

A New Basket Molecule Designed from Calix[6]arene by C_3 -Symmetrical Capping. Preorganization of Calix[6]arenes for Inclusion of Trimethylammonium Ions

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Summary: A C_3 -symmetrically upper rim capped calix[6]arene **5** which is the first example of the flipping motion restricted calix[6]arene is a well-preorganized host molecule for complexation of trimethylammonium ion by cation- π interactions.

The calixarene chemists have been accumulating the data that demonstrate that calixarenes act as a useful man-made receptor by appropriate functionalization.¹ In particular, modification of the lower rim has led to molecular design of artificial ionophores which frequently show ion selectivity superior to crown ethers.² In contrast, modification of the upper rim, which is expected to eventually lead to molecular recognition, has been attempted but the successful examples have been very limited.^{3,4} Probably, this is related to the difficulty in regioselective introduction of functional groups into the upper rim and to the conformational freedom remaining in calixarenes. Gutsche *et al.*⁴ thus described that "even the calix[6]arenes are rather flexible and further insight into their mode of action must await the construction of more rigid and conformationally-defined analogs". Recently, several groups have reported the synthetic efforts toward regioselective introduction of functional groups into the upper rim.⁵ To the best of our knowledge, however, there exists no precedent for immobilization of the calix[6]arene conformation,⁶ which is a compulsory process for successful molecular recognition using the calix[6]arene cavity. In this paper we report the first example for a calix[6]arene C_3 -symmetrically capped at the upper rim. This strategy has enabled us to attain not only the regioselective functionalization but also the restriction of the ring-flipping motion.

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(2) Sakaki, T.; Harada, T.; Deng, G.; Kawabata, H.; Kawahara, Y.; Shinkai, S. *J. Incl. Phenom.* **1992**, *14*, 285.

(3) (a) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 3214. (b) Gutsche, C. D.; Nam, K. C. *Ibid.* **1988**, *110*, 6153. (c) Shinkai, S.; Araki, K.; Manabe, O. *Ibid.* **1988**, *110*, 7214. (d) Shinkai, S.; Araki, K.; Grootenhuis, P. D. J.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1883.

(4) Gutsche, C. D.; Alam, I. *Tetrahedron* **1993**, *49*, 8933.

(5) (a) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639. (b) Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313. (c) Beer, P. D.; Drew, M. G. B.; Hazlewood, C.; Heseck, D.; Hodacova, J.; Stokes, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 229. (d) de Mendoza, J.; Carramolino, M.; Cuevas, F.; Nietro, P. M.; Parados, P.; Reinhoudt, D. N.; Verboom, W.; Ungaro, R.; Casnati, A. *Synthesis* **1994**, 47.

(6) Ungaro and his co-workers reported that they accomplished immobilization of the flipping motion in benzene rings of calix[6]arene.^{6a,b} However, Shinkai and his co-workers showed that this immobilization resulted from the observation of a "thermodynamically" stable conformer of calix[6]arene.^{6c} (a) Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413. (b) Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R.; Nijenhuis, W. F.; de Jong, F.; Reinhoudt, D. N. *Isr. J. Chem.* **1992**, *32*, 79. (c) Otsuka, H.; Araki, K.; Sakaki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, 7275.

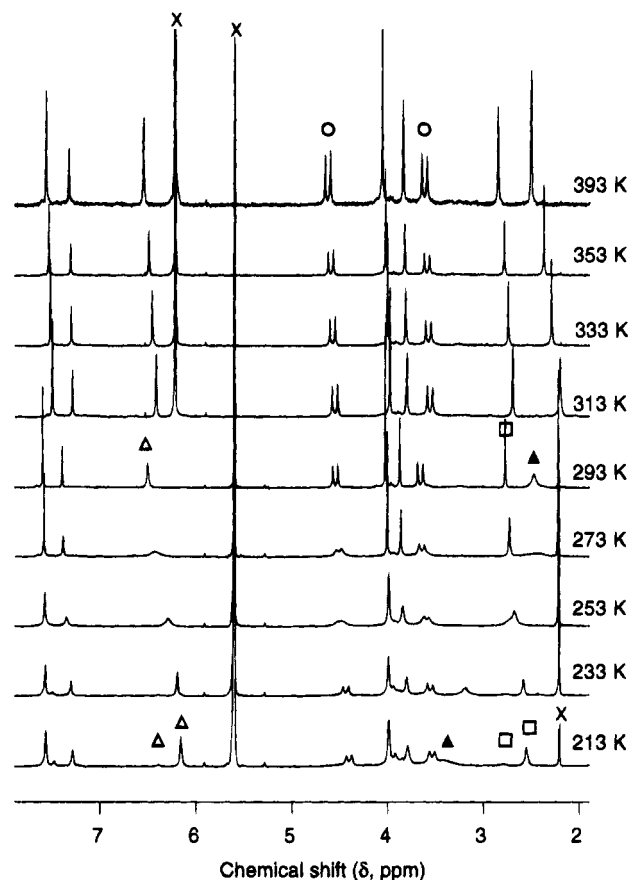


Figure 1. Dynamic ^1H NMR spectra of **5** (2.0 mol L^{-1}) in CD_2Cl_2 (below 293 K) and $\text{CDCl}_2\text{CDCl}_2$ (above 293 K): (E) a pair of doublets for ArCH_2Ar , (C) ArH and (H) OMe in the nonbridged phenyl units, and (G) OMe in the bridged phenyl units.

Treatment of 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trihydroxy-38,40,42-trimethoxycalix[6]arene (**1**)⁷ with AlCl_3 in the presence of MeNO_2 in PhH ⁸ afforded regioselectively de-*tert*-butylated calix[6]arene **2** in 34% yield.⁹ Compound **2** was converted to **3** by methylation in 60% yield. Chloromethylation of **3** afforded 37,38,39,40,41,42-hexamethoxy-11,23,35-tri-*tert*-butyl-5,17,29-tris(chloromethyl)calix[6]arene (**4**) in 87% yield. The intermolecular coupling reaction of the upper rim in **4** and 1,3,5-tris(mercaptomethyl)benzene¹⁰ under high-dilution conditions¹¹ in the presence of KOH in ethanol gave the desired capped calix[6]arene **5** in 28% yield (Scheme 1).¹²

(7) Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Ugozzori, F.; Ungaro, R.; Nietro, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380.

(8) For a general *trans-tert*-butylation method see: Tashiro, M. *Synthesis* **1979**, 921.

(9) This is the isolated yield. The HPLC analysis of the crude product showed 68% yield.

(10) Houk, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 6825.

(11) For example: Tashiro, M.; Yamato, T. *J. Org. Chem.* **1984**, *49*, 3380.

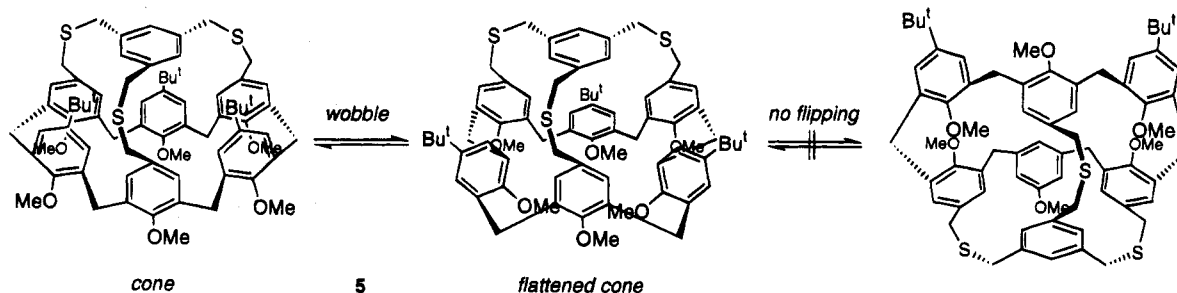


Figure 2. Conceivable motions of capped calix[6]arene **5** (some *tert*-butyl and methoxy groups are omitted for clarity).

Scheme 1

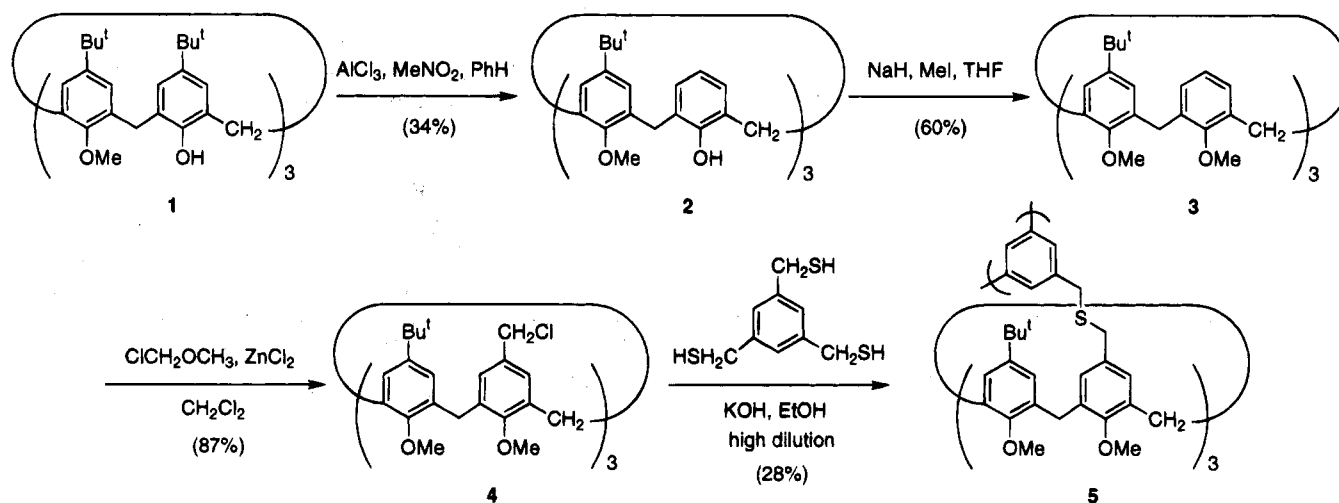


Figure 1 shows dynamic ^1H NMR spectra of calixarene **5** in CD_2Cl_2 (below 293 K) or in $\text{CDCl}_2\text{CDCl}_2$ (above 293 K). Between 213 and 393 K there is no coalescence for the geminal protons in the methylene bridge of **5** (doublet each), and NOESY spectra^{6b} at 295 K (in CDCl_3) and 373 K (in $\text{CDCl}_2\text{CDCl}_2$) showed no chemical exchange but only the positive NOE spectra between these two kinds of methylene protons. One can conclude, therefore, that there is no exchange in these protons: that is, no flipping motion exists in the linked benzene rings of calix[6]arene **5**. As seen from Figure 1, the peaks are sharp at 393 K. With lowering the temperature they at once become broad at around 273 K and again sharp below 233 K. As a pair of doublets for the ArCH_2Ar methylene protons appears throughout the whole temperature range, the cone conformation should be maintained firmly. Then, what is the origin of this line broadening? Careful examination of Figure 1 reveals that with lowering the temperature the OMe protons in the nonlinked phenyl units shift to lower magnetic field while the ArH protons in the nonlinked phenyl units shift to higher magnetic field. Furthermore, both peaks split into the two peaks with a 15:1 integral intensity ratio. This coalescence can be assigned to a "wobble" motion between a flattened cone and a regular cone.¹³ Since the major ArH peak in the nonlinked phenyl units appears at higher magnetic field than the minor one, the major and the minor peak can be assigned to a regular cone and a flattened cone, respectively.¹⁴

As shown above, the capped calix[6]arene **5** has a rigid C_3 -symmetric cavity composed of π -rich benzene rings.

Therefore, it is predictable that such a cavity can act as a well-preorganized host molecule for inclusion of trimethylammonium ions by cation- π interactions.¹⁵ Nonbridged calix[6]arene **6** was used as a reference compound. The ^1H NMR spectra (300 MHz) of **5** or **6** in the presence of trimethylanilinium iodide (PhNMe_3I) were measured in CD_2Cl_2 . The peak signals for PhNMe_3I included in **5** appeared separately from those for free PhNMe_3I ,¹² indicating that the complexation-decomplexation velocity is slower than the NMR time scale. For example, the Me protons included in **5** appeared in 2.90 ppm, which is shifted to higher magnetic field by 1.0 ppm. We repeated the ^1H NMR measurements at 293–228 K and determined the association constant (K_a) at each temperature. In Figure 3 $\ln K_a$ is plotted against T^{-1} , from which we estimated the thermodynamic parameters to be $\Delta H^\circ = -37 \text{ kJ mol}^{-1}$ and $\Delta S^\circ = -104 \text{ J mol}^{-1} \text{ K}^{-1}$. Also, it is worthy to mention that the peak broadening no longer takes place in the presence of PhNMe_3I . This implies that included guests can suppress the wobble motion of the nonbridged phenyl units. In contrast, addition of **6** did not result in the separate PhNMe_3I proton signals but only induced the upfield shift. We thus measured the shift as a function of the **6** concentration and determined the K_a .^{12,16} In Figure 3 $\ln K_a$ thus determined is plotted against T^{-1} : $\Delta H^\circ = -22 \text{ kJ mol}^{-1}$ and $\Delta S^\circ = -63 \text{ J mol}^{-1} \text{ K}^{-1}$. At 273 K, for example, the K_a for **5** is greater by a factor of 5.4 ($\Delta\Delta G^\circ_{273} = -3.8 \text{ kJ mol}^{-1}$) than that for **6**. Examination of thermodynamic parameters tells us that inclusion of PhNMe_3I in the **5**

(12) All experimental procedures and spectral data are shown in the supplementary material.

(13) Ungaro and his co-workers reported that the flattened cone conformation is the most stable in 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-trisubstituted calix[6]arene.^{6a}

(14) Computer-aided line shape analysis to obtain activation parameters of this motion will be reported in the near future.

(15) (a) Stauffer, D. A.; Dougherty, D. A. *Tetrahedron Lett.* **1988**, 29, 6039. (b) Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett.* **1993**, 205.

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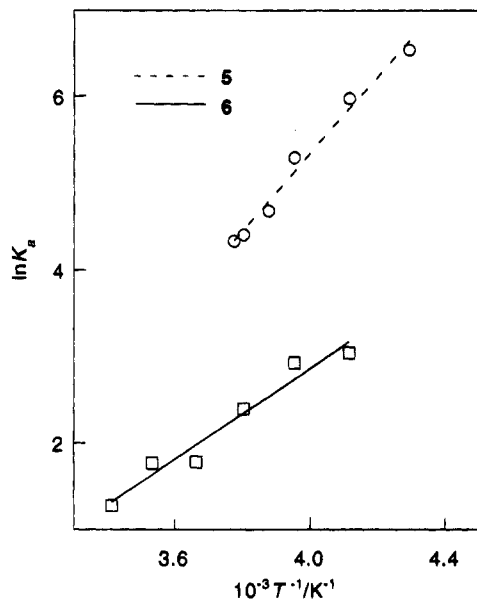
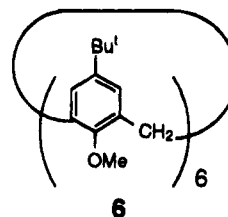


Figure 3. van't Hoff plot for complexation of **5** (E) or **6** (G) with PhNMe₃I in CD₂Cl₂.

cavity features the favorable ΔH° change (by 15 kJ mol⁻¹) and unfavorable ΔS° change (by 41 J mol T⁻¹); that is, with inclusion of C₃-symmetric RNMe₃⁺ guests, preorganization of calix[6]arene by a C₃-symmetric cap leads

to the enthalpy gain whereas rigidification of the ring leads to the entropy loss.



In conclusion, upper-rim capped calix[6]arene **5** is the first calix[6]arene whose benzene rings are restricted in the flipping motion, and a wobble motion still exists between cone and flattened cone conformers. Such immobilization results in good preorganization for complexation with ammonium ions such as PhNMe₃I by cation- π interactions.

Supplementary Material Available: Experimental procedures, characterization data, and figures for NOESY spectra of **5** at 205, 295, and 373 K, dynamic ¹H NMR spectra of **5** in the presence of PhNMe₃I, and concentration of **6** vs chemical shift of the *N*-methyl proton of PhNMe₃I in CD₂Cl₂ (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.