

# Recognition of Polyfluorinated Compounds Through Self-Aggregation in a Cavity

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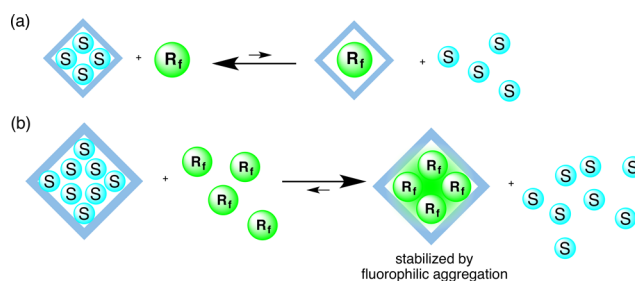
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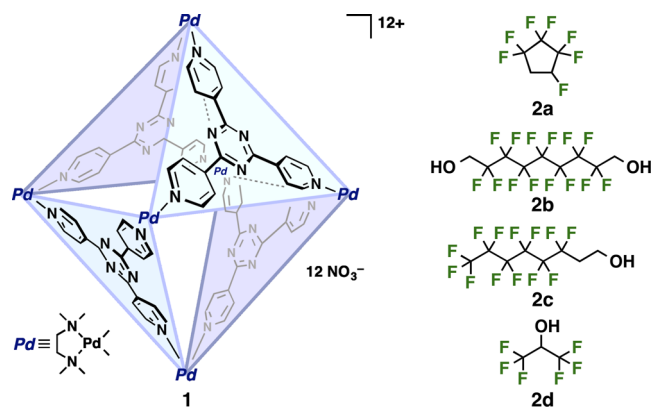
**ABSTRACT:** Polyfluorinated aliphatic compounds were encapsulated by a self-assembled  $M_6L_4$  coordination host in aqueous media. NMR titration and X-ray crystallographic analyses clearly revealed that the aggregation of the fluorinated moieties of the guests in the host cavity plays a significant role in the binding. Polyfluorinated aromatics did not show such aggregation in the cavity because of their “nonfluorous” nature.

Because of the highest electronegativity and extremely poor polarizability of fluorine atoms, polyfluorinated compounds exhibit unique physicochemical properties, particularly in that they are both hydrophobic and lipophobic.<sup>1</sup> At a molecular level, this amphiphobic nature reflects in the difficult design of synthetic hosts for fluorinated compounds which are important due to their environmental significance. Only a few host compounds for *fluorous* guests have been reported so far,<sup>2,3</sup> in which the driving force is a hydrophobic effect<sup>2</sup> or size compatibility.<sup>3</sup> The amphiphobicity of fluorinated compounds, however, brings about their distinct fluorophilicity that facilitates fluorous self-aggregation/segregation<sup>4</sup> or makes fluorinated compounds soluble in fluorous solvents.<sup>1</sup> Here, we report that the self-aggregation of polyfluorinated compounds in a confined cavity can be a driving force for their molecular recognition. Because of their amphiphobicity, fluorinated compounds cannot form stable 1:1 complexes with common synthetic cages (Figure 1a). However, when the cavity of the hosts is large enough to accommodate multiple fluorinated compounds, self-aggregation among the fluorous guests may result in the stabilization of the host–guest complex, pushing the equilibrium toward the complex (Figure 1b).

Self-assembled coordination cage **1**<sup>5a,d</sup> shows strong binding ability for organic molecules, especially for electron-rich ones with various sizes and shapes by virtue of its large hydrophobic cavity ( $\sim 460 \text{ \AA}^3$ ) surrounded by four electron-deficient triazine-coored panels (Figure 2).<sup>5</sup> Unlike common organic hosts, cage **1** can accommodate multiple (up to four) small molecules in the cavity. Since positive cooperativity is always observed in the binding of multiple guest molecules,<sup>5a–d</sup> the host–guest complexes are stabilized not only by host–guest interactions but also by guest–guest self-aggregation. We thus thought that the stabilization by self-aggregation is particularly enhanced



**Figure 1.** Schematic representations of (a) unimolecular and (b) multimolecular binding of polyfluorinated guests (S, solvent;  $R_f$ , polyfluorinated compounds). Unimolecular binding is dissociative because of the amphiphobicity of the guests (a), while multimolecular binding is associative because of the fluorophilicity among the guests (b).



**Figure 2.** Self-assembled coordination cage **1** and polyfluorinated aliphatic guests **2a–d**.

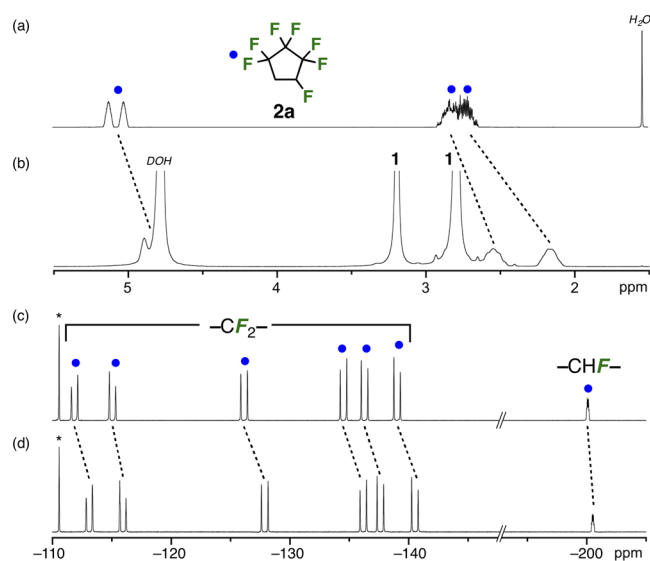
with polyfluorinated guests because of their distinct fluorophilic nature.

Recognition of polyfluorinated aliphatic compounds by cage **1** was examined in aqueous media. An excess amount of water-insoluble guests **2a–c** ( $\sim 10$  equiv) was suspended in an aqueous solution of cage **1** (5.0 mM, 1.0 mL) and stirred at room temperature or  $80 \text{ }^\circ\text{C}$  for 30 min. After removal of the excess guests by decantation or filtration, the guest encapsulation was confirmed by the upfield shift of the guest

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signals in  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra (Figure 3 and Figure S1 in Supporting Information [SI]). The host-guest ratios of **1** to

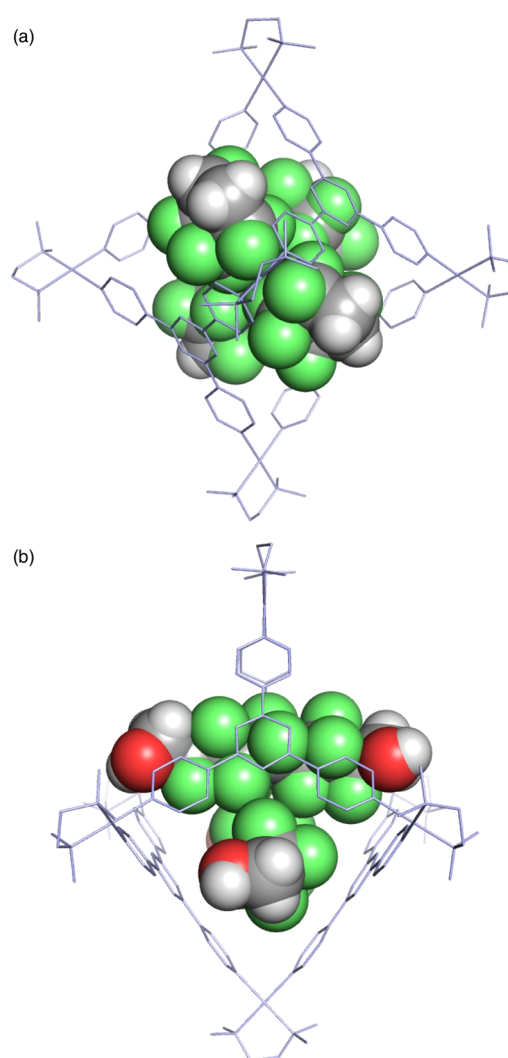


**Figure 3.**  $^1\text{H}$  NMR spectra (500 MHz, 300 K) of (a) **2a** in  $\text{CDCl}_3$  and (b)  $1\cdot(2a)_4$  in  $\text{D}_2\text{O}$ .  $^{19}\text{F}$  NMR spectra (470 MHz, 300 K) of (c) **2a** in  $\text{CDCl}_3$  and (d)  $1\cdot(2a)_4$  in  $\text{D}_2\text{O}$  (\* labels denote signals of internal standard, 1,3,5-trifluorobenzene).

**2a–c** were determined as 1:4 (**2a**), 1:2 (**2b**), and 1:2 (**2c**), respectively, by the integral ratios in the  $^1\text{H}$  NMR spectra (see the SI). In the case of  $1\cdot(2a)_4$ , upfield shifts of the proton signals and the fluorine signal of  $-\text{CHF}-$  in **2a** were moderate (0.3–0.6 ppm), while the fluorine signals of  $-\text{CF}_2-$  moieties were remarkably shifted (0.9–1.7 ppm). This result may indicate that the C–H bonds are located around the portal of **1** while the  $-\text{CF}_2-$  moieties are deeply embedded in the cavity to form a stable fluororous aggregate. The same behavior (moderate shifts of protons and significant shift of fluorine moieties in NMR spectra) was observed in  $1\cdot(2b)_2$  and  $1\cdot(2c)_2$ .

Aggregation of fluorinated moieties in the inclusion complexes was confirmed by the crystal structures of  $1\cdot(2a)_4$  and  $1\cdot(2b)_2$  (Figure 4). In the crystal structure of  $1\cdot(2a)_4$ , the fluorinated moieties of **2a** are aggregated at the core of the cavity, while the polar C–H moieties are exposed outside at the portal of **1** (Figure 4a). Similarly, in the inclusion complex  $1\cdot(2b)_2$ , the fluorinated moieties of **2b** are deeply shielded by the cavity of **1**, whereas both of the terminal hydroxyl groups of **2b** stick out at the portal of **1**. The exposure of the hydrophilic groups to water solvent is important to gain favorable hydrophilic interactions (Figure 4b). As a confirmation of this, fully fluorinated aliphatic compounds did not enter into **1** (see the SI), probably because of the unfavorable exposure of the highly hydrophobic fluorinated moieties to water solvent.

Even the highly water-soluble guest **2d** was encapsulated within **1**. The homogeneous host-guest complexation enabled us to carry out titration experiments by  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectroscopy that can elucidate the host-guest stoichiometry and the cooperativity in the multiple guest binding. A Job plot<sup>6</sup> indicated that compound **2d** gave a 1:4 host-guest complex with **1** (Figure S24, SI). In this 1:4 complexation, a strong positive cooperative effect, presumably due to self-aggregation of fluorinated moieties, was revealed by NMR titrations of **1** with **2d**. Guest **2d** was added to an aqueous solution of **1** (2.0 mM) and the chemical shift changes in  $\text{PyH}_\alpha$  of **1** were plotted



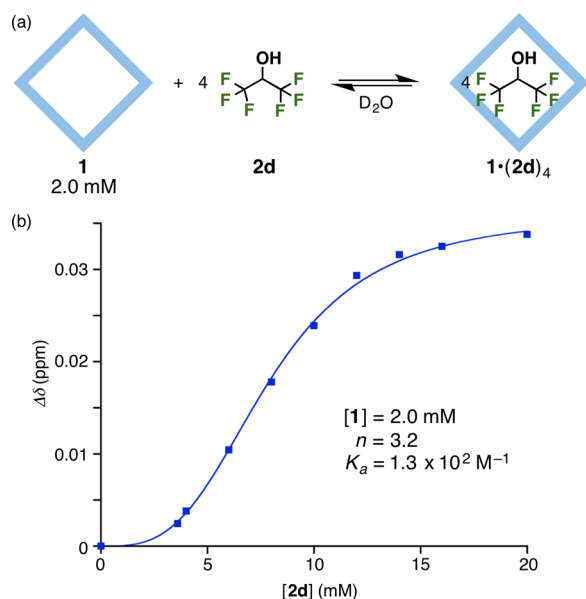
**Figure 4.** Crystal structures of (a)  $1\cdot(2a)_4$  and (b)  $1\cdot(2b)_2$  (C, gray; H, white; O, red; F, green). H atoms of **1**, nitrate anions, and solvent molecules have been omitted for clarity. Only one of the disordered structures was represented in  $1\cdot(2a)_4$ .

and fitted with a Hill function (Figure 5).<sup>6</sup> The plot showed sigmoidal change, and curve fitting revealed a Hill coefficient ( $n$ ) of 3.2, indicating a strong positive cooperative binding mode. The measured apparent association constant  $K_a$  was  $1.3 \times 10^2 \text{ M}^{-1}$ .

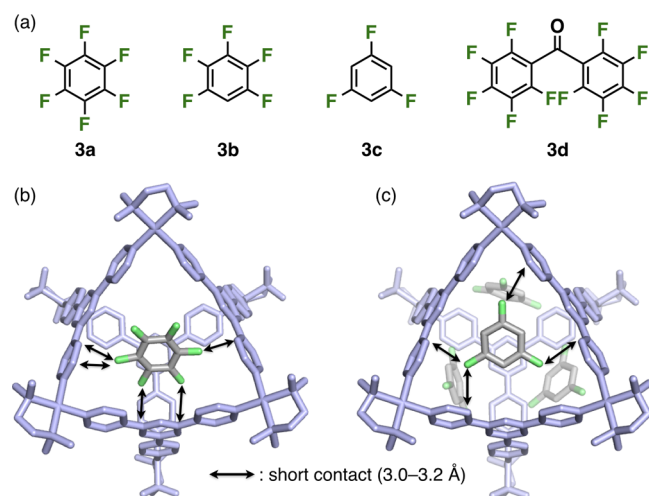
The cooperative inclusion behavior of **2d** is most probably derived from the effective self-aggregation of its fluorinated moieties. The hydrocarbon analogue of **2d** (2-propanol) showed much weaker binding behavior ( $K_a < 10$ ) under the same conditions.<sup>7</sup>

Inclusion behavior of polyfluorinated aromatic compounds **3a–d** by **1** was also investigated (Figure 6a). For these polyfluoroarenes, NMR analyses showed 1:2 to 1:4 host-guest complexations. Single crystals of inclusion complexes,  $1\cdot(3a)_2$ ,  $1\cdot(3b)_4$ ,  $1\cdot(3c)_4$ , and  $1\cdot(3d)_2$ , were obtained and subjected to crystallographic analysis (Figure 6b,c and S28–S31 in SI). The crystal structures revealed unique features in the guest binding:

(i) unlike aliphatic fluorinated compounds, the fluororous self-aggregation of the guests was not observed in any cases; (ii) unlike common aromatic guests,  $\pi$ - $\pi$  stacking with the triazine panel ligands was not observed; (iii) instead, all the



**Figure 5.** NMR titration of **1** with **2d**. (a) Schematic representation of the encapsulation of **2d** within **1** and (b) a Hill plot of **1·(2d)<sub>4</sub>**.



**Figure 6.** Encapsulation of polyfluorinated aromatic compounds **3**. (a) Guest compounds whose crystal structures of the inclusion complexes were determined (see the SI for details). Crystal structures of (b) **1·(3a)<sub>2</sub>** and (c) **1·(3c)<sub>4</sub>**. One of two disordered structures is represented in **1·(3a)<sub>2</sub>** and **1·(3c)<sub>4</sub>**. H atoms, nitrate anions, and solvent molecules have been omitted for clarity.

polyfluoroaromatic guests were located at the portals of the cage, exhibiting close C–F/ $\pi$  contacts (3.0–3.2 Å).<sup>8</sup>

Perfluoroarenes are often mistakenly assumed to be fluorous.<sup>1</sup> The observed encapsulation behavior in cage **1** shows that polyfluoroarenes **3a–d** are not to be considered fluorous as they possess negatively charged peripheries (i.e., sp<sup>2</sup> carbon–fluorine bonds) that electrostatically interact with the positively charged rings of the triazine ligands of **1**.

In summary, we found that even amphiphobic polyfluorinated compounds can be recognized in a synthetic cavity by gaining stability through the self-aggregation of the guests. The strategy for recognition of polyfluorinated compounds shown here gives new principles and guidelines for designing novel molecular receptors for poly- and perfluorinated compounds.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, physical properties, and crystallographic 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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