Definitive Evidence for Inhibition of Calix[6]arene Ring Inversion Obtained from a 1,3-Xylenyl-Bridged Chiral Calix[6]arene

Hideyuki Otsuka and Seiji Shinkai*

Contribution from the Department of Chemical Science & Technology, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan

Received October 30, 1995. Revised Manuscript Received February 21, 1996[⊗]

Abstract: To design calix[6]arene-based receptor molecules which show high affinity and high selectivity toward guest molecules, the construction of more rigid and conformationally-defined analogs has been long awaited (Gutsche; Alam *Tetrahedron* **1988**, *44*, 4689). It has been predicted that in certain sterically-hindered calix[6]arenes the ring inversion is suppressed. However, evidence presented so far (mainly from NMR spectroscopy) is indirect and is valid only in the range of the NMR time scale. To find definitive evidence for the immobilization we synthesized a calix[6]arene (**4**), the 1,3-phenyl units of which are bridged by an asymmetrical 4-methoxy-*m*-xylenyl unit, and optically resolved it by an HPLC method using a chiral packed column. Since ring inversion is obligatorily accompanied by racemization, one can easily discriminate between *true* immobilization and NMR time-scale immobilization. The ^{1}H NMR studies have established that **4** adopts a cone conformation, which is unaffected up to 130 °C. Very importantly, it was shown that **4** does not racemize even at 100 °C. This provides unambiguous evidence for the immobilization of the calix[6]arene ring in **4**. This paper demonstrates that the racemization of chiral calix[6]arenes is an effective (and probably sole at present) methodology to obtain the definitive evidence for ring immobilization.

Introduction

Calix[*n*]arenes are a class of cavity-shaped macrocycles composed of *n* molecules of phenol and *n* molecules of formaldehyde.[1−12] It is known that each phenol unit can enjoy rotational freedom, which creates a number of conformational isomers. On the other hand, the conformation of calix[4]arenes can be immobilized by *O*-substituents bulkier than the ethyl group: e.g., the *O*-propyl group in calix[4]arenes cannot engage in the oxygen-through-the-annulus rotation because of the bulkiness of the propyl group and the smallness of the calix[4]arene cavity.[9a,b] In contrast, conformational immobilization of calix[6]arenes has been left ambiguous. In 1991 Casnati et al.[13] reported ^{1}H NMR spectroscopic properties of 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris[(*tert*-butoxycarbonyl)methoxy]calix[6]arene. Although the line-broadening was scarcely induced over a wide temperature range,[13] it was later proven that the phenyl units in this compound can still rotate, the rate being slower than the NMR time scale.[14−16] Then, how can we suppress the ring inversion of calix[6]arenes? The importance of the ring immobilization was previously pointed out by Gutsche et al.[2c] as "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 1993, Biali et al.[17] succeeded in the immobilization using two dialkyl phosphates which can react with six phenol groups.

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1996.

(1) For comprehensive reviews see: (a) Gutsche, C. D. In *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) Vicens, J.; Böhmer, V., Eds. In *Calixarenes*; Kluwer Academic Press: Dordrecht, The Netherlands, 1991. (c) Shinkai, S. *Bioorg. Chem. Front.* **1990**, *1*, 161.

(2) (a) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652. (b) Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633. (c) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.

(3) (a) Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177. (b) Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 936.

(4) (a) Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313. (b) 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.

(5) (a) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409. (b) Shinkai, S.; Araki, K.; Tsubaki, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2297. (c) Arimura, T.; Nagasaki, T.; Shinkai, S.; Manabe, O. *J. Org. Chem.* **1989**, *54*, 3767. (d) Komori, T.; Shinkai, S. *Chem. Lett.* **1992**, 901.

(6) (a) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6059. (b) Gutsche, C. D.; Reddy, P. A. *J. Org. Chem.* **1991**, *56*, 4783. (c) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160.

(7) (a) Bocchi, V.; Foina, D.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *Tetrahedron* **1982**, *38*, 373. (b) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreetti, G. D.; Ugozzoli, F. *Tetrahedron* **1986**, *42*, 2089. (c) (d) Auduini, A.; Casnati, A.; Fabbi, M.; Minari, P.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Supramol. Chem.* **1993**, *1*, 235.

(8) (a) Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 1285. (b) Verboom, W.; Datta, S.; Asfari, Z.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 5394. (c) Groenen, L. C.; Ruel, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675.

(9) (a) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955. (b) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325. (c) Iwamoto, K.; Shinkai, S. *J. Org. Chem.* **1992**, *57*, 7066. (d) Shinkai, S.; Fujimoto, K.; Otsuka, T.; Ammon, H. L. *J. Org. Chem.* **1992**, *57*, 1516.

(10) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. *J. Chem. Soc., Chem. Commun.* **1985**, 388.

(11) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681.

(12) Arimura, T.; Kubota, M.; Matsuda, T.; Manabe, O.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1674.

(13) Casnati, A.; Minari, P.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413.

(14) Otsuka, H.; Araki, K.; Shinkai, S. *Chem. Express* **1993**, *8*, 479.

(15) Otsuka, H.; Araki, K.; Sakaki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 7275.

(16) van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 5814.

(17) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 13.

S0002-7863(95)03626-2 CCC: $12.00

We also synthesized triply-bridged calix[6]arenes at the upper rim side[18] or at the lower rim side.[19−21] Judging from the CPK molecular models it seems impossible for these capped calix[6]arenes to enjoy the ring inversion motion. Recently, Kanamathareddy and Gutsche[22] synthesized compound **1** in which the 1,4-phenyl units in calix[6]arene are bridged by a *p*-xylenyl unit. It was shown that **1** is capable of undergoing a conformational transformation in which the bridging moiety becomes threaded through the annulus to produce a "self-anchored rotaxane". It was also noted by these authors,[22] however, that the calix[6]arene bridged 1,4 with an anthrylene moiety does not form a self-anchored rotaxane but remaines conformationally immobile. Meanwhile, we synthesized compound **2** (as a reference compound for a triply-bridged calix[6]arene **3**) in which the 1,3-phenyl units are bridged by a *m*-xylenyl unit.[20b] Surprisingly, the ^{1}H NMR spectra (400 MHz) of **2** (as well as **3**) were scarcely changed at 30−130 °C.[20b] The two-dimensional (2D) EXSY measurements also indicated that the ring inversion in **2** and **3** is *apparently inhibited in terms of the NMR time scale*.[20b] Then, how can we obtain definitive evidence for immobilization of the ring inversion motion? The best and probably sole idea which comes to mind is the use of chiral calix[6]arenes with molecular asymmetry in which ring inversion is obligatorily accompanied by racemization. Molecular design of calix[4]arenes with molecular asymmetry has been reported by several groups,[23b] but the successful examples for optical resolution have still been very limited.[23−26] Molecular design of calix[6]arene with molecular asymmetry is more difficult than that of calix[4]arenes, and to the best of our knowledge no precedent exists for successful optical resolution of chiral calix[6]arenes. We noted that when the 1,3-phenyl units in calix[6]arene are bridged by a 4-methoxy-*m*-xylenyl unit, the product **4** is chiral, providing a compound suitable for testing the immobilization by measuring its enantiomeric stability. Fortunately, racemic **4** could be optically resolved by an HPLC method using a chiral packed column. We have found that racemization of enantiomeric **4** does not take place even at 100 °C. This is the first definitive evidence that the calix[6]arene ring **4** is *truly* immobilized.

Results and Discussion

Synthesis and Temperature-Dependent ^{1}H NMR Spectra. We previously reported that the reaction of 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetramethoxycalix[6]arene-40,42-diol (**5**) with α,α′-dibromo-*m*-xylene results in **2** in 93% yield.[20b] Compound **4** was synthesized from **5** and 4-methoxy-α,α′-dibromo-*m*-xylene in a similar manner used for the synthesis of **5**. The yield was 90%.

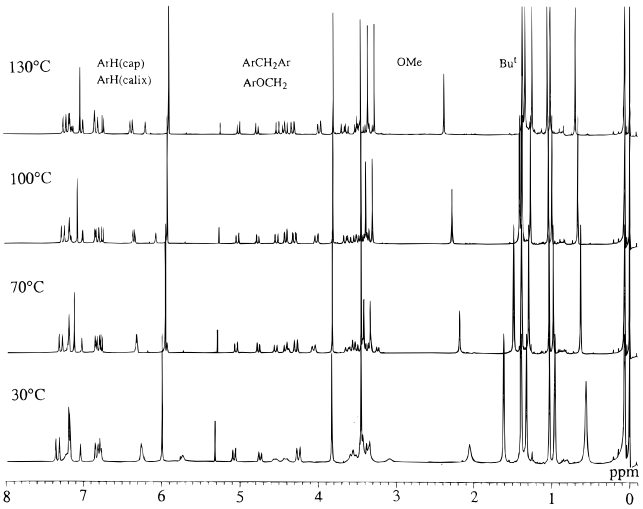


Figure 1. Temperature dependence of ^{1}H NMR spectra for **4** (400 MHz, $Cl_2CDCDCl_2$).

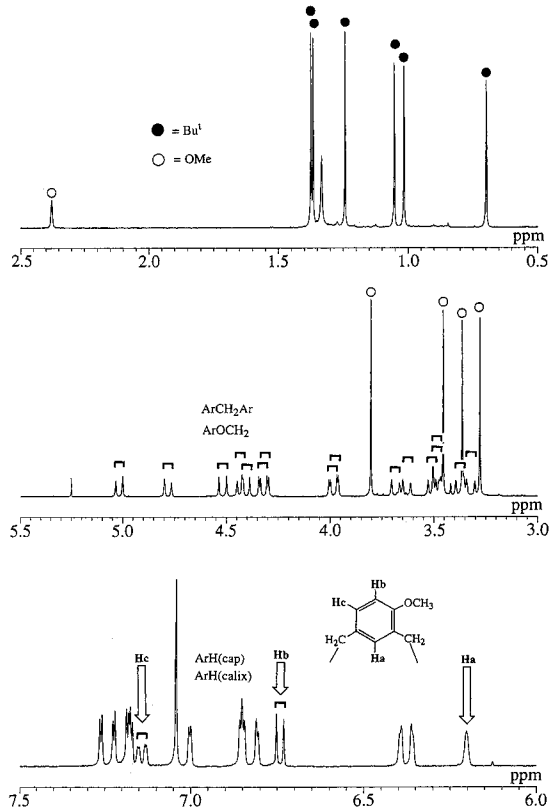
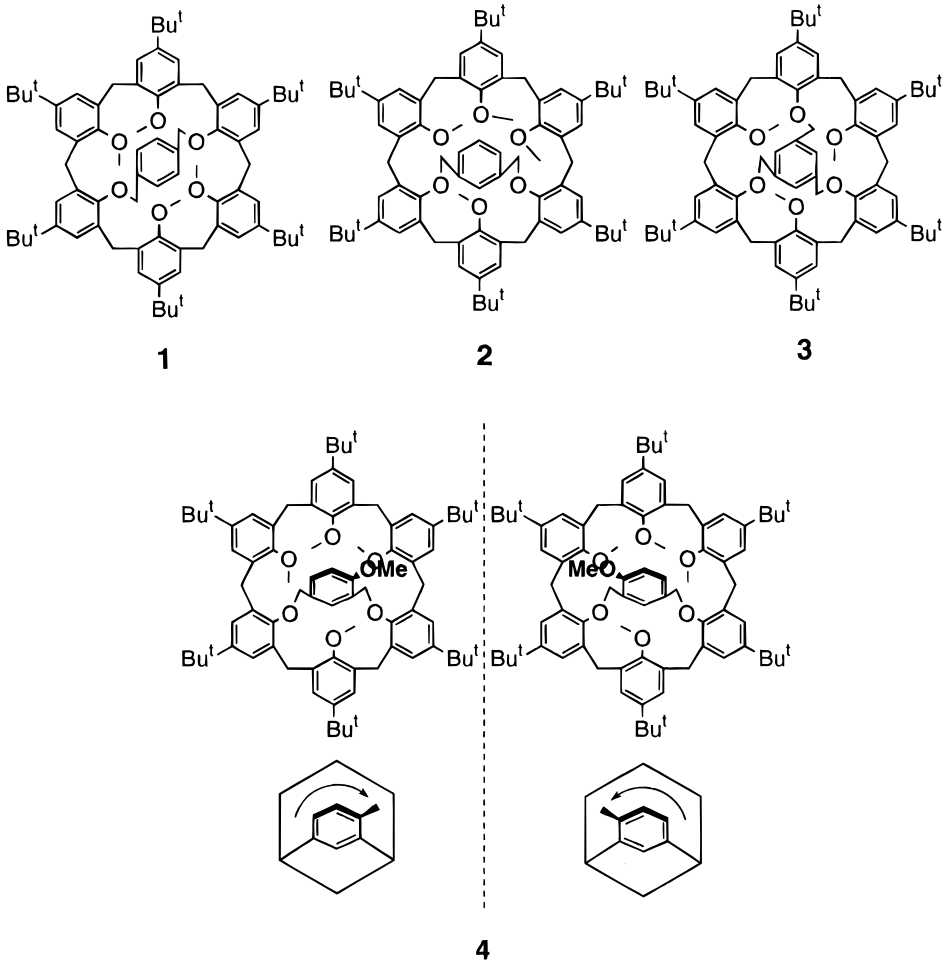


Figure 2. Proton assignment in the ^{1}H NMR spectrum for **4** at 130 °C.

Figures 1 and 2 show temperature-dependent ^{1}H NMR spectra of **4** in $Cl_2CDCDCl_2$. All peaks are sharpened at 130 °C, which are convenient for the peak assignments. Compound **2** without the MeO group gave four singlet *t*-Bu peaks in a 1:1:2:2 integral intensity ratio.[20b] On the other hand, **4** with the MeO group gives six singlet *t*-Bu peaks, indicating that all *t*-Bu groups are inequivalent. Similarly, compound **2** gave three singlet MeO (calix[6]arene) peaks in a 1:1:2 integral intensity ratio.[20b] In **4**, on the other hand, four singlet MeO (calix[6]arene) peaks are observable, indicating that they are all inequivalent. Obviously,

(18) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032.
(19) Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai, S. *Chem. Lett.* **1994**, 1251.
(20) (a) Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542. (b) Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862.
(21) Other examples for bridging or capping of calix[6]arenes (although their purposes are not necessarily immobilization of the conformation): (a) Janssen, R. G.; Verboom, W.; van Duynhoven, J. P. M.; van Velzen, E. J. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, *35*, 6555. (b) Kraft, K.; Böhmer, V.; Vogt, W.; Ferguson, G.; Gallagher, J. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1221.
(22) Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572.
(23) (a) Pickard, S. T.; Pirkle, W. H.; Tabatabai, M.; Vogt, W.; Böhmer, V. *Chirality* **1993**, *5*, 310. (b) For a comprehensive review for inherently chiral calixarenes see: Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom.* **1994**, *19*, 17.
(24) (a) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Araki, K.; Iwamoto K.; Matsuda, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1734. (b) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Iwamoto K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2429.
(25) (a) Iwamoto, K.; Yanagi, A.; Arimura, T.; Matsuda, T.; Shinkai, S. *Chem. Lett.* **1990**, 1901. (b) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1193**, *115*, 3997 (Corrigendum *Ibid.* **1993**, *115*, 3997).
(26) (a) Pappalardo, S.; Caccamese, S.; Giunta, L. *Tetrahedron Lett.* **1991**, *32*, 7747. (b) Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611.

Chart 1



1 **2** **3**

4

the inequivalence is induced by the 4-MeO group introduced into the *m*-xylenyl cap. As also observed for **2**,[20b] one MeO group in **4** appears at a higher magnetic field (δ_H 2.38 ppm: compare 2.32 ppm in **2**[20b]). This MeO group can be assigned to that in the phenyl unit farthest from the bridgehead which is considerably flattened, the MeO group undergoing the shielding effect of the benzene ring in the cap. In the methylene proton region we can find eight pairs of doublets, two of them being assigned to the methylene groups in the *m*-xylenyl cap and six of them being assigned to the $ArCH_2Ar$ protons in the calix[6]arene. Very importantly, the six pairs of doublets are firmly maintained even at 130 °C. For compound **2** we were able to assign four pairs of doublets to each $ArCH_2Ar$ methylene group by 2D COSY ^{1}H NMR spectroscopy and establish that it adopts a (partially) flattened cone conformation.[20b] Although the splitting pattern for the $ArCH_2Ar$ methylene protons in **4** is more complicated and therefore difficult to assign to each $ArCH_2Ar$ methylene group, the chemical shifts of each group are basically similar to those of **2**. One can consider, therefore, that **2** also adopts a (partially) flattened cone conformation. The line-broadening observed at 30 °C is attributable to the partial fluctuation of the cap, the nonbridged phenyl units, etc.[18−20] The foregoing ^{1}H NMR spectral data indicate that the calix[6]arene ring does not undergo inversion at least on the NMR time scale.

Optical Resolution. To confirm that **4** consists of a pair of enantiomers we measured its ^{1}H NMR spectrum in the presence of Pirkle's chiral shift reagents ((*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol). We found that this reagent is effective[24,25] to **4**: the peaks split into pairs with a 1:1 integral intensity ratio even at 30 °C. The cleanest split was observed for the methylene peaks

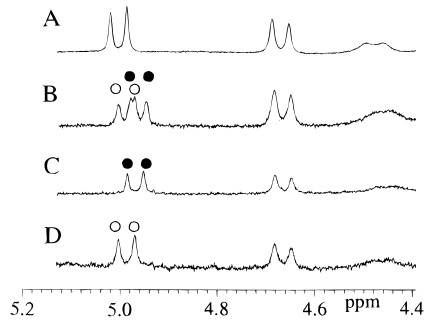


Figure 3. Partial ^{1}H NMR spectra for the methylene protons in **4** (2 mM) at 30 °C in $Cl_2CDCDCl_2$: (A) **4**; (B) **4** with Pirkle's reagent (20 mM); (C) **4a** with Pirkle's reagent; (D) **4b** with Pirkle's reagent.

(Figure 3). The finding suggests that the Pirkle's reagent interacts via hydrogen bonding with the MeO groups.

The optical resolution of **4** was carried out with Daicel Chiralpak AD (mobile phase: *n*-hexane/2-propanol, 98:2 v/v), a representive chromatogram for which is shown in Figure 4. Because of the favorable separation factor it was possible to recover **4a** (first fraction) in 50% yield and 100% ee and **4b** (second fraction) in 49% yield and 99% ee. As shown in Figure 5, the CD spectra of the two enantiomers are reciprocal to one another.

Thermal Racemization. Using optically-resolved **4**, we can now test whether the ring of **4** is immobilized or the rate of ring inversion is simply slower than the NMR time scale. We heated **4** in various solvents for 12 h and tested for racemization by an HPLC method. To obtain a general conclusion for the solvent effect on racemization we chose methanol, *n*-butanol,

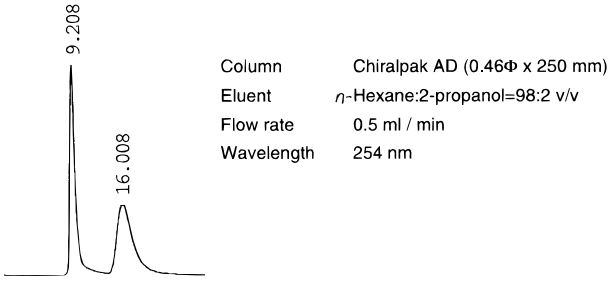


Figure 4. Chromatogram for resolution of racemic **4**. For separation conditions, see the data given in the figure. Numbers recorded on the peaks are the retention time (*t*/min).

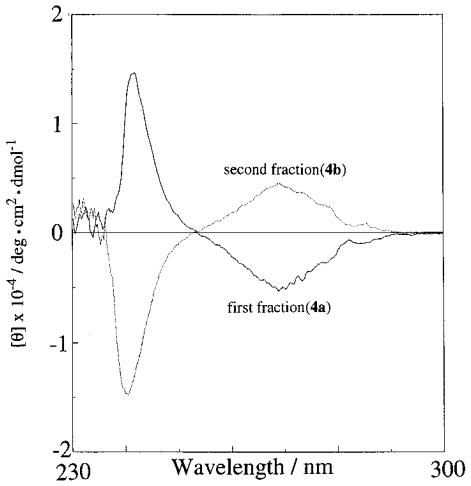


Figure 5. CD spectra of optically-resolved **4** at 25 °C in CD_2Cl_2.

n-octanol, *n*-octane, toluene, 1,1,2,2-tetrachloroethane, and DMF which cover most categories of polar vs apolar, protic vs. aprotic, halogenated, and aromatic solvents. When their boiling points are higher than 100 °C, the racemization test was carried out at 100 °C because **4** slowly decomposed above this temperature. When they are lower than 100 °C (e.g., methanol), we used the reflux temperature. From the HPLC analysis of these solutions we confirmed that the racemization does not take place in any solvent. In addition, we left *n*-octane solution at room temperature for 3 months. Again, the racemization was not observed. The findings unequivocally establish that *the ring inversion in **4** is inhibited*. This is the first experimental evidence that the calix[6]arene ring is *truly* immobilized on the temporal time scale.

We now discuss why **1** can undergo ring inversion,[22] whereas **4** cannot. The difference between **1** and **4** is only either the *p*-xylenyl-bridging on the 1,4-phenyl units or the *m*-xylenyl-bridging on the 1,3-phenyl units. It is known that **1** tends to adopt a 1,2,3-alternate conformation with a "self-anchored rotaxane" structure.[22] This structure can be a symmetrical intermediate in ring inversion, and the calix[6]arene annulus is large enough to include the self-anchored *p*-xylenyl unit. Furthermore, the 1,2,3-alternate conformation holds the 1,4-phenyl units in the *anti* direction which makes the *p*-xylenyl-bridging sterically advantageous. These stabilization effects act synergistically and allow the ring inversion. In **4**, on the other hand, the bridging of 1,3-phenyl units with the *m*-xylenyl unit creates a new small ring consisting of A−B−CAP−B′ phenyl units (see Figure 6). Although the D ring retains considerable conformational freedom (as shown by ^{1}H NMR spectroscopy), the rotation of the A ring is sterically impossible. The CAP ring stands nearly perpendicularly to the calix[6]arene plane to bridge the B and B′ rings to reduce the steric crowding with the C and C′ rings. When the A ring rotates, either the MeO group or the *t*-Bu group inevitably hits the CAP ring. Hence, this frame is firmly maintained and cannot undergo inversion. As shown in Figure 1, the ^{1}H NMR spectrum of **4** at 30 °C consists of a mixture of sharp and broad peaks. Most of the sharp peaks are assignable to protons in this firm frame, indicating that the molecular motion is highly restricted. This firm frame consists of 16 atoms, the number being the same as that in calix[4]arenes. In calix[4]arenes the MeO-through-the-annulus rotation is still allowed.[1] Hence, the cavity size of this firm frame should be smaller than that of calix[4]arenes. The difference stems from the *ortho* linkages employed in the B and B′ rings.

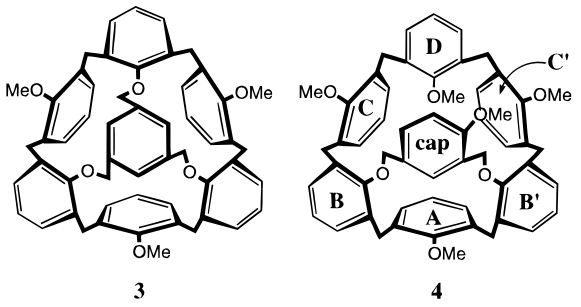


Figure 6. Schematic representation of a stereo view for aromatic rings in **3** and **4**. *p-tert*-Butyl groups are omitted for clarity.

Conclusion. The ring inversion problem in calix[6]arenes has been one of central interests in calixarene chemistry.[13−20] It is rather easy to obtain evidence for ring inversion from ^{1}H NMR spectroscopy using, for example, temperature-dependent ^{1}H NMR spectra and 2D EXSY measurements.[14−17] In contrast, it is very difficult to obtain unequivocal evidence for ring immobilization. Although the ^{1}H NMR spectra are unchanged over a wide temperature range, one has to always take the NMR time-scale problem into consideration. The present paper has demonstrated, for the first time, a novel method to obtain unequivocal evidence for ring immobilization in calix[6]arenes. The basic idea is to use a chiral calix[6]arene with molecular asymmetry: as ring inversion is obligatorily accompanied by racemization, one can conveniently determine whether or not the calix[6]arene ring is immobilized. We now consider that **4** is useful for testing several hypotheses in calix[6]arene chemistry which have been ambiguous for lack of the absence of appropriate calix[6]arenes: e.g., (i) the conformationally-defined analogs should show better shape selectivity for guest molecules,[2c] and (ii) guest inclusion into the invertible calix[*n*]arene cavities suppresses the ring inversion and therefore accompanies the loss of the conformational freedom: in this context, conformationally-immobilized analogs should give larger association constants,[27] etc.

Experimental Section

Materials. 2,4-Dimethylanisole was purchased from Janssen Chimica. Preparation of 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetramethoxycalix[6]arene-40,42-diol has already been described.[20a]

4-Methoxy-α,α′-dibromo-*m*-xylene. A mixture of 2,4-dimethylanisole (5 mL, 35.7 mmol), *N*-bromosuccinimide (12.7 g, 71.4 mmol), benzoyl peroxide (100 mg), and tetrachloromethane (100 mL) was heated at reflux temperature for 2 h under a N_2 stream. The reaction mixture was filtered to remove succinimide, washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to dryness and the residue was triturated with cold MeOH. The white solid was dissolved in CH_2Cl_2 and reprecipitated from cold MeOH to give the pure product: mp 96.8−98.2 °C, yield 72%; ^{1}H NMR ($CDCl_3$, 60 MHz,

(27) Shinkai, S.; Araki, K.; Matsuda, T.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3856.

25 °C) δ 3.91 (3H, s), 4.47 (2H, s), 5.53 (2H , s), 6.7−7.4 (3H, m). Anal. Calcd for $C_9H_{10}OBr_2$: C, 36.77; H, 3.43. Found: C, 37.28; H, 3.46.

Chiral Calix[6]arene (4). 5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,-39,41-tetramethoxycalix[6]arene-40,42-diol (32 mg, 0.03 mmol) was dispersed in acetone (30 mL) containing 4-methoxy-α,α′-dibromo-*m*-xylene (9.2 mg, 0.03 mmol) and Cs_2CO_3 (203 mg, 0.60 mmol), and the mixture was refluxed for 12 h under a N_2 stream. After evaporation, the solid residue was dispersed in aqueous 0.1 M HCl solution and then extracted with $CHCl_3$. The $CHCl_3$ layer was separated, washed with H_2O, and dried over $MgSO_4$. The solution was evaporated to dryness, and the residue dissolved in $CHCl_3$ was purified by reprecipitation from MeOH: mp >270 °C dec, yield 90%; IR(Nujol) no ν_{OH}; ^{1}H NMR ($(CDCl_2)_2$, 400 MHz, 130 °C) δ 0.70 (9H, s), 1.02 (9H, s), 1.05 (9H, s), 1.24 (9H, s), 1.37 (9H, s), 1.38 (9H, s), 2.38 (3H, s), 3.28 (3H, s), 3.36 (3H, s), 3.46 (3H, s), 3.32 (1H, d), 3.38 (1H, d), 3.47 (1H, d), 3.48 (1H, d), 3.51 (1H, d), 3.63 (1H, d), 3.68 (1H, d), 3.80 (3H, s), 3.97 (1H, d), 3.98 (1H, d), 4.32 (1H, d), 4.33 (1H, d), 4.41 (1H, d), 4.43 (1H, d), 4.52 (1H, d), 4.78 (1H, d), 5.02 (1H, d), 6.20 (1H, s), 6.36 (1H, d), 6.39 (1H, d), 6.74 (1H, d), 6.81 (1H, d), 6.84 (1H, d), 6.86 (1H, d), 7.00 (1H, d), 7.04 (2H, s), 7.14 (1H, m), 7.17 (1H, d), 7.18 (1H, d), 7.22 (1H, d), 7.26 (1H, d). Anal. Calcd for $C_{79}H_{100}O_7$: C, 81.68; H, 8.68. Found: C, 81.97; H, 8.57.

Optical Resolution. In order to optically resolve racemates we tested three chiral-packed HPLC columns: Daicel Chiralpak OP, Daicel Chiralpak AD, and Sumitomo Sumichiral. We found that Daicel Chiralpak AD shows satisfactory optical resolution ability for **4** (mobile phase, *n*-hexane−2-propanol = 98:2 (v/v)). We divided the eluent into two fractions and recovered one optical isomer from the first fraction and another optical isomer from the second fraction. Optically-resolved **4**: **4a** from the first fraction, mp >300 °C dec, recovery 50%, 100% ee (from HPLC analysis); **4b** from the second fraction, mp >300 °C dec, recovery 49%, 99% ee (from HPLC analysis).

Thermal Racemization. Enantiomer **4a** in various solvents was heated at 100 °C in an oil bath. The ee values were determined by an HPLC method (Daicel Chiralpak AD, mobile phase, *n*-hexane−2-propanol = 98:2 (v/v)). Even after 12 h, no production of another enantiomer **4b** was detected. The same result was obtained from thermal racemization of **4b**.

Miscellaneous. ^{1}H NMR, IR, and circular dichroism spectroscopic measurements were carried out with a JEOL GSX-400 spectrometer, a JASCO A-100 infrared spectrometer, and a JASCO spectropolarimeter J-720, respectively. HPLC experiments were performed on a JASCO PU-980 pump equipped with a JASCO UV-970 variable wavelength detector at a flow rate of 0.5 mL min^{-1} at room temperature and monitored at 254 nm.

JA953626B