UNIVERSITY OF SOUTHAMPTON

THE TEMPLATE EFFECT AND SYNTHESIS OF IONOPHOROUS MACROCYCLES

A thesis submitted for the degree of
Doctor of Philosophy

by

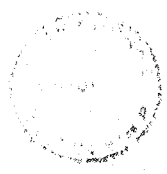
Brian Robert Bowsher

Department of Chemistry

November 1981

To

Mum and Dad



"One Ring to rule them all, One Ring to find them,

One Ring to bring them all and in the darkness bind them."

J.R.R. Tolkein, The Lord of the Rings.

This dissertation describes work carried out in the Department of Chemistry of the University of Southampton between October 1978 and October 1981. It is the result of my own work and, unless specifically stated to the contrary in the text, includes nothing which is the result of work done in collaboration.

None of the presented work has been previously submitted for a degree by me in this or any University.

[redacted]

5th December, 1981.

ACKNOWLEDGEMENTS

Primarily, I wish to thank my Supervisor, Dr. Tony Rest, for his continuous encouragement, advice and friendship during the course of this work.

I would like to thank Brian Main for his friendship and all his help, in particular with the synthetic chemistry and liposome work. I would also like to thank Brian, Andrew, Bryan and Dorothy for making my stay at ICI Pharmaceuticals such a memorable experience.

I would like to thank Mrs. Julie Broomfield for deciphering my handwriting, and typing this thesis.

I would particularly like to thank Janet and all my friends, both inside and outside the Department, especially those ever at 25 Westwood Gardens, for making my time at Southampton so enjoyable.

Finally I would like to thank the Science Research Council and ICI Ltd. (Pharmaceuticals Division) for the award of a CASE studentship.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

THE TEMPLATE EFFECT AND SYNTHESIS OF IONOPHOROUS MACROCYCLES

by Brian Robert Bowsher

The template role of alkali and alkaline-earth metals has been investigated in detail for the synthesis of some unsubstituted cyclic polyethers - 'crown ethers'. It was found that the concept of a template effect was more applicable to the role of alkali metals than alkaline-earth metals in the synthesis of crown ethers. The template effect however should not be used in isolation, but rather in conjunction with other factors, such as the charge density of the cation, solvent dependence and the base strength of the reaction medium in order to maximise macrocyclic yields.

Optimum synthetic conditions were used to make a series of alkyl and acid substituted crown ethers; chosen because of their similarity to natural ionophorous antibiotics. The ion-transporting abilities of these compounds was examined by use of a bulk chloroform membrane experiment and liposome studies. In the bulk chloroform membrane studies there was found to be a broad correlation between the fit of a cation:crown ether complex and the transport rate. The introduction of lipophilic substituents decreased sodium and potassium transport, but a certain degree of lipophilization assisted lithium transport. Preliminary work on the synthesis of acid substituted crown ethers suggested that transport may occur *via* a different mechanism from that of crown ethers with non-ionizable functional groups. A limited study of liposome experiments showed that bulk chloroform studies, whilst very useful, may not be directly applicable to biological membranes.

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CHAPTER 1 +

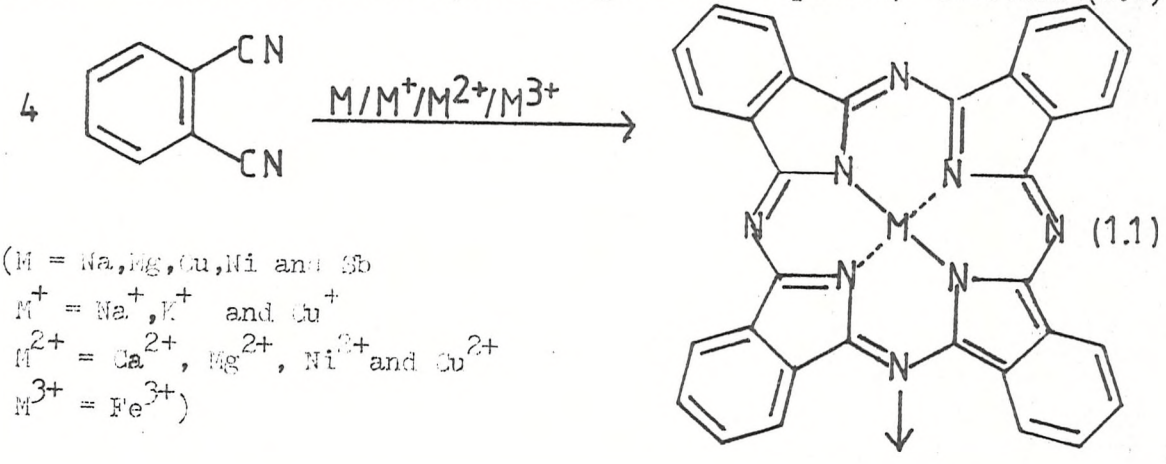
INTRODUCTION

1.1 INTRODUCTION TO MACROCYCLIC CHEMISTRY

1.1.1 History

For many years there has been strong interest in the synthesis of multidentate macrocyclic ligands and the complexes formed by these ligands with metal ions. In particular the comparison with naturally occurring nitrogen macrocycles such as the **porphyrin** structure in the prosthetic groups in haemoglobin, chlorophyll and vitamin B_{12}, has stimulated research into nitrogen containing **macrocycles.**

However for many years the synthesis of such macrocycles was unsuccessful due to low yields, the many side products of the reactions, and the large volumes of solvents that were needed in order to give sufficient dilution so as to minimize polymerization and encourage cyclization. One of the first examples where a metal salt was exploited in order to facilitate the formation of a macrocycle was the self condensation of **o-phthalonitrile** to give the metal complex from which the free phthalocyanine ligand was displaced,[1] reaction (1.1).



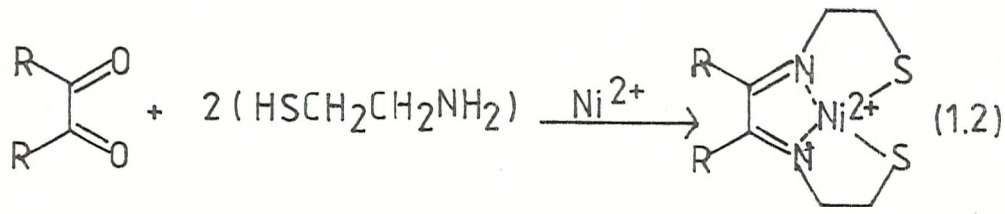
(M = Na, Mg, Cu, Ni and Sb
M^+ = Na^+, K^+ and Cu^+
M^{2+} = Ca^{2+}, Mg^{2+}, Ni^{2+} and Cu^{2+}
M^{3+} = Fe^{3+})

free macrocycle

The role of the metal ion in such reactions was recognized and developed in the main by **Busch**[2]. The use of Ni^{2+} ions in the formation

+ References for this chapter can be found on page 43.

of macrocycles, reactions (1.2) and (1.3), led Busch[3,4] to realize that



(1.2)

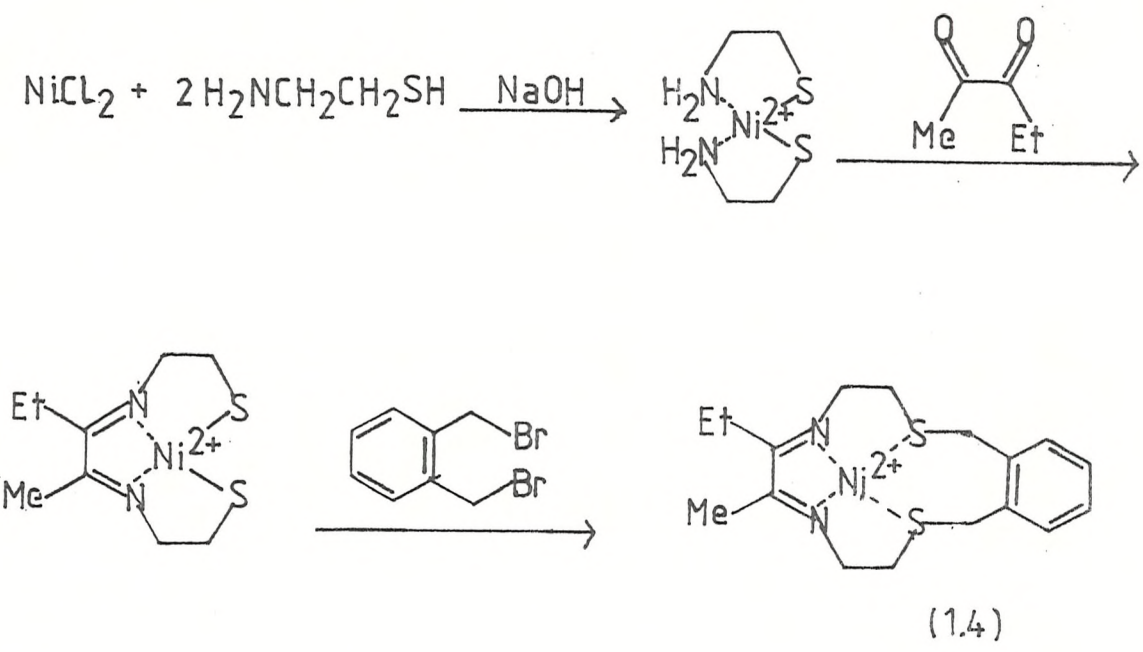
$$Ni(H_2NCH_2CH_2S)_2 + 2CH_3I \longrightarrow Ni(H_2NCH_2CH_2SCH_2)_2 \qquad (1.3)$$

the co-ordination sphere of the metal ion would hold the reacting groups in the correct positions for cyclization reactions, that is the metal ions acts as a 'mould' or 'template'. Since this time there have been many more examples of template driven closures of nitrogen containing macrocycles which are cited in various reviews[2,5-12].

1.1.2 The Template Effect

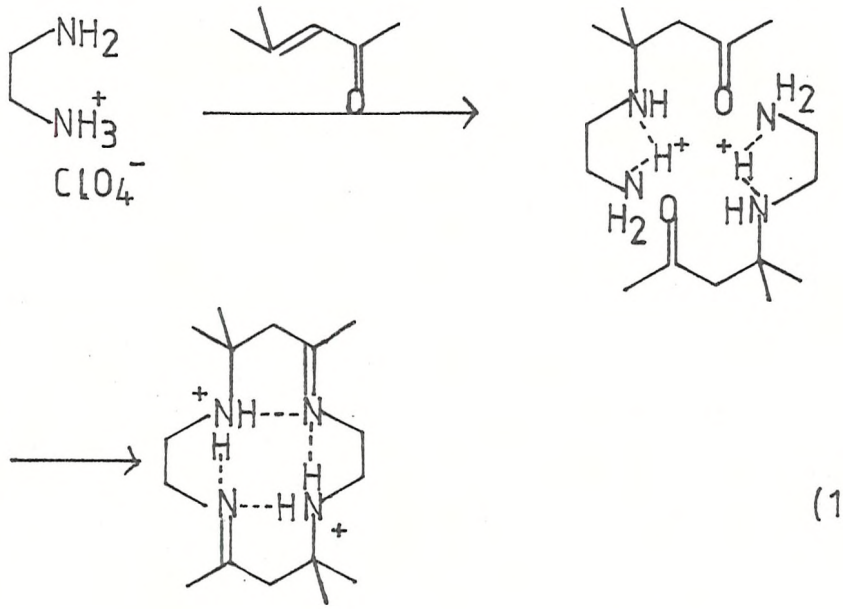
A template effect can be postulated if addition of a metal ion to a reaction mixture produces either an improvement in the yield of macrocycle, or an increase in the rate of reaction. The template effect may be divided into three categories, although it should be emphasised that these are not rigid divisions.

A. Kinetic A reaction has a kinetic template effect where a totally different chemical product is formed by addition of a metal ion than in its absence. An alternative title for this process is the co-ordination template effect[4], as the metal acts by co-ordinating to the reactants, forming a complex which undergoes a series of stereo-specifically controlled steps in a multi-step sequence, e.g. reaction (1.4)[3,13,14]

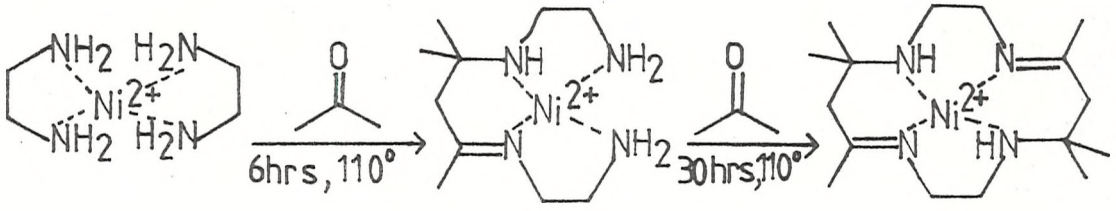


(1.4)

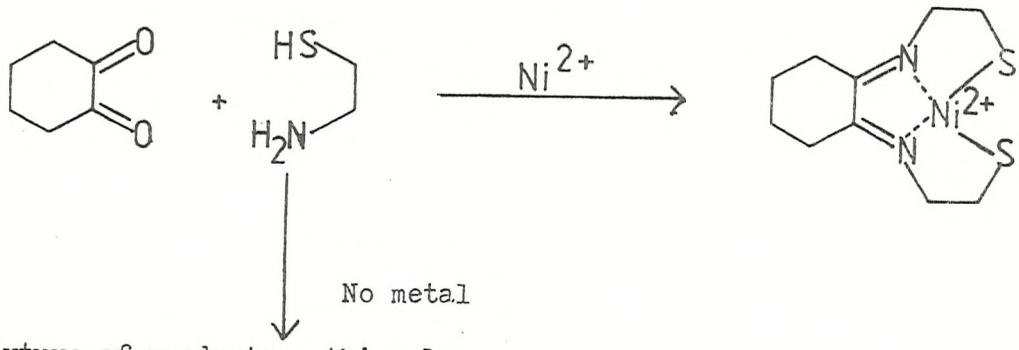
B. Thermodynamic A thermodynamic template effect is operating if the macrocycle formed could also be obtained in the absence of the metal ion, but the metal promotes formation of the macrocycle by removing it from the equilibrium as a metal complex, e.g. reaction (1.5)[15].



(1.5)



C. Equilibrium The equilibrium template effect[4], is a combination of the two previous effects and is characterized by the formation of different products in the metal-assisted and metal-free reactions, e.g. reaction (1.6)[14]



No metal

Mixture of products ; thiazoles, thiazolines and mercaptals

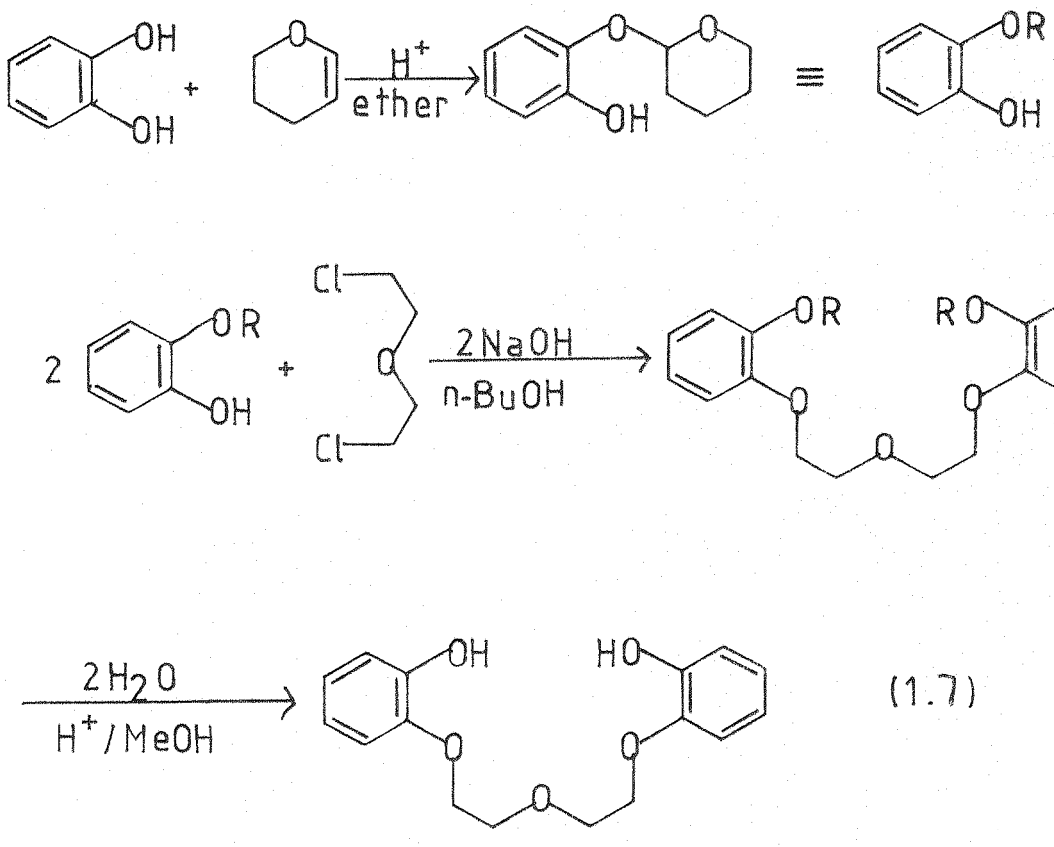
(1.6)

1.2 DISCOVERY AND DEVELOPMENT OF 'CROWN ETHER' CHEMISTRY

1.2.1 History

Although by 1966 many nitrogen containing macrocycles were known that could complex transition metal ions, the complexation of alkali and alkaline-earth cations as co-ordination compounds was a rarity[16,17] - stoichiometric complexes only being observed with natural antibiotics. Despite the vital importance of sodium, potassium, magnesium and calcium in biological systems[18,19], interest in the formation and isolation of complexes was low mainly because their chemistry was though to be rationalised by the ionic model.

Whilst investigating new vanadium containing catalysts for the polymerization of olefins, Charles Pedersen[20,21] decided to investigate the effects of multidentate phenolic ligands on the catalytic properties of the vanadyl group, VO. The quinquedentate ligand selected was bis - [2- (o - hydroxyphenoxy) ethyl] ether by the synthesis as in reaction (1.7). This reaction also gave a small quantity of white crystals (0.4% yield) which were investigated by UV absorption spectroscopy and found to be soluble in methanol containing any soluble sodium salt.



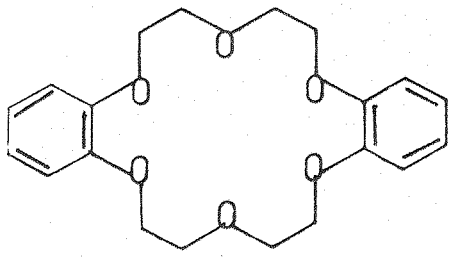
(1.7)

Further investigation showed the structure to be that of 2,3,11,12-dibenzo-1,4,7,10,13,16 - hexaoxacyclo-octadeca - 2,11 - diene (1). In classical papers, Pedersen[22-26] reported the synthesis of over fifty macrocyclic polyethers. Due to the very cumbersome names given to the polyethers by strict application of the IUPAC rules, Pedersen instigated the use of the generic name 'crown' because of the similarity of CPK molecular models to a regal crown and by the ability of these compounds to 'crown' cations by complexation. The names are made up of the ring substituents, the total number of atoms in the polyether ring, 'crown' and the number of oxygen atoms in the ring. Thus (1) is dibenzo-18-crown-6. Since this pioneering work, many more crown compounds have been synthesised ranging from rings of nine to sixty members. Some of these are illustrated in Plate 1.1.

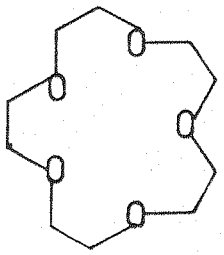
1.2.2 Functionalized Crown Ethers

Functionalized crown ethers can be broadly divided into two groups - those where the functionality is attached to an aromatic ring and is generally introduced by reaction of the relevant crown ether, and those where the functionality is directly attached to the carbon skeleton of the crown ether and is generally introduced at an early stage before cyclization.

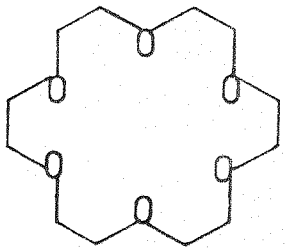
Plate 1.1 Selected Macrocyclic Compounds



(1)



(2)



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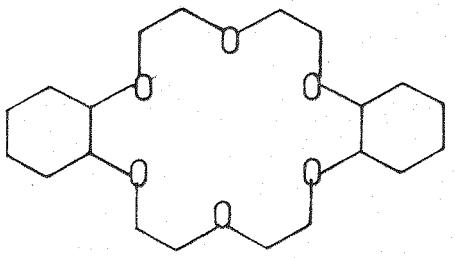

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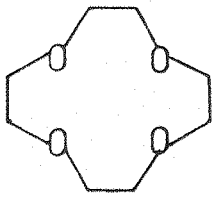

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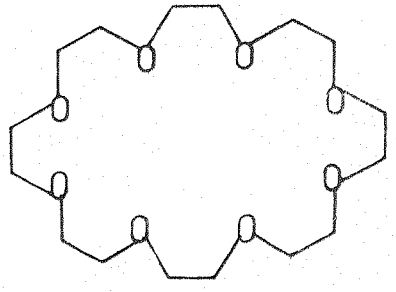

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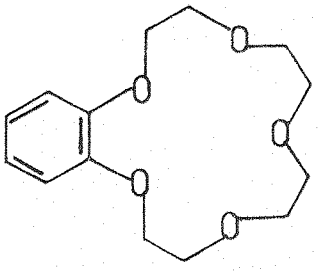

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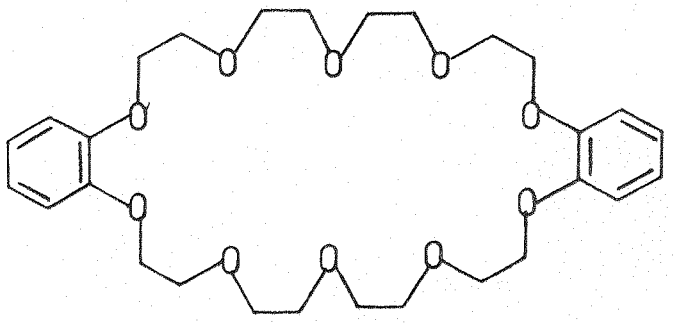

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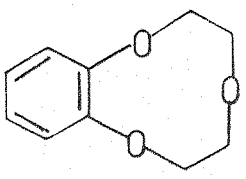

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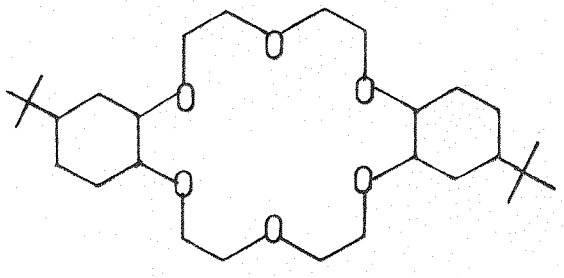

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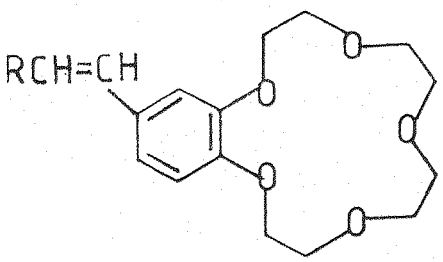
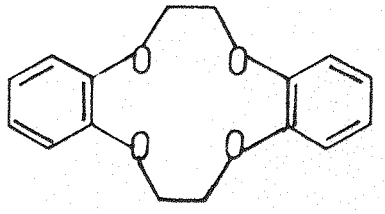


(12a) R = Ph
(12b) R = CO_2H



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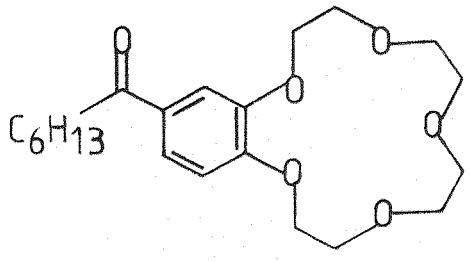

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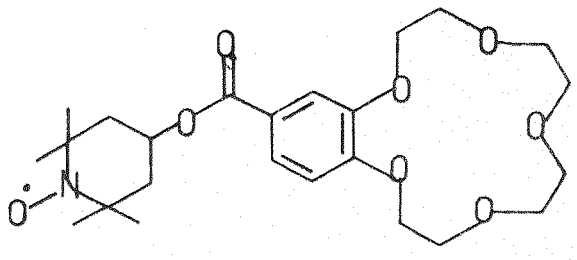

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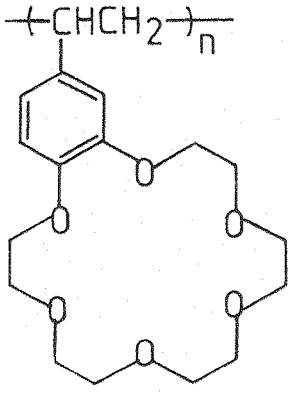

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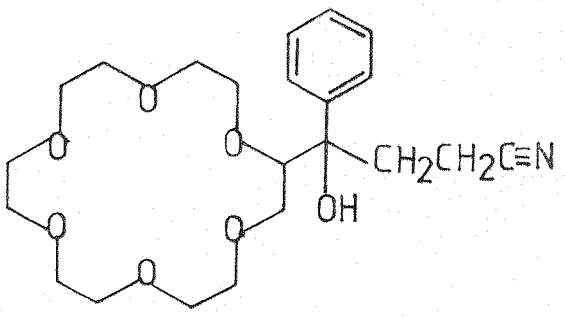

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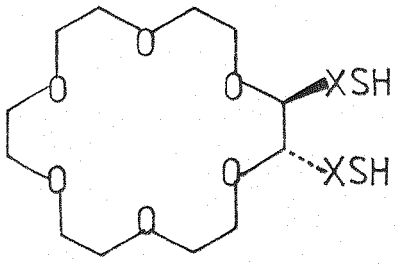
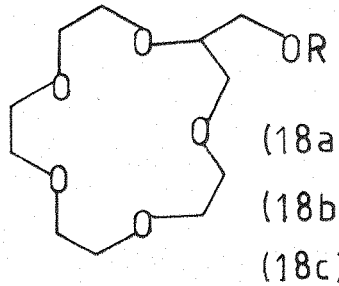


(17a) X = CH_2

(17b) X = $CH_2CH_2CH_2$

(17c) X = $CH_2OCH_2CH_2$

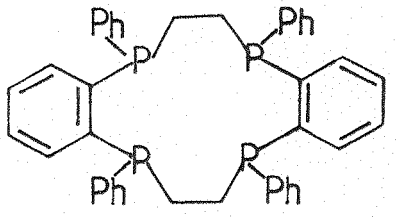


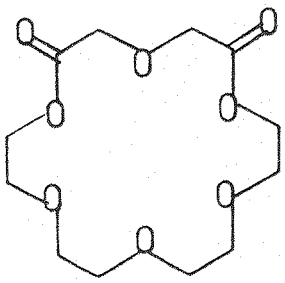
(18a) R = CH_2CH_2OMe

(18b) R = o$OMe.C_6H_4$

(18c) R = p$OMe.C_6H_4$

(21)





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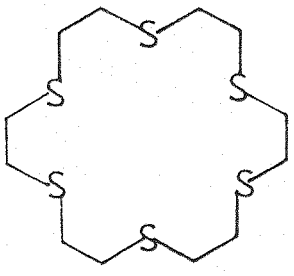

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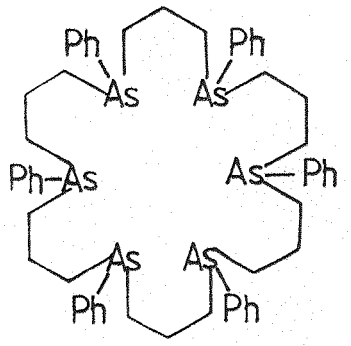

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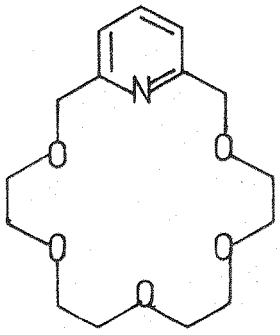

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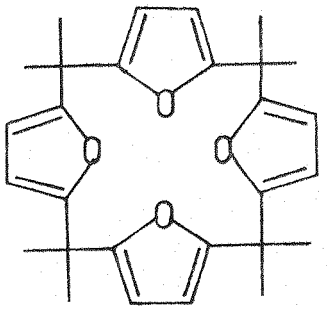

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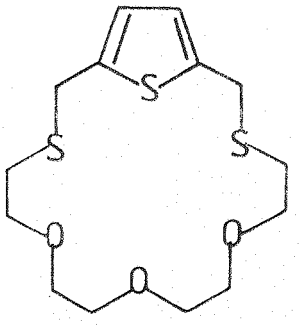

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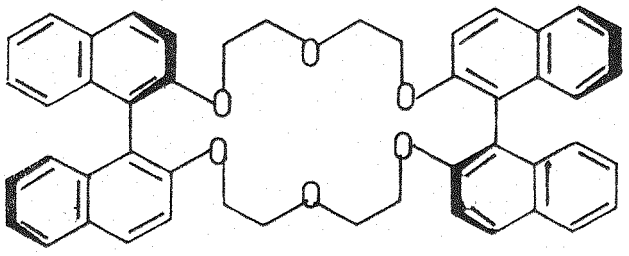

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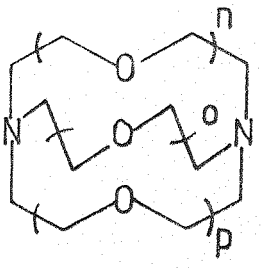

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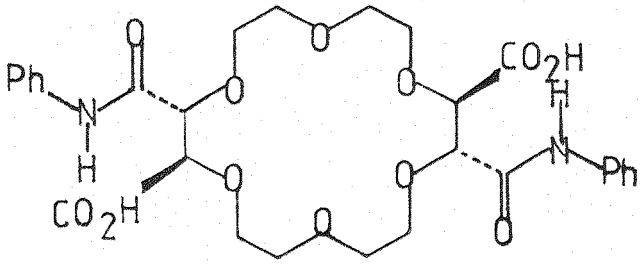

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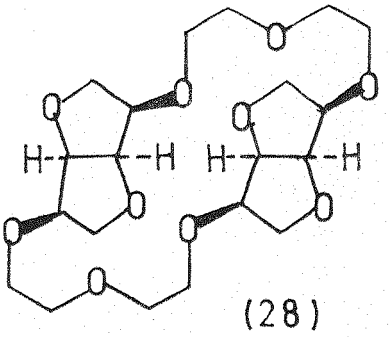

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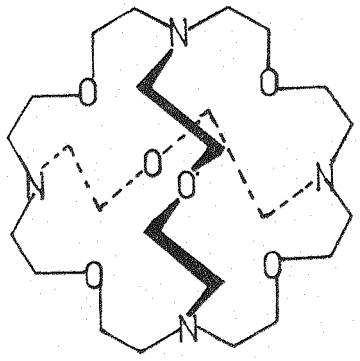

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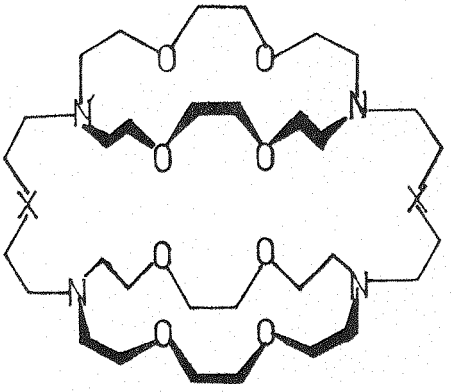
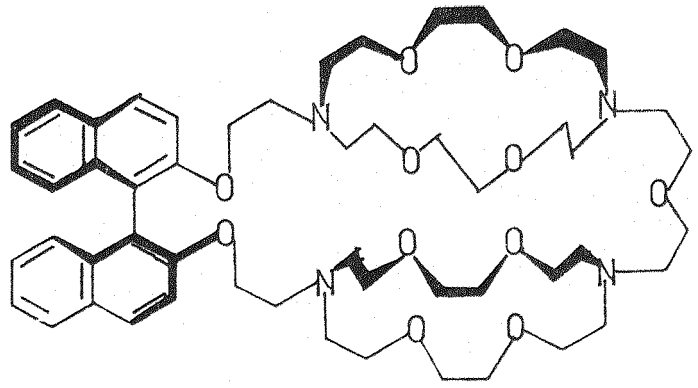


(31a) X=O

(31b) X=CH_2



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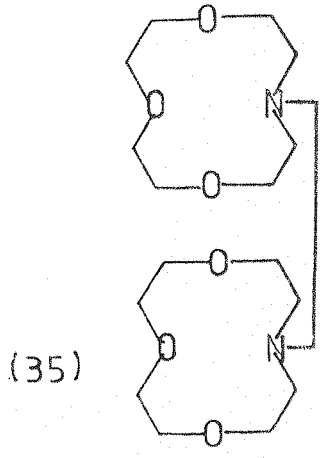

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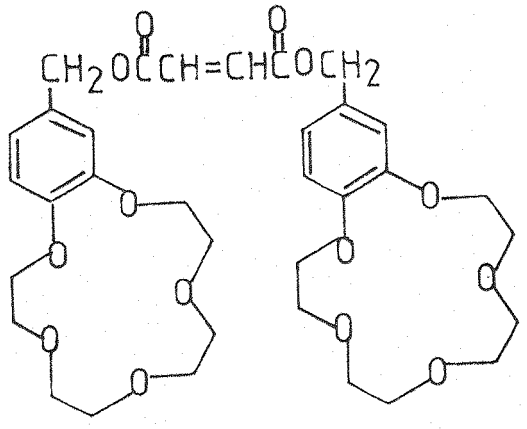

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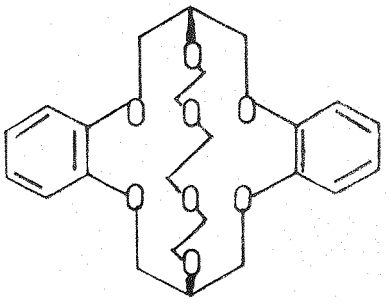

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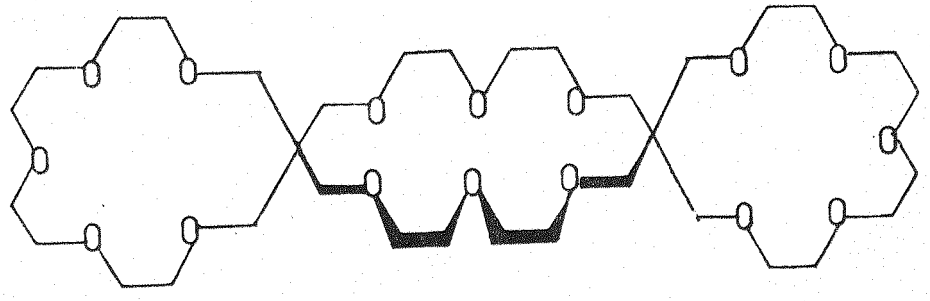
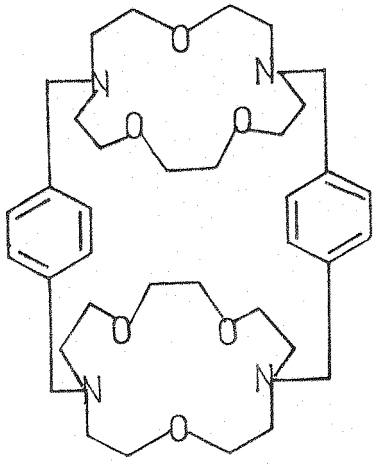
(37)





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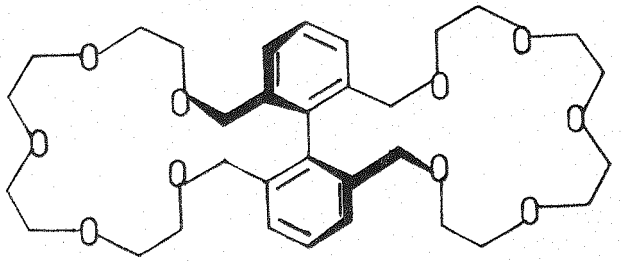

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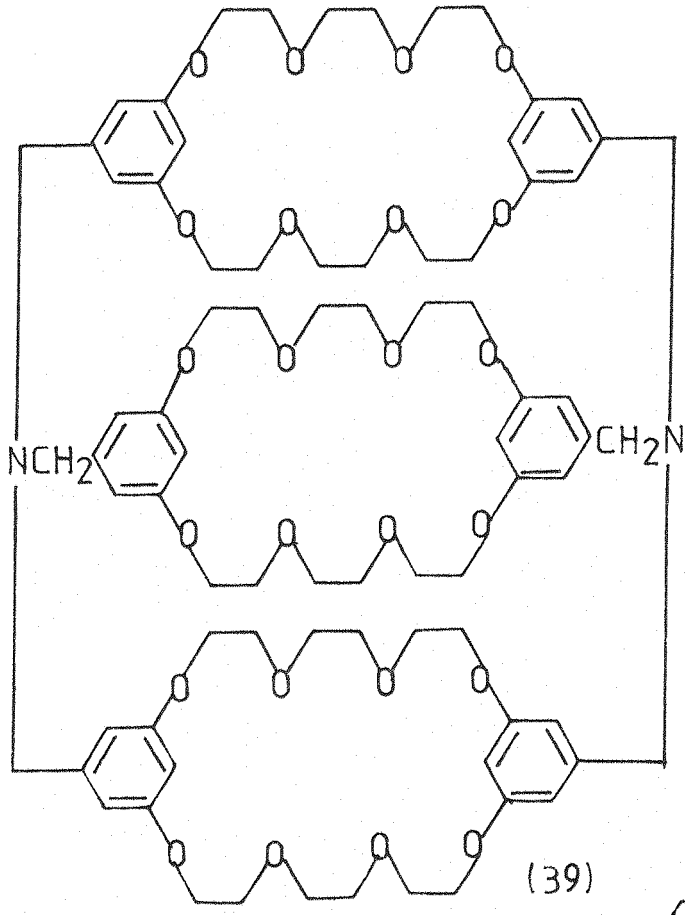

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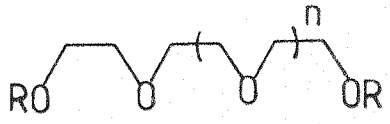
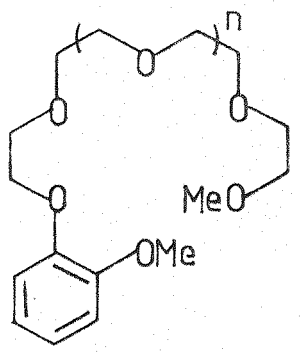


(44a) R = CH_3

(44b) R = H



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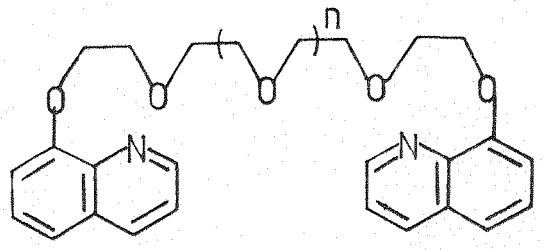

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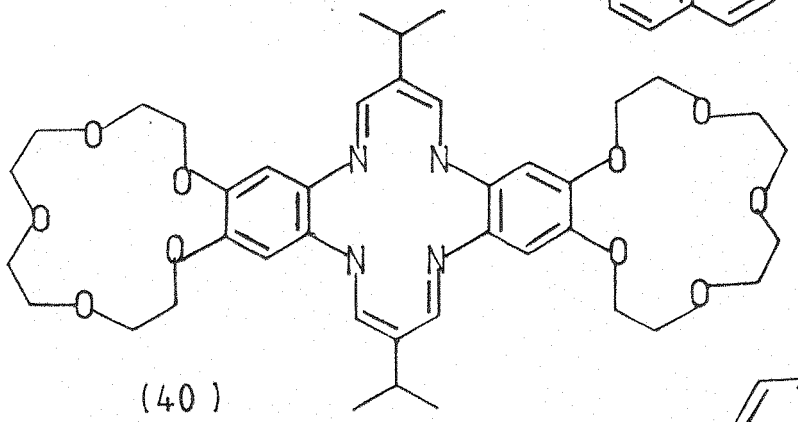

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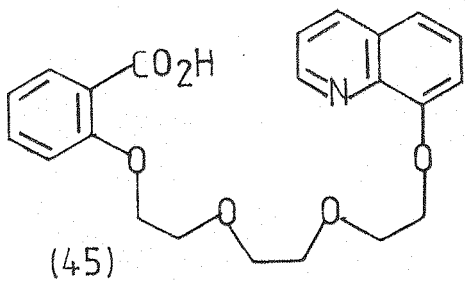

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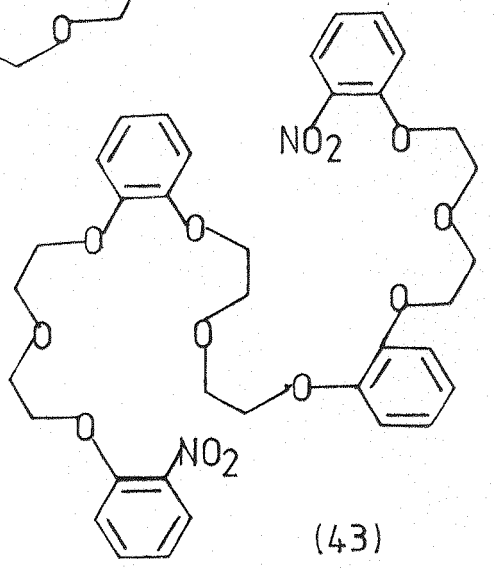

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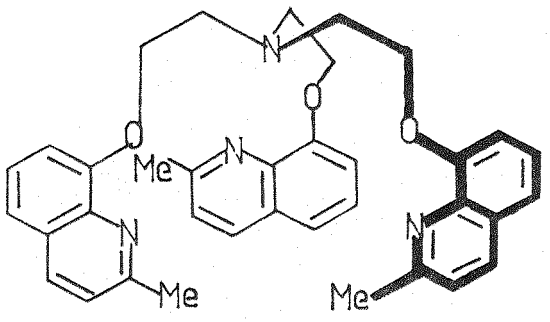

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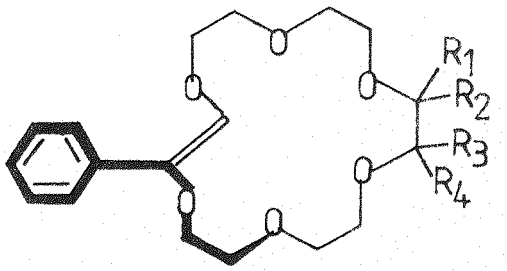

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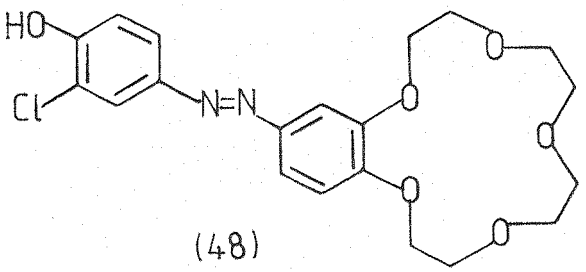

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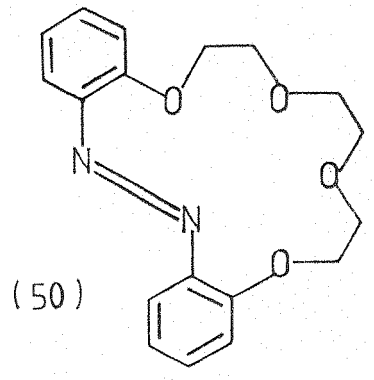

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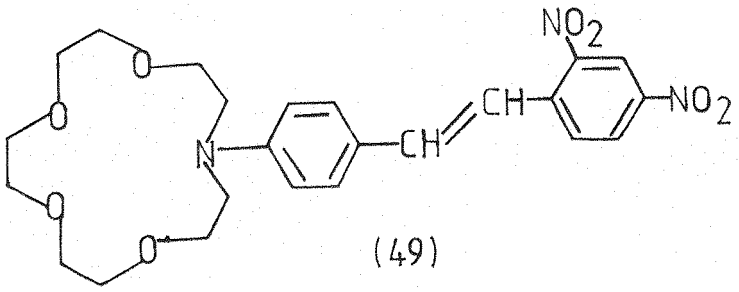

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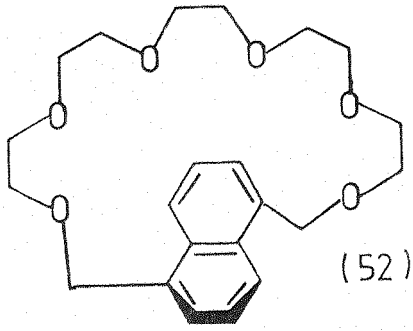

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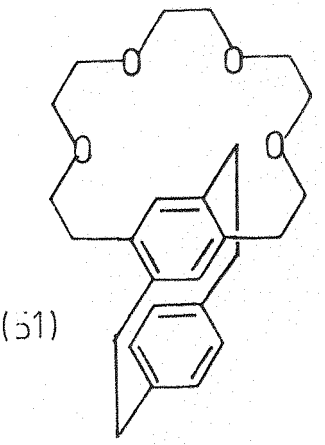

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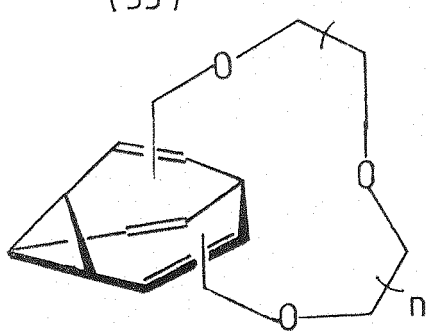

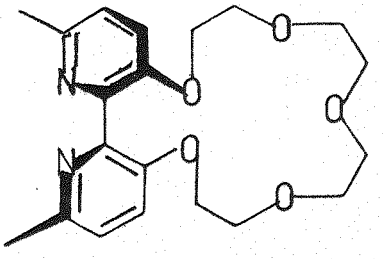

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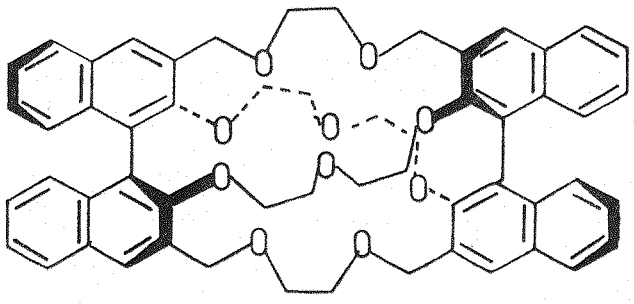

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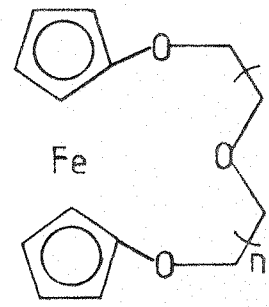

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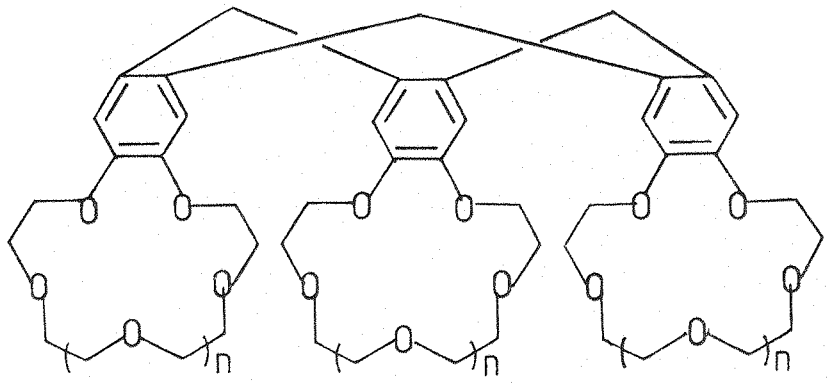

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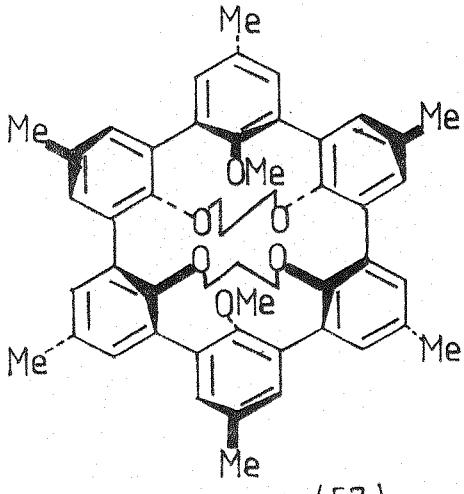

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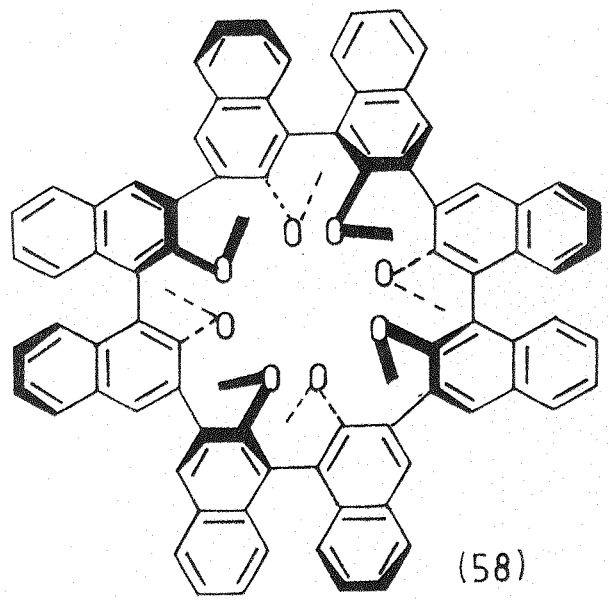

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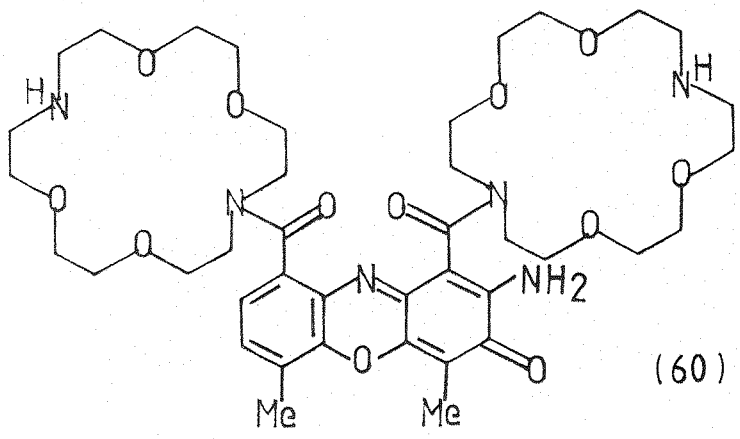
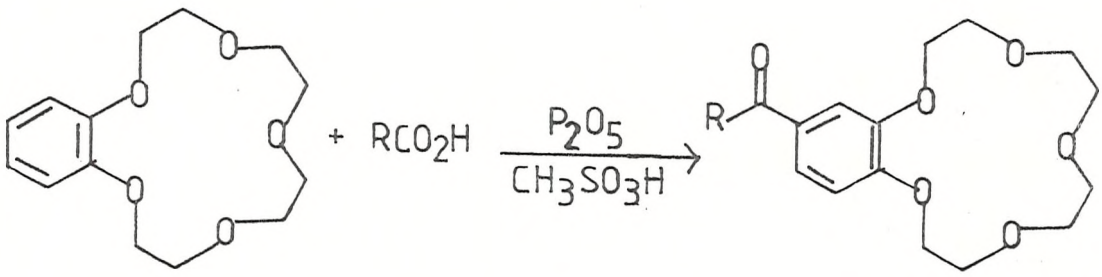


(60)

A. Functionalized on the Aromatic Ring[27] The majority of the substituted benzo crown ethers are prepared by nitration or acylation of the simple benzo crown compound[28]. The nitro derivatives are readily reduced to the corresponding amines[29] which can be further elaborated. Acylation has generally been achieved by the use of Eaton's reagent (phosphorus pentoxide in anhydrous methanesulphonic acid) as in reaction (1.8) to give the substituted crown ether which can undergo further reactions as desired[30 - 33].



(1.8)

Typical examples where functionality has been introduced on the aromatic ring of crown ethers are given in Plate 1.1, (11) - (15). This functionality gives many potential applications; for example it provides a site for the attachment of spin labels which can then be studied by electron spin resonance spectroscopy, (14)[34], and it may also provide a site for polymer support[29,35] (15).

B. Functionalized on the Macrocyclic Ring It is desirable to introduce functional groups onto the crown ether skeleton and so directly examine the effect of substituents. However this area has, until recently, received little attention because of the greater reactivity of the aromatic ring.

Alkyl-substituted 18-crown-6 ethers were first prepared by the rather laborious route of Cinquini and Tundo[36]. Optimization of template conditions greatly simplified this synthesis[37] to give alkyl-substituted 12-crown-4 and 15-crown-5 ethers. Okahara and co-workers[38 - 40] have also reported more convenient routes to the alkyl-substituted crown ethers via polyethylene glycol β-haloalkyl

ethers or via treatment of a substituted polyethylene glycol with p -toluenesulphonyl chloride in the presence of a suitable template base.

A novel method of introducing functionality to the crown ether skeleton is by the photochemical reaction[41] of alkyl aryl ketones with 18-crown-6 to give compounds typified by (16). Crown ethers bearing thiol groups (17) have also been reported[42,43]; these compounds catalyze reactions regioselectively. Recently Gokel and co-workers[44 - 46] have reported a series of crown ethers with side arms ('lariat ethers') which contain extra donor groups so as to give greater stability to complex cations. Two examples of this type of compound (18a), (18b) are given in Plate 1.1. Carbonyl groups may be introduced into the crown ether framework by reaction of diacids, or their derivatives, with glycols to produce di- and tetra-ester compounds, e.g. (19). Inclusion of the ester groups causes increased rigidity in the macrocycle and results in lower cation binding constants. This class of compounds has been thoroughly reviewed[47,48].

1.2.3 Crown Ethers with Hetero-atoms or -groups

Although the emphasis of the work described in this thesis is on purely oxygen containing macrocycles, it is worth noting the enormous amount of work that has been devoted to macrocycles containing atoms or groups other than oxygen. As well as oxygen and nitrogen donor macrocyles, macrocycles containing only sulphur, phosphorous and arsenic have been prepared, exemplified by (20)[49,50], (21)[51] and (22)[52]. The crown arsanes are air stable, unlike the macrocyclic phosphorus compounds. Recently there has been a decline of interest in the sulphur macrocycles due to their poor complexing ability for alkali and alkaline-earth metal ions. Although they do interact strongly with mercury and silver, generally the introduction of sulphur distorts the macrocyclic ring.

The introduction of hetero groups, in particular pyridine, furan and thiophene, into synthetic macrocyclic compounds, exemplified by (23), (24) and (25), has been thoroughly reviewed by Newkome and co-workers[53].

Whilst much of the mixed donor systems have been reviewed[5,10,12,27,53,54], it is worth emphasising the importance of the template effect in their synthesis. This is the case for the main class of mixed donor macrocycles - nitrogen/oxygen - especially for the case of Schiff base ligands, and this has recently been reviewed[12]. One very recent novel application of a template effect is the metal-ion controlled transamination in the synthesis of such ligands[55].

1.2.4 Chiral Crown Ethers[27,56]

Chiral crown ethers have been prepared by various methods, often utilizing chiral natural products. The introduction of chirality into the macrocyclic structure makes possible the selective binding of chiral substances. Thus, chiral crown ethers can be used as stereo-selective catalysts, enzyme models and for optical resolution of racemic substances. Chiral crown ethers may be divided into two main classes: those derived from binaphthyl substrates and those using natural chiral products such as tartaric acid and carbohydrates as precursers.

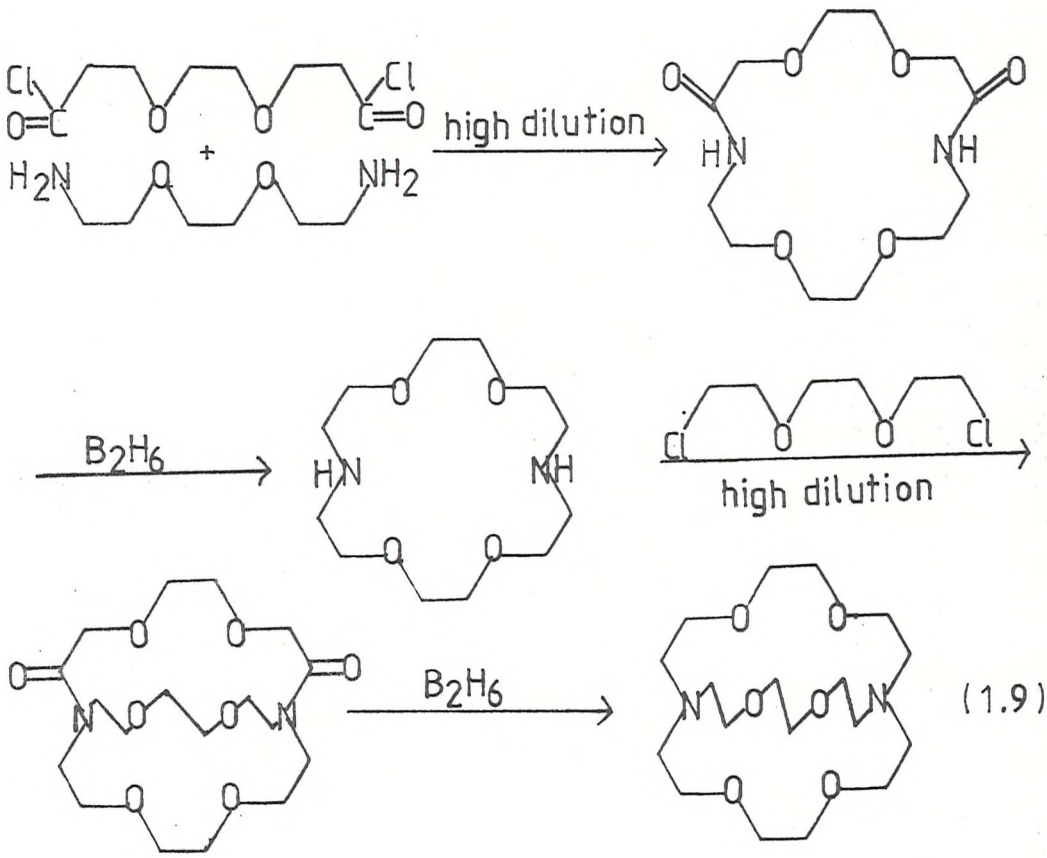
A. Chiral crown ethers derived from binaphthyl substrates The introduction of binaphthyl units into crown ethers, e.g. (26), has been developed in the main by Cram and co-workers. Recent articles by them and others gives a complete review of the field[56 - 61].

B. Chiral crown ethers derived from natural products Tartaric acid has been one of the most widely used precursers for making chiral crown ethers, due to the ready availability of both isomers and production of crown ethers with versatile functional groups. Various carbohydrates, e.g. D-manitol, D-glucose and D-galactose have also been reported as precursers, but in general these compounds do not exhibit a high degree of chiral recognition. This chemistry has largely been investigated by two research groups - those of Lehn[62,63] and Stoddart[64,65]. Compounds derived from tartaric acid (27)[66] and D-manitol (28)[67] are given in Plate1.1.

1.2.5 Cryptands and Other Macropolycyclic Compounds

Since the discovery of crown ethers was first reported, there have been numerous developments in macrocyclic chemistry. In particular, because of their ability to completely encapsulate an enclosed cation, much interest has centred on polycyclic compounds. These can be categorised into three areas: bicyclic compounds with nitrogen bridgeheads - cryptands, bicyclic compounds with carbon bridgeheads, and more complex species involving two or more 'crown ether rings'.

A. Cryptands Independently of Pedersen's work, Lehn and co-workers reported[68] a series of diaza-polyoxamacrobicyclic compounds in 1969 with the general structure of (29). These were produced in an elegant synthetic route asin reaction (1.9). Since this time many cryptands have been synthesized and their chemistry has been well reviewed[69-74]. Further interesting developments in this field are the spherical cryptates, e.g. (30)[75], where an enclosed cation is totally shielded from the environment, and dinuclear cryptates of polyoxamacrotricycles

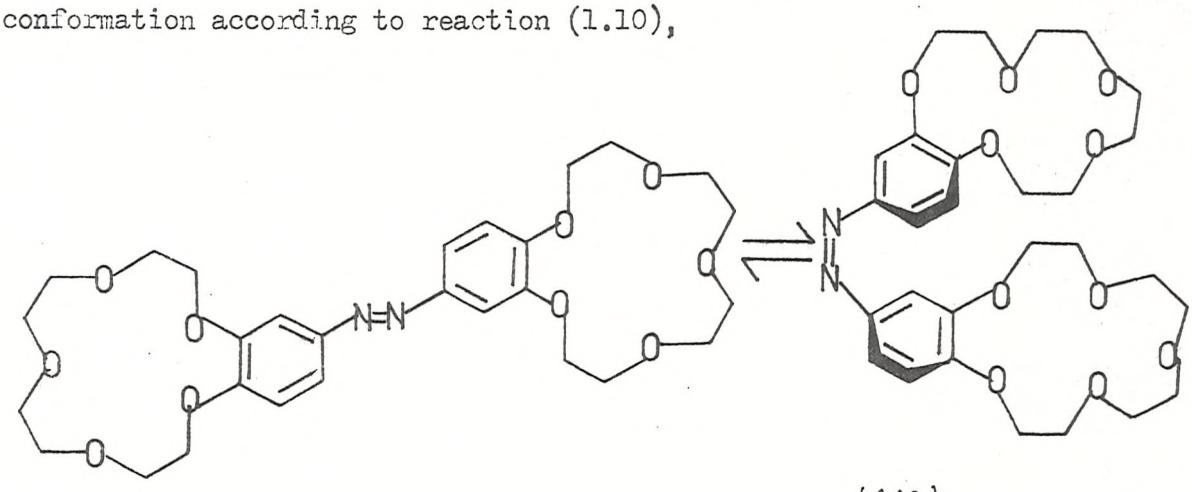


(1.9)

as typified by (31)[73], which incorporates two macrocyclic cavities for cation binding. One interesting example of this series is (32)[76] which incorporates a binaphthyl unit and so gives chiral discrimination.

B. Macrobicyclic Compounds with Carbon Bridgeheads Due to the difficulty of synthesising compounds with bridghead carbon atoms, examples of these compounds have only recently been made, in the main through the work of Truter and co-workers[77-79]. A typical compound (33) is given in Plate 1.1.

C. Miscellaneous Macropolycyclic Compounds Several workers have synthesized various 'bis-crown ethers', that is where two crown ether rings are joined by various length chains which often contain further donor groups. These compounds often have a much greater binding and selectivity for metal ions based on their ability to form sandwich-type complexes. In particular, Kimura and co-workers[80-83] have developed compounds of the type (34) with a view to investigating their ability as extracting reagents for alkali metal ions and their use as alkali metal selective electrodes. It should be noted that the cis isomers of (34) extract alkali metal picrates much better than the trans isomers, which, unlike the cis isomers can not form sandwich complexes[83]. Similar studies on compounds based on bis-benzo crown ethers have been reported by Wong and Ng[84]. An interesting related area is that investigated by Shinkai and co-workers[85-87] who have designed a photo responsive bis crown ether incorporating an azo linkage. Photochemical activiation of the compound changes the conformation according to reaction (1.10),



(1.10)

and this has been utilized to provide a basis for selective extraction and transport of alkali metal cations. The incorporation of nitrogen into a crown ether skeleton gives a simple way of linking two macrocycles as investigated by Lehn and co-workers.[71 - 74] This is exemplified in structures (35)[88] and (36)[89] in Plate 1.1. Other interesting macrocyclic compounds include the 'multi-loop' crown ethers, as reported by Weber[90], e.g. (37), which couple macrocycles by spiro carbon atoms. Recently a bicyclic compound (38)[91] has been reported to have an allosteric effect - the receptivity of one ether ring towards a second $Hg(CN)_2$ is enhanced by a factor of ten by the binding of the first $Hg(CN)_2$. One most unusual multicyclic compound (39) has recently been reported[92]. The synthesis of (40)[93] is most interesting in that it contains both a nitrogen macrocycle and oxygen macrocycles and so may independently bind both transition metal ions and alkali and alkaline-earth cations.

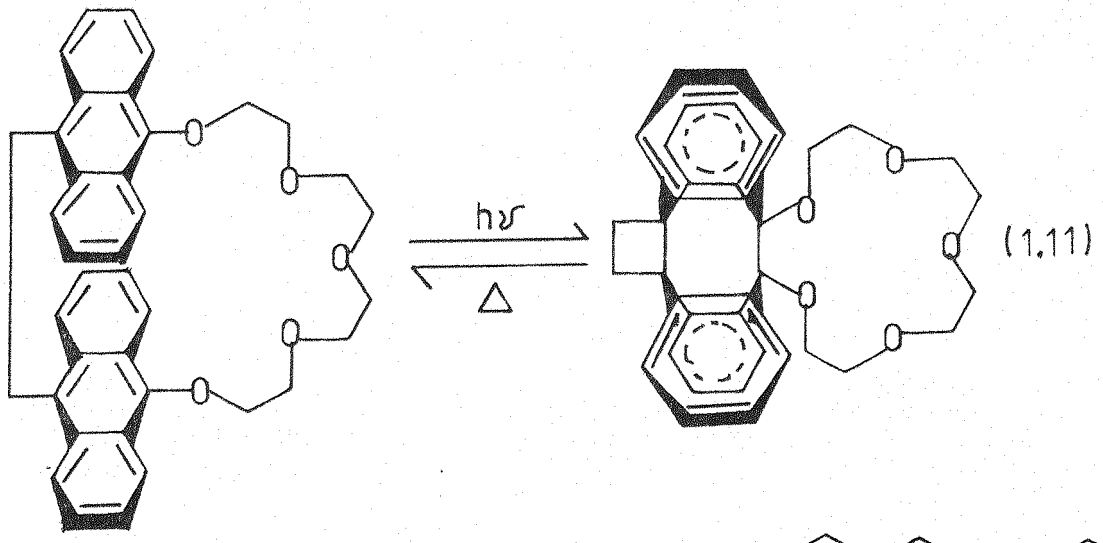
1.2.6. Open Chain Analogues

The linear, non-cyclic macropolyethers have received considerable attention due to their greater flexibility, and ability to form a pseudo-cyclic structure upon complexation in a similar way to that of the non-cyclic natural ionophorous antibiotics (see section 1.7.1). The investigation into their synthesis and properties has been led by Vögtle and co-workers[94 - 96]. In particular it has been found that for successful binding at least one of the terminal groups of the glymes should be a rigid donor group[97 - 100], as epitomised by (41) - (43) in Plate 1.1. In general, the simple oligo (ethylene glycol ethers), e.g. (44a), do not form stoichiometric complexes with Group 1A and 11A cations, although an exception to this is the formation of complexes of heptaglyme with $Ca(SCN)_2$ and $Ba(SCN)_2$[99]. Indeed recent studies[94,101,102] have shown the formation of stoichiometric alkaline-earth salt complexes with the higher oligoethylene glycols[101], (44b,$n \geqslant 3$); and the lower glycols (44b,$n \geqslant 0$) have been demonstrated[102] to act as lipophilizing and discriminating ligands for alkali and alkaline-earth salts. One particularly interesting non-cyclic compound is (45)[103] which is analogous to some natural ionophorous antibiotics - especially A23187 - and exhibits selective cation transport against a concentration

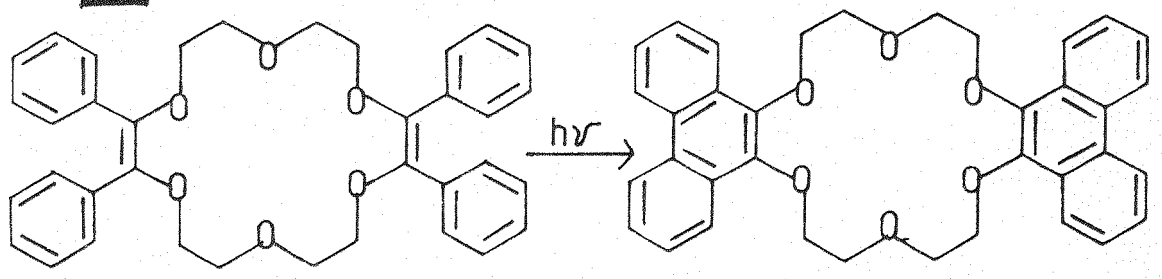
gradient. A further development is the synthesis of the non-cyclic, three-dimensional analogue of the cryptands[94,104,105] as in (46).

1.2.7 Novel and Unusual 'Crown Ethers'

Photochemical reactions often provide a useful synthetic route to unusual crown ethers. Some applications have already been examined[86,87] and the introduction of anthracenes into crown ethers to generate 'photo-crowns' has recently been reviewed[106]. Two further examples are given in reactions (1.11)[107] and (1.12)[108] respectively.



(1.11)



(1.12)

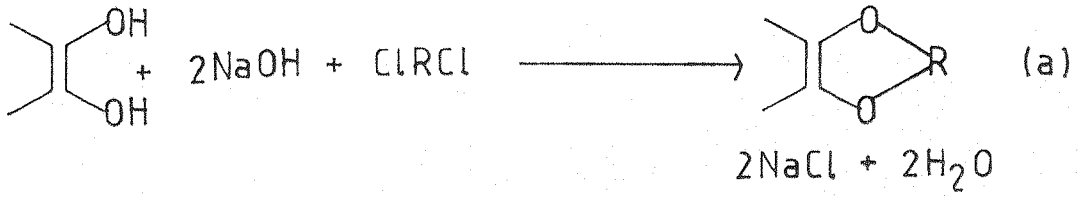
Reaction (1.12) illustrates the introduction of a trans double bond into the crown ether framework. Further examples of this type, of the general structure (47) have been reported[109]. The substitution of the aza-linkage into the aromatic part of a crown ether has already been referred to [86,87]. This gives a chromophore which may be sensitive to ion complexation, typified by (48)[110]. Further chromophores may be introduced, e.g. (49), and this whole field has been reviewed[111,112]. Another modification is to introduce the azo group directly into the crown ether framework, e.g. (50)[113].

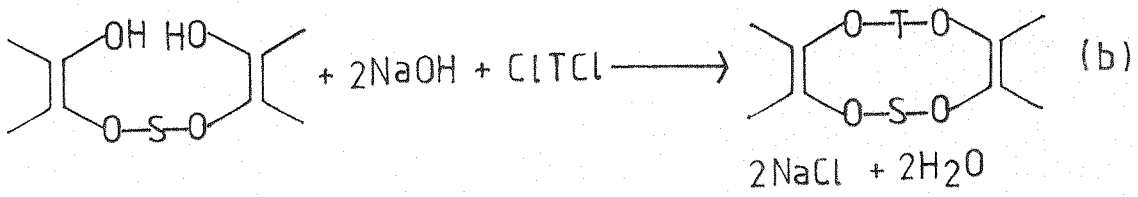
The introduction of aromatic groups to a crown ether has led to some interesting compounds. A series of crown ethers containing a π-donor sub-unit have been developed[114], e.g. (51), in order to investigate the effect of the aromatic ring. Similarly Larson and Sousa[115] have determined the effect of alkali metal ion complexation onto a crown ether containing naphthalene derivatives. Particularly interesting compounds are the 'rope-skipping' crown ethers, e.g. (52)[116], which give various enantiomeric conformations. A similar chemistry is observed for the introduction of bullvalero to give crown ethers of fluctuating size, e.g. (53)[117]. A bipyridyl moiety has been introduced into a crown ether, (54)[118], so as to give potential binding sites for both alkali and transition metal ions (cf ref.94). Further to section 1.2.6, other novel multicyclic macrocyles include (55)[119], and (56)[120] which incorporates a tri-veratrylene skeleton.

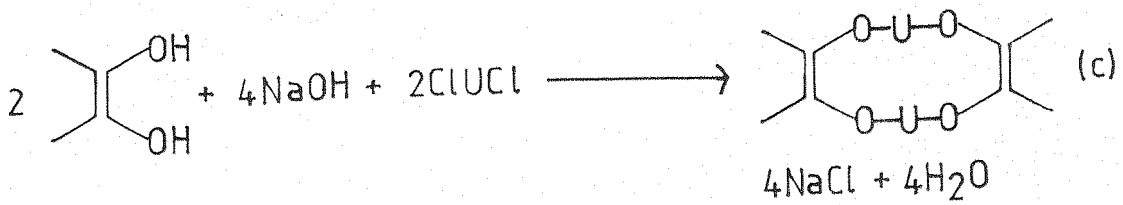
Cram and co-workers[121-3] have designed a series of ligands, exemplified by (57) and (58). Unlike the crown ethers, these contain an enforced cavity by means of a rigid support structure, and can selectively bind alkali metal ions. The ferrocene unit has been introduced into crown ethers, e.g. (59)[124,125], to give a novel series of macrocyclic compounds. Finally, a complex macrocyclic structure incorporating two diaza crown ethers, (60), has been synthesised[126] to act as an analogue of the actinomycins.

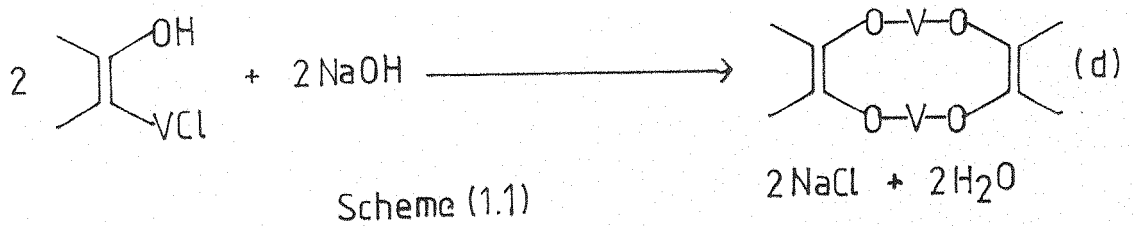
1.3 SYNTHESIS OF CROWN ETHERS[10,21,27,59,69,127]

Four different methods of producing the aromatic cyclic polyethers were given by Pedersen[21,23,26] as represented in Scheme(1.1).





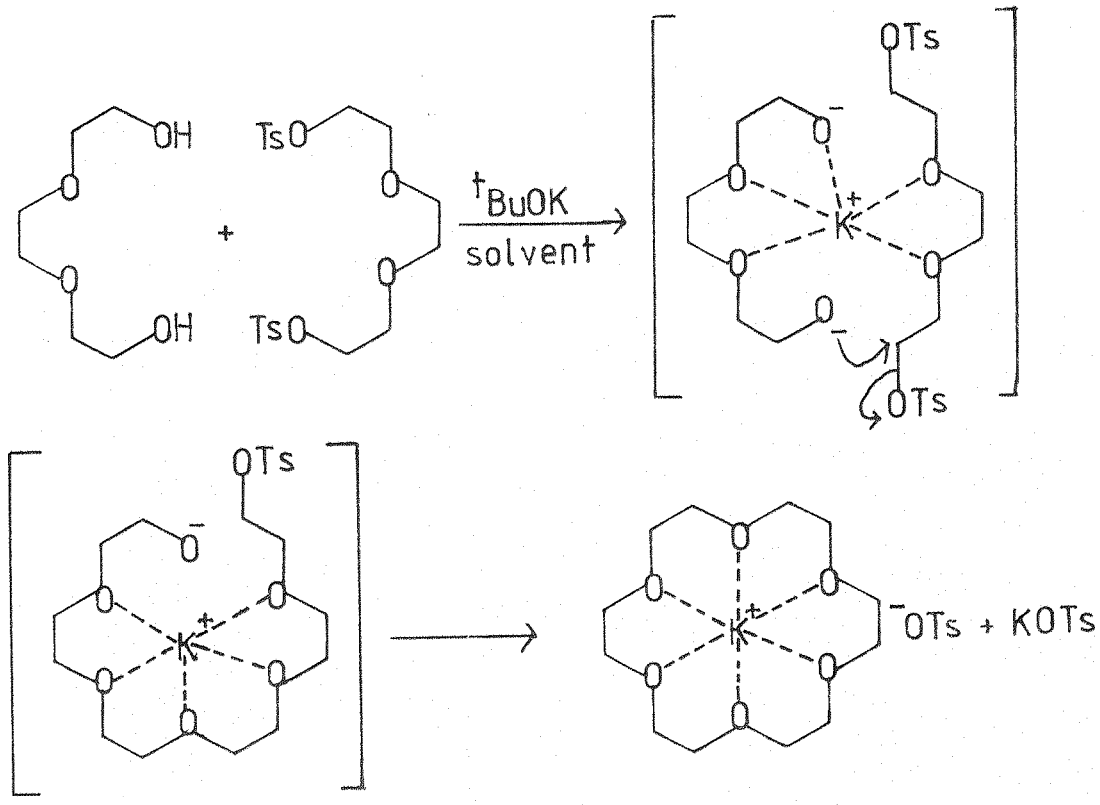




Scheme (1.1)

R,S,T,U and V are divalent organic groups, generally of the type $-(CH_2CH_2O)_nCH_2CH_2-$. In method (b) S and T may or may not be identical. This method is perhaps the most versatile for the synthesis of crown compounds containing two or more aromatic groups, particularly for an odd number of oxygen atoms in the polyether ring. Partially, or fully saturated crown compounds are prepared from the corresponding aromatic cyclic polyether by catalytic hydrogenation, typically in n-butanol at 100°C and 7 - 10 atm. over a ruthenium catalyst.

More recently, the yield of 18-crown-6, which originally was 2%, was greatly improved by utilization of a potassium template[128] according to Scheme (1.2).

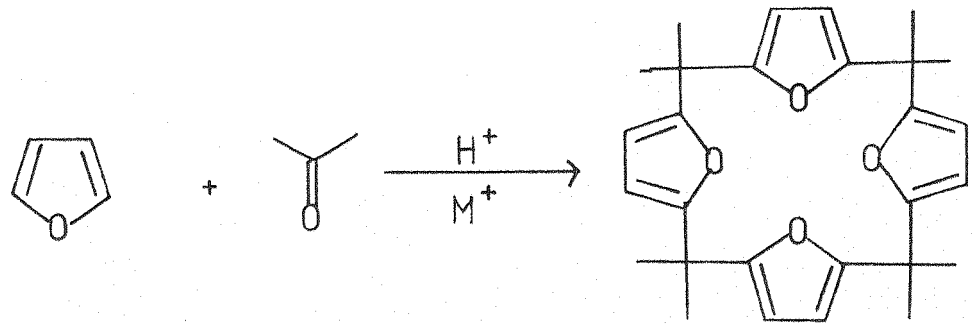


Scheme (1.2)

An excellent method of isolation of 18-crown-6,(3), has been reported by Cram[129] which utilizes an acetonitrile- crown ether complex. Liotta and co-workers[130] have shown the use of Na^+ and Li^+ templates in similar Williamson ether type syntheses of 15-crown-5,(2), and 12-crown-4,(5), respectively. The synthesis of 18-crown-6 and especially 15-crown-5 has been improved by Reese[131] by the use of an excess of bis (2-chloroethyl) ether with the relevant polyethylene glycol (see Chapter 2).

A different approach to the synthesis of crown ethers has been formulated by Dale and co-workers[132 - 134]. This involves the oligomerization of ethylene oxide using BF_3 in the presence of fluoroborate, fluorophosphate and fluoroantimonate salts of the alkali, alkaline-earth and transition metals. The product ratio is dependent on the choice of cation, although yields are only about 10% based on ethylene oxide.

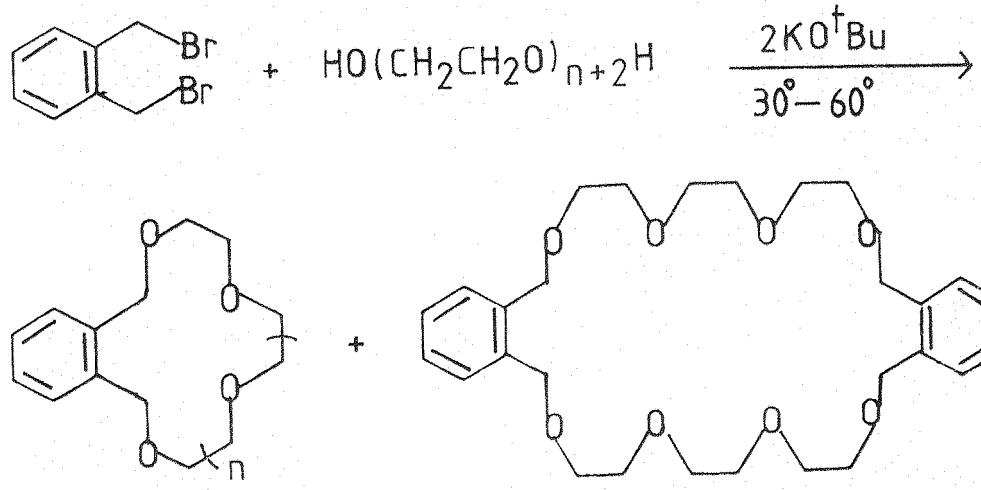
A Li^+ template was thought to be operating for the formation of the furan macrocycle (24) in the acid-catalyzed condensation of furan and acetone[135], as in reaction (1.13).



(1.13)

More recently transition metal ions have been shown to act as templates in this synthesis[136]. This reaction has been thoroughly investigated[137,138] (see section 2.3.2).

A template synthesis using group IA metal ions has been developed by Reinhoudt and co-workers,[139,140] which produces novel crown compounds from benzenes, furans and thiophenes as in reaction (1.14)

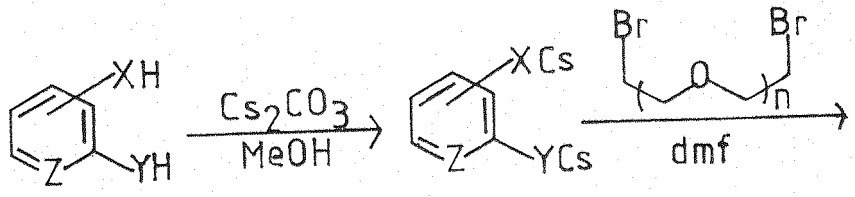


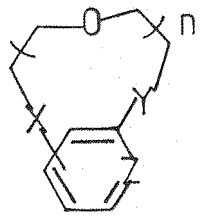
(1.14)

The same group of workers have also investigated[141] the use of metal fluorides as base in the template synthesis of crown ethers (see section 2.3.2). This has been extended by Ando et al[142] to the use of potassium fluoride on alumina as base for the synthesis of some

unsubstituted crown ethers.

Recently the use of caesium salts in crown ether synthesis has been reported[143] where the dicaesium salts of various dihydric phenols react with dibromo-polyethylene glycols to give crown ethers as in reaction (1.15).





(1.15)

a) X = Y = O(o), Z = CH

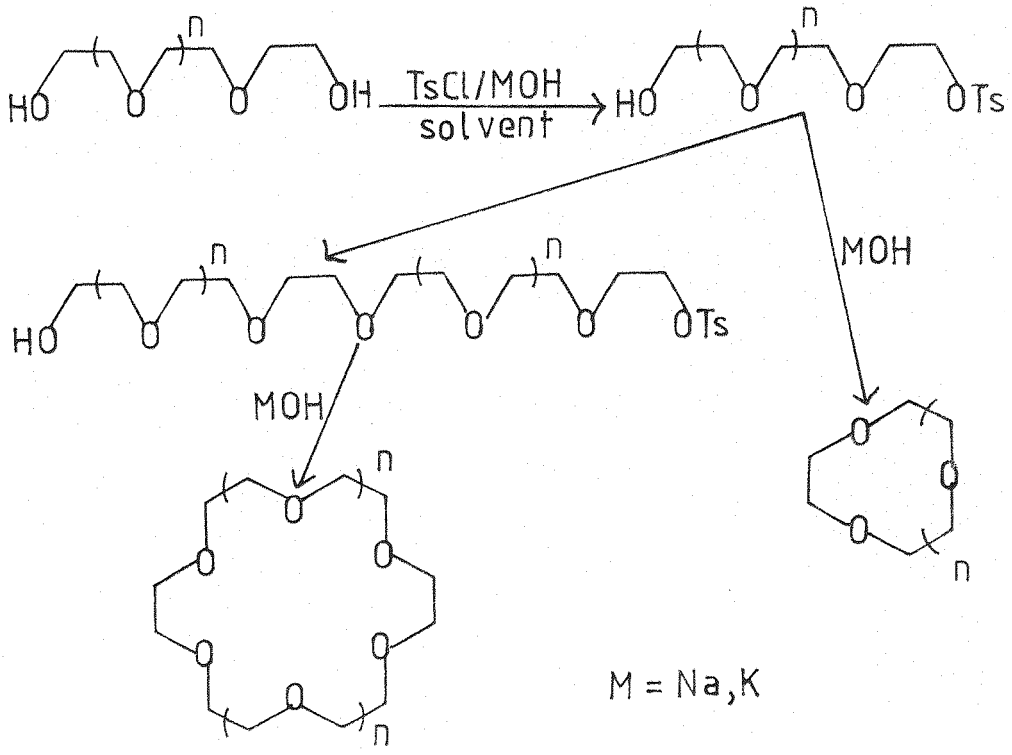
b) X = Y = O(m), Z = CH

c) X = O, Y = CO_2(o), Z = CH

d) X = Y = O(2,3), Z = N

Because of its large size (see section 2.3.1), it is uncertain as to whether Cs^+ is acting as a template, although this seems likely as the yields for n = 5 are greater than n = 4 which in turn are greater than n = 3, and Cs^+ would give the best fit to the cavity for n = 5. The use of alkali metal carbonates as templates has also been exploited [144,145] in the synthesis of diaza crown ethers (see section 2.3.3).

The use of Ba^{2+} and Sr^{2+} as template ions in crown ether syntheses in aqueous solution has been reported[146], employing polyethylene glycol monobromide, formed in situ from the dibromide by the action of hydroxide ion. A similar method for the synthesis of unsubstituted crown ethers from oligoethylene glycols by treatment with arenesulphonyl or alkanesulphonyl chlorides in the presence of the suitable alkali metal hydroxide or alkoxide template has been described[147] and is represented in Scheme (1.3). A similar method, starting from reaction of a substituted epoxide and the relevant polyethylene glycol



Scheme(1.3)

has been used[40] to give a series of substituted crown ethers. The same researchers[38,39] have used a novel approach to give substituted macrocycles via polyethylene glycol β-haloalkyl ethers prepared from the coupled addition of halogen cation and polyethylene glycol to a substituted olefin (see section 3.1.2). As referred to earlier, (1.2.2 (B)) Gokel et al[44 - 46] have utilized a traditional Williamson ether approach in conjunction with the optium template ion in order to give substituted crown ethers. It is worth noting that the template effect here is even more pronounced[44,148] where the substituent contains donor groups which can further interact with the metal cation and so enhance the template effect.

1.4 COMPLEXES OF CROWN ETHERS

The most striking property of the cyclic polyethers is their ability to complex various species[10,56,69,149]. These complexes will be classified as: alkali and alkaline-earth, other metals (lanthanides, actinides, transition metals), host-guest complexes

(complexation to protonated amines, neutral molecules) and anion bound complexes.

1.4.1 Complexes of Crown Ethers with Alkali and Alkaline-Earth Cations

Since the discovery of crown ethers and the realization that they could complex to alkali metal cations[23,26] a great deal of research has been devoted to this area[17,150-156]. Pedersen described four situations which can be used for the detection or measurement of metal ion complexation:

i) Observation of changes in the ultra-violet spectra of aromatic crown ethers
ii) Observation of changes in the solubilisation of salts and crown compounds in different solvents
iii) The isolation of crystalline complexes
iv) Two phase liquid extraction[157] - see section 1.5.3.

Initially it was thought[22,23] that the stoichiometry of the complexes was 1 : 1, but later investigations have shown this not always to be the case: 2 : 1, 3 : 2, 4 : 3 and 1 : 2 polyether: metal cation complexes have been isolated. In general the type of complex can be predicted from an examination of the relative sizes of the macrocyclic cavity and ionic diameter of the cation. The diameter of selected cations is given in Table 1.1[158] and the diameter of selected crown ethers is given in Table 1.2[158].

Table 1.1 Ionic diameter of selected Group IA and IIA Cations[158] in Angstroms

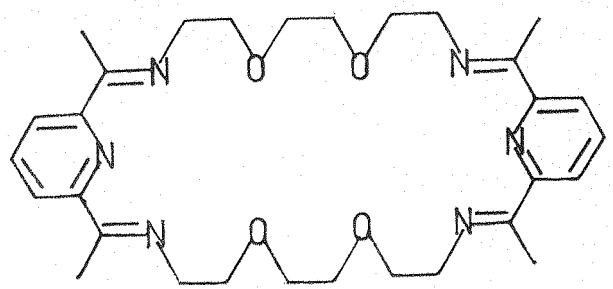
Li^+	1.36		
Na^+	1.94	Mg^{2+}	1.30
K^+	2.66	Ca^{2+}	1.98
Rb^+	2.94	Sr^{2+}	2.26
Cs^+	3.34	Ba^{2+}	2.68

Table 1.2 Cavity diameters of selected Crown Ethers[158] in Angstroms

All 12-crown-4	1.2 - 1.5
All 15-crown-5	1.7 - 2.2
All 18-crown-6	2.6 - 3.2
All 21-crown-7	3.4 - 4.3

In general, particularly for the alkali metal cations, if the size of the metal cation is similar to that of the macrocyclic cavity a 1 : 1 complex will be formed with the cation sitting in the centre of the cavity. This has been confirmed by X-ray crystallographic studies of the complexes - much work being done in this field by Truter and co-workers[150,152,159]. However this is not always the case. For example the complex formed by rubidium thiocyanate and dibenzo-18-crown-6 was found by X-ray studies[160] to have the rubidium ion at the exact centre, but just above, the macrocyclic plane.

Where the polyether ring is substantially larger than the cation this gives, in general, two possible modes of complexation. Firstly the macrocycle may undergo a conformational change to wrap around the cation. The classic example of this[161] is that of potassium iodide with dibenzo-30-crown-10 (8), where the potassium ion is totally encapsulated by the crown ether, co-ordinating to every oxygen of the polyether ring. Secondly a 2 : 1 metal ion: polyether will result. An example of this is the complex formed between dibenzo-30-crown-10 and two molecules of sodium isothiocyanate[162]. Similar cases of binuclear compounds are found in mixed donor, Schiff base ligands, a recent example is (61)[163] which can complex two Cu^{2+} ions. The field of dinuclear cryptates has recently been reviewed[73].



(61)

Conversely, when the polyether ring is substantially smaller than the cation, this generally gives rise to a sandwich type complex where the cation is between two polyether units. An example of this is the 2 : 1 sandwich complex formed between benzo-15-crown-5 (7) and potassium iodide[164], where the cation is located between the two parallel macrocycles.

Whilst the idea of cavity diameter: cation diameter to determine the stoichiometry and nature of complexes has in general been very successful for the alkali cations, there are exceptions. For example the formation of 1 : 1 complexes of the thallous ion with benzo-15-crown-5[165] as compared with 1 : 2 sandwich complexes formed with the similar sized potassium ion with the same crown ether[165]. Further examples are given by Poonia et al[17,156,166,167] in reviews of the subject. The concept breaks down even more when examining the structures of complexes formed by the alkaline-earth cations, particularly Mg^{2+} and Ca^{2+}, with crown ethers. Poonia and co-workers[17,156,166,167] found that complexation of magnesium and calcium was difficult due to the high charge density of these cations which favoured a higher interaction with the counter-ion. Indeed, the anion-philicity of calcium is such that a complex has been reported[168] where the calcium is in an exclusive anion-solvent environment, despite the presence of benzo-15-crown-5 which has the right cavity size for calcium. 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 (see section 2.3.1).

Hence, in summary, although the relative sizes of the cation and crown cavity are a useful guide to the nature of complexation, other factors, particularly the charge density of the metal cation, the nature of the anion, the solvent, and extent of solvation of the ion and the binding sites, must be considered.

1.4.2 Complexes of Crown Ethers with Other Metal Ions

A. Transition Metals Although there are innumerable transition metal complexes with nitrogen donor and mixed donor macrocycles, because of the very weak affinity of the 'soft' transition metal ions for the 'hard' oxygen donors, there are very few reported complexes with purely oxygen containing crown ethers. Most of the complexes reported do not have the metal ion sitting in the cavity of the macrocycle, but rather placed between two cyclic polyethers in a sandwich type structure so as to achieve optimum octahedral co-ordination. The first example of such a complex is between dicyclohexyl-18-crown-6 (4) and Co^{2+} [169]. Similar non-inclusive complexes have been reported[170], examples are those of Mn^{2+} with 18-crown-6,[171] Cu^{2+} with 15-crown-5,[172] Fe^{2+} with 18-crown-6 and dibenzo-18-crown-6[173]; and the X-ray structures were very recently reported[174] for non-inclusive Pt^{2+} complexes with 18-crown-6. Although rare, some inclusive complexes of the transition metal ions have been reported, for example those formed by niobium and tantalum with dibenzo-18-crown-6, 18-crown-6 and 15-crown-5,[175] and the complex formed by Hg^{2+} with the acyclic polyether 1, 15-bis (2-bromophenyl)-2,5, 8,11,14 - pentaoxapentadecane[176].

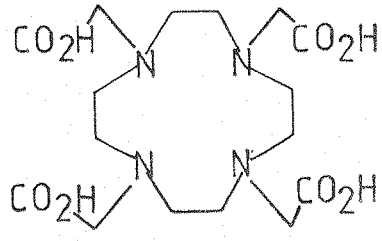
B. Lanthanide Metals After complexes of crown ethers with alkali and alkaline-earth cations, the complexes of the lanthanide metals have been the most widely studied. Two important general features are[177]:

i) Complexation behaviour depends on cavity size

ii) All crown ethers stabilize the +2 oxidation state in preference to +3.

Another interesting feature is the common occurrence of the unusual 4 : 3 metal ion : crown complex in addition to the 1 : 1 complex for most of the lanthanide metals. This has been investigated for the lanthanide nitrates with 15-crown-5 and 18-crown-6[178] and the lanthanide perchlorates and nitrates with 12-crown-4 and 15-crown-5[179]. The sandwich complexes of 12-crown-4 with lanthanide salts have been investigated[180] and show dependence on the anion. Whereas $Nd(NO_3)_3$ generates a 1 : 1 complex, perchlorate salts of La, Pr, Eu, Ho, Er, Tm and Yb generate 1 : 2 complexes. This is attributed[180] to the very weak complexing properties of ClO_4^-, whereas NO_3^- competes favourably with the polyether for complexation. The complexation of Sm is noteworthy[181] as it is a useful probe for transuranic elements. Complexation of lanthanides with crown ethers often gives rise to unusual spectral properties. For

example, there are remarkable changes in charge transfer, f-d and f-f transitions[182,183], and the quantum yields for photoreduction of Eu^{3+} are dramatically increased in the presence of 18-crown-6[182], confirming the potential of the crown ethers to stabilize the +2 oxidation state. Some aspects of the complexation of lanthanides with crown ethers have been reviewed[184]. In summary, lanthanide complexation is, like that of the alkali and alkaline-earth cations, not as simple as it might first appear. Complexation depends on not only the dimensions of the macrocyclic cavity, but also the rigidity of the macrocycle, the nature of its donor atoms and as the complexing properties of the counter-ion. It is worth noting that the most stable rare-earth complexes known are formed by the tetra-acetic, tetra-aza macrocycle (62)[177,184],



(62)

which might have great potential in separating rare earth ions from transition and alkali metal ions.

C. Actinides Practically the only actinide to receive attention with respect to crown ether complexation has been uranium[185], which forms both inclusive and exclusive complexes. Interest has centred on the ability of crown ethers to stabilize various oxidation states: e.g. U^{VI}, asin UO_2^{2+} $(NO_3)_2^-$. 18-crown-6[186];

U^{V}, formed by the photoreduction of UO_2^{2+}. 18-crown-6 $(ClO_4)_2^-$;[187]

U^{IV}, as in UCl_4. dicyclohexyl-18-crown-6[188];

U^{III}, as in UCl_3. 18-crown-6 or $U(BH_4)_3$. 18-crown-6[189].

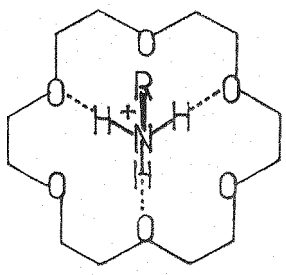
Indeed a case has been reported[190] of uranium^{IV} insertion into 18-crown-6 with co-existence of the metal in two oxidation states in the complex.

D. 'p' Block Elements The thallium cation, Tl^+, which, due to the inert s pair effect has a similar size to K^+ [191], and Pb^{2+}, which has a similar size to Sr^{2+}, are quite similar to the alkali and alkaline-earth cations in their macrocyclic binding properties and tend to form complexes even more stable than those of other metal ions of similar size[192]. However, with these exceptions, very little work

has been done on the other 'p' block metallic elements. Tin^{II} complexes with 18-crown-6 and dibenzo-18-crown-6 have been examined[193] as have $AlCl_3$ complexes with crown ethers[194]. In the latter case it was found that of a variety of crown ethers, only benzo-15-crown-5 and those with an electron releasing substituent formed complexes with $AlCl_3$.

1.4.3. Host-Guest Complexes

A. Protonated Amines Since the ammonium ion resembles the potassium ion with respect to charge and size, it is not surprising that it forms similar complexes with the cyclic polyethers. Complexes are formed in organic media with molecules containing guanidinium, arenediazonium and primary and secondary ammonium groups[195]. The complexation of potonated amines, RNH_3^+, by crown ethers differs in many aspects from complexation of metal cations[56]. Whereas metal cations derive most of their binding energy through electrostatic forces, complexes with ammonium ions are also stabilized through hydrogen bonds. Hence the favoured complexation is one that gives maximum hydrogen bonding, and this is illustrated for (63) and (64) for a primary amine complex with 18-crown-6 and guanidinium with tribenzo-



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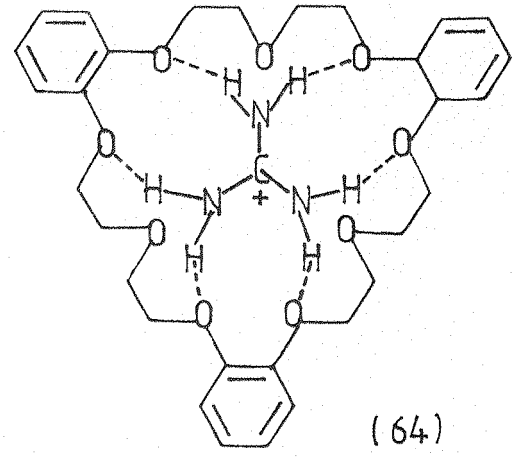
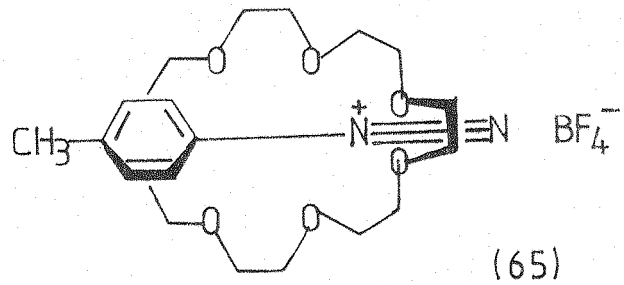


(64)

27-crown-9[196] respectively. Although not illustrated, it should be noted that further stabilization arises from electrostatic interactions of the remaining ether oxygens with the hydrogens. Structural variations - particularly the introduction of chirality (as in 1.2.4) - gives a potential method of resolving different enantiomers of amino acids due

to different complexations, and this has been developed in the main by Cram and co-workers[57,58]. The effect of the organic 'R' group on the stability of ammonium complexes of 18-crown-6 has been investigated[197], and it was found that formation constants decrease in the order NH_4^+, $RNH_3^+ > R_2NH_2^+ > R_3NH^+$, the association constants for alkylammonium ions being about one hundreth that of K^+. Some of the most studied host-guest complexes are those of the alkyl-and aryl-diazonium salts[56,198-200]. The structure of the arene-diazonium complex is shown below (65).



(65)

21-crown-7 is actually the preferred host for most diazonium salts. In summary, the discrimination arising from a combination of macrocyclic cavity size and choice of lateral interactions between the ligand and the substrate should lead to selective complexing agents for a wide variety of molecules with many potential applications.

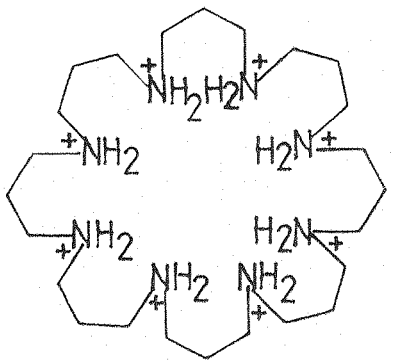
B. Neutral Molecules[56,112] Shortly after crown ethers were first synthesized, Pedersen[201] reported on a number of crystalline complexes of thiourea and related molecules of no fixed stoichiometry with the crown ethers. However, until recently, little work had been done on the complexation of crown ethers with neutral molecules despite the knowledge[129] that acetonitrile formed a solid adduct with 18-crown-6 (used to purify the polyether). However, there has been an upsurge of interest in this field and a whole host of neutral molecules have recently been reported[202-204] which stoichiometrically complex to crown ethers. These include benzenesulphonamide[202], urea, malodinitrile, dimethylsulphoxide, formamide and dimethyl formamide. Recantly 1 : 2 host:guest compounds of 18-crown-6 and 2,4-dinitrophenyl hydrazine were reported[205] and one interesting development is the first report[206] of an inclusive complex formed by aliphatic alcohols with a pyridino crown ether. One potentially very useful application is the fixation

of volatile, highly toxic alkylating and acylating reagents by crown ether complexation[112,207]. Such molecules as dimethyl sulphate, N,N-dimethyl nitrosamine, mesyl chloride, mesyl bromide and acetic anhydride can be complexed to crown ethers and used as the solid complex without any loss of efficiency.

1.4.4 Anion Binding Crown Type Compounds

Although crown ethers and similar compounds predominately complex positively charged, or neutral, species some compounds have been developed which can bind anions. This work has been done mainly by Lehn and co-workers[208-211], some of the typical anion-co-ordinating species are given in Plate 1.2. Typically the monocyclic species can bind to complex anions such as SO_4^{2-}, oxalate, malonate, succinate, tartrate, maleate, fumarate, squarate, citrate, $Co(CN)_6^{3-}$, $Fe(CN)_6^{4-}$, AMP^{2-}, ADP^{3-}, and ATP^{4-} whereas the multicyclic compounds e.g. (68) are more suited for the small mono-anions such as Cl^-, F^-, or Br^-.

Plate 1.2 Selected Anion Binding Macrocycles



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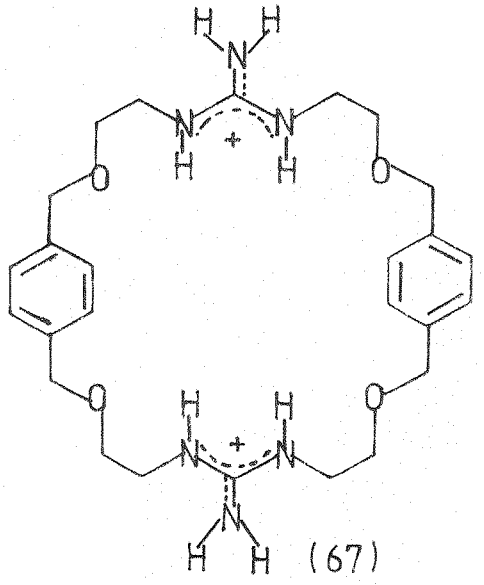

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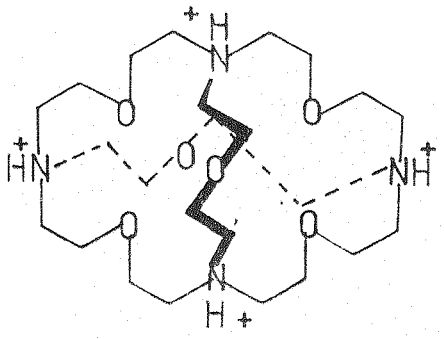


(68)

1.5 PHYSICAL STUDIES ON CROWN : CATION INTERACTION[155]

A variety of techniques may be used to detect complexation reactions, to determine the stability of the resulting complex and to determine the thermodynamic[149] and kinetic[212] parameters of complex formation[150]. These include spectroscopic, electrochemical, extraction, calorimetric and relaxation techniques.

1.5.1 Spectroscopic Techniques

A. Ultra-violet/visible spectroscopy All cyclic polyethers containing one or more benzo groups have characteristic absorption maxima at 275 nm in methanol and the shapes of the curves are altered upon complexations, the greatest change is assumed to be caused by the salt forming the most stable complex[23,213]. However in general ultra-violet/visible spectroscopy has limited applications and for the quantitative estimation of complex formation, other methods are simpler and more accurate.

B. Nuclear magnetic resonance spectroscopy[155,214,215]

i) ^{1}Hnmr Although sometimes limited by the small chemical shift between the complexed form and uncomplexed form, proton nmr is widely used because of the symmetric nature of the crown ethers and resulting simple spectra. Larger shifts have been observed[216] in the complexation of dimethyldibenzo-18-crown-6 and sodium fluorenyl in tetrahydrofuran solution for the ring protons, whilst those of the aromatic rings and methyl groups were much less affected. Lockhart et al[217] have reported ^{1}Hnmr measurements on benzo-15-crown-5 and benzo-21-crown-7 in the complexed and uncomplexed forms. Where both the 1 : 1 and 2 : 1 ligand metal ion complexes were formed, the ^{1}Hnmr moves initially downfield, but changes direction after formation of the first complex. Similar results have been reported[218] for the complexation of dibenzo-18-crown-6 with Cs^{+} in acetone. Whereas the behaviour of dibenzo-18-crown-6 and dibenzo-30-crown-10 is similar for potassium and caesium complexes, the addition of sodium to dibenzo-30-crown-10 changes the spectrum quite considerably. This indicates[218] a conformational change of the ligand upon formation of the sodium complex.

ii) ^{13}C nmr ^{13}C nmr is often used hand-in-hand with ^{1}Hnmr. The range of ^{13}C chemical shifts is much larger than for ^{1}Hnmr and are quite sensitive to small changes in the conformation or chemical environment, and ^{13}C nmr has often been used to confirm the results from ^{1}Hnmr - as in the case of the sodium complex with dibenzo-30-crown-10[218]. One particular application is to follow the protonation of cryptands and the resulting formation of an anionic complex[208], e.g. (68), Plate 1.2.

iii) Alkali metal nmr All the members of the alkali group have nmr active isotopes and the natural line widths of ^{23}Na, ^{39}K and particularly ^{7}Li and ^{133}Cs are quite narrow. The range of chemical shifts is directly dependent on atomic number, ranging from about 10 ppm, for ^{7}Li to several hundred for ^{133}Cs. As the nucleus of a complexed ion generally resonates at a different frequency than the uncomplexed ion, if the exchange between both forms is slow on the nmr time scale, then two signals will be observed. However, generally exchange between the two sites is fast and only one averaged signal is seen. From a knowledge of the observed signal, the signal of the free ion and the total concentrations of the metal and ligand, the formation constant may be obtained. This is a very successful technique for complexes with formation constants of 1 to 10^5 but, as with all spectroscopic techniques, nmr fails when dealing with very stable complexes.

^{7}Li nmr has been used[219] to demonstrate two signals for the free and complexed form when excess Li^+ is added to the cryptand C211, (29) n = o = 1, p = 2, Plate 1.1 . This cryptand accommodates Li^+ ideally[69], so causing slow exchange whereas for complexes with C222 (29), n = o = p = 2 and C221 (29), n = o = 2, p = 1 only an averaged signal is observed. Whilst the resonance frequency of the free cation is strongly solvent dependent, the limiting shift of Li^+ in the C211 cavity is almost completely independent of solvent demonstrating the complete encapsulation of the cation.

The ^{23}Na nmr resonance is broader than that of ^{7}Li, and this is especially true for crown ether complexes. However for the cryptand complexes, this is much less pronounced. Shchori et al[220] have used ^{23}Na nmr for kinetic studies of Na^+ complexation by several crown

ethers in different solvents. Both crowns and cryptands react with metal solutions in appropriate solvents to give the solvated alkali cation and an alkali anion. An example is the formation of C222.Na^+ Na^- in ethylamine[221], where exchange is slow and the Na^- resonance is shifted strongly upfield from the Na^+ resonance (for free and complexed forms).

^{39}K nmr measurements are difficulty due to a low sensitivity of the nucleus. However it has been used to examine the kinetics of complexation of K^+ with dibenzo-18-crown-6 in methanol[222], and its use, in conjunction with ^{13}Cnmr has recently been reported[223] in the examination of potassium cryptates.

^{87}Rb nmr studies do not look very promising due to the very broad line widths.

^{133} Cs nmr studies, in contrast to ^{87}Rb, seem to have great potential as the resonance is very narrow with relatively high sensitivity. ^{133}Cs nmr studies of Cs^+-18-crown-6 in pyridine solution were performed by Mei et al[224,225]. A plot of the ^{133}Cs chemical shift against the 18-crown-6/Cs^+ mole ratio at different temperatures revealed a downfield shift until a 1 : 1 ratio was achieved, when further addition of 18-crown-6 produced an upfield shift. This was attributed to the stepwise formation of 18-crown-6. Cs^+ and (18-crown-6)$_2$. Cs^+ complexes in a similar manner to reference[218]. One important use has been to differentiate between the exclusive and inclusive complex of Cs^+ with C222[215,226]. At low temperatures the cation is totally inside the ligand cavity and shielded from solvent, whereas at higher temperatures the cation is only partially inside the cavity (exclusive complex) and subject to solvent effects. These results have been confirmed by X-ray crystallographic studies[227].

iv) Nmr of other nuclei Due to its enormous, solvent dependent, chemical shift and chemical similarity to potassium[191], ^{205}Tl nmr is widely used. By competitive experiments the sequence of stability constants with respect to Tl^+ of the alkali metals for cyclic polyethers may be determined[228]. In addition ^{17}Onmr[229] and ^{15}N nmr have been used to follow crown ether and cryptand complexation, although both techniques are limited by the very low natural abundances and low sensitivities

C. Vibrational Spectroscopy Vibrational spectroscopy often yields additional information to other techniques about conformational changes, interaction with solvent and anion, and general complexation[155]. In particular, the greatest change in the infra-red spectrum of the crown ethers upon complexation is in the 900 - 1200 cm^{-1} region, and the appearance of low frequency bands in the 100 - 300 cm^{-1} region assigned to oxygen-metal vibrations[230].

D. Electron Spin Resonance Spectroscopy Spin labels have been introduced into crown ethers as in (14)[34] Plate1.1. A similar example is the galvinoxyl-labelled benzo-15-crown-5[231] where the esr spectra indicates the formation of a 1 : 1 complex with NaSCN and a 2 : 1 complex with KSCN. Radical anions of aromatic hydrocarbons, e.g. fluorenone[232], have been prepared by dissolution of sodium or potassium metal in crown ethers or cryptands which can then be followed by esr.

1.5.2 Electrochemical Techniques

A. Potentiometric Measurements Potentiometric determination of the free metal ion by using ion-selective electrodes is a simple technique and, unlike spectroscopic techniques, allows the determination of stability constants for very stable species. It does, however, possess two important limitations. Firstly the indicator electrodes are only selective -not specific- for cations, and consequently small impurities may affect results, particularly at high dilution. Secondly potentiometric methods are only suited to polar, 'water-like' solvents. The formation constants of a large number of crown ethers with several mono-valent ions have been determined by Frensdorff[233] using a potentiometric method in water and aqueous methanol solutions.

B. Conductometric Techniques Conductometric techniques have the advantage over potentiometric measurements in that they can be applied in non-aqueous solvents. However it is most sensitive to small amounts of conducting impurities. An example of its use is the study[220] of complexation of Na^+ with dibenzo-18-crown-6 in dimethylformamide. Conductometric titrations were also used by Pedersen and Frensdorff[26]

to determine the stoichiometries of crown complexes.

C. Other Techniques Other electrochemical techniques include polarography and cyclic voltammetry to follow the electrochemical reduction of various alkali metal salts and their crown ether/cryptand complexes. A recent application is the use of polarography to follow the reduction of alkali metal perchlorate complexes of 12-crown-4.[234]

1.5.3 Extraction Studies

This method is generally useful as it can be applied to all crown ethers and complexing efficiencies can be ranked numerically. When an aqueous solution of an alkali metal salt containing a very low concentration of the picrate of the same cation is mixed with an equal volume of an immiscible organic solvent, nearly all the picrate is present in the aqueous phase. On addition of a cyclic polyether the complexed picrate transfers to the organic phase, the extent of which is dependent on the binding of the polyether to the cation. This technique has been used[26,157,213] to study extractions of sodium and potassium picrates by various crown ethers in different solvents.

1.5.4 Calorimetric Techniques

Calorimetric techniques are extremely useful for the determination of thermodynamic parameters of complexation , and are ideally suited for non-aqueous solvents. As for spectroscopic methods, this technique is not suitable where formation constants are larger than 10^5. Work on the calorimetric measurement of crown ether complexation has been pioneered by Izatt and Christensen[149,154,192]. In particular they have applied calorimetric methods to make a systematic study of the effect of macrocycle ring size and donor atom type on the thermodynamic parameters of complexation for mono- and di-valent cations with crown ethers in methanol[235].

1.5.5 Relaxation Techniques

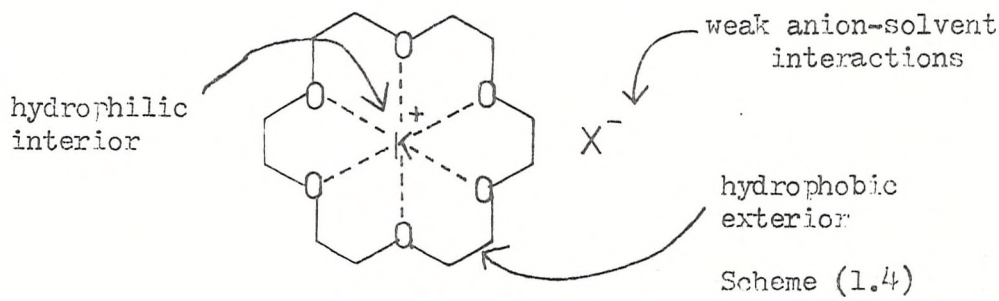
The kinetics of complex association and disassociation have been

studied by a variety of relaxation techniques[212] that include temperature jump, ultra-sonic absorption[236] and stopped-flow methods[237].

1.6 APPLICATIONS OF CROWN ETHERS

1.6.1 Synthetic Transformations

Crown ethers have two main roles in synthetic chemistry. The first is to act as phase-transfer agents by forming a complex with a metal salt, which can be represented as in Scheme(1.4),for the case of a potassium salt with 18-crown-6.



Scheme (1.4)

This gives the potassium salt a lipophilic exterior which renders it soluble in organic media. The classic example of this is that of 'purple benzene'[238] whereby potassium permanganate is rendered soluble in benzene by the addition of dicyclohexyl-18-crown-6, thus making possible permanganate oxidations in benzene. Crown ethers have the advantage over the traditional phase-transfer agents - the quaternary phosphonium and ammonium salts - of lack of steric hinderance and ligand neutrality so as to achieve solid-liquid phase transfer catalysis[127], but this is compensated for by their relatively high cost. A thorough review of all aspects of phase-transfer catalysis has been published[239].

The second, and main, use of crown ethers is in the field of activated anions. By complexation of the cation, as in Scheme 1.4, the anion is left relatively unsolvated - or 'naked' - and consequently has great potential as a nucleophile as well as a base.

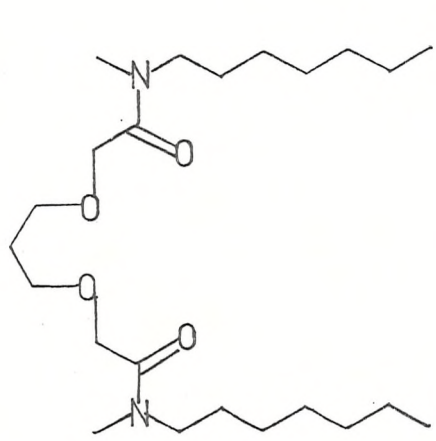
In particular, the activation of halide anions from common salts has great synthetic potential. Other reactions promoted by activated anions are those of carboxylate ions, cyanide ions, nitrite ions, nitrate ions, oxygen nucleophiles and bases, superoxides, hydride reductions, oxidation reactions, bromine addition reactions, sulphur nucleophiles, carbenes, carbanions and anion rearrangements, and alkali metals. This chemistry has been reported in various reviews[127,240,241].

1.6.2 Other Applications[242]

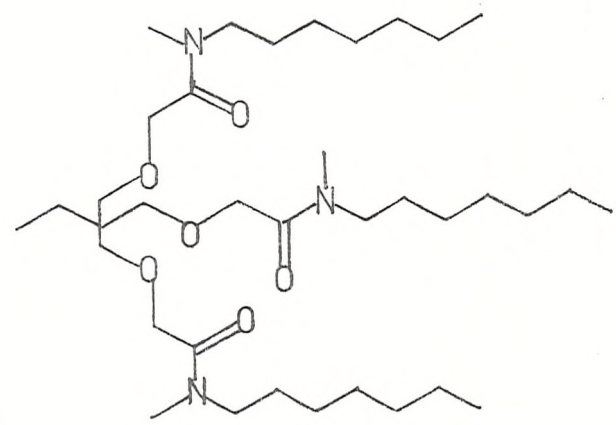
Because of their ability to selectively complex various cationic species, crown ethers have many potential applications in analytical chemistry and this has been the subject of a recent review[243]. One application, see sections 1.2.4 and 1.4.3, is the use of Cram's host-guest compounds. A development of this work is the incorporation of such molecules into a polystyrene resin for the chromatographic resolution of enantiomers of amino acids and ester salts[244]. Similarly crown ethers have been incorporated as anchor groups into exchangers[245] which have many potential applications including the separation of cations with a common anion and trace enrichment.

The field of liquid-liquid extractions is one where crown ethers have realised their potential and are used on a large scale. This is especially true for isotopic separations where, for example, dicyclohexyl-18-crown-6 has a preference for ^{40}Ca over ^{48}Ca of 1.008[242] and benzo-C222 has also been found[246] to have a promising separation for the same isotopes. Dicyclohexyl-18-crown-6 has also been used[247] to separate small amounts of ^{89}Sr and ^{90}Sr from a large amount of calcium in milk.

Crown ethers and similar compounds look to have promising future in the field of ion-selective electrodes, where already natural antibiotics such as valinomycin (see 1.7.1) have been used[248]. The most promising compounds in this field have been developed by Simon et al[249,230]. Although not crown ethers, they are thought to have similar complexing properties. Two examples, (69) and (70), are given below; (69) being lithium selective and (70) being potassium selective.



(69)



(70)

One final development has been the work of Grätzel and co-workers (251,253) who have utilized alkyl substituted diaza crown ethers which can form functional micelles for the purpose of electron transfer reactions. By incorporating Ag^+ into the crown ether cavity to act as the electron acceptor, these compounds might have a role to play in photography.

1.7 COMPARISON TO NATURAL IONOPHOROUS ANTIBIOTICS

1.7.1 Background

In 1964 Pressman discovered[254] that certain antibiotics could induce the selective movement of K^+ into rat liver mitochondria. Since this time there has been a great deal of interest in these antibiotics - termed ionophorous (ion-carrying) - due to their ability to transport the key biological ions K^+, Na^+, Ca^{2+} and Mg^{2+} across biological membranes. This has been the subject of several reviews[19,255-258]. In particular, there are two comprehensive reviews classifying ionophores either by mode of transport [259] or by chemical structure[260] which shall be used in this thesis due to its unambiguity. See Plate 1.3 for typical structures of all classes.

A. Peptides e.g. gramicidins A, B and C, alemethicin. These ionophores, although unable to form metal complexes, induce cationic permeability by forming stationary ion-conducting channels[261].

Plate 1.3 Selected Ionophorous Antibiotics

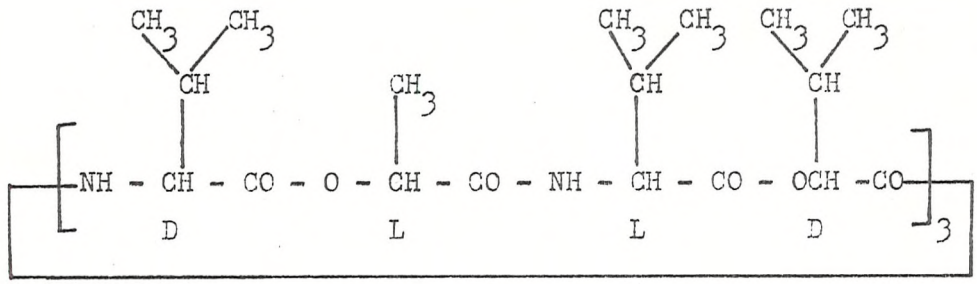
A. Peptides

HCO - L.Val - Gly - L. Ala - D.Leu - L.Ala - D.Val - L.Val
L.Val

$HOCH_2CH_2$ NH
D.Trp - L.Leu - D.Trp - L.Leu - D.AA* - L.Leu - D.Trp

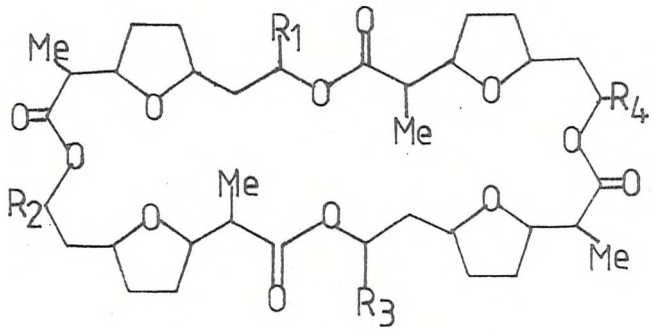
Gramicidin A	AA*	= Trp
B	AA*	= Phe
C	AA*	= Tyr

B. Cyclodepsipeptides



valinomycin

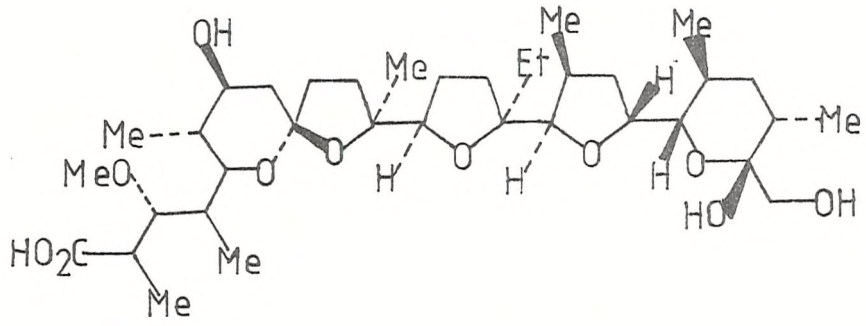
C. Macrotetralides



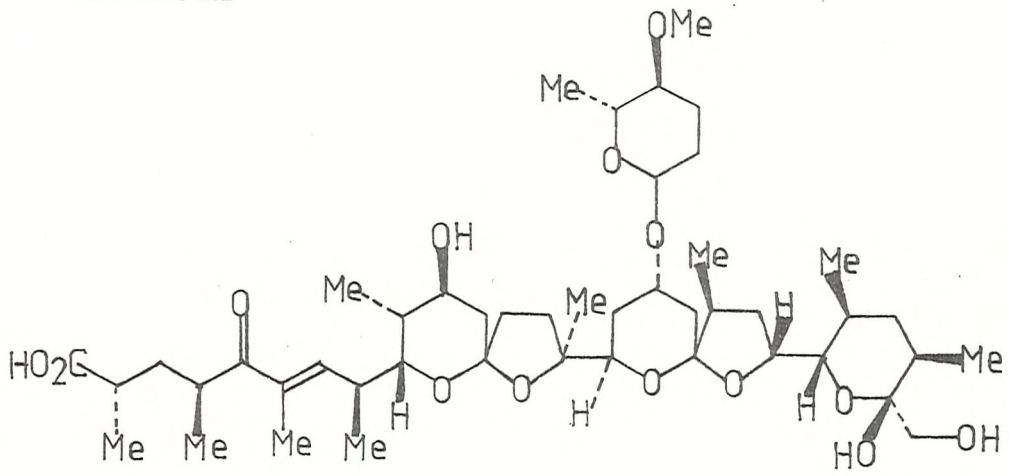
Nonactin $R_1 = R_2 = R_3 = R_4 = Me$
Monactin $R_1 = R_2 = R_3 = Me, R_4 = Et$
Dinactin $R_1 = R_2 = Me, R_2 = R_4 = Et$
Trinactin $R_1 = Me, R_2 = R_3 = R_4 = Et$
Tetranactin $R_1 = R_2 = R_3 = R_4 = Et$

D. Polyether antibiotics

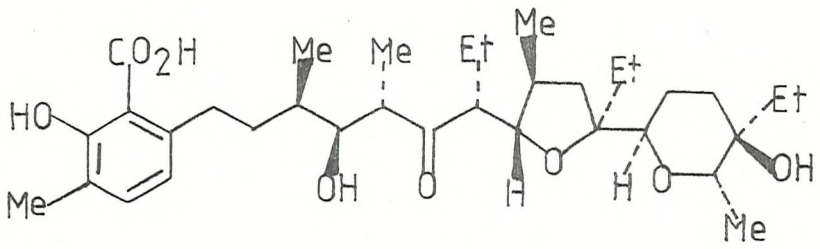
Ia monensin



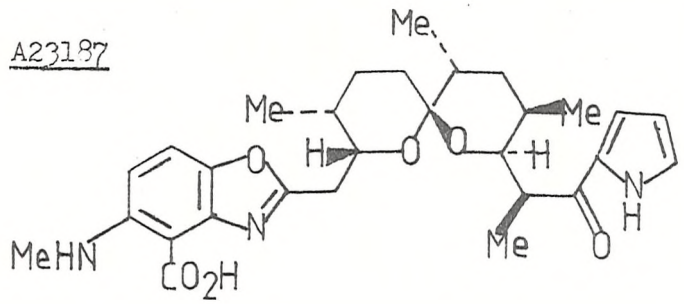
Ib dianemycin



IIa lasalocid A



IIb A23187



B. Cyclodepsipeptides[262] e.g. valinomycin, enniatins, beauvericin. These ionophores consist of alternating amino and hydroxy acids. Valinomycin has received much attention due to its very high selectivity for K^+ over Na^+ (10^4 : 1), whereas the enniatins have a much smaller selectivity (10 : 1) but can complex a broader range of cations.

C. Macrotetralides e.g. actin homologues. These ionophores, the most immediately analagous structures to the crown ethers, are constructed from four tetrahydrofuranyl hydroxyacids connected by lactone bonds.

D. Polyether antibiotics This group, sometimes known as the carboxylic acid ionophores, have been reviewed as a class[260,263,264], and can be sub-divided depending on their structure and ability to transport divalent cations.

Ia Monovalent polyethers, e.g. monensin, nigericin, laidlomycin, grisorixin, salinomycin, narasin, lonomycin, A206 and alborixin.

Ib Monovalent monoglycoside polyethers, e.g. dianemycin, lenoremycin, A204A, septamycin and etheromycin.

IIa Divalent polyethers, e.g. lasolocid A (X537A), isolasalocid A and lysocellin.

IIb Divalent pyrrole ethers, e.g. A23187. All the polyethers listed above were isolated from streptomyces. In general they are active against gram positive bacteria, mycobacteria and have an anti-coccidiostatic effect. In many instances these compounds have cardiotonic activity. As with many reports of their effects, this is probably associated with an ability to transport Ca^{2+}.

1.7.2 Ion Transport Experiments

Ion transport experiments fall into two main categories: those that utilize a bulk organic liquid (typically chloroform) to separate two aqueous phases, and those that use natural lipids to form a bilayer to imitate the natural cellular membrane. The advantage of the first system is its inherent simplicity although it is doubtful if it acts as a true representation of the complex cell membrane. There are many variants of this system, such as a 'U' tube which has a chloroform phase at the bottom and a receiving aqueous phase and salt solution respectively in both arms. In particular Izatt and Christensen and

co-workers[265,266] have exploited a variation of this technique (see sections 3.1.3 and 3.3.1) in order to examine the ionophorous abilities of various crown ethers.

The second method uses natural lipids such as cholesterol to form a bilayer to mimic the natural cell membrane[267-269]. The bilayer may then be formed into a sphere, or vesicle, which mimics a cell in that it is totally enclosed (see sections 3.1.3 and 3.3.2), or made to form a 'black lipid bilayer'. The apparatus for this second option consists[270] of a Teflon cell with two compartments containing an aqueous solution of an electrolyte which are separated by a partition with a small circular hole ($\sim$ 1mm diameter). The membrane solution (typically glycerol mono-oleate in n-decane 1% w/v) is introduced into the aperture and automatically thins, under the action of buoyancy and surface tension forces, to give an optically black membrane which is only a bilayer thick. This apparatus may then be used to follow the creation of conductance channels by the formation of a gramicidin dimer[258] and to investigate the effectiveness of ionophores at the transition point of the lipid bilayer. Ion carriers such as valinomycin and non actin drastically lose their effectiveness on freezing whereas channel formers such as gramicidin have the same effect on 'solid' and 'lipid' membranes[271].

1.8 AIMS OF RESEARCH PROJECT

Although there is an abundance of reports in the literature on the synthesis of new crown ethers, many of which invoke a template effect, there has been very little work done to quantify the importance of the template effect. This has become more important now that in recent cases the tacit assumption of a template effect has become less certain (see section 2.1). Consequently it was decided to examine the synthesis of the simple unsubstituted crown ethers in great detail in order to determine the importance of the template effect.

In conjunction with this, it was desired to make crown ethers that would be suitable ionophores, in particular by the introduction of substituents directly onto the crown ether skeleton. Two target

molecules were attempted - a series of alkyl substituted crown ethers and a series of carboxylic acid substituted crown ethers. The alkyl substituent was desirable as although crown ethers in general were poor ionophores in comparison to natural antibiotics[272,273], one compound which had shown more potential was bis-^{t} butylcyclohexyl-18-crown-6,(11), Plate 1.1, in lipid-bilayer experiments. This was attributed[274,275] to its ability to partition more strongly into an organic phase than the corresponding unsubstituted crown ether. The carboxylic acid substituent was desirable for two reasons. Firstly the acid function appears frequently in natural antibiotics and yet very little work indeed has been done on acid-substituted crown ethers. Secondly it is interesting to consider the effect of an additional binding site on the complexation and transport properties of the crown ether (see section 3.1).

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CHAPTER 2 +

THE TEMPLATE EFFECT IN THE SYNTHESIS OF CROWN ETHERS

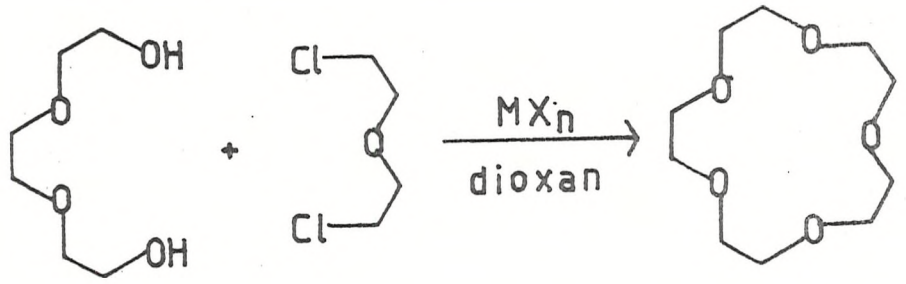
2.1 INTRODUCTION

Ever since the discovery of crown ethers by Pedersen[1], the synthesis of these cyclic polyethers has been assumed to involve a template effect[2] (see section 1.3). It should be noted, however, that some large macrocyclic compounds have been constructed without use of a template effect or resorting to high-dilution techniques where entropy considerations[3] or other factors favour the synthesis of macrocycles. These are unusual phenomena, and in the vast majority of cases, the synthesis of cyclic polyethers has invoked a template effect.

There has been little quantitative work to determine the importance of the template effect. Mostly the template effect is assumed on the basis of Na^+/K^+ selectivity for a particular macrocycle[4]. As interest in crown ether chemistry has grown it has become increasingly necessary to test the validity of the template effect. For example, Reinhoudt et al[5] 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 was higher with rubidium and caesium fluorides than with potassium fluoride and gave no reaction with lithium or sodium fluorides. Another example is the reported yield of 50%[6] for the synthesis of benzo-15-crown-5 from the dicaesium salt of catechol and dibromo-tetraethylene glycol, although it is uncertain as to whether the caesium ion is acting as a template ion in this case (see section 1.3). A further example is the difficulty of complexation of the lower alkaline-earth salts[7-9]. Although barium and strontium are known to act as suitable templates in the synthesis of crown ethers[10], it was not known whether the difficulty of complexation for

+References for this chapter can be found on page 85.

magnesium and calcium for crown ethers would extend to their ability to act in a templating role. 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 (2), reaction 2.1a, and 18-crown-6 (3), reaction 2.2, based on the initial syntheses by Reese and co-workers[11]. For comparison, the syntheses were also attempted with **tetrabutylammonium** hydroxide which due to its size, could not exert a template effect.

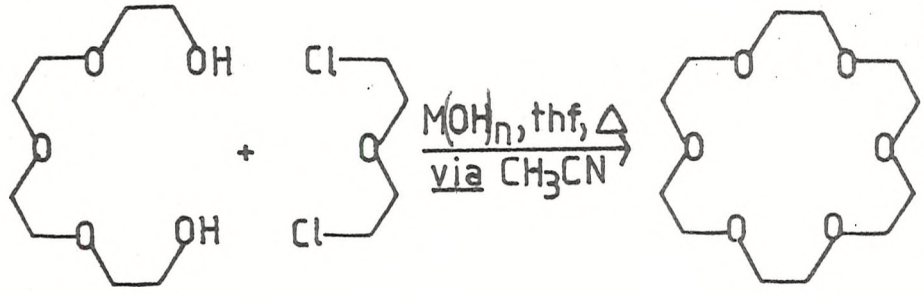


(2.1)

(2)

a) M = Li,Na,K,Rb,Cs,Mg,Ca,Sr,Ba,Tl or NBu_4^n ;
X = OH

b) M = Na, X = F, OH,OMe,NH_2 or H



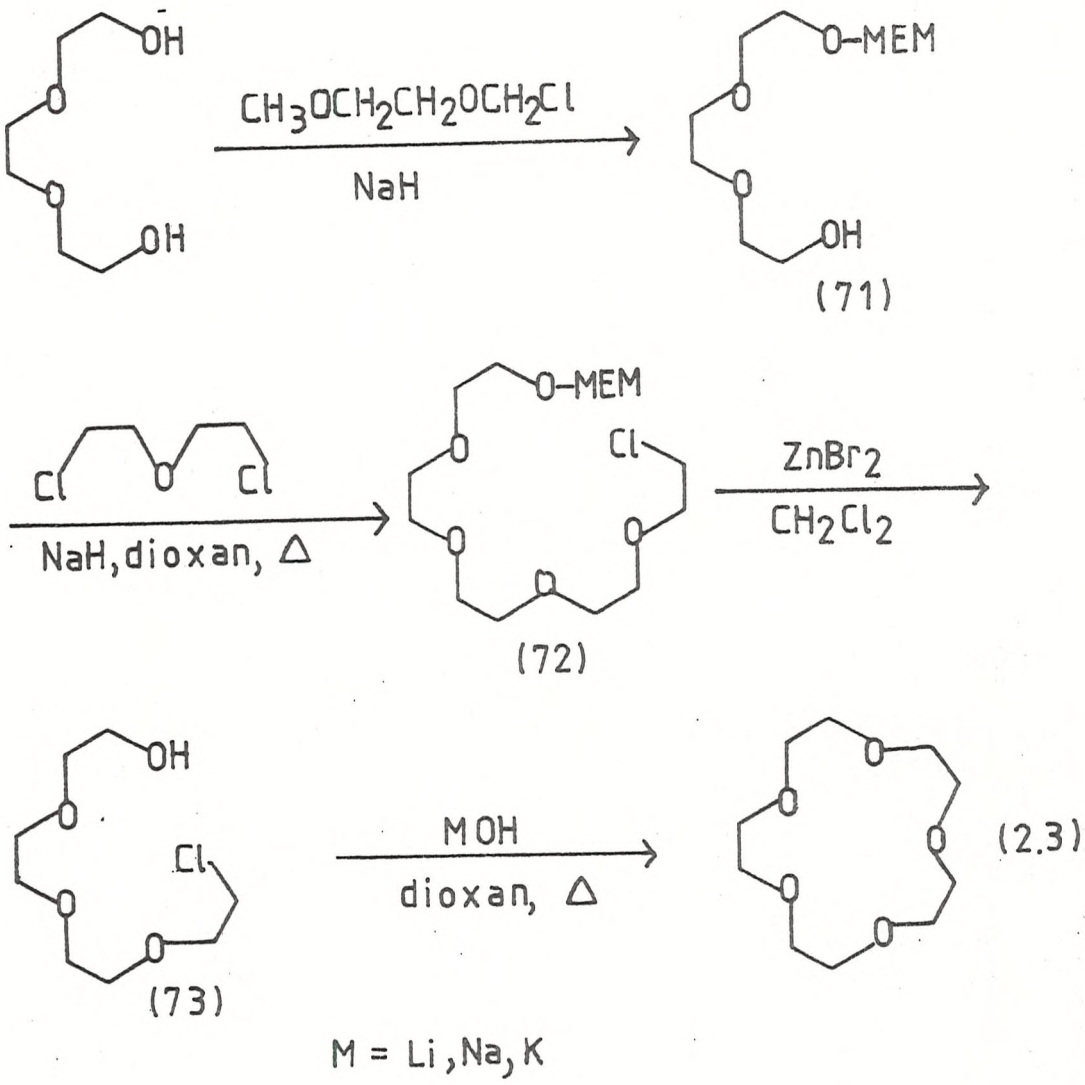
(2.2)

(3)

M = Li,Na,K,Rb,Cs,Mg,Ca,Sr,Ba,Tl or NBu_4^n

thf = tetrahydrofuran

A related synthesis of 15-crown-5 involved ring closure of molecule (7 3) in the presence of metal hydroxides, reaction 2.3. Molecule (7 3) was built up by mono-protecting triethylene glycol

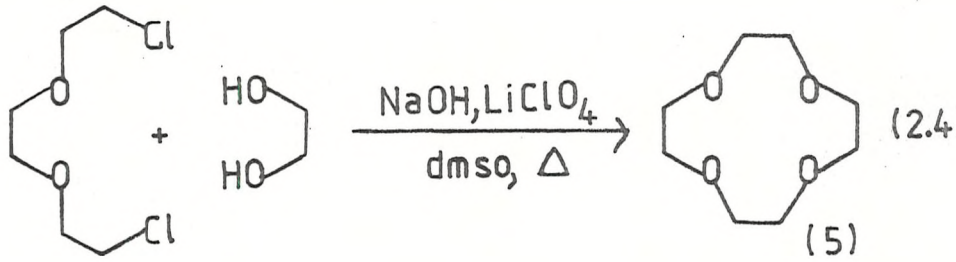


with the nethoxyethoxymethyl (MEM) group[12], reacting with bis (2-chloroethyl) ether and then deprotecting. The final cyclization step was then examined in the presence of some alkali metal hydroxides.

In the acid-catalyzed condensation of furan with acetone in the presence of some alkali, alkaline-earth, and transition metal salts, it has been shown[13] that the yield of the macrocyclic tetramer (24),

was related to changes in acidity or ionic strength of the reaction media 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, reaction 2.1b.

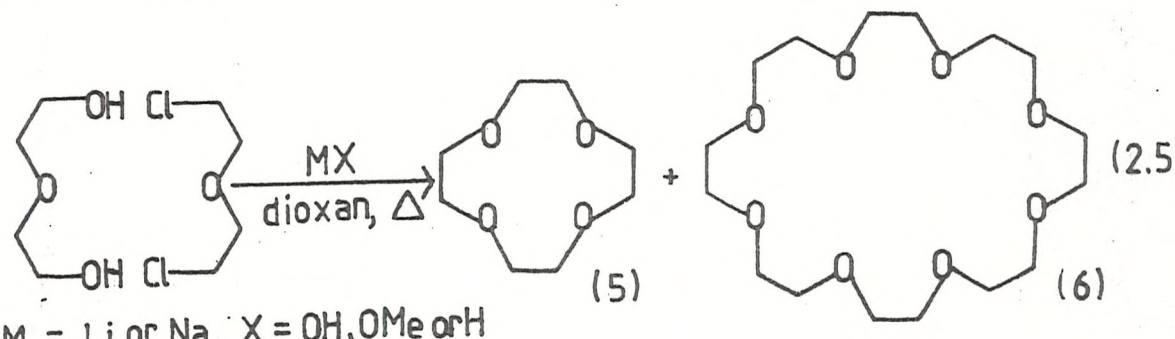
12-crown-4 (5) is a particularly interesting compound in that there are few reported syntheses and these tend to give low yields ($\lesssim$ 15%). The most successful synthesis of 12-crown-4 has been by the acid-catalyzed cyclic tetramerisation of ethylene oxide[14]. However, despite the 'gauche' effect[15], whereby the natural conformation[16] 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 products. 12-crown-4 has also been prepared[17] in a modified Williamson ether synthesis, reaction 2.4, in 13% yield. This is an unusual reaction because the 12-crown-4 was not obtained if



(2.4)

(5)

$LiClO_4$ was absent. Identical runs with $LiOH.H_2O$ rather than NaOH also gave no product, as did analogous runs with $LiClO_4$ in tetrahydrofuran (thf) instead of dimethyl sulphoxide (dmso). Consequently a study of the synthesis of 12-crown-4 using a new route, reaction 2.5, which also gave, depending on the cation, 24-crown-8 (6), was undertaken.



(2.5)

2.2 RESULTS[19]

2.2.1 Template Synthesis of 15-crown-5

The yields of 15-crown-5 with various metal hydroxides in a series of experiments are presented in Table 2.1. A preliminary report of this data has been published[19].

2.2.2 Template Synthesis of 18-crown-6

The yields of 18-crown-6 with various metal hydroxides in a series of experiments are presented in Table 2.2. The data in the first column of yields for each metal hydroxide is from Ref.20.

2.2.3 Cyclization of 14-chloro-3,6,9,12-tetraoxatetradecan-1-ol (monochloropenta-ethylene glycol) (73)

The yields of 15-crown-5 from cyclization of compound (73) with different metal hydroxides are presented in Table 2.3.

2.2.4 Template Syntheses of 12-crown-4 and 24-crown-8

The yields of 12-crown-4 with various bases are presented in Table 2.4. Figures in parentheses represent the yields of 24-crown-8. These results have been reported elsewhere[21].

2.2.5 Template Synthesis of 15-crown-5 with Different Bases

The yields of 15-crown-5 with various bases in a series of experiments are presented in Table 2.5.

2.3 DISCUSSION

2.3.1 The Template Effect

A mechanism for the template effect in the synthesis of 18-crown-6 has been proposed by Greene[22] as in Scheme 2.1.

Table 2.1 Yields of 15-crown-5 with various metal hydroxides in a series of experiments

Base	Yield(%)			Base	Yield (%)	
LiOH	5	4	-	$Mg(OH)_2$	1	2
NaOH	36	41	39	$Ca(OH)_2$	1	3
KOH	15	24	19	$Sr(OH)_2$	4	4
RbOH	15	15	-	$Ba(OH)_2$	5	8
CsOH	10	11	14			
TlOH	17	20	-	NBu^n_4OH	1	1

Table 2.2 Yields[a] of 18-crown-6 with various metal hydroxides in a series of experiments

Base	Yield (%)			Base	Yield (%)		
LiOH	1	2	2	$Mg(OH)_2$	-	1	2
NaOH	14	17	17	$Ca(OH)_2$	-	2	3
KOH	27	29	34	$Sr(OH)_2$	5	10	9
RbOH	-	20	27	$Ba(OH)_2$	-	20	25
CsOH	18	17	20				
TlOH	-	29	26	NBu^n_4OH	2	6	5

[a] Data in part from Ref. 20

Table 2.3 Yields of 15-crown-5 from cyclization of compound (73)

Base	Yield (%)
LiOH	3
NaOH	30
KOH	15

Table 2.4 Yields of 12-crown-4 with various bases in increasing basicity MOH to MH in a series of experiments

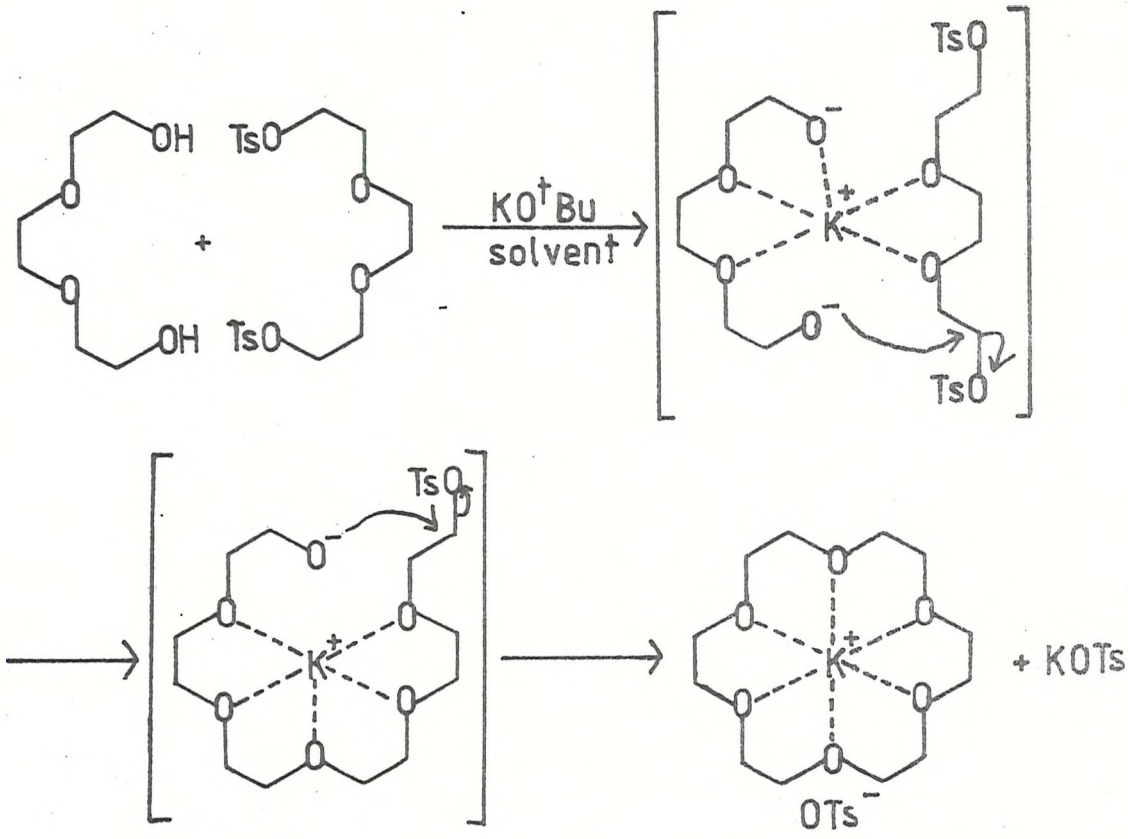
Base	Yield (%)		Base	Yield (%)[a]	
LiOH	0	-	NaOH	0(4)	1(4)
LiOMe	6	10	NaOMe	4(18)	4(22)
LiH[b]	10	15	NaH	6(11)	5(7)

a Figures parentheses represent yields of 24-crown-8

b Use of dmso as solvent, rather than dioxan, gave 12-crown-4 in a yield of 24%.

Table 2.5 Yields of 15-crown-5 with various bases in increasing basicity NaF to NaH in a series of experiments

Base	Yield (%)		
NaF	0	-	-
NaOH	36	41	39
NaOMe	65	66	-
$NaNH_2$	50	47	-
NaH	39	54	48



Scheme 2.1

It was proposed that the metal acts by complexing to the oxygen atoms before the second tosyl group is lost, so as to hold the cyclizing groups in close proximity and thus aid ring closure.

This mechanisim 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-butyl ammonium hydroxide, most of the cations gave an improved yield. Furthermore the maximum yield for each macrocyclic coincided with the use of the metal ion which most closely fitted the macrocyclic cavity. See Figures 2.1 and 2.2 which show the averaged yields for 15-crown-5 and 18-crown-6 respectively in the plots of yield(%) against ionic diameter, from X-ray data[23]. The cavity diameters of the crown ethers (from CPK models)[23] are also illustrated. The results were also confirmed by the use of thallium which, due to the inert 's' pair effect, has a similar size to potassium[24]. The asymmetry of the curves in Figures 2.1 and 2.2 should be noted. It indicates that, although in general crown ethers

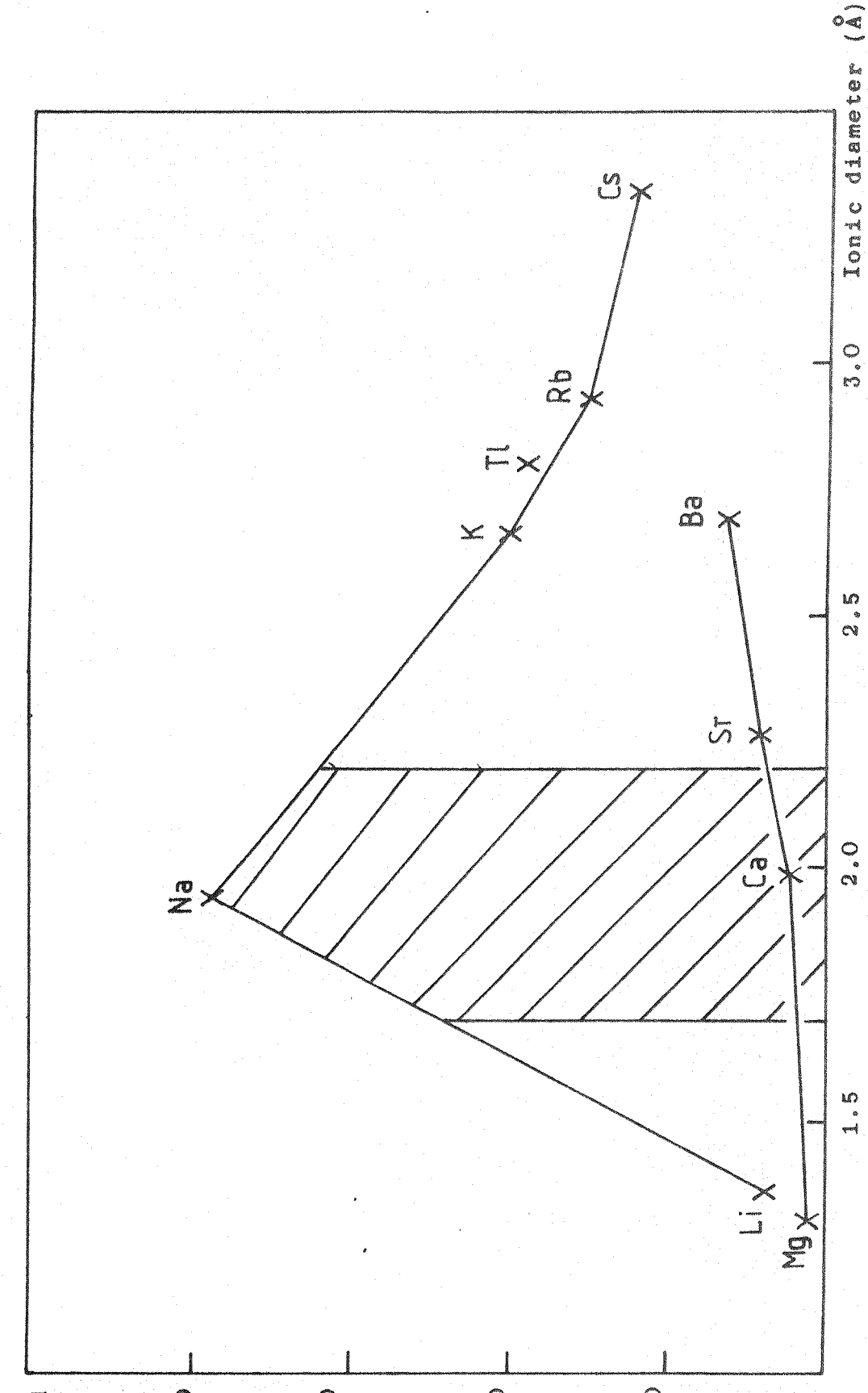


Figure 2.1 Yield of 15-crown-5 versus ionic diameter of metal ion template
(shaded region corresponds to the cavity diameter of 15-crown-5)

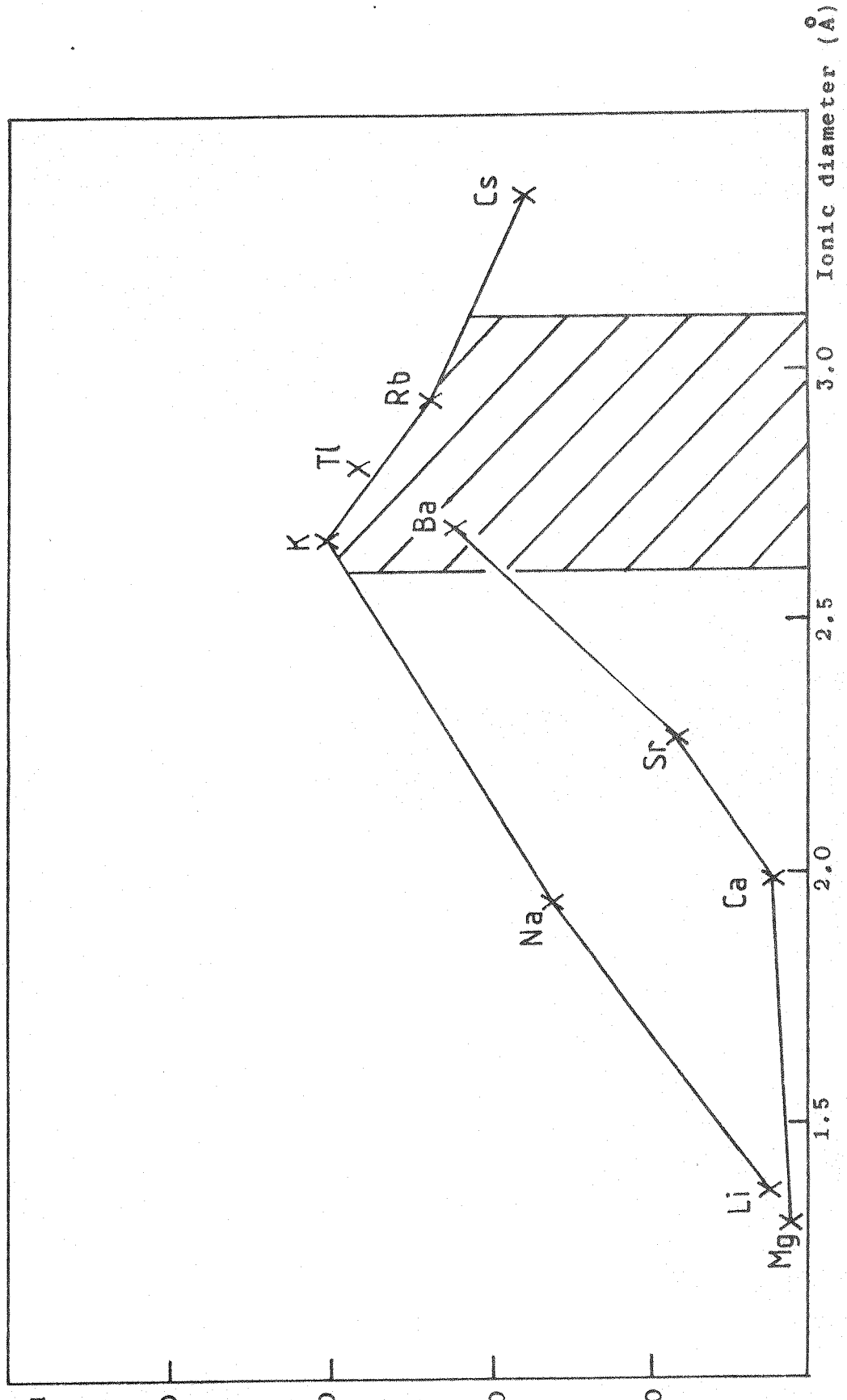


Figure 2.2 Yield of 18-crown-6 versus ionic diameter of metal ion template
(shaded region corresponds to the cavity diameter of 18-crown-6)

can not be synthesized in good yield employing cations of substantially smaller diameter than the cavity of the macrocycle, they can be produced in reasonable yields using cations that are substantially larger. This confirms the results of Reinhoudt et al[5]. where alkali metal fluorides were used as base, and presumably the lower fluorides were not sufficiently basic to generate the anion, but the higher fluorides generated benzo-crown ethers in reasonable yields. It is probably 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[7,25]. The crown ether complexes with larger cations are thought to occur because the macrocyclic cavity is not deformed and the cation tends to be polarised (ligand encapsulation)[7].

The template effect appears to be very important 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, 1.96Å [23], the cation can not fit into the cavity of 12-crown-4 (diameter 1.2 - 1.5 Å [23]) and consequently favours the synthesis of 24-crown-8[21], in relatively high yield, from two molecules of both diethylene glycol and bis (2-chloroethyl) ether. This is contrast to the use of lithium salts, 1.36Å [23], which, because of a better 'fit' gives 12-crown-4 almost exclusively as the cyclic product.

The synthesis of the cyclic polyethers, particularly 15-crown-5, using alkaline-earth metal hydroxides gave a different picture which is not accounted for by the template effect alone. This is exemplified by the very low yields for 15-crown-5 with calcium hydroxide despite being the ideal 'fit'. As stated, it is thought that there is a strong correlation between the template role and complexing ability of a metal, and therefore an insight into these results is afforded by an examination of the alkaline-earth complexes of crown ethers. Poonia

and co-workers[7,25] have investigated the binding of alkaline-earth metal ions 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 those cations which favoured a higher interaction with the counter-ion[8]. Indeed the anionophilicity of calcium is such that a complex has been reported[26] where the calcium is in an exclusive anion-solvent environment despite the presence of benzo-15-crown-5 which has the correct cavity size for calcium. 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 solubilization 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 with strontium and barium hydroxides. Indeed the highest yields of both crown ethers using alkaline-earth metal hydroxides were obtained with $Ba(OH)_2$ despite Ba^{2+} being the poorest 'fit' for 15-crown-5. In fact Mandolini and Masci[10] have reported the successful use of $Sr(OH)_2$ and $Ba(OH)_2$ as template bases 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 same group have recently reported[27] the results of an elegant study into the kinetics of cyclization of o-hydroxyphenyl-3,6,9,12-tetraoxa-14-bromo-tetradecyl ether to benzo-18-crown-6 in methanol solution in the presence of added alkali and alkaline-earth bromides. These results are independent of cation concentration and are summarised in Figure 2.3 in a plot of log of rate of reaction (relative to the case of no added metal template) for various alkali and alkaline-earth cations versus ionic diameter. These results for the effect of template ions on the rate of cyclization are in broad agreement with those achieved for the effect of template ions on the yield of macrocycle. It should be emphasised however that these results were obtained for benze-18-crown-6, unlike those for the unsubstituted crown ethers. The major difference is the more successful application

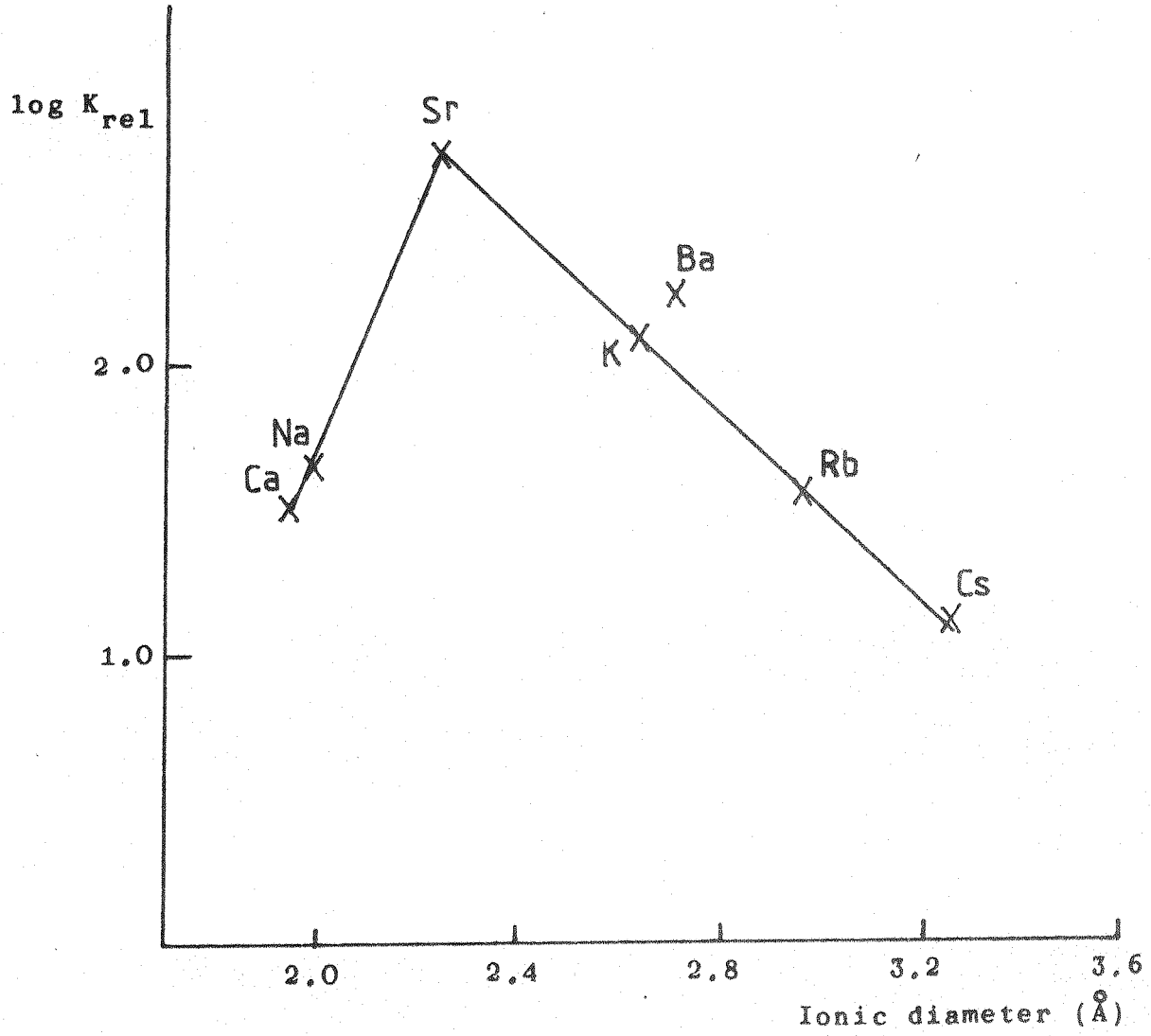


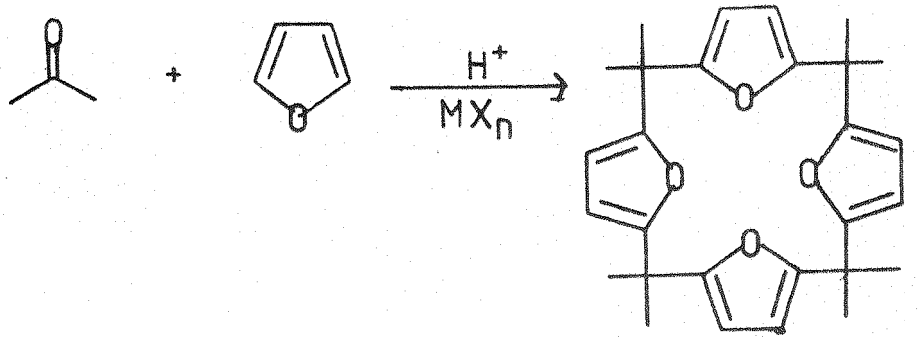
Figure 2.3 The Template Effect of Alkali and Alkaline-earth cations in the formation of benzo-18-crown-6 in methanol (from Ref.27)

of the alkaline-earth cations as templating agents - exemplified by strontium - in these kinetic studies. This was attributed[27] to the 'acidity-enhancing' ability of the alkaline-earth cations (about 10^3 times that of the alkali cations for the model compound o - HOC_6H_4 - $(OCH_2CH_2)_4$ OCH_3) in conjunction with proximity effects.

Finally, the results, Table 2.3, for the cyclization of 14-chloro-3,6,9,12-tetraoxatetra-decan-1-ol (73) to give 15-crown-5, where only one displacement reaction occurs, are similar to those obtained for the production of 15-crown-5 from triethylene glycol and bis (2-chloroethyl) ether, where two displacement reactions occur . This suggests that the mechanism for the template effect is to complex the intermediate species before the second leaving group is displaced - in agreement with the mechanism proposed by Greene[22].

2.3.2 The Effect of Base

The action of metal salts in the acid catalyzed condensation of acetone with furan to give the cyclic tetramer (24), as in reaction 2.6, has been reported[13] to affect the acidity, or ionic strength, of



(2.6)

(24)

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

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 2.1[28], will also increase the yield of the furan-acetone

macrocycle. In general, salts with

$$pH_m = pHo - 0.0555M_s\,(g^+ g^-)\left(\frac{h^+}{r^+} - \frac{h^-}{r^-}\right)$$

pH_m = pH to which a salt of concentration M has been added
pHo = pH of acid
g^+, g^- = charges of cation and anion of salt
r^+, r^- = ionic radii of cation, anion of salt
h^+, h^- = functions of hydration requirement of ions

Equation 2.1

a cation of small radius and high hydration function and anions which are poorly hydrated, e.g. $LiClO_4$, will increase the acidity and hence the yield of the macrocycle. It can also be seen that there is a close correlation between some of the parameters in Equation 2.1, and those that fulfill 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 15-crown-5 and 18-crown-6, that is the predominant factor in determining the yield of the product would 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, Table 2.6[29]. It can also be seen that the basicity of the alkali metal hydroxides is substantially higher than the corresponding alkaline-earth metal hydroxides. It is therefore probable that base strength is a contributory factor to the asymmetry of Figures 2.1 and 2.2 for the alkali metal hydroxides, as well as explaining the increased yields for the higher alkaline-earth metal hydroxides, $Ba(OH)_2$ and $Sr(OH)_2$, compared with $Ca(OH)_2$ and $Mg(OH)_2$.

Further examination of the effect of base, utilizing a common, ideal templating, cation in the synthesis of 15-crown-5, see Table 2.5, 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[5], to a maximum yield of 66% achieved with

Table 2.6 pKa values of various alkali and alkaline-earth metal hydroxides (at 25°C, in water), from Ref. 29.

Base	pKa	Base	pKa
LiOH	13.82	$Mg(OH)_2$	11.42
NaOH	14.77	$Ca(OH)_2$	12.9
KOH	16.0	$Ba(OH)_2$	13.36

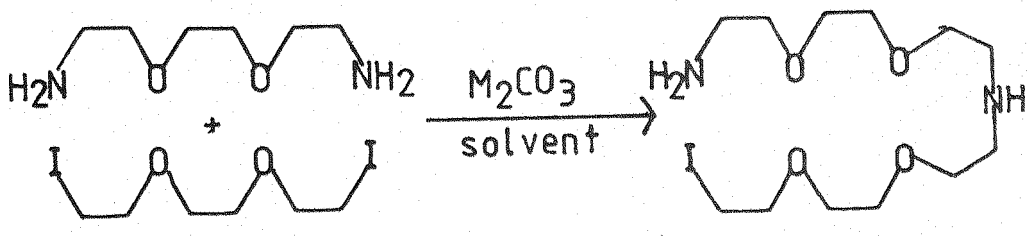
NaOMe which has a basicity of approximately 10^3 times that of NaOH[30]. There does seem to be an optium base strength as illustrated by the use of the very strong bases $NaNH_2$ and NaH where the yield of 15-crown-5 was lower than for NaOMe. For $NaNH_2$ and NaH complete dissociation occurs and the production of a large amount of polymer indicates the lowered effectiveness of any co-ordination template effect.

The importance of base strength is exemplified in the synthesis of 12-crown-4, as shown in Table 2.4, with the strongest base, LiH, giving the maximum yield of cyclic polyether. Similarly the yield of 24-crown-8 was maximised with the optium base, NaOMe, where, because of the template effect, the larger macrocycle was synthesized in preference to 12-crown-4[21]. These results may also explain the unusual results of Liotta et al[17], reaction 2.4, where perhaps the addition of $LiClO_4$ increased the ionic strength or basicity of the reaction medium, according to Equation 2.1, and thus favoured macrocycle formation. It also explains why the use of LiOH failed to give the desired product because, despite the template effect, it simply was not a strong enough base.

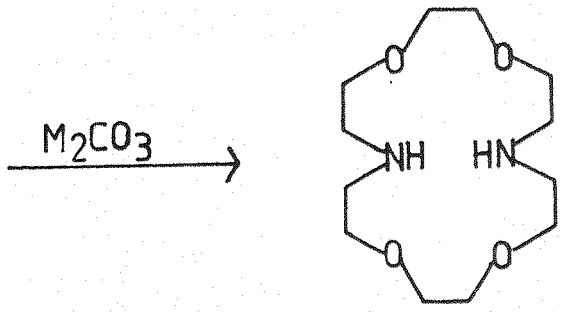
2.3.3 The Effect of Other Factors

The effect of solvent is a very important factor in giving various crown ether-cation complexes, e.g. a polar solvent may favour the stability of the complex. It was found that[7,25] for such complexes the selectivity of the crown ether for a larger over a smaller cation is enhanced as the solvating ability or donicity of the medium decreases, so that solvent competition towards M^+-crown ether interaction is reduced. This has been confirmed by various determinations of cation selectivity towards crown ethers, particularly utilizing alkali metal nuclear magnetic resonance spectroscopy[31] (see section 1.5.1). The same effect may be extended to the use of solvent in crown ether syntheses. The use of water as a medium for the barium template synthesis of crown ethers has been discussed[10]. The synthesis of the diaza crown ether (75) by Kulstad and Malmsten[32], reaction 2.7, ably illustrates the effect of solvent,

see Table 2.7, for the yields in various solvents with various alkali metal carbonates. As can be seen, in the protic solvent methanol,



(74)



(2.7)

(75)

the yield is very low compared to the aprotic solvents glyme and dioxan. Complex formation with the intermediate species (74) is at an optium when the interaction between the metal ion and solvent is weak, thus giving maximum yields, and this is illustrated by the use of acetonitrile which does not solvate alkali metal ions as strongly as glyme and dioxan, giving higher yields, with a maximum at sodium, than the other solvents[32]. This reaction is also noteworthy in its novel application of metal carbonates as non-nucleophilic bases which also provide the template ion after reaction with the ammonium salt formed.

Returning to reaction 2.4, this reaction again illustrates the importance of solvent in the synthesis of crown ethers. Liotta and co-workers[17] found that the synthesis of 12-crown-4 failed to proceed

Table 2.7 The yield of diaza crown ether (75) in various solvents using different alkali metal carbonates, from Ref.32.

Solvent	Li_2CO_3	Na_2CO_3	K_2CO_3	Cs_2CO_3
Acetonitrile	6	44	27	15
1,2-Dimethoxy-ethane	-	8	24	15
Dioxan	-	16	24	-
Methanol	-	-	5	-

in tetrahydrofuran and only went satisfactorily is dimethyl sulphoxide. Similarly the work presented in this thesis, see Table 2.4, having found the optimum base, LiH, gave a substantially higher yield of 12-crown-4 in dimethyl sulphoxide (24%) than in dioxan (13%). This is probably due to dimethyl sulphoxide being a more polar solvent than dioxan and consequently favouring the stability of the intermediate complex. However it is worth noting that the basicity increases by a factor of 10^{14} in going from a solution of 0.011 mol dm^{-3} tetramethylammonium hydroxide to a 95% dimethyl sulphoxide solution[30], due to the dimethyl sulphoxide and hydroxide ions competing for the solvent water, giving a less hydrogen bonded, more reactive hydroxide species as the amount of dimethyl sulphoxide is increased. Furthermore the addition of dimethyl sulphoxide to a solution of sodium methoxide in methanol results in a 10^{6} increase in basicity[30] as it changes from a solvent of pure water to 95% dimethyl sulphoxide, again due to the increased alkoxide ion activity. So again, this effect may be important in the synthesis of 12-crown-4.

Another factor that would seem to affect the synthesis of crown ethers is the reaction temperature. This was found to be the case[33] for the cyclization of oligoethylene glycol monotosylates in dioxan. Not only did this confirm the classical template effect with NaOH preferentially catalyzing the synthesis of 15-crown-5 over KOH, and the reverse being true for 18-crown-6, but also an optimum temperature of about 60°C was observed for maximum yield of both crown ethers. Temperature will also affect the basicity of a system[30], but this effect is small and would not appear to apply in these systems.

2.4 CONCLUSION

In conclusion, metal ion template enhancement of reactions cannot be treated as the only important factor in the synthesis of crown ethers. This is not to underestimate its potential use and conceptual value; indeed it has remarkable applications, particularly when using alkali metal hydroxides although it does begin to break down with other compounds, notably the lower alkaline-earth metal hydroxides. Rather, it should be used in conjunction with other factors, 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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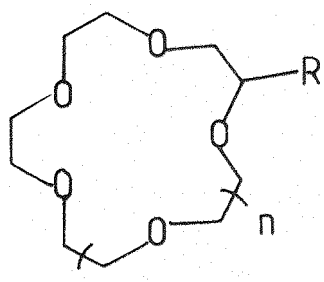
CHAPTER 3 +

THE SYNTHESIS AND IONOPHOROUS PROPERTIES OF SOME SUBSTITUTED CROWN ETHERS

3.1 INTRODUCTION

Whilst much of the interest in crown ethers has been due 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 $\frac{t}{}$ butylcyclohexyl-18-crown-6, (11), Plate 1.1[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 bilayer 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 synthesize a series of alkyl substituted crown ethers of the type (76) - (78). Particular emphases was placed

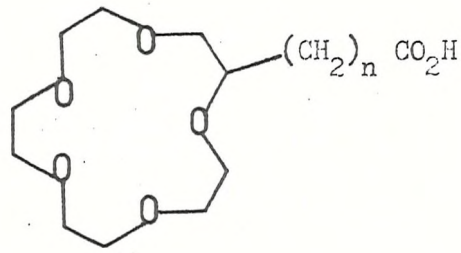


(76) n = 0
(77) n = 1
(78) n = 2

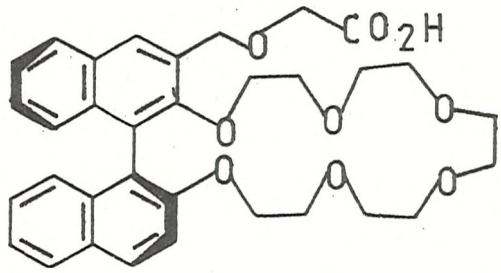
on substituted 15-crown-5 ethers (77) due to their specificity for Na^+, a property which many of the natural antibiotics, with the exception of monensin, do not possess.

The synthesis of a series of carboxylic acid substituted crown ethers, as below, based on the 15-crown-5 skeleton, was also attempted.

+ References for this chapter can be found on page 123.

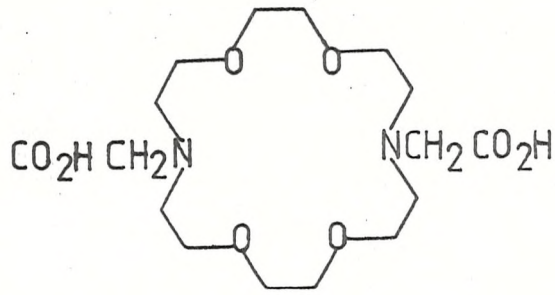


The synthesis of molecules of this type was desirable for two main reasons. Firstly the acid function frequently appears in natural ionophorous antibiotics (see section 1.7.1) and yet little work has been done on acid substituted crown ethers. In the main, acid substituents have been incorporated into the aromatic ring[9], rather than incorporating the acid function into the crown ether skeleton, e.g. (79)[10].



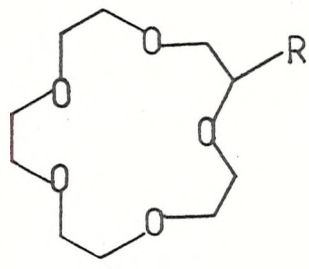
(79)

Another non-cyclic example is compound (45), see section 1.2.6. Reinhoudt and co-workers[11] have recently reported the results of a study of the effect of the introduction of additional donor groups, including carboxylic acids, onto the aromatic ring of crown ethers. It was found that intra-annular carboxylic acid substituents had little effect on complex stability and extra-annular carboxylic acid substituents were less stable than the corresponding methyl esters. A related area is that of the aza carboxylic acid substituted crown

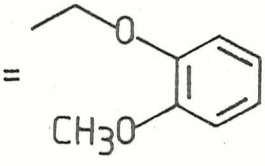


(80)

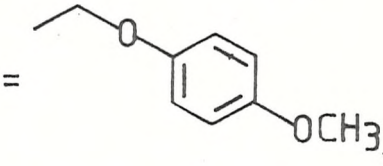
ether, (80),[12] which has been found to be a useful complexing agent for Ba^{2+}. Secondly it is interesting to consider the effect of an additional binding site on crown ether complexation. On reaching an optimum chain length, one might imagine the acid function folding over an encompassed cation, rather like a 'scorpion's tail', thus giving extra stability to the complex. Gokel and co-workers[13-15] have found this to be the case in their work on additional neutral binding sites, typically methyl ethers, in the side arm - 'lariat ethers'. Furthermore this effect has been demonstrated in their template syntheses[13,15] where the ortho derivative (18b), which can



(18b) R =



(18c) R =

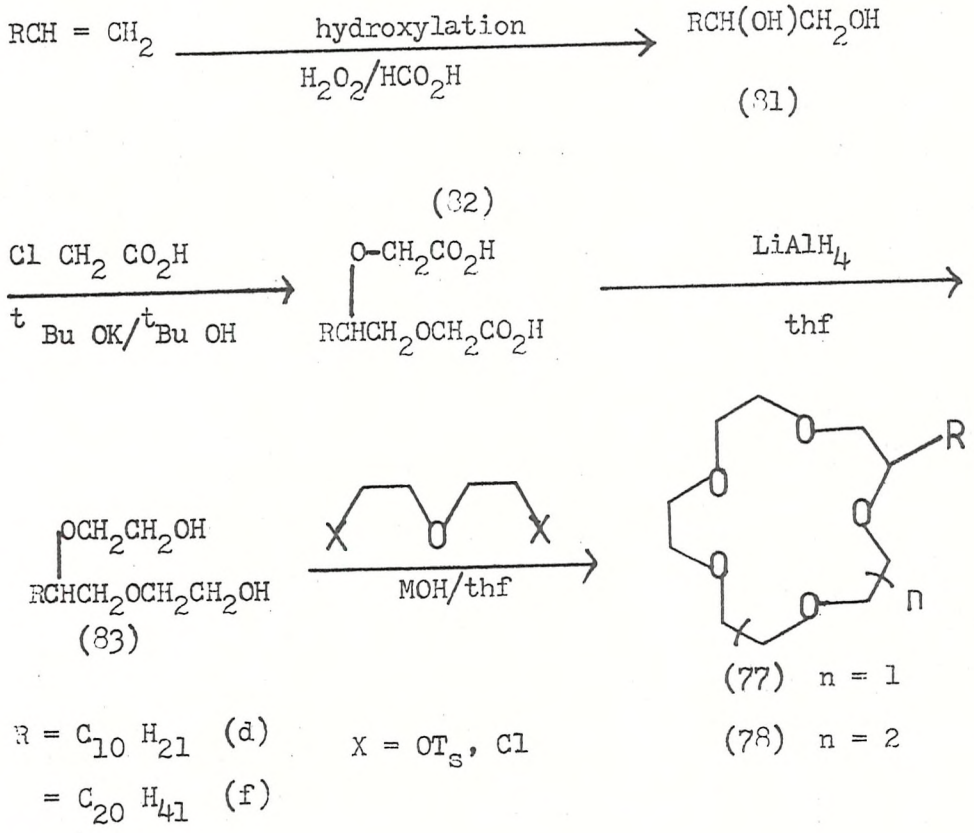


offer a further donor group, is synthesized in 70% yield, whereas the para derivative (18c), which does not give this additional stability, is synthesized in only 29% yield. However not only does the introduction of an acid function give extra stability, but it may also act as a natural counter-ion and thus may aid transport. The

effect of an acid function on ion transport has begun to receive attention[16-18], but a systematic study of the effect of chain length on binding and transport has not been undertaken. It should also be noted that a study of alkali metal transport across a 1-hexanol membrane has been conducted[19] for some non-cyclic carboxylic acid containing polyethers. It was concluded that the acid function was essential for transport. However, in this case, this could be just due to stabilization of a pseudo-cyclic structure through hydrogen bonding (cf.ref.[5]).

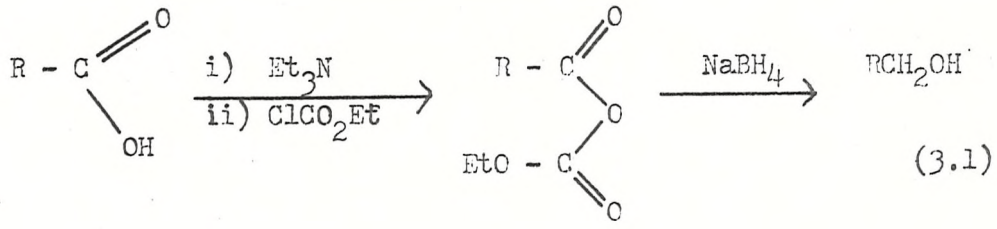
3.1.1 Alkyl Substituted Crown Ethers

Initially the route chosen to these compounds was based on the rather laborious route of Cinquini et al.[8], according to Scheme 3.1.



Scheme 3.1

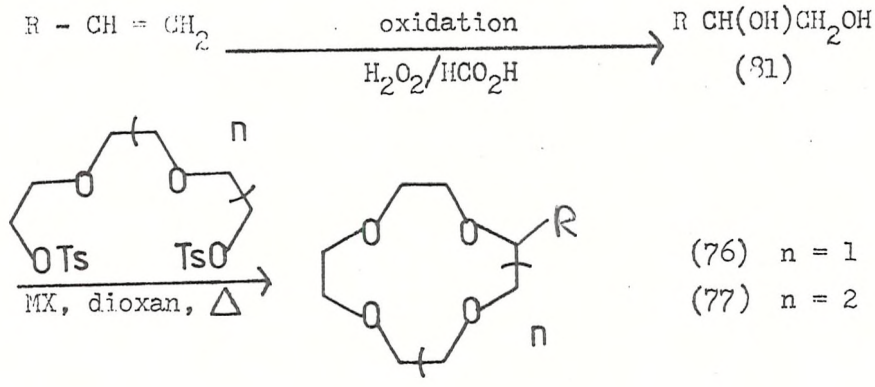
In this way, the syntheses of 2-eicosyl-18-crown-6 (78f), 2-decyl-18-crown-6 (78d) and 2-eicosyl-15-crown-5 (77f) were achieved in low overall yield. In particular, the reduction of the di-acid (82) to the corresponding diol (83) was difficult due to the formation of the dilithium salt of the di-acid. To overcome this, reduction was attempted using $NaBH_4$ through a mixed carbonic-carboxylic acid anhydride as in reaction (3.1)[20]. However this method failed to produce



(3.1)

appreciable quantities of the diol and repetition of the reduction using $LiAlH_4$ with different work-up procedures (see Chapter 4) gave the diol in satisfactory yields.

The synthesis of alkyl substituted crown ethers was greatly simplified by optimizing template conditions[21], thus overcoming the difficulty of cyclization of the secondary alcohol (81) as in Scheme 3.2. Gokel *et al*[13,14] have since used a similar cyclization reaction in the synthesis of various substituted crown ethers. Okahara *et al*[22-24] have also utilized the template effect in novel syntheses of substituted crown ethers (see sections 1.2.2, 1.3).

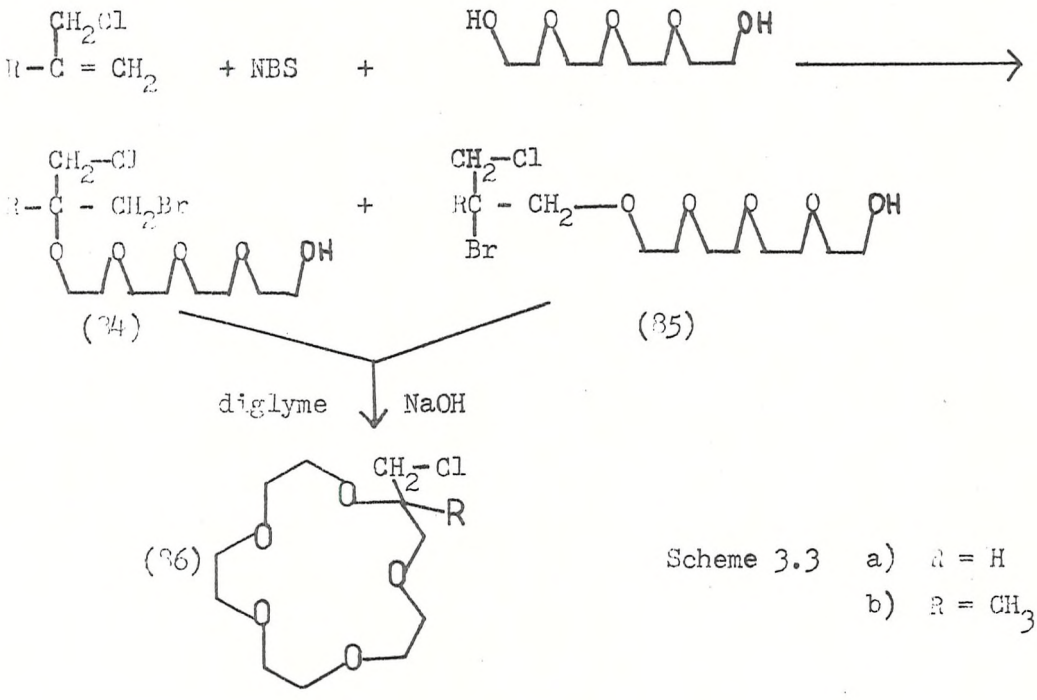


a) R = CH_3
b) R = C_2H_5
c) R = C_8H_{17}
d) R = $C_{10}H_{21}$
e) R = $C_{14}H_{21}$
f) R = $C_{20}H_{41}$
g) R = C_6H_5

Scheme 3.2

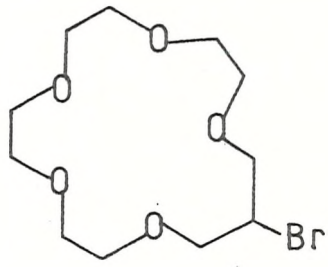
3.1.2 Acid Substituted Crown Ethers

The first attempt to synthesize the series of acid substituted crown ethers was based on the work of Okahara et al[23,24], according to Scheme 3.3. In this scheme there is a key chloromethyl substituted



Scheme 3.3 a) R = H
b) R = CH_3

product (86). Although the intermediate products (84,85), contain two different halogen atoms, Okahara and co-workers reported[24] that cyclization for the methyl-substituted products (84b, 85b) gave exclusively the chloromethyl substituted product (86b). However for the case where R = H, cyclization of the intermediates (84a, 85a) gave a mixture of products, containing predominately (87). This is



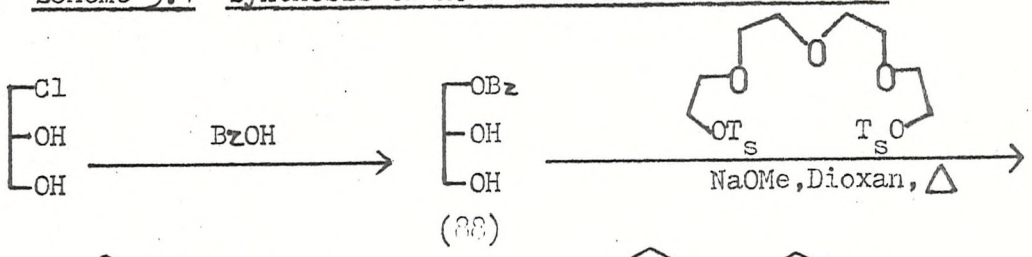
(87)

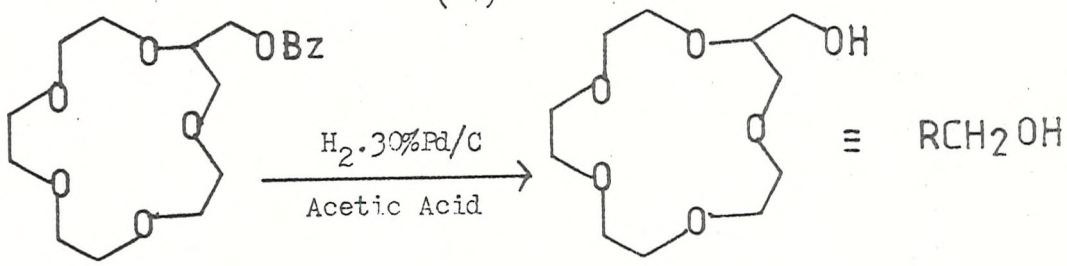
no doubt due to the elimination of the primary chloride rather than the secondary bromide. Consequently a novel route was devised to give the key hydroxymethyl substituted compound (90) which can then give the series of acid substituted crown ethers as in Scheme 3.4. It should be noted that since this time a similar approach to (90) has been reported by others[13,25] starting from the benzyl-protected 1-chloro-2,3-epoxypropane and the ditosylate of tetraethylene glycol.

3.1.3 Determination of Ionophorous Properties

A. Bulk Liquid Membrane Liquid membranes can serve as models of biological membranes, and their use has been developed in the main by Christensen, Izatt and their co-workers[26,27]. Details of apparatus are given in Chapter 4. Initially the dependence of transport rate on the concentration of ionophore was determined in a standard system for transport of sodium picrate by 15-crown-5 through a chloroform membrane. This showed that a reasonable transport rate for a good ionophore occurred at an ionophore concentration of 10^{-3}M. A matrix of results was then built up by examining the transport of lithium, sodium and potassium picrates for the various substituted and unsubstituted crown ethers in comparison to blank experiments.

Scheme 3.4 Synthesis of Acid Substituted Crown Ether





(89) (90)

n = 0 $RCH_2OH \xrightarrow[NaOH]{KMnO_4} RCO_2H$ (91)

n = 1 $RCH_2OH \xrightarrow[pyr]{T_sCl} RCH_2OT_s$ (92) $\xrightarrow[ii)\ cKOH, \triangle]{i)\ NaCN/dmso} RCH_2CO_2H$ (93)

n = 2A. $RCH_2OT_s \xrightarrow[ii)\ KOH/EtOH\ \ iii)\ HCl]{i)\ CH_2(CO_2Et)_2/NaOEt/EtOH} RCH_2CH_2CO_2H$ (94)

B. $RCH_2OH \xrightarrow[CF_3CO_2H/toluene]{DCC/dmso/pyr} RCHO$ (95)

$\xrightarrow{Ph_3P = CHCO_2Et} RCH = CHCO_2Et$ (96) $\xrightarrow[ii)\ NaOH]{i)H_2/cat} RCH_2CH_2CO_2H$ (94)

n = 3 A. $RCH_2OT_s \xrightarrow{^-C \equiv CCO_2^-} RCH_2C \equiv CO_2H$ (97) $\xrightarrow[cat.]{H_2} R(CH_2)_3CO_2H$ (98)

B. $RCH_2OT_s \xrightarrow[Li_2CuCl_4]{CH_2 = CHCH_2MgBr} RCH_2CH_2CH = CH_2$ (99)

$\xrightarrow{oxidation} R(CH_2)_3CO_2H$ (98)

B. Liposome Experiments Liposomes act as very good mimic of the cell membrane. By incorporating a crown ether into the liposome structure, the rate of transport of various trapped metal ions may be compared to a blank experiment. The overall concept of transport is summarised in Figure 3.1 with experimental details in Chapter 4.

3.2 RESULTS

3.2.1 Alkyl Substituted Crown Ethers[a]

The compounds made in this study are summarised in Table 3.1[28].

3.2.2 Acid Substituted Crown Ethers[a]

Protection of 3-chloro-1,2-propanediol, followed by cyclization with the ditosylate of tetraethylene glycol gave the benzyl protected crown ether (89) in good yield. The removal of the benzyl group was performed under strong reducing conditions[29] (30% Pd/C, glacial acetic acid) to give the hydroxymethyl-15-crown-5 (90). However initial misleading nmr and CH analysis data for (90) led to much fruitless elaboration of the compound until gas chromatographic data revealed it to be only 70% pure. This was corrected by use of a short path chromatographic separation of the benzyl-protected compound (89). Oxidation of (90) to the first member of the series (91) goes rapidly in almost quantitative yield. This is attributed to a self-catalytic process by complexation of the potassium ion to yield a 'naked' permanganate anion[30] which very effectively oxidizes the alcohol to give the subsequent acid (91).

The second acid of the series (93) was produced in low yield by reaction of (90) with tosylchloride in pyridine to give the tosylate (92) which was converted to the nitrile by reaction with sodium cyanide in dimethyl sulphoxide by the method of Friedman and Shechter[31,32], and then hydrolyzed to give the acid (93). It should be noted that a 'one-pot' conversion of primary alcohols to nitriles has since been reported[33], treating the alcohol with tributylphosphine, carbon tetrachloride and potassium cyanide in acetonitrile in the presence of 18-crown-6. This may well prove to be a superior method.

[a] Experimental, chemical and spectral data for all compounds in Chapter 4.

Figure 3.1 Liposome Experiments

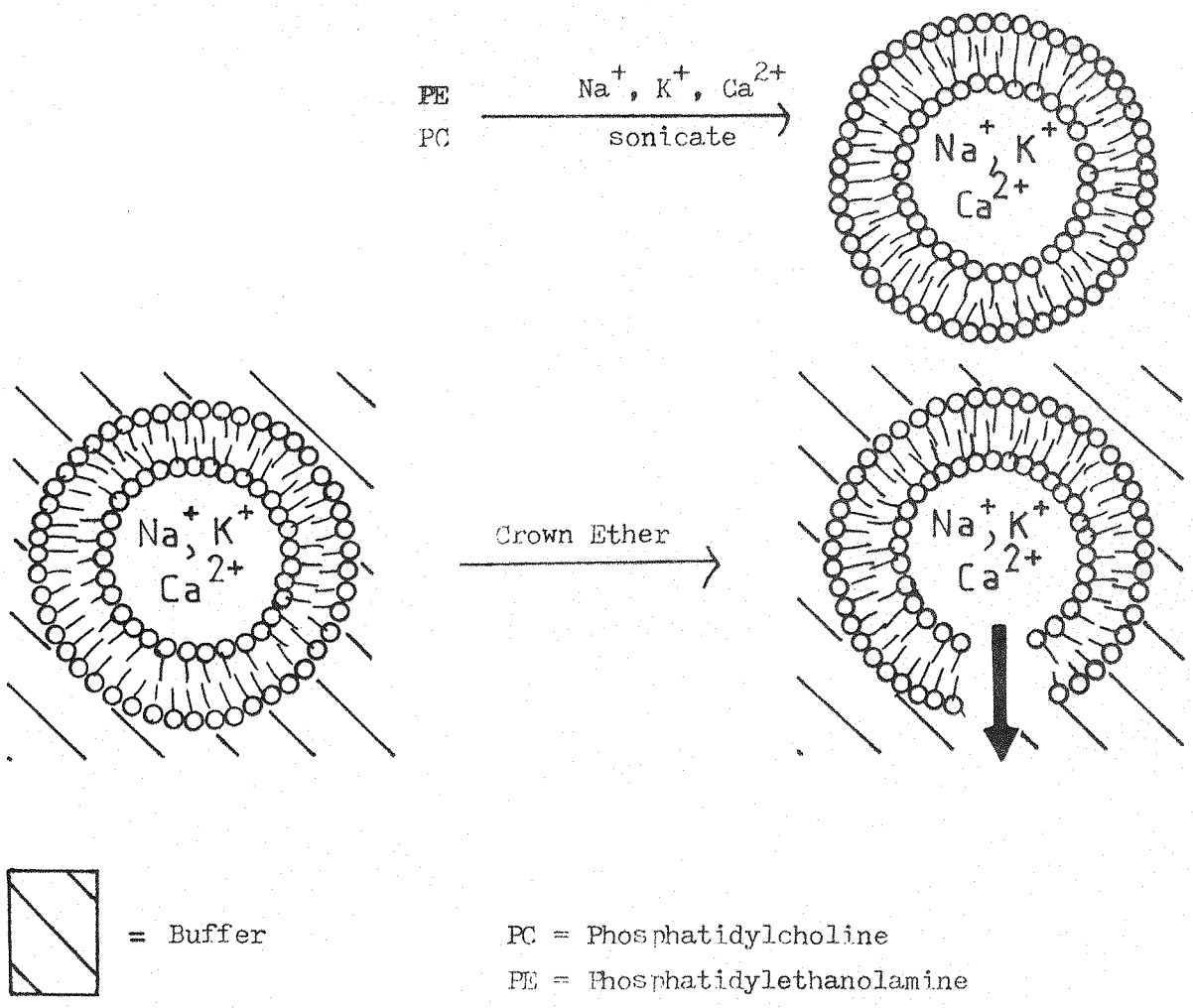


Table 3.1 Alkyl- Substituted Crown Ethers Prepared in this Study[28]

Substituent	'12-crown-4' (76)	'15-crown-5' (77)	'18-crown-6' (78)
a) CH_3-	√	√	-
b) C_2H_5-	-	√	-
c) C_8H_{17}-	-	√	-
d) $C_{10}H_{21}$-	-	√	$\surd^X$
e) $C_{14}H_{29}$-	-	√	-
f) $C_{20}H_{41}$-	√	√ $\surd^X$	$\surd^X$
g) C_6H_5-	⁄\	√	-

√ Prepared by method of Scheme 3.2

$\surd^X$ Prepared by method of Scheme 3.1[8]

⁄\ Crude product

Two possible approaches to the third acid of the series (94) were considered. Reaction of the tosylate (92) with sodium ethoxide and diethyl malonate in ethanol[34] gave the intermediate diethyl ester which was converted to the acid (94) by refluxing with potassium hydroxide in ethanol, followed by removal of the alcohol and acidification with conc.HCl. The yield, however, was disappointingly low. A second approach to the acid (94) was via the intermediate aldehyde (95) according to the method of Pfitzner and Moffatt[35]. Treatment of the alcohol (90) with dicyclohexylcarbodiimide (DCC) and dimethyl sulphoxide (dmso) in the presence of trifluoroacetic acid gave the aldehyde (95) in low yield. This represents the work completed in this study, but further synthetic work is contemplated to give the intermediate compound (96) by a Wittig reaction[36] followed by catalytic hydrogenation with PtO_2/1 atm. in EtOH and subsequent addition of sodium hydroxide to give the acid (94) as in Scheme 3.4.

Of the many potential ways of achieving the fourth member of the series (98), two are given in Scheme 3.4. The first is by reaction of the tosylate (92) with the di-anion of propiolic acid to give the alkyne intermediate (97) which is catalytically hydrogenated to the acid (98). The second method is by the reaction of the Grignard reagent in the presence of Li_2CuCl_4[37] to give the alkene (99) which under oxidation gives the desired acid (98). This last method may be suitable for achieving higher homologues by simply increasing the length of the Grignard reagent.

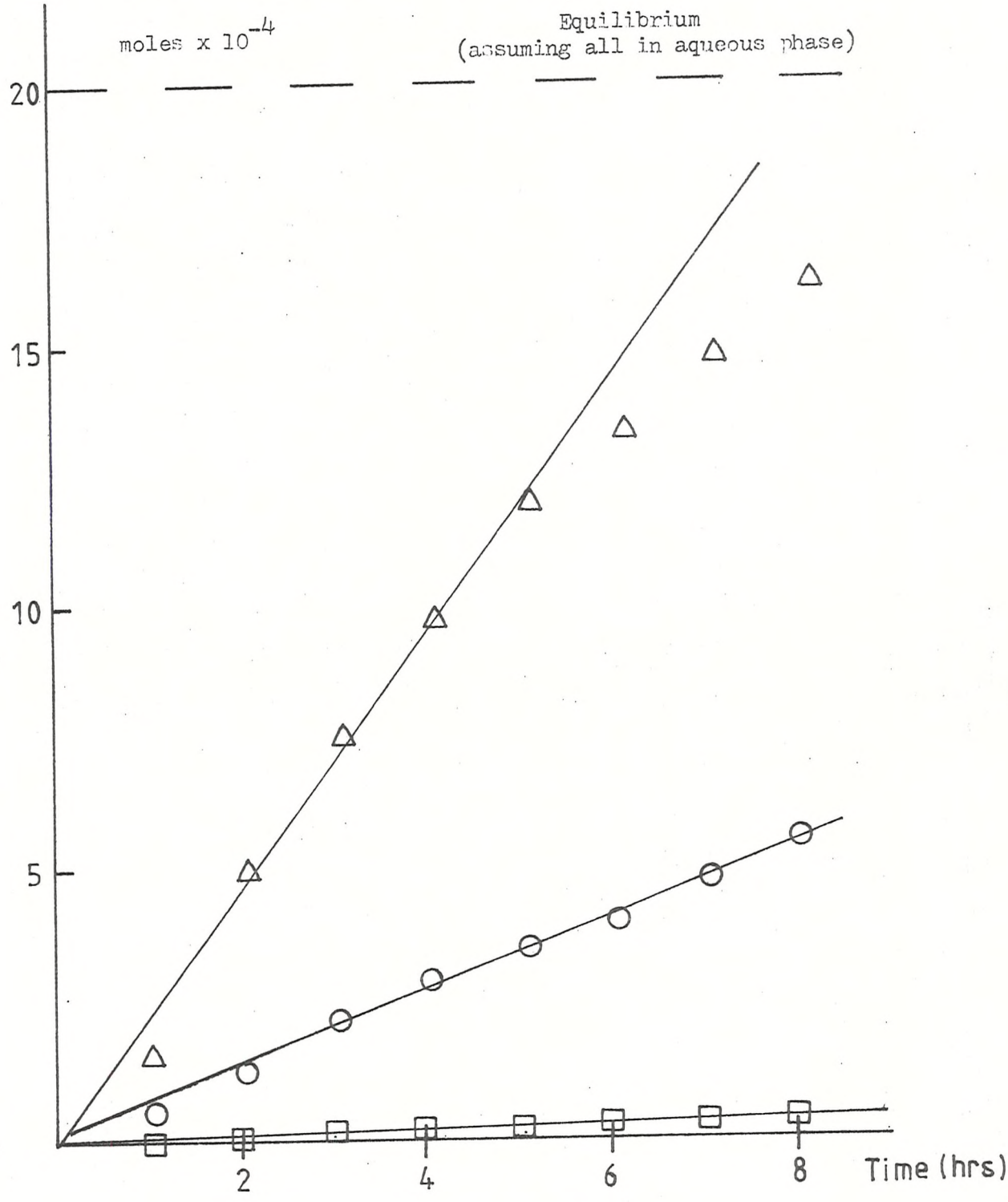
3.2.3 Determination of Ionophorous Properties

A. Bulk Liquid Membrane[b]

i) General Comments The addition of a 'good' ionophore to the chloroform membrane gave a plot as shown by the uppermost line (Δ) as in Figure 3.2. The rate of transport (moles^{-6}/hours) is given by taking a tangent to the curve at the start of the experiment, as in Figure 3.2. This 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

[b] See Chapter 4 for experimental details.

Figure 3.2 Transport of Li,Na,K Pic by 15-Crown-5



△ = Sodium (Transport Rate = 210 x 10^{-6} moles/hr)

□ = Lithium (Transport Rate = 2.7 x 10^{-6} moles/hr)

○ = Potassium (Transport Rate = 62 x 10^{-6} moles/hr)

(Corrected for Blank)

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 ($< 1.4 \times 10^{-4}$ mole) the solution could be removed, read and replaced, for high concentrations - in general by the use of good ionophores - error is introduced by the necessity to dilute the receiving phase in order to calculate the concentration. Therefore for high concentrations ($> 1.4 \times 10^{-4}$ mole) of the picrate solution, a 1 ml. sample of the receiving phase was removed, diluted as necessary, and subsequent readings were corrected for the 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 for all experiments.

ii) Effect of Ionophore Concentration These results were obtained for a series of two experiments on a range of ionophore concentrations (10^{-5} - 10^{-3}M) for the rate of transport of sodium picrate by 15-crown-5 in the standard experimental apparatus (see Chapter 4) and are summarised in Table 3.2.

iii) Ionophorous Ability of Substituted and Unsubstituted Crown Ethers The results for the ionophorous ability of various crown ethers for lithium, sodium and potassium picrates, all corrected for the blank experiments, are given in Table 3.3. An ionophore concentration of 10^{-3}M was used in all cases, except where otherwise stated.

B. Liposome Experiments The results from the liposome experiments are presented in Table 3.4.

3.3 DISCUSSION

3.3.1 Bulk Liquid Membrane

A. Mechanism of Transport Transfer of the metal salts is considered to be carrier facilitated transport whereby the species are moved across the membrane by selective carrier molecules which reside in the membrane. For neutral macrocyclic carriers this may be represented as in Figure 3.3.

Table 3.2 Rate of Transport of Sodium Picrate with 15-crown-5 Concentration

15-crown-5 Concentration (moles)	Transport Rate (moles x 10^{-6}/hr)
Blank (0)	10 (± 10)
10^{-5}	15 (± 5)
10^{-4}	35 (± 4)
2.5×10^{-4}	62 (± 5)
5×10^{-4}	120 (± 10)
7.5×10^{-4}	150 (± 10)
10^{-3}	210 (± 10)

Table 3.3 Rate of Transport of Various Crown Ethers for Lithium, Sodium and Potassium picrates

Ionophore	Rate of Transport$_+$ (moles x 10^{-6}/hr)		
	Li^+	Na^+	K^+
6-crown-2 (Dioxan)	0.1(± 0.1)	0(± 0.1)	0 (± 0.1)
tetraethyleneglycol	0.1 (± 0.1)	0(±0.1)	0 (± 0.1)
12-crown-4 (5)	4.5 (± 0.2)	34 (±5)	3 (± 0.2)
15-crown-5 (2)	2.7 (± 0.3)	210 (± 10)	62 (± 5)
18-crown-6 (3)	15 (± 1.0)	230 (± 15)	140 (± 40)
dibenzo-18-crown-6 (1)	1.8 (± 0.2)	50 (± 5)	50 (± 20)
24-crown-8 (6)	0.9 (± 0.2)	16 (± 2)	50 (± 10)
tetroxaquaterene (24)	13 (± 1)	17 (± 2)	1.5 (± 0.2)
CH_3-15-crown-5 (77a)	19 (± 2)	150 (± 10)	47 (± 5)
C_2H_5-15-crown-5 (77b)	--	150 (± 10)	--
C_8H_{17}-15-crown-5 (77c)	2.0 (± 0.2)	52 (± 5)	30 (± 5)
$C_{10}H_{21}$-15-crown-5 (77d)	2.0 (± 0.2)	49 (± 5)	31 (± 5)
$C_{14}H_{29}$-15-crown-5 (77e)	--	50 (± 5)	--
$C_{20}H_{41}$-15-crown-5 (77f)	1.5 (± 0.2)	42 (± 5)	24 (± 4)
C_6H_5-15-crown-5 (77g)	33 (± 3)	140 (± 10)	45 (± 5)
$C_{10}H_{21}$-18-crown-6 (78d)	--	30 (± 5)	30 (± 5)
$C_{20}H_{41}$-18-crown-6 (78f)	--	25 (± 5)	20 (± 5)
$BzOCH_2$-15-crown-5 (89)	7 (± 0.5)	125 (± 15)	54 (± 5)
$HOCH_2$-15-crown-5 (90)	--	240 (± 20)	85 (± 10)
HO_2C-15-crown-5 (91)[c]	--	80 (± 10)	50 (± 10)
monensin[cd]	--	230 (± 150)	25 (± 15)

[c] See text for explanation of mechanism

[d] Monensin concentration 10^{-5}M, results then scaled up by a factor of 100.

Table 3.4 Percentage Release of Trapped Metal Ions from Liposome in the Presence of Crown Ethers

Crown Ether	% Possible Release		
	Na^+	K^+	Ca^{2+}
Blank	0	0	0
18-crown-6 (3)	0	0	0
$C_{20}H_{41}$-18-crown-6 (78f)	0	13	23

This may be considered as four discreet steps:

1) Ion carrier association, whereby the cation, M^+, from the aqueous phase forms a complex with a carrier from the membrane phase at the membrane-solution interface.
2) Translocation of the resulting ion-carrier complex through the membrane to the second interface between the membrane and receiving phase.
3) Disassociation of the complex to release the cation, M^+, and picrate counter-ion into the receiving phase.
4) Diffusion of the carrier back across the membrane phase to repeat cycle.

Several characteristics are necessary for a ligand to qualify as a membrane cation carrier[26]:

i) It must be soluble in the membrane solvent;
ii) It must complex the cation strongly enough to overcome the cation's energy of hydration at the membrane-source interface and yet not so strongly so as not to release the cation into the receiving phase;
iii) It must diffuse rapidly through 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 3.4 which plots the results from Table 3.2 for rate of transport of sodium picrate with varying concentrations of 15-crown-5. This work confirms the results of other workers, in particular those of Christensen, Izatt and their co-workers[26,27,38,39]. Additionally they have assessed the effect of the counter-ion on transport of this type[38,40], and found that transport is strongly affected by anion type by up to eight orders of magnitude, see Figure 3.5, although the relative order of cation transport is unaffected. As can be seen from Figure 3.5, in addition to giving coloured solutions which give a very useful visual, and quantitative (by UV/vis.absorption) guide to transport, the picrate anion also gives the best rate of transport and so was chosen for this study. Christensen, Izatt *et al*[39] have derived a simplified equation 3.1, to represent the effect of rate of transport by various parameters. This equation has several interesting features.

Figure 3.3 Schematic Representation of Carrier-Facilitated Transport through Chloroform Membrane

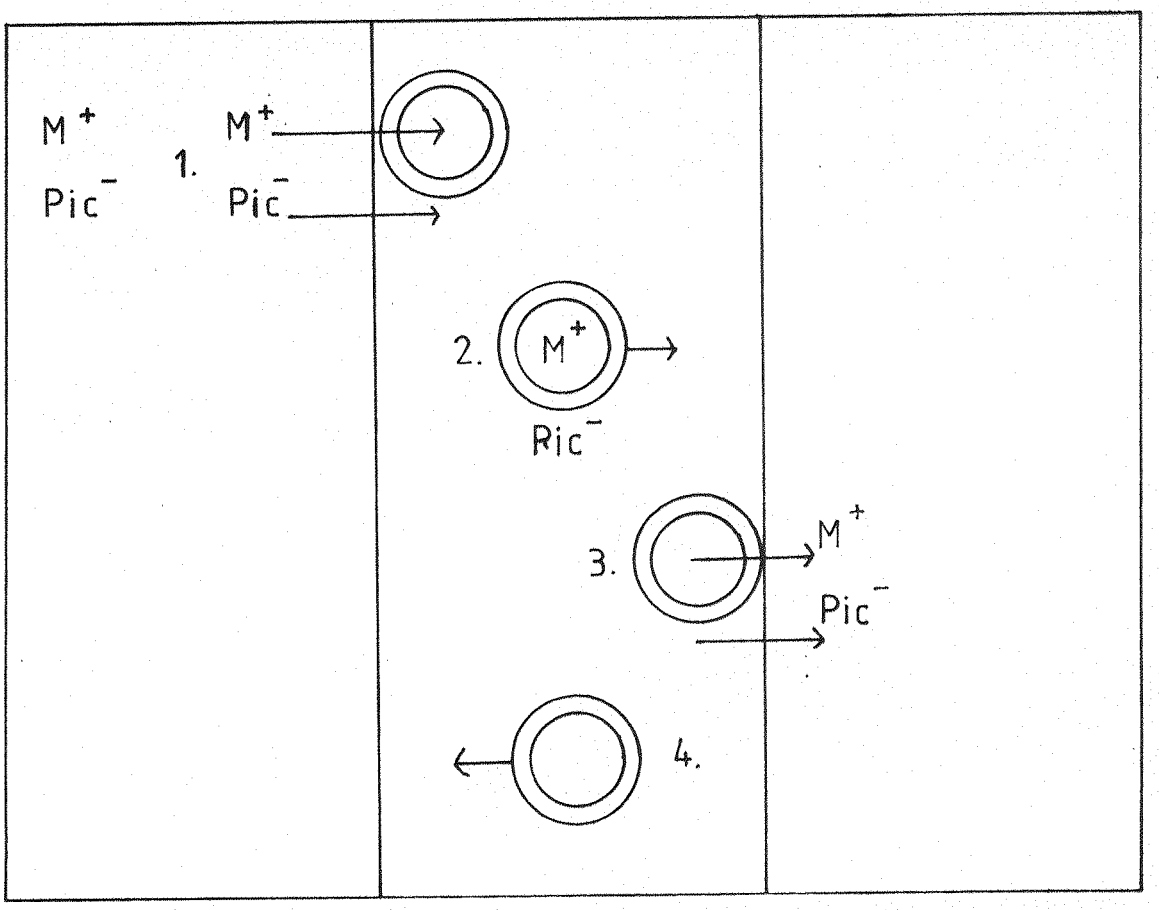


Figure 3.4 Rate of Transport of Sodium Picrate with 15-crown-5 Concentrati

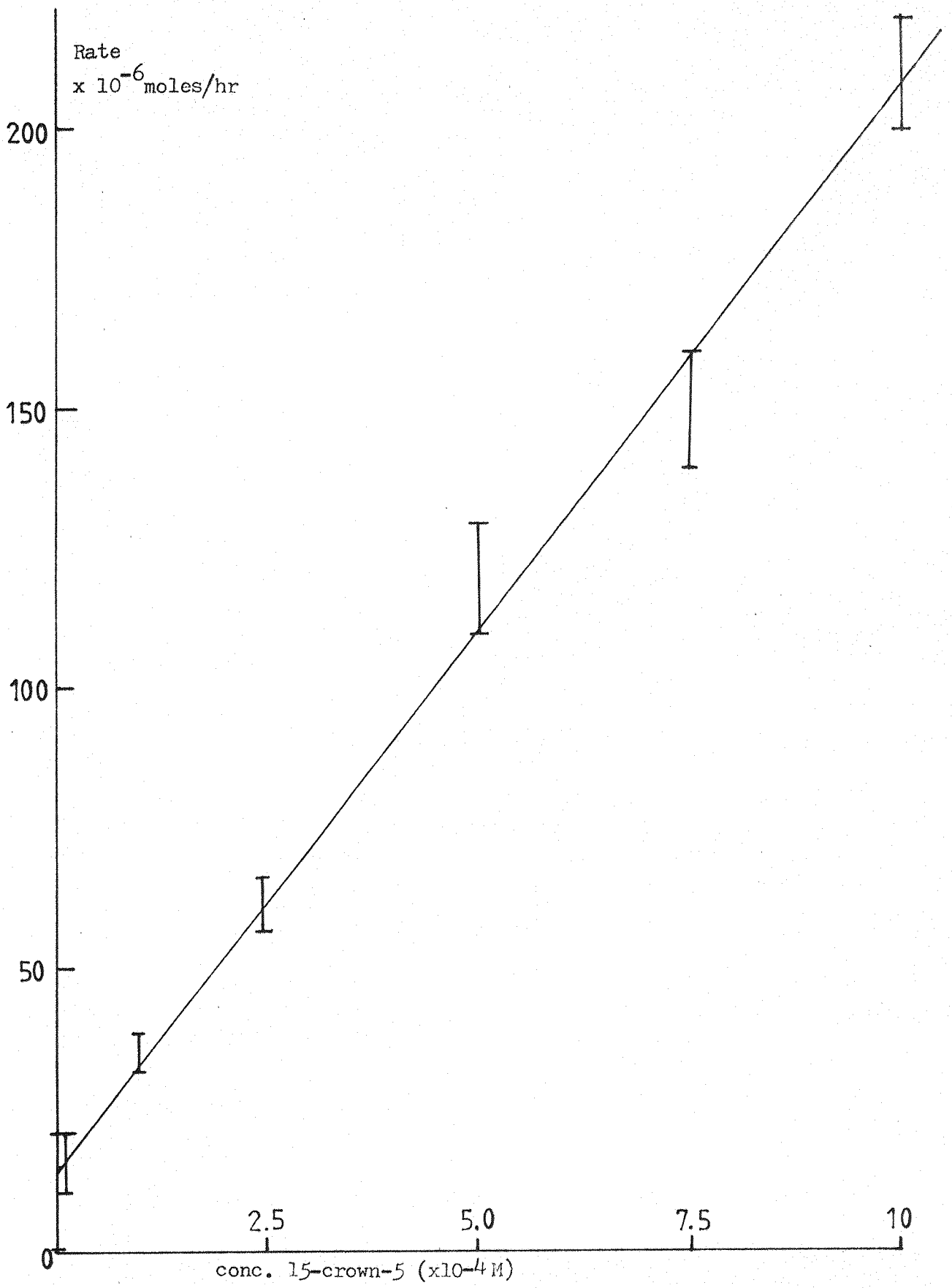
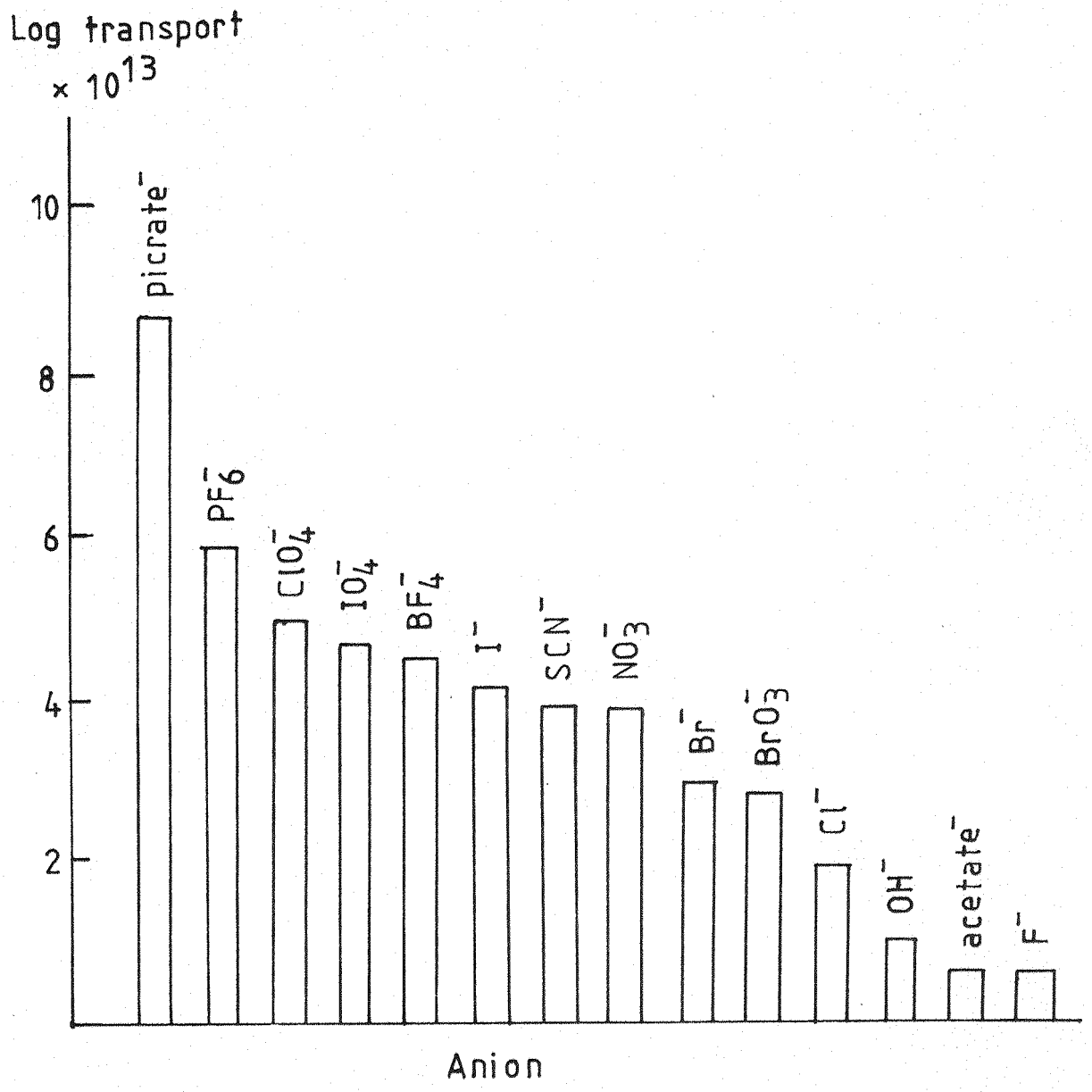


Figure 3.5 Variation of K^+ transport across a $CHCl_3$ membrane with anion (all salts adjusted to a source phase concentration of 0.002M) - from ref 38



$$J_M = \frac{D_c \, k \, K \, L_T \, M_1^2}{1} \qquad \text{Equation 3.1}$$

J_M = flux of salt across membrane
D_c = diffusion coefficient of complexed salt
k = partition coefficient of salt between water and membrane
K = equilibrium constant for salt-carrier complexation
L_T = total carrier ligand concentration
M_1 = source-phase salt concentration
1 = membrane thickness

Firstly it should be noted that there is a linear relationship between transport rate (J_M) and ionophore concentration (L_T), as found for the transport of sodium picrate by different concentrations of 15-crown-5, Figure 3.4. This relationship also encompasses the effect of anion which contributes to the partition coefficient (k)[38]. It should also be noted that for monovalent cation transport the flux is varied as the square of the source-phase salt concentration, although this begins to break down at high salt concentrations whereupon the cation activity rather than concentration becomes more appropriate[38]. One particularly interesting feature of this equation is the correlation of stability constants with transport rate. For maximum transport, an optimum range in value of the cation-carrier complex stability constant was shown to exist[39] with cation transport decreasing rapidly for stability constants outside this range. The maximum observed transport occurred for carriers having log K_{MeOH} values from 5.5 to 6.0 for K^+ and Rb^+ and 6.5 to 7.0 for Ba^{2+} and Sr^{2+}. For all cations little or not transport occurred with carriers having log K_{MeOH} less than 3.5 - 4.0[39]. This is a particularly useful equation, but it should be noted that although the introduction of an alkyl group has been reported[24] not to substantially effect the complexing ability and selectivity of crown ethers, clearly the introduction of an alkyl substituent does have an effect on ion transport and this will be discussed in the next section (section 3.3.1B).

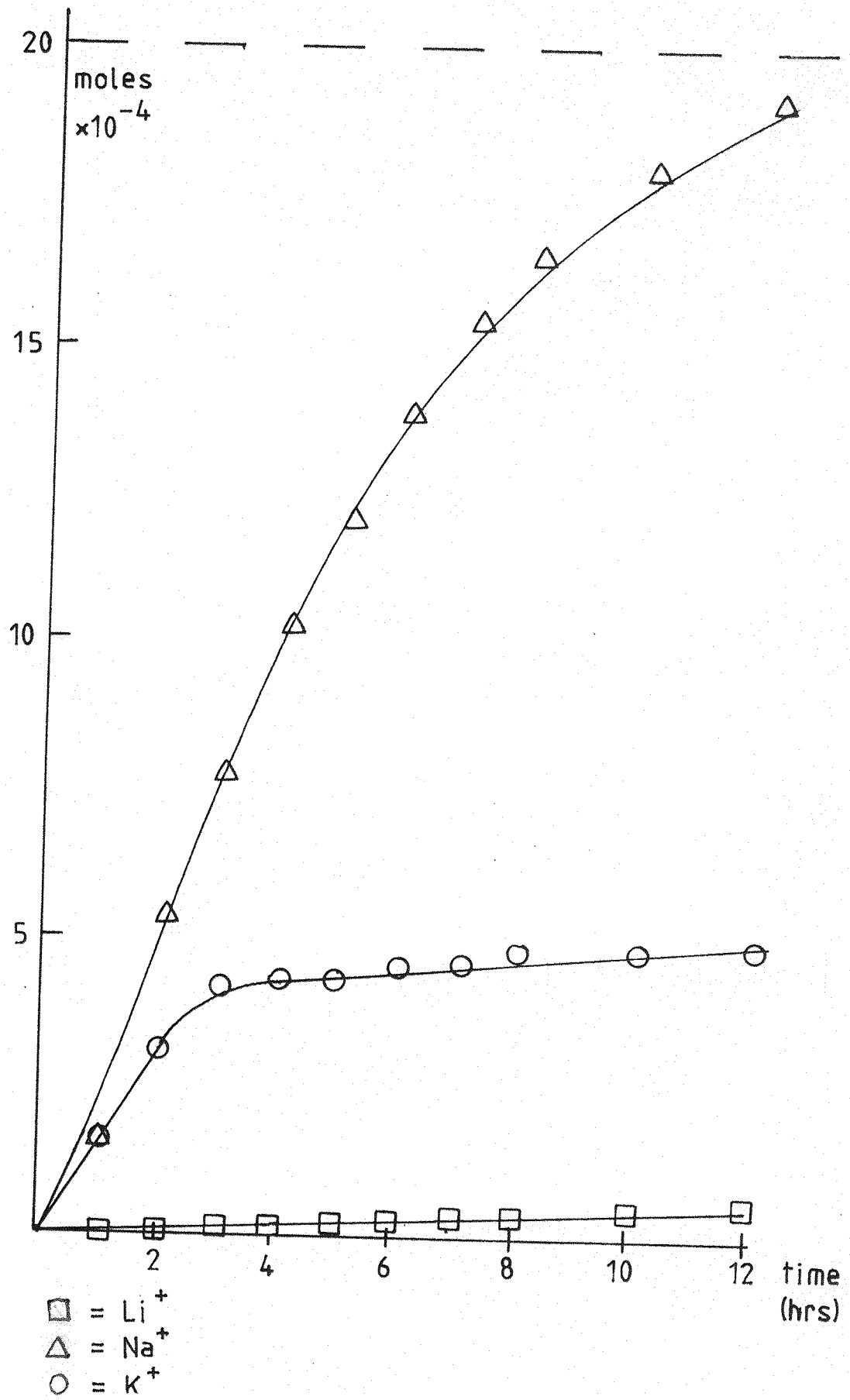
B. Ionophorous Properties of Substituted and Unsubstituted Crown Ethers

The results, Table 3.3, for the unsubstituted crown ethers confirm those of other workers[26,27,38-40] with the best transport rate being achieved

where the cation most closely fits the macrocycle, or provides the optimum stability constant for complexation[39]. 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[39]. However most of this data was concerned with more dilute solutions, not approaching equilbrium, whereas the data in this study is for far more concentrated solutions, where equilibrium was often reached within hours. Two important points deserve consideration. Firstly 18-crown-6 is soluble in water[41] and consequently may affect the concentration of ionophore in the membrane. Secondly, and most importantly, an equilibrium situation was reached very quickly for K^+ transport, see Figure 3.6, middle curve (O). Although it could be seen, visually, 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 ($\sim$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 found in a very recent paper by Okada *et al*[42], 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.

Further examination of the results for the unsubstituted crown ethers reveal 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*[39]. This might be due to an increase in the lipophilicity, see later, but could equally be due to lower stability constants for complexation, and could be related to the greater rigidity of the aromatic structure.

Figure 3.6 Transport of Li,Na and K Picrates by 18-crown-6

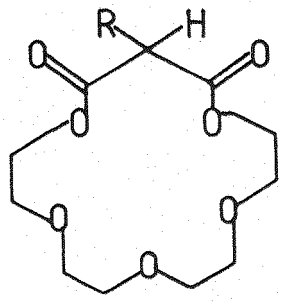


Tetraoxaquaterene (24) was found to be an effective transporter for Li^+ (about 3 x better than 12-crown-4, Table 3.3). This may be due to the fact that tetraoxaquaterene offers a larger macrocyclic cavity which fits Li^+ better than 12-crown-4. In a related study, Bradshaw et al[43] have reported that the introduction of tetrahydrofuran moiety to polyether-diester ligands assisted cation transport. Hence this effect might be due to a change in the stability constant. Another report of the transport properties of macrocycles composed of tetrahydrofuran rings[44] again stated that the best carrier was one that formed a moderately stable rather than a very stable complex. It should be noted that the effect of incorporating tetrahydrofuranyl units into crown ethers has been investigated[45], where it was found that it decreased the association constants for complexation.

Of the remaining unsubstituted crown ethers, it is possible that 1,4-dioxan (6-crown-2) is showing a tendency to transport lithium, possibly through the formation of a sandwich complex, but this may be within the measuring error of the experiment. It is not surprising that tetraethylene glycol does not transport the cations as it would partition almost entirely into the water layer. Of the related non-cyclic crown ethers, Lamb et al[39] reported that pentaglyme, (44a), n = 3, Plate 1.1, preferentially transports Na^+ over K^+ but by a factor of six times less than the equivalent cyclic crown ether. Poonia et al[46] similarly found that polyethylene glycols failed to transport cations, but that dichloro-pentaethylene glycol transported the cations more efficiently than the dichlorides of tetra-and triethylene glycol. The transfer selectivity was $Li^+ > Na^+ > K^+$.

Examination of the results for the alkyl and phenyl-substituted crown ethers, show that the introduction of a lipophilic group does not seem to assist sodium or potassium transport. Rather, the effect seems to make the ionophore more ready to remain in the chloroform layer; this can be seen by the drop in transport rate as the length of hydrocarbon chain increases. Indeed, the one case where a substituent increased the rate of transport of Na^+ and K^+ was for hydroxymethyl-15-crown-5 (90) which contains a polar group. Although the addition of an alkyl substituent has been reported[24] not to greatly affect the binding constants

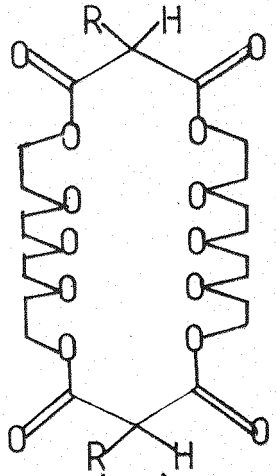
and therefore would not significantly alter the equilibrium constant for complexation (K) in Equation 3.1 - and therefore the rate of transport - this does not apply to some of the other ionophores, e.g. (77g), (89), (90) and (91). For example Gokel et al[14] have determined the binding constant of hydroxymethyl-15-crown-5 (90) to be 556 (90% w/v aq. MeOH at 25°) compared with 926 for 15-crown-5 (2). It would also be surprising if the introduction of an aromatic group as in (77g) or (89) did not affect the binding constants and hence transport rates. An insight into the results for the alkyl substituted crown ethers is given by an examination in the literature of similar ionophores. In particular Simon and co-workers[47] have examined the influence of lipophilicity on neutral ionophores, see compounds (69) and (70). They have reported that the ionophores behaviour of a series of lipophilic 3,6-dioxaoctanedioic diamides vanished with increasing lipophilicity. This loss was shown to be[47] due to kinetic limitations in the exchange reactions between the aqueous and membrane phases. Similarly Tashmukhamedova and co-workers[48] have investigated the effect of alkyl and aryl substituents on the ionophorous properties of dibenzo-18-crown-6, and found that after an optimum chain length was reached, transport declined as the lipophilicity was increased. A further recent example is the synthesis[49] of alkyl substituted di- and tetra-ester cyclic polyethers (100) and (101). Only the dimer (101)



(100)

a) R = C_8H_{17}

b) R = $C_{12}H_{25}$



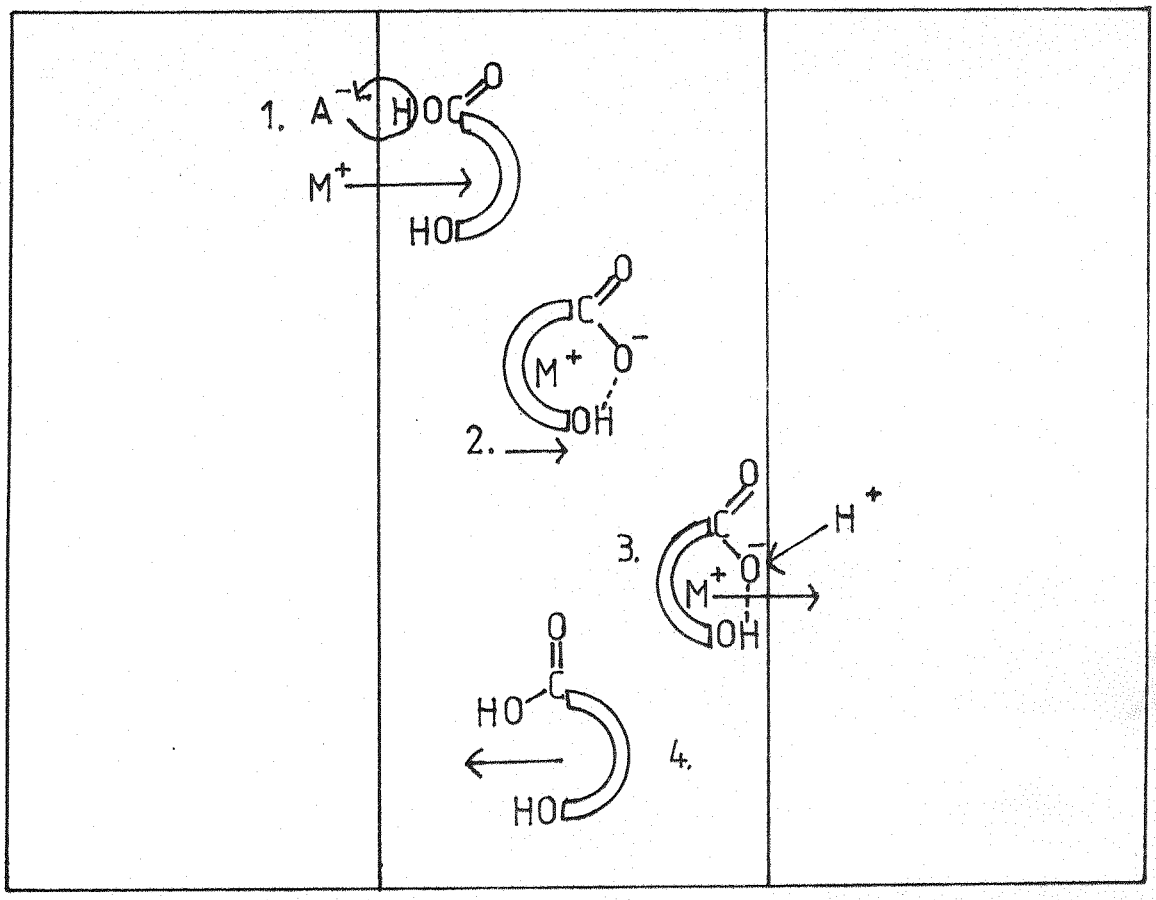
(101)

was reported to transport selectively but not very efficiently[49], the K^+ and NH_4^+ ions, but unfortunately no rates of transport were given.

It is possible that the increase lipophilicity accounts for the decreased rate of transport for sodium and potassium ions for the cases of dibenzo-18-crown-6 : 18-crown-6 and tetraoxaquaterene : 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 alkyl and other groups however does, to a certain extent, assist Li^+ transport. This is exemplified by phenyl-15-crown-5 (77g) which transports Li^+ about twelve times better than the corresponding unsubstituted 15-crown-5. Similarly the introduction of a methyl group (77a) increases transport, although the introduction of an octyl substitutent (77c) marginally decreases Li^+ transport, and larger hydrocarbon chains further decrease transport relative to 15-crown-5. It is uncertain why these results should contradict the transport of Na^+ and K^+, although it should be noted that the rate of transport of Li^+ is still small relative 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. As before this might be due to the unusual behaviour of 18-crown-6, but it is difficult to explain such an effect. The unusual results for Li^+ transport may reflect its unique position in the series of alkali metals[50], in that many of its properties are covalent rather than ionic. Also Li^+ has a hydration number of 25.3 compared to Na^+ of 16.6 or K^+ of 10.5[45] and this would necessitate a greater energy barrier to initial complexation. The anomalous chemistry of lithium may well explain the lack of previous investigations into crown ether complexes and transport properties.

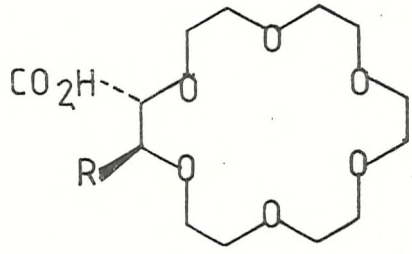
In order to explain the results of transport for monensin, and perhaps the acid substituted derivative (91), another mechanism for ion-transport, rather than that represented in Figure 3.3, needs to be considered. The mechanism of action of these charged ionophores is thought to be [26,51] as in Figure 3.7. Transport according to Figure 3.7 can be considered as four discreet steps:-

Figure 3.7 Transport of M^+ by monensin through a chloroform membrane



1) Cation is complexed by deprotonated ionophore at first interface
2) The neutral complex diffuses across the membrane
3) Rapid reaction with a proton at the second interface releases the cation into the receiving phase
4) Free monensin diffuses back across the membrane whereupon the proton reacts with an anion to repeat cycle.

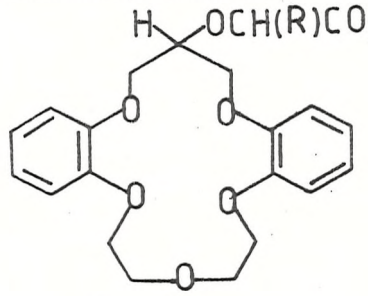
Inherent in this system, which is an electrically silent antiport system[51], is the counter-transport of protons. This has been demonstrated in two ways. Firstly, in a simple 'U' tube experiment[51], the movement of salts from an initially neutral solution through a chloroform membrane containing charged ionophores; monensin, nigericin and dianemychin; to distilled water was monitored. It was found that as transport occurred so the source phase became more acidic. Secondly, a more common approach has been to utilize a pH gradient by having buffered solutions of base and acid as the source and receiving phases respectively. A recent example of this is that of the non-cyclic carboxyl containing ionophore, (45), Plate 1.1,[52] which can transport alkali metal ions selectively through liquid membranes against their concentration gradient. A further example are the functionalized crown ethers (102 a,b,c), as below, which were found to transport potassium ions, through a chloroform membrane,



a) R = $COHN(CH_2)_7CH_3$
b) R = $CONH(CH_2)_3CH_3$
c) R = $CONH(CH_2)_{17}CH_3$

(102)

against their concentration gradient by the coupled counter-transport of protons[16,18]. In this mechanism of transport it should be emphasised that the counter-ion should not be transported. This has been born out by similar work on acid substituted crown ethers in the work of Fyles etal.[16,18] as above, and Bartsch et al.[17] who have examined a series of compounds as (103), and found that solvent



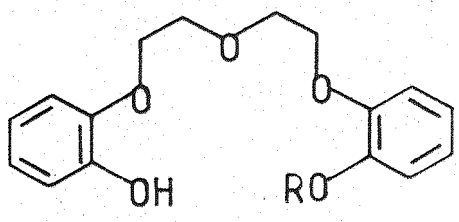
(103)

extraction of alkali and alkaline-earth cations from aqueous media into chloroform by (103) did not involve the transfer of the counter-anion.

In the study of (91) and monensin in this thesis, the picrate anion was detected in the receiving phase above the levels of a blank experiment and therefore this result is in conflict with the reported data. It should be emphasised that the results for monensin were based on an ionophore concentration of 10^{-5}M, compared with 10^{-3}M for all other compounds, and then scaled up in order to provide a comparison. In this way enormous error is built into the results, but nonetheless the results are still significant, particularly for (91) where this error factor is not introduced. There are three potential explanations to account for the transference of anion which might operate separately or, more likely, in conjunction with each other.

i) The picrate anion is simply so lipophilic, see Figure 3.5, that it transfers through the chloroform membrane in addition to a transport mechanism as in Figure 3.7[41].
ii) In conjunction with (i), the mechanism in Figure 3.7 inherently makes the source phase more acidic-generating picric acid. This then might transfer through the chloroform membrane in a passive transport mechanism in response to the pH gradient in association with the active cation transport[16].
iii) Despite the potential charged nature of the ionophore, the mechanism adopted, particularly for (91) which can not stabilize a cyclic structure through the carboxylate anion, is that of Figure 3.3 rather than Figure 3.7. That is, the free acid complexes the sodium and the picrate anion transfers in association with the complex. Results of a recent study by Wingfield and co-workers[53] indicate that this is the most likely possibility. They note that monensin forms complexes with sodium either in the deprotonated form as monensin$^-$.Na^+ or as the free acid as in its complex with sodium bromide, monensin H.NaBr. Furthermore in both structures, intramolecular hydrogen bonding between a hydroxyl and a carboxy end group of the ligand help to hold it in a cyclic conformation around the metal ion. In addition to this observation, they[53] synthesized a series of open

chain polyether hydroxyacids of the type (104) as illustrated below.



$R = CH_2\ CO_2H$

(104)

Again molecules of this type were found to complex with alkali metal ions as the free acid, but not as the deprotonated species. In addition, there was no evidence for hydrogen bonding to stabilize the pseudo-cyclic conformation. Assuming that complexation phenomena can be correlated to transport efficiency, which is generally applicable, see Equation 3.1, this indicates that acid substituted crown ethers, specifically (91), would be able to transport as the free acid and therefore co-transport the picrate anion as well.

It is apparent that further work is necessary to determine the mode of action of these carboxylic ionophores. In particular, work is in progress to determine the cation transport by other means *e.g.* atomic absorption, and to compare the results with those obtained from this picrate study.

3.3.2 Liposome Experiments

Examination of the limited results produced by the liposome transport experiments, Table 3.4, gives a completely different picture of ion-transport than for the bulk liquid membrane experiments. Here the introduction of an alkyl substituent was found to be essential for transport, and although the 18-crown-6 derivative (78f) showed the expected selectivity for K^+ over Na^+, it was also found to predominately transport Ca^{2+}. It is apparent that the mode of transport in a bulk chloroform membrane is not that adopted in a complex bilayer, which is far more analagous to the biological membrane.

Examination of a section of the liposome gives a cross-section of the lipid-bilayer as shown in Figure 3.8(a)[51,54]. An energy profile of a carrier molecule in a lipid bilayer is also shown, Figure 3.8(b)[54], together with the probable conformation of the uncomplexed eicosyl-18-crown-6 (78f), Figure 3.8(c). Figure 3.8 demonstrates why 18-crown-6 fails to transport in these systems. As discussed, section 3.3.1b, 18-crown-6 is water soluble[41] and consequently its expected position would be nearer the hydrophilic end of the bilayer. Therefore it would not be favourable for 18-crown-6 to complex the cation and cross the energy barrier, Figure 3.8(b), of the very hydrophobic region. However the eicosyl substituted 18-crown-6 (78f) would be able to pass through this hydrophobic region due to its greater lipophilicity. It should be noted that this would not involve a 'flip-flop' motion which is too slow[54], but more probably a conformational change as in Figure 3.9, so as to completely protect the cation during transport through the hydrophobic region. This mechanism can be thought of as four discreet steps:

1) Metal cation complexes with crown ether at first interface
2) Ionophore undergoes conformational change so as to pass through hydrophobic region of membrane
3) Ion carrier complex changes conformation at second interface so as to release cation
4) Ionophore diffuses back so as to repeat cycle.

The transport selectivity of (78f) for Ca^{2+}, K^{+} and Na^{+} is unexpected as 18-crown-6, and presumably[24] 2-eicosyl-18-crown-6 preferentially bind K^{+} over Na^{+} and Ca^{2+}. It should be stressed that good binding is not a pre-requisite for good transport, indeed sometimes the opposite is more accurate, c.f. K^{+} transport by 18-crown-6 in bulk liquid membrane studies, section 3.3.1B. It is important to note that the liposome experiments were competitive, that is a choice of cations was offered to the carrier molecule, whereas the bulk chloroform membrane experiments were for a single cationic species. It had previously been found[17] that the efficiencies and selectivities observed in competitive extractions show marked differences from predic tions based on single ion extraction

Figure 3.8

a) Schematic view of a liposome section
b) Energy profile of a carrier molecule in a lipid bilayer membrane, from ref.54.
c) Possible conformation of uncomplexed (78f) in a lipid bilayer

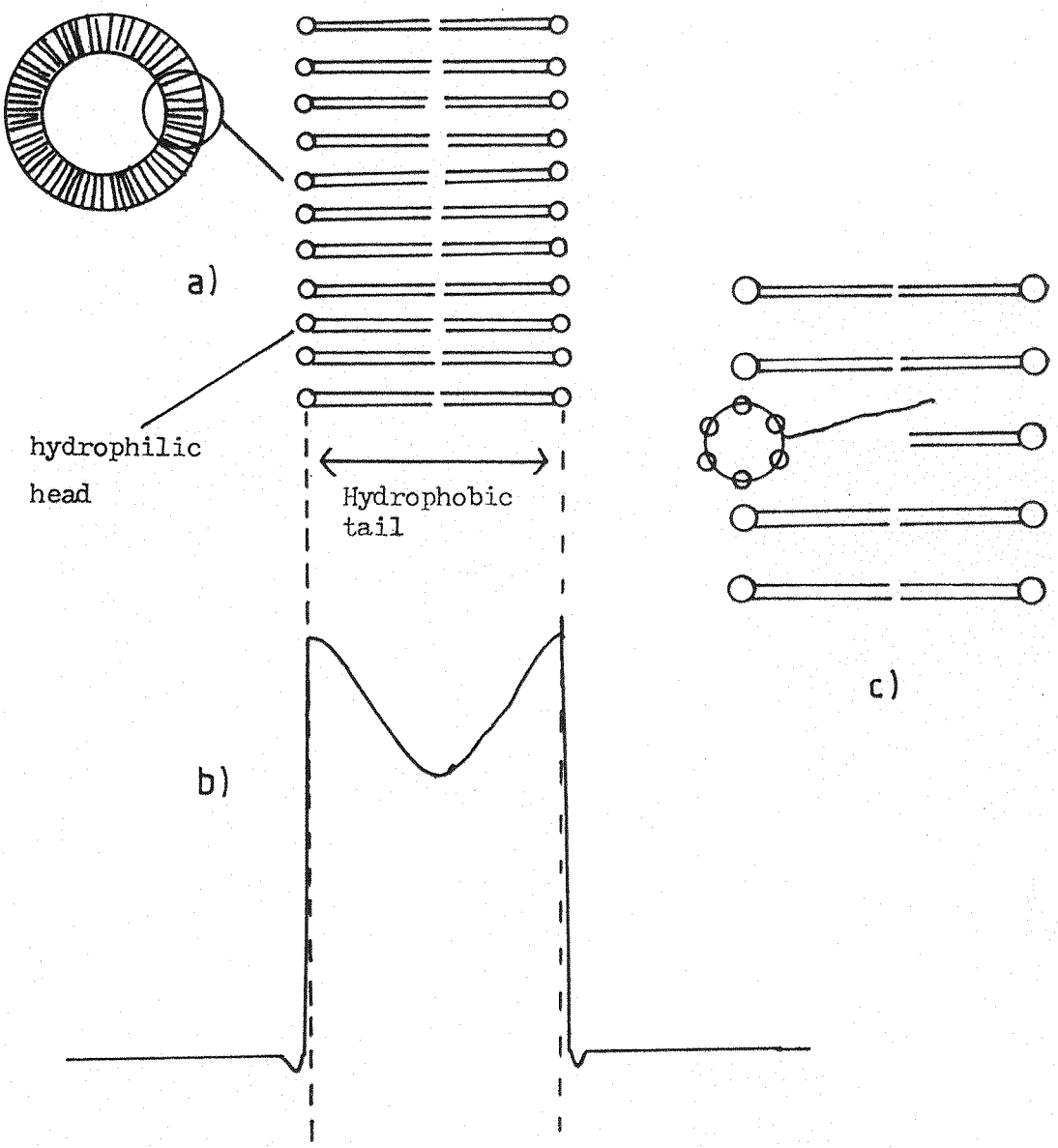
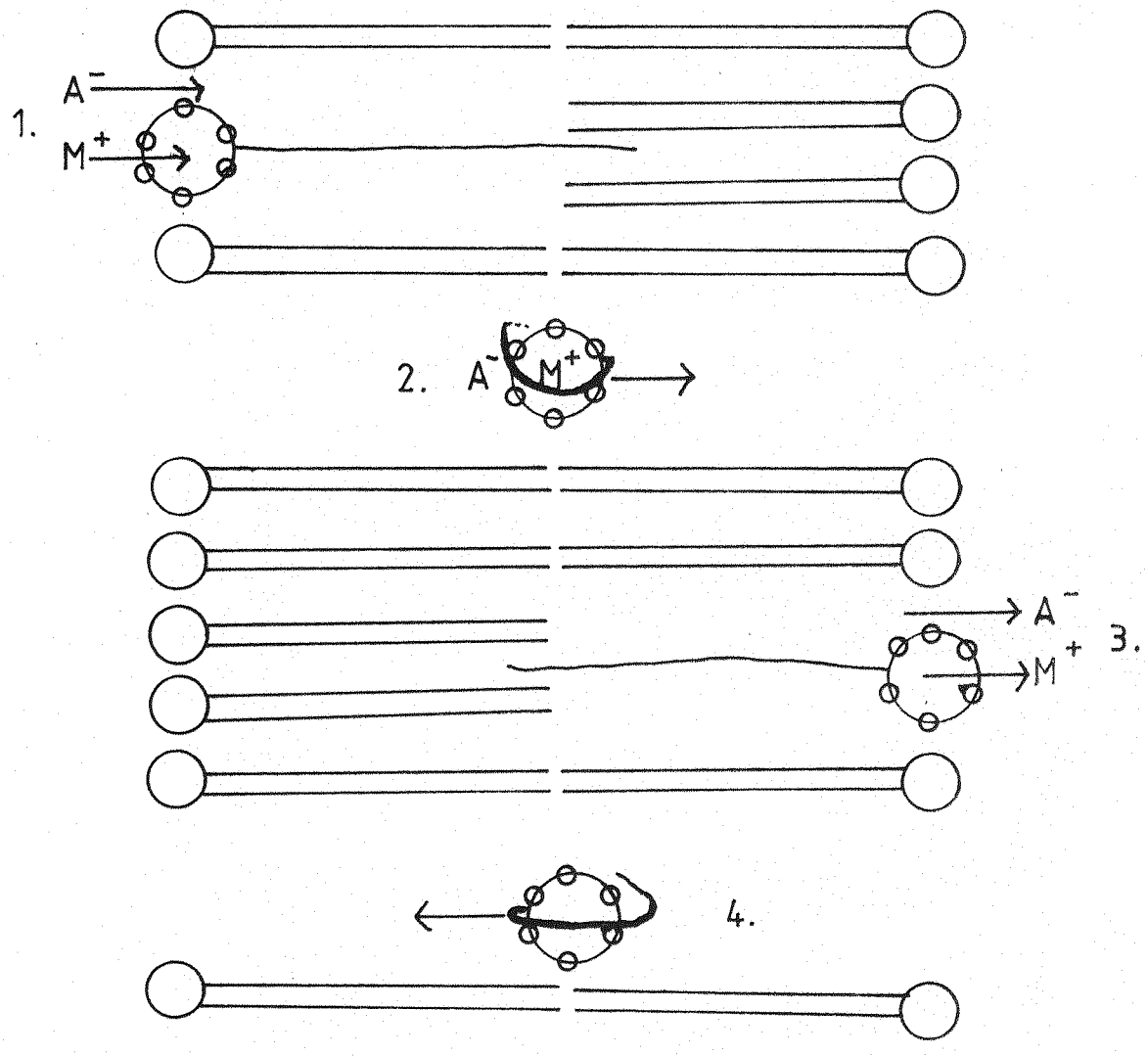


Figure 3.9 Suggested Mechanism of Transport by (78f) through Bilayer



results. Furthermore, at the pH used for the experiment, ethanolamine is in a protonated form, and consequently the surface charge of the bilayer[51,55] will influence transport by electrostatic effects. This would be expected to affect Ca^{2+} transport more than the transport of K^+ and Na^+.

3.4 CONCLUSION

In summary, a range of substituted and unsubstituted crown ethers have been synthesized and tested for their ionophorous properties by the use of bulk chloroform membrane and liposome experiments. Some of the results have been ambiguous, but certain general conclusions may be drawn:

A Bulk Chloroform Membrane Studies

1) For the unsubstituted crown ethers there is a broad correlation between the 'fit' or stability constant for a crown ether: cation complex and the transport rate.

2) Introduction of an alkyl substituent decreases sodium and potassium transport, but a certain degree of lipophilization favours lithium transport, as demonstrated by phenyl-15-crown-5 (77g).

3) Ionophores containing ionizable functional groups may transport via a different mechanism from that for non-ionizable functional groups, particularly for monensin where hydrogen bonding from the acid group to a hydroxy unit stabilizes a cyclic conformation. However, where this is not possible as in (91), transport probably occurs via the free acid, although the use of the very lipophilic picrate anion leads to confusing results.

B. Liposome Experiments Results from a limited study of liposome experiments show that the bulk chloroform membrane studies, whilst in themselves very useful, may not be directly applicable to biological membranes.

Further studies in this area should be concerned with the completion of the synthesis of the acid substituted crown ethers and their subsequent binding properties. Multinuclear nmr studies (see

Section 1.5.1) would seem ideal for this role. More work is also needed to determine the ionophorous abilities of various substituted crown ethers. In particular, emphasis should be placed on carboxylic acid substituted crown ethers in order to determine the ion-transporting mechanism, and further liposome work to quantify the ionophorous abilities of substituted crown ethers in a model more closely related to biological membranes than chloroform.

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CHAPTER 4[+]

EXPERIMENTAL

4.1 GENERAL

Proton nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz on a Perkin Elmer R-12 spectrometer or at 90 MHz on a Varian Associates E.M. 390 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are quoted as δ value. Splitting patterns are designated as follows: (s), singlet; (d), doublet; (t), triplet; (q), quartet; (d of d), doublet of doublets, (m), multiplet; (br), broad. Infrared (IR) spectra were recorded either on a Unicam SP200 spectrophotometer or on a Perkin Elmer 157 G spectrophotometer as thin films for oils and liquids, or nujol mulls for solids. Absorption bands are given in cm^{-1}. Intensities are described as strong (s), medium (m), weak (w) and broad (br). Ultraviolet (UV) spectra were recorded on a Pye Unican SP1800B spectrophotometer. Mass spectra (MS) were recorded either on a Kratos-AEl MS12 spectrometer with a Digispec PDP8 data system or on a Kratos-AEl MS30 spectrometer with a Digispec DS50 data system, generally at an ionization potential of 70eV. The mass to charge ratios of the major ion fragments together with those of special significance, if any, are quoted with the intensities, expressed as a percentage of base peak intensity, in parentheses.

Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. Elemental analysis was carried out by ICI Ltd, Pharmaceuticals Division, Alderley Edge or using a F. and M. Carbon Hydrogen Nitrogen Analyzer Model 185.

Analytical thin layer chromatography (tlc) was performed on Machery-Nagel precoated SIL G-50 UV_{254} plates. Compounds were visualised by observation under UV radiation or by exposure to iodine vapour unless otherwise stated. Column chromatography was performed

[+] References for this Chapter can be found on page 153.

with Grace standard silica gel, particle size 50 - 100.

Solvents were dried, where necessary, by published procedures unless otherwise specified.

4.2 THE TEMPLATE SYNTHESIS OF UNSUBSTITUTED CROWN ETHERS

1,4,7,10,13-pentaoxacyclopentadecane (2) Sodium Template A 500ml three necked round-bottomed flask, fitted with a mechanical stirrer, a reflux condenser and a 100ml dropping funnel, was charged with sodium hydroxide pellets (17.2g, 0.43mol), practical grade triethylene glycol (10.8g, 0.125mol) and dioxan (90mls). The reaction vessel was placed in a heating mantle and warmed gently with stirring. After 15 mins. a solution of bis (2-chloroethyl) ether (44.7g, 0.31mol) in dioxan (30mls) was added in a stream from the dropping funnel to the vigorously stirred reactants. The reaction mixture was then heated under reflux with stirring. 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. 24h). The products were cooled and evaporated under reduced pressure to give a brown slurry to which dichloromethane (60mls) was added. The resultant mixture was filtered and the residue washed with dichloromethane (20mls). The combined filtrate and washings were dried ($MgSO_4$), evaporated under reduced pressure, and then carefullly distilled through a lagged 10cm Vigreux column to give the cyclic polyether as a colourless liquid. (10.8g, 39%).

B.p.110 - 120°/ 2mm (lit. = 96°/0.02mm)[1]
NMR : 3.65(s), 20H, $C\underline{H}_2O C\underline{H}_2$
MS : 220(M^+), 133 (3%), 89 (35%), 45 (100%)
IR : 2880 (br.s), 1460 (m), 1360 (m), 1300 (m), 1250 (s), 1205 (w), 1120 (br.s), 970 (m), 940 (s), 855 (m).

Use of Other Metal Hydroxides[2] The synthesis of (2) was repeated using equimolar quantities of the following metal hydroxides (reagent grade from Aldrich Chemical Company or Alfa Products)

: LiOH, KOH, RbOH, CsOH, $Mg(OH)_2$, $Ca(OH)_2$, $Sr(OH)_2$, $Ba(OH)_2$ and TlOH. The synthesis was also attempted with tetra-n-butylammonium hydroxide (40% aqueous solution) to provide comparative experiments with a non-template ion.

Use of Different Bases[2] The synthesis of (2) was repeated using equimolar amounts of the following bases : NaF, NaOMe, $NaNH_2$ and NaH. For these reactions it is essential that the solvent was dry, so the dioxan was refluxed over lithium aluminium hydride for three hours and distilled immediately prior to use. All reactions of NaOMe, $NaNH_2$ and NaH were performed under nitrogen, and the glycol in dioxan, was added dropwise, over 30 min., carefully 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 the 50% mineral oil dispersion. At the end of the reaction, after removal of the dichloromethane, the mineral oil separated out and was removed.

1,4,7,10,13,16-hexaoxacyclo-octadecane (3)[1] Potassium Template A 500 ml three necked round-bottomed flask, fitted with an efficient mechanical stirrer, a reflux condenxer, and a 100ml dropping funnel was charged with potassium hydroxide pellets (41.6g, 0.63mol), practical grade tetraethylene glycol (24.3g, 0.125mol) and tetrahydrofuran (100mls). The reaction vessel was placed in a heating mantle and warmed gently. After 15 mins. a solution of bis (2-chloroethyl) ether (45.0g, 0.313mol) in tetrahydrofuran (20mls) was added in a stream from the dropping funnel to the vigorously stirred reactants. The reaction mixture was treated analogously to that for (2) and distillation gave a pale yellow liquid (20.3g).B.p. 120 - 155°/0.2mm. The distillate was purified by the method of Cram, Liotta et al[3], viz the crude cyclic polyether was dissolved in acetonitrile (50mls) and the solution slowly cooled with stirring to -55° (methanol/solid CO_2 bath) to give the acetonitrile-18-crown-6 complex as fine white crystals. The solid was collected by rapid filtration. On heating, the complex decomposed and the product was collected as a white crystalline solid. (10.1g, 30%).

M.p. = 37 - 39° (Lit. = 36.5 - 38°)[3]
NMR : 3.65 (s), 24H, $C\underline{H}_2$-O-$C\underline{H}_2$
MS : 264(M^+), 176 (2%), 89 (41%) 45 (100%)
IR : 2880 (br.s), 1460 (m), 1360 (s),
1300 (s), 1250 (s), 1115 (br.s),
970 (s), 855 (m).

Use of Other Metal Hydroxides[2] The synthesis of (3) was repeated using equimolar quantities of the following metal hydroxides : LiOH, NaOH, RbOH, CsOH, $Mg(OH)_2$, $Ca(OH)_2$, $Sr(OH)_2$, $Ba(OH)_2$ and TlOH. The synthesis was also attempted with tetra-n-butylammonium hydroxide to provide comparative experiments with a non-template ion.

1,4,7,10-tetraoxacyclododecane (5)[2,4]

Lithium Hydride Base A 250ml three necked round bottomed flask, fitted with an efficient mechanical stirrer, a reflux condenser, and a 100ml dropping funnel was charged with lithium hydride (3.5g, 0.44mol) and dry dioxan (60mls). Practical grade diethylene glycol (13.3g, 0.125mol) in dry dioxan (30mls) was added dropwise, over 30 mins, to the reaction mixture. When the vigorous reaction to give the glycolate anion was complete, a solution of bis (2-chloroethyl) ether (44.7g, 0.31mol) in dry dioxan (30mls) was added in a stream, over 5 mins, from the dropping funnel to the vigorously stirred reactants. The reaction was carried out, under nitrogen, as for compound (2). Distillation gave a colourless liquid. A sample of the distillate was taken and purified by column chromatography (silica gel, MeOH : CH_2Cl_2 (1 : 1 v/v) eluent) to give (5) as a colourless oil. (4.9g, 13%).

B.p. 58-65°/0.2mm (Lit. = 67-70°/0.5mm)[5]
NMR : 3.65 (s), 16H, CH_2OCH_2
MS : 176(M^+), 103 (3%), 89 (12%), 45 (100%)
IR : 2990 (br.s), 1465(m), 1365(m),
1290(m), 1250(s), 1125(br.s), 930(s).

Use of Different Bases The synthesis of (5) was repeated using equimolar amounts of the following bases : LiOH, LiOMe, NaOH, NaOMe and NaH.

Use of Dimethyl Sulphoxide (dmso) as Solvent The synthesis of (5) was repeated using equal volumes of dmso instead of dioxan. Due to its high boiling point, the dmso could not be evaporated at reduced pressure. Hence when the reaction was complete the solution was cooled, filtered and the filtrate added to distilled water (700 mls). The water solution was extracted with four 200 ml aliquots of dichloromethane, the combined extracts dried ($MgSO_4$) and the dichloromethane was removed by rotary evaporation. The product was then distilled and purified as before to give a colourless oil as the product. (9.0g, 24%).

1,4,7,10,13,16,19,22-octaoxacyclotetracosane (6)

Reaction was carried out as for (5) except for the substitution of lithium hydride by sodium methoxide as base. Distillation gave a pale yellow product (B.p. 170 - 205°/0.2 mm), which on recrystallization (dichloromethane) gave (6) as a white crystalline solid. (7.5 g, 20%).

M.p. 16 - 18°	(Lit = 19°)[6]
NMR:	3.65 (s), 32H, $C\underline{H}_2O C\underline{H}_2$
MS:	133 (4%), 107 (6%), 89 (24%) 87 (11%), 73 (8%) 63 (13%), 59 (19%), 45 (100%). No molecular ion was observed.
IR:	2880 (br.s), 1460 (m), 1360 (s), 1300 (s), 1250 (s), 1120 (br.s.), 970 (s), 855 (m).

3,6,9,11,14-pentaoxapentadecan-1-ol (71) (mono-methoxyethoxymethyl) triethylene glycol

The triethylene glycol was mono-protected by the methoxyethoxymethyl (MEM)[7] group, as in the synthesis of monoalkyl ethers of oligoethylene glycols[8]. Practical grade triethylene glycol (19.0 g, 0.125 mol) in dry dioxan (25 mls) was added to a well stirred solution of sodium hydride (50% oil dispersion, 2.5 g, 0.05 mol) in dry dioxan (30 mls). A solution of methoxyethoxymethyl chloride (6.0 g, 0.05 mol) in dry dioxan (25 mls) was slowly added, over 20 mins, to the vigorously stirred reactants. The reaction mixture was then gently heated (~60°), with stirring, and the reaction was followed by thin-layer chromatography (Sigel, EtOAc : MeOH (1 : 1 v/v) solvent) until the disappearance of the protecting group showed that reaction was complete (ca. 2 hrs). The products were then cooled and evaporated at reduced pressure to

give an off-white slurry to which chloroform (70 mls) was added. The resultant mixture was filtered and the residue washed with chloroform (20 mls). The combined filtrate and washings were washed with water (40 mls), dried ($MgSO_4$), and evaporated at reduced pressure to give the crude product as a yellow oil. A pure sample of (71) was obtained by careful distillation through a Vigreux column to give a clear oil. (8.9 g, 75%).

B.p. = 100 - 115°/0.4 mm
NMR: 4.86 (s), 2H, OCH_2O; 3.6 - 3.8 (m), 16H, CH_2OCH_2; 3.38 (s), 3H, OCH_3.

1-chloro-3,6,9,12,15,17,20-heptaoxaheneicosane (72)

A solution of (71), (7.2 g, 0.03 mol) in dioxan (25 mls) was slowly added, over 15 mins, to a well stirred mixture of sodium hydride (50% oil dispersion, 2.4 g, 0.05 mol) in dioxan (10 mls). A solution of bis (2-chloroethyl) ether (7.1 g, 0.05 mol) in dioxan (10 mls) was slowly added, over 10 mins, to the vigorously stirred reactants. The reaction mixture was then heated, with stirring and the reaction followed by thin-layer chromatography (Sigel, CH_2Cl_2 : MeOH (1 : 1 v/v) solvent) until disappearance of (71) showed that reaction was complete (ca. 3 hrs). The products were cooled and evaporated under reduced pressure to give a brown slurry to which dichloromethane (25 mls) was added. The resultant mixture was filtered and the residue washed with dichloromethane (5 mls). The combined filtrate and washings were dried ($MgSO_4$) and evaporated under reduced pressure. The mineral oil separated out and was removed to give the product as a yellow oil. Distillation of a portion of the crude product gave (72) as a pale yellow oil.(6.7 g, 65%).

B.p. = 160 - 180°/0.3 mm
NMR: 4.80 (s), 2H, OCH_2O; 3.6 - 3.9 (m), 24H, CH_2OCH_2, CH_2Cl; 3.38 (s), 3H, $O-CH_3$

14-chloro-3,6,9,12-tetraoxatetradecan-1-ol (73) (monochloropentaethylene glycol)

The cleavage of the MEM ether[7] was effected by reaction of (72)

(6.5 g, 0.019 mol) in dichloromethane (40 mls) with powdered zinc bromide (21.2 g, 0.094 mol) with efficient stirring at room temperature for 8 hours. The deprotected alcohol was afforded by washing the reaction mixture successively with saturated sodium bicarbonate solution and brine, extraction of the aqueous washings with dichloromethane, drying ($MgSO_4$) and evaporation at reduced pressure to give (73) as a pale yellow oil. (4.35 g, 90%).

NMR: 3.5 - 3.8 (m), 21H, CH_2O, CH_2Cl

IR: 3300 (br.s), 2880 (br.s), 1460 (m), 1360 (s), 1320 (s), 1250 (s), 1120 (br.s), 1070 (s), 970 (s), 855 (m), 720 (s).

Cyclization of (73)

A solution of (73) (1.28 g, 0.005 mol) in dioxan (5 mls) was added slowly, over 10 mins, to a vigorously stirred solution of sodium hydroxide (0.68 g, 0.017 mol) in dioxan (5 mls). The reaction mixture was then heated, under reflux, with stirring and treated analogously to that for (2) until distillation gave 1,4,7,10,13-pentaoxacyclopentadecane (2) as a colourless oil, identified by its chemical and spectral properties (see page 127). (0.33 g, 30%).

4.3 SYNTHESIS OF ALKYL AND ARYL SUBSTITUTED CROWN ETHERS

4.3.1 Route 1[9]

1,2-dodecanediol (81d)

The hydroxylation was based on the method of Swern et al[10]. Hydrogen peroxide (30% solution, 32.14 g, 0.28 mol) was added in one portion to a well stirred mixture of 1-dodecene (42.0 g, 0.25 mol) and 98 - 100% formic acid (125 mls) at room temperature. The mixture was heated and stirred at 40°C for 24 hrs to give a white slurry. The formic acid was recovered at reduced pressure and the distillation residue was heated under reflux for 1 hr. with excess alcoholic potassium hydroxide (3 M). Most of the alcohol was evaporated and a

large excess of hot water added to precipitate the crude glycol. When the mixture had cooled to room temperature, the aqueous layer was siphoned off and the hot water wash was repeated until the glycol was alkali free. The washings were extracted with diethyl ether to remove a small quantity of dissolved glycol and the residue obtained after evaporation of the ether was combined with the water washed product. Recrystallization from methanol (ca 500 mls) gave pure 1,2-dodecanediol as a cream coloured solid. (32.1 g, 63%).

M.p. =	57 - 59° (Lit = 60 - 61°)[10]
NMR:	3.5 (m), 3H, $C\underline{H}(OH)C\underline{H}_2OH$; 3.0 (br.s), 2H, $O\underline{H}$; 1.29 (s), 18H, $C\underline{H}_2C\underline{H}_2$, 0.90 (t), 3H, $CH_2C\underline{H}_3$
IR;	3500 (br.s), 2950 (s), 1470 (s), 1390 (s), 1130 (br.w), 740 (m).

1,2-docosanediol (81f)

Compound (81f) was prepared employing a similar route to that for (81d), but substituting an equimolar amount of 1-docosene for 1-dodecene and using 235 mls of formic acid to give the product as a cream coloured solid. (7.31 g, 86%).

M.p. =	85 - 87° (Lit. = 90 - 91°)[9]
NMR:	4.0 (br.s), 2H, $O\underline{H}$; 3.6 (m), 3H, $C\underline{H}(OH)C\underline{H}_2OH$; 1.29 (s), 38H, $C\underline{H}_2C\underline{H}_2$, 0.90 (t), 3H, $CH_2C\underline{H}_3$
IR:	3500 (br.s), 2950 (s), 1480 (s), 1395 (s), 740 (m).

1,2-dodecanediyldioxydiethanoic acid (82d)

Potassium (19.77 g, 0.51 mol) was added to a solution of 1,2-dodecanediol (81d) (20.2 g, 0.1 mol) in $\underline{t}$ butanol (350 mls), under a nitrogen atmosphere and the mixture was stirred until complete disappearance of the metal. The mixture was then heated to reflux and a solution of chloracetic acid (23.65 g, 0.25 mol) in $\underline{t}$ butanol (35 mls) was added over a period of 35 mins. After the addition was complete, the mixture was heated under reflux for three hours with stirring, then cooled and acidified with conc. HCl. The solvent was evaporated at reduced pressure,

benzene added and the residual water distilled off azeotropically. The residual liquid was filtered, the solvent evaporated and petroleum ether, b.p. 40 - 60°, (150 mls) added. On cooling to 0° white crystals of the di-acid were obtained. (19.1 g, 60%).

M.p. = 60 - 62° (Lit. = 60 - 62°)[9]

NMR: 9.5 (br.s), 2H, $CO_2\underline{H}$; 3.6 - 4.0 (m), 7H, $OC\underline{H}_2$, 1.29 (s), 18H, $C\underline{H}_2C\underline{H}_2$, 0.90 (t),3H, $CH_2C\underline{H}_3$

IR: 3000 (br.s), 1720 (s), 1470 (m), 1395 (s), 1140 (w), 730 (m).

1,2-docosanediyldioxydiethanoic acid (82f)

Compound (82f) was prepared from 1,2-dodecenediol (81f) using the method as for (82d) to give the product as a white solid.(20.2 g, 44%).

M.p. = 88 - 90° (Lit. = 88 - 89°)[9]

NMR: 9.8 (br.s), 2H, $CO_2\underline{H}$; 3.6 - 4.0 (m), 7H, $OC\underline{H}_2$, 1.29 (s), 38H, $C\underline{H}_2C\underline{H}_2$, 0,92 (t), 3H, $CH_2C\underline{H}_3$

IR: 2950 (br.s), 1720 (s), 1470 (m), 1395 (s), 1140 (w), 730 (m).

1,2-bis-(2-hydroxyethoxy)dodecane (83d)

A solution of (82d) (15.9 g, 0.05 mol) in dry tetrahydrofuran (50 mls) was added dropwise, over 20 mins., to a stirred refluxing suspension of lithium aluminium hydride (3.8g, 0.10 mol) in dry tetrahydrofuran under a nitrogen atmosphere. The mixture was heated under reflux for an hour, then aqueous sodium hydroxide (2M, 10 mls) was added with stirring. The mixture was filtered, the solvent removed at reduced pressure, and the crude product, an oily green solid, was distilled (B.p. 195 - 203°/0.2 mms) (Lit. = 180 - 182°/ 0.6 mm)[9] before recrystallization from dichloromethane gave (83d) as an oily white solid. (4.35 g, 30%).

M.p. = 28 - 31° (Lit. = 32 - 33°)[9]

NMR: 3.4 - 3.8 (m), 11H, $C\underline{H}_2O$; 2.95 (s), 2H, $O\underline{H}$; 1.22(s), 18H, $C\underline{H}_2C\underline{H}_2$; 0.9 (t), 3H, $CH_2\ C\underline{H}_3$

IR: 3500 (br.s), 2950 (s), 1470 (s), 1390 (s), 1130 (br.w), 740 (m).

1,2-bis (2-hydroxyethoxy) docosane (83f)

Compound (83f) was prepared from (82f) using the method as for (83d) to give the product as a white solid, recrystallized from petroleum ether (40 - 60°). (5.05 g, 24%).

M.p. = 57 - 59° (Lit. = 60 - 61°)[9]

NMR: 4.1 (s), 2H, $O\underline{H}$; 3.6 - 3.9 (m), 11H, $OC\underline{H}_2$; 1.25 (s), 38H, $C\underline{H}_2C\underline{H}_2$; 0.9 (t), 3H, $CH_2C\underline{H}_3$

CH analysis: C 71.4 % (72.5%)
H 12.1 % (12.5%)

MS: 458 (M^+), 355 (5%), 85 (21%), 57 (34%), 45 (100%).

IR: 3450 (br.s), 2950 (s), 1480 (s), 1395 (s), 1250 (br.w), 1100 (br.m.), 730 (m).

1,2-bis (2-tosyloxyethoxy) ethane[11]

A solution of triethylene glycol (10.59 g, 0.071 mol) in pyridine (150 mls) from a freshly opened bottle, in a 250 ml glass stoppered flask was cooled to 0°, and treated with p-toluenesulphonyl chloride (45.63 g, 0.23 mol), purified before use by Pelletier's method[11]. After solution was complete the flask was kept at -20° for 24 hrs and the reaction was followed by development of a light brown colour followed by separation of pyridine. HCl as long needles. When the reaction was complete, the entire mixture was poured into an ice/water

mixture (∿700g). The ditosylate crystallized immediately and the cream coloured solid was filtered, washed with cold water and recrystallized from ethanol to give the product as a white solid.(22.4 g, 69%).

M.p. = 67 - 69° (Lit. = 78°)[6]

NMR: 7.65 (d of d), J = 8Hz, 8H, $C_6\underline{H}_4$; 4.2 (m), 4H, $C\underline{H}_2OTs$; 3.6 (m), 8H, $C\underline{H}_2O$; 2.43 (s), 6H, $C_6H_4C\underline{H}_3$.

MS: 458 (M^+), 172 (100%), 79 (64%).

IR: 2900 (br.s), 1610 (s), 1500 (w), 1460 (m), 1360 (br.s), 1320 (w), 1300 (w), 1250 (m), 1180 (m), 1130 (br.m), 925 (s), 825 (m), 770 (m), 725 (s).

2-eicosyl-1,4,7,10,13-pentaoxacyclopentadecane (77f)

A solution of 1,2-bis (2-hydroxyethoxy) docosane (83f), (4.21 g, 0.01 mol) and sodium hydroxide (1.0 g, 0.025 mol) in dioxan (20 mls) was gently heated with stirring. To this solution bis (2-chloroethyl) ether (2.15 g, 0.015 mol) was added with stirring. The mixture was heated under reflux and followed by thin layer chromatography (Si gel, CH_2Cl_2 : MeOH (9 : 1 v/v) solvent) until the disappearance of the diol showed the reaction to be complete (ca. 5 hours). After allowing the mixture to cool, dichloromethane (18 mls) was added, the mixture filtered, the filtrate washed with water (2 x 10 mls) and dried ($MgSO_4$). The solvent was removed at reduced pressure to give the crude product as a brown oil. This was purified by column chromatography (Si gel, acetone : petrol (40-60°) (1 : 1 v/v) eluent) and/or by a small scale distillation (generally using a Kugelrohr apparatus) to give (77f) as a cream coloured, waxy solid. (1.70 g, 34%).

M.p. = 31 - 34°

B.p. = 170 - 180°/0.05 mm

NMR: 3.2 - 3.8 (m), 19H, $C\underline{H}_2O$; 1.28 (s), 38H, $C\underline{H}_2C\underline{H}_2$; 0.91 (t), 3H, $CH_2C\underline{H}_3$

CH analysis: C 69.7% (72.0%)
H 10.9% (12.0%)

MS: 498 (1%) (M±2), 354 (100%), 125 (35%), 111 (62%), 57 (60%)

IR: 2860 (br.s), 1460 (s), 1355 (s), 1290 (m), 1250 (m), 1110 (br.s), 970 (s), 845 (m), 730 (w).

2-decyl-1,4,7,10,13,16-hexaoxacyclo-octadecane (78d)

A solution of 1,2-bis (2-hydroxyethoxy) dodecane (83d), (2.90 g, 0.01 mol) and potassium hydroxide (1.40 g, 0.025 mol) in tetrahydrofuran (12 mls) and water (1.2 mls) was heated to boiling. To this solution 1,2-bis (2-tosyloxyethoxy) ethane (6.87 g, 0.015 mol) was added with stirring. The mixture was heated under reflux for 3 hours and then allowed to cool. The pure compound was then obtained by similar work-up and purification procedures as for (77f) to give a cream coloured waxy solid which was recrystallized from n-hexane. (1.13 g, 28%).

M.p. = 25 - 28°

NMR: 3.3 - 3.9 (m), 23H, $C\underline{H}_2O$; 1.28 (s), 18H, $C\underline{H}_2C\underline{H}_2$; 0.90 (t), 3H, $CH_2C\underline{H}_3$.

CH analysis: C 63.5 % (65.3%)
H 10.1 % (10.9%)

IR: 2880 (s), 1450 (m), 1370 (s), 1300 (m), 1255 (m), 1105 (br.s), 980 (m), 840 (s), 730 (w).

2-eicosyl-1,4,7,10,13,16-hexaoxacyclo-octadecane(78f)

Compound (78f) was prepared from (83f) in a similar manner as (78d) to give the product as a waxy pale yellow solid.(1.25 g, 23%).

M.p. = 40 - 43° (Lit. = 41 - 42°)[9]

B.p. = 180 - 192°/0.05 mms

NMR: 3.3 - 3.9 (m), 2H, $C\underline{H}_2O$; 1.25 (s), 38H, $C\underline{H}_2C\underline{H}_2$, 0.90 (t), 3H, $CH_2C\underline{H}_3$

CH analysis: C 70.0 % (70.6%)
H 11.2 % (11.7%)

MS: 458 (0.2%), 354 (100%), 199 (33%), 154 (52%), 91 (78%) 45 (48%)

IR: 2860 (br.s), 1450 (m), 1360 (s), 1295 (m), 1250 (m), 1110 (br.s), 930 (s), 850 (s), 725 (w).

4.3.2 Route 2

1,2-decanediol (81c)

Compound (81c) was prepared from 1-decene in a similar manner to that for (81d) to give the product as a white solid.(21.3 g, 49%).

M.p. = 47 - 49° (Lit. = 48 - 49°)[10]

NMR: 3.5 (m), 3H, $C\underline{H}(OH)C\underline{H}_2OH$; 3.0 (br.s), 2H, $O\underline{H}$; 1.25 (s) 14H, $C\underline{H}_2C\underline{H}_2$, 0.88 (t), 3H, $CH_2C\underline{H}_3$

1,2-hexadecanediol (81e)

Compound (81e) was prepared from 1-hexadecene in a similar manner to that for (81d) to give the product as a white solid.(34.7 g, 56%).

M.p. = 68 - 69° (Lit. = 75 - 76)[10]

NMR: 3.5 (m), 3H, $C\underline{H}(OH)C\underline{H}_2OH$; 3.0 (br.s), 2H, $O\underline{H}$; 1.25 (s), 26H, $C\underline{H}_2C\underline{H}_2$; 0.89 (t), 3H, $CH_2C\underline{H}_3$

1,2-bis (2-tosyloxyethoxy) diethyl ether (ditosylate of tetraethylene glycol)

Tetraethylene glycol (92.0g, 0.5 mol) was dissolved in pyridine (Analar grade, 400 mls) and cooled to 5° in an ice bath. It was stirred at 5 - 10° while purified[11] p-toluene sulphonyl chloride (190.5 g, 1.0 mol) was added in portions over 2 hrs. The reaction mixture was then stirred at 10° for 4 hrs. The mixture was then poured onto ice (500 g) and acidified with conc.HCl before extracting the product with dichloromethane (3 x 200 mls). The extracts were washed with a saturated sodium bicarbonate solution (100 mls) and brine (100 mls), dried ($MgSO_4$), and the solvent evaporated at reduced pressure to give the product as a colourless, viscous oil. (213.0 g, 85%).

NMR: 7.65 (d of d), J = 8Hz, 8H, $C_6\underline{H}_4$; 4.1 - 4.3 (m), 4H, $C\underline{H}_2OTs$; 3.57 - 3.76 (m), 12H, $C\underline{H}_2O$; 2.45 (s), 6H, $C_6H_4C\underline{H}_3$.

MS: No molecular peak, 425 (0.1%), 172 (50%), 107 (100%), 91 (55%), 79 (78%), 65 (53%).

IR: 2900 (br.s), 1610 (s), 1500 (m), 1460 (m), 1360 (br.s), 1320 (m), 1300 (w), 1250 (m), 1180 (m), 1130 (br.m), 925 (s), 825 (m), 770 (m), 725 (s).

2-methyl-1,4,7,10,13-pentaoxacyclopentadecane (77a)

A 100 ml three necked round bottomed flask fitted with an efficient mechanical stirrer, a reflux condenser and a 50 ml dropping funnel was charged with sodium methoxide (2.16 g, 0.04 mol) and dry dioxan (12 mls). To the reaction mixture was added, with stirring, 1,2-propanediol (81a) (1.22 g, 0.016 mol) in dry dioxan (5 mls) dropwise, over 10 mins. When reaction to give the glycolate anion was complete, a solution of

1,2-bis (2-tosyloxy-ethoxy) diethyl ether (10.0 g, 0.02 mol) in dry dioxan (8 mls) was added slowly, over 5 mins, 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 (Si gel, MeOH: CH_2Cl_2 (1 : 1 v/v) solvent) until disappearance of the glycol showed that the reaction was complete. The pure compound was obtained by similar work-up and purification procedures as for (77f) to give a colourless oil.(1.11 g, 30%).

B.p. = 105 - 120°/0.05 mm

NMR: 3.3 - 3.65 (m), 19H, $C\underline{H}_2O$; 1.08(d), 3H, $C\underline{H}_3$

MS: 234 (M^+, 0.1%), 133 (0.8%), 103 (10%), 89 (5%), 59 (100%), 45 (35%).

2-ethyl-1,4,7,10,13-pentaoxacyclopentadecane (77b)

Compound (77b) was prepared in an analogous way to (77a) from 1,2-butanediol (81b) to give the product as a pale yellow oil.(1.11 g, 28%).

B.p. = 105 - 120/0.05 mms

NMR: 3.4 - 3.65 (m), 19H, $C\underline{H}_2O$; 1.25 - 1.55 (m), 2H, $C\underline{H}_2CH_3$; 0.89 (t), 3H, $CH_2C\underline{H}_3$

2-octyl-1,4,7,10,13-pentaoxacyclopentadecane (77c)

Compound (77c) was prepared in an analogous way to (77a) from 1,2-decanediol (81c) to give the product as a pale yellow viscous oil. (1.33 g, 25%).

B.p. = 170 - 185°/0.05 mm

NMR: 3.25 - 3.70 (m), 19H, $OC\underline{H}_2$; 1.25 (s), 14H, $C\underline{H}_2$; 0.89 (t), 3H, $C\underline{H}_3$

2-decyl-1,4,7,10,13-pentaoxacyclopentadecane (77d)

Compound (77d) was prepared in an analogous way to (77a) from 1,2-dodecanediol (81d) to give the product as a pale yellow viscous liquid.(1.22 g, 21%).

B.p. = 175 - 188°/0.05 mm

NMR: 3.25 - 3.70 (m), 19H, OCH_2; 1.28 (s), 18H, CH_2; 0.90 (t), 3H, CH_3

2-tetradecyl-1,4,7,10,13-pentaoxacyclopentadecane (77e)

Compound (77e) was prepared in an analogous way to (77a) from 1,2-hexadecanediol (81e) to give the product as a yellow viscous oil. (1.53 g, 23%).

B.p. = 182- 193°/0.05 mm

NMR: 3.25 - 3.70 (m), 19H, CH_2O; 1.29 (s), 26H, CH_2; 0.90 (t), 3H, CH_3

2-eicosyl-1,4,7,10,13-pentaoxacyclopentadecane (77f)

Compound (77f) was prepared in an analogous way to (77a) from 1,2-docosanediol (81f) to give the product as a pale yellow waxy solid, which was identified by chemical and spectral properties, (see Route 1, page 136). (1.36 g, 17%).

2-phenyl-1,4,7,10,13-pentaoxacyclopentadecane (77g)

Compound (77g) was prepared in an analogous way to (77a) from 1-phenyl-1,2-ethanediol (81g) to give the product as a pale yellow oil. (1.92 g, 41%).

B.p. = 156 - 168°/0.05 mm

NMR; 7.24 (s), 5H, $C_6\underline{H}_5$; 4.60 (m), 1H, OC(Ph)$\underline{H}$; 3.4 - 3.7 (m), 13H, O$C\underline{H}_2$

IR: 2940 (s), 2865 (br.s), 1450 (m), 1360 (s), 1295 (m), 1250 (m), 1110 (br.s), 980 (s), 930 (m), 760 (s), 690 (s).

2-methyl-1,4,7,10-tetraoxacyclododecane (76a)

A 100 ml three necked round bottomed flask fitted with an efficient mechanical stirrer, a reflux condenser and a 50 ml dropping funnel was charged with lithium hydride (0.32 g, 0.04 mol) and dry dioxan (12 mls). To the reaction mixture was added, with stirring, 1,2-propanediol (81a) (1.22 g, 0.016 mol) in dry dioxan (5 mls) dropwise, over 10 mins. When reaction to give the glycolate anion was complete, a solution of 1,2-bis (2-tosyloxyethoxy) ethane (9.16 g, 0.02 mol) in dry dioxan (8 mls) was added slowly, over 5 mins, from the dropping funnel to the vigorously stirred reactants. The reaction was then treated and purified as for (77f) to give a pale yellow oil.(0.33 g, 11%).

B.p. 74 - 79°/0.05 mm

NMR: 3.25 - 3.65 (m), 15H, $C\underline{H}_2O$; 1.04(d), 3H, $C\underline{H}_3$

2-eicosyl-1,4,7,10-tetraoxacyclododecane (76f)

Compound (76f) was prepared in an analgous way to (76a) from 1,2-docosanediol (81f) to give the product as a viscous, pale yellow oil. (0.58 g, 8%).

B.p. = 142 - 150°/0.05 mm

NMR: 3.25 - 3.70 (m), 15H, $C\underline{H}_2O$; 1.25 (s), 38H, $C\underline{H}_2C\underline{H}_2$; 0.90 (t), 3H, $C\underline{H}_3$

2-phenyl-1,4,7,10-tetraoxacyclododecane (76g)

Compound (76g) was prepared in an analogous way to (76a) from 1-phenyl-1,2-ethanediol (81g) to give the product as a viscous, yellow oil.(0.49 g, 12%).

B.p. = 110 - 126°/0.05 mm

NMR: 7.20 (s), 5H, $C_6\underline{H}_5$; 4.60 (m), 1H, OC(Ph)$\underline{H}$; 3.2 - 3.9 (m), 14H, $C\underline{H}_2O$

4.4 SYNTHESIS OF ACID SUBSTITUTED CROWN ETHERS

4.4.1 Route 1[12,13]

Polyethylene Glycol β-haloalkyl ether (84a/85a)

To a stirred suspension of tetraethylene glycol (13.6 g, 0.07 mol) and N-bromosuccimide (3.56 g, 0.02 mol) was added, dropwise over 15 min, allyl chloride (1.68 g, 0.22 mol) at 45 - 50°. The mixture was then stirred at that temperature for 2 hrs until the positive halogen had been consumed. The reaction mixture was cooled to room temperature, added to water (70 mls) and extracted with diethyl ether (3 x 20 mls). The ether extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure to give the crude product as a brown oil. (3.62 g, 51%).

NMR: 3.4 - 3.95 (m), 22H, $C\underline{H}_2O$, $C\underline{H}_2X$

2-chloromethyl-1,4,7,10,13-pentaoxacyclopentadecane (86a)

To stirred suspension of sodium hydroxide (3.0 g, 0.07 mol) in diglyme (100 mls) was added, dropwise over a 2 hr period, a solution of crude (84a/85a) (18.2 g, 0.05 mol) in diglyme (25 mls) at a reaction temperature of 100°. The reaction was then stirred for 6 hrs at 110 - 120° before allowing the resultant mixture to cool to room temperature. The mixture was filtered and the filtrate was evaporated at reduced pressure to give a brown viscous oil. A portion of this liquid was

purified by column chromatography (Si gel, pentane:acetone (5 : 1 v/v) eluent) to give a yellow oil. Analysis showed this to be a mixture of products, predominated by 3-bromo-1,5,8,11,13-pentaoxacyclohexadecane (87).

NMR: 3.5 - 4.3 (m)

CH analysis:			
	C	41.3%	(49.2%)
	H	6.3%	(7.8%)
	Cl	4.6%	(13.2%)
	Br	12.3%	(-)

4.4.2 Route 2[a]

3-benzyloxy-1,2-propanediol (88)[16]

Sodium hydroxide (27.0 g, 0.67 mol) was stirred in benzyl alcohol (500 mls) at 140° for 1 hr, then cooled to 90°. 3-chloro-1,2-propanediol (78.5 g, 0.71 mol) was added to the reaction mixture, over 1 hr, and then it was heated at 140° for one further hour. The reaction was followed by thin layer chromatography (Si gel, CH_2Cl_2 : EtOAc (1 : 1 v/v) solvent), and when complete the reaction mixture was cooled to room temperature, washed with water (2 x 100 mls), and distilled to give the product as a colourless oil.(96.0 g, 65%).

B.p. = 140 - 146°/0.15 mm (Lit. = 164 - 166°/2mms)[16]

NMR: 7.28 (s), 5H, $C_6\underline{H}_5$; 4.48 (s), 2H, $OC\underline{H}_2$ Ph; 3.3 - 4.0 (m), 7H, $O\underline{H}$, $C\underline{H}O$, $C\underline{H}_2O$

2-(benzyloxy)methyl)-1,4,7,10,13-pentaoxacyclopentadecane (89)

A 3-litre three necked round bottomed flask, fitted with a mechanical stirrer, a reflux condenser and a 500 ml dropping funnel was charged with sodium methoxide (40.8 g, 0.80 mol) and dry dioxan (400 mls). 3-benzyloxy-1,2-propanediol (88), (72.0 g, 0.40 mol) in dry dioxan

[a]Similar routes to the hydroxymethyl-15-crown-5 (90) have since been reported by Czech[14] and Gokel et al[15].

(300 mls) was added slowly (over 1 hr) with stirring to the reaction mixture. After reaction to give the dianion was complete a solution of 1,2-bis (2-tosyloxyethoxy) diethyl ether (203 g, 0.41 mol) in dry dioxan (250 mls) was slowly added, over 2 hrs, to the reaction mixture and the reaction mixture was heated to 80°. The reaction was followed by thin layer chromatography (Si gel, EtOAc solvent) until completion (ca. 12 hrs) and the solvent was removed at reduced pressure. Chloroform (500 mls) was added to the resultant brown slurry and the solution was filtered and the residue was washed with chloroform (100 mls). The combined filtrate and washings were washed with water (2 x 150 mls), dried ($MgSO_4$), and the solvent was evaporated to give the product as a brown oil (61 g,45%). Although apparently pure from NMR data, gas-liquid chromatography (30% Silicone SE-30) showed this compound to be only 70% pure. An analytically pure sample was prepared by use of column chromatography (silica, CH_2Cl_2 : EtOAc (1 : 1 v/v) then MeOH eluent). The bulk product was purified by passing through a short column of silica (≈250 g) to give (89) as a clear yellow oil.(28.5 g 21%).

B.p. 162 - 168°/0.05 mm

NMR: 7.38 (s), 5H, $C_6\underline{H}_5$; 4.59 (s), 2H, $OC\underline{H}_2Ph$; 3.45 - 3.85 (m), 21H, $OC\underline{H}_2$

CH analysis:

C	61.1%	(63.5%)
H	8.2%	(8.2%)

MS: 341 (M^++1), 219 (10%), 91 (35%), 87 (82%), 45 (100%)

IR: 2860 (br.s), 1545 (m), 1450 (m), 1350 (m), 1250 (m), 1120 (br.s), 1000 (br.m), 770 (s).

2-(hydroxymethyl)-1,4,7,10,13-pentaoxacyclopentadecane (90)

Compound (89), (12.1 g, 0.036 mol) was placed in a hydrogenation flask in absolute ethanol (50 mls) and glacial acetic acid (50 mls). 30% Pd on carbon in glacial acetic acid was added to the flask and the

compound was hydrogenated with stirring at 50°C. The reaction was followed by thin-layer chromatography (Si gel, CH_2Cl_2: MeOH (9 : 1 v/v) solvent) and uptake of hydrogen into the flask (estimated 810 mls). When the reaction was complete, the solution was filtered and the solvent removed at reduced pressure to give the product as a pale yellow oil.(7.65 g, 85%). An analytically pure sample was obtained by a small scale distillation.

B.p. 143 - 149°/0.05 mm

NMR: 3.3 - 3.8 (m), 21H, $C\underline{H}_2O$, 2.8 (s), 1H, $O\underline{H}$

CH analysis:			
	C	52.9%	(52.8%)
	H	8.7 %	(8.8%)

MS: 249 (M ±1) (1%), 219 (32%), 177 (31%), 87 (50%), 45 (100%)

IR: 3300 (br.s), 2860 (br.s), 1440 (m), 1350 (m), 1250 (m), 1120 (br.s), 1030 (m), 910 (m), 850 (m).

2-(carboxy)-1,4,7,10,13-pentaoxacyclopentadecane (91)[17]

Potassium permanganate (1.70 g, 0.011 mol) in water (15 mls) was added to a well stirred mixture of hydroxymethyl-15-crown-5 (90), (1.25 g, 0.005 mol) and sodium hydroxide (0.15 g) dissolved in water (2 mls). After 12 hrs of stirring, the mixture was acidified with conc. sulphuric acid and sulphur dioxide. The sulphur dioxide was passed through the reaction mixture until the MnO_2 had completely dissolved (colourless solution). The solution was then extracted with diethyl ether (2 x 20 mls) and the solvent was evaporated at reduced pressure to give the product as a pale oil.(1.12 g, 85%).

NMR: 9.0 (br.s), 1H, $CO_2\underline{H}$; 3.3 - 3.8 (m), 19H, $C\underline{H}_2O$

CH analysis:			
	C	51.6%	(50.0%)
	H	6.9%	(7.6%)

MS: 264(M^+) 219 (3%), 199 (11%), 149 (25%), 105 (94%), 45 (100%)

IR: 3400 - 2500 (br,m), 2860 (s), 1700 (s), 1450 (m), 1375 (w), 1320 (w), 1290 (m), 1100 (br,w), 935 (m), 710 (s)

2-(p-tolylsulphonyloxy) methyl-1,4,7,10,13-pentaoxacyclopentadecane (92)

The alcohol (90) (5.0 g, 0.02 mol) was dissolved in pyridine (Analar, 100 mls) and cooled to 5° in an ice bath. It was stirred at 5 - 10° while tosyl chloride (7.62 g, 0.04 mol) was added in portions over 1 hr. The mixture was stirred for 4 hrs at 10° before pouring the entire mixture onto ice (50 g). The mixture was acidified with conc. HCl and extracted with chloroform (3 x 20 mls). The extracts were washed with saturated sodium bicarbonate solution and brine, dried ($MgSO_4$), and the solvent evaporated to give a yellow oil.(3.07 g, 38%).

NMR: 7.6 (d of d) J = 8Hz, 4H, $C_6\underline{H}_4$; 4.10 (m) 2H, $C\underline{H}_2OTs$; 3.64 (s), 19H, $OC\underline{H}_2$; 2.40 (s), 3H, $C_6H_4\ C\underline{H}_3$.

MS: 405 (M + H), 229 (6%), 199 (31%), 155 (65%), 91 (100%), 45 (100%).

IR: 2860 (br.s), 1600 (m), 1450 (m), 1355 (s),1310 (w), 1290 (w), 1250 (w), 1190 (m), 1120 (br.s), 980 (m), 940 (m), 830 (m), 750 (m), 665 (s).

2-(carboxymethyl)-1,4,7,10,13-pentaoxacyclopentadecane (93)

Compound (93) was prepared *via* an intermediate nitrile compound which was prepared according to the method of Friedman *et al*[18]. The tosylate (92), (2.02 g, 0.005 mol) in dimethyl sulphoxide (10 mls) was added slowly, over 10 mins, to a well stirred mixture of sodium cyanide (0.31 g, 0.0064 mol) in dimethyl sulphoxide (10 mls) at 40°. When the reaction was complete, the reaction mixture was cooled, diluted

with water (70 mls) and extracted with diethyl ether. The ether extracts were washed with hydrochloric acid (2M, 50 mls), brine (50 mls) and water (50 mls), dried ($MgSO_4$), and the solvent evaporated to give the intermediate cyanide product as a yellow oil.(0.34 g, 25%).

NMR: 3.4 - 3.9 (m), 19H, $C\underline{H}_2O$; 2.38 (d), 2H, $C\underline{H}_2CN$

A mixture of the intermediate nitrile (0.30 g, 0.0011 mol) was heated, under reflux,with an aqueous solution of potassium hydroxide (5M, 10mls) for 1 hr, when hydrolysis was complete. The solution was cooled and acidified (sulphuric acid). The product was extracted with chloroform (20 mls), washed with saturated sodium bicarbonate (5 mls), water (5 mls), dried ($MgSO_4$) and the solvent removed at reduced pressure to give the product as a yellow oil.(0.21 g,67%).

NMR: 10.5 (br.s), H, $CO_2\underline{H}$; 3.3 - 3.8 (m), 19H, $C\underline{H}_2O$; 2.84 (d), 2H, $C\underline{H}_2CO_2H$

MS: 278 (M^+), 219 (10%), 149 (12%), 105 (72%), 45 (100%)

IR: 3400 - 2600 (br.w), 2360 (s), 1710 (s), 1450 (m), 1375 (m), 1290 (m), 1120 (br.s), 940 (m), 720 (s).

2-(carboxyethyl)-1,4,7,10,13-pentaoxacyclopentadecane (94)[19]

To a solution of sodium metal (0.06 g, 0.0025 mol) in dry ethanol (2.5 mls), diethyl malonate (0.40 g, 0.0025 mol) was added and the temperature raised to 60°. Then 2-(tosyloxy)methyl-15-crown-5 (92), (1.01 g, 0.0025 mol) in dry ethanol (1 ml) was added dropwise, over 5 min, with stirring, and the reaction mixture was heated under reflux for 24 hrs. The sodium tosylate salt was filtered off and the filtrate was heated under reflux for 2 hrs with potassium hydroxide (0.30 g, 0.0053 mol) in ethanol (1.0 ml) until neutral. Then water (0.5 mls) was added, the alcohol removed at reduced pressure, the residue acidified with conc.HCl and heated under reflux for 5 hrs. The product was extracted with dichloromethane (2 x 5 mls), washed with saturated sodium bicarbonate (5 mls), water (5 mls), dried ($MgSO_4$) and the solvent

evaporated at reduced pressure to give the product as a yellow oil. (0.15 g, 21%).

NMR: 10.5 (br.s), 1H, $CO_2\underline{H}$; 3. 4 - 3.7 (m), 19H, $C\underline{H}_2O$; 2.42 (m), 2H, $C\underline{H}_2CO_2H$; 1.35 - 1.60 (m), 2H, $C\underline{H}_2CH_2CO_2H$

IR: 3100 - 2600 (br.w), 2860 (s), 1710 (s), 1450 (m), 1375 (m), 1280 (m), 1110 (br.m), 940 (m), 710 (s).

2-(formyl)-1,4,7,10,13-pentaoxacyclopentadecane (95)[20]

2-(Hydroxymethyl)-1,4,7,10,13-pentaoxacyclopentadecane (90), (2.5 g, 0.01 mol) was dissolved in anhydrous dimethyl sulphoxide (15 mls) and toluene (20 mls) containing pyridine (0.80 ml, 0.01 mol) and trifluoroacetic acid (0.4 mls, 0.005 mol). After the addition of dicyclohexylcarbodiimide (DCC), (6.2 g, 0.03 mol), the stoppered reaction flask was kept overnight at room temperature. Diethyl ether (250 mls) was added followed by solution of oxalic acid (2.70 g, 0.03 mol) in methanol (25 mls). After gas evolution had ceased (about 30 mins), water (250 mls) was added and the insoluble dicyclohexylurea was removal by filtration. The organic phase was then washed with saturated sodium bicarbonate (2 x 50 mls) and water (1 x 50 mls), dried ($MgSO_4$), and evaporated at reduced pressure to give the product as a yellow oil. (0.87 g, 35%).

tlc: MeOH : CH_2Cl_2 (1 : 1 v/v) solvent, 2,4-dinitrophenylhydrazone development) Rf = 0.36, yellow colour (characteristic of aldehyde)

NMR: 9.6 (br.d), 1H, $C\underline{H}O$; 3.2 - 3.8 (m), 19H, $C\underline{H}_2O$

IR: 3320 (w), 2900 (br.s), 2730 (w), 1700 (s), 1450 (s), 1375 (m), 1140 (br.m), 725 (m).

4.5 STUDIES ON THE IONOPHOROUS PROPERTIES OF CROWN ETHERS

4.5.1 Bulk Chloroform Membrane

The apparatus for this experiment was based on that developed by Christensen, Izatt and co-workers[21] and is schematically represented in Figure 4.1.

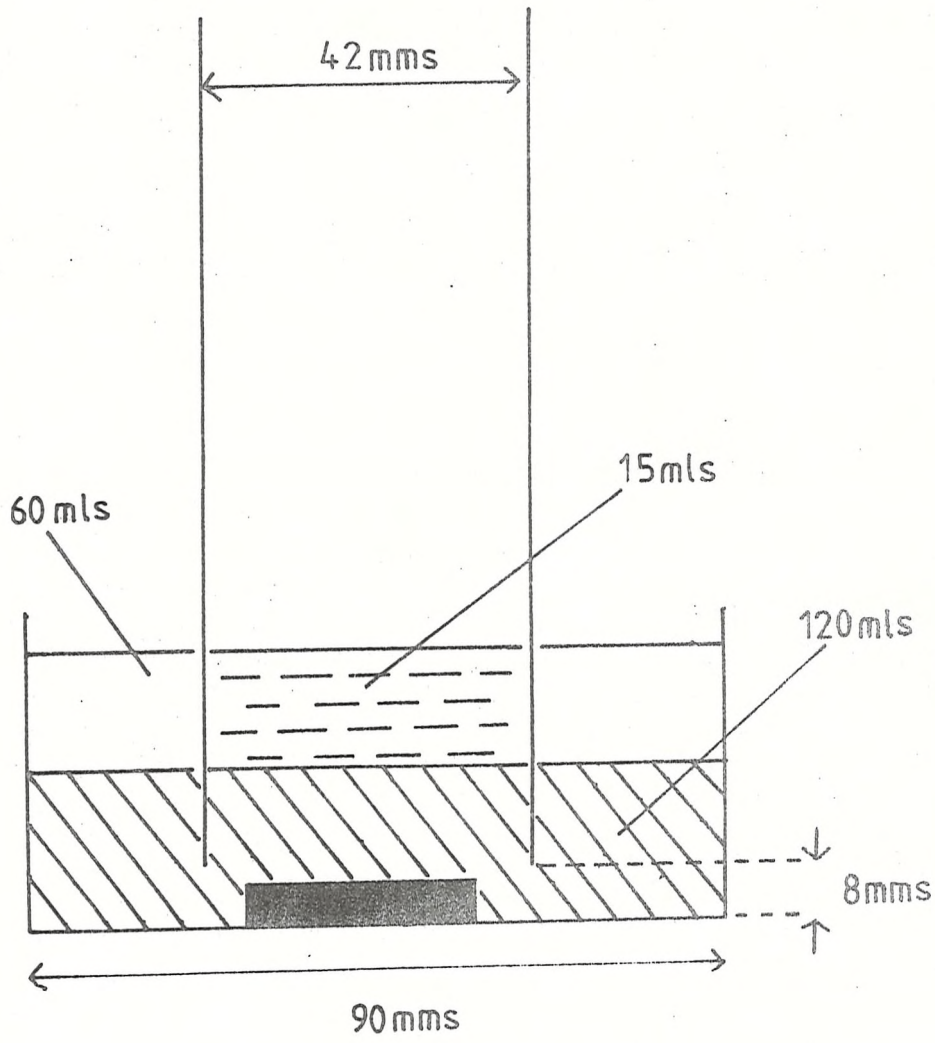
A 120 ml sample of the liquid membrane, chloroform (Analar) containing the crown ether, typically 10^{-3} mol, was placed in a 90 mm diameter evaporating dish with a 24 mm magnetic follower. A 42 mm diameter glass cylinder was inserted partly into the chloroform layer, as in Figure 4.1, and clamped into position. Distilled water (60 mls) was carefully introduced to the outer ring as the receiving phase, and a picrate solution (15 mls, 0.01 M) was similarly introduced to the inner cylinder above the chloroform layer as the source phase. The membrane was stirred at approximately 80 rpm. Samples were withdrawn from the receiving phase at 1 hr intervals and the absorption of picrate recorded at 360 nms.

The picrate solutions were prepared by titrating picric acid against 10^{-2}M solutions of lithium, sodium and potassium hydroxides. Standard spectra were then run to obtain λmax and Emax values. For example sodium picrate gave values λ max = 360 nms, Emax = 1.42×10^{4}, which agrees well with the literature values (λ max = 353 nms, Emax = 1.41×10^{4})[22]. A calibration graph was used to convert absorbance values into picrate concentrations.

4.5.2 Liposome Experiments[23]

Liposomes were prepared by adding egg lecithin solution (1.5 mls) phosphatidyl ethanolamine (1.05 mls) and cholesterol (23.16 mgs) to a round bottomed flask. All the solvent was evaporated at reduced pressure and the solution to be trapped inside the liposome, Buffer 1

Figure 4.1 Bulk Chloroform Membrance Experiments



= $CHCl_3$, membrane phase

= 0.01 M metal picrate, source phase

= H_2O, receiving phase

(5 mls)[a], was added. The flask was flushed with nitrogen, sealed, and placed in a vortex mixer for 1 min. The mixture was then sonicated to produce the liposomes. 10 µl of the mixture was then taken and added to a phase combining system (PCS, 4 mls) and counted for radioactivity (^{45}Ca). In order to separate the liposomes, the mixture was placed on top of a sephadex column (sephadex G -50 medium) and eluted with the K^+/Na^+ Free Buffer 2[b], at a rate of 1 ml/ 4 mins. The liposome fraction (pink colouration) was placed in a 250 ml conical flask, counted (500 µl in 4 mls PCS), and diluted with Buffer 2[b] to 100 mls.

100 ppm (1 ml) of the crown ether was added to the liposome solution (3.5 mls) and placed in an insulator at 37°C for 1 hr. The solution was then tipped into centriflo membrane cones (cut off 50,000 MW) and centrifuged at 500 G for 10 mins. The filtrate was then analyzed for Na, K and Ca content (Na and K by atomic absorption, Ca by ^{45}Ca radioactivity count).

[a]Buffer 1
0.14 M NaCl (Analar)
0.14 M K Cl (Analar)
0.05 M Trizma Base (Reagent grade)
0.14 M $CaCl_2.2H_2O$ (Analar)
100 Cu ^{45}Ca + Lissamine Red B
Make up to 1 litre with deionised water,
pH 7.4, (HCl).

[b]Buffer 2
0.05 M Trizma Base (Reagent grade)
0.105 M $CaCl_2.2H_2O$ (Analar)
Make up to 1 litre with deionised water,
pH 7.4, (HCl).

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23. Liposome experiments were conducted with technical assistance at ICI Ltd., Pharmaceuticals Division, Alderley Edge.