Difunctional 28-Membered Cyclic Arylene Ethers

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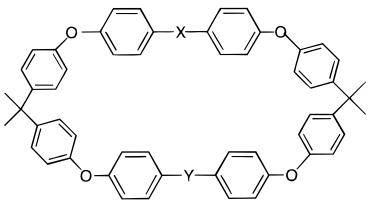
Received May 30, 1997

Introduction

We have prepared a number of mono- and difunctional derivatives of bis(*m*-phenylene)crown ethers.[1] We have also synthesized nonfunctionalized arylene ether macrocycles.[2] For example, 40-membered cyclic arylene ether disulfone **1a** was synthesized starting from bisphenol-A and bis(*p*-fluorophenyl) sulfone;[2a,b] sulfone ketone **1b** and sulfone phosphine oxide **1c** were made analogously.[2b,f,g] These macrocycles are building blocks for supramolecular chemistry.[3]



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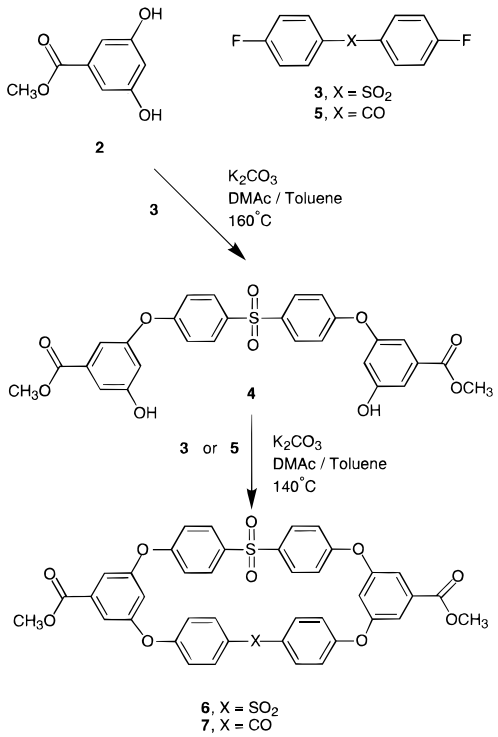
a. X = Y = SO_2
b. X = SO_2, Y = CO
c. X = SO_2, Y = $P(O)C_6H_5$

Herein we describe the synthesis and characterization of functionalized cyclic arylene ethers in order to provide reactive macrocycles with high thermal stabilities.

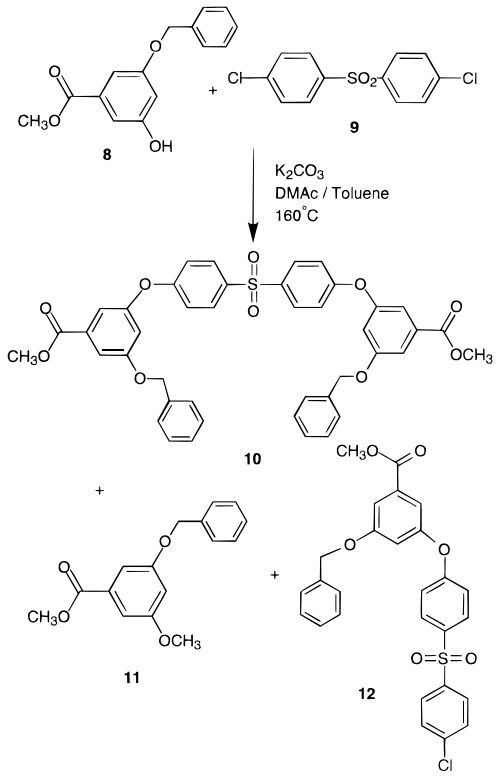
Results and Discussion

The syntheses of 28-membered cyclic arylene ether diesters **6** and **7** were accomplished via a two-step method (Scheme 1). Bis[*p*-(3-carbomethoxy-5-hydroxyphenoxy)-phenyl] sulfone (**4**) was made in 49% yield by nucleophilic aromatic substitution of bis(*p*-fluorophenyl) sulfone (**3**) using excess methyl 3,5-dihydroxybenzoate (**2**). The ^{1}H NMR and FAB mass spectra were consistent with the structure of **4**. This compound exhibited a broad softening range; attempts to crystallize **4** were futile.

Scheme 1



Scheme 2



4 was also synthesized via the bis(benzyl ether) **10** (Scheme 2). Methyl 3-(benzyloxy)-5-hydroxybenzoate (**8**) and bis(*p*-chlorophenyl) sulfone (**9**) yielded **10** (5%) along with the byproducts methyl 3-(benzyloxy)-5-methoxybenzoate (**11**) and *p*-[3-carbomethoxy-5-(benzyloxy)phenoxy]-phenyl *p*-chlorophenyl sulfone (**12**) in 25% and 16% yields, respectively. **11** probably arose by transesterifi-

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S0022-3263(97)00954-7 CCC: $14.00

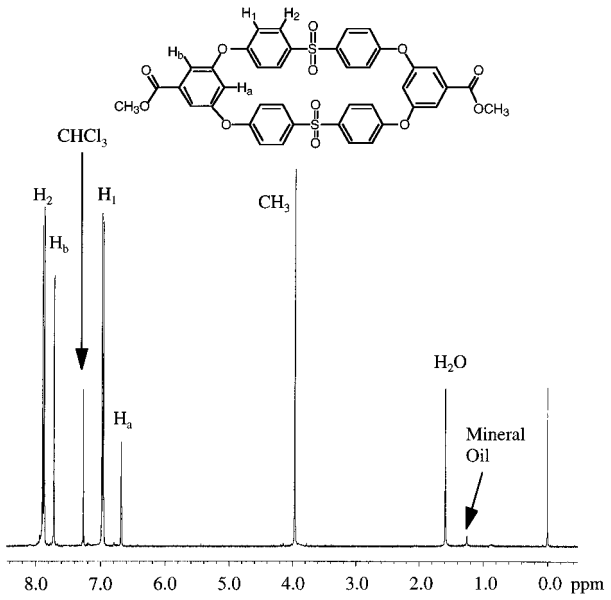

Figure 1. ^{1}H NMR spectrum (400 MHz) of **6** in $CDCl_3$.

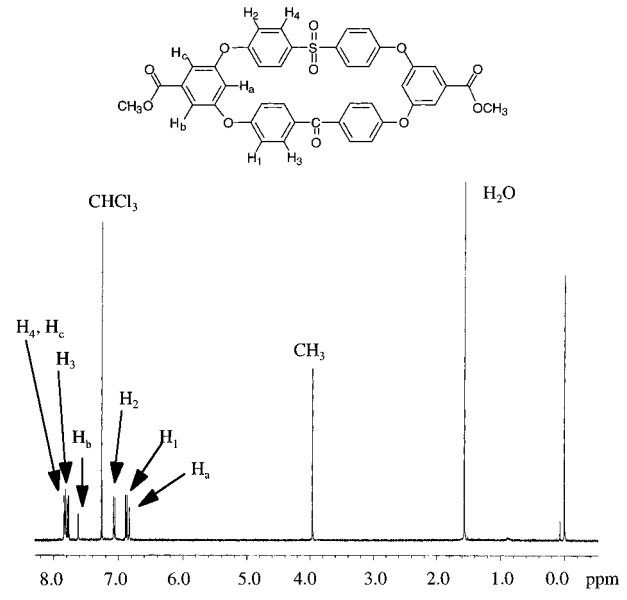

Figure 2. ^{1}H NMR spectrum (400 MHz) of **7** in $CDCl_3$.

cation of **8**, the carboxylate ion serving as a leaving group. **12** represents conversion of only one of the two halide groups of **9** to the desired phenoxy derivative, probably because of the low reactivity of the dichloride **9** and depletion of **8** by its side reaction to form **11**. However, **10** was successfully converted (88%) to **4** by hydrogenolysis.

The syntheses of macrocycles **6** and **7** were accomplished via 1 + 1 condensation of bisphenol **4** with bis(*p*-fluorophenyl) sulfone (**3**) or 4,4′-difluorobenzophenone (**5**), respectively, by aromatic nucleophilic substitution reactions using a syringe pump to maintain psuedo-high-dilution conditions[4] (Scheme 1). These macrocycles were obtained in low yields (19% and 10%, respectively) as compared to **1a** (67%) and **1b** (68%) made under identical conditions.[2f,g] The lower yields in case of **6** and **7** are probably a direct result of the lower nucleophilicity of the phenolates of linear precursor **4** because of the electron-withdrawing carbomethoxy groups and the smaller, more strained rings of **6** and **7** relative to **1a**,**b**. Low reactivity was evident from the significant amounts of starting materials which were identified during the purification process. Transetherification is also a common side reaction during aromatic nucleophilic substitution reactions on activated dihalides.[5]

The proton NMR spectrum of **6** (Figure 1), apart from a sharp singlet due to the methyl protons, also contains one triplet (H_a) and three doublets (H_b, H_1, and H_2), consistent with the symmetrical nature of the macrocycle **6**. The proton NMR spectrum of macrocycle **7** (Figure 2) contains four doublets (H_1-H_4), the most downfield one of which is appropriate for the aromatic proton next to the sulfone linkage (H_4), and three sets of triplets (H_a-H_c), consistent with the unsymmetrical nature of the macrocycle. The ^{13}C NMR spectrum of **6** contained 10 signals and that of **7** indicated 17 nonequivalent carbons, consistent with the structures of the macrocycles.

Figures 3 and 4 show the FAB mass spectra of macrocycles **6** and **7**, respectively. In each case the

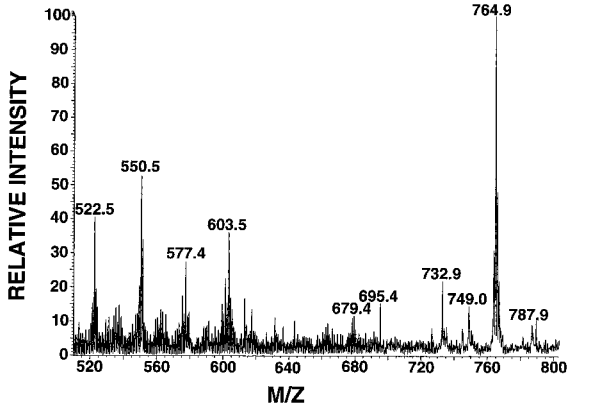

Figure 3. FAB mass spectrum of **6** in 3-nitrobenzyl alcohol matrix.

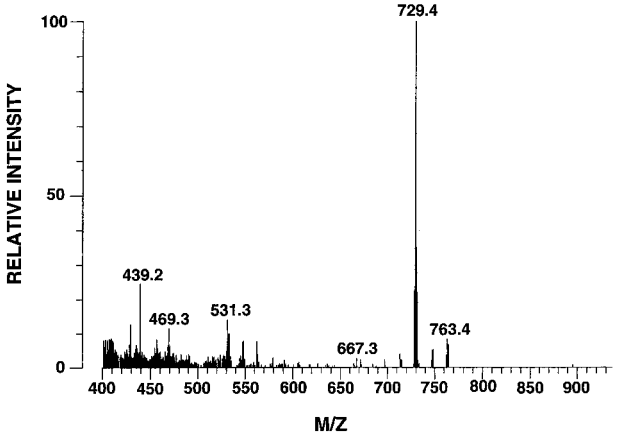

Figure 4. FAB mass spectrum of **7** in 3-nitrobenzyl alcohol/glycerol/trifluoroacetic acid matrix.

parent ion corresponds to the mass of the pseudomolecular ion $(M + H)^+$, and a sodium complex ion is also observed. In the case of **6** the Na complex ion is observed at *m*/*z* 787.9; the loss of a methyl fragment from the pseudomolecular ion (*m*/*z* 764.9) yields *m*/*z* 749 with a relative intensity of 15%, and loss of methanol from the pseudomolecular ion is also evident (*m*/*z* 732.9, 22). For **7** the sodium complex ion appears at *m*/*z* 763.4; loss of

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two methoxy fragments from the pseudomolecular ion (*m*/*z* 729.4) yields *m*/*z* 667.3 (3); the peak at *m*/*z* 531 corresponds to the loss of two methyl groups and a $C_6H_4OC_6H_4$ unit. The high-resolution mass spectra of **6** and **7** confirm their structures.

Both macrocycles exhibited good thermal stability by thermogravimetric analysis (TGA) under nitrogen: 453 and 405 °C for **6** and **7**, respectively.

Conclusions

Two new 28-membered cyclic arylene ether diesters were synthesized via a two-step approach. The linear precursor **4** synthesized in the first step was cyclized with either bis(*p*-fluorophenyl) sulfone (**3**) or 4,4′-difluorobenzophenone (**5**) to give macrocycle **6** or **7** in 19% and 10% yields, respectively. These are building blocks for supramolecular chemistry, including polyrotaxanes.[3]

Experimental Section

Materials and Measurements. These have been previously reported.[1f,i] Mass spectra (MS) were measured at the Nebraska Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, NE, and the Washington University Mass Spectrometry Resource in St. Louis, MO; HRFAB, high-resolution FAB. TGA was performed at 10 °C/min.

Bis[*p*-(3-carbomethoxy-5-hydroxyphenoxy)phenyl] Sulfone (4). K_2CO_3 (48.45 g, 350.6 mmol) was added to a solution of **2**[1d,j] (53.09 g, 315.7 mmol) in a mixture of DMAc (250 mL) and toluene (170 mL). The suspension was mechanically stirred and purged with N_2 while heating in an oil bath whose temperature was 170 °C. H_2O generated was azeotroped by toluene into a Dean−Stark trap. After refluxing for 15 h most of the toluene was removed and then **3** (4.10 g, 16.1 mmol) was added. The reaction was allowed to continue for 20 h (oil bath at 140 °C). After cooling, the mixture was filtered and solvent was evaporated. The resultant brown liquid was precipitated into aq HCl. The solution was decanted to recover oily material. The oil was boiled in water to remove excess **2**. After decantation the oil was dissolved in $CHCl_3$. Pure **4**, 4.35 g (49%), "mp" 77.4−88.3 °C, was obtained by flash silica gel column chromatography with $CHCl_3$/EtOAc (20:1) as the solvent system. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.82 (s, 6H), 6.79 (t, J = 2.2 Hz, 2H), 7.04 (dd, J = 2.2, 1.2 Hz, 2H), 7.19 (d, J = 9.0 Hz, 4H), 7.26 (dd, J = 2.2, 1.2 Hz, 2H), 7.97 (d, J = 9.0 Hz, 4H), 10.28 (s, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 52.35, 110.84, 111.79, 112.70, 118.45, 129.95, 132.35, 135.62, 155.87, 159.28, 160.81, 165.39 (12 peaks as required). MS (FAB) *m*/*z* [assignment, rel int.]: 551.3 [$(M + H)^+$, 32], 519.3 [$(M - OCH_3)^+$, 84], 400.3 [$(M + H)^+ - C_8H_7O_3$, 7.3], 337.2 [100]. HRFAB calcd for $C_{28}H_{24S}O_{10}$ [$M + H]^+$ *m*/*z* 551.1012, found 551.1023 (error 2.0 ppm).

Cyclobis[oxy-1,4-phenylenesulfonyl-1,4-phenyleneoxy-5-(methoxycarbonyl)-1,3-phenylene] (6). A solution of **4** (1.008 g, 1.825 mmol) and **3** (464 mg, 1.83 mmol) in DMAc (20 mL) was injected into a refluxing suspension of DMAc (400 mL), toluene (240 mL), and K_2CO_3 (410 mg, 3.00 mmol) at the rate of 1.0 mL/h. The suspension was mechanically stirred and purged with N_2. H_2O generated was azeotroped by toluene into a Dean−Stark trap. After injection, the reaction was allowed to continue for 12 h. After cooling, the mixture was filtered and solvent was evaporated; the resultant brown liquid was precipitated into aq HCl. The crude solid was filtered. Pure **6** (270 mg, 19.3%, mp 347−349 °C) was obtained by flash silica gel column chromatography using $CHCl_3$/EtOAc (20:1) as the solvent system and recrystallization from $CHCl_3$. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.86 (s, 6H), 6.68 (t, J = 2.2 Hz, 2H), 6.97 (d, J = 9.0 Hz, 8H), 7.72 (d, J = 2.2 Hz, 4H), 7.88 (d, J = 9.0 Hz, 8H) (Figure 1). ^{13}C NMR ($CDCl_3$) δ (ppm): 52.75, 115.18, 117.72, 119.01, 130.11, 134.52, 136.49, 155.87, 160.87, 165.11 (10 peaks as required). MS (FAB) *m*/*z* [rel int.]: 787.9 [$(M + Na)^+$, 9], 764.9 [$(M + H)^+$, 100], 749.0 [$(M + H)^+ - CH_3$, 15], 732.9 [$(M - OCH_3)^+$, 22] (Figure 3). HRFAB calcd for $C_{40}H_{29}S_2O_{12}$ [$M + H]^+$ *m*/*z* 765.1100, found 765.1117 (error 2.1 ppm).

Cyclo[oxy-1,4-phenylenesulfonyl-1,4-phenyleneoxy-5-(methoxycarbonyl)-1,3-phenyleneoxy-1,4-benzoyl-1,4-phenyleneoxy-5-(methoxycarbonyl)-1,3-phenylene] (7). A solution of **4** (1.10 g, 2.00 mmol) and **5** (436 mg, 2.00 mmol) in DMAc (25 mL) was injected into a refluxing suspension of DMAc (400 mL), toluene (240 mL), and K_2CO_3 (416 mg, 3.01 mmol) at the rate of 1.0 mL/h. The suspension was mechanically stirred and purged with N_2. H_2O generated was azeotroped by toluene into a Dean−Stark trap. After injection, the reaction was allowed to continue for 12 h. After cooling, the mixture was filtered and solvent was evaporated; the resultant brown liquid was then precipitated into aq HCl. The crude solid was filtered. Pure **7** (143 mg, 9.8%, mp 342.0−344.6 °C) was obtained by flash silica gel column chromatography using $CHCl_3$/EtOAc (20:1) as the solvent system. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.96 (s, 6H), 6.83 (t, J = 2.2 Hz, 2H), 6.88 (d, J = 8.8 Hz, 4H), 7.07 (d, J = 8.8 Hz, 4H), 7.62 (t, J = 2.2 Hz, 2H), 7.78 (d, J = 8.8 Hz, 4H), 7.83 (m, 6H) (Figure 2). ^{13}C NMR ($CDCl_3$) δ (ppm): 52.71, 115.42, 115.85, 118.00, 118.94, 119.02, 129.96, 132.37, 133.18, 134.37, 135.36, 154.23, 157.58, 159.15, 162.18, 165.26, 193.56 (17 peaks as required). MS (FAB) *m*/*z* [rel int.]: 729.4 [$(M + H)^+$, 100], 667.3 [$(M + H)^+ - 2 \times OCH_3$, 3], 531.3 [$(M + H)^+ - C_{14}H_{14}O$, 15] (Figure 4). HRFAB calcd for $C_{41}H_{30}SO_{11}$ [$M + H]^+$ *m*/*z* 729.1430, found 729.1425 (error 0.7 ppm).

Methyl 3-(Benzyloxy)-5-hydroxybenzoate (8). A mixture of 29.76 g (177 mmol) of **2**, 9.07 g (375 mmol) of NaH, and 350 mL of DMF was stirred at 110 °C for 5 h and then cooled to rt. A solution of 18.6 mL (156 mmol) of benzyl bromide in 5 mL of DMF was added via syringe pump at a rate of 1 mL/h. After addition the mixture was stirred at rt for 3 days, the DMF was removed by rotary evaporation, and the residue was extracted with Et_2O. Evaporation of the extract gave 40.9 g of a gummy, light brown product. Trituration with CH_2Cl_2 (DCM) produced 8.01 g of a light yellow solid, which was the starting **2**; the filtrate was evaporated to produce a gummy material. Silica gel chromatography using DCM gave the dibenzyl ether [12.4 g, 28%, mp 65.1−67.6 °C (lit.[6] mp 65.1−67.6 °C)] as the first fraction, a mixture as the second fraction, and the third eluted fraction as pure **8** (14.5 g, 43%), mp 96.2−97.6 °C (lit.[6] mp 97−98 °C). IR (KBr) cm^{-1}: 3376 (br, OH), 1715 (C=O), 1602 (C=C). ^{1}H NMR (acetone-d_6) δ (ppm): 3.85 (s, 3H), 5.14 (s, 2H), 6.74 (t, J = 2.2 Hz, 1H), 7.1−7.4 (m, 5H), 7.51 (m, 2H, J = 2.2 Hz), 8.84 (s, 1H).

Bis[*p*-[3-(benzyloxy)-5-carbomethoxyphenoxy]phenyl] Sulfone (10). A mixture of 10.40 g (75.2 mmol) of K_2CO_3, 16.25 g (63.0 mmol) of **8**, 400 mL of DMAC, and 250 mL of toluene was stirred for 25 h under reflux (oil bath at 140 °C) while H_2O was removed by azeotropic distillation into a Dean−Stark trap. The toluene was then completely removed, and the oil bath temperature was increased to 190 °C. **9** (8.96 g, 31.2 mmol) was added all at once, and the reaction was continued for 24 h. DMAc was then removed on a rotary evaporator, and the residue was diluted with DCM and filtered through Celite. Evaporation of the solvent left a gummy residue. TLC indicated four products. Flash column chromatography with 4:1 hexane/EtOAc yielded as the fourth fraction pure **10**, as a glassy solid (1.11 g, 4.9%). IR (KBr) cm^{-1}: 1722 (C=O), 1582 (C=C), 1330 (asymm SO_2), 1151 (symm SO_2). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.89 (s, 6H), 5.09 (s, 4H), 6.84 (t, J = 2.3 Hz, 2H), 7.03 (d, J = 8.8 Hz, 4H), 7.30 (m, 2H), 7.4 (m, 10H), 7.51 (m, 2H), 7.88 (d, J = 8.8 Hz, 4H). Anal. Calcd for $C_{42}H_{34}SO_{10}\cdot H_2O$: C, 67.37; H, 4.85. Found: C, 66.92; H, 4.78.

Methyl 3-(Benzyloxy)-5-methoxybenzoate (11). 11 was obtained as an oil (4.2 g, 25%) (lit.[7] mp 46.5−47.0 °C) as the first fraction from the chromatography above. IR (neat) cm^{-1}: 3090−3003 (=CH), 2844 (CH), 1722 (C=O), 1596 (C=C), 1237 (asymm COC), 1058 (symm COC). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.91 (s, 3H), 5.08 (s, 2H), 6.73 (t, J = 2.3 Hz, 1H), 7.20 (t, J = 2.3 Hz, 1H), 7.28 (t, J = 2.3 Hz, 1H), 7.38 (m, 5H).

***p*-[3-(Benzyloxy)-5-carbomethoxyphenoxy]phenyl *p*-Chlorophenyl Sulfone (12). 12** was obtained as an amorphous yellow solid, "mp" 56−88 °C (1.57 g, 16%), as the second fraction from the above chromatography. IR (neat) cm^{-1}: 1722 (C=O),

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1582 (C=C), 1330 (asymm SO_2), 1151 (symm SO_2). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.90 (s, 3H), 5.09 (s, 2H), 6.84 (t, J = 2.3 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.20−7.45 (m, 6H), 7.48 (d, J = 8.8 Hz, 4H), 7.52 (m, 1H), 7.87 (d, J = 8.6, 2H). MS (FAB, NaI) m/z {rel. int.}: 853.3 {[M(^{35}Cl) + 2Na + 2NaI]$^+$, 0.8}, 705.4 {[M(^{37}Cl) + 2Na + NaI]$^+$, 6}, 703.4 {[M(^{35}Cl) + 2Na + NaI]$^+$, 14}, 682.9 {[M(^{37}Cl) + Na + NaI]$^+$, 5}, 680.9 {[M(^{35}Cl) + Na + NaI]$^+$, 12}, 533.0 {[M(^{37}Cl) + Na]$^+$, 12}, 531.0 {[M(^{35}Cl) + Na]$^+$, 28}, 501.0 {[M(^{37}Cl) + Na − 2O]$^+$, 1}, 499.0 {[M(^{35}Cl) + Na − 2O]$^+$, 6}, 477.8 {[M(^{37}Cl) − 2O]$^+$, 3}, 475.8 {[M(^{35}Cl) − 2O]$^+$, 7}, 348.9 {[M(^{35}Cl) + Na − 2O − $COOCH_3$ − $CH_2C_6H_5$]$^+$, 13}, 327.3 {[M(^{37}Cl) − 2O − $COOCH_3$ − $CH_2C_6H_5$]$^+$, 14}, 325.3 {[M(^{35}Cl) − 2O − $COOCH_3$ − $CH_2C_6H_5$]$^+$, 28}, 199.0 {37}, 176.0 {100}. HRFAB calcd for $C_{27}H_{22}ClSO_6$ [M + H]$^+$ m/z 509.0825, found 509.0808 (error 3.2 ppm).

Bis[*p*-(3-carbomethoxy-5-hydroxyphenoxy)phenyl] Sulfone (4). A mixture of 570 mg (0.78 mmol) of **10**, 30 mg of Pd/C, and 15 mL of EtOAc was exposed to 60 psi of H_2 for 30 min. After filtration of the catalyst the solution was concentrated and subjected to silica gel column chromatography using ether to afford **4** as a colorless solid, 380 mg (88%), "mp" 77.7−84.9 °C, identical in all respects to the sample described above.

Acknowledgment. We acknowledge support from NSF (DMR93-20196, CHE95-21738) for the work described here. Partial support was also provided by the NSF Science & Technology Center for High Performance Polymeric Adhesives and Composites (Grant DMR91-2004). MS were provided by the Nebraska Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, and by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant P41RR0954).

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