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Synthesis of Unsubstituted Thia Crown Ethers *via* Intramolecular Cyclization

Yohji Nakatsuji, Yoshitaka Watanabe, and Mitsuo Okahara*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565

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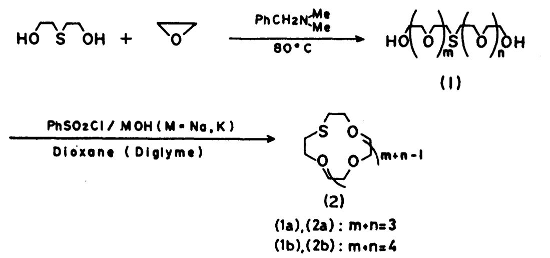
Synopsis. A remarkable temperature dependence of the template effect of alkali metal cations was found in the cyclization of thio analogs of penta- or hexaethylene glycols to thia 15-crown-5 or 18-crown-6. The optimum range of the reaction temperature was found to be 80—100 °C.

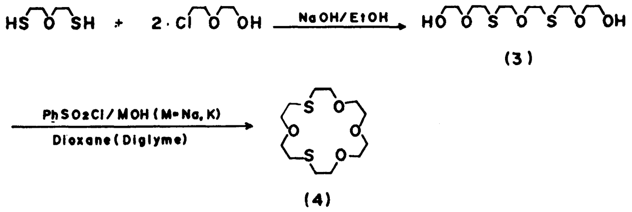
Thia crown ethers are interesting compounds because they can complex with transition metal cations, unlike normal crown ethers.[1—3] The known synthetic methods, however, are mostly restricted to the condensation reactions between two molecules.[4—6] We previously developed a new synthetic method of preparing crown ethers *via* intramolecular cyclization.[7] Template ions are important in obtaining macrocyclic compounds in good yields. The template effect of alkali metal cations in cyclization of oligoethylene glycols to the corresponding crown ethers was found to be dependent on the reaction temperature.[8] We here applied the intramolecular cyclization method to the synthesis of unsubstituted mono and dithia crown ethers and observed a more remarkable temperature effect on the reaction than occurred in the reaction of oligoethylene glycol.

Monothio oligoethylene glycol (**1**), the precursor of monothia crown ether (**2**), was prepared by the addition of ethylene oxide to 2,2′-thiodiethanol at 80 °C using *N*,*N*-dimethylbenzylamine as a catalyst. The three and four mole ethylene oxide adducts were separated from other adducts by distillation under reduced pressure.



A dioxane solution of **1** and an equimolar amount of benzenesulfonyl chloride was added dropwise to a stirred suspension of powdered sodium hydroxide in dioxane at a fixed temperature for 4 h. The mixture was stirred for another hour to give monothia crown ether (**2**). The yield was best at 100 °C for 15-crown-5 (**2a**) and at 80 °C for 18-crown-6 (**2b**) respectively, as shown in Table 1. It is noteworthy that reaction temperatures over 100 °C drastically lowered the yield. These optimum reaction temperatures (80—100 °C) in the synthesis of thia crown ethers are relatively higher than those of normal crown ethers (60—80 °C[8]). In addition, the temperature dependence of the template effect is remarkable in the reaction of **1**, compared with that of the oligoethylene glycols, so the consideration of the reaction temperature is more important in this case. The stability constant (log K') of **2a** toward Na^+ in methanol at 25 °C was determined to be 2.1 by using a cation-selective electrode, while that toward K^+ was too low to measure. Christensen and coworkers[3] reported that the value for **2b** was 2.57 toward Na^+ and 3.61 toward K^+. This trend in the stability constant may explain why K^+ does not display any template effects in the synthesis of **2a** and yet is suitable as the template ion for **2b**.

3,9,15-Trioxa-6,12-dithiaheptadecane-1,17-diol (**3**), which was obtained from the reaction between bis(2-mercaptoethyl) ether and 2-(2-chloroethoxy)ethanol, was successfully cyclized to 1,7-dithia-18-crown-6 (**4**) according to the procedure mentioned above. The trend of the template effect of sodium and potassium cations in this case was similar to the case of **2b**.



However, the cyclization of 6,9-dioxa-3,12-dithiatetradecane-1,14-diol (**5**) gave very little of the desired crown ether (1,7-dithia-15-crown-5 (**6**)). Instead, a small

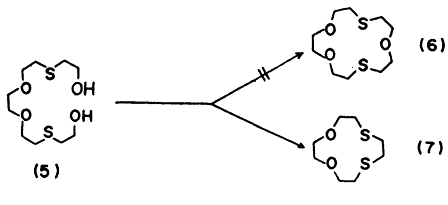


Table 1. Synthesis of thia crown ethers

Temperature/°C	Monothia-15-crown-5 (**2a**)		Monothia-18-crown-6 (**2b**)		Dithia-18-crown-6 (**4**)	
	NaOH	KOH	NaOH	KOH	NaOH	KOH
40	24	22	19	43	10	14
60	55	27*	31	53	30	42
80	80	22, 23*	56	62	51	66
100	92	19	52	57	40	51
120	20*	11*	9*	13*	—	8*

Solvent: Dioxane, *diglyme. Yields were determined by GLC.

amount of 1,4-dithia-12-crown-4 (**7**) was isolated by preparative GLC together with the unreacted **5**. The template effect is not effective in this case and **5** may be cyclized to **7** after the removal of ethylene oxide.

Experimental

The ^{1}H NMR spectra were taken at 100 MHz on a JEOL JNM-PS-100 spectrometer using tetramethylsilane as the internal standard. The infrared spectra were obtained on a Hitachi 260-10 spectrometer. The mass spectra were measured with a Hitachi RMU-6E mass spectrometer at an ionization potential of 70 eV.

*Monothia-15-crown-5(**2a**)(1,4,7,10-tetraoxa-13-thiacyclopentadecane).* A dioxane solution (40 ml) of monothio pentaethylene glycol (**1a**) (3.0 g, 0.012 mol) and benzenesulfonyl chloride (2.12 g, 0.012 mol) was added dropwise to a stirred suspension of sodium hydroxide (1.90 g, 0.048 mol) in dioxane (60 ml) over 4 h at a fixed temperature; then the mixture was stirred for one more hour at that temperature. The insoluble salt was removed by filtration and washed with dichloromethane. The solvent was removed *in vacuo* to give the crude product. The yields were determined by GLC (Shimadzu GC 3BF, FID, 2 m×3 mm packed with 10% Silicone Gum SE-30 on Celite 545, 60—80 mesh, 220 °C) using methyl myristate as the internal standard. Bp 110—114 °C/0.06 Torr† (Kugelrohr apparatus). NMR (CDCl$_3$, δ): 2.66 (t, 4H), 3.55 (s, 12H), and 3.68 ppm (t, 4H). MS (*m/e*): 236 (M$^+$), 203, 174, 149, 133, 104, 86, 73, 60, and 45. IR (Neat): 2920 (s), 1460 (m), 1355 (m), 1300 (m), 1245 (m), and 1115 cm^{-1} (s). The NMR spectrum of **2a** was coincident with that in the literature.[4]

*Monothia-18-crown-6 (**2b**) (1,4,7,10,13-pentaoxa-16-thiacyclooctadecane).* Monothia-18-crown-6 (**2b**) was prepared according to the procedure mentioned above. The yields were determined by GLC using dihexyl sebacate as the internal standard. The NMR spectrum of **2b** was coincident with that in the literature.[5]

3,9,15-Trioxa-6,12-dithiaheptadecane-1,17-diol (3). A suspended mixture of bis(2-mercaptoethyl) ether (27.0 g, 0.195 mol) and sodium hydroxide (24.6 g, 0.585 mol) in ethanol (230 ml) was stirred for 1.5 h. Then, 2-(2-chloroethoxy)ethanol (53.44 g, 0.429 mol) was added dropwise to the resultant mixture at 78 °C. The mixture was refluxed for another 1.5 h. The insoluble salt was removed by filtration and washed with ethanol. The solution was neutralized with aq hydrochloric acid and concentrated. The residue was dissolved in a mixed solvent of ethanol and ether and the insoluble salt was removed by filtration again. The solvent was concentrated to give the crude product of **3** (51.3 g, 84%). The crude product was distilled (190—200 °C/0.007 Torr) by using flash distillation apparatus to give **3** in a 48% yield. NMR (CDCl$_3$, δ): 2.75 (t, 8H), 3.00 (s, 2H), and 3.55—3.85 ppm (m, 16H). MS (*m/e*): 314 (M$^+$), 296, 283, 252, 149, 117, 105, 88, 75, and 45. IR (Neat): 3400 (s), 2920 (s), 1460 (m), 1355 (m), 1200 (m), and 1115 cm^{-1} (s).

1,7-Dithia-18-crown-6 (4) (1,4,7,13-tetraoxa-10,16-dithiacyclooctadecane). 1,7-Dithia-18-crown-6 was prepared according to the procedure mentioned above. The yields were determined by GLC using ethyl stearate as the internal standard. The NMR spectrum of **4** was coincident with that in the literature.[4]

6,9-Dioxa-3,12-dithiatetradecane-1,14-diol (5). Purified Yield: 37%. Bp 184—190 °C/0.03 Torr (Kugelrohr apparatus). NMR (CDCl$_3$, δ): 2.75 (t, 8H), 3.30 (s, 2H), and 3.60—3.85 ppm (m, 12H). MS (*m/e*): 252 (M$^+$ $-$H$_2$O), 149, 105, 87, 61, and 45. IR (Neat): 3400 (s), 2900 (s), 1640 (m), 1405 (m), 1350 (m), 1100 cm^{-1} (s).

Cyclization Reaction of 5. The cyclization reaction of **5** was carried out according to an analogous procedure. 1,4-Dithia-12-crown-4 (**7**) was detected by GLC, together with unreacted **5**, and isolated by preparative GLC. The analytical data of **7** were as follows: NMR (CDCl$_3$, δ): 2.73 (t, 4H), 2.88 (s, 4H), 3.68 (s, 4H), and 3.78 ppm (t, 4H). MS (*m/e*): 208 (M$^+$), 149, 120, 104, 86, 73, 61, and 45. IR (Neat): 2870 (s), 1650 (m), 1460 (m), 1350 (m), 1300 (m), and 1130 cm^{-1} (s). The NMR spectrum of this compound was coincident with that in the literature.[4]

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† 1 Torr≈133.322 Pa.