Synthesis of 2-Oxo-Crown Ethers

Yohji Nakatsui, Norio Kawamura, Misao Okahara

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

Kenji Matsushima

Department of Applied Chemistry, Faculty of Science and Technology, Kinki University, Kowakae, Higashi-osaka, Osaka, Japan

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 and the cation-complexing ability of some of diester-type crown ethers was found to be different from that of the normal crown ethers. Although a convenient synthesis of macrocyclic polyethers developed by our group could be successfully applied to the synthesis of monooester-type crown ethers, we now describe alternative routes to these compounds.

\[
\begin{align*}
1a & \quad n = 1 \\
b & \quad n = 2 \\
c & \quad n = 3
\end{align*}
\]

Method A: \(\text{diglyme} / \text{Na}_2\text{CO}_3 / 150^\circ \text{C} / 5 \text{h}\)
Method B: Li\(_2\)CO\(_3\)/heat/vacuum
Method C: C\(_6\)H\(_5\)-SO\(_2\)-Cl/M\(_2\)CO\(_3\)/dioxane/60\(^\circ\)C/5h

Sodium salts of oligoethylene glycol mono-carboxymethyl ethers (3) were prepared by the reaction of bromoacetic acid (2) and the sodium alkoxide of the corresponding oligoethylene glycols (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 oligoethylene glycol mono-methoxycarbonylmethyl ethers (4) were obtained in a pure state. Oligoethylene glycol 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 arenesulfonil chloride.

The template effect in the cyclization of 5 to monooester-type crown ethers (Method C) was examined at 60\(^\circ\)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 that the potassium cation is the most suitable as the template ion in the synthesis of 18-crown-6 ether.

Oligoethylene glycol Mono-methoxycarbonylmethyl Ethers (4):
Metallic sodium (15.5 g, 0.67 mol) is dissolved in the oligoethylene glycol 1 (360 mL, 2.68 mol), bromoacetic acid (2, 50.88 g, 0.337 mol) is added to the resultant solution at 100\(^\circ\)C; the mixture is then stirred at 100\(^\circ\)C for 10 h. The excess oligoethylene glycol 1 is removed in vacuum.

\[
\begin{align*}
1 & \quad \text{HCl} \\
2 & \quad \text{H}_2\text{SO}_4 / \text{CH}_3\text{OH}
\end{align*}
\]

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 \times 100 mL). The first and second fractions contain 4 and a small
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/10−2 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 treated with ion-exchange resin (50 g; Amberlyte IR-120B) using ethanol as the eluent. The combined ether 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 (1.69 g, 10.3 mmol) in diglyme (32 g) is stirred at 130 °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 Kugelrohr apparatus under reduced pressure (~200°C/0.4 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.

Method B: The mixture of 5a and its equimolar amount of lithium carbonate is heated in a Kugelrohr 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 dioxane (50 ml) is added drop-wise benzenesulfonyl chloride (1.10 g, 61.7 mmol) in dioxane (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 Monoether-type Crown Ethers (6) (Method C)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Li+</th>
<th>Na+</th>
<th>K+</th>
<th>Cs+</th>
</tr>
</thead>
<tbody>
<tr>
<td>6b</td>
<td>30</td>
<td>39</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>6c</td>
<td>82</td>
<td>49</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Molecular formula*</th>
<th>I.R. (neat) [cm⁻¹]</th>
<th>¹H-N.M.R. (solvent) δ [ppm]</th>
<th>M.S. (70 eV) m/e (relative intensity %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a (n = 1)</td>
<td>C₂H₅O₂</td>
<td>—</td>
<td>(CCL₄) 3.06 (s, 1H), 3.4-3.7 (m, 12H + 31H), 4.05 (s, 2 H)</td>
<td>190: 163 (160), 147 (111), 133 (117), 28 (102), 49 (101), 53 (89), 28 (86), 28 (73), 21 (59), 45 (58), 34 (58), 45 (40), 43 (53), 266 (M⁺)</td>
</tr>
<tr>
<td>4b (n = 2)</td>
<td>C₅H₁₀O₄ (266,3)</td>
<td>3400 (b): 2870, 1750 (s); 1450, 1440, 1370, 1350, 1280, 1260, 1220, 1120 (bs); 940, 880, 855, 700</td>
<td>(CCL₄) 3.12 (s, 1H), 3.4-3.7 (m, 16H + 31H), 4.05 (s, 2 H)</td>
<td>190: 163 (160), 147 (111), 133 (117), 28 (102), 49 (101), 53 (89), 28 (86), 28 (73), 21 (59), 45 (58), 34 (58), 45 (40), 43 (53), 266 (M⁺)</td>
</tr>
<tr>
<td>4c (n = 3)</td>
<td>C₇H₁₄O₄ (310,3)</td>
<td>3400 (b): 2860, 1750 (s); 1450, 1435, 1370, 1345, 1280, 1250, 1220, 1120 (bs); 940, 880, 855, 700</td>
<td>(CCL₄) 2.76 (bs, 1H), 3.4-3.8 (m, 20H + 31H), 4.05 (s, 2 H)</td>
<td>190: 163 (160), 147 (111), 133 (117), 28 (102), 49 (101), 53 (89), 28 (86), 28 (73), 21 (59), 45 (58), 34 (58), 45 (40), 43 (53), 266 (M⁺)</td>
</tr>
<tr>
<td>5a (n = 1)</td>
<td>—</td>
<td>—</td>
<td>(CDCl₃) 3.5-3.9 (m, 12H), 4.11 (s, 2 H), 7.29 (s, 2 H)</td>
<td>177, 147 (2), 146 (2), 133 (3), 119 (7), 103 (32), 102 (15), 99 (19), 75 (8), 59 (13), 58 (18), 45 (100), 44 (11), 43 (8), 31 (11), 28 (14)</td>
</tr>
<tr>
<td>5b (n = 2)</td>
<td>—</td>
<td>—</td>
<td>(CDCl₃) 3.5-3.9 (m, 16H), 4.14 (s, 2 H), 7.09 (s, 2 H)</td>
<td>211, 209, 190, 177, 163 (13), 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)</td>
</tr>
<tr>
<td>5c (n = 3)</td>
<td>—</td>
<td>—</td>
<td>(CDCl₃) 3.5-3.8 (m, 20H), 4.12 (s, 2 H), 6.63 (s, 2 H)</td>
<td>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)</td>
</tr>
<tr>
<td>6a (n = 1)</td>
<td>C₅H₄O₂ (190,2)</td>
<td>2900: 2800, 1745, 1725, 1442, 1348, 1280, 1195, 1140, 1110, 1070, 1040, 1018, 960, 840</td>
<td>(CCL₄) 3.4-3.8 (m, 10H), 4.00 (s, 2 H), 4.2-4.4 (m, 2 H)</td>
<td>190 (M⁺), 147 (17), 146 (14), 103 (88), 102 (92), 86 (24), 73 (36), 58 (44), 45 (100), 44 (44), 43 (80), 42 (72), 42 (72)</td>
</tr>
<tr>
<td>6b (n = 2)</td>
<td>—</td>
<td>spectral data identical to that previously reported</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>6c (n = 3)</td>
<td>—</td>
<td>spectral data identical to that previously reported</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* Satisfactory microanalyses obtained (C ± 0.30, H ± 0.10).
* 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.