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Tunable Capsule Space: Self-Assembly of Hemispherical Cavitands with Hydrogen-Bonding Linkers

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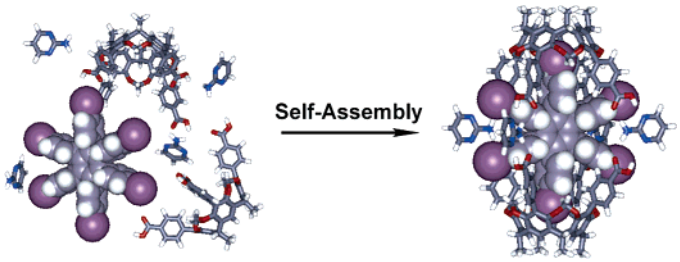
Received July 20, 2006



Fine and/or drastic tuning of capsule space has been attained by alteration of the hydrogen-bonding linker and/or hemispherical cavitand, respectively. Two molecules of tetracarboxyl-cavitand **1** or tetrakis-(4-carboxyphenyl)-cavitand **2** as a hemisphere and four molecules of 2-aminopyrimidine (2-AP) or tetrahydro-2-pyrimidinone (THP) as an equatorial hydrogen-bonding linker self-assemble into a capsule $[(\mathbf{1})_2\cdot(2\text{-AP})_4]$ (**3**), $[(\mathbf{1})_2\cdot(\text{THP})_4]$ (**4**), $[(\mathbf{2})_2\cdot(2\text{-AP})_4]$ (**5**), or $[(\mathbf{2})_2\cdot(\text{THP})_4]$ (**6**), respectively, via 16 hydrogen bonds. These capsules provide isolated nanospace and can encapsulate one guest molecule (**7**−**13**) in solution. Each capsule has a different cavity size and shows particular guest selectivity on the competitive encapsulation experiments.

Introduction

Supramolecular capsules constructed from self-assembly of preorganized molecules provide an isolated nanospace.[1] Guest molecules encapsulated in the capsules often show unique properties that are not observed in bulk phases.[2−4] A fit between guest and cavity of capsule in shape and size is essential for the encapsulation.[5] The strategy for the construction of hydrogen-bonding supramolecular capsules has so far been mainly based on (self-) complementary assemblies of two molecules. In contrast, capsule formation via multimolecule assemblies is rare.[6−10] Assembly of multicomponents and -molecules through hydrogen bonds is one of interesting topics in supramolecular chemistry, with a view to mimicking biological processes, as well as the construction of a variety of cavity libraries by

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(1) (a) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018−1033. (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382−2426. (c) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488−1508. (d) Fujita, M.; Tominaga, M.; Hori, A.; Therrien, B. *Acc. Chem. Res.* **2005**, *38*, 369−378.

(2) (a) Körner, S. K.; Tucci, F. C.; Rudkevich, D. M.; Heinz, T.; Rebek, J., Jr. *Chem.−Eur. J.* **2000**, *6*, 187−195. (b) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 6311−6312. (c) Ziegler, M.; Brumaghim, J. L.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4119−4121.

(3) (a) Kang, J.; Rebek, J., Jr. *Nature (London)* **1997**, *385*, 50−52. (b) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748−6751. (c) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251−254.

(4) (a) Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 12074−12075. (b) Shivanyuk, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 684−686. (c) Yamanaka, M.; Rebek, J., Jr. *Chem. Commun.* **2004**, 1690−1691.

(5) Mecozzi, S.; Rebek, J., Jr. *Chem.−Eur. J.* **1998**, *4*, 1016−1022.

(6) (a) Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1215−1218. (b) Jolliffe, K. A.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 933−937. (c) Paraschiv, V.; Crego-Calama, M.; Ishi-I, T.; Padberg, C. J.; Timmerman, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 7638−7639. (d) Kerckhoffs, J. M. C. A.; ten Cate, M. G. J.; Mateos-Timoneda, M. A.; van Leeuwen, F. W. B.; Snellink-Ruël, B.; Spek, A. L.; Kooijman, H.; Crego-Calama, M.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2005**, *127*, 12697−12708.

(7) (a) MacGillivray, L. R.; Atwood, J. L. *Nature (London)* **1997**, *389*, 469−472. (b) Gerkensmeier, T.; Iwanek, W.; Agena, C.; Fröhlich, R.; Kotila, S.; Näther, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, *2257*, 7−2262. (c) Yamanaka, M.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 2939−2943. (d) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11556−11563.

10.1021/jo061516p CCC: $33.50
Published on Web 10/13/2006

CHART 1. Hemisphere Cavitands and Hydrogen-Bonding Linkers

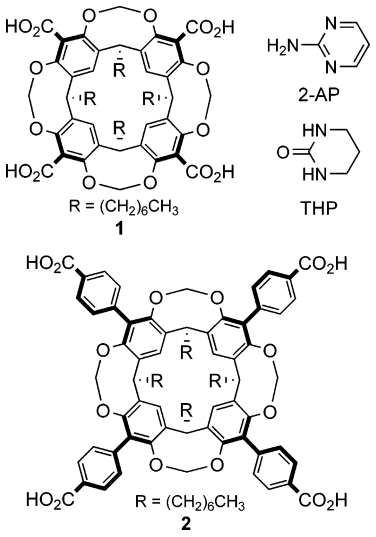
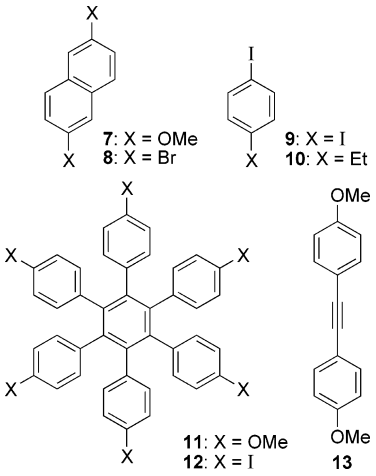


CHART 2. Guest Molecules

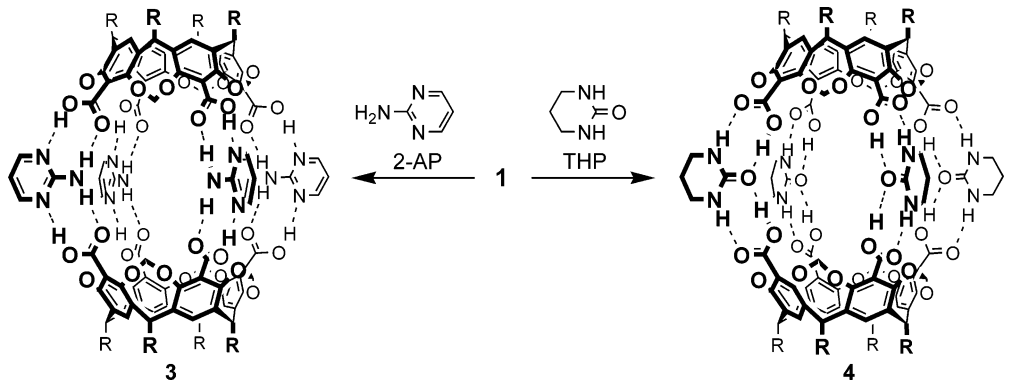


increasing the tunable factors. We report here the formation of a capsule with a highly tunable cavity via self-assembly of six molecules, i.e., two molecules of hemispherical cavitands and four molecules of hydrogen-bonding equatorial linkers. A combination of cavitands (**1** and **2**) with linkers (2-AP and THP) (Chart 1) provides four kinds of supramolecular capsules **3**, **4**, **5**, and **6**. Encapsulation of guest molecules (Chart 2) is attained in solution and their exchanges are slow enough on the NMR time scale. Fine-tuning of the cavity is attained by alteration of the linker. Modification of the cavitand provides a dramatic variation in cavity size. Each capsule has a different cavity size and shows particular guest selectivity.

Results and Discussion

Encapsulation of Guest in [(1)$_2$·(2-AP)$_4$] and [(1)$_2$·(THP)$_4$]. Previously, we have reported the formation of capsule [(**1**)$_2$·(2-AP)$_4$] (**3**) via self-assembly of two molecules of tetracarboxylcavitand **1** and four molecules of 2-aminopyrimidine (2-AP) (Scheme 1 and Figure 1a).[11] At that time, however, encapsulation of a guest molecule in **3** was not observed in solution. The relatively large equatorial windows of **3** may result in too little surface for guest-binding. Recently, we have demonstrated that guest-capsule CH-π, halogen-π, and/or CH-halogen interactions as supplemental forces play important roles in the formation of encapsulation complexes in another system.[12] This concept enabled us to observe encapsulation of a guest molecule in capsule **3** in solution. We found that 2,6-dimethoxynaphthalene (**7**), 2,6-dibromonaphthalene (**8**), and *p*-diiodobenzene (**9**) are encapsulated in **3** in C_6D_6. In the ^{1}H NMR spectrum of encapsulation complex **7**@**3**, the $\Delta\delta$ values ($\delta_{\text{encapsulated guest}} - \delta_{\text{free guest}}$) of the methoxy protons and the aromatic protons at the 1,3,4 (5,7,8)-positions of **7** were −2.57, 0.08, 0.64, and 0.35 ppm, respectively (Figure 1b).[13] This result indicates that the methoxy groups of **7** are oriented to the both aromatic cavity ends of **3**, namely, the guest encapsulated in **3** is oriented with the long axis of the guest along the long axis of **3**. The integration ratio of the ^{1}H NMR spectra resulting from a titration experiment confirmed that one molecule of **7** is accommodated in **3**. Similarly, aromatic protons of encapsulated 2,6-dibromonaphthalene (**8**) were shifted downfield (Figure 1c). The ^{1}H NMR spectra for the titration of **3** (15 mM) in C_6D_6 upon addition of *p*-diiodobenzene (**9**) are shown in Figure 1d−f. In a mixture of **3**/**9** = 1:0.5, encapsulation complex **9**@**3** and guest-free **3** were observed in a 1:1 mole ratio based on the ^{1}H NMR integration ratio (Figure 1d). In a mixture of **3**/**9** = 1:1, only **9**@**3** was observed (Figure 1e). Upon mixing **3**/**9** = 1:2, **9**@**3** and free **9** were observed in a 1:1 mole ratio (Figure 1f). These results indicate that one molecule of **9** is accommodated in **3**, and exchanges between **9**@**3** and guest-free **3** and between **9**@**3** and free **9** are slow on the NMR time scale. The signal of the inner proton of the methylene bridge rim (O−$CH_{in}H_{out}$−O) of **9**@**3** was shifted downfield by 0.18 to 0.21 ppm relative to those of **7**@**3** and **8**@**3** (Figure 1e vs 1b,c). This result is characteristic of CH−I interaction between cavitand-based capsule and iodo-containing guest.[12,14]

SCHEME 1. Self-Assembly of Tetracarboxyl-Cavitand 1 and 2-Aminopyrimidine (2-AP) or Tetrahydro-2-pyrimidinone (THP) into a Capsule 3 or 4, Respectively



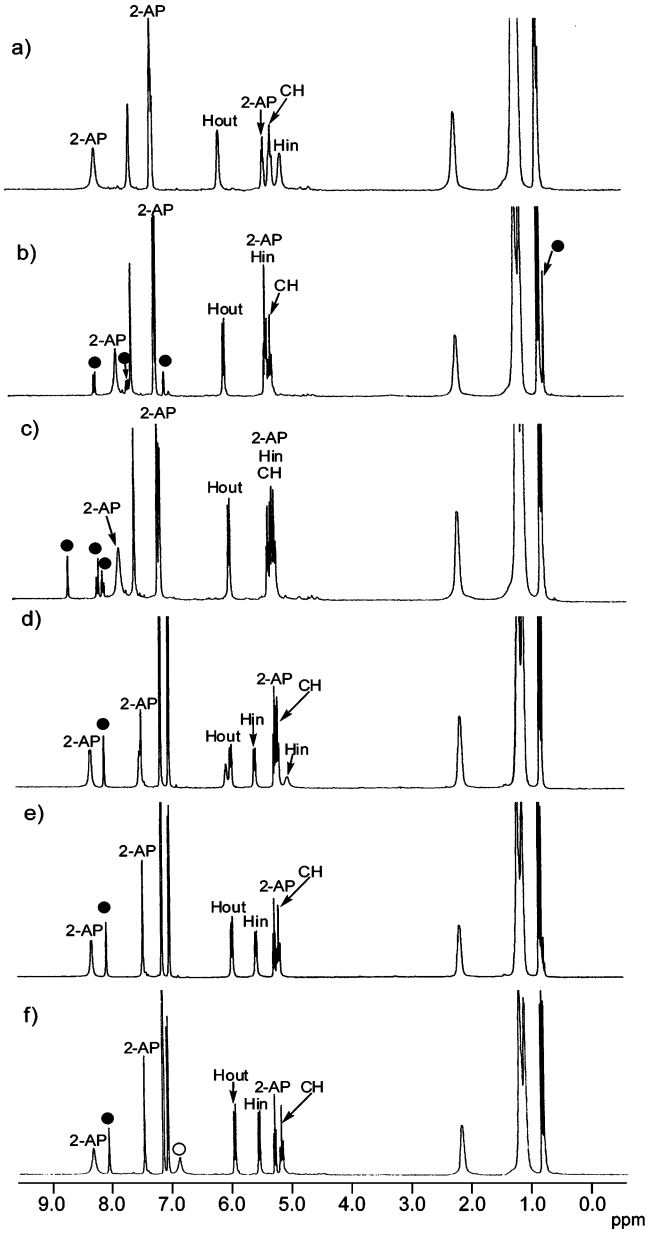


FIGURE 1. ^{1}H NMR spectra (C_6D_6 at 23 °C) of (a) [**3**] = 15 mM, (b) [**3**] = [**7**] = 15 mM, (c) [**3**] = [**8**] = 15 mM, (d) [**3**] = 15 mM and [**9**] = 7.5 mM, (e) [**3**] = [**9**] = 15 mM, and (f) [**3**] = 15 mM and [**9**] = 30 mM. The signals of the encapsulated and free guests are marked with solid and open circles, respectively. The inner and outer protons of methylene bridge and methyne proton in the **1** unit of capsule **3** are marked with Hin, Hout, and CH, respectively.

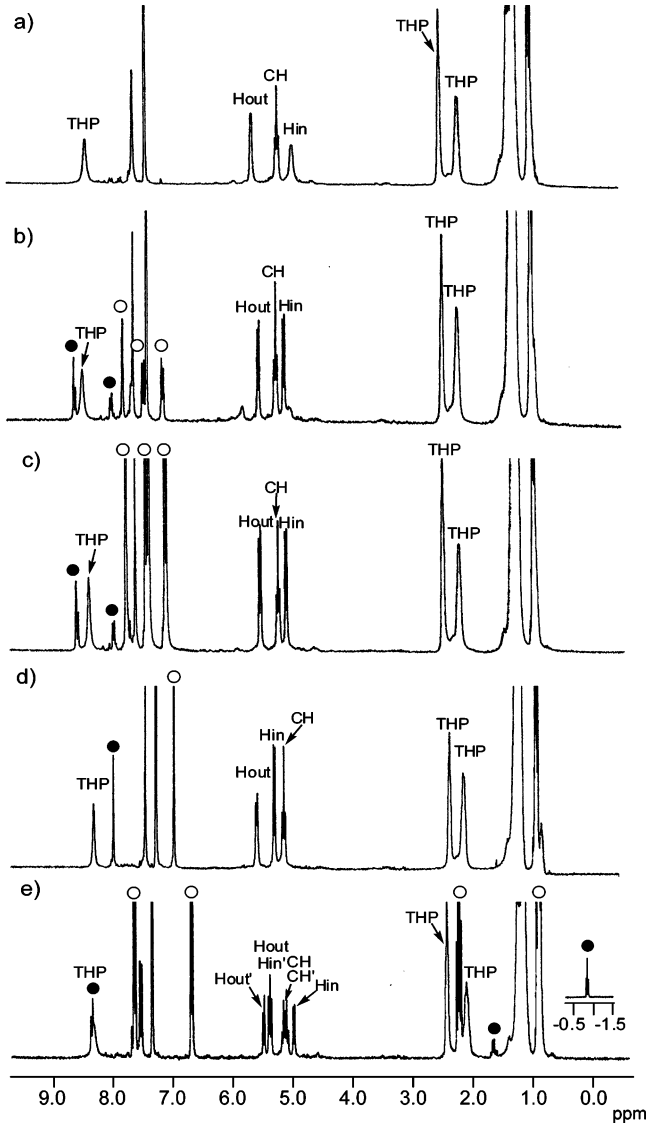


FIGURE 2. ^{1}H NMR spectra (C_6D_6 at 23 °C) of (a) [**4**] = 10 mM, (b) [**4**] = 10 mM and [**8**] = 20 mM, (c) [**4**] = 10 mM and [**8**] = 200 mM, (d) [**4**] = 10 mM and [**9**] = 20 mM, and (e) [**4**] = 10 mM and [**10**] = 100 mM. The signals of the encapsulated and free guests are marked with solid and open circles, respectively. The inner and outer protons of methylene bridge and methyne proton in the **1** unit of capsule **4** are marked with Hin, Hout, and CH, respectively.

We also found that two molecules of **1** and four molecules of tetrahydro-2-pyrimidinone (THP), as an alternative to 2-AP, self-assemble into the capsule [(**1**)$_2$·(THP)$_4$] (**4**) (Scheme 1). The ^{1}H NMR spectrum of a 1:2 mixture of **1** (20 mM) and THP (40 mM) in C_6D_6 showed a single highly symmetrical species (D_{4h} symmetry) of **4**, wherein the NH proton of the THP unit in **4** was shifted downfield by ca. 3 ppm relative to free THP, because of hydrogen bonds between **1** and THP (Figure 2a). On the basis of the analysis of energy minimized structures (PM3) for the 1:2 complexes of 2-AP or THP with acetic acid, it was estimated that the long axis of the THP-based capsule **4** is ca. 0.7 Å shorter than that of the 2-AP-based capsule **3**. The carbonyl moieties of the carboxyl groups in the complex of THP·(RCO$_2$H)$_2$ are directed outward,[15] whereas those in the

(8) (a) Martín, T.; Obst, U.; Rebek, J., Jr. *Science* **1998**, *281*, 1842−1845. (b) Hof, F.; Nuckolls, C.; Craig, S. L.; Martín, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10991−10996. (c) Johnson, D. W.; Hof, F.; Iovine, P. M.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 3793−3796.

(9) Ajami, D.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 5314−5315.

(10) For capsule formation via multimolecule assemblies based on covalent bonds, see (a) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967. (b) Barrett, E. S.; Irwin, J. L.; Edward, A. J.; Sherburn, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 16747−16749. (c) Makeiff, D. A.; Sherman, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 12363−12367. (d) Liu, X.; Liu, Y.; Li, G.; Warmuth, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 901−904.

(11) Kobayashi, K.; Shirasaka, T.; Yamaguchi, K.; Sakamoto, S.; Horn, E.; Furukawa, N. *Chem. Commun.* **2000**, 41−42.

(12) (a) Kobayashi, K.; Ishii, K.; Sakamoto, S.; Shirasaka, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 10615−10624. (b) Kobayashi, K.; Ishii, K.; Yamanaka, M. *Chem.—Eur. J.* **2005**, *11*, 4725−4734.

TABLE 1. Guest Selectivity in the Competitive Encapsulation[a]

entry	capsule	guest-A	guest-B	guest selectivity (guest-A/guest-B)[b]
1	**3**	**7**	**8**	0.4:1
2	**4**	**7**	**8**	0:1
3	**3**	**8**	**9**	1:1
4	**4**	**8**	**9**	0:1

[a] The same amount of guest-A and guest-B was used. [b] Determined by the ^{1}H NMR integration ratio.

complex of 2-AP·$(RCO_2H)_2$ are directed inward.[11,16] Capsule **4** also encapsulates various guest molecules such as **8**, **9**, and 1-ethyl-4-iodobenzene (**10**) in C_6D_6 as capsule/guest = 1:1 complexes (Figure 2b,e). As shown in Figure 2b, 100% encapsulation of **8** in **4** was not attained (ca. 90% encapsulation) under the conditions of [**4**] = 10 mM and [**8**] = 20 mM, while the complete encapsulation of **8** in **3** was attained under the conditions of [**3**] = [**8**] = 15 mM (Figure 1c). Guest **7** was scarcely accommodated in **4**, although **7** was encapsulated in **3**. The slight change (less than 1 Å) in cavity size caused a great difference of guest recognition between capsules **3** and **4**. It is noted that symmetrical **4** was desymmetrized by the encapsulation of unsymmetrical **10**, as shown in the ^{1}H NMR spectrum (Figure 2e). The result indicates that the guest molecule does not tumble within **4** on the NMR time scale.

The competitive encapsulation experiments of two guest molecules in capsule **3** or **4** also showed a significant difference in the guest selectivity (Table 1). In the 2-AP-based capsule **3**, the competitive encapsulation of **7** and **8** showed moderate selectivity for **8** (entry 1), whereas **8** was specifically encapsulated in the shorter THP-based capsule **4** (entry 2). The 2-AP-based capsule **3** had no selectivity for the competitive encapsulation of **8** and **9** (entry 3).[17] In contrast, the THP-based capsule **4** encapsulated **9** in a perfect manner (entry 4). Thus, fine-tuning of the cavity size was achieved by alteration of the linker molecules (2-AP vs THP), leading to a dramatic variation in guest selectivity.

Encapsulation of Guest in [$(2)_2$·(2-AP)$_4$] and [$(2)_2$·(THP)$_4$]. Next we focused on the drastic expansion in cavity size by introduction of a phenyl group as a spacer to cavitand **1**.[18] Tetrakis(4-carboxyphenyl)-cavitand **2** was synthesized by the Suzuki-Miyaura cross-coupling reaction of tetraiodo-cavitand with 4-(methoxycarbonyl)phenylboronic acid pinacol ester,[19] followed by hydrolysis of the tetraester. A 1:2 mixture of **2** (2 mM) and 2-AP (4 mM) was scarcely soluble in $CDCl_3$ and gave an obscure ^{1}H NMR spectrum (Figure 3a). This heterogeneous mixture changed to a clear solution upon addition of 0.5 equiv of hexakis(4-methoxyphenyl)benzene (**11**).[20] The ^{1}H NMR showed the capsule formation of [($\mathbf{2}$)$_2$·(2-AP)$_4$] (**5**), as well as the encapsulation of **11** (Scheme 2 and Figure 3b). It is noteworthy that the encapsulated **11** was restricted not only in tumbling but also rotation in the cavity of **5** on the NMR time scale. In **11**@**5**, restriction in tumbling causes desymmetrization of the encapsulated **11** (Figure 4a). The two methoxy groups of **11** existing at the cavity ends of **5** show a large upfield shift ($\Delta\delta$ = −2.87 ppm). The other four methoxy groups, overhanging obliquely from the large equatorial windows of **5**, show a relatively small upfield shift ($\Delta\delta$ = −0.58 ppm). Desymmetrization of the cavitand part in **5**, namely, two sets of inner and outer protons of methylene bridge rim (O−$CH_{in}H_{out}$−O) and two sets of methyne proton, were observed as a result of the restriction in free rotation of the encapsulated **11** along the cavity axis (Figure 4b). Expanded capsule **5** also encapsulated hexakis(4-iodophenyl)benzene (**12**)[21] in the same manner (Figure 3c).

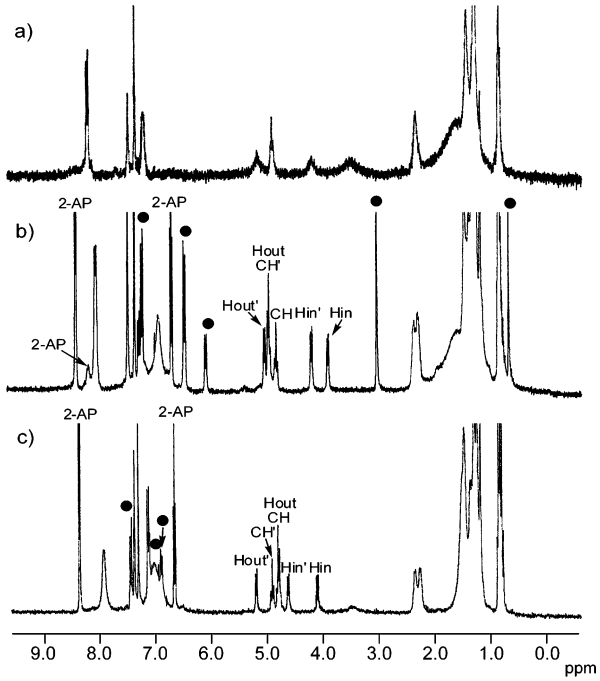


FIGURE 3. ^{1}H NMR spectra ($CDCl_3$ at 23 °C) of (a) [**2**] = 2 mM and [2-AP] = 4 mM, (b) [**5**] = [**11**] = 1 mM, and (c) [**5**] = [**12**] = 1 mM. The signals of the encapsulated guests are marked with solid circles. The inner and outer protons of methylene bridge and methyne proton in the **2** unit of capsule **5** are marked with Hin (Hin′), Hout (Hout′), and CH (CH′), respectively.

A 1:2 mixture of **2** (2 mM) and THP (4 mM) in $CDCl_3$ gave a homogeneous solution and the ^{1}H NMR spectrum showed a

(13) The $\Delta\delta$ values of the methoxy protons and the aromatic protons at the 1, 3, 4 (5, 7, 8)-positions of **7** in $CDCl_3$ were −3.58, −0.90, nd, and −0.78 ppm, respectively. The $\Delta\delta$ values of **7** in C_6D_6 were shifted downfield by ca. 1.0 ppm relative to those in $CDCl_3$. This result can be interpreted as follows. (1) Free **7** is solvated by C_6D_6 and is subject to the ring current effect of C_6D_6-solvation. (2) Upon encapsulation of **7** in **3**, desolvation of C_6D_6 from **7** occurs, and the **7** encapsulated in **3** is no longer subject to the ring current effect of C_6D_6-solvation. (3) Instead, the **7** encapsulated in **3** is subject to the ring current effect of the aromatic cavity of **3**. Consequently, the $\Delta\delta$ values of **7** in C_6D_6 are canceled and seemingly shifted downfield relative to those in $CDCl_3$.

(14) Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *J. Am. Chem. Soc*. **2001**, *123*, 5849−5850. (b) Laughrey, Z. R.; Gibb, C. L. D.; Senechal, T.; Gibb, B. C. *Chem.—Eur. J*. **2003**, *9*, 130−139.

(15) Ikeda, C.; Yoon, Z.-S.; Park, M.; Inoue, H.; Kim, D.; Osuka, A. *J. Am. Chem. Soc*. **2005**, *127*, 534−535.

(16) Etter, M. C.; Adsmond, D. A. *J. Chem. Soc., Chem. Commun*. **1990**, 589−591.

(17) The molecular volume and molecular length along the long axis of **9** (144 Å^3, 11.1 Å including van der Waals radii) are smaller than those of **8** (184 Å^3, 12.5 Å). The CPK model study suggests that **8** fits the cavity of **3** better than **9**. Nevertheless, the binding ability of **9** encapsulated in **3** was the same as that of **8** encapsulated in **3**. These results suggest that CH−I and I−π interactions in **9**@**3** are more favorable than CH−Br and Br− π interactions in **8**@**3**.[12]

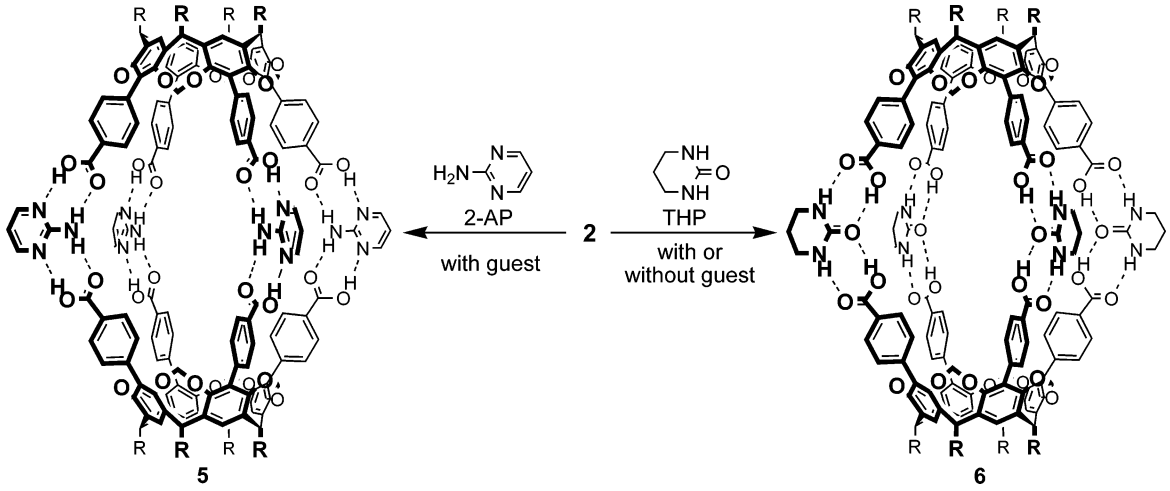
(18) Cho, Y. L.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc*.. **2000**, *122*, 9868−9869.

(19) (a) Bussche-Hünnefeld, C. v. d.; Helgeson, R. C.; Bühring, D.; Knobler, C. B.; Cram, D. J. *Croat. Chim. Acta* **1996**, *69*, 447−458. (b) Sebo, L.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **2000**, *83*, 93−113.

(20) Kobayashi, K.; Shirasaka, T.; Sato, A.; Horn, E.; Furukawa, N. *Angew. Chem., Int. Ed*. **1999**, *38*, 3483−3486.

(21) Kobayashi, K.; Kobayashi, N.; Ikuta, M.; Therrien, B.; Sakamoto, S.; Yamaguchi, K. *J. Org. Chem*. **2005**, *70*, 749−752.

SCHEME 2. Self-Assembly of Tetrakis(4-carboxyphenyl)-Cavitand 2 and 2-AP or THP into a Capsule 5 or 6, Respectively



single highly symmetrical species (D_{4h} symmetry), wherein the NH proton signal of the THP unit was shifted downfield by 1.98 ppm relative to that of free THP, owing to hydrogen bonds between **2** and THP (Figure 5a). This result indicates the formation of capsule $[(\mathbf{2})_2 \cdot (\mathrm{THP})_4]$ (**6**) (Scheme 2). THP-based capsule **6** also has enough space for guest encapsulation, and addition of 1 equiv of **11** to **6** (1 mM) leads to complete complexation (Figure 5b). Again, the encapsulated **11** did not tumble and rotate in **6** on the NMR time scale to cause desymmetrization of guest and cavitand, wherein the $\Delta\delta$ values of the methoxy groups of **11** are −3.48 and −0.52 ppm, and the inner and outer protons of methylene bridge and methyne proton of the cavitand part in **6** appear as two sets of signals. A 1:1 mixture of **6** (1 mM) and **12** gave encapsulation complex **12**@**6** and guest-free **6** in a 2:1 mole ratio (Figure 5c), although addition of 10 equiv of **12** to **6** led to complete encapsulation (Figure 5d). An encapsulation complex was also formed from **6** and excess amount of bis(4-methoxyphenyl)acetylene (**13**) (Figure 5e). In this complex, desymmetrization of the cavitand protons, caused by restriction of guest rotation along the cavity axis, was not observed in contrast to the encapsulation complexes of **11** and **12**. This result indicates that the restriction of the guest molecule is derived from its bulkiness.

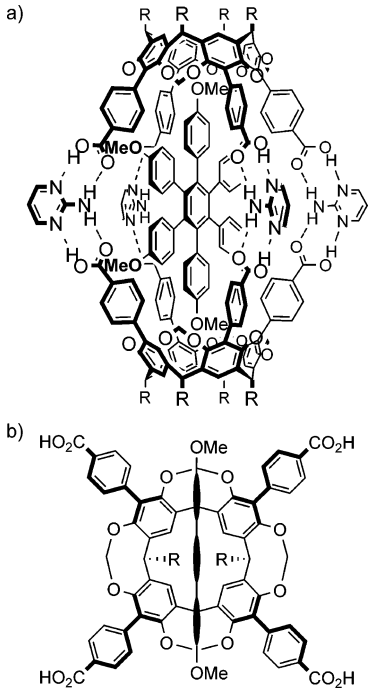
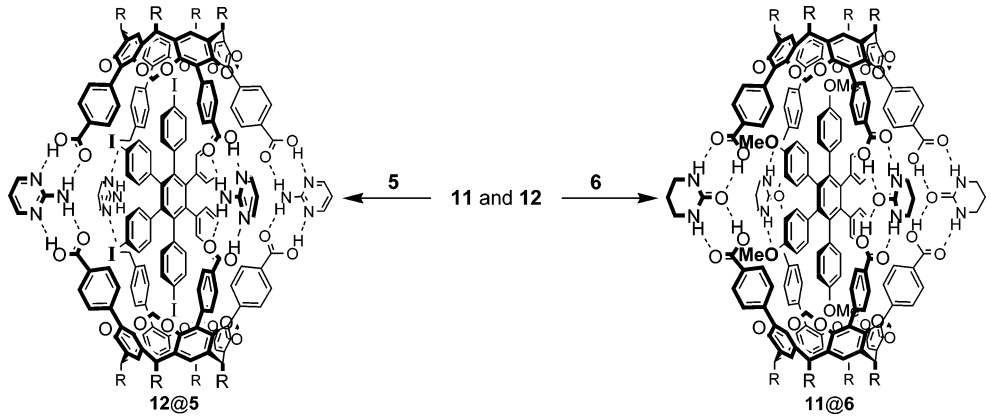


FIGURE 4. Schematic representation of **11**@**5**: (a) front view and (b) top view of half of the complex.

Competitive encapsulation experiments were carried out for capsule **5** or **6** (Scheme 3). The 2-AP-based capsule **5** specifically encapsulated **12** in the presence of the same amounts of **11** and **12**. In marked contrast, **11** was specifically encapsulated in the THP-based capsule **6**. The difference in encapsulation ability of the guest between **5** and **6** would result from the

SCHEME 3. Guest Selective Encapsulation in the Competitive Experiment



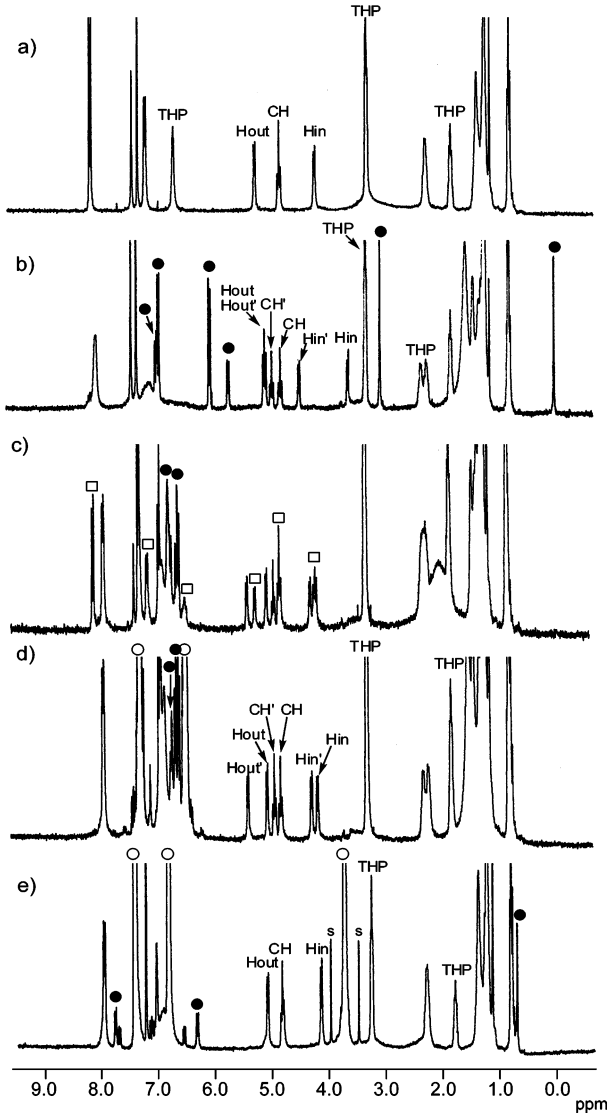


FIGURE 5. ^{1}H NMR spectra ($CDCl_3$ at 23 °C) of (a) [**6**] = 1 mM, (b) [**6**] = [**11**] = 1 mM, (c) [**6**] = [**12**] = 1 mM, (d) [**6**] = 1 mM and [**12**] = 10 mM, and (e) [**6**] = 1mM and [**13**] = 50 mM. The signals of the encapsulated and free guests are marked with solid and open circles, respectively. The inner and outer protons of methylene bridge and methyne proton in the **2** unit of capsule **6** are marked with Hin (Hin′), Hout (Hout′), and CH (CH′), respectively. In Figure 5c, the signals of guest-free **6** are marked with open squares.

slightly smaller cavity size of **6** compared with **5**. Smaller **11** (563 Å^3) fits as a favorable guest in **6** rather than **12** (632 Å^3).

Conclusion

We have found the formation of four kinds of capsules [(**1**)$_2$·(2-AP)$_4$] (**3**), [(**1**)$_2$·(THP)$_4$] (**4**), [(**2**)$_2$·(2-AP)$_4$] (**5**), and [(**2**)$_2$·(THP)$_4$] (**6**) via self-assembly of two molecules of hemispherical cavitands (**1** or **2**) and four molecules of hydrogen-bonding equatorial linkers (2-AP or THP), and their encapsulation abilities for appropriate guests. Alteration of hydrogen-bonding linkers (2-AP vs THP) enables fine adjustment of the cavity size (**3** vs **4** or **5** vs **6**). Introduction of an aromatic spacer to the cavitand (**1** vs **2**) results in drastic expansion of the cavity size (**3** vs **5** or **4** vs **6**). Thus, a simple operation based on the combination of cavitands and hydrogen-bonding linkers provides highly tunable capsule space which brings about a dramatic change of the guest-encapsulation selectivity.

Experimental Section

General. THF was distilled from sodium-benzophenone ketyl under an argon atmosphere. The other solvents and all commercially available reagents were used without any purification. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.3 MHz, respectively. $CDCl_3$ and C_6D_6 were dried over anhydrous K_2CO_3 and molecular sieves 4A, respectively, prior to use.

Tetracarboxyl-Cavitand (1). Host **1** was prepared by the modified procedure of the literature.[22] To a solution of tetrabromocavitand[23] (2.49 g, 2.0 mmol) in dry THF (150 mL) was added *n*-BuLi (1.6 M in hexane, 10 mL, 16 mmol) at −78 °C under an argon atmosphere. After the mixture was stirred at −78 °C for 1 h, the argon balloon was replaced with a CO_2 balloon, which was exchanged to a fresh CO_2 balloon two or three times until absorption of CO_2 gas into the reaction solution ceased at −78 °C. The reaction mixture was warmed to room temperature under CO_2 atmosphere overnight. A NaOH (1 M) aqueous solution (150 mL) was added to the reaction mixture at room temperature. After evaporation of THF, the aqueous layer was washed with Et_2O (200 mL × 2) and then acidified with concentrated HCl at 0 °C. The resulting precipitate in aqueous layer was extracted with Et_2O (300 mL × 2). The organic layer was washed with water (100 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was taken up in hexane (200 mL) and then filtered off. The resulting solid was recrystallized from EtOH−hexane and dried in vacuo at 40 °C for 6 h to give **1** as an off-white solid (1.85 g, 84% yield):[24] mp. 230 °C dec. ^{1}H NMR (DMSO-d_6): δ 0.85 (t, J = 6.5 Hz, 12H), 1.25 (m, 40H), 2.41 (brm, 8H), 4.37 (d, J = 7.7 Hz, 4H), 4.57 (t, J = 8.3 Hz, 4H), 5.74 (d, J = 7.7 Hz, 4H), 7.63 (s, 4H). FAB-MS (*m*-NBA): *m*/*z* 1128 ([M + Na]$^+$, 100). IR (KBr): ν 2500−3500, 1715 cm^{-1}. Anal. Calcd for $C_{64}H_{80}O_{16}$·0.5H_2O: C, 68.98; H, 7.33. Found: C, 69.19; H, 7.16.

Tetrakis(4-carboxyphenyl)-Cavitand (2). To a mixture of tetraiodo-cavitand[19b] (143 mg, 0.10 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 0.025 mmol), $AsPh_3$ (61.2 mg, 0.20 mmol), 4-(methoxycarbonyl)-phenylboronic acid pinacol ester (262 mg, 1.0 mmol), and Cs_2CO_3 (488 mg, 1.5 mmol) under an argon atmosphere were added 1,4-dioxane (20 mL) and H_2O (1.0 mL). The resulting mixture was stirred at 110 °C for 19 h. After it was cooled to room temperature, the reaction mixture was filtered. The filtrate was partitioned between EtOAc and H_2O. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of solvents, the residue was purified with column chromatography on silica gel eluted with EtOAc−hexane (5:2), followed by reprecipitation with EtOAc−hexane to give tetrakis(4-methoxycarbonylphenyl)-cavitand[19a] (105 mg, 72%) as a pale yellow solid.

To a mixture of tetrakis(4-methoxycarbonylphenyl)-cavitand (60.1 mg, 0.041 mmol) in THF (7.0 mL) was added KOH (48.2 mg, 0.73 mmol) in H_2O (8.0 mL). The resulting mixture was stirred at 70 °C for 19 h under an argon atmosphere. After it was cooled to room temperature, the mixture was acidified with 2 M HCl at 0 °C, and then extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of solvents, the residue was purified by reprecipitation with EtOAc−

(22) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826−5828.

(23) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167−2172.

(24) If **1** is heated at 50 °C for more than 8 h, **1** changes to a rearranged compound in part. Choi, H.-J.; Bühring, D.; Quan, M. L. C.; Knobler, C. B.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1733−1735.

hexane to give **2** (49.0 mg, 85%) as a white solid: mp. 270 °C dec. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, J = 6.5 Hz, 12H), 1.27 (m, 40H), 2.46 (brm, 8H), 4.33 (d, J = 7.1 Hz, 4H), 4.69 (t, J = 8.0 Hz, 4H), 5.19 (d, J = 7.1 Hz, 4H), 7.19 (d, J = 8.3 Hz, 4H), 7.82 (s, 4H), 7.88 (d, J = 8.3 Hz, 4H). ^{13}C NMR (DMSO-d_6): δ 13.9, 22.0, 27.6, 28.9, 29.1, 29.5, 31.2, 37.1, 99.0, 122.1, 128.3, 128.6, 129.4, 130.3, 137.9, 138.2, 151.8, 167.2. IR (KBr): ν 2500−3500,1698 cm^{-1}. Anal. Calcd for $C_{88}H_{96}O_{16}\cdot H_2O$: C, 74.03; H, 6.92. Found: C, 73.96; H, 6.76.

Acknowledgment. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science, Sports, Culture, and Technology, Japan (Grant No. 17350067).

JO061516P