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The Use of Alkali Metal Hydroxides in the Template Synthesis of 15-Crown-5

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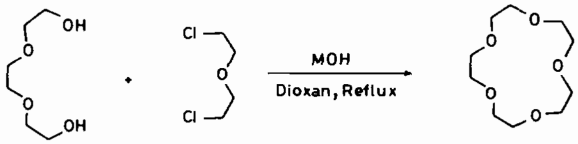
Since the discovery of crown ethers in 1967 by Pedersen [1], a great deal of interest has centred upon their synthesis [2] due to numerous applications such as the selective complexation of cations [3], use as phase-transfer agents and application to synthetic transformations, in particular in the generation of nucleophiles [4]. However few methods are available for the synthesis of crown ethers and these generally assume a template effect [5] in typical modified Williamson ether syntheses. Although a sodium template has always been assumed for the synthesis of 15-Crown-5 ethers [6], recent work has made this less certain. Reinhoudt *et al.* [7] investigated the use of metal fluorides as base for the template synthesis of benzo crown ethers and found that the yield of benzo 15-Crown-5 from reaction of catechol and tetraethylene glycol ditosylate was higher with rubidium and caesium fluoride than potassium fluoride and gave no reaction with lithium or sodium fluoride. Kellogg *et al.* [8] has reported a yield of 50% for the synthesis of benzo 15-Crown-5 from reaction of the dicaesium salt of catechol with dibromotetraethylene glycol, although it is uncertain as to whether the caesium is acting as a template ion in this case. Consequently it was decided to investigate in detail the synthesis of 15-Crown-5, from triethylene glycol and bis-(2-chloroethyl) ether, as performed initially by Reese *et al.* [9], with various alkali metal hydroxides.

The reaction was followed by TLC until the disappearance of the glycol showed that the reaction was complete. The experiment was conducted three times for each metal hydroxide to give a uniform yield (±5% of quoted figure).

The results, presented in Table I, show a template effect for all the metal ions as shown by the comparitive experiment with tetrabutyl ammonium hydroxide, and give a classical template effect as shown by the plot of yield *vs.* ionic diameter [10] in Fig. 1. In particular the use of thallium which, due to the inert s pair effect, has a similar size to potassium and has often been used as a probe for it in biological systems because of its chemical similarity [11], confirms that the yield is dependent in this case mainly on the metal cation size.

TABLE I. Yield of 15-Crown-5 from Alkali Metal Hydroxides.



Metal Hydroxide	Yield (%)
LiOH	4
NaOH	39
KOH	20
RbOH	15
CsOH	12
$Tl^{I}OH$	19
$N(nBu)_4OH$	<1

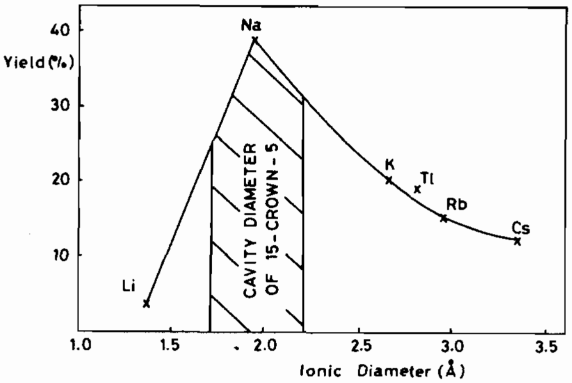


Fig. 1. Yield of 15-Crown-5 *vs.* ionic diameter of metal cation.

The asymmetry of the curve in Fig. 1 should be noted, indicating that although the reaction can proceed in a reasonable yield with a larger metal ion than the cavity diameter this is not the case for a smaller metal ion. Presumably this is because a larger metal ion, unlike a smaller one, could still give the correct conformation for the final cyclization step. This confirms the results of Reinhoudt *et al.* [7] and Kellogg *et al.* [8] where good yields of crown ethers were still obtained despite the metal cation being larger than the cavity hole; where other factors, such as the nature of the counter-ion as a base in promoting the formation of an ether bond, rule out the use of the 'ideal' metal cation.

Preliminary results from investigation of a similar reaction as catalyzed by alkaline-earth metal hydroxides show that yields are substantially lower than might be predicted on purely a template effect;

presumably due to the higher charge density of the alkaline-earth cations causing a stronger interaction with the anion. This demonstrates once again that this is a complex field and shows the difficulty of isolating a single factor as the only reason for the production or yield of a particular product. In particular the nature of the anion and solvent require further study.

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