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## Guest inclusion properties of a novel cage molecule composed of two calix[4]arenes

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### Abstract

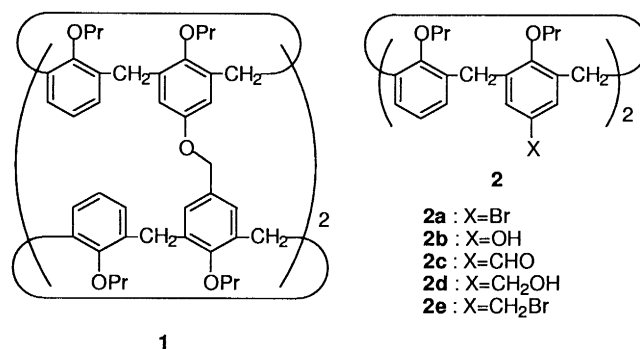
The biscalix[4]arene was synthesized by connecting the upper rims with two spacers. The inclusion ability and the selectivity for various quaternary ammonium ions were enhanced due to the cooperative action of the cation– $\pi$  interaction in the two bowl-shaped calix[4]arenes. The very slow dynamic process during complexation and decomplexation and the separation of the cationic guest and the counter anion were caused by encapsulation of the biscalix[4]arene. © 2000 Elsevier Science Ltd. All rights reserved.

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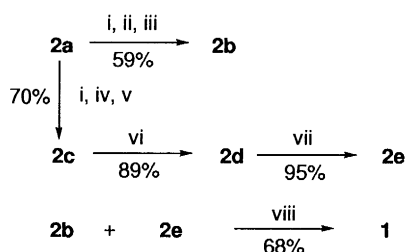
Calixarenes, a new class of synthetic macrocycles having phenolic units linked by methylene groups, have received considerable attention for host guest chemistry in the last decade. The architecture of the calixarene can provide a  $\pi$ -basic cavity. Hence, they are useful for designing a globular  $\pi$ -basic cavity by binding the upper rims of two calixarenes.<sup>1–8</sup> We previously demonstrated that conformational isomers derived from calix[4]arenes are very useful for estimating the contribution of the cation– $\pi$  interaction<sup>9</sup> to the host–guest process,<sup>10–12</sup> and a biscalix[4]arene prepared by connecting two conformationally immobile calix[4]arenes with two ethylene glycol spacers at the upper rims has significant inclusion ability for cationic guests.<sup>13</sup> The guest molecule passes through the spacing between the upper rims of two calixarenes in the biscalix[4]arene during the complexation and decomplexation process. One can then easily realize that biscalix[4]arenes connected by shorter spacers should provide a slow exchange between the included and free guest and increase the cooperative action of the two bowl-shaped calix[4]arenes. They may also encapsulate a guest molecule in their spherical cavity and act as a molecular capsule. We now report the synthesis and the inclusion properties of the biscalix[4]arene **1** connected with two spacers at the upper rim.

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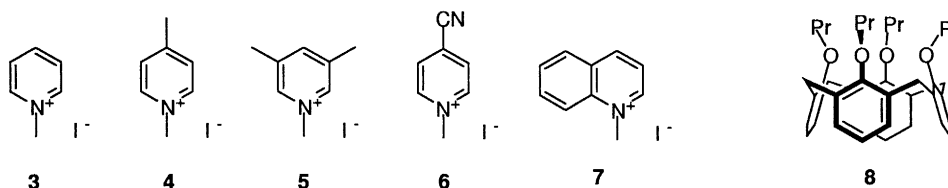


The bis(calix[4]arene) **1** was synthesized from cone-5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene<sup>13</sup> **2a** according to Scheme 1. The products were identified by IR, <sup>1</sup>H NMR and mass spectral evidence and elemental analysis.



Scheme 1. (i) *n*-BuLi, THF,  $-78^{\circ}\text{C}$  (ii) B(OMe)<sub>3</sub> (iii) H<sub>2</sub>O<sub>2</sub>, AcOH (iv) DMF (v) H<sub>3</sub>O<sup>+</sup> (vi) NaBH<sub>4</sub>, THF, EtOH (vii) PBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> (viii) Cs<sub>2</sub>CO<sub>3</sub>, THF

The inclusion properties of **1** for *N*-methylpyridinium iodide **3** and analogues **4–7** were examined using 500 MHz <sup>1</sup>H NMR measurements. It is reported that the chemical shifts for the protons in the quaternary ammonium ions are only slightly shifted to a higher magnetic field in the presence of cone-tetrapropoxycalix[4]arene **8** and the cation- $\pi$  interaction between **8** and the cationic guests is quite weak.<sup>10</sup> The dynamic process during the complexation and the decomplexation of **8** is also faster than the NMR time scale.<sup>10</sup> The <sup>1</sup>H NMR spectrum of *N*-methyl- $\gamma$ -picolinium iodide **4** in the presence of **1**, on the other hand, gave two separated peaks for each proton at  $0^{\circ}\text{C}$  in CDCl<sub>3</sub>, which are assigned to the complexed and uncomplexed **4**. These peaks did not coalesce into an average peak even at  $50^{\circ}\text{C}$ . This remarkably high coalescence temperature,  $T_c$ , reveals that the dynamic process during the complexation and the decomplexation is much slower than the NMR time scale. The transition state of the complexation and the decomplexation, on which **4** passes through the spacing between the upper rims of two calix[4]arenes in **1**, is unstabilized due to the steric factor, compared with the known bis(calix[4]arenes) having relatively long spacers.<sup>4,12</sup> This quite slow exchange of guest results from the narrow space between the two calix[4]arenes connected with the two short linkages. The slow exchange was not observed for the complexation process of the bis(calix[4]arenes) possessing relatively long spacers.<sup>4,13</sup> The <sup>1</sup>H NMR spectrum for **3** in the presence of **1** gave split peaks similar to that for **4** at  $-30^{\circ}\text{C}$ . However, the coalesced and significantly broadened peaks above  $25^{\circ}\text{C}$  indicated that the exchanging process of **3** during the complexation is faster than that of **4**.



The peaks for all the protons in **4** were shifted to the upper magnetic field upon complexation, i.e., the chemical shifts of the  $\alpha$ -,  $\beta$ -,  $\gamma$ -methyl and *N*-methyl protons in the complexed **4** were 3.89, 2.89, 1.24 and 1.73 ppm and those in the free **4** were 9.14, 7.85, 2.67 and 4.59 ppm, respectively. These significant up-field shifts rationalized by the shielding effect of the benzene rings in **1** imply that **4** is included in the spherical cavity of **1**. Indeed, these up-field shifts were not observed for nonionic guests such as pyridine, picoline, benzene or toluene. The essential cationic charge in the guests establishes the significant contribution of the cation- $\pi$  interaction to the formation of the complex in **1**. As shown in Fig. 1, the magnitude of up-field shift for the  $\alpha$ - and  $\beta$ -protons in **4** is larger than that for the protons in the *N*- and  $\gamma$ -methyl groups. This result suggests that **4** is tightly included in the cavity of **1**. Therefore, in the inner sphere of **1**, the molecular motion of **4** is strongly restricted and **4** is fixed in an orientation in which the  $\alpha$ - and  $\beta$ -protons in **4** are significantly affected by shielding of the benzene rings in **1**, as shown in Fig. 2.<sup>14</sup> Similar splitting and up-field shift for **6** were also observed, but no evidence of complexation for **5** and **7** was obtained during the  $^1\text{H}$  NMR study of **1**.

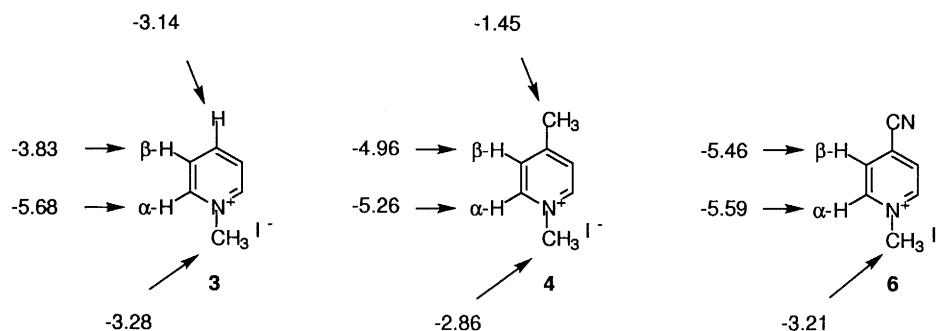


Fig. 1. Induced up-field shifts in the  $^1\text{H}$  NMR of **3**, **4** and **6** during the complexation with **1** at  $-30^\circ\text{C}$ .  $[\mathbf{1}] = [\text{guest}] = 5.0 \text{ mmol dm}^{-3}$ . Data for **3** and **4** in  $\text{CDCl}_3$  and that for **6** in  $\text{CDCl}_3:\text{CD}_3\text{CN} = 10:1 \text{ v/v}$ . The minus value denotes the up-field shift in ppm

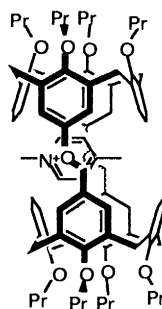


Fig. 2. Schematic structure proposed for the complex of **1** and **4**

The association constants  $K_a$  of **1** for **3–7** were estimated using UV-vis spectroscopy. For example, the UV-vis spectra of **6** gave an absorbance maximum at 454 nm in the absence of **1** in  $\text{CHCl}_3:\text{CH}_3\text{CN}$  10:1 (v/v) which is assigned to the charge transfer (CT) band from the iodide anion to the pyridinium cation. By the addition of **1**, the absorbance at 454 nm decreased and that at 364 nm assigned to the complex

increased, showing an isosbestic point at 446 nm. The disappearance of the CT band in **6** suggests that only the cationic guest ion was encapsulated in **1** and the counter anion was left outside of **1**. Therefore, *p*-cyanopyridinium and iodide in **6** were separated by the complexation. This behavior of **1** as a molecular capsule is characterized by the interruption of the contact of iodide to *p*-cyanopyridinium. The plot of the absorbance versus  $[1]/[\text{guest}]$  gave the gradual curve indicating the 1:1 stoichiometry of host and guest for the complex. The  $K_a$  values were determined by the curve fit method for these plots with the computer-assisted nonlinear least square procedure.

The  $K_a$  values for **1** and **8** are summarized in Table 1. The largest  $K_a$  was obtained for the complex of **1** and **3**. This value in  $\text{CHCl}_3$  is greater by 500-fold than that of **8** and **3**. This significant enhancement in  $K_a$  is attributed to the cooperative action of the two  $\pi$ -basic cavities of the confronted cone-calix[4]arenes in the globular shaped **1**. The decreased  $K_a$  for **4** indicates that the introduction of an additional methyl group to **3** reduces the stability of the complex. No formation of a complex for **5**, in which three methyl groups are attached, was observed. These results establish the fact that the inner sphere of **1** is suitable to be fully occupied with **3** and the inclusion of the bulkier **4** provides a less stable complex. The inner sphere in **1** is probably somewhat too tight to form a stable complex with **4**. This is supported by the very slow dynamic process during the complexation and the decomplexation of **4**. It is likely that **5** and **7** are too bulky to be included in the inner sphere of **1**. The high selectivity of **1** is readily rationalized by the reduced freedom of the conformation in **1** and by the closed and restricted space, which is surrounded by the two  $\pi$ -basic cavities of the calix[4]arenes. The biscalix[4]arenes with the flexible conformation did not show these high selectivity,<sup>4,13</sup> indicating an importance of connecting the two calix[4]arenes with appropriate spacers and reducing the conformational freedom of host.

Table 1  
Association constants ( $K_a$ ) for inclusion of **3–7**<sup>a</sup>

Calix[4]arene	$K_a / \text{dm}^3 \text{mol}^{-1}$				
	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>1</b>	3310 <sup>cg</sup> 5250 <sup>dg</sup>	166 <sup>cg</sup> 600 <sup>dg</sup>	- <sup>b</sup>	3390 <sup>dg</sup>	- <sup>b</sup>
<b>8</b>	6.4±0.4 <sup>eh</sup>	1.1±0.4 <sup>eh</sup>	< 1 <sup>eh</sup>	6.6±0.1 <sup>fh</sup>	3.6±1.3 <sup>eh</sup>

<sup>a</sup>at 25 °C; <sup>b</sup>No formation of the complex was observed.; <sup>c</sup>in  $\text{CHCl}_3$ ; <sup>d</sup>in  $\text{CHCl}_3:\text{CH}_3\text{CN}=10:1$  v/v; <sup>e</sup>in  $\text{CDCl}_3$ ; <sup>f</sup>in  $\text{CDCl}_3:\text{CD}_3\text{CN}=10:1$  v/v; <sup>g</sup>The values were estimated from the change in the UV-Vis absorption spectrum.; <sup>h</sup>The values were estimated from the change in the  $^1\text{H}$  NMR chemical shift.

In conclusion, the present study showed that the biscalix[4]arene prepared by connecting the two conformationally-immobilized calix[4]arenes at the upper rims has strong inclusion ability for the cationic guest molecules due to the cooperative action of the cation- $\pi$  interaction. The very slow dynamic process during the complexation and decomplexation and the separation of the cationic guest and the counter anion were caused by the encapsulation of the biscalix[4]arene. This study was partially supported by Nissan Science Foundation.

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14. The  $^1\text{H}$  NMR peaks for the aromatic protons in the benzene rings bearing the spacers in **1** were split upon the complexation with **4**. This lowering of symmetry in **1** strongly supports the complex structure as shown in Fig. 2.