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Template-Directed Synthesis of a Covalent Organic Capsule Based on a 3 nm-Sized Metallocapsule

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Molecular capsules have been of continuing interest to many researchers because they provide a specific, confined nanospace as a site for recognition and catalysis.[1a,2] Since the birth of a covalent organic capsule, carcerand, by Cram et al.,[2] a number of excellent molecular capsules have been reported to exhibit the usefulness of the isolated internal space. Because of their synthetic facility, many of them are constructed by self-assembly with the aid of reversible chemical bonding such as H bonding and metal coordination.[1] In contrast, covalent organic capsules, which have a higher chemical and thermal stability than self-assembled capsules, are synthetically more difficult.[3] At this stage, template-directed synthesis is expected to be a rational strategy for constructing elaborate 3D architectures.[4] Among a series of possible template species, metal-assisted self-assembled molecules have great advantages, such as their relative stability and the fact that the relative position of the metal ligands is precisely defined by directional coordination bonding. Previously, we reported 3 nm-sized octahedron-shaped metallocapsules $[M_6\mathbf{1}_8]^{12+}$ constructed from eight tris(monodentate) ligands **1** and six divalent transition-metal ions M^{2+} (M = Mn, Co, Fe, Ni, Cu, Zn, Cd, Hg, Pd, Pt) (Figure 1).[5] The six metal ions and eight ligands **1** occupy the six vertexes and eight faces of the octahedron, respectively, and as a result, two methyl groups on two ligands lying side-by-side come close to each other. Accordingly, the introduction of terminal olefins at these positions with an appropriate linker would lead to cross-linkage of the adjacent metal ligands by olefin metathesis reactions. To achieve this, we designed the modified tris(monodentate) ligands **2**−**4**, in which three terminal olefins are attached to benzene rings in **1** through alkoxy linkers having different chain lengths. In view of its high thermal stability and inertness to Grubbs catalyst, a Pd(II) capsule was chosen. Here we demonstrate the highly efficient synthesis of covalent organic capsule **6** (from **3**) starting from $Pd_6\mathbf{3}_8\cdot(BF_4)_{12}$ via the following three steps (Figure 1): (1) olefin metathesis reaction between the nearest-neighbor olefins on the Pd(II) capsule; (2) removal of the Pd^{2+} ions; and (3) reduction of the internal olefins. The 24 pyridyl groups of the resulting organic capsule **6** were fully methylated to afford 5 nm-sized $\mathbf{7}\cdot I_{24}$, which was found to be larger than the 4 nm-sized neutral capsule **6**.

To determine the optimal chain length of the linker for the olefin metathesis reaction, three ligands having different chain lengths, **2**−**4**, were synthesized. The metallocapsules $Pd_6L_8\cdot(BF_4)_{12}$ (L = **2**−**4**) were quantitatively constructed by mixing L and $Pd(CH_3CN)_4\cdot(BF_4)_2$ in a 4:3 ratio in a 1:1 $CH_3CN/CHCl_3$ mixed solvent at 70 °C for 10 h. The formation of the hexanuclear Pd(II) capsules was confirmed by ^1H NMR and ESI-TOF MS measurements. For example, ^1H NMR and ESI-TOF MS spectra of $Pd_6\mathbf{3}_8\cdot(BF_4)_{12}$ are shown in Figures 2b and 3a, respectively. The olefin metathesis reactions of hexanuclear capsules having different chain lengths were then carried out at a capsule concentration of 0.5 mM in the presence of Grubbs catalyst **5** in CH_2Cl_2 at 293 K. Each reaction was monitored by ESI-TOF MS (Figure S6 in the Supporting Information). The 12-point metathesis reactions of the capsules having longer alkoxy chains, $[Pd_6L_8]^{12+}$ (L = **3**, **4**), completed within two days, while the reaction did not proceed in the case of $[Pd_6\mathbf{2}_8]^{12+}$ having shorter alkoxy linkers.[6]

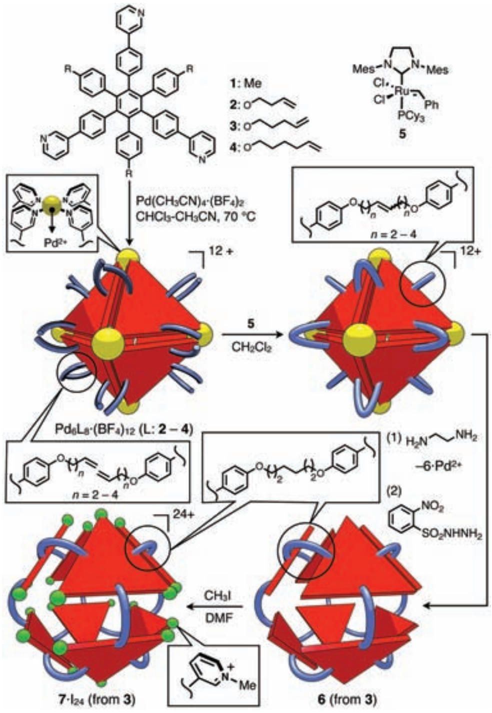

Figure 1. Schematic representation of the formation of covalent organic capsules based on a template-directed approach.

Next, we investigated the effect of concentration on the metathesis reaction for the $[Pd_6\mathbf{3}_8]^{12+}$ and $[Pd_6\mathbf{4}_8]^{12+}$ capsules. In the case of $[Pd_3\mathbf{3}_8]^{12+}$, decreasing the concentration of the capsule to 0.08 mM led to completion of the reaction within 1 day, and the ESI-TOF MS spectrum of this reaction mixture showed only one species for the capsule, which lost 12 C_2H_4 molecules (Figure 3b). On the other hand, the metathesis reaction of $[Pd_6\mathbf{4}_8]^{12+}$ at the lower concentration was found to be too slow (Figure S7).

The olefin metathesis reaction with the $Pd_6\mathbf{3}_8\cdot(BF_4)_{12}$ capsule was then performed under the optimal conditions, after which the six Pd^{2+} ions were removed from the resulting complex by the addition of ethylenediamine. The subsequent reduction of the internal olefins by

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a sulfonylhydrazide reagent produced the desired covalent organic capsule **6** in 43% yield in three steps from $\mathrm{Pd}_6\mathbf{3}_8\cdot(\mathrm{BF}_4)_{12}$. The organic capsule **6** was fully characterized by NMR and MS measurements. The ^{1}H NMR spectrum of **6** in $\mathrm{CDCl_3}$ displayed only 12 proton signals in the aromatic region (Figure 2c), indicating a highly symmetrical structure. This was also confirmed by the ^{13}C NMR spectrum. All of the proton and carbon signals were fully characterized by H−H COSY, HMQC, and HMBC measurements (Figures S1−S3). It is noteworthy that no signals for methyl groups were observed in these spectra, indicating that the cross-linking of the terminal olefins was complete at all 12 positions.[7] The MALDI-TOF MS spectrum showed only one intense signal at *m/z* 7833.4, which is consistent with $\mathbf{6}^+$ (Figure 3c).

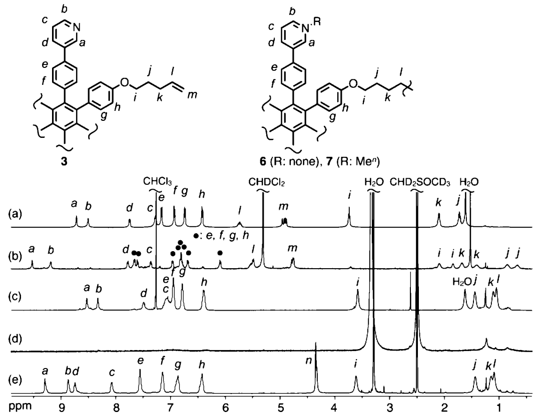

Figure 2. ^{1}H NMR spectra (500 MHz, 293 K). (a) **3** in $\mathrm{CDCl_3}$; (b) $\mathrm{Pd}_6\mathbf{3}_8\cdot(\mathrm{BF}_4)_{12}$ in $\mathrm{CD_2Cl_2}$; (c) **6** in $\mathrm{CDCl_3}$; (d) **6** in DMSO-d_6; (e) $\mathbf{7}\cdot\mathrm{I}_{24}$ in DMSO-d_6.

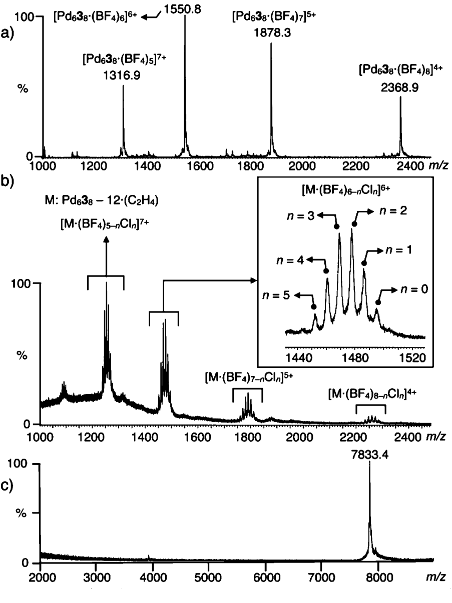

Figure 3. (a, b) ESI(+)-TOF MS spectra: (a) $\mathrm{Pd}_6\mathbf{3}_8\cdot(\mathrm{BF}_4)_{12}$; (b) measured after the olefin metathesis reaction. (c) MALDI-TOF MS spectrum of **6**. α-Cyano-4-hydroxycinnamic acid (CHCA) was used as a matrix.

The molecular size of the capsule in solution was estimated by ^{1}H DOSY measurements (Figure S4). The hydrodynamic radius of **6** in $\mathrm{CDCl_3}$, $r_\mathrm{h} = 1.9$ nm, is larger than that of the original Pd(II) capsule ($r_\mathrm{h} = 1.5$ nm), indicating that the eight panels are farther apart from each other in **6** than in the metallocapsule. In contrast, the ^{1}H NMR spectrum of **6** in DMSO-d_6 was extremely broadened, suggesting a compacted structure as the result of condensation of the immiscible apolar alkoxy chains and phenylene groups in the polar medium.[8]

The finding that the solution structure of the capsule is flexible prompted us to conduct *N*-methylation of the 24 pyridyl groups in **6** to form the polycationic capsule $\mathbf{7}^{24+}$. It was expected that in this molecule, the electrostatic repulsion between the positive charges on the nitrogen atoms would destabilize the folded conformation, causing $\mathbf{7}^{24+}$ to be larger than **6**. *N*-methylation of **6** with $\mathrm{CH_3I}$ gave $\mathbf{7}\cdot\mathrm{I}_{24}$ quantitatively. The ^{1}H NMR spectrum of $\mathbf{7}\cdot\mathrm{I}_{24}$ in DMSO-d_6 became relatively sharp (Figure 2e). As expected, $\mathbf{7}\cdot\mathrm{I}_{24}$ was found to have a significantly larger hydrodynamic radius of 2.4 nm (Figure S5), which is comparable to that of the fully expanded capsule structure as estimated from molecular modeling.[9]

In summary, a covalent organic capsule **6** was synthesized from a template capsule, $\mathrm{Pd}_6\mathbf{3}_8\cdot(\mathrm{BF}_4)_{12}$, in extremely high yield. The molecular size of the capsule can be enlarged by *N*-methylation of the 24 pyridyl groups of **6**. Research on molecular recognition and chemical reactions utilizing both neutral and polycationic nanosized capsules as platforms is currently underway.

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Supporting Information Available: Synthetic procedures, NMR spectra, and ESI-TOF MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The template effect of the metallocapsule is obvious, since the same reaction of ligand **3** at low concentration ([**3**] = 4.3 mM) resulted in no reaction, whereas the reaction at higher concentration ([**3**] = 33 mM) gave only insoluble material that may be a polymeric structure.

(7) When the metathesis reaction was incomplete, signals for the methyl groups of the linkers in the *N*-methylated capsule were found at 0.74 and 13.6 ppm in the ^{1}H and ^{13}C NMR spectra, respectively.

(8) The DOSY measurement of **6** in DMSO-d_6 failed because of the extremely broadened ^{1}H NMR spectrum.

(9) A detailed discussion of the larger molecular size of the polycationic capsule is provided in the Supporting Information.

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