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SYNTHESIS OF NEW BENZOSULFOXIDE MACROCYCLIC COMPOUNDS

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Bis(dibenzosulfoxo)-27,30,35,38-tetramethyl-24-crown-6, bis(dibenzosulfoxo)-21,24,29,32-tetramethyl-18-crown-4, dibenzosulfoxo-15,18-dimethyl-12-crown-3 and dibenzosulfoxo-12,15-dimethyl-9-crown-2 macrocycles are synthesized by the reaction of 2,2′-sulfinyl-bis(4-methyl phenol)and 1,2-dibromoethane and diethyleneglycol di-p-toluenesulfonate.

Keywords: Benzosulfoxide; crown ether; macrocycle; template effect

Various classes of macrocyclic compounds have been known since Pedersen has synthesized the first macrocyclic crown ether.[1] These compounds have attracted great attention in respect of the synthesis, physico-chemical investigation of various new representative of various substances. The search for applications has solved many significant potential tasks in different fields of science and engineering (e.g., chemistry preparative organic synthesis, medicine, biophysics, catalysis, agriculture, and ecology).[2,3]

In addition to discovery of Pedersen's crown, polyethers are actively used in host-guest chemistry and the template effects of alkali metal ions played a paramount role.[4–6] They are often synthesized by Williamson's reaction, by direct cyclization of glycols with dialkylating agents under moderat or high dilution conditions to suppress linear polymerization.[7,8]

We have used Williamson's reaction of 1[9,*] with two ligsons (diethyleneglycol di-p-toluenesulfonate and 1,2-dibromoethane) to

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*Synthesis of the substrate 1 as 2,2′-Sulfinyl bis(4-methyl phenol): To a cold suspension of anhydrous aluminum chloride (25 g, 0.187 mmol) in 100 ml of dichloromethane p-cresol (20 g, 19.34 cc, 0.185 mmol) in 50 ml of dichloromethane was added portionwisely.

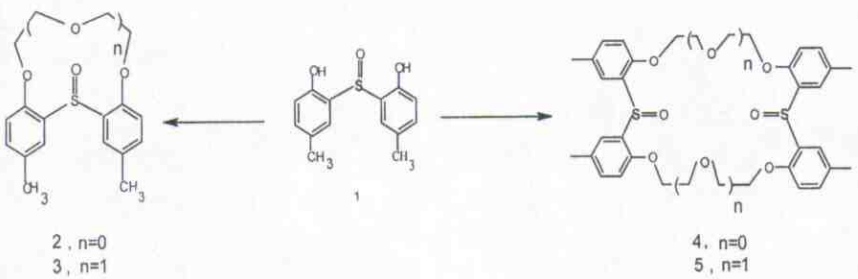


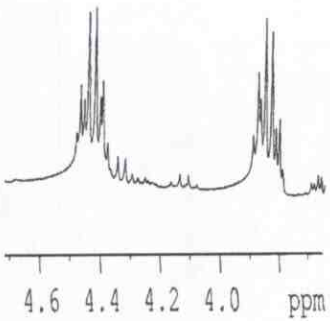
FIGURE 1 Benzosulfoxide macrocycles 2–5.

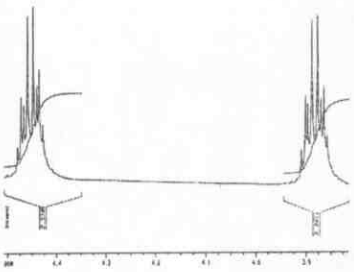
synthesis benzosulfoxide macrocycles **2**, **3**, **4**, and **5** in which the conformational flexibility and then cavity dimensions increase respectively (Figure 1). Dispite the high reactivity of the end groups (bromides and tosylates) in the ligsons it seems that the yields are controlled by template effect of ions Li^+, Na^+, K^+ to a certain extent (in the absence of these ions the yields were in the range of 5–17%). The hydrogens of the methylene groups are diastereotopic and their splitting patterns appear as "ddd" in ^1H NMR spectra (Figure 2).

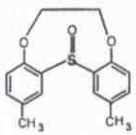
RESULTS AND DISCUSSION

The essential problem in the synthesis of these benzosulfoxide macrocycles was performance of Williamson's reaction of the phenoxide groups with 1,2-dibromoethane and diethyleneglycol di-p-toluenesulfonate. This problem was partially solved by using the compounds such as LiCl, NaOH, KOH, in the synthesis of macrocycles **2**, **3**, **4**, and **5** and the yields were increased due to template effect (in the absence of these ions the yields were in the range of 5–17%). Still, modification of the conditions and probably more improvement in the yields needs more investigations. The most interesting point in this research was found in the structure determination of these macrocycles. The larger the macrocycle the more flexible the cavity. The flexibility and rigidity of these macrocycles affect the diastereotopic character of methylene groups.

The mixture was stirred for 30 min and then thionyl chloride (11 g, 6.75 cc, 0.093 mmol) in 50 ml of dichloromethane was added dropwise. The stirring was continued for 24 h and left overnight. The resulting viscose mixture was slowly poured into a container of ice-water and was stirred for 5 min. The precipitate was filtered, dried, and recrystallized from ethanol to afford substrate 1 in 90% yield and m.p. 194–195°C. IR (KBr) 3200, 1600, 1520, 1250, 1050 cm^{-1}; ^1H NMR (60 MHz, acetone-d6, ppm) δ 1.8 (s, 6H), 6.35 (d, j = 6 Hz, 2H), 6.7 (d, j = 6 Hz, 2H), 7.0 (s, 2H), 9.3 (s, 1H).







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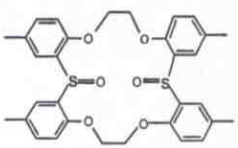

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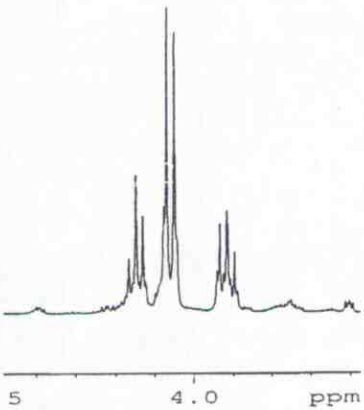

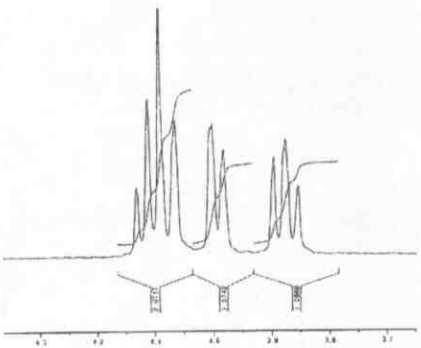

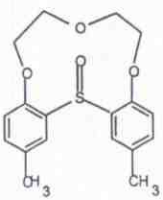

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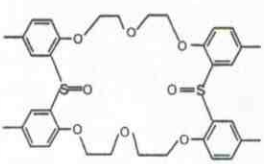

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FIGURE 2 The methylene region of marocycles in ^{1}H NMR spectra.

This is obvious by analysis of ^{1}H NMR spectra. Due to the repulsion effects of the sulfoxide group (S=O) either with oxygens or other sulfoxide group in the cavity, the macrocycles are twisted. The more twisted the cavity or macrocycle, the more difference in the diastereotopic character of CH_2 protons. This difference also results in the difference of the chemical shifts. The more rigid the macrocycle the more difference in the chemical shifts of the protons. The splitting patterns follow as AA'BB' and "ddd." Splitting patterns of methylene of these macrocycles are shown in Figure 2 for comparison. It is interesting that the rigidity of the macrocycle **2** shows almost the same rigidity as the macrocycle **4**. This may be due to the strong repulsions between two sulfoxide groups in the macrocycle **4**. The same rationalisation could be involved in the comparison of the two macrocycles **3** and **5**.

EXPERIMENTAL

The reactions were carried out in an efficient hood. All the materials were purchased from Merck, BDH and Aldrich chemical companies and applied without further purification. The melting points (uncorrected) were measured with a Stuart Scientific SMP1 apparatus. IR spectra were measured on a Perkin-Elmer model 543; the ^{1}H NMR and ^{13}C NMR spectra were obtained at 500 and 125 MHz using BRUKER DRX 500 AVANCE apparatus and mass spectra were obtained with Shimadzu GC-MS-QP 1100 EX model.

Synthesis of 2,3,5,6-Dibenzo-12,15-dimethyl-4-sulfoxo-9-crown-2 (2)

To a round-bottomed flask containing 50 ml of dried DMF, 4.32 g (0.015 mmol) of **1** and 5.64 g (0.03 mmol) of 1,2-dibromoethane and 10 g of K_2CO_3 were added and the mixture was heated at 60°C while stirring vigorously for 48 h. Then 150 ml of water were added and stirred for 30 min. The precipitate was filtered and washed with water and was dissolved in 150 ml of CH_2Cl_2. The CH_2Cl_2 was washed with aqueous NaOH(5%) twice and washed with distilled water until the filterate was neutral. The solvent was dried by Na_2SO_4 and evaporated under reduced pressure. The precipitate was recrystallized from ethyl acetate/ethanol (1:1), the yield was 29% (m.p. 188–192°C).

IR (KBr) 3010, 2990, 1620, 1590, 1270, 1150, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 2.35 (s, 6H), 3.80–3.88 (ddd, j = 13.8, 8.5, 5.7 Hz, 2H), 4.4–4.47 (ddd, j = 13.8, 8.8, 5.7 Hz, 2H), 6.96 (d, j = 8.8, 2H),

7.14–7.18 (dd, j = 8.8, j = 1 Hz, 2H), 7.6 (d, j = 1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 152.53, 139.83, 136.17, 133.20, 124.48, 121.77, 72.21, 21.39; MS (EI) *m/z* (rel intensity) 288(M^+, cal. M = 288) (5%), 271(28%), 245(15%), 215(24%), 139(15%), 133(30%), 105(35%), 91(32%), 77(100%).

Synthesis of 2,3,5,6,14,15,17,18-Tetrabenzo-27,30,35,38-tetramethyl-4,16-di sulfoxo-24-crown-6 (5) and 2,3,5,6-dibenzo-15,18-dimethyl-4-sulfoxo-12-crown-3 (3)

To a 500 ml three-necked flask, 800 ml of acetonitrile, 1.48 g (0.004 mmol) of **1** and 4 g (0.028 mmol) of K_2CO_3, one peace of sodium hydroxide (0.09 g) and 0.24 g of lithium chloride were added. The mixture was refluxed for 15 min and then 1.528 g (0.004 mmol) of diethylene glycol di-p-toluenesulfonate was added dropwise (one drop/sec). The reflux was continued for 30 h and then 200 ml of distilled water and 20 g of K_2CO_3 were added to the reaction mixture and then extracted with chloroform (5 × 20 ml). The combined chloroform layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure to afford the crude product. The crude product was purified by column chromatography on silica gel 40 (70–230 mesh) and eluted by petroleum ether/ethyl acetate (4:1) to give two macrocycles, **3** and **5**. The yield was 55% (the yield of **3** was 62% and **5**, 38%) and melting points for **3** and **5** were 205–207°C and 171–172°C respectively.

Spectral Data for 3

IR (KBr) 3005, 1600, 1475, 1000, 1300, 1250 Cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 2.84 (s, 8 H), 3.90–4.05 (ddd, 4H); (j = 1.42, 2.85, 12.8), 4.05–4.20 (ddd, 4H), 6.73 (d, j = 8.79, 2H), 7.12 (dd, j = 8.79, 2.17 Hz, 2H), 7.63 (d, j_m = 2.17 Hz, 2H); MS (EI) *m/z* (rel intensity) 333 (M + 1, cal. M = 332) (10%), 262(13%), 244 (15%), 228 (10%), 201(18%), 151(53%), 110(100%), 108(43%), 77(62%), 49(61%).

Spectral Data for 5

IR (KBr) 3000–3200, 2900–2980, 1500, 1450, 1250, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 2.34 (s, 12H), 3.85–3.89 (ddd, J = 10, 10 Hz, 4H), 3.98–4.00 (ddd, J = 10, 1.5 Hz, 4H), 4.06–4.13 (ddd, J = 35, 15, 10 Hz, 8H), 6.63–6.65 (d, J = 10 Hz, 4H), 7.05–7.06 (dd, J = 10 Hz, 4H), 7.57 (S, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 20.55, 69.17, 72.17, 95.96, 111.66, 125.25, 130.89, 131.89, 134.47, 153.25; MS (EI) *m/z* (rel intensity) 666 (M + 2, cal. M = 664) (5%), 568(7%), 513(8%), 453(6%), 406(35%), 386(48%), 333(67%), 262(17%), 177(25%), 151(56%), 110(100%), 77(68%), 45(76%).

Synthesis of 2,3,5,6,11,12,14,15-Tetrabenzo-21,24,29,32-tetramethyl-4,13-disulfoxo-18-crown-4 (4)

0.52 g (2 mmol) of **1** and 0.12 g (2 mmol) of KOH were poured into a round bottomed flask containing 100 ml of dry acetonitrile. The solution mixture was refluxed for 30 min then excess amounts of 1,2-dibromoethane (4 ml) and 0.3 g of polyethylene glycol 6000 (as phase transfer catalyst) were added. The reaction mixture was refluxed for 8 h and then the solvent was removed under reduced pressure. A colourless precipitate was obtained, washed with aqueous NaOH (10%), filtered, and dissolved in 10 ml of acetone. The acetone solution was filtered and the filterate was evaporated. The colorless pricipitate was recrystallized from ethanol. Fine needle crystals were formed (25%) with m.p. 194–195°C.

IR (KBr) 3005, 2985, 2970, 1480, 1300, 1150, 1050, 1000 cm^{-1}; ^1H NMR (500 MHz, acetone-d6, ppm) δ 2.33 (s, 6H), 3.85–3.90 (ddd, two CH_2 groups), 4.41–4.47 (ddd, two CH_2 groups), 7.07–7.10 (d, j = 8 Hz, 4 Hz), 7.23–7.25 (dd, j = 8 Hz, j = 1.5 Hz, 4H), 7.58 (d, j = 1.5 Hz, 4H); ^{13}C NMR (acetone-d6, ppm) δ 152.47, 140.34, 135.27, 132.87, 123.59, 121.75, 71.69, 20.09; MS (EI) *m/z* (rel intensity) 577(M + 1, cal. M = 576) (35%), 477(15%), 393(24%), 289(100%), 272(90%), 262(20%), 245(51%), 155(48%), 133 (70%), 77(15%), 45(20%).

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