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Networked-Cage Microcrystals for Evaluation of Host–Guest Interactions

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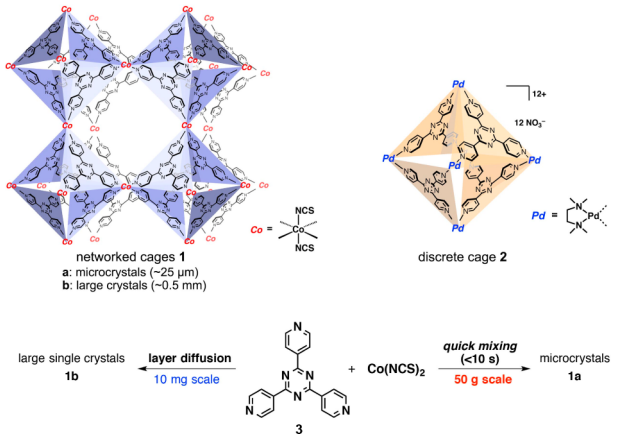
Supporting Information

ABSTRACT: We have developed a new synthetic protocol for the preparation of a microcrystalline powder (median size: X_{50} = 25 μm) of networked M_6L_4 cages **1a** for the stationary phase of an affinity column on a greater than 50 g scale. Analogously to large single crystals **1b** (X_{50} ≈ 0.5 mm), microcrystals **1a** accommodate guest molecules tetrathiafulvalene (TTF) and fullerene (C_{60}) at up to 32 and 35 wt %, respectively. Importantly, the host–guest interactions within networked cages could be evaluated in terms of the retention time from HPLC analysis by using microcrystals **1a** as the stationary phase. In this way, favorable guests for networked cages **1** and even solution M_6L_4 cage **2** could easily be assessed by HPLC.

Finding a matching host–guest pair is the key to taking full advantage of non-covalent interactions in supramolecular chemistry,[1] sensing technology,[2] and enzyme engineering.[3] Affinity column chromatography is a conventional technique that is frequently employed for guest screening.[4] However, immobilization of host counterparts[5] onto a solid-phase support is not always successful because of the difficulty in the synthetic modification of the properties of the solid support. We recently reported networked molecular cages **1**, which are composed of M_6L_4 octahedral molecular cages that are isostructural to Pd cage **2**, and showed that the host–guest chemistry in solution can be qualitatively transferred into the crystalline state.[6,7] Specifically, the M_6L_4 cage units in crystals **1** accommodate guest molecules such as tetrathiafulvalene (TTF) upon soaking of the crystals in guest solutions and release these guests upon washing with an appropriate solvent. This reversible host–guest complexation prompted us to use networked cages **1** as the stationary phase of an affinity column for the facile evaluation of host–guest interactions between the octahedral M_6L_4 cage and guest molecules. Here we report a new synthetic method for the size-controlled preparation of microcrystals of networked cages **1** suitable for the stationary phase of an HPLC column on a >50 g scale that simply requires the quick mixing of ligand and metal salt solutions. Using a column packed with microcrystals of **1**, host–guest interactions between the M_6L_4 cage and several guest molecules were evaluated in terms of their retention times, and this allowed us to screen guests for accommodation in both discrete and crystal cages. Unlike previously reported MOF-packed columns,[8] the guest affinity is well-correlated with that of discrete counterpart cage **2**, a highly efficient solution host for a variety of organic guests.

In our previous method,[6] networked cages **1** were synthesized on a 10 mg scale as ca. 0.5 mm-sized orange single crystals (denoted **1b**) by slow layer diffusion between an *o*-dichlorobenzene/MeOH solution of tris(4-pyridyl)triazine (**3**) (4 mM) and an MeOH solution of $Co(NCS)_2$ (40 mM) over 1 week (Scheme 1). We found that quick mixing of the

Scheme 1. Synthesis of Networked and Discrete Cages 1 and 2



two solutions (<10 s) provided fine orange microcrystals of **1** (denoted **1a**) on up to a >50 g scale (Scheme 1 and Figure S4 in the Supporting Information). To a solution of ligand **3** (4.0 mM, 9.0 L) was quickly added a solution of $Co(NCS)_2$ (40 mM, 1.8 L) in one portion (<10 s) with vigorous stirring. After 30 s of stirring, a large amount of orange crystalline powder formed and was collected by filtration to give 52 g of microcrystals **1a** (62% yield).

The powder X-ray diffraction (PXRD) pattern of microcrystals **1a** was consistent with that of single crystals **1b**, which indicates that networked M_6L_4 cages were exclusively synthesized (Figure S2). The median grain size of microcrystals **1a** was determined by laser diffraction analysis to be X_{50} = 25 μm (Figure S5), which is markedly smaller than that of **1b** (X_{50} = 0.52 mm). Scanning electron microscopy measurements confirmed the cuboctahedral shape of **1a** with an average

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diameter of ~25 μm (Figure S7). Quick mixing of the two components within <10 s by manual stirring with a paddle was essential for obtaining a homogeneous powder of **1a** (Figure S1); preparation with only magnetic stirring gave much poorer crystallinity.

To evaluate the purity of the obtained microcrystalline powder **1a**, we compared the guest encapsulation behaviors of **1a** and single crystals **1b** using TTF and C_{60}, which are suitable guest molecules for networked cages. When microcrystals **1a** (70 mg) were immersed in a saturated TTF solution in toluene (4 mL), the microcrystals immediately turned black, which indicated the rapid penetration of TTF (Figure 1b). The diffuse

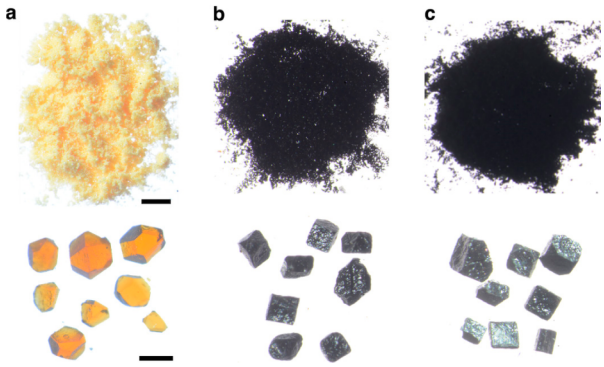

Figure 1. Photographs of (a) as-synthesized, (b) TTF-included, and (c) fullerene C_{60}-included networked cage complexes: (top) microcrystalline powder **1a**; (bottom) large single crystals **1b**. Scale bars are 500 μm.

reflectance spectrum of **1a** recorded after immersion for 1 h was almost identical to that of **1b**·(TTF), in which four TTF molecules are accommodated in every M_6L_4 chamber. The guest content of **1a**·(TTF) was determined to be 32 wt % by elemental analysis and extraction experiments; this is comparable to that of single crystals **1b**·(TTF) (30 wt %). In a similar fashion, microcrystals **1a** accommodated C_{60} at 35 wt % upon soaking in a saturated toluene solution of C_{60}, which also matches the value of large single crystals **1b** (35 wt %). Therefore, it was concluded in terms of guest binding ability that microcrystals of networked M_6L_4 cages **1a** were obtained qualitatively in pure form.

To our delight, the inclusion of TTF in microcrystals **1a** was markedly faster than the inclusion within single crystals **1b**. The inclusion amount for microcrystals **1a** reached 23 wt % after soaking for 1 min, whereas only 15 wt % TTF was enclathrated in large crystals **1b** during the same time period. Although inclusion in both **1a** and **1b** had almost reached the maximum amount after 60 min, a distinct difference was observed during the initial 1 min. This is attributable to the larger surface area of microcrystals **1a** compared with large single crystals **1b**.

Harnessing the fine grain size and fast guest-inclusion behavior of **1a**, we prepared a packed column of microcrystals **1a** for the screening of suitable guest molecules for M_6L_4 cages. As a benchmark test, we examined the separation of a mixture of three aldehyde compounds, 2-naphthylaldehyde (**4**), 5-formyl-2,2′-bithiophene (**5**), and formyltetrathiafulvalene (**6**), which are known to be encapsulated into Pd cage **2** in solution. All three compounds were eluted, and the retention times were 4.7, 7.9, and 17.9 min, respectively (Figure 2a). The order of elution is consistent with the electron-donating character of the π-conjugated rings for **4**–**6** (Figure S11).

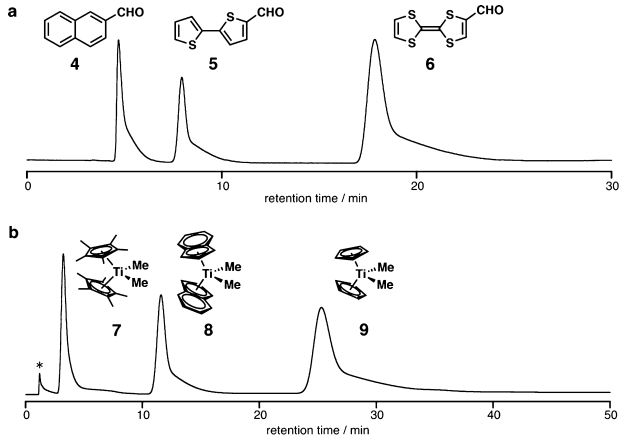

Figure 2. Chromatograms of mixtures of compounds (a) **4**, **5**, and **6** and (b) 7, **8**, and **9** recorded using a column packed with microcrystals **1a** as the stationary phase (column diameter, 4 mm; length, 15 cm; flow rate, 1.0 mL/min; mobile phase, toluene; detector, 380 nm; *, impurity).

In solution chemistry, it is known that guest molecules with electron-donating character are strongly accommodated into the cavity of molecular cage **2** as a result of π–π or charge-transfer interactions with electron-deficient triazine ligand **3**.[1a] Therefore, the order of the retention times for guests **4**–**6** qualitatively indicate the affinities of the guests for M_6L_4 cages.

To investigate the influence of the bulkiness of the guests, we also compared the retention times of titanocene compounds **7**–**9**. In our previous report, we showed that ruthenium complexes with cyclopentadienyl (Cp) or indenyl ligands can be encapsulated into cage **2**, whereas the pentamethylcyclopentadienyl (Cp*) ligand is too bulky to be accommodated.[9] Cp*-titanocene **7** was eluted from the **1a**-packed column much faster than titanocene guests **8** and **9** (Figure 2b), despite the fact that the electron-donating characteristics of **7**–**9** are not significantly different. Compound **9** has the longest retention time and thus appears to be the most favorable guest for the cage. Although the influence of host–guest interactions in the large interstitial pores of **1** cannot be ruled out, the retention times of the guests reflect both the electronic and size compatibility with the M_6L_4 cage.

In light of the chromatogram in Figure 2b, host–guest complexes with titanocene compounds **7**–**9** were prepared with large single crystals **1b** and analyzed by inductively coupled plasma (ICP) spectroscopy and single-crystal diffraction. As expected, inclusion complex **1b**·**9**, prepared by soaking crystals **1b** in a saturated toluene solution of dimethyltitanocene **9**, showed the highest guest inclusion in the crystals (7.6 molecules/cage unit by ICP). Inclusion of titanocene compounds **7** and **8** was also confirmed by ICP analysis, but these molecules were enclathrated to a lesser extent (guest/cage = 3.0 for **1b**·**7** and 3.0 for **1b**·**8**).

Single-crystal analysis confirmed the structure of inclusion complex **1b**·**9**, in which a titanocene molecule **9** is clearly encapsulated inside the cage and rather disordered guests **9** are found around the portals (Figure 3). Two Cp rings of guest **9** inside the cage are favorably stacked on the π plane of ligand **3** and exhibit the strongest host–guest interactions, while other guests **9** are weakly trapped by the cage. Although inclusion of titanocene compounds **7** and **8** was also confirmed by ICP analysis, single crystal X-ray analysis was unsuccessful in both cases. This can be attributed to the disorder and low occupancy

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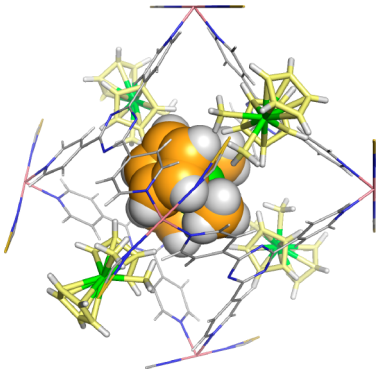

Figure 3. X-ray crystal structure of host–guest complex **1b**·**9** (line model, M_6L_4 cage; stick model, guest **9** at the portals; CPK model, guest **9** inside the cage).

of the guests due to the weaker host–guest interactions compared with titanocene **9**.

In summary, we have developed an instant and large-scale synthesis of microcrystals of networked M_6L_4 cages **1** that accommodate a variety of guest molecules in the cavity. Because of the fine grain size, as-synthesized microcrystals **1a** can be directly used as the stationary phase of an affinity column. The affinity column packed with microcrystals **1a** can resolve several compounds depending on the host–guest interactions with the M_6L_4 cage unit, thus allowing the facile screening of suitable guests for networked cages **1**. Finally, we succeeded in selecting the most favorable guest in a series of titanocene compounds and determined the structure of the host–guest complex by single-crystal X-ray analysis. Unlike other MOF-packed column systems, the host–guest chemistry of our networked cages can be transferred into the solution state using discrete host **2**. Therefore, guest screening with a **1a**-packed column would also be beneficial for finding a good host–guest pair for **2**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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