Synthesis of Monoaza Crown Ethers from *N,N*-Di[oligo(oxyalkylene)]amines and Oligoethylene Glycol Di(*p*-toluenesulfonates) or Corresponding Dichlorides

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(Received May 21, 1982)

Monoaza crown ethers were prepared in satisfactory yields by the one-step reaction between diethanolamine or *N,N*-di[oligo(oxyethylene)]amines and oligoethylene glycol di(*p*-toluenesulfonates) or corresponding dichlorides in *t*-butyl alcohol/dioxane in the presence of sodium or potassium *t*-butoxide. The reaction conditions in the preparation of monoaza 15- and 18-crown ethers were studied. Various monoaza crown ethers having substituents were also prepared and their properties were investigated.

N-Unsubstituted monoaza crown ethers, which are the reactive crown ethers, have complexing ability with metal[1,2] and ammonium cations.[3] Using their reactive amino group, they can be readily transformed to bis-crown compounds,[4–7] lariat ethers,[3,8–10] or *N*-alkyl derivatives useful as surfactants with special properties.[11–13]

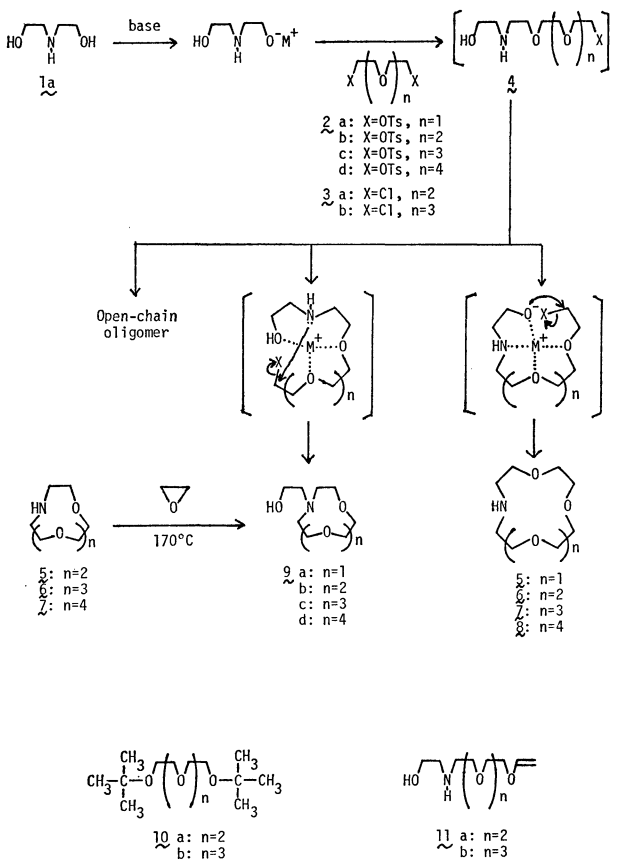
The synthetic methods of monoaza crown ethers can be classified into two categories; with or without employing amino protection. In the former, after the preparation of *N*-substituted monoaza crown ethers (*N*-cyano,[14] *N*-(*p*-tolylsulfonyl),[15] *N*-benzyl,[1,4] or *N*-trityl monoaza crown ether[16]), the deprotection of them by proper means gave *N*-unsubstituted crown ethers. However, these methods are more or less laborious, since the introduction and elimination processes of *N*-substituent are necessary.

On the other hand, 1,4,10,13-tetraoxa-7-azacyclohexadecane possessing oxetane ring was prepared by Krespan[17] by the reaction of 3,3-bis(chloromethyl)-oxetane with bis[2-(2-hydroxyethoxy)ethyl]amine without using amino protection. In accordance with the observation in the synthesis of 18-methylene-1,7,10,16-tetraoxa-4,13-diazacyclononadecane by Tomoi *et al.*,[18] and the synthesis of α,ω-diamino-substituted oligo(oxyethylenes) by Böhmer *et al.*,[19] the results substantiate that *O*-alkylation is far more predominant than *N*-alkylation under the basic conditions which generate an alkoxide.

We have previously reported that *N*-unsubstituted monoaza crown ethers can be obtained in satisfactory yields by the reaction of commercially available dialkanolamines with oligoethylene glycol di(*p*-toluenesulfonates) or corresponding dichlorides without protection of the amino group.[20] In the present paper, the detailed results of the synthesis of monoaza crown ethers from diethanolamine or *N,N*-di[oligo(oxyethylene)]amines are described. Monoaza crown ethers bearing various substituents were also prepared and the scope and the limitations of this method were discussed.

Results and Discussion

Diethanolamine (**1a**) was allowed to react with oligoethylene glycol di(*p*-toluenesulfonates) (**2**) or corresponding dichlorides (**3**) in *t*-butyl alcohol/dioxane in the presence of sodium or potassium *t*-butoxide. After



Scheme 1.

the reaction, the crude products of monoaza crown ethers were separated by extraction and the pure compounds were obtained by Kugelrohr distillation.

As shown in Scheme 1, the *in-situ* generated alkoxide anion of one hydroxyl group may react with di(*p*-toluenesulfonate) or its corresponding dichloride to give an intermediate (**4**), which subsequently cyclizes to monoaza crown ether *via* the intramolecular nucleophilic substitution by the aid of a template ion. However, the alternative attack of amino nitrogen may lead to the formation of *N*-(2-hydroxyethyl) monoaza crown ether (**9**).

The synthesis of monoaza-15-crown-5 (**6**) was carried out under the various reaction conditions by changing solvents, bases, temperature and molar ratio of the reactants. The reaction products were carefully

Table 1. Synthesis of monoaza-15-crown-5 (**6**)[a]

Run	Solvent	**2b** or **3a**	**1a**/**2b** or **3a**/Base (Molar ratio)	Base	Reaction temp/°C	Yield/%[b]	
						6	**10a**
1	*t*-BuOH/Dioxane	**2b**	1.0/1.0/2.4	*t*-BuONa	40	53(43)[c]	4
2	*t*-BuOH/Benzene	**2b**	1.0/1.0/2.4	*t*-BuONa	40	57	3
3	*t*-BuOH/Dioxane	**2b**	2.0/1.0/2.4	*t*-BuONa	40	77(59)[d]	1
4	*t*-BuOH/Dioxane	**2b**	1.0/1.0/2.4	*t*-BuONa	60	54(41)	4
5	*t*-BuOH/Dioxane	**2b**	1.0/1.0/6.0	*t*-BuONa	60	43	38
6	*t*-BuOH/Dioxane	**2b**	1.0/1.0/2.4	*t*-BuONa	80	56	6
7	*t*-BuOH/Dioxane	**2b**	1.0/1.0/2.4	*t*-BuOK	40	36	3
8	*t*-BuOH/Dioxane	**2b**	1.0/1.0/2.4	*t*-BuOK	60	38	4
9	*t*-BuOH/Dioxane	**2b**	1.0/1.0/2.4	*t*-BuOK	80	34	4
10	*t*-BuOH/Dioxane	**2b**	1.0/1.0/2.4	NaOH	40	14	0
11	Dioxane	**2b**	1.0/1.0/2.4	NaOH	40	1	0
12	Dioxane	**2b**	1.0/1.0/2.4	*t*-BuOK	40	2	1
13	*t*-BuOH	**3a**	1.0/1.0/2.4	*t*-BuONa	40	30[e]	0
14	*t*-BuOH	**3a**	1.0/1.0/2.4	*t*-BuONa	60	37(12)[e,f]	0
15	*t*-BuOH	**3a**	1.0/1.0/2.4	*t*-BuONa	80	35[e]	0

a) **2b** or **3a**, 0.01 mol; solvent, 200 ml; reaction time, 4 h. b) Based on **2b** or **3a** and determined by GLC. c) Values in parentheses are isolated yields obtained on larger scale by extraction and distillation. d) The yield obtained in higher concentration; **2b**, 0.12 mol; solvent, 550 ml. e) Reaction time, 40 h. f) Further purified by thermolyzing the complex of **6** with sodium thiocyante.

examined by GLC and NMR to make a survey of the reaction (Table 1).

Triethylene glycol di(*p*-toluenesulfonate) was dissolved in dioxane or benzene because of its insolubility in *t*-butyl alcohol. The reaction proceeded very little in dioxane whichever base, sodium hydroxide or *t*-butoxide, was used, and **2b** was recovered unchanged. This result may be ascribed to the insolubility of the alkoxide. In the range of 40 to 80 °C, the reactions using sodium or potassium *t*-butoxide as a base gave around 55 and 35% yields of monoaza-15-crown-5, respectively. Thus, the reaction temperature does not seem to affect the reaction, but with respect to the effect of the template ion, the sodium cation is superior to the potassium one, as described in the previous investigations.[21-23] Furthermore, when a two molar quantity of diethanolamine was used, the yield of **6** increased to 77%. On the contrary, use of excess base increased the formation of triethylene glycol di-*t*-butyl ether (**10a**) and caused the reduction of the yield of **6**.

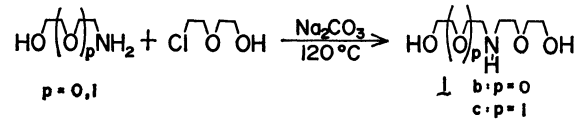
Triethylene glycol di-*t*-butyl ether, which was produced by the attack of *t*-butoxide anion to **2b**, was found in the reactions using **2b**.[24]

When sodium hydroxide was used instead of sodium *t*-butoxide, monoaza-15-crown-5 was obtained in a lower yield.

In the reaction using dichloride (**3a**), the reaction was continued for 40 h, because of its low reactivity. The yields of monoaza-15-crown-5 were found to be low compared with those using di(*p*-toluenesulfonate). In these cases, vinyl ether derivative (**11a**), which was supposed to be generated by the elimination of HCl from the intermediate (**4**), was isolated instead of di-*t*-butyl ether (**10a**). As the by-product (**11a**) could not be separated from crude product by extraction, **6** was isolated by thermolyzing monoaza-15-crown-5 complex with sodium thiocyanate in acetone/hexane. Consequently, the difference between isolated yield and GLC yield was larger than that obtained using **2b**.

The products obtained from all reactions showed a single peak in their gas chromatograms using various columns, and were identified unambiguously as monoaza-15-crown-5 by spectral analyses (^{1}H NMR, IR, and MS). However, to make sure that the possible isomer, *N*-(2-hydroxyethyl)monoaza-12-crown-4 (**9b**), is not formed in the reactions, the authentic **9b** was prepared by the ethoxylation of monoaza-12-crown-4. No indication of the presence of **9b** in the reaction products was obtained, despite a precise check by GLC.

Monoaza-18-crown-6 (**7**) was prepared from the reaction between diethanolamine and tetraethylene glycol di(*p*-toluenesulfonate) (**2c**) or corresponding dichloride (**3b**), and yields were determined by GLC (Table 2). In addition, **7** was also prepared from the reactions of the corresponding oligoethylene glycol di(*p*-toluenesulfonate) with *N*-(2-hydroxyethyl)-2-(2-hydroxyethoxy)ethylamine (**1b**) or bis[2-(2-hydroxyethoxy)ethyl]amine (**1c**), which were obtained by the reactions of oligo(oxyethylene)amines with 2-(2-chloroethoxy)ethanol (Scheme 2).



Scheme 2.

In the reactions using **2c**, no remarkable temperature effect was observed. However, unlike the results of monoaza-15-crown-5, use of both sodium and potassium *t*-butoxides gave almost the same yields. Although a small amount of tetraethylene glycol di-*t*-butyl ether was also formed in these cases, improvement of the yield of **7** to about 80% was attained by using excess diethanolamine or by using the amines

with oligo(oxyethylene) units (**1b** and **1c**). This fact may be interpreted by the increased solubilities of alkoxides of these amines in the solvent.

It was confirmed by the comparison with the authentic sample by GLC that the possible isomer (**9c**) by *N,O*-alkylation was not formed in these reactions.

Furthermore, monoaza-21-crown-7 (**8**) was prepared in a 33% yield by the reaction of diethanolamine with pentaethylene glycol di(*p*-toluenesulfonate) (**2d**). In this case, however, presence of a small amount of the isomer, *N*-(2-hydroxyethyl)monoaza-18-crown-6 (**9d**) was observed by GLC analysis, probably because of the ease of 18-crown ring formation. Similarly, treatment of diethanolamine with diethylene glycol di-(*p*-toluenesulfonate) (**2a**) afforded monoaza-12-crown-4 in very low yield (3%).

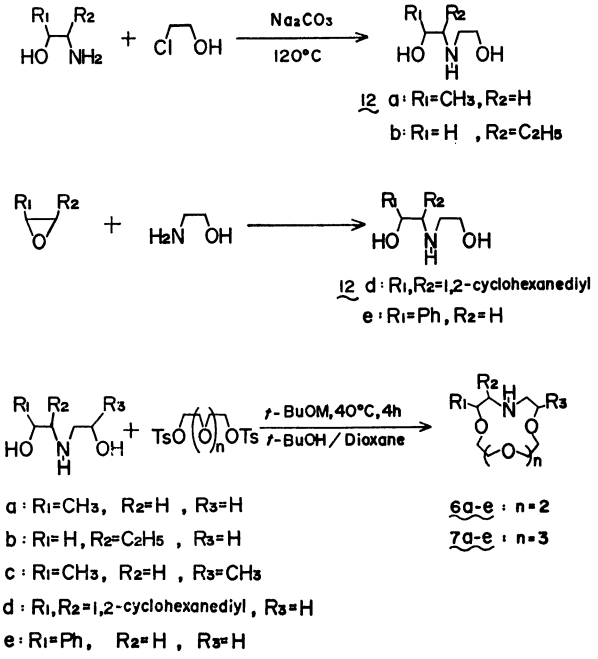
TABLE 2. SYNTHESIS OF MONOAZA-18-CROWN-6 (**7**)[a]

Run	**1**	**2** or **3**	Base	Reaction temp/°C	Yield of **7**/%[b]
1	**1a**	**2c**	*t*-BuONa	40	62
2	**1a**	**2c**	*t*-BuONa	60	62
3	**1a**	**2c**	*t*-BuONa	80	58
4	**1a**	**2c**	*t*-BuOK	25	61
5	**1a**	**2c**	*t*-BuOK	40	63 (45)[c]
6	**1a**[d]	**2c**	*t*-BuOK	40	78 (65)[e]
7	**1b**	**2b**	*t*-BuOK	40	69
8	**1c**	**2a**	*t*-BuOK	40	84
9	**1a**	**2c**	*t*-BuOK	60	60
10	**1a**	**2c**	*t*-BuOK	80	59
11	**1a**	**3b**	*t*-BuONa	40	27[f]
12	**1a**	**3b**	*t*-BuOK	40	37[f]
13	**1a**	**3b**	*t*-BuOK	60	35 (11)[f,g]

a) **1**, 0.01 mol; **2** or **3**, 0.01 mol; base, 0.024 mol; *t*-BuOH/dioxane, 200 ml; reaction time, 4 h. b) Based on **2** or **3** and determined by GLC. c) Values in parentheses are isolated yields obtained on larger scale by extraction and distillation. d) Excess **1a** was used (0.02 mol). e) The yield in higher concentration; **1a**, 0.24 mol; **2c**, 0.12 mol; base, 0.29 mol; *t*-BuOH/dioxane, 550 ml. f) Solvent, *t*-BuOH; reaction time, 40 h. g) Further purified by recrystallization from hexane.

This method was successfully applied for the preparation of the monoaza crown ethers bearing various substituents. *N*-(2-hydroxyethyl)-2-hydroxyalkylamines (**12**) were prepared by two procedures, as shown in Scheme 3. Equimolar reactions of **12** with oligoethylene glycol di(*p*-toluenesulfonates) were performed in a similar manner to give the substituted monoaza 15- and 18-crown ethers (Table 3).

The yields of crown compounds of which R^1 or R^3 is methyl were observed to be lower than those of crown compounds of which R^2 is ethyl or those of unsubstituted crowns (**6**, **7**). Such results may be attributed to the competitive formation of di-*t*-butyl ethers, because of the lower reactivity of secondary alkoxide than that of normal alkoxide due to a steric effect. The better yields of crown compounds with cyclohexane ring, however, may be explained by the higher solubility of its alkoxide in the solvent. Phenyl monoaza crown ethers (**6e** and **7e**) were also obtained



Scheme 3.

TABLE 3. YIELDS AND PROPERTIES OF SUBSTITUTED MONOAZA CROWN ETHERS[a]

Crown ether	**2**	Starting amine (**12**)	R^1	R^2	R^3	Base	Yield %	Refractive index (20 °C)	Amine number (Calcd)
6a	**2b**	**12a**	CH_3	H	H	*t*-BuONa	26	1.4661	237.0(240.5)
6b	**2b**	**12b**	H	C_2H_5	H	*t*-BuONa	46	1.4671	224.2(226.8)
6c	**2b**	**12c**	CH_3	H	CH_3	*t*-BuONa	26	1.4609	218.9(226.8)
6d	**2b**	**12d**	1,2-Cyclohexanediyl		H	*t*-BuONa	52	1.4852[b]	204.7(205.2)
6e	**2b**	**12e**	Ph	H	H	*t*-BuONa	33	1.5171	187.3(189.9)
7a	**2c**	**12a**	CH_3	H	H	*t*-BuOK	39	1.4672	199.8(202.3)
7b	**2c**	**12b**	H	C_2H_5	H	*t*-BuOK	41	1.4689	189.9(192.5)
7c	**2c**	**12c**	CH_3	H	CH_3	*t*-BuOK	28	1.4625[b]	188.8(192.5)
7d	**2c**	**12d**	1,2-Cyclohexanediyl		H	*t*-BuOK	43	1.4837	173.6(176.7)
7e	**2c**	**12e**	Ph	H	H	*t*-BuOK	33	1.5127	159.9(165.3)

a) **2**, 0.02 mol; **12**, 0.02 mol; base, 0.048 mol; *t*-BuOH/dioxane, 360 ml; 40 °C: 4 h. b) Measured at 40 °C: white waxy solid at 20 °C.

in satisfactory yields.

Most of the reactions in this study were run on a rather small scale in dilute solution (0.01 mol of **2**/200 ml of solvent). However, in the practical preparation on a larger scale in higher concentration (0.12 mol of **2**/550 ml of solvent), monoaza crown ethers were obtained in 50 to 70% yields by using the excess dialkanolamines. Thus, together with the high selectivity and ready accessibility of the starting materials, this method is useful for the practical production of monoaza crown ethers.

Experimental

The infrared spectra were taken on a Hitachi 260-10 spectrometer. The ^{1}H NMR spectra were recorded at 100 MHz on a JEOL JNM-PS 100 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. The mass spectra were measured with a Hitachi RMU-6E mass spectrometer at an ionization potential of 70 eV. The GLC analyses were performed on a Shimadzu gas chromatograph GC-3BF using 1 m×3 mm column packed with 10% Silicone SE-30 on 60—80 mesh Celite 545 or on a Shimadzu gas chromatograph GC-3BT using 0.7 m×3 mm column packed with 10% Carbowax on 60—80 mesh Celite 545. Amine contents were determined by a conventional titration procedure.[25]

Starting Materials. Starting materials were the commercial products of analytical grade. Their purities were checked by GLC and they were purified by distillation when necessary. Oligoethylene glycol di(*p*-toluenesulfonates) were prepared as reported.[26] α-(2-Chloroethyl)-ω-chlorooligo(oxyethylenes) were prepared from the corresponding glycols and thionyl chloride.

*N-(2-Hydroxyethyl)-2-(2-hydroxyethoxy)ethylamine (**1b**).* 2-(2-Chloroethoxy)ethanol (62.3 g, 0.50 mol) was added to a suspension of powdered sodium carbonate (39.8 g, 0.38 mol) in 2-aminoethanol (91.7 g, 1.50 mol) and the mixture was heated at 120 °C with stirring. After 24 h of reaction, it was cooled to room temperature, filtered and excess 2-aminoethanol was recovered from the filtrate. The residue was purified by fractional distillation at 150—152 °C (0.1 Torr) to give 46.1 g (50%) of **1b** as a pale yellow liquid: ^{1}H NMR δ 2.65—2.97 (m, NCH_2, 4H), 3.46—3.89 (m, OCH_2, 8H), 4.38 (s, OH, NH, 3H); IR (neat) 3350, 3300, 2950, 2860, 1460, 1360, 1120, 1070 cm^{-1}.

Found: C, 48.06; H, 10.29; N, 9.52%. Calcd for $C_6H_{15}NO_3$: C, 48.31; H, 10.13; N, 9.39%.

*Bis[2-(2-hydroxyethoxy)ethyl]amine (**1c**).* The above procedure was followed, using 2-(2-aminoethoxy)ethanol and 2-(2-chloroethoxy)ethanol: bp 154—156 °C (0.05 Torr)**; pale yellow liquid; 55% yield; ^{1}H NMR δ 2.79 (t, 4H), 3.44—3.78 (m, 12H), 3.82 (s, 3H); IR (neat) 3320, 3280, 2950, 2850, 1460, 1350, 1120, 1070 cm^{-1}.

Found: C, 49.93; H, 10.04; N, 7.50%. Calcd for $C_8H_{19}NO_4$: C, 49.72; H, 9.91; N, 7.25%.

*N-(2-Hydroxyethyl)-2-hydroxypropylamine (**12a**).* The above procedure was followed with 1-amino-2-propanol and 2-chloroethanol as reactants: bp 96—98 °C (0.015 Torr, Kugelrohr distillation); colorless liquid; 61% yield; ^{1}H NMR δ 1.17 (d, 3H), 2.37—2.68 (m, 2H), 2.77 (t, 2H), 3.56—4.07 (m, 3H), 3.66 (s, 3H); IR (neat) 3300, 2925, 2850, 1460, 1375, 1040 cm^{-1}.

Found: C, 50.20; H, 11.09; N, 11.69%. Calcd for $C_5H_{13}NO_2$: C, 50.40; H, 11.00; N, 11.75%.

** 1 Torr ≈ 133.322 Pa.

*N-(2-Hydroxyethyl)-1-hydroxymethylpropylamine (**12b**).* The above procedure was used with 2-amino-1-butanol and 2-chloroethanol as reactants: bp 90—95 °C (0.015 Torr, Kugelrohr distillation); pale yellow liquid; ^{1}H NMR δ 0.90 (t, 3H), 1.12—1.76 (m, 2H), 2.32—2.98 (m, 3H), 2.99—3.83 (s+m, 7H); IR (neat) 3300, 2930, 2850, 1460, 1370, 1050 cm^{-1}.

Found: C, 53.97; H, 11.46; N, 10.51%. Calcd for $C_6H_{15}NO_2$: C, 54.11; H, 11.35; N, 10.52%.

*N-(2-Hydroxyethyl)-2-hydroxycyclohexylamine (**12d**).* Cyclohexene oxide (4.91 g, 0.05 mol) was added in drops to 2-aminoethanol (15.27 g, 0.25 mol) during 1 h, at 125 °C. After the addition, the reaction was continued for 3 h and excess 2-aminoethanol was removed. The crude product (8.3 g) was purified by Kugelrohr distillation at 115—120 °C (0.05 Torr) to give 7.6 g (95%) of **12d** as a pale yellow liquid: ^{1}H NMR δ 0.88—2.14 (m, CH_2, 8H), 2.15—2.46 (m, NCH, 1H), 2.47—3.02 (m, NCH_2, 2H), 3.14—3.47 (m, OCH, 1H), 3.69 (t, OCH_2, 2H), 4.01 (s, OH, NH, 3H); IR (neat) 3300, 2940, 2860, 1450, 1375, 1130, 1060 cm^{-1}.

Found: C, 60.12; H, 10.74; N, 9.04%. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80%.

*N-(2-Hydroxyethyl)-2-hydroxy-2-phenylethylamine (**12e**).* By a procedure similar to that used for **12d**, the reaction between styrene oxide (6.01 g, 0.05 mol) and 2-aminoethanol (15.27 g, 0.05 mol) was performed. The crude product (9.90 g) was purified by recrystallization from benzene to give 7.07 g (78%) of **12e** as a white solid: mp 98.5—100.5 °C; ^{1}H NMR δ 2.58—2.88 (m, 4H), 3.44 (s, 3H), 3.64 (t, 2H), 4.76 (t, 1H), 7.31 (s, 5H); IR (KBr) 3380, 3250, 3050, 2910, 2850, 1460, 1070, 710 cm^{-1}.

Found: C, 65.96; H, 8.24; N, 7.72%. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73%.

*2,2,13,13-Tetramethyl-3,6,9,12-tetraoxatetradecane (**10a**).* Potassium metal (5.9 g, 0.15 mol) was dissolved in *t*-butyl alcohol (200 ml), and triethylene glycol di(*p*-toluenesulfonate) (**2b**, 22.9 g, 0.05 mol) was added at 60 °C. After 4 h of reaction, the mixture was filtered and the solvent was evaporated off. Water (30 ml) was added to the residue and the solution was extracted several times with hexane. The hexane extracts were combined, the solvent was removed, and the crude product (11.0 g) was distilled by Kugelrohr apparatus at 78—81 °C (0.05 Torr) to give 4.2 g (32%) of **10a** as a colorless liquid: ^{1}H NMR δ 2.18 (s, 18H), 3.45—3.73 (m, 12H); IR (neat) 2990, 2880, 1460, 1365, 1130, 1100 cm^{-1}.

Found: C, 63.62; H, 11.48%. Calcd for $C_{14}H_{30}O_4$: C, 64.09; H, 11.52%.

*Preparation of 1,4,7,10-Tetraoxa-13-azacyclopentadecane (**6**). (i) Reaction of Triethylene Glycol Di(p-toluenesulfonate) (**2b**) with Diethanolamine (**1a**):* Diethanolamine (**1a**, 3.15 g, 0.03 mol) and sodium metal (1.66 g, 0.072 mol) were dissolved in 420 ml of *t*-butyl alcohol, and triethylene glycol di(*p*-toluenesulfonate) (**2b**, 13.8 g, 0.03 mol) in 180 ml of dioxane was slowly added, drop by drop, into the solution over a period of 2 h under stirring at 40 °C. After the addition, the reaction was continued for two more hours and the reaction product was filtered. The precipitate was washed with dichloromethane, and the solvent was removed from the combined solution of filtrate and washings. Water (20 ml) was added to the residue and the solution was extracted two times with hexane to remove hexane-soluble by-products and then extracted several times with dichloromethane. Hexane was recovered from the hexane extracts, and the main by-product was isolated from the residue by preparative GLC and identified as **10a**. The dichloromethane extracts were combined, the solvent was evaporated off, and the

residue (5.21 g) was distilled by Kugelrohr apparatus at 77—81 °C (0.01 Torr) to give **6** (2.83 g, 43%) as a colorless solid: mp 29—32 °C (lit,[20] 30—32 °C); ^{1}H NMR δ 2.78 (t, 4H), 2.96 (s, 1H), 2.55—3.76 (m, 16H); MS, *m/e* (relative intensity) 219 (M^+, 11), 188 (22), 162 (32), 132 (26), 116 (9), 100 (61), 45 (100); IR (neat) 3320, 2940, 2860, 1460, 1350, 1120 cm^{-1}.

Found: C, 54.81; H, 9.71; N, 6.27%. Calcd for $C_{10}H_{21}NO_4$: C, 54.78; H, 9.65; N, 6.39%.

A larger scale experiment in higher concentration was carried out in a similar manner to that described above. Triethylene glycol di(*p*-toluenesulfonate) (55.0 g, 0.12 mol) in dioxane (200 ml) was added to the solution of diethanolamine (25.2 g, 0.24 mol) and sodium metal (6.6 g, 0.29 mol) dissolved in *t*-butyl alcohol (350 ml). The crude product (23.4 g) was distilled by Kugelrohr apparatus to give **6** (15.5 g, 59%).

GLC analyses for the investigation of the reaction conditions were performed using 0.7 m × 3 mm column packed with 10% Carbowax on 60—80 mesh Celite 545. Triethylene glycol di(*p*-toluenesulfonate) (0.01 mol) in a solvent (60 ml) was slowly added to the solution of diethanolamine and base in a solvent (140 ml) during 2 h. After the reaction was continued for 2 h, the mixture was filtered and the precipitate was washed with dichloromethane. The solvent was removed from the combined solution. The GLC analysis was performed on a diluted sample of the residue, and each yield of **6** and **10a** was determined.

*(ii) Reaction of 1,8-Dichloro-3,6-dioxaoctane (**3a**) with Diethanolamine (**1a**)*: Diethanolamine (3.15 g, 0.03 mol) and sodium metal (1.66 g, 0.072 mol) were dissolved in 420 ml of *t*-butyl alcohol. Into the solution, 1,8-dichloro-3,6-dioxaoctane (5.61 g, 0.03 mol) in 180 ml of *t*-butyl alcohol was slowly added over a period of 2 h under stirring at 60 °C. After the addition, the reaction continued for 38 h, and a work-up was performed similarly to the case of di(*p*-toluenesulfonate). The product (2.60 g) obtained by Kugelrohr distillation showed a single peak in the GLC, using Silicone SE-30 on Celite 545. On the more polar column (10% Carbowax on Celite 545), however, it showed two peaks. Then, the by-product was isolated from the distillation product by preparative GLC: ^{1}H NMR δ 2.39 (s, 2H), 2.68—2.94 (m, 4H), 3.53—3.96 (m, 12H), 4.03 (dd, 1H), 4.20 (dd, 1H), 6.52 (dd, 1H); MS, *m/e* (relative intensity) 219 (M^+, 2), 188 (47), 74 (100); IR (neat) 3320, 2940, 2870, 1620, 1460, 1330, 1110, 990 cm^{-1}. From these data this product was identified as **11a**, but the possible isomer, *N*-(2-hydroxyethyl)monoaza-12-crown-4 (**9b**) was not detected in this reaction. The distillation product was further purified by thermolyzing the monoaza-15-crown-5 complex with sodium thiocyanate in acetone/hexane to give the pure product of **6** (0.79 g, 12%).

*1,4,7,10,13-Pentaoxa-16-azacyclooctadecane (**7**).* This compound was prepared, using a method similar to that used for **6**, from diethanolamine (25.2 g, 0.24 mol), tetraethylene glycol di(*p*-toluenesulfonate) (**2c**, 60.3 g, 0.12 mol), and potassium metal (11.3 g, 0.29 mol). The crude product was distilled by Kugelrohr apparatus at 95—99 °C (0.02 Torr) to give 20.5 g (65%) of **7** as a colorless solid: mp 48—51 °C (lit,[15] 49—51 °C); ^{1}H NMR δ 2.70 (s, 1H), 2.79 (t, 4H), 3.56—3.78 (m, 20H); MS *m/e* (relative intensity) 263 (M^+, 6), 233 (20), 220 (18), 204 (19), 188 (9), 176 (35), 100 (60), 45 (100); IR (neat) 3300, 2940, 2850, 1460, 1350, 1120 cm^{-1}.

Found: C, 54.59; H, 9.88; N, 5.60%. Calcd for $C_{12}H_{25}NO_5$: C, 54.73; H, 9.57; N, 5.32%.

In the same manner as in the preparation of **6** using **3a**, the reaction of 1,11-dichloro-3,6,9-trioxaundecane (**3b**, 6.93 g, 0.03 mol) with diethanolamine (3.15 g, 0.03 mol) was carried out. Since the distillation product (3.12 g) was found as a mixture of **7** and **11b**, it was further purified by recrystallization from hexane to give the pure product of **7** (0.87 g, 11%).

Small-scale experiments for the investigation of the reaction conditions were carried out, using oligoethylene glycol di(*p*-toluenesulfonate) or 1,11-dichloro-3,6,9-trioxaundecane (0.01 mol) and corresponding dihydroxy amines (**1a—c**) in the same manner as that used for **6**.

*1,4,7,10,13,16-Hexaoxa-19-azacycloheneicosane (**8**).* Diethanolamine (10.5 g, 0.1 mol) and potassium metal (9.4 g, 0.24 mol) dissolved in 300 ml of *t*-butyl alcohol and pentaethylene glycol di(*p*-toluenesulfonate) (**2d**, 54.7 g, 0.1 mol) in 250 ml of dioxane were allowed to react, using a method similar to **6**. In the GLC analysis of the crude product (27.6 g), a small peak which was ascribed to **9d** was observed. The product was distilled by Kugelrohr apparatus at 111—114 °C (0.001 Torr) to afford 10.0 g (33%) of **8** as a colorless liquid: n_D^{20} 1.4700; ^{1}H NMR δ 2.64 (s, 1H), 2.79 (t, 4H), 3.56—3.80 (m, 24H); MS, *m/e* (relative intensity) 307 (M^+, 4), 276 (7), 232 (10), 220 (17), 204 (19), 176 (15), 100 (35), 45 (100); IR (neat) 3340, 2940, 2860, 1450, 1350, 1120 cm^{-1}.

Found: C, 54.88; H, 9.79; N, 4.50%. Calcd for $C_{14}H_{29}NO_6$: C, 54.70; H, 9.51; N, 4.56%.

*1,4,7-Trioxa-10-azacyclododecane (**5**).* This compound was prepared using a method similar to that for the macrocycle **6**, from diethanolamine (42.1 g, 0.4 mol), sodium metal (11.0 g, 0.48 mol), and diethylene glycol di(*p*-toluenesulfonate) (82.9 g, 0.2 mol). The crude product was purified by Kugelrohr apparatus giving colorless crystals: bp 58—62 °C (0.005 Torr); mp 57—59 °C (lit,[4] 60 °C); 3% yield; ^{1}H NMR δ 2.52 (s, NH, 1H), 2.72 (t, NCH_2, 4H), 3.48—3.89 (m, OCH_2, 12H); MS, *m/e* (relative intensity) 175 (M^+, 10), 144 (15), 118 (35), 100 (33), 86 (61), 74 (21), 72 (21), 57 (100); IR (neat) 3300, 2940, 2870, 1460, 1360, 1130, 1090 cm^{-1}.

Found: C, 54.89; H, 9.91; N, 7.91%. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99%.

*11-Methyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (**6a**).* *N*-(2-Hydroxyethyl)-2-hydroxypropylamine (**12a**, 2.38 g, 0.02 mol) and sodium metal (1.10 g, 0.048 mol) were dissolved in 240 ml of *t*-butyl alcohol and triethylene glycol di(*p*-toluenesulfonate) (9.16 g, 0.02 mol) in 120 ml of dioxane was added in drops to the solution over a period of 2 h under stirring at 40 °C. After the addition, the reaction was continued for two more hours, then the reaction mixture was filtered. The precipitate was washed with dichloromethane, and the solvent was removed from the combined solution of filtrate and washings. Water (15 ml) was added to the residue and the solution was extracted two times with hexane to remove hexane-soluble materials and then extracted several times with dichloromethane. The dichloromethane extracts were combined, the solvent was evaporated off, and the residue was distilled by Kugelrohr apparatus at 80—83 °C (0.01 Torr) to give 1.21 g (26%) of **6a** as a pale yellow liquid: ^{1}H NMR δ 1.10 (d, CH_3, 3H), 2.52—2.80 (m, NCH_2, 4H), 2.83 (s, NH, 1H), 2.42—2.92 (m, OCH, OCH_2, 15H); MS, *m/e* (relative intensity) 233 (M^+, 9), 218 (4), 188 (12), 161 (10), 132 (10), 114 (11), 45 (100); IR (neat) 3330, 2930, 2850, 1460, 1360, 1130 cm^{-1}.

Found: C, 56.35; H, 10.00; N, 6.04%. Calcd for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00%.

This procedure is typical for the preparation of other *N*-unsubstituted monoaza crown ethers bearing substituents.

Monoaza 15- and 18-crown ethers were prepared from the reaction of dihydroxy amines (**12a—e**) with triethylene and tetraethylene glycol di(*p*-toluenesulfonates), respectively.

*11,15-Dimethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (**6c**).* Bp 75—80 °C (0.01 Torr, Kugelrohr distillation); colorless liquid; 26% yield; ^{1}H NMR δ 1.05—1.22 (m, 6H), 2.59 (s, 1H), 2.42—2.80 (m, 4H), 3.40—3.84 (m, 14H); MS, *m/e* (relative intensity) 247 (M^+, 6), 232 (5), 202 (37), 174 (7), 158 (6), 146 (6), 114 (18), 101 (49), 45 (100); IR (neat) 3330, 2970, 2870, 1460, 1340, 1110 cm^{-1}.

Found: C, 58.04; H, 10.38; N, 5.60%. Calcd for $C_{12}H_{25}NO_4$: C, 58.27; H, 10.19; N, 5.66%.

*12-Ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (**6b**).* Bp 90—93 °C (0.02 Torr, Kugelrohr distillation); colorless liquid; 46% yield; ^{1}H NMR δ 0.89 (t, 3H), 1.28—1.62 (m, 2H), 2.01 (s, 1H), 2.60—2.92 (m, 3H), 3.18—3.80 (m, 16H); MS, *m/e* (relative intensity) 247 (M^+, 23), 218 (95), 188 (57), 172 (21), 159 (42), 128 (29), 69 (100); IR (neat) 3320, 2930, 2860, 1460, 1350, 1120 cm^{-1}.

Found: C, 58.13; H, 10.05; N, 5.63%. Calcd for $C_{12}H_{25}NO_4$: C, 58.27; H, 10.19; N, 5.66%.

*Perhydro-11,12-benzo-1,4,7,10-tetraoxa-13-azacyclopentadecane (**6d**).* Bp 125—128 °C (0.03 Torr, Kugelrohr distillation); white waxy solid at 20 °C; 52% yield; ^{1}H NMR δ 0.88—2.33 (m, 8H), 2.34—2.51 (m, 1H), 2.72 (t, 2H), 2.98 (s, 1H), 2.88—3.09 (m, 1H), 3.30—4.04 (m, 14H); MS, *m/e* (relative intensity) 273 (M^+, 13), 244 (8), 230 (11), 188 (21), 154 (37), 142 (23), 128 (25), 126 (33), 45 (100); IR (neat) 3320, 2940, 2860, 1460, 1355, 1130 cm^{-1}.

Found: C, 61.11; H, 10.33; N, 4.99%. Calcd for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.95; N, 5.12%.

*11-Phenyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (**6e**).* Bp 139—143 °C (0.02 Torr, Kugelrohr distillation); pale yellow liquid; 33% yield; ^{1}H NMR δ 2.47 (s, 1H), 2.72 (t, 2H), 2.74—3.07 (m, 2H), 3.36—4.04 (m, 14H), 4.40—4.64 (m, 1H), 7.12—7.52 (m, 5H); MS, *m/e* (relative intensity) 295 (M^+, 35), 265 (10), 220 (9), 207 (11), 176 (16), 165 (17), 74 (100); IR (neat) 3325, 3050, 2920, 2880, 1460, 1350, 1110, 760, 700 cm^{-1}.

Found: C, 65.02; H, 8.59; N, 4.98%. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74%.

*14-Methyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**7a**).* By a similar procedure to that used for **6a**, the reaction between *N*-(2-hydroxyethyl)-2-hydroxypropylamine (**12a**, 2.38 g, 0.02 mol) and tetraethylene glycol di(*p*-toluenesulfonate) (**2c**, 10.04 g, 0.02 mol) was performed in the presence of potassium metal (1.87 g, 0.048 mol) dissolved in *t*-butyl alcohol: bp 102—107 °C (0.01 Torr); colorless liquid; 39% yield; ^{1}H NMR δ 1.12 (d, 3H), 2.52—2.84 (m, 4H), 2.65 (s, 1H), 3.40—3.90 (m, 19H); MS, *m/e* (relative intensity) 277 (M^+, 7), 232 (19), 205 (14), 190 (13), 176 (16), 144 (13), 45 (100); IR (neat) 3350, 2930, 2890, 1460, 1350, 1120 cm^{-1}.

Found: C, 55.89; H, 10.00; N, 4.94%. Calcd for $C_{13}H_{27}NO_5$: C, 56.30; H, 9.81; N, 5.05%.

*14,18-Dimethyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**7c**).* Bp 97—101 °C (0.001 Torr, Kugelrohr distillation); white waxy solid at 20 °C; 28% yield; ^{1}H NMR δ 1.06—1.22 (m, 6H), 2.54 (s, 1H), 2.38—2.83 (m, 4H), 3.37—3.89 (m, 18H); MS, *m/e* (relative intensity) 291 (M^+, 3), 276 (4), 246 (20), 190 (10), 146 (7), 133 (8), 116 (14), 101 (24), 45 (100); IR (neat) 3340, 2970, 2870, 1460, 1350, 1120 cm^{-1}.

Found: C, 57.56; H, 10.24; N, 4.39%. Calcd for $C_{14}H_{29}NO_5$: C, 57.71; H, 10.03; N, 4.81%.

*15-Ethyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**7b**).* Bp 120—124 °C (0.04 Torr, Kugelrohr distillation); pale yellow liquid; 41% yield; ^{1}H NMR δ 0.88 (t, 3H), 1.27—1.64 (m, 2H), 2.23 (s, 1H), 2.63—2.86 (m, 3H), 3.23—3.78 (m, 20H); MS, *m/e* (relative intensity) 291 (M^+, 23), 262 (100), 232 (79), 216 (57), 188 (32), 174 (47), 159 (50); IR (neat) 3370, 2920, 2870, 1460, 1360, 1120 cm^{-1}.

Found: C, 57.38; H, 10.15; N, 4.78%. Calcd for $C_{14}H_{29}NO_5$: C, 57.71; H, 10.03; N, 4.81%.

*Perhydro-14,15-benzo-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**7d**).* Bp 145—150 °C (0.03 Torr, Kugelrohr distillation); pale yellow liquid; 43% yield; ^{1}H NMR δ 0.92—2.23 (m, 8H), 2.24—2.68 (m, 1H), 2.64 (s, 1H), 2.75 (t, 2H), 2.86—3.28 (m, 1H), 3.32—4.04 (m, 18H); MS, *m/e* (relative intensity) 317 (M^+, 8), 288 (9), 274 (9), 242 (14), 205 (15), 154 (36), 143 (27), 45 (100); IR (neat) 3325, 2930, 2860, 1460, 1350, 1120 cm^{-1}.

Found: C, 60.42; H, 9.87; N, 4.50%. Calcd for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41%.

*14-Phenyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**7e**).* Bp 153—157 °C (0.02 Torr, Kugelrohr distillation); yellow liquid; 33% yield; ^{1}H NMR δ 2.38 (s, 1H), 2.74 (t, 2H), 2.72—3.08 (m, 2H), 3.38—3.90 (m, 18H), 4.42—4.68 (m, 1H), 7.12—7.45 (m, 5H); MS, *m/e* (relative intensity) 339 (M^+, 14), 309 (9), 280 (7), 264 (8), 205 (11), 176 (19), 74 (100); IR (neat) 3325, 3050, 2930, 2880, 1450, 1350, 1110, 760, 700 cm^{-1}.

Found: C, 63.35; H, 8.77; N, 4.42%. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13%.

*10-(2-Hydroxyethyl)-1,4,7-trioxa-10-azacyclododecane (**9b**).* After ethylene oxide was passed through 35% NaOH aqueous solution and dried over NaOH and soda lime, it was introduced to 1,4,7-trioxa-10-azacyclododecane (**5**, 0.88 g, 0.005 mol) at 170 °C for 6 h. By distilling the reaction mixture at 80—85 °C (0.03 Torr) using Kugelrohr apparatus, 0.47 g (43%) of **9b** was obtained as a pale yellow liquid. ^{1}H NMR δ 2.67 (t, NCH_2, 2H), 2.72 (t, NCH_2, 4H), 3.39—3.92 (s+m, OH, OCH_2, 15H); MS, *m/e* (relative intensity) 219 (M^+, 6.2), 188 (100); IR (neat) 3300, 2910, 2840, 1640, 1450, 1360, 1130, 1100 cm^{-1}.

Found: C, 54.21; H, 9.85; N, 6.05%. Calcd for $C_{10}H_{21}NO_4$: C, 54.77; H, 9.65; N, 6.39%.

Using a similar procedure, **9c** and **9d** were also obtained.

*13-(2-Hydroxyethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**9c**).* Bp 80—85 °C (0.005 Torr, Kugelrohr distillation); pale yellow liquid; 41% yield; ^{1}H NMR δ 2.65 (t, 2H), 2.75 (t, 4H), 3.48—3.76 (s+m, 19H); MS, *m/e* (relative intensity) 363 (M^+, 2.7), 232 (100); IR (neat) 3300, 2910, 2840, 1640, 1460, 1360, 1110, 1090 cm^{-1}.

Found: C, 54.55; H, 9.69; N, 5.45%. Calcd for $C_{12}H_{25}NO_5$: C, 54.73; H, 9.57; N, 5.32%.

*16-(2-Hydroxyethyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**9d**).* Bp 138—142 °C (0.005 Torr, Kugelrohr distillation); pale yellow liquid; 52% yield; ^{1}H NMR δ 2.65 (t, 2H), 2.75 (t, 4H), 3.48—3.74 (s+m, 23H), MS, *m/e* (relative intensity) 307 (M^+, 0.6), 276 (100); IR (neat) 3250, 2900, 2840, 1640, 1460, 1360, 1100 cm^{-1}.

Found: C, 54.33; H, 9.65; N, 4.75%. Calcd for $C_{14}H_{29}NO_6$: C, 54.70; H, 9.51; N, 4.56%.

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