Synthesis and Inclusion Properties of a Upper-rim-connected Biscalix[4]arene

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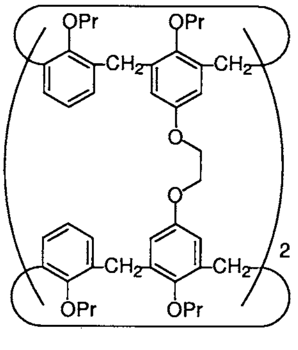
The conformationally-immobile biscalix[4]arene was synthesized by connecting the upper rims with two spacers. It showed high inclusion ability and selectivity for quaternary ammonium ions. A comparison with reference compounds established that the enhanced selectivity is due to the cooperative action of two bowl-shaped calix[4]arenes.

Calixarenes, a new class of synthetic macrocycles having phenolic units linked by methylene groups at the *ortho*-position to the hydroxy groups, have received considerable attention for the host-guest chemistry in the last decade. The architecture of the calix[4]arenes can provide a π-basic cavity. Hence, they are useful for designing a globular π-basic cavity by connecting the upper rim of two calix[4]arenes.[1-5] We previously demonstrated that conformational isomers derived from calix[4]arenes are very useful for estimating the contribution of the cation-π interaction[6] to the host-guest process,[7,8] because one can easily prepare conformationally-immobilized π-basic cavities composed of four differently pre-organized benzene rings. We have found that a significant contribution of the cation-π interaction is observed for the cone isomer providing a bowl-shaped cavity.[7] To establish the cooperative action of the two π-basic cavities in the calix[4]arenes, several biscalix[4]arenes were synthesized by connecting the upper rim. While the binding ability of the biscalix[4]arenes to guests was enhanced, the selectivity was not very high due to the conformational freedom in the linkage.[4,9] It prompted us to synthesize the conformationally-immobile biscalix[4]arene which is connected at the upper rims and should provide a π-basic sphere composed of two confronted hemispherical cavities. We now report the synthesis and the inclusion properties of biscalix[4]arene **1**.



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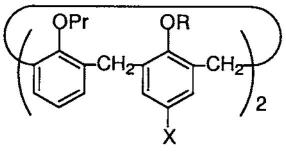

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2a : R=H, X=H
2b : R=H, X=Br
2c : R=Pr, X=Br
2d : R=Pr, X=OH
2e : R=Pr, X=OCH2COOEt
2f : R=Pr, X=OCH2CH2OH
2g : R=Pr, X=OCH2CH2Br

The target biscalix[4]arene **1** was synthesized from cone-25,27-dihydroxy-26,28-dipropoxycalix[4]arene[10] **2a** according to Scheme 1. The products were identified by IR, ^{1}H NMR, and mass spectral evidence and elemental analysis. The temperature-independent ^{1}H NMR peaks for the ArCH$_2$Ar methylene protons in **1** showed one pair of doublets at 3.09 and 4.43 ppm at 25 °C in CDCl$_3$. This finding reveals that the two calix[4]arene skeletons are immobilized in the cone conformation and possess high symmetry.

Scheme 1.

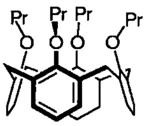
$$\mathbf{2a} \xrightarrow[93\ \%]{\text{i}} \mathbf{2b} \xrightarrow[55\ \%]{\text{ii}} \mathbf{2c} \xrightarrow[59\ \%]{\text{iii, iv, v}} \mathbf{2d} \xrightarrow[37\ \%]{\text{vi}}$$

$$\mathbf{2e} \xrightarrow[83\ \%]{\text{vii}} \mathbf{2f} \xrightarrow[80\ \%]{\text{viii}} \mathbf{2g}$$

$$\mathbf{2d} + \mathbf{2g} \xrightarrow[45\ \%]{\text{ix}} \mathbf{1}$$

i) Br$_2$, CHCl$_3$ ii) *n*-PrI, NaH, DMF iii) BuLi, THF, -78 °C iv) B(OMe)$_3$ v) H$_2$O$_2$, AcOH vi) BrCH$_2$COOEt, *t*-BuOK, THF vii) LiAlH$_4$, THF viii) CBr$_4$, PPh$_3$, CH$_2$Cl$_2$ ix) CS$_2$CO$_3$, THF

The inclusion abilities of **1** for N-methylpyridinium and homologous cationic guest molecules were examined using a 500 MHz ^{1}H NMR. The protons in **4** - **6** gave the averaged NMR peaks of the free and complexed guests at 25 °C. These peaks did not split even at -35 °C. This fact implies that the dynamic process on complexation and decomplexation is faster than the NMR time scale. The NMR peaks for **7**, on the other hand, were significantly broadened at 25 °C and completely split into the free and complexed peaks at -35 °C. This suggests that **7** is suitable for the inner sphere in **1** and the dynamic process of complexation and decomplexation is sterically suppressed.



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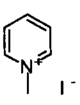

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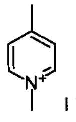

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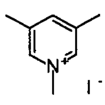

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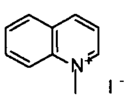

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As summarized in Table 1, the chemical shifts for the NCH$_3$ in **4** - **7** were scarcely shifted to a higher magnetic field in the presence of **3**. The similar up-field shifts were also observed for other protons in **4** - **7**. These up-field shifts caused by the shielding effect of the benzene rings in **3** imply that the cationic guest is included in the cavity of **3**. This result indicates that the cation-π interaction[11] between **3** and the cationic guests is considerably weak although **4** - **7** are bound to the π-basic cavity in **3**. In the presence of **1**, in contrast, the chemical shifts for NCH$_3$ in **4** - **7** were largely moved to a higher magnetic field. The remarkably large shift was observed for N-methylquinolinium **7**, which was much greater than that for the pyridinium derivatives **4** - **6**. This result suggests that the inner sphere in **1** is too large to be filled up by **4** - **6** but **7** is suitable

Table 1. ^{1}H NMR chemical shifts of NCH_3 in guests in the absence and the presence of calix[4]arenes[a]

Calix[4]arene	Chemical shifts for NCH_3			
	4[b]	**5**[b]	**6**[b]	**7**
None	4.73	4.64	4.59	4.96[c] 4.93[d]
1	4.49	4.58	4.58	2.94[c]
3	4.69	4.62	4.59	4.92[d]

[a] 500 MHz, $CDCl_3$, internal standard TMS. [b] [calix[4]arene] = [guest] = 5.0 mmol dm^{-3}, 24 °C. [c] [calix[4]arene] = [**7**] = 1.0 mmol dm^{-3}, -35 °C. [d] [calix[4]arene] = [**7**] = 3.0 mmol dm^{-3}, 24 °C.

Table 2. Association constants (K_{ass}) for inclusion of **4** - **7**[a]

Calix[4]arene	K_{ass} / dm^3 mol^{-1}			
	4	**5**	**6**	**7**
1	35.5±3.4[b]	9.3±1.0[b]	5.5±2.9[b]	323[c]
3	6.4±0.4[b]	1.1±0.4[b]	<1[b]	3.6±1.3[b]

[a] 25 °C. [b] The values were estimated from the change of ^{1}H NMR chemical shift in $CDCl_3$. [c] The value was estimated from the change in the UV-Vis absorption spectrum in $CHCl_3$. The error is ±5%.

to be fully included in **1**. This is consistent with the fact that the dynamic process of complexation and decomplexation between **1** and **7** observed in the ^{1}H NMR spectra is quite slow.

The association constants, K_{ass}, were estimated from the plots of the chemical shifts for the protons in guests *vs.* [calix[4]arenes] or the change in the UV-Vis absorption spectrum assuming the formation of a 1:1 complex.[12] The determined K_{ass} values are summarized in Table 2. The largest K_{ass} was observed for the complex of **1** and **7**. This result suggests that the size of the inner sphere in **1** is exactly suitable to include **7**. The CPK model examination and the molecular mechanics calculation also supported the size fit between **1** and **7**. The selectivity in K_{ass} is consistent with the magnitudes of the chemical shift changes. The K_{ass} of **1** for **7** is greater by 90-fold than that of **3**. This enhancement of the inclusion ability is due to the cooperative action of two bowl shaped calix[4]arenes providing π-basic cavities. The trend in the selectivity of **1** is different from that of the biscalix[4]arene connected with a spacer.[9] The high selectivity of **1** rationalized by the size fit of the guests and the inner sphere in **1** results in the orientaion of two calix[4]arenes fixed by two linkages.

In conclusion, the present study showed that the biscalix[4]arene prepared by connecting two conformationally-immobilized calix[4]arenes at the upper rims has the strong inclusion ability and the high selectivity for the cationic guest molecules.

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11 The similar chemical shift changes were not observed for nonionic guests such as pyridine, quinoline, benzene or naphthalene. The essential cationic charge in the guests establishes the significant contribution of the cation-π interaction to the formation of the complex.

12 In the FAB-MS analyses, the only host:guest 1:1 complex was observed. No formation of the complex with other stoichiometries was confirmed for all the hosts and the guests.