J. Org. Chem. **1997,** *62,* 6441−6443

Synthesis and Structure of a Capped Calix[6]arene: Capping Calix[6]arene with 1,2,4,5-Tetrakis(bromomethyl)benzene

Kye Chun Nam,* Young Joo Choi, Dae Soon Kim, Jong Min Kim, and Jong Chul Chun

Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea

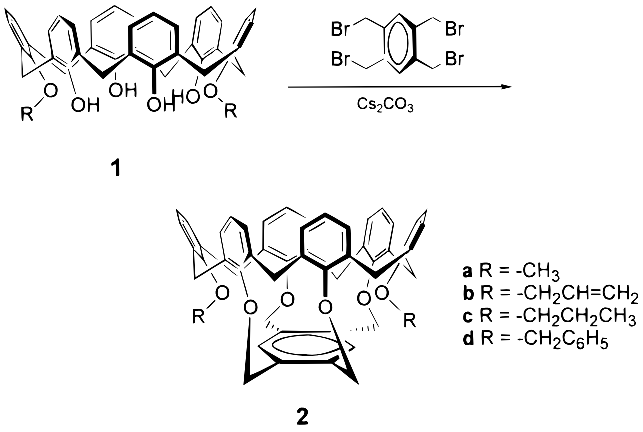
Received April 23, 1997

Introduction

Calixarenes[1] are a class of [1_n]cyclophanes possessing a cavity capable of accepting a guest molecule. In the calix[4]arenes the cavity size is such that only very small guests can enter, while in the calix[6]arenes it is larger and can allow larger guests[2−4] to be accepted. A basic rule for the precise recognition of guest molecules is that the host must have a rigid, well-defined cavity complementary in shape to that of the guest. The parent calixarenes, however, are conformationally mobile, and to make them immobile they must be altered in some fashion. One approach has been to introduce bulky groups[5−7] on the phenolic oxygens, which works very well with the calix[4]arenes but less well with the larger calix[6]arenes. A more effective approach in the latter case is to build a bridge at the lower or upper rim.[4,8−10] In 1993, Kanamathareddy and Gutsche[11] synthesized the first lower rim-bridged calix[6]arene using phenylene and durylene bridges. The first case, shown to be conformationally flexible, was O-methylation of the calix[6]arene bridged with a phenylene moiety producing a “self-anchored rotaxane” in which the phenylene group is threaded through the annulus of the calixarene. With the durylene bridge, however, a conformationally immobile cone conformer was established. More recently Otsuka *et al.*[12] reported a lower rim-bridged calix[6]arene with triple attachment via alkylation with 1,3,5-tris(bromomethyl)benzene.

Although ring inversion is, indeed, inhibited, the methylene protons of the mesitylenyl bridge were not observed as diastereotopic in the ^{1}H NMR spectrum, sufficient local conformational mobility remaining to make them equivalent on the ^{1}H NMR time scale.[8,12] Therefore, to obtain an even more rigid and well-defined cavity, a calix[6]arene bridged by quadruple attachment at the lower rim has been explored and is the subject of the present note.

Scheme 1



Results and Discussion

The bridging of the calix[6]arene was accomplished by first converting it to a 1,4-dialkyl ether[11,13] which was then treated with 1,2,4,5-tetrakis(bromomethyl)benzene in the presence of Cs$_2$CO$_3$ in dilute solution, as shown in Scheme 1. Reasonably good yields of 65−80% were obtained in spite of Shinkai’s observation[12] that steric crowding in calix[6]arenes bridged by triple attachment is so great that additional attachment should be difficult. This result suggests that the second, third, and fourth alkylations, which all are intramolecular, are much faster than the initial alkylation and that crowding at the lower rim is of less serious consequence than might have been thought.

Figure 1 shows the 2D COSY ^{1}H NMR spectrum of **2a** which confirms the correlation of the three pairs of doublets for the 20 methylene protons and 20 aromatic protons. It is known that the methylene protons (ArOCH$_2$Ar) in the capping durenyl group usually appear at lower magnetic fields than those in the calixarene bridge (ArCH$_2$Ar).[13,14] The usual coupling of the calixarene bridge methylene protons is about 17 Hz. The coupling of the A and B pairs is observed as 17.4 Hz, but the coupling of the C pair is 11.1 Hz. Hence, among the three pairs (A, B, and C in Figure 1), the C pair could be assigned to the ArOCH$_2$Ar methylene protons. The integration ratio of A and B pairs of doublets is 2:1; therefore the A pair should be assigned to the eight bridge methylene protons directly connected with the phenol ring containing the R group. The remaining B pair then could be assigned to the four methylene protons connecting two phenolic units bound to the durenyl cap.

In contrast to the calix[6]arene bridged by triple attachment (**4**),[9] the calix[6]arenes bridged by quadruple attachments (**2**) show the protons of the bridging methylene groups as two pairs of doublets that remain invariant upon heating up to 50 °C in CDCl$_3$. This is a consequence of the inherently diastereotopic relationships in a 2,3,5,6-tetrasubstituted calix[6]arene system in which no plane of symmetry passes through these methylene groups. The resonances arising from the aro-

---

(1) (a) Gutsche, C. D. Calixarenes. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: London, 1989. (b) *Calixarenes, A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745.

(2) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.

(3) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032.

(4) Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591.

(5) Araki, K.; Iwamoto, K.; Shinkai, S.; Mastanda, J. *Chem. Lett.* **1989**, 1747.

(6) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.

(7) Shinkai, S.; Arimura, T.; Kawabata, H.; Iwamoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2429.

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

(9) Takeshita, M.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1088.

(10) Saiki, T.; Goto, K.; Tokitoh, N.; Okazaki, R. *J. Org. Chem.* **1996**, *61*, 2924.

(11) Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572.

(12) Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862.

(13) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1993**, *115*, 6572.

(14) (a) Friedrich, E. C.; Runkle, K. G. *J. Chem. Educ.* **1984**, *61*, 830; (b) **1986**, *63*, 127.

S0022-3263(97)00729-9 CCC: $14.00

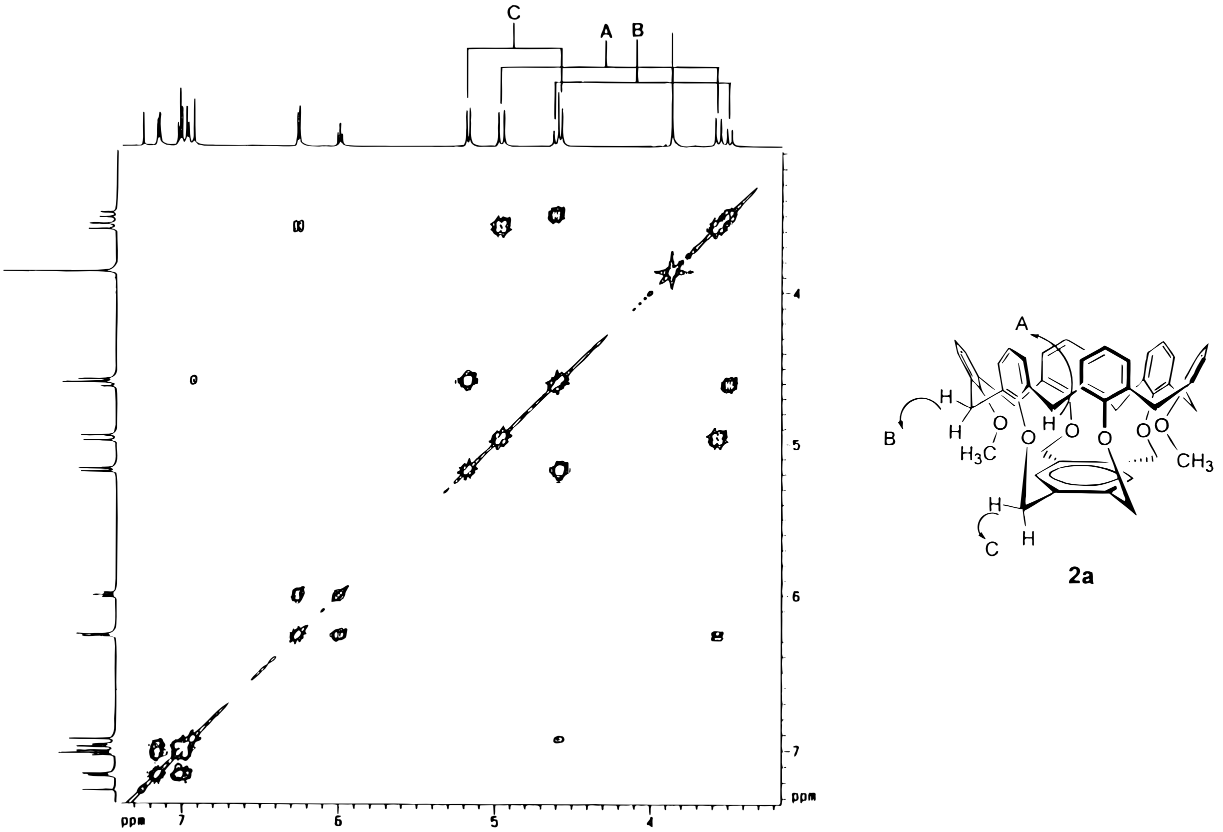
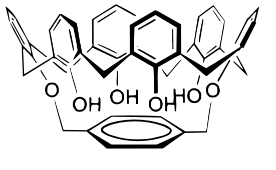
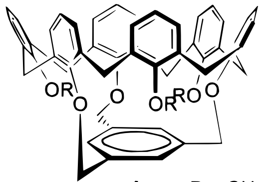


Figure 1. 2D COSY ^{1}H NMR (300 MHz) spectrum and correlation of the $ArCH_2Ar$ and $ArOCH_2Ar$ methylene protons in **2a**.

matic protons of the ArOR units of the calixarene appear as a triplet at 6.0 ppm and a doublet at 6.3 ppm. The upfield shift suggests that these moieties are tilted inward toward one another, bringing the Ar-H protons in closer proximity to the other aromatic rings of the cavity. The resonances of the other aromatic protons of the calixarene appear in the 6.9−7.2 ppm region. The resonance arising from the aromatic protons of the durenyl bridge in **2** appear as a singlet at 6.91 ppm, which is 0.94 and 0.62 ppm upfield from those observed for **3** and **4**, respectively. The resonances arising from the MeO protons of **2a** appear at 3.84 ppm which is close to those in **1a**, suggesting that there is little change in their environment upon adding the bridge. To investigate the effect of R groups for a capping reaction, three other substituents were tested such as allyl, propyl, and benzyl groups. The capping reaction with 1,2,4,5-tetrakis(bromomethyl)benzene proceeded without much difference regardless of the size of the R groups, suggesting that R groups were situated outward when the capping reaction took place.



3



4 R = CH_3

The present ^{1}H NMR studies demonstrate that the capped durenyl unit can inhibit the ring inversion of calix[6]arenes. The cavities provided by these capped calix[6]arenes should be rigid and conformationally well defined. We believe that they are useful for recognizing guest molecules. Further studies are currently under way in our laboratory.

Experimental Section[15]

Dialkylation of Calix[6]arene. The compounds **1a**−**1e** were synthesized by the procedure reported[13,16] previously.

Capping of Dialkylcalix[6]arene. Compound 2a. To a solution of 1.2 g (1.8 mmol) of **1a** and 4.7 g of Cs_2CO_3 in 700 mL of acetonitrile was added 1.0 g of 1,2,4,5-tetrakis(bromomethyl)benzene (2.2 mmol). The mixture was refluxed for 16 h, and the solvents were removed. The residue was treated with $CHCl_3$ and H_2O (each 250 mL), and the organic layer was separated and removed under reduced pressure. The residue was triturated with MeOH to give 1.0 g (66%) of **2a**: mp >197 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.14−6.90 (m, 14, ArH), 6.25 (d, 4, ArH with methoxy group, J = 7.5 Hz), 6.00 (t, 2, ArH with methoxy group), 5.18 (d, 4, $ArOCH_2-$, J = 11.1 Hz), 4.94 (d, 4, $ArCH_2Ar$, J = 17.4 Hz), 4.57 (d, 4, $ArOCH_2-$, J = 11.1 Hz), 4.55 (d, 2, $ArCH_2Ar$, J = 15.4 Hz), 3.54 (d, 4, $ArCH_2Ar$, J = 17.4 Hz), 3.48 (d, 2, $ArCH_2Ar$, J = 15.4 Hz), 3.67 (s, 6, $-OCH_3$); ^{13}C NMR ($CDCl_3$) δ 154.42, 153.03, 135.96, 135.73, 131.66, 130.83, 129.09, 126.12, 122.68, and 122.56 (Ar), 68.37 ($-OCH_2-$), 57.81 ($-OCH_3$), 33.72 and 29.65 ($ArCH_2Ar$); MS (FAB) m/z 790 (M^+). Anal. Calcd for $C_{54}H_{46}O_6CH_3OH$: C, 80.29; H, 6.08. Found: C, 80.58; H, 5.84.

Compound 2b. Following the same procedure described for **2a**, 1.1 g (72%) of **2b** was obtained: mp >234 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.20−6.96 (m, 14, ArH), 6.28 (d, 4, ArH with allyloxy group, J = 7.5 Hz), 6.02 (t, 2, ArH with allyloxy group, J = 7.5 Hz), 6.26 (m, 2, $-CH=$, partially hidden under the aromatic doublets at 6.28 ppm), 5.55−5.34 (2 m, 4, $=CH_2$), 5.19 (d, 4, $ArOCH_2-$, J = 11.1 Hz), 4.98 (d, 4, $ArCH_2Ar$, J = 17.4 Hz), 4.63

---

[15] Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. The melting points of all compounds were recorded on a Mel-Temp apparatus without calibration. Infrared (IR) spectra were determined on a FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a 300 MHz spectrometer. Thin layer chromatography (TLC) analyses were carried out on silica gel plates.

[16] Nam, K. C.; Park, K. S. *Bull. Korean Chem. Soc.* **1995**, *16*, 153.

(d, 2, $ArCH_2Ar$, $J = 15.5$ Hz), 4.61 (d, 4, $ArOCH_2-$, $J = 11.1$ Hz), 3.56 (d, 4, $ArCH_2Ar$, $J = 17.4$ Hz), 3.50 (d, 2, $ArCH_2Ar$, $J = 15.5$ Hz), 4.46 (d, 4H, $-OCH_2-$); ^{13}C NMR ($CDCl_3$) δ 153.56, 153.00, 135.96, 135.69, 134.30, 131.98, 131.67, 130.96, 130.81, 129.08, 126.14, 122.70, 122.55, and 117.37 (Ar and $-CH{=}CH_2$), 73.44 and 68.37 ($-OCH_2-$), 33.70 and 30.12 ($ArCH_2Ar$); MS (FAB) m/z 840 (M^+). Anal. Calcd for $C_{58}H_{50}O_6CH_3OH$: C, 81.01; H, 6.18. Found: C, 81.18; H, 5.72.

Compound 2c. Following the same procedure described for **2a**, 1.0 g (65%) of **2c** was obtained: mp >210 °C dec; ^1H NMR ($CDCl_3$) δ 7.17−6.95 (m, 14, ArH), 6.26 (d, 4, ArH with propyloxy group, $J = 7.5$ Hz), 5.98 (t, 2, ArH with propyloxy group, $J = 7.5$ Hz), 5.20 (d, 4, $ArOCH_2-$, $J = 11.1$ Hz), 4.94 (d, 4, $ArCH_2Ar$, $J = 17.4$ Hz), 4.60 (d, 2, $ArCH_2Ar$, $J = 15.5$ Hz), 4.59 (d, 4, $ArOCH_2-$, $J = 11.1$ Hz), 3.54 (d, 4, $ArCH_2Ar$, $J = 17.4$ Hz), 3.48 (d, 2, $ArCH_2Ar$, $J = 15.5$ Hz), 3.86 (t, 4, $-OCH_2-$, $J = 6.6$ Hz), 1.97 (m, 4, $-CH_2-$), 1.18 (t, 6, $-CH_3$, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 153.65, 153.02, 135.97, 135.68, 132.01, 131.82, 130.91, 130.82, 129.04, 126.09, 122.55, and 122.48 (Ar), 74.00 and 68.42 ($-OCH_2-$), 33.71 and 30.00 ($ArCH_2Ar$), 23.74 and 10.89 ($-CH_2CH_3$); MS (FAB) m/z 846 (M^+). Anal. Calcd for $C_{58}H_{54}O_6CH_3OH$: C, 80.64; H, 6.15. Found: C, 78.62; H, 6.16.

Compound 2d. Following the same procedure described for **2a**, 0.7 g (40%) of **2d** was obtained after 36 h of refluxing in acetonitrile: mp >203 °C dec; ^1H NMR ($CDCl_3$) δ 7.63−6.95 (m, 24, ArH), 6.30 (d, 4, ArH with benzyloxy, $J = 7.6$ Hz), 6.03 (t, 2, ArH with benzyloxy, $J = 7.6$ Hz), 5.15 (d, 4, $ArOCH_2-$, $J = 11.1$ Hz), 5.03 (d, 4, $ArCH_2Ar$, $J = 17.4$ Hz), 4.59 (d, 2, $ArCH_2Ar$, $J = 15.2$ Hz), 4.57 (d, 4, $ArOCH_2-$, $J = 11.1$ Hz), 3.53 (d, 4, $ArCH_2Ar$, $J = 17.4$ Hz), 3.48 (d, 2, $ArCH_2Ar$, $J = 15.2$ Hz), 4.94 (s, 4, $-OCH_2-$); ^{13}C NMR ($CDCl_3$) δ 153.34, 153.02, 137.66, 135.96, 135.67, 131.63, 131.05, 130.85, 129.12, 128.59, 128.33, 128.10, 127.59, 126.29, 122.84, and 122.57 (Ar), 74.23 and 68.43 ($-OCH_2-$), 33.71 and 30.12 ($ArCH_2Ar$); MS (FAB) m/z 942 (M^+). Anal. Calcd for $C_{66}H_{54}O_6CH_3OH$: C, 82.25; H, 5.95. Found: C, 82.37; H, 5.61.

Acknowledgment. We are indebted to the Basic Science Research Institute Program, Ministry of Education of Korea (BSRI 96-3429) for generous support of this work. Special thanks are expressed to Professor David Gutsche for his helpful discussion on this work.

JO970729Z