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The Importance of the Template Effect in the Synthesis of Crown Ethers: a New Synthesis of 24-Crown-8

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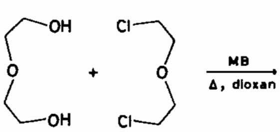
Since the discovery of crown ethers [1], a great deal of interest has centred on these compounds because of their importance as phase-transfer catalysts [2] and in synthetic applications based on the generation of nucleophilic anions [3]. However, this interest has mainly focused on crown ethers which incorporate benzene rings. Relatively little work has been done on the simple unsubstituted cyclic ethers, particularly the larger macrocycles, *e.g.* 21-crown-7 and 24-crown-8. The synthesis of these large macrocycles has been achieved either by oligomerisation of ethylene oxide in the presence of BF_3 and other similar fluorine compounds, *e.g.* PF_5 and SbF_5, or by a modified Williamson ether synthesis. Using the former route, a 2% yield of 24-crown-8 was obtained but this route necessitated the separation of other cyclic homologues [4]. Using the second route, Dale *et al.* [5] have reported at 15% yield of 24-crown-8 from the reaction of tetraethylene glycol and its ditosylate in benzene in the presence of potassium *tert*-butoxide. Greene [6] has also reported a 15% yield of 24-crown-8 from an unspecified combination of polyethylene glycol and a ditosylate of another polyethylene glycol. We have also obtained a 12% yield of 24-crown-8 from the reaction of tetraethylene glycol and its ditosylate in dioxan using potassium hydroxide as the base. As a continuation of our work on the template effect [7] in the synthesis of crown ethers [8], we report a new improved yield synthesis of 24-crown-8 from inexpensive starting materials (eqn. 1).



(1)

M = Li, Na; B = OH, OMe, H

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Experimental

Diethylene glycol in dry dioxan (refluxed over $LiAlH_4$ and distilled immediately prior to use) was added dropwise to a solution of base in dioxan. When the vigorous reaction to give the glycolate anion was complete, a solution of bis(2-chloroethyl)-ether in dry dioxan was added in a stream (5 min) to the stirred reactants. The reaction proceeded at reflux temperature and was followed by TLC (MeOH: CH_2Cl_2 = 1:1 solvent, silica, iodine development) until disappearance of glycol showed that the reaction was complete (4 hours). After extracting with CH_2Cl_2, the product was washed with H_2O and dried ($MgSO_4$). The product was distilled to give primarily 12-crown-4 (b.p. 58–65 °C at 0.2 torr) with lithium bases, and primarily 24-crown-8 (b.p. 170–205 °C at 0.2 torr, m.p. 16–18 °C) with sodium bases. The yields for the various bases are given in Table I.

TABLE I. Yields of 12-Crown-4 and 24-Crown-8 with Increasing Basicity of Bases in the Series MOH–MH.

Base	Yield(%) of 12-crown-4	Yield(%) of 24-crown-8
LiOH	0	0
LiOMe	8	<2
LiH	13	<2
NaOH	<1	4
NaOMe	4	20
NaH	6	9

Discussion

The results summarised in Table I are significant for two main reasons. Firstly the nature of base in the synthesis of macrocycles is shown to be important. Secondly, the template ion is shown to have a major effect in determining the ring size of the product. Despite the 'gauche effect' [9], whereby the natural conformation of an oligo-oxyethylene chain augments the synthesis of 12-crown-4, the use of sodium bases favours the synthesis of 24-crown-8. This is because, unlike the lithium ion (ionic diameter 1.36 Å [10]) which fits the cavity of 12-crown-4 (cavity diameter 1.4–1.7 Å [10],) the sodium ion (ionic diameter 1.96 Å [10]) is too big for the cavity of 12-crown-4 and consequently favours the formation of the larger macrocycle. It should be noted, however, that, although the template effect is obviously important in determining the product, the highest yield of 24-crown-8 was obtained with sodium methoxide, *i.e.* the nature of the base is important. Other factors which could be important are: the nature of the leaving group, *e.g.* chloride as compared to tosylate, and the solvent. For example, in the synthesis of 12-crown-4 (eqn. 1) we obtained a 24% yield using dimethylsulphoxide as solvent compared to 13% using dioxan [8b]. A detailed description of the factors affecting the synthesis of 12-crown-4 appears elsewhere [8b].

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References

1 C. J. Pedersen, 'Synthetic Multidentate Macrocyclic Compounds', Academic Press, New York, Ch. 1, (1978).
2 C. M. Starks and C. Liotta, 'Phase Transfer Catalysis, Principles and Techniques', Academic Press, New York, (1978).
3 C. Liotta, 'Synthetic Multidentate Macrocyclic Compounds', Academic Press, New York, Ch. 3, (1978)
4 J. Dale, G. Borgen and K. Daasuati, *Acta Chem. Scand., B28* 378 (1974), *Ger. Offen.*, 2,401,126 (1974); J. Dale, *Ger. Offen.*, 2,523,542 (1975).
5 J. Dale and P. O. Kirstiansen, *J. Chem. Soc. Chem. Comm.*, 670 (1971), *Acta Chem. Scand., B26,* 1471 (1972).
6 R. N. Greene, *Tetrahedron Letts.*, 1793 (1972), *Ger. Offen.*, 2,153,844 (1972).
7 M. de Sousa Healy and A. J. Rest, *Adv. Inorg. Chem. Radiochem., 28,* 1 (1978).
8 (a) B. R. Bowsher and A. J. Rest, *Inorg. Chim. Acta, 45,* L1 (1980). (b) *J. Chem. Soc. Dalton,* accepted for publication (paper no. 0/1211).
9 J. F. Stoddart, *Chem. Soc. Rev., 8,* 85 (1979).
10 Ionic diameters of cations and cavity diameters of crown ethers from X-ray diffraction data and CPK models respectively as quoted by: N. K. Dalley, 'Synthetic Multidentate Macrocyclic Compounds', Academic Press, New York, Ch. 4, p. 207 (1978).