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A Facile One-pot Synthesis of Hydroxy-substituted Crown Ethers

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Hydroxy-substituted crown ethers were prepared in one-pot synthesis by treatment of oligoethylene glycols with epichlorohydrin in the presence of alkali metals, alkali metal hydride or alkali metal hydroxides. The stability constants of complexes with sodium and potassium cations in methanol were determined.

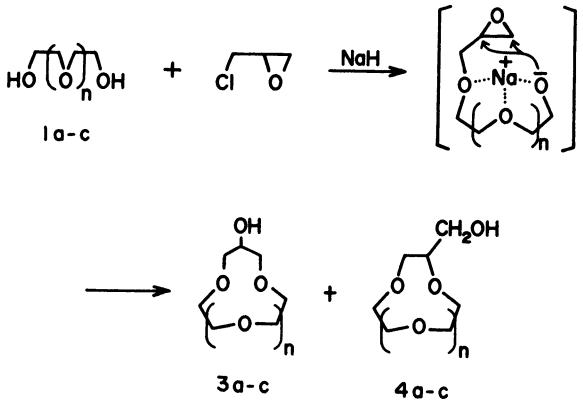
Crown compounds having a functional group are useful for designing phase transfer catalysts, ion-selective electrodes, ion carriers or polymer supported crown compounds. Hydroxy-functionalized derivatives have recently attracted attention as one of the most promising intermediates for these purposes, and various syntheses[1-9] and applications[10-14] have been reported.

We now describe a facile one-pot synthesis of hydroxy-substituted 13-, 16-, and 19-crown ethers using epichlorohydrin and oligoethylene glycols, which are industrially available inexpensive raw materials. Although one of these crown ethers has already been prepared by Tomoi *et al.*[4] *via* several steps starting from 3-chloro-2-chloromethyl-1-propene, the improvement in preparation procedure should enhance the usefulness of these unique functional compounds. Furthermore, some trials to synthesize hydroxy crown ethers using epichlorohydrin were reported,[1,2,8] but in these cases this material was restrictively used as a coupling agent for two phenolic hydroxyl groups in a multi-step synthesis.

Results and Discussion

The reaction of oligoethylene glycols (**1**) with epichlorohydrin in the presence of base may afford oligoethylene glycol monoglycidyl ethers (**2**), which may successively cyclize to the hydroxy-substituted crown ethers (**3**) and/or (**4**) by the intramolecular attack of the alkoxide anion to the epoxy ring, as shown in the Scheme.

In practice, the reaction product showed only one peak in the expected region of the gas chromatogram. In order to confirm their formation, the possible compounds **3** and **4** were synthesized by alternative methods. The authentic compound **3b** were prepared by the coupling reaction of 2-benzyloxy-1,3-propanediol[15] and tetraethylene glycol ditosylate, and **4a—c** by the reported method,[7] followed by debenzylation.



a, $n=2$ *b*, $n=3$ *c*, $n=4$

Scheme. Probable pathway of the reaction.

From GLC analysis, only **3b** was confirmed to be formed and **4b** could not be detected in the reaction product (Shimadzu GC-4CPT, Silicone OV-1 on Uniport KS 60—80 mesh, 1 m, started from 100 °C, 20 °C/min, retention time; **3b**, 4.5 min; **4b**, 4.8 min). The isolated product was characterized by spectral and elemental analyses. For the purpose of further confir-

Table 1. Spectra of hydroxy-substituted crown ethers and their acetates

Crown ether	IR ($\tilde{\nu}$/cm^{-1})	MS (*m/e*)	NMR (CCl_4, δ)
3a	1120, 3400	206(M^+), 188(M^+-H_2O), 163($M^+-C_2H_3O$)	2.75(s, 1H), 3.40—3.80(m, 17H)
5a (Acetate of **3a**)	1120, 1235, 1735	249(M^++1), 247(M^+-1), 188(M^+-CH_3COOH)	2.00(s, 3H), 3.60—3.80 (d+m, 16H), 4.96(quint, 1H)
3b	1120, 3400	250(M^+), 232(M^+-H_2O), 203($M^+-C_2H_3O$)	2.75(s, 1H), 3.40—3.80 (m, 21H)
5b (Acetate of **3b**)	1120, 1235, 1730	293(M^+-1), 232(M^+-CH_3COOH)	2.00(s, 3H), 3.50—3.80(d+m, 20H), 4.92 (quint, 1H)
3c	1120, 3400	294(M^+), 276(M^+-H_2O), 251($M^+-C_2H_3O$)	2.75(s, 1H), 3.40—3.80(m, 25H)
5c (Acetate of **3c**)	1120, 1235, 1730	337(M^++1), 335(M^+-1), 276(M^+-CH_3COOH)	2.00(s, 3H), 3.50—3.80(d+m, 24H), 4.96 (quint, 1H)

TABLE 2. THE REACTION CONDITIONS AND THE YIELDS OF **3**

Crown ether[a]	Base	(mol)	**1** (mol)	Ech[b] (mol)	Reaction temp/°C	Reaction time/h	Yield[d] %
3a	LiOH	0.10	0.02	0.02	Reflux[c]	20	40
	Li	0.04	0.024	0.02	Reflux[c]	20	23, 16[e]
3b	NaH	0.004	0.002	0.002	60	3	55, 31[e]
	NaOH	0.10	0.02	0.02	Reflux[c]	2	35
	Na	0.04	0.024	0.02	Reflux[c]	2	54
	Na	0.04	0.024	0.02	Reflux[c]	20	69
	K	0.04	0.024	0.02	Reflux[c]	2	14
3c	KOH	0.10	0.02	0.02	Reflux[c]	2	28
	K	0.0021	0.002	0.002	60	20	42[e,f]

a) Bp: **3a**; 115—120 °C/0.05 Torr, **3b**; 128—135 °C/0.02 Torr, 150 °C/0.05 Torr (Kugelrohr distillation), **3c**; 185 °C/0.04 Torr (Kugelrohr distillation). b) Epichlorohydrin. c) Dioxane was used as the solvent. d) Calculated by GLC. e) Isolated. f) KBF_4 (0.002 mol) was added in the reaction system.

mation, the product was acetylated by treatment with acetic anhydride in pyridine.

From the reactions between epichlorohydrin and tri- and pentaethylene glycol, hydroxy-13-crown-4 (**3a**, $n=2$), and hydroxy-19-crown-6 (**3c**, $n=4$) were obtained. No detectable amount of **4a** nor **4c** could be observed in any run by GLC (the same conditions as for **3b**, retention time; **3a**, 3.0 min; **4a**, 3.3 min; **3c**, 5.8 min; **4c**, 6.1 min). Spectral data of the products and their acetates are summarized in Table 1.

In the case of the reaction of tetraethylene glycol and epichlorohydrin, sodium hydroxide and metallic sodium also worked well to give the objective crown ether (**3b**), but metallic potassium gave it in a poorer yield. To obtain **3a** and **3c**, metallic lithium and potassium or their hydroxides were used and showed good yields. The reaction conditions and the yields are listed in Table 2.

The fractional distillation afforded the oligoethylene glycol-free **3**, but it is usually difficult to remove a small amount of contaminates, mainly oligoethylene glycols, from the objective compounds by Kugelrohr distillation, which is convenient in a small scale preparation. The compounds **3**, however, could be freed of the last traces of oligoethylene glycols by either of following methods: a) passing through an ion-exchange resin (metal form) column, or b) extracting from the aqueous solution with chloroform. In the case of hydroxy-16-crown-5 (**3b**), the pyrolysis of $MgBr_2$·complex also afforded the purified compound.

In order to verify the complexing property of **3**, the stability constants of the complexes with sodium and potassium cations in methanol were measured,[16] and are summarized in Table 3. The complexing ability of **3a** with both cations was too low to give reliable stability constant values. Compounds **3b** and **3c**, however, showed the good and rather selective complexing ability toward sodium and potassium cations.

TABLE 3. STABILITY CONSTANTS OF **3b** AND **3c** COMPLEXES

Crown ether	log K'[a]	
	Sodium cation	Potassium cation
3b	3.03 ± 0.01	2.53 ± 0.005
3c	2.62 ± 0.03	4.03 ± 0.03

a) Crown ether + $M^+ \overset{K'_1}{\rightleftharpoons}$ (Crown ether·M)$^+$ In methanol, 25 °C. Values with the standard deviation at the 95% confidence level.

Experimental

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

Preparation of Hydroxy-16-crown-5 (3b). As a typical procedure for the preparation of **3**: tetraethylene glycol (**1b**, $n=3$, 3.9 g, 0.002 mol) was added dropwise to a suspension of sodium hydride (50% oil suspension, 2.0 g, 0.004 mol, washed with dioxane by decantation) in dioxane (50 ml). After the evolution of hydrogen gas had ceased, epichlorohydrin (1.9 g, 0.002 mol) was added in one quantity and the mixture was stirred for 1 h during which time the temperature was carefully regulated not to exceed 40 °C. Then the mixture was heated to 60 °C and was stirred for an additional 3 h at this temperature. The reaction mixture was neutralized with hydrochloric acid (1 : 1 ethanol), filtered and washed with dichloromethane. The solvent was removed from the filtrate combined with washings and the resultant viscous material was washed with hexane to give 4.5 g of the crude product. The hydroxy-substituted crown ether (**3b**) was obtained as a pale yellow oil by distilling a portion of the crude product (2.72 g) on a Kugelrohr distillation apparatus. Yield, 0.95 g (31%, 55% by GLC analysis).

Purification of 3b by an Ion-exchange Resin Column. Amberlite CG-120 (Type 1, Na form, 30 g) was washed 3 times with a plenty of water, and then 3 times with acetone. A little contaminated distillate (0.5 g) of **3b** dissolved in acetone was charged into the column packed with this washed resin, and eluted with 200 ml of acetone. Evaporation of the solvent afforded 0.38 g of oligoethylene glycol-free **3b**, checked by GLC.

Preparation and Pyrolysis of $MgBr_2$·Complex of 3b. The acetone solution of **3b** contaminated with a small amount of **2b** was added to acetone saturated with $MgBr_2 \cdot 6H_2O$ under stirring. White precipitates which appeared immediately were collected by filtration, washed with acetone repeatedly, and dried under reduced pressure. The white solid was heated to 200 °C in a Kugelrohr distillation apparatus at

0.015 Torr (1 Torr=133.322 Pa) to release purified **3b**, which was checked to be free of **2b** by GLC.

Synthesis of Authentic 3b. Although the synthesis of **3b** was reported,[6] from the point of availability of the starting material, an alternative method was employed to obtain the authentic compound. The starting material 2-benzyloxy-1,3-propanediol (137—140 °C/0.004 Torr, Kugelrohr distillation) was obtained by hydrolysis of *cis*-5-benzyloxy-2-phenyl-1,3-dioxane (mp 79.0—80.0 °C), which was prepared by benzylation of *cis*-2-phenyl-1,3-dioxan-5-ol (mp 84.5—85.5 °C).[15] 2-Benzyloxy-1,3-propanediol (1.8 g, 0.01 mol) was added to *t*-butyl alcohol (30 ml) containing 0.02 mol of *t*-BuONa at 60 °C under stirring. To the resulting solution was added dropwise a solution of tetraethylene glycol ditosylate (5.0 g, 0.01 mol)[17] in *t*-butyl alcohol (20 ml), and the mixture was stirred for 2 h at 60 °C. After the removal of solid salt by filtration, the *t*-butyl alcohol was evaporated off under reduced pressure to leave a viscous oil (3.5 g). An aliquot of the oil (1.6 g) was fractionated by Kugelrohr distillation. The distillate of 150 °C/0.05 Torr (0.48 g, 31%) was hydrogenated with hydrogen gas in the presence of Pd/C and *p*-toluenesulfonic acid.[7] After the work-up, the viscous oil was fractionated by Kugelrohr distillation to give a pale yellow oil (0.23 g, bp 150 °C/0.1 Torr, Kugelrohr distillation). This fraction showed the same GLC retention time and spectral data as those of **3b** shown in Table 1.

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