Template Synthesis and Ionophorous Properties of Substituted Crown Ethers towards Alkali-metal Ions

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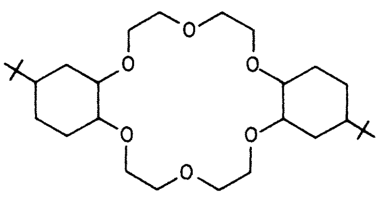
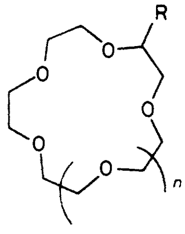
A number of alkyl-substituted crown ethers of the type 2-R-12-crown-4, 2-R-15-crown-5, and 2-R-18-crown-6 (R = Me, Et, octyl, decyl, tetradecyl, icosyl, or Ph) have been prepared in relatively good yields by a novel synthetic route employing the metal-ion template effect. The ionophorous properties of these crown ethers with respect to the transport of lithium, sodium, and potassium picrates across a bulk liquid chloroform membrane were measured and have been compared to those of crown ethers already used as ionophores. Substitution of alkyl and phenyl groups on the crown ethers, making them more lipophilic, does not seem to assist the transport of Na^+ and K^+ as their picrate salts, but rather appears to make the ionophore more susceptible to remain in the chloroform phase, as the chain length increases, and thereby leads to a reduction in transport. Introduction of alkyl and other groups, however, does seem to assist the transport of Li^+ as lithium picrate, although the overall rate of transport is considerably slower for Li^+ than the rate for Na^+.

Whilst much of the interest in crown ethers may be ascribed to their similarity to natural ionophorous antibiotics, it had been noted that preliminary results for the ion-transporting abilities of crown ethers had been disappointing when compared with these antibiotics.[1-5] However one compound which showed more potential as a model ionophore was bis(t-butylcyclohexyl)-18-crown-6 {2,13-bis(t-butyl)icosahydro-dibenzo-[*b*,*k*][1,4,7,10,13,16]hexaoxacyclo-octadecin} (1).[6,7] This was attributed to its greater lipophilicity, causing greater partitioning into an organic phase than the corresponding unsubstituted dicyclohexyl-18-crown-6, and therefore enhancing the conductance of the bi-layer membrane.[6,7] Similarly it had been found that organophilic crown ethers were most successful as phase-transfer agents.[8] Consequently it was decided to synthesise a series of alkyl (R) substituted crown ethers of the types (2)—(4). Particular emphasis was placed on substituted 15-crown-5 ethers (3) due to their specificity for Na^+, a property which many of the natural antibiotics, with the exception of monensin, do not possess. The bulk liquid membrane technique, developed by Christensen,[9] and Izatt and co-workers[10] as a model for biological membranes, was used to measure the ionophorous properties of the new crown ethers.



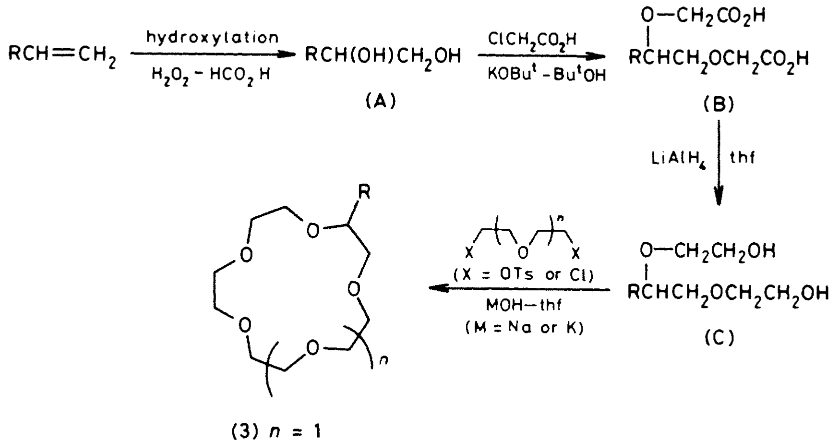
(1)



(2) *n* = 0
(3) *n* = 1
(4) *n* = 2

Experimental

Synthesis of Alkyl-substituted Crown Ethers.—Initially the route chosen to compounds of types (3) and (4) was the multistep route of Cinquini and Tundo[8] [equation (i);

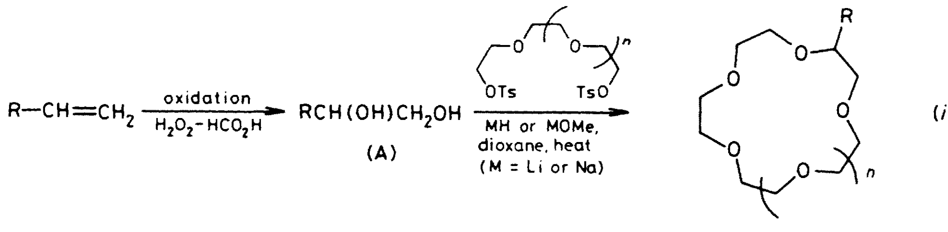


(*i*)

(3) *n* = 1
(4) *n* = 2
R = $C_{10}H_{21}$(d) or $C_{20}H_{41}$(f)

Ts = toluene-*p*-sulphonyl, thf = tetrahydrofuran]. In this way, the syntheses of 2-icosyl-15-crown-5 * (3f), 2-decyl-18-crown-6 (4d), and 2-icosyl-18-crown-6 (4f) were achieved in low overall yields.

The synthesis of alkyl-substituted crown ethers was greatly simplified and improved [equation (ii)] by using optimum template [11] conditions developed through a study of the unsubstituted crown ethers.[12] This approach overcame the difficulty of cyclisation of the secondary alcohol (A). While this work was in progress,[13] Gokel and co-workers[14-16] reported the use of similar cyclisation reactions in the preparation of various substituted crown ethers. Okahara and co-workers [17-19] have also utilised the template effect in novel syntheses of substituted crown ethers.



(*ii*)

(2) *n* = 0
(3) *n* = 1

R = CH_3 (a), C_2H_5 (b), C_8H_{17} (c), $C_{10}H_{21}$ (d), $C_{14}H_{29}$ (e) $C_{20}H_{41}$ (f), or C_6H_5 (g)

15-Crown-5, 18-crown-6, 12-crown-4, and 24-crown-8 were prepared by a previously reported procedure.[12] The syntheses of 2-icosyl-15-crown-5 (3f), 2-decyl-18-crown-6 (4d), and 2-icosyl-18-crown-6 (4f) employed the route [equation (i)] of Cinquini and Tundo.[8] Diols were prepared on the basis of the synthesis of Swern *et al.*[20]

General Method for the Preparation of Substituted 15-*Crown*-5 *Ethers*.—A 100-cm^3 three-necked round-bottomed flask fitted with an efficient mechanical stirrer, a reflux condenser, and a 50-cm^3 dropping funnel was charged with sodium methoxide (2.16 g, 0.04 mol) and dry dioxane (12 cm^3). To the reaction mixture was added, with stirring, the diol (0.016 mol) in dry dioxane (5 cm^3) dropwise, over 10 min. When reaction to give the glycolate anion was complete, a solution of 1,2-bis[2′-(toluene-*p*-sulphonyloxy)ethoxy]ethane (10.0 g, 0.02 mol) in dry dioxane (8 cm^3) was added slowly, over 5 min, from the dropping funnel to the vigorously stirred reactants. The reaction mixture was then heated, under reflux, with stirring and followed by thin-layer chromatography [silica gel, MeOH–CH_2Cl_2 (1 : 1 v/v) solvent] until disappearance of the glycol showed that the reaction was complete. After allowing the reaction to cool, dichloromethane (25 cm^3) was added, the mixture filtered, the filtrate washed with water (2 × 10 cm^3), and dried ($MgSO_4$). The solvent was removed at reduced pressure to give the crude product as a brown oil. This was either purified by column chromatography [silica gel, acetone–light petroleum (b.p. 40—60 °C) (1 : 1 v/v) eluant] or by a small scale distillation, generally using a Kugelrohr apparatus.

General Method for the Preparation of Substituted 12-*Crown*-4 *Ethers*.—A similar method of preparing the substituted 12-crown-4 ethers to that of the 15-crown-5 ethers was employed but equivalent amounts of lithium hydride and bis[2-(toluene-*p*-sulphonyloxy)ethyl] ether (ditosylate of triethylene glycol) were substituted for the sodium methoxide and 1,2-bis[2′-(toluene-*p*-sulphonyloxy)ethoxy]ethane respectively.

The compounds prepared in this work (Table 1) were characterised primarily by ^{1}H n.m.r. spectroscopy with supportive i.r. and mass spectral data (Table 2). The ^{1}H n.m.r. data for some compounds prepared according to equation (ii) agreed with data for the same compounds prepared by different routes. Attempts to obtain C and H analyses were unsuccessful possibly due to the hygroscopic nature of the compounds.

Table 1. A summary of the alkyl-substituted crown ethers prepared in this study

Substituent R	‘ 12-crown-4 ’ (2)	‘ 15-crown-5 ’ (3)	‘ 18-crown-6 ’ (4)
(a) CH_3	*a*	*a*	—
(b) C_2H_5	—	*a*	—
(c) C_8H_{17}	—	*a*	—
(d) $C_{10}H_{21}$	—	*a*	*b*
(e) $C_{14}H_{29}$	—	*a*	—
(f) $C_{20}H_{41}$	*a*	*a*, *b*	*b*
(g) C_6H_5	*a*	*a*	—

[a] Prepared by the novel synthetic route shown in equation (ii). [b] Prepared by the method shown in equation (i) (ref. 8).

Ion-transport Experiments.—The apparatus for these experiments [13] was based on that developed by Christensen and co-workers.[21] A 120-cm^3 sample of the liquid membrane, chloroform (AnalaR) containing the crown ether (typically 10^{-3} mol) was placed in a 90-mm diameter glass crystallising dish with a 24-mm magnetic follower. A 42-mm diameter glass cylinder was inserted partly into the chloroform layer and clamped into position. Distilled water (60 cm^3) was carefully introduced to the outer ring as the receiving phase, and a picrate solution (15 cm^3, 0.01 mol cm^{-3}) was similarly introduced to the inner cylinder above the chloroform layer as the source phase. The membrane was stirred at approximately 80 r.p.m. Samples were withdrawn from the receiving phase at 1-h intervals and the absorption of picrate recorded at 360 nm.

Results

Determination of Ionophorous Properties.—(*i*) *General comments*. The addition of a ‘ good ’ ionophore to the chloroform membrane gave the plot shown in Figure 1(*a*). The rate

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* 2-Icosyl-1,4,7,10,13-pentaoxacyclopentadecane.

Table 2. Yields, physical properties, and spectroscopic properties of the new crown ethers prepared in this study

Compound	Yield (%)	B.p. (°C)/mmHg	^{1}H N.m.r. [a] (δ vs. $SiMe_4$)	Mass spectrum	I.r. [b]/cm^{-1}
(2g) 2-Phenyl-12-crown-4	12	110—126/0.05	7.20 (s, 5 H, C_6H_5), 4.60 (m, 1 H, OC*H*Ph), 3.2—3.9 (m, 14 H, CH_2O)		
(3e) 2-Tetradecyl-15-crown-5	23	182—193/0.05	3.25—3.70 (m, 19 H, CH_2O), 1.29 (s, 26 H, CH_2), 0.90 (t, 3 H, CH_3)		
(3f) 2-Icosyl-15-crown-5 [c]	17	170—180/0.05	3.2—3.8 (m, 19 H, CH_2O), 1.28 (s, 38 H, CH_2), 0.91 (t, 3 H, CH_3)	498 ($M^+ - 2$, 1%), 354 (100%), 125 (35%), 111 (62%), 57 (60%)	2 860br, s, 1 460s, 1 355s, 1 290m, 1 250m, 1 110br, s, 970s, 845m, 730w
(3g) 2-Phenyl-15-crown-5	41	156—168/0.05	7.24 (s, 5 H, C_6H_5), 4.60 (m, 1 H, OC*H*Ph), 3.4—3.7 (m, 18 H, CH_2O)		2 940s, 2 865br, s, 1 450m, 1 360s, 1 295m, 1 250m, 1 110br, s, 980s, 930m, 760s, 690s

[a] $CDCl_3$ solution containing 1% $SiMe_4$; s = singlet, d = doublet, t = triplet, m = multiplet. [b] Thin films between NaCl plates; br = broad, s = strong, m = medium, w = weak. [c] M.p. 31—34 °C.

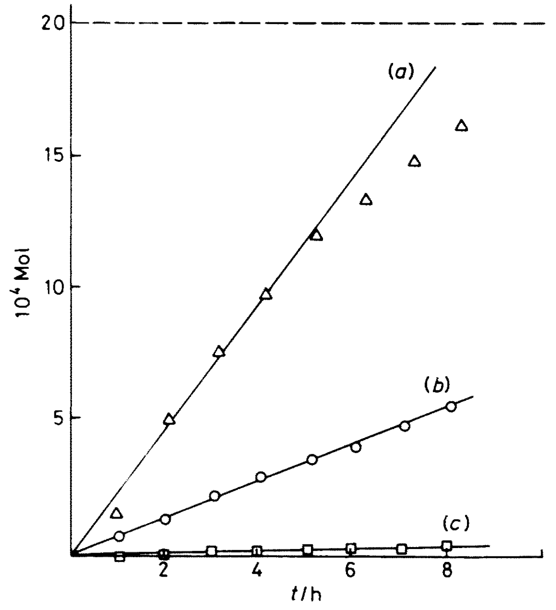


Figure 1. Graph showing the transport of (*a*) Na^+ (transport rate = 210 × 10^{-6} mol h^{-1}), (*b*) K^+ (transport rate = 62 × 10^{-6} mol h^{-1}), and (*c*) Li^+ picrates (transport rate = 2.7 × 10^{-6} mol h^{-1}) by 15-crown-5. The horizontal dashed line represents equilibrium (assuming all alkali-metal ions are in the aqueous phase)

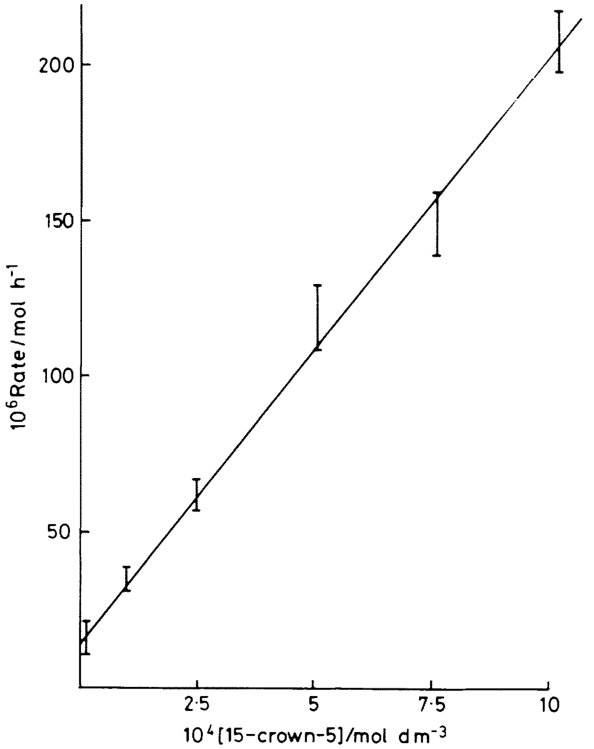


Figure 2. Graph showing the rate of transport of sodium picrate as a function of 15-crown-5 concentration in $CHCl_3$

of transport (mol h^{-1}) is given by taking a tangent to the curve at the start of the experiment, as in Figure 1, and represents the maximum transport rate for each cation. It should be noted that, particularly for poor ionophores, it is difficult to ascertain this initial transport rate due to other factors such as initial slow diffusion into the chloroform layer, and this is reflected in the wide error limits for some compounds. Whereas for low concentrations of metal picrate in the receiving phase ($<1.4 \times 10^{-4}$ mol) the solution samples could be removed, analysed, and replaced, for high concentrations it was necessary to dilute the samples from the receiving phase in order to calculate the concentration. Therefore for high concentrations ($>1.4 \times 10^{-4}$ mol) of the picrate solution, a 1-cm^3 sample of the receiving phase was removed, diluted as necessary, and subsequent experimental readings were corrected for the resulting change in volume. Stirring rate and variation in room temperature may affect the results and these factors were kept nearly constant by the use of the same apparatus and instrumental settings for all experiments.

(*ii*) *The effect of ionophore concentration.* Results were obtained for a series of experiments on a range of ionophore concentrations (10^{-5}—10^{-3} mol dm^{-3}) for the rate of transport of sodium picrate by 15-crown-5 in the standard experimental apparatus and are summarised in Figure 2.

(*iii*) *The ionophorous ability of substituted and unsubstituted crown ethers.* The results for the ionophorous ability of

Table 3. Comparison of the transporting efficiencies of various crown ethers with respect to lithium, sodium, and potassium picrates

Ionophore	Rate of transport (10^6 mol h^{-1})		
	Li^+	Na^+	K^+
6-Crown-2 (dioxane)	0.1 (±0.1)	0 (±0.1)	0 (±0.1)
Tetraethylene glycol	0.1 (±0.1)	0 (±0.1)	0 (±0.1)
12-Crown-4	4.5 (±0.2)	34 (±5)	3 (±0.2)
15-Crown-5	2.7 (±0.3)	210 (±10)	62 (±5)
18-Crown-6	15 (±0.1)	230 (±15)	140 (±40)
Dibenzo-18-crown-6	1.8 (±0.2)	50 (±5)	50 (±20)
24-Crown-8	0.9 (±0.2)	16 (±2)	50 (±10)
(5)	13 (±1)	17 (±2)	1.5 (±0.2)
(3a) 2-Methyl-15-crown-5	19 (±2)	150 (±10)	47 (±5)
(3b) 2-Ethyl-15-crown-5	—	150 (±10)	—
(3c) 2-Octyl-15-crown-5	2.0 (±0.2)	52 (±5)	30 (±5)
(3d) 2-Decyl-15-crown-5	2.0 (±0.2)	49 (±5)	31 (±5)
(3e) 2-Tetradecyl-15-crown-5	—	50 (±5)	—
(3f) 2-Icosyl-15-crown-5	1.5 (±0.2)	42 (±5)	24 (±4)
(3g) 2-Phenyl-15-crown-5	33 (±3)	140 (±10)	45 (±5)
(4d) 2-Decyl-18-crown-6	—	30 (±5)	30 (±5)
(4f) 2-Icosyl-18-crown-6	—	25 (±5)	20 (±5)

various crown ethers for lithium, sodium, and potassium picrates, all corrected for blank experiments, are given in Table 3.

Discussion

(*i*) *Mechanism of Transport.*—Transfer of the metal salts is considered to be a carrier facilitated transport whereby the species are moved across the membrane by selective carrier molecules which reside in the membrane. Consistent with this scheme of a single carrier transporting a single ion is the prediction that as the concentration of ionophore is increased, the rate of transport will also directly increase. This is seen to be verified in Figure 2.

(*ii*) *Ionophorous Properties of Substituted and Unsubstituted Crown Ethers.*—The results, Table 3, for the unsubstituted crown ethers confirm those of other workers,[9,10,21–23] with the best transport rate being achieved where the cation most closely fits the macrocycle and provides the optimum stability constant for complexation.[21] This is especially applicable for 15-crown-5 which preferentially transports Na^+, and 24-crown-8 which preferentially transports K^+. The one anomalous result is that for 18-crown-6 which was repeatedly found to transport Na^+ better than K^+. This is in contrast to most of the reported data.[21] However most of these other data were concerned with more dilute solutions, not approaching equilibrium, whereas the data in this study are for far more concentrated solutions, where equilibrium was often reached within hours. An equilibrium situation was reached very quickly for K^+ transport, see Figure 3(*b*). Although it could be seen that initial diffusion into the chloroform was very rapid, and that the transport into the receiving phase after one hour was the same as for sodium, equilibrium is reached with a large proportion (~70%) of the potassium picrate in the chloroform layer. Whereas it had generally been assumed that at final equilibrium all the metal picrate would be in aqueous media, here this is not the case. Support for these unusual observations has been reported by Okada and co-workers,[24] who, whilst investigating related macrolides containing tetrahydrofuran moieties, found that transport of potassium picrate by 18-crown-6 ceased after only 35% of the picrate had been transported into the receiving phase, despite, again, a very rapid initial transport rate into the organic phase. This was attributed to a rate-determining step of ion release, due to the high specific binding of 18-crown-6 for K^+, preventing transport through the organic membrane.

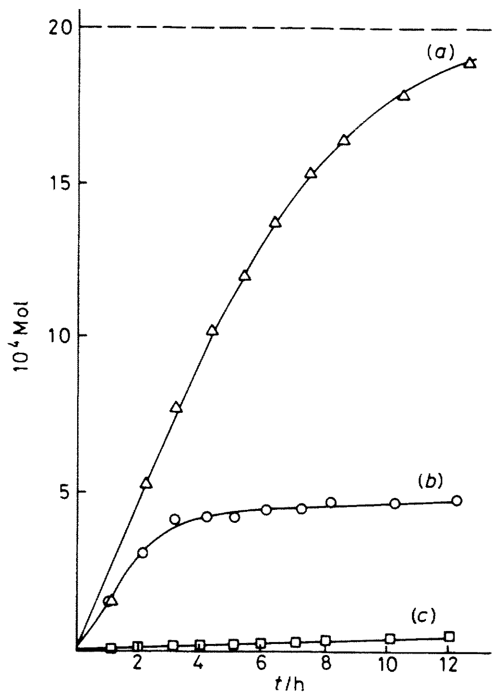
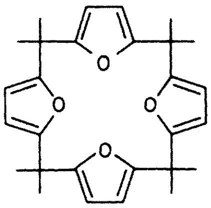


Figure 3. Graph showing the transport of (*a*) Na^+, (*b*) K^+, and (*c* Li^+ picrates by 18-crown-6. The horizontal dashed line represents equilibrium (assuming all Na^+ ions are in the aqueous phase)

Further examination of the results for the unsubstituted crown ethers reveals that dibenzo-18-crown-6 transports Li^+, Na^+, and K^+ at a slower rate than the corresponding 18-crown-6, in agreement with the work of Lamb *et al.*[21] This might be due to an increase in the lipophilicity but is more probably associated with lower stability constants for complexation arising from the greater rigidity of the aromatic structure. The cyclic tetramer (5) was found to be a more effective Li^+ transporter than 12-crown-4 (Table 3). This is due to the fact that (5) offers a larger cavity which fits Li^+ better than does 12-crown-4.



(5)

Introduction of lipophilic groups [(3a)—(3f), (4d), and (4f); Table 3] causes a drop in Na^+ and K^+ transport rates as the length of the hydrocarbon chain increases. It is possible that the increased lipophilicity accounts for the decreased rate of transport for sodium and potassium ions for the cases of dibenzo-18-crown-6 compared to 18-crown-6 and (5) compared to 12-crown-4. However, in these cases, other factors, such as the increased rigidity of conformation, because of the aromatic sub-units, may well be equally important.

The introduction of some alkyl and other groups, however, does assist Li^+ transport. This is exemplified by phenyl-15-crown-5 (3g) which transports Li^+ about 12 times better than the corresponding unsubstituted 15-crown-5. It is unclear why these results are the opposite to those for the transport of Na^+ and K^+, although it should be noted that the rate of transport of Li^+ is still relatively small compared to that for Na^+. A further anomalous result is the relatively high transport of Li^+ by 18-crown-6, when compared to 12-crown-4, 15-crown-5, and 24-crown-8. The unusual results for Li^+ transport may reflect its unique position in the series of alkali metals,[25] in that many of its properties are covalent rather than ionic. Also Li^+ has a larger hydration number (25.3) compared to Na^+ (16.6) and K^+ (10.5) [25] and this would necessitate a greater energy barrier to initial complexation.

Acknowledgements

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