

## A,C-Bridged Calix[6]arene: Relationship between the Length of Bridge and Conformation

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Three new A,C-diamide bridged *p*-*tert*-butylcalix[6]arenes were synthesized from *p*-*tert*-butylcalix[6]arenes by bridging ClCH<sub>2</sub>CONH(CH<sub>2</sub>)<sub>n</sub>NHCOCH<sub>2</sub>Cl (*n*=3, 4, 6) in acetonitrile using K<sub>2</sub>CO<sub>3</sub> as a base in 17%—25% yields. It was found that the bridged calix[6]arenes with shorter bridges (*n*=2, 3, 4 in *N,N'*-bischloroacetodiamines) adopt cone conformation, but the last one (*n*=6) adopts alternate conformation, *i.e.*, accompanying the lengthening of bridge, the conformation of A,C-bridged calix[6]arenes changes from cone to alternate.

**Keywords** calixarene, calix[6]arene, conformation, bridging, diamide bridge

### Introduction

Calixarenes are a class of host molecules with a three dimensional cavity which can recognize guest molecules. Owing to the limitedly restricted rotation about the  $\sigma$  bonds of the Ar-CH<sub>2</sub>-Ar groups, calixarenes possess a lot of conformers. A rigid, conformationally defined calixarene is essential for recognizing guest molecules selectively. For calix[4]arenes, which are composed of four phenolic units with four possible basic conformations, this task is easily realized by introducing substituents bulkier than ethyl onto the lower-rim of calix[4]arene.

As for calix[6]arenes, which possess six phenolic units and at least eight basic conformations. It is not the case. As the conformational interconversion can occur not only via the oxygen through the annulus but also by the *para*-substituent through the annulus pathway, it is difficult to immobilize the conformation of calix[6]arene simply by introducing bulky substituents, even if the substituents are as bulky as chloesteryl group.<sup>1</sup> The more sites (six hydroxyl groups) being attacked and greater conformational flexibility of calix[6]arenes caused much difficulty in selective functionalization and immobilization of conformation.

An effective route to freeze the conformation of calix[6]arene is bridging of two phenolic rings. To distinguish which phenolic rings being linked, the phenolic rings are numbered by letters A, B, C, D, E, F instead of 1, 2, 3, 4, 5, 6 used in old literatures. Three kinds of bridged calix[6]arenes are possible: A,B-bridged, A,C-bridged and A,D-bridged. It was reported that the calix[6]arene bridged on A,D-phenolic rings could slow the ring inversion, and it is also the case for A,B-bridged one, whereas in the case of calix[6]arene bridged on A,

C-phenolic rings, ring inversion was virtually suppressed because of destabilization of the transitional state.<sup>2</sup> It is to say that the A,C-bridging is the most effective method to immobilize the conformation of bridged calix[6]arene.

There are a few papers concerning the A,C-bridging of calix[6]arene. The first example, 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetramethoxy-40,42-*m*-xylynyloxy-calix[6]arene, in cone conformation was reported by Shinkai *et al.*<sup>2</sup> in 1995 as mentioned above. Another example, 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetramethoxy-40,42-*m*-(4'-methoxyxylynyloxy)-calix[6]arene was reported in the next year, which was also in cone conformation.<sup>3</sup> The latter work has attracted much attention as providing a non-spectral methodology to obtain unambiguous evidence for the immobilization of the conformation of the calix[6]arene. It should be noted that the above mentioned A,C-bridged calix[6]arenes were synthesized constrainedly by the reaction of  $\alpha,\alpha'$ -dibromo-*m*-xylenes with the corresponding tetrasubstituted calix[6]arene. If  $\alpha,\alpha'$ -dibromo-*m*-xylene reacted with unsubstituted calix[6]arene, *i.e.*, *p*-*tert*-butylcalix[6]arene itself, only the A,D-bridged product was obtained. However, using pyridine-2,6-dicarboxylic acid dichloride instead of  $\alpha,\alpha'$ -dibromo-*m*-xylene, the A,C-bridged calix[6]arene could be obtained in 24% yield.<sup>4</sup> The first A,C-bridged calix[6]arene possessing a long and flexible chain, *i.e.*, *p*-*tert*-butylcalix[6]-crown-3, was prepared by reacting *p*-*tert*-butylcalix[6]arene with diethylene glycol ditosylate in 1999.<sup>5</sup> A,C-*p*-*tert*-Butylcalix[6]crown-4 and A,C-*p*-*tert*-butylcalix[6]-crown-5 have also been synthesized.<sup>6</sup>

Recently, it has been found that the condensation of

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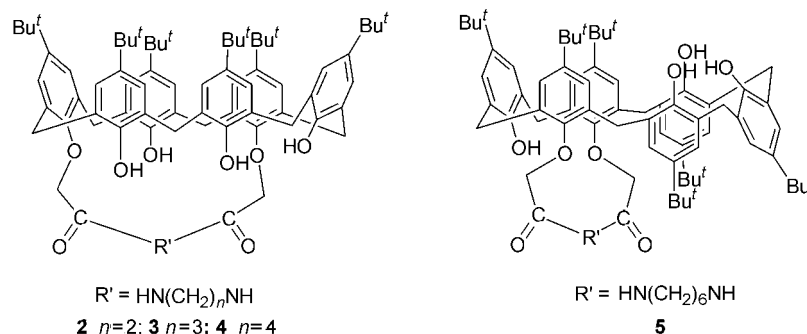
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*N,N'*-bis-(chloromethylcarbonyl)ethylenediamine with *p*-*tert*-butylcalix[6]arene (**1**) proceeded smoothly and the A,C-bridgedcalix[6]arene, *p*-*tert*-butyl-1,3-[oxy-(2', 7'-dioxo-3',6'-diazaoctamethylene)oxy]calix[6]arene (**2**) existing in cone conformation was obtained selectively in 35% yield.<sup>7</sup> In this paper, the condensation of ClCH<sub>2</sub>-CONH(CH<sub>2</sub>)<sub>n</sub>NHCOC-H<sub>2</sub>Cl (*n*=3, 4, 6) with *p*-*tert*-butylcalix[6]arene (**1**) is reported. It is the first example of A,C-bridged calix[6]arene existing in defined 1,2,3-alternate conformation (Figure 1 and Scheme 1).

## Results and discussion

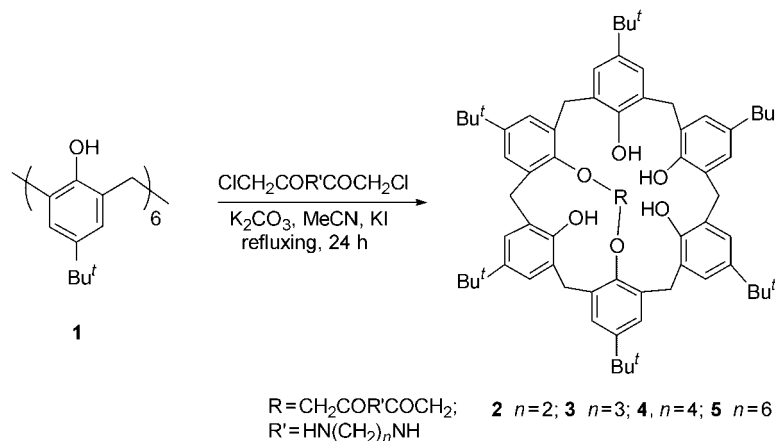
The structures of **2**–**5** were characterized by FAB-MS, elemental analyses and <sup>1</sup>H NMR spectra. The <sup>1</sup>H NMR spectrum of **3** shows four singlets in a 2 : 1 : 2 : 1 ratio at  $\delta$  1.31, 1.29, 1.24 and 1.12 for the *tert*-butyl groups, indicating that the calixarene moiety of **3** is A,C-bridged. Three pairs of doublets in a 1 : 1 : 1 ratio in the  $\delta$  4.7–3.3 region, in accord with three sets of nonequivalent ArCH<sub>2</sub>Ar groups, or three sets of AB system, support that **3** adopts cone (*syn*-) conformation at ambient temperature. The <sup>1</sup>H NMR spectrum of **4** is similar. Four singlets in a ratio of 1 : 2 : 2 : 1 at  $\delta$  1.30, 1.29, 1.21 and 1.01, and three pairs of doublets in a ratio of 1 : 1 : 1 in the  $\delta$  4.8–3.4 region, in accord with three sets of nonequivalent ArCH<sub>2</sub>Ar groups, support **4**

being A,C-bridged and adopting cone (*syn*-) conformation at ambient temperature too. This is not the case for compound **5**. In the <sup>1</sup>H NMR spectrum of **5**, four singlets in a 1 : 2 : 2 : 1 ratio at  $\delta$  1.39, 1.33, 1.11 and 0.85 for the *tert*-butyl groups, also indicate the compound being A,C-bridged. However, The signal pattern in the diarylmethylene region shows two pairs of doublets and one singlet in a ratio of 1 : 1 : 1. It is known that a doublet for the methylene hydrogen atoms means that the aryl groups are *syn* to each other, and the two hydrogen atoms situates various chemical environment, coupled each other to construct an AB quartets. On the other hand, a singlet for the methylene hydrogen atoms indicates that the aryl groups are *anti* to each other resulting in the two methylene hydrogen atoms with a similar environment, and no couple exists between the hydrogen atoms.<sup>2,3</sup> Thus, it should be postulated that **5** exists in 1,2,3-alternate conformation at ambient temperature. Furthermore, in comparison with signals of NCH<sub>2</sub> and C(CH<sub>2</sub>)<sub>n</sub>C in compounds **2**–**5** ( $\delta$  3.60, 3.60, 3.58, 3.46 for protons in NCH<sub>2</sub>: none,  $\delta$  1.30, 1.29, 1.20 for protons in C(CH<sub>2</sub>)<sub>n</sub>C, respectively), remarkably up-field shifts were found from compound **4** to compound **5**. This is also in agreement with that the conformation has changed from cone to 1,2,3-alternate one, *i.e.*, the bridge is threaded through the annulus of the macro ring system.<sup>2,8,9</sup>



**Figure 1** Conformations of A,C-diamide-bridged calix[6]arenes.

## Scheme 1 Synthesis of A,C-diamide-bridged calix[6]arene



The conversion of conformation from cone to alternate is often accompanied with methylation of A,D-bridged calixarenes in cone conformation.<sup>9</sup> Opposite example is also known.<sup>10</sup> It is seldom reported that lengthening the bridge causes change of conformation from cone to alternate. An example could be found for A,D-bridged calix[6]arenes recently. It was reported that *p*-*tert*-butylcalix[6]-1,4-crown-3 adopts a special flattened cone conformation,<sup>6</sup> *p*-*tert*-butylcalix[6]-1,4-crown-4 adopts a cone conformation,<sup>6</sup> and *p*-*tert*-butylcalix[6]-1,4-crown-5 adopts an alternate conformation.<sup>10</sup> Although similar A,C-calix[6]crowns have been prepared, and *p*-*tert*-butylcalix[6]crown-3 adopts cone conformation, but no defined conformations of *p*-*tert*-butylcalix[6]crown-4 and *p*-*tert*-butylcalix[6]crown-5 can be postulated from their <sup>1</sup>H NMR spectra.<sup>6</sup> Thus, it is the first time to report that A,C-bridged calix[6]arene can adopt a defined alternate conformation, and lengthening the bridge can convert the conformation of A,C-bridged calix[6]arene from cone to alternate.

## Experimental

$\text{ClCH}_2\text{CONH}(\text{CH}_2)_n\text{NHCOCH}_2\text{Cl}$  ( $n=2, 3, 4, 6$ ) were prepared according to the reported method.<sup>11</sup> Melting points are uncorrected. <sup>1</sup>H NMR spectra were recorded on Bruker-ARX 300 instruments at ambient temperature. TMS was used as an internal standard. FAB-MS was obtained from a Kratos MS80RF mass spectrometry service, with *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were performed by the Analytical Laboratory of the Department of Chemistry. Precoated silica gel plates (G60) were used for analytical TLC. All other chemicals are of analytically pure and used without further purification.

### Preparation of 2,3,4,5(A,C-diamide-bridged *p*-*tert*-butyl-calix[6]arene)

**General procedure** A mixture of *p*-*tert*-butylcalix[6]arene (3 mmol) and  $\text{ClCH}_2\text{CONH}(\text{CH}_2)_n\text{NHCOCH}_2\text{Cl}$  ( $n=2, 3, 4, 6$ ) (3 mmol) in dry  $\text{CH}_3\text{CN}$  (250 mL) was refluxed under nitrogen atmosphere in the presence of  $\text{K}_2\text{CO}_3$  (7 mmol) and KI (6 mmol) for 24 h. After the evaporation of  $\text{CH}_3\text{CN}$  under reduced pressure, a portion of 100 mL of  $\text{CH}_2\text{Cl}_2$  was added and the organic phase was washed with water ( $2 \times 100$  mL) and dried over  $\text{MgSO}_4$ . The solvent was evaporated and the crude product was purified by column chromatography (silica gel,  $\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH} = 50 : 1, V : V$ ) and recrystallized from  $\text{CHCl}_3 : \text{CH}_3\text{OH}$ .

**5,11,17,23,29,35-Hexa-*tert*-butyl-38,40,41,42-tetrahydroxy-37,39-[oxy(2',7'-dioxo-3',6'-diazaoctamethylene)oxy]calix[6]arene (2)** <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.15 [(s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.23 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 1.29 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.31 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 3.45 (d,  $J=13.8$  Hz, 4H, ArCH<sub>2</sub>Ar), 3.56—3.60 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>N), 3.80 (d,  $J=13.8$  Hz, 4H, ArCH<sub>2</sub>Ar), 4.34

(d,  $J=14.1$  Hz, 2H, ArCH<sub>2</sub>Ar), 4.40 (d,  $J=7.2$  Hz, 2H, OCH<sub>2</sub>), 4.48 (d,  $J=7.2$  Hz, 2H, OCH<sub>2</sub>), 4.65 (d,  $J=14.1$  Hz, 2H, ArCH<sub>2</sub>Ar), 7.01 (s, 4H, ArH), 7.20 (s, 8H, ArH), 7.26 (s, 4H, ArOH), 8.40 (bs, 2H, NH). The data were cited from literature 7 for comparison.

**5,11,17,23,29,35-Hexa-*tert*-butyl-38,40,41,42-tertahydroxy-37,39-[oxy(2',8'-dioxo-3',7'-diazanona-methylene)oxy]calix[6]arene (3)**  $R_f=0.3$  (TLC,  $\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH}=50 : 1, V : V$ ), yield 25%, m.p. 258 °C (dec.). <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.12 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.24 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 1.29 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.30 [overlap, 2H, CH<sub>2</sub>(CH<sub>2</sub>NH)<sub>2</sub>], 1.31 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 3.38 (d,  $J=13.8$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.44 (d,  $J=14.1$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.51 (d,  $J=14.7$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.60—3.80 (m, 4H, NCH<sub>2</sub>), 4.17 (d,  $J=13.8$  Hz, 2H, ArCH<sub>2</sub>Ar), 4.34 (d,  $J=14.1$  Hz, 2H, ArCH<sub>2</sub>Ar), 4.38 (d,  $J=6.0$  Hz, 2H, OCH<sub>2</sub>), 4.46 (d,  $J=6.0$  Hz, 2H, OCH<sub>2</sub>), 4.65 (d,  $J=14.7$  Hz, 2H, ArCH<sub>2</sub>Ar), 6.95 (s, 2H, ArH), 7.02 (d,  $J=2.4$  Hz, 2H, ArH), 7.06 (d,  $J=2.1$  Hz, 2H, ArH), 7.09 (d,  $J=2.1$  Hz, 2H, ArH), 7.12 (d,  $J=2.4$  Hz, 2H, ArH), 7.16 (s, 3H, ArH and one ArOH), 7.21 (s, 2H, ArOH), 7.30 (s, 1H, ArOH), 8.34 (bs, 2H, NH); MS (FAB)  $m/z$ : 1126 [ $\text{M}^+$ ]. Anal. calcd for C<sub>73</sub>H<sub>94</sub>N<sub>2</sub>O<sub>8</sub>: C 77.76, H 8.40, N 2.48; found C 77.46, H 8.50, N 2.34.

**5,11,17,23,29,35-Hexa-*tert*-butyl-38,40,41,42-tertahydroxy-37,39-[oxy(2',9'-dioxo-3',8'-diazadecamethylene)oxy]calix[6]arene (4)**  $R_f=0.34$  (TLC,  $\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH}=50 : 1, V : V$ ), yield 22%, m.p. 258 °C (dec.). <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.01 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.21 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 1.288 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 1.29 [overlap, 4H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>NH)<sub>2</sub>], 1.30 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 3.42 (d,  $J=14.1$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.44 (d,  $J=13.8$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.46 (d,  $J=14.4$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.58—3.60 (m, 4H, NCH<sub>2</sub>), 4.29 (d,  $J=14.1$  Hz, 2H, ArCH<sub>2</sub>Ar), 4.34 (d,  $J=13.8$  Hz, 2H, ArCH<sub>2</sub>Ar), 4.40 (d,  $J=5.7$  Hz, 2H, OCH<sub>2</sub>), 4.46 (d,  $J=5.7$  Hz, 2H, OCH<sub>2</sub>), 4.80 (d,  $J=14.4$  Hz, 2H, ArCH<sub>2</sub>Ar), 6.85 (s, 2H, ArH), 6.98 (d,  $J=2.4$  Hz, 2H, ArH), 7.02 (d,  $J=2.1$  Hz, 2H, ArH), 7.04 (d,  $J=2.4$  Hz, 2H, ArH), 7.12 (d,  $J=2.1$  Hz, 2H, ArH), 7.11 (s, 2H, ArH), 7.21 (s, 2H, ArOH), 7.30 (s, 2H, ArOH), 8.45 (bs, 2H, NH); MS(FAB)  $m/z$ : 1141 [ $\text{M}+\text{H}^+$ ]. Anal. calcd for C<sub>74</sub>H<sub>96</sub>N<sub>2</sub>O<sub>8</sub>: C 77.86, H 8.48, N 2.45; found C 77.56, H 8.37, N 2.31.

**5,11,17,23,29,35-Hexa-*tert*-butyl-38,40,41,42-tertahydroxy-37,39-[oxy(2',11'-dioxo-3',10'-diazadodecamethylene)oxy]calix[6]arene (5)**  $R_f=0.67$  (TLC,  $\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH}=50 : 1, V : V$ ), yield 17%, m.p. 278 °C (dec.); <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 0.85 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 1.11 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 1.20—1.26 [m, 8H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>NH)<sub>2</sub>], 1.33 [s, 18H, C(CH<sub>3</sub>)<sub>3</sub>], 1.39 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 3.40 (d,  $J=13.8$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.46—3.50 (m, 4H,  $2 \times \text{NCH}_2$ ), 3.75 (d,  $J=15.6$  Hz, 2H, ArCH<sub>2</sub>Ar), 3.99 (s, 4H, ArCH<sub>2</sub>Ar), 4.14 (d,  $J=13.8$  Hz, 2H, ArCH<sub>2</sub>Ar), 4.21 (d,  $J=15.6$  Hz, 2H, ArCH<sub>2</sub>Ar), 4.45 (d,  $J=6.6$  Hz, 2H, OCH<sub>2</sub>), 4.49 (d,  $J=6.6$  Hz, 2H, OCH<sub>2</sub>), 6.50 (bs, 1H, NH), 6.67 (s, 2H,

ArH), 6.77 (s, 2H, ArH), 7.03 (s, 4H, ArH), 7.07 (s, 2H, ArH), 7.13 (s, 2H, ArH), 7.20 (s, 2H, ArOH), 7.27 (s, 2H, ArOH), 8.05 (bs, 1H, NH); MS(FAB)  $m/z$ : 1168 [ $M^+$ ]. Anal. calcd for  $C_{76}H_{100}N_2O_8$ : C 78.04, H 8.62, N 2.40; found C 78.14; H 8.55; N 2.28.

## References

- 1 Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713.
- 2 Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862.
- 3 Otsuki, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271.
- 4 Ross, H.; Lüning U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2555.
- 5 Chen, Y.-Y.; Li, J.-S.; Xin, J.; Zhong, Z.-L.; Gong, S.-L.; Lu, X.-R. *Synth. Commun.* **1999**, *29*, 705.
- 6 Li, J.-S.; Chen, Y.-Y.; Lu, X.-R. *Tetrahedron* **1999**, *55*, 10365.
- 7 Chen, Y.-K.; Chen, Y.-Y. *Org. Lett.* **2000**, *2*, 743.
- 8 Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160.
- 9 Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572.
- 10 Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591.
- 11 Speziale, A. J. *US 2 864 684*, **1958** [*Chem. Abstr.* **1960**, *54*, 2006.]

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