Synthesis of an Upper-rim-connected Biscalix[4]arene and Its Improved Inclusion Ability Based on the Cooperative Action

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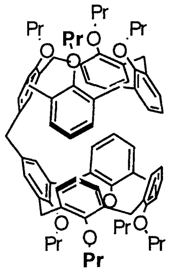
Conformationally-immobile biscalix[4]arene made by connecting the upper rims showed the high inclusion ability for N-methylpyridimium and homologous cationic guest molecules. Comparison with reference compounds established that the enhanced inclusion ability is due to the cooperative action of two upper-rim-confronted calix[4]arenes.

The architecture of calix[n]arenes can provide a π-basic bowl-shaped hemisphere. Hence, they are useful to design a globular π-basic cavity by connecting the upper rim of two calix[n]arenes.[1-5] In contrast to not a few examples for the synthetic reports, the studies of dynamic guest-binding properties of these biscalix[n]arenes have been very limited.[3,5-7] Meanwhile, we previously demonstrated that conformational isomers derived from calix[4]arenes are very useful to estimate the contribution of the cation (RN^+Me_3) -π interaction[8] to the guest-binding process[9, 10] because one can easily prepare conformationally-immobilized π-basic cavities composed of differently pre-organized four benzene rings. We have found that the significant contribution of the RN^+Me_3-π interaction is observed for cone isomers in which four benzene rings are pre-organized so that they can provide a bowl-shaped cavity. It thus occurred to us that if two cone-calix[4]arenes are connected at the upper rim, they should provide a π-basic sphere composed of confronted two hemispherical cavities. To begin with this hypothesis we synthesized a biscalix[4]arene **1**. The CPK molecular model suggests that the inner sphere in **1** is exactly suitable to inclusion of N-methylpyridinium ion (**2**). We here report the inclusion properties for four guest molecules **2** - **5**. Compounds **6** and **7** were used as reference compounds.



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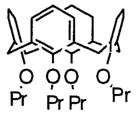

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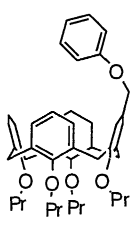

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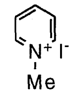

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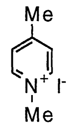

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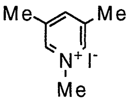

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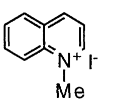

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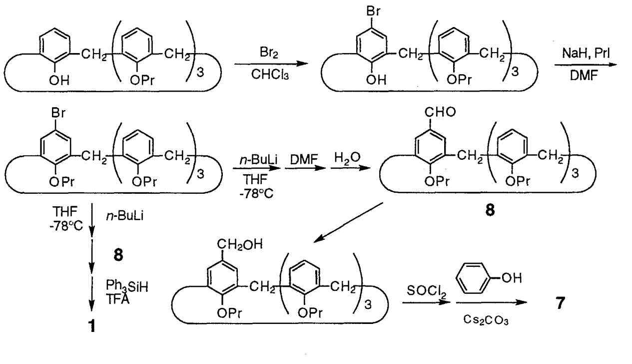
Compounds **1** and **7** were synthesized from cone-25-hydroxy-26,27,28-tripropoxycalix[4]arene[11] according to Scheme 1. The products were identified by IR, ^1H NMR, and mass spectral evidence and elemental analyses. The temperature-independent peaks for the $ArCH_2Ar$ methylene protons (two pairs of doublets at 4.45, 4.41, 3.14, and 3.07 ppm: 24 °C, $CDCl_3$) in **1** reveal that the two calix[4]arenes are immobilized to a cone.

Scheme 1.



As summarized in Table 1, the δ_H for the NCH_3 protons in **2** - **5** shifted to higher magnetic field in the presence of **6**. The particularly large shifts (0.46 - 0.66 ppm) were observed for **2** - **4**, which were much greater than that for **5** (0.13 ppm). The results indicate that the NCH_3 group in **2** - **4** are strongly bound to the π-basic **6** cavity owing to the cation-π interaction (although the partial contribution of the charge-transfer interaction cannot be ruled out) [9] whereas **5** is a little too large to be fully included in **6**. In the presence of **7**, in contrast, the δ_H scarcely moved to higher magnetic field. We have found that substituents present on the upper rim of cone-calix[4]arenes sterically hamper inclusion of guest molecules.[9] This is also the case in **7**.

Compound **1** may be comparable with **7** in a sense that it has a substituents on the upper rim. When **1** was added, the δ_H further moved to higher magnetic field (except **4**). The results

Table 1. δ_H for NCH_3 of **2** - **5** in the absence and the presence of calix[4]arenes [a]

Calix[4]arene	δ_H[b]			
	2	**3**	**4**	**5**
None	4.56	4.47	4.45	4.79
1	3.92	3.52	3.90	4.49
6	4.10	3.81	3.90	4.66

[a] 250 MHz, $CDCl_3$: CD_3CN = 10 : 2 v/v, 24 °C, [calix[4]arene] = 5.0 mmol dm^{-3}.

[b] The saturated δ_H value for plots of δ_H *vs.* [calixarene] / [guest] as shown in Figure 1.

support the view that **1** can wrap **2**, **3** and **5** by a cooperative action of two calix[4]arene bowls. In **4** two protruding methyl groups interfere with such a cooperative inclusion action.

In the presence of **6**, the magnitude of the δ_H shift in **2** appeared in the order of NCH_3 ($\Delta\delta = 0.46$ ppm) > γ-H (0.43 ppm) > α-H (0.25 ppm) (β-H overlaps with **6**). This trend suggests that **2** enters into the **6** cavity either from NCH_3 or from γ-H. In the presence of **1**, the δ_H shifts compared with **6** are furthter greater by 0.18 ppm for NCH_3, 0.53 ppm for γ-H, and 0.43 ppm for α-H. The result suggests that the second calix[4]arene in **1** mainly covers the pyridine protons.

The association constants (K_{ass}) were estimated from plots of δ_H for NCH_3 *vs.* [guest (**2** - **5**)] assuming the formation of a 1 : 1 complex. The typical plots are illustrated in Figure 1 and the K_{ass} values thus determined are summarized in Table 2. Estimation of Table 2 reveals that the K_{ass} for **1** + **2** is greater by 70-fold than that for **6** + **2**. This clearly supports that two calix[4]arenes in **1** act cooperatively, like a pearl oyster, in the inclusion of **2**. The high inclusion ability is due to the size agreement between **2** and the inner space of **1** and the presence of acidic protons (α, β, γ and NCH_3) useful for the CH-π interaction at the periphery of **2**. The similar K_{ass} increase in **1** (respect to **6**) was also observed for **3** (10-fold) and **5** (2-fold). On the other hand, the K_{ass} for **1** + **4** is relatively small and not different from that for **6** + **4**. This trend is compatible with the δ_H shift in Table 1. Conceivably, the NCH_3 moiety is included in the π-basic calix[4]arene cavity but the 3,5-dimethylpyridine moiety is so bulky that the second calix[4]arene is almost useless.

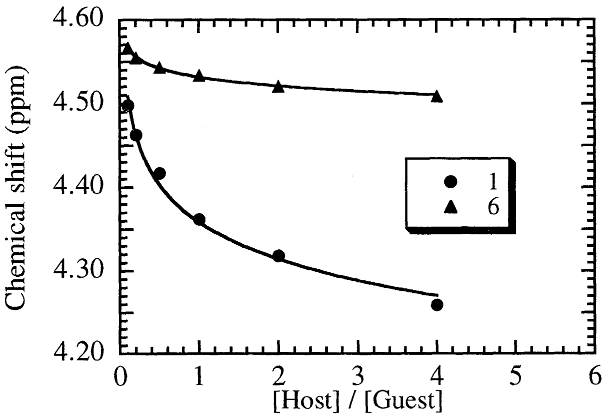


Figure 1. Plots of δ_H for NCH_3 *vs.* [calix[4]arene] / [**2**]: The measurement conditions are similar to those in Table 1. The calix[4]arene concentration (5.0 mmol dm^{-3}) was kept constant while the **2** concentration was varied (0.125 - 50 mmol dm^{-3}). The solid lines are calculated curves.

Table 2. Association constants (K_{ass}) for inclusion of **2** - **5** [a]

Calix[4]arene	K_{ass} / dm^3 mol^{-1}			
	2	**3**	**4**	**5**
1	480	36	2.0	97
6	6.9	3.5	2.0	47

[a] 250 MHz, $CDCl_3$: CD_3CN = 10 : 2 v/v, 24 °C, [calix[4]arene] = 5.0 mmol dm^{-3}, [**2** - **5**] = (0.10 - 1.25) mmol dm^{-3}.

In conclusion, the present study shows that a biscalix[4]arene made by connecting the upper rims of two conformationally-immobile calix[4]arenes has a strong inclusion ability for cationic guest molecules. To further enhance the ability by reducing the conformational freedom we are now synthesizing the homologous biscalix[4]arenes with two-to-four connectors.

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