Synthesis of Polyethylene Glycol β-Haloalkyl Ethers. A New Synthetic Route to Alkyl-Substituted Crown Ethers.

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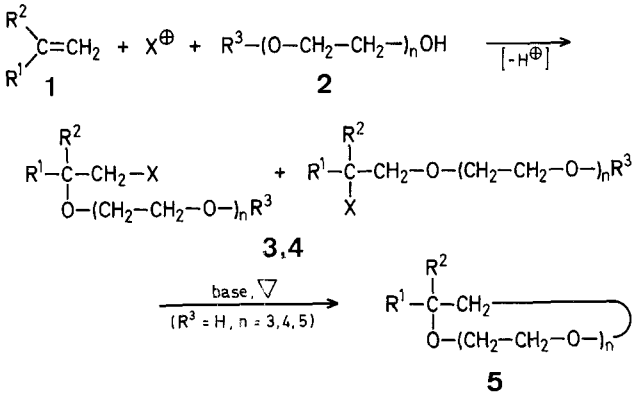
The syntheses and applications of macrocyclic polyethers and related macroheterocycles have been a subject of increasing interest in recent years[1,2,3]. Especially, alkyl-substituted crown ethers[4] and cryptands[5] were recently synthesized and found to be effective as phase-transfer catalysts in the anion-promoted two phase reactions[4].

We wish to describe the preparation of polyethylene glycol β-haloalkyl ethers **3** by the coupled addition of halogen cation and polyethylene glycol **2** to olefins **1**[6,7,8], and their conversion to the alkyl-substituted crown ethers **5**.



3 (isomeric mixture): R^1 = alkyl, aryl; R^2 = H, CH_3; R^3 = H; X = Cl; n = 2, 3, 4, 5

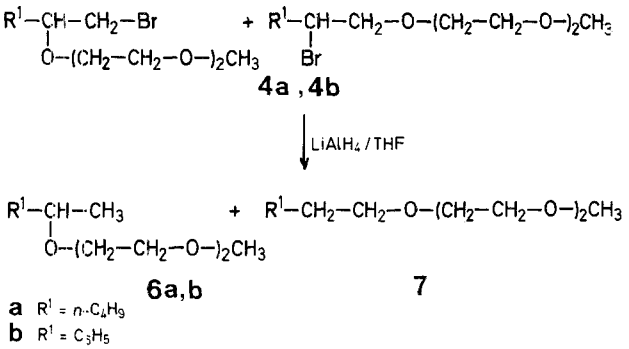
4 (isomeric mixture): R^1 = alkyl, aryl; R^2 = H, CH_3; X = Br; n = 2

5: R^1 = alkyl, aryl; R^2 = H, CH_3; n = 3, 4, 5

Olefins were added dropwise to (or passed through) a mixture of halogenating agent (NBS, NBA, or NCS) and polyethylene glycol at 40–50° until the positive halogen was consumed. The addition products **3** and **4** were obtained in fair yields as shown in Table 1. No marked difference between *N*-bromosuccinimide and *N*-bromoacetamide (NBS and NBA) in reactivity and yields of adducts was observed, while a relatively lower reactivity was observed in the reaction of *N*-chlorosuccinimide (NCS).

The β-haloalkyl ethers obtained by haloalkoxylation of 1-alkene are known as mostly the isomeric mixtures of Markownikoff (M) and anti-Markownikoff (AM) addition products[6,7,9] and the former (M) may be more preferable to the latter (AM) for the synthesis of crown ethers. To determine the composition of the isomeric mixtures, the compounds **4a, b** prepared by the reaction of diethylene glycol monomethyl ether with 1-hexene or styrene in the presence of NBS were reduced by with lithium tetrahydroaluminate respectively and the reduction products were analyzed by G.L.C.

In the chromatogram (Silicone gum SE-30) of the reduction product of **4a**, two peaks were observed and each component was separated in pure form by preparative G.L.C. The



a R^1 = n-C_4H_9
b R^1 = C_3H_5

compound of shorter retention time (87%) was identified as **6a** and the other compound (13%) was identified as **7a**. Accordingly, the isomer ratio (M/AM) of original product **4a** was found to be nearly five to one and this result agreed well with that reported by Jovtscheff in haloformyloxylation of 1-alkenes[10].

On the other hand, the reduction product of **4b** showed only one peak in G.L.C. and this was identified as **6b** by M.S. ($M^+ - CH_3$ fragment peak) and ^{1}H-N.M.R. [δ = 1.34 ppm (d, 3H)].

The alkali metal salts of β-haloalkyl polyethylene glycol ethers are "self-solvating bases"[11] and are expected to be converted to the alkyl-substituted crown ethers by intramolecular substitution under the proper reaction conditions.

Thus, compounds **3g** and **3j** were treated with sodium hydroxide in dioxan[12,13], respectively and the corresponding alkyl-substituted 15-crown-5 ethers **5g** and **5j** (n = 4) were obtained in ~30% yields. This method may be more convenient than the reported procedure[4] because the crown ethers are prepared in two steps from readily accessible materials. The preparation of other crown ethers is in progress.

Preparation of Polyethylene Glycol β-Haloalkyl Ethers 3 and 4; General Procedure:

1-Hexene (0.22 mol) is added dropwise with stirring to a mixture of *N*-bromosuccimide (0.2 mol) and tetraethylene glycol (0.8 mol) at 40–50° and the reaction is continued until the positive bromine completely disappeared (~3 h). [When gaseous olefin is used, it is passed through the mixture of NBS and polyethylene glycol with vigorous stirring at 40–50°]. The reaction product is extracted with ether, the combined extracts are washed with water, dried over anhydrous magnesium sulfate, and a yellow liquid is obtained after evaporating the solvent in vacuo.

β-Haloalkyl ethers with C_8–C_{12} alkyl chains are surface active and, in some cases, a stable emulsion is formed when the ether extract is washed with water. However, the problem can be avoided by extracting the aqueous hot solution of the crude reaction products with xylene.

The crude products are analyzed by G.L.C. with various columns such as Silicone SE-30, Apiezon grease L, Ucon Oils, or Carbowax 20 M, but only one large peak which is determined to be the isomeric mixture (**3** or **4**) and a few preceding small peaks of impurities are observed. The β-haloalkyl ethers with lower alkyl groups or shorter polyoxyethylene chains could be purified by distillation under reduced pressure. The results of the syntheses are shown in Table 1 and the spectral data of purified products (isomeric mixture) are summarized in Table 2.

Reduction of Diethylene Glycol β-Haloalkyl Methyl Ethers 4 (R^3 = CH_3) with Lithium Tetrahydroaluminate:

A tetrahydrofuran solution of **4a** (3.0 g, 0.016 mol/15 ml) is added to a suspension of lithium tetrahydroaluminate in tetrahyd-

Table 1. Synthesis of Polyethylene Glycol β-Haloalkyl Ethers **3** and **4**

Product	Olefin **1** R^1	R^2	Glycol **2** R^3	n	Halogenating Agent	Yield [%]	b.p./torr	Bromine analysis [%] (Calc.)
3a	C_2H_5	H	H	3	NBS	24	113–114°/0.06	28.3 (28.0)
3b	C_2H_5	H	H	4	NBS	44[a]	131–133°/0.16	24.5 (24.3)
3c	CH_3	CH_3	H	3	NBS	38	125–126°/0.08	28.2 (28.0)
3d	CH_3	CH_3	H	4	NBS	36[a]	143–144°/0.04	25.1 (24.3)
3e	C_4H_9	H	H	2	NBA	51	103–105°/0.07	29.8 (29.7)
3f	C_4H_9	H	H	3	NBS	62[a]	144–146°/1.7	25.6 (25.5)
3g	C_4H_9	H	H	4	NBA	62[a]	155–158°/0.3	22.3 (22.4)
3h	C_3H_7	CH_3	H	4	NBS	67[a,b]	–[c]	23.0 (22.4)
3i	C_6H_{13}	H	H	3	NBS	37	145–147°/0.09	24.6 (23.4)
3j	C_6H_{13}	H	H	4	NBS	85[a,b]	–[c]	21.0 (20.7)
3k	C_6H_{13}	H	H	5	NBS	67[a,b]	–[c]	20.8 (18.6)
3m	C_8H_{17}	H	H	4	NBS	77[a,b]	–[c]	21.6 (19.3)
3n	$C_{10}H_{21}$	H	H	4	NBA	74[a,b]	–[c]	22.7 (18.1)
3p	$C_{12}H_{25}$	H	H	4	NBS	84[a,b]	–[c]	17.5 (17.0)
3q	C_6H_5	H	H	2	NCS	40	153–155°/0.8	27.4 (27.6)[d]
3r	C_6H_5	H	H	4	NBS	71[a,b]	–[c]	22.6 (21.2)
3s	C_6H_5	CH_3	H	2	NBS	87[a,b]	–[c]	26.2 (26.4)
4a	C_4H_9	H	CH_3	2	NBS	54	83–85°/0.15	27.8 (28.2)
4b	C_6H_5	H	CH_3	2	NBS	34	151–154°/1.0	26.9 (26.4)

[a] Crude yields.
[b] Presence of small amount of dibromoalkane, bromohydrin and an unknown carbonyl compound was shown by G.L.C.
[c] Could not be distilled because of decomposition.
[d] Chlorine analysis.

Table 2. Polyethylene Glycol β-Haloalkyl Ethers

Product	Molecular formula	M.S. (*m/e*)[a]	I.R. (neat)[b] ν_{max} [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
3a	$C_{10}H_{21}BrO_4$ (285.16)	244*, 253, 209*, 191, 178*, 135*, 133, 119, 89, 55, 45	3430; 1060–1140	0.86–1.13 (two t, 3H); 1.25–2.20 (m, 2H); 3.26–3.40 (s+m, 3H); 3.40–3.67 (m, 14H)
3b	$C_{12}H_{25}BrO_5$ (329.23)	253*, 239*, 235, 135*, 89, 55, 45	3420; 1060–1150	0.86–1.13 (two t, 3H); 1.24–2.20 (m, 2H); 3.15–3.40 (s+m, 3H); 3.40–4.10 (m, 17H)
3c	$C_{10}H_{21}BrO_4$ (285.16)	222*, 191, 178*, 135*, 133 119, 89, 55, 45	3400; 1060–1140	1.28 (s, 6H); 3.32 (s+s, 3H); 3.40–3.65 (m, 12H)
3d	$C_{12}H_{25}BrO_5$ (329.23)	277*, 267*, 177, 135*, 119, 89, 55, 45	3400; 1060–1140	1.30 (s, 6H); 3.11 (s, 1H); 3.34 (s, 2H); 3.45–3.70 (m, 15.7H)
3e	$C_{10}H_{21}BrO_3$ (269.18)	193*, 185, 158, 101, 89, 87, 83, 58, 55, 45	3400; 1060–1140	0.91 (t, 3H); 1.18–1.95 (m, 6H); 3.06 (s, 1H); 3.20–4.15 (m, 11.1H)
3f	$C_{12}H_{25}BrO_4$ (313.22)	281*, 255*, 237*, 219, 163*, 133, 119, 107*, 99, 83, 55, 45	3420; 1060–1140	0.96 (t, 3H); 1.40 (m, 6H); 2.96 (s, 1H); 3.30–4.00 (m, 15H)
3g	$C_{14}H_{29}BrO_5$ (357.29)	313*, 299*, 263, 177, 163*, 133, 89, 83, 55, 45	3420; 1060–1140	0.92 (t, 3H); 1.36 (m, 6H); 3.06 (s, 1H); 3.20–3.70 (m, 19H)
3q	$C_{12}H_{17}BrO_3$ (289.17)	257*, 195, 183*, 165, 104, 89, 88, 78, 79, 45	3420; 1495; 1060–1140; 760; 700	3.40 (s, 1H); 3.48–3.80 (m, 10H); 4.51 (t, 1H); 7.27 (s, 4.9H)
4a	$C_{11}H_{23}BrO_3$ (283.21)	237*, 225*, 189, 163*, 113, 103, 83, 59, 58, 55, 45	1105	0.95 (t, 3H); 1.18–1.80 (m, 6H); 3.20–4.10 (s+m, 14H)
4b	$C_{13}H_{19}BrO_3$ (303.20)	223*, 209, 183*, 163, 149, 104, 103, 78, 77, 59, 45	3030; 1495; 1100; 755; 700	3.22 (s, 3H); 3.41 (s, 2H); 3.50–3.70 (m, 8.2H); 4.53 (d, d, 1H); 7.28 (s, 4.8H)

[a] The main and the characteristic fragment ion peaks were recorded. The asterisked peaks are accompanied by an isotope peak.
[b] The characteristic absorptions were recorded.

rofuran (0.8 g, 0.0212 mol/100 ml) and the reaction is continued at 40–60° for 10h until **4a** can no longer be detected by G.L.C. analysis. By the usual work-up procedures[14], an almost colorless liquid is obtained; yield: 2.1 g (97%). In the G.L.C. (Silicone gum-SE-30, 10% on Celite 545, with FID) of the reduction products, two peaks (i and ii, area ratio, 83:17) are observed and the components are separated by preparative G.L.C.

(i) **6a**: M.S.: *m/e*=204 (M^+), 189 (M^+-CH_3), 147, 103, 85, 84, 59, 45, 43.

I.R. (neat): ν_{max}=2890; 2840; 1460; 1375; 1195; 1090–1140 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ=0.90 (t, 3H); 1.08 (d, 3.1H); 1.32 (m, 6.2H); 3.27–3.60 ppm (s+m, 11.6H).

(ii) **7a**: M.S.: *m/e*=204 (M^+), 159, 145, 133, 113, 89, 85, 82, 59, 45, 43.

I.R. (neat): ν_{max}=2890; 2850; 1465; 1355; 1195; 1090–1140 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ=0.91 (t, 3H); 1.20–1.72 (m, 8H); 3.28–3.60 ppm (s+m, 13.0H).

Reduction of **4b** with lithium tetrahydroaluminate in a similar procedure affords a colorless liquid identified as **6b**; yield: 92%.

6b: M.S.: $m/e = 224$ (M^+), 209 ($M^+ - CH_3$), 121, 105, 89, 77, 59.

I.R. (neat): $\nu_{max} = 2900$; 1600; 1490; 1460; 1380; 1103; 760; 698 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 1.34$ (d, 3H); 3.28 (s, 3.0H); 3.30–3.60 (m, 8.1H); 4.36 (q, 0.9H); 7.28 ppm (s, 5.0H).

Preparation of Alkyl-Substituted 15-Crown-5 Ethers 5 (n = 4):

Compound **3g** (35.7 g, 0.1 mol) is dissolved in dioxan (120 ml) and the solution is added to a suspension of powdered sodium hydroxide (5.0 g) in dioxan (100 ml) at room temperature. The mixture is stirred for 10 h at 80° and for further 8 h at 100°. After sodium bromide has been filtered off, the dioxan is removed from the filtrate to leave a yellow liquid; yield: 24.4 g. The product is distilled in vacuo and the fractions of b.p. 120–125°/0.2 torr are collected; yield: 8.8 g (32%). Further purification on a column (Silica gel, hexane/acetone, 5:1) affords pure 2-butyl-15-crown-5 (**5g**, $R^1 = C_4H_9$, $R^2 = H$, $n = 4$) as a colorless liquid; $n_D^{20} = 1.4635$.

$C_{14}H_{28}O_5$	calc.	C 60.84	H 10.21
(276.3)	found	60.56	10.10

M.S.: $m/e = 276$ (M^+), 219, 133, 89, 87, 73, 59, 45; relative intensities: 0.5, 3, 21, 63, 45, 40, 68, 100%, respectively.

I.R. (neat): $\nu_{max} = 2910$; 2830; 1470; 1350; 1295; 1130; 985; 940; 850 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 0.90$ (t, 3H); 1.34 (m, 6H); 3.24–3.72 ppm (multiplets, 19H).

By a similar procedure, 2-hexyl-15-crown-5 (**5j**, $R^1 = C_6H_{13}$, $R^2 = H$, $n = 4$) is obtained from **3j** as a colorless liquid; crude yield: 29%; b.p. 130–134°/0.1 torr; $n_D^{20} = 1.4620$.

$C_{16}H_{32}O_5$	calc.	C 63.12	H 10.60
(304.4)	found	62.72	10.68

M.S.: $m/e = 304$ (M^+), 219, 133, 89, 87, 73, 59, 45; relative intensities: 0.5, 5, 18, 60, 38, 32, 60, 100%, respectively.

I.R. (neat): $\nu_{max} = 2910$, 2830, 1470, 1350, 1295, 1130, 980, 940, 850 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 0.90$ (t, 3.1H), 1.32 (m, 9.8H), 3.16–3.72 ppm (multiplets, 19H).

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