Synthesis of a Molecular Container Having an Open Door that Closes on Guest Binding

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A molecular container composed of monodeoxy-calix[4]-arene and calix[4]arene is synthesized. The host binds planar cationic guests. The deoxy-aromatic ring acts as an open door when the guest is absent and closes on guest binding.

Host molecules that drastically change their shape upon the binding of a guest molecule are uncommon, with the Venus fly-trap type Zn–porphyrin[1] being one such example. Specifically, molecular containers having a door that opens and closes depending on guest molecule binding is of substantial interest in the chemistry of molecular recognition. A wide-open host portal can facilitate the insertion of guest molecules, and the closing the portal after the ingress of the guest molecule can facilitate guest binding. In this vein, we design a globular molecular container **1** having both monodeoxycalix[4]arene[2] and calix[4]arene[3] as upper and lower hemispheres, respectively (Figure 1).

Head to head linked double calixarenes have been extensively investigated as molecular containers;[4] however, the idea of a guest-mediated open–close door has not been achieved in literature. The trimethyl ether of a monodeoxycalix[4]arene has a partial cone structure,[5] wherein the deoxy-aromatic ring is inverted. The inverted deoxy ring acts as a wide-open door in the so-designed globular molecular container. The flipping motion of the deoxy ring closes the door to encapsulate the guest into the container. In this paper, we report a convenient synthesis of a doubly bridged double calix[4]arene receptor **1** via amide linkages, starting from the upper rim-functionalized monodeoxycalix[4]arene and the corresponding derivative of the calix[4]arene, and its binding properties towards various planar cationic guests.

The synthesis of double-bridged container **1** started from **2**[6] according to Scheme 1.[7] Propylation of the phenolic hydroxy groups of **2** gave **3**. Two iodine groups of **3** were treated with *n*-butyllithium, followed by the addition of dimethylformamide to afford **4** a good yield. Oxidation of the dialdehyde produced diacid **5**, which was converted to acid chloride **6**. Coupling the reaction of **6** and diaminocalix[4]arene **7**[8] furnished the desired container molecule **1**.

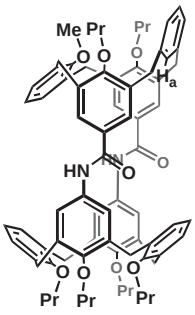
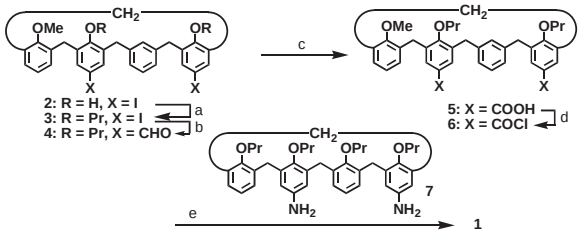


Figure 1. Molecular container **1**.



Scheme 1. Synthesis of **1**. Reagents: (a) PrI, NaH, DMF, (40%); (b) *n*-BuLi, THF then DMF (69%); (c) $KMnO_4$, acetone, H_2O (98%); (d) $(COCl)_2$, THF (quant.); (e) **7**, THF (25%).

The open door conformation of **1** in the absence of a guest is supported by the comparison of the ^{1}H NMR chemical shifts of the methoxy groups of **1** (3.655 ppm in $CDCl_3$) and **3** (3.594 ppm) or **5** (3.386 ppm). As can be seen, compound **3** has a partial cone conformation with an inverted deoxy-aromatic ring and a coexisting cone form in the same crystal[9] (Figure 2). In the partial cone conformation, the methoxy group is susceptible to the shielding effect of the inverted aromatic ring. Actually, these signals appeared in a high magnetic field as compared with that of the cone form in **2** (OMe: 4.168 ppm).

The molecular container was found to encapsulate various planar cationic guests in its spherical cavity to give a 1:1 inclusion complex in solution. The association constant of the complex of **1** and $C_7H_7^+BF_4^-$ (**8**) was estimated using UV–vis spectroscopy to be $6.4 \pm 0.4 \times 10^4\ M^{-1}$ in $CHCl_3/CH_3CN$ (4/1 (v/v)) by non-linear curve fitting.[10]

The addition of **8** to a solution of **1** in $CDCl_3/CD_3CN$ (4/1 (v/v)) caused significant changes in the ^{1}H NMR spectra. Specifically, the signal changes observed in the methoxy group and the aromatic proton (Ha) are striking.[7] The signal of the methoxy group appeared at 3.492 ppm, suggesting that **1** has an open door conformation. The signal shifted to a lower magnetic field with a simultaneous broadening upon the addition of the guest. The signal was quenched with an 0.2 equivalent of the guest, and reappeared as a broad signal at a lower field, gradually sharpening with increasing concentration of the guest. The signal reached the limiting value of 4.04 ppm when three

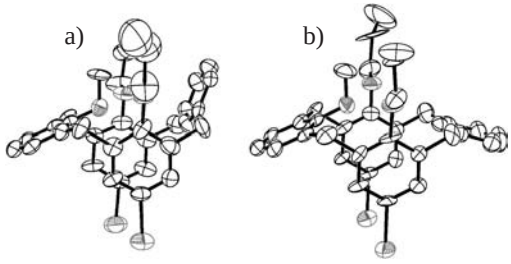


Figure 2. X-ray structure of compound **3**, a) partial cone, b) cone.

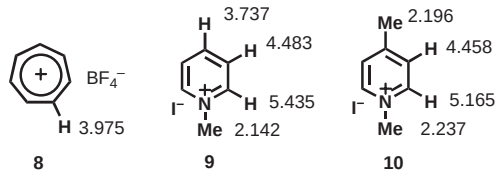


Figure 3. Complexation induced up-field shifts of encapsulated guests **8**, **9**, and **10**.

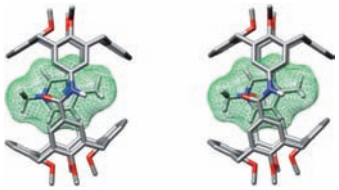


Figure 4. Stereoplot of the structure of the complex with **1** and **10** calculated by using MacroModel 9.1 with AMBER* force field.

equivalent of the guest was added. Similar signal behavior was observed in the aromatic proton of the deoxy ring (Ha). The signal of the aromatic proton Ha appeared at 5.798 ppm, and shifted to 6.903 ppm when 3 equivalent of the guest was added.

These signal changes suggest a conformational change of the deoxy-aromatic ring in the presence of a guest. The open door conformation has an inverted deoxy ring that causes an up-field shift to the methoxy group due to the deoxy-aromatic ring closely facing the methoxy group of the diagonally arranged anisole ring. In the closed door conformation, the inverted ring flips down to have the cone form of the upper hemisphere and the methoxy signal reverts back to its original position of the cone form. Similar signal behavior of the aromatic proton Ha can also be explained by this conformational change of the door with the complexation of the guest in the host cavity. In the open door conformation, Ha is susceptible to the shielding effect of the diagonally oriented anisole ring, and moves to the down-field in the closed door conformation because of the deshielding effects of the nearby ether groups of the three aromatic rings of the cone form.

The association constants of **1** towards *N*-methylpyridinium ion guests **9** and **10** were estimated using UV–vis spectroscopy to be $(1.3 \pm 0.5) \times 10^5$, and $(3.9 \pm 0.5) \times 10^3\ M^{-1}$, respectively. Similar signal shifts of the OMe group of the host were observed in the case of **9** (4.087 ppm) and **10** (4.081 ppm). Thus the guest-induced closing of the host open door is common in the case of **1**.

The ^{1}H NMR spectrum of **10** in the presence of **1** provided two sets of peaks assignable to the complexed and free guest. The peaks for all protons of **10** were shifted to the higher magnetic field upon complexation. The chemical shifts of α- and β-protons, γ-methyl, and *N*-methyl of the complexed guest were 3.927, 3.371, 0.473, and 2.385 ppm and those of the free guest were 9.092, 7.829, 2.669, and 4.622 ppm, respectively. These significant up-field shifts verify the inclusion of the guest into the host cavity. Similar splitting and up-field shift of the bound guest was observed in every cationic guest (Figure 3). The lateral orientation of the included guest **10**[4k,4l] within the host cavity is more indicated by the larger up-field shifts of α- and β-protons than those of the methyl protons (Figure 4).[11]

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References and Notes

1 M. Mazzanti, J.-C. Marchon, M. Shang, W. R. Scheidt, S. Jia, J. A. Shelnutt, *J. Am. Chem. Soc.* **1997**, *119*, 12400.
2 a) Y. Fukazawa, K. Deyama, S. Usui, *Tetrahedron Lett.* **1992**, *33*, 5803. b) F. Grynszpan, Z. Goren, S. E. Biali, *J. Org. Chem.* **1991**, *56*, 532. c) Y. Ting, W. Verboom, L. C. Groenen, J.-D. van Loon, D. N. Reinhoudt, *J. Chem. Soc., Chem. Commun.* **1990**, 1432.
3 C. D. Gutsche, *Calixarene. Monograph in Supramolecular Chemistry*, RSC, Cambridge, **1989**.
4 a) V. Böhmer, H. Goldmann, W. Vogt, J. Vicens, Z. Asfari, *Tetrahedron Lett.* **1989**, *30*, 1391. b) A. Arduini, G. Manfredi, A. Pochini, A. R. Sicuri, R. Ungaro, *J. Chem. Soc., Chem. Commun.* **1991**, 936. c) K. Araki, K. Sisido, K. Hisaichi, S. Shinkai, *Tetrahedron Lett.* **1993**, *34*, 8297. d) K. Araki, K. Hisaichi, T. Kanai, S. Shinkai, *Chem. Lett.* **1995**, 569. e) J.-A. Pérez-Adelmar, H. Abraham, C. Sánchez, K. Rissanen, P. Prados, J. de Mendoza, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1009. f) O. Struck, L. A. J. Chrisstoffels, R. J. W. Lugtenberg, W. Verboom, G. J. van Hummel, S. Harkema, D. N. Reinhoudt, *J. Org. Chem.* **1997**, *62*, 2487. g) M. Jørgensen, M. Larsen, P. Sommer-Larsen, W. B. Petersen, H. Eggert, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2851. h) P. Neri, A. Bottino, F. Cunsolo, M. Piattelli, E. Gavuzzo, *Angew. Chem., Int. Ed.* **1998**, *37*, 166. i) Z. Zhong, A. Ikeda, S. Shinkai, *J. Am. Chem. Soc.* **1999**, *121*, 11906. j) G. T. Hwang, B. H. Kim, *Tetrahedron Lett.* **2000**, *41*, 5917. k) J. Wang, S. G. Bodige, W. H. Watson, C. D. Gutsche, *J. Org. Chem.* **2000**, *65*, 8260. l) K. Araki, H. Hayashida, *Tetrahedron Lett.* **2000**, *41*, 1209. m) K. Araki, T. Watanabe, M. Oda, H. Hayashida, M. Yasutake, T. Shimmyozu, *Tetrahedron Lett.* **2001**, *42*, 7465.
5 Y. Fukazawa, K. Yoshimura, S. Sasaki, M. Yamazaki, T. Okajima, *Tetrahedron* **1996**, *52*, 2301.
6 T. Haino, H. Akii, Y. Fukazawa, *Synlett* **1998**, 1016.
7 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
8 P. Timmerman, H. Boerrigter, W. Verboom, D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 103.
9 Crystal structure have been deposited at the Cambridge Crystallographic Data Center and allocated the depossition numbers CCDC No. 671328.
10 K. A. Connors, *Binding Constants: The Measurement of Molecular Complex Stability*, Wiley, New York, **1987**, pp. 189–216.
11 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440.

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