SYNTHESIS OF A NOVEL WATER-SOLUBLE CYCLOPHANE HAVING EIGHT CARBOXYMETHYLTHIOMETHYL GROUPS ON THE AROMATIC RINGS[1]

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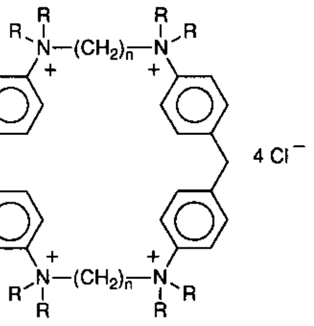
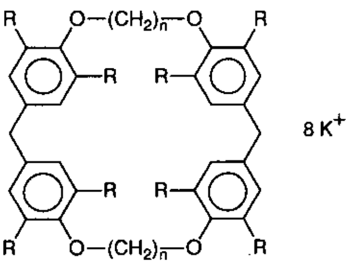
Abstract- A novel cyclophane (**9**) having eight carboxyl groups that are attached on the aromatic rings via a spacer (-CH_2SCH_2-) was designed and synthesized as a host for cationic, anionic, and neutral aromatic guests in alkaline water. Macrocyclization of **7** with **6** was carried out under high dilution condition to give the objective **8** in 17% yield.

Water-soluble cyclophanes having a hydrophobic cavity constitute a promising class of totally synthetic hosts to capture organic guests in aqueous solution.[2] We have previously reported a series of cationic cyclophanes (**1**) which are composed from two diphenylmethane units and two bridging chains that are connected *via* four nitrogens. Evidence of the formation of 1:1 inclusion complexes with neutral and anionic aromatic guests was



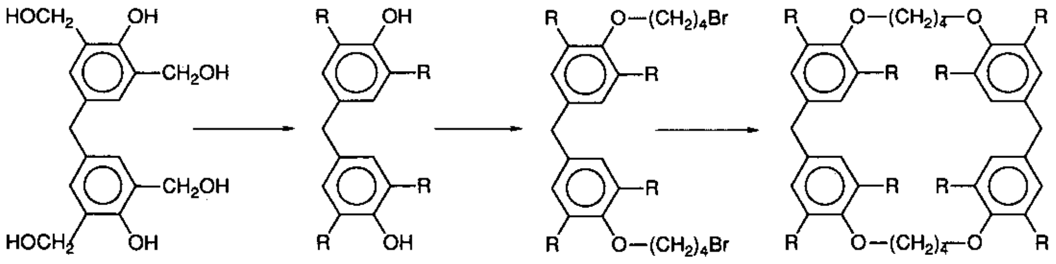
1 R = H, Me; n ≥ 4



2 R = CO_2^- ; n = 4, 6
3 R = $CH_2SCH_2CO_2^-$; n = 4

obtained by X-ray crystallographic studies. ^{1}H-Nmr and fluorescence spectroscopic studies have confirmed that the inclusion complex formation occurs not only in the crystalline state but also in aqueous solution.[2a,e,3] The complexation was found to occur with a particular geometry and with marked selectivity. We have also reported anionic cyclophanes (**2**), which are composed from two diphenylmethane units and two bridging chains that are connected *via* four oxygens, and have eight carboxylate groups that are attached directly on the aromatic rings. ^{1}H-Nmr spectral studies have shown that anionic cyclophanes (**2**) form 1:1 inclusion complexes selectively with cationic aromatic guests.[4] These data suggest that charge interactions in addition to hydrophobic interactions between the host and the guest are operating at complexation using **1** and **2** as hosts, which carry charges at the periphery of their cavities.

We assumed that cyclophanes having charges remote from their cavities would work as hosts for any of the cationic, anionic, and neutral aromatic guests.[5] Guided by CPK model studies, we designed an anionic water-soluble cyclophane (**3**), which has two diphenylmethane units and two tetramethylene bridges that are connected *via* four oxygens, and has eight carboxylate groups that are attached on the aromatic rings via a spacer (-CH_2SCH_2-). By ^{1}H-nmr spectral studies, we have recently shown that **3** forms 1:1 inclusion complexes in particular geometries with any of the cationic, anionic, and neutral aromatic guests in weakly alkaline D_2O.[6] We describe here the details of the synthesis and characterization of **9**, which is expected to exist as **3** in aqueous potassium hydroxide.[7]



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5 R = CH_2Cl

6 R = $CH_2SCH_2CO_2Et$

7 R = $CH_2SCH_2CO_2Et$

8 R = $CH_2SCH_2CO_2Et$

9 R = $CH_2SCH_2CO_2H$

As shown in the Scheme, the parent cyclophane (**9**) was synthesized from the known **4**,[8] which is easily accessible from phenol. Treatment of **4** with thionyl chloride afforded the corresponding tetrachloride (**5**), which was converted to the tetraester (**6**) using ethyl mercaptoacetate in dimethylformamide (DMF) in the presence of potassium carbonate (K_2CO_3). The reaction of **6** with excess tetramethylene dibromide in DMF in the presence of K_2CO_3 gave the corresponding dibromide (**7**). Macrocyclization of **7** with **6** was carried out under high dilution condition. The objective **8** was isolated in 17% yield after careful separation and purification. Hydrolysis of **8** gave the desired octacarboxylic acid (**9**). The cyclized structures of **8** and **9** were confirmed on the basis of molecular ion peaks in their mass spectra.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on a JASCO IRA-1 infrared spectrophotometer. ^{1}H-Nmr spectra were recorded on a JEOL JNM-GSX 400 Fourier transform nmr spectrometer using tetramethylsilane (TMS) as an internal standard when measured in organic solvents, and as an external standard when measured in aqueous solvents. Mass spectra were recorded on a JEOL JMS-SX 102A mass spectrometer or on a HITACHI M-2000 double-focusing mass spectrometer.

3,5,3',5'-Tetrakis(chloromethyl)-4,4'-dihydroxydiphenylmethane (5) Thionyl chloride (20 ml, 270 mmol) was added slowly to a suspension of **4**[8] (3.2 g, 10 mmol) in $CHCl_3$ (60 ml), and the whole was stirred at room temperature for 3 days. The reaction mixture was concentrated to dryness *in vacuo*, the residue was mixed with benzene, and the whole was again concentrated to dryness to give a slightly dark solid. Recrystallization from acetone-hexane gave **5** (3.52 g, 89 %) as colorless needles of mp 155-156 °C. Ir (KBr) cm^{-1}: 3550, 1605. ^{1}H-Nmr ($CDCl_3$) δ: 3.83 (2H, s, Ph-C*H*$_2$-Ph), 4.66 (8H, s, Ph-C*H*$_2$-Cl), 5.65 (2H, s, O*H*), 7.07 (4H, s, Ar-*H*). *Anal.* Calcd for $C_{17}H_{16}O_2Cl_4$: C, 51.81; H, 4.09. Found: C, 51.84; H, 4.04.

3,5,3',5'-Tetrakis(ethoxycarbonylmethylthiomethyl)-4,4'-dihydroxydiphenylmethane (6) A mixture of **5** (8.13 g, 20.6 mmol), ethyl mercaptoacetate (9.90 g, 82.4 mmol), and anhydrous K_2CO_3 (11.4 g, 82.4 mmol) in DMF (20 ml) was stirred at 60 °C for 4 h. The reaction mixture was filtered, and the filtrate was mixed with AcOEt (200 ml). After washing with brine (200 ml x 3), the AcOEt layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a yellow oil. Purification by column chromatography (silica gel, AcOEt-hexane (1:1)) afforded **6** (7.55 g, 50 %) as a pale yellow oil. Ir (film) cm^{-1}: 3380, 1728. ^{1}H-Nmr ($CDCl_3$) δ: 1.29 (12H, t, J=7, OCH_2CH_3), 3.15 (8H, s, $SCH_2COOC_2H_5$), 3.76 (2H, s, Ph-C*H*$_2$-Ph), 3.85 (8H, s, Ar-C*H*$_2$-S), 4.20 (8H, q, J=7, OCH_2CH_3), 6.94 (4H, s, Ar-*H*), 7.45 (2H, s, O*H*). Ms m/z: 728 (M+). *Anal.* Calcd for $C_{33}H_{44}O_{10}S_4$: C, 54.37; H, 6.08. Found: C, 54.66; H, 5.95.

4,4'-Bis(4-bromobutoxy)-3,5,3',5'-tetrakis(ethoxycarbonylmethylthiomethyl)diphenylmethane (7) A mixture of **6** (3.67 g, 5.0 mmol), 1,4-dibromobutane (5.44 g, 25.0 mmol) and anhydrous K_2CO_3 (3.47 g, 25.0 mmol) in DMF (300 ml) was stirred at room temperature for 8 h. After cooling, the reaction mixture was filtered, the filtrate was mixed with AcOEt (200 ml), and the whole was washed with brine

(300 ml x 3). The AcOEt layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a pale yellow oil. Purification by column chromatography (silica gel, AcOEt-hexane (1: 2)) afforded **7** (3.50 g, 70 %) as a pale yellow oil. Ir (film) cm^{-1}: 1729. ^{1}H-Nmr ($CDCl_3$) δ: 1.28 (12H, t, J=7, OCH_2CH_3), 1.9-2.2 (8H, m, $OCH_2CH_2CH_2CH_2Br$), 3.17 (8H, s, $SCH_2COOC_2H_5$), 3.52 (4H, t, J=7, CH_2CH_2Br), 3.82 (10H, s, Ph-CH_2-Ph, Ar-CH_2S), 3.98 (4H, t, J=7, OCH_2CH_2), 4.18 (8H, q, J=7, OCH_2CH_3), 7.09 (4H, s, Ar-*H*). *Anal.* Calcd for $C_{41}H_{58}O_{10}Br_2S_4$: C, 49.29; H, 5.85. Found: C, 49.41; H, 5.81.

5,14,20,29,32,33,36,37-Octakis(ethoxycarbonylmethylthiomethyl)-7,12,22,27-tetraoxa-[6.1.6.1]paracyclophane (8)[9] A solution of **7** (998 mg, 1.0 mmol) and **6** (728 mg, 1.0 mmol) in DMF (30 ml) was added dropwise over a period of 2 h to a stirred and heated (60-70 °C) suspension of anhydrous K_2CO_3 (690 mg, 5.0 mmol) in DMF (50 ml), and the stirring was continued at the same temperature for 5 h. The reaction mixture was filtered, and the filtrate was mixed with AcOEt (150 ml). After washing with brine (300 ml x 3), the AcOEt layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a pale yellow oil. Purification by column chromatography (silica gel, AcOEt-hexane (1: 2)) afforded **8** as a colorless oil, which became colorless powder (0.26 g, 17 %) on trituration in MeOH. Ir (KBr) cm^{-1}: 1735. ^{1}H-Nmr ($CDCl_3$) δ : 1.30 (24H, t, J=7, OCH_2CH_3), 1.9-2.0 (8H, m, $OCH_2CH_2CH_2CH_2O$), 3.11 (16H, s, $SCH_2COOC_2H_5$), 3.69 (4H, s, Ph-CH_2-Ph), 3.75 (8H, s, Ar-CH_2S), ~3.8 (8H, m, $OCH_2CH_2CH_2CH_2O$), 4.20 (16H, q, J=7, OCH_2CH_3), 7.07 (8H, s, Ar-*H*). Ms (Fd) *m/z*: 1565 (M^++1). *Anal.* Calcd for $C_{74}H_{100}O_{20}S_8$: C, 56.75; H, 6.44. Found: C, 56.94; H, 6.41.

5,14,20,29,32,33,36,37-Octakis(carboxymethylthiomethyl)-7,12,22,27-tetraoxa[6.1.6.1]-paracyclophane (9)[9] To a suspension of **8** (780 mg, 0.5 mmol) in MeOH (20 ml) was added 5N KOH-MeOH (10 ml), and the whole was heated under reflux for 4 h. The reaction mixture was evaporated to dryness *in vacuo* to give a residue, which was dissolved in H_2O (20 ml). After acidification to pH 1 by addition of 1N HCl, the whole was extracted with AcOEt. The extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was triturated in AcOEt-hexane to give a colorless solid, which was recrystallized from acetone-AcOEt to give **9** (500 mg, 75 %) as colorless fine needles of mp 174-175 °C. Ir (KBr) cm^{-1}: 1702. ^{1}H-Nmr (KD_2PO_4-KOD-D_2O buffer, pD 7.9) δ: ~1.6 (8H, m, OCH_2CH_2-CH_2CH_2O), 2.78 (16H, s, SCH_2COOH), 3.36 (16H, s, Ar-CH_2S), 3.57 (2H, s, $PhCH_2Ph$), 3.68 (8H, m, $OCH_2CH_2CH_2CH_2O$), 6.82 (8H, s, Ar-*H*). Ms(Fd) *m/z:* 1341 (M^++1). *Anal.* Calcd for $C_{58}H_{68}O_{20}S_8$: C, 51.92; H, 5.11. Found: C, 51.72; H, 5.04

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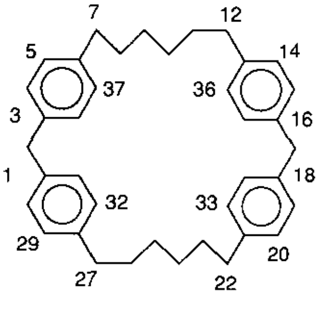
7. Due to the hygroscopic nature, it was not possible to isolate **3** in analytically pure state.
8. F. Seebach, *Ber.*, 1939, **72**, 1635.
9. For convenience, a conventional cyclophane nomenclature is used according to the numbering of the parent skeleton (i), which is named as [6.1.6.1]paracyclophane.



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