Synthesis of 2-Oxo-Crown Ethers

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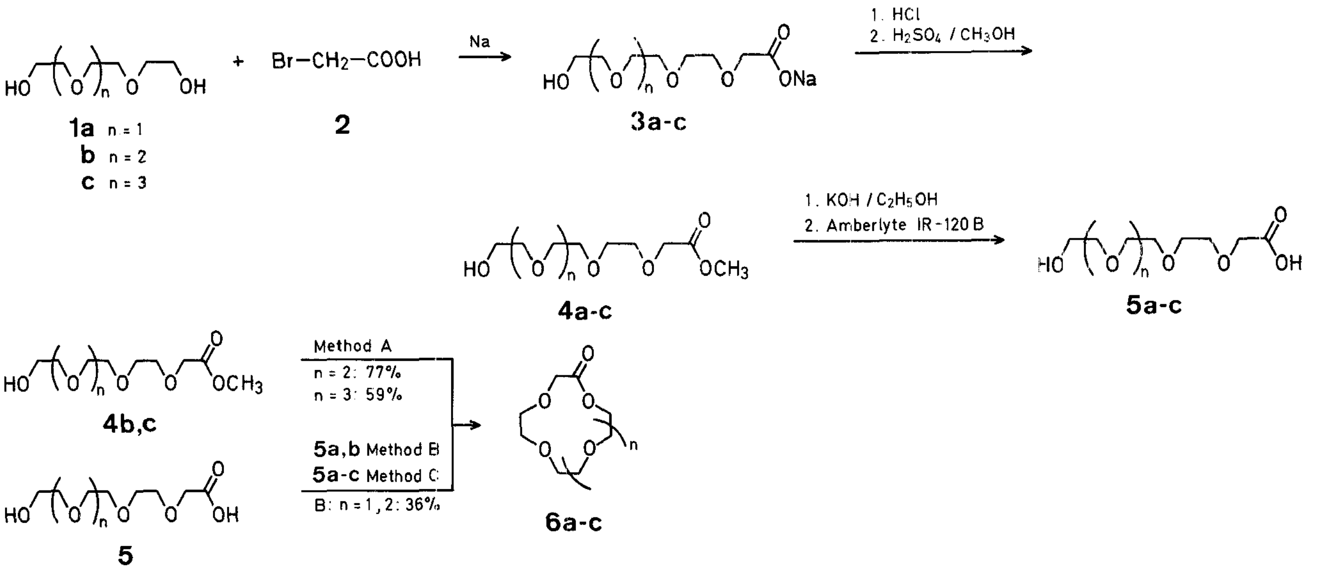
One of the important factors determining the selectivity or the stability of the cation-complexing ability of macrocyclic compounds is interaction between the cation and the electron-donating group. From this standpoint, modifications of the electron-donating part have received attention in recent years[1-6] and the cation-complexing ability of some of diester-type crown ethers was found to be different from that of the normal crown ethers[7]. Although a convenient synthesis of macrocyclic polyethers developed by our group[8,9] could be successfully applied to the synthesis of monoester-type crown ethers[10], we now describe alternative routes to these compounds



Method A: diglyme/Na_2CO_3/150°C/5 h
Method B: Li_2CO_3/heat/vacuum
Method C: $C_6H_5-SO_2-Cl/M_2CO_3$/dioxan/60°C/5 h

Sodium salts of oligoethyleneglycol mono-carboxymethyl ethers (3) were prepared by the reaction of bromoacetic acid (2) and the sodium alkoxide of the corresponding oligoethyleneglycols (1a-c). Free acids 5 could not be obtained in a pure state simply by neutralization of 3 with hydrochloric acid since their separation from other by-products was difficult. However, crude free acids 5 were easily esterified according to the conventional method using methanol and sulfuric acid and then oligoethyleneglycol mono-methoxycarbonylmethyl ethers (4) were obtained in a pure state. Oligoethyleneglycol mono-carboxymethyl ethers (5) were obtained pure by saponification of 4 followed by treatment with an ion-exchange resin.

Cyclization to the 2-oxo-crown ethers 6 is achieved by two methods:

Method A is intramolecular transesterification of 4. By using sodium carbonate, 2-oxo-15-crown-5 (6b) and 2-oxo-18-crown-6 (6c) ethers were obtained in 77% and 59% yields, respectively. However, the starting material 4 was recovered in the case when lithium carbonate was used as the base and the intended product was scarcely obtained in the case when potassium carbonate was used.

Method B is intramolecular dehydration of 5. This method afforded 2-oxo-12-crown-4 ether (6a), which could hardly be obtained by other methods, in 36% yield. These two methods (A and B) may have the advantage of preparing 2-oxo-crown ethers without the necessity of using an arenesulfonyl chloride.

The template effect in the cyclization of 5 to monoester-type crown ethers (Method C) was examined at 60°C. The results are shown in Table 1. A remarkable difference among alkali metal cations in the yield was not detected in the synthesis of 2-oxo-15-crown-5 ether (6b). However, use of the sodium cation gave an excellent result in the synthesis of 2-oxo-18-crown-6 ether (6c). This result differs from the finding[11] that the potassium cation is the most suitable as the template ion in the synthesis of 18-crown-6 ether.

Oligoethyleneglycol Mono-methoxycarbonylmethyl Ethers (4):
Metallic sodium (15.5 g, 0.67 mol) is dissolved in the oligoethyleneglycol 1 (360–370 ml, 2.698 mol), bromoacetic acid (2; 50.88 g, 0.337 mol) is added to the resultant solution at 100°C; the mixture is then stirred at 100°C for 10 h. The excess oligoethyleneglycol 1 is removed in vacuo. Water (100 ml) and 35% hydrochloric acid (35 ml) are added to the distillation residue, then sodium halides (NaBr and NaCl) are removed by filtration. After evaporating the water, methanol (600 ml) and sulfuric acid (10 ml) are added to the residue and the resultant mixture is refluxed for 10 h. The solution is neutralized with aqueous sodium carbonate solution and then the solvent is evaporated under reduced pressure. Water (400 ml) is added to the residue and the mixture is extracted with dichloromethane (3 × 100 ml). The first and second fractions contain 4 and a small

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amount of diether. The third fraction contains the desired product **4** in the pure state. This extraction procedure is repeated several times to give **4** in 70–80% yield. The product is further purified by flash distillation below 150 °C to give **4** as a slightly yellowish liquid (**4b**: 120 °C/10^{-3} torr; purified yield: 63%). Characterization of products **4**, see Table 2.

Oligoethyleneglycol Mono-carboxymethyl Ethers (5):

An ethanol solution (60 ml) of **4** (20.3 mmol) and 85% potassium hydroxide (1.35 g, 20.5 mmol) is refluxed for 1 h. The solution is cooled to room temperature and then is treated with ion-exchange resin (50 g; Amberlyte IR-120B) using ethanol as the eluent. The combined ethanol solution is concentrated to give **5** as a slightly yellowish viscous liquid; yield: ~100% (see Table 2).

2-Oxo-Crown Ethers 6:

Method A: A suspension of **4c** (3.2 g, 10.3 mmol) and sodium carbonate (1.09 g, 10.3 mmol) in diglyme (32 g) is stirred at 150 °C for 5 h. After the reaction mixture is cooled to room temperature, insoluble matter is removed by filtration and washed with dichloromethane. The combined solution is concentrated to give a viscous substance; 2-oxo-18-crown-6 ether (**6c**) is isolated in 59% yield by thermolysis of this substance using a Kugel-rohr apparatus under reduced pressure (~200 °C/0.1 torr). The yield of 2-oxo-15-crown-5 ether (**6b**) by this method is 77%. The analytical data of **6b** and **6c** are coincident with those reported previously[10].

Method B: The mixture of **5a** and its equimolar amount of lithium carbonate is heated in a Kugel-rohr apparatus under reduced pressure (~240 °C/0.1–0.05 torr) to give 2-oxo-12-crown-4 (**6a**) in 36% yield; use of a similar procedure gives 2-oxo-15-crown-5 (**6b**) in 36% yield.

Method C: To a stirred suspension of sodium carbonate (2.52 g, 23.8 mmol) and **5b** (1.50 g, 59.5 mmol) in dioxan (50 ml) is added, drop-wise benzenesulfonyl chloride (1.10 g, 61.7 mmol) in dioxan (10 ml) over 1.5 h at 60 °C, and then the mixture is stirred for 3.5 h at 60 °C. 2-Oxo-15-crown-5 ether (**6b**) is then obtained according to a purification procedure similar to that described for Method A.

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Table 1. The Template Effect of Alkali Metal Cations on the Yield of Monoester-type Crown Ethers (**6**) (Method C)[a]

Compound	Li_2CO_3	Na_2CO_3	K_2CO_3	Cs_2CO_3
6b	—[b]	30	39	28[c]
6c	—[d]	82	49	23[c]

[a] Reaction conditions: reaction temp. 60 °C, reaction time 5 h. The yields listed in this table are yields [%] of isolated products.

[b] Benzenesulfonyl chloride was recovered (71%). 14% of **6b** was isolated. However, the stage of formation of **6b** is not clear because the purification procedure in a Kugelrohr possibly gives **6b**.

[c] A hygroscopic matter sticked to the walls of the apparatus.

[d] This experiment was not tried.

Table 2. Characterization of Products **4, 5**, and **6**

Product	Molecular formula[a]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]	M.S. (70 eV) m/e (relative intensity %)
4a (n = 1)	$C_9H_{18}O_6$ (222.2)	—	(CCl_4): 3.06 (s, 1 H); 3.4–3.7 (m, 12 H + 3 H); 4.05 (s, 2 H)	190; 163; 160; 147 (11); 133; 117 (28); 102 (49); 101 (53); 89 (28); 86 (28); 73 (21); 59 (45); 58 (34); 45 (100); 43 (53)
4b (n = 2)	$C_{11}H_{22}O_7$ (266.3)	3480 (b); 2870; 1750 (s); 1450; 1440; 1370; 1350; 1280; 1240; 1220; 1120 (bs); 940; 880; 855; 700	(CCl_4): 3.12 (s, 1 H); 3.4–3.7 (m, 16 H + 3 H); 4.05 (s, 2 H)	266 (M^+), 234, 223, 207, 204, 190, 160; 147 (11); 133 (6); 117 (36); 102 (36); 99 (30); 73 (17); 59 (38); 45 (100); 43 (28); 31 (22); 28 (26)
4c (n = 3)	$C_{13}H_{26}O_8$ (310.3)	3480 (b); 2860; 1750 (s); 1450; 1435; 1370; 1345; 1280; 1250; 1220; 1120 (bs); 940; 880; 850; 700	(CCl_4): 2.76 (bs, 1 H); 3.4–3.8 (m, 20 H + 3 H); 4.05 (s, 2 H)	—
5a (n = 1)	—[b]	3400 (b); 2800; 2600; 2500; 1730; 1460; 1420; 1350; 1320; 1280; 1240; 1120; 1100; 1060; 925; 880	($CDCl_3$): 3.5–3.9 (m, 12 H); 4.11 (s, 2 H); 7.29 (s, 2 H)	177; 147 (2); 146 (2); 133 (3); 119 (7); 103 (32); 102 (15); 89 (18); 75 (8); 59 (13); 58 (18); 45 (100); 44 (11); 43 (8); 31 (11); 28 (14)
5b (n = 2)	—[b]	—	($CDCl_3$): 3.5–3.9 (m, 16 H); 4.14 (s, 2 H); 7.09 (s, 2 H)	211; 209; 190; 177; 163 (3); 147 (4); 146 (5); 133 (4); 119 (6); 103 (41); 102 (17); 89 (27); 87 (15); 75 (7); 59 (14); 58 (16); 45 (100); 44 (12); 43 (11); 31 (8); 28 (10)
5c (n = 3)	—[b]	3400 (b); 2800; 2750; 2600; 2500; 1730; 1440; 1340; 1320; 1280; 1240; 1220; 1120; 940; 880; 850	($CDCl_3$): 3.5–3.8 (m, 20 H); 4.12 (s, 2 H); 6.63 (s, 2 H)	221; 209; 207; 191; 190; 177; 163 (4); 147 (5); 146 (4); 133 (7); 119 (5); 103 (44); 102 (17); 89 (35); 87 (18); 75 (6); 73 (7); 72 (5); 59 (15); 58 (12); 45 (100); 44 (12); 43 (12); 31 (7); 29 (5); 28 (9)
6a (n = 1)	$C_8H_{14}O_5$ (190.2)	2900; 2800; 1745; 1725; 1442; 1348; 1280; 1195; 1140; 1110; 1070; 1040; 1018; 960; 840	(CCl_4): 3.4–3.8 (m, 10 H); 4.00 (s, 2 H); 4.2–4.4 (m, 2 H)	190 (M^+); 147 (17); 146 (14); 103 (88); 102 (92); 86 (24); 73 (36); 58 (44); 45 (100); 44 (44); 43 (80); 42 (72); 28 (72)
6b (n = 2)	—	spectral data identical to that previously reported[10]		
6c (n = 3)	—	spectral data identical to that previously reported[10]		

[a] Satisfactory microanalyses obtained (C ±0.30, H ±0.10).

[b] Compounds **5** were difficult to purify and so were used directly in the next step. The structural assignments are fully supported by the spectral data.

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