Synthesis and Properties of Pentahomothiazacalix[3]arene Derivatives Constructed from Phenol-Formaldehyde Trimer and Aminoethanethiol Unit

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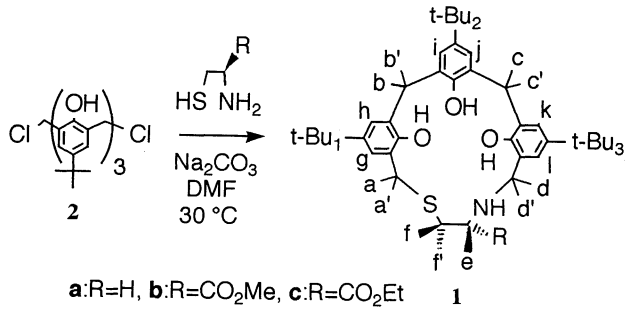
Chiral calixarene analogs incorporating aminoethanethiol unit such as *L*-cysteine alkyl ester into their rings were prepared. NMR studies of the macrocycles reveal that their preferred conformations in solution are a cone form and the introduction of aminoethanethiol unit in their rings causes the ring fluctuation.

Many efforts have been paid on the modification of calixarenes at lower and upper lims from viewpoint of the introduction of the additional functionalities.[1] Despite such progress, there has been a relatively small number of researches describing the modification of the methylene group owing to the relatively inert reactivity on this site.[2] As another direction for the modification of the methylene moiety the synthses of calixarene analogs have been described, which constrcuted by changing the methylene bridges to trimethylene bridge or dimethylene heteroatom bridges such as homo-oxa-, homo-aza-, and homo-thiacalixarenes.[3] However, we are unaware of the calixarene analogs incorporating chiral unit into the macrocyclic ring. The introduction of chiral unit into the macrocyclic ring is expected to deduce the effective discrimination of enantiomers of guest, which have attracted attention on the enzyme mimic.[4]

We now report here the synthesis of novel calixarene analogs constructed from phenol-formaldehyde trimer and aminoethanethiol unit such as *L*-cysteine alkyl ester and also the clarification of their conformational properties and molecular mobilities by NMR study.

Calixarene analogs (**1**) were conveniently synthesized by the reaction of bis(chloromethyl)phenol-formaldehyde trimer (**2**)[5] with equimolecular amount of aminoethanethiol in the presence of sodium carbonate in dry DMF at 30 ° C under a nitrogen atmosphere to give a 1:1 cyclic compound (**1a**) in 50% yield. The similar reactions using *L*-cysteine methyl and ethyl ester afforded the corresponding cyclic compounds (**1b** and **1c**) in 30 and 30% yields, respectively. Contrary to this, the reaction using bis(chloromethyl)phenol-formaldehyde tetramer or pentamer instead of **2** did not give any products except for polymeric materials.



Scheme 1.

The structural determination of these macrocycles (**1**) was accomplished on the bases of their elemental analyses, FAB-MS, NMR, and IR spectra.[6] The assignment of the protons was confirmed by H-H COSY and NOE experiments. The assignment of the carbon atoms of the $ArCH_2Ar$ was deduced from C-H COSY spectra.

In the IR spectra of **1** in chloroform, the OH absorptions of streching vibration appeared in the region of 3300-3290 cm^{-1} as broad bands. The phenolic OH protons of those in ^{1}H-NMR spectra were observed at 8.7~9.3 ppm at 25 °C. Lowering of the temperature to -60 °C slows down the rate of proton exchange, and the three signals with equal intensities appear (**1a**: 7.1, 9.3, and 11.1, **1b**: 8.8, 10.0, and 12.3, **1c**: 8.7, 9.9, and 12.3 ppm). Considering the nitrogen atom is a good proton acceptor, the OH signals observed at the lowest fields (11~12 ppm) are assigned to the OH protons adjacent to the amine moieties, which form hydrogen bonds not only with OH groups but also with the nitrogen atom. Comparing the IR and ^{1}H-NMR spectra of the phenolic OH groups of **1** with those of calix[4]arene (ν_{OH}= 3138 cm^{-1}, δ_{OH}= 10.2 ppm),[1a] the intramolecular hydrogen bonds in **1** are weaker than that of calix[4]arene owing to the introduction of aminoethanethiol unit.

The conformational property of **1a** is investigated by ^{1}H-NMR measurement at variable temperatures and ^{13}C-NMR chemical shift values of the $ArCH_2Ar$ methylene carbons. In the ^{1}H-NMR spectrum of **1a** at -60 °C in $CDCl_3$, three pairs of doublets are observed. The doublets with the larger chemical shift difference is assigned to the methylene protons of the $ArCH_2Ar$ [3.48 ppm (J=13 Hz), 4.22 ppm (J=13 Hz)], the pair appeared at relatively higher field is ascribed to the $ArCH_2S$ protons [3.45 ppm (J=13 Hz), 3.93 ppm (J=13 Hz)], and the pair observed at relatively lower field is ascribed to the $ArCH_2N$ protons [3.73 ppm (J=13 Hz), 4.22 ppm (J=13 Hz)] by using a double resonance technique. The difference of the chemical shifts ($\Delta\delta$) of **1a** between high- and low-fields resonances arising from the

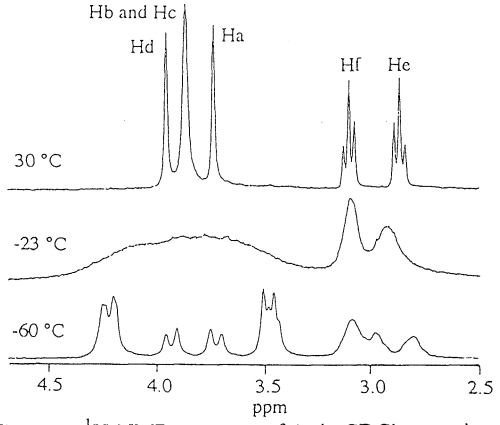


Figure 1. ^{1}H-NMR spectrum of **1a** in $CDCl_3$ at various temperatures.

$ArCH_2Ar$ protons was 0.74 ppm, indicating that the adjacent aryl rings are preferable to the *syn*-conformation.[1a] The coalescence temperature (T_c) of the methylene protons of $ArCH_2Ar$ is -23 °C ($\Delta\nu$ = 200 Hz), which corresponds to a free energy barrier ($\Delta G^{\ddagger}$) of 11.7 kcal/mol.[7] This value is similar to that of trihydroxy-*p*-*t*-butyl-calix[4]arene (T_c = -27 °C, $\Delta G^{\ddagger}$ = 11.6 kcal/mol in $CDCl_3$).[8] On the other hand, analyses of the conformations of other macrocycles (**1b** and **1c**) were difficult because of overlapping of the proton signals between $ArCH_2Ar$ and the alkyl ester. Recently, the ^{13}C-NMR chemical shifts of the $ArCH_2Ar$ for calixarenes have come into use as a means for assessing their conformations.[9] Applying it to **1a**, the chemical shift values (32.4 and 32.7 ppm) of the $ArCH_2Ar$ carbon atoms deduced the *syn*-conformation of the adjacent aryl rings, which was in agreement with the result derived from VT-NMR experiment. The result indicates that this rule is applicable to the similar structural compounds.[10] As the rule applies to other macrocycles (**1b**: 31.9 and 32.9, **1c**: 31.9 and 32.8 ppm), the *syn*-conformation of the aromatic rings is proposed in all cases. From these results on the spectral data, these macrocycles (**1**) are considered to adopt a cone conformation in solution.

In order to clarify the molecular motions of **1a** in more detail, we carried out measurements of ^{1}H-NMR relaxation time (T_1) by using inversion recovery method[11] at 25 °C in $CDCl_3$ at 270 MHz and the results were shown in Figure 2.[12] T_1 measurement of **1a** reveals that the T_1 values of the methylene protons of $ArCH_2Ar$ (H_b and H_c) are remakably small. This means that the motion of the aromatic units in **1a** is characterized by up and down motions around the methylene moieties as axes. The T_1 values of the methylene protons (H_d and H_e) adjacent to the nitrogen atom are smaller than those of the methylene protons (H_a and H_f) neighboring the sulfur atom. The smaller T_1 values observed suggest that the hydrogen bond between the nitrogen atom and the adjacent phenolic hydroxyl group suppresses the motions of the methylene moieties. Comparing the values of the aromatic protons among them, the larger T_1 values were observed for H_g and H_l, which placed in the neighborhood of aminoethanethiol unit. This implies that the introduction of aminoethanethiol unit into the macrocyclic ring causes the ring fluctuation in macrocycles.

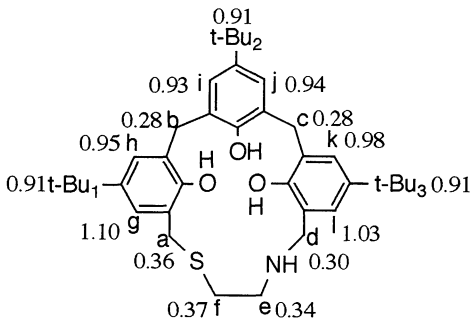


Figure 2. T_1 Values of **1a** at 25 °C in $CDCl_3$ / [s].

In conclusion, this study demostrated the first synthesis of chiral calixarene analogs which incorporated aminoethanethiol units such as *L*-cysteine alkyl ester into their rings and the elucidation of their flexible structures by NMR studies.

References and Notes

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5 Compound (**2**) was synthesized from the reaction of bis(hydroxymethyl) phenol-formaldehyde trimer[3a] with thionyl chloride in dry benzene at room temperature for 5 h in 97% yield. Spectral data of **2**: mp 115-116 °C. ^{1}H-NMR ($CDCl_3$) δ 1.27 (27H, s, *t*-Bu X 3), 3.93 (4H, s, $ArCH_2Ar$), 4.66 (4H, s, $ArCH_2Cl$), 7.00-7.41 (6H, m, aromatic protons).

6 Spectral data of **1a**: mp 199-201 °C(from dichloromethane - ethyl acetate). MS (FAB) m/z 576 $[M+1]^+$. IR ($CHCl_3$) 3300, 3014, 2964, 2908, 2866, 1484, 1209 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.23 (18, s, *t*-Bu X 2), 1.27 (9H, s, *t*-Bu), 2.88 (2H, t, H_f and $H_{f'}$, J=7.1 Hz), 3.11 (2H, t, H_e and $H_{e'}$, J=7.1 Hz), 3.73 (2H, s, H_a and $H_{a'}$), 3.86 (4H, bs, H_b, $H_{b'}$, H_c, and $H_{c'}$), 3.94 (2H, s, H_d and $H_{d'}$), 6.79 (1H, d, H_j), 6.87 (1H, d, H_g), 7.11 (1H, d, H_j), 7.13 (1H, d, H_h), 7.17 (1H, d, H_i), 7.22 (1H, d, H_k), 8.70 (3H, br s, OH). Coupling constants in Hz; J_{ef}=$J_{e'f}$=$J_{ef'}$=$J_{e'f'}$= 7.1, J_{gh}=2.3, J_{ij}=2.3, J_{kl}=2.3. ^{13}C-NMR ($CDCl_3$) δ 31.5, 32.3, 32.4, 32.6, 32.7, 33.8, 33.9, 46.9, 52.3, 120.3, 123.2, 125.3, 125.5, 126.4, 127.1, 127.7, 127.8, 128.3, 128.6, 142.3, 142.5, 143.4, 148.3, 150.0, 152.3. Anal. Found : C, 75.26; H, 8.79; N, 2.24%. Calcd for $C_{36}H_{49}NO_3S$: C, 75.09; H, 8.58; N, 2.43%.
Spectral data of **1b**: mp 211-213 °C (from ethyl acetate) $[\alpha]_D^{20}$=-20° ($CHCl_3$). MS (FAB) m/z 634 $[M+1]^+$. IR ($CHCl_3$) 3290, 3008, 2964, 2867, 1739, 1486, 1209 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.22 (9H, s, *t*-Bu), 1.24 (9H, s, *t*-Bu), 1.28 (9H, s, *t*-Bu), 3.11 (1H, dd, H_f), 3.19 (1H, dd, $H_{f'}$), 3.48 (1H, dd, H_e), 3.66 (2H, d, H_a and H_d), 3.77 (1H, d, $H_{d'}$), 3.78 (3H, s, CO_2Me), 3.87 (4H, br s, H_b, $H_{b'}$, H_c, and $H_{c'}$), 4.02 (1H, d, $H_{a'}$), 6.81 (1H, d, H_j), 6.82 (1H, d, H_g), 7.11 (d, H_h and H_j), 7.18 (1H, d, H_i), 7.26 (1H, d, H_k), 9.40 (3H, br s, OH). Coupling constants in Hz; $J_{aa'}$=13.5, $J_{dd'}$=13.5, J_{ef}=7.3, $J_{ef'}$=5.1, $J_{ff'}$=10.8, J_{gh}=2.4, J_{ij}=2.4, J_{kl}=2.4.^{13}C-NMR ($CDCl_3$) δ 31.4, 31.9, 32.5, 32.8, 33.8, 33.9, 36.3, 50.8, 52.3, 58.5, 121.2, 123.8, 125.1, 125.4, 125.7, 126.4, 126.6,126.8, 127.1, 127.6, 128.2, 128.7, 142.4, 143.3, 144.1, 147.5, 149.8, 150.8, 172.4. Anal. Found: C,72.14; H, 8.16; N, 2.08%. Calcd for $C_{38}H_{51}NO_5S$: C, 72.01; H, 8.11; N, 2.21%.
Spectral data of **1c**: mp 212-213.5 °C (from ethyl acetate) $[\alpha]_D^{20}$ = +21° ($CHCl_3$). MS (FAB) m/z 648 $[M+1]^+$. IR ($CHCl_3$) 3290, 3012, 2966, 2906, 2869, 1733, 1485, 1209 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.22 (9H, s, *t*-Bu) 1.24 (9H, s, *t*-Bu), 1.28 (9H, s, *t*-Bu), 1.31 (3H, t, $CO_2CH_2CH_3$, J=7.2 Hz), 3.14 (1H, dd, H_f), 3.20 (1H, dd, $H_{f'}$), 3.45 (1H, dd, H_e), 3.65 (1H, d, H_d), 3.66 (1H, d, H_a), 3.79 (1H, d, $H_{d'}$), 3.86 (4H, s, H_b, $H_{b'}$, H_c, and $H_{c'}$), 4.02 (1H, d, $H_{a'}$), 4.24 (2H, q, $CO_2CH_2CH_3$, J=7.2 Hz), 6.81 (1H, d, H_j), 6.82 (1H, d, H_g), 7.11 (2H, d, H_h and H_j), 7.18 (1H, d, H_i), 7.26 (1H, d, H_k). Coupling constants in Hz; $J_{aa'}$=13.5, $J_{dd'}$=13.5, J_{ef}=7.3, $J_{ef'}$=5.1, $J_{ff'}$=10.8, J_{gh}=2.4, J_{ij}=2.4, J_{kl}=2.4.^{13}C-NMR ($CDCl_3$) δ 14.2, 31.5, 31.9, 32.5, 32.9, 33.8, 34.0, 36.4, 50.8, 58.6, 61.6, 121.3, 123.8, 125.2, 125.5, 125.8, 126.4, 126.6, 126.9, 127.1, 127.6, 128.2, 128.7, 142.4, 143.3, 144.1, 147.5, 149.8, 150.8, 171.9. Anal. Found : C, 72.57; H, 8.32; N, 2.04%. Calcd for $C_{39}H_{53}NO_5S$: C, 72.30; H,8.25; N, 2.16%.

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