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Mutual Induced Fit in a Synthetic Host–Guest System

Tomohisa Sawada, Hayato Hisada, and Makoto Fujita*

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

Supporting Information

ABSTRACT: Mutual induced fit is an important phenomenon in biological molecular recognition, but it is still rare in artificial systems. Here we report an artificial host–guest system in which a flexible calix[4]arene is enclathrated in a dynamic self-assembled host and both molecules mutually adopt specific three-dimensional structures. NMR data revealed the conformational changes, and crystallographic studies clearly established the precise structures at each stage.

Induced fit is a molecular recognition mechanism commonly observed when large biomolecules (mostly enzymes) recognize small substrate molecule(s) at their binding sites.[1] In most cases, a rigid substrate induces the organization of the flexible recognition site of an enzyme to show high substrate specificity. However, for molecular recognition between biomolecules (for example, protein–protein or protein-RNA interactions), the recognition sites of both molecules are usually flexible or poorly organized before the event. Yet, interestingly, they mutually induce the organization of each other so that the two biomolecules interact strongly and with a high specificity (Figure 1).[2] Such a mutual induced fit is an important

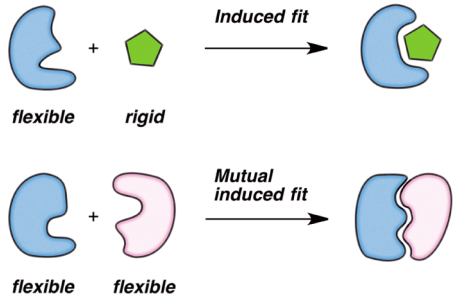

Figure 1. Cartoon representation of induced fit and mutual induced fit.

mechanism for biomolecular recognition, but has rarely been designed or achieved for artificial host–guest systems, in contrast to the numerous examples of lock-and-key or induced-fit molecular recognition.[3−5] Here we report the self-assembly of a "host-in-a-host" complex in which the two hosts are flexible and dynamic, but their conformation or composition is firmly fixed when they recognize each other. Triangular panel ligands **1** can potentially generate the host library shown in Figure 2b upon complexation with (en)$Pd(NO_3)_2$. Dynamic host library **3** generated from **1** was complexed with calix[4]arene **2**, a

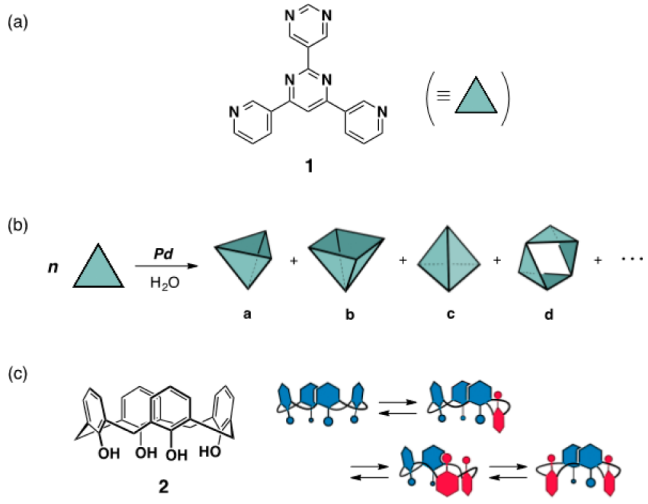

Figure 2. (a) Structure of ligand **1**. (b) Cartoon representations of potential dynamic host library from ligand **1** and (en)$Pd(NO_3)_2$. (c) Structure of calix[4]arene (**2**) and its conformational isomers.

conformationally mobile molecule with cone, partial cone, 1,2-alternate, and 1,3-alternate conformers in rapid equilibrium (Figure 2c).[6] We show that complexation of this dynamic host library with a flexible molecule gives conformationally and compositionally unique, well-defined host-in-a-host structure **2**·**3**. The fixed cavity of **2**·**3** shows enhanced molecular recognition abilities and is capable of binding a guest which cannot be recognized by host **2** alone.

Triangular ligand **1**, newly synthesized in this study (12.5 mg, 40 μmol), was complexed with (en)$Pd(NO_3)_2$ (23.2 mg, 80 μmol) in D_2O (1 mL) for 24 h at ambient temperature. ^{1}H NMR spectroscopy showed the formation of M_6L_3 trigonal pyramid **3a** and M_8L_4 tetragonal pyramid **3b** in a 94:6 ratio (Figure 3b, middle). Other potential structures **3c** and **3d**, which formed from similar triangular ligands in our previous works, were not observed. The trigonal pyramidal structure of **3a** was confirmed by crystallographic analysis after crystallization from the reaction mixture.[7,8] When an excess amount of calixarene **2** was suspended in the solution during the complexation (70 °C, 12 h), however, the equilibrium between **3a** and **3b** was pushed exclusively to **3b** by the formation of the **2**·**3b** complex. In the ^{1}H NMR spectrum, the two aromatic signals of **2** were shifted highly upfield (5.60 and 5.92 ppm) and the 1:1 complexation was confirmed by the integral ratio

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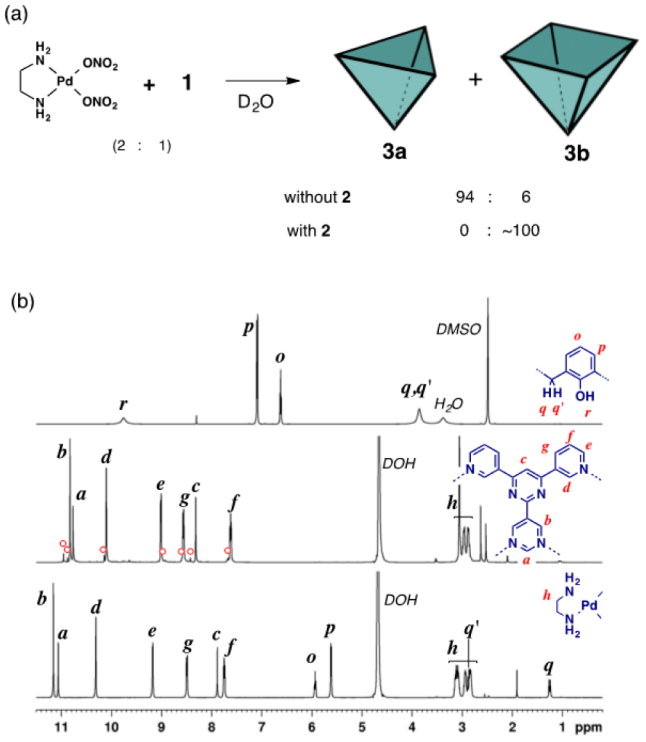

Figure 3. (a) Formation of **3a**,**b** and (b) ^{1}H NMR spectra (500 MHz, 300 K) of **2** in DMSO-d_6 (top), **3a** in D_2O (middle), and **2**·**3b** in D_2O (bottom). Red circles show presence of **3b**.

(Figure 3b, bottom). Notably, two doublet signals were observed for the methylene protons of **2** at 1.23 and 2.85 ppm (geminal coupling, J = 13.4 Hz); this represents the conformational fixation of **2** in the cone conformation. Clearly, the equilibration between the two host structures **3a** and **3b**, and between the four conformers of **2**, was suppressed, and the single host-in-a-host structure **2**·**3b** was formed. No signal broadening was observed, which indicates the tight and strong interaction between **3b** and **2**.

The structure of the **2**·**3b** complex was confirmed by single crystal X-ray analysis. For better crystallinity, bulky chelate ligand (*S*,*S*)-1,2-diaminocyclohexane (chxn) was employed as an end-capping ligand on the palladium ions.[9] Single crystals of **2**·**3b**′, an analog of **2**·**3b** where en is replaced with chxn, were obtained from an aqueous solution by slow evaporation of water. The crystal structure clearly showed the M_8L_4 tetragonal pyramidal structure of **3b**′ and the cone conformation of **2** (Figure 4a). The mutual stabilization of both structures can be explained by the effective $\pi-\pi$ interactions between the

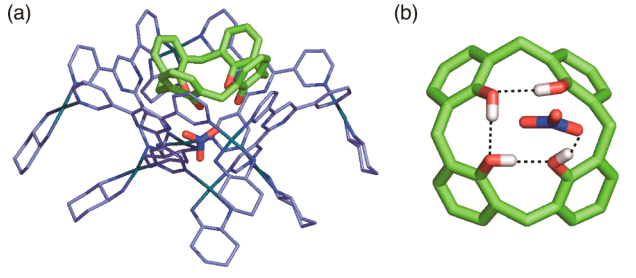

Figure 4. (a) Crystal structure of **2**·**3b**′ (solvents and nitrate ions outside the cavity have been omitted for clarity). (b) Major H-bond networks observed within the cavity.

electron-deficient pyrimidine rings of **3b**′and the electron-rich phenol rings of **2**, as observed in the crystal structure ($\pi-\pi$ distances 3.41−3.57 Å). One counteranion (NO_3^-) of **3b**′ was trapped around the bottom of the cationic cavity.[10,11] One typical H-bond was observed between the nitrate oxygen atom and one of the phenolic oxygen atoms of **2** (O···O distance: 2.66 Å, Figure 4b). The other three phenolic oxygen atoms formed a H-bonded network (O···O distances: 2.61, 2.69, and 2.78 Å), and the cone conformation of **2** was thereby additionally stabilized.[12]

With a related tridentate ligand **4**, previous studies have shown that two conformational isomers, bowl-shaped **5b** and box-shaped **5d**, in rapid equilibration are formed (Figure 5b).[14]

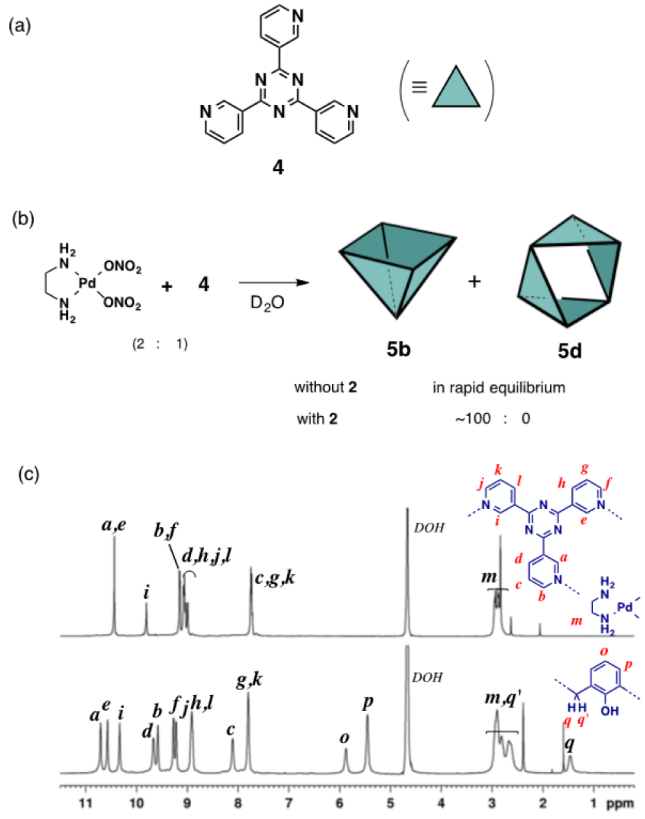

Figure 5. (a) Structure of ligand **4**. (b) Formation of **5b**,**d**. (c) ^{1}H NMR spectra (500 MHz, 300 K, D_2O) of the flexible M_6L_4 host **5** (top) and **2**·**5b** (bottom).

Again, the mutual induced fit was observed between the conformationally flexible host **5** and calix[4]arene, **2**. Due to the host dynamics, the ^{1}H NMR spectrum of **5** shows only two sets of 3-pyridyl groups in a 2:1 ratio for ligand **4** (Figure 5c, top), which is consistent with its pseudo C_{2v} symmetry. However, when an excess amount of calix[4]arene **2** was suspended in a D_2O solution of host **5** (5 mM) for 12 h at 70 °C, the host dynamics was frozen and the formation of host-in-a-host complex **2**·**5b** in a fixed conformation was indicated by ^{1}H NMR spectroscopy (Figure 5c, bottom). The three pyridyl groups on the triangular panels of **4** were clearly distinguished, which indicates that the equilibrium between **5b** and **5d** was completely suppressed. The 1:1 host−guest ratio was confirmed by the integral ratio. The mutual induced fit between conformationally flexible **2** and **5** can be well explained by the tightly combined host−guest structure of **2**·**5b**.

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The three-dimensional structure of the **2**·**5b** complex was elucidated by X-ray analysis. Slow evaporation of water from an aqueous solution of **2**·**5b** (10 mM) at ambient temperature over three weeks afforded single crystals suitable for a diffraction study. In the crystal structure, the host-in-a-host structure was clearly confirmed (Figure 6). Each phenol ring of

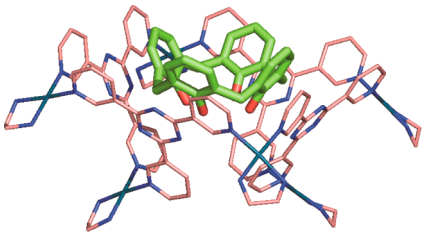

Figure 6. (a) Crystal structure of **2**·**5b** (solvents and nitrate ions outside of the cavity have been omitted for clarity).

2 contacts with the tridentate panels of **5b** through $\pi-\pi$ interactions as observed in the analogous **2**·**3b**′ complex. However, unlike **2**·**3b**′, enclathrated calixarene **2** does not show nitrate capture in the crystalline state. All phenolic oxygen atoms of **2** form H-bonds with the neighboring oxygen atoms (Figure S5).

Moreover, the mutual induced fit enhanced the guest binding ability of nonsubstituted calix[4]arene **2**. Host-in-a-host complex **2**·**5b** could further accommodate one molecule of nitrobenzene in aqueous solution (Figure S6). No such behavior was observed for **2** alone. The 1:1 complexation, confirmed by NMR, was different from that of nitrobenzene with **5b** alone where several guests were accommodated in the large cavity of **5b**. In a similar way, bromocyclopropane was trapped in the fixed cavity of the **2**·**5b** complex in aqueous solution, while not in the flexible cavity of **2** alone.

In conclusion, we have successfully demonstrated mutual induced fit in a synthetic system between conformationally and compositionally flexible host molecules. It is noteworthy that the mutual induced fit distinctly tuned the nature of nonsubstituted calix[4]arene, the most basic of the calixarene family, without any chemical modification. In our system, the calix[4]arene is conformationally fixed, water-soluble, and wrapped in a cationic environment. It thus exhibits unusual binding abilities, which cannot be observed for free calix[4]-arene. Mutual induced fit is a new way of controlling the properties of dynamic molecules or self-assemblies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

All experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mfujita@appchem.t.u-tokyo.ac.jp

Notes

The authors declare no competing financial interest.

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(7) Characterization of **3a** by NMR and crystallographic studies are described in the Supporting Information.

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(10) To the best of our knowledge, there is no report of anion binding behavior by nonsubstituted calix[4]arene.

(11) There is an example of unusual nitrate capture by an anionic nucleotide guest within a cationic nanocavity. See ref 9c.

(12) Although cationic cavities can enhance the acidity of guests,[13] we consider all phenolic protons in the **2**·**3b**′ complex to participate in the H-bonded network. See Figure S5 in the Supporting Information for details.

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