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Synthesis of Some New Macrocyclic Bis-sulfonamides by Fast Addition Method

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Abstract: Novel macrocyclic bis-sulfonamides that structurally related to the proton-ionizable crown compounds have been synthesized. These compounds were obtained in the macrocyclization step by the fast addition method, and the results were compared with both high dilution and solvent-free conditions.

Keywords: Fast addition, high dilution technique, macrocyclization, proton-ionizable, solvent-free conditions, sulfonamides

Various modifications have been made to the basic crown ether structure to enhance the sensing and selectivity of these ligands and the stability of the complex formed.[1] Among these modifications are the substitutions of ligand donor atoms with nitrogen or sulfur atoms or the inclusion of ester and amide linkages in the polyether ring.[2] There has been much attention paid to the chemistry of proton-ionizable crown ethers.[3] The nature of the proton-ionizable group, particularly its acidity, controls the metal ion complexation properties of such ligands. Arylsulfonamides offer an advantage over other proton-ionizable crown compounds by increasing the acidity of the amide protons by stabilizing the nitrogen anions.[4] Bradshaw et al.[4,5] have reported bis-sulfonamide crown compounds as excellent alkali metal cation carriers in bulk liquid membranes. These macrocycles have been prepared mainly by the reaction of bis-sulfonyl chlorides and diamines in high dilution conditions, which suffer from disadvantages such as long reaction time, low yields, tedious procedures, and use of high volumes of organic solvents.

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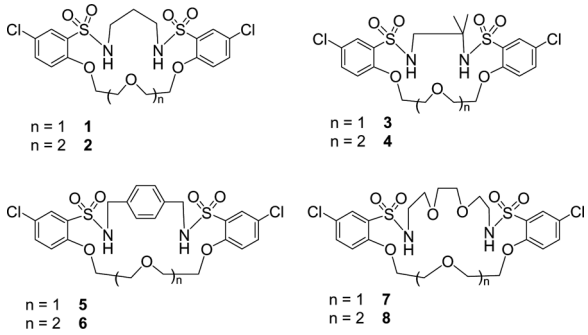
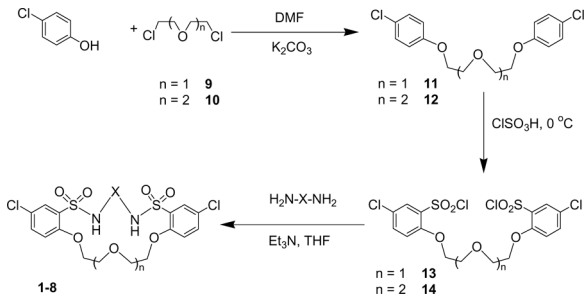


Scheme 1. New macrocyclic bis-sulfonamides.

Herein, we report the synthesis of novel macrocyclic bis-sulfonamides **1–8** (Scheme 1), in which the acidity of these proton-ionizable macrocycles are increased by electronegative chloride substituents. As shown in Scheme 2, these compounds were prepared by reacting the bis-sulfonyl chlorides **13** and **14** and diamines in the fast addition method.

The reaction of *p*-chlorophenol with dichlorides **9** and **10** in N,N-dimethylformamide (DMF) using potassium carbonate as a base gave podands **11** and **12** in 76 and 64% yields, respectively. Bis-sulfonyl chlorides **13** and **14** were obtained by chlorosulfonation of podands in 86 and 73% yields, respectively. The cyclization was carried out with vigorously stirring and fast addition of a mixture of the diamine and triethylamine into a suspension of bis-sulfonyl chlorides **13** and **14** in tetrahydrofuran (THF) over 5 s at 25 °C (Scheme 2).

A typical preparation of macrocyclic bis-sulfonamides is as follows: a solution of 1,3-diaminopropane (2 mmol) and triethylamine (4 mmol) in THF (20 ml) was added rapidly (5 s.) into a vigorously stirred suspension of bis-sulfonyl chlorides **13** (2 mmol) in THF (20 ml) at 25 °C. After the usual workup and purification, bis-sulfonamide macrocyle **1** was



Scheme 2. Synthesis of macrocyclic bis-sulfonamides.

Table 1. Comparison of the macrocyclization methods for the synthesis of bis-sulfonamides **1** and **2**

Entry[a]	1			2		
	Solvent (ml)	Time	Yield[c]	Solvent (ml)	Time	Yield[c]
Fast addition	40	5 s	45	40	5 s	35
Solvent free	0	10 min	18	0	10 min	15
High dilution[b]	400	4 h	25	400	4 h	19

[a]All reactions were carried out using 2 mmol of bis-sulfonyl chloride **13** or **14**, 2 mmol of 1,3-diaminopropane, and 4 mmol of triethylamine in THF (except the solvent-free entry).

[b]According to Ref. 4.

[c]Yields refer to isolated yield.

obtained in 45% yield. As shown in Scheme 1, a series of macrocyclic bis-sulfonamides was obtained by this procedure in 18–45% yields. As pointed in our previous study,[6] the less-reactive substrates in a solvent-presence procedure failed in solvent-free reaction conditions. To test this opinion and possibly increase the isolated yield, we treated the 1,3-diaminopropane (2 mmol) and bis-sulfonyl chlorides **13** and **14** (2 mmol) in the presence of triethylamine (4 mmol) in solvent-free conditions by simply grinding the mixture for 10 min. The corresponding bis-sulfonamide macrocyles **1** and **2** were obtained in low yields, 18 and 15%, respectively. The results are summarized in Table 1 and are compared with the corresponding results obtained in both high dilution and fast addition methods. As shown in Table 1, yields of macrocyclization with the fast addition method are quite good. However, bis-sulfonyl chlorides **13** and **14** are solid, bulky, and much less reactive than dicarboxylic acid dichlorides, which decreased the yields in all procedures, especially in the solvent-free condition. On the other hand, these sulfonamide-containing crowns with high melting points and so low solubility in common solvents were recrystallized in acetic acid, which seriously decreased the isolated yields.

The structures proposed for the macrocyclic compounds are consistent with data derived from IR and ^{1}HNMR spectra and molecular weights determined by mass spectrometric analysis. The proton-ionizable properties and ion recognition ability of these novel compounds are in progress in our laboratories.

EXPERIMENTAL

Melting points were recorded in open capillary tubes in an Electrothermal IA 9100 melting-point apparatus. IR spectra were recorded on a

Shimadzu IR 470 spectrophotometer. ^{1}HNMR spectra were recorded on a Bruker 100-MHz instrument using tetramethylsilane (TMS) as an internal standard. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV. All chemicals were purchased from Merck and Fluka Co. and used without further purification.

Preparation of Podands 11 and 12

A mixture of *p*-chlorophenol (0.1 mol, 12.8 g) and potassium carbonate (0.1 mol, 14 g) in DMF (60 mL) was refluxed for 30 min. Then a solution of dichlorides **9** or **10** (0.05 mol) in DMF (20 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred under reflux for 20 h. After cooling, the mixture was poured into water (200 mL) and extracted with chloroform (2×75 mL). The organic layer was washed with brine (6×100 mL) and dried over calcium chloride. The solvent was evaporated to give a bright white solid of the corresponding podands **11** and **12** after recrystallization from ethanol.

Data

1-Chloro-4-(2-[2-(4-chlorophenoxy)ethoxy]ethoxy)benzene (11): yield 12.4 g (76%); mp = 88–90 °C; IR (KBr): 740, 840, 1062, 1125, 1440, 1490, 1580, 2920, 3070 cm^{-1}; ^{1}HNMR ($CDCl_3$, 100 MHz) δ 7.2 (d, 4 H, $J = 8.5$ Hz), 6.8 (d, 4 H, $J = 8.5$ Hz), 4.1 (m, 4H), 3.9 (m, 4H). MS m/z 330 ($M^+ + 4$), 328 ($M^+ + 2$), 327 ($M^+ + 1$), 326(M^+), 218,170, 157, 140, 128 (base peak), 106.

1-Chloro-4-(2-[2-(2-[4-chlorophenoxy]ethoxy)ethoxy]ethoxy)benzene (12): yield 11.85 g (64%); mp = 78–80 °C; IR (KBr): 760, 870, 1050, 1120, 1510, 1595, 2960, 3070 cm^{-1}; ^{1}HNMR ($CDCl_3$, 100 MHz) δ 7.8 (d, 4 H, $J = 8.5$ Hz), 7.35 (d, 4 H, $J = 8.5$ Hz), 4.16 (m, 4 H), 3.7 (m, 4 H), 3.6 (s, 4 H). MS m/z 374 ($M^+ + 4$), 372 ($M^+ + 2$), 371 ($M^+ + 1$), 370 (M^+, base peak), 356, 342, 313, 299, 279, 243, 231, 198,172, 159, 140, 128.

Preparation of Bis-sulfonyl Chlorides 13 and 14

Podands **11** or **12** (0.01 mol) were added to a string chlorosulfonic acid solution (5 mL) at 0 °C over a 45-min period. The resulting mixture was stirred at 0 °C for an additional 5 h. The mixture was then diluted with chloroform (30 mL) and poured onto crushed ice. The mixture was saturated with sodium chloride. The separated organic layer was washed with saturated sodium bicarbonate (2×15 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a white solid of

the corresponding bis-sulfonyl chlorides **13** and **14** after recrystallization from ethyl acetate.

Data

5-Chloro-2-(2-[2-(4-chloro-2-chlorosulfonylphenoxy)ethoxy]ethoxy)-1-benzenesulfonyl chloride (13): yield 4.5 g (86%); mp = 118–120 °C; IR (KBr): 760, 830, 920, 1080, 1120, 1160, 1180, 1205, 1290, 1330, 1440, 1470, 1500, 1620, 2960, 3070 cm^{-1}; ^{1}HNMR (DMSO-d^6, 100 MHz) δ 7.65 (d, 2 H, $J = 1.5$ Hz), 7.35 (dd, 2 H, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz), 7.05 (d, 2 H, $J = 8.0$ Hz), 4.15 (m, 4 H), 3.90 (m, 4 H). MS m/z 526 ($M^+ + 4$), 524 ($M^+ + 2$), 523 ($M^+ + 1$), 522 (M^+), 519, 426, 333, 326, 296, 282, 252, 235, 217, 198, 126, 107 (base peak).

5-Chloro-2-(2-[2-(2-[4-chloro-2-chlorosulfonylphenoxy]ethoxy)ethoxy]ethoxy)-1-benzenesulfonyl chloride (14): yield 4.12 g (73%); mp = 105 °C; IR (KBr): 760, 850, 940, 1050, 1120, 1250, 1290, 1340, 1450, 1500, 1620, 2960, 3070 cm^{-1}; ^{1}HNMR (DMSO-d^6, 100 MHz) δ 7.70 (d, 2 H, $J = 1.5$ Hz), 7.40 (dd, 2 H, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz), 7.10 (d, 2 H, $J = 8.0$ Hz), 4.25 (m, 4 H), 3.75 (m, 4 H), 3.6 (s, 4 H). MS m/z 567 ($M^+ + 1$), 566 (M^+), 564, 562, 499, 466, 370, 342, 325, 296, 252, 234, 216 (base peak), 188, 160, 128.

General Procedure for the Synthesis of Macrocyclic Bis-sulfonamides (1–8) by Fast Addition Method

A solution of diamine (2 mmol) and triethylamine (0.41 g, 4 mmol) in THF (20 mL) was added quickly (5 s) to a vigorously stirring suspension of bis-sulfonyl chlorides **13** or **14** (2 mmol) in THF (20 mL) at 25 °C. The reaction mixture was stirred at room temperature for 30 min. The precipitate was filtered off, and the filtrate was washed with water (2×50 mL), saturated aqueous sodium bicarbonate solution (2×50 mL), and water (100 mL). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated to give a solid product. The crude product was purified by recrystallization from acetic acid and subsequent washing with water.

Data

3,13-Dichloro-7,8,9,10,17,18,20,21-octahydro-5H-5λ^6,11λ^6-dibenzo[b,k][1,13,16,4,10,5,9]trioxadithiadiazacyclooctadecine-5,5,11,11,(6H)-tetraone (1): 45% yield; white solids; mp = 285 °C (decomposed); IR (KBr): 760, 850, 940, 1050, 1250, 1500, 1620, 2960, 3260 cm^{-1}. ^{1}HNMR (DMSO-

d^6, 100 MHz): δ 7.65 (d, 2 H, $J = 1.5$ Hz), 7.40 (dd, 2 H, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz), 7.20 (d, 2 H, $J = 8.0$ Hz), 6.60 (br s, 2 H, NH), 4.20 (m, 4 H), 3.90 (m, 4 H), 3.0 (m, 4 H), 1.70 (m, 2 H). MS m/z 528 ($M^+ + 4$), 526 ($M^+ + 2$), 524 (M^+), 521, 459, 427, 324, 306, 283, 256 (base peak), 217, 199, 173, 143, 128, 108.

2,17-Dichloro-6,7,9,10,12,13,21,22,23,24-decahydro-19H-19λ^6,25λ^6-dibenzo [b,k] [1,13,16,19,4,10,5,9]tetraoxadithiadiazacyclohenicosine-19,19,25,25, (20H)-tetraone (2): 35% yield; white solids; mp = 280 °C (decomposed); IR (KBr): 760, 950, 1050, 1250, 1450, 1500, 1600, 2960, 3240 cm^{-1}. ^{1}HNMR (DMSO-d^6, 100 MHz): δ 7.70 (d, 2 H, $J = 1.5$ Hz), 7.40 (dd, 2 H, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz), 7.10 (d, 2 H, $J = 8.0$ Hz), 6.60 (br s, 2 H, NH), 4.20 (m, 4 H), 3.80 (m, 4 H), 3.60 (s, 4 H), 3.10 (m, 4 H), 1.60 (m, 2 H). MS m/z 572 ($M^+ + 4$), 570 ($M^+ + 2$), 568 (M^+), 486, 369, 339, 264, 230 (base peak), 200, 149, 136, 107.

3,12-Dichloro-7,7-dimethyl-6,7,8,9,16,17,19,20-octahydro-5λ^6,10λ^6-dibenzo [b,j][1,12,15,4,9,5,8]trioxadithiadiazacycloheptadecine-5,5,10,10-tetraone (3): 45% yield; white solids; mp = 295 °C (decomposed); IR (KBr): 760, 850, 950, 1150, 1450, 1500, 1620, 2920, 2960, 3280 cm^{-1}. ^{1}HNMR (DMSO-d^6, 100 MHz): δ 7.70 (m, 2 H), 7.40 (m, 2 H), 7.10 (m, 2 H), 6.60 (br s, 2 H, NH), 4.10 (m, 8 H), 3.90 (m, 2 H), 1.25 (s, 6 H). MS m/z 539 ($M^+ + 1$), 538 (M^+), 536, 533, 453, 356, 340, 325, 296, 256, 244 (base peak), 217, 200, 173, 121.

2,17-Dichloro-21,21-dimethyl-6,7,9,10,12,13,20,21,22,23-decahydro-19λ^6, 24λ^6-dibenzo[b,j][1,12,15,18,4,9,5,8]tetraoxadithiadiazacycloicosine-19,19, 24,24-tetraone (4): 18% yield; white solids; mp = 283 °C (decomposed); IR (KBr): 800, 900, 1050, 1150, 1200, 1350, 1485, 1600, 3200 cm^{-1}. ^{1}HNMR (DMSO-d^6, 100 MHz): δ 7.62 (m, 2 H), 7.35 (m, 2 H), 7.05 (m, 2 H), 6.70 (br s, 2 H, NH), 4.30 (m, 8 H), 4.10 (s, 4 H), 3.85 (m, 2 H), 1.20 (s, 6 H). MS m/z 582 (M^+), 552, 536, 530, 457, 359, 345, 320, 291, 255, 243 (base peak), 217, 199, 176, 121.

7,21-Dichloro-11,14,17-trioxa-4λ^6,24λ^6-dithia-3,25-diazatetracyclo[25.2.2.0^{5,10}. 0^{18,23}]hentriaconta-1(29),5,7,9,18(23),19,21,27,30-nonaene-4,4,24,24-tetraone (5): 40% yield; white solids; mp = 263 °C; IR (KBr): 750, 800, 850, 1095, 1180, 1265, 1485, 1600, 3400 cm^{-1}. ^{1}HNMR (DMSO-d^6, 100 MHz): δ 7.55 (m, 2 H), 7.25 (m, 2 H), 7.05 (m, 2 H), 6.90 (s, 4H), 6.80 (br s, 2 H, NH), 4.20 (m, 4 H), 4.05 (m, 4 H), 3.70 (m, 4 H). MS m/z 587 ($M^+ + 1$), 586 (M^+), 585, 581, 451, 413, 336, 296, 282, 253, 236, 217, 200, 172, 136, 104, 64 (base peak).

7,24-Dichloro-11,14,17,20-tetraoxa-4λ^6,27λ^6-dithia-3,28-diazatetracyclo [28.2.2.0^{5,10}.0^{21,26}]tetratriaconta-1(32),5,7,9,21(26),22,24,30,33-nonaene-4,4, 27,27-tetraone (6): 25% yield; white solids; mp = 245 °C; IR (KBr): 750, 850, 950, 1100, 1150, 1350, 1500, 1600, 3400 cm^{-1}. ^{1}HNMR (DMSO-d^6, 100 MHz): δ 9.30 (br s, 2 H, NH), 7.60 (m, 2 H), 7.30 (m, 2 H), 6.90 (s, 4H), 6.80 (m, 2 H), 4.25 (m, 4 H), 4.0 (m, 4 H), 3.80 (m, 4 H), 3.60 (s, 4 H). MS m/z 631 ($M^+ + 1$), 630 (M^+), 629, 401, 368, 334, 325, 290, 246, 230, 200, 134, 124, 86, 64, 56 (base peak).

3,18-Dichloro-7,8,10,11,14,15,22,23,25,26-decahydro-5λ^6,16λ^6-dibenzo[b,p] [1,8,11,18,21,4,15,5,14]pentaoxadithiadiazacyclotricosine-5,5,16,16(6H,13H)-tetraone (7): 35% yield; white solids; mp = 270 °C; IR (KBr): 750, 850, 1050, 1150, 1250, 1350, 1500, 1600, 3350 cm^{-1}. ^{1}H-NMR (DMSO-d^6, 100 MHz): δ 7.60 (d, 2 H, $J = 1.5$ Hz), 7.35 (dd, 2 H, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz), 7.05 (d, 2 H, $J = 8.0$ Hz), 6.20 (br s, 2 H, NH), 4.15 (m, 4 H), 3.90 (m, 4 H), 3.50 (m, 4 H), 3.4 (s, 4 H), 3.05 (m, 4 H). MS m/z 602 ($M^+ + 4$), 600 ($M^+ + 2$), 598 (M^+), 457, 425, 407, 348, 333, 291, 278, 250, 234, 217, 200, 174, 131, 126 (base peak).

3,18-Dichloro-7,8,10,11,14,15,22,23,25,26,28,29-dodecahydro-5λ^6,16λ^6-dibenzo[b,p][1,8,11,18,21,24,4,15,5,14]hexaoxadithiadiazacyclohexacosine-5,5,16,16(6H,13H)-tetraone (8): 23% yield; white solids; mp = 256 °C; IR (KBr): 750, 800, 1050, 1190, 1300, 1520, 1600, 3300 cm^{-1}. ^{1}HNMR ($CDCl_3$, 100 MHz): δ 7.85 (m, 2 H), 7.50 (m, 2 H), 6.95 (d, 2 H, $J = 8.0$ Hz), 6.10 (br s, 2 H, NH), 4.30 (m, 4 H), 3.95 (m, 4 H), 3.80 (s, 4 H), 3.50 (m, 8 H), 3.0 (m, 4 H). MS m/z 642 (M^+), 641, 620, 598, 550, 457, 425, 407, 350, 330, 295, 278, 258, 234, 217, 200, 174, 131, 126 (base peak).

General Procedure for the Solvent-Free Synthesis of Macrocyclic Bis-sulfonamides (1 and 2)

A mixture of 1,3-diaminopropane (0.15 g, 2 mmol), triethylamine (0.4 g, 4 mmol), and bis-sulfonyl chloride **13** or **14** (2 mmol) was grinded in a mortar and pestle for 10 min. The reaction mixture was treated with water (500 ml), and the precipitate was filtered off. The crude product was purified by recrystallization from acetic acid and subsequent washing with water. Compounds **1** and **2** were obtained by this procedure in **18** and 15% yields, respectively, with the same characterization as reported previously for the fast addition procedure.

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