Synthesis and Properties of Cholesteryl Esters Bearing 32- and 16-Membered Crown Ethers

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The cholesteryl esters (**3b** and **3a**) of 5-carboxy-1,3-phenylene-16-crown-5 and 5-carboxy-4,6-dichloro-1,3-phenylene-16-crown-5 show cholesteric liquid crystalline behavior but only upon heating samples that were rapidly cooled from the isotropic melt in the case of **3a** and a monotropic phase for **3b**. The dichloro compound **3a** was formed by treatment of the corresponding acid **2** with $SOCl_2$ first and then cholesterol; it is believed that the $SOCl_2$ was contaminated with SO_2Cl_2, leading to the chlorination of the aromatic ring. The dichloro compound **3a** was structurally characterized using single crystal X-ray diffraction. **3a** crystallizes in the orthorhombic space group $P2_12_12_1$ with unit cell parameters of $a = 12.76(4)$ Å, $b = 17.511(5)$ Å, and $c = 18.213$ Å. Use of freshly opened $SOCl_2$ produced **3b**. The reaction of the acid **2** and cholesterol in the presence of dicyclohexylcarbodiimide yielded the acylisourea **4** as the major product (64%) along with **3b** (36%) upon treatment with cholesterol. The dicholesteryl ester **9** of bis(5-carboxy-1,3-phenylene)-32-crown-10 (**8a**) was also synthesized, and by differential scanning calorimetry (DSC) and polarized optical microscopy no liquid crystalline behavior was observed with this system. Apparently the presence of the semirigid crown in the molecule prevents the two cholesteryl moieties from organizing in independent helices. The complexation ability of this cholesteryl crown (**9**) with methyl viologen bis(hexafluorophosphate) ([paraquat]·2[PF_6]) (**12**) in acetone has been examined by ^{1}H NMR spectroscopy; it showed weaker binding than its simple dimethyl ester analog **8b**.

Introduction

The idea of exploring the ordering of molecules in liquid crystalline phases for the optimization of various types of functionality is appealing. Lehn[1] and Ringsdorf[2] have explored the use of this concept in a number of areas: photochemical control of phase changes, optical memory devices, "one-dimensional" conductors and photoconductors. The synthesis and cation binding properties of steroidal aza-crown ethers were reported by Gokel et al.[3] Later Shinkai and co-workers[4−7] also reported the synthesis of cholesteric liquid crystals bearing crown ethers. They studied the cation binding,[4] ion permeation,[5] detection,[6] and chirality recognition[7] abilities of these compounds in the liquid crystalline state. Ming-Gui and coworkers also reported synthesis and properties of cholesteryl derivatives of crown ethers.[8]

Aware of these previous studies and having available 5-carboxy-1,3-phenylene-16-crown-5 (**2**)[9] and bis(5-carboxy-1,3-phenylene)-32-crown-10 (**8a**)[9], we chose to make the corresponding cholesteryl esters and examine their ability to form mesophases. Here we report the synthesis and properties of these compounds.

Results and Discussion

A. Synthesis and Molecular Characterization. The reactions for the synthesis of the cholesteryl esters of the 16-membered crown ether acid **2** are shown in Scheme 1. 5-Carbomethoxy-16-crown-5 (**1**)[9] was converted into the corresponding 5-carboxy-1,3-phenylene-16-crown-5 (**2**) in quantitative yield by reaction with NaOH in ethanol. The acid **2** was reacted with $SOCl_2$ in an attempt to produce 5-(chlorocarbonyl)-1,3-phenylene-16-crown-5. Then cholesterol (along with a few drops of pyridine) was added to the chlorocarbonyl crown ether at room temperature. However, the cholesteryl ester **3a**, in which two chlorine atoms had been introduced in the aromatic ring, was isolated in 92% yield.

The structure was confirmed by elemental analysis, spectroscopy, and X-ray crystal structure determination. The elemental analysis and mass spectral data are entirely consistent with this structure (**3a**); the MS contains the molecular ion and the proper ratios of isotopic peaks. The proton NMR shows that there is only one aromatic proton; it is a singlet at δ 7.39, shifted downfield relative to proton "a" of **1**. The molecular structure (Figure 1 and 2) deduced from single crystal X-ray diffraction clearly shows the presence and locations of the two chlorine atoms. Figure 1 shows the entire structure of the molecule, revealing the facts that the carbonyl group is not coplanar with the aromatic ring probably due to the steric effects of the *o*-chloro substituents and the essential coplanarity of the aromatic ring

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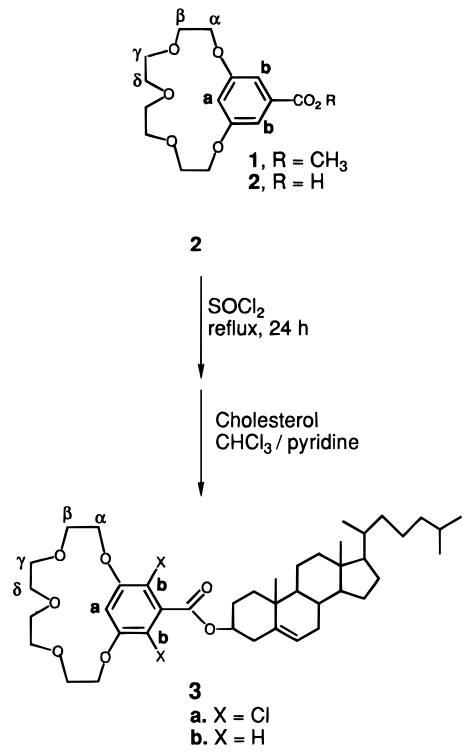
Scheme 1



with the cholesteryl nucleus. Figure 2 shows only the crown ether portion of the molecule; the carbonyl group's orthogonality to the aromatic ring is evident, as is the "bent" nature of the ring, in close similarity to the conformation of **1**.[10] It is believed that the $SOCl_2$ contained some amount of SO_2Cl_2, a good chlorinating agent[11] for aromatic compounds.

We decided to synthesize cholesteryl ester **3b** via an alternate method involving DCC (dicyclohexylcarbodiimide), a dehydrating agent. This procedure is particularly widely used for the acylation step in the synthesis of polypeptides from amino acids.[12,13] Carboxylic acids are known to react with carbodiimides to give acylisoureas. The acyl group is highly reactive in this environment because the cleavage of the acyl−oxygen bond converts the carbon−nitrogen double bond of the isourea to a more stable carbon−oxygen double bond.[14−16] An attempt was made to synthesize cholesteryl ester **3b** (Scheme 2) by reacting 5-carboxy-1,3-phenylene-16-crown-5 (**2**) with cholesterol in the presence of DCC with catalytic amounts of 4-(dimethylamino)pyridine (DMAP). After 30 h of reflux TLC indicated complete consumption of the starting acid crown **2**. Insoluble dicyclohexylurea obtained as a byproduct was filtered, and the crude material was subjected to flash silica column chromatography with diethyl ether (Et_2O) as solvent. Of the two compounds that were isolated one was found to be the desired compound **3b** isolated in 36%. The other component upon analysis by NMR was found to be *N*,*N*-dicyclohexyl-*O*-(5-carbonyl-1,3-phenylene-16-crown-5)-isourea (**4**). The proton NMR spectrum corresponded to this structure. IR spectroscopy showed two different absorptions (1675.8 and 1642.6 cm^{-1}) for the C═N moiety of the acyl isourea, consistent with two geometrical isomers of **4**. The structure of **4** was further confirmed by FAB mass spectrometry which revealed the molecular ion. The fragmentation pattern was consistent with **4**.

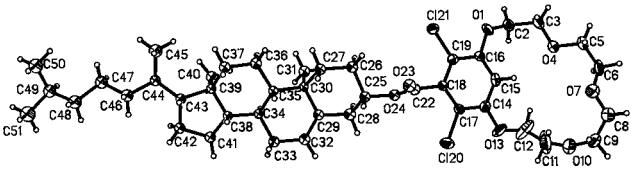


Figure 1. Molecular conformation of compound **3a** in the crystalline state as determined by X-ray crystallography.

It is well known[14] that acylisoureas are very reactive toward alcohols due to the formation of a very stable compound, urea, which contains the more stable carbon oxygen double bond as compared to carbon−nitrogen double bond. The isolated intermediate **4** was therefore reacted with cholesterol with a catalytic amount of base, DMAP (Scheme 2). After 24 h of reflux the TLC in ethyl acetate (EtOAc) indicated substantial amounts of the starting materials. Both cholesterol and acylisourea **4** were separated by first eluting with Et_2O, followed by EtOAc to give product **5**. The proton NMR spectrum of product **5** was similar to that of acylisourea **4**. The main difference was the change in the chemical shift of the NH proton upfield by about 0.56 ppm as compared to the acylisourea **4**. The ^{13}C NMR spectrum of **5** indicated eight carbon atoms in the aliphatic region, four due to the cyclohexyl unit and four due to the oxyethylene moieties and a loss of one carbon atom (absence of extra C═O resonance) in the sp^2 region. The ^{13}C APT NMR spectrum indicated the presence of the methine carbon of the cyclohexyl urea moiety in **5**. Similarly IR spectroscopy indicated the absence of C═N stretch and only one absorption for carbonyl moiety. This data indicates that there may be a rearrangement ocurring via a four-membered transition state (**6**, Scheme 3) to give *N*-(5-carbonyl-1,3-phenylene-16-crown-5)-*N*,*N*′-dicyclohexylurea (**7**). The four membered transition state, however uncommon, may be possible due to (1) the presence of the aza-enamine moiety in the acylisourea intermediate **4** and (2) the formation of the stable carbon−oxygen double bond in **7**. This intermediate may react with water to eliminate CO_2 and cyclohexylamine, to give the observed amide **5**. We were able to detect cyclohexylamine from the carbon-13 NMR spectrum of the crude material which indicated four sets of carbons for the cyclohexyl moiety. Thus this result indicates that the presence of the crown moiety makes the acylisourea **4** too sterically bulky to react with cholesterol. It is this particular reason that the reaction results in lower yields of **3b** in the DCC reaction.

Acid chlorides are widely used for ester synthesis, especially for the preparation of cholesteryl esters from benzo-15-crown-5[4] and benzo-18-crown-6[5] derivatives. The acid crown **2** was reacted with freshly opened $SOCl_2$ (Scheme 1) to produce 5-(chlorocarbonyl)-1,3-phenylene-16-crown-5. Cholesterol and 2 equiv of pyridine were added to the acid chloride, and the mixture was refluxed for 30 h. TLC indicated the presence of unreacted starting material, cholesterol. This reaction gave a 60% yield of the desired product [5-(cholesteryloxycarbonyl)-

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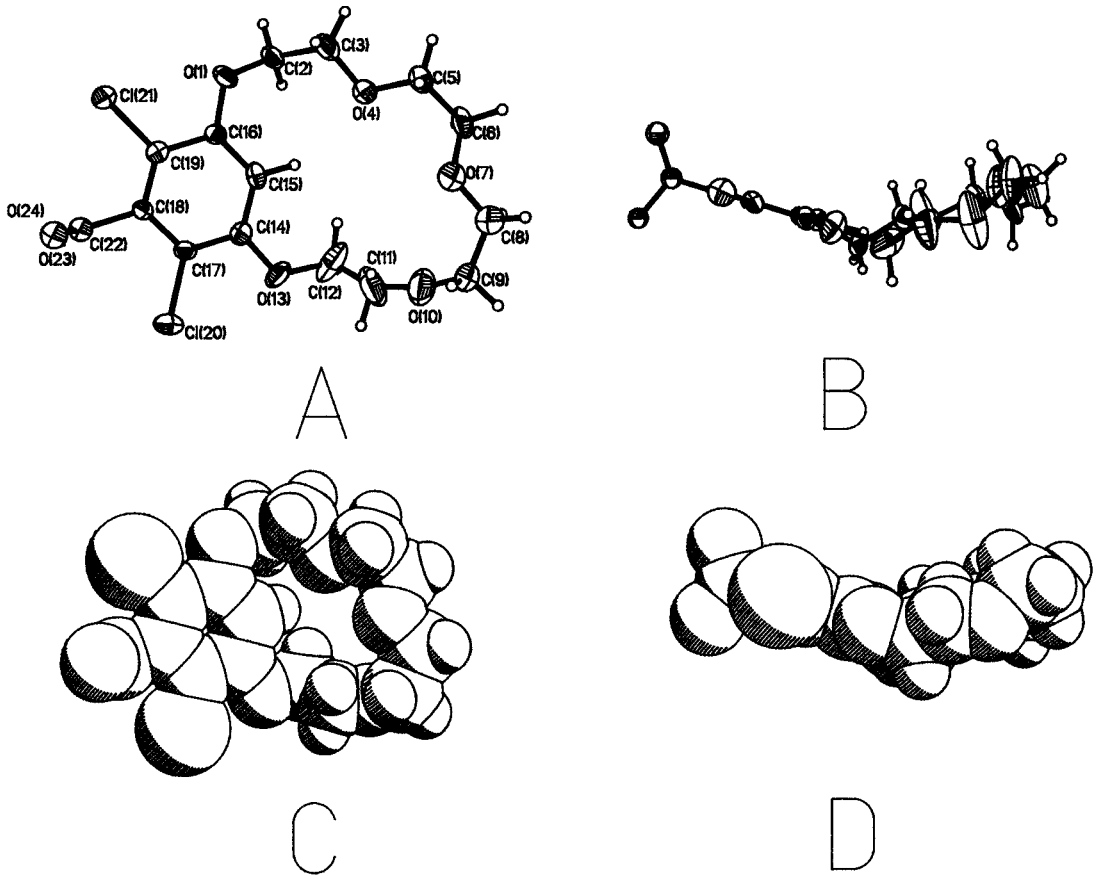
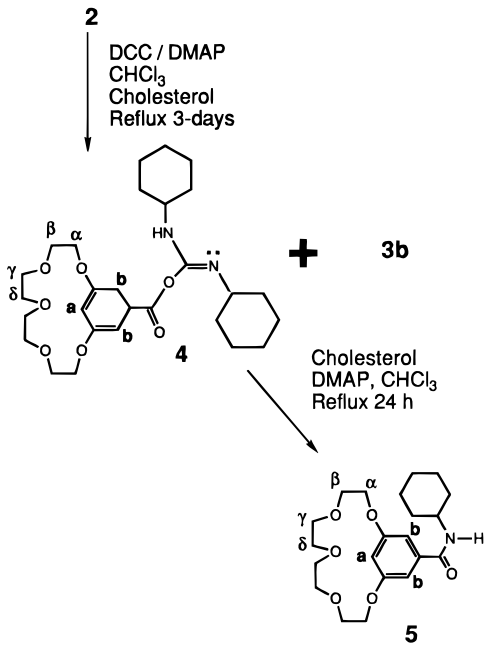
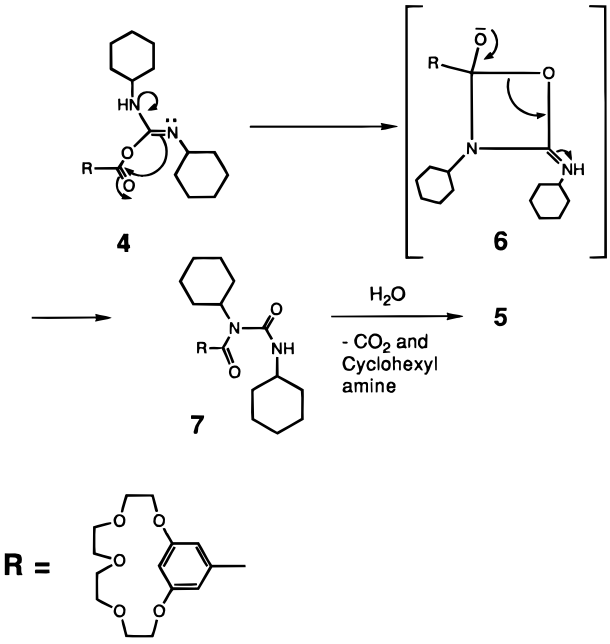


Figure 2. Conformation of 5-carbonyl-4,6-dichloro-1,3-phenylene-16-crown-5 portion of **3a**: (a) top view, ball and stick; (b) side view, ball and stick; (c) top view, space filling; (d) side view, space filling.

Scheme 2



Scheme 3



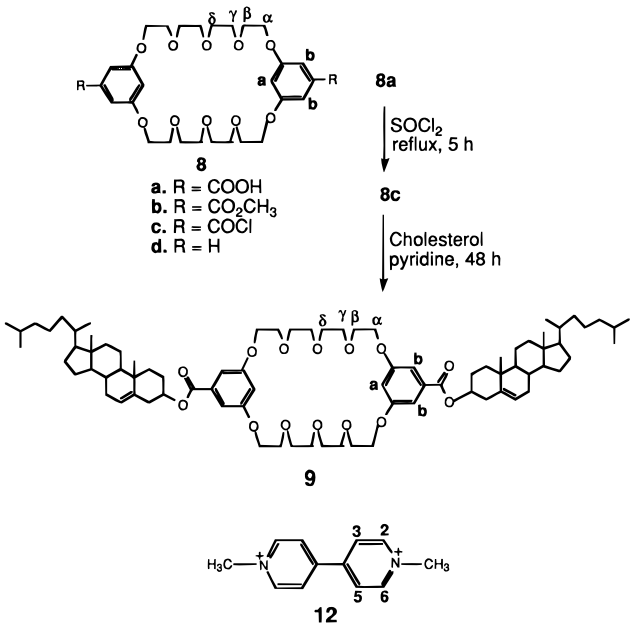
1,3-phenylene-1,6-crown-5 (**3b**)], which was characterized both by DSC and polarized optical microscopy.

The same procedure used for the synthesis of **3b** was followed for the synthesis of the dicholesteryl diester **9** (Scheme 4) in 70% yield, except that a brief reaction time was used to convert acid **8a** to its acid chloride **8c**.

B. Thermal Properties of the Crown Derivatives. a. Compound 3a. Figure 3 shows some DSC scans obtained with monoester **3a**. Figure 3a shows the scan obtained on cooling the sample from the isotropic melt. Two prominent peaks are seen at 117 and 130 °C. When this sample is heated, the thermogram is characterized by a single sharp endotherm at 213 °C (Figure 3b). When the sample is quenched, the heating scan (Figure 3c) is characterized by two exotherms at 58 and 130 °C and two melting endotherms at 147 and 212 °C.

In order to understand the origin of the transition behavior observed by DSC, polarized optical microscopy

Scheme 4



measurements were made. Figure 4 shows characteristic micrographs obtained for compound **3a**. In this case the sample was quenched from 240 °C to room temperature. Figure 4a shows a micrograph taken at 25 °C and Figure 4b shows one taken at 110 °C. Both the micrographs show birefringence due to the spherulitic nature of the sample; on close examination one can observe that in Figure 4b the birefringence has increased. Therefore, we attribute the small exotherm at 58 °C in Figure 3c to further crystallization. Figure 4c shows a micrograph obtained at 120 °C; the spherulitic texture disappears and instead a rodlike smectic phase appears. This temperature is very close to the second exotherm observed in the DSC scan (Figure 3c) at 130 °C. Therefore, it would seem that this exotherm is due to the formation of the smectic phase. Figure 4d shows a micrograph obtained at 130 °C, where one can see a fully developed anisotropic phase. Figure 4e shows a micrograph obtained at 150 °C; the smectic phase of Figure 4d disappeared and was replaced by a very different type of anisotropic phase, which is a cholesteric liquid crystalline phase. The endotherm observed in Figure 3c at 147 °C is close to the temperature observed by microscopy. In Figure 4e disclination lines characteristic of the cholesteric phase are discerned. On heating, isotropization occurs at 215 °C. This temperature agrees with the DSC endotherm (Figure 3c) at 213 °C. Thus based on the DSC and microscopy results, it is concluded that compound **3a** shows two liquid crystalline phases, a smectic of some type and a cholesteric.

b. Compound 3b. Figure 5 shows some typical DSC scans for 5-cholesteryloxycarbonyl-1,3-phenylene-16-crown-5 (**3b**) obtained upon heating (Figure 5a), cooling (Figure 5b), and reheating (Figure 5c). Upon heating, the thermogram shows only one transition for melting at 155.4 °C. Upon cooling at a rate of 5 °C/min, a sharp transition due to the cholesteric mesophase is seen at 48.2 °C followed by the glass transition temperature, T_g, at 19.2 °C. No further transitions are observed upon cooling to −50 °C. When the sample was reheated four transitions were observed. These were due to the glass transition (20.8 °C), melting of the cholesteric mesophase

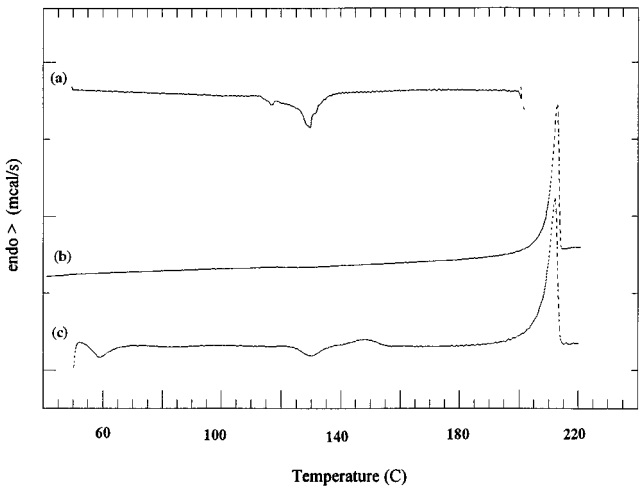


Figure 3. DSC scans (5 °C/min) on compound **3a**: (a) cooled from the isotropic melt, (b) second heating, and (c) heating scan of a sample rapidly cooled from the isotropic melt.

(51.4 °C), crystallization (80 °C) and finally the isotropization of the crystals (154.5 °C).

Figure 6 shows micrographs obtained for compound **3b**. Upon cooling of the freshly melted sample, one observes a typical cholesteric mesophase (Figure 6a) at 11 °C. The DSC (Figure 5b) exotherm at 48 °C, probably due to the formation of the cholesteric phase, does not seem to result in birefringence at this temperature. This may be due to the homeotropic alignment of the molecules. This phenomenon cannot be checked by pressing the cover slip due to instrumentation constraints. The birefringence observed at 11 °C persists as low as −50 °C without any significant crystallization. Upon heating the quenched cholesteric liquid crystal phase on a hot stage at a rate of 5 °C/min, complete melting of this phase to an isotropic melt occurs at 45 °C. The isotropic liquid upon further heating generates a spherulitic texture (Figure 6b) at 85 °C which corresponds quite well to the exotherm observed for crystallization at 91 °C in the DSC scan (Figure 5c). The crystallized spherulites upon further heating undergo isotropization at 156 °C (Figure 6c).

On the basis of results obtained from polarized optical microscopy and DSC, sample **3b** exhibits monotropic cholesteric liquid crystalline behavior, similar to compound **3a**. The main difference between the two cholesteryl esters is that there is a significant decrease in the melting and cholesteric mesophase transitions in **3b** as compared to **3a**. The relatively higher transition temperatures in **3a** are perhaps due to the presence of a bulky chlorine atoms, which restrict conformational changes. These results are not surprising since compounds with similar structural features such as 4-(cholesteryloxycarbonyl)benzo-15-crown-5 (**10**) and 4-(cholesteryloxycarbonyl) benzo-18-crown-6 (**11**) exhibit cholesteric phases. **10** displays an enantiotropic cholesteric phase from 133−143 °C and **11** a monotropic cholesteric phase from 125−165 °C (mp 182 °C).[3]

c. Compound 9. Figure 7 shows DSC scans for the diester **9**. In Figure 7a three exotherms are observed at 70, 94, and 98 °C, respectively, upon cooling the sample from the melt. Heating the slowly cooled sample produces a sharp endotherm at 170 °C (Figure 7b). If the sample is quenched, upon heating, the glass transition occurs at 52 °C (Figure 7c), followed by a sharp exotherm at 70 °C and a small exotherm at 117 °C, and two

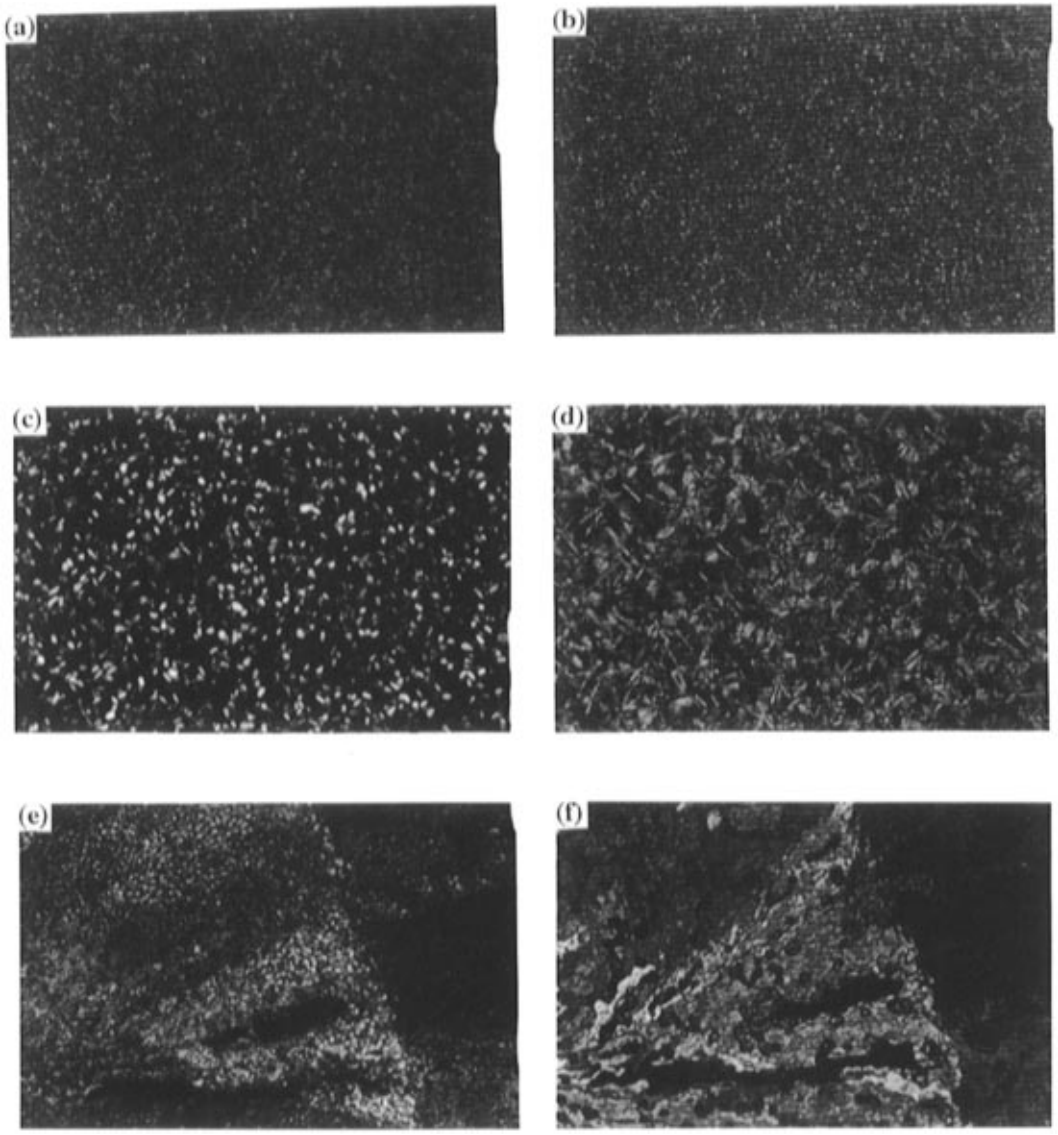


Figure 4. Polarized optical micrographs obtained upon heating of compound **3a** rapidly cooled from 240 °C to room temperature at (a) 25 °C, (b) 110 °C, (c) 120 °C, (d) 130 °C, (e) 150 °C, and (f) at 205 °C, respectively.

endotherms, a very small one at 150 °C and a large one at 170 °C. This compound therefore, gives no evidence of liquid crystallinity.

Optical micrographs obtained for compound **9** upon heating the quenched sample show only the formation of a spherulitic crystalline texture and no evidence of a mesophase. Upon reheating, the sample becomes isotropic at 180 °C. Thus, microscopic observations on **9** confirm that it is not liquid crystalline.

c. Solution Complexation of 9 with [Paraquat]·2[PF_6] (12). Stoddart and co-workers[17] studied the complexation of bis(*m*-phenylene)-32-crown-10 (BMP32C10, **8d**) with paraquat **12** or diquat bis(hexafluorophosphate)s. They found that **8d** forms a 1:1 complex with paraquat in organic solvents such as acetone (K_a = 760 M^{-1}). When a colorless solution of dimethyl ester **8b** is mixed with a colorless solution of paraquat·2[PF_6] (**12**) on an equimolar basis, a yellow-orange solution is formed immediately as a result of the charge transfer complexation. Comparison (Table 1) of the ^{1}H NMR spectra of **8b** and the complex of **8b** with [paraquat]·2[PF6] (**12**) reveals upfield shifts for most protons on complexation. These observations as stated by Stoddart and co-workers[17] "are the results of a combination of [C- -H- - -O] hydrogen bonding, [N^+- - -O] electrostatic interactions, and charge transfer between the π-electron-rich resorcinol rings and π-electron-deficient bipyridinium dication, which clearly stablize the 1:1 complex. The charge transfer interactions account for the yellowish-orange color of the complex."

Equimolar solutions of dicholesteryl ester **9** with paraquat **12** in acetone displayed a light yellow color. The comparison of the chemical shifts of the protons of paraquat and crown moieties in the complex with those of the dimethyl ester analog **8b** (Table 1) shows smaller changes, especially for H_a, H_b-aromatic, and α-OCH_2 protons. Also the β-OCH_2 protons show a downfield shift (positive) in comparison to the complex with **9b** (Table 1). The less intense color and smaller chemical shift changes for the cholesteryl diester are qualitative evidence of weaker complexation than for analog **8b**. Gokel

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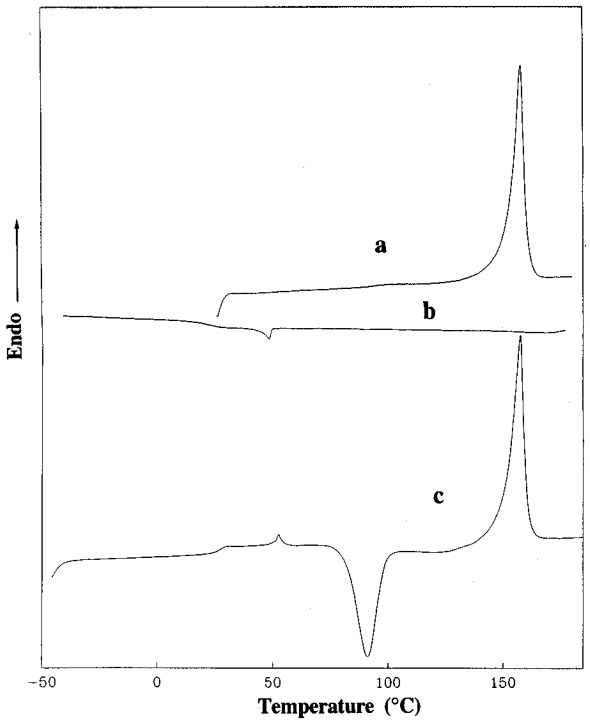

Figure 5. DSC scans (5 °C/min) on compound **3b**. (a) heating, (b) cooling, and (c) reheating the cooled sample.

and co-workers also found that steroidal lariat ethers generally show weak cation binding; the presence of the lipophilic cholesteryl side arm does not enhance the cation binding strength.[3]

Conclusions

A variety of compounds were obtained during the attempted synthesis of 5-(cholesteryloxycarbonyl)-1,3-phenylene-16-crown-5 (**3b**). The structural elucidation was done by IR, NMR, and mass spectral techniques; the crystal structure of **3a** was obtained. The cholesteryl-containing monoesters **3a** and **3b** and diester **9** were examined for mesomorphic behavior by both DSC and polarized optical microscopy. Both **3a** and **3b** exhibit monotropic cholesteric liquid crystalline behavior. No liquid crystalline behavior was observed for dicholesteryl ester **9** due to the difficulty of organizing the two cholesteryl moieties into separate helices. Furthermore the complexation of **9** with **12** was studied and was found to be weaker than the parent dimethyl ester analog **8b** with **12**.

Experimental Section

Materials. Unless specified otherwise, reagent grade reactants and solvents were used as received from chemical suppliers. Pyridine was distilled over calcium hydride prior to use.

Measurements. Melting points are corrected. Infrared spectra were recorded in KBr. ^{1}H NMR spectra were recorded at ambient temperature on a 400 MHz spectrometer using deuterated acetone, dimethyl sulfoxide, and chloroform (as about 15% solutions) with CD_2HCOCD_2H (δ = 2.04) or TMS (δ = 0) as internal standards, respectively. Chemical shifts are reported in parts per million (δ) in comparison to internal standards in order: chemical shift, spin multiplicity (br = broad; s = singlet; d = doublet; t = triplet; q = quartet; h = heptet; m = multiplet), coupling constants in hertz and integration. Mass spectra were measured with a analytical

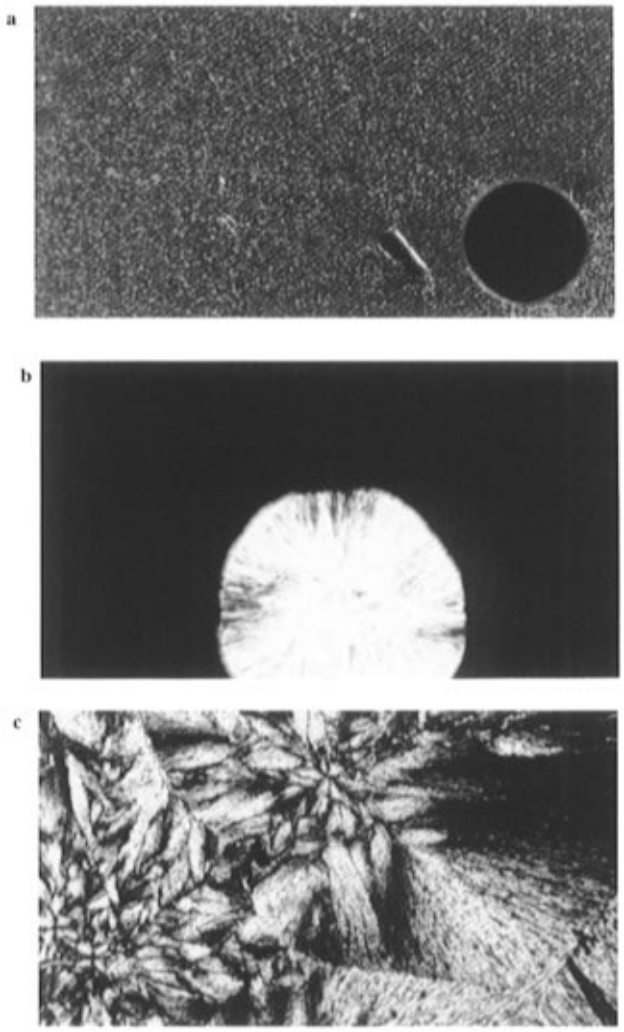

Figure 6. Polarized optical micrographs of **3b** obtained upon (a) cooling from the isotropic melt to 11 °C and (b) reheating the cooled sample to 85 °C where crystallization begins, followed by (c) further heating of the crystallized sample to the beginning of isotropization at 156 °C.

mass spectrometer. Elemental analyses were performed by Atlantic Microlab of Norcross, GA.

X-ray crystallographic data[18] were obtained using a single crystal diffractometer and the structure was solved and refined using the SHELXTL PLUS software package. Data collection was carried out at room temperature using Mo Kα radiation with a graphite monochromator. All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were added in at calculated positions and allowed to ride on the carbon atom to which they were attached.

Thermal properties were determined with a DSC calorimeter under a nitrogen purge. Typically heating and cooling rates of 5 °C/min were used. The peak temperatures of the exo- and the endotherms were used as the values of the transitions. Indium was used for calibration. For optical microscopy, thin films (5−10 μm) were melt pressed between the cover slips in a hot stage. A polarizing optical photomicroscope equipped with a hot stage was used to observe morphological changes. The hot stage was calibrated using indium.

5-Carboxy-1,3-phenylene-16-crown-5 (**2**). A mixture of 5-carbomethoxy-l,3-phenylene-16-crown-5[9] (**1**, 5.0 g, 15 mmol), ethanol (430 mL), and NaOH (4 M, 100 mL) was refluxed for

(18) The authors have deposited complete atomic coordinates for **3a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

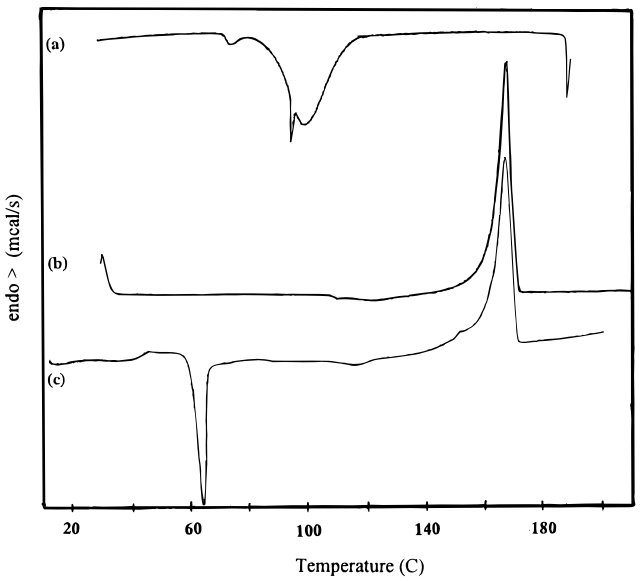

Figure 7. DSC scans (5 °C/min) on compound **9**: (a) cooled from the isotropic melt, (b) second heating, and (c) heating scan on a sample rapidly cooled from the isotropic melt.

24 h, allowed to cool to room temperature, and acidified with 4 M HCl solution. The acid crown **2** which precipitated after cooling to 0−5 °C was filtered and washed with cold H_2O. Recrystallization from EtOH afforded 4.5 g (95%) of pure acid crown **2**, mp 141−142 °C. IR ν: 3501 (OH), 1690 (C=O), 1600 (C=C), 1129 (C−O−C) cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 12.90 (1H, br, exchangeable), 7.22 (t, J = 2.4 Hz, 1H), 7.00 (d, J = 2.4 Hz, 2H), 4.28 (t, J = 4.6 Hz, 4H), 3.69 (t, J = 4.6 Hz, 4H), 3.53 (t, J = 4.6 Hz, 4H), 3.44 (t, J = 4.6 Hz, 4H). Anal. Calcd for $C_{15}H_{20}O_7$: C 57.68, H 6.45, O 35.86. Found: C 57.45, H 6.42.

5-(Cholesteryloxycarbonyl)-4,6-dichloro-1,3-phenylene-16-crown-5 (3a). 5-Carboxy-1,3-phenylene-16-crown-5 (**2**, 0.50 g, 1.6 mmol) was heated with $SOCl_2$ under reflux for 24 h. The excess $SOCl_2$ was removed in vacuo. Cholesterol (0.93 g, 2.4 mmol) was dissolved in dry $CHCl_3$ (10 mL) and along with a few drops of pyridine was added to the acid chloride. After stirring under N_2 for 24 h at room temperature, the reaction mixture was poured into H_2O (25 mL). The product was extracted with $CHCl_3$ (2 × 25 mL). The combined organic phases were dried with Na_2SO_4 and evaporated to produce a solid residue, which was purified by column chromatography (silica gel, EtOAc/hexanes 20:80) and recrystallized from EtOAc to produce the cholesteryl ester **3a** as thin platelike crystals, 1.0 g (92%), mp 215−216 °C. IR (thin film on NaCl disk) ν 1729 (C=O), 1581 (C=C, aromatics), 1540 (C=C, olefinic), 1228 (CO−O−C), 1114 (C−O−C) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ: 7.39 (s, 1H), 5.46 (d, J = 5 Hz, 1H), 4.96 (h, J = 6 Hz, 1H), 4.35 (t, J = 4.9 Hz, 4H), 3.83 (t, J = 4.9 Hz, 4H), 3.69 (t, J = 5.7 Hz, 4H), 3.62 (t, J = 5.7 Hz, 4H), 2.5 (m, 2H), 2.1−0.06 (m, 41H). Anal. Calcd for $C_{42}H_{62}Cl_2O_7$ (MW 749.86): C 67.27, H 8.33. Found: C 67.30, H 8.39. MS (CI): 750 [60%, M^+], 714 [42%, (M^+- Cl)], 678 [100%, (M^+ − 2C1)], 369 [100%, $C_{27}H_{44}^+$], 363 [80%, (M^+ − $C_{27}H_{45}O$)].

***N,N*-Dicyclohexyl-*O*-(5-carbonyl-1,3-phenylene-16-crown-5)isourea (4) and 5-(Cholesteryloxycarbonyl)-1,3-phenylene-16-crown-5 (3b).** A mixture containing 5-carboxy-1,3-phenylene-16-crown-5 (**2,** 0.2453 g, 0.7854 mmol), cholesterol (0.3109 g, 0.8040 mmol), DCC (0.1662 g, 0.8055 mmol), and a catalytic amount of DMAP (10 mg) was refluxed in $CHCl_3$ (50 mL) for 30 h. Upon cooling to 0 °C, dicyclohexylurea was filtered and the filtrate was evaporated. The pure product was isolated via flash silica gel column chromatography using Et_2O as an eluent. The white product was further purified by recrystallization from EtOAc which gave *N,N*-dicyclohexyl-*O*-(5-carbonyl-1,3-phenylene-16-crown-5)isourea (**4**), 0.26 g (64%), mp 171.4−171.6 °C. IR (KBr) ν: 3303 (NH), 2930 and 2857 (-CH), 1702 (C=O), 1675 and 1642 (C=N, isomers), 1589 (C=C) and 1111 (C−O−C). ^1H NMR ($CDCl_3$) δ: 7.20 (t, J = 2.1 Hz, 1H), 6.66 (d, J = 2.1 Hz, 2H), 6.48 (br d, J = 6.0 Hz, 1H), 4.29 (t, J = 4.6 Hz, 4H), 4.01 (br t, J = 12 Hz, 1H), 3.78 (t, J = 4.7 Hz, 4H), 3.66 (t, J = 3.8 Hz, 4H), 3.57 (t, J = 3.8, 4H), 3.52 (m, 1H), 2.09 (m, 2H), 1.78 (m, 4H), 1.70 (m, 2H), 1.57 (m, 4H), 1.37−1.06 (m, 6H), 0.96 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 24.567, 25.219, 25.409, 26.251, 30.628, 32.350, 49.524, 57.960, 69.005, 70.287, 70.690, 70.757, 106.190, 108.170, 138.301, 154.110, 160.406, 171.458 (18 peaks as required). MS (FAB): m/z 519.3 [22%, (M + H)$^+$], 349.2 [66%, (M^+ − $C_7H_{11}NO$)], 295.1 [100%, (M^+ − $C_{13}H_{23}N_2O$)].

Upon further elution with Et_2O, compound **3b** was isolated and further purified by recrystallization from acetone, 0.20 g (36%), mp 155.4−155.6 °C, identical in all respects to that reported below.

5-(*N*-Cyclohexylcarbamoyl-1,3-phenylene-16-crown-5 (5). A mixture containing **4** (0.4503 g, 0.8693 mmol), cholesterol (0.3368 g, 0.8710 mmol), and a catalytic amount of DMAP (15 mg) was refluxed in $CHCl_3$ (25 mL) for 24 h. Upon cooling, the solvent was removed by rotary evaporator. The separation via silica gel column chromatography using Et_2O followed by EtOAc gave **6**, 0.210 g (49.3%), mp 141.3−143.0 °C. IR (KBr) ν: 3329 and 3249 (NH), 2930 and 2857 (CH), 1629 (C=O), 1589 (C=C), 1104 (C−O−C). ^1H NMR ($CDCl_3$) δ: 7.22 (br t, J = 2.1 Hz, 1H), 6.70 (d, J = 2.1 Hz, 2H), 5.93 (br d, J = 7.6 Hz, 1H), 4.31 (t, J = 4.6 Hz, 4H), 3.93 (m, 1H), 3.79 (t, J = 4.6 Hz, 4H), 3.65 (t, J = 3.8 Hz, 4H) 3.57 (t, J = 3.8 Hz, 4H), 2.00 (br d, J = 9.2 Hz, 2H), 1.74 (m, 2H), 1.64 (m, 1H), 1.41 (m, 2H) and 1.22 (m, 3H). ^{13}C-APT NMR ($CDCl_3$) δ: 24.787 (CH_2), 25.516 (CH_2), 33.101, 48.508 (CH), 68.758 (CH_2), 70.302 (CH_2), 70.613 (CH_2), 70.719 (CH_2), 106.464 (CH), 108.451 (CH), 136.830 (quat-C), 160.224 (quat-C) and 166.217 (C=O) (13 peaks as required). MS (FAB): m/z 394 [100%, (M + H)$^+$], 295 [74%, (M^+ − $C_6H_{12}N$)].

5-(Cholesteryloxycarbonyl)-1,3-phenylene-16-crown-5 (3b). 5-Carboxy-1,3-phenylene-16-crown-5 (**2**, 0.3083 g, 0.9871 mmol) was heated with freshly opened $SOCl_2$ (10 mL) under reflux for 4 h. The excess $SOCl_2$ was removed in vacuo. Upon addition of cholesterol (0.4208 g, 1.088 mmol) and pyridine (0.16 mL, 2.0 mmol), the mixture was diluted with $CHCl_3$ (20 mL), refluxed for 30 h, and poured into H_2O, and the product was extracted with $CHCl_3$ (3 × 50 mL). The organic layer was washed with HCl (2 N, 20 mL) and H_2O (2 × 25 mL). Upon evaporation the material was subjected to column chromatography which gave 5-(cholesteryloxycarbonyl)-1,3-phenylene-16-crown-5 (**3b**). Further purification was achieved by recrystallization from acetone, 0.402 g (60%), mp

Table 1. ^1H NMR Chemical Shift Data [δ values ($\Delta\delta$ values)]^a in CD_3COCD_3

compound or complex	[paraquat]$^{2+}$			crown				
	2-,6-H^b	3-,5-H^b	CH_3^{b}	H_b^{c}	H_a^{d}	α-OCH_2^{b}	β-OCH_2^{b}	γ/δ-OCH_2^{b}
12	9.35	8.81	4.72					
8b	−	−	−	7.08	6.71	4.11	3.80	3.83
12:8b	9.23 (−0.12)	8.50 (−0.31)	4.69 (−0.03)	6.80 (−0.28)	6.37 (−0.34)	3.89 (−0.22)	3.76 (−0.04)	3.73 (−0.10)
9	−	−	−	7.08	6.71	4.11	3.80	3.83
12:9	9.26 (−0.09)	8.58 (−0.23)	4.70 (−0.02)	7.00 (−0.08)	6.54 (−0.17)	4.01 (−0.10)	3.84 (+0.04)	3.70 (−0.13)

^{a} The $\Delta\delta$ values indicated in parentheses next to the respective δ values relate to the chemical shift changes experienced upon complex formation; concentrations 4 mM in each component. ^{b} The chemical shift assignments were taken from rf. 17. ^{c} The assignment of H_b was based on its multiplicity (doublet) and coupling to H_a. ^{d} The assignment of H_a was based on its multiplicity (triplet) and coupling to H_b.

155.4−155.6 °C. IR (KBr) ν: 2937 (CH), 1715 (C═O), 1596, 1496 (C═C), and 1137 (C−O−C). ^{1}H NMR ($CDCl_3$) δ: 7.30 (t, J = 2.2 Hz, 1H), 7.21 (d, J = 2.2 Hz, 2H), 5.42 (m, 1H), 4.80 (m, 1H), 4.32 (t, J = 4.6 Hz, 4H), 3.80 (t, J = 4.6 Hz, 4H), 3.65 (m, 4H), 3.59 (m, 4H), 0.69−2.43 (43H, m). MS (FAB): m/z 703.4 [100%, $(M + Na)^+$], 295.1 [8%, $(M^+ - C_{27}H_{45}O)$]

Bis[5-(cholesteryloxycarbonyl)-1,3-phenylene]-32-crown-10 (**9**). Bis(5-carboxy-1,3-phenylene)-32-crown-10[6] (**8a**, 0.10 g, 0.16 mmol) was converted into the corresponding bis-[5-(chlorocarbonyl)-1,3-phenylene]-32-crown-10 by heating with $SOCl_2$ under reflux for 5 h. The excess $SOCl_2$ was removed under vacuo. Cholesterol (0.18 g, 0.48 mmol) dissolved in $CHCl_3$ (3 mL) along with few drops of pyridine was added to the diacid chloride. After stirring under N_2 for 24 h at rt, the reaction mixture was poured into H_2O (25 mL). The product was extracted with $CHCl_3$ (2 × 25 mL). The combined organic phases were dried with Na_2SO_4; the solvent was removed under vacuum to produce a solid residue, which was purified by column chromatography (silica gel, EtOAc/hexanes 20:80) and recrystallized (once) from EtOAc to produce the cholesteryl crown ether **9** as a spherulitic crystalline solid, 0.15 g (70%), mp 171−173 °C. IR (thin film on NaCl disk) ν: 1717 (C═O), 1594 (C═C, aromatics), 1450 (C═C, olefinic), 1177 (CO−OC), 1136 (C−O−C) cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS) δ: 7.15 (d, J = 3 Hz, 4H), 6.64 (t, J = 3 Hz, 2H), 5.40 (d, J = 4 Hz, 2H), 4.80 (m, 2H), 4.10 (t, J = 5 Hz, 8H), 3.84 (t, J = 5 Hz, 8H), 3.70 (m, 16H), 2.1−0.6 (m, 82H); m/z (desorption CI) (MW 1361): 1362 [30%, $(M + 1)^+$], 994 [100%, $((M + 1)^+ - C_{27}H_{44})$].

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