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Macrocyclic Polyether Sulfide Syntheses. The Preparation of Thia-Crown-3,4, and 5 Compounds (1)

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Macrocyclic polyether sulfides have been prepared by reacting an oligoethylene glycol dichloride with a dithiol or sodium sulfide in ethanol. The trivial naming system for these compounds is an extension of the trivial crown nomenclature (5). A thia prefix is used to show that sulfur atoms have replaced ether oxygen atoms in the polyether ring. The following new compounds were prepared: 1-thia-(15-crown-5) (II); 1,4-dithia-(15-crown-5) (III); 1,7-dithia-(15-crown-5) (IV); 1,4-dithia-(12-crown-4) (VII); 1,4,7-trithia-(12-crown-4) (VIII); 1-thia-(9-crown-3) (IX); and 1,4-dithia-(9-crown-3) (X). Four other previously reported macrocyclic polyether sulfides were also prepared. The symmetry of the nmr spectra of these compounds gives added evidence for the proposed ring structures.

Since the macrocyclic polyethers were reported by Pedersen (5), a considerable volume of literature has appeared concerning this class of compounds. Of special interest have been their unusual cation binding properties (6). In general, they have high affinities for certain of the alkali and alkaline earth cations with the affinity increasing markedly with increasing cation charge (same cationic radius). For example, log K values for the formation of the K^+ and Ba^{2+} complexes with dicylcohexyl-18-crown-6 in aqueous solution at 25° are 2.02 and 3.57, respectively (7,8). The increased stability with increasing cation charge has been interpreted as showing that the metal-oxygen bond in cyclic polyether complexes is predominantly ionic (8). It was also shown that, in the case of dicyclohexyl-18-crown-6, the most stable complexes were found for both +1 and +2 cations when the ratio of the diameter of the cation to that of the crown cavity was about 0.80 (8). Substitution of sulfur for part or all of the oxygen atoms in the crown compounds should markedly affect their complexing properties. Despite their potential interest as selective complexing agents, very few compounds where sulfur replaces oxygen have been prepared (9) thus their chemistry has not been extensively studied.

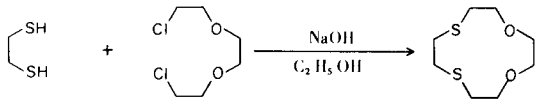
A symmetrical 18-crown-6 compound (I) having two sulfur and four oxygen atoms has been synthesized and log K values have been reported for several of its metal complexes (10). Log K values for the formation of the Ag^+ and K^+ complexes with I in aqueous solution are 4.34 and 1.15, respectively (10). The four fold increase in the binding constant for Ag^+ over that for K^+ was attributed to the ability of Ag^+ to form strong covalent bonds with the sulfur atoms (10) whereas K^+ can only form ionic bonds. Of particular interest is the high log K value (4.34) for the formation of the Ag^+ complex with I compared to that (1.59) for the Ag^+ complex with dicylcohexyl 18-crown-6 in aqueous solution (8).

We have embarked on a program to synthesize selected cyclic polyether sulfides and determine log K, ΔH, and $\Delta S°$ values for their interaction with selected cations. In the present study is reported the synthesis of several 15-crown-5, 12-crown-4, and 9-crown-3 compounds with both sulfur and oxygen heteroatoms (compounds II-X, Figure 1). Thermochemical results indicate that the cavity sizes of II, III and IV are too small to accomodate a metal ion in the cavity and that binding involves a 2:1 ligand:metal complex (11).

The trivial naming system for these compounds is an extension of the crown nomenclature used by Pedersen (5). A thia (or oligothia) prefix is used to show that one (or more) of the ether oxygen atoms has been replaced by one (or more) sulfur atom. Thus, the trivial name for compound III is 1,4-dithia-(15-crown-5). Compounds II, III, IV, VII, VIII, IX and X have not been reported previously.

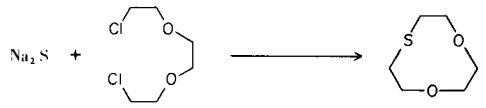
Results and Discussion.

The macrocyclic polyether sulfides were prepared in a manner similar to that reported by Dann, Chiesa and Gates (12). An oligoethylene glycol dichloride was allowed to react with a dithiol or sodium sulfide. Both our yields and theirs were generally low (5-30%) due to extensive polymer formation.



VII

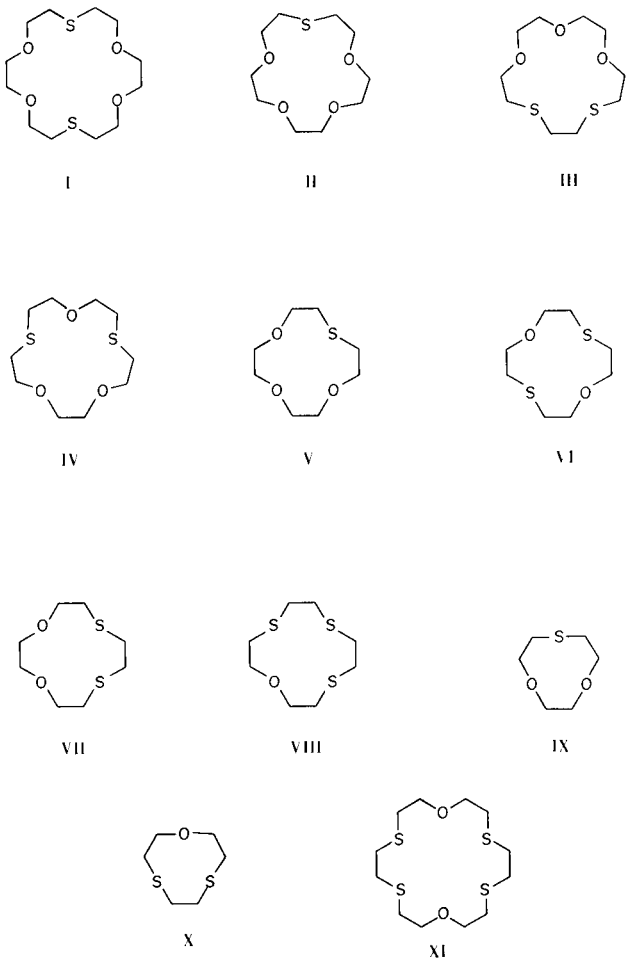
Dann and coworkers (12) allowed 1,2-bis(2-chloroethoxy)ethane to react with sodium sulfide to prepare 1,10-dithia-(18-crown-5) (I). They were unable to isolate 1-thia-(9-crown-3) (IX). Using higher dilutions, we were able to isolate IX in a 5% yield along with compound I.



IX

Figure 1

Crown Compounds Prepared in this Study



Meadow and Reid (13) attempted to prepare 1,4-dithia-(9-crown-3) (X) from the reaction of ethylene mercaptan and bis(2-chloroethyl) ether. They were unable to isolate X but rather isolated 1,4,10,13-tetrathia-(18-crown-6) (XI). We were able to isolate X in a 6% yield by using high dilution techniques. Compound XI was also isolated in our reaction. Although compound XI had the same physical properties as those reported by Meadow and Reid (13), Black and McLean (14) reported a much lower melting point for XI. The reason for this discrepancy in melting points is not known. The physical properties of our compound are consistent with structure XI.

The nmr spectra for these crown compounds are very distinctive. 1,4-Dithia-(12-crown-4) (VII), for example, has four different peak types. The singlet peaks at δ = 2.91 and 3.56 are caused by ethylene hydrogens between the two sulfur and oxygen atoms, respectively. The triplet peaks at δ = 2.62 are caused by the methylene hydrogens α to sulfur and β to oxygen while those at δ = 3.78 are caused by the methylene hydrogens δ to oxygen but β to sulfur. The singlet peaks correspond very closely to those of *p*-dithiane and *p*-dioxane. It is interesting to note that hydrogen atoms on carbon atoms β to sulfur atoms are more deshielded than those β to oxygen atoms. The β hydrogen atoms of tetrahydrothiophene gave peaks at δ = 1.91 while those of tetrahydrofuran are at δ = 1.82. Thus one could expect that the hydrogen atoms β to the sulfur atom in compound VII (but α to the oxygen atom) would be shifted downfield. This is indeed the case as shown by the fact that the triplet at δ = 3.78 is shifted from the singlet δ = 3.56.

The triplet nmr peaks, attributable to the ethylene hydrogen atoms between the oxygen and sulfur atoms, appear to be first order for the crown-4 and 5 compounds which contain only one sulfur atom (compounds II and V). For all other compounds herein studied, triplet nmr peaks

show broadening and/or complex splitting. No change in this splitting was observed for compound VII when the temperature was lowered to -60°. Models show that when two or more sulfur atoms are in the crown-4 and 5 rings, the ring is puckered and cannot easily change conformations; the splitting of the triplet nmr peaks is a further evidence of the ring puckering. The crown-3 compounds are puckered with only one sulfur atom.

It is interesting to note that the nmr spectra for the two crown-3 compounds (IX and X) are in effect "mirror images" of each other. The triplet peaks near δ = 2.7 and 3.9 corresponding to CH_2 next to sulfur and oxygen, respectively, do not change. The singlet peak, however, changes from δ = 3.58 (OCH_2CH_2O in IX) to δ = 3.02 (SCH_2CH_2S in X). Thus, the nmr spectrum can be used to accurately describe the structures of these compounds.

EXPERIMENTAL

All infrared (ir) spectra were obtained on a Perkin-Elmer 457 spectrophotometer. A Varian A-60 A spectrometer was used to obtain the nuclear magnetic resonance (nmr) spectra. Elemental analyses were performed by MHW Laboratories, Garden City, Michigan. Molecular weights were determined by osmometry in benzene or chloroform and indicate all complexes are monomers. Melting points were obtained on a Thomas-Hoover capillary type melting apparatus and are uncorrected.

General Synthesis.

A solution of reagent sodium hydroxide dissolved in 600-1000 ml. of ethanol was placed in a large round bottom flask equipped with two addition funnels, a gas inlet, reflux condenser, and mechanical stirrer. The reaction was performed in an atmosphere of nitrogen and with vigorous sitrring. The appropriate dichloride and dithiol were dissolved in 300 ml. of ethanol and placed in the two addition funnels. The two solutions were added slowly at the same rate over a period of six hours. For the crown-4 and crown-3 compounds, an equal molar mixture of the dichloride and the dithiol in 500 ml. of ethanol was added slowly from one addition funnel. In the case of the synthesis of crown compounds with only one sulfur heteroatom, the dichloride in ethanol was added slowly to a solution of sodium sulfide and small amounts of sodium hydroxide in ethanol. The resulting mixture was refluxed for an additional 1 to 8 hours and then cooled to room temperature. The excess base was neutralized with hydrochloric acid, the solid was filtered and the ethanol removed under vacuum. The remaining viscous liquid was extracted with three 300 ml. portions of diethyl ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered. The yellow liquid which remained after the ether was removed was subjected to vacuum distillation and/or recrystallization to obtain the pure product. The products were colorless and had almost no odor. No -SH or $-CH_2Cl$ absorption bands appeared in the ir or nmr spectra. Specific synthetic details are given for each compound prepared.

Starting Materials.

Most of the starting materials were used as purchased. The dichlorides were prepared from the corresponding glycols. 1,14-Dichloro-3,6,9,12-tetraoxatetradecane was prepared from pentaethylene glycol (Columbia) and thionyl chloride. 1,11-Dichloro-3,6,9-trioxaundecane was prepared from tetraethylene glycol (Aldrich) and thionyl chloride.

1-Thia(15-crown-5) (II) (4,7,10,13-Tetraoxa-1-thiacyclopentadecane).

1,14-Dichloro-3,6,9,12-tetraoxatetradecane (135.6 g., 0.5 mole) was added to 2.0 g. of sodium hydroxide and 120.1 g. (0.5 mole) of sodium sulfide nonahydrate. The product was a colorless liquid, 34.2 g. (29%), b.p. 123-124°/0.1 mm.; nmr: δ = 2.66 (t, 4H, SCH_2O), δ = 3.57 (s, 12H, OCH_2CHO) and δ = 3.68 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_{10}H_{20}O_4S$: C, 50.80; H, 8.53; S, 13.57. Found: C, 50.57; H, 8.73; S, 13.73.

1,4-Dithia(15-crown-5) (III) (7,10,13-Trioxa-1,4-dithiacyclopentadecane).

1,11-Dichloro-3,6,9-trioxaundecane (115.6 g., 0.5 mole) and 47.1 g. (0.5 mole) of 1,2-ethanedithiol (Aldrich) were added to 44.0 g. of sodium hydroxide in ethanol. The product was first distilled (147-148°/0.1 mm.) and then recrystallized from a 50:50 benzene-hexane mixture to yield 25.2 g. (20%) of large prisms, m.p. 51-52°, nmr: δ = 2.63 (t, 4H, SCH_2CH_2O), δ = 2.78 (s, 4H, SCH_2CH_2S), δ = 3.55 (s, 8H, OCH_2CH_2O) and δ = 3.69 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_{10}H_{20}O_3S_2$: C, 47.59; H, 7.99; S, 25.41. Found: C, 47.54; H, 8.20; S, 25.21.

1,7-Dithia-(15-crown-5) (IV) (4,10,13-Trioxa-1,7-dithiacyclopentadecane).

Bis-(2-mercaptoethyl) ether (Aldrich, 69.2 g., 0.5 mole) and 93.5 g. (0.5 mole) of 1,8-dichloro-3,6-dioxaoctane (Eastman) were added to 44.0 g. of sodium hydroxide in ethanol. The product was a viscous liquid, 34.2 g. (27%), b.p. 150-151°/0.1 mm.; nmr: δ = 2.62 (t, 4H, SCH_2CH_2O), δ = 2.78 (t, 4H, SCH_2CH_2O), δ = 3.56 (s, 4H, OCH_2CH_2O), δ = 3.58 (t, 4H, OCH_2CH_2S), and δ = 3.73 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_{10}H_{20}O_3S_2$: C, 47.59; H, 7.99; S, 25.41. Found: C, 47.64; H, 8.15; S, 25.47.

1-Thia-(12-crown-4) (V) (4,7,10-Trioxa-1-thiacyclododecane).

1,11-Dichloro-3,6,9-trioxaundecane (77 g., 0.33 mole) was added to 80.0 g. (0.33 mole) of sodium sulfide nonahydrate and 2 g. of sodium hydroxide in ethanol. The product was a colorless liquid, 5.3 g. (14%), b.p. 80-87°/1 mm. (lit. 90-95°/1 mm. (12)); nmr: δ = 2.68 (t, 4H, SCH_2CH_2O), δ = 3.57 (s, 8H, OCH_2CH_2O) and δ = 3.77 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_8H_{16}O_3S$: C, 49.97; H, 8.39; S, 16.68. Found: C, 50.02; H, 8.55; S, 16.47.

1,7-Dithia-(12-crown-4) (VI) (4,10-Dioxa-1,7-dithiacyclododecane).

Bis-(2-mercaptoethyl) ether (46.1 g., 0.33 mole) and 47.7 g. (0.33 mole) of bis-(2-chloroethyl) ether (Aldrich) were added to 30 g. of sodium hydroxide in ethanol. The product, 8 g. (12%), was a colorless liquid, b.p. 118-120°/0.1 mm. (lit. 133-142°/0.17 mm. (12)); nmr: δ = 2.77 (t, 8H, SCH_2CH_2O) and δ = 3.74 (t, 8H, OCH_2CH_2S).

Anal. Calcd. for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74; S, 30.78. Found: C, 45.96; H, 7.59; S, 31.00.

1,4-Dithia-(12-crown-4) (VII) (7,10-Dioxa-1,4-dithiacyclododecane).

1,2-Bis-(2-chloroethoxy) ethane (Eastman, 62.41 g., 0.33 mole) and 31.4 g. (0.33 mole) of 1,2-ethanedithiol (Aldrich) were added

to 30 g. of sodium hydroxide in ethanol. The product, 12.4 g. (19%) was a colorless liquid, b.p. 134-136°/0.1 mm.; nmr: δ = 2.61 (t, 4H, SCH_2CH_2O), δ = 2.91 (s, 4H, SCH_2CH_2S), δ = 3.56 (s, 4H, OCH_2CH_2O), and δ 3.77 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74; S, 30.78. Found: C, 46.38; H, 7.65; S, 30.55.

1,4,7-Trithia-(12-crown-4) (VIII) (10-Oxa-1,4,7-trithiacyclododecane).

Bis-(2-chloroethyl) ether (Aldrich, 31.5 g., 0.22 mole) and 34.2 g. (0.22 mole) of bis-(2-mercaptoethyl)sulfide (K and K) were added to 25 g. of sodium hydroxide in ethanol. The product, 14.6 g. (26%) of large crystals, was recrystallized from benzene, m.p. 89-91°; nmr: δ = 2.73 (t, 4H, SCH_2CH_2O), δ = 2.90 (s, 8H, SCH_2CH_2S) and δ = 3.78 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_8H_{16}OS_3$: C, 43.82; H, 7.19; S, 42.86. Found: C, 42.87; H, 7.03; S, 42.95.

1-Thia-(9-crown-3) (IX) (4,7-Dioxa-1-thiacyclononane).

Bis-(2-chloroethoxy) ethane (Eastman, 37.4 g., 0.2 mole) was added to 48 g. (0.2 mole) of sodium nonahydrate and 0.7 g. of sodium hydroxide in ethanol. The product, 1.3 g. (5%) was a colorless liquid, b.p. 40-48°/0.15 mm.; nmr: δ = 2.79 (t, 4H, SCH_2CH_2O), δ = 3.58 (s, 4H, OCH_2CH_2O) and δ = 3.88 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_6H_{12}O_2S$: C, 48.62; H, 8.16; S, 21.63. Found: C, 48.35; H, 8.31; S, 21.76.

A solid by-product formed in the ether extract. This was isolated before the ether extract was distilled for the above isolation of liquid product IX. The solid, 3.6 g. (12%) was recrystallized from chloroform-hexane to yield 1,10-dithia(18-crown-6) (I), m.p. 88-90° (lit. 90-91° (12)); nmr: δ = 2.82 (t, 8H, SCH_2CH_2O), δ = 3.63 (s, 8H, OCH_2CH_2O) and δ = 3.72 (t, 8H, OCH_2CH_2S).

Anal. Calcd. for $C_{12}H_{24}O_4S_2$: C, 48.62; H, 8.16; S, 21.63. Found: C, 48.41; H, 8.31; S, 21.67.

1,4-Dithia-(9-crown-3) (X) (7-Oxa-1,4-dithiacyclononane).

Bis-(2-chloroethyl) ether (Aldrich, 35.8 g., 0.25 mole) and 23.6 g. (0.25 mole) of 1,2-ethanedithiol were added to 25 g. of sodium hydroxide in ethanol. The product, 2.3 g. (6%), was collected by vacuum distillation, b.p. 62-64°/0.1 mm.; nmr: δ = 2.73 (t, 4H, SCH_2CH_2O), δ = 3.02 (s, 4H, SCH_2CH_2S) and δ = 3.89 (t, 4H, OCH_2CH_2S).

Anal. Calcd. for $C_6H_{12}OS_2$: C, 43.87; H, 7.36; S, 39.03. Found: C, 43.76. H, 7.43; S, 38.83.

The solid from the acidified ethanol solution was extracted continuously for two days with hexane. A solid formed in the hexane layer. This solid was repeatedly recrystallized in chloroform-hexane to yield 1,4,10,13-tetrathia-(18-crown-6) (XI), 1.8 g. (4%), m.p. 125-126° (lit. 50° (14) and 125° (13)); nmr: δ = 2.74 (t, 8H, SCH_2CH_2O), δ = 2.85 (s, 8H, SCH_2CH_2S) and δ = 3.67 (t, 8H, SCH_2CH_2S).

Anal. Calcd. for $C_{12}H_{24}O_2S_4$: C, 43.87; H, 7.36; S, 39.03. Found: C, 44.14; H, 7.36; S, 38.88.

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(1) This research was supported by the National Science Foundation Grant No. GP 33536-X and National Institute of Health Grant AM 15615-02.

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