Synthesis and Properties of Chiral Calixarene Analogs Bridged by a (*R,R*)-Cystine Unit

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(Received June 17, 1996)

The chiral calixarene analogs bridged by a (*R,R*)-cystine unit were synthesized. NMR studies reveal that the phenol-formaldehyde moieties of the macrocycles adopt a chiral helical geometry induced by the cystine bridge and the macrocycles form a twisted concave. This helicity is enhanced at low temperature.

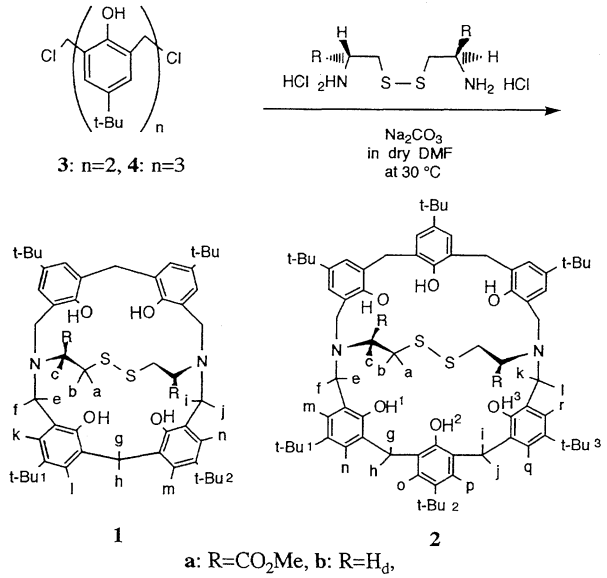
The ability of chiral receptors to serve as enzyme models along with their remarkable selectivity for the substrate lends great importance to the syntheses of such compounds.[1] Since amino acids are versatile and inexpensive sources of chirality, they were frequently used as building blocks of chiral receptors.[2] Although there has been some work on the syntheses of bridged calixarenes[3] and receptors composed of amino acid units,[2] we are unaware of the examples of the chiral bridged calixarenes or its analogs, which were expected to form concave containing chiral recognition sites. We synthesized the chiral bridged calixarene analogs, which are constructed from the phenol-formaldehyde oligomer moieties and the (*R,R*)-cystine bridge, and elucidated that the calixarene analogs form a chiral twisted concave.

The bridged macrocycle **1a**[4] was prepared by the cyclization reaction of the (*R,R*)-cystine dimethyl ester and two equimolar amounts of the bis(chloromethyl) phenol-formaldehyde dimer **3**[5] in dry DMF in the presence of sodium carbonate at 30 °C under a nitrogen atmosphere in 42% yield. An analogous reaction using the corresponding trimer **4**[6] gave the macrocycle **2a** in 24% yield. The reactions using cystamine instead of cystine gave **1b** and **2b** in 48 and 27% yields, respectively. The formation of similar homoazacalixarenes was previously reported by Takemura *et al.*[7]

The structures of macrocycles **1** and **2** were confirmed by elemental analysis, FAB-MS, and NMR and IR spectra. The assignment of the proton and carbon atoms was done using NOE, DEPT, H-H and C-H COSY NMR experiments.[8]

The IR spectra of **1** and **2** in $CHCl_3$ show the absorption for the hydroxy stretching band at 3200 ~ 3260 cm^{-1}. In the ^{1}H-NMR spectra in $CDCl_3$ at 30 °C, OH signals were observed at 9.31 and 10.85 ppm for **1a**, 10.93 ppm for **1b**, 9.06, 10.69, and 13.13 ppm for **2a**, 9.51, 12.24, and 15.27 ppm for **2b**. These spectral data indicate the existence of strong hydrogen bonds which are comparable to that of the calixarenes (ν_{OH} = ca. 3200 cm^{-1}, δ_{OH} = ca. 10 ppm).[9]

The conformations of this system have been studied by means of NMR spectroscopy. The $ArCH_2Ar$ methylene protons of **1** and **2** appear as pairs of doublets due to the geminal coupling between H_{exo} and H_{endo}. The differences between the chemical shifts of the doublets ($\Delta\delta$) are 0.86 ppm for **1a**, 0.88 ppm for **1b**, 0.73 and 0.83 ppm for **2a**, and 0.73 and 0.89 ppm for **2b**, indicating that the adjacent aryl rings adopt a *syn*-conformation.[9,10] The chemical shifts of the $ArCH_2Ar$ carbon atoms (31.1 ppm for **1a**, 31.5 ppm for **1b**, 32.4 and 32.5 ppm for **2a**, 32.8 and 33.3 ppm for **2b**) provided further support for the all-*syn* conformation.[6,11] The observation of the aromatic proton H_m of **2** (6.62 ppm for **2a** and 6.68 ppm for **2b**) at relatively high field indicates that the proton is shielded by the π cavity of another phenol-formaldehyde



a: R=CO_2Me, **b**: R=H_d,

Scheme 1.

oligomer moiety of the macrocycle. This means that the two phenol-formaldehyde oligomer moieties in **2** are facing each other. These facts demonstrate that the preferred conformation of **2** in solution is a cone. A similar up-field shift of the aromatic protons of **1** was not observed. The CPK model consideration of **1** indicates that it adopts a cone conformation because it is difficult to construct a 1,2-alternate model.

The small $\Delta\delta$ values between H_{exo} and H_{endo} (0.73 and 0.83 ppm for **2a** and 0.73 and 0.89 ppm for **2b**) of **2** compared with that (0.9 ppm)[9] of cone-calixarene indicate that the aryl rings of **2** are twisted together. The signals of *t*-Bu[1] (1.21 ppm for **2a** and 1.23 ppm for **2b**) and the aromatic proton H_m (6.62 ppm for **2a** and 6.68 ppm for **2b**) of **2** are observed at higher field, indicating that *t*-Bu[1] and H_m protons are located inside the cavity. The observation of the hydroxyl proton signal (OH^3) at lowest field (13.13 ppm for **2a** and 15.27 ppm for **2b**) is attributed to the strong hydrogen bond formation not only with oxygen but also with nitrogen atoms.[6,7] Thus, the hydroxyl proton (OH^3) is located inside the cavity due to the formation of the hydrogen bond with an nitrogen atom. From these consideration, the phenol-formaldehyde moieties of **2** are considered to adopt a helical structure as shown in Figure 1.[12] The chirality of the cystine bridge causes the predominant formation of the left-hand isomer in Figure 1. Therefore, the phenol-formaldehyde moieties of **2a** form chiral helicity and give chiral twisted concaves. Although it is reasonable to assume that the macrocycle (**1**) also possesses similar helicity ($\Delta\delta$ values ; 0.86 ppm for **1a** and 0.88 ppm for **1b**, OH^2; 10.85 ppm for **1a**[13]), the degree must be smaller than that of **2**. Figure 2 shows circular dichroism (CD) spectra of **1a** and **2a**. CD spectrum of **2a** was clearly observed at 238 nm (θ -71600) due to phenol chromophore[14] in hexane at 20 °C, suggesting the existence of the helicity of phenol-formaldehyde

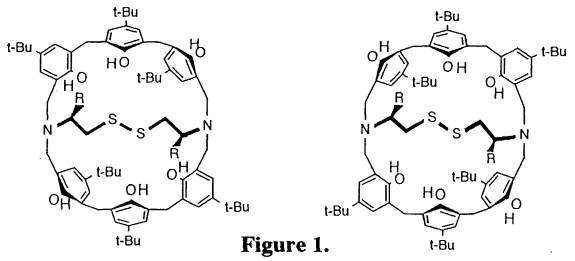


Figure 1.

units. In contrast, **1a** did not give a similar CD spectrum in this region. This discrepancy indicate that the degree of the helicity of **1a** must be small. It is consistent with the results derived from NMR spectroscopy.

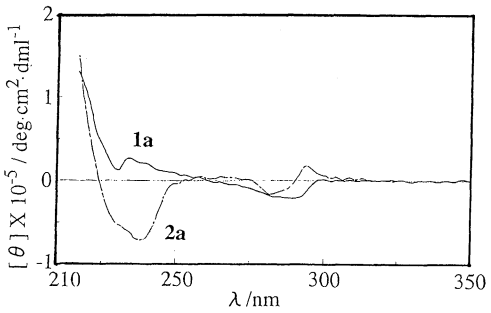


Figure 2. CD spectra of **1a** and **2a**.

In order to elucidate the temperature dependence of this helicity, we carried out the variable temperature ^{1}H-NMR measurement in the range of 55 to -60 °C in $CDCl_3$ and the results are summarized in Table 1. Lowering the temperature resulted in the decrease of $\Delta\delta$ values of the $ArCH_2Ar$ methylene protons and down-field shifts of OH signals. These results suggest that the helicity is enhanced by cooling due to the stronger hydrogen bond between the OH proton and nitrogen atoms.

Table 1. Observed proton chemical shift and the differnce ($\Delta\delta$) of the chemical shifts between H_{exo} and H_{endo} of the $ArCH_2Ar$ protons at various temperatures in $CDCl_3$ at 270 MHz

	1a				**2a**				
°C	$\Delta\delta$	H_k	*t*-Bu^1	OH^2	$\Delta\delta$	H_m	*t*-Bu^1	OH^2	OH^3
55	0.88	6.81	1.26	9.40[a]	0.85	0.74	6.65	1.22	13.03
30	0.86	6.80	1.26	10.85	0.83	0.73	6.62	1.21	13.13
0	0.85	6.80	1.26	11.35	0.79	0.71	6.60	1.19	13.24
-30	0.83	6.80	1.26	11.80	0.77	0.70	6.57	1.16	13.34
-60	0.81	6.80	1.25	12.11	0.73	0.68	6.55	1.14	13.41

[a] OH^2 signal coalesced with OH^1.

In conclusion, we demonstrated that the first synthesis of the chiral bridged calixarene analogs, which are constructed from the phenol-formaldehyde oligomers and the (*R*,*R*)-cystine bridge, and the formation of the chiral helical phenol-formaldehyde moieties, which is induced from the chirality of the cystine bridge. VT-NMR experiments indicated that the chiral helicity is enhanced at low temperature. The present system is a unique concept from the viewpoint of the transmisson of the chirality from the bridge to the concave.

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8 Spectral data. **1a**: colorless crystals mp 250-255 °C (decomp.) (ethyl acetate - hexane). $[\alpha]_D^{20}$+31° ($CHCl_3$). MS (FAB) m/z 941 $[M+1]^+$. IR ($CHCl_3$) 3260, 3050, 3000, 2960, 2910, 2870, 1730, 1490 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.28 (s, *t*-Bu^2, 18H), 1.29 (s, *t*-Bu^1, 18H), 2.26 (dd, H_a, 2H), 2.41 (dd, H_b, 2H), 3.46 (d, H_g, 2H), 3.61 (d, H_c, 2H), 3.74 (s, CO_2Me, 6H), 3.88 (d, H_e, 2H), 3.91 (d, H_i, 2H), 4.16 (d, H_h, 2H), 4.32 (d, H_f, 2H), 4.43 (d, H_d, 2H), 6.81 (d, H_m, 2H), 6.93 (d, H_j, 2H), 7.28 (d, H_k, 2H), 7.31 (d, H_l, 2H), 9.31 (bs, OH^1, 2H), 10.85 (bs, OH^2, 2H). Coupling Constants in Hz; J_{ab}=14.0, J_{ac}=8.6, J_{bc}=5.9, J_{de}=12.0, J_{fh}=13.9, J_{hi}=15.3, J_{jk}=2.3, J_{lm}=2.3. **1b**: colorless crystals mp 238-241 °C (dichloromethane-hexane). MS (FAB) m/z 825 $[M+1]^+$. IR ($CHCl_3$) 3260, 2960, 2910, 2870, 2840, 1490 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.29 (s, *t*-Bu, 36H), 2.11 (t, H_a and H_b, 4H), 2.55 (t, H_c and H_d, 4H), 3.33 (d, H_e, 4H), 3.45 (d, H_h, 2H), 4.33 (d, H_g, 2H), 4.36 (d, H_f, 4H), 6.85 (d, H_k, 4H), 7.27 (d, H_l, 4H), 10.93 (s, OH, 4H). Coupling constants in Hz; J_{ac}= J_{ad}= J_{bc}= J_{bd}= 6.5, J_{ef}= 13.5, J_{gh}= 14.0, J_{kl}= 2.2. **2a**: pale yellow crystals. mp 203-207 °C (ethyl acetate). $[\alpha]_D^{20}$+127° ($CHCl_3$). MS (FAB) m/z 1265 $[M+1]^+$. IR ($CHCl_3$) 3260, 3170, 3050, 3000, 2960, 2910, 2870, 1730, 1490 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.21 (s, *t*-Bu^1, 18H), 1.26 (s, *t*-Bu^3, 18H), 1.27 (s, *t*-Bu^2, 18H), 3.37 (d, H_e, 2H), 3.52 (d, H_h and H_j, 4H), 3.64 (s, CO_2CH_3, 6H), 3.79 (dd, H_a, 2H), 3.83 (s, H_k and H_l, 4H), 3.87 (dd, H_b, 2H), 4.25 (d, H_i, 2H), 4.33 (d, H_f, 2H), 4.35 (d, H_g, 2H), 4.71 (dd, H_c, 2H), 6.62 (d, H_m, 2H), 6.91 (d, H_r, 2H), 7.17 (d, H_o, 2H), 7.18 (d, H_p, 2H), 7.24 (d, H_n, 2H), 7.27 (d, H_q, 2H), 9.06 (s, OH^1, 2H), 10.69 (s, OH^2, 2H), 13.13 (s, OH^3, 2H). Coupling Constants in Hz; J_{ab}=13.7, J_{ac}=7.3, J_{bc}=6.8, J_{ef}=14.5, J_{gh}=13.9, J_{ij}=13.9, J_{mn}=2.3, J_{op}=2.3, J_{qr}=2.3. **2b**: colorless crystals. mp 233-236 °C (dichloromethane-hexane). MS (FAB) m/z 1149 $[M+1]^+$. IR ($CHCl_3$) 3240, 3020, 2960, 1480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.23 (s, *t*-Bu^1, 18H), 1.27 (s, *t*-Bu^2 and *t*-Bu^3, 36H), 2.79 (m, H_c or H_d, 2H), 3.34 (d, H_e, 2H), 3.51 (d, H_h, 2H), 3.52 (d, H_j, 2H), 3.63 (m, H_a and H_b, 4H), 3.84 (d, H_k, 2H), 3.88 (d, H_l, 2H), 4.09 (m, H_d or H_c, 2H), 4.25 (d, H_i, 2H), 4.30 (d, H_f, 2H), 4.40 (d, H_g, 2H), 6.68 (d, H_m, 2H), 6.89 (d, H_r, 2H), 7.17 (s, H_o and H_p, 4H), 7.28 (d, H_q, 2H), 7.29 (d, H_n, 2H), 9.51 (s, OH^1, 2H), 12.24 (s, OH^2, 2H), 15.27 (s, OH^3, 2H). Coupling constants in Hz; J_{ef}= 14.0, J_{gh}=13.5, J_{ij}=13.8, J_{kl}=14.9, J_{mn}= 2.2, J_{qr}= 2.2.
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