Synthesis and Properties of Bowl-Shaped Homotriazacalix[3 and 6] arenes and the Acyclic Analogues

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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 corresponding acyclic phenol-formaldehyde oligomers were also synthesized. The structural analysis of the macrocycles by nmr and circular dichroism spectra imply the existence of chiral transmission from the point chirality of the cysteine bridge to the cyclophane moiety. Their cyclic and acyclic compounds have a π-base cavity large enough to include the ammonium ion.

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Introduction.

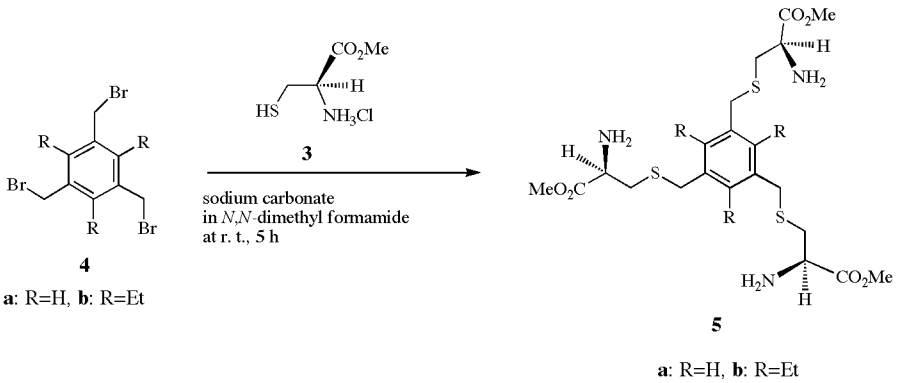
Calixarenes are well known for their unique molecular architecture, which is extensively used in the supramolecular chemistry to build up more complex synthetic receptors for ion and neutral molecules [1]. Despite such progress of the calixarene chemistry, little effort has been directed towards the methylene bridge [2]. This situation inspired us to exploit the synthesis of calixarene analogs, which were modified on the methylene moiety to other unit. Introduction of other unit into the cyclic array easily affect the entire molecules, thus providing the possibility for other properties effectively. Therefore, we report syntheses of bowl-shaped homoazacalixarenes in which three methylene bridges (-CH_2-) were replaced by three dihomoaza bridges (-CH_2NRCH_2-), their structural detail based on their nmr and circular dichroism spectra, and their complexation toward ammonium ion. We also prepared the corresponding acyclic compounds to compare with the properties of the cyclic compounds.

Results and Discussion.

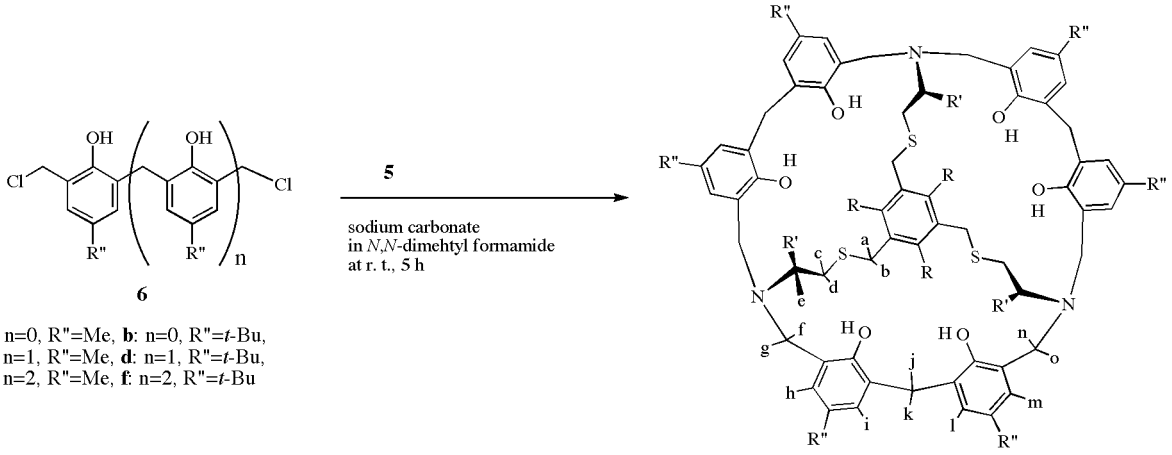
Chiral triamines **5** bearing three cysteine residues were synthesized by the reactions of 1,3,5-tris(bromomethyl)-benzenes **4a** and **4b** with cysteine methyl ester **3** in *N*,*N*-dimethyl formaldehyde at 30 °C in the presence of sodium carbonate in 75 % (**4a**) and 97 % (**4b**) yields, respectively. Treatment of **5a** with three equimolar amount of bis(chloromethyl) phenols (**6a** and **6b**) or bis(chloromethyl)phenol-formaldehyde dimer **6c** afforded macrocycles (**1a**, **1b**, and **1c**) in 14, 13, and 6 % yields, respectively (Scheme 1). Analogous reactions using **4b** with **6a** and **6c** also gave the corresponding macrocycles (**1d** and **1e**) in 5 and 15 % yields, respectively. However, the same reactions of **4** with **6d**, **6e**, or **6f** did not give any product except polymeric materials. Corresponding acyclic compounds **2** were prepared from the condensation reaction between **4** and **7** in refluxing benzene, followed by reduction using sodium borohydride, in moderate yields (Scheme 2 and 3).

The structure of macrocycles **1** and acyclic compounds **2** 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 intramolecular hydrogen bonding [3]. The ir spectral absorption band corresponding to OH stretching of the phenol unit was observed at 3100-3300 cm^{-1}, indicating the formation of strong intramolecular hydrogen bonding (Table 1)[3]. The ^{1}H and ^{13}C nmr spectra of **1** showed C_3 symmetry signal pattern [4]. The $ArCH_2N$ and $ArCH_2Ar$ methylene protons

Scheme 1



Scheme 2



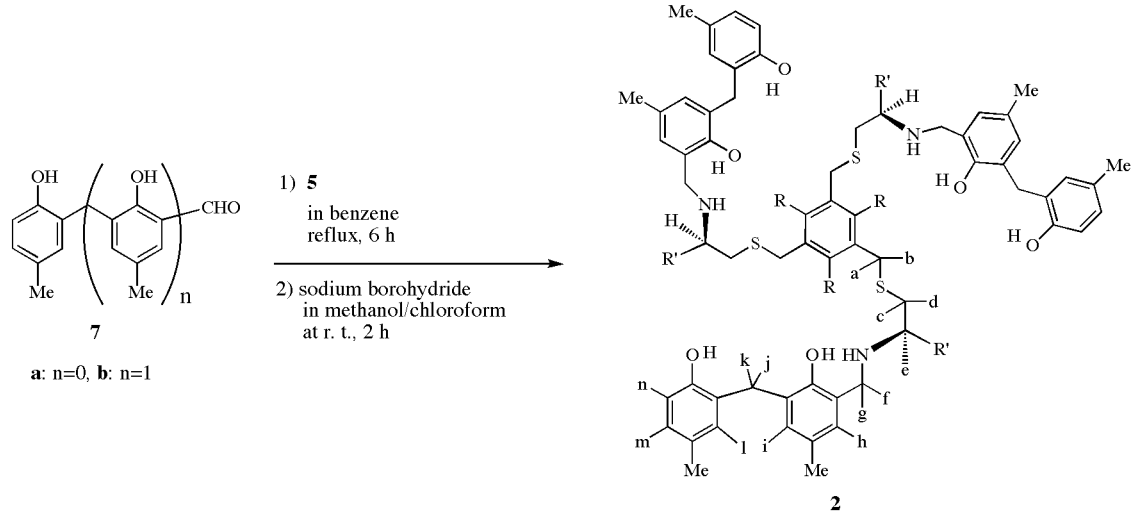
6

a: n=0, R"=Me, **b**: n=0, R"=*t*-Bu,
c: n=1, R"=Me, **d**: n=1, R"=*t*-Bu,
e: n=2, R"=Me, **f**: n=2, R"=*t*-Bu

1

a: n=0, R=H, R'=CO_2Me, R"=Me,
b: n=0, R=H, R'=CO_2Me, R"=*t*-Bu,
c: n=1, R=H, R'=CO_2Me, R"=Me,
d: n=0, R=Et, R'=CO_2Me, R"=Me,
e: n=1, R=Et, R'=CO_2Me, R"=Me

Scheme 3



7

a: n=0, **b**: n=1

2

a: n=0, R=H, R'=CO_2Me, **c**: n=0, R=Et, R'=CO_2Me,
b: n=1, R=H, R'=CO_2Me, **d**: n=1, R=Et, R'=CO_2Me,

of **1** appeared as two (for **1a**, **1b**, and **1d**) or three (for **1c** and **1e**) pair of doublets due to the geminal coupling between H_{exo} and H_{endo} protons at room temperature (Table 2). These pairs did not coalesce at 55 °C in deuteriochloroform, indicating that **1** exists as a rigid structure. Conformational analysis of the phenol-formaldehyde dimer moiety in **1c** and **1e** was carried out by using nmr spectroscopy. The $ArCH_2Ar$ methylene region is informative and diagnostic for conformational assignments. The $ArCH_2Ar$ methylene protons of **1c** and **1e** were observed as AB systems. It is known that the $\Delta\delta$ values between H_{exo} and H_{endo} of the $ArCH_2Ar$ methylene protons of calixarenes is generally *ca*. 0.9±0.2 ppm for *syn* orientation of the aryl rings and zero for *anti* [5]. Applying this rule to **1c** and **1e**, the $\Delta\delta$ values (1.00 ppm for **1c** and 0.98 ppm for **1e**) indicate that the phenol-formaldehyde dimer moiety adopts a *syn* orientation. This is further supported by the chemical shift values of the $ArCH_2Ar$ methylene carbon atoms (δ 30.9 ppm for **1c** and δ 30.8 ppm for **1e**) [6]. Based on these results, the cone-like form may adopt a preferable conformation in **1**.

The different $\Delta\delta$ values of the $ArCH_2N$ methylene protons ($\Delta\delta H_fH_g$ and $\Delta\delta H_nH_o$) imply that the cyclophane

Table 1

Chemical Shifts of Hydroxy Protons in the ^{1}H NMR Spectra in deuteriochloroform at 20 °C (500MHz) and IR Spectral Absorptions of OH and CO Groups in chloroform at 20 °C.

Cyclic and Acyclic Compound	δ_{OH} [ppm]	ν_{OH} [cm^{-1}]	ν_{CO} [cm^{-1}]
1a	10.60	3089	1732
1b	10.60	3111	1732
1c	8.76, 11.20	3288	1726
1d	10.40	3107	1732
1e	8.73, 11.20	3288	1726
2a	a	3313	1739
2b	a	3319	1732
2c	a	3313	1732
2d	a	3319	1739

a: too broad to observe as a signal

the dihedral angle between the methylene protons and the plane of the adjacent aromatic rings as shown in Figure 1. Since the smaller $\Delta\delta$ values are 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 steric repulsion between the hydroxyl group of the phenol ring and methyl ester group of the cysteine moiety. Therefore, it is reasonable to assume that the direction of the intramolecular hydrogen bonding of **1** is effected by the point chirality of the cysteine unit. In this case, the chirality of the *L*-cysteine bridge cause the predominate formation of the left-hand isomer in Figure 2. In other words, the point chirality of the cysteine unit transfers to the cyclophane moiety. To prove the existence

Table 2

Chemical Shifts of Methylene Protons in deuteriochloroform at 20 °C (500 MHz)

Cyclic and Acyclic Compound	NCH_fH_gAr (*J* [Hz], $\Delta\delta$ [ppm])	$ArCH_jH_kAr$ (*J* [Hz], $\Delta\delta$ [ppm])	$ArCH_nH_oN$ (*J* [Hz], $\Delta\delta$ [ppm])
1a	3.55, 3.86 (15.5, 0.31)	-	3.11, 4.24 (13.0, 1.13)
1b	3.61, 3.88 (15.5, 0.27)	-	3.16, 4.28 (14.0, 1.12)
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)
1d	3.43, 3.75 (16.0, 0.32)	-	3.09, 4.13 (13.0, 1.04)
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)
2a	3.66, 3.94 (13.5, 0.28)	-	-
2b	3.60, 3.89 (14.0, 0.29)	3.78, 3.84 (14.0, 0.06)	-
2c	3.77, 4.00 (13.5, 0.23)	-	-
2d	3.73, 3.96 (13.5, 0.23)	3.79, 3.84 (14.5, 0.05)	-

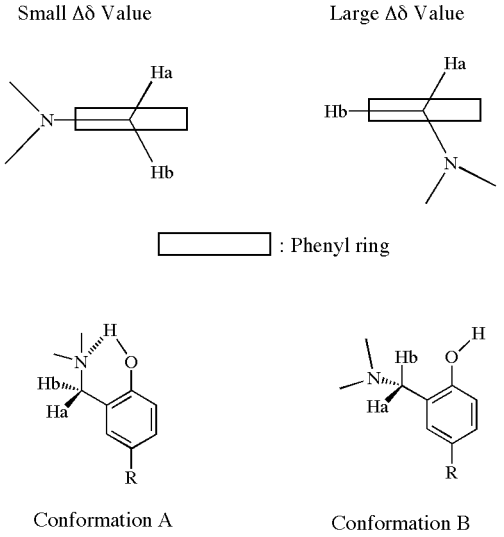


Figure 1

moiety is twisted. The $\Delta\delta$ values of the methylene protons of the cyclophane moiety are expected to be sensitive to

Table 3

Circular Dichroism and Uv Spectra of **1** and **2** in Chloroform at 20 °C

Cyclic and Acyclic Compound	λ_{ext} [nm] (θ [deg cm^2 dmol^{-1}])	λ_{max} [nm] (ε [cm^{-1} mol dml^{-3}])
1a	297 (50700)	289 (7000)
1b	293 (13600)	286 (7600)
1c	298 (56300)	293 (16100)
1d	296 (35900)	289 (10100)
1e	298 (67600)	293 (21600)
2a	294 (-700)	284 (7000)
2b	294 (-1700)	290 (14500)
2c	294 (-900)	284 (8300)
2d	294 (-2000)	292 (19100)

of the chiral cyclophane moiety, circular dichroism spectral measurement was employed. The circular dichroism spectral absorptions were observed at *ca*. 295 nm, which were corresponding to the phenol unit (Figure 3 and Table 3)[7]. Therefore, circular dichroism spectra supported the assumption that the cyclophane unit is chiral. In contrast, circular dichroism spectral absorptions of acyclic compounds **2** were fairly small.

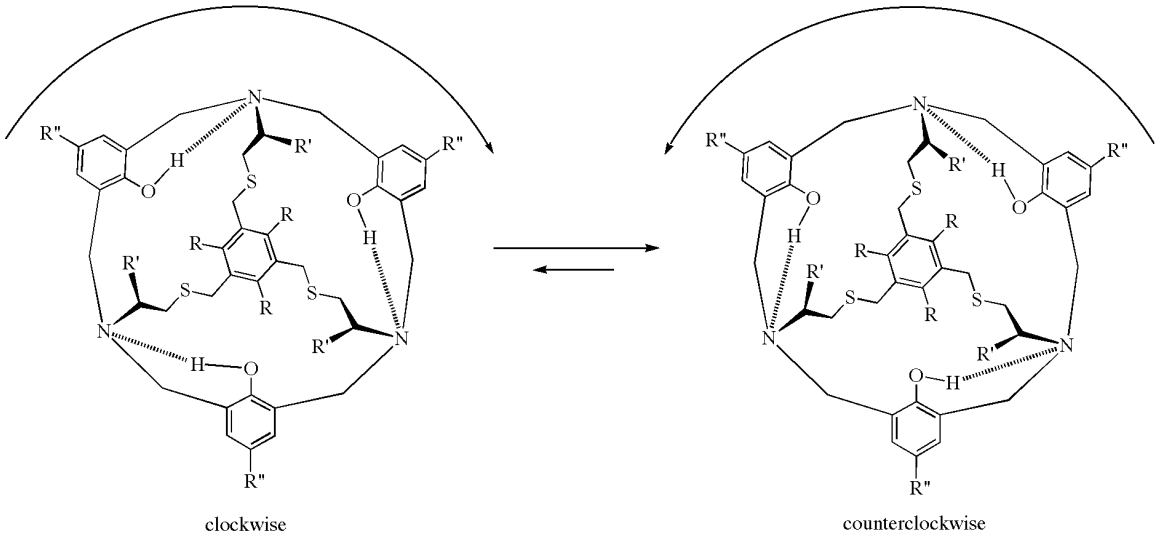
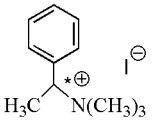


Figure 2

Table 4

Induced Chemical Shift of the Complexation of α-Phenethyl Trimethylammonium Iodide **8** with **1** or **2** in Deuterochloroform at 20 °C (500 MHz, [**1**] or [**2**] = [**8**] = 10 mM).

Cyclic and Acyclic Compounds	α-phenethyl trimethyl ammonium iodide **8**			
	CH_3	$N^+(CH_3)_3$	CH	Ph
	δ ppm (Δδ pp)	δ ppm (Δδ pp)	δ ppm (Δδ pp)	δ ppm (Δδ pp)
none	1.857	3.388	5.430	7.630
1a	1.856 (-0.001)	3.387 (-0.001)	5.432 (+0.002)	7.629 (-0.001)
1e	1.816 (-0.041)	3.322 (-0.060)	5.407 (-0.023)	7.610 (-0.020)
2a	1.831 (-0.026)	3.340 (-0.048)	5.385 (-0.045)	7.605 (-0.025)
2d	1.767 (-0.090)	3.236 (-0.152)	5.294 (-0.136)	7.563 (-0.067)



8

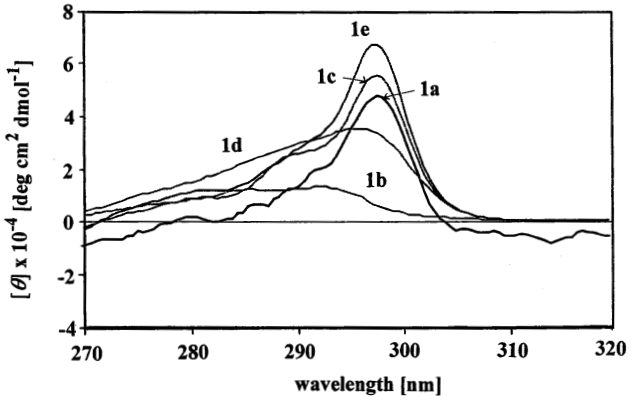


Figure 3. Circular Dichroism Spectra of **1** in chloroform at 20 °C.

It is known that the cyclophanes form complexes with ammonium ions [8]. Therefore, we examined the complexation ability of these macrocycles **1** and the corresponding acyclic oligomers **2** with racemic α-methyl benzyl trimethyl ammonium iodide **8** using ^1H nmr spectroscopy. In the presence of **1e**, homoazacalix[6]arene, all proton resonances of **8** moved to a high field due to the ring current effect of the π-cavity of **1e** during the formation of the complex **1e**-**8** (Table 4). The highest induced shifts of methyl protons of $N^+(CH_3)_3$ of **8** suggest that the cation moiety is included in the aromatic π-cavity of **1e**. However chiral selectivity with **1e** was not observed [9]. In the same experiment using **1a**, homoazacalix[3]arene, however, the chemical shift of **8** scarcely changes due to the small π-cavity of **1a**. Interestingly, the methyl signals of $N^+(CH_3)_3$ of **8** in the presence of the corresponding acyclic compounds (**2a** and **2d**) shifted to a high field. Compound **2** may show behavior consistent with the induce-fit model when encapsulating the ammonium ion **8**.

In summary, we prepared the bowl-shaped chiral homotriazacalixarenes and the corresponding acyclic compounds in moderate yields. Their nmr and circular dichloroism spectra of macrocycles imply the existence of the chiral transmission from the point chirality of the bridge to the molecule as a whole. Their cyclic and acyclic compounds contain a π-base cavity large enough to include ammonium ion.

EXPERIMENTAL

1D and 2D nmr measurements were performed on Varian Mercury 200 and INOVA 500 spectrophotometers in solvents as indicated. Chemical shifts are reported as part per militon (δ) relative to tetramethylsilane. Melting points were obtained on Yanagimoto micro melting point apparatus and are uncorrected. Ir and uv spectra were recorded on Horiba FT-200 and Hitachi 228A spectrophotometers, respectively. Fab-mass spectra were obtained on a JEOL AX-505 HA spectrometer using *m*-nitorobenzyl alcohol as a matrix. Circular dichroism spectra were collected by Jasco J720WI spectrophotometer. All commercially available compounds were used without further purification unless otherwise indicated. Column chromatography was performed on Merck Silica (kieselgel 60, 63-200 mm, 70-230 mesh). 1,3,5-Tris(bromomethyl)benzene (**4a**) [10] and 1,3,5-tris- (bromomethyl)-2,4,6-triethylbenzene (**4b**) [11], bis(chloromethyl)-*p*-substituted phenols (**6a**, **6b**) [12] and bis(chloromethyl)-*p*-substituted phenol-formaldehyde oligomers (**6c**-**6f**) [13,14], and 2-hydroxyl-5-methyl benzaldhyde (**7a**) [15] and 2-hydroxyl-3-(2-hydroxyl-5-methylphenyl)methyl-5-methylbenzaldehyde (**7b**) [15] were prepared according to the literature.

Synthesis of Amine Derivatives (**5**).

A mixture of *L*-cysteine methyl ester monohydrochloride **3** (1.54 g, 9.0 mmol), sodium carbonate (4.4 g, 41 mmol), and *N*,*N*-dimethyl formaldehyde (20 ml) was added to a solution of **4** (2.0 mmol) in *N*,*N*-dimethyl formaldehyde (20 ml) over 0.5 h at room temperature. After the addition was completed, the mixture was allowed to stir at room temperature for 4 h. Removal of *N*,*N*-dimethyl formaldehyde under a reduced pressure gave yellow oily residue, which was dissolved with chloroform. The solution was washed with water, 5% $NaHCO_3$ aqueous solution, and water again. The organic layer was dried over anhydrous sodium sulfate. Removal of solvent gave **5** as a colorless oil.

2-Amino-3-[3,5-bis-(2-amino-2-methoxycarbonylethylsulfanyl-methyl)benzylsulfanyl]propionic Acid Methyl Ester (**5a**).

The yield was 75 %. Colorless oil. ^{1}H nmr (deuteriochloroform): δ 2.67 (dd, 3H, *J*=7.2, 13.5 Hz, CH x 3), 2.83 (dd, 3H, *J*=4.8, 13.5 Hz, CH x 3), 3.61 (dd, 3H, *J*=4.8, 7.2 Hz, CH x 3), 3.72 (s, 6H, CH_2 x 3), 3.74 (s, 9H, CO_2CH_3 x 3), 7.17 (s, 3H, Ar-H x 3). ^{13}C nmr (deuteriochloroform): δ 36.4, 36.5, 52.2, 54.0, 128.3, 138.7, 174.3. Ir (oil): 1732 (ν_{CO}) cm^{-1}. Fab-mass 520 $(M+H)^+$.

Anal. Calcd. for $C_{21}H_{33}N_3O_6S_3$: C, 48.53; H, 6.40; N, 8.09. Found: C, 48.30; H, 6.60; N, 7.98.

Amino-3-[3,5-bis-(2-amino-2-methoxycarbonylethylsulfanyl-methyl)-2,4,6-triethylbenzylsulfanyl]propionic Acid Methyl Ester (**5b**).

The yield was 97 %. Colorless oil. ^{1}H nmr (deuteriochloroform): δ 1.29 (t, 9H, *J*=7.0 Hz, CH_2CH_3 x 3), 2.89 (q, 6H, *J*=7.0 Hz, CH_2CH_3 x 3), 2.89 (dd, 3H, *J*=7.0, 13.5 Hz, CH x 3), 3.00 (dd, 3H, *J*=5.0, 13.5 Hz, CH x 3), 3.71 (dd, 3H, *J*=5.0, 7.0 Hz, CH x 3), 3.77 (s, 9H, CO_2CH_3 x 3), 3.79 (s, 6H, CH_2 x 3). ^{13}C nmr (deuteriochloroform): δ 16.2, 22.9, 31.9, 38.7, 52.2, 54.3, 131.2, 142.6, 174.5. Ir (oil): 1739 (ν_{CO}) cm^{-1}. Fab-mass: 604 $(M+H)^+$.

Anal. Calcd. for $C_{27}H_{45}N_3O_6S_3$: C, 53.70; H, 7.51; N, 6.96. Found: 53.50; H, 7.20; N, 6.70.

General Procedure for the Preparation of Homotriaza-calixarenes (**1**).

To a suspension of sodium carbonate (318 mg, 2.0 mmol) in *N*,*N*-dimethyl formaldehyde (10 ml) were added a solution of **5** (173 mg, 0.33 mmol) in *N*,*N*-dimethyl formaldehyde (30 ml) and a solution of **6** (mmol) in *N*,*N*-dimethyl formaldehyde (30 ml) simultaneously at 30 °C over 2 h. After the addition was complete, the mixture was allowed to stir at 30 °C for 5 h. Removal of *N*,*N*-dimethyl formaldehyde under a reduced pressure below 40 °C gave an yellow oily residue, which was subjected to column chromatography on silica gel using hexane:ethyl acetate 2:3 as an eluent to give **1** as colorless crystals.

Compound **1a** was obtained in 14 % yield. Mp 270-273 °C. ^{1}H nmr (deuteriochloroform): δ 2.13 (s, 9H, CH_3 x 3), 2.79 (d, 3H, *J*=10.0 Hz, H_c x 3), 3.11 (d, 3H, *J*=12.0 Hz, H_o x 3), 3.21 (dd, 3H, *J*=10.0, 12.0 Hz, H_d x 3), 3.47 (d, 3H, *J*=12.0 Hz, H_e x 3), 3.55 (d, 3H, *J*=15.5 Hz, H_g x 3), 3.63 (d, 3H, *J*=14.0 Hz, H_b x 3), 3.74 (d, 3H, *J*=14.0 Hz, H_a x 3), 3.82 (s, 9H, CO_2CH_3 x 3), 3.86 (d, 3H, *J*=15.5 Hz, H_f x 3), 4.24 (s, 3H, *J*=13.0 Hz, H_n x 3), 6.60 (s, 3H, H_h x 3), 6.74 (s, 3H, H_i x 3), 7.16 (s, 3H, Ar-H x 3), 10.60 (s, 3H, OH x 3). ^{13}C nmr (deuteriochloroform): δ 20.3, 31.5, 37.2, 51.6, 51.8, 53.5, 59.7, 120.1, 122.3, 127.2, 128.3, 129.4, 130.5, 138.8, 153.0, 170.3. Ir (chloroform): 3089 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}. Fab-mass 917 $(M+H)^+$.

Anal. Calcd. for $C_{48}H_{57}N_3O_9S_3$: C, 62.93; H, 6.27; N, 4.59. Found C, 63.10; H, 6.10; N, 4.55.

Compound **1b** was obtained in 13 % yield. Mp 155-157 °C. ^{1}H nmr (deuteriochlorofrom): δ 1.19 (s, 27H, *t*-Bu x 3), 2.83 (d, 3H, *J*=8.5 Hz, H_c x 3), 3.16 (d, 3H, *J*=13.5 Hz, H_o x 3), 3.22 (dd, 3H, *J*=8.5, 11.0 Hz, H_d x 3), 3.52 (d, 3H, *J*=11.0 Hz, H_e x 3), 3.61 (d, 3H, *J*=15.5 Hz, H_g x 3), 3.64 (d, 3H, *J*=14.5 Hz, H_b x 3), 3.75 (d, 3H, *J*=14.5 Hz, H_a x 3), 3.84 (s, 9H, CO_2CH_3 x 3), 3.88 (d, 3H, *J*=15.5 Hz, H_f x 3), 4.28 (d, 3H, *J*=13.5 Hz, H_n x 3), 6.79 (s, 3H, H_h x 3), 6.91 (s, 3H, H_i x 3), 7.17 (s 3H, Ar-H x 3), 10.60 (s, 3H, OH x 3). ^{13}C nmr (deuteriochlorofrom): δ 31.4, 31.5, 33.8, 37.2, 51.6, 52.2, 53.8, 59.8, 119.7, 121.9, 125.6, 126.8, 128.3, 138.8, 140.8, 153.0, 170.5. Ir (chloroform): 3111 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}. Fab-mass 1043 $(M+H)^+$.

Anal. Calcd. for $C_{57}H_{75}N_3O_9S_3$: C, 65.68; H, 7.25; N, 4.03. Found C, 65.70; H, 7.30; N, 3.89.

Compound **1c** was obtained in 6 % yield. Mp 245-248 °C. ^{1}H nmr (deuteriochloroform): δ 2.10 (s, 9H, CH_3 x 3), 2.21 (s, 9H, CH_3 x 3), 2.55 (d, 3H, *J*=14.0 Hz, H_c x 3), 2.84 (d, 3H, *J*=12.0 Hz, H_o x 3), 3.00 (dd, 3H, *J*=12.0, 14.0 Hz, H_d x 3), 3.30 (s, 3H, *J*=14.0 Hz, H_k x 3), 3.34 (d, 3H, *J*=14.5 Hz, H_g x 3), 3.47 (s, 3H, *J*=12.5 Hz, H_a x 3), 3.58 (d, 3H, *J*=12.5 Hz, H_e x 3), 3.69 (d, 3H, *J*=13.0 Hz, H_b x 3), 3.90 (d, 3H, *J*=14.0 Hz, H_f x 3), 3.90 (s, 9H, CO_2CH_3 x 3), 4.30 (d, 3H, *J*=13.5 Hz, H_j x 3), 4.69 (d, 3H, *J*=12.0 Hz, H_n x 3), 6.61 (s, 3H, H_h x 3), 6.74 (s, 3H, H_m x 3), 6.97 (s, 3H, H_i x 3), 7.01 (s, 3H, H_l x 3), 7.38 (s, 3H, Ar-H x 3), 8.76 (s, 3H, OH x 3), 11.20 (s, 3H, OH x 3). ^{13}C nmr (deuteriochloroform): δ 20.3, 20.5, 25.1, 30.9, 36.1, 51.4, 51.5, 53.4, 63.4, 121.4, 122.9, 127.6, 128.2, 128.3, 128.4, 128.9, 129.4, 129.5, 131.3, 131.9, 139.7, 149.5, 150.9, 170.6. Ir (chloroform): 3288 (ν_{OH}), 1726 (ν_{CO}) cm^{-1}. Fab-mass 1276 $(M+H)^+$.

Anal. Calcd. for $C_{72}H_{81}N_3O_{12}S_3$: C, 67.74; H, 6.40; N, 3.29. C, 67.80; H, 6.30; N, 3.36.

Compound **1d** was obtained in 5 % yield. Mp 178-181 °C. ^{1}H nmr (deuteriochloroform): δ 1.12 (t, 9H, *J*=7.5 Hz, CH_2CH_3 x 3), 2.14 (s, 9H, CH_3 x 3), 2.76-2.80 (m, 9H, CH_2CH_3 x 2 and H_c x

3), 3.18 (d, 3H, *J*=13.0 Hz, H_o x 3), 3.29 (dd, 3H, *J*=7.5, 14.5 Hz, H_d x 3), 3.44-3.53 (m, 9H, H_g, H_b, and H_e), 3.82 (s, 9H, CO_2CH_3 x 3), 3.86 (d, 3H, *J*=14.5 Hz, H_a x 3), 4.19 (d, 3H, *J*=13.5 Hz, H_f x 3), 4.22 (d, 3H, *J*=12.0 Hz, H_n x 3), 6.60 (s, 3H, H_h x 3), 6.75 (s, 3H, H_i x 3), 10.5 (s, 3H, OH x 3). ^{13}C nmr (deuteriochloroform): δ 15.3, 20.3, 29.1, 29.8, 51.5, 53.2, 60.1, 120.1, 122.3, 127.0, 129.5, 130.6, 131.1, 142.7, 153.0, 170.6. Ir (chloroform): 3107 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}. Fab-mass 999 $(M+H)^+$.

Anal. Calcd. for $C_{54}H_{69}N_3O_9S_3$: C, 64.86; H, 6.91; N, 4.20. C, 64.78; H, 6.80; N, 4.10.

Compound **1e** was obtained in 15 % yield. Mp 273-276 °C. ^{1}H nmr (deuteriochloroform): δ 1.07 (t, 9H, *J*=7.5 Hz, -CH_2CH_3 x 3), 2.17 (s, 9H, CH_3 x 3), 2.21 (s, 9H, CH_3 x 3), 2.52 (d, 3H, *J*=13.5 Hz, H_c x 3), 2.96 (dd, 3H, *J*=13.0, 13.5 Hz, H_d x 3), 3.02 (d, 3H, *J*=12.0 Hz, H_n x 3), 3.08 (m, 3H, -$CHCH_3$ x 3), 3.14 (d, 3H, *J*=14.5 Hz, H_a x 3), 3.27 (d, 3H, *J*=14.0 Hz, H_j x 3), 3.33 (d, 3H, *J*=14.0 Hz, H_f x 3), 3.53 (m, 6H, He x 3 and $CHHCH_3$ x 3), 3.82 (d, 3H, *J*=14.5 Hz, H_b x 3), 3.84 (s, 9H, CO_2CH_3 x 3), 4.13 (d, 3H, *J*=14.0 Hz, H_g x 3), 4.25 (d, 3H, *J*=14.0 Hz, H_k x 3), 4.48 (d, 3H, *J*=12.0 Hz, H_o x 3), 6.57 (s, 3H, H_h x 3), 6.76 (s, 3H, H_m x 3), 6.97 (s, 3H, H_i x 3), 7.00 (s, 3H, H_l x 3), 8.73 (s, 3H, OH x 3), 11.12 (s, 3H, OH x 3). ^{13}C nmr (deuteriochloroform): δ 16.4, 20.3, 20.5, 22.2, 25.3, 30.0, 30.8, 50.3, 51.1, 53.4, 62.7, 121.1, 123.1, 127.3, 128.2, 128.3, 128.4, 129.2, 129.4, 131.2, 131.7, 132.7, 142.2, 149.6, 151.0, 169.8. Ir (chloroform) : 3288 (ν_{OH}), 1726 (ν_{CO}) cm^{-1}. Fab-mass 1360 $(M+H)^+$.

Anal. Calcd. for $C_{78}H_{93}N_3O_{12}S_3$: C, 68.85; H, 6.89; N, 3.09. Found C, 69.10; H, 6.80; N, 3.20.

Synthesis of Acyclic Compounds (**2**).

A mixture of **4** (1.3 mmol) and **7** (4.2 mmol) in dry benzene (50 ml) was refluxed for 6 h. Removal of benzene gave yellow oily residue, which was dissolved with methanol (70 ml) and dichloromethane (30 ml). The solution was cooled to 0 °C in an ice bath, and then sodium borohydride (11 mmol) was added small portion over 0.5 h. After the addition was completed, the mixture was allowed to stir at room temperature for 2 h. After removing the solvent, the residue was dissolved with chloroform. The solution was washed with water several times. The organic layer was dried over anhydrous sodium sulfate. Condensation of the solution gave yellow oily residue, which was subjected to column chromatography on silica gel using ethyl acetate: hexane 1:1 as an eluent to give **2** as pale yellow crystals.

Compound **2a** was obtained in 34 % yield. Mp 65-69 °C. ^{1}H nmr (deuteriochloroform): δ 2.22 (s, 9H, CH_3 x 3), 2.67 (dd, 3H, *J*=7.0, 13.5 Hz, 3H, H_c x 3), 2.79 (dd, 3H, *J*=5.0, 13.5 Hz, H_d x 3), 3.43 (dd, 3H, *J*=5.0, 7.0 Hz, H_e x 3), 3.65 (s, 6H, H_a x 3 and H_b x 3), 3.66 (d, 3H, *J*=13.5 Hz, H_f x 3), 3.75 (s, 9H, CO_2CH_3 x 3), 3.94 (d, 3H, *J*=13.5 Hz, H_g x 3), 6.74 (d, 3H, *J*=1.5 Hz, H_l x 3), 6.75 (d, 3H, *J*=8.5 Hz, H_n x 3), 6.97 (dd, 3H, *J*=1.5, 8.0 Hz, H_m x 3), 7.13 (s, 3H, Ar-H x 3), 9.70 (s, 3H, OH x 3). ^{13}C nmr (deuteriochloroform): δ 20.4, 34.2, 36.3, 50.9, 52.4, 59.1, 116.3, 121.8, 128.3, 128.4, 129.2, 129.5, 138.6, 155.3, 172.9. Ir (chloroform): 3313 (ν_{OH}), 1739 (ν_{CO}) cm^{-1}. Fab-mass 880 $(M+H)^+$.

Anal. Calcd. for $C_{45}H_{57}N_3O_9S_3$: C, 61.43; H, 6.48; N, 4.78. Found C, 61.54; H, 6.38; N, 4.90.

Compound **2b** was obtained in 58 % yield. Mp 70-78 °C. ^{1}H nmr (deuteriochloroform): δ 2.18 (s, 9H, CH_3 x 3), 2.23 (s, 9H, CH_3 x 3), 2.66 (dd, 3H, *J*=8.0, 14.0 Hz, H_c x 3), 2.78 (dd, 3H, *J*=4.5, 14.0 Hz, H_d x 3), 3.36 (dd, 3H, *J*=4.5, 8.0 Hz, H_e x 3), 3.60 (d, 3H, *J*=14.0 Hz, H_f x 3), 3.64 (s, 6H, H_a x 3 and H_b x 3), 3.70 (s, 9H, CO_2CH_3 x 3), 3.78 (d, 3H, *J*=14.0 Hz, H_j x 3), 3.84 (d, 3H, *J*=14.0 Hz, H_k x 3), 3.89 (d, 3H, *J*=14.0 Hz, H_g x 3), 6.57 (d, 3H, *J*=2.0 Hz, H_h x 3), 6.74 (d, 3H, *J*=8.0 Hz, H_n x 3), 6.85 (dd, 3H, *J*=2.0, 8.0 Hz, H_m x 3), 7.00 (d, 3H, *J*=2.0 Hz, H_l x 3), 7.02 (d, 3H, *J*=2.0 Hz, H_i x 3), 7.17 (s, 3H, Ar-H x 3). ^{13}C nmr (deuteriochloroform): δ 20.4, 20.5, 30.8, 34.0, 36.4, 50.6, 52.5, 59.0, 116.7, 121.3, 127.1, 127.6, 127.8, 128.4, 128.5, 129.3, 129.4, 130.5, 130.9, 138.7, 151.0, 152.0, 172.3. Ir (chloroform): 3319 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}. Fab-mass 1240 $(M+H)^+$.

Anal. Calcd. for $C_{69}H_{81}N_3O_{12}S_3$: C, 66.83; H, 6.54; N, 3.39. Found C, 66.60; H, 6.60; N, 3.50.

Compound **2c** was obtained in 22 % yield. Mp 69-78 °C. ^{1}H nmr (deuteriochloroform): δ 1.20-1.27 (m, 9H, CH_2CH_3 x 3), 2.23 (s, 9H, CH_3 x 3), 2.81-2.96 (m, 12H, CH_2CH_3 x 3, H_c x 3 and H_d x 3), 3.53 (dd, 3H, *J*=5.5, 6.5 Hz, H_e x 3), 3.77 (d, 3H, *J*=13.5 Hz, H_f x 3), 3.78 (s, 9H, CO_2CH_3 x 3), 4.00 (d, 3H, *J*=13.5 Hz, H_g x 3), 6.76 (d, 3H, *J*=8.0 Hz, H_n x 3), 6.78 (d, 3H, *J*=2.0 Hz, H_l x 3), 6.97 (dd, 3H, *J*=2.0, 8.0 Hz, H_m x 3). ^{13}C nmr (deuteriochloroform): δ 16.2, 20.4, 23.0, 31.9, 36.3, 50.9, 52.4, 59.3, 116.4, 121.7, 128.4, 129.3, 129.5, 131.0, 142.8, 155.3, 172.8. IR ($CHCl_3$): 3313 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}. Fab-mass 964. $(M+H)^+$.

Anal. Calcd. for $C_{51}H_{69}N_3O_9S_3$: C, 63.55; H, 7.17; N, 4.36. Found C, 63.60; H, 7.30; N, 4.50.

Compound **2d** was obtained in 44 % yield. mp 83-93 °C. ^{1}H nmr (deuteriochloroform): δ 1.23-1.26 (m, 9H, CH_2CH_3 x 3), 2.20 (s, 9H, CH_3 x 3), 2.24 (s, 9H, CH_3 x 3), 2.80-3.00 (m, 12H, CH_2CH_3 x 3, H_c x 3 and H_d x 3), 3.48 (dd, 3H, *J*=5.5, 6.0 Hz, H_e x 3), 3.74 (d, 3H, *J*=13.5 Hz, H_f x 3), 3.75 (s, 9H, CO_2CH_3 x 3), 3.77 (s, 6H, H_a x 3 and H_b x 3), 3.79 (d, 3H, *J*=14.5 Hz, H_j x 3), 3.84 (d, 3H, *J*=14.5 Hz, H_k x 3), 3.96 (d, 3H, *J*=13.5 Hz, H_g x 3), 6.62 (d, 3H, *J*=2.0 Hz, H_h x 3), 6.74 (d, 3H, *J*=8.0 Hz, H_n x 3), 6.87 (dd, 3H, *J*=2.0, 8.0 Hz, H_m x 3), 7.01 (d, 3H, *J*=2.0 Hz, H_l x 3), 7.03 (d, 3H, *J*=2.0 Hz, H_i x 3). ^{13}C nmr (deuteriochloroform): δ 16.2, 20.5 x 2, 23.0, 30.8, 31.8, 35.8, 50.6, 52.5, 58.9, 116.7, 121.1, 127.1, 127.7, 127.8, 128.4, 129.3, 129.5, 130.5, 130.8, 130.9, 142.9, 151.0, 152.0, 172.4. Ir (chloroform): 3319 (ν_{OH}), 1739 (ν_{CO}) cm^{-1}. Fab-mass 1324 $(M+H)^+$.

Anal Calcd for $C_{75}H_{93}N_3O_{12}S_3$: C, 68.03; H, 7.03; N, 3.17. Found C, 67.89; H, 6.88; N, 3.30.

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