**Supramolecular Chemistry**

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# Capsule–Capsule Conversion by Guest Encapsulation

*Shitao Wang, Tomohisa Sawada, Kazuaki Ohara, Kentaro Yamaguchi, and Makoto Fujita**

***Abstract:*** *Guest-induced $M_{18}L_6$–$M_{24}L_8$ capsule–capsule conversion is reported. Both capsules are composed of $Pd^{II}$ ethylenediamine units (M) and 1,3,5-tris(3,5-pyrimidyl)pyrimidine (L), and form trigonal bipyramidal ($M_{18}L_6$) and octahedral ($M_{24}L_8$) closed-shell structures with huge hydrophobic inner spaces. The $M_{18}L_6$ trigonal bipyramid is converted to the $M_{24}L_8$ octahedron through encapsulation of large aromatic guests, with the latter capsule possessing a cavity volume three times larger than the former. Despite the dynamic properties of the capsule host, the encapsulated guests are difficult to extract and are thus isolated from the external environment.*

Molecular capsules show unique host properties that are different from those of other synthetic hosts in that they possess isolated nanocavities that allow the properties and reactivities of encapsulated guests to be maintained.[1] Recently, a lot of effort has been put into constructing capsular structures of ever-increasing size,[2] but relatively few of these capsules show distinct guest-binding properties in their large cavities, thus demonstrating that simple cavity expansion does not automatically lead to large guest encapsulation. We have previously reported trigonal bipyramidal $M_{18}L_6$ coordination capsule **1a**, but, unlike similar $M_6L_4$ open cages that bind various organic guests in their cavities,[3] capsule **1a** did not show any encapsulation behavior toward organic guests in water.[2b] We assumed that, in addition to the open framework, the highly electron-deficient environment of the $M_6L_4$ cages offered by the metal-coordinated tris(4-pyridyl)triazine ligand is essential for guest binding. We therefore redesigned the panel ligand of capsule **1a** to give a more electron-deficient 1,3-pyrimidine-cored panel, and created the more electron-deficient $M_{18}L_6$ capsule **1b**. Herein, we report that capsule **1b** does indeed encapsulate large guests and, unexpectedly and surprisingly, the large guest encapsulation triggers the conversion of $M_{18}L_6$ capsule **1b** into cavity-expanded $M_{24}L_8$ octahedral capsule **2b** (Figure 1). This guest-triggered $M_{18}L_6$–$M_{24}L_8$ switch presents a rare example of capsule–capsule conversion with concurrent dramatic cavity expansion.[4]

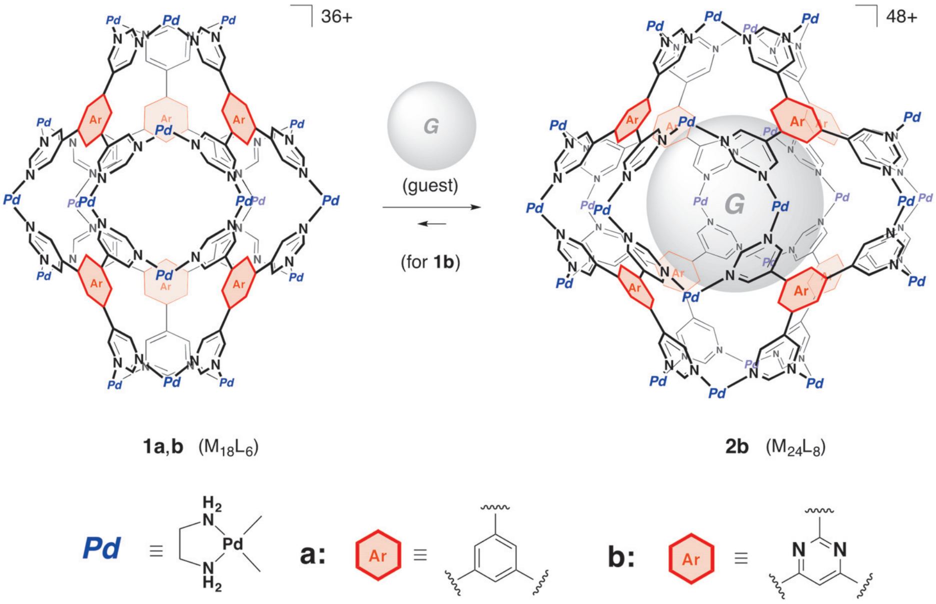

***Figure 1.*** Guest-induced $M_{18}L_6$–$M_{24}L_8$ capsule–capsule conversion.

By simply mixing [(en)Pd($ONO_2$)$_2$] (**3**; en = ethylenediamine) and our new ligand 2,4,6-tris(3,5-pyrimidyl)pyrimidine (**4**) in water, trigonal bipyramidal $M_{18}L_6$ coordination capsule **1b** was obtained. A mixture of **3** (34.9 mg, 120 μmol) and **4** (12.6 mg, 40 μmol) was stirred in $D_2O$ solution at 70 °C for 24 h, and the $^1$H NMR spectrum after the complexation clearly showed the formation of a single product with panel ligand **4** placed in a $C_{2v}$ environment. Six aromatic signals were observed in a 1:2:2:2:2:1 integral ratio (Figure 2a), thus suggesting that **3** and **4** were assembled into trigonal bipyramid **1b** with $D_{3h}$ symmetry and a mirror plane ($\sigma_h$) vertical to the main apical $C_3$ axis. There are many possible isomers of this $M_{18}L_6$ capsular structure because ligand **4** does not have a $C_3$ symmetry axis. However, the NMR analysis revealed that a single isomer was selectively formed in the reaction.[5] Crystallization was achieved by slow diffusion of

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[*] S. Wang, Dr. T. Sawada, Prof. Dr. M. Fujita
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
E-mail: mfujita@appchem.t.u-tokyo.ac.jp
Dr. K. Ohara, Prof. Dr. K. Yamaguchi
Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University
1314-1, Shido, Sanuki, Kagawa 769-2193 (Japan)

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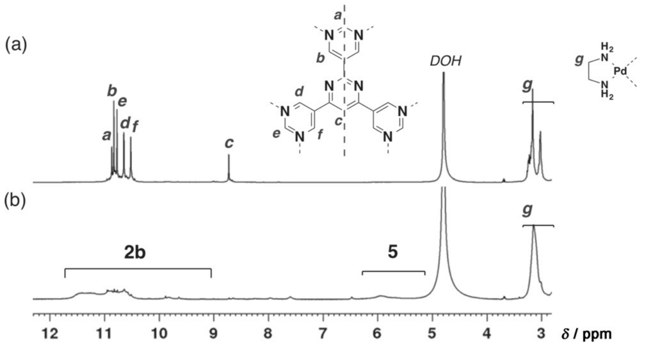


*Figure 2.* $^1$H NMR spectra of a) trigonal bipyramidal capsule **1b** and b) encapsulation complex of octahedral capsule **2b** containing four acenaphtylene molecules **2b**·(**5**)$_4$ (500 MHz, $D_2O$, 300 K).

methanol into the aqueous NMR sample over 2 weeks, and subsequent crystallographic analysis of a yellow single crystal clearly confirmed the trigonal bipyramidal structure of **1b** (Figure 3a).

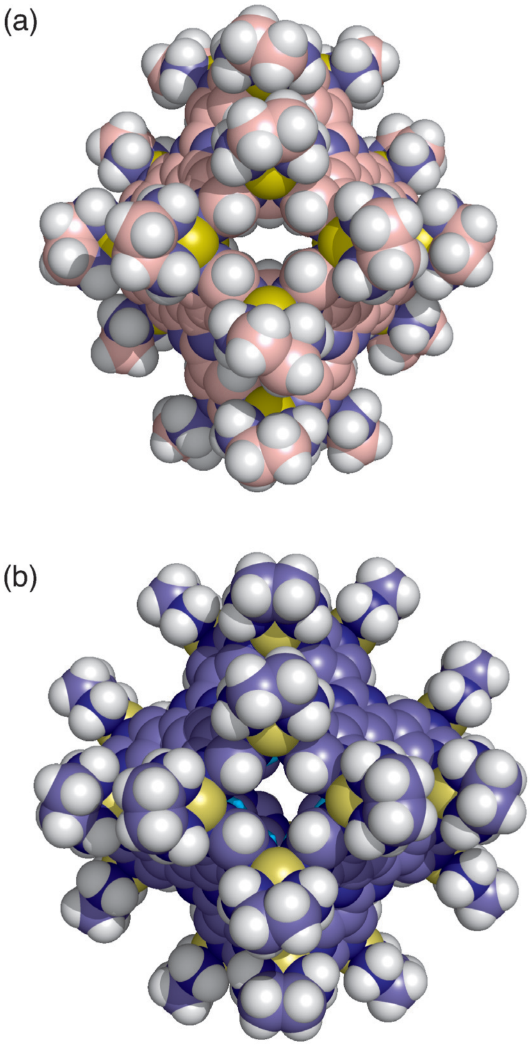
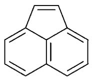
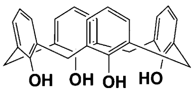


*Figure 3.* Crystal structures of a) trigonal bipyramidal capsule **1b** and b) octahedral capsule **2b**·(**5**)$_4$ in space-filling representation (solvents and nitrate ions are omitted for clarity).

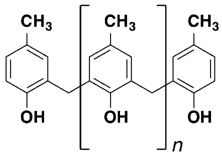
We next examined the guest encapsulation ability of **1b**. A large rigid aromatic molecule, acenaphthylene **5**, was found to be a suitable guest for this capsule. When an excess of **5** (36.5 mg, 240 μmol) was suspended in a $D_2O$ solution of $M_{18}L_6$ capsule **1b** (6.7 mM, 1 mL) at 70°C for 24 h, all of the aromatic signals in the $^1$H NMR spectrum became severely broadened (Figure 2b). Diffusion-ordered spectroscopy (DOSY) measurement of the newly assembled complex suggested the formation of a single structure with $\log D = -9.9$ ($D$: diffusion coefficient, $m^2 s^{-1}$). This value corresponds to a much larger species than hexahedron **1b** ($\log D = -9.7$). The signals of guest **5** were also severely broadened, and showed a high upfield shift to around 5–6 ppm, thus suggesting the encapsulation of **5** within the newly assembled structure. In addition, the methylene proton signals of the $Pd^{II}$ capping ligand in the $^1$H NMR spectrum changed from multiple singlets in **1b** to almost overlapping signals at approximately 3 ppm, which indicated that the newly formed species was more symmetric.



**5**



**6**



$n = 2$: **7**

$n = 1$: **8**

The encapsulation product was crystallized by slow evaporation of the solvent over 1 week. Single-crystal X-ray analysis unambiguously confirmed the octahedral structure of $M_{24}L_8$ capsule **2b** (Figure 3b). Four molecules of large aromatic guest **5** were encapsulated within the pseudo-$O_h$-symmetric cavity (Figure 4a).[6,7] Strong π–π interactions were observed between electron-rich **5** and the electron-deficient panel of **4** on octahedral capsule **2b**, (distances between π planes: 3.28–3.43 Å).

When single crystals of **2b**·(**5**)$_4$ of a quality suitable for X-ray analysis were redissolved in $D_2O$, we again observed the same broad NMR spectrum as for the as-synthesized complex in solution. The variable-temperature NMR measurement of **2b**·(**5**)$_4$ showed that the broad signals did not become sharper over the temperature range 280–340 K. These results indicate that the broad signals are not due to any dynamic processes (such as slow guest tumbling in the capsule or slow comformational change of the ligand) but to the existence of structural isomers of **2b**. Unlike the pyrimidine ligands in **1b**, those in **2b** can presumably adopt three different orientations in the octahedral capsule structure to generate numerous isomers (up to $3^8$, given a fixed $C_1$ orientation of the encapsulated guests). The monodispersity of **2b**·(**5**)$_4$ complex was also confirmed by a DLS study that showed monomodal scattering with a hydrodynamic radius of 1.25 nm, which reasonably corresponded to that of the $M_{24}L_8$ capsule (ca. 2.5 nm diameter from the crystal structure; Figure S33).

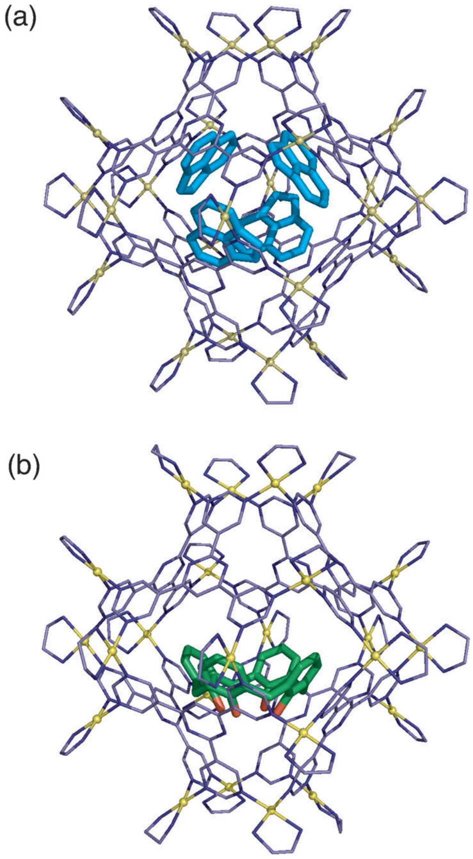


*Figure 4.* Orientations of guests: a) four molecules of acenaphtylene **5** and b) one molecule of calix[4]arene **6**, within octahedral capsule **2b** in the crystalline state. Only one orientation of the disordered guest is shown. Solvents and nitrate ions are omitted for clarity.

Recently, we reported an artificial mutual induced fit system, in which a flexible host and a self-assembled host mutually interacted and adopted a single host-in-host structure.[8] We thus decided to examine the encapsulation behavior of **1b** with flexible oligomeric hosts as guest molecules. Flexible calix[4]arene **6**, known for its rapid equilibration between four major conformers, was chosen for this demonstration. The encapsulation of **6** in **1b** was carried out according to the same procedure as used for **5** (excess of **6**, stirring at 70 °C for 24 h). After guest encapsulation, the $^1$H NMR spectrum showed broadened signals but the DOSY spectrum showed a single band with $\log D = -9.85$, which indicated the formation of a single species and suggested the selective formation of $M_{24}L_8$ capsule **2b** (Figure S28). FT-ICR ESI-MS measurements were undertaken to further characterize the solution structure. The MS spectrum was directly obtained from an aqueous solution of **2b·6** complex, and the most intense ion peak at $m/z$ 1920 was assigned to $[\mathbf{2b{\cdot}6}-5(NO_3)]^{5+}$ at high resolution (error 2 ppm; Figure S29).

The crystal structure of the encapsulation complex clearly confirmed the $M_{24}L_8$ octahedral structure (Figure 4b). Within the cavity, one guest molecule was disordered over two sites;[9] in both cases, only the cone conformation of **6** that fitted perfectly into the pyramidal corner of **2** (mutual induced fit) was observed. Presumably, strong π–π interactions between the phenol part of **6** and the electron-deficient capsule framework simultaneously triggered both the dynamic capsule–capsule conversion (**1b**→**2b**) and the guest encapsulation. The more flexible linear tetramer **7** was also encapsulated in the cavity of **2b**. In contrast, when trimer **8** was employed, neither the structural switch from **1b** to **2b** nor the encapsulation of **8** within trigonal bipyramidal capsule **1b** was observed in the $^1$H NMR spectrum.

Molecular mechanics calculations indicated a relatively small energy difference between the two capsules. The total energy of the empty framework of the two capsules was 205 and 214 kJ mol$^{-1}$ per $M_3L$ unit for **1b** and **2b**, respectively, slightly in favor of **1b**.[10] This energy difference is reversed upon guest encapsulation. Although the energy difference is relatively small, the difference in cavity volume between **1b** and **2b** is very large. We used the VOIDOO program[11] to calculate the cavity volumes from the crystal structures, and Figure S8 shows the visualized cavity volume when a spherical probe with a radius of 3.36 Å was used. Octahedron **2b** has a very large cavity volume of 943 Å$^3$, whereas the cavity of trigonal bipyramidal **1b** has a volume of only 381 Å$^3$.

The cavity of the octahedral capsule provided protection from guest exchange. Because of the reversible nature of Pd$^{II}$–pyrimidine bonding, the capsule framework is in equilibrium with its partially dissociated forms (although these exist at very low concentrations). Nevertheless, once encapsulated within **2b**, guest **5** could no longer be extracted with chloroform. Even after vigorous stirring of the aqueous solution of $\mathbf{2b}{\cdot}(\mathbf{5})_4$ with chloroform at room temperature for 24 h, no guest molecules were detected in the chloroform phase (Figure S9). Only after stirring at high temperature (ca. 60 °C) for 24 h, could **5** be extracted from the cavity of **2b**. Thus, the inside of the closed-shell structure of $\mathbf{2b}{\cdot}(\mathbf{5})_4$ only becomes accessible at high temperatures. After guest extraction, the octahedral structure was immediately reconverted to trigonal bipyramidal capsule **1b**. This behavior sharply contrasts to that of an open $M_6L_4$ cage, from which **5** could be immediately extracted with chloroform (Figure S10).

In conclusion, we have successfully developed a large $M_{18}L_6$ trigonal bipyramidal capsule with a cavity that can be dramatically expanded upon large guest encapsulation by conversion into a larger octahedral $M_{24}L_8$ capsule. To the best of our knowledge, the cavity volume of this octahedral capsule (> 900 Å$^3$) is one of the largest reported among self-assembled capsules with guest-binding properties.[12,13] Large guests are fully encapsulated within the $M_{24}L_8$ octahedral cavity and are unable to interact with the outside environment, meaning that our results have established a step toward the development of giant synthetic capsules with strong guest encapsulation abilities.

## Experimental Section

Crystallographic diffraction data were measured on a Bruker APEX-II/CCD diffractometer equipped with a focusing mirror (Mo Kα radiation $\lambda = 0.71073$ Å) with a cryostat system equipped with a $N_2$ generator. The crystals were removed from the solution, quickly attached to a loop of nylon fiber with antifreeze reagent (paraton-N, Hampton research), and mounted on a goniometer.

Crystal data for **1b**: Hexagonal space group $P\bar{6}$, $T = 90(2)$ K, $a = b = 22.749(3)$, $c = 31.459(4)$ Å, $\alpha = \beta = 90$, $\gamma = 120°$, $V = 14099(3)$ Å$^3$, $Z = 2$, $\rho_{calcd} = 1.704$ Mg m$^{-3}$, $F(000) = 7206$, reflections collected/unique 161898/22553 ($R_{int} = 0.0407$). The structure was solved by direct methods (SHELXS) and refined by fill-matrix least-squares methods (SHELXL) on $F^2$ with 768 parameters. $R_1 = 0.0940$ ($I > 2\sigma(I)$), $\omega R_2 = 0.2519$. GOF 1.082, CCDC 1402529 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Crystal data for **2b·(5)**$_4$: Monoclinic space group $I2/m$, $T = 90(2)$ K, $a = 27.068(4)$, $b = 26.615(3)$, $c = 30.276(6)$ Å, $\alpha = \gamma = 90$, $\beta = 92.9030(10)°$, $V = 21783(6)$ Å$^3$, $Z = 2$, $\rho_{calcd} = 1.577$ Mg m$^{-3}$, $F(000) = 10333$, reflections collected/unique 129837/27005 ($R_{int} = 0.0393$). 1218 parameters. $R_1 = 0.1163$ ($I > 2\sigma(I)$), $\omega R_2 = 0.3441$. GOF 1.514, CCDC 1402528 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Crystal data for **2b·6**: Monoclinic space group $C2/m$, $T = 90(2)$ K, $a = 39.459(5)$, $b = 26.488(4)$, $c = 27.040(4)$ Å, $\alpha = \gamma = 90$, $\beta = 130.2970(10)°$, $V = 21555(5)$ Å$^3$, $Z = 2$, $\rho_{calcd} = 1.554$ Mg m$^{-3}$, $F(000) = 10062$, reflections collected/unique 113364/22789 ($R_{int} = 0.0475$). 1071 parameters. $R_1 = 0.1421$ ($I > 2\sigma(I)$), $\omega R_2 = 0.4490$. GOF 1.334, CCDC 1402527 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[6] See the Supporting Information for details.

[7] Elemental analysis of the crystals supported the formation of the **2b·(5)**$_4$ complex: calcd for $C_{176}H_{272}N_{160}O_{144}Pd_{24}\cdot 4(C_{12}H_8)\cdot 50\,H_2O$, C 24.47 %, H 3.70 %, O 20.38 %; found, C 24.10 %, H 3.86 %, O 20.21 %.

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