

# Diamide Bridged Calix[8]arenes

Jun Li, Wei Wang, Shuling Gong, Yuanyin Chen,\* Xiaojun Wu

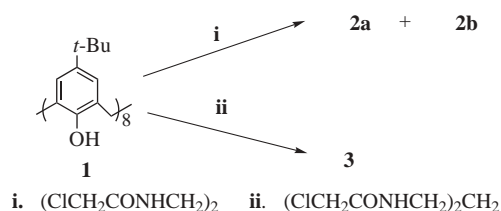
Department of Chemistry, Wuhan University, Wuhan 430072, P. R. China  
Fax +86(27)87647617; E-mail: yychen@whu.edu.cn

Received 21 October 2003

**Abstract:** 1,5-Diamide-bridged and 1,3;5,7-doubly diamide-bridged calix[8]arene were obtained by reacting *p*-*tert*-butylcalix[8]arene with *N,N'*-bis(chloroacetyl)alkylenediamine using  $K_2CO_3$  as a base in acetone.

**Key words:** calixarenes, macrocycles, amines, regioselectivity

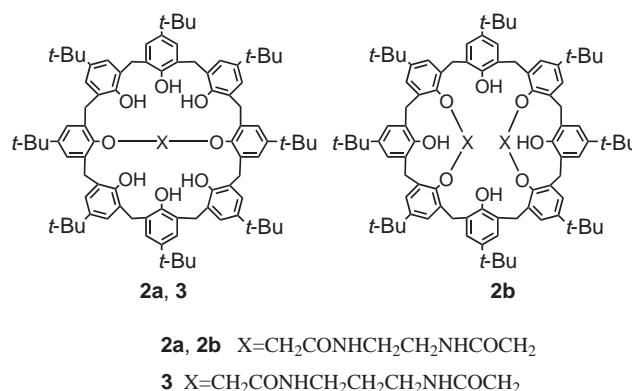
It is well known that the intramolecular bridging of calix[8]arenes is an efficient route to immobilize the conformation, or to at least reduce the conformational mobility.<sup>1</sup> In the last decade, much work has appeared along this line, especially for regioselective bridging at the lower rim.<sup>1,2</sup> In 1994, Neri et al. reported the first example of singly-bridged calix[8]arenes by alkylation of 1,3;5,7-tetrasubstituted calix[8]arenes with 1,4-bis(bromomethyl)benzene.<sup>3</sup> Shinkai et al. synthesized several arene-bridged calix[8]arenes by NaH-promoted direct alkylation of *p*-*tert*-butylcalix[8]arene with various bis(bromomethyl)arenes.<sup>4</sup> Direct alkylation of *p*-*tert*-butylcalix[8]arene with oligoethylene glycol ditosylates gave calix[8]crowns-n, and the bridging pattern depended on the nature of the base used.<sup>5,6</sup> Using oligoethylene glycol bischloroacetates in place of oligoethylene glycol ditosylates, a series of ester-containing 1,2-bridged calix[8]crowns have been obtained in reasonable yields.<sup>7</sup> Other diester bridged *p*-*tert*-butylcalix[8]arenes were obtained from *p*-*tert*-butylcalix[8]arene by reacting with adipoyl chloride in the presence of NaH.<sup>8</sup> As for doubly-bridged *p*-*tert*-butylcalix[8]arenes, with two identical bridging elements, there are twenty-two possible regioisomers.<sup>2</sup> Only a few of them are known. For example, 1,3;5,7-, 1,5;3,7-, as well as 1,4;2,5-, 1,4;5,8- etc. doubly-bridged calix[8]arenes.<sup>1,4,9–11</sup>



**Scheme 1** Reaction conditions:  $K_2CO_3$ /acetone, KI, reflux, 24 h

Amide-containing calix[4]arenes have been investigated extensively, and those compounds can selectively recognize cations and anions (via hydrogen bonds).<sup>12</sup> Amide-bridged calixarenes can be reduced to calixazacrowns by  $LiAlH_4$ .<sup>13</sup> Recently, we have synthesized a 1,3-diamide bridged calix[6]arene and an asymmetrical 1,3;4,5-doubly bridged derivative by reacting *p*-*tert*-butylcalix[6]arene with *N,N'*-bis(chloroacetyl)ethylenediamine.<sup>14</sup> As an extension of the above work and to prepare calix[8]azacrown, the reaction of such a reagent and its homologue, *N,N'*-bis(chloroacetyl)propylenediamine with *p*-*tert*-butylcalix[8]arene was investigated, and 1,5-diamide bridged *p*-*tert*-butylcalix[8]arenes and a 1,3;5,7-doubly diamide bridged *p*-*tert*-butylcalix[8]arene were obtained. (Scheme 1) The results are presented in the following.

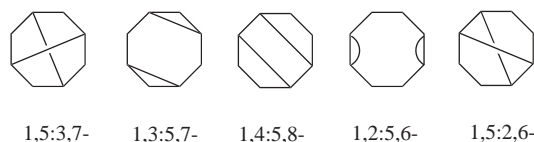
Reaction of *p*-*tert*-butylcalix[8]arene **1** with *bis*(chloroacetyl)ethylenediamine (1.38 equiv) in the presence of  $K_2CO_3$  (3 equiv) and KI (2.76 equiv) in acetone, under reflux, gave 1,5-diamide bridged *p*-*tert*-butylcalix[8]arene **2a** in 40% yield along with a 1,3;5,7-doubly-bridged compound **2b** in 10% yield. Using *N,N'*-bis(chloroacetyl)propylenediamine in place of *N,N'*-bis(chloroacetyl)ethylenediamine, 1,5-bridged product **3** was obtained in 10% yield, and no doubly-bridged compound was formed (Figure 1).



**Figure 1**

Their structures were characterized by FAB-MS spectra,  $^1H$  NMR spectra and  $^{13}C$  NMR spectra.<sup>15</sup> The  $^1H$  NMR spectrum of **2a** shows three singlets at  $\delta = 1.22, 1.25, 1.26$  for the *tert*-butyl (ratio 1:2:1) and the  $^{13}C$  NMR spectrum shows six signals at 143.27, 143.73, 144.38, 147.46, 148.49, 149.55 in the region of 140–155 ppm ascribing to aromatic carbons bearing either an oxygen or a *tert*-butyl

group, which certainly indicates that the *p*-*tert*-butyl-calix[8]arene is intramolecularly bridged by a diamide spacer at 1,5-positions.<sup>5,6</sup> This is further proved by the MS datum (FAB–MS:  $m/z = 1437$ ) and the peaks of hydroxyl appeared at 8.40 and 8.75 in a ratio of 1:2.<sup>16</sup> Two broad single singlets ( $\delta = 3.86, 3.69$ ) for  $\text{ArCH}_2\text{Ar}$  methylene protons and no discriminated doublets being observed indicate that the ring inversion is not inhibited. The structure of **3** is similarly deduced.



**Figure 2** Five doubly bridged calix[8]arenes with higher symmetry

The presence of two bridges for compound **2b** is deduced from FAB–MS spectrum, which shows a protonated molecular ion peak at  $m/z = 1577$ . Three singlet for the *tert*-butyl at 1.16, 1.18 and 1.25 in a ratio of 1:1:2, a single singlet for  $\text{NCH}_2\text{CH}_2\text{N}$  ( $\delta = 3.64$ ), a single singlet for  $\text{OCH}_2\text{CO}$  ( $\delta = 4.35$ ) in  $^1\text{H}$  NMR spectrum as well as a singlet appearing at  $\delta = 169.23$  for the C of carbonyl in the  $^{13}\text{C}$  NMR spectrum indicate that the compound possesses high symmetry. There are twenty-two possible regioisomers when introducing two identical bridging elements in the calix[8]arene skeleton, seven of them being completely asymmetric, ten with a single symmetry element and remaining five with higher symmetry as shown in Figure 2.

It is clear that only the 1,3:5,7-isomer possesses three kinds of *tert*-butyl and in a ratio of 1:1:2. The 1,3:5,7-structure is also evidenced by the presence of six signals for aromatic carbons bearing oxygen or *tert*-Bu groups, three singlets for three types of oxygen-bearing carbons ( $\delta = 149.55, \text{C-OR}, 149.43, \text{C-OH}, 149.12, \text{C-OH}$ ) and three singlets for three types of the *tert*-Bu-bearing aromatic carbons ( $\delta = 148.57, 143.42, 143.09$ ) in the  $^{13}\text{C}$  NMR spectrum. Again, a sharp singlet at  $\delta = 3.90$  and a broad singlet at 3.79 for  $\text{ArCH}_2\text{Ar}$  imply that double bridges still cannot inhibit the mobility of calix[8]arene ring. Two sharp singlets for  $\text{ArCH}_2\text{Ar}$  are observed from temperature of 343 K and higher in  $\text{CDCl}_3$ . And when temperature is below 243 K, only broader signals can be observed, which means **2b** exists as possible mixture of conformers.

$\text{Cs}_2\text{CO}_3$  and NaH are generally used in the synthesis of 1,5-isomer.<sup>4–6,17</sup> However, using these bases in the reaction, either calix[8]arene remains unchanged or the products are too complex to be separated. Increasing of  $\text{K}_2\text{CO}_3$  to 8 equivalents has no remarkable effect on the distribution of products.

To test this potentiality two-phase picrate extraction and  $^1\text{H}$  NMR experiments were performed. In both cases, none of compounds **2a**, **2b** and **3** showed noteworthy complexing properties for  $\text{Cs}^+$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ , or  $\text{Zn}^{2+}$  ions.

## Acknowledgment

Financial supports from the National Natural Science Foundation of China (20272044) and Wangguoqi & Luoqinghua Foundation of Wuhan University are gratefully acknowledged.

## References

- (1) Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, 36, 5429.
- (2) Neri, P.; Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Piattelli, M. *Calixarenes 2001*; Asfari, Z.; Bohmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, **2001**, Chap. 5, 89.
- (3) Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917.
- (4) Ikeda, A.; Akao, K.; Harada, T.; Shinkai, S. *Tetrahedron Lett.* **1996**, 37, 1621.
- (5) Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, 37, 3899.
- (6) Geraci, C.; Piattelli, M.; Chessari, G.; Neri, P. *J. Org. Chem.* **2000**, 65, 5143.
- (7) Yang, F. F.; Chen, Y. Y. *Eur. J. Org. Chem.* **2001**, 365.
- (8) Consoli, G. M. L.; Geraci, C.; Cunsolo, F.; Neri, P. *Tetrahedron Lett.* **2003**, 44, 53.
- (9) Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, 37, 715.
- (10) Ikeda, A.; Suzuki, Y.; Shinkai, S. *Tetrahedron: Asymmetry* **1998**, 9, 97.
- (11) Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, 37, 7627.
- (12) (a) Bohmer, V.; Ferguson, G.; John, F. *J. Chem. Soc., Perkin Trans 1* **1993**, 1521. (b) Beer, P. D.; Drew, M. G. B.; Hazlewood, C. *J. Chem. Soc., Chem. Commun.* **1993**, 229.
- (13) Zheng, Q. Y.; Chen, C. F.; Huang, Z. T. *Chin. J. Chem.* **2000**, 18, 104.
- (14) Chen, Y. K.; Chen, Y. Y. *Org. Lett.* **2000**, 2, 743.
- (15) **General Procedure for Preparation of Compound 2a, 2b and 3:** To a suspension of compound **1** (2 mmol) and  $\text{K}_2\text{CO}_3$  (6 mmol) in acetone (250 mL) were added appropriate bridging agent (2.76 mmol) and KI (5.52 mmol). The mixture was stirred at 58 °C for 24 h. After concentration under vacuum, the residue was triturated with HCl, collected by filtration, washed with MeOH and dried. Compound **2a**, **2b** and **3** were isolated by chromatograph on silica gel (eluent:  $\text{CH}_2\text{Cl}_2$ –MeOH). Compound **2a**: Mp >270 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta = 1.22$  [s, 18 H,  $(\text{CH}_3)_3$ ], 1.25 [s, 36 H,  $(\text{CH}_3)_3$ ], 1.26 [s, 18 H,  $(\text{CH}_3)_3$ ], 3.56 (s, 4 H,  $\text{NCH}_2\text{CH}_2\text{N}$ ), 3.86 (br s, 12 H,  $\text{ArCH}_2\text{Ar}$ ), 3.96 (br s, 4 H,  $\text{ArCH}_2\text{Ar}$ ), 4.31 (s, 4 H,  $\text{OCH}_2\text{CO}$ ), 7.00–7.28 (m, 16 H,  $\text{ArH}$ ), 7.76 (br s, 2 H, NH), 8.40 (br s, 2 H, OH), 8.75 (br s, 4 H, OH).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta = 30.97, 31.49, 31.62, 31.75, 32.52, 34.21, 34.58, 39.39, 72.55, 125.89, 126.17, 126.43, 126.67, 127.10, 127.46, 127.77, 127.85, 132.98, 143.27, 143.73, 144.48, 147.46, 148.49, 149.55, 169.79$ . MS–FAB:  $m/z = 1437$  [ $\text{MH}^+$ ]. Compound **3**: Mp >250.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta = 1.24$  [s, 18 H,  $(\text{CH}_3)_3$ ], 1.26 [s, 36 H,  $(\text{CH}_3)_3$ ], 1.27 [s, 18 H,  $(\text{CH}_3)_3$ ], 1.67 (overlapped, 2 H,  $\text{CH}_2$ ), 3.65 (br s, 4 H,  $\text{NCH}_2$ ), 3.83 [br s, 4 H,  $\text{ArCH}_2\text{Ar}$ ], 3.90 [br s, 8 H,  $\text{ArCH}_2\text{Ar}$ ], 4.02 (br s, 4 H,  $\text{ArCH}_2\text{Ar}$ ), 4.38 (s, 4 H,  $\text{OCH}_2\text{CO}$ ), 7.05–7.27 (m, 16 H,  $\text{ArH}$ ), 7.96 (br s, 2 H, NH), 8.75 (br s, 2 H, OH), 9.42 (br s, 4 H, OH).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta = 30.58, 31.73, 31.86, 32.81, 34.37, 34.74, 36.63, 72.22, 125.26, 126.01, 126.74, 127.04, 127.17, 127.41, 128.14, 132.99, 143.12, 143.72, 144.47, 147.24, 148.29, 149.71, 169.82$ . MS–FAB:  $m/z = 1451$  [ $\text{MH}^+$ ]. Compound **2b**: mp >250 °C.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta$  = 1.16 [s, 36 H,  $(\text{CH}_3)_3$ ], 1.18 [s, 18 H,  $(\text{CH}_3)_3$ ], 1.25 [s, 18 H,  $(\text{CH}_3)_3$ ], 3.64 (br s, 8 H,  $\text{NCH}_2\text{CH}_2\text{N}$ ), 3.79 (br s, 8 H,  $\text{ArCH}_2\text{Ar}$ ), 3.90 (s, 8 H,  $\text{ArCH}_2\text{Ar}$ ), 4.35 (s, 8 H,  $\text{OCH}_2\text{CO}$ ), 6.91 [s, 8 H,  $\text{ArH}$ ], 7.16 [s, 4 H,  $\text{ArH}$ ], 7.24 (s,  $\text{ArH}$ , 4 H), 7.20 (overlapped, 4 H, OH, disappeared after 2 h after the addition of  $\text{D}_2\text{O}$ ), 8.00 (br s, 4 H, NH, partially disappeared after 2 d after the addition of  $\text{D}_2\text{O}$ ).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta$  = 30.55, 30.89, 31.45, 31.72, 31.74, 34.16, 34.52, 39.60, 73.23, 126.02, 126.24, 126.49, 126.77, 126.82, 132.72,

143.09, 143.42, 148.57, 149.12, 149.43, 149.55, 169.22.

MS–FAB:  $m/z$  = 1577 [ $\text{MH}^+$ ].

- (16) It was suggested that ‘isolated OH groups usually resonate at  $\delta < 7.7$ ’, ‘singly-bonded hydroxyls give signals at  $7.7 < \delta < 8.7$ ’, ‘doubly-bonded hydroxyls resonate at  $\delta > 8.7$ ’, cited from: Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *J. Org. Chem.* **1998**, *64*, 6852.
- (17) (a) Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Neri, P. *Org. Lett.* **2001**, *3*, 1605. (b) Gaeta, C.; Gregoli, L.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2002**, *43*, 8875.