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Temperature Controls Guest Uptake and Release from Zn_4L_4 Tetrahedra

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Supporting Information

ABSTRACT: We report the preparation of triazatruxene-faced tetrahedral cage **1**, which exhibits two diastereomeric configurations (**T1** and **T2**) that differ in the handedness of the ligand faces relative to that of the octahedrally coordinated metal centers. At lower temperatures, **T1** is favored, whereas **T2** predominates at higher temperatures. Host−guest studies show that **T1** binds small aliphatic guests, whereas **T2** binds larger aromatic molecules, with these changes in binding preference resulting from differences in cavity size and degree of enclosure. Thus, by a change in temperature the cage system can be triggered to eject one bound guest and take up another.

Stimuli-responsive molecules[1] and molecular hosts[2] that are capable of adapting to changes in their environments have attracted substantial attention.[3] The ability of these species to switch between distinct states can enable them to be built into artificial molecular systems with useful functions.[4] One such function is the stimulus-controlled uptake and release of guests by molecular containers.[5] Such behavior has the potential to direct the outcome of chemical processes,[4h,6] control the transport and storage of chemicals,[7] and enable new means of drug delivery.[8]

Subcomponent self-assembled capsules are attractive candidates to achieve guest uptake and release, as the reversible formation of the dynamic covalent and coordinative bonds that hold the structures together provide different potential modes of opening.[9] Systems have thus been designed containing two or three capsules, where the application of chemical signals led to selective disassembly of individual cages and the release of their guests.[10] An alternative route for achieving guest uptake and release is the interconversion between supramolecular hosts with different guest preferences. However, these host transformations have been irreversible to date, in many cases resulting from the addition of new ligands[11] or templates.[12] Reversibility can be achieved in some cases by noninvasive stimuli, such as light,[5c,13] or by a change in solvent[14] or concentration,[15] enabling uptake and release of a single guest.

We hypothesized that stimuli-induced reconfiguration between two metal−organic hosts[16] with different guest preferences could lead to a system exhibiting switchable and reversible uptake and release of different guests. In this work, we demonstrate the functioning of such a system for the first time. Our system consists of a mixture of two thermally interconverting Zn_4L_4 tetrahedral diastereomers (Figure 1).

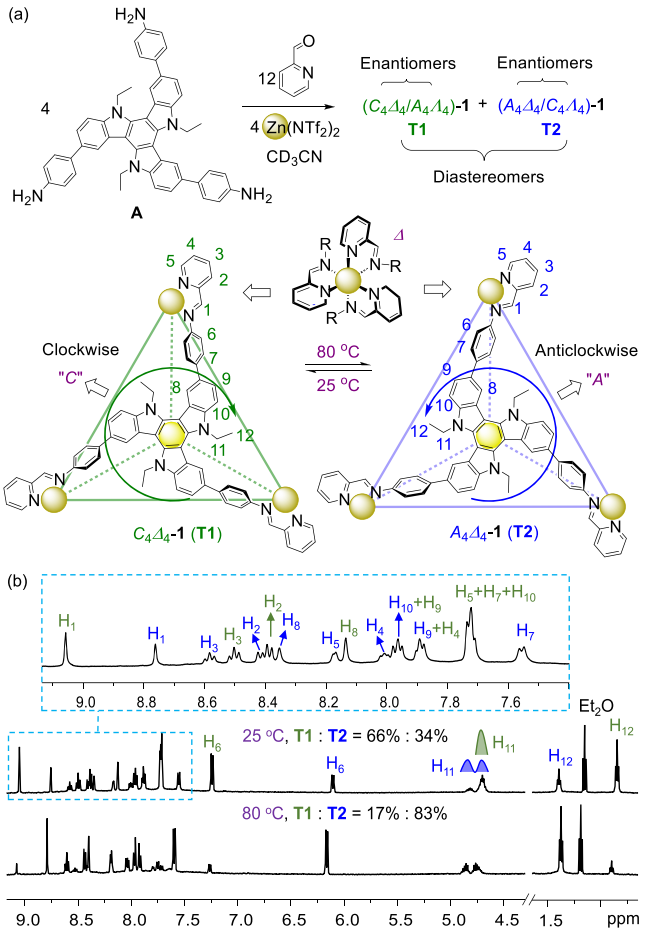

Figure 1. (a) Subcomponent self-assembly of **A** with 2-formylpyridine and Zn^{II} produced two diastereomeric pairs of enantiomers, as illustrated by the structures of $C_4\Delta_4$-**1** and $A_4\Delta_4$-**1**. (b) ^{1}H NMR spectra (CD_3CN, 500 MHz) of **1** at 25 and 80 °C. The protons of $(C_4\Delta_4/A_4\Lambda_4)$-**1** (**T1**) and $(A_4\Delta_4/C_4\Lambda_4)$-**1** (**T2**) have been assigned and are indicated by green and blue labels, respectively.

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Triazatruxene subcomponent **A** (4 equiv) reacted with 2-formylpyridine (12 equiv) and zinc(II) bis-(trifluoromethanesulfonyl)imide (triflimide, Tf_2N^-) (4 equiv) in acetonitrile to give tetrahedron **1** (Figure 1a). The Zn_4L_4 stoichiometry of the assembly was confirmed by ESI-MS (Figure S10). The triazatruxene moieties can be oriented either clockwise (*C*) or anticlockwise (*A*) within the faces of **1** (Figure 1a), and each trischelated octahedral vertex of the tetrahedron may adopt either Λ or Δ handedness. The combination of these two stereochemical elements can thus produce diastereomers.[17] The ^{1}H NMR spectrum of **1** exhibited two sets of ligand signals with the same DOSY diffusion coefficients (Figures 1b and S8), consistent with the presence of two distinct diastereomeric pairs of enantiomers, each belonging to the *T* point group, $(C_4\Delta_4/A_4\Lambda_4)$-**1** (**T1**) and $(A_4\Delta_4/C_4\Lambda_4)$-**1** (**T2**). In contrast, when iron(II) triflimide was used to produce an analogous tetrahedron from the same subcomponent precursors, only one of the two diastereomeric pairs was observed, exclusively $(A_4\Delta_4/C_4\Lambda_4)$-$Fe^{II}_4L_4$.[18] Comparison of the ^{1}H NMR spectral features of Zn_4L_4 **1** and the previous Fe_4L_4 structure, along with observations of their guest binding properties, allowed us to assign each of the two sets of signals in the ^{1}H NMR spectrum of **1** to the corresponding isomer (see section 2.2 in the Supporting Information).

Density functional theory (DFT) calculations provided insight into the structural properties of the two diastereomers of **1**. The optimized structures showed that **T2** has larger pores between pairs of triazatruxene faces, rendering the tetrahedral framework more open than that of **T1**, as illustrated in Figure 2, and greatly increasing the void cavity size. Moreover, the

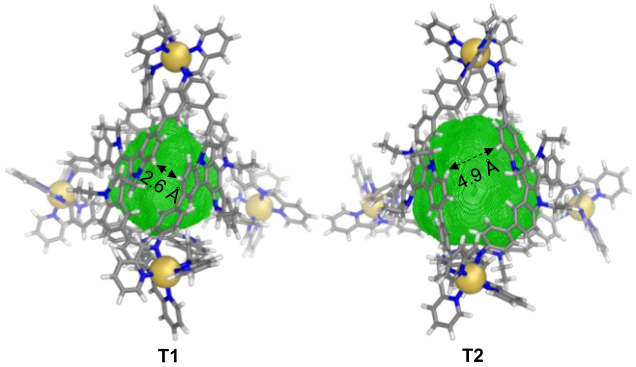

Figure 2. VOIDOO-calculated void spaces (green meshes) within the DFT-optimized models of $C_4\Delta_4$-**1** (**T1**) (volume = 423 Å^3) and $A_4\Delta_4$-**1** (**T2**) (volume = 902 Å^3) with all of the ethyl groups pointing outside of the cavities, viewed down a pore between two faces. Distances between the closest protons across adjacent faces are shown, highlighting the different degrees of cavity enclosure.

orientation of the ethyl groups on the triazatruxene faces of the tetrahedron, either toward or away from the center, was also found to affect the degree of enclosure, cavity volume, and cage stability (see section 4 in the Supporting Information).

The two cage isomers **T1** and **T2** were observed to interconvert in a temperature-dependent equilibrium (Figures 1 and S15). At 25 °C, a **T1**:**T2** ratio of 66:34 was observed, with **T1** predominating. The proportion of **T2** increased with temperature, leading to a **T1**:**T2** ratio of 17:83 at 80 °C. Re-equilibration back to the original proportions was observed after the mixture had been cooled back to 25 °C for 12 h. A van't Hoff analysis revealed **T1** to be enthalpically favorable ($\Delta H = -8.51$ kcal mol^{-1}), whereas **T2** is entropically favored ($\Delta S = 2.73 \times 10^{-2}$ kcal K^{-1} mol^{-1}) (Figure S16). Computation of the vibrational frequencies of the two structures also indicated enhancement of the relative stability of **T2** versus **T1** with increased temperature (see section 4 in the Supporting Information), consistent with the experimental trend.

Cage **1** was first investigated as a host for smaller aliphatic guests. All of the guests shown in Figure 3a were observed to

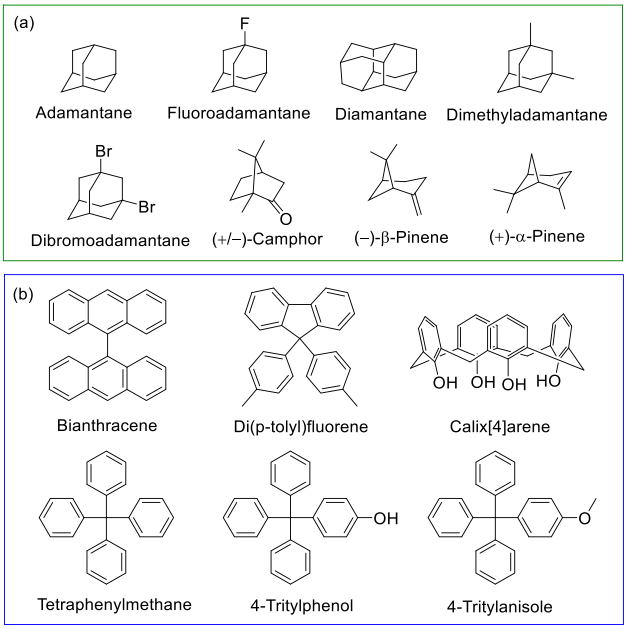

Figure 3. Guests investigated for **1**. (a) Smaller aliphatic guests and (b) larger aromatic guests were bound respectively by **T1** and **T2** in slow exchange on the NMR time scale at room temperature.

be encapsulated within **T1** in slow exchange on the NMR time scale at room temperature (Figures 4a and S22–S41). Titration of a guest into the host solution resulted in the appearance and increase in intensity of characteristically upfield-shifted signals for the bound guests in the range between −2.7 and −0.6 ppm, corresponding to 1:1 guest⊂**T1** complexes by ^{1}H NMR integration. NOESY cross-peaks between the bound guest signals and the aromatic and methyl peaks of occupied **T1** were observed (see section 6.1 in the Supporting Information); no correlations were observed with those of **T2**. Slight shifts in the phenyl and methyl signals of **T2** (H_6 and H_{12}) were also observed in the presence of these guests, suggesting rapid guest exchange on the NMR time scale at room temperature. The presence of multiple equilibria in solution (Figure S21) prevented quantification of the binding strengths of these small guests.

Cage **1** was then investigated as a receptor for the larger guests bearing aromatic rings listed in Figure 3b. These guests were found to interact only with **T2** in slow exchange on the NMR time scale at room temperature (Figures 4b and S43–S61). Upon titration with each guest, new guest⊂**T2** ^{1}H NMR signals were observed between 4.0 and 6.5 ppm, increasing in intensity as the guest was added. NOESY spectra exhibited cross-peaks between the signals of the bound guests and the aromatic protons of occupied **T2** (see section 6.2 in the Supporting Information); no such correlations were observed between signals from the guests shown in Figure 3b and those

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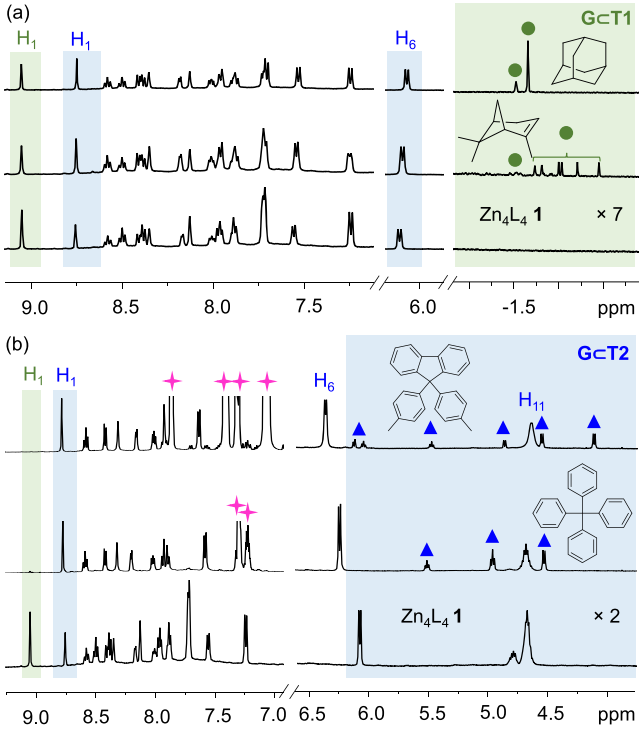

Figure 4. ^{1}H NMR spectra (CD_3CN, 500 MHz, 25 °C) of **1** in the presence of excess representative (a) aliphatic and (b) aromatic guests. Peak assignments are given in Figure 1. Green solid circles and blue solid triangles indicate the peaks of the guests bound in **T1** and **T2**, respectively. The peaks of the free aromatic guests in (b) are marked with magenta crosses.

of **T1**. Integration of the host–guest signals indicated a 1:1 binding stoichiometry in all cases. On the basis of ^{1}H NMR titrations, the binding constants of **T2** for these larger guests were determined and showed a binding hierarchy of bianthracene > di(*p*-tolyl)fluorine > tetraphenylmethane > other guests (Table 1). We infer that both the abundance of aromatic rings and the three-dimensional structures of the guests play important roles in the favorable binding interactions.

Table 1. Binding Constants of T2 for Large Aromatic Guests in CD_3CN at 25 °C

guest	K_a (M^{-1})
bianthracene	$(2.3 \pm 0.1) \times 10^5$
di(*p*-tolyl)fluorene	$(4.6 \pm 0.4) \times 10^4$
calix[4]arene	$(2.6 \pm 0.1) \times 10^3$
tetraphenylmethane	$(1.2 \pm 0.1) \times 10^4$
4-tritylphenol	$(1.7 \pm 0.2) \times 10^3$
4-tritylanisole	$(7.7 \pm 0.1) \times 10^3$

We noted that the addition of these guests also drove the equilibrium from **T1** to **T2** and that the presence of a large excess of guest resulted in the formation of the guest⊂**T2** complex exclusively (Figure S43). The effect of guest binding on the equilibrium between **T1** and **T2** was investigated by considering the guest-induced change in the apparent Gibbs free energy difference ($\Delta G'$) between the total concentrations of **T1** and **T2** (see section 6.2 in the Supporting Information). Our results showed that the progressive addition of each guest gradually switched the sign of $\Delta G'$ from positive to negative (Tables S7–S12), thus favoring species **T2** to a progressively greater degree by the end of the titration.

We infer that the different binding preferences of **T1** and **T2** derive from the differences in their cavity sizes and degrees of cavity enclosure. The smaller and more enclosed cavity of **T1** is more suitable for encapsulation of small aliphatic guests, in contrast to the larger and more open cavity of **T2** (Figure 2), which is better adapted to larger aromatic molecules.

We then explored the use of temperature to trigger the uptake and release of the different guests. Heating a mixture of **1** with one of the aliphatic guests listed in Figure 3a from 25 to 80 °C led to a significant decrease in the peak intensities of **T1** with a concomitant increase of those of **T2** (Figures S62–S69). The peaks of the bound guests within **T1** became nearly undetectable at 80 °C, indicating the release of these guests from **T1**. Cooling the mixture back to 25 °C for 2 days regenerated the initial ratio of **T1** and **T2**, leading to reuptake of the released guests by **T1**. For instance, the equilibrium mixture of **1** and dibromoadamantane contained 50% and 9% guest⊂**T1** at 25 and 80 °C, respectively (Table S13). Switching the temperature thus enabled the reversible uptake and release of dibromoadamantane from **T1** due to the 41% change in the population of guest⊂**T1**.

In contrast, heating a mixture of **1** and one of the aromatic guests listed in Figure 3b increased the population of guest⊂**T2** (Figures S70–S73) because of the greater thermodynamic stability of **T2** at higher temperatures, which drove the uptake of the guest. Re-equilibration of the mixture at 25 °C for 2 days led to a decrease in the **T2** population and the release of the **T2**-bound guest. This process is exemplified by the case of calix[4]arene, which showed a 15% change in the population of guest⊂**T2**, switching between 24% and 39% when the temperature was changed between 25 and 80 °C, leading to the reversible uptake and release of calix[4]arene from **T2** (Table S14). It should be noted that the temperature-dependent capture and release by **T2** is impracticable in the presence of a large excess of an aromatic guest from Figure 3b because of the complete formation of guest⊂**T2** even at 25 °C, as discussed above (Figure S43).

We then investigated the simultaneous uptake and release of a pair of different guests, dibromoadamantane (**G1**) and calix[4]arene (**G2**), within a single system (Figure 5). The initial equilibrium mixture at 25 °C contained **G1**⊂**T1** as the major species (52%), relative to the populations of **G2**⊂**T2** (16%) and empty **T1** and **T2** (32% in total) (Figure S74 and Table S18). This hierarchy was inverted at 80 °C, with only 3% **G1**⊂**T1** and 50% **G2**⊂**T2**. The temperature increase thus

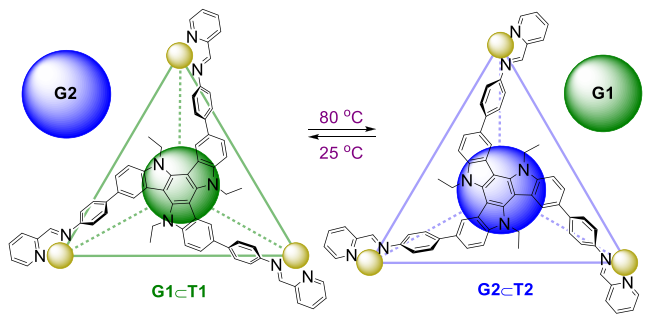

Figure 5. Schematic representation of reversible uptake and release of the guests dibromoadamantane (**G1**) and calix[4]arene (**G2**) by **T1** and **T2**, respectively, via thermoswitching.

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resulted in the release of **G1** from **T1** and the uptake of **G2** by **T2**. Conversely, the release of **G2** from **T2** and the uptake of **G1** by **T1** occurred as the initial equilibrium population was re-established when the mixture re-equilibrated at 25 °C over 2 days.

In summary, a new and straightforward means of stimulus-directed guest uptake and release has been developed that is based upon the different thermodynamic stabilities of the two diastereomers of tetrahedral host **1** and their differential guest preferences. This ability to reversibly catch and release guests may prove useful in the context of new switchable catalytic systems, where a catalyst is released only when needed, or in new modes of chemical purification, where a cargo molecule may be selectively taken up from a mixture, moved to where it is needed, and released in pure form following a temperature change.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07307.

Complete experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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