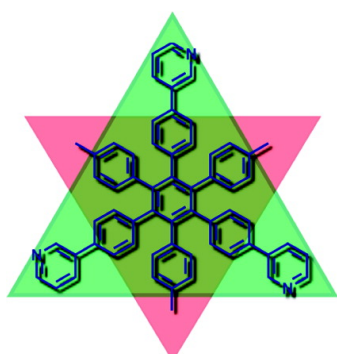## Communication

A Self-Assembled Organic Capsule Formed from the Union of Six Hexagram-Shaped Amphiphile Molecules

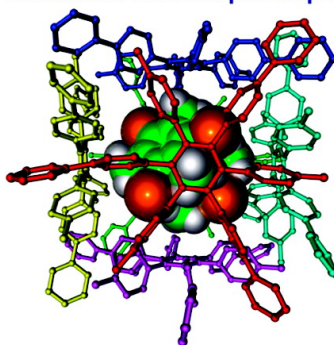Shuichi Hiraoka, Koji Harano, Motoo Shiro, and Mitsuhiko Shionoya

Hexameric Box-Shaped Capsule

Hexagram-Shaped Amphiphile

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A Self-Assembled Organic Capsule Formed from the Union of Six Hexagram-Shaped Amphiphile Molecules

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Self-assembled hollow nanostructures have a great potential for providing highly functional spaces for molecular recognition, transport, reaction, and catalysis. A number of excellent examples of discrete molecular capsules have been reported,[1,2] and most are constructed by directional, noncovalent bonding such as H-bonding[1] and metal coordination bonding.[2] Another key assembly strategy is to use amphiphile molecules with hydrophilic and hydrophobic parts, as seen in a variety of regular aggregates[3] such as micelles, vesicles, and tubes triggered by the hydrophobic effect in aqueous media. In general, however, the number of components is uncertain in these aggregates. This is because each building component has no strict structural information to define a discrete structure due to the nature of less-directional interactions between the chemical components. Thus, the ensemble of hydrophobic effect and multi-point weak interactions is critical to define an entire discrete structure. Herein we present a hexagram-shaped amphiphile (**1**) with three hydrophilic pyridyl groups attached to a hydrophobic hexaphenyl benzene core. This molecule aggregates in aqueous methanol to form a box-shaped structure comprised of six molecules of **1**. These six components are assembled by the hydrophobic effect, van der Waals forces, and CH–π interactions. In addition, the entity can encapsulate a couple of hexa-substituted benzene molecules (**3**) in the hydrophobic interior space (Figure 1).

Recently, we have reported octahedron-shaped metallo-capsules, $[M_6\mathbf{1}_8]^{12+}$, constructed from six transition metal ions M^{2+} (M: Mn, Fe, Co, Ni, Pd, Pt, Cu, Zn, Cd, and Hg) and eight metal ligands (**1**) having three 3-pyridyl groups,[2j] and found that the $[Hg_6\mathbf{1}_8]^{12+}$ capsule is interconvertible with a $[Hg_6\mathbf{1}_4]^{12+}$ cage by changing the ratio of ligand to metal.[2k] We found that this molecule aggregates to form a discrete structure in aqueous methanol solution. The ^1H NMR spectrum of **1** in CD_3OD showed simple signals indicating the C_3 symmetric monomer (Figure 2a), whereas that in a mixed solvent of $D_2O/CD_3OD = 25:75$ (v/v) was rather complicated and some of signals appeared in an upper field region (Figure 2d).[4,5] These results indicated that the aggregation in aqueous methanol was induced by the hydrophobic effect. It should be noted that three separate signals with the same integral values were observed for three methyl groups (H^i). The (H, H) COSY spectrum of **1** in a mixed solvent of $D_2O/CD_3OD = 25:75$ (v/v) displayed 36 signals in the aromatic region, which contain 12 pyridyl and 24 p-phenylene protons (Figure 2f). The ^1H DOSY measurement of the solution showed that all the signals have the same log D values of -9.91 ($D = 1.2 \times 10^{-10}$ m^2 s^{-1}) (Figure S4), indicating the existence of a single component. These results raised two possibilities. The first one was that the solution includes the same amount of three chemically inequivalent **1** with C_3 symmetry. The second possibility
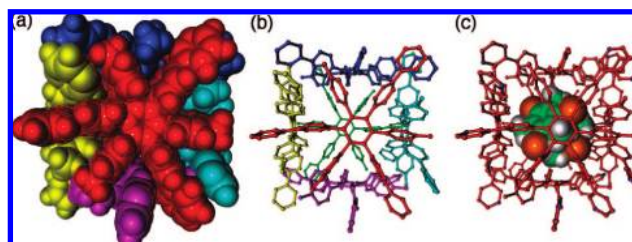

Figure 1. Crystal structure of $\mathbf{3}_2\subset\mathbf{1}_6$. (a) Space-filling models. Each **1** is shown in a different color. (b) Cylinder model. Hydrogens and **3** are omitted. (c) Color in $\mathbf{1}_6$: red, C; blue, N. Color in **3**: green: C, white, H; brown, Br.

was that all the components of the aggregate are chemically equivalent but each component has a lower C_1 symmetry where all the pyridyl and p-tolyl groups are inequivalent. The ESI-TOF mass spectrum of **1** in CH_3OH showed three prominent signals at $m/z = 1235.1$, 1638.8, and 2446.6 assignable to $[\mathbf{1}_6\cdot Na_4]^{4+}$, $[\mathbf{1}_6\cdot Na_3]^{3+}$, and $[\mathbf{1}_6\cdot Na_2]^{2+}$, respectively (Figure S2), indicating the formation of a hexameric aggregate.

We tried to obtain a single crystal of the aggregate from a saturated solution of **1** in aqueous methanol, but a suitable crystal was not obtained.[6] However, a single crystal suitable for X-ray analysis was obtained in the presence of tribromomesitylene (**3**).[7] In the inclusion complex $\mathbf{3}_2\subset\mathbf{1}_6$, six hexagram-shaped ligands **1** assemble to form a box-shaped hexameric capsule, which encapsulates a couple of the guest **3** stacked face to face (Figure 1). The hexagram-shaped molecules in $\mathbf{3}_2\subset\mathbf{1}_6$ lost their original C_3 symmetry of **1** because the pyridyl and p-tolyl groups in **1** became inequivalent. This is consistent with the symmetry of the solution structure observed in the ^1H NMR spectrum of the inclusion complex in aqueous methanol. The methyl groups of **1** are in close proximity to the pyridyl and p-phenylene groups of the neighboring molecules. This result is in good accordance with the observation that the proton signals of the methyl groups, H^i, in the aggregate were shifted to higher field. A pair of **3** appears to move about freely in the hydrophobic space of $\mathbf{1}_6$ as the guest molecules were disordered in the X-ray analysis (Figure 1 shows only one of the three possible structures). This agrees with the result that the symmetries of $\mathbf{1}_6$ and the encapsulated **3** in solution are independent of each other as shown by the ^1H NMR study.

The formation of the hexameric aggregate depends heavily on the structure of the hexagram-shaped amphiphile. **2**, in which three methyl groups of **1** are hydrogen-modified, exists as a monomer in aqueous methanol regardless of the solvent composition (Figure S10). Furthermore, the X-ray analysis of a single crystal obtained from an aqueous methanol solution of **2** established not a hexameric capsule but a multilayered structure (Figure S9). These results indicate that van der Waals forces and/or CH–π interactions between the methyl groups and the adjacent aromatic rings help to stabilize the discrete capsule structure of $\mathbf{1}_6$ to a great extent.

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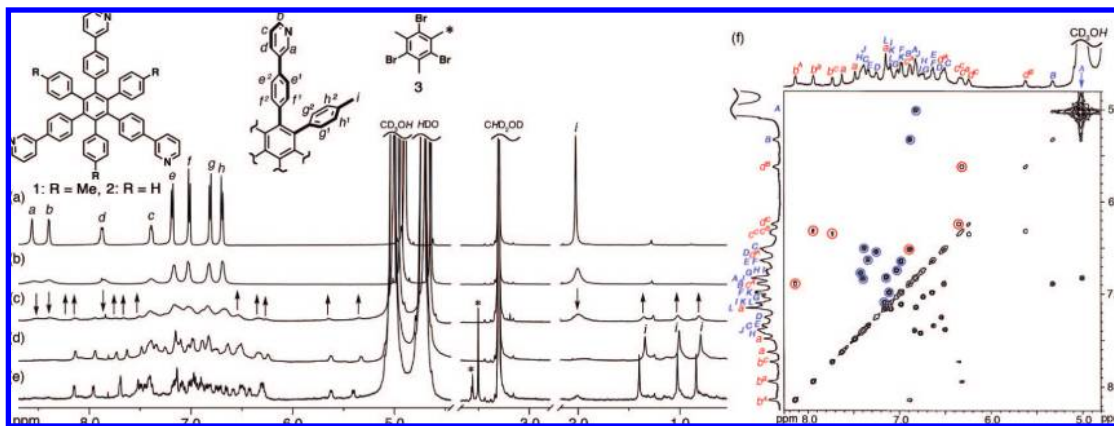‡ PRESTO.
§ Rigaku Co. LTD.

Figure 2. (a–d) ^{1}H NMR spectra (500 MHz, 293 K, [**1**] = 2.0 mM) in a mixed solvent of D_2O and CD_3OD in various ratios (D_2O/CD_3OD = X:Y). X:Y = (a) 0:100; (b) 5:95; (c) 15:85; (d) 25:75; (e) ^{1}H NMR spectra of $\mathbf{3}_2 \subset \mathbf{1}_6$ (500 MHz, D_2O/CD_3OD = 25:75 (v/v), 293 K, [**1**] = 2.0 mM). (f) (H–H) COSY NMR spectrum of $\mathbf{1}_6$ (500 MHz, D_2O/CD_3OD = 25:75 (v/v), 293 K, [**1**] = 2.0 mM). Small red letters denote proton signals for the pyridyl groups a–d. Superscripts (A–C) indicate the protons in the same pyridine ring. Blue capital letters denote 12 coupling pairs for the phenylene and p-tolyl protons (e–f and g–h, respectively).

The ^{1}H NMR titration study verified that a couple of the guest **3** were encapsulated in the box-shaped capsule $\mathbf{1}_6$ in solution (Figure S11), which is consistent with the crystal structure. Upon addition of 2 equiv of **3** to an aqueous methanol solution of the capsule $\mathbf{1}_6$, the ^{1}H NMR signals for the capsule became sharpened (Figure 2e). This should be due to the formation of an inclusion complex $\mathbf{3}_2 \subset \mathbf{1}_6$.

In the presence of excess **3**, proton signals of free **3** appeared separately, at $\delta = 2.63$ ppm, indicating that the inclusion/release of the guest molecules is relatively slow compared with the NMR time scale. The signals for encapsulated **3** were observed in the lower field region ($\Delta\delta = 0.87$ ppm) compared to those of free **3**.[8] This is best explained by the deshielding of the neighboring aromatic rings in $\mathbf{1}_6$. Indeed, an (H, H) NOESY spectrum of the inclusion complex showed two cross peaks between the signals of **1** and **3** (Figure S7), indicating that both are close to each other as was observed in the crystal structure. A ^{1}H DOSY measurement showed that the ^{1}H signals for **3** showed a log D value of -9.88 ($D = 1.3 \times 10^{-10}$ m^2 s^{-1}), which is identical to that of $\mathbf{1}_6$ (Figure S5). These results demonstrate that a couple of the guest molecules **3** are encapsulated in $\mathbf{1}_6$ in solution. Other benzene derivatives were also tested for the encapsulation in the capsule (Figure S12). As a result, hexamethylbenzene, mesitylene, and hexafluorobenzene were encapsulated into $\mathbf{1}_6$, while a larger hexabromobenzene and a smaller 1,3,5-trichlorobenzene were not. These results indicate that a high size and shape selectivity observed in the molecular recognition should arise not only from a hydrophobic effect but also from van der Waals forces that work between $\mathbf{1}_6$ and the guest molecules.

In conclusion, a self-assembled organic capsule was formed from the union of six hexagram-shaped amphiphile molecules **1** in aqueous methanol due to the hydrophobic effect, van der Waals forces, and CH–π interactions. Such an integration of noncovalent weak interactions between multiple chemical components is critical in maintaining well-defined discrete self-assembled structures of large molecules, as seen in many biological events in Nature. The present study would provide a new roadmap to more complex and larger self-assembled molecules and molecular systems by means of not only directional but also directionless binding forces.

Note Added after ASAP Publication. Production errors in the definition of M in the second paragraph and the notation for the inclusion complex were corrected on October 29, 2008.

Supporting Information Available: Synthetic procedures, NMR spectra, mass spectra, and crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) The critical concentration of the capsule formation was determined to be ~1 mM by a variable-concentration ^{1}H NMR experiment.

(5) When the fraction of water is set over 30%, the capsule gradually precipitated due to its lower solubility.

(6) A single crystal of box-shaped $\mathbf{1}_6$ was obtained from a saturated solution of **1** in CH_3CN. This aggregate contains a hexameric CH_3CN cluster inside which may act as a template, whereas **1** exists as a monomer in both dilute CH_3CN and aqueous CH_3CN solutions (Figure S8).

(7) Crystallographic data for $\mathbf{3}_2 \subset \mathbf{1}_6$: $C_{386}H_{348}Br_6N_{18}O_{22}$, $M = 6070.53$, $T = 93.1$ K, trigonal, $R\overline{3}$, $Z = 3$, $a = 23.8917(6)$, $b = 23.8971(6)$, $c = 50.1378(12)$ Å, $\alpha = 90.0000°$, $\beta = 90.0000°$, $\gamma = 120.0000°$, $V = 24796.3(11)$ Å^3, $R = 0.1545$, $wR = 0.4376$, GOF = 1.484. Material details for the crystal structure are available free of charge from the Cambridge Crystallographic Data Centre under Deposition No. CCDC 692402.

(8) Three ^{1}H NMR signals were separately observed in a 1:2:6 integral ratio for the methyl groups of a pair of **3** in the capsule. This is probably because a pair of the guest molecules tumbles in the cavity in a somewhat restricted way to make these signals inequivalent.

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