Notes

Synthesis and Properties of Chiral Tetrahomodiazacalix[4]- and -[6]arenes Bridged by a Cystine Unit

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Introduction

Calixarenes are becoming an important class of macrocyclic compounds in supramolecular chemistry for the design of new host molecules due to their chemical versatility and conformational properties.[1] Although many studies on the modification of calixarenes have so far been made at the large and small rims of the calixarene skeleton to introduce additional functionality, modification of the methylene backbone has not been exploited to any great extent.[2,3,4] This situation inspired us to make calixarene analogues, which were constructed by changing the methylene moiety to another unit. Therefore, we designed calixarene analogues bridged by a cystine unit, which is known as an important structural element of peptide and protein molecules, because the disulfide unit in the proteins plays an important functional role in redox processes and in restricting their conformation.[5] These properties are useful for the design of artificial host molecules.[6] Here, we present the facile formation of chiral calixarene analogues bridged by a cystine unit and their structural details based on NMR and CD spectra.

Results and Discussion

Bis(chloromethyl)phenol−formaldehyde oligomers (**5** and **6**) were prepared by a previously reported method.[7] Cystine peptides (**7d** and **7e**) were synthesized by a solution-phase synthetic method according to the literature.[6a,b] We examined the cyclization reaction of the bis(chloromethyl)phenol−formaldehyde dimer (**5a**) and cystine peptide (**7d**) under several reaction conditions as shown in Table 1 (entries 7−14). The reaction **5a** with **7d** in chloroform in the presence of triethylamine did not gave any macrocyclic compound (entry 7). In contrast, the same reaction in DMF gave a macrocycle (**3a**) in 21% yield (entry 8). To evaluate the effect of the base in this reaction, we carried out the reaction using Na_2CO_3, K_2CO_3, and Cs_2CO_3 instead of triethylamine (entries 9, 10, and 11, respectively) and found that this cyclization was best effected by employing Na_2CO_3 (entry 9). The low and high reaction temperature (entries 12 and 13) and the dilution condition (entry 14) tended to decrease the yield. We also carried out analogous reactions of the bis(chloromethyl)phenol−formaldehyde oligomer (**5** or **6**) with a diamine derivative such as cystine dimethyl ester (**7a** and **7c**), cystaime (**7b**), or cystine peptide (**7d** and **7e**) and obtained corresponding macrocycles (**1**−**4**) in moderate yields (Table 1, Scheme 1).

The structures of macrocycles (**1**−**4**) were established on the basis of their elemental analyses, FAB-mass, and NMR and IR spectra. The assignment of proton and carbon atoms was done using 2D NMR experiments.

IR spectra of macrocycles (**1**−**4**) in $CHCl_3$ show the absorption for the hydroxyl stretching band at 3200−3260 cm^{-1} (Table 2). In ^1H NMR spectra in $CDCl_3$ at 30 °C, the OH signals were observed in the range of 9.40−15.27 ppm. These spectral data indicate the existence of strong hydrogen bonds which are comparable to that of calixarenes (ν_{OH} = ca. 3200 cm^{-1}, δ_{OH} = ca. 10 ppm).[8]

The conformation of macrocycles (**1**−**4**) have been studied using NMR spectroscopy. The $ArCH_2Ar$ methylene protons of **1**−**4** appear as pairs of doublets due to the geminal coupling between H_{exo} and H_{endo}. It is known that the chemical shift difference ($\Delta\delta$) between the high- and low-field magnetic resonances arising from the $ArCH_2Ar$ methylene protons in calix[4]arenes is generally 0.9 ± 0.2 ppm for the cone conformation and zero for the 1,3-alternate conformation.[9] Provided that the rule established for calix[4]arene is also applicable to this system, it follows that the adjacent aryl rings of the oligomer moieties of macrocycles ($\Delta\delta$ = 0.73−0.88 ppm)

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(8) Page 100 in ref 1a.

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Table 1. Reaction Conditions and Yield of Products

entry	oligomer	peptide	solvent	base	temp, °C	product (yield %)
1	**5a**	**7a**	DMF	Na_2CO_3	30	**1a** (20%)
2	**5b**	**7a**	DMF	Na_2CO_3	30	**1b** (42%)
3	**5b**	**7b**	DMF	Na_2CO_3	30	**1c** (24%)
4	**5b**	**7c**	DMF	Na_2CO_3	30	**1d** (37%)
5	**6b**	**7a**	DMF	Na_2CO_3	30	**2b** (48%)
6	**6b**	**7b**	DMF	Na_2CO_3	30	**2c** (27%)
7	**5a**	**7d**	$CHCl_3$	NEt_3	30	polymeric materials
8	**5a**	**7d**	DMF	NEt_3	30	**3a** (21%)
9	**5a**	**7d**	DMF	Na_2CO_3	30	**3a** (24%)
10	**5a**	**7d**	DMF	K_2CO_3	30	**3a** (6%)
11	**5a**	**7d**	DMF	Cs_2CO_3	30	**3a** (11%)
12	**5a**	**7d**	DMF	Na_2CO_3	0	**3a** (19%)
13	**5a**	**7d**	DMF	Na_2CO_3	50	**3a** (13%)
14[a]	**5a**	**7d**	DMF	Na_2CO_3	30	**3a** (18%)
15	**5a**	**7e**	DMF	Na_2CO_3	30	**3b** (14%)
16	**5b**	**7d**	DMF	Na_2CO_3	30	**3c** (14%)
17	**5b**	**7e**	DMF	Na_2CO_3	30	polymeric materials
18	**6a**	**7d**	DMF	Na_2CO_3	30	**4a** (10%)
19	**6b**	**7d**	DMF	Na_2CO_3	30	**4b** (18%)

[a] The reaction was carried out under a 10 times dilution condition.

take the preferable *syn*-orientation. The ^{13}C NMR chemical shifts of the methylene carbon atoms of the $ArCH_2Ar$ for calixarenes are now being used as a means for assessing conformations. The methylene carbon resonances for the calixarenes appear at ca. 30−33 ppm when the adjacent aryl rings are *syn* and at ca. 36−38 ppm when they are anti.[10] Applying this information to this system, all the *syn*-orientations of the adjacent aromatic rings were confirmed (Table 2). The CPK model consideration of **1**−**4** indicates that it adopts a cone conformation because it is difficult to construct a 1,2-alternate model. The crystal structure of **1a**, which was given in Figure 1, also supports the fact that **1**−**4** adopt a cone form.

Considering that the $\Delta\delta$ values of the NCH_2Ar methylene protons are expected to be sensitive to the dihedral angle between the methylene proton and the adjacent aromatic ring,[9] the difference between $\Delta\delta$ H_eH_f and $\Delta\delta$ H_qH_r for **1**−**4** implies that phenol−formaldehyde oligomer moieties are considered to adopt a twisted form (Figure 2). Since the smaller $\Delta\delta$ values are ascribed to the methylene protons H_qH_r (Table 3), it is reasonable to assume that the methylene protons are located in an equivalent magnetic field (conformation A in Figure 3). This assumption was supported by the fact that the hydroxyl proton signals (OH^2 for **1** and **3**, and OH^3 for **2** and **4**) were observed at the lowest field due to the formation of the hydrogen bonding not only with the hydroxyl group but also with the adjacent nitrogen atom. In contrast, the larger $\Delta\delta$ values (H_eH_f) indicate that the adjacent aromatic ring is considered to adopt a somewhat standup form (conformation B in Figure 3). On the basis of these considerations, phenol−formaldehyde oligomer moieties of **1** are considered to adopt a twisted structure as shown in Figure 2. The chirality of the cystine bridge causes the formation of the left-hand isomer in Figure 2.[3d] Therefore, phenol−formaldehyde oligomer moieties form a chiral helicity and produce the chiral cyclophane moiety.

Figures 4 and 5 showed the circular dichroism (CD) spectra of the macrocycles (**1**−**4**). The CD spectra were clearly observed at ca. 290 nm due to the phenol chromophore[11] in chloroform at 20 °C, supporting the assumption that phenol−formaldehyde oligomer moieties are chiral.

To elucidate the temperature dependence of the $\Delta\delta$ values of the $ArCH_2Ar$ methylene protons and the phenolic OH proton chemical shifts, we carried out a variable temperature ^1H NMR measurement in the range of 55 to −60 °C in $CDCl_3$, and these results are summarized in Table 6. Lowering the temperature resulted in a decrease in the $\Delta\delta$ values of the $ArCH_2Ar$ methylene protons and downfield shifts of the OH signals. These results suggest that the contribution of the twisted form is enhanced by cooling.

Conclusion

In conclusion, we demonstrated the facile synthesis of chiral bridged calixarene analogues, which were constructed from phenol−formaldehyde oligomers and the cystine unit. The ^1H NMR and CD spectra indicated that the chirality of the phenol−formaldehyde oligomer moieties were induced from the chirality of the cystine bridge. The present system is a unique concept from the viewpoint of the transmisson of the chirality from the bridge to the cyclophane moiety.

Experimental Section

General Procedure of the Preparation of Bis(chloromethyl)phenol−Formaldehyde Oligomers (5 and 6). To a solution of bis(hydroxymethyl)phenol−formaldehyde oligomer[7] (1.1 mol) in 10 mL of dry benzene was added a solution of thionyl chloride (1.0 g, 8.0 mmol) in 10 mL of dry benzene over 0.5 h at room temperature. After the addition was complete, the mixture was allowed to stir at room temperature for 3 h. Removal of benzene and excess thionyl chloride below 25 °C under a reduced pressure gave bis(chloromethyl)phenol−formaldehyde oligomer as a colorless powder, which was recrystallized from benzene to give pure crystals, whose spectral chracteristics were identical with those reported.[7]

General Procedure of the Preparation of Cystine Peptides (7d and 7e). To a mixture of l-cystine dimethyl ester dihydrochloride (1.71 g, 5.0 mmol), *N*-methylmorpholine (1.11 g, 11 mmol), and *N*-Boc protected amino acid (11 mmol) in 100 mL of chloroform was added a solution of DCC (2.27 g, 11 mmol) in 12 mL of chloroform at 0 °C over 1 h. After the addition was complete, the mixture was stirred at room temperature overnight. The precipitated dicyclohexylurea was filtered off, and the filtrate was condensed. The residue was subjected to column chromatography on silica gel using hexane:ethyl acetate 1:1 as an eluent to afford *N*-Boc protected cystine peptide in good yield. The spectral chracteristics of *N*-Boc protected cystine peptides were identical with those reported.[6] Cystine peptides (**7d** and **7e**) were prepared by treatment of the protected peptide with excess HCl−ethyl acetate reagent at 0 °C for 2 h. The residue was directly used for the next cyclization reaction.

General Procedure of the Preparation of the Calixarene Analogues (1, 2, 3, and 4) Bridged by Cystine Unit. To a suspension of sodium carbonate (636 mg, 6.0 mmol) in 50 mL of dry DMF were added a solution of bis(chloromethyl)-phenol−formaldehyde oligomer (2.0 mmol) in 50 mL of dry DMF and a solution of cystine dimethyl ester, cystamine, or cystine peptide (1.0 mmol) in 50 mL of dry DMF at 30 °C over 6 h under

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Scheme 1

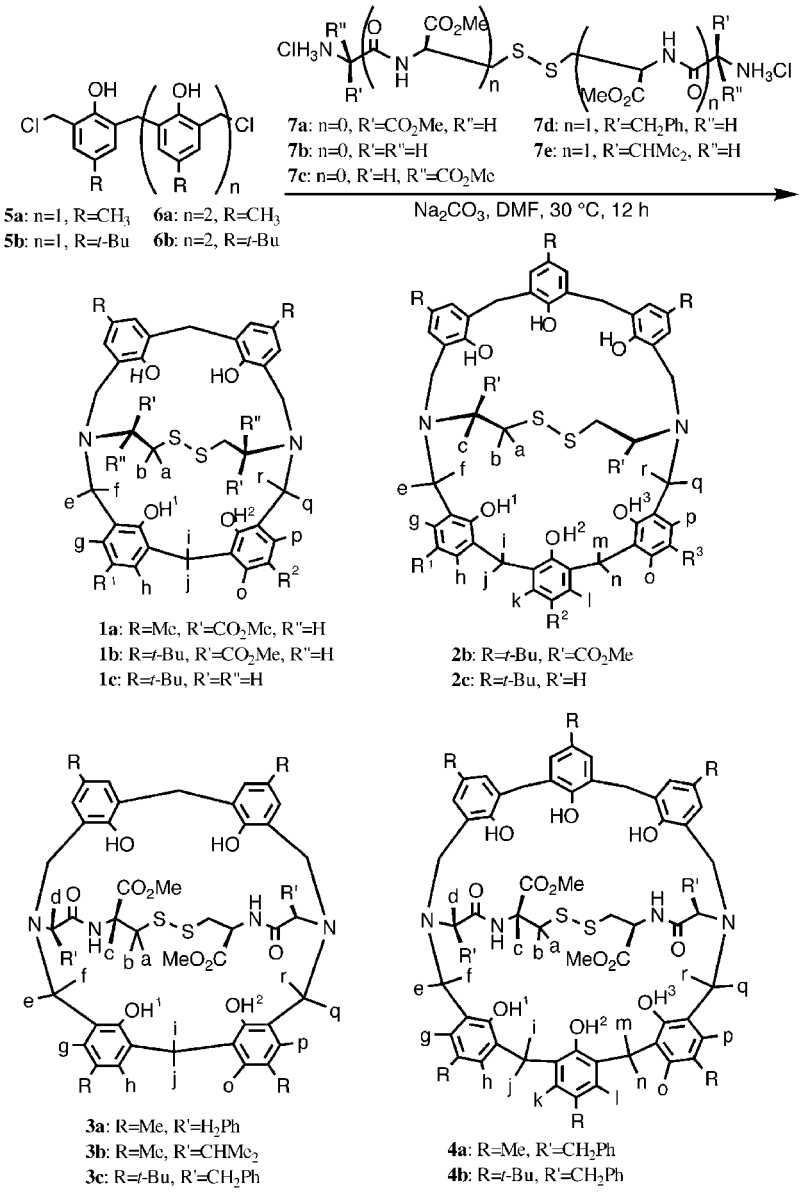

Table 2. Proton Signals in ^{1}H NMR Spectra and Stretching Vibrations of the Hydroxyl Group, and the Chemical Shifts of the Methylene Carbon Atom

	δ_{OH} [ppm]	ν_{OH} [cm^{-1}]	$\nu_{C=O}$ [cm^{-1}]	amide I [cm^{-1}]	^{13}C NMR ArCH$_2$Ar [ppm]
1a	9.40, 11.15	3260	1730	-	30.8
1b	9.31, 10.85	3260	1730	-	31.1
1c	10.93	3260	-	-	31.5
2b	9.06, 10.69, 13.13	3260	1730	-	32.4, 32.5
2c	9.51, 12.24, 15.27	3240	-	-	32.8, 33.3
3a	10.50	3332, 3242	1747	1681	31.2
3b	10.28	3334, 3255	1747	1674	31.1
3c	10.60	3303, 3222	1747	1681	32.0
4a	8.55, 9.05, 10.10	3363, 3291	1743	1654	31.0, 31.7
4b	8.45, 9.15, 10.60	3363, 3309	1743	1655	30.4, 31.9

a nitrogen atmosphere. After the addition was complete, the mixture was allowed to stir at 30 °C for 12 h. Removal of DMF under a reduced pressure gave pale yellow oily residue, which was separated with column chromatography on silica gel to give a calixarene analogue as a white powder.

1a: colorless crystals mp 250−253 °C (decomp) (from dichloromethane−hexane). $[\alpha]^{20}_D$ +21° (c = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.15 (bs, 2H), 9.40 (bs, 2H), 7.10 (s, 4H), 6.71 (d, 2H, J = 1.9 Hz), 6.62 (d, 2H, J = 1.9 Hz), 4.42 (d, 2H, J = 11.9 Hz), 4.28 (d, 2H, J = 13.5 Hz), 4.10 (d, 2H, J = 14.3 Hz), 3.90 (d, 2H, J = 15.4 Hz), 3.83 (d, 2H, J = 12.4 Hz), 3.72 (s, 6H), 3.55 (dd, 2H, J = 7.0, 8.0 Hz), 3.40 (d, 2H, J = 13.8 Hz), 2.50 (dd, 2H, J = 7.0, 14.3 Hz), 2.42 (dd, 2H, J = 8.0, 14.3 Hz), 2.24 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 151.5, 151.2, 131.5, 130.8, 130.0, 129.9, 129.1, 128.1, 127.7, 126.9, 123.6, 122.1, 60.7, 60.3, 58.9, 55.6, 51.4, 38.3, 30.7, 20.5, 20.4. FAB MS m/z: 773 $[M + H]^+$. Anal. Found: C, 65.42; H, 6.41; N, 3.54. Calcd for $C_{42}H_{48}N_2O_8S_2$: C, 65.26; H, 6.26; N, 3.62.

1b: colorless crystals mp 250−255 °C (decomp) (from ethyl acetate−hexane). $[\alpha]^{20}_D$ +31° (c = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.85 (bs, 2H), 9.31 (bs, 2H), 7.31 (d, 2H, J = 2.4 Hz), 7.28 (d, 2H, J = 2.4 Hz), 6.93 (d, 2H, J = 2.4 Hz), 6.81 (d, 2H, J = 2.4 Hz), 4.43 (d, 2H, J = 12.0 Hz), 4.32 (d, 2H, J = 13.9 Hz), 4.16 (d, 2H, J = 15.3 Hz), 3.91 (d, 2H, J = 15.3 Hz), 3.88 (d, 2H, J = 12.0 Hz), 3.74 (s, 6H), 3.61 (dd, 2H, J = 5.9, 8.6 Hz), 3.46 (d, 2H, J = 13.9 Hz), 2.41 (dd, 2H, 5.9, J = 14.0 Hz), 2.26 (dd, 2H, J = 8.6, 14.0 Hz), 1.29 (s, 18H), 1.28 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 151.2, 151.1, 143.3, 142.4, 127.8, 127.6, 127.3, 127.1, 126.3, 123.2, 122.8, 121.6, 60.2, 59.2, 56.0, 51.4, 37.5, 33.9, 33.7, 31.5, 31.4, 31.1. FAB MS m/z: 941 $[M + H]^+$. Anal. Found: C, 68.93; H, 7.77; N, 2.99. Calcd for $C_{54}H_{72}N_2O_8S_2$: C, 68.91; H, 7.71; N, 2.98.

1c: colorless crystals mp 238−241 °C (from dichloromethane−hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 4H), 7.27 (d,

Table 3. Chemical Shifts of Methylene Protons in $CDCl_3$ at 500 MHz at 20 °C

	H_eH_f (J, Hz; $\Delta\delta^a$, ppm)	H_iH_j (J, Hz; $\Delta\delta^a$, ppm)	H_mH_n (J, Hz; $\Delta\delta^a$, ppm)	H_qH_r (J, Hz; $\Delta\delta^a$, ppm)
1a	3.83, 4.42 (12.0, 0.59)	3.40, 4.28 (14.0, 0.88)		3.90, 4.10 (15.5, 0.20)
1b	3.88, 4.43 (12.0, 0.55)	3.46, 4.32 (14.0, 0.86)		3.91, 4.16 (15.3, 0.25)
1c	3.33, 4.36 (13.5, 1.03)	3.45, 4.33 (13.9, 0.88)		
2b	3.37, 4.33 (14.0, 0.96)	3.52, 4.35 (13.5, 0.83)	3.52, 4.25 (13.8, 0.73)	3.83[b]
2c	3.34, 4.30 (14.5, 0.96)	3.51, 4.40 (13.9, 0.84)	3.52, 4.25 (13.9, 0.73)	3.84, 3.88 (14.9, 0.04)
3a	3.45, 4.51 (14.0, 1.06)	3.36, 4.25 (14.0, 0.89)		3.11, 4.13 (12.5, 1.02)
3b	3.68, 4.92 (14.5, 1.24)	3.43, 4.36 (13.5, 0.93)		3.34, 4.16 (12.5, 0.82)
3c	3.56, 4.61 (15.0, 1.05)	3.53, 4.39 (14.0, 0.86)		3.36, 4.32 (13.0, 0.96)
4a	3.53, 4.42 (12.5, 0.89)	3.37, 4.55 (14.0, 1.18)	3.40, 4.28 (13.5, 0.88)	2.99, 3.64 (14.0, 0.65)
4b	3.56, 4.45 (12.5, 0.86)	3.44, 4.60 (14.0, 1.16)	3.49, 4.36 (14.0, 0.87)	3.13, 3.72 (14.0, 0.59)

[a] $\Delta\delta$ $H_xH_y = \delta H_x - \delta H_y$. [b] Observed as a singlet.

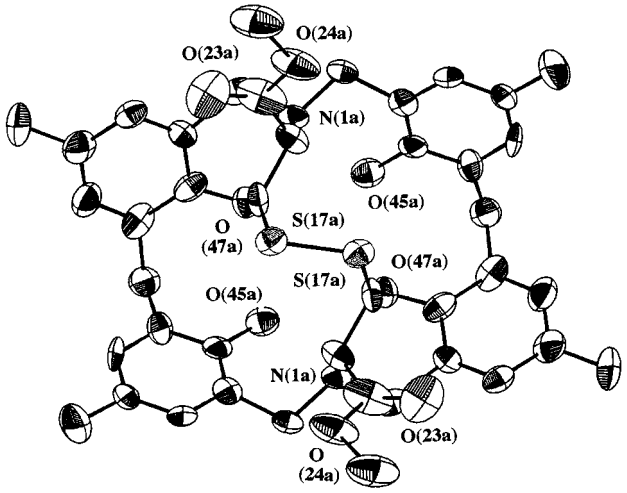

Figure 1. X-ray crystallograhic structure of the calixarene analogue (**1a**). The proton atoms are omitted.

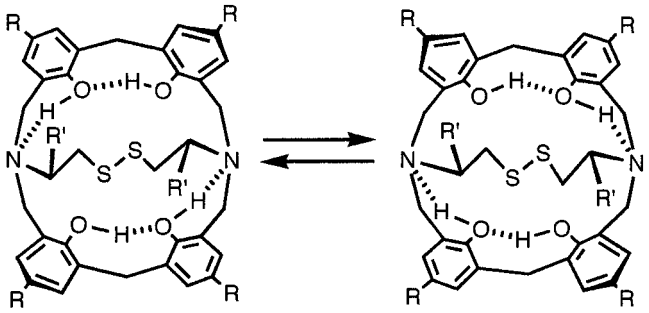

Figure 2.

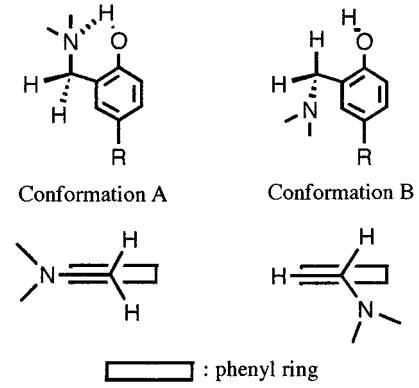

Figure 3.

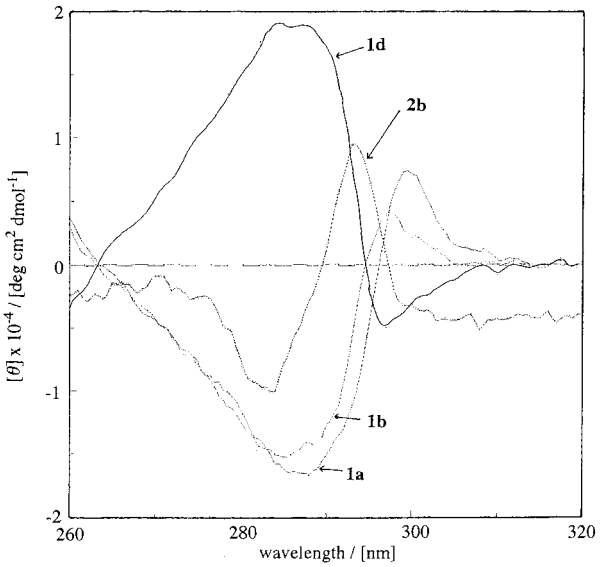

Figure 4. CD spectra of **1** and **2** in $CHCl_3$ at 20 °C.

4H, J = 2.2 Hz), 6.85 (d, 4H, J = 2.2 Hz), 4.36 (d, 4H, J = 13.5 Hz), 4.33 (d, 2H, J = 14.0 Hz), 3.45 (d, 2H, J = 14.0 Hz), 3.33 (d, 4H, J = 13.5 Hz), 2.55 (t, 4H, J = 6.5 Hz), 2.11 (t, 4H, J = 6.5 Hz), 1.29 (s, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 142.6, 128.0, 126.8, 124.3, 122.5, 61.8, 53.4, 35.4, 33.9, 31.8, 31.5. FAB MS m/z: 825 $[M + H]^+$. Anal. Found: C, 72.86; H, 8.39; N, 3.18. Calcd for $C_{50}H_{68}N_2O_4S_2$: C, 72.76; H, 8.31; N, 3.39.

1d: colorless crystals mp 258−260 °C (decomp) (from ethyl acetate−hexane). $[\alpha]^{20}_D$ −35° (c = 0.1, $CHCl_3$). FAB MS m/z: 941 $[M + H]^+$. Anal. Found: C, 69.10; H, 7.61; N, 3.10. Calcd for $C_{54}H_{72}N_2O_8S_2$: C, 68.91; H, 7.71; N, 2.98.

2b: pale yellow crystals. mp 203−207 °C (from ethyl acetate). $[\alpha]^{20}_D$ +127° (c = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.13 (s, 2H), 10.69 (s, 2H), 9.06 (s, 2H), 7.27 (d, 2H, J = 2.3 Hz), 7.24 (d, 2H, J = 2.3 Hz), 7.18 (d, 2H, J = 2.3 Hz), 7.17 (d, 2H, J = 2.3 Hz), 6.91 (d, 2H, J = 2.3 Hz), 6.62 (d, 2H, J = 2.3 Hz), 4.71 (dd, 2H, J = 6.8, 7.3 Hz), 4.35 (d, 2H, J = 14.0 Hz), 4.33 (d, 2H, J = 14.5 Hz), 4.25 (d, 2H, J = 13.9 Hz), 3.87 (dd, 2H, J = 6.8, 13.7 Hz), 3.83 (s, 4H), 3.79 (dd, 2H, J = 7.3, 13.7 Hz), 3.64 (s, 6H), 3.52 (m, 4H), 3.37 (d, 2H, J = 14.5 Hz), 1.27 (s, 18H), 1.26 (s, 18H), 1.21 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 152.0, 151.4, 147.5, 143.6, 143.4, 141.4, 128.5, 127.7, 127.5, 127.4, 126.9, 126.2, 125.7, 123.8, 119.8, 119.0, 64.5, 52.0, 50.9, 48.4, 44.8, 34.1, 34.0, 33.7, 32.5, 32.4, 31.7, 31.6, 31.5. FAB MS m/z: 1265 $[M + H]^+$. Anal. Found: C, 72.06; H, 7.98; N, 2.21. Calcd for $C_{76}H_{100}N_2O_{10}S_2$: C, 72.12; H, 7.96; N, 2.21.

2c: colorless crystals. mp 233−236 °C (from dichloromethane−hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.27 (s, 2H), 12.24 (s, 2H), 9.51 (s, 2H), 7.29 (d, 2H, J = 2.2 Hz), 7.28 (d, 2H, J = 2.2 Hz), 7.17 (s, 4H), 6.89 (d, 2H, J = 2.2 Hz), 6.68 (d, 2H, J = 2.2 Hz), 4.40 (d, 2H, J = 13.5 Hz), 4.30 (d, 2H, J = 14.0 Hz), 4.25 (d, 2H, J = 13.8 Hz), 4.09 (m, 2H), 3.88 (d, 2H, J = 14.9 Hz), 3.84 (d, 2H, J = 14.9 Hz), 3.63 (m, 4H), 3.52 (d, 2H, J = 13.8 Hz), 3.51 (d, 2H, J = 13.5 Hz), 3.34 (d, 2H, J = 14.0 Hz), 2.79 (m, 4H), 1.27 (s, 36H), 1.23 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 152.3, 148.3, 143.2, 142.0, 141.6, 129.1, 128.2, 128.1, 127.7, 127.5, 127.3, 127.0, 126.2, 125.6, 123.2, 118.8, 117.4, 55.2, 52.7, 47.7, 41.8, 34.1, 34.0, 33.8, 31.7, 31.5. FAB MS m/z: 1149

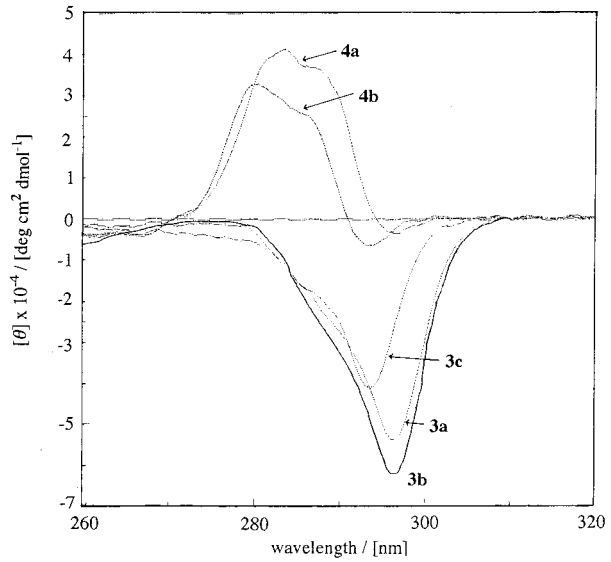

Figure 5. CD spectra of **3** and **4** in $CHCl_3$ at 20 °C.

Table 4. Summary of Crystal Data and Data Collection

	1a
formula	$C_{42}H_{48}O_{10}N_2S_2$
molar mass	804.97
color	colorless
crystal size, mm	0.30 × 0.25 × 0.25
crystal system	monoclinic C
space group	C2
a, Å	17.054(2)
b, Å	13.840(3)
c, Å	16.541(3)
β, deg	92.39(1)
V, Å^3	3900(1)
Z	4
scan mode	$\omega-2\theta$
$2\theta_{max}$, deg	48.5
d_{calcd}, g cm^{-3}	1.371
λ (Mo Kα)	0.71069
μ(Mo Kα), cm^{-1}	1.99
T, K	293
F(000)	1704.00
no. of refls obsd	3471
no. of refls used ($I_0 > 3\sigma I_0$)	1277
R	0.057
R_w	0.047

Table 5. CD Spectral Absorption in $CHCl_3$ at 20 °C

	λ_{ext} [nm]	
macrocycle	(θ[deg cm^2 dmol^{-1}])	
1a	288 (−16600)	299 (7500)
1b	285 (−15200)	298 (4300)
1d	285 (19200)	297 (−5000)
2b	284 (−10100)	293 (9500)
3a	297 (−53900)	
3b	297 (−62400)	
3c	294 (−41200)	
4a	284 (41100)	297 (−3400)
4b	281 (32800)	294 (−6400)

$[M + H]^+$. Anal. Found: C, 75.37; H, 8.42; N, 2.44. Calcd for $C_{72}H_{96}N_2O_6S_2$: C, 75.22; H, 8.42; N, 2.44.

3a: mp 202−205 °C (from dichloromethane−hexane). $[\alpha]^{20}_D$ −123° (*c* = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 10.50 (br s, 4H), 7.02−7.12 (m, 19H), 6.98 (s, 2H), 6.81 (m, 2H), 6.65 (s, 2H), 6.63 (s, 2H), 4.62 (m, 2H), 4.51 (d, 2H, *J* = 14.0 Hz), 4.25 (d, 2H, *J* = 14.0 Hz), 4.13 (d, 2H, *J* = 12.5 Hz), 3.54 (s, 6H), 3.45 (d, 2H, *J* = 14.0 Hz), 3.36 (d, 2H, *J* = 14.0 Hz), 3.32 (d, 2H, *J* = 9.0 Hz), 3.19 (dd, 2H, *J* = 3.5, 14.5 Hz), 3.11 (d, 2H, *J* = 12.5 Hz), 3.09 (dd, 2H, *J* = 9.0, 11.0 Hz), 2.99 (dd, 2H, *J* = 8.0, 14.5 Hz), 2.67 (d, 2H, *J* = 11.0 Hz), 2.20 (s, 6H), 2.15 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 171.1, 170.5, 150.5, 150.4, 138.2, 131.6, 131.0, 129.7, 129.6, 129.5, 129.4, 128.6, 128.1, 127.7, 126.8, 126.1, 122.7, 120.5, 62.8, 55.9, 54.4, 52.5, 52.4, 40.9, 31.2, 27.5, 20.4, 20.3. FAB MS *m*/*z*: 1067 $[M + H]^+$. Anal. Found C, 67.62; H, 6.55; N, 5.50. Anal. Calcd for $C_{60}H_{66}N_4O_{10}S_2$: C, 67.52; H, 6.23; N, 5.25.

Table 6. Observed Proton Chemical Shifts and the Difference (Δ*δ*) of the Chemical Shifts Between H_{exo} and H_{endo} of the $ArCH_2Ar$ Protons at Various Temperatures in $CDCl_3$ at 500 MHz

	°C	Δ*δ* H_eH_f	Δ*δ* H_iH_j	Δ*δ* H_mH_n	Δ*δ* H_rH_q	*δ*OH^1	*δ*OH^2	*δ*OH^3
	55	0.54	0.88	−	0.31	9.40	9.40	−
	30	0.55	0.86	−	0.27	9.30	10.85	−
1b	0	0.60	0.85	−	0.18	9.38	11.35	−
	−30	0.65	0.83	−	0.13	9.50	11.80	−
	−60	0.68	0.81	−	0.10	9.58	12.11	−
	55	0.96	0.85	0.74	0.0	9.03	10.65	13.03
	30	0.94	0.83	0.73	0.0	9.06	10.69	13.13
2b	0	0.92	0.79	0.71	0.0	9.07	10.73	13.24
	−30	0.90	0.77	0.70	0.0	9.07	10.74	13.34
	−60	0.90	0.73	0.68	0.0	9.04	10.72	13.41

3b: mp 211−214 °C (from dichloromethane−hexane). $[\alpha]^{20}_D$ −256° (*c* = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 10.28 (br s, 4H), 7.13 (d, 2H, *J* = 1.5 Hz), 7.04 (d, 2H, *J* = 1.5 Hz), 7.02 (d, 2H, *J* = 3.5 Hz), 6.70 (d, 2H, *J* = 1.5 Hz), 6.67 (d, 2H, *J* = 1.5 Hz), 4.92 (d, 2H, *J* = 14.5 Hz), 4.72 (ddd, 2H, *J* = 4.0, 11.0, 14.0 Hz), 4.36 (d, 2H, *J* = 13.5 Hz), 4.16 (d, 2H, *J* = 12.5 Hz), 3.76 (s, 6H), 3.68 (d, 2H, *J* = 14.5 Hz), 3.43 (d, 2H, *J* = 13.5 Hz), 3.34 (d, 2H, *J* = 12.5 Hz), 3.32 (dd, 2H, *J* = 4.0, 14.0 Hz), 2.87 (d, 2H, *J* = 10.5 Hz), 2.85 (dd, 2H, *J* = 11.0, 14.0 Hz), 2.49 (m, 2H), 2.23 (s, 6H), 2.22 (s, 6H), 1.06 (d, 6H, *J* = 7.0 Hz), 0.75 (d, 6H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.8, 171.5, 150.7, 150.6, 131.8, 131.3, 129.6, 129.4, 129.3, 128.6, 127.7, 126.9, 123.2, 121.1, 64.3, 57.3, 53.6, 52.6, 52.0, 36.9, 31.1, 27.2, 21.0, 20.7, 20.5, 20.4. FAB MS *m*/*z*: 943 $[M + H]^+$. Found C, 65.98; H, 7.18; N, 3.01. Anal. Calcd for $C_{52}H_{66}N_2O_{10}S_2$: C, 66.22; H, 7.05; N, 2.97.

3c: mp 210−217 °C (from dichloromethane−hexane). $[\alpha]^{20}_D$ −120° (*c* = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 10.60 (br s, 4H), 7.38 (d, 2H, *J* = 2.0 Hz), 7.30−7.35 (m, 10H), 7.28 (d, 2H, *J* = 2.0 Hz), 7.19 (d, 2H, *J* = 6.0 Hz), 7.06 (d, 2H, *J* = 2.0 Hz), 6.91 (s, 2H), 4.67 (m, 2H), 4.61 (d, 2H, *J* = 15.0 Hz), 4.39 (d, 2H, *J* = 14.0 Hz), 4.31 (d, 2H, *J* = 15.0 Hz), 3.61 (s, 6H), 3.56 (d, 2H, *J* = 15.0 Hz), 3.53 (d, 2H, *J* = 14.0 Hz), 3.44 (d, 2H, *J* = 9.5 Hz), 3.36 (d, 2H, *J* = 13.0 Hz), 3.25 (dd, 2H, *J* = 9.5, 11.5 Hz), 3.24 (dd, 2H, *J* = 4.5, 14.5 Hz), 3.07 (dd, 2H, *J* = 7.5, 14.5 Hz), 2.73 (d, 2H, *J* = 11.5 Hz), 1.33 (s, 18H), 1.28 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 170.9, 170.5, 150.5, 143.0, 142.9, 138.2, 129.5, 128.7, 128.3, 128.1, 126.8, 126.0, 123.9, 122.4, 120.0, 63.1, 56.6, 54.8, 52.5, 52.4, 41.1, 34.0, 32.0, 31.5, 27.2. FAB MS *m*/*z*: 1236 $[M + H]^+$. Anal. Found C, 69.74; H, 7.12; N, 4.82. Anal. Calcd for $C_{72}H_{90}N_4O_{10}S_2$: C, 69.99; H, 7.34; N, 4.53.

4a: mp 202−206 °C (from dichloromethane−hexane). $[\alpha]^{20}_D$ −140° (*c* = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 10.10 (br s, 2H), 9.05 (br s, 2H), 8.55 (br s, 2H), 8.33 (d, 2H, *J* = 6.0 Hz), 7.22−7.32 (m, 10H), 7.04 (d, 2H, *J* = 1.5 Hz), 7.00 (d, 2H, *J* = 1.0 Hz), 6.86 (d, 2H, *J* = 2.0 Hz), 6.84 (d, 2H, *J* = 2.0 Hz), 6.77 (d, 2H, *J* = 1.5 Hz), 6.10 (s, 2H), 4.55 (d, 2H, *J* = 14.0 Hz), 4.42 (d, 2H, *J* = 12.5 Hz), 4.34 (m, 2H), 4.28 (d, 2H, *J* = 13.5 Hz), 3.77 (dd, 2H, *J* = 6.5, 6.5 Hz), 3.75 (s, 6H), 3.64 (d, 2H, *J* = 13.5 Hz), 3.53 (d, 2H, *J* = 12.5 Hz), 3.47 (dd, 2H, *J* = 3.0, 14.5 Hz), 3.41 (dd, 2H, *J* = 7.0, 14.0 Hz), 3.40 (d, 2H, *J* = 13.5 Hz), 3.37 (d, 2H, *J* = 14.0 Hz), 3.28 (dd, 2H, *J* = 8.5, 14.5 Hz), 3.10 (dd, 2H, *J* = 7.0, 14.0 Hz), 2.99 (d, 2H, *J* = 14.0 Hz), 2.24 (s, 6H), 2.16 (s, 6H), 2.14 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 171.4, 170.4, 150.5, 150.1, 146.5, 140.1, 131.9, 131.8, 131.5, 130.1, 129.6, 129.5, 129.4, 129.3, 129.0, 128.5, 128.4, 128.0, 126.3, 122.4, 120.9, 63.8, 54.0, 52.6 × 2, 52.4, 40.4, 31.7, 31.0, 30.6, 20.5, 20.4, 20.2. FAB MS *m*/*z*: 1306 $[M + H]^+$. Anal. Found C, 70.02; H, 6.22; N, 4.10. Anal. Calcd for $C_{76}H_{80}N_4O_{12}S_2$: C, 69.92; H, 6.18; N, 4.29.

4b: mp 130−134 °C (from dichloromethane−hexane). $[\alpha]^{20}_D$ −93° (*c* = 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 10.60 (br s, 2H), 9.15 (br s, 2H), 8.45 (br s, 2H), 8.48 (d, 2H, *J* = 6.5 Hz),

7.21−7.30 (m, 10H), 7.27 (d, 2H, J = 2.0 Hz), 7.23 (d, 3H, J = 2.0 Hz), 7.09 (s, 4H), 6.93 (d, 2H, J = 2.0 Hz), 6.50 (d, 2H, J = 2.0 Hz), 4.60 (d, 2H, J = 14.0 Hz), 4.45 (d, 2H, J = 12.5 Hz), 4.40 (m, 2H), 4.36 (d, 2H, J = 14.0 Hz), 3.80 (dd, 2H, J = 6.5, 6.5 Hz), 3.76 (s, 6H), 3.72 (d, 2H, J = 14.0 Hz), 3.56 (d, 2H, J = 12.5 Hz), 3.49 (d, 2H, J = 14.0 Hz), 3.45 (dd, 2H, J = 3.5, 14.5 Hz), 3.44 (d, 2H, J = 14.0 Hz), 3.38 (dd, 2H, J = 6.5, 14.5 Hz), 3.28 (dd, 2H, J = 8.0, 14.5 Hz), 3.13 (d, 2H, J = 14.0 Hz), 3.12 (dd, 2H, J = 6.5, 14.5 Hz), 1.28 (s, 18H), 1.23 (s, 18H), 1.17 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 170.4, 150.3, 150.0, 146.5, 144.5, 143.2, 140.1, 129.3 × 2, 129.2, 128.5 × 2, 128.4, 128.3, 127.8, 127.6, 126.3, 126.2, 126.1, 125.0, 124.9, 121.9, 120.4, 63.8, 53.8, 53.0, 52.7, 52.6, 40.3, 34.0, 33.9, 33.8, 31.9, 31.6, 31.5, 31.4, 31.3, 30.4. FAB MS m/z: 1560 $[M + H]^+$. Anal. Found C, 72.55; H, 7.69; N, 3.84. Anal. Calcd for $C_{94}H_{118}N_4O_{12}S_2$: C, 72.37; H, 7.62; N, 3.59.

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Supporting Information Available: X-ray crystallographic data for **1a**. This material is available free of charge via Internet at http://pubs.acs.org.

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