The Synthesis and Cation-complexing Ability of Alkyl Crown Ethers

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Alkyl-15-crown-5 and alkyl-12-crown-4 were prepared *via* polyethylene glycol β-haloalkyl ethers in two steps from terminal olefins, and their complexing ability with cations of alkali and alkaline earth metals was measured by using ^{1}H NMR; it was found to be almost identified with that of the corresponding unsubstituted crown ether. A new type of alkyl crown ether with a chloro substituent could also be synthesized according to this method.

Synthetic macrocyclic polyethers have received attention in recent years, as phase-transfer catalysts in a variety of organic reactions because they possess the ability to form complexes with salts of the alkali and alkaline earth metals to raise the reactivity of the counter anion; they are also expected to be useful selective carriers for the transport of cations through a liquid membrane.[1,2]

Modifications of their solubilities in various organic solvents by introducing lipophilic groups into the macrocyclic ring seem to be desirable for these purposes. For substituted macrocyclic compounds, the balance between lipophilic and hydrophilic parts is supposed to be one of the important factors influencing their properties; this balance can easily be adjusted by changing the substituents and the ring size.

From this standpoint, alkyl-substituted crown ethers, cryptands, and cyclic tetraamines were synthesized *via* the multi-step reactions reported by Cinquini,[3,4] Lehn,[5] and Tundo[6] and found to show high catalytic activity in several two-phase reactions. On the other hand, alkyl-substituted cyclams were synthesized and successfully used as the extraction of heavy metal ions from an aqueous solution by Tabushi.[7]

In the course of our investigation, a convenient method of synthesizing these alkyl crown ethers *via* polyethylene glycol β-haloalkyl ethers was found and previously reported in a preliminary paper.[8]

In this paper, we will describe the preparation of alkyl-15-crown-5 and alkyl-12-crown-4 and their complexing ability with alkali and alkaline earth cations, as measured by means of the ^{1}H NMR method.

Experimental

The ^{1}H NMR spectra were taken at 100 MHz on a JEOL JNM-PS-100 spectrometer, using tetramethylsilane as the internal standard, except for the measurement of the complexing ability. The infrared spectra were obtained on a JASCO IR-E spectrometer. The mass spectra were measured with a Hitachi RMU-6E mass spectrometer at an ionization potential of 70 eV. The GLC analyses were done on a Shimadzu GC-3A using a 1 m×3 mm column packed with 10% Silicone SE-30 on 60—80 mesh Celite 545. The halogen contents of the polyethylene glycol β-haloalkyl ethers were measured according to the conventional method.[9]

Preparation of Polyethylene Glycol β-Haloalkyl Ether (1 or 2). To a stirred suspension of 136.0 g (0.7 mol) of tetraethylene glycol and 35.6 g (0.2 mol) of NBS we added, drop by drop, 18.5 g (0.22 mol) of 2-methyl-1-pentene over a 15-min period at 45—50 °C; the mixture was then stirred at that temperature for 2 h until the positive halogen had been consumed. The reaction mixture was cooled to room temperature and worked up adding water and then extracting with ether. The ether extracts were dried over anhydrous magnesium sulfate and concentrated to give 47.8 g (67%) of the crude product (**1h**). Some of the results are shown in Table 1.

Preparation of Alkyl-15-crown-5 (3); 2-Methyl-2-propyl-15-crown-5 (3h). To a stirred suspension of 4.7 g (0.11 mol) of sodium hydroxide in 174 ml of diglyme we added, drop by drop, 35.7 g (0.1 mol) of **1h** over a 3.5-h period at 120—125 °C; the mixture was then stirred at 110—140 °C for 7 h. The reaction was followed by GLC and continued until the starting material (**1h**) had been completely consumed. The resultant mixture was cooled to room temperature, and sodium bromide was removed by filtration. The filtrate was evaporated under reduced pressure to give 29.3 g of a brown viscous liquid. A portion of the crude product (9.6 g) was distilled to give 3.83 g (43%) of a colorless liquid. The product was further purified on a silica-gel column (hexane: acetone=10: 1) to afford the following analytical sample (**3h**): n_D^{20}, 1.4636; IR max (neat) 2980, 2880, 1465, 1360, 1297, 1200, and 1125 cm^{-1}; mass: 276 (M) and 233 (M−R); NMR (CCl$_4$) δ 0.90 (t, 3H), 1.06 (s, 3H), 1.38 (m, 4H), and 3.28—3.68 (m, 18H). Found: C, 60.88; H, 10.27%. Calcd for $C_{14}H_{28}O_5$: C, 60.84; H, 10.21%.

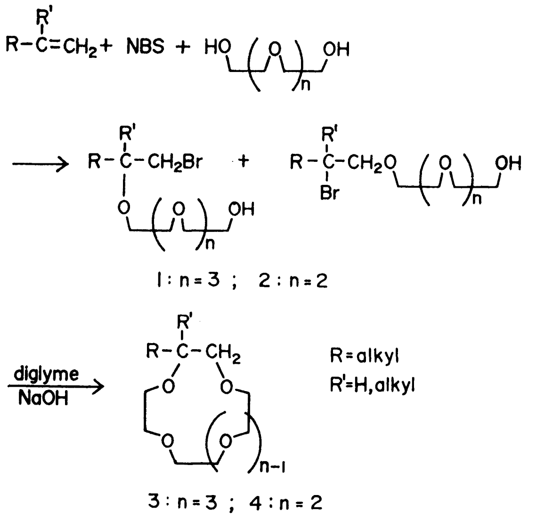
Preparation of Alkyl-12-crown-4 (4); 2-Methyl-2-propyl-12-crown-4 (4d). A suspended mixture of 20.0 g (0.064 mol) of **2d** and 5.92 g (0.14 mol) of sodium hydroxide in 165 ml of diglyme was stirred at 130—145 °C for 19 h until the starting material (**2d**) had been completely consumed. A brown viscous liquid (14.2 g) was then obtained according to the procedure mentioned above. A portion of the crude product (9.0 g) was distilled to give 1.93 g (21%) of **4d** as a colorless liquid. All the spectroscopic analytical results shown in Table 4 support the expected structure.

Preparation of Crown Ether Containing a Chloro Substituent; 2-Chloromethyl-2-methyl-15-crown-5 (3i). To a stirred suspension of 3.0 g (0.07 mol) of sodium hydroxide in 100 ml of diglyme we added, drop by drop, 18.2 g (0.05 mol) of **1i** in 25 ml of diglyme over a 4.5-h period at 80—125 °C, and then the mixture was stirred for 6 h at 110—120 °C. A purification procedure similar to that described above afforded the following analytical sample (**3i**): IR max (neat) 2900, 2850, 1455, 1350, 1250, 1100, 930, 770, and 730 cm^{-1}; mass: 233 (M−R); NMR (CCl$_4$) δ 1.18 (s, 3H) and 3.40—3.76 (m, 20H). Found: C, 51.90; H, 8.44; Cl,[9] 12.1%. Calcd for $C_{12}H_{23}O_5Cl$: C, 50.97; H, 8.20; Cl, 12.5%.

Measurement of Complexing Ability Using ^{1}H NMR. The ^{1}H NMR were measured as a 1% solution of crown ether in acetone-d_6, with 8% dioxane in benzene used as an external standard. The chemical shift of ^{1}H NMR signals of the main oxyethylene protons in the crown ether was compared with that in a sample containing an equimolar amount of the metal salt (thiocyanate).[10] The difference in the chemical shifts of these two samples was regarded as the downfield shift, based on the formation of the complex. The results are summarized in Tables 5 and 6.

Results and Discussion

Preparation of Alkyl-substituted Crown Ethers via *Polyethylene Glycol β-Haloalkyl Ethers.* The overall reaction process is shown in Scheme 1.



Scheme 1.

The polyethylene glycol β-haloalkyl ether was prepared by adding 1-alkene to a suspension of polyethylene glycol and a halogenating agent (NBS or NBA) and was then converted to the alkyl-substituted crown ether by heating with sodium hydroxide in diglyme. The β-haloalkyl ethers were obtained as a mixture of two isomers (Markownikoff and *anti*-Markownikoff adducts of the terminal olefins[11,12]). However the two isomers afford only one type of alkyl-substituted crown ether after a cyclization reaction.

Table 1 shows the halogenating agents used, the yields, and the halogen contents of the products in the preparation of polyethylene glycol β-haloalkyl ethers. Although the intermediate haloethers (**1** or **2**) were cyclized to crown ethers without further purification,[13] the halogen contents of the crude products coincided well with the calculated values.

TABLE 1. SYNTHESIS OF POLYETHYLENE GLYCOL β-HALOALKYL ETHERS

Compd	R	R′	*n*	Halogenating agent	Yield %	Found (Calcd) Halogen(%)
1a	n-C_4H_9	H	3	NBA	62	22.3 (22.4)
1b	n-C_6H_{13}	H	3	NBS	85	21.0 (20.7)
1c	n-C_8H_{17}	H	3	NBS	77	21.6 (19.3)
1d	n-$C_{10}H_{21}$	H	3	NBA	74	22.7 (18.1)
1e	n-$C_{12}H_{25}$	H	3	NBS	84	17.5 (17.0)
1f	CH_3	CH_3	3	NBS	36	25.1 (24.3)
1g	C_2H_5	CH_3	3	NBS	76	22.4 (23.3)
1h	n-C_3H_7	CH_3	3	NBS	67	23.0 (22.4)
1i	CH_2Cl	CH_3	3	NBS	77	30.5 (31.7)
1j	C_2H_5	C_2H_5	3	NBS	74	22.7 (22.4)
2a	C_2H_5	H	2	NBS	24	25.6 (25.5)
2b	CH_3	CH_3	2	NBS	38	28.2 (28.0)
2c	C_2H_5	CH_3	2	NBS	76	24.9 (26.7)
2d	n-C_3H_7	CH_3	2	NBS	65	25.6 (25.5)
2e	CH_2Cl	CH_3	2	NBS	73	35.7 (36.3)

The results of the cyclization to alkyl-15-crown-5 are shown in Table 2, while the analytical data are shown in Table 3. A reaction temperature above 100 °C was found to be optimal for the cyclization without any undesirable formation of olefins. The use of a high-dilution technique with a varied dropping rate of polyethylene glycol β-haloalkyl ether did not improve the yield appreciably. Dioxane had been used as the solvent in the preparation of alkyl-15-crown-5 in the previous paper,[8] but diglyme was preferable to dioxane from the viewpoint of making it possible to adopt higher reaction temperatures.

The yield of alkyl-12-crown-4 (**4**) was lower than that of the corresponding alkyl-15-crown-5 (**3**) in spite of the severer reaction conditions, as is shown in Tables 2 and 4; this finding suggests that the sodium cation did not function effectively as the template ion in the formation of the former.[14]

A new type of crown ether (**3i** and **4e**) with a chloro substituent, which is potentially useful for the preparation of variously functionalized crown ethers, could also be synthesized according to this method. Although the intermediate product (**1i** or **2e**) possesses two different halogen atoms, the results of the NMR and elementary analyses showed that the chlorine atom was preferentially conserved in the final product (**3i** or **4e**) after the cyclization reaction (Scheme 2).

TABLE 2. SYNTHESIS OF ALKYL-15-CROWN-5 (**3**)

Compd	R	R′	Solvent	LiCl/**1**[a]	Reaction temp/°C	Time/h	Yield/%[b]
3a	n-C_4H_9	H	Dioxane	2.0	reflux	30	12
3b	n-C_6H_{13}	H	Diglyme	1.7	80—100	18	35
3c	n-C_8H_{17}	H	Dioxane	—	25—80	53	6
3d	n-$C_{10}H_{21}$	H	Diglyme	3.0	90—120	27	30
3e	n-$C_{12}H_{25}$	H	Diglyme	1.2	90—120	27	36
3f	CH_3	CH_3	Diglyme	—	80—125	6	38
3g	C_2H_5	CH_3	Diglyme	—	105—130	9	39
3h	C_3H_7	CH_3	Diglyme	—	110—140	7	43
3i	CH_2Cl	CH_3	Diglyme	—	110—120	6	25
3j	C_2H_5	C_2H_5	Diglyme	—	105—140	12	22

a) mol/mol. b) After purification.

TABLE 3. ANALYSIS OF ALKYL-15-CROWN-5 (**3**)

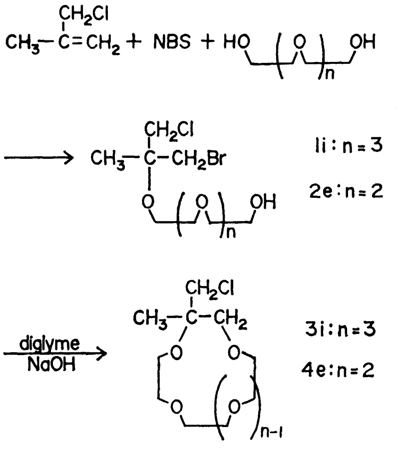
Compd	MS	NMR (CCl_4, δ)	Bp (°C/Torr)
3a	276 (M) 219 (M−R)	0.90 (t, 3H), 1.34 (s, 6H) 3.22—3.72 (m, 19H)	—[a]
3b	304 (M) 219 (M−R)	0.90 (t, 3H), 1.32 (s, 10H) 3.16—3.76 (m, 19H)	—[a]
3c	332 (M) 219 (M−R)	0.88 (t, 3H), 1.26 (s, 14H) 3.24—3.70 (m, 19H)	—[a]
3d	360 (M) 219 (M−R)	0.88 (t, 3H), 1.26 (s, 18H) 3.26—3.70 (m, 19H)	—[a]
3e	388 (M) 219 (M−R)	0.88 (t, 3H), 1.26 (s, 22H) 3.30—3.70 (m, 19H)	—[a]
3f	248 (M) 233 (M−R)	1.12 (s, 6H) 3.28—3.68 (m, 18H)	89—91/0.05
3g	262 (M) 233 (M−R)	0.83 (t, 3H), 1.04 (s, 3H) 1.46 (m, 2H), 3.28—3.68 (m, 18H)	98—100/0.04
3h	276 (M) 233 (M−R)	0.90 (t, 3H), 1.06 (s, 3H) 1.38 (m, 4H), 3.28—3.68 (m, 18H)	103—105/0.10
3i	233 (M−R)	1.18 (s, 3H) 3.40—3.76 (m, 20H)	—[a]
3j	276 (M) 247 (M−R)	0.81 (t, 6H), 1.48 (q, 4H) 3.32—3.72 (m, 18H)	108—110/0.05

a) Purified on a silica-gel column.

TABLE 4. SYNTHESIS AND ANALYSIS OF ALKYL-12-CROWN-4 (**4**)

Compd	R	R′	Reaction temp/°C	Time/h	Yield/%[b]	MS	NMR (CCl_4, δ)	Bp (°C/Torr)
4a	C_2H_5	H	100—110	24	15	204 (M) 175 (M−R)	0.91 (t, 3H), 1.38 (m, 2H) 3.27—3.70 (m, 15 H)	—[a]
4b	CH_3	CH_3	120—140	11	12	204 (M) 189 (M−R)	1.06 (s, 6H) 3.20—3.72 (m, 14H)	64/0.09
4c	C_2H_5	CH_3	120—140	14	23	218 (M) 189 (M−R)	0.84 (t, 3H), 1.04 (s, 3H) 1.45 (m, 2H), 3.24—3.72 (m, 14H)	63/0.06
4d	*n*-C_3H_7	CH_3	130—145	19	21	232 (M) 189 (M−R)	0.90 (t, 3H), 1.04 (s, 3H) 1.38 (m, 4H), 3.20—3.80 (m, 14H)	71/0.09
4e	CH_2Cl	CH_3	100—110	7	14	189 (M−R)	1.16 (s, 3H) 3.32—3.76 (m, 16H)	—[a]

a) Purified on a silica-gel column. b) After purification.



Scheme 2.

Complexing Ability of Alkyl-substituted Crown Ethers. The lipophilicity of crown ethers may be supposed to be important, together with their complexing properties, when they are used as phase-transfer catalysts, as is the case with quaternary ammonium salts, which were discussed recently.[15] The lipophilicity of alkyl crown ethers can be controlled by changing the number or the chain length of the alkyl group. However, the introduction of the alkyl group into the crown ether rings may cause a decrease in their complexing ability toward the metal cations because of the steric effect or the loss of symmetry.[16]

Therefore, we investigated the complexing ability of some of the alkyl crown ethers prepared in this study and compared it with that of the unsubstituted crown ethers. The ^1H NMR spectrum of each alkyl crown

TABLE 5. DOWNFIELD SHIFT IN 100 MHz NMR OF ALKYL-15-CROWN-5 CAUSED BY MSCN (Hz)

Cation	Compd									
	3[a]	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3f**
Na^+	13.9	13.1	13.7	14.7	13.5	13.9	10.6	13.9	13.8	12.6
K^+	11.2	12.3	12.3	12.8	13.0	12.1	10.1	11.1	11.9	10.9

a) Unsubstituted 15-crown-5.

ether as a 1% solution in acetone-d_6 was measured, with or without an equimolar amount of the metal salt. An 8% solution of dioxane in benzene was used as the external standard.

The influence of the change in the alkyl group in alkyl-15-crown-5 (Table 5) and alkyl-12-crown-4 (Table 6) on the complexing ability toward sodium and potassium cations was found to be almost the same as that of the corresponding unsubstituted crown ether. This finding suggests that it is possible to adjust the lipophilic/hydrophilic balance of crown ethers without changing the complexing ability toward alkali metal cations. In other words, there is possibility of designing a suitable crown compound for a specified purpose without imparing their complexing ability and selectivity.

TABLE 6. DOWNFIELD SHIFT IN 100 MHz NMR OF ALKYL-12-CROWN-4 CAUSED BY MSCN OR $M(SCN)_2$ (Hz)

Cation	Compd			
	4[a)]	**4b**	**4c**	**4d**
Na^+	15.6	13.2	15.8	14.7
K^+	10.6	8.2	9.7	9.2
Mg^{2+}	2.2	0.8	2.2	3.3
Ca^{2+}	—[b)]	20.2	24.5	20.1

a) Unsubstituted 12-crown-4. b) Precipitation of insoluble salts.

Table 6 also demonstrates the complexing ability of alkyl and unsubstituted 12-crown-4 for magnesium and calcium cations. The complexing ability of unsubstituted 12-crown-4 for the calcium cation could not be measured because of the formation of an insoluble complex in the acetone-d_6 solution.[17)] About a 20 Hz downfield shift was observed in the combination of 12-crown-4 and the calcium cation, but in the case of the magnesium cation the shift was little. The selectivity of alkyl-12-crown-4 for magnesium and calcium cations was similar to that of unsubstituted 12-crown-4.

Consequently, the complexing ability and the selectivity of alkyl-15-crown-5 and alkyl-12-crown-4 for alkali and alkaline earth metal cations were found to be almost equal to those of the corresponding unsubstituted one, and the raise in the lipophilicity of crown ethers can be expected to bring about a favorable result when crown ether is used as a phase-transfer catalyst or a selective carrier for the transport of cations.

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