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INTRAMOLECULAR CYCLIZATION OF N,N-Di(OLIGOOXYETHYLENE)AMINES: A NEW SYNTHESIS OF MONOAZA CROWN ETHERS

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Abstract—The reaction of N,N-di(oligooxyethylene)amines with arenesulfonyl chloride in the presence of alkali metal hydroxide was investigated. It was found that the monoarenesulfonates of N,N-di(oligooxyethylene)amines were first formed as intermediates, and their subsequent intramolecular cyclization gave N-unsubstituted monoaza crown ethers rather selectively.

Studies on macrocyclic compounds have recently been developed because of their unique ability to complex selectively with metal or ammonium cations.[1-4] However, interest in their synthesis has mainly been directed to new macrocyclic ligands with higher complexing ability and selectivity, and less attention has been paid to the research aimed at for the development of the practically available preparation methods of the known crown compounds.

We have previously reported one-step synthesis of substituted and unsubstituted crown ethers via treatment with sulfonyl chlorides in the presence of alkali metal hydroxide.[5-8] This method could also be successfully applied to the synthesis of 2-oxo-crown ethers,[9,10] N-alkyl monoaza crown ethers,[11,12] and thia crown ethers.[13]

We have found that, by applying this method to N,N-di(oligooxyethylene)amines which have a reactive sec-amino group, monoaza crown ethers were obtained in satisfactory yield, contrary to the presumed formation of the complicated reaction mixtures.

RESULTS AND DISCUSSION

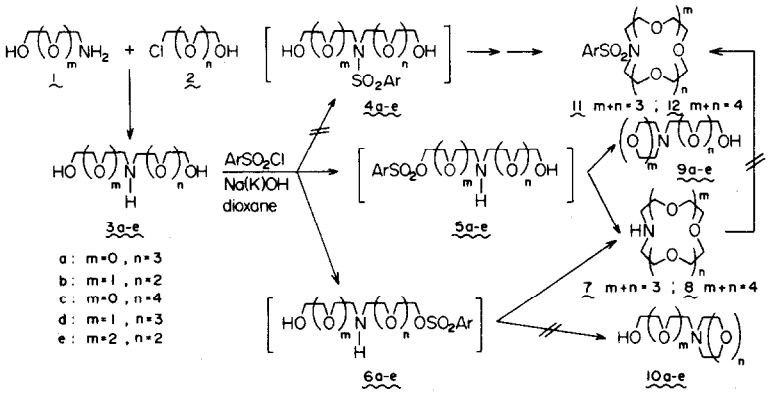
N,N-Di(oligooxyethylene)amines (**3**), prepared by the reaction between oligoethylene glycol monoamines (**1**) and oligoethylene glycol monochlorides (**2**), were treated with an equimolar amount of arenesulfonyl chlorides in dioxane suspension of alkali metal hydroxide.

The reaction of arenesulfonyl chloride with N,N-di(oligooxyethylene)amine which has three reactive sites—one secondary amino and two OH groups—may first afford two types of intermediates. Thus, as shown in Scheme 1, arenesulfonyl chloride is attacked by alkoxide anion to give the monosulfonates (**5** and **6**), whereas the alternative attack by amino N may generate sulfonamide (**4**).

Compounds **5** and **6** may subsequently cyclize to unsubstituted monoaza crown ethers (**7**, **8**) or N-alkylated cyclic compounds (**9**, **10**) by the intramolecular nucleophilic attack, either by the alkoxide anion or by the amino N, respectively. On the other hand, further reactions of the sulfonamide intermediates (**4**) with arenesulfonyl chloride may result in the formation of N-arenesulfonyl monoaza crown ethers (**11**, **12**), and furthermore, there is a fair chance for the intermolecular reactions between these intermediates to give linear oligomers.

However, the reaction was observed to proceed rather selectively. In the reaction of N-(dioxyethylene)-N-(trioxyethylene)amine (**3b**), the product obtained by Kugelrohr distillation showed almost a single peak in the gas chromatogram using Silicone SE-30 on Celite 545. On the more polar column (10% Carbowax on Celite 545), however, it showed two peaks, which were respectively identified as monoaza 15-crown-5 (**7**) and N-(trioxyethylene)morpholine (**9b**). Their respective yields were determined by ^{1}H NMR based on the integrated intensities of the protons adjacent to N (δ 2.78 for **7** and δ 2.51 for **9b**).

The results of the synthesis of monoaza 15-crown-5 (**7**)



Scheme 1. Reaction of N,N-Di(oligooxyethylene)amines with arenesulfonyl chlorides.

Table 1. Synthesis of monoaza 15-crown-5[a] by the reaction from **3a** or **3b**

Starting material (3)	Arenesulfonyl chloride	Base	Temp. (°C)	Yield[b] (Crude yield[c]) (%) (7)	(9)
3a	TsCl	NaOH	60	59 (87)	9a 0 (5)
3b	TsCl	NaOH	20	48 (68)	9b 10 (21)
3b	TsCl	NaOH	40	56	9b 8
3b	TsCl[d]	NaOH	60	42 (64)	9b 8 (19)
3b	TsCl	NaOH	60	59	9b 6
3b	$PhSO_2Cl$	NaOH	60	48	9b 4
3b	TsCl	KOH	60	30	9b 10
3b	TsCl	NaOH	80	58 (74)	9b 4 (16)
3b	TsCl	NaOH	100	58	9b 4

a. 3, 0.03mol; $ArSO_2Cl$, 0.03mol; Base, 0.23mol; Dioxane, 120ml. b. The ratio of both compounds was determined by NMR. c. Before distillation. d. Excess TsCl was used (0.04mol).

from N-(2(hydroxyethyl)-N-(tetraoxyethylene)amine (**3a**) and N-(dioxyethylene)-N-(trioxyethylene)amine (**3b**) are shown in Table 1.

Monoaza 15-crown-5 (**7**) was obtained in good yield (55 to 60%) from **3b**, with the by-formation of morpholine derivative (**9b**) the yield of which was found to decrease with the increase of temperature. The fact that the formation of monoaza 15-crown-5 is more favorable than that of **9b**, in spite of the ease of 6-membered ring formation, suggests that the substitution by alkoxide anion was preferred to that of amino group under the conditions described. This finding is in accord with the observation in the previously reported synthesis of monoaza crown ethers,[14] and the synthesis of aza crown ethers with oxetane reported by Krespan.[15] The apparent higher proportions of **9b** in the crude products may be explained by assuming the formation of oligomers including the morpholine ring, which remains in the residue after distillation.

Regarding the sulfonyl chlorides, p-toluenesulfonyl chloride was observed to give a slightly higher yield than benzenesulfonyl chloride. In addition, the use of Na cation as a template ion gave a better yield than that of K cation.

A similar treatment of N-(2-hydroxyethyl)-N-(tetraoxyethylene)amine (**3a**) at 60° gave monoaza 15-crown-5 (**7**) in almost the same yield as **3b**. In this reaction, the possible isomers, N-(2-hydroxyethyl)-monoaza 12-crown-4 (**10a**) and N-tetraoxyethylene aziridine (**9a**), were not detected by GLC and ^1H NMR in the product obtained by distillation. In the ^1H NMR spectrum of the crude product before distillation, however, absorptions were observed at δ 1.13 and 1.72 which were ascribed to the protons on the aziridine ring. The reactive aziridine compound (**9c**) may be lost by further reactions during distillation.

Even in the reaction of **3b** with excess p-toluenesulfonyl chloride, N-(p-tolylsulfonyl)-monoaza-15-crown-5 (**11**) was scarcely detected by comparison with the authentic sample by GLC.

By a method similar to that used for monoaza 15-crown-5 (**7**), monoaza 18-crown-6 (**8**) was prepared from N,N-di(oligooxyethylene)amines (**3c**, **3d** and **3e**). The results are summarized in Table 2.

Table 2. Synthesis of monoaza 18-crown-6[a] by the reaction of N,N-di(oligooxyethylene)amines with TsCl

Starting material (3)	Base	Yield[b] (Crude yield[c]) (%) (8)	(9)
3c	NaOH	48 (80)	9c 1 (7)
3c	KOH	60 (86)	9c 0 (3)
3d	NaOH	45 (68)	9d 7 (21)
3d	KOH	59 (81)	9d 4 (11)
3e	NaOH	49	9e 0
3e	KOH	63	9e 0

a. 3, 0.03mol; TsCl, 0.03mol; Base, 0.23mol; Dioxane, 120ml; 60°C. b. The ratio of both compounds was determined by NMR. c. Before distillation.

A small amount of aziridine derivative (**9c**) was observed, in the distillation product of the reaction of N-(2-hydroxyethyl)-N-(pentaoxyethylene)amine (**3c**) using sodium hydroxide as a base. However, evidence for the formation of N-(2-hydroxyethyl)-monoaza 15-crown-5 (**10c**) was not found even by careful analysis of the product by GLC. On the other hand, in the reaction of N-(dioxyethylene)-N-(tetraoxyethylene)amine (**3d**), a small amount of morpholine derivative (**9d**) was detected by GLC, whereas monoaza 18-crown-6 (**8**) was the only cyclic product in the reaction of di(trioxyethylene)amine (**3e**), probably because of the difficulty of 9-membered ring formation.

In the preparation of **8**, use of K cation as the template ion was observed to give better yields than use of Na cation, in accordance with the generally accepted trend that K cation is more favorable as a template than Na cation in the synthesis of 18-crown ethers.[8,16-18] Also it is notable that the cyclic by-products were formed to a limited extent in the reactions using potassium hydroxide.

In conclusion, the reaction seems to be controlled by two factors: (1) The competition between alkoxide anion and amino group for both the arenesulfonyl chloride and

the intermediate monosulfonate (4). (2) Ease of ring formation in the presence of the template cation. However, due to the poor reactivity of the amino group and the preferable template effect, monoaza crown ethers were obtained selectively from these reactions.

EXPERIMENTAL

The IR and ^{1}H NMR spectra were recorded on Hitachi 260 spectrometer and a JEOL JNM-PS-100 spectrometer respectively. The GLC analyses were performed on a Shimadzu gas chromatograph GC-3BF using two 1 m × 3 mm columns packed with 10% Silicone SE-30 on Celite 545 and with Silicone OV-1 on Uniport KS or on a Shimadzu gas chromatograph GC-3BT employing 0.7 m × 3 mm column packed with 10% Carbowax on Celite 545.

2-Aminoethanol, 2-(2-aminoethoxy)ethanol, 2-chloroethanol, 2-(2-chloroethoxy)ethanol, and 2-(2-(2-chloroethoxy)ethoxy)ethanol were products of analytical grade. Their purity was checked by GLC and they were purified by distillation when necessary. 11-Chloro-3,6,9-trioxaundecanol and 14-chloro-3,6,9,12-tetraoxatetradecanol were prepared as previously reported method.[12] N-(2-Hydroxyethyl)-monoaza crown ethers were prepared by the reaction of the corresponding monoaza crown ethers with ethylene oxide at 170°. Compound **11** was also prepared by reaction of monoaza 15-crown-5 with p-toluene sulfonyl chloride in the presence of excess Et_3N.

2-(2-(2-Aminoethoxy)ethoxy)ethanol. 2 - (2 - (2 - Chloroethoxy)ethoxy)ethanol (33.7 g, 0.2 mol) was added to a soln of potassium phthalimide (40.8 g, 0.22 mol) in DMF (40 ml) and the mixture was stirred at 120° for 5 hr. After removal of DMF, water (60 ml) was added and the soln was extracted several times with benzene. The extracts were combined, the solvent was evaporated, and the crude product was recrystallized from benzene/hexane (6:4) to give 2-(2-(2-phthalimidoethoxy)ethoxy)ethanol (38.0 g, 68%) as a white solid: m.p. 54.5–56.0°; ^{1}H NMR ($CDCl_3$) δ 2.95 (s, OH, 1H), 3.45–4.01 (m, NCH_2, OCH_2, 12H), 7.63–7.96 (m, Ar, 4H); IR (neat) 3360, 2910, 2870, 1770, 1710, 1465, 1120, 720 cm^{-1}. (Found: C, 60.88; H, 6.19; N, 4.92. Calc for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.02%). The phthalimide derivative (36.3 g, 0.13 mol) was dissolved in EtOH (400 ml) under reflux and hydrazine hydrate (6 ml of 90%) was added. After heating under reflux for 3 hr, 10N HCl (40 ml) was added and the mixture was refluxed for 0.5 hr. The solvent was distilled off, water (50 ml) was added, and the precipitated phthalhydrazide filtered off. NaOH (20.0 g, 0.5 mol) was added to the filtrate and the aqueous soln was extracted by continuous liquid–liquid extraction with CH_2Cl_2. The solvent was evaporated off, and the residue was distilled by Kugelrohr apparatus to give 13.6 g (70%) of 2-(2-(2-aminoethoxy)ethoxy)ethanol as a pale yellow liquid: b.p. 95–100°/0.1 torr; ^{1}H NMR ($CDCl_3$) δ 2.78 (s, OH, NH_2, 3H), 2.85 (t, NCH_2, 2H), 3.43–3.79 (m, OCH_2, 10H); IR (neat) 3350, 3300, 3290, 2930, 2870, 1600, 1460, 1350, 1120, 1080 cm^{-1}. (Found: C, 48.13; H, 10.32; N, 9.11. Calc for $C_6H_{13}NO_3$: C, 48.30; H, 10.14; N, 9.39%).

3,6,9-Trioxa-12-azatetradecane-1,14-diol (**3a**). 11-Chloro-3,6,9-trioxaundecanol (17.0 g, 0.08 mol) was added to a suspension of powdered Na_2CO_3 (6.4 g, 0.06 mol) in 2-aminoethanol (24.4 g, 0.4 mol) and the mixture was heated at 120° with stirring. After 24 hr, it was cooled to room temp, filtered and excess 2-aminoethanol was recovered from the filtrate. The residue was purified by Kugelrohr distillation at 165–170°/0.04 torr to give 12.2 g (64%) of **3a** as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 2.72 (t, NCH_2, 2H), 2.79 (t, NCH_2, 2H), 3.38 (s, OH, NH, 3H), 3.50–3.78 (m, OCH_2, 16H); IR (neat) 3350, 3300, 2950, 2880, 1460, 1360, 1120, 1070 cm^{-1}. (Found: C, 50.48; H, 9.94; N, 6.21. Calc for $C_{10}H_{23}NO_5$: C, 50.62; H, 9.77; N, 5.90%). Using a similar procedure, **3b**, **3c**, **3d** and **3e** were also obtained from the corresponding oligoethylene glycol monoamines and monochlorides.

3,6,12-Trioxa-9-azatetradecane-1,14-diol (**3b**). **3b** was obtained from the reaction between 2-(2-aminoethoxy)ethanol and 2-(2-(2-chloroethoxy)ethoxy)ethanol: b.p. 155–160° (0.02 torr, Kugelrohr distillation); pale yellow liquid; 74% yield; ^{1}H NMR ($CDCl_3$) δ 2.80 (t, NCH_2, 4H), 3.50–3.79 (m, OCH_2, 16H), 3.67 (s, OH, NH, 3H); IR (neat) 3350, 3300, 2950, 2880, 1460, 1360, 1120, 1070 cm^{-1}. (Found: C, 50.37; H, 9.96; N, 6.20. Calc for $C_{10}H_{23}NO_5$: C, 50.62; H, 9.77; N, 5.90%).

3,6,9,12-Tetraoxa-15-azaheptadecane-1,17-diol (**3c**). 2-Aminoethanol and 14-chloro-3,6,9,12-tetraoxatetradecanol were used: b.p. 170–175° (0.01 torr, Kugelrohr distillation); pale yellow liquid; 62% yield; ^{1}H NMR ($CDCl_3$) δ 2.73 (t, NCH_2, 2H), 2.79 (t, NCH_2, 2H), 3.34 (s, OH, NH, 3H), 3.51–3.77 (m, OCH_2, 20H); IR (neat) 3350, 3300, 2950, 2870, 1460, 1360, 1120, 1080 cm^{-1}. (Found: C, 50.95; H, 9.72; N, 5.21. Calc for $C_{12}H_{27}NO_6$: C, 51.23; H, 9.67; N, 4.98%).

3,6,9,15-Tetraoxa-12-azaheptadecane-1,17-diol (**3d**). 2-(2-Aminoethoxy)ethanol and 11-chloro-3,6,9-trioxaundecanol were employed: b.p. 175–180° (0.02 torr, Kugelrohr distillation); pale yellow liquid; 59% yield; ^{1}H NMR ($CDCl_3$) δ 2.79 (t, NCH_2, 4H), 3.48–3.85 (m, OCH_2, 20H), 3.74 (s, OH, NH, 3H); IR (neat) 3350, 3300, 2950, 2870, 1460, 1360, 1120, 1080 cm^{-1}. (Found: C, 50.96; H, 9.80; N, 5.31. Calc for $C_{12}H_{27}NO_6$: C, 51.23; H, 9.67; N, 4.98%).

3,6,12,15-Tetraoxa-9-azaheptadecane-1,17-diol (**3e**). 2-(2-(2-Aminoethoxy)ethoxy)ethanol (13.4 g, 0.09 mol), 2-(2-(2-chloroethoxy)ethoxy)ethanol (10.1 g, 0.06 mol), and Na_2CO_3 (5.3 g, 0.05 mol) were reacted at 110° for 36 hr: b.p. 170–175° (0.01 torr, Kugelrohr distillation); pale yellow liquid; 55% yield; ^{1}H NMR ($CDCl_3$) δ 2.79 (t, NCH_2, 4H), 3.51–3.82 (m, OCH_2, 2OH), 3.64 (s, OH, NH, 3H); IR (neat) 3400, 3350, 2950, 2880, 1460, 1360, 1120, 1080 cm^{-1}. (Found: C, 50.99; H, 9.83; N, 5.15. Calc for $C_{12}H_{27}NO_6$: C, 51.23; H, 9.67; N, 4.98%).

Monoaza 15-crown-5 (**7**) *from* **3a**. p-Toluenesulfonyl chloride (5.72 g, 0.03 mol) dissolved in 30 ml dioxane, was slowly added in drops to a suspension of powdered NaOH (9.7 g, 0.23 mol, 95%) and **3a** (7.12 g, 0.03 mol) in 90 ml dioxane over a period of 2 hr at 60°. After the addition was complete, the reaction was continued for 3 hr, and the mixture filtered. The ppt was washed with CH_2Cl_2, and the solvent was recovered from the combined soln of filtrate and washings. Water (15 ml) was added to the residue and the soln was extracted five times with CH_2Cl_2. The solvent was removed from the extracts to give the crude product (6.04 g, 92%). In the ^{1}H NMR (D_2O) spectrum, small absorptions were observed at δ 1.13 and 1.72, which were ascribed to the aziridine ring protons. The ratio of **7** and **9a** in the crude product was calculated as 95:5, from the integrated intensities of protons adjacent to N for **7** (δ 2.78) and aziridine ring protons. After the crude product was neutralized by HCl, it was distilled in the presence of Na_2CO_3 (2.12 g, 0.02 mol) by Kugelrohr distillation at 70–100° (0.01 torr) to give 3.88 g (59%) of **7** as a white solid: m.p. 29–31° (lit.,[14] 30–32°). The product showed a single peak in the GLC using column packed with 10% Carbowax on Celite 545 and the ^{1}H NMR spectra agreed well with that of the authentic compound. 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}.

Monoaza 15-crown-5 (**7**) *from* **3b**. The above procedure was followed using **3b** (7.12 g, 0.03 mol), p-toluenesulfonyl chloride (5.72 g, 0.03 mol), and NaOH (9.5 g, 0.23 mol). As the product (4.27 g) was a mixture of **7** and **9b**, their respective yields were calculated by ^{1}H NMR (D_2O) based on the integrated intensities of the protons adjacent to N. It was further purified by thermolyzing monoaza 15-crown-5 complex with sodium thiocyanate in acetone/hexane to give the pure product of **7** (3.29 g, 50%). In addition, the reaction with **3b** (7.12 g, 0.03 mol) with excess p-toluenesulfonyl chloride (7.63 g, 0.04 mol) was carried out. The ratio of **7** and **9b** in the crude product (5.45 g, 83%) was found as 77:23, but **11** was hardly observed by comparison with the authentic sample by GLC.

Monoaza 18-crown-6 (**8**) *from* **3c**. The procedure adopted for **7** from **3a** was followed using **3c** (8.44 g, 0.03 mol), p-toluenesulfonyl chloride (5.72 g, 0.03 mol) and KOH (15.2 g, 0.23 mol, 85%). The crude product of **8** was distilled by Kugelrohr distillation at 90–120° (0.01 torr) to give 4.73 g (60%) of **8** as a white solid: m.p. 48.5–51.0° (lit.,[19] 49–51°). MS, *m/e* (relative intensity) 263 (M^+, 6), 233 (20), 220 (18), 204 (19), 188 (9), 176 (35), 100 (60), 45 (100); IR (neat) 3330, 2940, 2850, 1460, 1350, 1120 cm^{-1}.

Monoaza 18-crown-6 (**8**) *from* **3d**. The procedure used for **7**

from **3b** was followed with **3d** (8.44 g, 0.03 mol) and p-toluenesulfonyl chloride (5.72 g, 0.03 mol) as reactants. The product (5.01 g, 63%) obtained by Kugelrohr distillation was further purified by recrystallization from hexane to give the pure **8** (3.79 g, 48%).

Monoaza 18-*crown*-6 (**8**) *from* **3e**. By a similar procedure, 3.87 g (49%) and 4.97 g (63%) of **8** were obtained from **3e** by using NaOH and KOH, respectively.

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