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THE SYNTHESIS OF NOVEL CROWN ETHERS

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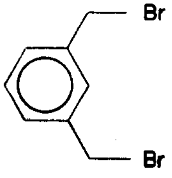
The synthesis and chemistry of macrocyclic polyethers are currently receiving a great deal of attention. Very recently Cram and co-workers[1,2] have reported the synthesis of two crown ethers (3c and 7b). We have prepared two series of novel crown ethers in which respectively, the 1,3- and 2,5-positions of a benzene and a furan ring are linked via a polyethylene glycol chain. As 3c and 7b are members of these series, the communications of Cram et al. have prompted us to disclose the preliminary results of our work.

A series of disodium or dipotassium polyethylene glycolates (derived from 2a) were reacted with equimolar amounts of 1,3-bis(bromomethyl)benzene (1) in apolar solvents without using high dilution conditions (0.1 M concentration)[3]. Reaction times of 1 to 3 hours at 110 °C were sufficient to effect complete conversion of the starting materials.



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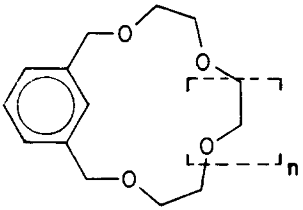
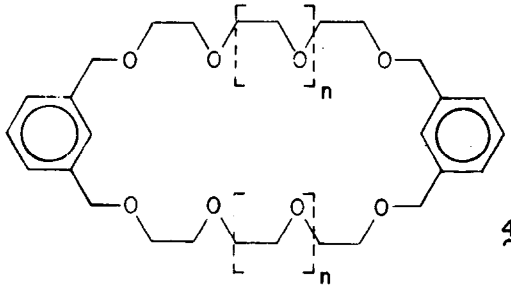
$RO(CH_2CH_2O)_{n+2}R$

2a, R=H, n=0 to 6
2b, R=Ts, n=1, 2, 4



3a, n=0
b, n=1
c, n=2
d, n=3
e, n=4
f, n=5
g, n=6



4a, n=0
b, n=1

The product mixtures could be completely separated by chromatography and subsequent distillation*. Three fractions were obtained, a 1:1 cyclic reaction product (3), a 2:2 cyclic reaction product (4), and products of higher molecular weight[4]. The yields of the isolated low molecular weight cyclic products (3 and 4) varied from 2 to 67 % when formed from the dipotassium glycolates (see Table 1).

TABLE 1

Reaction between 1,3-bis(Bromomethyl)benzene and Dipotassium Glycolates

Glycol 2a	Cyclic products % [a)]	3 in cyclic product % [b)]	Yield of 3 after isolation	Yield of 4 after isolation	Selectivity[c)] of 3
n = 0	72	10	2	30	0.1
n = 1	83	32	16	9	0.4
n = 2	81	88	67	--	2.5
n = 3	79	72	49	--	1.3
n = 4	70	40	18	--	0.4
n = 5	46	65	21	--	0.4
n = 6	59	45	21	--	0.4

a) after chromatography over neutral alumina with tetrahydrofuran

b) as determined by PMR

c) defined as yield of 3/yield of all other products.

The observed selectivity towards 1:1 cyclic products (3) is greatly dependent upon the chain length of the glycol (Table 1)[5]. This dependence can be interpreted in terms of a "template effect" of the potassium ion. Such a template effect has been suggested by others in order to explain the unexpectedly high yields of macrocyclic polyethers containing rings of 18-21 atoms[6]. Apart from the above-mentioned selectivity in the synthesis of the crown ethers 3, there are two other arguments which support the existence of a template effect for this system.

Firstly, extension of the period of addition of 1 to dipotassium tetraethylene glycolate from one to ten hours gave no marked difference in the yield of 3c (see Table 2)[7]. This means that

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* Boiling points were in the range of 150-250 °C at 1 Pa.

TABLE 2

Effect of varying the Period of Addition of 1 to Dipotassium Tetraethyleneglycolate

Addition time h	Crude product %	Cyclic[a)] product %	3c in cyclic[b)] product %
1	91	62	82
2	91	61	84
10	87	56	82

a) after chromatography over neutral alumina with tetrahydrofuran

b) as determined by PMR

the second step in the synthesis of 3c, the intramolecular displacement of the second bromomethyl group, is much faster than the competitive intermolecular displacement, which leads to polymerization. The difference in rate between an intermolecular and an intramolecular solvolysis must be attributed to a larger entropy contribution in the transition state of the latter, which in turn must be due to the formation of a highly ordered conformation during the first step of the synthesis (see Fig. 1). The obvious explanation for such a large difference in entropy contribution is a coordination of the polyether chain by the potassium ion[8].

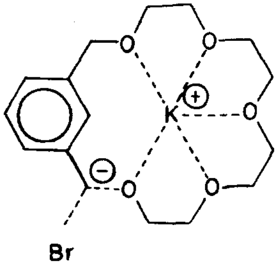
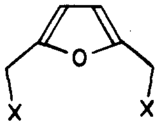


FIGURE 1

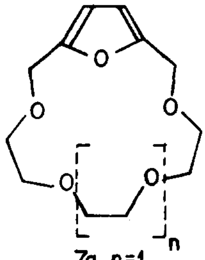
Secondly, the yields of 3 are low for 12- and 15- membered rings, reach a maximum for an 18-membered ring (3c, n =2) and gradually level out at a lower value for larger rings. We have been able to relate the marked difference between the yields of the 15- and the 18-membered rings with a difference between their relative complexity abilities with respect to potassium ions (complexation constants). For the complexation with Zeise's salt[9], e.g., $K_{3b}/K_{3c} = 7.5 \times 10^{-2}/9.00$.

A heteroaromatic compound containing two halomethyl substituents in the 1,3-positions, 2,5-bis(chloromethyl)furan (5)[10], was also reacted with the polyethylene glycolates derived from 2a. The yields of crown ethers were low, suggesting that this very reactive dihalide gives rise to side reactions under the prevailing reaction conditions[2].

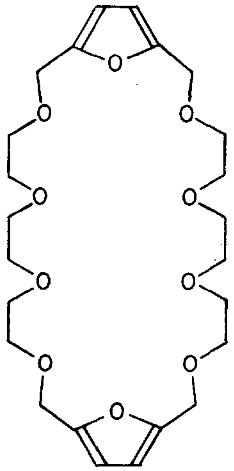
However, by using an alternative procedure in which the disodium or dipotassium salt of 2,5-bis(hydroxymethyl)furan (6) was reacted with polyethylene glycol ditosylates (2b) we obtained crown ethers 7 (10-30 % yield) and in one case 8 (~ 10 % yield).



5, X=CL
6, X=OH



7a, n=1
b, n=2
c, n=4



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2. J.M. Timko and D.J. Cram, J. Amer. Chem. Soc. 96, 7159 (1974).
3. a) F. Vögtle and M. Zuber, Tetrahedron Letters, 1972, 561;
   b) F. Vögtle and E. Weber, Angew. Chem. Internat. Edit, 13, 149 (1974).
4. All products were fully characterized by PMR, ^{13}CMR and mass spectrometry. Strong molecular ion peaks were observed in the mass spectra of all compounds at 70 eV.
5. With other bases, too, such as NaH or BuLi, a dependence of yield on glycol chain length was observed, but the yields of the isolated 1:1 cyclic adducts were generally lower.
6. See, for example, R.N. Greene, Tetrahedron Letters, 1972, 1793.
7. At slow addition rates the ratio of glycolate to 1,3-bis(bromomethyl)benzene is at least 10^3:1 during the first period of the reaction.
8. As discussed in reference 1, the ratio of the complexing powers of pentaethylene glycol dimethyl ether and of 18-crown-6 at 24 °C in $CHCl_3$ is $4.0/7.5 \times 10^4$.
9. R.T. Gray and D.N. Reinhoudt, Tetrahedron Letters, 1975, 000.
10. Prepared in five steps from 2-furoic acid in 29 % overall yield, or in two steps from sucrose [W.N. Haworth and W.G.M. Jones, J. Chem. Soc. 1944, 667].