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Immobilization of the Ring Inversion Motion in Calix[6]arene by a Cap with C_3-Symmetry

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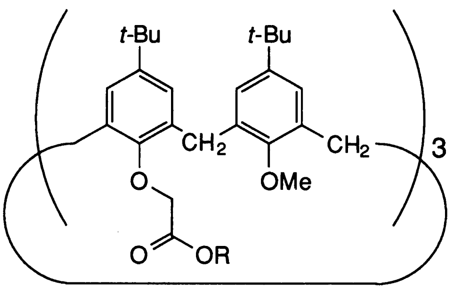
A conformationally-immobilized calix[6]arene (**2**) was synthesized for the first time. The immobilization was attained by capping calix[6]aryl 1,3,5-tricarboxylic acid chloride with C_3-symmetrical triol. The ^{1}H NMR spectral examination with 2D EXSY established that **2** is immobilized in a cone conformation. Compound **2** showed the high affinity for guanidinium ion because of rigidification of the conformation.

It has been established that the rotation of phenyl units in calix[4]arenes can be suppressed by introduction of *O*-substituents bulkier than the ethyl group.$^{1)}$ Thus, one can derive conformationally-immobilized four different conformers (cone, partial-cone, 1,2-alternate, and 1,3-alternate) and enjoy metal recognition by utilizing the ionophoric cavities provided from these conformers.$^{2-4)}$ In contrast, calix[6]arenes possess a cavity larger than calix[4]arenes and probably are more suitable to molecular recognition. However, the attempts to apply calix[6]arenes as hosts to specific molecular recognition$^{5-7)}$ have so far been unsuccessful because of their large conformational freedom. Gutsche *et al.*$^{5)}$ thus described reluctantly 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*".

In 1991 Casnati *et al.*$^{8)}$ reported compound **1a**. They proposed on the basis of ^{1}H NMR spectral examinations that "***1a** is the first example of calix[6]arenes frozen in the cone conformation*".$^{8)}$ This proposal was incompatible with our observation that in calix[6]arene-37,38,39,40,41,42-hexol ring inversion can still take place even though very bulky *O*-substituents are introduced$^{9)}$: that is, not only the oxygen-through-the-annulus rotation but also the para-substituent-through-the-annulus rotation can occur in calix[6]arenes. Our recent ^{1}H NMR spectral examinations (2D EXSY) established that **1a** is not truly immobilized but the rate of ring inversion is just slower than that of the NMR time-scale.$^{10)}$ Then, how can we immobilize the conformation of calix[6]arenes? We considered that the remaining and probably sole strategy is "capping". Here, we report the first example of conformationally-immobilized calix[6]arene **2**, which was synthesized by condensation of a C_3-symmetrical calix[6]arene and a C_3-symmetrical cap.$^{11)}$

Compound **2** was synthesized from **1b** according to Scheme 1. Examination of CPK molecular models predicted that if the distance between terminal OH groups in the cap is short, the carbonyl groups which are



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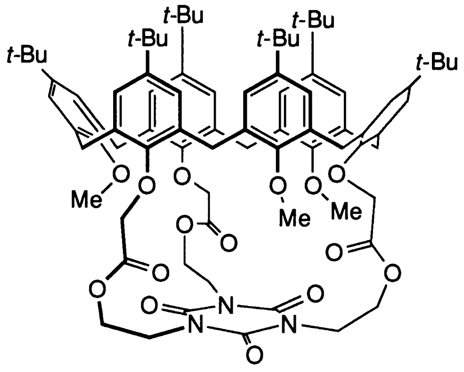
a: R = t-Bu
b: R = Et



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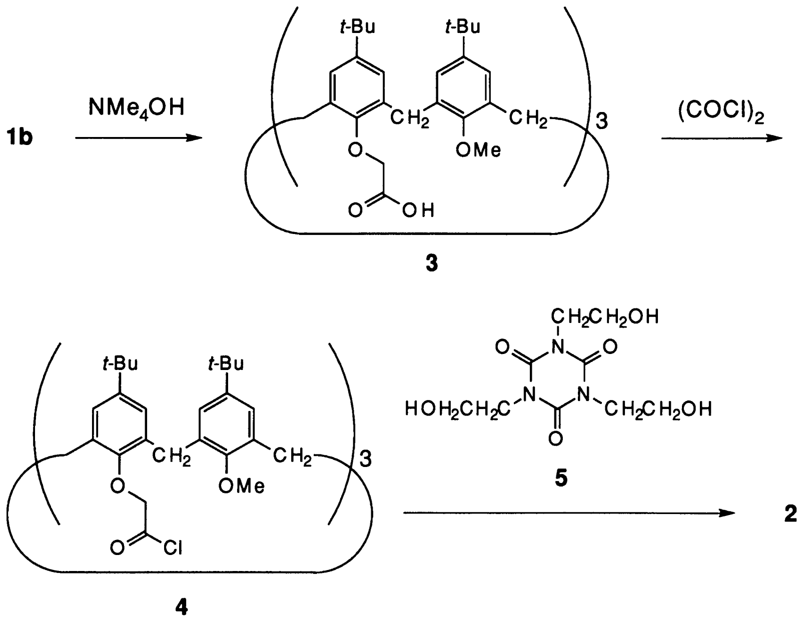
essential for the guest-binding are enforced to turn outward. In tris(2-hydroxyethyl)isocyanurate (**5**) used as a cap, on the other hand, the distance is long enough to hold the carbonyl groups inward. The key step in the synthesis is the reaction of **4** and **5** under the high-dilution conditions. The esterification of **4** (0.21 mmol) and **5** (0.21 mmol) was carried out in THF (350 ml) at the reflux temperature in the presence of pyridine (0.99 mmol) under a nitrogen atmosphere. **2** was isolated by a preparative TLC method (silica gel, chloroform:methanol = 30:1 v/v) and identified by IR, mass and ^{1}H NMR spectral evidence and elemental analysis[12]: yield 2.5%,[13] mp > 290 °C (decomp.).



Scheme 1.

Figure 1 shows the temperature-dependent ^{1}H NMR spectra of **2**. At 40 °C a pair of doublets appeared at 3.43 and 4.43 ppm, indicating that **2** adopts a cone conformation. The spectral pattern scarcely changed up to 110 °C. This implies that the rate of ring inversion, even if it occurs, is much slower than that of the NMR time-scale. In **1a** which showed the similar temperature-dependence,[8] the rotation of the phenyl groups was evidenced by 2D EXSY in ^{1}H NMR spectroscopy: that is, the exchange between H_{ax} and H_{eq} in the ArCH$_2$Ar methylene protons was clearly observed.[10)] We thus applied the similar method to the present system (Brucker ARX-300, NOESYTP with Time Proportional Phase Increment: [**2**] = 8.4 mmol dm^{-3}, $Cl_2CDCDCl_2$, τ_m 800 msec). At 40 - 110 °C the correlation arising from the exchange between H_{ax} and H_{eq} was not observed. The result unequivocally evidences that **2** is firmly immobilized in a cone conformation: that is, flip-flop-type inversion of the "basket" cannot take place.

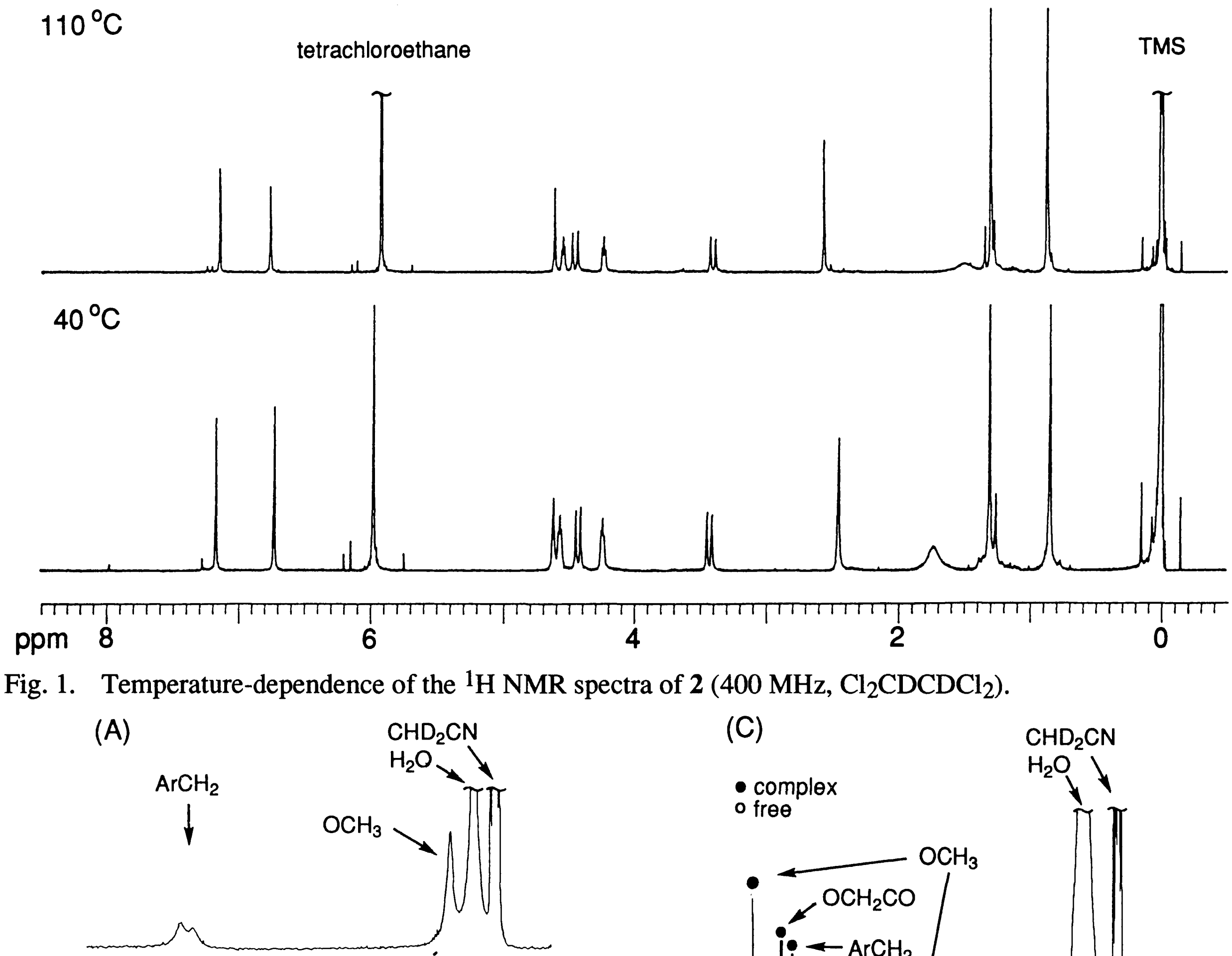


Fig. 1. Temperature-dependence of the ^1H NMR spectra of **2** (400 MHz, $Cl_2CDCDCl_2$).

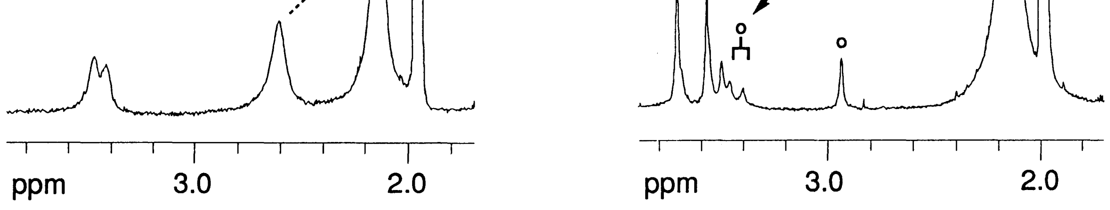


Fig. 2. Partial ^1H NMR spectra of (A) **1b** (2.8 mmol dm^{-3}), (B) **1b** (2.8 mmol dm^{-3}) + guanidinium tetraphenylborate (2.8 mmol dm^{-3}), and (C) **2** (2.8 mmol dm^{-3}) + guanidinium tetraphenylborate (2.8 mmol dm^{-3}) (250 MHz, $Cl_2CDCDCl_2$:CD_3CN = 4:1 v/v, 24 °C).

It is known that **1a** binds guanidinium ion because of the hole-size selectivity and the C_3-symmetrical complementarity.[8)] We considered that the capped, C_3-symmetrical cavity in **2** should bind guanidinium ion more strongly and via a kinetically slower process. Figure 2 shows the ^1H NMR spectra of **1b** and **2** in the presence of 1.0 equivalent of guanidinium ion. Upon addition of guanidinium ion the ^{1}H NMR spectrum of **2** separated into two components assignable to the complex and free **2** whereas that of **1b** did not separate but only caused a change in the chemical shifts. The finding shows that the rates for the association and the dissociation in the complexation of **2** and guanidinium ion are much slower than those in **1b**. The association constant (K) for **2** was directly estimated from the ratio of the integral intensities to be $K = 2300$ dm^3 mol^{-1}. On the other hand, the K for **1b** was determined from a plot of δ_H *vs*. [guanidinium ion] to be $K = 880$ dm^3 mol^{-1}. The K for **2** in which the functional groups for guest-binding are well-preorganized is larger by a factor of 3 than that for **1b**.

In conclusion, the present paper demonstrates that capping of calix[6]arenes at the 1,3,5-positions is a potential strategy to suppress their conformational change. We believe that the door to molecular recognition by calix[6]arenes has been opened by **2**, which is classified, as Gutsche said,5) as "a more rigid and conformationally-defined analog".14)

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11) The similar attempt to use cyclotriveratrilene as a cap was reported by Reinhoudt *et al.* in the 2nd Workshop on Calixarenes and Related Compounds (1993, June, Kurume).
12) **2** was isolated as a complex with $CHCl_3$ which was used in the TLC purification process. IR(nujol) $\nu_{c=o}$ 1690 and 1770 cm^{-1}; MS (positive SIMS in the presence of guanidinium chloride) m/e 1455 $[M+C(NH_2)_3]^+$; ^{1}H NMR (250 MHz, $CDCl_3$, 24 °C) δ_H 7.10 (s, 6H, ArH), 6.81 (s, 6H, ArH), 4.56 (t, 6H, CH_2OCO), 4.49 (s, 6H, OCH_2CO), 4.43 (d, 6H, J = 15.5 Hz, $ArCH_2Ar$), 4.24 (t, 6H, NCH_2), 3.46 (d, 6H, J = 15.5 Hz, $ArCH_2Ar$), 2.69 (s, 9H, OCH_3), 1.24 (s, 27H, $C(CH_3)_3$), 0.94 (s, 27H, $C(CH_3)_3$). Found: C, 67.89; H, 7.67; N, 2.84%. Calcd for $C_{84}H_{105}O_{15}N_3 \cdot CHCl_3$: C, 67.34; H, 7.05; N, 2.77%.
13) The HPLC analysis of the raw product showed that the yield was *ca.* 10% but **2** decomposed on the silica gel plate during the isolation process.
14) Gutsche *et al.* recently reported calix[6]arenes bridged at the 1,4-positions but the ring inversion was not suppressed: S. Kanamathareddy and C. D. Gutsche, *J. Am. Chem. Soc.*, **115**, 6572 (1993).

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