SYNTHESIS OF BOWL-SHAPED CHIRAL HOMOTRIAZACALIXARENES: CHIRAL TRANSMISSION FROM THE POINT CHIRALITY OF THE BRIDGE TO THE CYCLOPHANE MOIETY

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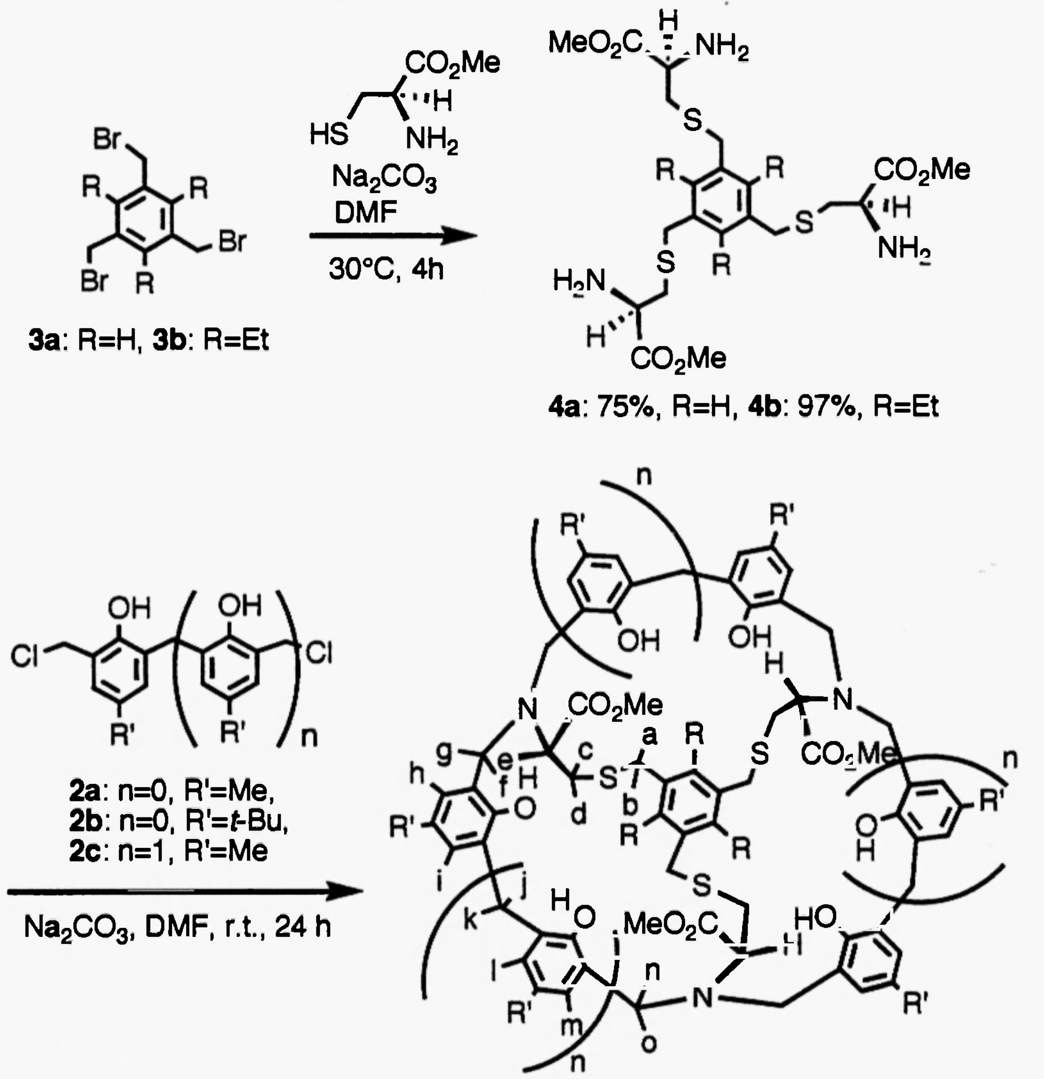
Abstract Bowl-shaped chiral homotriazacalixarenes were prepared by the cyclization reactions of chiral triamines with three equimolar amounts of bis(chloromethyl)phenols or bis(chloromethyl)-phenol-formaldehyde dimers in moderate yields. The structural analysis of the macrocycles by the NMR and CD spectra imply the existence of the chiral transmission from the point chirality of the cysteine bridge to the cyclophane moiety.

Calixarenes are well known for their unique molecular architecture which is extensively used in the supramolecular chemistry to build up more complex synthetic receptors for ion and neutral molecules (1). Despite such progress of the calixarene chemistry, little effort has been directed towards the construction of calixarenes bearing the functional groups at the methylene bridges (2). This situation inspired us to exploit the synthesis of calxiarene analogs, which were modified on the methylene moiety (3). We now report a facile synthesis of bowl-shaped chiral homoazacalixarenes and discuss their structural feature.

Chiral triamines **4** bearing three cysteine residues were synthesized by the reactions of 1,3,5-tris(bromomethyl)benzenes **3a** and **3b** with cysteine methylester in DMF at 30 °C in the presence of sodium carbonate in 75 % (**4a**) and 97 % (**4b**) yields, respectively (4,5). Treatment of a chiral triamine **4a** with three equimolecular amount of bis(chloromethyl)phenols **2a** and **2b** or bis(chloromethyl)phenol-formaldehyde dimer **2c** afforded macrocycles **1a**, **1b**, and **1c** in 14, 13, and 6 % yields, respectively (6). Analogous reactions using **4b** with **2a** and **2c** also gave the corresponding macrocycles **1d** and **1e** in 5 and 15 % yields, respectively.

The structure of macrocycles **1** was determined on the bases of their elemental analysis and spectral data, especially NMR spectra. The phenolic OH protons in ^{1}H NMR spectra were observed at the range of δ 8.73-11.20 ppm, indicating the existence of the intramolecular hydrogen bonding. The IR spectral absorption band corresponding to OH stretching of phenol unit was observed at 3100-3200 cm^{-1}, indicating the formation of the strong intramolecular hydrogen bonding (Table 1) (7). The ^1H and ^{13}C NMR spectra of macrocycles **1** showed C_3 symmetry signal pattern. The $ArCH_2N$ and $ArCH_2Ar$ methylene protons of macrocycles **1** appeared as two (for **1a**, **1b**, and **1d**) or three (for **1c** and **1e**) pairs of doublets due to the geminal coupling between H_{exo} and H_{endo} protons at room temperature (Table 2) (8). These pairs did not coalesce at 55 °C in $CDCl_3$, indicating that macrocycles **1** form a rigid structure. Based on these results, the cone-like form may adopt a preferable conformation in this system.



3a: R=H, **3b**: R=Et

4a: 75%, R=H, **4b**: 97%, R=Et

2a: n=0, R'=Me,
2b: n=0, R'=*t*-Bu,
2c: n=1, R'=Me

1a: 14%, n=0, R=H, R'=Me,
1b: 13%, n=0, R=H, R'=*t*-Bu
1c: 6%, n=1, R=H, R'=Me
1d: 5%, n=0, R=Et, R'=Me
1e: 15%, n=1, R=Et, R'=Me

Scheme 1.

Table 1: Melting point, chemical shifts of hydroxy protons, IR absorptions of OH and CO groups.

macrocycles	mp [°C]	δ_{OH}[a] [ppm]	ν_{OH}[b] [cm^{-1}]	ν_{CO}[b] [cm^{-1}]	FAB mass[c] m/z $(M+H)^+$
1a	273	10.60	3089	1732	917
1b	157	10.60	3111	1732	1043
1c	248	8.76, 11.20	3288	1726	1277
1d	181	10.40	3107	1732	1000
1e	276	8.73, 11.20	3288	1726	1362

a) In $CDCl_3$ at 20 °C at 500 MHz. b) In $CHCl_3$ at 20 °C.
c) Used *m*-nitrobenzyl alcohol as a matrix.

Table 2: Chemical shifts of methylene protons (at 500 MHz for ^1H) and carbons (at 125 MHz for ^{13}C) in $CDCl_3$ at 20 °C.

	ArH_fH_gN (*J*, Hz; Δδ, ppm)	ArH_jH_kAr (*J*, Hz; Δδ, ppm)	ArH_nH_oN (*J*, Hz; Δδ, ppm)	$\delta ArCH_2N$	$\delta ArCH_2Ar$
1a	3.55, 3.86 (15.5, 0.31)	-	3.11, 4.24 (13.0, 1.13)	51.8, 53.5	-
1b	3.61, 3.88 (15.5, 0.27)	-	3.16, 4.28 (14.0, 1.12)	52.2, 53.8	-
1c	3.34, 3.90 (14.0, 0.56)	3.30, 4.30 (14.0, 1.00)	2.84, 4.69 (12.0, 1.85)	51.5, 53.4	30.9
1d	3.43, 3.75 (16.0, 0.32)	-	3.09, 4.13 (13.0, 1.04)	51.6, 53.2	-
1e	3.34, 4.13 (14.0, 0.79)	3.28, 4.26 (14.0, 0.98)	3.02, 4.48 (12.0, 1.46)	50.3, 53.4	30.8

Table 3: CD and UV spectral data at 20 °C in $CHCl_3$.

macrocycle	λ_{ext} [nm] (*θ* [deg cm^2 dmol^{-1}])	λ_{max} [nm] (ε [cm^{-1} mol dml^{-3}])
1a	297 (50700)	289 (7010)
1b	293 (13600)	286 (7620)
1c	298 (56300)	293 (16122)
1d	296 (35900)	289 (10114)
1e	298 (67600)	293 (21644)

The different Δδ values of the $ArCH_2N$ methylene protons ($\Delta\delta H_fH_g$ and $\Delta\delta H_nH_o$) imply that the cyclophane moiety is twisted form, because the Δδ values of the methylene protons of the cyclophane moiety are expected to be sensitive to the dihedral angle between the methylene protons and the plane of the adjacent aromatic rings as shown in Figure 1. Since the smaller Δδ values is ascribed to the H_fH_g methylene protons, it is reasonable to assume that the phenol ring adjacent to the H_fH_g

methylene moiety adopt a conformation A in Figure 1. The CPK model consideration also supports the fact that the phenol rings somewhat flatten owing to the steric repulsion between the hydroxy group of the phenol ring and methyl ester group of cysteine moiety. Therefore, it is reasonable to assume that the direction of the intramolecular hydrogen bonding of macrocycles **1** is effected by the point chirality of the cysteine unit as shown in Figure 2. In other words, the point chirality of the cysteine unit transfers to the cyclophane moiety. To prove the existence of the chiral cyclophane moiety, CD spectral measurement was employed. The CD spectral absorptions were observed at *ca.* 290 nm, which were corresponding to the phenol unit (9). Therefore, CD spectra supported the assumption that the cyclophane unit is chiral. In this case, the chirality of the *L*-cysteine bridge cause the predominant formation of the left-hand isomer in Figure 2.

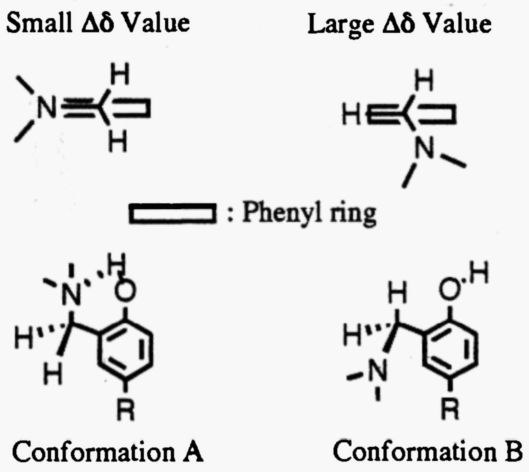
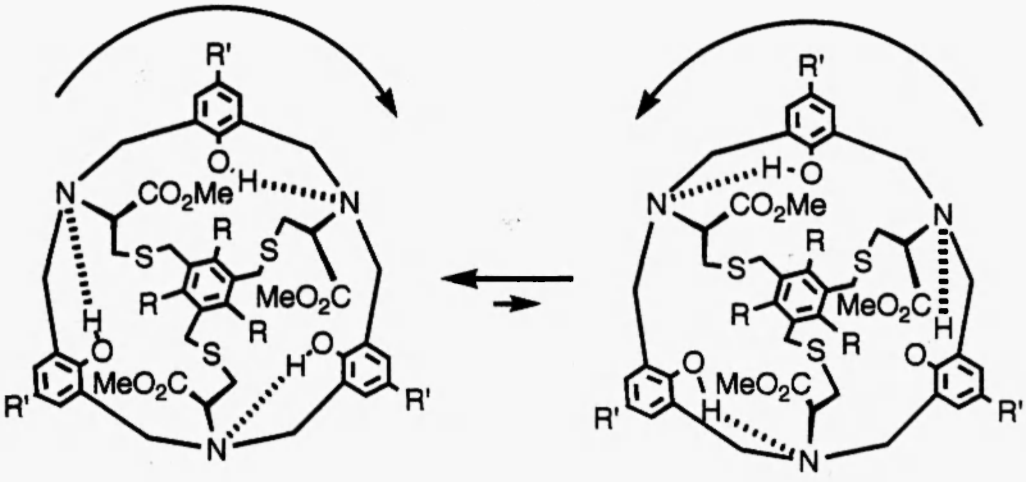


Figure 1.



clockwise counterclockwise

Figure 2. The direction of the intramolecular hydrogen bonding.

In summary, we prepared the bowl-shaped chiral homotriazacalixarenes in moderate yields. The NMR and CD spectra imply the existence of the chiral transmission from the point chirality of the bridge to the whole of the molecule.

References and Notes

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(4) 1,3,5-Tris(bromomethyl)benzene **3a** and 1,3,5-tris(boromomethyl)-2,4,6-triethylbenzene **3b** were prepared by reported methods in literature. (a) W. P. Cochrane, P. L. Pauso, and T. S. Stevens, *J. Chem. Soc. (C)*, 630 (1968); (b) A. Metzger and E. A. Anslyn, *Angew. Chem., Int. Ed. Engl.*, **36**, 862 (1997).

(5) Selected spectral data for chiral triamines **4**. **4a**: colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.67 (3H, dd, H_b, J=7.2, 13.5 Hz), 2.83 (3H, dd, H_c, J=4.8, 13.5 Hz), 3.61 (dd, dd, H_d, J=4.8, 7.2 Hz), 3.72 (6H, s, H_a), 3.74 (9H, s, CO_2CH_3), 7.17 (3H, s, Ar-H); ^{13}C NMR ($CDCl_3$) δ 36.4 (CH_2), 36.5 (CH_2), 52.2 (CH_3), 54.0 (CH), 128.3 (Ar-CH), 138.7 (Ar-C), 174.3 (CO); FAB-MS : 520 $(M+H)^+$; **4b**: colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.29 (9H, t, CH_3, J= 7.5 Hz), 2.87 (6H, q, CH_2, J= 7.5 Hz), 2.90 (3H, dd, CH, J= 7.0, 13.5 Hz), 3.00 (3H, dd, CH, J= 5.0, 13.5 Hz), 3.71 (3H, dd, CH, J= 5.0, 7.0 Hz), 3.77 (9H, s, CO_2CH_3), 3.79 (6H, s, NH_2); ^{13}C NMR ($CDCl_3$) δ 16.2, 22.9, 31.9, 52.2, 131.2, 142.6, 174.5; FAB-MS : 604 $(M+H)^+$.

(6) Bis(chloromethyl)phenols **2a** and **2b** and bis(chloromethyl)phenol-formaldehyde dimer **2c** were prepared by the methods reported in literature. (a) K. Ito, Y. Ohba , and T. Sone, *Heterocycles*, **51**, 2203 (1999); (b) K. Ito, T. Ohta, Y. Ohba, and T. Sone, *J. Heterocycl. Chem.*, **37**, 79 (2000).

(7) In **1c** and **1e**, two phenolic protons were observed. Considering that a nitrogen atom is good proton acceptor, OH peaks observed at lower magnetic field are assigned to the OH proton formed the intramolecular hydrogen bonding not only with a hydroxy group but also with adjacent nitrogen atom.

(8) Conformational analysis of the phenol-formaldehyde dimer moiety in **1c** and **1e** were carried out

by using NMR spectroscopy. The ArCH2Ar methylene region is the informative and diagnostic for conformational assignments. The ArCH2Ar methylene protons of the macrocycles **1c** and **1e** were observed as AB systems. It is known that the Δδ values between Hexo and Hendo of the ArCH2Ar methylene protons of calixarenes is generally *ca.* 0.9±0.2 ppm for *syn* orientation of the ary rings and zero for *anti* (1a). Applied to this rule on macrocycles **1c** and **1e**, the Δδ values (1.00 ppm for **1c** and 0.98 ppm for **1e**) indicate that the phenol-formaldehyde dimer moiety adopt a *syn* orientation. This is further supported by the chemical shift values of the ArCH2Ar methylene carbon atoms (δ 30.9 ppm for **1c** and 30.8 ppm for **1e**). C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto, and S. Sanchez, *J. Org. Chem.*, **56**, 3372 (1991).

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