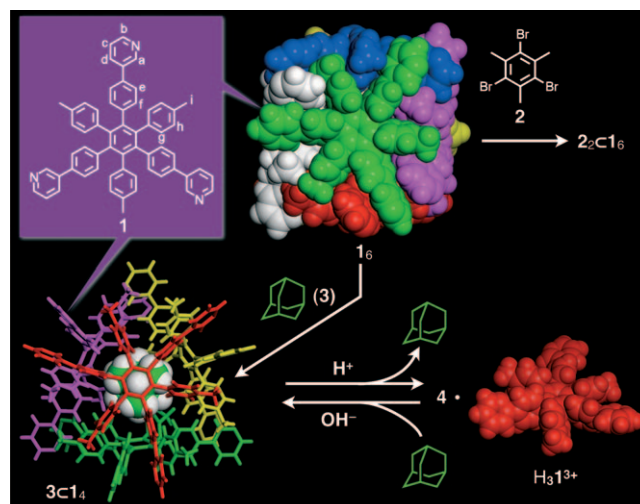


# Induced-Fit Formation of a Tetrameric Organic Capsule Consisting of Hexagram-Shaped Amphiphile Molecules\*\*

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Induced-fit molecular recognition is a key event in signal transduction,<sup>[1a]</sup> activation of reaction centers,<sup>[1b]</sup> and allosteric regulation,<sup>[1c,d]</sup> and is accompanied by conformational changes around the recognition sites. The general concept that a suitable guest molecule can alter the structure of its host molecule to result in a stable host–guest complex has been widely applied to the selective formation of self-assembled host molecules that are in dynamic equilibrium with a template guest species.<sup>[2]</sup> Such a system would allow the size-, shape-, and number-dependent inclusion of guest species by host molecules that are formed in a highly adaptive manner from elaborate building blocks under given conditions.

Recently, we reported that a hexameric box-shaped aggregate **1<sub>6</sub>** is formed from hexagram-shaped amphiphile molecules **1** in aqueous methanol.<sup>[3]</sup> As the building block **1** has a hydrophobic hexaphenylbenzene core and three hydrophilic 3-pyridyl groups, **1** forms aggregates in H<sub>2</sub>O/CH<sub>3</sub>OH (1:3) through the hydrophobic effect,<sup>[4k,5]</sup> while it exists as a monomer in pure CH<sub>3</sub>OH. In addition, the discrete hexameric capsule structure is well-stabilized by van der Waals interactions between the hydrophobic surfaces of **1**. The hexameric capsule **1<sub>6</sub>** allows bimolecular guest inclusion with hexasubstituted benzene derivatives such as 2,4,6-tribromomesitylene (**2**). Herein, we report that a smaller sized spherical molecule, adamantane (**3**), serves as a template guest for the formation of a fourfold, tetrahedron-shaped capsule **3C1<sub>4</sub>**, resulting in significant changes in the capsule structure (Figure 1). The phenomenon that the observed



**Figure 1.** Induced-fit formation of a tetrahedron-shaped tetrameric capsule from hexagram-shaped amphiphile molecules **1**, and the reversible encapsulation and release of a guest molecule **3** by acid–base regulation.

nanoscopic aggregation is highly dependant on the size and shape of the template guest molecule is notable. Furthermore, this inclusion complex exhibited a unique function to reversibly encapsulate and release a guest molecule as a result of dissociation and reconstruction of the tetrameric capsule **1<sub>4</sub>** by acid–base regulation.<sup>[6]</sup>

The <sup>1</sup>H NMR spectrum of the hexameric aggregate **1<sub>6</sub>** formed in D<sub>2</sub>O/CD<sub>3</sub>OD (1:3) shows rather complex signals because each component **1** of the capsule loses its original C<sub>3</sub> symmetry (Figure 2a). For example, the three methyl proton signals (H<sup>i</sup>) in the <sup>1</sup>H NMR spectrum indicated that all the methyl groups became inequivalent in the hexameric capsule. The aggregate **1<sub>6</sub>** has a cubic cavity with sides of 7 Å, and thereby can encapsulate two molecules of 2,4,6-tribromomesitylene (**2**) as guests to form **2<sub>2</sub>C1<sub>6</sub>** through van der Waals interaction between the host and guest molecules.<sup>[3]</sup> As less-substituted benzene derivatives are not encapsulated in **1<sub>6</sub>**, the recognition behavior was believed to be highly shape-dependent. During the course of investigating the encapsulation properties of **1<sub>6</sub>**, we found that **3**, which is not a suitable guest for **1<sub>6</sub>**, can induce an alternative supramolecular aggregate. Upon addition of **3** to a solution of **1<sub>6</sub>** in D<sub>2</sub>O/CD<sub>3</sub>OD (1:3), the intensity of the signals in the <sup>1</sup>H NMR spectrum of **1<sub>6</sub>** decreased while new signals appeared (Figure 2b). When 1.5 equivalents (based on [1<sub>6</sub>]) of **3** were added to **1<sub>6</sub>** ([1]/[3] = 4:1), the <sup>1</sup>H NMR spectrum showed only new signals (Figure 2c), and addition of extra **3** did not show any

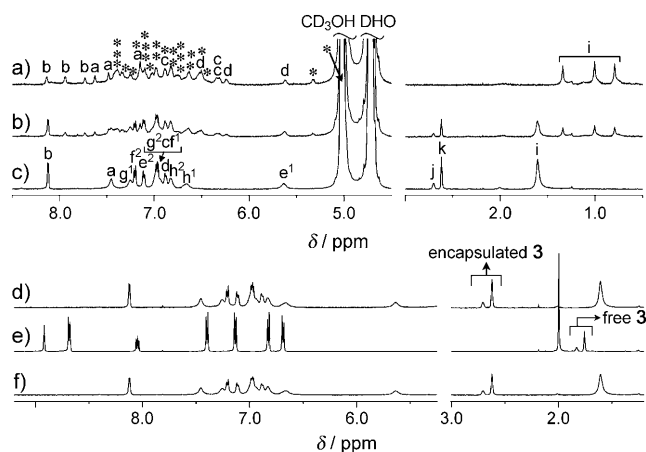
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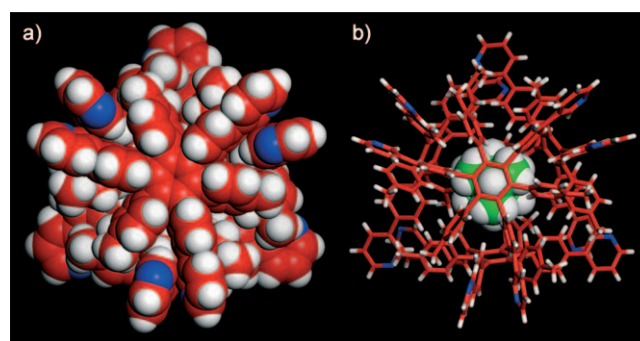
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.200902652>.



**Figure 2.** Partial  $^1\text{H}$  NMR spectra (500 MHz,  $\text{D}_2\text{O}/\text{CD}_3\text{OD}$  (1:3 v/v),  $[\mathbf{1}]=2.0$  mM, 293 K). a) Box-shaped capsule  $\mathbf{1}_6$ . \* denotes  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{H}^c$ , and  $\text{H}^d$ . b) 0.75 equiv (based on  $[\mathbf{1}_6]$ ) of  $\mathbf{3}$  was added to a solution of  $\mathbf{1}_6$ . c) Inclusion complex  $\mathbf{3}@\mathbf{1}_4$  obtained upon addition of 1.5 equiv of  $\mathbf{3}$  to a solution of  $\mathbf{1}_6$ . d) Dissociation and reconstruction of  $\mathbf{1}_4$  by acid–base control. e) 12 equiv (based on  $[\mathbf{1}_4]$ ) of DCl was added to a solution of  $\mathbf{3}@\mathbf{1}_4$ . f) 12 equiv of NaOD was added to the solution in (e).

changes except for the appearance of signals of free  $\mathbf{3}$ . Similar to the  $^1\text{H}$  NMR spectrum of  $\mathbf{1}_6$ , a highly shielded aromatic signal was observed at  $\delta=5.6$  ppm in the  $^1\text{H}$  NMR spectrum (Figure 2c), thus indicating the aggregation of  $\mathbf{1}$ . It should be noted that the  $^1\text{H}$  NMR spectrum of the mixture of  $\mathbf{1}$  and  $\mathbf{3}$  is simpler than that of  $\mathbf{1}_6$ , as every methyl group ( $\text{H}^i$ ) is equivalent (Figure 2c). These results suggest that the new aggregate formed in the presence of  $\mathbf{3}$  should contain molecules of  $\mathbf{1}$  with  $C_3$  symmetry. The ESI-TOF mass spectrum of the solution showed three signals at  $m/z$  1145.5, 1696.3, and 1706.8, which are assignable to  $[\mathbf{1}_4\cdot\mathbf{3}\cdot\text{Na}_3]^{3+}$ ,  $[\mathbf{1}_4\cdot\mathbf{3}\cdot\text{D}\cdot\text{Na}]^{2+}$ , and  $[\mathbf{1}_4\cdot\mathbf{3}\cdot\text{Na}_2]^{2+}$ , respectively. This result suggests that a tetrameric aggregate forms a complex with one molecule of  $\mathbf{3}$ . A  $^1\text{H}$  NMR titration study also revealed that the complex consists of  $\mathbf{1}$  and  $\mathbf{3}$  in a 4:1 ratio. The significant downfield shift of the signals for  $\mathbf{3}$  ( $\Delta\delta=0.86$  and  $0.88$  ppm) suggests that the guest molecule  $\mathbf{3}$  is located in the deshielding region of the aromatic ring current of  $\mathbf{1}$  within a tetrameric aggregate  $\mathbf{1}_4$ .

The structure of the aggregate was unambiguously determined by single-crystal X-ray analysis (Figure 3).<sup>[7]</sup> Crystals suitable for X-ray crystallography were obtained from a saturated solution of  $\mathbf{3}@\mathbf{1}_4$  in  $\text{H}_2\text{O}/\text{CH}_3\text{OH}$  (1:3) at room temperature after one day. The crystal structure showed that hexagram-shaped molecules of  $\mathbf{1}$  with  $C_3$  symmetry assemble to form a tetrahedron-shaped capsule structure with one adamantane molecule in the hydrophobic inner space of the capsule. This result is consistent with those obtained from the  $^1\text{H}$  NMR spectra. The pyridine rings are situated between a cleft formed by other hexagram-shaped molecules. Six pairs of stacked pyridine rings are located on the six sides of the tetrahedron, and the two nitrogen atoms in each pair are oppositely oriented so as to minimize the molecular dipole moment that arises from the pyridine rings. The nearest distance between the protons on the inner surface of the host



**Figure 3.** Crystal structure of inclusion complex  $\mathbf{3}@\mathbf{1}_4$ . a) Space-filling model. b) Cylinder model. The guest molecule  $\mathbf{3}$  is shown by a space-filling model. C in  $\mathbf{1}$  is red, N is blue, H is white, C in  $\mathbf{3}$  is green.

( $\text{H}^f$  and  $\text{H}^g$  in  $\mathbf{1}$ ) and the guest  $\mathbf{3}$  is  $2.7$  Å, which indicates a negligible van der Waals interaction between the host and the guest. This observation suggests that the encapsulation of  $\mathbf{3}$  in the capsule should arise mainly from the hydrophobic effect.

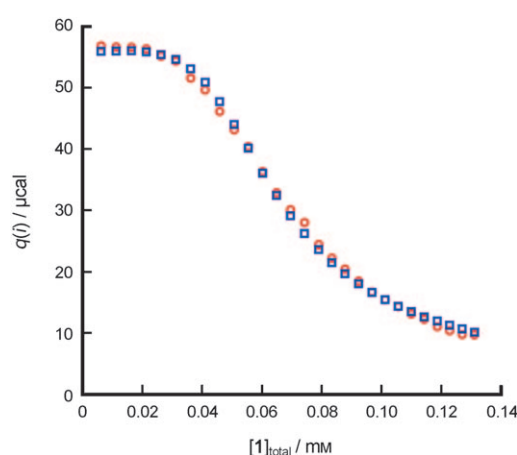
All the  $^1\text{H}$  NMR signals for the inclusion complex  $\mathbf{3}@\mathbf{1}_4$  shown in Figure 2c were fully characterized by  $^1\text{H}$ – $^1\text{H}$  COSY and  $^1\text{H}$ – $^1\text{H}$  NOESY measurements (Figure S2 in the Supporting Information). One of the phenylene proton signals,  $\text{H}^{e1}$ , was observed at a high field because of the strong shielding effect of the assembled structure. This feature is in good agreement with the crystal structure of the capsule. The inclusion of guest molecule  $\mathbf{3}$  within the capsule  $\mathbf{1}_4$  in solution was evidenced by  $^1\text{H}$ – $^1\text{H}$  NOESY and  $^1\text{H}$  DOSY measurements. A strong correlation was observed in the NOESY spectrum between  $\text{H}^k$  of  $\mathbf{3}$  and the protons on the inner surface of the capsule,  $\text{H}^{f1}$  and  $\text{H}^{g1}$  (Figure S3 in the Supporting Information). In the  $^1\text{H}$  DOSY spectrum (Figure S4 in the Supporting Information), both proton signals for  $\mathbf{1}_4$  and  $\mathbf{3}$  exhibited the same  $\log D$  values of  $-9.82$  (diffusion coefficient  $D=1.5\times 10^{-10}$  m $^2$ s $^{-1}$ ). These results indicate that the guest molecule  $\mathbf{3}$  is included inside the capsule.

As a spherical, hydrophobic molecule,  $\mathbf{3}$  (volume  $140$  Å $^3$ )<sup>[8]</sup> was found to serve as an excellent template for the formation of capsule  $\mathbf{1}_4$ . We then examined effects of other spherical molecules such as  $\text{Me}_4\text{Si}$  ( $113$  Å $^3$ ),  $\text{CBr}_4$  ( $103$  Å $^3$ ), and norbornane ( $115$  Å $^3$ ) on the formation of the tetrameric capsule. Upon addition of each guest molecule to a solution of  $\mathbf{1}_6$ , a tetrameric inclusion complex, guest $@\mathbf{1}_4$ , was formed immediately.<sup>[9]</sup>

As demonstrated by the crystal structure analysis, the hexagram-shaped amphiphile molecules  $\mathbf{1}$  assemble into the tetrameric inclusion complex  $\mathbf{3}@\mathbf{1}_4$ , in which the two neighboring pyridyl nitrogen atoms are  $4.1$  Å apart. Accordingly, the protonation of the nitrogen atoms of  $\mathbf{1}$  in the capsule was expected to break the assembled structure into monomeric ligands because of the electrostatic repulsion between the positively charged nitrogen atoms. Indeed, upon addition of 12 equivalents of DCl to a solution of the inclusion complex  $\mathbf{3}@\mathbf{1}_4$  in  $\text{D}_2\text{O}/\text{CD}_3\text{OD}$  (1:3), the signals for the complex in the  $^1\text{H}$  NMR spectrum immediately disappeared, and then those of the deuterated monomeric amphiphile molecule  $\text{D}_3\mathbf{1}^{3+}$  and the free guest molecule appeared (Figure 2e). Furthermore, when the resulting solution was neutralized with NaOD, the

inclusion complex  $3\text{C}1_4$  was regenerated (Figure 2 f). These results indicate that the encapsulation and release of the guest molecule in the capsule can be reversibly controlled by acid–base regulation, with the dissociation and reconstruction of the complex.<sup>[6]</sup>

In  $\text{H}_2\text{O}/\text{CH}_3\text{OH}$  (1:3), the ligand **1** forms both hexameric and tetrameric capsules  $1_6$  and  $3\text{C}1_4$  in the absence and presence of **3**, respectively. In  $\text{CH}_3\text{OH}$ , **1** exists as a monomer only. This result suggests that the hexagram-shaped molecule **1** has hydrophobic portions to facilitate its aggregation in aqueous media. To reveal the thermodynamic profile of the aggregation process in detail, the thermodynamic parameters for the capsule formation ( $6\cdot 1 \rightleftharpoons 1_6$ )<sup>[10]</sup> was determined by isothermal titration calorimetry (ITC). ITC dilution experiments are a powerful tool for analyzing the aggregation of single components.<sup>[11]</sup> In the titration experiment, a solution of the hexameric capsule  $1_6$  was injected by increments at fixed time intervals into the calorimetric cell filled with solvent only; an endothermic heat pulse was subsequently obtained (Figure 4 and Figure S6 in the Supporting Information). The data thus obtained were analyzed according to the method described in the Supporting Information, and the thermodynamic parameters for the hexameric capsule formation ( $6\cdot 1 \rightleftharpoons 1_6$ ) were determined:  $\Delta G_{293} = -18 \text{ kJ mol}^{-1}$ ,  $\Delta H = -36 \text{ kJ mol}^{-1}$ , and  $\Delta S = -59 \text{ J mol}^{-1} \text{ K}^{-1}$ . The hexameric capsule formation is enthalpically favorable but entropically unfavorable. Such an enthalpy-driven molecular interaction in aqueous media is known as the “nonclassical hydrophobic effect”.<sup>[12]</sup> Under the classical hydrophobic effect, hydrophobic residues such as long alkyl chains in amphiphiles tend to avoid contact with the aqueous environment and aggregate to form a hydrophobic core with the release of solvent molecules around the hydrophobic surfaces. Hence, the hydrophobic effect is normally considered an entropic phenomenon. However, when the hydrophobic groups have large areas of  $\pi$  surfaces that consist of aromatic rings, the aggregation is enthalpically favorable because of the  $\pi$ – $\pi$  interactions between the components. In the present case, the



**Figure 4.** Plots of the integrated heat  $q(i)$  measured by ITC for each injection of a solution of  $1_6$  ( $[1] = 0.75 \text{ mM}$ ) to  $\text{H}_2\text{O}/\text{CH}_3\text{OH}$  (1:3) in the cell, with respect to the total concentration of **1** in the cell,  $[1]_{\text{total}}$ . Red open circles and blue open squares are experimental ( $q_{\text{obs}}(i)$ ) and calculated ( $q_{\text{fit}}(i)$ ) values, respectively.

negative enthalpy change is explained by the multipoint van der Waals interactions in the capsule, as suggested by the crystal structure of  $1_6$  in which the hexagram-shaped hydrophobic surfaces of the components are in contact with each other (Figure 1). The negative entropy change observed in the capsule formation is probably due to 1) a decrease in the number of molecules upon aggregation, 2) less spacial degrees of freedom for the aromatic rings in the meshing structure, and 3) a relatively small entropic gain arising from the release of the solvent molecules around **1** in  $\text{H}_2\text{O}/\text{CH}_3\text{OH}$  (1:3). These results indicate that an indented hexagram-shaped hydrophobic surface in **1** is essential for the formation of well-defined discrete aggregates.<sup>[13]</sup>

In conclusion, a self-assembled tetrameric capsule guest $\text{C}1_4$  that results from the union of four hexagram-shaped molecules **1**, was formed exclusively in an induced-fit manner in the presence of a spherical template molecule. In contrast, a hexameric box-shaped capsule  $1_6$  was formed without the template molecule. In addition, the reversible encapsulation and release of the guest molecule as a result of the dissociation and reconstruction of the capsule was achieved by acid–base control. The ITC dilution experiment for the capsule formation of the hexameric capsule  $1_6$  clearly indicated that the hexagram-shaped molecules **1** are assembled to form  $1_6$  by virtue of the nonclassical hydrophobic effect that arises from van der Waals interactions between the adjacent molecules in the meshing structure. We are currently exploring water-soluble capsules as an extension of the discrete aggregation of hexagram-shaped amphiphile molecules. Applications of these molecular architectures to functional devices will be reported elsewhere.

## Experimental Section

**Formation of  $3\text{C}1_4$ :** Adamantane (0.18  $\mu\text{mol}$ , 0.25 equiv) in  $\text{D}_2\text{O}/\text{CD}_3\text{OD}$  (1:3, 20  $\mu\text{L}$ ) was added to a solution of  $\text{D}_2\text{O}/\text{CD}_3\text{OD}$  (1:3, 0.40 mL) containing **1** (0.73  $\mu\text{mol}$ ), and the solution was allowed to stand at 293 K for 5 min. The  $^1\text{H}$  NMR spectrum of this solution showed the quantitative formation of  $3\text{C}1_4$ .

$^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}/\text{CD}_3\text{OD}$  (1:3 v/v)):  $\delta = 8.12$  (d,  $J = 4.7 \text{ Hz}$ , 12H), 7.45 (br, 12H), 7.26 (br, 12H), 7.21 (d,  $J = 8.0 \text{ Hz}$ , 12H), 7.11 (d,  $J = 8.0 \text{ Hz}$ , 12H), 6.99–6.92 (m, 36H), 6.88 (br, 12H), 6.83 (br, 12H), 6.66 (br, 12H), 5.63 (br, 12H), 2.71 (br, 4H), 2.62 (br, 12H), 1.61 ppm (br s, 36H); ESI-TOF MS (positive mode,  $\text{D}_2\text{O}/\text{CD}_3\text{OD}$  (1:3 v/v))  $m/z$  1145.5:  $[3\text{C}1_4\cdot\text{Na}_3]^{3+}$ , 1696.3:  $[3\text{C}1_4\cdot\text{D}\cdot\text{Na}]^{2+}$ , 1706.8:  $[3\text{C}1_4\cdot\text{Na}_2]^{2+}$ .

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- [8] The volume of each molecule was calculated by the Connolly surface method (Connolly radius:  $1.00\text{ Å}$ ) using the Material Studio molecular modeling package (ver. 4.0, Accelrys, San Diego, CA).
- [9] The host–guest stoichiometry in the complex was determined by  $^1\text{H}$  integral ratios, except  $\text{CBr}_4$ .  $^1\text{H}$  NMR spectra are shown in Figure S5 in the Supporting Information.
- [10] Even when a solution of  $\text{I}_6$  was highly diluted, no species other than the monomer and hexamer was found in the  $^1\text{H}$  NMR spectrum, thus indicating the presence of the monomer–hexamer equilibrium ( $6\cdot\text{I} \rightleftharpoons \text{I}_6$ ) in solution.
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