

The Synthesis of Unsubstituted Crown Ethers by the Reaction of Oligoethylene Glycols with Arenesulfonyl or Alkanesulfonyl Chlorides

Ping-Lin KUO, Norio KAWAMURA, Masaki MIKI, and Mitsuo OKAHARA*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka 565

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A new facile method of synthesizing crown ethers from oligoethylene glycols by treating them with arenesulfonyl or alkanesulfonyl chlorides in the presence of alkali metal hydroxide or alkoxide was described. 15-Crown-5 and 21-crown-7 were synthesized from pentaethylene glycol and heptaethylene glycol respectively in good yields, while 18-crown-6 was obtained from both hexaethylene glycol and triethylene glycol. Although the main product was 24-crown-8 in the reaction of tetraethylene glycol/TsCl/Na(K)OH in dioxane, 12-crown-4 was obtained in a moderate yield from the reaction of tetraethylene glycol/benzenesulfonyl chloride/*t*-BuOLi in *t*-BuOH. Furthermore, the analogous treatment of PEG 200 afforded a mixture of 15-, 18-, 21-, and 24-crown ethers. The reaction conditions were investigated, and the scope of the reaction was discussed.

One feature of the remarkable recent developments in the field of macrocyclic compounds has been the publication of numerous reports during the past ten years.^{1,2)}

The various methods proposed for the synthesis of crown compounds may be classified into two categories: 1) A modified Williamson ether synthesis by means of a reaction between oligoethylene glycols or aromatic dihydroxy compounds, and oligoethylene glycol dichlorides or ditosylates, in the presence of alkali, which has the appropriate template atom,³⁻⁷⁾ and 2) a Lewis acid-catalyzed cyclo-oligomerization of ethylene oxide using special metal salts.^{8,9)}

Although the former method has been widely adopted for the synthesis of crown compounds, the intramolecular cyclization of a polyoxyethylene compound with a hydroxyl group at one end and a leaving group at the other end, which corresponds to the intermediate in the former method, may be a more convenient way to get crown compounds.¹⁰⁾

In view of this, an attempt was undertaken in our laboratory to get such compounds,¹¹⁾ and we have recently reported a new method of obtaining a variety of crown compounds through the *in situ* formation of such precursors.^{12,13)}

The detailed results of the synthesis of unsubstituted crown ethers from oligoethylene glycols by treatment with arenesulfonyl or alkanesulfonyl chlorides in the presence of alkali metal hydroxide will be described in this paper.

Experimental

The IR and ¹H NMR spectra were recorded on a JASCO IR-E spectrophotometer and a JEOL JMN-PS-100 spectrometer respectively. The GLC analyses were performed on a Shimadzu gas chromatograph GC-3BF, equipped with a flame-ionization detector.

Oligoethylene Glycols. The penta-, hexa-, and heptaethylene glycols were each purely separated from a polyethylene glycol mixture with an average molecular weight of 250 by distillation at a reduced pressure. The di-, tri-, and tetraethylene glycols were commercial products and were used without purification.

Synthesis of 15-Crown-5 (IIc) from Pentaethylene Glycol.

Pentaethylene glycol (4.8 g, 0.02 mol) and *p*-toluenesulfonyl chloride (4.0 g, 0.02 mol) were dissolved in 30 ml of monoglyme, after which the solution was slowly added, drop by drop, into a suspension of powdered sodium hydroxide (6.0 g, 0.15 mol) in 30 ml of monoglyme over a period of 2 h at room temperature. After the addition was complete, the reaction was continued for one more hour, and the reaction product was filtered. The precipitate was washed with dichloromethane, and then the solvent was removed from the combined solution of filtrate and washings to leave the 15-crown-5 complex as an almost colorless liquid. It was found by GLC to consist 61% of 15-crown-5 (10% Carbowax 20 M or Silicone DC 550 on Celite 545, 220 °C, carrier gas N₂). When a part of the complexes (3.6 g) was thermolyzed using Kugelrohr distillation apparatus, free 15-crown-5 (IIc, 1.7 g, 50%) was obtained as a viscous liquid. NMR (CCl₄, δ): 3.53 s, MS (*m/e*): 220 (M⁺).

Small-scale experiments for the investigation of the reaction conditions were carried out using 1.0 g (4.2 mmol) glycol in 60 ml of a solvent in manner similar to that described above.

Synthesis of 18-Crown-6 (IIId) from Hexaethylene Glycol.

Hexaethylene glycol (3.0 g, 0.011 mol) and *p*-toluenesulfonyl chloride (2.0 g, 0.011 mol) were dissolved in 40 ml of dioxane, after which the solution was added, drop by drop, into a suspension of powdered potassium hydroxide (2.4 g, in 40 ml dioxane) at 40 °C. The white solid (4.8 g) thus obtained was found to contain 2.68 g (92%) of 18-crown-6 (IIId) and no unreacted glycol by GLC. When a part of the crude product (3.5 g) was thermolyzed by means of a Kugelrohr apparatus at reduced pressure, IIId (1.6 g, 75%) was isolated in a pure state. MS (*m/e*): 264 (M⁺), NMR (CCl₄, δ): 3.50 s.

Synthesis of 21-Crown-7 (IIe) from Heptaethylene Glycol.

Heptaethylene glycol (3.0 g, 9.2 mmol) was treated with *p*-toluenesulfonyl chloride (1.75 g, 9.2 mmol) in 80 ml of dioxane in a manner similar to that described above at 50 °C. The crude complex (3.3 g) was extracted by the use of hexane in a continuous extractor to give 1.67 g (59%) of pure 21-crown-7 (IIe) as a colorless liquid. IR (neat): 2880 s, 1465 m, 1360 m, 1300 m, 1255 m, 1115 s, 945 m, and 850 w cm⁻¹. MS (*m/e*, rel. intensity): 308 (M⁺, amplified), 133 (20), 89 (49), 87 (29), 73 (21), 72 (13), 59 (18), 58 (17), 45 (100), 44 (23), and 43 (29). NMR (CCl₄, δ): 3.54 s. Analysis for C₁₄H₂₈O₇: C, 53.98 (Calcd. 54.53); H, 8.99 (9.15).

Reaction of Tetraethylene Glycol with Sulfonyl Chloride.

a): A solution of tetraethylene glycol (3.9 g, 0.02 mol) and *p*-toluenesulfonyl chloride (4.0 g, 0.02 mol) in monoglyme (30 ml) was added into a suspension of sodium hydroxide

(6.0 g) in 30 ml of monoglyme at 20 °C. The crude product (3.3 g), which was found by GLC to contain 3% of 12-crown-4, was treated on a silica-gel column to give a low-melting solid (0.42 g) from an acetone-hexane eluent. IR (neat): 2880 s, 1460 w, 1350 m, 1300 w, 1250 w, 1150–1110 s, 950 w, and 850 w cm^{-1} . MS (m/e , rel. intensity): 352 (M^+ , 5), 177 (5), 133 (24), 117 (24), 101 (14), 89 (60), 87 (37), 73 (30), 59 (25), 58 (25), 45 (100), 44 (32), and 43 (40). NMR (CCl_4 , δ): 3.52 s. From the above spectral data, it was identified as 24-crown-8 (II f). Yield: 12%, b): Tetraethylene glycol (7.77 g, 0.04 mol) and benzenesulfonyl chloride (7.36 g, 0.04 mol) were dissolved in 90 ml of *t*-butyl alcohol, after which the solution was added, drop by drop, into a suspension of lithium *t*-butoxide (12.8 g, 0.16 mol) in 90 ml of *t*-butyl alcohol over a period of 2 h. After the reaction was complete, the *t*-butyl alcohol was removed *in vacuo* and dichloromethane (100 ml) was added to the residue and filtrate. After the solvent had then been removed, the crude complex was thermolyzed to give a colorless liquid (3.5 g). It was further purified by distillation at reduced pressure. II b , 1.93 g (27%). IR (neat): 2925 s, 1465 w, 1375 m, 1300 m, 1255 m, 1140 s, 1100 s, 1095 m, 1020 m, 920 m, and 850 m cm^{-1} . MS (m/e , rel. intensity): 176 (M^+ , amplified), 133 (8), 89 (30), 87 (18), 73 (15), 59 (15), 58 (19), 57 (11), 45 (100), 44 (33), 43 (40), and 28 (29). NMR (CCl_4 , δ): 3.56 s.

Also, the crude complex of II b (3.95 g; II b content, 38%), obtained in another reaction, was dissolved in methanol (10 ml), after which the solution was extracted continuously by hexane for 9 h. The colorless liquid thus obtained (1.96 g) was distilled under reduced pressure to afford II b (0.65 g, 31%) in a pure state.

Reaction of Mixture of Glycols with Sulfonyl Chloride. a): Tetraethylene glycol (3.9 g, 0.02 mol), triethylene glycol (3.0 g, 0.02 mol), *p*-toluenesulfonyl chloride (8.0 g, 0.04 mol), and potassium hydroxide (10 g) was allowed to react at 60 °C in dioxane to afford a crude product (9.8 g). It was found by GLC determination to contain three kinds of crown ethers: 18-crown-6 (1.02 g, 19%), 21-crown-7 (2.06 g, 33%), and 24-crown-8 (0.98 g, 14%), b): Tetraethylene glycol (1.94 g, 0.01 mol), diethylene glycol (1.06 g, 0.01 mol), *p*-toluenesulfonyl chloride (4.0 g, 0.02 mol), and potassium hydroxide (2.7 g) were allowed to react in dioxane at 60 °C. The crude complex (2.2 g) was analyzed by GLC and found to contain 18-crown-6 (0.60 g, 23%) as the major product, together with small amounts of 24-crown-8 (3%) and 12-crown-4 (<1%).

Conversion of Polyethylene Glycol 200 to Crown Ethers. 3.0 g of commercial polyethylene glycol 200, which was a mixture of di- (1 wt%), tri- (26%), tetra- (36%), penta- (29%), and hexaethylene glycol (8%), was treated with *p*-toluenesulfonyl chloride (2.9 g) in the presence of sodium hydroxide (1.3 g)

TABLE 1. SYNTHESIS OF 15-CROWN-5 FROM PENTAETHYLENE GLYCOL

Exp. No.	Solvent	Concn mol/l	Sulfonyl chloride	Alkali	React. temp/°C	Yield/% ^{a)}
1	Monoglyme	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	0	36
2	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	20	70 (50) ^{b)}
3	THF	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	20	69
4	Dioxane	0.35 ^{e)}	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	20	62 (48)
5	Dioxane	0.70 ^{d)}	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	20	55 (45)
6	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	40	81
7	Monoglyme	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	40	82
8	Diglyme	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	40	81
9	THF	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	40	81
10	Ether	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	f)	63
11	Benzene	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	40	44
12	Hexane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	40	15
13	Dioxane	0.07	<i>o</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	40	79
14	Dioxane	0.07	<i>p</i> -Cl-C ₆ H ₄ SO ₂ Cl	NaOH	40	68
15	Dioxane	0.07	C ₆ H ₅ SO ₂ Cl	NaOH	40	85
16	Dioxane	0.07	CH ₃ SO ₂ Cl	NaOH	40	64
17	Dioxane	0.07	C ₂ H ₅ SO ₂ Cl	NaOH	40	55
18	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	60	82
19	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	80	80
20	Dioxane	0.28 ^{e)}	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	80	82 (75)
21	Diglyme	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	100	82
22	Diglyme	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	NaOH	120	59
23	Monoglyme	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	KOH	0	26
24	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	KOH	20	37
25	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	KOH	40	53
26	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	KOH	60	57
27	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	KOH	80	54
28	Dioxane	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	KOH	100	53
29	Diglyme	0.07	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ Cl	KOH	120	48

a) Determined by GLC. b) Values in parentheses are the purified, isolated yields obtained by thermolysis (Nos. 2, 4, and 20) or by hexane extraction (No. 5). c) Glycol 5.0 g/TsCl 4.1 g/NaOH 3.6 g/dioxane 60 ml. d) Glycol 5.0 g/TsCl 4.1 g/NaOH 3.6 g/dioxane 30 ml. e) Glycol 47 g/TsCl 38 g/NaOH 32 g/dioxane 700 ml. f) Reflux temperature.

TABLE 2. SYNTHESIS OF CROWN ETHERS FROM OLIGOETHYLENE GLYCOLS

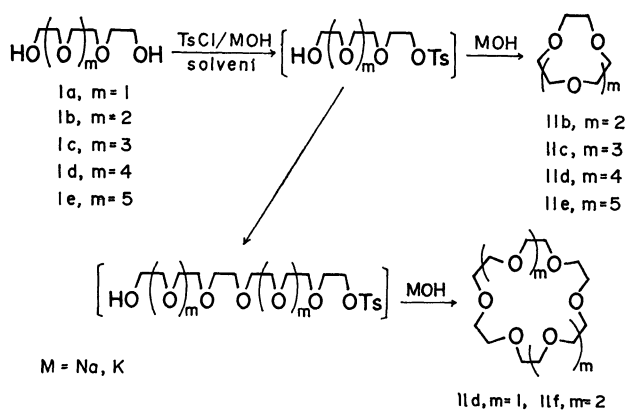
Exp. No.	PEG	Solvent	Concn mol/l	Sulfonyl chloride	Alkali	React. temp/°C	Yield of crown ether/% ^{a,b}	
1	Hexa E.G.	dioxane	0.060	TsCl	NaOH	20	18-crown-6	44
2	Hexa E.G.	dioxane	0.060	TsCl	NaOH	40	18-crown-6	57
3	Hexa E.G.	dioxane	0.060	TsCl	NaOH	60	18-crown-6	71
4	Hexa E.G.	dioxane	0.060	TsCl	NaOH	80	18-crown-6	70
5	Hexa E.G.	diglyme	0.060	TsCl	NaOH	100	18-crown-6	67
6	Hexa E.G.	diglyme	0.060	TsCl	NaOH	120	18-crown-6	50
7	Hexa E.G.	dioxane	0.060	TsCl	KOH	20	18-crown-6	77 (52) ^b
8	Hexa E.G.	dioxane	0.060	TsCl	KOH	40	18-crown-6	95
9	Hexa E.G.	dioxane	0.138	TsCl	KOH	40	18-crown-6	92 (75)
10	Hexa E.G.	dioxane	0.060	TsCl	KOH	60	18-crown-6	98 (75)
11	Hexa E.G.	dioxane	0.060	TsCl	KOH	80	18-crown-6	94
12	Hexa E.G.	diglyme	0.060	TsCl	KOH	100	18-crown-6	89
13	Hexa E.G.	diglyme	0.060	TsCl	KOH	120	18-crown-6	84
14	Hepta E.G.	dioxane	0.052	TsCl	NaOH	40	21-crown-7	28
15	Hepta E.G.	dioxane	0.052	TsCl	NaOH	60	21-crown-7	38
16	Hepta E.G.	dioxane	0.052	TsCl	NaOH	80	21-crown-7	36
17	Hepta E.G.	dioxane	0.052	TsCl	KOH	20	21-crown-7	48
18	Hepta E.G.	dioxane	0.052	TsCl	KOH	40	21-crown-7	73
19	Hepta E.G.	dioxane	0.115	TsCl	KOH	50	21-crown-7	75 (59)
20	Hepta E.G.	dioxane	0.052	TsCl	KOH	60	21-crown-7	79
21	Hepta E.G.	dioxane	0.052	TsCl	KOH	80	21-crown-7	80
22	Hepta E.G.	diglyme	0.052	TsCl	KOH	100	21-crown-7	73
23	Hepta E.G.	diglyme	0.052	TsCl	KOH	120	21-crown-7	62
24	Tetra E.G.	dioxane	0.085	TsCl	NaOH	20	12-crown-4	3
							24-crown-8	18 (12)
25	Tetra E.G.	dioxane	0.085	TsCl	<i>t</i> -BuOLi	60	12-crown-4	22
26	Tetra E.G.	dioxane	0.085	TsCl	<i>t</i> -BuOLi	80	12-crown-4	25
27	Tetra E.G.	<i>t</i> -BuOH	0.220	TsCl	<i>t</i> -BuOLi	80 ^c	12-crown-4	39 (27)
28	Tetra E.G.	<i>t</i> -BuOH	0.085	BzSO ₂ Cl	<i>t</i> -BuOLi	40	12-crown-4	34
29	Tetra E.G.	<i>t</i> -BuOH	0.085	BzSO ₂ Cl	<i>t</i> -BuOLi	60	12-crown-4	41
30	Tetra E.G.	<i>t</i> -BuOH	0.085	BzSO ₂ Cl	<i>t</i> -BuOLi	80 ^c	12-crown-4	49

a) Determined by GLC. b) Values in parentheses are the yields of crown ethers isolated by thermolysis (Nos. 7, 9, 10, and 27), hexane extraction (No. 19), or column chromatography (No. 24). c) Reflux temperature.

and potassium hydroxide (3.0 g) in 60 ml of dioxane at 60 °C. The crude complex (3.5 g) thus obtained was found by GLC analysis to contain 15-crown-5 (0.67 g), 18-crown-6 (0.38 g), 21-crown-7 (0.49 g), and 24-crown-8 (0.40 g).

Results and Discussion

The overall reaction scheme for the synthesis of crown



Scheme 1. Synthesis of crown ethers from oligoethylene glycols.

ethers is shown in Scheme 1.

Pentaethylene glycol, hexaethylene glycol, and heptaethylene glycol were converted easily to the corresponding crown ethers, *i.e.*, 15-crown-5, 18-crown-6, and 21-crown-7 respectively. The results are shown in Tables 1 and 2.

On the other hand, tetraethylene glycol gave only a very small amount of 12-crown-4 (3%) under reaction conditions similar to those of the higher homologues, in spite of complete consumption of the starting glycol. Instead, 24-crown-8 was isolated in a 12% yield from the reaction product, suggesting that the template effect was not effective for the cyclization of tetraethylene glycol to 12-crown-4.¹⁴⁾

However, the yield of 12-crown-4 could be increased up to 49% by altering the alkali/solvent system from Na(K)OH/dioxane to *t*-BuOLi/*t*-BuOH.

The solvent may play an important role in this reaction.¹⁵⁾ In the reactions in dioxane, THF, monoglyme, and diglyme, the yields of crown ethers were almost all the same and well satisfactory, while the reactions in ether, acetonitrile, and benzene gave somewhat poorer yields, and in hexane, the yield was very low, probably because of the limited solubility of

glycol. On the other hand, although a slight amount of 15-crown-5 was obtained in the reaction in DMF, no crown ether was obtained in the DMSO solvent and the glycols were recovered unchanged. Sulfonyl chlorides seemed to react with these solvents in preference to glycols when alkali metal hydroxide was present.

The kind of sulfonyl chloride also has some effect on the reaction. Among the sulfonyl chlorides investigated, benzenesulfonyl chloride was most effective with the *o*- and *p*-toluenesulfonyl chlorides following. The alkanesulfonyl chlorides seemed less effective than arenesulfonyl chlorides.

With respect to the effect of the alkali metal cation as the template ion, results almost the same as in the previous investigations were obtained.^{5,6} The order of the effectiveness of sodium cation for the oligoethylene glycol was: *penta* > *hexa* > *hepta* > *octa* >> *tetra*, while that of the potassium cation was: *hexa* > *hepta* > *penta* > *octa* >> *tetra*. Other cations, such as Li⁺, Ba⁺⁺, and Ca⁺⁺ were found to be ineffective.

The temperature effect has already been reported briefly.¹⁶ A temperature of around 60 °C was found to be optimum for the synthesis of most of the crown ethers investigated.

The concentration of the glycols and the addition rate may also affect the reaction, because the intramolecular cyclization to a crown ether may be preferable to the intramolecular oligomerization in a dilute solution. However, the addition time was settled as 2 h for the convenience of comparison, while the concentration was changed over the range from 0.07 to 0.7 mol/l in the synthesis of 15-crown-5.

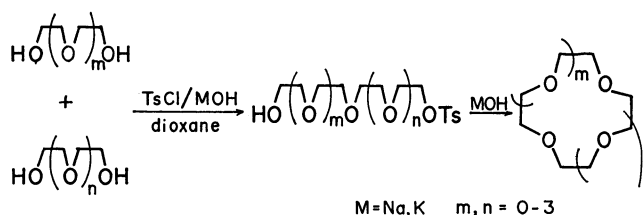
Although the yield was observed to decrease slightly in concentrations (0.7 mol/l) higher than that in the dilute solution (0.07 mol/l), the difference in the yields between the concentrations was not so remarkable that, by controlling the addition rate, a satisfactory result can be expected even in production on a large scale.

Furthermore, as to such glycols as tri- and tetraethylene glycol, which are difficult to cyclize to the

corresponding crown ethers, cyclization was observed to occur after the dimerization or trimerization of glycol, as 24-crown-8 instead of 12-crown-4 was obtained in the reaction of tetraethylene glycol. Thus, when triethylene glycol was treated with an equimolar amount of *p*-toluenesulfonyl chloride, 18-crown-6 was obtained in the maximum yield of 72%, as is shown in Fig. 1 (Curve II).

The yield was somewhat lower than that of the cyclization of hexaethylene glycol (Curve I), but better than that of the condensation between triethylene glycol and triethylene glycol ditosylate (Curve III).^{4,16}

Similarly, the three expected crown ethers, *i.e.*, 18-crown-6, 21-crown-7, and 24-crown-8, were obtained in the molar ratio of 4:7:3 from the reaction of an equimolar mixture of triethylene glycol and tetraethylene glycol (Scheme 2 and Table 3).



Scheme 2. Synthesis of crown ethers from mixtures of oligoethylene glycols.

TABLE 3. SYNTHESIS OF CROWN ETHERS BY THE COUPLING REACTION OF GLYCOLS

Exp. No.	<i>m</i>	<i>n</i>	MOH	Product	Yield/(% ^a)
1	3	0	NaOH	15-crown-5	trace ^b
2	3	1	KOH	18-crown-6	23 ^b
3	3	2	NaOH	18-crown-6	19
			KOH	21-crown-7	33
				24-crown-8	14
4	3	3	KOH	12-crown-4	2
				24-crown-8	24

a) Determined by GLC. b) The presence of a small amount of 24-crown-8 was detected.

However, our attempts to prepare crown ethers using ethylene glycol or diethylene glycol were not successful because of their prompt conversion to ethylene oxide or dioxane.

Furthermore, the treatment of the commercial polyethylene glycol 200, which is composed mainly of tri-, tetra-, penta-, and hexaethylene glycols, with *p*-toluenesulfonyl chloride at 60 °C in the presence of

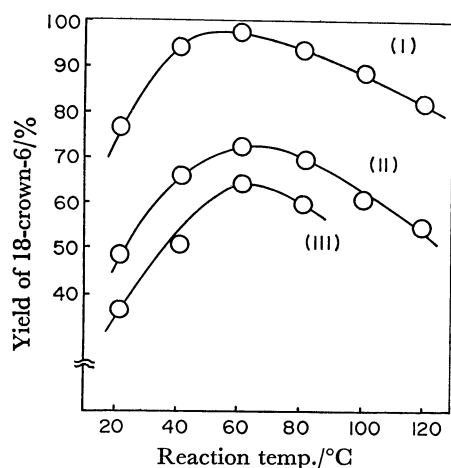


Fig. 1. Yield of 18-crown-6 in various reactions.

Curve I : Cyclization of hexaethylene glycol by TsCl.

Curve II : Condensation of two moles of triethylene glycol by TsCl.

Curve III: Condensation of triethylene glycol and triethylene glycol ditosylate.

TABLE 4. SYNTHESIS OF CROWN ETHERS FROM POLYETHYLENE GLYCOL 200

Product	PEG Source	Yield/(wt% ^a)
15-Crown-5	penta	26
18-Crown-6	hexa, tri × 2	15
21-Crown-7	tri + tetra	20
24-Crown-8	tetra × 2, tri + penta	16

a) Determined by GLC.

NaOH/KOH afforded a mixture of 15-, 18-, 21-, and 24-crown ethers, with the complete consumption of the glycols (Table 4).

Free crown ethers were isolated from their complexes with sodium (potassium) chloride or *p*-toluenesulfonate by thermal decomposition under reduced pressure using a Kugelrohr distillation apparatus, column chromatography or continuous extraction by hydrocarbon solvents. The last means was preferable to the others, especially for the separation of 15- and 21-crown ethers from their complexes.

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