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Recognition of Polyfluorinated Compounds Through Self-Aggregation in a Cavity

Hiroki Takezawa,[†] Takashi Murase,[†] Giuseppe Resnati,[‡] Pierangelo Metrangolo,*[,‡] and Makoto Fujita*[,†]

[†]Department of Applied Chemistry, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

[‡]Laboratory of Nanostructured Fluorinated Materials, Politecnico di Milano, Via L. Mancinelli 7, IT-20131 Milano, Italy

Supporting Information

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.[1] 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,[2,3] in which the driving force is a hydrophobic effect[2] or size compatibility.[3] The amphiphobicity of fluorinated compounds, however, brings about their distinct fluorophilicity that facilitates fluorous self-aggregation/segregation[4] or makes fluorinated compounds soluble in fluorous solvents.[1] 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**[5a,d] shows strong binding ability for organic molecules, especially for electron-rich ones with various sizes and shapes by virtue of its large hydrophobic cavity (~460 Å^3) surrounded by four electron-deficient triazine-cored panels (Figure 2).[5] 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,[5a–d] 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

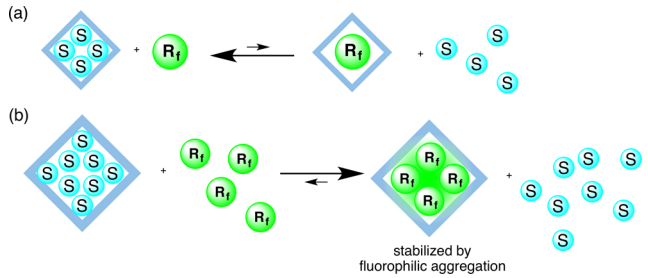

Figure 1. Schematic representations of (a) unimolecular and (b) multimolecular binding of polyfluorinated guests (S, solvent; R_f, polyfluorinated compounds). Unimolecular binding is dissociative because of the amphiphobicity of the guests (a), while multimolecular binding is associative because of the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

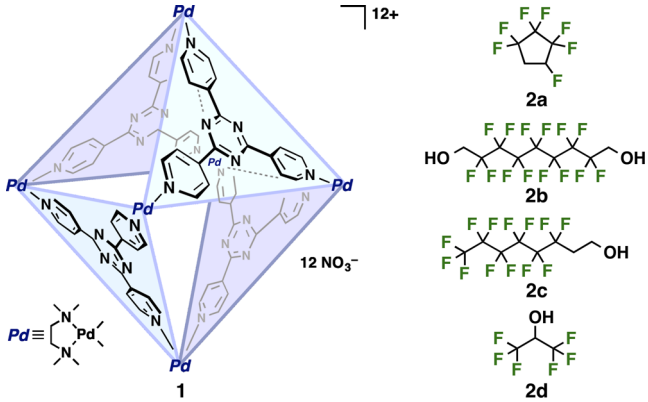

Figure 2. Self-assembled coordination cage **1** and polyfluorinated aliphatic guests **2a–d**.

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** (~10 equiv) was suspended in an aqueous solution of cage **1** (5.0 mM, 1.0 mL) and stirred at room temperature or 80 °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}H and ^{19}F NMR spectra (Figure 3 and Figure S1 in Supporting Information [SI]). The host–guest ratios of **1** to

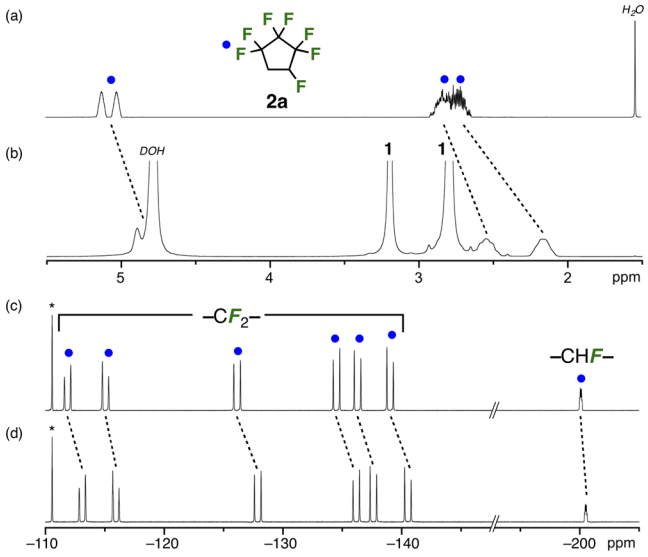

Figure 3. ^{1}H NMR spectra (500 MHz, 300 K) of (a) **2a** in $CDCl_3$ and (b) **1**·(**2a**)$_4$ in D_2O. ^{19}F NMR spectra (470 MHz, 300 K) of (c) **2a** in $CDCl_3$ and (d) **1**·(**2a**)$_4$ in D_2O (* labels denote signals of internal standard, 1,3,5-trifluorobenzene).

2a–c were determined as 1:4 (**2a**), 1:2 (**2b**), and 1:2 (**2c**), respectively, by the integral ratios in the ^{1}H NMR spectra (see the SI). In the case of **1**·(**2a**)$_4$, upfield shifts of the proton signals and the fluorine signal of $-CHF-$ in **2a** were moderate (0.3–0.6 ppm), while the fluorine signals of $-CF_2-$ 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 $-CF_2-$ moieties are deeply embedded in the cavity to form a stable fluorous aggregate. The same behavior (moderate shifts of protons and significant shift of fluorine moieties in NMR spectra) was observed in **1**·(**2b**)$_2$ and **1**·(**2c**)$_2$.

Aggregation of fluorinated moieties in the inclusion complexes was confirmed by the crystal structures of **1**·(**2a**)$_4$ and **1**·(**2b**)$_2$ (Figure 4). In the crystal structure of **1**·(**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**·(**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}H and ^{19}F NMR spectroscopy that can elucidate the host–guest stoichiometry and the cooperativity in the multiple guest binding. A Job plot[6] 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 PyH_α of **1** were plotted

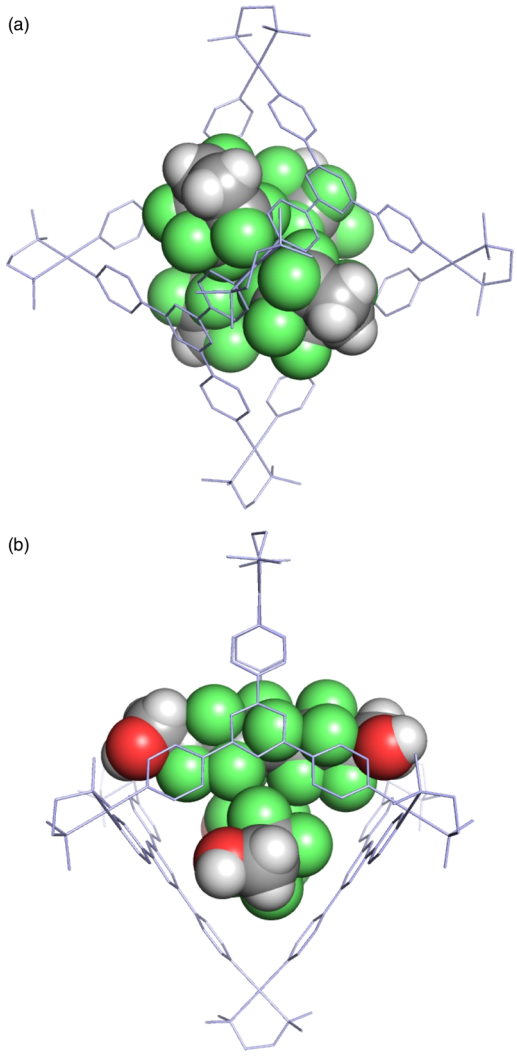

Figure 4. Crystal structures of (a) **1**·(**2a**)$_4$ and (b) **1**·(**2b**)$_2$ (C, gray; H, white; O, red; F, green). H atoms of **1**, nitrate anions, and solvent molecules have been omitted for clarity. Only one of the disordered structures was represented in **1**·(**2a**)$_4$.

and fitted with a Hill function (Figure 5).[6] 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 × 10^2 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.[7]

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**·(**3a**)$_2$, **1**·(**3b**)$_4$, **1**·(**3c**)$_4$, and **1**·(**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 fluorous self-aggregation of the guests was not observed in any cases; (ii) unlike common aromatic guests, π–π stacking with the triazine panel ligands was not observed; (iii) instead, all the

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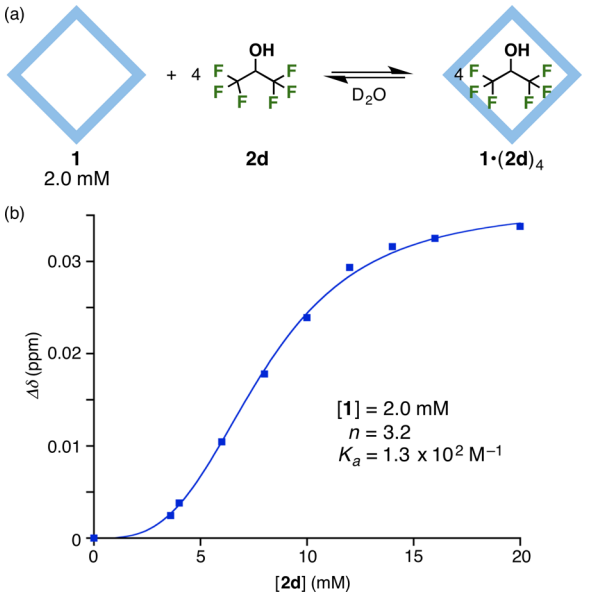

Figure 5. NMR titration of **1** with **2d**. (a) Schematic representation of the encapsulation of **2d** within **1** and (b) a Hill plot of **1**·(**2d**)$_4$.

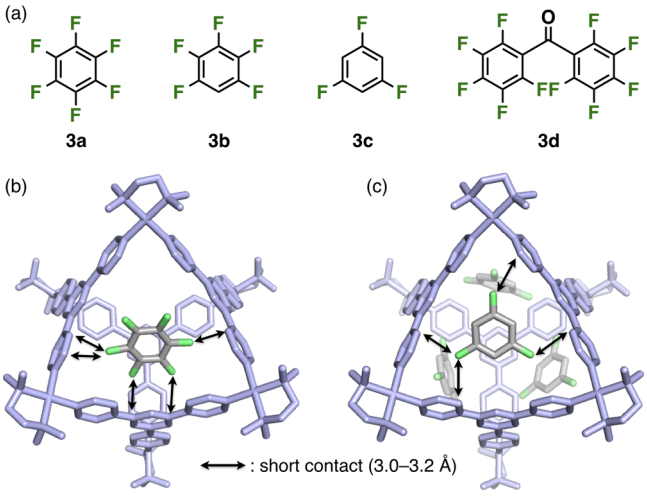

Figure 6. Encapsulation of polyfluorinated aromatic compounds **3**. (a) Guest compounds whose crystal structures of the inclusion complexes were determined (see the SI for details). Crystal structures of (b) **1**·(**3a**)$_2$ and (c) **1**·(**3c**)$_4$. One of two disordered structures is represented in **1**·(**3a**)$_2$ and **1**·(**3c**)$_4$. 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/π contacts (3.0−3.2 Å).[8]

Perfluoroarenes are often mistakenly assumed to be fluorous.[1] 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^2 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.

■ AUTHOR INFORMATION

Corresponding Authors

mfujita@appchem.t.u-tokyo.ac.jp;
pierangelo.metrangolo@polimi.it

Notes

The authors declare no competing financial interest.

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