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Subcomponent Exchange Transforms an Fe$^{II}_4$L$_4$ Cage from High- to Low-Spin, Switching Guest Release in a Two-Cage System

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Ⓢ *Supporting Information*

ABSTRACT: Subcomponent exchange transformed new high-spin Fe$^{II}_4$L$_4$ cage **1** into previously-reported low-spin Fe$^{II}_4$L$_4$ cage **2**: 2-formyl-6-methylpyridine was ejected in favor of the less sterically hindered 2-formylpyridine, with concomitant high- to low-spin transition of the cage's Fe^{II} centers. High-spin **1** also reacted more readily with electron-rich anilines than **2**, enabling the design of a system consisting of two cages that could release their guests in response to combinations of different stimuli. The addition of *p*-anisidine to a mixture of high-spin **1** and previously-reported low-spin Fe$^{II}_4$L$_6$ cage **3** resulted in the destruction of **1** and the release of its guest. However, initial addition of 2-formylpyridine to an identical mixture of **1** and **3** resulted in the transformation of **1** into **2**; added *p*-anisidine then reacted preferentially with **3** releasing its guest. The addition of 2-formylpyridine thus modulated the system's behavior, fundamentally altering its response to the subsequent signal *p*-anisidine.

Stimuli-responsive container molecules,[1] whose uptake and release of guests can be controlled through the application of external signals,[2] are useful building blocks for molecular networks.[3] The development of new stimuli-responsive behaviors[1f,4] allows for these networks to increase in complexity, as cages may be addressed individually within mixtures,[5] or signals may be passed between network members in order to construct complex responses.[6] An ultimate goal is to approach the functional complexity exhibited by the signaling pathways in biological systems.

Structures prepared via subcomponent self-assembly[7] can transform in response to external stimuli through the reversible reconfiguration of the dynamic covalent and coordinative bonds holding the structures together;[8] examples include the rearrangements of a Schiff-base ligand[7b] and *meso*-helicates[7e] via aldehyde exchange, and the imine exchanges undergone by dynamic cages when an electron-rich amine substitutes an electron-poor amine residue.[9]

In this study, we envisaged a new approach whereby a chemical stimulus transforms a high-spin Fe$^{II}_4$L$_4$ cage into a low-spin analog through exchange of a more bulky aldehyde subcomponent for a less bulky one. Others[10] and our group[11] have reported Fe^{II} cages and helicates that undergo spin-crossover[12] induced by heat and light. Mononuclear Fe^{II} complexes incorporating 2-formyl-6-methylpyridine undergo spin-crossover,[13] attributed to a steric clash between methyl groups and adjacent pyridine rings destabilizing the low-spin

state relative to the high-spin state.[14] Fe^{II} mononuclear complexes are observed to preferentially incorporate 2-formylpyridine over 2-formyl-6-methylpyridine.[14] Thus, alleviation of steric clash might drive exchange of 2-formylpyridine for 2-formyl-6-methylpyridine, transforming an Fe^{II} cage from high-spin to low-spin.

Here we report the self-assembly of high-spin Fe$^{II}_4$L$_4$ cage **1** incorporating 2-formyl-6-methylpyridine as a subcomponent. Cage **1** binds a variety of neutral guests in acetonitrile. Paramagnetic ^{1}H NMR spectroscopy provides a sensitive means for detecting guest encapsulation and determining guest identity due to the isotropic shifts of the paramagnetic Fe^{II} centers.[15] High-spin **1** did not transition to a low-spin state upon lowering the temperature to 268 K; however, the chemical stimulus 2-formylpyridine transformed high-spin **1** into previously reported low-spin Fe$^{II}_4$L$_4$ cage **2**,[16] as a consequence of aldehyde exchange. This transformation was used to set up a system such that either one of a pair of cages could be opened, and its guest released, following the addition of a different chemical stimulus, *p*-anisidine.

Cage **1** was prepared by reaction of iron(II) triflate, triamine **A**[16] and commercially available 2-formyl-6-methylpyridine (1:1:3) in CD$_3$CN (Scheme 1). The [Fe$^{II}_4$L$_4$] composition was confirmed by high-resolution ESI-MS (Figure S4). Unlike previously reported low-spin **2**,[16] which contains 2-formylpyridine residues, the Fe^{II} centers of **1** are high-spin between 268 and 318 K (Figure S5). The ^{1}H NMR spectrum of **1** has the eight proton signals expected for a *T*-symmetric structure spread over ca. 240 ppm (Figure S1), displaying Curie–Weiss behavior above 268 K (Figure S6).[17] We infer the high-spin character of **1** to be a consequence of steric clash between methyl groups and adjacent pyridine rings.[13,14]

The paramagnetic signals of **1** were assigned following the methods employed by Raehm[18] and Ward[19] for paramagnetic Co^{II} complexes. T_1 relaxation times were measured and correlated to the distances between the paramagnetic center and proton according to the Solomon equation (Table S1, Figure S7).[20] Cross-peaks observed in the COSY spectrum (Figure S3) and comparison to the calculated chemical shifts for a related high-spin Fe^{II} mononuclear complex[21] provide additional support for our ^{1}H NMR assignments and proposed solution structure of **1**.

Host–guest studies revealed that cage **1** (2 mM) encapsulated a similar range of guests (10–15 equiv) to cage **2**[16] in acetonitrile at 298 K, although guest uptake was faster

Scheme 1. Self-Assembly of High-Spin Fe$^{II}_4$L$_4$ Cage 1 and Transformation to Low-Spin Cage 2
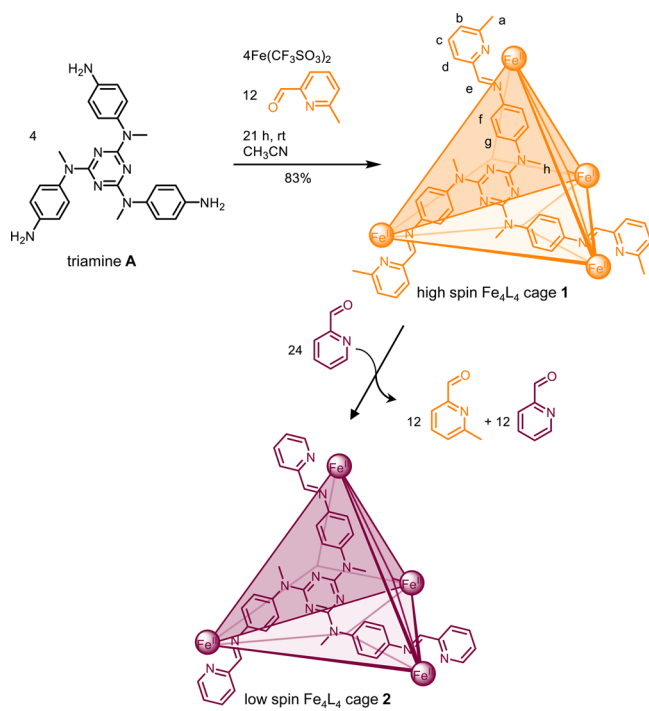
(approaching equilibrium within 4 h) because high-spin Fe^{II} complexes have more labile N→Fe^{II} bonds than their low-spin analogs. In the ^{1}H NMR spectra, each guest was bound in slow exchange, with shifts of both the cage and guest peaks observed upon encapsulation. Encapsulated guest signals were observed in all cases between −10 and −20 ppm and their T_1 values were of a similar magnitude to the T_1 value for proton **h**, reflecting the isotropic shifts experienced by the guests within the paramagnetic host cavity (Table S2).

Prospective guests for **1** were divided into three groups based upon the extent of host−guest complexation (Figure 1). Complete conversion to the host−guest complex was observed for guests that matched the size and shape of the cavity well, such as adamantane (Figures 1a, S8), whereas two sets of NMR signals corresponding to the empty cage and host−guest complex were observed for guests with a poorer match for the cavity, such as *o*-xylene (Figures 1b, S9). *m*- and *p*-Xylene
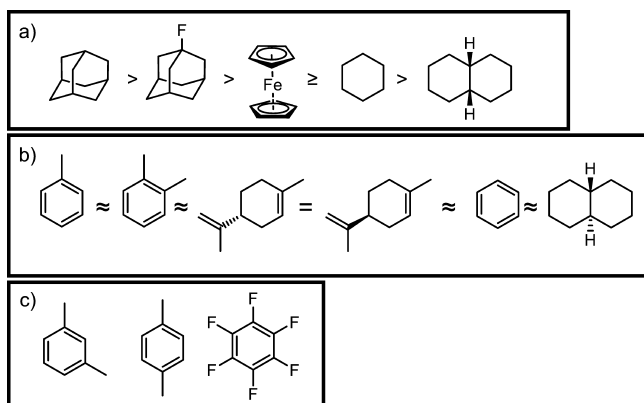

Figure 1. Guests for cage **1** that **a)** bind strongly, **b)** bind weakly and **c)** are not observed to bind.

bound in trace amounts (Figures S49−52) and hexafluorobenzene did not bind at all, which we attribute to unfavorable interactions between this electron deficient guest and the electron deficient cavity (Figure 1c). The relative binding affinities of the guests in Figure 1a were estimated from competition experiments (Figures S53−S66).

The paramagnetic Fe^{II} centers in cage **1** enabled the sensitive detection of guest encapsulation and straightforward discrimination of signals belonging to different isomers by ^{1}H NMR spectroscopy. Encapsulated NMR signals are spread over a wider chemical shift range, thus reducing signal overlap and improving dispersion upon encapsulation.[15b] For strongly bound guests, such as adamantane, minor sets of encapsulated guest signals were observed alongside the major set of peaks corresponding to bound adamantane (Figure S14). GC−MS analysis of these guests (commercial claimed purity of 98+%) revealed trace impurities (Figures S10−13). We infer the minor NMR signals to correspond to these impurities encapsulated within cage **1**. Thus, cage **1** can enable the detection of trace quantities of strongly binding guests within mixtures by NMR spectroscopy in a manner that would not be possible using diamagnetic hosts.

Similarly, trace *cis*-decalin could be sensed as an impurity in commercial *trans*-decalin (Figures S9, S65). Cage **1** also binds *o*-xylene over the other xylene isomers (Figure S66). The separation of xylene isomers from mixed hydrocarbons is costly and inefficient due to the close similarity in the physicochemical properties of the isomers.[22] Host−guest complexation within **1** could thus enable the separation of *o*-xylene.[23]

Subcomponent exchange within cage **1**, empty or with bound 1-fluoroadamantane (1-FA), proceeded in anhydrous CD$_3$CN upon addition of 2-formylpyridine (24 equiv), resulting in a color change from orange to red-purple. The use of excess 2-formylpyridine was found to result in sharper ^{1}H NMR spectra, rendering the process easier to follow. Released 2-formyl-6-methylpyridine was observed by ^{1}H NMR spectroscopy with a concomitant decrease in the intensities of the peaks for cage **1** and appearance of new paramagnetic species after 16 h at 50 °C (Figures S69, S72). However, no NMR peaks corresponding to cage **2** (Figure S70) or its host−guest complex (Figure S73) were observed until 5% D$_2$O (v/v) was added, resulting in a color change to dark purple (Figure S67). The requirement for water to complete the transformation implies that hydrolyzed species are intermediates during the exchange process, as reported by Hahn[7b] and Hooley.[7e] When no guest was present, the transformation was complete within 1 day at 50 °C (Figure S70) whereas the equilibration process was slower for the full cage, with kinetics depending on the amount of water added (Figure S75). In addition to the encapsulated 1-FA within **2**, a putative intermediate encapsulated 1-FA species was observed in the ^{19}F NMR spectrum during equilibration (Figure S74), suggesting that the guest remained bound during the transformation.

Selective cage breakdown and guest release could be triggered by the chemical signal *p*-anisidine, which opens cages through imine exchange.[3a,24] As cage **1** was thermodynamically unstable with respect to **2** in the presence of 2-formylpyridine, we hypothesized that **1** might react more readily with *p*-anisidine and that a low-spin Fe$^{II}_4$L$_6$ cage **3**[25] (Scheme 2) might react with *p*-anisidine at a rate intermediate between those of **1** and **2**. This differential reactivity would allow for the functioning of the system shown in Scheme 2. A mixture of **1** and **3** would thus react with *p*-anisidine to

Scheme 2. Cage Disassembly and Guest Release Triggered by *p*-Anisidine[a]
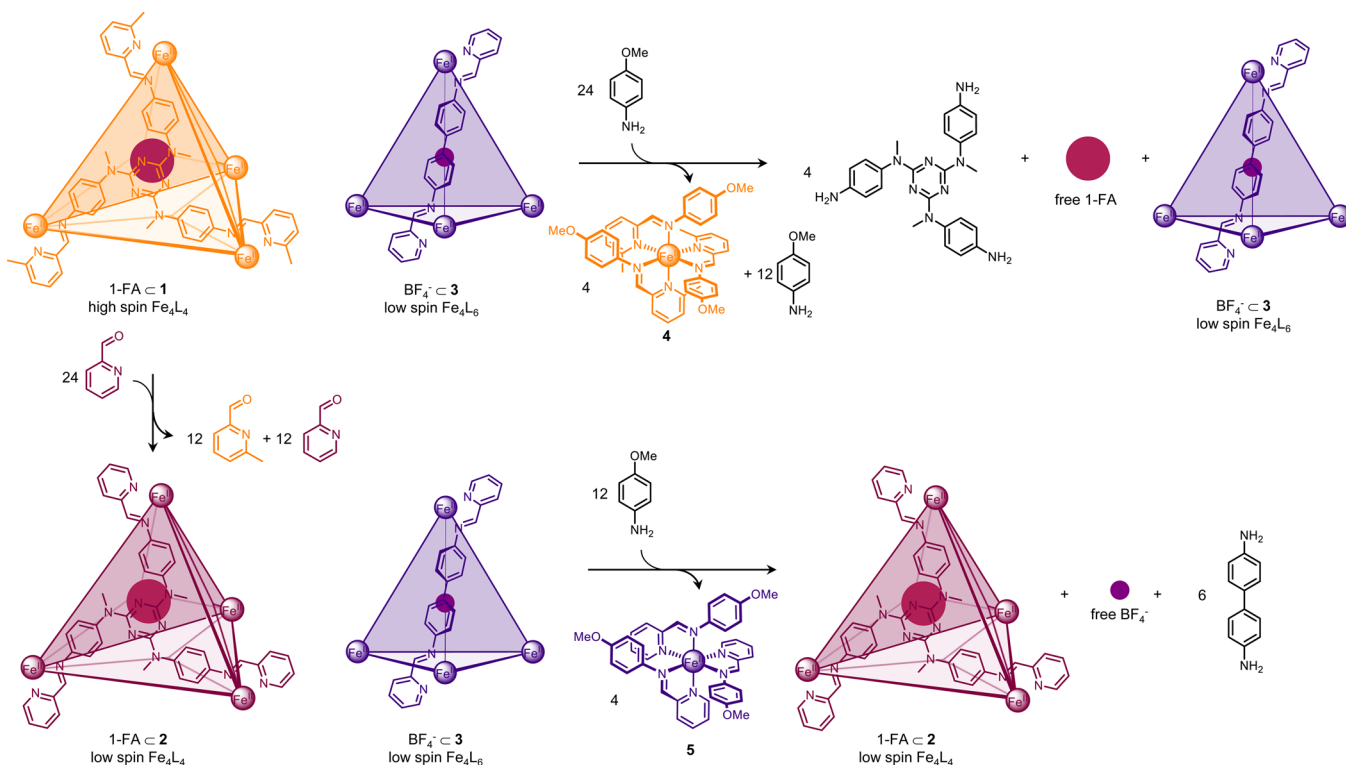
[a]High-spin $Fe^{II}_4L_4$ cage **1** reacted with *p*-anisidine in the presence of low-spin $Fe^{II}_4L_6$ cage **3**, releasing the guest 1-fluoroadamantane (1-FA) and forming mononuclear complex **4**. Following the transformation from high-spin cage **1** to low-spin cage **2**, low-spin $Fe^{II}_4L_6$ cage **3** was instead broken down by *p*-anisidine releasing the guest BF_4^- and forming **5**. Each transformation was performed in the presence of an excess of 1-FA (10 equiv per cage **1** or **2**).

selectively liberate the guest of **1**, whereas initial treatment with 2-formylpyridine would result in a mixture of **2** and **3**, whose reaction with *p*-anisidine would selectively liberate the guest of **3**. Guests containing fluorine (BF_4^- for **3** and 1-FA for **1** and **2**) were chosen so that guest release could be monitored by ^{19}F NMR spectroscopy. Importantly, control experiments revealed there was no aldehyde or guest exchange between $[BF_4^- \subset 3]$ and $[1\text{-FA} \subset 1]$ and the aldehyde exchange process was unaffected by the presence of $[BF_4^- \subset 3]$ (Figures S95–S97).

The selectivity of cage disassembly and guest release was first investigated for an equimolar mixture of $[1\text{-FA} \subset 1]$ and $[BF_4^- \subset 3]$. As *p*-anisidine (24 equiv) was progressively added, the ^1H NMR signals corresponding to $[1\text{-FA} \subset 1]$ were observed to disappear whereas those for $[BF_4^- \subset 3]$ remained (Figures S88–S89). Control titrations with each cage separately revealed *p*-anisidine to react with both cages, but more readily with $[1\text{-FA} \subset 1]$ (Figures S91–S94). The addition of excess *p*-anisidine (24 equiv) to $[1\text{-FA} \subset 1]$ thus resulted in its complete disassembly at room temperature in the presence of $[BF_4^- \subset 3]$, releasing 1-FA (Figures S85–S87). The encapsulated 1-FA signal disappeared in the ^{19}F NMR spectrum, whereas BF_4^- remained encapsulated within **3** (Figure S87).

In contrast, the selectivity of cage disassembly was inverted for an equimolar mixture of $[1\text{-FA} \subset 2]$ and $[BF_4^- \subset 3]$ due to the increased thermodynamic stability of face-capped compared with edge-bridged tetrahedra;[24] only the NMR signals for $[BF_4^- \subset 3]$ disappeared following progressive addition of *p*-anisidine (12 equiv) and heating (Figures S100–S101). Control experiments were also carried out for the individual

cages (Figures S102–S105). The mixture of $[1\text{-FA} \subset 2]$ and $[BF_4^- \subset 3]$ resulting from aldehyde exchange reacted similarly with stoichiometric *p*-anisidine (12 equiv) upon heating (Figure S98), resulting in disassembly of $[BF_4^- \subset 3]$ and release of BF_4^-, whereas 1-FA remained bound within the transformed cage **2** (Figure S99).

We have demonstrated the transformation of Fe^{II} centers in a $Fe^{II}_4L_4$ cage from high- to low-spin for the first time via selective aldehyde exchange. In the presence of low-spin $Fe^{II}_4L_6$ cage **3**, this transformation was employed to switch the guest release outcome following application of the chemical signal *p*-anisidine, due to the difference in the relative reactivities of the high- and low-spin cages. Switching the spin state of a cage is thus a promising new strategy for signal transduction. Future work will focus upon integrating these processes into larger signaling networks.[6]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01478.

Complete experimental procedures including full characterization, NMR data and ESI mass spectra (PDF)

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Notes

The authors declare no competing financial interest.

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