Use of Alkali- and Alkaline-earth-metal Ions in the Template Synthesis of 12-Crown-4, 15-Crown-5, and 18-Crown-6 †

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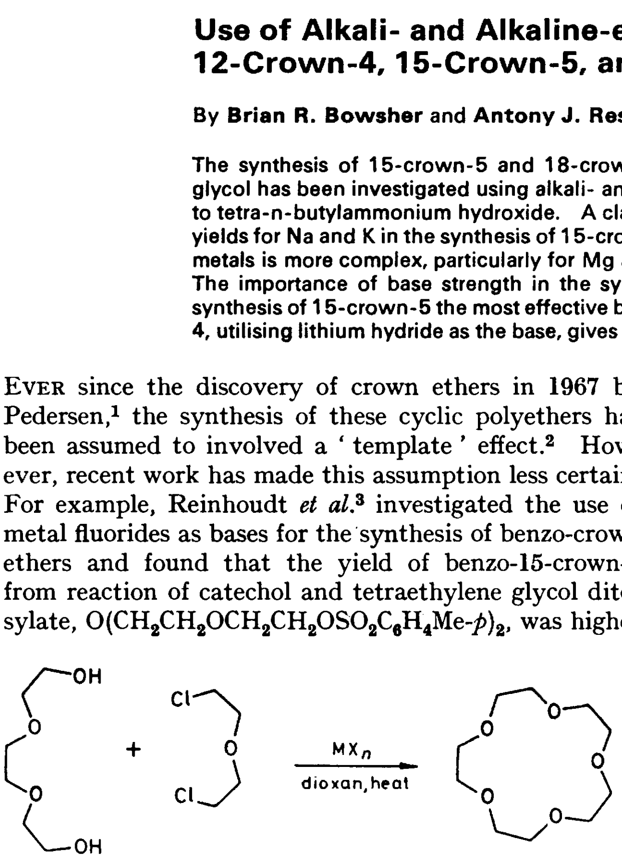
The synthesis of 15-crown-5 and 18-crown-6 from bis(2-chloroethyl) ether and the appropriate polyethylene glycol has been investigated using alkali- and alkaline-earth-metal hydroxides as ' template ' agents in comparison to tetra-n-butylammonium hydroxide. A classical template effect is observed for the alkali metals, giving optimum yields for Na and K in the synthesis of 15-crown-5 and 18-crown-6 respectively, but the action of the alkaline-earth metals is more complex, particularly for Mg and Ca where involvement with the counter ion prevents a good yield. The importance of base strength in the synthesis of 15-crown-5 and 12-crown-4 is demonstrated, *e.g.* in the synthesis of 15-crown-5 the most effective base is found to be sodium methoxide. A novel synthesis of 12-crown-4, utilising lithium hydride as the base, gives a 24% yield, the highest yield so far reported.

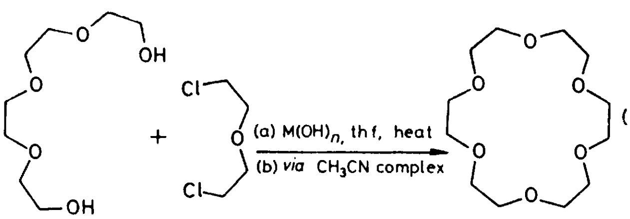
EVER since the discovery of crown ethers in 1967 by Pedersen,[1] the synthesis of these cyclic polyethers has been assumed to involved a ' template ' effect.[2] However, recent work has made this assumption less certain. For example, Reinhoudt *et al.*[3] investigated the use of metal fluorides as bases for the synthesis of benzo-crown ethers and found that the yield of benzo-15-crown-5 from reaction of catechol and tetraethylene glycol ditosylate, $O(CH_2CH_2OCH_2CH_2OSO_2C_6H_4Me\text{-}p)_2$, was higher with rubidium and caesium fluorides than with potassium fluoride and gave no reaction with lithium or sodium fluorides. A further example is the reported[4] yield of 50% for the synthesis of benzo-15-crown-5 from the dicaesium salt of catechol and dibromotetraethylene glycol, $O(CH_2CH_2OCH_2CH_2Br)_2$, although it is uncertain as to whether the caesium ion is acting as a template ion in this case. Consequently it was decided to investigate in detail the template action of various alkali- and alkaline-earth-metal hydroxides in the synthesis of 15-crown-5 (1) [equation (i) (a)] and 18-crown-6 [equation (ii)].



(i)

(1)

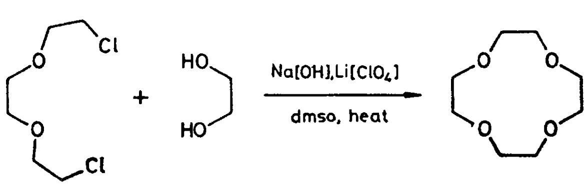
(a) M = Li, Na, K, Rb, Cs, Mg, Ca, Sr, Ba, Tl, or NBu^n_4 ; X = OH
(b) M = Na ; X = F, OH, OMe, NH_2, or H



(ii)

(2)

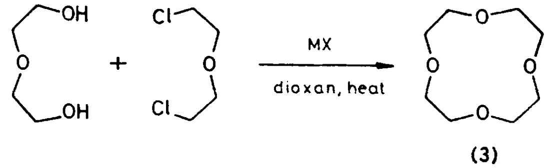
M = Li, Na, K, Rb, Cs, Mg, Ca, Sr, Ba, Tl, or NBu^n_4
thf = tetrahydrofuran



(iii)

(3)

In the acid-catalysed condensation of furan with acetone in the presence of some alkali-, alkaline-earth-, and transition-metal salts it has recently been shown[5] that the yield of the cyclic tetrameric macrocycle was related to changes in the acidity of the reaction medium rather than to specific template-effect properties of the metal ions. Hence the effect of different bases with a common cation was examined for the synthesis of 15-crown-5 [equation (i) (b)].



(iv)

(3)

M = Li or Na; X = OH, OMe, or H

12-Crown-4 is a particularly interesting compound in that there are few reported syntheses and these tend to give low yields (≤15%). In the main the synthesis of unsubstituted 12-crown-4 has been by the acid-catalysed cyclic tetramerisation of ethylene oxide.[6] However, despite the '*gauche*' effect[7] whereby the natural conformation of the growing oligo-oxyethylene chain augments the synthesis of 12-crown-4, and the use of template ions, these syntheses give a low yield (15%) of 12-crown-4 as well as a mixture of other cyclic polyether products. 12-Crown-4 has been prepared in a modified Williamson ether synthesis [equation (iii), 13% yield].[8] This is an unusual reaction because the

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† 1,4,7,10-Tetraoxacyclododecane, 1,4,7,10,13-pentaoxacyclopentadecane, and 1,4,7,10,13,16-hexaoxacyclo-octadecane respectively.

12-crown-4 was not obtained if $Li[ClO_4]$ was absent. Identical runs with $Li[OH]·H_2O$ rather than Na[OH] also gave no product, as did analogous runs with $Li[ClO_4]$ in thf instead of dimethyl sulphoxide (dmso). Consequently a study of the synthesis of 12-crown-4 using a new route [equation (iv)] was undertaken together with an investigation of the role of various bases in this reaction and also the role of the solvent.

EXPERIMENTAL

1,4,7,10,13-*Pentaoxacyclopentadecane* (1)–*Sodium Template.*[9]—A three-necked round-bottomed flask (500 cm^3), fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel (100 cm^3), was charged with 96% Na[OH] pellets (17.2 g, 0.43 mol dm^{-3}), practical grade triethylene glycol (10.8 g, 0.125 mol dm^{-3}), and dioxan (90 cm^3). The reaction vessel was placed in a heating mantle and warmed gently with stirring. After 15 min a solution of bis(2-chloroethyl) ether (44.7 g, 0.31 mol dm^{-3}) in dioxan (30 cm^3) was added in a stream from the dropping funnel to the vigorously stirred reactants. The reaction mixture was then heated, under reflux, with stirring and the reaction was followed by thin-layer chromatography [Si gel, MeOH–CH_2Cl_2 (1 : 1 v/v) solvent] until the disappearance of the glycol showed that the reaction was complete (*ca.* 24 h). The products were cooled and evaporated under reduced pressure to give a brown slurry to which dichloromethane (60 cm^3) was added. The resultant mixture was filtered and the residue washed with dichloromethane (20 cm^3). The combined filtrate and washings were dried ($Mg[SO_4]$), evaporated under reduced pressure, and then carefully distilled through a lagged 10-cm Vigreux column to give the cyclic polyether (10.8 g, 39%) as a colourless liquid (b.p. 96—100 °C at 0.02 Torr).*

Use of other metal hydroxides. The synthesis of (1) was repeated using equimolar quantities of the following metal hydroxides (reagent grade from Aldrich Chemical Company or Alfa Products): Li[OH], K[OH], Rb[OH], Cs[OH], $Mg[OH]_2$, $Ca[OH]_2$, $Sr[OH]_2$, $Ba[OH]_2$, and Tl[OH]. The synthesis was also attempted with tetra-n-butylammonium hydroxide (40% aqueous solution from Aldrich) to provide comparative experiments with a non-template ion.

Use of different bases. The synthesis of (1) was repeated using equimolar amounts of the following bases: NaF, Na[OMe], $Na[NH_2]$, and NaH. For these reactions it was found to be essential that the solvent was dry so the dioxan was refluxed over $Li[AlH_4]$ for 3 h and distilled immediately prior to use. Reactions of Na[OMe], $Na[NH_2]$, and NaH were carried out under nitrogen, and the glycol in dioxan was slowly and very carefully added dropwise (30 min) to the base, also in dioxan. This modification was necessary because of the extremely vigorous reaction to give the glycolate anion. Sodium hydride was used directly as its 50% mineral-oil dispersion; after removal of dichloromethane, the mineral oil separated out and was removed.

1,4,7,10,13,16-*Hexaoxacyclo-octadecane* (2)–*Potassium Template.*[9]—A three-necked round-bottomed flask (500 cm^3), fitted with an efficient mechanical stirrer, a reflux condenser, and a dropping funnel (100 cm^3), was charged with 85% potassium hydroxide pellets (41.6 g, *ca.* 0.63 mol dm^{-3}), practical grade tetraethylene glycol (24.3 g, 0.125 mol dm^{-3}), and tetrahydrofuran (100 cm^3). The reaction vessel was placed in a heating mantle and warmed gently. After 15 min a solution of bis(2-chloroethyl) ether (45.0 g, 0.313 mol dm^{-3}) in thf (20 cm^3) was added in a stream from the dropping funnel to the vigorously stirred reactants. The reaction mixture was treated analogously to that for 15-crown-5 and distillation gave a discoloured liquid (20.3 g), b.p. 110—200 °C (0.02 Torr). The distillate was then purified by the method of Cram and co-workers,[9] *viz.* the crude 18-crown-6 was dissolved in acetonitrile (50 cm^3) and the solution was slowly cooled with stirring to −55 °C (methanol–solid CO_2 bath) to give the acetonitrile–18-crown-6 complex as fine white crystals. The solid was filtered off. On heating it decomposed and pure 18-crown-6 (10.1 g, 30%) collected as a white crystalline solid (m.p. 37—39 °C) on the walls of the flask.

TABLE 1

Yields of 15-crown-5 with various metal hydroxides in a number of series of experiments

Base	Yield/%			Base	Yield/%	
Li[OH]	5	4		$Mg[OH]_2$	<1	2
Na[OH]	36	41	39	$Ca[OH]_2$	<1	3
K[OH]	15	24	19	$Sr[OH]_2$	4	4
Rb[OH]	15	15		$Ba[OH]_3$	5	8
Cs[OH]	10	11	14			
Tl[OH]	17	20		$[NBu^n_4][OH]$	<1	<1

Use of other metal hydroxides. The synthesis of (2) was repeated using equimolar quantities of the following metal hydroxides: Li[OH], Na[OH], Rb[OH], Cs[OH], $Mg[OH]_2$, $Ca[OH]_2$, $Sr[OH]_2$, $Ba[OH]_2$, and Tl[OH]. The synthesis was also attempted with tetra-n-butylammonium hydroxide to provide comparative experiments with a ' non-template ' ion.

1,4,7,10-*Tetraoxacyclododecane* (3)–LiH *Base.*—A three-necked round-bottomed flask (250 cm^3), fitted with an efficient mechanical stirrer, a reflux condenser, and a dropping funnel (100 cm^3), was charged with 98% lithium hydride (3.5 g, 0.44 mol dm^{-3}) and dry dioxan (60 cm^3) (freshly distilled after refluxing over $Li[AlH_4]$ for 3 h). Practical grade diethylene glycol (13.3 g, 0.125 mol dm^{-3}) in dry dioxan (30 cm^3) was added dropwise to the reaction mixture. When the vigorous reaction to give the glycolate anion was complete, a solution of bis(2-chloroethyl) ether (44.7 g, 0.31 mol dm^{-3}) in dry dioxan (30 cm^3) was added in a stream from the dropping funnel to the vigorously stirred reactants. The reaction proceeded, under nitrogen, as for 15-crown-5 until distillation gave a colourless liquid (4.9 g), b.p. 58—65 °C (0.2 Torr). A sample of the distillate was taken and purified by column chromatography [silica gel, MeOH–CH_2Cl_2 (50 : 50) eluant] to give a pure sample of 12-crown-4 (13%).

TABLE 2

Yields * of 18-crown-6 with various metal hydroxides in a number of series of experiments

Base	Yield/%			Base	Yield/%		
Li[OH]	1	2	2	$Mg[OH]_2$		1	2
Na[OH]	14	17	17	$Ca[OH]_2$		2	3
K[OH]	27	29	34	$Sr[OH]_2$	5	10	9
Rb[OH]		20	27	$Ba[OH]_2$		20	25
Cs[OH]	18	17	20				
Tl[OH]		29	26	$[NBu^n_4][OH]$	<2	6	5

* Data in part from ref. 12.

Use of different bases. The synthesis of (3) was repeated

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* Throughout this paper: 1 Torr = (101 325/760) Pa.

using equimolar amounts of the following bases: Li[OH], Li[OMe], Na[OH], Na[OMe], and NaH.

Use of dimethyl sulphoxide (dmso) as solvent. The synthesis of (3) was repeated using equal volumes of dmso instead of dioxan. Due to its high boiling point the dmso could not be removed by evaporation at reduced pressure. Hence when the reaction was complete the solution was cooled, filtered, and the fitrate added to distilled water (700 cm^3). The water solution was extracted with four 700-ml aliquots of methylene chloride, the combined extracts dried (Mg[SO$_4$]), and the CH_2Cl_2 removed by rotary evaporation. The product was then distilled and purified as before to give a pure sample of 12-crown-4 (24%).

RESULTS

(*a*) *Template Synthesis of* 15-*Crown*-5 *and* 18-*Crown*-6.—The yields of 15-crown-5 and 18-crown-6 are presented in Tables 1 and 2. The averaged yields are shown in Figures 1 and 2 respectively in the plots of yield (%) *vs.* ionic diameter (from *X*-ray data).[10] The cavity diameters (from CPK models) [10] of 15-crown-5 and 18-crown-6 are superimposed on Figures 1 and 2. A preliminary report of the data for 15-crown-5 has appeared elsewhere.[11]

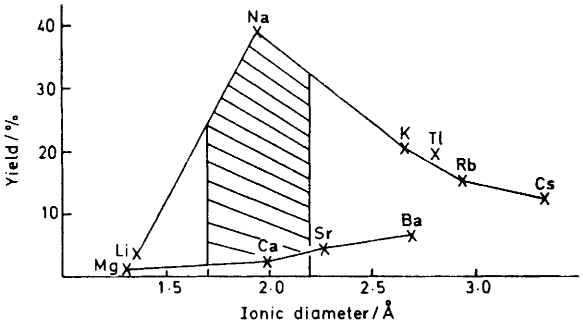


FIGURE 1 Plot of yield of 15-crown-5 *versus* ionic diameter of metal-ion template (shaded region corresponds to the cavity diameter of 15-crown-5)

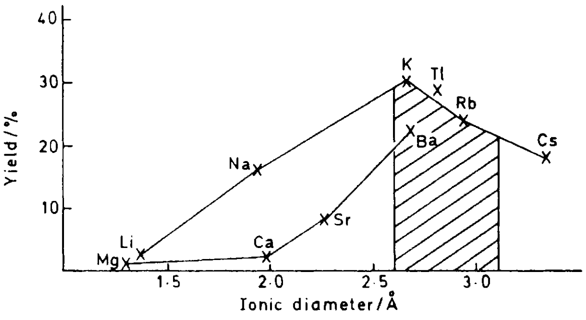


FIGURE 2 Plot of yield of 18-crown-6 *versus* ionic diameter of metal-ion template (shaded region corresponds to the cavity diameter of 18-crown-6)

(*b*) *Synthesis of* 15-*Crown*-5 *and* 12-*Crown*-4 *with Different Bases*.[12]—The yields of 15-crown-5 and 12-crown-4 utilising various bases are presented in Tables 3 and 4 respectively.

DISCUSSION

The Template Effect.—In general the synthesis of macrocycles is not favoured kinetically and has to be performed either in highly dilute solutions or in the presence of a metal cation. A mechanism for the template effect in the synthesis of 18-crown-6 has been proposed by Greene [13] as shown in equation (v). It was proposed that the metal acts by complexing to the oxygens, before the second Ts (tosyl = toluene-*p*-sulphonyl) group is lost, so as to hold the cyclising groups in close proximity and thus aid ring closure.

TABLE 3

Yields of 15-crown-5 with various bases in increasing basicity NaF to NaH in several series of experiments

Base	Yield/%			Average yield/%
NaF	0			0
Na[OH]	36	41	39	39
Na[OMe]	65	66		66
Na[NH$_2$]	50	47		48
NaH	39	54	48	47

The proposed mechanism appears to be valid for the synthesis of 15-crown-5 and 18-crown-6 using alkali-metal hydroxides because it was found that in comparison to tetra-n-butylammonium hydroxide, which due to its size could not exert a template effect, most of the cations gave an improved yield. Furthermore, the maximum yield for each macrocycle coincided with the use of the metal ion which most closely fitted the macrocyclic cavity. The results were also confirmed by the use of thallium which, due to the inert *s*-pair effect, has a similar size to potassium.[14]

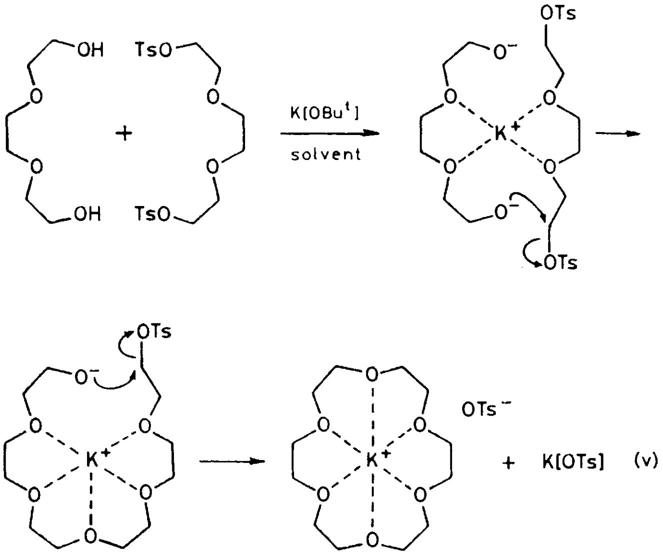


TABLE 4

Yields of 12-crown-4 with various bases in increasing basicity M[OH] to MH in several series of experiments

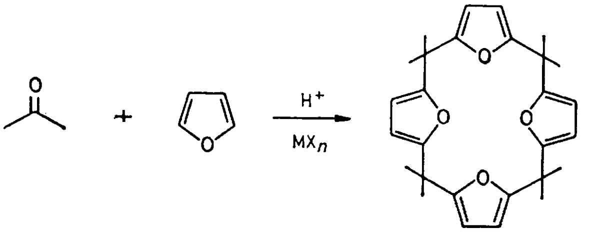
Base	Yield [a]/%		Average yield/%
Li[OH]	0		0
Li[OMe]	6	10	8
LiH [b]	10	15	13
Na[OH]	0	1	<1
Na[OMe]	4(18)	4(22)	4(20)
NaH	6(11)	5(7)	6(9)

[a] Figures in parentheses represent yield of 24-crown-8.
[b] Use of dmso as solvent rather than dioxan gave a yield of 24%.

The asymmetry of the curves in Figures 1 and 2 should be noted. It indicates that, although in general crown ethers cannot be synthesised employing cations of substantially smaller diameter than the cavity of the macrocycle, they can be produced in quite reasonable yields using cations that are substantially larger. This is confirmed by the results of Reinhoudt *et al.*[3] where alkali-metal fluorides were used as base. We believe that the ability of a metal cation to act as a co-ordination template in the formation of a macrocycle is strongly related to its ability to form a complex with that macrocycle. Consequently further evidence of this asymmetry is to be found in the wide variety of alkali metals that are known to complex with crown ethers of much smaller size.[15] The crown ether complexes with larger cations occur because the macrocyclic cavity is not deformed and the cation tends to be polarised (ligand encapsulation).[15] The template effect appears to be particularly predominant in the synthesis of 12-crown-4 where the lithium salt of the base gave a higher yield of 12-crown-4 than did the sodium salt of the same base. The template effect is manifested when sodium bases are used where, because of its large size, 1.96 Å,[10] the cation cannot fit into the cavity of 12-crown-4, 1.4—1.7 Å,[10] and consequently favours the synthesis of 24-crown-8, in relatively high yield, from two molecules of both diethylene glycol and bis(2-chloroethyl) ether. This is in contrast with the use of lithium salts, 1.36 Å,[10] which because of a better 'fit' give 12-crown-4 almost exclusively as the only cyclic product.

However, the synthesis of the cyclic polyethers, particularly 15-crown-5, using the alkaline-earth-metal hydroxides gave a different picture which is not accounted for by the template effect above. As stated above, we believe in a strong correlation between the template role and the complexing ability of a metal and therefore an insight into these results is afforded by an examination of the alkali- and alkaline-earth-metal complexes of crown ethers. Poonia and co-workers [15] have investigated the binding of alkaline-earth metals to cyclic polyethers and have found that the complexation of magnesium and calcium to crown ethers was difficult due to the high charge density of these cations which favoured a higher interaction with the counter ion. Indeed the anionophilicity of calcium is such that a complex has recently been reported [16] where the calcium is in an exclusive anion–solvent environment, despite the presence of a crown ether with the right cavity size. The synthesis of calcium and magnesium complexes with crown ethers is possible only when the crown ether is potentially nucleophilic and such factors as the nature of the counter ion, which should favour solubilisation of the salt in an organic environment, and the polarity of the solvent greatly influence complexation. It is apparent that the difficulties associated with complexation are extended to the role of the alkaline-earth metals as template ions. As the size of the cation increases, the involvement with the counter ion (in this case OH^-) becomes less, as shown by the improved yields of both 15-crown-5 and 18-crown-6 using strontium and barium hydroxides (Tables 1 and 2). Indeed, the highest yields of both crown ethers using alkaline-earth-metal hydroxides were obtained with $Ba[OH]_2$ despite Ba having the poorest 'fit' for 15-crown-5. In fact $Sr[OH]_2$ and $Ba[OH]_2$ have previously been successfully used [17] as template ions in crown-ether syntheses, although it should be noted that this was reported for aqueous solutions which, as proton donors, would favour such complexation.

The Effect of Base.—The action of metal salts in the acid-catalysed condensation of acetone with furan to give the cyclic tetramer (4), as shown in equation (vi), has recently been reported [5] to affect the acidity of the reaction medium rather than to involve a template role for the metal ions. The reaction is favoured by the use of strong acid ($HClO_4$), and salts, which further increase the acidity of the medium according to equation (vii),[18] will also increase the yield of the furan–acetone macrocycle. In general, salts with a cation of small radius



(4) (vi)

M = alkali-, alkaline-earth-, or transition-metal
X = Cl, Br, I, SCN, or ClO_4

$$pH_m = pH_0 - 0.0555M_s(Z^+Z^-)\left(\frac{h_+}{r_+} - \frac{h_-}{r_-}\right) \quad \text{(vii)}$$

where pH_m = pH to which a salt of concentration M has been added
pH_0 = pH of acid
Z_+, Z_- = charges of cation and anion of salt
r_+, r_- = ionic radii of cation and anion of salt
h_+, h_- = functions of hydration requirement of ion

and high hydration function and anions which are poorly hydrated, *e.g.* Li[ClO_4], will increase the acidity and hence the yield of macrocycle. It can also be seen that there is a close correlation between some of the parameters in equation (vii) and those that fulfil the requirements for a template action, thus explaining the initial proposal of a template effect.

It was thought that a similar effect may be responsible for the yields of the crown ethers 15-crown-5 and 18-crown-6, *i.e.* the predominant factor in determining the yield of products will be the strength of the base. In this connection it should be noted that the basicity of the alkali- and alkaline-earth-metal hydroxides increases with ionic diameter as given in Table 5.[19] It can also be seen that the basicity of the alkali-metal hydroxides is substantially higher than the corresponding alkaline-earth-metal hydroxide. It is therefore probable that base strength is a contributory factor to the asymmetry of Figures 1 and 2 for the alkali-metal hydroxides as well as increased yields for the higher alkaline-earth-metal hydroxides (Sr, Ba) compared to $Ca[OH]_2$ and $Mg[OH]_2$.

Further examination of the effect of base utilising a common cation, in the synthesis of 15-crown-5, as given in Table 3, shows a strong dependence on base strength. This ranges from the zero yield with NaF, which presumably is not a strong enough base to promote anion formation unlike the fluorides of potassium, rubidium, and caesium,[3] to a maximum yield of 66% achieved with Na[OMe] which has a basicity of *ca.* 10^3 times that of Na[OH].[20] There does seem to be an optimum base strength as illustrated by the use of the very strong bases $Na[NH_2]$ and NaH where the yield of 15-crown-5 was lower than for Na[OMe]. For $Na[NH_2]$ and NaH complete dissociation occurs, and the production of a large amount of polymer indicates the lowered effectiveness of any co-ordination template effect. The synthesis of 12-crown-4 however exemplifies the importance of base-strength effects as shown in Table 4, with the strongest base, LiH, giving the maximum yield of cyclic polyether. Similarly the yield of 24-crown-8 was maximised with the strongest base, NaH, where, because of the template effect, the larger macrocycle was synthesised in preference to 12-crown-4. These results may also explain the unusual results of Liotta and co-workers,[8] equation (iii), where only the addition of $Li[ClO_4]$ to the reaction media gave 12-crown-4. That is, addition of $Li[ClO_4]$ increased the basicity of the reaction media according to equation (vii) and thus favoured macrocycle formation. It also explains why the use of Li[OH] failed to give the desired product because, despite the template effect, it was simply not a strong enough base.

TABLE 5

pK_a values of various alkali- and alkaline-earth-metal hydroxides (at 25 °C, in water) *

Base	pK_a	Base	pK_a
Li[OH]	13.82	$Mg[OH]_2$	11.42
Na[OH]	14.77	$Ca[OH]_2$	12.9
K[OH]	16.0	$Ba[OH]_2$	13.36

* Data from ref. 19.

This reaction also illustrates the importance of solvent in the synthesis of crown ethers. Liotta and co-workers [8] found that the synthesis of 12-crown-4 according to equation (iii) failed to proceed in thf and only went in dmso. Similarly, our results having found the optimum base, gave a substantially higher yield of 12-crown-4 in dmso (24%) than in dioxan (13%). This is mainly due to dmso being a more polar solvent than dioxan and consequently favouring the stability of the intermediate complex. However, it is worth noting that basicity increases by a factor of 10^{14} in going from a solution of 0.011 mol dm^{-3} tetramethylammonium hydroxide to 95% dmso solution,[20] due to the dmso and OH ions competing for the solvent water, giving a less hydrogen-bonded, more reactive hydroxide species as the amount of dmso is increased. So once again this effect may at least be partly attributed to base strength.

Conclusion.—In conclusion, it has been demonstrated that, although the template effect does apply for the synthesis of crown ethers using alkali-metal hydroxides, on the whole metal-ion template enhancement of reactions cannot be treated as the only factor in the synthesis of macrocycles. This is because of the importance of other considerations apart from the size of the metal cation in relation to the size of the crown ether cavity, such as the charge density of the cation, solvent dependence, and, perhaps above all, the base strength of the reaction medium.

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