Syntheses and Properties of Chiral Pentahomothiazacalix[3]arenes

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Chiral calixarene analogs incorporating an aminoethanethiol unit such as *L*-cysteine into their rings were prepared. Conformational analysis of the macrocycles by using ^1H and ^{13}C nmr spectroscopy revealed that their preferred conformation was a cone, which was more stable in chloroform than in toluene. The introduction of an aminoethanethiol moiety into the macrocyclic ring caused ring fluctuation, however, the carboxylic acid derivative was a highly rigid structure in the cone form. The ^1H nmr and circular dichroism spectra of the macrocycles showed the existence of chirality of the phenol-formaldehyde unit, which was induced by the chirality of the cysteine moiety.

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Introduction.

Much effort has been made toward modification of calixarenes at the lower and upper rims from the viewpoint of the introduction of additional functionalities [1]. Despite much progress, there has been relatively little work describing the modification of the methylene group due to the relatively low reactivity at this site [2]. The modification of the methylene moiety for the syntheses of calixarene analogs has been performed by changing the methylene bridges to a trimethylene bridge or to dimethylene heteroatom bridges such as homooxa, homoaza, and homothiacalixarenes [3]. However, we are unaware of calixarene analogs incorporating chiral units into the macrocyclic ring.

The chiral calixarene derivatives previously prepared have been synthesized by the introduction of chiral residues at the upper or lower rim of the calixarene skeleton [4] and by the use of the inherent chirality of the calixarene through the absence of symmetry elements [5]. Therefore, we synthesized chiral calixarene analogs constructed from phenol-formaldehyde trimers and aminoethanethiol moieties such as an *L*-cysteine alkyl ester. This macrocycle is of interest due to the introduction of a chiral unit into the macrocyclic ring. We report here the synthesis of macrocycles and the determination of their conformational properties, molecular mobility, and molecular chirality by using nmr and circular dichroism studies.

Results and Discussion.

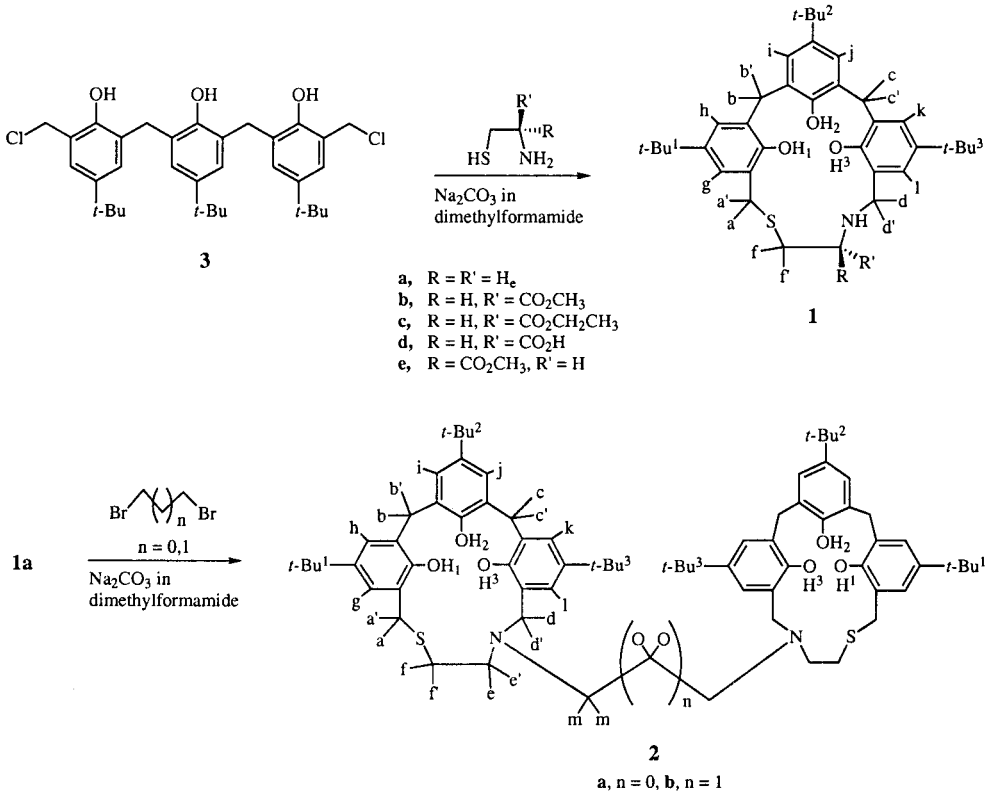
Macrocycle **1a** was conveniently synthesized by the reaction of bis(chloromethyl) phenol-formaldehyde trimer **3** with an equimolecular amount of aminoethanethiol in the presence of sodium carbonate in dry *N,N*-dimethylformamide at 30° under a nitrogen atmosphere in 50% yield. A similar reaction using *L*-cysteine methyl and ethyl esters afforded the corresponding cyclic compounds **1b** and **1c** in 30% yields. In contrast, the reaction using bis(chloromethyl) phenol-formaldehyde tetramer or pentamer in place of **3** did not produce any products except polymeric materials. Basic hydrolysis of **1b** at 0° gave carboxylic acid derivative **1d** in 90% yield. In order to modify the amine moiety on the aminoethanethiol unit of **1a**, we changed the methylene bridging reaction of **1a** by using dibromoalkanes. The reaction of **1a** with a 0.5 molar equivalent of dibromoethane in the presence of sodium carbonate in dry *N,N*-dimethylformamide at room temperature for 7 days afforded methylene bridged macrocycle **2a** in 70% yield. A similar reaction using dibromopropane under the same reaction conditions gave the corresponding product **2b** in 80% yield.

The structures of macrocycles **1** and **2** were determined on the basis of elemental analysis, fab-mass, nmr, and ir spectra. 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 made by C-H COSY spectra.

In the ir spectra of **1** and **2** in chloroform, the OH stretching vibration appeared in the region of 3300-3270 cm^{-1}, except for **1d** (3140 cm^{-1}), as broad bands. The phenolic OH protons of **1** in the ^1H nmr spectra in deuteriochloroform were observed at 8.7~9.4 ppm. Lowering the temperature to -60° slows down the rate of proton exchange, and the three signals with equal intensities appear: **1a** at 7.09, 9.28, 11.10; **1b** at 8.79, 10.01, 12.31; **1c** at 8.79, 9.98, 12.30 ppm. The phenolic protons of **2** were observed separately as three signals even at 20°: **2a** at 8.70, 9.63, 13.09; **2b** at 8.76, 9.87, 13.45 ppm. Considering that the nitrogen atom is a good proton acceptor, the OH signals observed at the lowest fields (11~13 ppm) are assigned to the OH protons adjacent to the amine moieties which form hydrogen bonds not only between OH groups but also between the OH and the nitrogen atoms. Comparing the ir and ^1H nmr spectra of the phenolic OH groups of **1** and **2** with those of calix[4]arene (ν_{OH} = 3200 cm^{-1}, δ_{OH} =10 ppm) [1a], the intramolecular hydrogen bonds in **1** and **2** are weaker due to the introduction of the arninoethanethiol unit.

The conformational properties of **1** were investigated by using ^1H and ^{13}C nmr spectroscopy. In the ^1H nmr

Scheme 1



spectrum of **1a** at 20° in deuteriochloroform, the methylene protons appeared as three singlets. Upon lowering the temperature, the methylene signals coalesced into three AB systems. The pair of doublets with the largest chemical shift difference is assigned to the methylene protons of the $ArCH_2Ar$ [3.48 ppm (J = 13 Hz), 4.22 ppm (J = 13

Table 1

Chemical Shifts of Methylene Protons, Coalescence Temperature (T_c), and Energy Barriers ($\Delta G^{\ddagger}$).

		$\delta SCH_aH_{a'}Ar$ (J, Hz; $\Delta\delta$, ppm)	$\delta ArCH_bH_{b'}Ar$ (J, Hz; $\Delta\delta$, ppm)	$\delta ArCH_cH_{c'}Ar$ (J, Hz; $\Delta\delta$, ppm)	$\delta NCH_dH_{d'}Ar$ (J, Hz; $\Delta\delta$, ppm)	T_c [°C]	$\Delta G^{\ddagger}$ [kcal/mol]
in deuteriochloroform							
1a	20°	3.73 [a]	3.86 [a]	3.86 [a]	3.94 [a]	-15	11.7
	-60°	3.45, 3.93 (13.0, 0.49)	3.48, 4.22 (13.0, 0.74)	3.48, 4.22 (13.0, 0.74)	3.73, 4.12 (13.0, 0.49)		
1b	20°	3.66, 177 (13.5, 0.11)	3.87 [a]	3.87 [a]	3.66, 4.02 (13.5, 0.36)	-10	12.0
	-60°	3.38, 197 (13.5, 0.39)	3.45, 4.23 (13.0, 0.78)	3.50, 4.18 (13.0, 0.68)	3.74, 3.82 (12.5, 0.08) 3.76, 182 (12.5, 0.06)		
1c	20°	3.65, 179 (13.5, 0.14)	3.86 [a]	3.86 [a]	3.66, 4.02 (13.5, 0.36)	-10	12.0
	-60°	3.42, 4.03 (13.5, 0.61)	3.50, 4.28 (13.0, 0.78)	3.55, 423 (13.0, 0.68)	3.77, 3.85 (12.5, 0.08) 3.79, 3.85 (12.5, 0.06)		
1d	55°[c]	3.72, 4.26 (12.0, 0.34)	3.55, 4.21 (14.0, 0.66)	3.58, 4.20 (13.5, 0.62)	4.00, 4.82 (13.5, 0.82)	>55	>15.2
in toluene-d_8							
1a	20°	4.07 [a]	4.25 [a]	4.16 [a]	3.39 [a]	–	–
	-70°	- [b]	- [b]	- [b]	- [b]		
1b	60° [c]	3.91, 4.01 (13.0, 0.10)	4.15, 4.26 (13.5, 0.11)	4.07, 4.15 (13.5, 0.08)	3.43, 3.80 (13.5, 0.37)	-20	11.5
	-70°	3.39, 4.58 (13.0, 1.19)	3.68, 4.93 (13.5, 1.25)	3.61, 4.71 (13.5, 1.09)	3.10, 3.45 (13.5, 0.25) 3.12, 3.45 (13.5, 0.23)		
1c	60°[c]	3.94, 3.99 (14.0, 0.05)	4.17, 4.24 (14.0, 0.07)	4.09, 4.14 (14.0, 0.18)	3.45, 3.85 (13.5, 0.40)	-20	11.5
	-70°	3.40, 4.56 (13.5, 1.16)	3.68, 4.93 (14.0, 1.25)	3.61, 4.71 (14.0, 1.10)	3.13, 3.52 (13.5, 0.39) 3.15, 3.52 (13.5, 0.37)		

[a] The signal was observed as a broad singlet. [b] Too broad and complex to assign the signals. [c] Too broad to assign the signals at 20°.

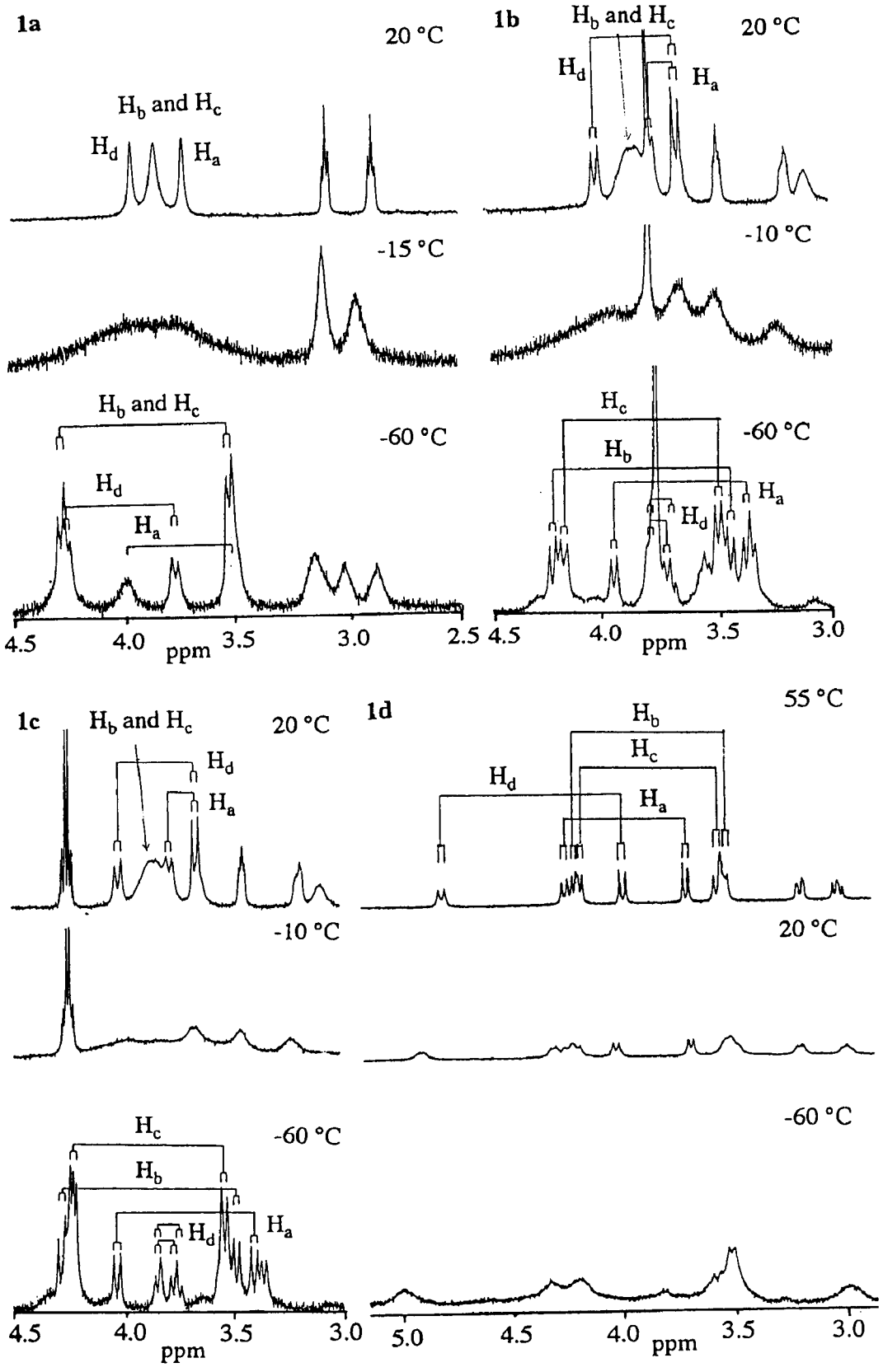


Figure 1. Partial ^{1}H nmr spectra for methylene protons in macrocycles **1a**, **1b**, **1c**, and **1d** in deuteriochloroform at variable temperatures at 500 MHz.

Hz)], which are two sets of overlapping pairs of doublets. The pair appearing at relatively high field as broad signals is ascribed to the $ArCH_2S$ protons [3.45 ppm, 3.93 ppm], and the pair observed at relatively low field is ascribed to the $ArCH_2N$ protons [3.73 ppm (J = 13 Hz), 4.22 ppm (J = 13 Hz)]. It is known that the chemical shift difference ($\Delta\delta$) between high- and low-field resonances arising from the $ArCH_2Ar$ methylene protons in calix[4]arenes is generally 0.9 ±0.2 ppm for cone conformation and zero for the alternate 1,3-conformation [1a]. Provided the rule established for calix[4]arene is also applicable to this system, it follows that the adjacent aryl rings of **1a**, whose $\Delta\delta$ values are 0.74 ppm, are preferable to the *syn* orientation. Analogous macrocycles **1b** and **1c** showed a similar temperature dependent ^1H nmr behavior characteristic of **1a**, namely a broad singlet signal arising from $ArCH_2Ar$ methylene groups at 20° resolved into two pairs of doublets at -60°. In the case of carboxylic acid derivative **1d**, the $ArCH_2Ar$ methylene protons were observed as two pairs of doublets even at 55°. The magnitude of the chemical shifts difference of **1b**, **1c**, and **1d** ($\Delta\delta$ = 0.62~0.78 ppm) is commensurate with the *syn* orientation.

The ^{13}C nmr chemical shifts of the methylene carbon atom of the $ArCH_2Ar$ for calixarenes have come into use as a mean for assessing conformations [6]. Appling these to **1**, the *syn* orientation of the adjacent aryl rings was deduced from the chemical shift values: **1a** at 32.4, 32.7 ppm; **1b** at 31.9, 32.9 ppm; **1c** at 31.9, 32.8 ppm; and **1d** at 32.4, 32.7 ppm) of the $ArCH_2Ar$ carbon atoms. It was in agreement with the results derived from the variable temperature ^1H nmr experiment.

The coalescence temperatures (T_c) and the barriers to ring inversion ($\Delta G^{\ddagger}$) for **1** were derived from variable temperature ^1H nmr spectroscopy at 500 MHz [7]. The results are shown in Table 1. The $\Delta G^{\ddagger}$ value (11.7 kcal/mol in deuteriochloroform) of **1a** is similar to that of trihydroxy-*p*-*tert*-butylcalix[4]arene (11.6 kcal/mol in deuteriochloroform) [8] and is somewhat lower than those of **1b** and **1c** (12.0 kcal/mol in deuteriochloroform). In **1d**, a pair of doublets corresponding to the $ArCH_2Ar$ methylene protons did not coalesce in deuteriochloroform up to 55° ($\Delta G^{\ddagger}$ > 15.2 kcal/mol). This means that **1d** is a highly rigid structure in the cone form, which can be ascribed to participation of the amino acid moiety in the hydrogen bond array of the hydroxy groups. In the ^1H nmr spectra of **1b** and **1c** at -60° two types of H_{exo} protons of the NCH_2Ar methylene protons were observed. Considering that this proton is located close to the chiral center of a cysteine moiety and this phenomenon is not observed in **1a**, it is reasonable to assume that two diastereomeric cone conformations (A and B in Figure 2) were observed. The ratio of these species is approximately 1:1 at -60°.

The conformational properties of **1b** and **1c** in toluene-d_8 are similar to those in deuteriochloroform. The $ArCH_2Ar$ methylene protons appear as broad signals at 20° in the ^1H nmr spectra. The signals coalesced at -20° (T_c) and finally appeared as two pairs of doublet signals below -70°. The magnitude of the chemical shift difference ($\Delta\delta$ = 1.09-1.25 ppm) is proportional to the *syn* orientation. Therefore the prefered conformation of **1b** and **1c** is a cone. The activation energy ($\Delta G^{\ddagger}$) of ring inversion is 11.5 kcal/mol, which is somewhat lower than that in deuteriochloroform (12.0 kcal/mol). Variable temperature ^1H nmr spectral behavior of **1a** and **1d** in toluene-d_8 is quite different in deuteriochloroform. The aromatic and methylene proton resonances showed a more complex pattern than those in deuteriochloroform at -60°, indicating that a few conformers existed in toluene-d_8. From these results the cone conformation of **1** is stabilized more by chloroform than by toluene. It may relate to the complexing ability of **1** toward solvents [7b].

As mentioned above, the $\Delta\delta$ values of $ArCH_2Ar$ methylene protons are expected to be sensitive to the dihedral angle between the methylene protons and the plane of the aromatic ring. Thus, the different $\Delta\delta$ values (0.78 and 0.68 ppm) observed at **1b** and **1c** imply that the phenol-formaldehyde trimer moiety has no plane of symmetry and is considered to adopt a twisted form. Since the smaller $\Delta\delta$ value (0.68 ppm) is ascribed to the methylene protons H_c and $H_{c'}$ and the hydroxy proton (OH^3) is located inside the cavity due to the hydrogen bond with a nitrogen atom, it is reasonable to assume that the aromatic ring with the attached hydroxy proton (OH^3) is somewhat flattened as shown in Figure 2. This assumption was also

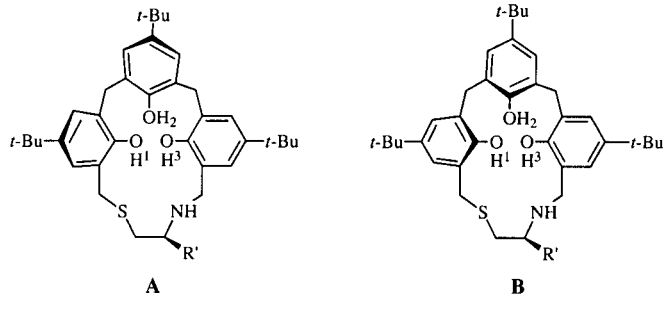


Figure 2.

supported by the $\Delta\delta$ values (approximately 0.0 ppm) of the NCH_2Ar methylene protons. This implies that the methylene protons are located in the equivalent magnetic field, namely the dihedral angle between the CN bond of NCH_2Ar moiety and the aromatic ring was *ca.* zero degrees. The circular dichroism spectral absorptions of **1b** were observed at 231 nm (θ+22000), 274 nm (θ-2600), and 290 nm (θ+7800). The corresponding enantiomer **1e**, which was synthesized from the reaction of *D*-cysteine

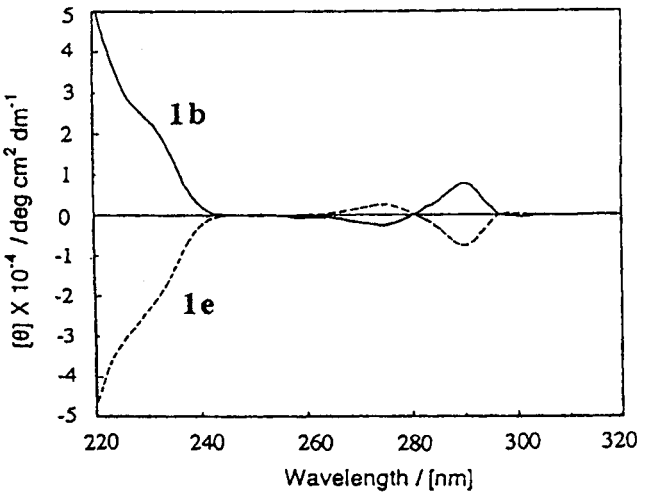


Figure 3. Circular dichroism spectra of the macrocycles **1b** and **1e** in hexane at 20°.

methyl ester with **3** in 21% yield, showed the completely opposite circular dichroism spectrum (231 nm (θ-22000), 274 nm (θ+2600), and 290 nm (θ-7800)). The circular dichroism spectral absorption patterns of **1b** and **1e** are quite similar to that of known chiral calixarenes [5], supporting the assumption that the phenol-formaldehyde units are chiral. These observations clearly indicate that the chirality of the phenol-formaldehyde trimer unit was induced by the cysteine moiety and the twist direction was controlled by the hydrogen bond.

In order to clarify the molecular motions of macrocycle **1a**, we carried out the measurement of its ^{1}H nmr relaxation time (T_1) by using an inversion recovery method in deuteriochloroform at 25° [2b,9]. The T_1 measurement of **1a** reveals that the T_1 values of the methylene protons of $ArCH_2Ar$ (H_b and H_c) is remarkably small. This means that the motion of the aromatic units in **1a** is characterized by up and down motions around the methylene moiefies as axes. The T_1 values of the methylene protons of $ArCH_2N$ (H_d and H_e) are smaller than those of the methylene protons of $ArCH_2S$ (H_a and H_f). The smaller T_1 values observed suggest that the hydrogen bond between the nitrogen atom and the adjacet phenolic hydroxyl group (OH^3) suppress the

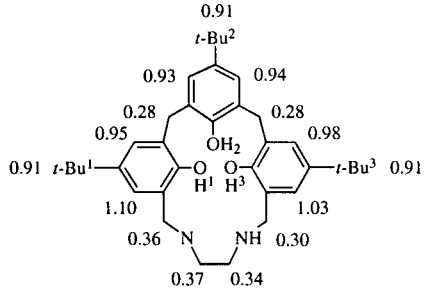


Figure 4. T_1 values of **1a**/[s].

motions of the methylene moieties. Comparing the aromatic protons, the larger T_1 values were observed for H_g and H_1, which were placed in the neighborhood of aminoethanethiol moiety. This implies that the introduction of the aminoethanethiol moiety into the macrocyclic ring causes the ring fluctuation in macrocycles.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H and ^{13}C nmr spectra were measured with JEOL EX-270 and Varian 500 INOVA spectrophotometers, using tetramethylsilane as the internal standard. The ir and uv spectra were taken on Horiba FF-200 and Hitachi 228A spectrophotometers, respectively. The circular dichroism spectra were obtained on a Jasco J-720WI spectrophotometer. The mass spectra (FAB) were recorded on a JEOL JMS AX-505HA spectrometer, using *m*-nitrobenzyl alcohol the matrix. Optical rotations were measured on a Atago AA-5 digital polarimeter. Column chromatography was performed using silica gel (Kieselgel 60, 63-200 μm, 70-230 mesh, Merck). All chemicals were reagent grade and were used without further purification. 3-[3-(3-Hydroxymethyl-5-*tert*-butylsalicyl)-5-*tert*-butylsalicyl)-5-*tert*-butyl-2-hydroxybenzyl alcohol was prepared by a literature procedure [3a].

Synthesis of 2-[3-(3-Chloromethyl-5-*tert*-butylsalicyl)-5-*tert*-butylsalicyl]-6-chloromethyl-4-*tert*-butylphenol (**3**).

To a solution of 3-[3-(3-hydroxymethyl-5-*tert*-butylsalicyl)-5-*tert*-butylsalicyl]-5-*tert*-butyl-2-hydroxybenzylalcohol (5.00 g, 9.4 mmoles) in 100 ml of dry benzene was added a solution of thionyl chloride (6.00 g, 50 mmoles) in 20 ml of dry benzene over 30 minutes. After the addition was completed, the mixture was allowed to stir at room temperature for 5 hours. Removal of benzene and excess thionyl chloride *in vacuo* gave colorless crystals, which were recrystallized from benzene:hexane 1:5 to give **3** as colorless crystals (5.20 g, 97% yield), mp 115-116°; ir (potassium bromide): 3394 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1. 27 (s, 27H, *t*-Bu x 3), 3.93 (s, 4H, $ArCH_2Ar$), 4.66 (s, 4H, $ArCH_2Cl$), 7.00-7.41 (m, 6H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 31.3, 31.4, 31.7, 34.0, 34.1, 43.6, 123.3, 125.5, 125.9, 126.9, 127.9, 128.3, 144.1, 144.5, 147.1, 149.3; (FAB) ms: m/z 571 $(M+1)^+$.

Anal. Calcd. for $C_{34}H_{44}O_3Cl_2$: C, 71.43; H, 7.76. Found: C, 71.34; H, 7.90.

General Procedure for the Preparation of Macrocycles **1.**

To a solution of **3** (0.57 g, 1.0 mmole) and sodium carbonate (0.32 g, 3.0 mmoles) in dry dimethylformamide (30 ml) was slowly added a solution of aminoethanethiol hydrochloride or cysteine alkyl ester hydrochloride (1.0 mmole) in dry *N,N*-dimethylformamide (10 ml) over a period of 1 hour at 30°. After the addition was complete, the mixture was allowed to stir for 2 hour at 30°. Removal of *N,N*-dimethylformamide *in vacuo* gave pale yellow oily residue which was separated by column chromatography on silica gel (chloroform:ethyl acetate 1:1 for **1a**, hexane:ethyl acetate 9:1 for **1b**, **1c**, and **1e** as an eluent) to give **1** as crystals.

10,16,22-Tri-*tert*-butyl-24,25,26-trihydroxy-2,3,4,5,6-pentahomo-3-thia-6-azatetracyclo[18.3.1.1^{8,12}.1^{14,18}]hexacosane-1(24),8,10,12(25),14,16,18(26),20,22-nonene (**1a**).

The yield of **1a** was 50% as pale yellow crystals, mp 199-201° (from dichloromethane-ethyl acetate); ir (chloroform): 3300 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.23 (s, 18H, *t*-Bu^1 and *t*-Bu^3), 1.27 (s, 9H, *t*-Bu^2), 2.88 (t, 2H, H_f and $H_{f'}$, J = 7.1 Hz), 3.11 (t, 2H, H_e and $H_{e'}$, J = 7.1 Hz), 3.73 (s, 2H, H_a and $H_{a'}$), 3.86 (br s, 4H, H_b, $H_{b'}$, H_c, and $H_{c'}$), 3.94 (s, 2H, H_d and $H_{d'}$), 6.79 (d, 1H, H_1, J = 2.3 Hz), 6.87 (d, 1H, H_g, J = 2.3 Hz), 7.11 (d, 1H, H_j, J = 2.3 Hz), 7.13 (d, 1H, H_h, J = 2.3 Hz), 7.17 (d, 1H, H_i, J = 2.3 Hz), 7.22 (d, 1H, H_k, J = 2.3 Hz), 8.70 (br s, 3H, OH); ^{13}C nmr (deuteriochloroform): 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; (FAB) ms: m/z 576 (M+1)$^+$.

Anal. Calcd. for $C_{36}H_{49}NO_3S$: C, 75.09; H, 8.58; N, 2.43. Found: C, 75.26; H, 8.79; N, 2.24.

(5R)-10,16,22-Tri-*tert*-butyl-5-methoxycarbonyl-24,25,26-trihydroxy-2,3,4,5,6-pentahomo-3-thia-6-azatetracyclo-[18.3.1.1^{8,12}.1^{14,18}]hexacosane-1(24),8,10,12(25),14,16,18(26),-20,22-nonene (**1b**).

The yield of **1b** was 30% as colorless crystals, mp 211-213° (from ethyl acetate), $[\alpha]_D^{20}$ = +20° (c 0.1, chloroform); ir (chloroform): 3290 (OH), 1739 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22 (s, 9H, *t*-Bu^1), 1.24 (s, 9H, *t*-Bu^3), 1.28 (s, 9H, *t*-Bu^2), 3.11 (dd, 1H, H_f, J = 10.8, 7.3 Hz), 3.19 (dd, 1H, $H_{f'}$, J = 10.8, 5.1 Hz), 3.48 (dd, 1H, H_e, J = 7.3, 5.1 Hz), 3.66 (d, 2H, H_a and H_d, J = 13.5 Hz), 3.77 (d, 1H, $H_{a'}$, J = 13.5 Hz), 3.78 (s, 3H, CO_2Me), 3.87 (br s, 4H, H_b, $H_{b'}$, H_c, and $H_{c'}$), 4.02 (d, 1H, $H_{d'}$, J = 13.5 Hz), 6.81 (d, 1H, H_1, J = 2.4 Hz), 6.82 (d, 1H, H_g, J = 2.4 Hz), 7.11 (d, 2H, H_h and H_j, J = 2.4 Hz), 7.18 (d, 1H, H_i, J = 2.4 Hz), 7.26 (d, 1H, H_k, J = 2.4 Hz), 9.40 (br s, 3H, OH); ^{13}C nmr (deuteriochloroform): 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; (FAB) ms: m/z 634 (M+1)$^+$.

Anal. Calcd. for $C_{38}H_{51}NO_5S$: C, 72.01; H, 8.11; N, 2.21. Found: C, 72.14; H, 8.16; N, 2.08.

(5*R*)-10,16,22-Tri-*tert*-butyl-5-ethoxycarbonyl-24,25,26-trihydroxy-2,3,4,5,6-pentahomo-3-thia-6-azatetracyclo[18.3.1.1^{8,12}.1^{14,18}]hexacosane-1(24),8,10,12(25),-14,16,18(26),20,22-nonene (**1c**).

The yield of **1c** was 30% of colorless crystals, mp 212-213.5° (from ethyl acetate), $[\alpha]_D^{20}$ = +21° (c 0.1, chloroform); ir (chloroform): 3290 (OH), 1733 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22 (s, 9H, *t*-Bu^1), 1.24 (s, 9H, *t*-Bu^3), 1.28 (s, 9H, *t*-Bu^2), 1.31 (t, 3H, $CO_2CH_2CH_3$, J = 7.2 Hz), 3.14 (dd, 1H, H_f, J = 10.8, 7.3 Hz), 3.20 (dd, 1H, $H_{f'}$, J = 10 8, 5.1 Hz), 3.45 (dd, 1H, H_e, J = 7.3, 5.1 Hz), 3.65 (d, 1H, H_d, J = 13.5 Hz), 3.66 (d, 1H, H_a, J = 13.5 Hz), 3.79 (d, 1H, $H_{a'}$, J = 13.5 Hz), 3.86 (br s, 4H, H_b, $H_{b'}$, H_c, and $H_{c'}$), 4.02 (d, 1H, $H_{d'}$, J = 13.5 Hz), 4.24 (q, 2H, $CO_2CH_2CH_3$, J = 7.2 Hz), 6.81 (d, 1H, H_1, J = 2.4 Hz), 6.82 (d, 1H, H_g, J = 2.4 Hz), 7.11 (d, 2H, H_h and H_j, J = 2.4 Hz), 7.18 (d, 1H, H_i, J = 2.4 Hz), 7.26 (d, 1H, H_k, J = 2.4 Hz), 9.40 (br s, 3H, OH); ^{13}C nmr (deuteriochloroform): 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; (FAB) ms: m/z 648 (M+1)$^+$.

Anal. Calcd. for $C_{39}H_{53}NO_5S$: C, 72.30; H, 8.25; N, 2.16. Found: C, 72.57; H, 8.32; N, 2.04.

(5*S*)-10,16,22-Tri-*tert*-butyl-5-methoxycarbonyl-24,25,26-trihydroxy-2,3,4,5,6-pentahomo-3-thia-6-azatetracyclo[18.3.1.1^{8,12}.1^{14,18}]hexacosane-1(24),8,10,12(25),14,16,18(26),20,22-nonene (**1e**).

The yield of **1e** was 21% as colorless crystals, mp 218-221° (from ethyl acetate), $[\alpha]_D^{20}$ = -20° (c 0.1, chloroform); ir (chloroform): (OH) 3290, (CO) 1739 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22 (s, 9H, *t*-Bu^1), 1.24 (s, 9H, *t*-Bu^3), 1.28 (s, 9H, *t*-Bu^2), 3.11 (dd, 1H, H_f, J = 10.8, 7.3 Hz), 3.19 (dd, 1H, $H_{f'}$, J = 10.8, 5.1 Hz), 3.48 (dd, 1H, H_e, J = 7.3, 5.1 Hz), 3.66 (d, 2H, H_a and H_d, J = 13.5 Hz), 3.77 (d, 1H, $H_{a'}$, J = 13.5 Hz), 3.78 (s, 3H, CO_2Me), 3.87 (broad s, 4H, H_b, $H_{b'}$, H_c, and $H_{c'}$), 4.02 (d, 1H, $H_{d'}$, J = 13.5 Hz), 6.81 (d, 1H, H_1, J = 2.4 Hz), 6.82 (d, 1H, H_g, J = 2.4 Hz), 9.40 (br s, 3H, OH), 7.11 (d, 2H, H_h and H_j, J = 2.4 Hz), 7.18 (d, 1H, H_i, J = 2.4 Hz), 7.26 (d, 1H, H_k, J = 2.4 Hz); ^{13}C nmr (deuteriochloroform): 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; (FAB) ms: m/z 634 (M+1)$^+$.

Anal. Calcd. for $C_{38}H_{51}NO_5S$: C, 72.01; H, 8.11; N, 2.21. Found: C, 72.18; H, 7.82; N, 2.17.

Basic Hydrolysis of Macrocycle **1b** Leading to Carboxylic Acid Compound **1d**.

To a solution of **1b** (240 mg, 3.8 mmoles) in 10 ml of methanol and 20 ml of 1,4-dioxane was slowly added a solution of 5% sodium hydroxide (20 ml) over 5 minutes at 0°. After the addition was complete, the mixture was allowed to stir at 0° for 6 hours and then 10% aqueous hydrochloric acid solution was added to the solution until the *p*H reached 2. The white precipitate was collected by filtration and dried *in vacuo* at 80°. Recrystallization of the precipitates from chloroform-hexane gave **1d** (211 mg) as colorless crystals.

(5*R*)-10,16,22-Tri-*tert*-butyl-5-carboxy-24,25,26-trihydroxy-2,3,4,5,6-pentahomo-3-thia-6-azatetracyclo[18.3.1.1^{8,12}.1^{14,18}]-hexacosane-1(24),8,10,12(25),14,16,18(26),20,22-nonene (**1d**).

The yield of **1d** was 90% as colorless crystals, mp 195-197°, $[\alpha]_D^{20}$ = -2.2° (c 0.1, chloroform); ir (chloroform): 3140 (OH), 1641 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform at 60°: δ 1.19 (s, 9H, *t*-Bu^1), 1.26 (s, 9H, *t*-Bu^3), 1.28 (s, 9H, *t*-Bu^2), 3.05 (dd, 1H, H_f, J = 13.0, 9.0 Hz), 3.21 (dd, 1H, $H_{f'}$, J = 13.0, 3.5 Hz), 3.54 (dd, 1H, H_e, J = 9.0 Hz), 3.55 (d, 1H, H_b, J = 14.0 Hz), 3.58 (d, 1H, H_c, J = 14.0 Hz), 3.72 (d, 1H, H_a, J = 11.0 Hz), 4.00 (d, 1H, H_d, J = 13.5 Hz), 4.20 (d, 1H, $H_{c'}$, J = 14.0 Hz), 4.21 (d, 1H, $H_{b'}$, J = 14.0 Hz), 4.26 (d, 1H, $H_{a'}$, J = 11.0 Hz), 4.82 (d, 1H, $H_{d'}$, J = 13.5 Hz), 6.90 (d, 1H, H_g, J = 2.5 Hz), 7.02 (d, 1H, H_1, J = 2.5 Hz), 7.11 (d, 1H, H_i, J = 2.5 Hz), 7.14 (d, 1H, H_j, J = 2.5 Hz), 7.15 (d, 1H, H_h, J = 2.5 Hz), 7.30 (d, 1H, H_k, J = 2.5 Hz); ^{13}C nmr (deuteriochloroform): δ 31.5, 32.4, 32.7, 32.8, 33.8, 33.9, 35.4, 50.6, 59.1, 120.5, 124.4, 125.2, 125.4, 125.6, 126.1, 127.0, 127.6, 127.9, 128.3, 142.5, 142.7, 143.8, 148.0, 149.8, 151.6, 172.2; (FAB) ms: m/z 642 (M+Na)$^+$.

Anal. Calcd. for $C_{37}H_{49}NO_5S$: C, 71.69; H, 7.97; N, 2.26. Found: C, 71.39; H, 8.19; N, 2.27.

General Procedure for Methylene Bridging Reaction.

A mixture of **1a** (190 mg, 0.33 mmole), dibromoalkane (0.16 mmole) and sodium carbonate (53 mg, 0.50 mmole) in dry *N,N*-

dimethylformamide (5 ml) was allowed to stir at 30° for 7 days. Removal of dimethylformamide under reduced pressure gave a pale yellow oily residue which was separated by column chromatography on silica gel using hexane:ethyl acetate 4:1 as an eluent to give **2** as colorless crystals.

1,2-Bis(10,16,22-Tri-*tert*-butyl-24,25,26-trihydroxy-2,3,4,5,6-pentabomo-3-thia-6-azatetracyclo[18.3.1.1^{8,12}.1^{14,18}]hexacosane-1(24),8,10,12(25),14,16,18(26),20,22-nonene)ethane (**2a**).

Compound 2a was obtianed in 70% yield as colorless powder, mp 163-166° (dichloromethane-ethyl acetate); ir (chloroform): 3270 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.23 (s, 18H, *t*-Bu^1), 1.24 (s, 18H, *t*-Bu^3), 1.29 (s, 18H, *t*-Bu^2), 2.60~4.50 (m, 28H, H_a, $H_{a'}$, H_b, $H_{b'}$, H_c, $H_{c'}$, H_d, $H_{d'}$, H_e, $H_{e'}$, H_f, $H_{f'}$, H_m, and $H_{m'}$), 6.78 (d, 2H, H_1, J = 2.4 Hz), 6.93 (d, 2H, H_g, J = 2.4 Hz), 7.13 (d, 2H, H_j, J = 2.4 Hz), 7.14 (d, 2H, H_h, J = 2.4 Hz), 7.17 (d, 2H, H_i, J = 2.4 Hz), 7.24 (d, 2H, H_k, J = 2.4 Hz), 8.70 (br s, 2H, OH), 9.63 (br s, 2H, OH), 13.09 (2H, br s, OH); ^{13}C nmr (deuteriochloroform): δ 30.0, 31.5, 32.5, 33.9, 34.0, 53.5, 55.0, 59.7, 119.7, 123.1, 125.4, 125.6, 125.8, 126.0, 126.3, 126.7, 126.8, 127.6, 127.9, 128.0, 128.2, 143.2, 143.4, 144.0, 147.6, 149.3, 150.8; (FAB) ms: m/z 1176 (M+1)$^+$.

Anal. Calcd. for $C_{74}H_{100}N_2O_6S_2$: C, 75.47; H, 8.56; N, 2.38. Found: C, 75.55; H, 8.67; N, 2.29.

1,3-Bis(10,16,22-Tri-*tert*-butyl-24,25,26-trihydroxy-2,3,4,5,6-pentahomo-3-thia-6-azatetracyclo[18.3.1.1^{18,12}.1^{14,18}]hexacosane-1(24),8,10,12(25),14,16,18(26),20,22-nonene)propane (**2b**).

The yield was 80% as a colorless powder, mp 251-254° dec (from dichloromethane-ethyl acetate); ir (chloroform): 3270 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.23 (s, 18H, *t*-Bu^1), 1.24 (s, 18H, *t*-Bu^3), 1.28 (s, 18H, *t*-Bu^2), 2.04 (m, 2H, H_o), 2.70~4.50 (m, 28H, H_a, $H_{a'}$, H_b, $H_{b'}$, H_c, $H_{c'}$, H_d, $H_{d'}$, H_e, $H_{e'}$, H_f, $H_{f'}$, H_m, and $H_{m'}$), 6.77 (d, 2H, H_1, J = 2.4 Hz), 6.93 (d, 2H, H_g, J = 2.4 Hz), 7.13 (d, 4H, H_h and H_j, J = 2.4 Hz), 7.17 (d, 2H, H_i, J = 2.4 Hz), 7.20 (d, 2H, H_k, J = 2.4 Hz), 8.76 (br s, 2H, OH), 9.87 (br s, 2H, OH), 13.45 (br s, 2H, OH); ^{13}C nmr (deuteriochloroform): δ 29.8, 31.1, 31.5, 31.8, 32.5, 34.0, 54.0, 54.6, 59.2, 119.9, 122.9, 125.4, 125.6, 125.8, 126.2, 126.5, 127.0, 127.6, 128.0, 143.1, 143.2, 144.0, 147.5, 149.3, 151.1; (FAB) ms: m/z 1190 (M+1)$^+$.

Anal. Calcd. for $C_{75}H_{102}N_2O_6S_2$: C, 75.59; H, 8.63; N, 2.35. Found: C, 75.58; H, 8.73; N, 2.23.

T_1 Measurements.

The T_1 values were obtained in deuteriochloroform at 25° by using an inversion recovery method. The nmr sample was sealed under vacuum after degassing by five freeze-pump-thaw cycles. The T_1 values for protons showed good reproducibility within the 5% relative standard deviation.

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