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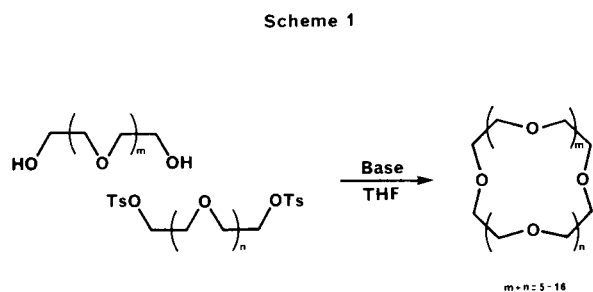
Received April 15, 1986

The synthesis of large ring crown compounds with the general structure 3n-crown-n where n is 9 to 20 is reported.

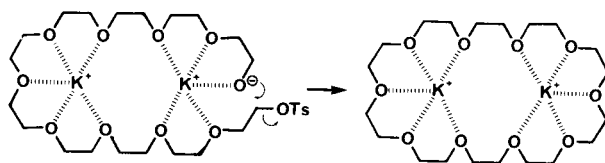
J. Heterocyclic Chem., **23**, 1785 (1986).

The synthesis of macrocyclic ligands capable of complexing metal ions, organic ions and uncharged molecules has stimulated a variety of research efforts in many fields of chemistry [1]. The possibilities for structural changes are large and efforts continue to modify the properties of such compounds by variation of all possible structural parameters, such as the number and type of heteroatoms, ring size, length of the methylene bridge, introduction of substituents and asymmetry in the ring [2]. One neglected area is the synthesis of large ring crown compounds. These compounds are important from several standpoints. First, there is an interest in binuclear complexes where two cations are embedded in a large ring [3,4], as in the complex of dibenzo-24-crown-8 with two molecules of sodium nitrophenolate [5] or potassium isothiocyanate [6]. Secondly, many natural ionophores have rings substantially larger than the ring of 18-crown-6 or 15-crown-5. Gramicidin S, antamanide, valinomycin, nonactins, candidin and amphotericin have rings with 30-38 members [7]. These natural ionophores have lower binding constants than crown compounds but they are better transport agents because of a stepwise-low energy pathway for the decomplexation process. Finally, as the size of the ring increases, greater conformational flexibility is possible and, consequently, different structural types result. Dibenzo-30-crown-10 forms a 1:1 complex with potassium iodide in which all 10 oxygens wrap around and bind to the cation in a shape resembling the seams of a tennis ball [8]. This paper deals with the systematic synthesis of large ring crown compounds [9] with the general structure 3n-crown-n where n is 9 to 20.

The large ring crown ethers were obtained by double condensation of an appropriate polyethylene glycol with a



Scheme 2



polyethylene glycol ditosylate in the presence of an alkali metal hydride [10] (Scheme 1). The results are summarized in Table 1. These cyclic oligomers of ethylene glycol have similar spectral data (Table 2) characteristic of crown compounds. For such compounds, the molecular weight which establishes the ring size cannot be determined by electron impact mass spectrometry. The molecular weights were determined by desorption chemical ionization (DCI) and fast atom bombardment (FAB) mass spectrometry. For 33-crown-11 and larger crowns, the yields are in the range of 20-30% when potassium hydride is used as base and replacement of potassium hydride by sodium hydride does not change the yields significantly. However, for 27-crown-9 and 30-crown-10, much better yields (~50%) are obtained with sodium hydride than with potassium hydride (14-18%). The synthesis of macrocyclic polyethers in high yields mostly by Williamson ether synthesis has led to the recognition of a template effect [11]; the cation is ion-paired with the alkoxide and the remainder of the chain is wrapped around it in such a way that the two ends of the molecule are held in proximity allowing the reaction to occur even at high concentration. Yields above 20% in the ring closure reactions to give 27 to 60 membered macrocycles must be explained by some kind of template effect. In view of the fact that the size of the cation and the size of the chain are not complementary, we suggest the operation of a double or multiple template effect as depicted in Scheme 2. Studies on the ion binding properties of these large crown ethers are in progress.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were taken on a Beckman

Table 1
Synthesis of Large Ring Crowns

Starting materials		Products	Yields (%)	Mp (°C)	Elemental Analyses		
Ethylene glycols	Ethylene glycol ditosylates				Calcd. for C _{2n} H _{4n} O _n : C, 54.55; H, 9.09	Found:	C
penta	tetra	27-crown-9	14 (KH) 47 (NaH)	oil	—	ref [12]	—
penta	penta	30-crown-10	18 (KH) 55 (NaH)	oil	—	ref [13]	—
hexa	penta	33-crown-11	22 (KH) 19 (NaH)	oil	54.66		9.01
hexa	hexa	36-crown-12	22 (KH) 28 (NaH)	oil	54.71		9.23
hepta	hexa	39-crown-13	24	oil	54.78		9.39
hepta	hepta	42-crown-14	20	28.5-31	54.39		8.97
octa	hepta	45-crown-15	24	38-41.5	54.28		8.93
octa	octa	48-crown-16	22	40-43	54.42		9.31
nona	octa	51-crown-17	22	44-47	54.77		8.94
nona	nona	54-crown-18	24	47-50	54.40		9.27
deca	nona	57-crown-19	28	51-53.5	54.71		8.90
deca	deca	60-crown-20	26	46-50.5	54.28		9.36

Table 2
Spectral Data of Large Ring Crowns

Compounds	IR (ν /max, cm ⁻¹)	PMR (deuteriochloroform)	CMR (deuteriochloroform)	MS (M + H) ⁺
27-crown-9	2865, 1450, 1345, 1295, 1245, 1120-1095, 935, 840, 745, 655	3.67	70.53	397 (DCI)
30-crown-10	2860, 1455, 1350, 1295, 1250, 1120-1105, 940, 850, 750	3.67	70.55	441 (DCI)
33-crown-11	2860, 1445, 1345, 1290, 1245 1130-1090, 935, 845, 745, 660	3.67	70.50	485 (DCI)
36-crown-12	2860, 1450, 1350, 1295, 1120- 1085, 920, 815, 775, 600	3.66	70.46	529 (DCI)
39-crown-13	2860, 1445, 1340, 1285, 1240, 1130-1090, 930, 835	3.66	70.47	573 (DCI)
42-crown-14	2840, 1450, 1340, 1290, 1240, 1110-1090, 935, 840	3.66	70.43	617 (DCI)
45-crown-15	2840, 1450, 1340, 1275, 1235, 1100, 945, 835	3.65	70.45	661 (DCI)
48-crown-16	2850, 1465, 1345, 1285, 1245 1100, 955, 845	3.66	70.44	705 (FAB)
51-crown-17	2850, 1460, 1355, 1275, 1240, 1105, 940, 840	3.65	70.50	750 (FAB)
54-crown-18	2840, 1465, 1375, 1340, 1280, 1240, 1105, 960, 840	3.63	70.48	794 (FAB)
57-crown-19	2840, 1465, 1375, 1340, 1280, 1240, 1105, 960, 840	3.64	70.43	838 (FAB)
60-crown-20	2840, 1465, 1375, 1345, 1280, 1240, 1110, 940, 840	3.64	70.44	882 (FAB)

IR-4240 spectrophotometer. Neat liquids or Nujol mulls (solid compounds) were obtained between Irtran-4 (ZnSe) windows. The nmr spectra were recorded on a Varian XL-200 multinuclear spectrometer. Chemical shifts are recorded in parts per million downfield from internal reference tetramethylsilane (δ). The elemental analyses were carried out in a Hewlett-Packard F and M Scientific 185 apparatus. Electron impact mass spectra were obtained on a Hewlett-Packard 5992 (GC-MS system) spectrometer. DCI and FAB mass spectra were obtained on a quadrupole VG-Micromass 1212 and a Kratos MS-50-TATC, respectively, at the "Centre Régional de Spectrométrie de Masse de l'Université de Montréal".

Reagents.

Tetra-, penta- and hexaethylene glycols are commercially available from Aldrich Chem. Co. Polyethylene glycols ($n = 7$ to 10) [14] and their ditosylates [15] are known compounds.

Synthesis of Crown Ethers. General Procedure.

The appropriate ethylene glycol (5 mmoles) was dissolved in anhydrous tetrahydrofuran (125 ml) under a nitrogen atmosphere and potassium hydride (20 mmoles) was added slowly (15 minutes). The appropriate ditosylate (5 mmoles) in anhydrous tetrahydrofuran (125 ml) was added

over a period of two hours and the mixture was stirred overnight at room temperature. The excess potassium hydride was destroyed by careful addition of water and the solvent was evaporated under reduced pressure. The aqueous solution was then extracted with chloroform (3 x 100 ml) and the chloroform phase was dried over magnesium sulfate and evaporated. The oily residue was purified by column chromatography (neutral alumina) with first benzene and then chloroform as eluents. Solid crowns were recrystallized from acetone.

Acknowledgements.

The authors are grateful to Dr. Michel Bertrand (University of Montreal) for obtaining the DCI and FAB mass spectra. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada and by the "Ministère de l'Éducation du Québec".

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