cages**

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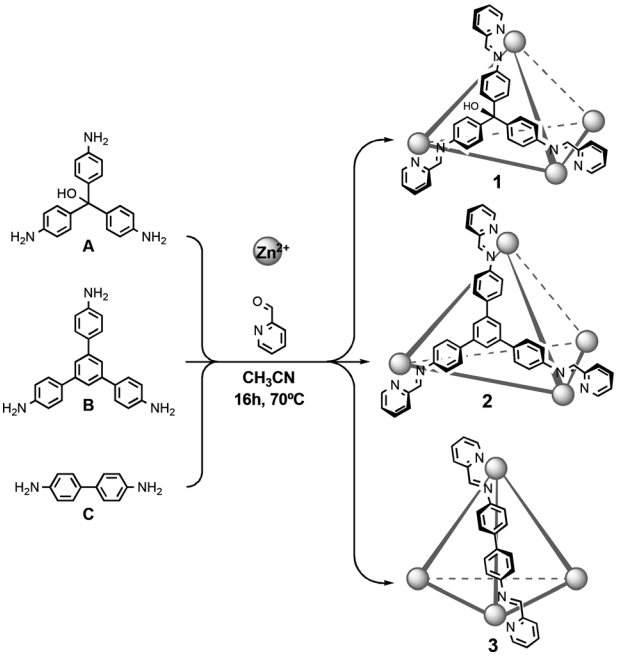
Dedicated to T. Don Tilley on the occasion of his 60th birthday

Abstract: *A mixture of two triamines, one diamine, 2-formylpyridine and a Zn^{II} salt was found to self-sort, cleanly producing a mixture of three different tetrahedral cages. Each cage bound one of three guests selectively. These guests could be released in a specific sequence following the addition of 4-methoxyaniline, which reacted with the cages, opening each in turn and releasing its guest. The system here described thus behaved in an organized way in three distinct contexts: cage formation, guest encapsulation, and guest release. Such behavior could be used in the context of a more complex system, where released guests serve as signals to other chemical actors.*

Chemical self-sorting is a process in which molecules are able to distinguish "self" from "non-self" within a mixture of related components.[1] Examples of artificial self-sorting systems[2] have been reported based on hydrogen bonding,[3] solvophobic effects,[4] reversible covalent bonds[5] and metal–ligand interactions.[6]

Others[7] and our group[8] have explored the preparation of metal–organic architectures[9] by self-assembly[10] of amine- and 2-formylpyridine-containing subcomponents around metal-ion templates, wherein both reversible covalent bonds and metal-coordination bonds form in a single reaction process.[8] The final geometry of the structure ultimately depends on several factors, including the subcomponents' sizes and geometries. Self-sorting could thus be observed in cases where subcomponents had substantially different geometries and sizes,[11] whereas similarly sized subcomponents were observed to interchangeably form heteroleptic capsules.[12] In order to design more complex systems of container molecules than what has been achieved to date,[13] it is necessary to explore and understand how multiple guests interact with multiple hosts when all are present in the same solution. The preparation of multiple hosts together, in turn, requires their building blocks to self-sort during the self-assembly process.

Here we report the one-pot synthesis of three discrete metal–organic capsules **1**–**3** from a combination of five subcomponents: amines **A**–**C**, 2-formylpyridine and a Zn^{II} salt (Scheme 1). Each of the three capsules was observed to selectively bind a single guest from among a mixture of prospective guests, and the cages' guests can be released in a specific sequence[14] following the addition of a chemical stimulus.[15]



Scheme 1. One-pot synthesis of cages **1**, **2** and **3** through the self-sorting of the three amine subcomponents (**A**, **B** and **C**), 2-formyl pyridine and a Zn^{II} salt.

We envisaged that structurally distinct amine subcomponents would self-sort to yield homoleptic structures, whereby each amine assembles with its congeners due to geometry and shape constraints.[1c,2f,6a,b] Zinc(II) was chosen as a suitable

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Supporting information for this article (full synthetic procedures, characterization data, X-ray crystallographic analyses and further experimental details) is available on the WWW under http://dx.doi.org/10.1002/anie.201400541.

metal ion due to the lability of Zn–L coordination bonds. Therefore, to accomplish this goal, two triamines, that is, tris(4-aminophenol)methanol (**A**) and 1,3,5-tris(4′-aminophenyl)benzene (**B**), and a linear diamine, that is, 4,4′-diaminobiphenyl (**C**), were selected following consideration of their sizes and geometries. It was anticipated that the C_2-symmetric **C** would not form heteroleptic structures with the C_3-symmetric amines, and the triamines **A** and **B** would discriminate between themselves based on their incompatible sizes, thus forming only homoleptic face-capped tetrahedra, as observed for their Fe^{II} face-capped analogues.[12]

Individual tetrahedral Zn_4L_4 complexes **1**, **2** and Zn_4L_6 complex **3** were first prepared starting from **A**, **B** and **C**, respectively, together with 2-formylpyridine and $Zn(NTf_2)_2$, and characterized by MS and NMR analyses (see the Supporting Information, Figure S1–S7). The ^{1}H NMR spectra of cages **1** and **2** showed one signal for each proton environment and were consistent with exclusive formation of the homochiral *T*-symmetric configurations, wherein all metal centers have the same Δ or Λ stereochemistry. Cage **3**, in contrast, displayed a complex ^{1}H NMR spectrum, consistent with an equilibrium between the homochiral *T* (ΔΔΔΔ/ΛΛΛΛ), heterochiral C_3 (ΔΔΔΛ/ΛΛΛΔ), and achiral S_4 (ΔΔΛΛ) diastereomers, as observed for analogous iron(II)-based systems.[16]

The solid-state structures of cages **1**, **2**, and **3** were determined through X-ray crystallography (Figure 1).[17] Each cage crystallized with approximate *T* point-group symmetry, such that all of the zinc(II) stereocenters within each cage share the same Δ or Λ stereochemistry. In each case the M–M distances are 0.2–0.3 Å longer than in their iron(II) analogues;[12,16,18] these longer distances are reflected in larger internal cavity volumes. As expected, cage **1** has the smallest cavity, as calculated using VOIDOO,[19] followed by **3** and then **2**. The cages' volumes were found to increase with their Zn–Zn distances (Figure S29); the cavity of **1** is smaller than expected because its ligands' C–H groups protrude inside to a greater degree than for **2** or **3**. The face-capped arrangement of **2** resulted in a larger ligand surface area and smaller pore sizes than cage **3**, where the ligands define the edges of the tetrahedron. Cage **3** was found to encapsulate a single PF_6^- anion in the solid state (Figure 1). The PF_6^- encapsulated within **3** benefits from non-classical hydrogen-bonding interactions with the internally directed biphenyl protons of the cage.[20]

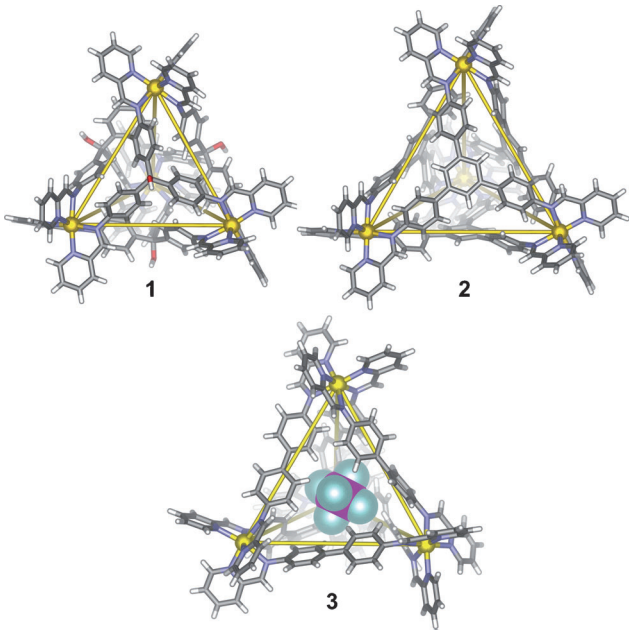


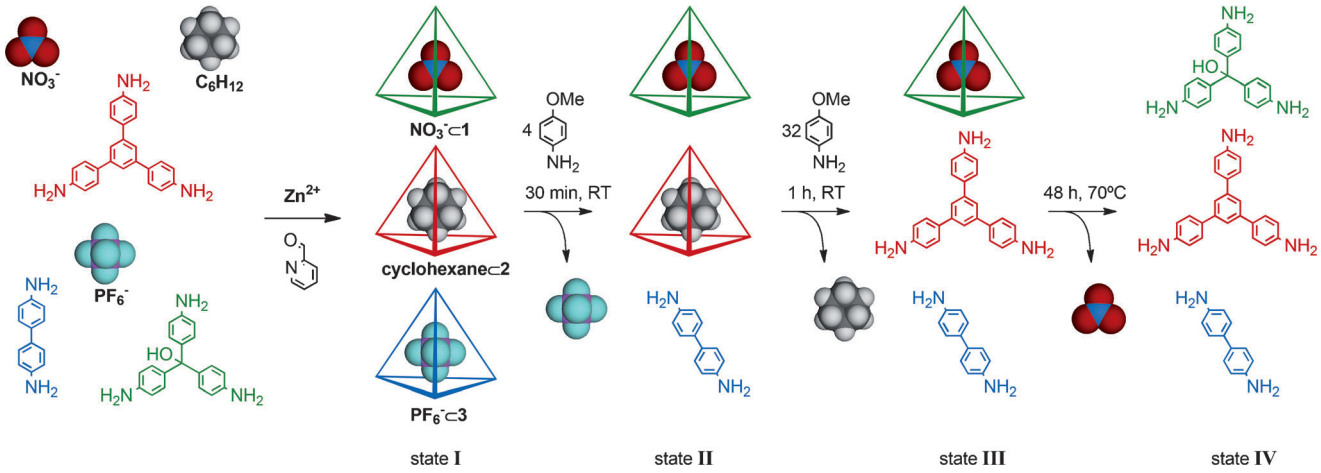
Figure 1. X-ray crystal structures of cages **1**, **2** and **3**. Solvent molecules and non-encapsulated counterions are not shown for clarity. For **1**, the average Zn–Zn separation (shown in yellow) and cavity volume were calculated to be 12.1 Å and 50.5(4) Å^3, respectively; for **2**, these values were 14.6 Å and 187.9(5) Å^3, and for [PF_6^-⊂**3**], 13.0 Å and 116(1) Å^3. The PF_6^- anion encapsulated within **3** is shown in space-filling mode.[24]

Having shown that the three cages could be assembled individually, we then explored the one-pot synthesis of all three cages. For this reaction, diamine **C** (6 equiv), triamines **A** and **B** (4 equiv each), 2-formylpyridine (36 equiv) and zinc(II) triflimide ($Zn(NTf_2)_2$, 12 equiv), were mixed in acetonitrile (Scheme 1). After 16 h at 70 °C, these starting materials had been converted into a clean mixture of the homoleptic cages **1**, **2** and **3**, as confirmed by ^{1}H NMR and ESI-MS (Figures S8 and S9). Similar results were observed when using $Zn(BF_4)_2$ or $Zn(OTf)_2$ in place of the triflimide salt.

Previously we have shown the Fe^{II}-containing analogue of **2** to accommodate neutral hydrophobic guests,[12] and the analogue of **3** to serve as a good anion receptor.[16] We thus investigated the guest-binding behavior of cages **1**, **2** and **3** with the aim of finding guests which could be selectively recognized within a mixture. Since the Zn^{II}-containing capsules differed only slightly in size from their Fe^{II} analogues, we expected similar host–guest behavior.

Cages **1** and **3** were both observed to bind anionic guests such as ClO_4^-, NO_3^-, I^-, and BF_4^-, but did not show affinity for *t*BuOH or cyclohexane. Cage **2** was observed to bind these two neutral molecules, whereas it gave no evidence of anion encapsulation (Table S1). However, only cage **3** was observed to bind the larger anion PF_6^- (see Table S1, Figure S12–S13). The cages' anion-binding behavior was followed in all cases by NMR spectroscopy, because UV/Vis and fluorescence properties were observed to undergo only minimal changes upon guest binding. PF_6^- was thus chosen as the specific guest for **3**, and cyclohexane was selected for **2**. Since the anions ClO_4^-, NO_3^-, I^- and BF_4^- were observed to be encapsulated by both cages **1** and **3**, it was necessary to optimize the conditions to selectively encapsulate PF_6^- into cage **3** such that the other anion was taken up by **1**. Addition of PF_6^- (40 equiv) and NO_3^- (2 equiv) to a 0.3 mM solution of all three of the cages resulted in selective encapsulation of PF_6^- in cage **3**, whereas NO_3^- was uniquely encapsulated in cage **1** (Figures S14 and S15). Subsequent addition of cyclohexane (4 equiv) showed, as expected, the formation of the cyclohexane⊂**2**, without perturbing the selective anion encapsulation within cages **1** and **3** (Supporting Information, Section 5.2).

In ^{1}H NMR spectra, NO_3^-⊂**1** and cyclohexane⊂**2** appeared as new sets of peaks, indicative of slow guest



Scheme 2. One-pot self-sorting system of encapsulation and release of the guests from the corresponding cages. Cages **1**, **2** and **3** are represented in green, red and blue, respectively.

exchange on the NMR timescale. The encapsulation of PF_6^- within **3** resulted in broadening of the ^{1}H NMR signals (Figure S15), however guest binding could be readily followed in the ^{19}F NMR spectrum (Figure S16), which displayed three new doublets, each assigned to PF_6^- encapsulated in one of the cage diastereoisomers (*T*, C_3 or S_4).[21] NMR analyses revealed encapsulation not to proceed to completion, with the empty cages **1**, **2** and **3** existing in equilibrium with the corresponding host–guest complexes $NO_3^-\subset$**1**, cyclohexane⊂**2**, and $PF_6^-\subset$**3**. At the host and guest concentrations noted above, NMR spectroscopy helped us to estimate the degree of encapsulation of nitrate in **1** to be 52% (Figure S17), cyclohexane in **2** to be 41% (Figure S18), and hexafluorophosphate in **3** to be 43% (Figure S19). These modest affinities are inferred to be a result of the only moderate fit of these guests to the host cavities and of the absence of strong solvophobic effects to drive encapsulation.

Having worked out conditions under which selective encapsulation could be achieved, we hypothesized that differences in stability might allow for selective guest release through sequential disassembly of the capsules upon the application of a chemical stimulus. Electron-rich 4-methoxyaniline was selected for this purpose[22] as it has previously been reported to displace less electron-rich amine residues within Fe^{II}-containing tris(pyridylimine) complexes through imine exchange. The disassembly of each individual Zn^{II}-containing cage was observed to result from the addition of 12 equiv of 4-methoxyaniline per capsule. Cages **2** and **3** were observed to undergo near-complete disassembly following the addition of 4 equiv of 4-methoxyaniline, after 1 h at 25 °C, whereas the disassembly of cage **1** required the addition of 12 equiv of 4-methoxyaniline followed by heating to 70 °C for 48 h (Figure S20–S23). The difference in stability between cages **1** and **2** may be a result of a slight strain within the framework of **2**, as evidenced by the singular tendency of the Fe^{II} analogue of **2** to reconfigure into a larger $M_{12}L_{12}$ structure.[18] Moreover, the addition of 4 equiv of 4-methoxyaniline to the mixture of the three host–guest complexes resulted in total disassembly of cage **3**, indicating it to be less stable than cage **2** (Figure S24 a,b).

Taking advantage of the observed differences in relative stabilities between the three capsules, we achieved sequential release of the three guests by modulating the amount of 4-methoxyaniline added and the reaction temperature (states **I**–**IV**, Scheme 2). Addition of 4 equiv of 4-methoxyaniline to a 1:1:1 mixture of cages **1**, **2** and **3**, in the presence of the three guests, at room temperature (state **I**) resulted in the specific disassembly of cage **3** after 30 min (state **II**), and consequently, the release of the guest (PF_6^-) as indicated by the absence of signals for the host–guest complex $PF_6^-\subset$**3** in the ^{19}F NMR spectrum (Figure S24,S25). A slight decrease (ca. 17% by NMR integration) in the total amount of cage **2** and cyclohexane⊂**2** was also observed, while cage **1** remained intact. Subsequently, addition of a further 32 equiv of 4-methoxyaniline, providing the amount of aniline stoichiometrically required to completely disassemble the complexes (i.e. 36 equiv in total) brought the system to State **III**, wherein the disassembly of cage **2** had occurred with consequent release of the encapsulated cyclohexane after 1 h at 25 °C, as confirmed by the absence of the peak from the encapsulated guest (at −0.6 ppm) in the ^{1}H NMR spectrum (Figure S24). No changes were observed for the signals corresponding to $NO_3^-\subset$**1** by ^{1}H NMR. However, heating the mixture to 70 °C for 48 h brought the system to state **IV**, wherein the release of the remaining guest, NO_3^-, had occurred through disassembly of cage **1**, thus achieving a complete and sequential release of the guests as follows: PF_6^- first, then cyclohexane, and finally NO_3^-. This result was also confirmed by ESI-MS, which showed no signals for the empty cages or their host–guest complexes (Figure S26).

The self-sorting synthesis, selective encapsulation and guest release processes described above could be sequentially accomplished in a one-pot reaction. The reaction sequence shown in Scheme 2 was carried out in an NMR tube and monitored by ^{1}H NMR and ^{19}F NMR spectroscopy (see the Supporting Information, Figure S28 and S29).

In conclusion, we have reported a straightforward parallel synthesis of three distinct Zn^{II}-containing tetrahedral cages **1**, **2** and **3** through self-sorting. Each cage has been shown to selectively recognize and accommodate a single guest from

within a mixture of three, and each guest could be sequentially released in a controlled manner using a chemical signal. Lastly, we have demonstrated that these three complex processes could be carried out in a one-pot reaction. This study paves the way towards the design of more complex chemical systems where individual cage-catalyzed processes[23] could be turned on and off in parallel reaction systems, allowing substrates to be directed along specific pathways in biomimetic fashion.

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[21] One of the doublets was barely observed when the concentration of cage **3** was less than 0.3 mM. When the concentration of cage **3** was greater than 0.3 mM the third doublet was clearly visible, thus giving evidence of the encapsulation in all three diastereoisomers (Figure S13).

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[24] CCDC 978020 (**1**), 978019 (**2**), and 978018 (**3**) contain 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.

