

## Complete Selection of a Self-Assembling Homo- or Hetero-Cavitand Cage via Metal Coordination Based on Ligand Tuning

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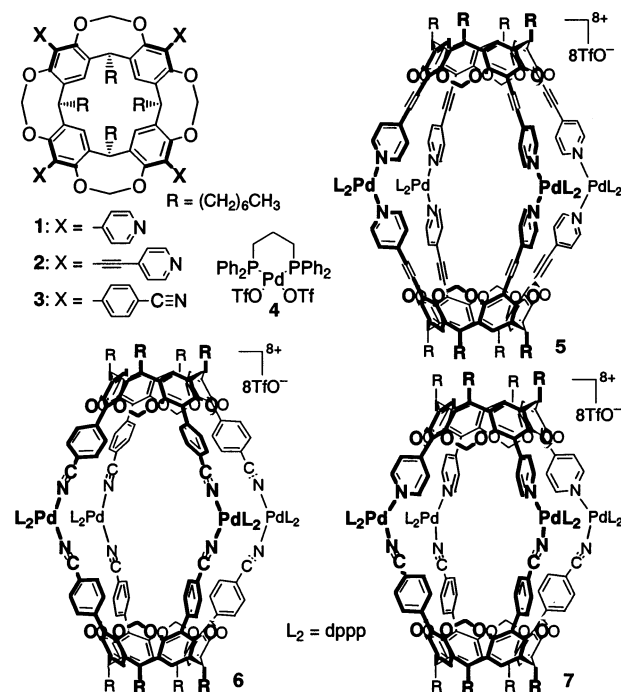
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The construction and utilization of nanospace are among the important subjects of nanotechnology directed toward material and life sciences. The self-assembly of cages (or capsules) via hydrogen bonds or metal coordination has been extensively studied as a promising candidate for providing nanospace isolated from bulk phases.<sup>1–3</sup> The formation of hydrogen-bonded hetero-cages of bowl-shaped cavitands or calix[4]arenes (i.e., assembly of north and south hemispheres) is of considerable interest in light of a dynamic combinatorial library of assemblies, and as the basis of building blocks for molecular devices.<sup>4</sup> However, metal-coordination hetero-cages have been rarely reported owing to the difficulty in controlling the simultaneous *cis*-coordination of two kinds of ligands with different coordination ability as donors on a metal as an acceptor.<sup>5,6</sup> Herein, we report the selective self-assembly of a homo- or hetero-cavitand cage via metal coordination based on ligand tuning, wherein a combination of factors such as coordination ability and steric demand of cavitand ligands would play an important role.

Deep cavitands, tetra(4-pyridyl)-cavitand (**1**), tetrakis(4-pyridylethynyl)-cavitand (**2**), and tetrakis(4-cyanophenyl)-cavitand (**3**),<sup>3d</sup> were synthesized by the Suzuki or Sonogashira coupling reaction.<sup>7</sup> The homo-cavitand cages {2(2)·4[Pd(dppp)]}<sup>8+</sup>·8(TfO<sup>-</sup>) (**5**) and {2(3)·4[Pd(dppp)]}<sup>8+</sup>·8(TfO<sup>-</sup>) (**6**) and the hetero-cavitand cage {1·3·4[Pd(dppp)]}<sup>8+</sup>·8(TfO<sup>-</sup>) (**7**) were instantaneously formed in CDCl<sub>3</sub> by four square-planar Pd(dppp)(OTf)<sub>2</sub> (**4**) complexes in the equatorial region, connecting the two homo- or hetero-cavitand ligands **1–3** (Chart 1 and Figure 1).

The <sup>1</sup>H NMR spectrum of a 2:4 mixture of **1** and **4** showed broad and complicated signals, indicating various species of aggregates. On the other hand, the <sup>1</sup>H NMR spectrum of a 2:4 mixture of **2** and **4** exhibited a new set of signals (Figure 1c), indicative of a single highly symmetrical species (*D*<sub>4h</sub> symmetry), a homo-cavitand cage **5**. The pyridyl α-proton of **5** was shifted downfield by 0.32 ppm, and the pyridyl β-proton and the outer and inner protons of the methylene bridge were shifted upfield by 0.30, 0.10, and 0.34 ppm, relative to those of free **2**. The <sup>1</sup>H NMR spectra of a mixture of **2** and **4** in 2:1, 2:2, and 2:3 molar ratios showed only two sets of signals of the homo-cavitand cage **5** and free **2**, and the spectrum of a 2:8 mixture of **2** and **4** exhibited another two sets of signals of **5** and free **4** (Figure S1).<sup>7</sup> In all cases, the chemical shifts of **5** remained unchanged and other species such as intermediates were not observed, which was also supported by the <sup>31</sup>P NMR (Figure S2).<sup>7</sup> These results indicate that **5** is highly stable and the self-assembly of **5** is a concerted process. Further evidence for the formation of **5** was provided by the cold-spray ionization mass spectrum (CSI-MS)<sup>8</sup> of a 2:4 mixture of **2** and **4** (Figure S5),<sup>7</sup> wherein the molecular ion peaks of **5** were observed at *m/z* 5785.1

Chart 1



[M – TfO<sup>-</sup>]<sup>+</sup> (calcd 5786.28), 2818.2 [M – 2(TfO<sup>-</sup>)]<sup>2+</sup> (2818.16), and 1828.8 [M – 3(TfO<sup>-</sup>)]<sup>3+</sup> (1829.12).

A 2:4 mixture of **3** (2 mM) and **4** was also self-assembled into a homo-cavitand cage **6** (Figure 1e).<sup>3d</sup> The chemical shift changes of the α- and β-protons of the *p*-cyanophenyl group and the outer and inner protons of the methylene bridge of **6** relative to those of free **3** ( $\Delta\delta = \delta_{\text{cage}} - \delta_{\text{free ligand}}$ ) were –0.25, 0.09, –0.31, and 0.10 ppm, respectively. The **6** is less stable than **5**. A dilution experiment of **6** monitored by <sup>1</sup>H NMR, where the ratio of **3**:**4** is maintained at 2:4, showed that the  $\Delta\delta$  of **6** gradually decreased upon dilution, indicating that the exchange between **6** and free **3** is fast on the NMR time scale.

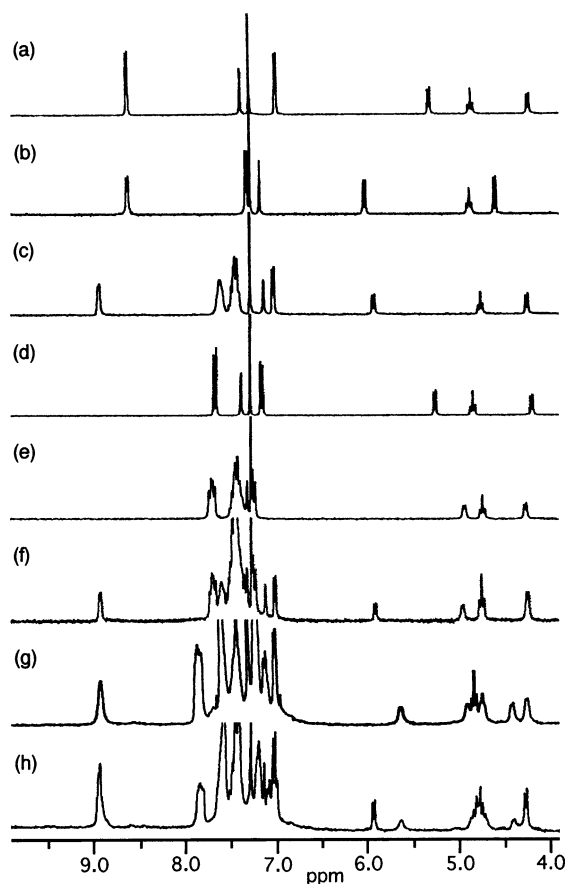
Thus, in the <sup>1</sup>H NMR spectrum of a 1:1:4 mixture of **2** (1 mM), **3**, and **4**, two homo-cavitand cages **5** and **6** were individually observed in a 1:1 molar ratio (Figure 1f). A hetero-cavitand cage composed of **2**, **3**, and **4** was not detected under these conditions. A 1:1:4 mixture of **1**, **2**, and **4** produced **5** and complicated aggregates derived from **1** and **4**, but not a hetero-cavitand cage.

In marked contrast, a 1:1:4 mixture of **1**, **3**, and **4** was exclusively self-assembled into a hetero-cavitand cage **7**, the <sup>1</sup>H NMR spectrum of which indicated a single highly symmetrical species (*C*<sub>4v</sub> symmetry) (Figure 1g). In the **1** unit of **7**, the  $\Delta\delta$  values of the pyridyl α- and β-protons and the outer and inner protons of the methylene bridge were 0.29, 0.00, 0.32, and 0.16 ppm, respectively.

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**Figure 1.** Association behavior of deep cavitands **1–3** with Pd complex **4** monitored by  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 23  $^\circ\text{C}$ ): (a) **1** alone; (b) **2** alone; (c)  $[\text{2}] = 2 \text{ mM}$  and  $[\text{4}] = 4 \text{ mM}$  (homo-cage **5**); (d) **3** alone; (e)  $[\text{3}] = 2 \text{ mM}$  and  $[\text{4}] = 4 \text{ mM}$  (homo-cage **6**); (f)  $[\text{2}] = [\text{3}] = 1 \text{ mM}$  and  $[\text{4}] = 4 \text{ mM}$  (**5:6** = 1:1); (g)  $[\text{1}] = [\text{3}] = 1 \text{ mM}$  and  $[\text{4}] = 4 \text{ mM}$  (hetero-cage **7**); and (h)  $[\text{1}] = [\text{2}] = [\text{3}] = 2 \text{ mM}$  and  $[\text{4}] = 12 \text{ mM}$  (**5:7** = 1:2).

In the **3** unit of **7**, the  $\Delta\delta$  values of the  $\alpha$ - and  $\beta$ -protons of the *p*-cyanophenyl group and the outer and inner protons of the methylene bridge were  $-0.09$ ,  $0.05$ ,  $-0.39$ , and  $0.06$  ppm, respectively. The chemical shifts of **7** remained unchanged, at least at concentrations greater than  $0.1 \text{ mM}$ . The  $^{31}\text{P}$  NMR of **7** showed two doublet peaks at  $6.39$  and  $9.51$  ppm with  $^3J_{\text{pp}} = 27.3 \text{ Hz}$  due to the dppp desymmetrized by the hetero-cage (Figure S4).<sup>7</sup> Further evidence for the formation of **7** was given by CSI-MS of a 1:1:4 mixture of **1**, **3**, and **4** (Figure S5), wherein the molecular ion peaks of **7** were observed at  $m/z$  5687.4  $[\text{M} - \text{TfO}^-]^+$  (calcd 5690.28), 2769.0  $[\text{M} - 2(\text{TfO}^-)]^{2+}$  (2770.16), and 1796.9  $[\text{M} - 3(\text{TfO}^-)]^{3+}$  (1797.12). In the  $^1\text{H}$  NMR, however, the  $\Delta\delta$  of the **3** unit of **7** gradually decreased upon addition of aliquots of **3** to the solution of **7**, although the chemical shifts of the **1** unit of **7** remained unchanged (Figure S3).<sup>7</sup> Upon addition of 1 equiv of **1**, the hetero-cavitand cage **7** was changed to a mixture of free **3** and complicated aggregates derived from **1** and **4**. These results indicate that the **3** unit of **7** is labile and the exchange between the **3** unit of **7** and free **3** is fast on the NMR time scale. Upon addition of 1 equiv of **3**, aggregates derived from a 1:4 mixture of **1** and **4** were converted to **7** (Figure S3). Therefore, the strict stoichiometry of **1:3:4** = 1:1:4 is required for the formation of **7**.

The  $^{19}\text{F}$  NMR of **5**, **6**, and **7** showed a single peak at ca.  $-80$  ppm, respectively, indicating no encapsulation of  $\text{TfO}^-$ .<sup>3c-e</sup> In the competition experiments, a 2:2:2:12 mixture of **1**, **2**, **3**, and **4** immediately gave **5** and **7** in a 1:2 molar ratio (Figure 1h), whereas a mixture of **1–4** in a 2:2:2:8 ratio produced **5**, free **3**, and aggregates derived from **1** and **4**, concomitantly with a small amount of **7**. Thus, the stability of the cages increases in the order  $\mathbf{6} < \mathbf{7} < \mathbf{5}$ . The observed selectivity for the self-assembly of the homo- or hetero-cavitand cages **5–7** via metal coordination would arise from combinations of differences of (i) the inherent coordination ability of cavitand ligands ( $\mathbf{1} \geq \mathbf{2} > \mathbf{3}$ ),<sup>9</sup> (ii) the flexibility of dihedral angle between ligand moiety and the cavitand scaffold ( $\mathbf{2} > \mathbf{3} \approx \mathbf{1}$ ), and (iii) the steric hindrance between dppp and ligands on the Pd ( $\mathbf{1} > \mathbf{2} > \mathbf{3}$ ). The deviation of the biting angles of  $\text{X-Pd-X'}$ (X), where X and X' are ligands on the cavitand, from that of **4** would also be an important factor for the cage assembly.<sup>3c</sup>

In summary, we have demonstrated that tuning the ligands on the basis of a combination of factors such as coordination ability and steric demand of cavitand ligands can control the selection of a self-assembling homo- or hetero-cavitand coordination cage. Studies on the encapsulation abilities of these cages are currently underway in our laboratory.

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**Supporting Information Available:** Synthetic procedures and spectral data of **1–3** and **5–7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) The addition of 2 equiv of **1** to the solution of **5** gave a 1:1 mixture of **5** and free **2**, concomitantly with aggregates derived from **1** and **4**.

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