Synthetic ionophores for cations

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SYNTHETIC IONOPHORES FOR CATIONS

by

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MEMORANDUM

The work for this thesis has been carried out in the Department of Chemistry at the University of Durham between October 1990 and September 1993. It is the work solely of the author unless stated otherwise. None of the work has been submitted for any other degree.

To my parents

He giveth power to the faint; and to them that have no might he increaseth strength. Even the youths shall faint and be weary, and the young men shall utterly fall: But they that wait upon the LORD shall renew their strength; they shall mount up with wings as eagles; they shall run and not be weary, and they shall walk, and not faint.

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ABSTRACT

A series of 14-crown-4 derivatives bearing amide substituents have been prepared in order to develop ionophores selective for lithium. Complexation with lithium ions was monitored using ^{13}C and IR spectroscopy and liquid membrane electrodes prepared and evaluated using a fixed interference method. The highest selectivities with respect to sodium ions were obtained for di-n-butylamide-oNPOE and a di-n-benzylamide-oNPOE derivatives; $\log K^{POT}_{Li,Na}$ = -2.92 and -2.93 respectively.

A series of amide and amide-ester N-functionalised coronands based upon [12]-N_2O_2 , [15]-N_2O_3 and [18]-N_2O_4 parent macrocycles has been prepared. Complexation of certain alkali and alkaline-earth cations was monitored by ^{13}C NMR and IR spectroscopy, enthalpies of complexation measured in methanolic solution using micro-calorimetry and stability constants measured in aqueous media by potentiometric methods. Strong complexation of Ca^{2+} in aqueous media was observed with good selectivity over Na^+ and K^+. Lower free energies of binding for IIa cations were displayed by the tertiary amide derivative (of [12]N_2O_2), than by its secondary analogue, despite displaying higher enthalpies of complexation. Thus the lower free energies result from significantly lower entropies of complexation.

Two sets of oxa-amide and oxa-ester tripodal ligands have been prepared and solvent membranes fabricated. The effects of the nature of the plasticiser, bis (butylpentyl)adipate (BBPA) verses *o* -nitrophenyl octyl ether (oNPOE), the ligand structure and the ionic strength of the analyte solution on the electrode response to Ia and IIa cations were studied. The performance of the oxa-amides was superior to that of the oxa-esters particularly at higher ionic strengths, however super-Nernstian responses were observed with the more charge-dense ions in the presence of chloride and/or with the less polar plasticiser BBPA. Measurements of intracellular sodium concentration could be effected with a sensor based upon bis (N,N',N"-tributyl)-4,4',4"-propylidintris(3-oxabutanamide) and oNPOE for which -log $K^{POT}_{Na,K}$ = 2.64 and -log $K^{POT}_{Na,Mg}$ =3.0, whilst bis (N,N',N"-tributyl) -2,2',2"-phenylmethylidintris(3-oxabutamide) and oNPOE functioned as a calcium sensor, displaying excellent selectivity over Mg. -log $K^{POT}_{Ca,Mg}$= 4.8.

Additionally a triamide based upon a cyclohexane triol skeleton was prepared, a membrane fabricated and its performance assessed as a sodium sensor.

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CHAPTER I

INTRODUCTION

1.1 SUPRA MOLECULAR CHEMISTRY:- HOST GUEST CONCEPT

Supra molecular chemistry has been defined as the study of the intermolecular bonding forces [1] present in complexes which are formed by the association of two or more chemical species.

A complex is defined as being composed of two or more molecules or ions held together by non-covalent forces in a well defined structural relationship [2,3] It is usually a combination of non covalent forces which are involved in defining the structure of the complex. The possible forces involved include combinations of hydrogen bonding, Van der Waals attractions and ion-pairing.

Often a complex can be defined in terms of a host-guest relationship [4] involving a complementary arrangement of binding sites. A host is a compound whose binding sites converge in the complex and those of the guest diverge. An association of the two leads to the formation of a host-guest complex (Figure 1.01).

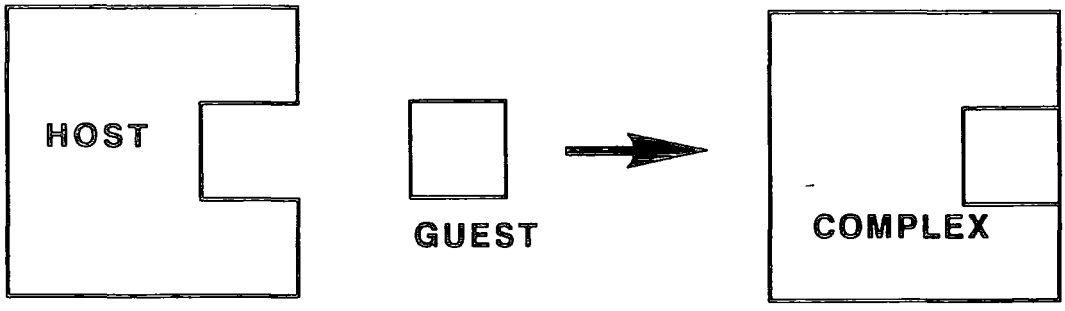


Figure 1.01 Formation of a Host-Guest Complex

An intrinsic requirement of the host is that not only must it bind a guest species but also it must do so selectively. In order to achieve this, the host should exhibit a degree of molecular recognition. Thus it should possess structural features which facilitate the binding a particular guest species but

prevent or at least render unfavourable the binding of a different but often closely related guest species.

There are several factors which govern selectivity in complexation, principally cavity dimensions, conformational flexibility/rigidity, shape, donor atom type, number and arrangement. Rigid preorganised macrocycles such as calixarenes, spherands and some small cryptands possess a relatively well defined cavity. Their lack of conformational flexibility prevents significant changes in conformation upon complexation and thus they exhibit size selectivity [5]. Selectivity can often be enhanced by the incorporation of rigid sub-structures into the host, such as benzene or pyridine rings. An example of this is the incorporation of a 1,8-naphthyridine ring into a 20-membered crown ether, the resultant structure exhibiting selectivity for Ba^{2+} (Log K = 7.16) over Ca^{2+} (Log K = 4.91) [6] . This can be taken a stage further by the incorporation of chiral sub-structures into the molecular framework of the host in order to effect chiral discrimination [7]. Cram developed a chiral crown ether which was used to resolve chiral ammonium salts, such as amino acid ester salts. The NH_4^+ cation binds to the 18-crown-6, the strength of the binding interaction depending upon the geometry at the chiral centre i.e. one enantiomer binds more strongly than the other. A difficulty inherent in such rigid structures is that while they may possess an elegant and well defined structure they generally possess very poor complexation dynamics. The quest of the macrocyclic chemist thus is not only to design structures which exhibit excellent structural preorganisation but also possess a certain degree of flexibility and good complexation dynamics.

In addition to steric and spatial factors, the nature and number of the donor atoms is also critical in determining the selectivity of the host. Oxygen donor atoms favour binding of alkali and alkaline earth cations, whereas nitrogen donor atoms favour transition metals, particularly Cu^{2+}

and sulphur donors may interact preferentially with Ag^{+}, Pb^{2+} and Hg^{2+}. The number of donors is also an important factor particularly in the binding of metal cations since different cations have different co-ordination number preferences. The incorporation of side-arm donors has also been shown to enhance selectivity. The attachment of pendant amide substituents to oxa-aza macrocycles for example has been demonstrated to enhance discrimination in favour of cations with a higher charge density. [8,9]

Thus it can be seen that a number of different criteria can be used in designing a synthetic host compound in order to enhance selectivity in favour of a preferred guest compound or ion.

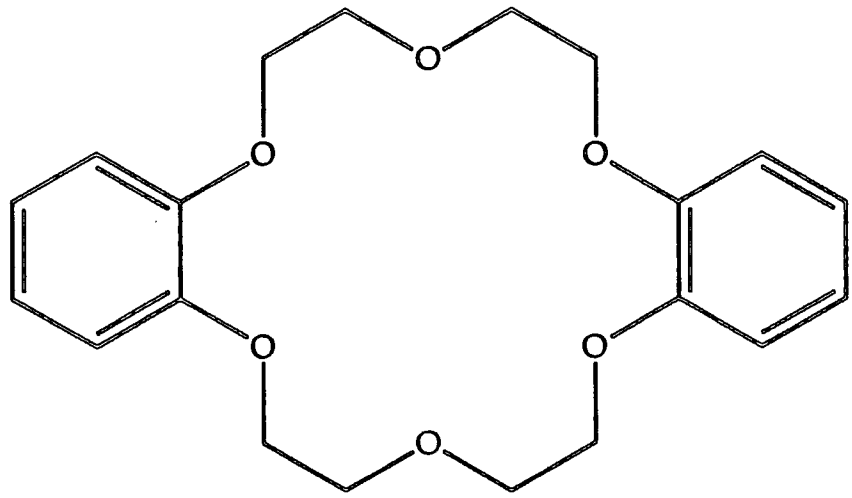
Because this thesis is predominantly concerned with the complexation properties of cyclic ionophores this introduction concentrates on the parameters affecting the binding properties of these ligands. The part of the work concerned with acyclic and anionic ionophores will be discussed separately as a brief introduction to the relevant chapter.

1.2. MACROCYCLIC HOSTS FOR CATIONIC GUEST SPECIES

1.2.1 CROWN ETHER

This class of compounds was discovered by Pedersen in 1962 [10]. At the time he was investigating the use of vanadium as a catalyst in oxidation and polymerisation reactions. When attempting to synthesise bis [2-o-(hydroxyphenoxy)ethyl] ether from 2-(o-hydroxyphenoxy) tetrahydropyran he isolated a very small amount of a white crystalline substance.

Subsequent identification of this compound showed it to be 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene (usually referred to as dibenzo-18-crown-6) (Figure 1.02) (1).



(1)

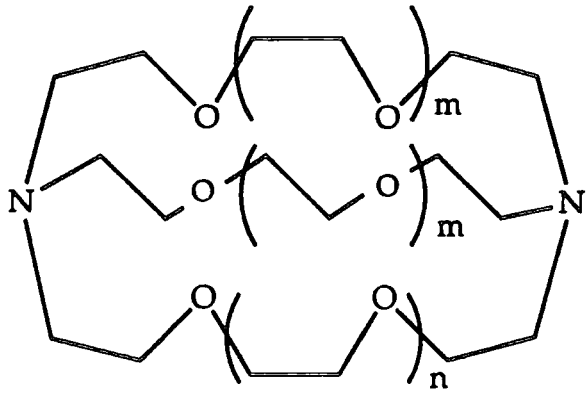
Figure 1.02: Dibenzo-18-crown-6

This compound was found to be only sparingly soluble in protic solvents. However upon the addition of sodium ions the solubility was seen to increase markedly. Pedersen proposed that this was the result of the sodium ions entering the cavity of the crown ether and being held there by an electrostatic interaction between the positively charged cation and the negative dipole charge on the six oxygen atoms.

Following this observation, Pedersen synthesised a range of macrocyclic poly-ethers containing four to ten oxygen atoms and demonstrated that selectivity for a particular cation appeared to depend upon the size of the macrocyclic ring.[11] This is however an over-simplification, and a more detailed discussion of the factors affecting selectivity in such systems is given in section 1.3. The selectivity achieved with simple parent crown ethers is modest, for example, the selectivity for potassium over sodium with 18 crown 6 is only of the order of 40:1. The low selectivity is due to a lack of encapsulation, the crown ether presenting only a "2D" array of binding sites rather than a "3D" encapsulation.

1.2.2 CRYPTANDS

In order to enhance selectivity, Lehn [12] designed and synthesised the macrobicyclic ligands referred to as cryptands, derived from the Greek word *cryptos* meaning cave. These consist of three polyether chains linked together via two bridgehead nitrogens, to provide a 3D intramolecular cavity lined with N and O binding sites. (Figure 1.03).



2 = [2.1.1]: m=0, n=1
3 = [2.2.1]: m=1, n=0
4 = [2.2.2]: m=1, n=1

Figure 1.03: Common Cryptands

Cryptands show enhanced stability and selectivity over comparable monocyclic analogues, for example the potassium complex of [2.2.2] cryptand is 10^5 more stable than that of its monocyclic equivalent diaza 18[N_2O_4]. The reason for this enhanced stability is enthalpic in origin. Less energy is expended in ligand reorganisation prior to complexation than in the more flexible monocyclic systems. Furthermore cations are encapsulated in a three dimensional array and this prevents the interaction of solvents with the encapsulated cation.

However even in the cryptate systems the cavity is relatively poorly defined prior to complexation (Figure 1.04)

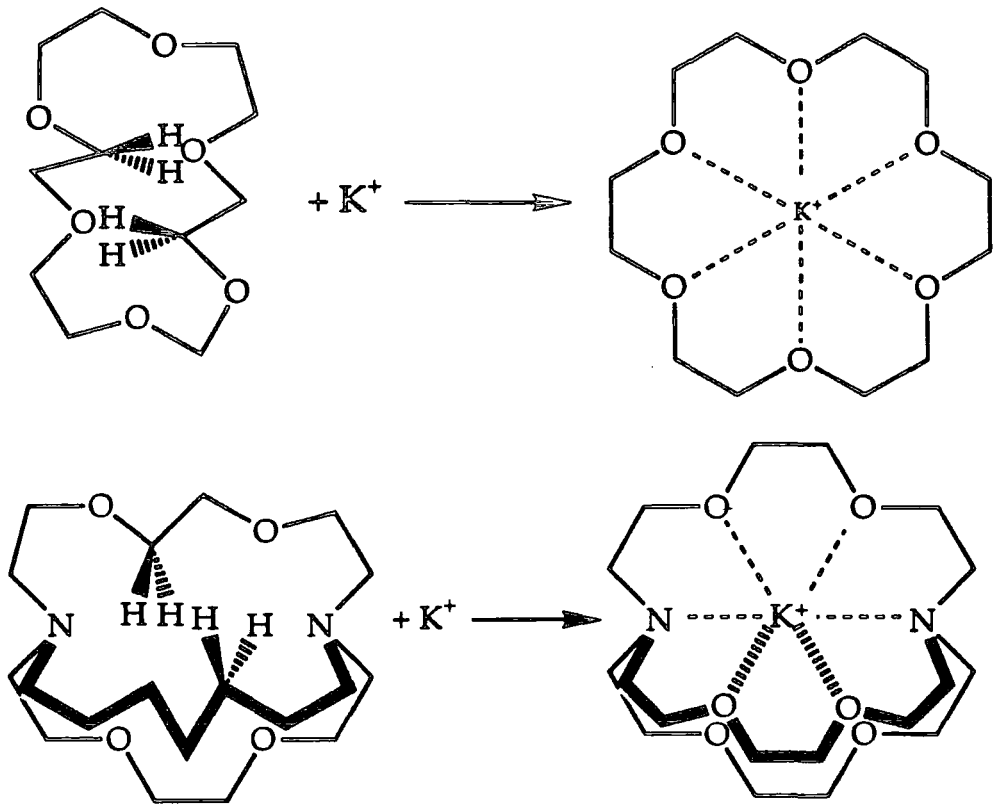


Figure 1.04: Illustration of the lack of a defined cavity with both crowns and cryptands prior to complexation.

1.2.3 SPHERANDS

Unlike the crowns and cryptands, spherands possess a well defined cavity prior to complexation which becomes filled upon complexation. The lone pairs on the oxygen are focused into the centre of the cavity in an octahedral arrangement with the 24 unpaired electrons lining the inside of the cavity.[2, 3, 13]

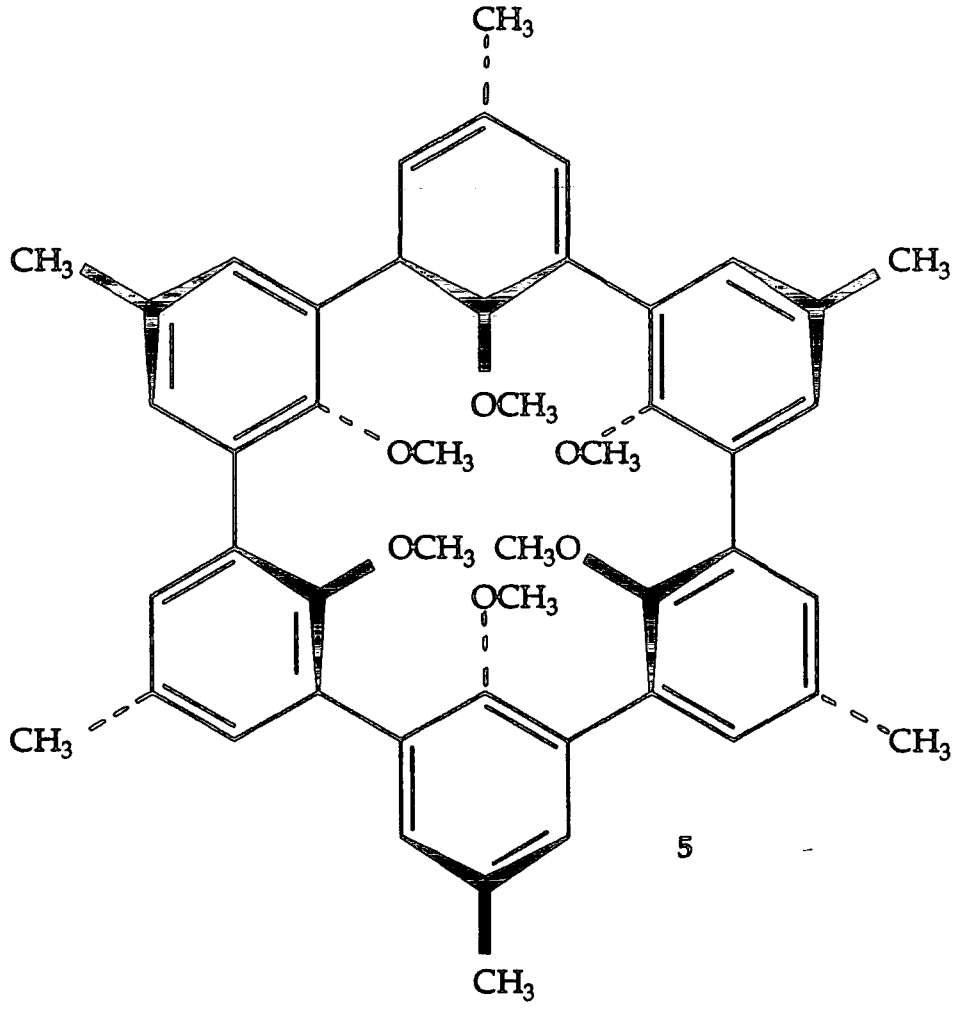


Figure 1.05: Spherand Structure

The rigidity of the cavity is maintained by the benzene rings and the spatial requirements of the methoxy groups. There is very little rotation about the aryl-aryl bond and the methyl groups prevent rotation about the Ar-O bonds. Thus very little reorganisation of the spherand is required prior to complexation. These molecules exhibit the highest stability constants known for many alkali and alkaline earth metal cation complexes and also

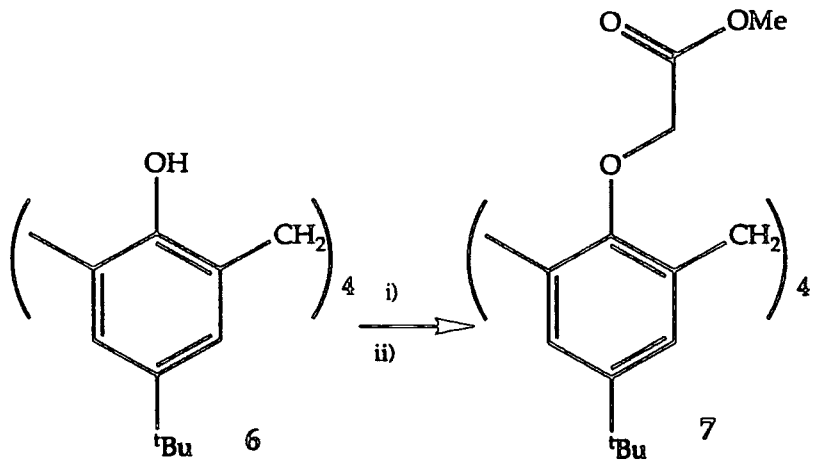
known for many alkali and alkaline earth metal cation complexes and also show very high size exclusion selectivity. For example Spherand 6 (5) exhibits a Li^+ / Na^+ selectivity factor of 600, and will not bind potassium at all. However the use of such ligands is limited because of the slow kinetics of complexation exhibited. In fact, it is often difficult to measure stability constants because the slow dissociation rates prevent the process from reaching equilibrium.

1.2.4 CALIXARENES

The term calixarenes was introduced by Gutsche [14] to describe a homologous series of macrocyclic phenol-formaldehyde condensates. The origin of the term lies in the (cuplike or) chalice like appearance of the smallest member of the series. The complexation properties exhibited by calixarenes are similar to those of spherands and the naturally occurring cyclodextrins. There is also similarity between calixarenes and cyclodextrins in that both can adopt conformations in which several hydroxyl groups are arranged around a central cavity. However calixarenes are insoluble in water.

Recently attention has been focused on the functionalisation of the parent calixarenes particularly the p-*tert* - butyl-calix [N] arenes, the phenol pendant groups of p-*tert* -butyl calix[4]arene (6) being converted to ketones and esters by McKervey *et al* [15] (Figure 1.06).

The resultant structures were found to exhibit high sodium selectivity over potassium and other cations and the methyl ester derivative of calix-4-arene (7) has been used as an ionophore in the construction of a sodium selective electrode.[16, 17]



STEPS i) ethylbromoacetate, K_2CO_3, Acetone
ii) Tosic acid, Methanol

Figure 1.06: Synthesis of the methyl ester tetramer

The sodium ion sits inside the cavity defined by the four ester groups and is held there in an electrostatic interaction with the four ether oxygens and the four ester carbonyls. The calixarene is found to adopt a cone conformation (Figure 1.07).

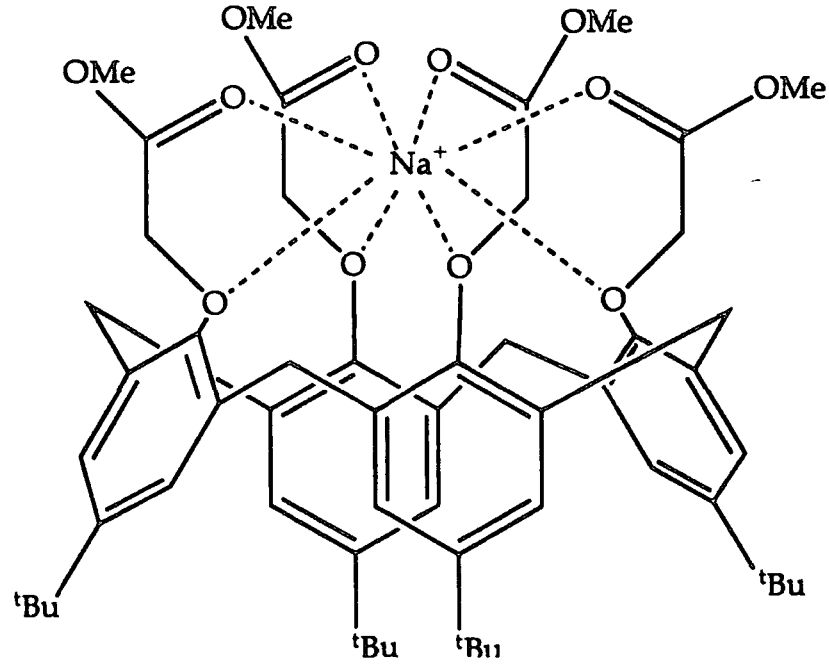


Fig 1.07: Encapsulation of a sodium ion by a tetrameric calixarene ester.

1.2.5 LARIAT ETHERS

In a desire to augment the fast reaction kinetics of the crown ethers with the selectivity seen with the cryptands the idea of attaching side arms to simple macrocycles was devised [5,18,19,20,21,22,23,24]. A monocyclic ligand possessing pivoting ligating side-arms ought to combine the rapid exchange kinetics of the unsubstituted macrocycle with the high selectivity and stability associated with the bicyclic equivalent.

These are characterised by parent macrocyclic ligands functionalised with flexible cation ligating side-arms. These then form three dimensional "psuedo-cryptate" metal complexes via side-arm macroring co-operative binding. Attention has been focused on N-pivot polyaza-polyoxa lariat ethers in the search for discrimination although C-pivot lariat ethers have also been prepared and shown to bind in the same manner (see section 1.3.3 for a detailed discussion). The side-arms have usually incorporated amide donors in order to enhance discrimination in favour of cations with higher charge density, the high ground state dipole moment of amides favouring binding to hard cations. This effect has been utilised to optimise Li^+/ Na^+ selectivity in a C-substituted 14 crown 4 derivative[22] and to enhance the transport of cations using functionalised aza macrocycles [24,25]

As stated earlier many factors influence the binding of macrocyclic polyether analogues to alkali and alkaline earth metal cations and these will now be discussed in detail.

1.3 FACTORS AFFECTING THE SELECTIVITY OF BINDING IN CYCLIC IONOPHORES

1.3.1. THERMODYNAMIC PARAMETERS OF COMPLEXATION

The interaction between alkali and alkaline earth metal cations and ligands can be thought of in terms of electro-static interactions and may be represented by the following equation (1.1.):-

$$M^{n+}_{(s)} + L_{(s)} \rightleftharpoons ML^{n+}_{(s)} \qquad (1.1)$$

where M^+ = metal cation

L = ligand

(s) = solvent

The equilibrium stability constant (Ks) can thus be defined as :-

$$Ks = \frac{[ML^{n+}]}{[M^{n+}]\,[L]} \qquad (1.2)$$

where $[ML^{n+}]$ = concentration of complex at equilibrium.

$[M^{n+}]$ = free cation concentration " "

$[L]$ = free ligand concentration " "

The relationship between the equilibrium stability constant and the free energy change associated with complexation, ΔG°, is given by equation 1.3:-

$$\Delta G^\circ = -RT \ln K_s \qquad (1.3)$$

The free energy term itself can be expressed in terms of the corresponding enthalpy and entropy changes using the Gibbs-Helmoltz equation (1.4):-

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \qquad (1.4)$$

There are four possible combinations of $T\Delta S^\circ$ and ΔH° which lead to the formation of stable complexes ($\Delta G^\circ < 0$).

(a) $\Delta H < 0$ (dominant), $T\Delta S > 0$

(b) $\Delta H < 0$ (dominant), $T\Delta S < 0$

(c) $\Delta H < 0$, $T\Delta S > 0$ (dominant).

(d) $\Delta H > 0$, $T\Delta S > 0$ (dominant).

In the first two equations the complexation process is enthalpy driven, whereas in equations (c) and (d) the reactions are entropically favoured. In the following sections the influence upon complexation of several factors will be considered in terms of enthalpic and entropic contributions. The actual techniques used in the determination of such parameters can be found in section 1. 4.

1.3.2. MACROCYCLIC AND CRYPTATE EFFECT

The stability of a metal cation/ ligand complex is found to increase in the progression:-

monodentate < acyclic < monocyclic < bicyclic.

These increases in stability can be explained in terms of the chelate effect (monodentate to acyclic) [26], macrocyclic effect and the cryptate effect. Of these, the latter two are of particular interest to the macrocyclic chemist.

The increase in stability seen when an open chain ligand is replaced by a macro-ring analogue was first noted by Cabbiness and Margerum [27] and

given the term macrocyclic effect They compared the stability constants of the Cu^{2+} complex of the acyclic ligand (9) with that of the macrocyclic analogue (8) and noted an increase in stability of the order of 10^4 (Figure 1.08).

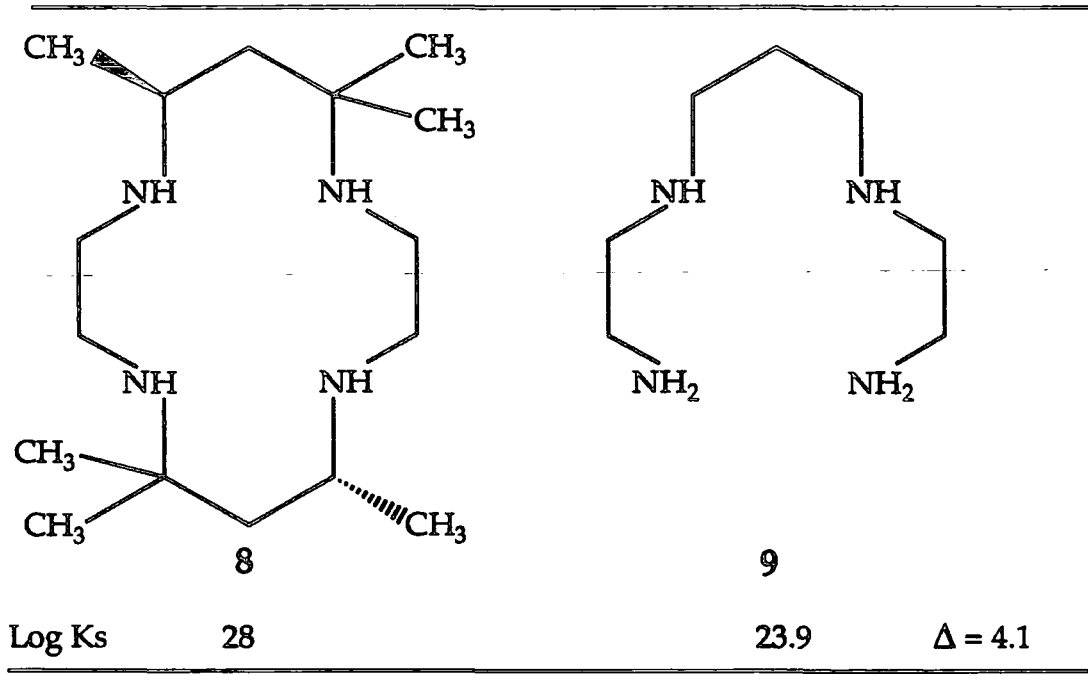
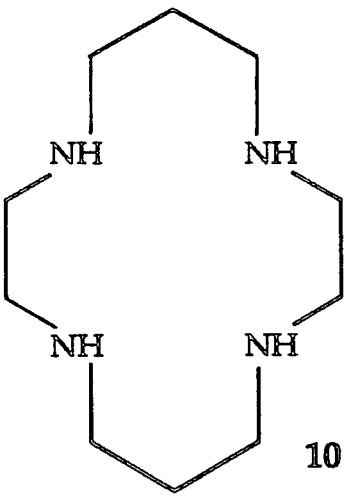


Figure 1.08: Influence of the macrocyclic effect upon the stabilities of 1:1 Copper (II) : tetraamines in water.

Further studies were then performed in order to ascertain the origin of the enhanced stability of the macrocyclic complex. The macrocyclic ligand **(10)** forms a complex with nickel (II), the stability constant of which is $>10^6$ of that displayed by its acyclic analogue **(9)**[28]. The dominant effect was seen to be enthalpic in origin (Figure 1.09); in fact entropy favours complexation with the acyclic ionophore. The difference in reaction enthalpy arises from the fact that the macrocyclic ligand requires significantly less energy to be desolvated prior to complexation.



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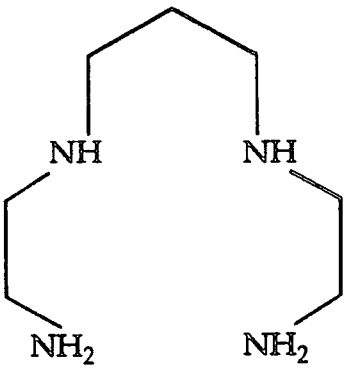

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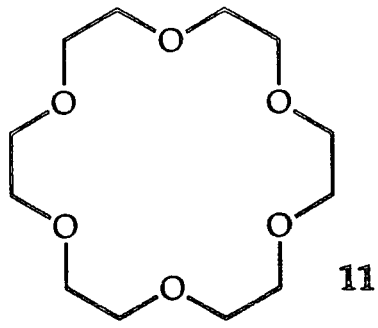
	10	9	Macrocyclic Effect
Log Ks	22.2	15.3	Δ = 6.9
$\Delta H°$/ KJmol^{-1}	-130	-70.3	Δ = -59.7
$\Delta S°$ / KJmol^{-1}	-8.4	57.7	Δ = -66.1

Figure 1.09: Influence of the macrocyclic effect upon the stabilities, in water.

However further work on the influence of the macrocyclic effect upon the thermodynamic parameters of a series of tetra-aza macrocycle / copper (II) complexes [29] complicated the picture somewhat as it indicated that ring size was also an important factor. For smaller rings in which large conformational changes occur upon complexation, entropic factors become dominant. The stereo-chemical factors associated with ligands of this nature make it very difficult to assign any stability enhancement to a macrocyclic effect, because of the difficulty in finding macrocyclic and related acyclic structures which are sufficiently similar in structure to allow reliable comparisons.

A study of alkali and alkaline earth metal / crown ether complexes is preferential since the cations impose less stereo-chemical demands than transition metal ions. Haymore *et al* [30] studied the thermodynamic parameters of complexation of the macrocycle 18 crown 6 **(11)** and its acyclic analogue **(12)** for complexation with a range of cations (figure 1.10.). The

results indicate that the major contribution to enhanced stability was enthalpic, although for potassium and barium, entropy also favoured macrocyclic complexation.



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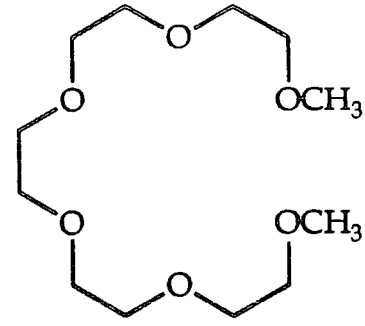

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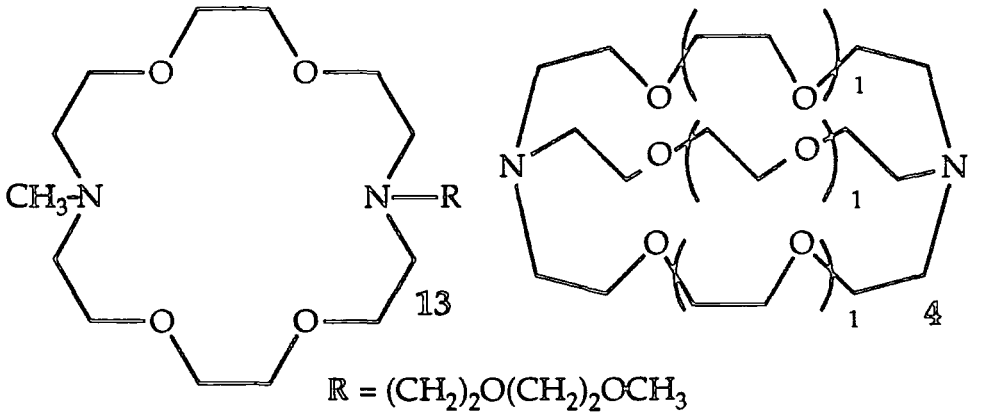
cation	ligand	Log Ks	ΔH° (KJmol^{-1})	ΔS (JK^{-1} mol^{-1})
	11	4.36	-35.0	-33.8
Na^+	12	1.44	-16.8	-28.9
macrocyclic effect		Δ = 2.92	Δ = -18.2	Δ = -4.9
	11	6.06	-56.1	-72.1
K^+	12	2.1	-36.4	-81.4
macrocyclic effect		Δ = 4.0	Δ = -19.7	Δ = 9.3
	11	7.04	-43.6	-11.2
Ba^{2+}	12	2.3	-23.2	-33.7
macrocyclic effect		Δ = 4.7	Δ = -20.4	Δ = 22.5

Figure 1.10: Influence of the macrocyclic effect upon the stabilities, enthalpies and entropies of complexation of 18 crown 6 in comparison with pentaglyme .

When the stability constants of monocyclic complexes are compared to macrobicyclic analogues (cryptates) a large increase is observed. This has been termed the **cryptate** effect [31] . For instance a comparison of 2,2,2 cryptand **(4)** with its diaza-crown analogue **(13)** revealed an enhancement in stability of the order of 10^4 to 10^5 (Figure 1.11).



CATION	13	4
Na^+	3.26	7.21
K^+	4.38	9.75

Figure 1.11: Stability constants (Log Ks) values in methanol/ water (95:5) for sodium and potassium complexes of monocyclic and bicyclic ligands.

1.3.3 EFFECT OF RING SIZE:- CAVITY SIZE- CATION SIZE CORRELATION

The correlation between cavity size and cation size is not as well defined for crown ethers as in other more rigid preorganised structures such as spherands. However monocyclic ionophores show peak selectivities in Log Ks values and these have been used to provide an estimate of the cavity dimensions using the radii of the cations which form the strongest complexes. Although this approach is simplistic, the data collated in Table 1.01 does seem to indicate that, with the help of CPK models, some simple crown ethers do indeed show a partial correlation between cavity radius and cation radius [32]. However this approach is too simplistic and fundamentally flawed in that it fails to take into account that the number of donor atoms also varies directly with the cavity size.

Ligand	cavity radius/Å CPK models	ion of maximum log Ks value	cation radii (Å)
12-crown-4	0.6	Na^+	1.02
15-crown-5	0.85	Na^+, K^+	1.02,1.38
18-crown-6	1.3	K^+	1.38
21-crown-7	1.7	Rb^+	1.49

Table 1.01: Cavity Radii of crown ethers.

A more detailed study performed by Gokel *et al* [33] contradicted the notion of a cation diameter/ cavity size correlation. He recorded the binding constants for a series of crown ethers (14) to (18) with a range of cations, Na^+, K^+, NH_4^+ and Ca^{2+} and found that K^+ was bound more strongly by all the crowns and that all cations exhibited their highest binding constants with 18 crown 6.

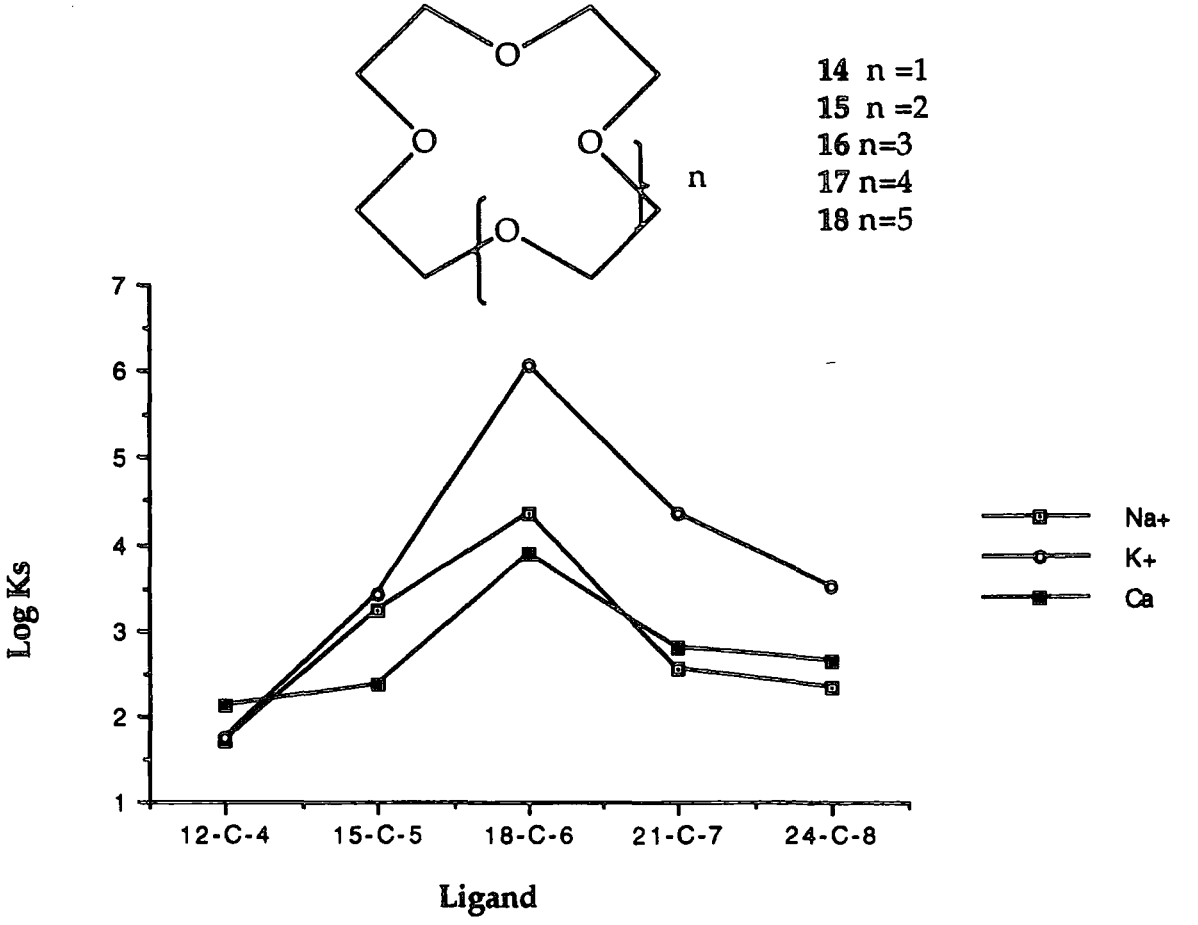


Figure 1.12:-Profile of Cation Binding by simple crowns

These findings were mirrored by Michaux and Reisse [34] who also concluded that no correlation existed between cavity and cation size.

It appears therefore that although hole size correlation may make some minor contribution to cation binding, the flexible nature of the ligands allows them to adopt conformations suited to the binding of a range of cations of varying radii and thus other factors contributing to cation binding will predominate. Furthermore the fact that the highest binding constants for cations for simple crown ethers are observed for 18 crown 6 can be surmised to be due to the fact that the optimum number of donor atoms for the cations examined is six.

Although the actual cavity size is not a predominating factor in the binding of cations, the size of the ring becomes an important factor when the size of the chelate rings formed upon complexation are considered. Molecular mechanics calculations performed by Hancock [35,36] indicated that the size of chelate rings formed upon complexation play an important role in determining the strain involved in the subsequent complexes and thus their stability. The formation of six-membered ring chelates is favoured when binding small cations because the hydrogen atoms can adopt a staggered conformation (see Figure. 1.13) [37]

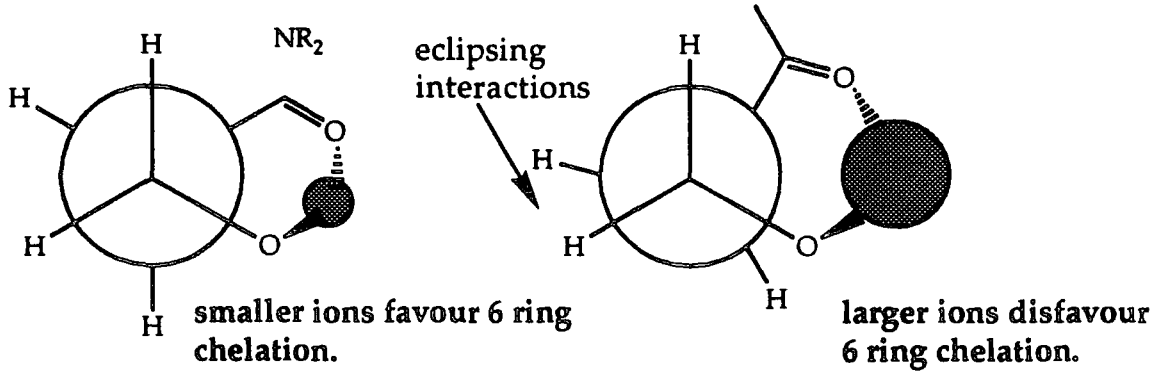
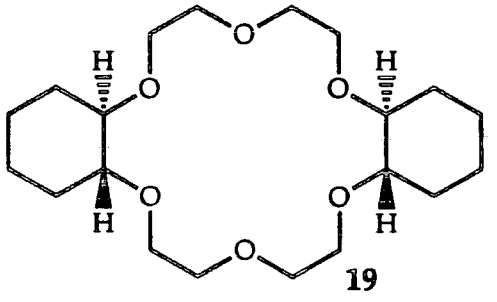


Figure 1.13:- Preference of small cations to form 6 ring chelates upon complexation.

When larger cations are held in a 6 ring chelate the hydrogens become eclipsed and strain is introduced into the structure. With 5 ring chelates staggering is not possible and the effect is less marked.

The conformation of the macrocycle prior to complexation can also significantly influence the complexation characteristics displayed by the ligand. For example dicyclohexane 18-crown-6 can adopt any one of five different stable conformations [38] (Figure 1.14).



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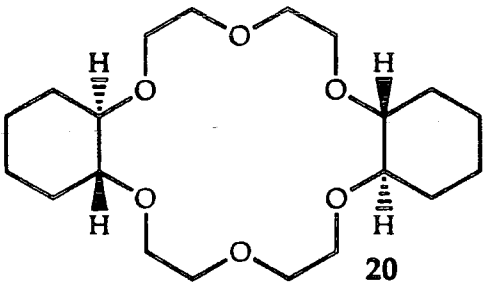
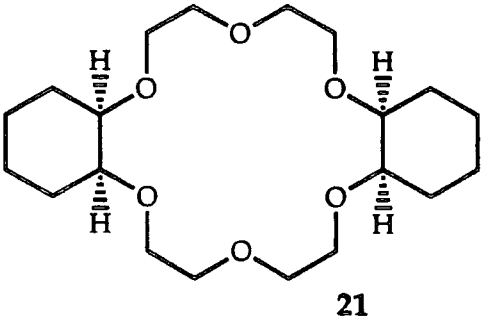
trans,syn,trans



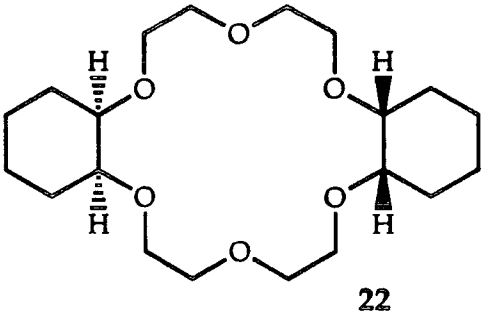
20

trans,anti,trans



21

cis, syn, cis



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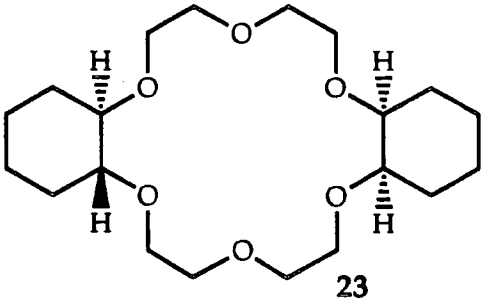
cis, anti, cis



23

trans, cis

Figure 1.14: Five possible stereo isomers of dicyclohexane 18-crown-6.

A study of the complexation characteristics of these diastereomers revealed a considerable difference in terms of binding strengths (Table 1.02). The data, illustrated below, indicated that the trans isomers formed weaker complexes with alkali metal cations than the corresponding cis isomers . Furthermore the syn isomer was favoured over the anti. The reason for these differences lies in the orientation of oxygen donors prior to complexation, the trans isomers requiring considerably more structural reorganisation prior to complexation, resulting in an unfavourable enthalpy term. X-ray crystallographic studies confirmed this hypothesis,[39] showing that the conformational orientation of the trans-anti-trans stereo isomer was such that only one oxygen atom was pointed towards the centre, whereas the cis-syn-cis isomer had all six oxygens focused into the cavity.

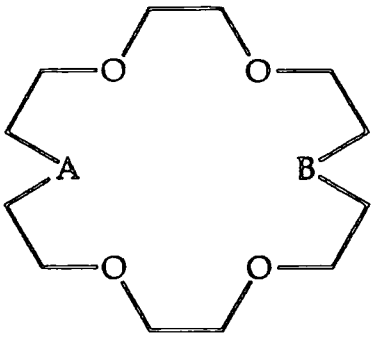
Ligand	Na^+	K^+	Rb^+	Cs^+
18-crown-6	4.32	6.10	5.35	4.70
cis -syn-*cis* isomer	4.08	6.01		4.61
cis -anti-*cis* isomer	3.68	5.38		3.49
trans -syn-*trans* isomer	2.99	4.14	3.42	3.00
trans -anti-*trans* isomer	2.52	3.26	2.73	2.27

Table 1.02 Stability constants (log Ks) values for complexation of 18-crown-6 and the stereo-isomers of dicyclohexano-18-crown-6 with alkali metal cations in methanol 25° C.

1.3.4. NATURE OF DONOR ATOMS

Alkali and alkaline earth metal cations can be classified as hard Lewis acids. Hard cations interact most favourably with hard donors such as oxygen and therefore cations in this group interact most strongly with oxygen containing donor groups. Frensdorff and others[40,41,42] studied the effect of replacing oxygen by nitrogen and thio ether donors for a fixed ring

size and recording the stability constants of the subsequent ligands with potassium in methanol (Table 1.03).

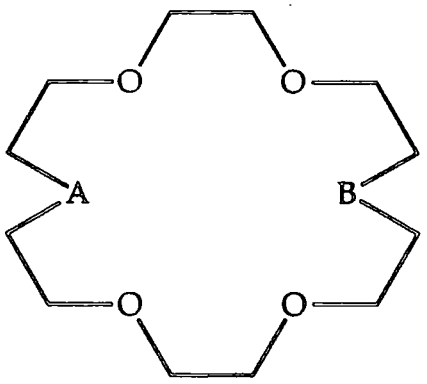


Ligand		Cation (log 10 K)			
A	B	Na^+	K^+	Ag^+	Pb^{2+}
O	O	4.38[a]	6.10[b]	4.58[c]	6.99[g]
NH	O	2.69[d]	3.90[b]	n/d	9.11[e]
NH	NH	1.0[b]	2.04	10.02	9.48[e]
S	S	n/d	1.15	10.33[f]	4.76[g]

[a] reference 34, [b] ref 41, [c] ref 45, [d] ref 42, [e] ref 43, [f]ref 46, [g]ref 47.

Table1.03:- The effect of substituting ether donors with amine and thio ether donors in 18 membered rings and the subsequent effect upon the stability of complexation with a range of cations, in methanol.

The replacement of oxygen by nitrogen[43] or sulphur led to a strong destabilisation of the complexes formed with potassium and sodium. This is partly due to less favourable enthalpic changes upon complexation, i.e. nitrogen and sulphur interact poorly with the hard potassium and sodium cations. However softer cations such as silver and lead interact more favourably with the diamino and di-thio ether derivatives. The extent to which the enthalpy of complexation for the potassium ion is decreased as the nature of the ligand is modified and is illustrated below in Table 1.04 [44,45,46,47] .



POLYETHER		ΔH
A	B	kJ mol^{-1}
O	O	-54.9
NH	NH	- 4.7
O	S	-37.7
S	S	----

Table 1.04: The effect of substituting amine and thio ether groups for ether donors in 18-crown-6 upon the enthalpy of complexation with K^+ in methanol at 25°C.

The strength of the binding interaction between a cation and a donor atom is linked to the electron density at the donor atom. This will be largely determined by the dipole moment possessed by the donor atom and the higher the dipole moment the more electron density will lie on the donor and hence the more favourable the interaction with the hard cation, since the positive charge can be dissipated more effectively. Thus the incorporation of an electron withdrawing group such as a benzo group in place of an ethylene group in 18 crown 6 will result in a reduction in electron density at the two oxygen atoms attached to this sub-unit, and correspondingly a reduction in the stability of the complex formed (Table 1.05).

The only exceptions to this are the sodium complexes. The smaller size of the sodium cation prevents its optimal accommodation within the macrocycle and thus complexation is aided by the increased rigidity resulting from the incorporation of the benzo group.

Ligand	Na^+	K^+	Rb^+	Cs^+	Ag^+	Tl^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
18C6	4.32	6.10	5.35	4.62	4.58	5.16	3.86	>5.5	7.0
B18C6	4.35	5.20	4.62	4.05		4.60	3.50	4.92	5.35
$B_2$18C6	4.36	5.00	4.23	3.55	4.04	4.00		3.55	4.28

Table 1.05:- Stability constants (log Ks) of metal ion complexes with 18 crown 6, benzo 18 crown 6 (B18C6) and dibenzo 18 crown 6 ($B_2$18C6) in MeOH [48].

The highest dipole moments are possessed by amides and their use as complementary side arm donors to ring systems will be covered extensively in chapter 3 of this thesis.

1.3.4. NUMBER OF DONOR ATOMS

In order to optimise binding the number of donor atoms must match the co-ordination number of the cation in order to ensure that binding sites can replace all co-ordinated solvent molecules. Table 1.06 lists the co-ordination numbers of several alkali and alkaline earth metal cations.

CATION	CO-ORDINATION NUMBER	CATION	CO-ORDINATION NUMBER
Li^+	4, 6	Mg^{2+}	6
Na^+	6	Ca^{2+}	6, 8
K^+	6	Sr^{2+}	8
Rb^+	6, 8	Ba^{2+}	8, 9
Cs^+	8		

Table 1.06: Common Co-ordination numbers of Alkali and Alkaline Earth metal cations.

Buschmann[44, 46] studied the enthalpies of complexation of a series of cations with a range of simple oxa crown ethers and ascertained that when the number of donor atoms present in the ligand was less than the co-ordination number of the cation, the enthalpies displayed were less than that displayed by 18-crown-6 (Figure 1.15).

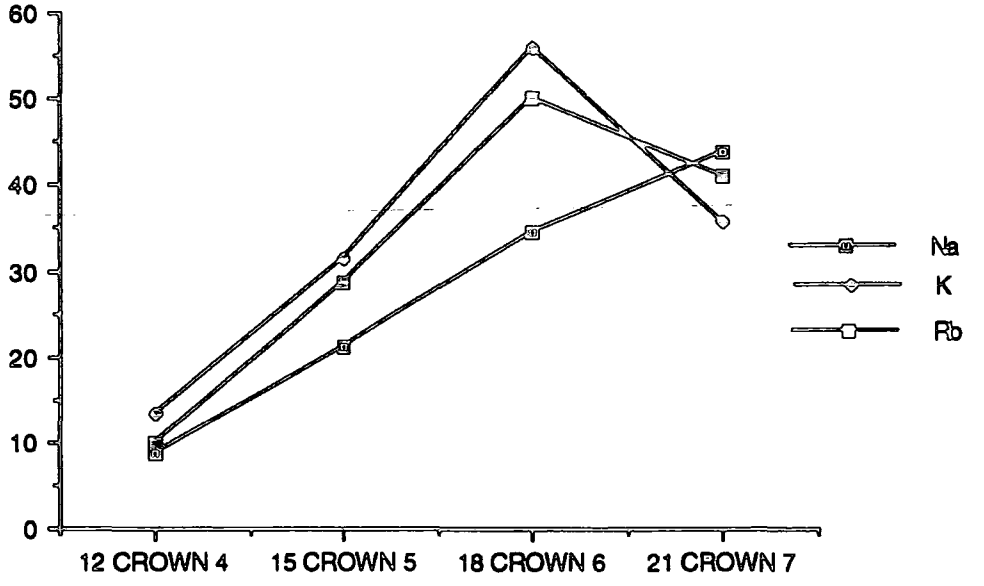


Figure 1.15:- Enthalpy of complexation for a series of crown ethers with Alkali metal cations.

Interestingly the enthalpy of complexation displayed by the 21 crown 7 / sodium complex was seen to be greater than that displayed by 18 crown 6 indicating a greater cation/ donor interaction. However the stability constant for this complex is lower than that of 18 crown 6 with sodium. Thus it can be surmised that although a larger cation/donor interaction is possible with 21 crown 7 this is offset by an unfavourable enthalpy term associated with ligand reorganisation.

1.3.6. INFLUENCE OF CATION AND LIGAND SOLVATION UPON COMPLEXATION

Ion Solvation:-

The strength of ion-solvent interactions is a crucial factor in determining both the stability and the kinetics of complexation. The solvation energies involved are very large, of the order of hundreds to several thousands of kilojoules per mole. The extent of the solvation is dependent upon the nature of the solvent and although the differences from solvent to solvent are small compared to the absolute value, nevertheless they are sufficient to exert considerable influence upon the strengths of complexation.

Ligand Solvation:-

Although the extent of ligand solvation may be small in comparison to that of the cation it still exerts a significant influence on the strength of complexation. Again as with cation solvation the extent of solvation is solvent dependent. The complexation of a cation with a ligand results in the displacement of solvent molecules. This process of desolvation is energetically "expensive" and results in an unfavourable enthalpy term , although this effect is counter-balanced by a favourable entropy term.

The enthalpy term is greatly influenced by the nature of the solvent: the higher the dielectric constant the solvent possess the greater the energy expended on desolvation. Thus enthalpies of complexation are significantly lower when recorded in water than in a less polar solvent such as methanol. Table 1.07 illustrates this point, the potassium and sodium complexes of 18 crown 6 can be seen to possess much lower enthalpies in water than in methanol.

Structural features present in a ligand can also significantly influence enthalpies and entropies of complexation and a detailed discussion of the influence of H bonding upon such parameters can be found in chapter 3.

LIGAND	SOLVENT	CATION	ΔH (KJ mol^{-1})
18 crown 6	H_2O	Na^+	-9.41
"	H_2O	K^+	-26.00
"	MeOH	Na^+	-31.38 [34]
"	MeOH	K^+	-53.14 [34]

Table 1.07:- Enthalpies of complexation of 18 crown 6 with sodium and potassium both in water and methanol.

1.3.7 THE ANION EFFECT

Depending upon the nature of the anion and the solvent involved, the anion can significantly influence the complexation process:-

(1) The nature of the anion, its size, shape and polarisability will effect the strength of the cation/anion association. Small anions tend to associate more strongly with the complex than larger anions as a result of the shorter complex-anion distance.

(2) The nature of the solvent; In solvents such as water with a high dielectric constant both the complex and the counter-ion are heavily solvated and little interaction occurs. By contrast, in less polar solvents, solvation is poor and ion-pairing and/or aggregation can occur. When such associations do occur it can be thought of in terms of the formation of a new complex (equation 1.5).

$$ML + X \rightleftharpoons MLX \qquad \text{(eqtn 1.5)}$$

where ML = metal-ligand complex.
X = counter-ion.
MLX = Association complex.

Not only does the counter-ion influence the strength of the complex, it also effects the solvation properties of the complex. If the counter-ion is a

large organic anion then the solubility of the complex may be seen to increase.

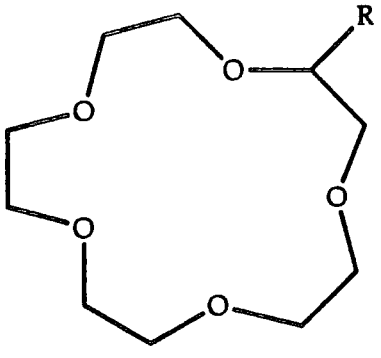
1.3.8 EFFECT OF THE ADDITION OF LIGATING SIDE ARMS

Greater binding strengths and selectivities can often be achieved by the incorporation of side-arms possessing ligating functional groups, provided the spatial orientation of the side arms allows the functional groups to locate at a suitable distance from the metal centre.

1.3.8.1 C-pivot Lariat ethers

Gokel [49,50] has synthesised a series of structures based upon a simple 3n crown n macroring incorporating a flexible ligating side arm in order to ascertain the effect of such donor arms upon cation binding strengths.

In this series the side arm is attached directly to the macroring about a carbon atom pivot, **(25)** to **(30)**. Extraction studies were performed in a CH_2Cl_2 / H_2O system at 25° C using both sodium and potassium picrate salts (Table 1.08)



LIGAND	Na^+	K^+
(25) R = H	7.6	5.7
(26) R = CH_2OMe	5.1	3.3
(27) R = $CH_2O(CH_2)_2OMe$	18.0	13.7
(28) R = $CH_2(OCH_2CH_2)_2OMe$	15.7	24.4
(29) R = $CH_2OC_6H_4OMe$ (para)	6.4	
(30) R = $CH_2OC_6H_4OMe$ (ortho)	15.7	

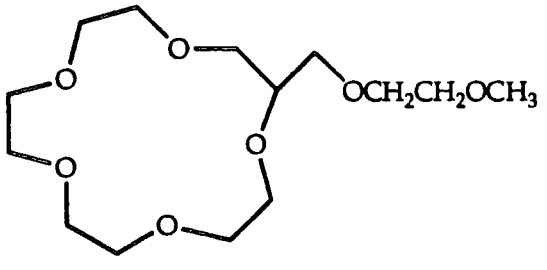
Table 1.08:- Extraction coefficients for a series of C-pivot lariat ethers with sodium and potassium picrates at 25° C (dichloromethane / water).

The position of the donor atom in the side chain was found to be critical. With derivative **(26)** the side arm ether oxygen is sterically prevented from binding to the cation and furthermore it also inhibits the

access of the cation to the macro-ring resulting in diminished binding compared to the unsubstituted derivative (25). The need to have the required side arm donor orientation is even more vividly illustrated with a comparison of the ortho and para methoxyphenoxymethyl side armed derivatives (29) and (30). The ortho substituted ligand was found to show a greatly enhanced extraction coefficient in comparison to the para derivative. CPK models had in fact indicated that the ortho derivative was capable of interacting with the ring bound cation and that the para could not.

Studies by Okahara *et al* [51,52] further complicated the picture; showing that replacing the hydrogen atom at the C-pivot position with a methyl group significantly enhanced binding strength. When the side-arm is $CH_2OCH_2CH_2OCH_3$ (27) the H substituted derivative exhibited a Log Ks $_{(Na)}$ = 3.01, however the derivative possessing a geminal methyl group displayed a Log Ks $_{(Na)}$ = 3.48. It is believed that this enhanced binding is as a result of a conformational effect, the methyl group "fixing" the conformation of the ligand prior to complexation in a conformer which favours binding. Such an effect may be related to the original Thorpe-Ingold (or gem-dimethyl) affect.

^{13}C NMR relaxation time solution studies also offered an insight into the strengths and dynamics of cation binding displayed by such C-pivot lariat ethers [53] . The change in relaxation time, T_1, reflecting the change in motility of the ligand upon complexation.



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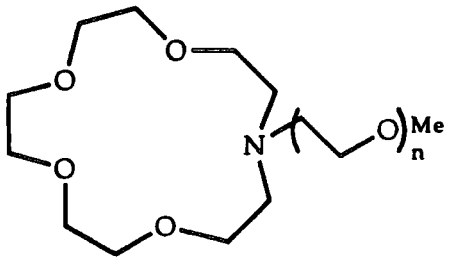
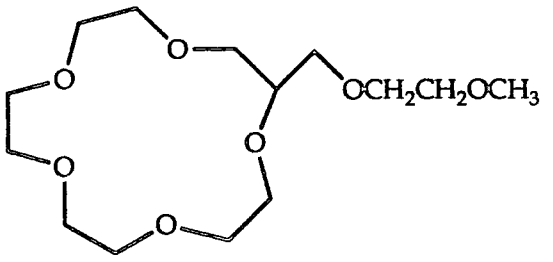


31 n = 1
32 n = 2



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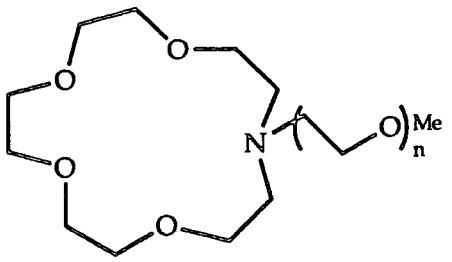
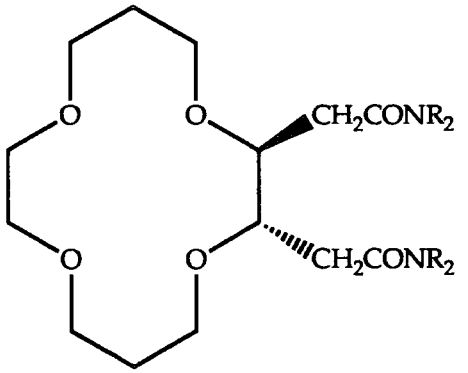


31 n = 1
32 n = 2

For the C-pivot lariat ether (27) a reduction in T_1 of 42% was observed for the ring carbon. However for the N-pivot lariats (31) and (32) a much smaller reduction in T_1 was observed, indicating a much smaller reduction in ring motility upon complexation than that seen for the C-pivot lariats. In addition the sodium binding constants of the N-pivot lariat ethers are larger than those for the C-lariat analogue. Thus it can be surmised that N-pivot lariat ethers offer enhanced flexibility over the C-pivot counterparts and generally exhibit higher binding constants . However provided that the lack of flexibility of the C-pivots can in some way be circumvented then these structures can offer valuable alternatives to N-pivot structures particularly as ionophores, since the pH sensitivity of N-pivots occludes their use. Parker *et al* [22] avoided the problem of flexibility in such structures by designing a lithium sensor based upon a chiral 14 crown 4 sub-structure (33)



(33)

By the incorporation of a chiral sub-unit into the ring it is possible to build the required donor arm stereo chemistry into the ligand and thus the lack of flexibility about the C-pivot becomes beneficial in that the donor arms are effectively locked in position.

being sterically hindered by the side arm, as the side arm can simply flip out of the way.

A series of 12, 15 and 18 membered ring N-pivot lariat ethers having a $(CH_2CH_2O)_nCH_3$ side arm were studied by Gokel [55,56] . He measured the stability of complexation of these monoaza crowns with sodium in methanol and plotted the values determined against the number of available oxygen donor atoms.

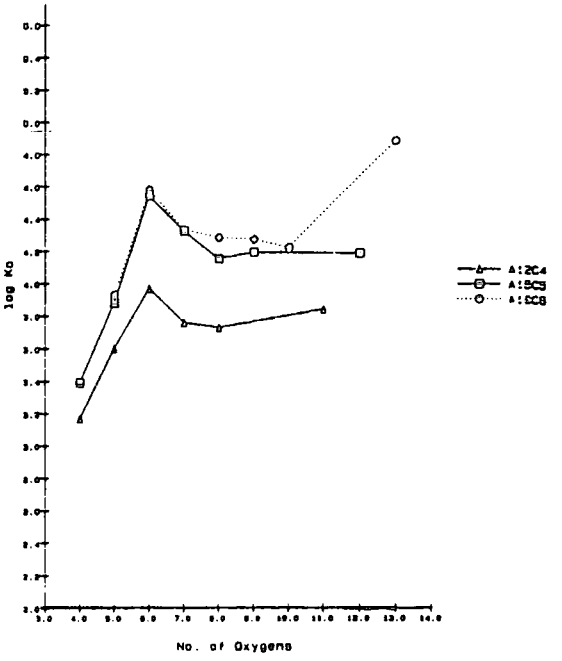


Figure 1.16:-Plot of Stability constants for sodium complexation for a range of mono-aza crowns of differing ring size in methanol, using a sodium I.S.E. (25°C).

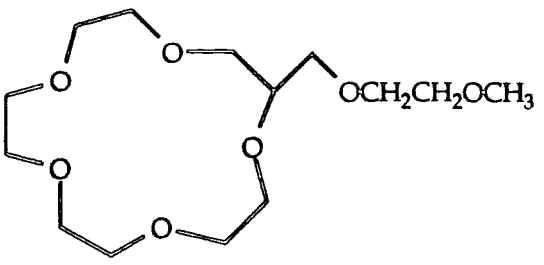
Peak binding for sodium was observed when six oxygen donor atoms were present in the ligand independent of ring size. This suggests that these ligands are sufficiently flexible to allow them to adopt the optimal conformation for binding sodium in which six donor atoms are located at a suitable distance from the metal ion centre.

Gokel suggested that the data indicated that the nitrogen atom is redundant as a donor in such systems and plays no part in ligating the cation. This is however unlikely, it is more probable that the nitrogens do in

fact ligate the cation, but to a much lesser extent than the ether donors also present.

As well as the strength of binding, the dynamics of cation complexation are of paramount importance in determining the use of such ionophores as cation carriers, rapid exchange being vital in such cases. It is possible to determine exchange rates using NMR techniques and Gokel *et al* [53] used such a technique based upon ^{23}Na NMR. He compared line widths as a variant of temperature for two related N-pivot and C-pivot lariat ethers (Table 1.09).

If sharp lines are retained at low temperatures this is indicative of rapid cation exchange; slow exchange is accompanied by significant line broadening at low temperatures. Thus it can be clearly seen from the data listed above that N-pivot lariats exhibit faster exchange rates than C-pivot lariats, as considerably less line-broadening is observed at lower temperatures.



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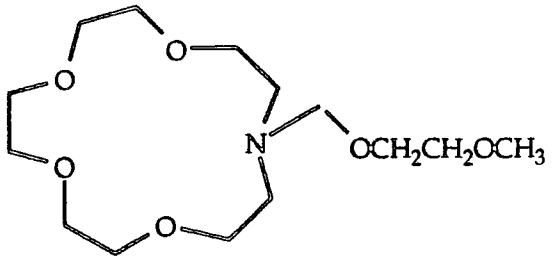


31

TEMPERATURE (°C)	LINE WIDTHS ($\omega_{1/2}$, Hz)	
	27	31
25	96	58
0	202	87
-25	587	190
-50	≈2500	490
-75	>2500	≈1300

Table 1.09:- ^{23}Na Relaxation times of sodium complexes of C-pivot and N-pivot lariat ethers recorded in methanol : D_2O (9:1)

The scope of these investigations was extended further by the study of two armed lariat systems possessing differing secondary donor groups Gokel referring to these structures as **bibracchial lariat ethers** from the Latin term **bracchium** meaning "arm". The question posed by these structures was whether the two arms would interact from the same or opposite sides. Crystallographic studies [20,54,57], revealed that for sodium N, N'-bis (2-methoxyethyl)-4,13-diaza-18-crown-6 (34) iodide monohydrate a syn conformation is adopted with the macro-ring donor atoms adopting a "twist-boat" conformation. The oxygen atom in each side-arm occupies a "flag-pole" position, with the sodium atom lying on the line connecting the two nitrogens. This is represented below in skeletal form (Figure. 1.17)

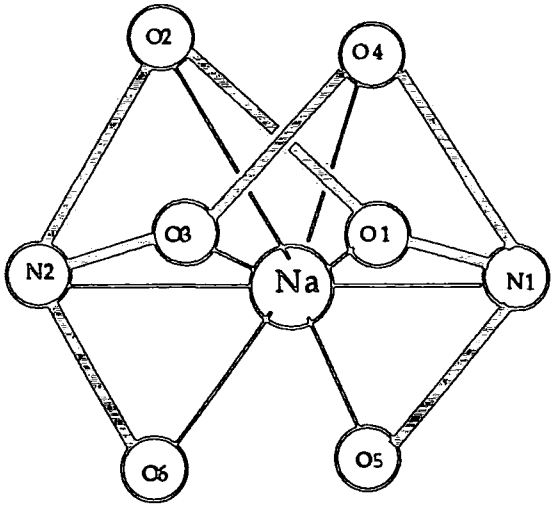


Figure 1.17:- Skeletal representation illustrating the sodium complex of **(34)**

All ligands similar to **(34)** have been found to adopt this syn conformation when complexed to sodium. With potassium the situation is not as straight-forward, although the cryptate like conformation is favoured, the larger steric bulk of the potassium cation can sterically prevent the adoption of such a conformation and thus the less favoured anti conformation is adopted (Figure 1.18).

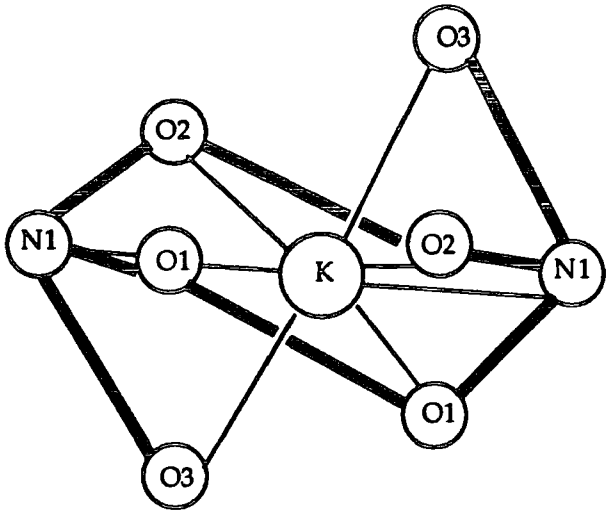
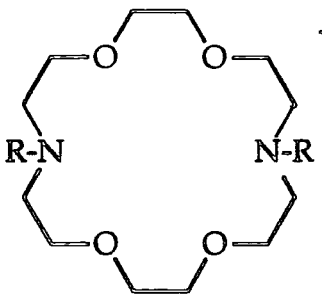


Figure 1.18:- Skeletal representation of KI complex of **(34)** illustrating D3d conformation

Gokel[54] synthesised several such 'BIBLE's' **(35)** - **(38)** the nature of the side arm donor being the variable factor (Table 1.10)



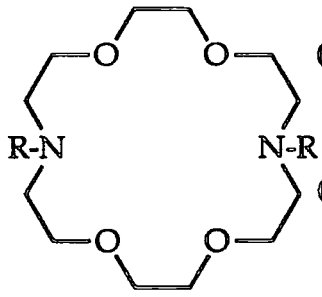
LIGAND	Na	K	Ca
(35) R = H	1.5	1.8	
(36) R = CH_2CH_2OMe	4.75	5.46	4.48
(37) R = CH_2CH_2OH	4.87	5.08	6.02
(38) R = CH_2COOEt	5.51	5.78	6.78

Table 1.10: Stability constants for a series of N-pivot BIBLE's complexed with sodium, potassium and calcium ions in Methanol at 25° C.

From the data it is apparent that the addition of side-arms significantly enhances the binding strengths displayed by the ligand. It is also important to note the effect the nature of the donor groups present in the side-arms has upon complexation characteristics. For a cation possessing a high charge density, such as calcium, the stability constant displayed by the ester derivative (38) is significantly higher than that exhibited by the ether derivative (36). This is undoubtedly due to the higher dipole moment possessed by the ester group which slightly favours the binding of high charge density cations. This effect is further enhanced by the incorporation of amides into the side-arms and has been used to optimise Li^+ / Na^+ selectivity in a C-pivot 14-crown-4 derivative [22].

Further studies have been performed in order to ascertain the thermodynamic basis for this enhanced stability. Determinations of the complexation enthalpy and entropy values were performed on a series of N-pivot BIBLE's with various ligating side-arms in complexation with sodium and potassium[57] (Table 1.11).

The data clearly indicated that the enhanced stability of such ligands was enthalpic in origin.



LIGAND	Cation	LogKs	ΔH (Kcal mol^{-1})	TΔS
(39) R = $(CH_2)_3$	Na^+	2.86	-2.82	1.08
	K^+	3.77	-6.28	-1.14
(37) R = CH_2CH_2OH	Na^+	4.83	-5.82	0.76
	K^+	5.07	-8.80	-1.89
(38) R = CH_2COOEt	Na^+	4.77	-7.24	-0.73
	K^+	5.52	-8.81	-1.28

Table 1.11:- Thermodynamic parameters for the complexation of a series of N-pivot BIBLE's with sodium and potassium in methanol.

Gokel [20,18], reasoned somewhat optimistically that these structures could be used to provide models for the natural ionophore valinomycin. Valinomycin (Figure 1.19) is a 36 membered ring of alternating amino and hydroxy acids. Thus it possesses alternate amide and ester carbonyl donor groups. Each of the amino or hydroxy acids possesses a side-chain. Thus nine-isopropyl and three methyl groups are present on the periphery. The presence of these hydrophobic chains is important since valinomycin must be able to cross a hydrophobic membrane.

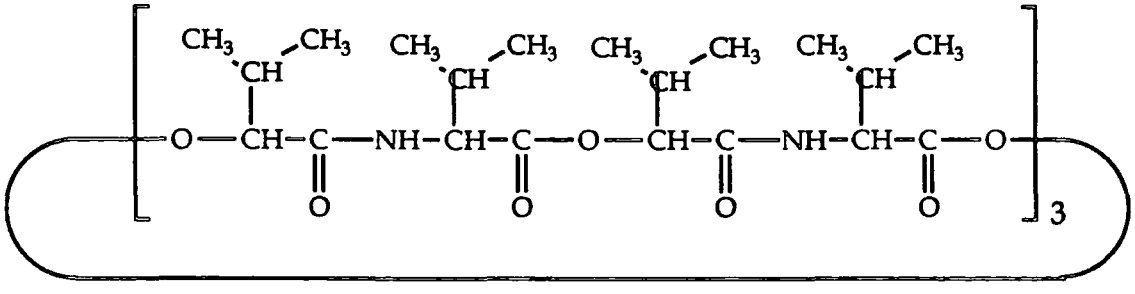


Figure 1.19:- Schematic representation of valinomycin

One may postulate that the amide carbonyls would function as donors for hard metal ions, in fact the amides are involved in conformation

holding H-bonds[58] leaving only ester groups to bind the cation. It has been shown the large ring folds into a "tennis ball-like" seam [59]

In order to attempt to mimic valinomycin, a variety of N-pivot lariat ethers bearing peptide and dipeptide side-arms were experimented with[18,20]. This approach would however seem a little simplistic bearing in mind firstly, that valinomycin binds potassium using only ester donor atoms and yet in the systems studied the cation is primarily bound by the ring ether oxygens and secondly the conformation of valinomycin is such that it exhibits size selectivity, such selectivity is unlikely to be exhibited by the systems studied. Not surprisingly, these lariat ethers failed to mimic valinomycin's binding profile they did however exhibit a number of interesting features. These features and their implications are discussed in full in chapter 3.

1.4. TECHNIQUES USED TO DETERMINE THE STABILITY AND SELECTIVITY OF COMPLEXATION

Many techniques are available for the chemist to utilise in order to assess the stability and selectivity of complexation between cations and ligands. The following section will outline the most common techniques used and discuss the limitations of each. It must be noted that direct comparison of selectivities and stabilities determined by one technique cannot be made with data derived from other techniques. In order to make such comparisons strict criteria must be adhered to such as i) constant temperature, ii) ensuring the solvent system is the same and iii) where possible use the same counter-ion.

1.4.1. ^{13}C AND ^{1}H NMR TECHNIQUES

NMR experiments can be used to determine the stoichiometry of complexation, to give a semi-quantitive assessment of cation binding strengths and also to gain information as to the dynamics of the complexation process. The techniques used are predominantly ^{1}H and ^{13}C NMR, however an examination of the chemical shifts of nuclei bound within the ligand cavity, such as cations, can also be used to gain an insight into the stoichiometries and stabilities of complexes. The major draw back of such techniques lies in the fact that by no means all common cations are NMR active. Furthermore the natural abundance of the active isotope is often low and this coupled with low sensitivity makes the acquisition of data difficult.

^{13}C NMR is a useful technique for assessing both the stoichiometry and sometimes the actual stability constant associated with complexation. The technique involves the admixture of stoichiometric quantities of solid alkali or alkaline earth metal salts to a deuterated methanolic solution of

the ligand. Complexation is accompanied by a shift in the resonance of the ligand carbon atoms. If strong complexation occurs then discrete lines are observed for free and complexed ligand at intermediate stiochiometries, as result of slow kinetics on the NMR time scale. This is indicative of Log K values greater than about four, although a more accurate assessment of the exact value cannot be reliably made using this technique. However an assessment of the stoichiometry of complexation can be made from the mole ratio of metal to ligand at the point at which the signals for free ligand disappear. The shift displacements are often larger for ring carbons than for those present in the side-arm, this is often indicative of a change in ring conformation upon complex formation [60, 61]

With weaker complexation time averaged signals are seen at intermediate stoichiometries, indicative of fast exchange on the NMR time scale. It is possible to determine the stoichiometry in such cases by plotting the ^{13}C NMR chemical shift displacement ($\Delta\delta$) for a particular carbon atom against salt:ligand ratio, the stoichiometry being derived from the position of the curve bend (Figure 1.20)

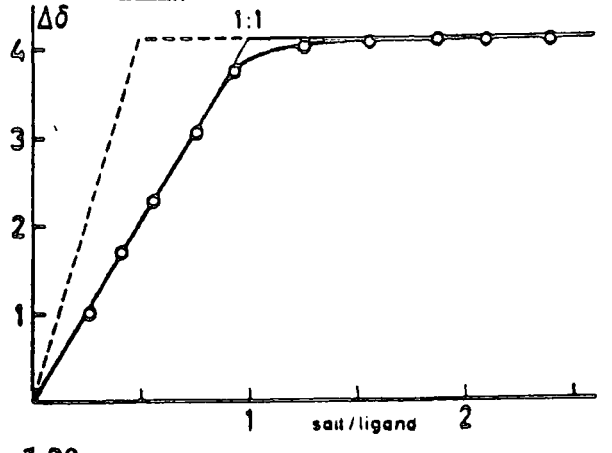


Figure 1.20

Provided the stoichiometry of complexation is known then the strength of binding i.e. the stability constant can be calculated. The method used involves detailed analysis of a specific resonance, full descriptions of the technique are given in the papers of Lenkinski[62] and Reuben.[63]

NMR has also been used extensively to calculate free energies of activation, for ligands displaying strong complexation i.e. discrete signals for free and complexed states [64]. The technique involves recording the differences in chemical shift between free and complexed states as a function of temperature, until the lines are seen to coalesce. From the chemical shift differences the dissociation rate constants at a series of temperatures, including the temperature at which coalescence is observed, are calculated by line shape analysis. From these the free energy of activation at the coalescence temperature can be determined.

Finally NMR can also be used to qualitatively study the dynamics of complexation by measuring relaxation times (T_1). In fact it was this technique which Gokel [53] utilised in order to demonstrate the greater flexibility of N-pivot lariat ethers over C-pivots (see section 1.3.8.2).

1.4.2. CALORIMETRY

The technique of titration calorimetry is one of the most widely used to determine thermodynamic parameters.[65] By measuring the variation in reaction temperature during the titration it is possible to determine not only the enthalpy of complexation but also the equilibrium stability constant. Once these two terms have been determined, then the entropy associated with complexation can also be calculated (see equation1.4).

As the titration of the ligand solution against a metal ion solution proceeds, a thermogram of the reaction is plotted and from this log Ks and ΔH° can be deduced. A typical reaction thermogram is illustrated below in Figure 1.21.

The non-chemical heat effects seen prior to and after the completion of the reaction result from several factors and are compensated for in the

analysis of the data. At equilibrium the reaction occurring in the calorimeter can be described using equation 1.1

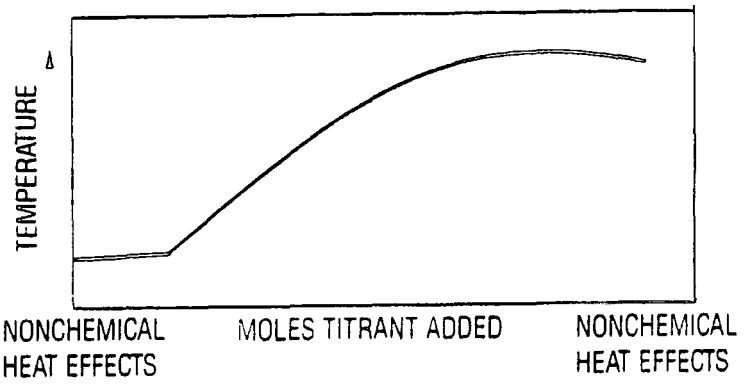


Figure 1.21 Illustration of the appearance of a typical thermogram showing the variation of temperature against time.

$$M^{n+}_{(s)} + L_{(s)} \rightleftharpoons ML^{n+}_{(s)} \qquad (1.1)$$

where M^{+} = metal cation

L = ligand

(s) = solvent

Generally four steps are involved in the determination of Ks by this technique [66], [1] The total heat evolved in the reaction vessel is determined as a function of the volume of titrant added. [2] The data is corrected in order to compensate for the 'non chemical' heat effects. [3] Further corrections are then made to compensate for energy contributions arising from reactions other than that of interest and finally [4] the corrected value for total heat evolved is used to determine Ks.

The only limitation of this technique lies in the fact that only reactions whose stability constants are less than five can be studied directly by this technique. However recently Buschmann[67] has developed a technique whereby the thermodynamic parameters of complexation can be determined indirectly, using a competitive titration, allowing the semi-quantitative assessment of stability constants in excess of five.

1.4.3. FAST ATOM BOMBARDMENT MASS SPECTROMETRY (FAB-MS) TECHNIQUES

This technique is relatively new[68] and offers a quick and easy assessment of competitive selectivity. The species of interest is introduced into the probe in the form of a glycerol matrix and then bombarded by a beam of high energy, fast atoms, usually argon or xenon. FAB-MS allows the detection of the molecular ions of interest with little fragmentation occurring. This stems from the fact that FAB-MS yields ions from involatile species without heating the sample, thus it is possible to obtain spectra for thermally labile samples which would simply fragment if ionised by a different technique such as CI or EI.

Johnstone and Rose[69] reported that complex formation between several macrocyclic ligands and a range of alkali metal cations could be observed, furthermore the abundances of gas phase ions at m/e values were found to closely fit the calculated concentrations of these complexes. Thus FAB-MS can be used to determine the selectivity of a ligand for a range of cations, the relative abundances of the m/e peaks reflecting the selectivity of the ligand.

However the data obtained from such a study is not directly comparable with selectivity coefficients determined potentiometrically since the solvent used for FAB-MS purposes is a glycerol-water mixture and to date no potentiometric data has been obtained in such a solvent system.

1.4.4. EXTRACTION TECHNIQUES

Extraction techniques have found widespread application in the determination of selectivity of a ligand for a particular cation. The technique, in basic terms involves the extraction of cations into an organic phase from an aqueous phase. The technique was originally devised by Pedersen[10, 11, 33] and usually involves the use of a coloured anion, usually a picrate, as the counter-ion. The picrate salt is then dissolved in water, when shaken with an organic solvent, initially no extraction is observed and thus the organic phase remains colourless. However when a ligand is present extraction of the ion-pair occurs in part and thus the organic phase becomes coloured. Thus UV spectrophotometry can be used to determine the picrate concentration via Beer's Law:-

$A = \varepsilon.c.l$ where ε = Molar absorptivity (L cm^{-1} mol^{-1})

C = concentration (mol l^{-1})

l = path length

Beer's Law is a limiting law and only describes the behaviour of dilute solutions.

There are however several variables associated with this technique and care must be taken to assure that as many variables as possible remain unaltered. These variables include cation and anion concentrations, temperature, volumes of aqueous and organic phases, ionic strength, salt to ligand ratio and even the mixing procedure. Furthermore extraction coefficients may not accurately reflect equilibrium binding constants. For instance extraction data suggests that the 15 crown 5 ortho-methoxy phenyl derivative **(24)** binds sodium more strongly than both the para derivative **(25)** and the parent macrocycle **(20)**. However the stability constant data showed that not only did the two substituted derivatives exhibit similar

sodium binding strengths, but also that both bound sodium less well than the parent macrocycle (Table 1.12).

LIGAND	Extraction Coeff	Solvent Pair	Stability Const (LogKs)	Solvent
25 R=H	7.6%	CH_2Cl_2/ H_2O	3.25	MeOH
29 R= $CH_2OC_6H_4$-o-OCH_3	15.7%	"	3.24	"
29 R= $CH_2OC_6H_4$-p-OCH_3	6.4%	"	2.91	"

Table 1.12: Comparison of Extraction and Equilibrium Stabilities for substituted lariat ethers.

1.4.5. POTENTIOMETRIC METHODS

A) pH METRIC TITRATION

Potentiometric methods can be used in order to precisely determine the stability constants for complexation between basic ligands and metal cations. The analysis of the pH-metric curve produced following titration of a solution of the protonated ligand with tetramethylammonium hydroxide solution allows the acid dissociation constants to be determined . Once these have been calculated, the titration procedure is repeated in the presence of metal cations and from the plot stability constants can be determined. [70, 71, 72]

The reason tetramethylammonium hydroxide is used as the base instead of a more conventional alkali is because cations such as sodium or potassium could interact with the ligand cavity, however the tetramethylammonium cation is sufficiently large to discount such interactions. The addition of metal cations to the protonated ligand solution

results in the deprotonation of the ligand upon complexation and thus the pH of the solution is decreased. The data produced by the titration is then evaluated using a least squares regression analysis program, either Superquad[73] or SCOGS[74].

The limitations of this procedure are minor:-

[1] The ligand must be soluble in aqueous or methanolic media.

[2] The ligand must possess basic sites.

[3] The kinetics of the protonation / deprotonation process must be rapid and

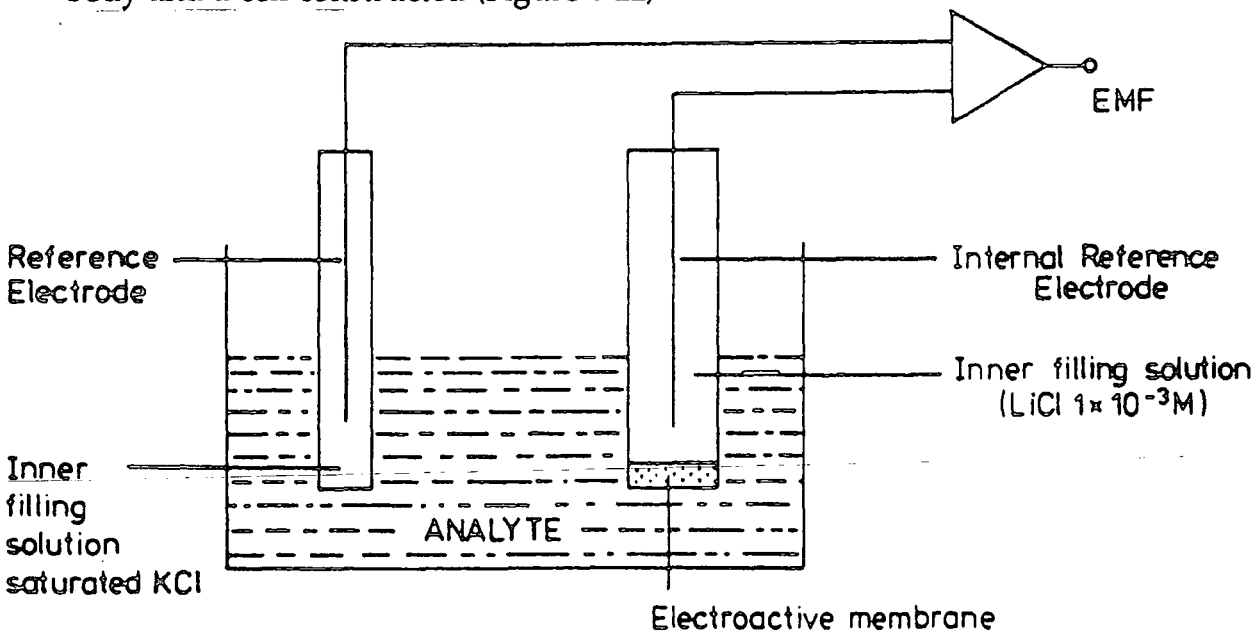
[4] The accuracy of stability constants determined by this technique will be influenced by any problems arising from either half cell or the salt bridge, thus great care must be taken to ensure the electrodes are well conditioned and that the liquid junction potential remains constant throughout the determination.

The advantages certainly outweigh the disadvantages provided care is taken to ensure electrodes are well conditioned. It offers a quick and very accurate means of assessing the stability constants for complexes formed between basic ligands and cations. Furthermore a great deal of data has already been collated for a large number of ligands using this technique and therefore this technique offers the best means whereby complexation characteristics of new ligands can be compared to those possessed by ligands previously prepared.

B ION SELECTIVE ELECTRODES

The use of ion selective electrodes allows the direct measurement of metal ion activity in aqueous or methanolic solutions. The ion-selective electrode itself usually takes the form of a glass type or membrane electrode.

A membrane electrode is fabricated by the incorporation of an organic sensor into a polymeric matrix.[75] The matrix is then attached to an electrode body and a cell constructed (Figure 1.22)



$$Hg \mid HgCl_2 \mid \text{Saturated KCl} \mid \text{ANALYTE} \mid \text{Electroactive PVC Membrane} \mid \text{Inner Filling Solutions} \mid AgCl \mid Ag$$

Figure 1.22:- Typical cell construction

All measurements are referenced against an internal silver/silver chloride electrode. After conditioning the electrode is calibrated using a constant dilution technique. [76] The selectivity of the ionophore can then be assessed using a fixed interference method. The exact procedure for this can be found in the experimental section.

Additionally ion-selective electrodes can be used to determine stability constants, using the technique originally developed by Frensdorff. [77] The e.m.f. response of the calibrated electrode is directly proportional to the concentration of the free cation and thus $E = E_0 + k \log [M^+]$, where k is a constant determined by calibrating the electrode. Thus the value of $[M^+]$ can be measured and log Ks calculated. ΔH and ΔS values can also be evaluated using this technique by examining a plot of log Ks vs. 1/T. The gradient of

the line is $-\Delta H/R$ and the intercept $\Delta S/R$. The technique has been used to determine binding constants for sodium[78], potassium[79] and calcium [18]. However it must be noted that the electrode is only selective for the cation of interest, not specific, thus care must be taken to ensure readings of free cation concentrations lie within the linear response range of the electrode.

In addition to the techniques described above, several other techniques have been used to study complexation, these include polarography,[80] cyclic voltammetry,[81] electrical conductivity[82] and uv spectrometry [11,83,84].

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CHAPTER II

DEVELOPMENT OF LITHIUM SELECTIVE IONOPHORES

2. DEVELOPMENT OF LITHIUM SELECTIVE IONOPHORES

2.1 MEDICAL APPLICATIONS OF LITHIUM

At present lithium carbonate (Priadel) is the only available mood stabiliser, and it is used in the treatment of manic depression. After administration, lithium is completely absorbed in the intestines within 8 hours and blood levels peak 1-3 hours after intake. Lithium is not metabolised and is excreted almost entirely by the kidneys. Thus patients must have good renal function in order to undertake lithium therapy.

The mechanism by which lithium operates is not entirely understood. However lithium does alter the chemical balance of the body and probably influences the chemical systems which regulate emotional states[1].

Lithium is generally well tolerated, although some adverse effects have been noted (Figure 2.01). Toxic effects (see Figure 2.01) usually appear over 1.5 mmol dm^{-3} (therapeutic range 0.5-1.00 mmol dm^{-3}); however there is a great deal of individual variability and it is this variability which necessitates the need for very careful monitoring of blood/ plasma levels in order to secure a therapeutic effect and to avoid toxic side-effects. It is therefore clinically desirable to develop a lithium selective I.S.E. (ion selective electrode) for the simple and rapid assay of lithium in aqueous and physiological media.

Present in plasma are ions which may interfere with the measurement of lithium levels. The level of sodium present in plasma, in particular, is very high compared to expected lithium levels (Table 2.01).Thus any prospective lithium ISE must have sufficient selectivity so as to operate against the high background interference. In fact in order to accurately measure the lithium levels (with <1% interference from interferent cations) in plasma, a lithium ISE. must exhibit a selectivity for

Li^+ over Na^+ of the order of log $K^{POT}_{Li, Na}$= -4.5. At present the best value achieved is around -3.25 [2,3].

ADVERSE

Gastrointestinal(mild)
-Nausea
-Vomiting
-Diarrhoea

Renal
-polyurea
-polydypsia
-nephrogenic diabetes insipidus
-kidney damage

Cardiovascular
-EKG changes

Neurological
-tremor
-EEG changes

Haematological
-leukocytosis

Thyroid
-Hypothyroidism

Weight gain

Skin
-acne
-worsening of psoriasis

Reproduction
-tetratogenic

Oedema

TOXIC

Moderate
-persistent nausea &/or diarrhoea
-lethargy, muscle weakness
-ataxia, muscle irritability
-coarse tremor

Severe
-arrhythmias,hypotension
-anuria, shock
-seizures
-incontinence
-confusion, stupor
-coma, death.

Figure 2.01 Illustration of the possible side affects of lithium therapy[1]

Cation	Concentration range (mmol dm^{-3})
Na^+	135 - 150
K^+	3.4 - 5.2
Ca^{2+}	1.04 - 1.52
Li^+	0.5 - 1.0

Table2.01:- Interferent cation concentrations in human plasma

2.2 DESIGN OF LITHIUM IONOPHORES

Any potential lithium ionophore must possess the following properties in order to facilitate its use as a sensor in a potentiometric lithium ion-selective electrode (I.S.E.).

(1) It must exhibit lithium selectivity over other alkali and alkaline earth metal cations, particularly sodium.

(2) The kinetics of complexation must be sufficiently rapid to allow equilibrium to be quickly established.

(3) It must be sufficiently lipophilic in order to prevent it dissolving in the aqueous media.

(4) It should be charge neutral and non-basic to avoid pH interference.

Presently the highest selectivities for lithium are displayed by spherand **(5)** [4] and cryptand-2,1,1. **(4)**. Both exhibit selectivity on the basis of ion-size, however in both cases the kinetics of complexation are too slow to allow their use as an ionophore incorporated into an electrode. Furthermore cryptand 2,1,1 **(4)** is pH sensitive. Thus the search for lithium ionophores has focused on more flexible ligand systems which display rapid complexation kinetics.

2.2.1 ACYCLIC LIGANDS

A number of acyclic quadridentate amide-ethers have been developed which exhibit selectivity for lithium over other cations.[5,6]

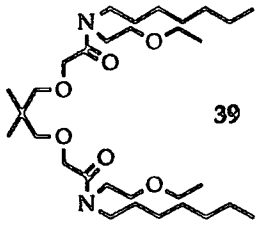
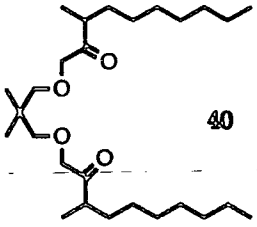
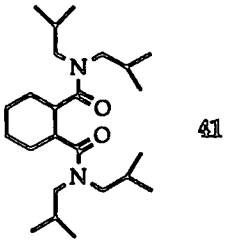
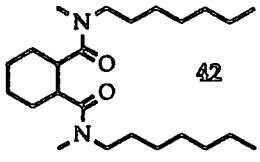
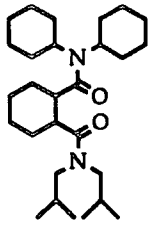
IONOPHORE	membrane composition (mass%) Solvent mediator	PVC	Sensor	Selectivity coeff. $K^{pot}_{Li/M}$ Separate Soln. method	Mixed Soln. method
 39	TEHP (66.7)	29.4	3.9	Na 0.051 K 5.3×10^{-3} Ca 3.6×10^{-3} Mg 4.0×10^{-4}	0.063 0.104 7.1×10^{-3} 2.5×10^{-4}
 40	TEHP (62.8)	31.4	5.8	Na 0.05 K 7.0×10^{-3} NH_4 7.9×10^{-3} Ca 5×10^{-4}	
	oNPOE (65-66)	33	1-2	Mg 1.99×10^{-4} Na 0.08	
 41	oNPOE (65-66)	33	1-2	Na 7.9×10^{-3} K 6.3×10^{-3} NH_4 7.9×10^{-3} Ca 10^{-3} Mg 6.3×10^{-3}	
	TEHP (64.6)	28.5	6.9	Na	0.15
 42	oNPOE (65-66)	33	1.2	Na 0.4	
 43	oNPOE (65.6) +0.4% TpClPB	32.8	1.2	Na 5×10^{-3}	3.16×10^{-3} 3.55×10^{-3}
	BPA (65.6) +0.4% TpClPB	32.8	1.2		0.032

Figure 2.02 Lithium Selective Acyclic Ionophores

The best selectivity achieved with such acyclic systems is log $K^{POT}_{Li/Na}$ = -2.5 (43, Figure 2.02). At present this ligand is the best commercially available acyclic lithium ionophore. NMR and X ray studies

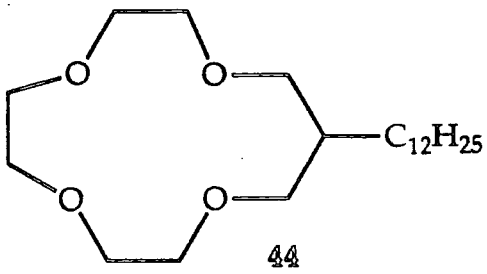
of this ligand have revealed that it forms a 2:1 "sandwich complex" with lithium, the four carbonyl oxygens interacting with the lithium ion in a tetrahedral array.

2.2.2 MONOCYCLIC IONOPHORES

2.2.2.1 Ring Size

The selectivity achieved with the acyclic ligands is insufficient to facilitate their use as lithium ionophores in clinical media and thus attention has focused on the development of ionophores based upon a crown ether skeleton. Kitazawa *et al* [7] attempted to establish a relationship between the cavity size of crown-4 derivatives and lithium selectivity by examining the potentiometric behaviour of a series of lipophilic crown-4 derivatives varying in ring size from 13 to 16 (Figure. 2.03).

The study showed that the 13 membered ring analogue (**44**) was much less selective than the 14 and 15 membered ring derivatives. Rather than being due to the size of the ring cavity, the enhanced selectivity seen with the 14 and 15 membered rings results from the fact that on complexation with lithium two and three six ring chelates respectively, are formed. As stated earlier (section 1.3.2), 6 ring chelation is favoured by small cations [8] such as lithium as the hydrogen atoms in the linking methylene groups can adopt a staggered conformation. The trend was seen to be reversed with the 16 membered ring (**47**). This results from the increased steric crowding introduced by the formation of four, 6 ring chelates.



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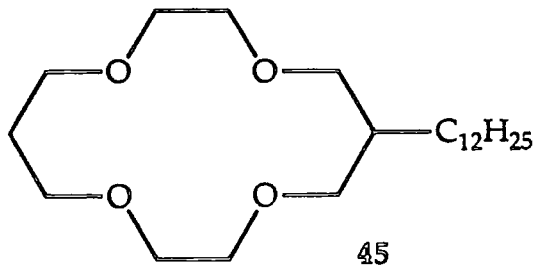

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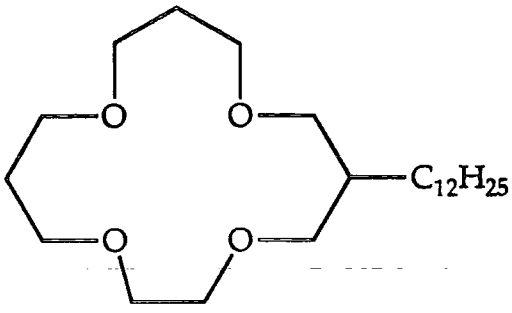

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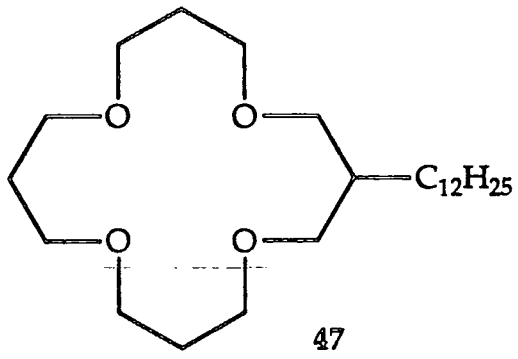

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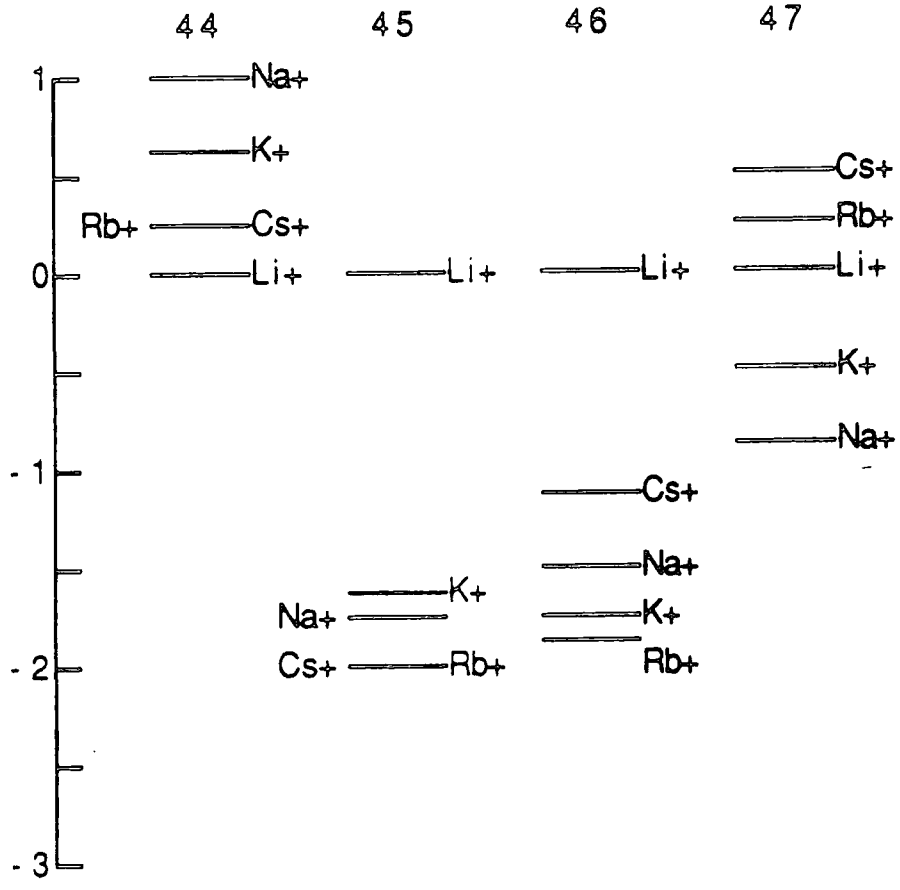


Fig 2.03 Influence of ring size upon lithium complexation

Kitizawa [9] also showed that lithium selectivity was affected considerably by the existence and the nature of the geminal substituents. He examined four 14-crown-4 derivatives with varying geminal substituents and discovered that the presence of a methyl group geminal to a dodecyl group led to an enhanced lithium/sodium selectivity (Figure 2.04).

This increase in selectivity is thought to result from the steric influence exerted by the methyl group. Both sodium and potassium although too large to fit inside the ring cavity can form 2:1 (ligand: metal) "sandwich" complexes and it is the formation of such complexes which is sterically inhibited by the geminal dialkyl group. Both **(49)** and **(50)** were found to exhibit a similarly enhanced Li^+ / Na^+ selectivity compared to the simple dodecyl derivative **(48)**. However ligand **(50)**, in which both neo-pentyl carbons possess geminal methyl groups, did not show the same extent of enhancement in selectivity. It is thought that although the substituents of **(50)** inhibit 2:1 complexation with sodium and potassium they also tend to inhibit 1:1 complexation with lithium as a result of steric inaccessibility. The effect was further enhanced by the incorporation of a more bulky benzyl group in the geminal position **(51)**.[10]

A slightly different approach to preventing the formation of 2:1 "sandwich" complexes was more recently undertaken by Suzuki *et al* .[11] They incorporated a decalino sub-unit at the ethanato bridge, **(53)**.

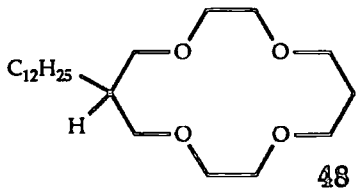
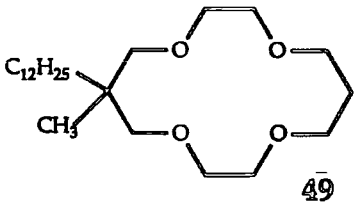
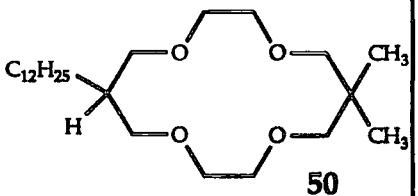
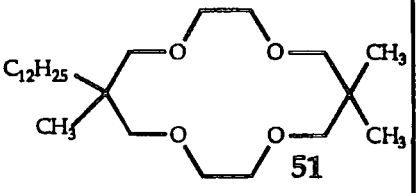
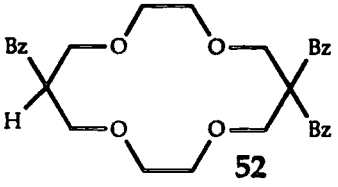
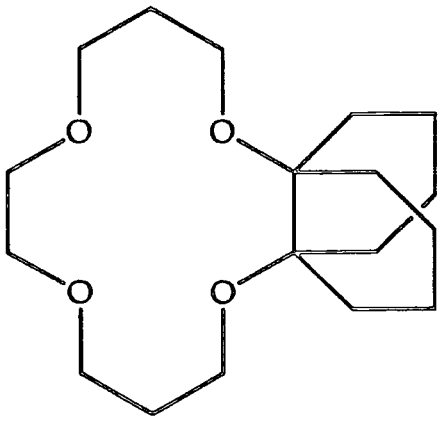
IONOPHORE	Membrane composition (%mass)			Selectivity coefficient $K^{pot}_{Li/M}$
	Solvent mediator	PVC	Sensor	Mixed solution method
 48	2-NPOE (70.2)	28.1	1.0 + 0.7% KTpClPB	0.016
 49	2-NPOE (70.2)	28.1	1.0 + 0.7% KTpCLPB	6.6×10^{-3} 2×10^{-3} For membrane with TOPO (1%).
 50	2-NPOE (70.2)	28.1	1.0 + 0.7% KTpCLPB	6.2×10^{-3}
 51	2-NPOE (70.2)	28.1	1.0 + 0.7% KTpCLPB +1% TOPO	7.2×10^{-3}
 52	2-NPOE (70.2)	28.1	1.0 + 0.7% KTpCLPB	3.39×10^{-3}

Figure 2.04: Characteristics of lithium ISE`s based upon a 14-crown-4 skeleton



(53)

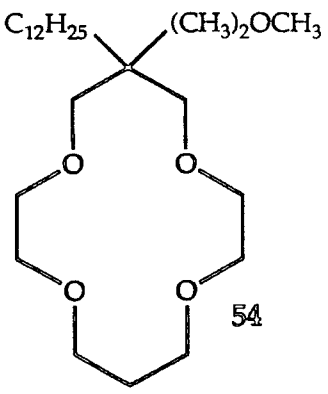
CPK molecular modelling studies suggest that the decalino sub-unit forms a steric barrier above and below the plane of the ring and thus prevents the formation of 2:1 "sandwich" complexes with larger cations.

This ionophore when incorporated into a PVC membrane (BBPA plasticizer) was shown to exhibit excellent Li/Na selectivity, $\log^{POT}_{Li/Na}$ =-3.3. However its behaviour in serum or plasma has yet to be reported.

2.2.2.2 Effect of donating substituents upon lithium selectivity

Whilst high selectivity for lithium can be achieved using sterically hindered four co-ordinate ring systems, crystallographic studies,[12,13] indicated a co-ordination number of five or six for lithium. This suggested the possibility of enhancing selectivity and complex stability of 14-crown-4 complexes by attaching ligating side-arms to the macro-ring. The orientation of these donors must be such that they allow the binding of the donor atoms present in the side-arm to the centrally held lithium cation.

Kitizawa *et al* [14] synthesised a number of 14-crown-4 derivatives **(54)** to **(60)** (figure 2.05) and embedded them in a PVC / NPOE membrane and assessed each one potentiometrically using a fixed interference method.



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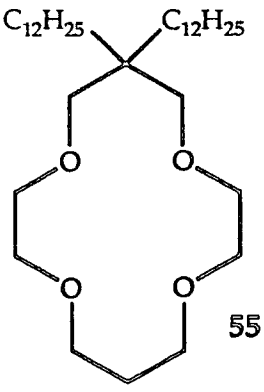
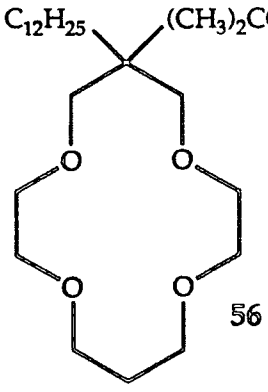


55



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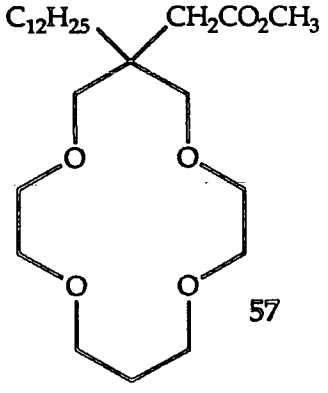

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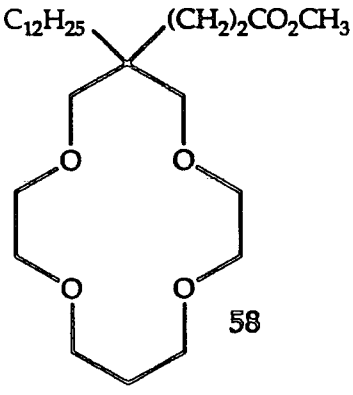

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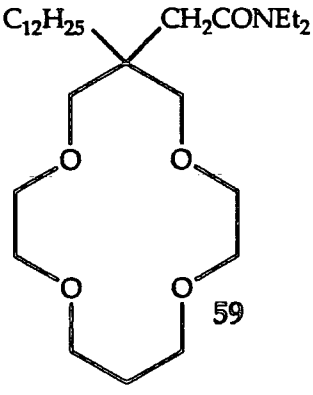

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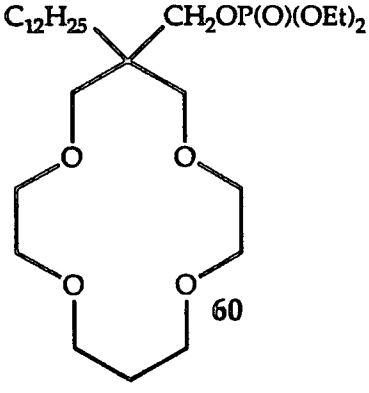


60

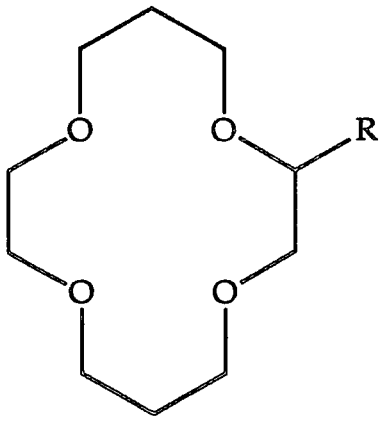
LIGAND	$1/K^{pot}_{Li/Na}$	$1/K^{pot}_{Li/K}$
54	91	54
55	145	91
56	129	162
57	105	93
58	72	38
59	229	316
60	182	288

Figure 2.05: Lithium selectivity of some 14-crown-4 derivatives bearing additional axial donor sites.

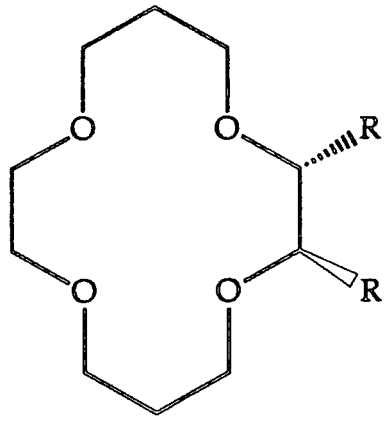
Of the derivatives examined, only the amide derivative (59) and the phosphonate derivative (60) exhibit enhanced selectivity relative to the selectivity displayed by the four co-ordinate parent macrocycle (55). The enhanced selectivity results from the fact that amide and phosphonate groups have a high ground state dipole moment and thus favour binding of the small highly charged lithium cation over sodium and potassium.

The idea of incorporating ligating side-arm donors into a parent 14-crown-4 skeleton was also studied by Parker *et al*.[2,3]A series of 14-crown-4 derivatives were prepared so as to vary systematically the nature of the additional donor groups and their number (fig 2.06).

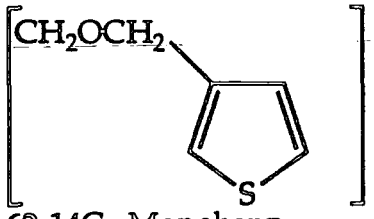
Because lithium can exhibit octahedral co-ordination it was surmised that the incorporation of two additional "axial" donors on the 14-crown-4 skeleton would enhance 1:1 complexation of lithium whilst at the same time sterically inhibiting the formation of 2:1 "sandwich" complexes with sodium and potassium. The length of the donor arm, with a methylene group spacer, was deduced to be the most suitable since it permitted the binding of lithium in a six ring chelate. Small cations, such as lithium are known to form more stable complexes with six ring chelates than do larger cations (see section 1.3.2). This preference has been noted in both macrocyclic chemistry,[15]and other fields of organic chemistry such as stereo-selective lithiation.[16]



61 $14C_4$ Thio



63 $14C_4$ dibenz
(CH_2OCH_2Ph)



62 $14C_4$ Monobenz
(CH_2OCH_2Ph)

64 $14C_4$ Diol
(CH_2OH)

65 $14C_4$ Ol
(CH_2OH)

66 $14C_4$ Diest
(CH_2CO_2Me)

67 $14C_4$ Est
(CH_2CO_2Me)

68 $14C_4$ Dibutam
(CH_2CONBu_2)

69 $14C_4$ Butam
(CH_2CONBu_2)

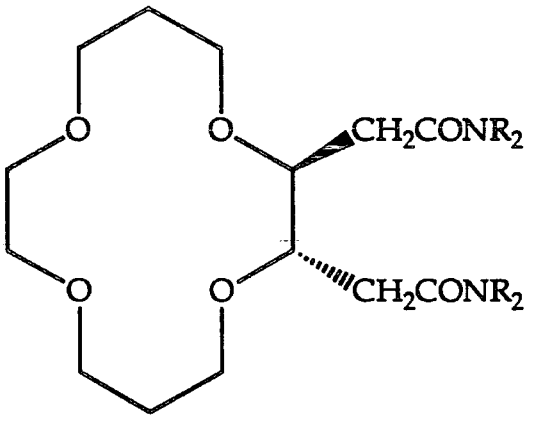
70 $14C_4$ Diibutam
[$CH_2CON(iBu)_2$]

Figure 2.06: Series of 14-crown-4 coronands synthesised for evaluation as potential lithium selective ionophores.

Of those examined, ion selective electrodes fabricated using ligands **(68)** and **(70)** as the ionophore were found to display the highest selectivity for lithium, as expected, since both have two axial amide donors. The di-isobutyl amide derivative **(70)** was found to exhibit slightly higher lithium/sodium selectivity than the di-n-butyl derivative **(68)**; Log $K^{POT}_{Li,Na}$ = -3.25 compared to -2.92. However **(70)** behaves poorly in serum, whereas **(68)** has a relatively long life span in serum and exhibits a fast response (10-15s).

2.3. AIMS AND OBJECTIVES

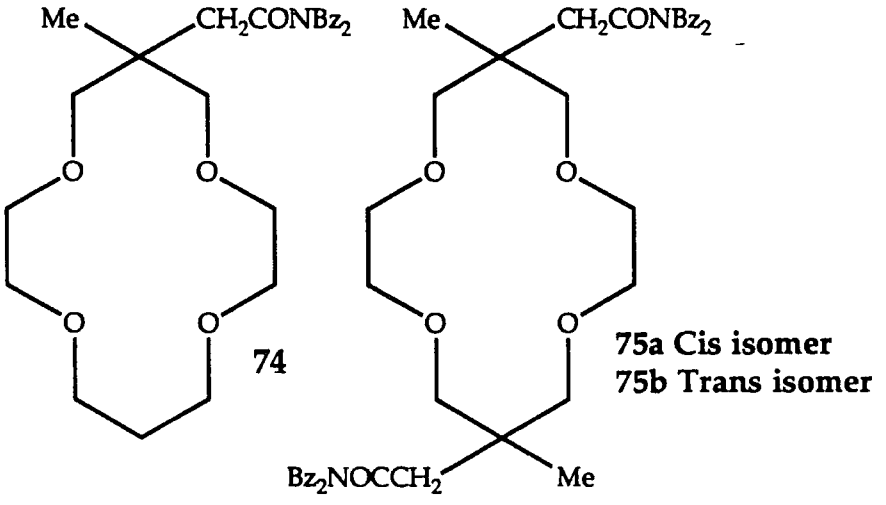
The aim of this work was firstly to synthesise a series of amide difunctionalised 14-crown-4 coronands (68) to (73), in order to further study the effect that varying the nature of the amide donors has upon lithium selectivity.



68 R = butyl
70 R = ^{i}butyl
71 R = octyl
72 R = benzyl
73 R = ethyl

Figure 2.07: Target Ionophores

Latterly attention was focused upon amide functionalised 14-crown-4 derivatives where the ligating side-arm(s) were positioned at the neo-pentyl site(s). Figure 2.08 illustrates the two ligands in question.



74

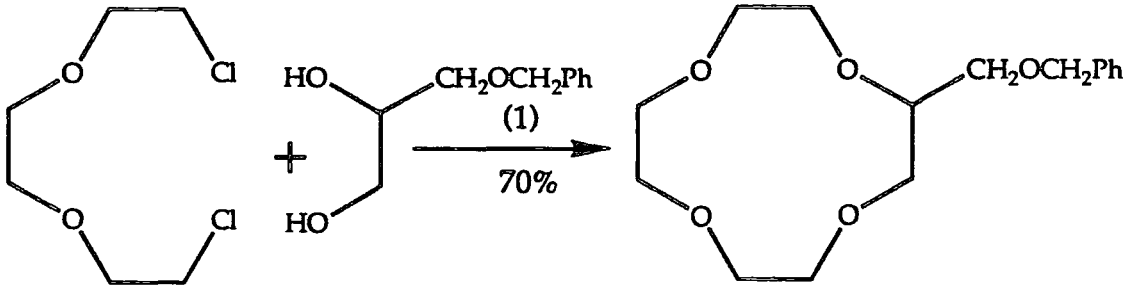
75a Cis isomer
75b Trans isomer

Figure 2.08: Proposed neo-pentyl substituted 14-crown-4 analogues.

It was hoped that not only would the amide(s) present in the side-arm(s) ligate the centrally held lithium cation but also that the geminal methyl groups would suppress 2:1 "sandwich" complex formation in much the same manner as that observed by Kitizawa. [9]

2.4 LIGAND SYNTHESIS

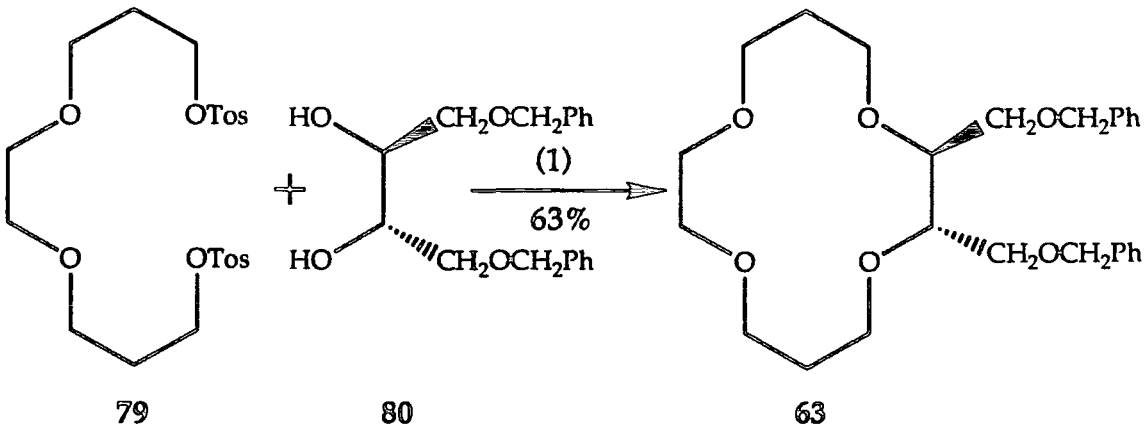
Ligands (68) to (73) were all synthesised using procedures analogous to those devised by Parker *et al*. [15] The cyclisation was performed using a modified procedure of that developed by Okahara *et al* [17] (Figure 2.09). The success of the procedure was attributed to the fact that the lithium salt of the diol (77) was insoluble in the reaction solvent, ^{t}BuOH and thus the reaction occurred heterogeneously under the influence of the lithium template effect.



76 77 78

Figure 2.09: (1) Li(s), ^{t}BuOH, LiBr, Reflux (N_2).

The actual procedure used is illustrated below (Figure 2.10). Instead of using a halide atom as the leaving group a tosyl group was used instead. This offered several advantages over the previous procedure [15]. Firstly the ditosylate could be prepared in significantly higher yield than the dihalide, secondly the reaction time required for the cyclisation reaction was reduced from two weeks to seventy-two hours and finally the yields achieved for the cyclisation were slightly improved.



79 80 63

Figure 2.10: (1) Li(s), ^{t}BuOH, LiBr, 60°C (nitrogen).

The di-tosylate was synthesised using the scheme outlined below (Figure 2.11), starting firstly with the addition of two equivalents of acrylonitrile to a stirred two phase solution comprised of one equivalent of ethane-1,2-diol and a 2% solution of sodium hydroxide maintained at O° C. This afforded the dinitrile **(82)**, which, in turn, was converted to the diester **(83)** by refluxing with sulphuric acid(conc) and ethanol. It was found necessary to alter slightly the procedure used previously [15], the presence of a small measure of water being necessary in order to effect ethanolysis.

Reduction of the diester **(83)** to the diol **(84)** was first attempted using a Bouveault-Blanc procedure i.e. a dissolving metal reduction. However this was unsuccessful and instead of the required product being recovered several reverse Michael addition type products were isolated. The proposed mechanism for this process is given in Figure 2.12. Thus a different approach was required and metal hydride reduction using lithium aluminium hydride was used. The yield of this reaction was found to be greatly improved if the lithium and magnesium salts were extracted by refluxing in chloroform/methanol (9:1) for two hours. Finally the diol **(84)** was tosylated under basic conditions, pyridine, to give the required tosylate **(79)**.

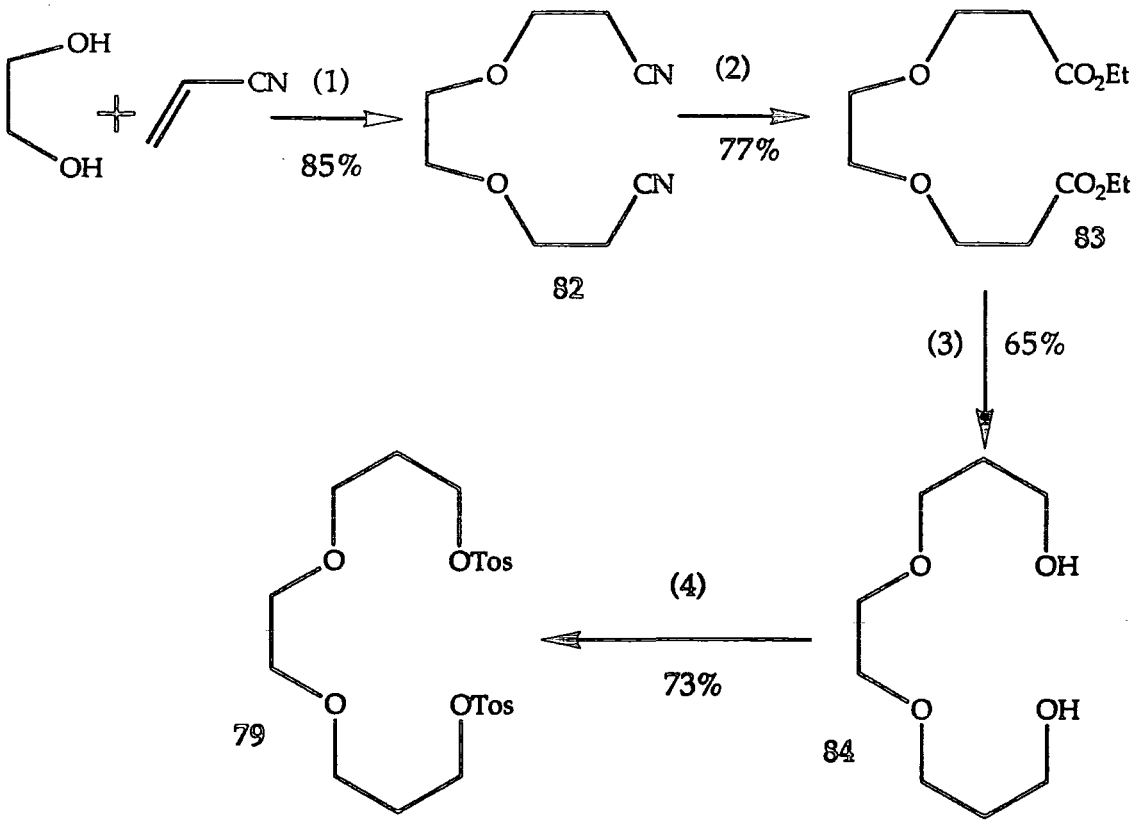


Figure 2.11: (1) NaOH (2%), RT. (2) EtOH, H_2SO_4 & H_2O, reflux (3) $LiAlH_4$, diethyl ether, N_2, reflux. (4) Tosyl Chloride, pyridine, -15° C.

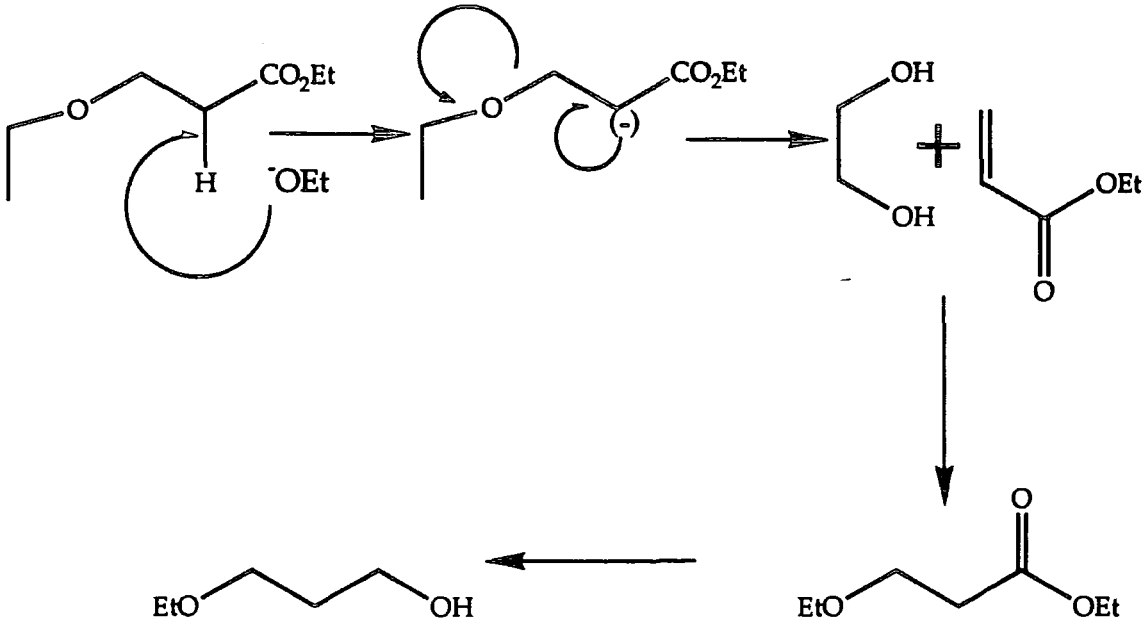


Figure 2.12: Proposed fragmentation mechanism for the decomposition of (83).

Synthesis of the dibenzylated diol (80) (Figure 2.13) was effected starting with R,R-(+)-dimethyl-L-tartrate (85). The first step involved the protection of the two alcohol groups of R,R-(+)-dimethyl-L-tartrate (85) as a ketal (86) by reaction with dimethoxypropane, using a p-toluene sulphonic acid catalyst. A Soxhlet apparatus filled with 4Å molecular sieves was used in order to remove the methanol produced during the reaction thus altering the equilibrium in favour of the ketal product (86). The ester groups were then reduced using lithium aluminium hydride to yield a diol (87) which was subsequently protected by benzylation.

The conditions required for benzylation were slightly modified from those used previously,[15] instead of using tetrapropylammonium bromide, tetra-butyl ammonium hydrogen sulphate was used as a phase transfer catalyst. This was found to improve both the rate of reaction and the isolated yield. Finally the ketal protection was removed by hydrolysis. The procedure described previously [15] (using acetone as the reaction solvent) was found to be unsuccessful, and methanol was found to be a more suitable solvent.

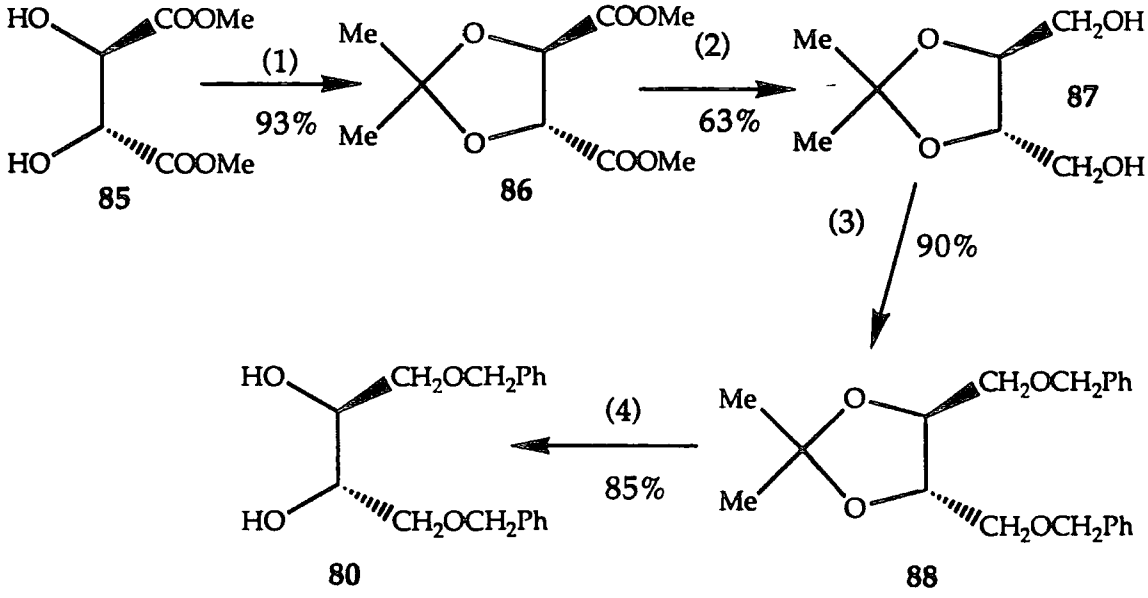


Figure 2.13: (1) dimethoxypropane, $CHCl_3$, Tosic acid, N_2, reflux. (2) $LiAlH_4$, Et_2O, reflux, Ar. (3) $PhCH_2Cl$, THF, $Bu_4N^+HSO_4^-$. (4) MeOH, HCl (6M).

After cyclisation the protective benzyl groups were removed by catalytic hydrogenation. This was achieved using Pearlman's catalyst [$Pd(OH)_2$ on C, 30% $^{v}/_{v}$ H_2O], with a catalytic amount of p-toluene sulphonic acid in ethanol under a hydrogen gas pressure of three atmospheres at room temperature (Figure 2.14).

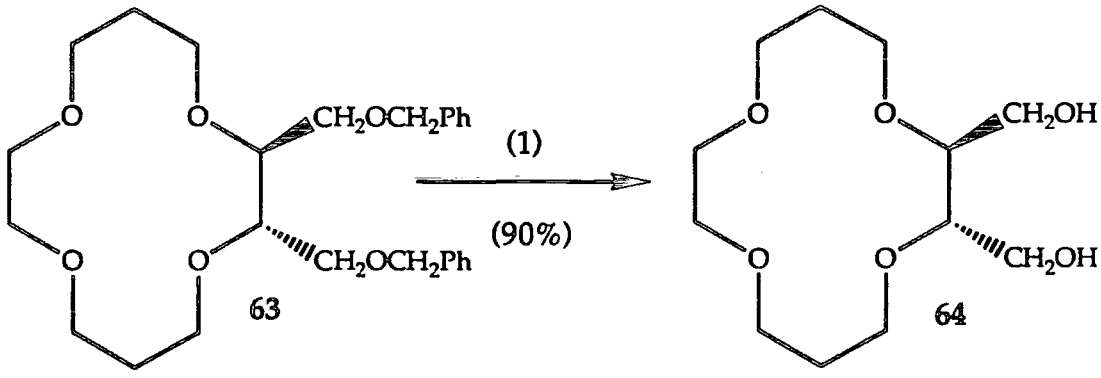


Figure 2.14: (1) Pearlman's Catalyst, p-toluene sulphonic acid, ethanol, H_2 (3 atm), RT.

In order to extend the length of the axial substituents by one carbon atom (Figure 2.15), the diol was first tosylated and then cyanated, thus introducing the required extra carbon atom. It was found to be necessary to alter the work-up procedure from that used previously ,[15] since this was found to give very poor yields (<10%) due to a poor extraction technique. The DMSO used as the reaction solvent was removed completely prior to extraction of the required dinitrile using chloroform.

The dinitrile **(90)** was then converted to a di-ester **(66)** by ethanolysis, which was subsequently hydrolysed under basic conditions to give a di-acid **(91)**. All the required amide derivatives were prepared from this di-acid via the acid chloride.

Optical rotation measurements $[\alpha]_d$, suggested that no racemisation occurred during the reaction scheme. Thus, as required, one axial donor is

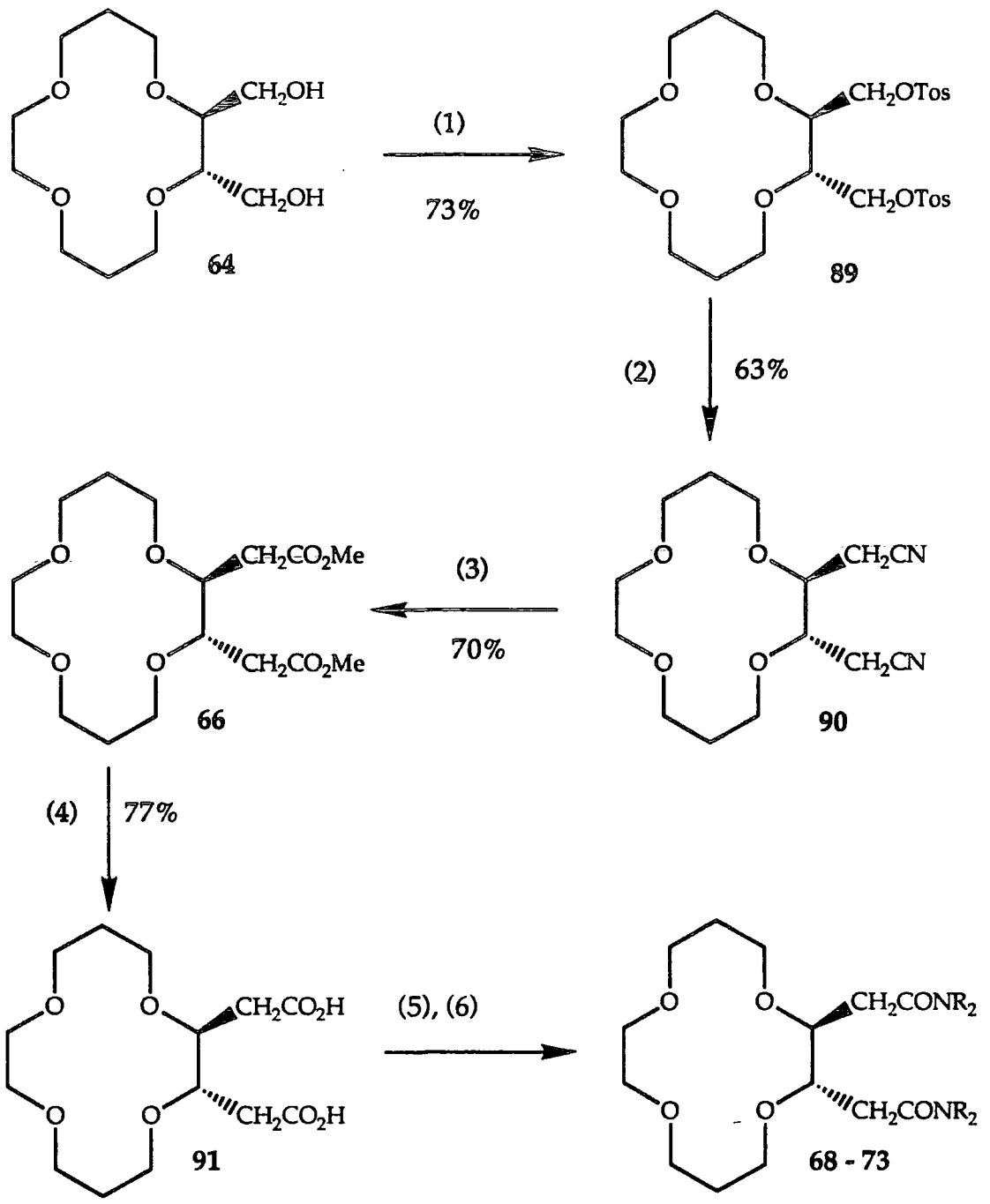


Figure 2.15: (1) TosCl, Pyridine, -15°C; (2) KCN, DMSO(dry), N_2, 90° C; (3) MeOH, HCl(g), reflux, N_2. (4) Me_4NOH, H_2O/MeOH, reflux. (5) PCl_5, CH_2Cl_2(dry), RT, N_2; (6) Et_3N, R_2NH [R = Et, ^nBu, ^iBu, Bz, Oct], CH_2Cl_2, N_2, 0° C.

located above and the other, below, the plane of the macrocycle, allowing the octahedral complexation of the lithium cation.

The neopentyl 14-crown-4 analogues (74) and (75) were both prepared using 2-hydroxymethyl 2-methyl, propane 1,3 diol (92) as the starting material, (Figure 2.16). The first step simply involved protecting two of the hydroxyl groups as a ketal by treatment of (92) with dimethoxypropane in the presence of a p-toluene sulphonic acid catalyst, again as with (86) using a Soxhlet apparatus containing molecular sieves. The third hydroxyl group was subsequently benzylated under the same conditions described previously for the benzylation of (87). However approximately 25% of the crude reaction product was found to be di-benzyl ether, formed as a by-product. Separation of (94) and di-benzyl ether was found to be very difficult therefore the crude product was hydrolysed to yield a diol (95) without further purification. Separation of the diol from dibenzyl ether was more easily achieved, by recrystallisation.

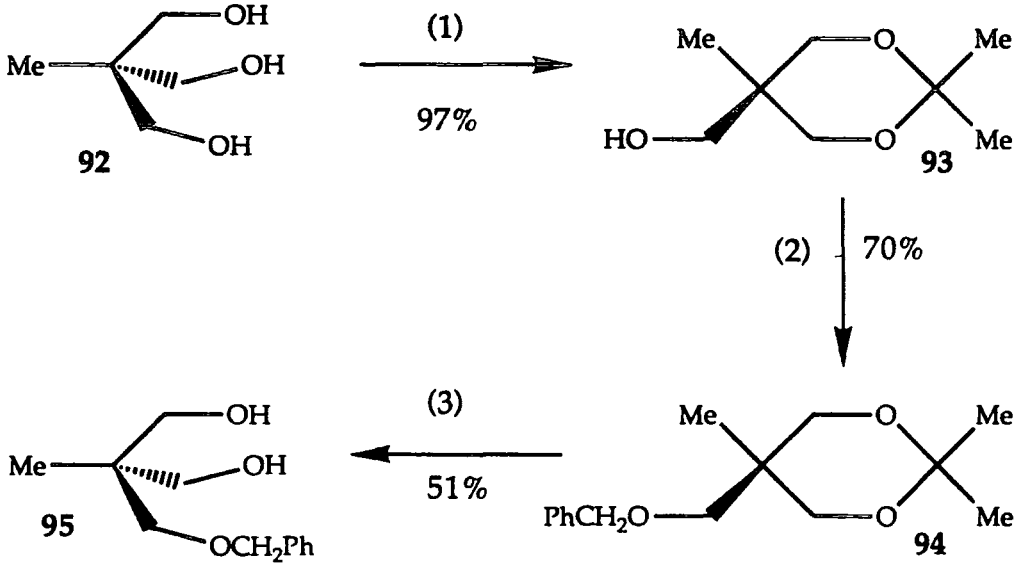


Figure 2.16: (1) dimethoxypropane, $CHCl_3$, Tosic acid, N_2, reflux. (2) $PhCH_2Cl$, $NaOH_{(s)}$, THF, $Bu_4N^+HSO_4^{+,}$ reflux. (3) MeOH, HCl (6M), reflux.

For the monosubstituted derivative (74) cyclisation was simply performed using the benzylated diol (95) described above and

1,11 di (toluene-p-sulphonyl) - 4,7 - dioxanonane. [9] (Figure 2.17). The reaction conditions used for the cyclisation were identical to those described previously.

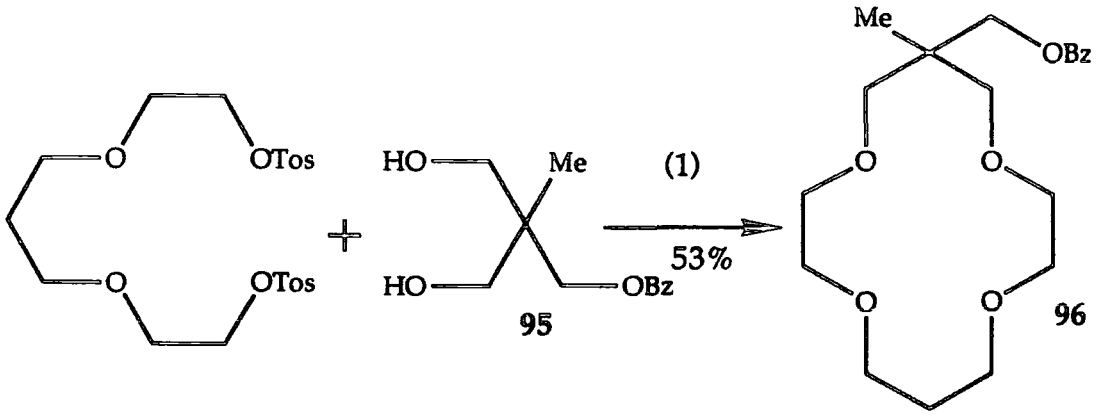


Figure 2.17: (1) $Li_{(s)}$, LiBr, ^tBuOH, 60°C, Argon.

In order to synthesise the dibenzylated analogue of **(100)**, firstly the neo-pentyl functionalised ditosylate **(99)** had to be synthesised. The first step involved treatment of **(95)** with ethyl diazoacetate, in the presence of a BF_3-etherate catalyst, in order to introduce the required two carbon extension. The diester **(97)** resulting from this alkylation was then reduced using $LiAlH_4$ to give a diol **(98)** which was subsequently tosylated to give the required tosylate **(99)** (Figure 2.18).

The cyclic dibenzylated derivative **(100)** was, as expected, found to consist of a mixture of cis and trans diastereo-isomers. When cyclisation was performed on a small scale (4g of **95**) a ratio of approximately 7:3 for the two diastereo-isomers was observed (^{13}C NMR), Separation of these isomers could not be achieved at this stage. Both the mono **(96)** and dibenzylated **(100)** compounds were then dibenzylated, again under the same conditions as those described previously. The mixture of cis and trans diols **(102)** resulting from the debenzylation of **(100)** were successfully separated

chromatographically.

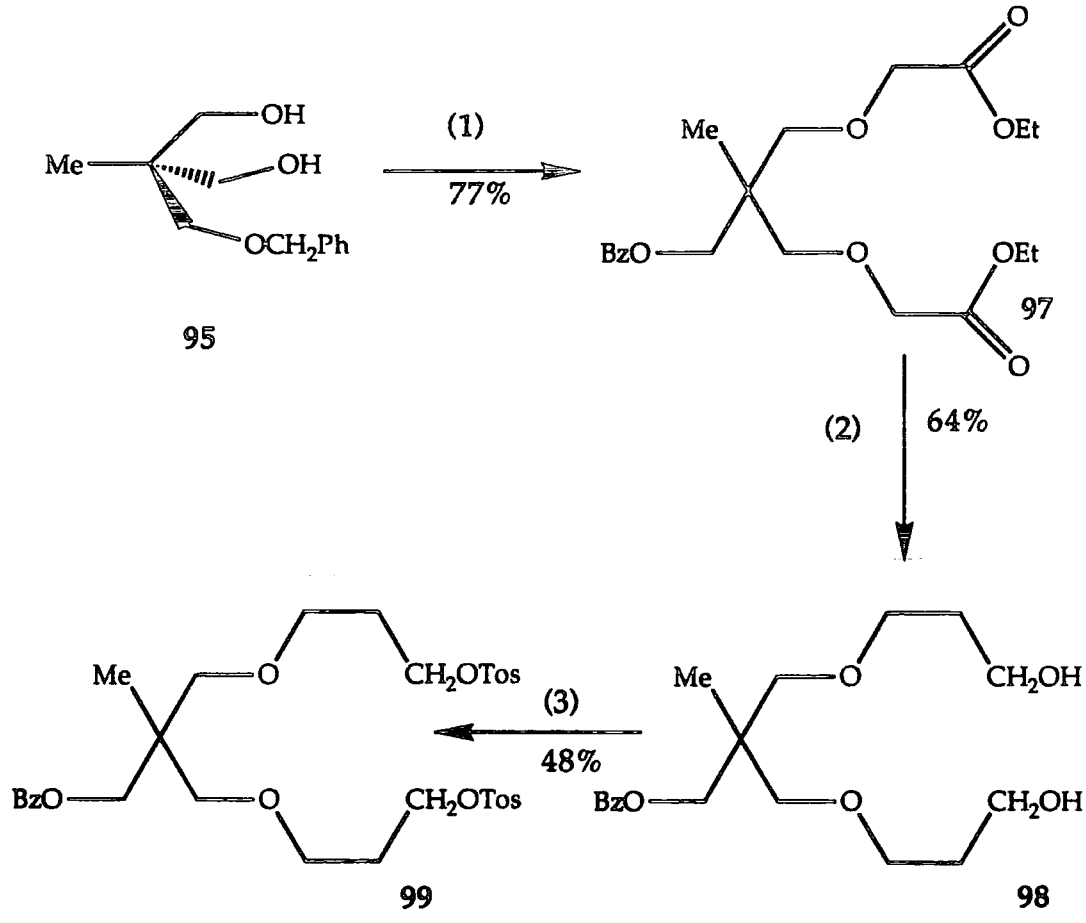


Figure 2.18: (1) $N_2CH_2CO_2Et$, CH_2Cl_2, BF_3-etherate, 40°C, (2) $LiAlH_4$, ether, argon, reflux. (3) Tosyl chloride, pyridine ,-20°C.

The assumption that the major isomer would be the trans was made on the basis that, firstly this would be the favoured orientation during cyclisation since it would allow the "lithium template" to be bound in a favoured octahedral arrangement and secondly on a more practical point the trans isomer should elute faster than the cis isomer on alumina, since only one hydroxyl group can bind to the alumina surface whereas both hydroxyls present in the cis isomer can bind simultaneously. The major spot being the faster eluting component. [These assumptions were later proved to be correct when a crystal structure was obtained for the di-nitrile analogue **(106)** of the major component (Figure 2.19)].

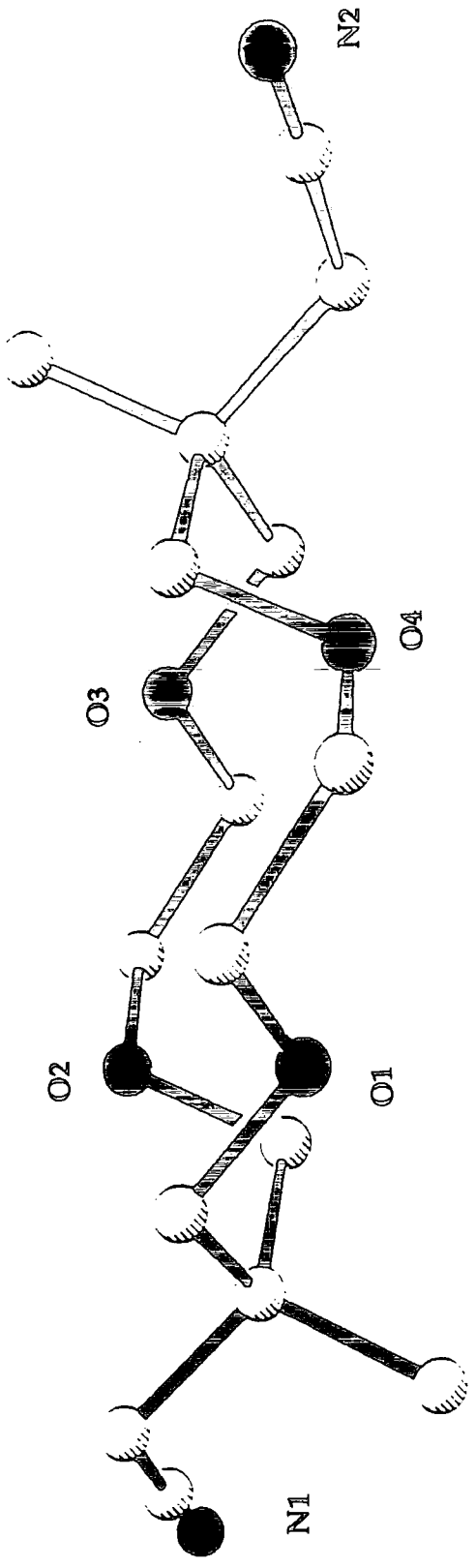


Figure2.22:- Crystal structure of 3,10 - Bis (cyanomethyl), 3,10 bis-methyl - 1,5,8,12 - tetraoxacyclotetradecane **(106)**

However due to difficulties encountered during the hydrolysis step (nitrile to carboxylic acid, see page 80), the need to carry out the cyclisation again, arose. This was performed on a larger scale and for reasons which are

unclear, the isomeric ratio was closer to 1:1. Therefore separation of the diastereomeric diols was much more difficult and because of this it was decided to attempt separation of the isomers after completion of the final step.

Again as in the previous scheme, tosylation was performed to give the tosylate (**103**) and ditosylate (**104**) (Figures 2.20 and 2.21).However conversion of the tosylates to nitriles, in order to introduce the required extra carbon atom, proved to be more difficult than the conversion described previously. The reason for this undoubtedly lies in the greater steric hindrance present in these neo-pentyl derivatives compared to the simple secondary tosylates cyanated previously.

Conversion was eventually achieved using potassium cyanide in DMSO at 150°C, in the presence of an 18-crown-6 catalyst. The 18-crown-6 serving to increase the nucleophilicity of the cyanide ion by binding the potassium ion and thus freeing the "naked" anion. Ethanolysis of the resultant nitriles (**105**) and (**106**) proved unsuccessful. The sterically hindered neo-pentyl site proving inaccessible to attack by the relatively large ethanol nucleophile. Methanolysis was similarly unsuccessful. Thus rather than synthesise the required carboxylic acids via an intermediate ester derivative, direct nitrile hydrolysis was attempted. Initially acid hydrolysis was attempted. Although this proved successful in converting the nitrile functionality it unfortunately also resulted in a degradation of the macrocyclic ring itself as a result of cleavage of the ether linkages. Hydrolysis of the mono-derivative (**105**) was eventually achieved using NaOH in ethylene glycol / water, 24 hours at 150°C.[18]

Attempts to convert this mono-acid (**107**) to an acid chloride using PCl_5 proved unsuccessful, again it appeared that the ring structure itself was degraded. Thus it was decided to attempt to synthesise the required amide

(74) directly using a coupling reaction, utilising dicyclohexyl carbodiimide (DCC), rather than proceeding via an intermediate acid chloride. This proved successful even though the yield achieved was very poor (at around 15% in the worst case). The hydrolysis of the dinitrile (106), proved more awkward. When the procedure was attempted using ethylene glycol/water as the solvent system hydrolysis occurred, but it proved very difficult to remove residual ethylene glycol. Therefore, methoxyethanol was used in place of ethylene glycol, since its lower boiling point allowed it to be removed more easily.

Again synthesis of the diamide (75) was achieved using a coupling reaction (DCC, DMAP, dibenzylamine). The resultant mixture of cis and trans diastereomers proved inseparable by simple column chromatography on either alumina or silica. Therefore separation was attempted using preparative HPLC. Both normal phase (silica gel) and reversed phase (hypersil ODS) columns were examined using several solvent systems, however no separation was achieved. Unfortunately, therefore, the potential of the two diastereomers as ionophores for lithium could not be assessed separately instead a membrane was fabricated containing the mixture of diastereomers.

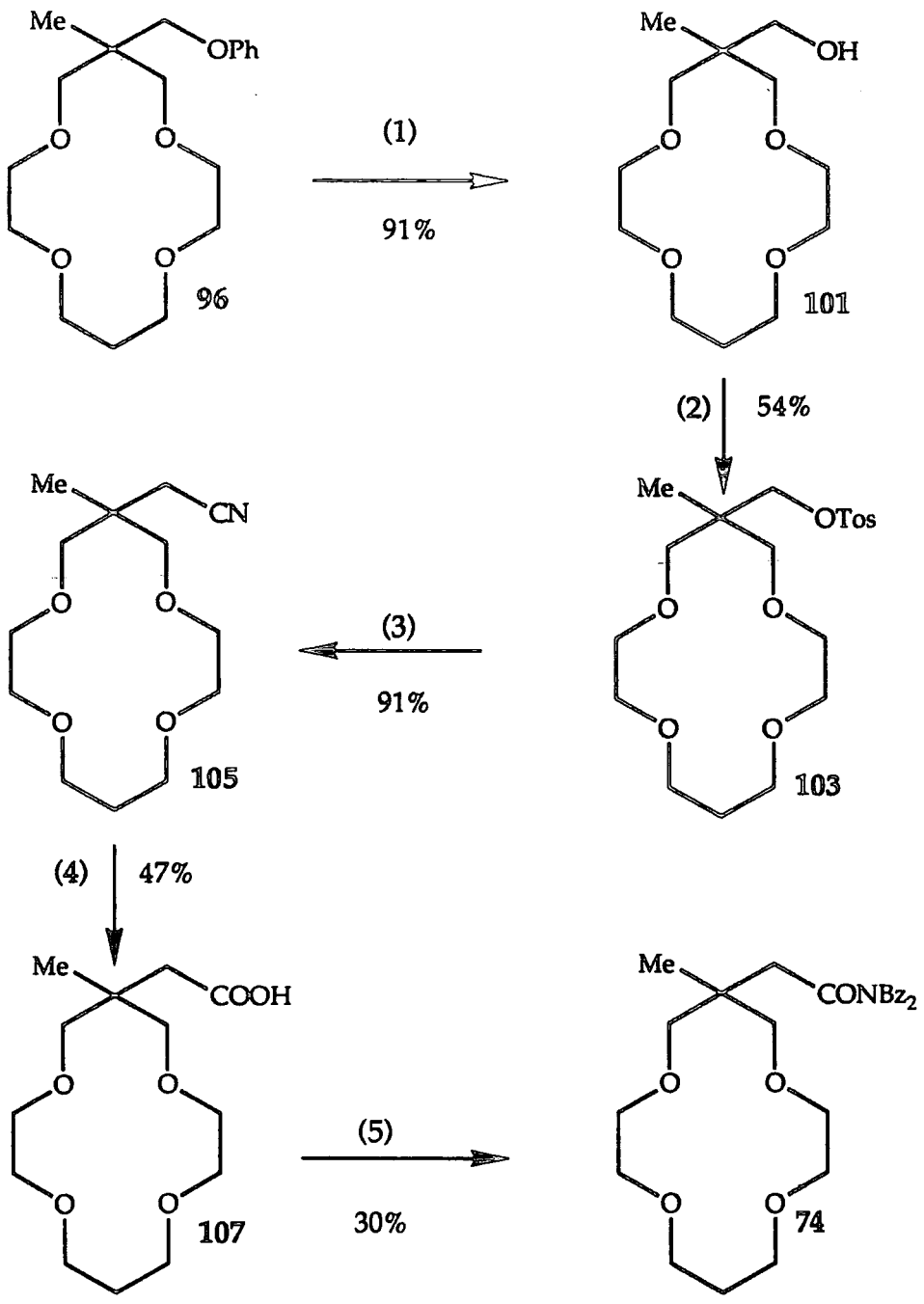
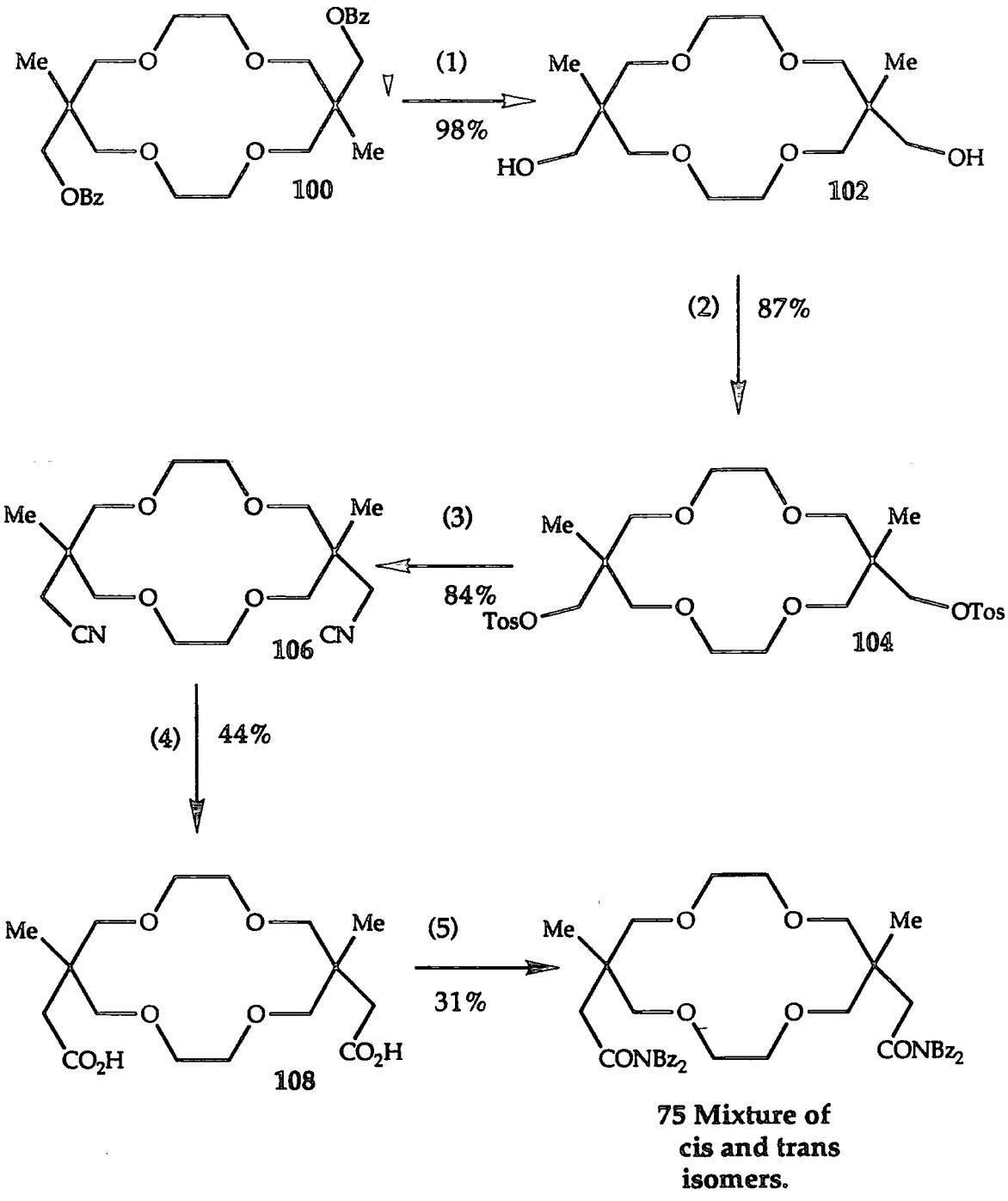


Figure 2.21: (1) Pearlman's Catalyst [Pd $(OH)_2$ on C, 15% H_2O], ethanol, tosic acid, H_2 (3atm). (2) Tosyl chloride, pyridine (-20°C). (3) KCN, 18-crown-6, DMSO (150°C). (4) NaOH (2M), $H_2O/HOCH_2CH_2OH$, reflux. (5) Bz_2NH, DCC, DMAP, CH_2Cl_2.



75 Mixture of cis and trans isomers.

Figure 2.22: (1) Pearlman's Catalyst [Pd $(OH)_2$ on C, 15% H_2O], ethanol, tosic acid, H_2 (3atm). (2) Tosyl chloride, pyridine (-20°C). (3) KCN, 18-crown-6, DMSO (150°C). (4) $NaOH_{(aq)}$ (2M), methoxyethanol. (5) Bz_2NH, DCC, DMAP, CH_2Cl_2.

In addition to the amide derivatives described above, several other 14-crown-4 analogues were examined as potential lithium ionophores and their synthesis is described below.

In a previous study Kitizawa *et al* [14] had shown that incorporation of a phosphonate ester donor (60) enhanced lithium selectivity to a similar extent to that shown by the amide derivative (59) also studied. Therefore it was decided to attempt to incorporate two phosphonate ester donors into a 14 crown 4 skeleton. The approach adopted is illustrated in Figure 2.23. Firstly the ditosylate (89) was treated with potassium iodide and converted into a di-iodide (109). A Michaelis-Arbuzov rearrangement[19] was then attempted in order to form the required carbon-phosphorus bonds. This procedure involves treatment of an alkyl halide with tri-valent phosphorus ester, in this case dimethoxyphenylphosphine, yielding an alkylphosphonate.

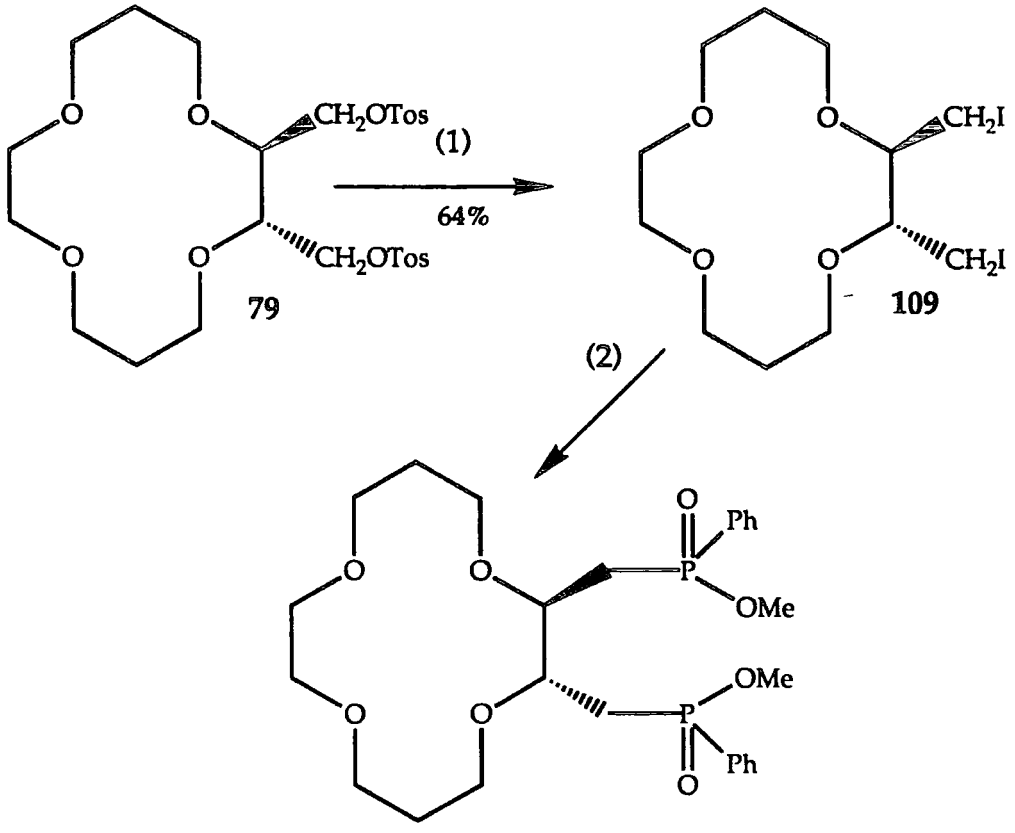
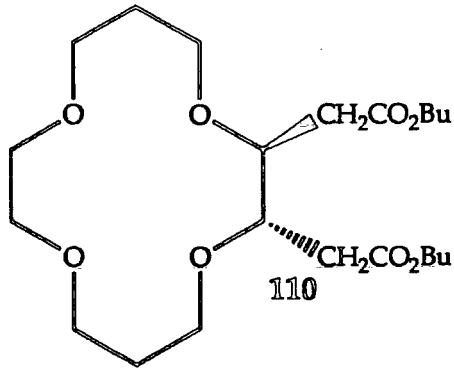


Figure 2.23 (1) KI, DMF, 60°C.

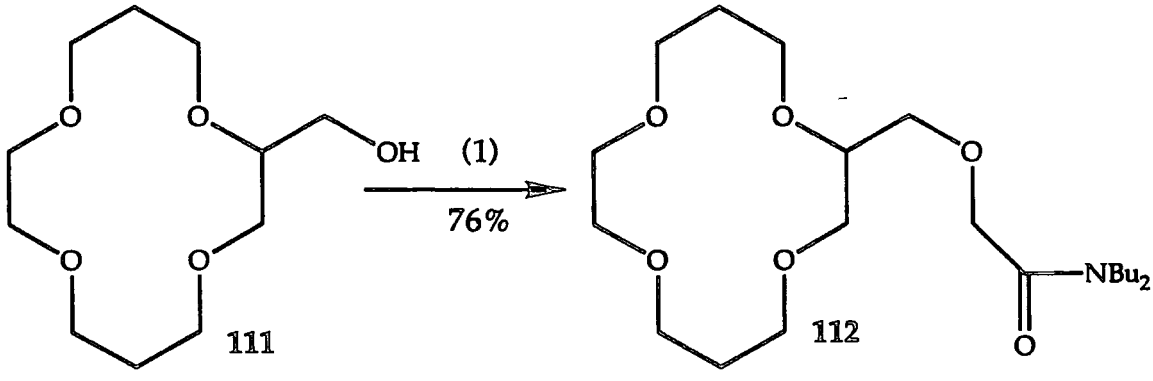
The reason for the failure was unclear. Both mass spectrometry and NMR indicated that ring degradation had possibly occurred.

In addition to the dimethyl ester (66) described previously, a dibutyl analogue (110) was also prepared from the dinitrile (90), simply by substituting n-butanol for methanol in the alcoholysis reaction.



110

Finally a monofunctionalised analogue (112) was examined. This was prepared from 2-hydroxymethyl-1,4,8,11-teraoxacyclotetradecane (111) which was prepared using the procedure described by Parker *et al* [15] (figure 2.24). It was hoped that both the ether oxygen and the amide carbonyl present in the side-arm could adopt a conformer in which simultaneous ligation of the lithium cation was possible.



111 112

Figure 2.24 (1) NaH, N,N- dibutylchloroethamide, THF.

2.5 ^{13}C NMR and IR COMPLEXATION STUDIES

A ligand: metal titration was performed between ligand (72) and lithium chloride and the data (see Figure 2.25) compared to that obtained previously for (63) [20] (Figure 2.26).

Ligand (72):-

Ligand (72) was dissolved in d^4 - MeOH and titrated with anhydrous lithium chloride. Figure 2.25 illustrates the ^{13}C shift changes which were observed as the Ligand: Lithium ratio altered. Carbons 2 and 7 are not plotted since at intermediate stoichiometries these two are seen to coalesce.

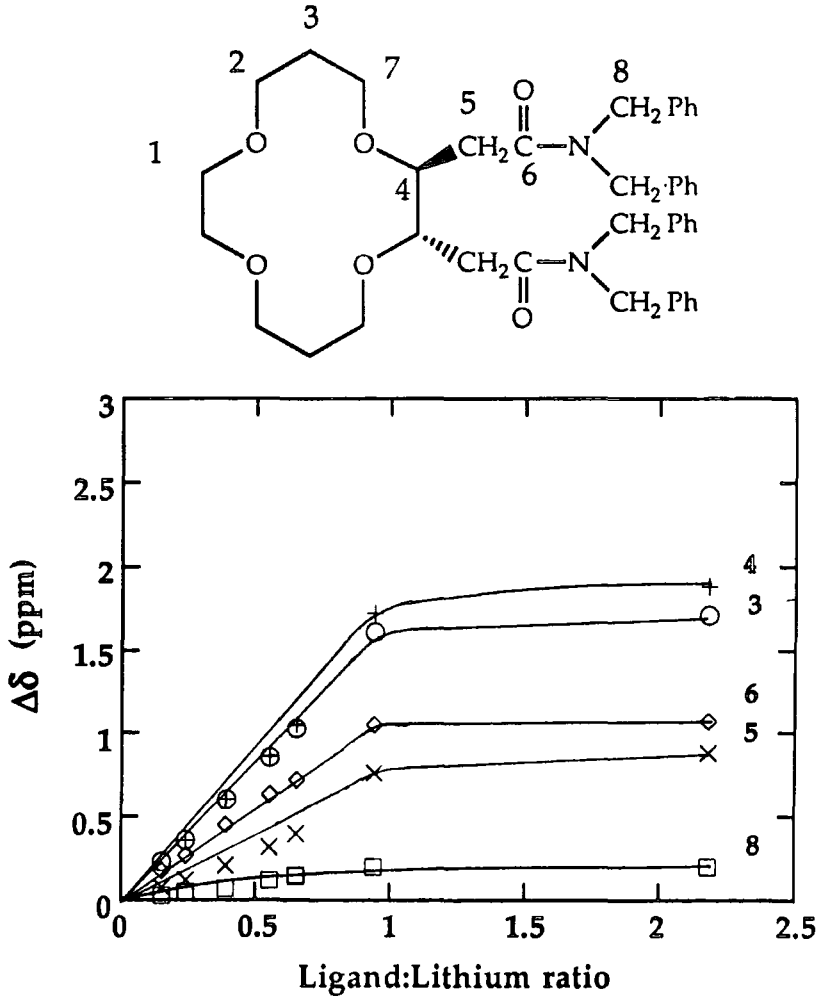


Figure 2.25:- ^{13}C Chemical shift displacements for carbon atoms of Ligand (72) in d^4 - MeOH relative to the Ligand: Lithium ratio.

Ligand (63)

Figure 2.26 illustrates the ^{13}C shift changes which were observed as the Ligand: Lithium ratio altered for the titration of Ligand **(63)** with lithium chloride. [22]

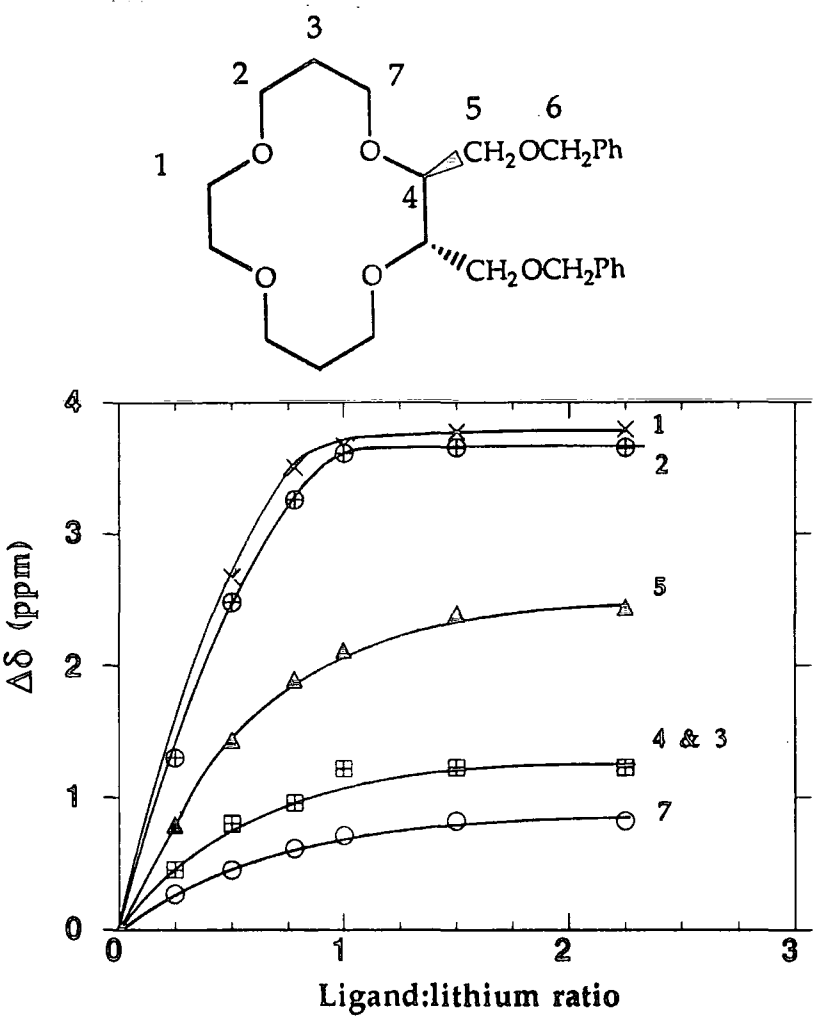


Figure 2.26:- ^{13}C Chemical shift displacements for carbon atoms of Ligand **(63)** in d^4 - MeOH relative to the Ligand: Lithium ratio.

Points to note:-

1/ In both cases a limiting chemical shift was reached when one equivalent of lithium chloride had been added. This indicated the formation of a relatively strong complex with 1:1 stoichiometry. However although the sharp curve bends observed indicated strong complexation, the fact that

time-averaged signals, as opposed to discrete lines, were observed at intermediate stoichiometries inferred that in both cases Log K < 4.

2/ The ring carbon atoms in ligand (63) exhibit appreciably higher $\Delta\delta$ values than those displayed by the ring carbons of ligand (72), upon lithium complexation. This suggests that a greater degree of conformational reorientation is required for ligand (63) to bind lithium. This may be in part due to the fact that the side-arm ether oxygens form a 5 ring chelate with the ring bound lithium, whereas with ligand (72) the carbonyl oxygens bind lithium in a favoured six ring chelate.

3/ The participation of the carbonyl groups present in ligand (72) in cation ligation was confirmed by IR spectroscopy, complexation being accompanied by a shift to a lower frequency of the carbonyl stretching frequency (1642 cm^{-1} to 1627 cm^{-1}.)

2.6 POTENTIOMETRIC STUDIES

The selectivities of ligands (64) (68) (70)-(75), (110) and (112) for lithium were measured potentiometrically using the fixed interference method. Membranes containing the ligands were fabricated according to published procedures.[21] i.e.

1.2% Sensor (ligand)

65.6% Plasticizer (oNPOE)

32.8% PVC (high molecular weight)

0.4% Lipophilic anion (KpTClPB).

The purpose of the plasticizer is to have a good non-volatile solvent medium in which to incorporate the ionophore. The lipophilic anion is present in the membrane for two reasons. Firstly it serves to reduce anionic interference and secondly it reduces membrane resistance.

2.6.1 Electrode Calibration

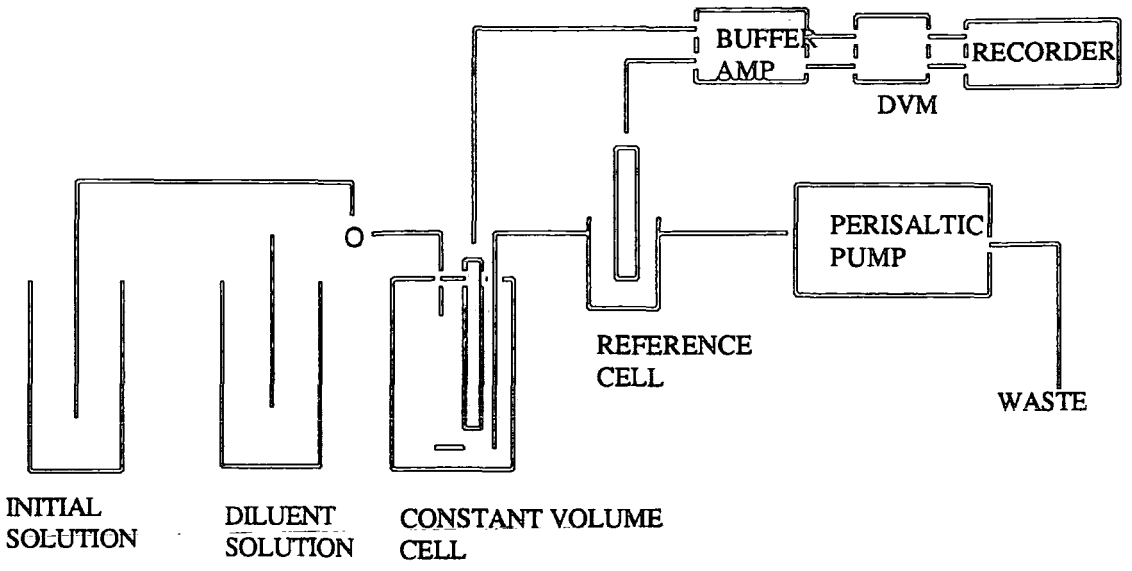


Figure 2.27:- Schematic representation of constant flow system used to evaluate I.S.E's.

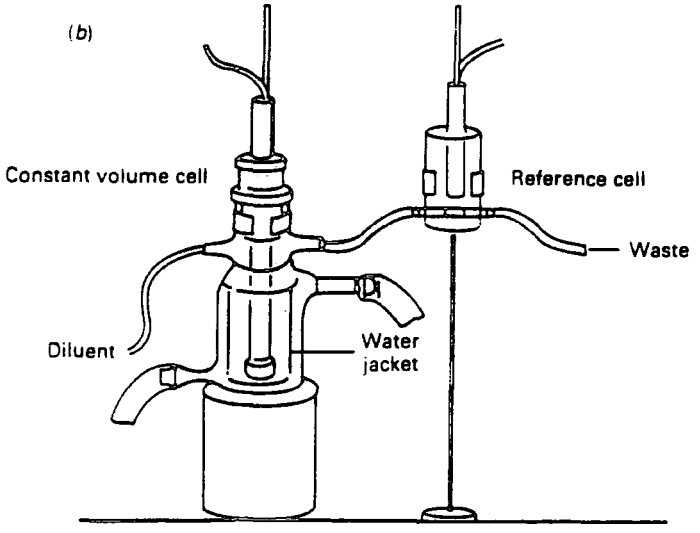


Figure 2.28 Constant flow cell

The ion-selective electrodes were calibrated using a constant dilution technique. The experimental apparatus used in these determinations is illustrated in Figure 2.27. and in basic terms involves the monitoring of electrode output as the ion concentration is continuously reduced.

Prior to examination all electrodes were conditioned for 24 hours in 10^{-3} M LiCl solution at 25°C. Thereafter they were thoroughly rinsed and immersed in a constant volume cell, which initially contained a 10^{-1}M LiCl solution, maintained at 37°C. This solution was then diluted continuously with double de-ionised water, pumped into the constant volume cell (Figure 2.28) at a rate of 6 ml/min using a peristaltic pump. As the Li concentration decreased the electrode response was plotted on a Y/t chart recorder.

Slopes and limits of detection were recorded for ligands **(64)** **(68)** **(70)-(75)**, **(110)** and **(112)** and compared to those determined previously [15].

There are several points to note from this data:-

(1) When an electrode behaves ideally it is said to exhibit a Nernstian response to variations in a specific cation concentration and is defined by the Nernst equation:-

$$E = E^{\circ} + \frac{RT}{nF} \cdot \ln [M^{+}] \quad \textbf{Equation 2.01}$$

where R = the gas constant.

F = Faraday constant.

n = the number of electrons transferred.

This in fact can be abbreviated to :-

$$E = E^{\circ} + \frac{0.06154}{n} \cdot \log_{10} [M^{+}] \text{ at } 37^{\circ}C. \quad \textbf{Equation 2.02}$$

Thus at 37°C the electrode response to a monovalent ion should exhibit a slope corresponding to a 61.54 mV/decade change.

(2) Limits of detection were measured according to IUPAC recommendations. These define the limit of detection as the concentration of primary ion at which the electrode response deviates from the linear portion of the calibration graph by 18.5 mV (see section 2.6.2 for derivation).

(3) Response times were also noted.

Results for the calibration of ligands (64) (68) (70)-(75), (110) and (112) over the lithium concentration range are illustrated below in Table 2.01.

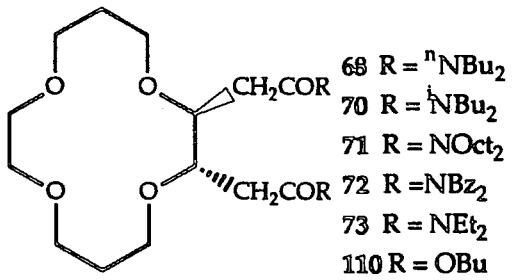
There are several points to note from this data:-

(1) The limits of detection displayed by the amide derivatives (68), (70) and (72) offer a significant improvement upon those displayed by the commercially available Philips electrode.

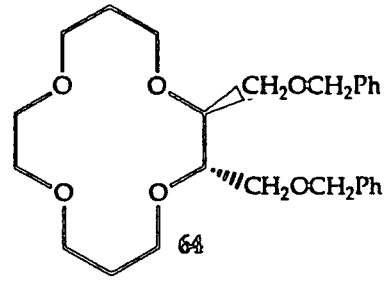
(2) Somewhat surprisingly, the dioctylamide derivative (71) exhibited an extremely slow response time when incorporated into a membrane, thus precluding its use as an ionophore. The reason for this slow response is not fully understood. Two possible explanations exist:-

a) The octyl chains sterically inhibit the complexation of the lithium cation. Although possible, one may expect a similar effect to have occurred to some extent with the di^{n}butyl derivative (68).

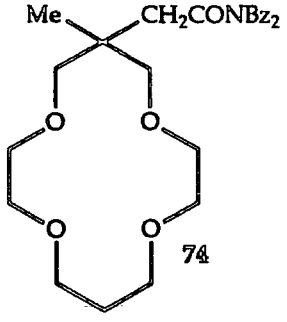
b) A more likely hypothesis is that the lipophilicity of the octyl side-chains is such that the ionophore interacts with the plasticiser as the result of hydrophobic interactions and thus becomes locally "ordered" within the membrane. Thus the ionophore is no longer capable of moving freely within the membrane.



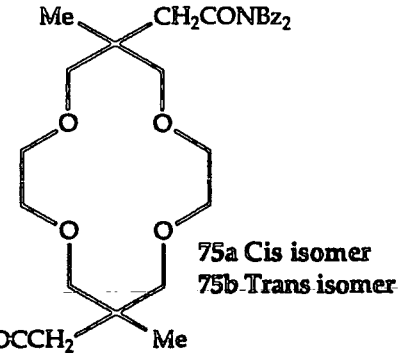
68 R = $^{n}NBu_2$
70 R = $^{i}NBu_2$
71 R = $NOct_2$
72 R = NBz_2
73 R = NEt_2
110 R = OBu



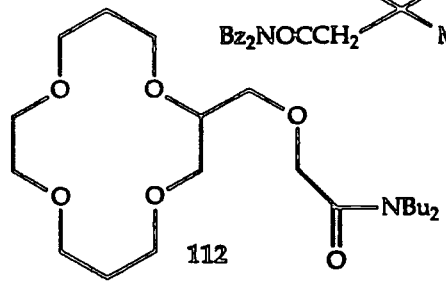
64



74



75a Cis isomer
75b Trans isomer



112

LIGAND	SLOPE (mV /Decade)	LIMIT OF DETECTION (Log [c])
14-C-4 dibenz (64)	60.0	-4.6[a]
14-C-4 di^{n}butylamide (68)	60.0	-5.0[b]
14-C-4 di^{i}butylamide (70)	50.0	-5.0
14-C-4 dioctylamide (71)	---	---
14-C-4 dibenzylamide (72)	61.0	-5.5
14-C-4 diethylamide (73)	52.0	-4.5
14-C-4 monobenz (74)	60.0	-4.5
14-C-4 dibenz (75)	61.5	-5.0
14-C-4 dibutyl ester (110)	60.0	-4.4
Philips	62.0	-4.5
14-C-4 mono amide (112)	60.0	-3.7

a) Reference 2. b) Reference 3

Table 2.01:- Calibration of Electrodes in Pure Lithium Chloride Solution ($1x\ 10^{-1}$ - $1x\ 10^{-6}$ M).

2.6.2 Lithium Selectivity Measurements

Lithium selectivity measurements were made using the fixed interference methods. This involved measuring ΔE values for changes in LiCl concentration against a constant interference background of:-

a) 150mM NaCl (upper concentration limit of Na^+ in whole blood).

b) 4.3mM KCl (upper concentration limit of K^+ in whole blood)

c) 1.26mM $CaCl_2$ (upper concentration limit of Ca^{2+} in whole blood).

Although certain ionophores are selective for a particular cation they do not respond exclusively to this ion and therefore, particularly at low concentrations, interferent ions start to influence the response of the electrode. Selectivity of the electrode is defined in terms of the selectivity coefficient $K^{POT}_{Li,\,M}$. This itself is defined by the Nicholsky-Eisenmann equation:-

$$E = E^{\circ} + 0.06154 \text{ Log} \left\{ [Li^+] + \Sigma K^{POT}_{Li\,M} [M]^+ . z_{Li} / z_M \right\} \quad \textbf{Equation 2.03}$$

Where M = interferent ion.

If a plot of electrode output against primary ion concentration is studied closely, it is possible to assign three distinct regions to the plot.

In the region A to B ,the electrode is responding to the primary ion Li^+ and exhibits a Nernstian response. In the second region B to C, as the primary ion concentration decreases the response of the electrode becomes increasingly influenced by the interferent ion M^+ and finally in the third region of the plot the electrode responds solely to the interferent ion.

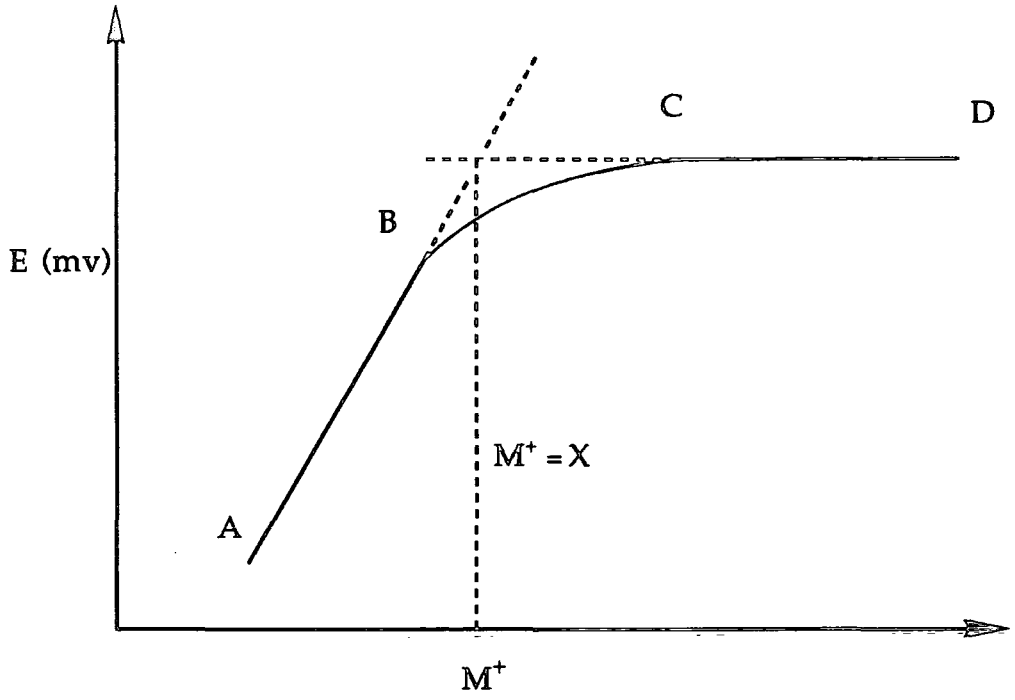


Figure 2.29 : Plot of electrode potential against primary ion concentration with a fixed interference background.

At the point where both ions contribute equally to the electrode response:-

$$[Li^+]^1 = K^{POT}_{Li,M} \cdot [M^+]^{z_{Li}/z_m},$$

Thus:-

$$E = E^\circ + 0.06154 \log \left\{ 2[Li^+]^1 \right\}.$$

The difference between this value and the emf were no interference present can be expressed as:-

$$E = E^\circ + 0.06154 \log \left\{ 2[Li^+]^1 - [Li^+] \right\}$$

$$E = E^\circ + 0.06154 \log \left\{ 2 \right\}$$

$$E = 18.5 \text{ mV (at } 37^\circ C).$$

The point at which the experimental curve deviates by this margin from the linear portion of the plot is referred to as the selectivity coefficient.

Measurements of lithium selectivity for ligands (64) (68) (70)-(75), (110) and (112) were made against a fixed interference background of 150mM NaCl, 4.3 mM KCl and 1.26mM $CaCl_2$using the constant dilution technique described above. The technique used was virtually identical to that used to calibrate the electrodes differing only in terms of the nature of the diluent solution, substituting simulated plasma for di-ionised water. Thus selectivity coefficients were calculated directly from the plotted curves (see Figures 2.30-Figure 2.36) and are displayed in Table 2.02

LIGAND	SLOPE (mV/ dec) (±2.0)	LIMIT OF DETECTION (Log [c])	Log K_{ij}^{POT} (±0.05)
14-C-4 dibenz (64)	62.0	-2.6	-1.77
14-C-4 di^{n}butylamide (68)	61.0	-3.8	-2.92
14-C-4 di^{i}butylamide (70)	61.0	-4.1	-3.25
14-C-4 dioctylamide (71)	---a	---	---
14-C-4 dibenzylamide (72)	54.0	-3.75	-2.93
14-C-4 diethylamide (73)	---b	---	---
14-C-4 monobenz (74)	60.0	-3.10	-2.30
14-C-4 dibenz (75)	59.0	-3.10	-2.30
14-C-4 dibutyl ester (110)	61.0	-3.25	-2.25
Philips	47.0	-2.6	-1.89
14-C-4 mono amide (112)	---	---	---

a) Due to the very slow response time exhibited by this electrode during calibration no selectivity coefficient determinations were performed.

b) Severe interference was observed

Table 2.02:- Lithium Selectivity Measurements, determined using the Fixed Interference Method, at 37°C.

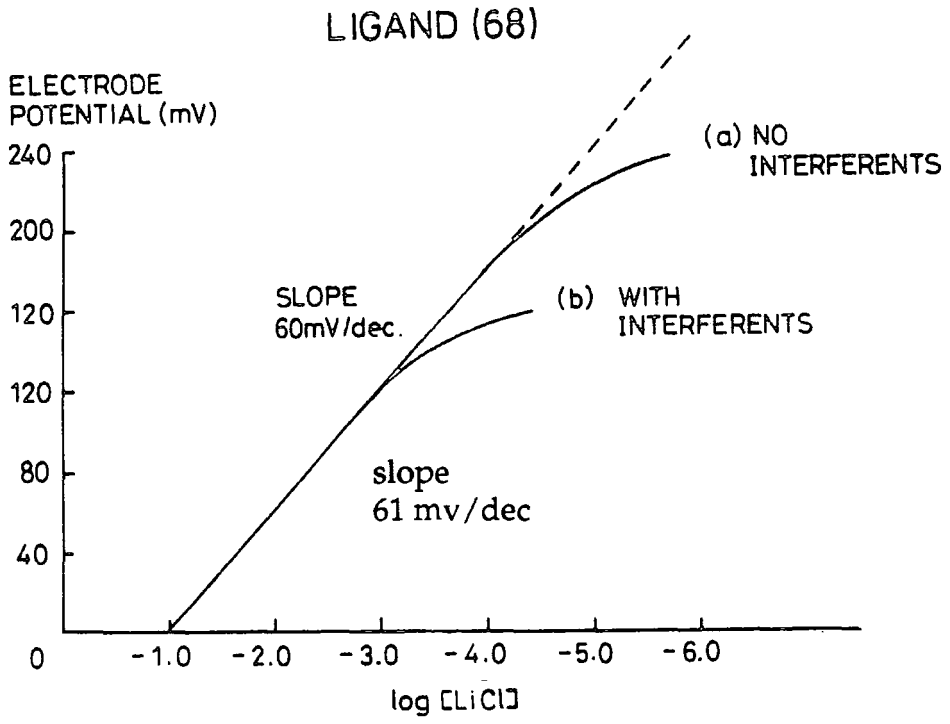


Figure 2.30:- Graph of Electrode Potential Against Lithium Chloride Concentration for Ligand **(68)** at 37°C (a) Pure LiCl and b) Fixed interference background of 150mM $CaCl_2$, 4.3 mM KCl and 1.26mM $CaCl_2$

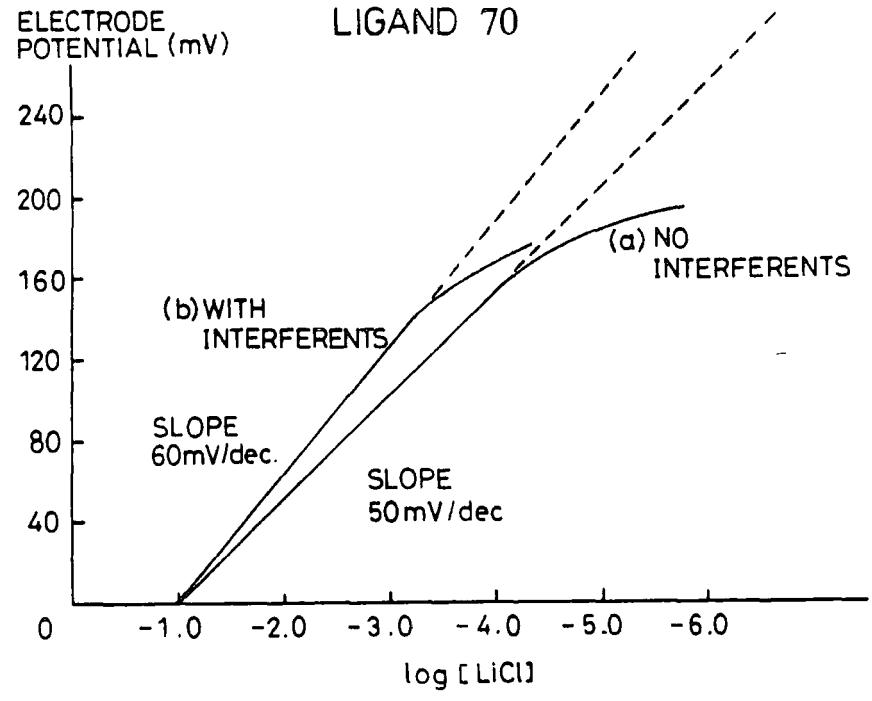


Figure 2.31:- Graph of Electrode Potential Against Lithium Chloride Concentration for Ligand **(69)** at 37°C (a) Pure LiCl and b) Fixed interference background of 150mM $CaCl_2$, 4.3 mM KCl and 1.26mM $CaCl_2$

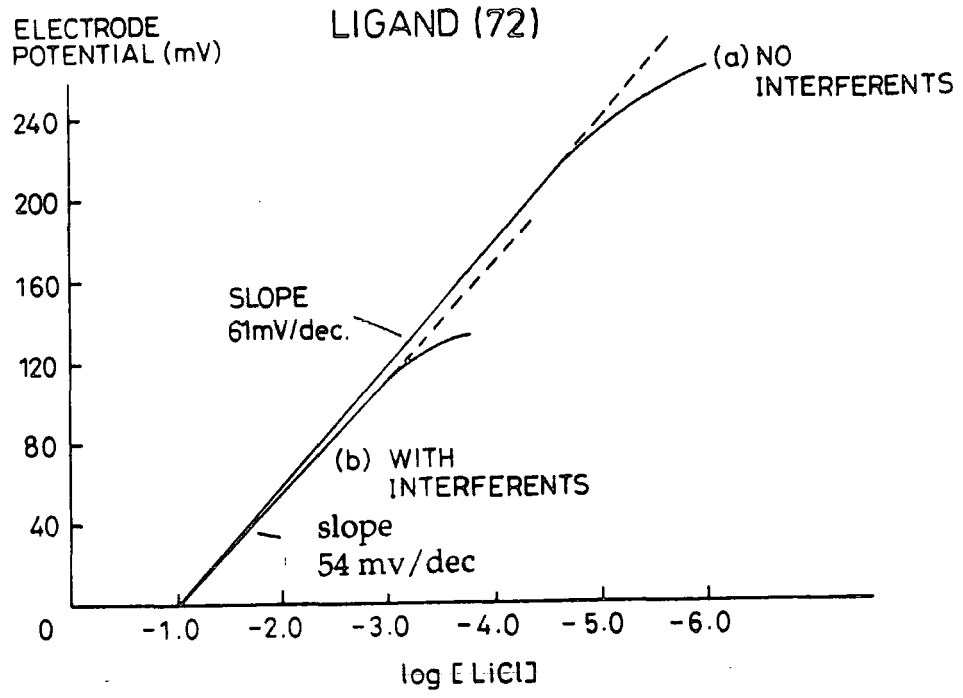


Figure 2.32:- Graph of Electrode Potential Against Lithium Chloride Concentration for Ligand (72) at 37°C (a) Pure LiCl and b) Fixed interference background of 150mM $CaCl_2$, 4.3 mM KCl and 1.26mM $CaCl_2$

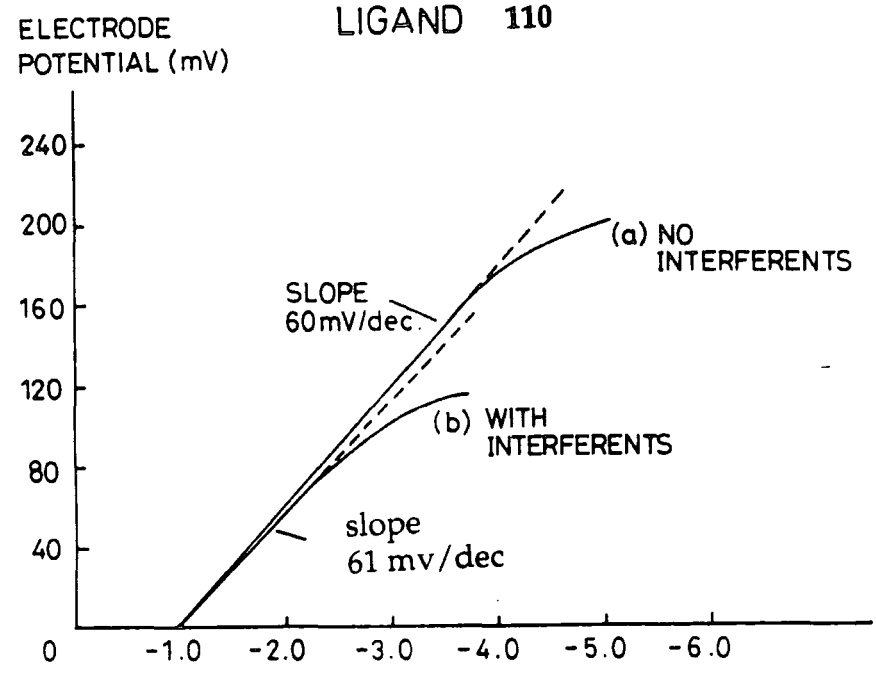


Figure 2.33:- Graph of Electrode Potential Against Lithium Chloride Concentration for Ligand (110) at 37°C (a) Pure LiCl and b) Fixed interference background of 150mM $CaCl_2$, 4.3 mM KCl and 1.26mM $CaCl_2$

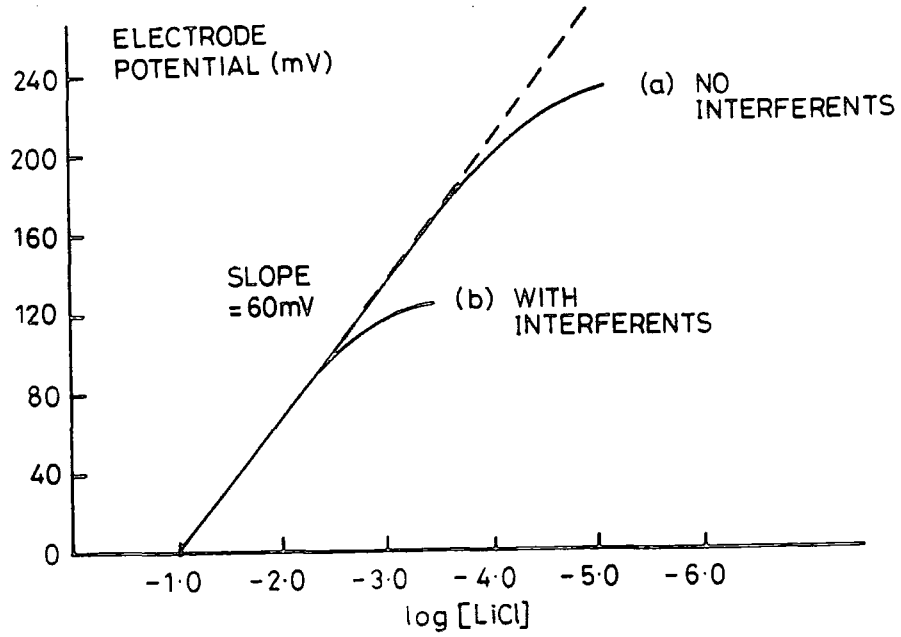


Figure 2.34:- Graph of Electrode Potential Against Lithium Chloride Concentration for Ligand **(74)** at 37°C (a) Pure LiCl and b) Fixed interference background of 150mM $CaCl_2$, 4.3 mM KCl and 1.26mM $CaCl_2$

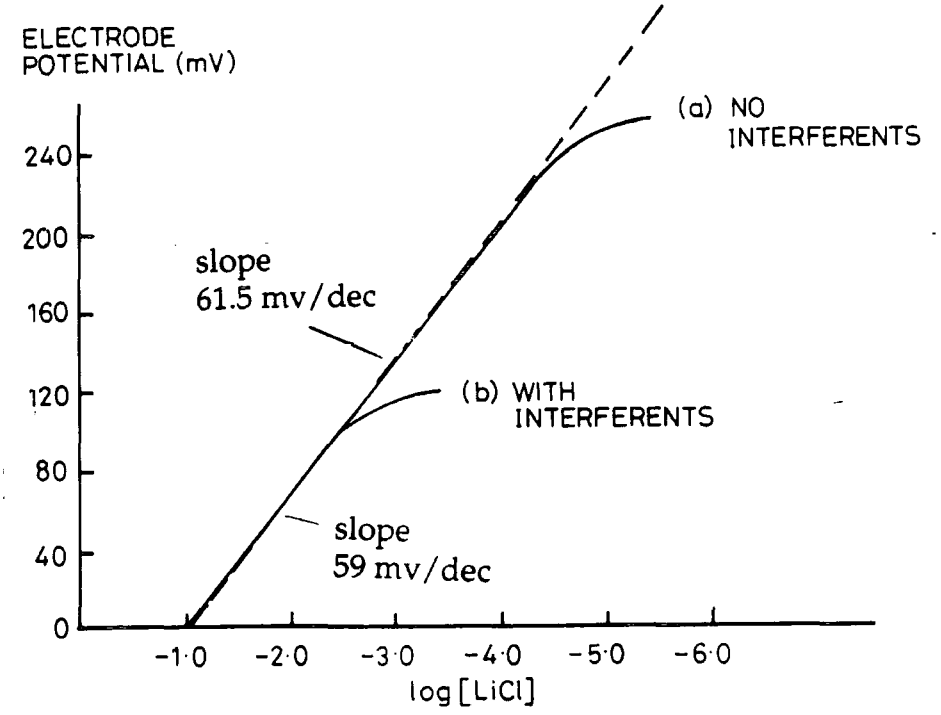


Figure 2.35:- Graph of Electrode Potential Against Lithium Chloride Concentration for Ligand **(75)** at 37°C (a) Pure LiCl and b) Fixed interference background of 150mM $CaCl_2$, 4.3 mM KCl and 1.26mM $CaCl_2$

There are several points to note from the results:-

(1) Previous studies [2,3] have shown that interference from both potassium and calcium does not define a limit of detection within the lithium concentration range examined ($1x\ 10^{-1}$ to $1x\ 10^{-4}$) and therefore any interference which leads to a limit of detection is presumed to be due entirely to sodium ions.

(2) The slopes observed for the amide ionophores, with the exception of the the diethyl amide (**73**), and the extended amide (**112**), remained similar to those observed in pure LiCl. Indeed for the di^{i}butyl amide derivative (**70**) the slope improves slightly when evaluated in simulated plasma. The reason for this improvement is unclear.

(3) Both the diethyl amide derivative (**73**) and the extended amide (**112**) performed very badly in this media. Both experiencing severe sodium interference even at high lithium concentrations. For (**112**) IR studies revealed that the side-arm was flexible enough to allow the carbonyl group to ligate both lithium and the larger sodium cation, hence no Li^+/ Na^+ selectivity was observed.

(4) The greatest selectivity was displayed by the hexacoordinate amide derivatives (**68**), (**70**) and (**72**), as expected. It is believed that the enhanced selectivity arises as a result of the following factors:-

a) The di-amides coordinate lithium more strongly than the previously described mono-amide (**69**) by virtue of their possession of a sixth donor site, thus matching the preferred coordination number of lithium.

b) The presence of the two donor arms, one positioned above and the other below, the plane of the ring, sterically inhibits the possible formation of two to one ligand:metal sandwich complexes with cations such as sodium.

c) Upon ligation of the ring bound lithium cation by the side-arm carbonyls, two six ring chelates are formed. As stated earlier, the formation of six-ring chelates favours the complexation of smaller cations (see section 1.3.3).[17]

d) Amides possess a high ground state dipole moment and this again favours the complexation of small "charge dense" cations. This is well illustrated by a comparision of the selectivity coefficients displayed by (68) and (110). These derivatives differ only in terms of the relative σ donor ability of the side-arms carbonyl groups (amide vs ester). The derivative possessing amide side-arm donors (68) and hence stronger σ donor potential exhibits significantly greater lithium/ sodium selectivity than the ester functionalised analogue (110). [Log $K^{POT}_{Li/Na}$ = -2.92 (68); Log $K^{POT}_{Li/Na}$ = -2.25 (110)].

e) The values displayed by (68), (70) and (72) are a significant improvement upon those displayed by the commercially available Philips electrode and although the Li^+/ Na^+ selectivity is still lower than that required for the 'ideal' measurement of Li^+ in whole blood ($Log^{POT}_{Li,Na}$ = -4.20), measurements of Lithium concentrations could be performed for Li^+ conentrations within the therapeutic range (0.5-1.5 mmol dm^{-3}).

(5)The selectivity displayed by the diamide derivative (75) was, somewhat disappointingly, identical to that displayed by the closely related mono-amide (74) ($-\log^{POT}_{Li/Na}$ = 2.30). It was proposed, as previous studies had shown [2], that the hexacoordinate ligand might display enhanced lithium selectivity in comparison to that displayed by the five-coordinate analogue. It was suggested that this might result from the fact that the ligand possesses an additional ligating donor atom and also because of the increased steric hindrance introduced by the extra donor arm, thus inhibiting competitive two to one "sandwich" complexation, with sodium in particular. The lack of

any enhanced selectivity displayed by the diamide (75) may therefore have resulted from either of two factors:-

a) The ionophore was evaluated as a mixture of the two diasteromers for the reasons described above. It may be that the cis isomer dominates the complexation kinetics and therefore governs the selectivity displayed by the ionophore. If this were the case then it would be expected that the selectivity might be the same as that displayed by the mono-amide.

b) A more likely explanation is that the selectivity displayed by (74) and (75) are identical because, in both cases, the origin of the selectivity exhibited by these ligands arises predominantly from steric factors. Indeed, the selectivity values obtained for (74) and (75) are very similar to that obtained with ligand (50), a 14 membered ring analogue posessing two methyl groups at one apex and a dodecyl group at the other where some degree of selectivity was achieved by sterically hindering 2:1 sandwich complexation(see page 63) [10], ($-\log K^{POT}_{Li,Na} = 2.30$ for (74) and (75) compared to 2.21 for (50).)

That is to say that in both cases there is little participation of the side-arm amide carbonyls in cation ligation. This would appear to be backed up by IR studies which indicated that only very weak carbonyl ligation occurred upon complexation (a shift in the carbonyl stretching frequency of only 3 cm^{-1} being observed, 1640 to 1637 cm^{-1}). It is probable, therefore, that in both cases the ligands are not capable of orientating the side-arms in such a way as to allow the adoption of a conformation in which the amide carbonyls can significantly ligate the lithium cation.

Furthermore the findings contradict the assumption made by *Kitizawa* [14] that the amide derivative **(59)** displays enhanced selectivity ($-\log K^{POT}_{Li,Na} = 2.34$ over closely related analogues as a result of amide ligation

of the cation (no evidence to substantiate this claim was provided). Instead it would appear that any enhancement was entirely steric in origin.

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CHAPTER III

BINDING PROPERTIES OF AMIDE AND AMIDE ESTER N-FUNCTIONALISED POLYAZA, POLYOXAMACROCYCLES

3.1 INTRODUCTION

Lariet ethers, side-arm bearing crown ethers, have attracted considerable interest (see section 1.3.8), because selectivity has been shown to be enhanced by the incorporation of appropriate ligating peripheral donors. Recently an attempt has been made to mimic the properties of the naturally occuring ionophore valinomycin[1,2] which exhibits extremely high potassium selectivity (see section 1.3.8.2). Gokel [3] synthesised a series of peptide derivatives of 4,13-diaza-18-crown-6 and reported that although they did not mimic valinomycin, they apparently formed extremely stable complexes with calcium [log K > 7 in H_2O] and that they exhibited very high Ca^{2+}/ Na^+ selectivity. The values reported were in fact higher than those obtained for the tetra-amide derivative of [12]-N-4 **(115)** which was previously thought to exhibit the highest stability constant for Ca^{2+} for a neutral ligand, 10 $^{6.82}$ in aqueous solution [4].

Thus it was decided to investigate these findings [5], in particular to study the possible role of the ester carbonyls in the enhancement of binding. Accordingly the difunctionalised secondary amide derivatives of the [12]-N_2O_2, [15]-N_2O_3 and [18]-N_2O_4 coronands **(116)** **(118)** and **(120)** were prepared and their binding ability compared to derivatives **(117)** **(119)** and **(122)** in which the N-methyl substituent has been replaced by a potentially ligating CH_2CO_2Et group. Additionally a tertiary diamide derivative of [12]N_2O_2 **(123)** was prepared and its binding properties examined in comparision to those of the secondary amide in order to determine the role that, H-bonding, between the ligand and solvent molecules, plays in determining the relative importance of the enthalpies and entopies of complexation.

3.2 LIGAND SYNTHESIS

Alkylation of the parent diamines with N-methyl-2-bromoethanamide under basic conditions [K_2CO_3, CH_3CN, NaI] afforded the required diamides **(116)** **(118)** and **(120)** in yields of 71, 67 and 88% respectively. The related compounds **(117)** **(119)** and **(122)** were similarly prepared using ethyl (N-2-bromoethanoyl)glycinate in yields of 68,69 and 59% respectively. The tertiary diamide **(121)** again involved alkylation under basic conditions, the alkylating agent being N,N'-dimethyl-2-bromoethanamide,with an isolated yield of 83% (Figure 3.01).

3.3 ^{13}C NMR AND IR STUDIES OF COMPLEXATION

A series of ligand:metal ^{13}C NMR titrations were performed for several ligands both with calcium and sodium as the cation. Admixture of increasing amounts of anhydrous calcium chloride to a solution of ligand **(116)** resulted in changes in the ^{13}C NMR chemical shifts of all the carbons present in the ligand (Figure 3.02). At stoichiometries between 0.1:1.0 and 1.0:1.0 (salt:ligand) discrete lines were observed for all carbons except for the carbonyl carbon.

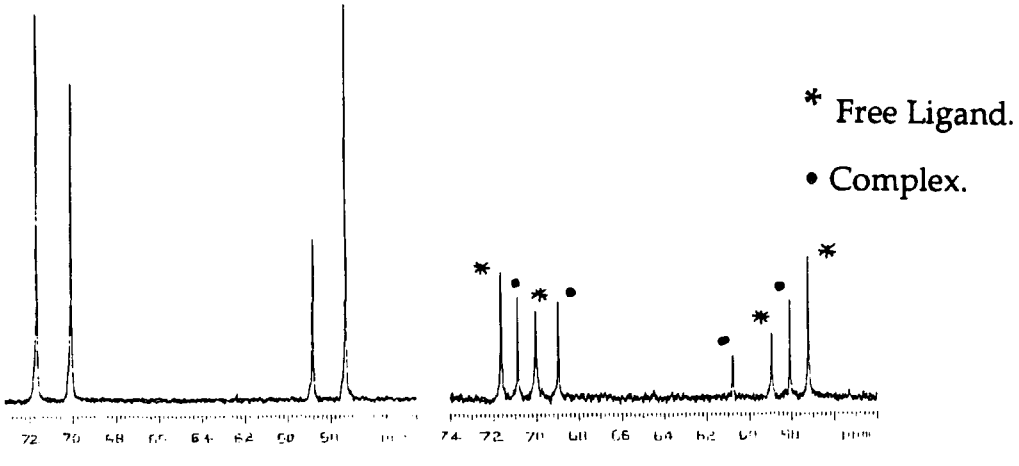
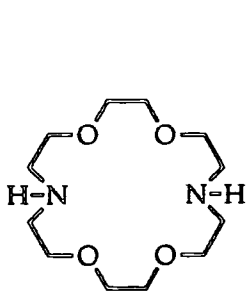
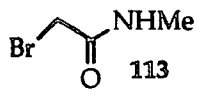


Figure 3.02 Illustration of the discrete lines observed for free and complexed ligand at intermediate stoichiometries.

PARENT MACROCYCLE	ALKYLATING AGENT	FUNCTIONALISED MACROCYCLE





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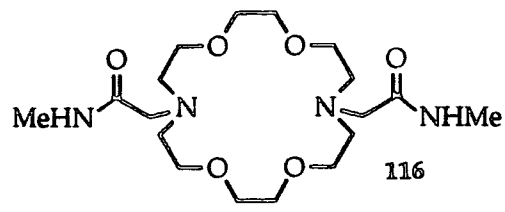

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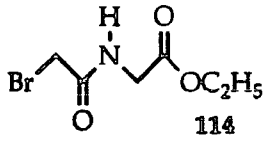

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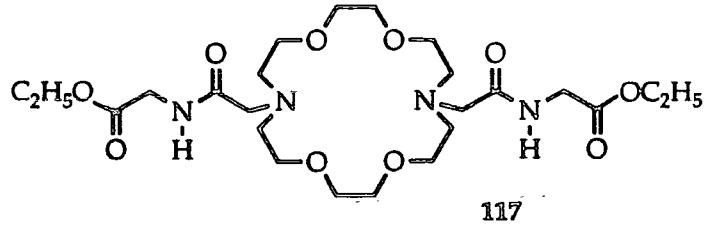

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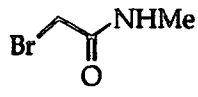

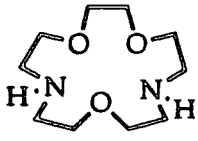

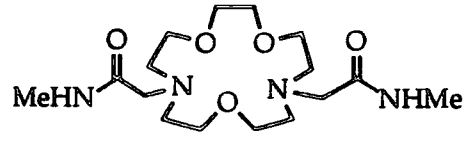

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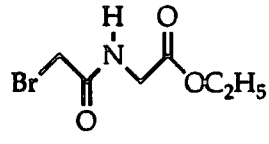

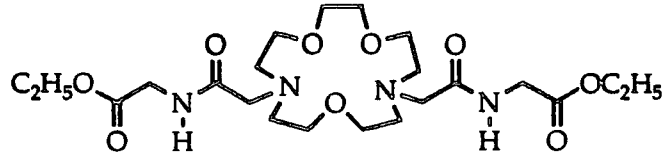

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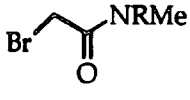
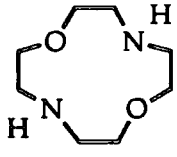
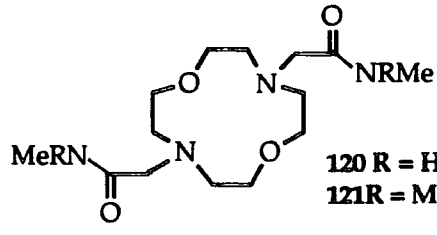


R =H or Me

(115)

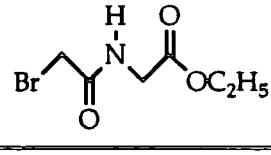


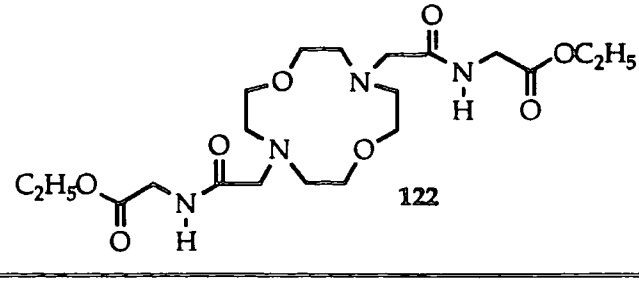


120 R = H

121R = Me

Figure 3.01





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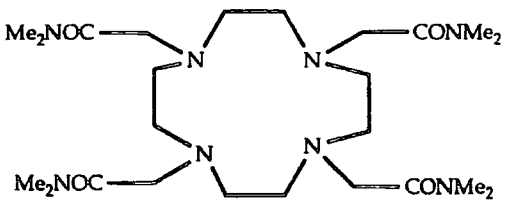

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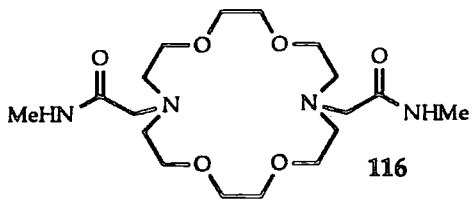

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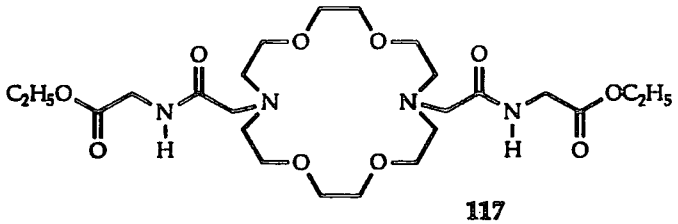

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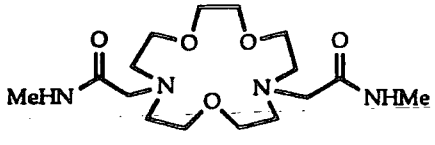

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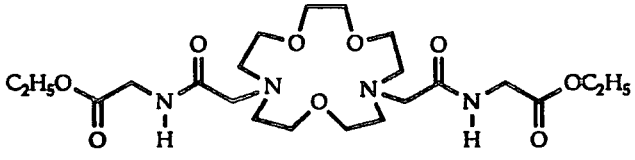

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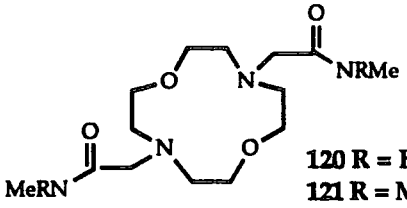
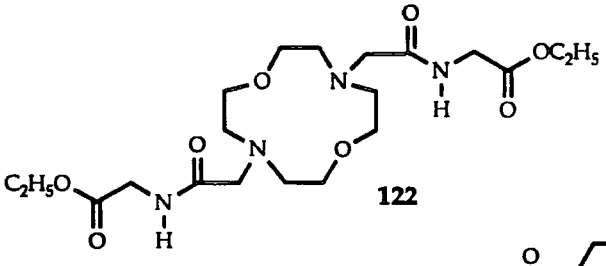
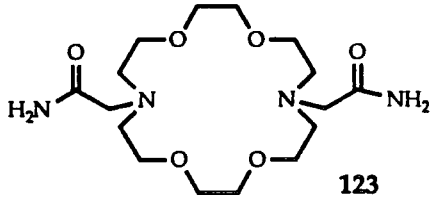


120 R = H
121 R = Me

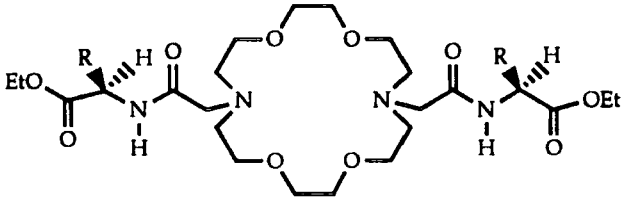
Figure 3.01b



122



123



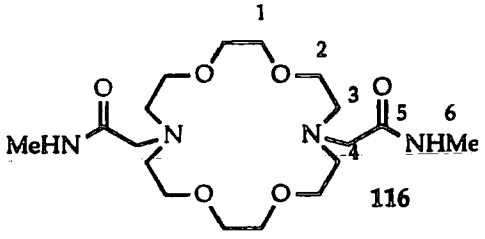
124 R = CH_3
125 R = iPr
126 R = iBu

This is indicative of slow cation exchange (on the NMR timescale) and is typical of a complex possessing a 1:1 stability constant of greater than 10^4. The resonance of the carbonyl carbon was seen to broaden at stoichiometries between 0.1:1 and 0.5:1 (salt : ligand) and sharpen thereafter. This is consistent with the amide donor exchanging rapidly between free and bound states prior to formation of the 1:1 complex. No resonances due to free ligand were observed following admixture of one equivalent of $CaCl_2$. This indicated the formation of a 1:1 complex, and upon addition of further increments of $CaCl_2$ no further change in chemical shift was observed. In fact with all the ligands examined 1:1 complexation was observed, for complexation with both sodium and calcium. (see Figure 3.04).

The magnitude of the shifts in the ^{13}C resonances seen upon complexation reflects the differing degree of conformational change both in the ring and the side-arms that occurs upon complexation, rather than being indicative of the binding strength. Additionally the introduction of a cation, may perturb the magnetic shielding. Thus although a change in the chemical shift is indicative of binding, its magnitude cannot be used as the basis for approximating the strength of the interaction. However an estimate of the strength of complexation can be made by analysing the curve shape. ^{13}C NMR is often used in tandem with IR spectroscopy where the decrease in stretching frequency gives an indication of the strength of an interaction between the cation and carbonyls present in the ligand.

Complexation with sodium was also studied, again by the admixture of stoichiometric quantities of sodium (anhydrous sodium acetate) to a ligand solution (in CD_3OD). As stated above, 1:1 complexation was observed. Time averaged signals were observed for free and complexed ligand at intermediate stoichiometries. This is indicative of fast exchange kinetics [on the NMR timescale] and is associated with weaker complexation ($\log K_s < 4$). With sodium complexation, coordination shifts were generally larger

than with the corresponding calcium complex and this may reflect the greater ligand reorganisation required in order to complex sodium. No evidence was obtained to suggest the formation of 2:1 ligand : metal "sandwich" complexes at intermediate stoichiometries. Figure 3.03 shows the smooth progression in coordination shift for all the carbon atoms of ligand (116) up to a limiting value at 1:1 sodium:ligand stoichiometry.



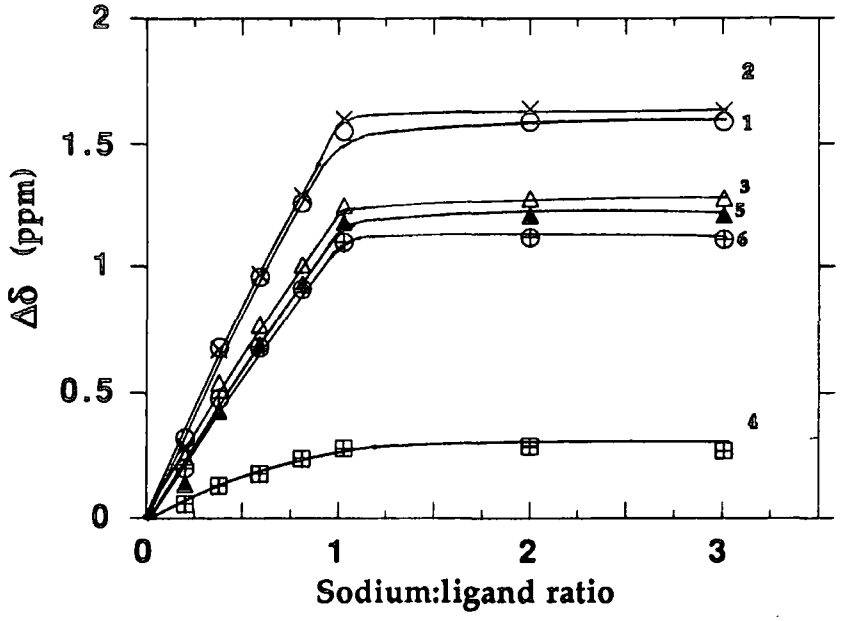


Figure 3.03 ^{13}C NMR coordination shifts for the carbon atoms of ligand **(116)** following incremental addition of solid NaOAc (298K, d^4MeOH).

An estimate of the binding strength of ligand **(116)** with sodium was made using an iterative data analysis devised by Dr. F. O'Carroll at Durham. Provided the exact concentration of the ligand and the limiting chemical shift for a particular carbon are known, the data curve can be used (see

appendix) to ascertain the binding strength, semi-quantitively. Figure 3.03 (b) illustrates the analysis performed on ligand (116).

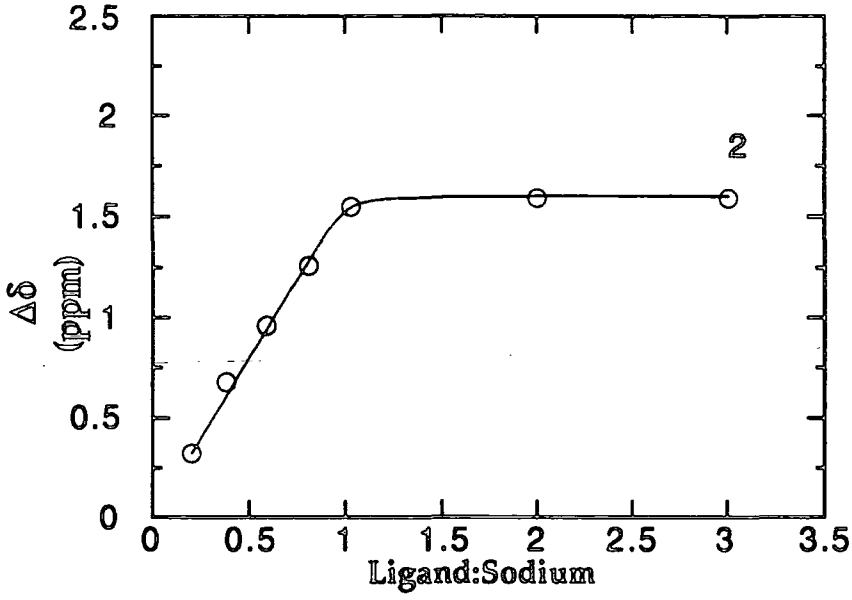
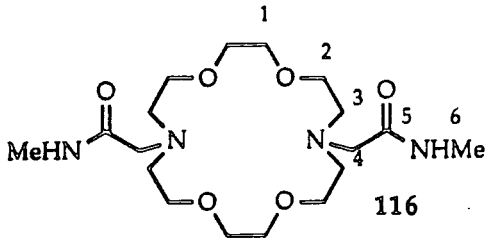


Figure 3.03 (b) :- ^{13}C NMR coordination shifts for carbon 2 of ligand (116) following incremental addition of solid NaOAc (298K, d^4MeOH).

Analysis of the slope produced a value of K = 1583 (log K = 3.2) for the complexation of sodium. As can be seen from figure 3.03 (b) the curve "fit" is extremely good and this is reflected in the correlation coefficient, a value of R = 0.9978 being obtained. The actual value, Log K = 3.2, correlates quite well with those values determined potentiometrically (log K = 3.77 for the related primary amide analogue (123) [6, 9]).

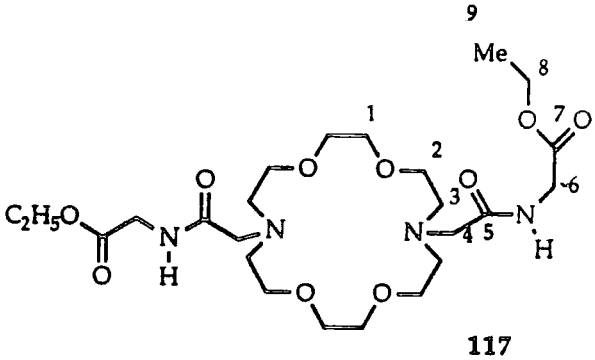
In order to confirm the participation of the side-arm carbonyl groups in cation complexation, thin films of the ligands and the subsequent complex were studied using IR spectroscopy. In all the ligands studied amide ligation was confirmed both in the calcium and sodium complexes. With ligand (117) a reduction in the amide carbonyl stretching of 22 cm^{-1} was accompanied by a reduction in the ester carbonyl stretching frequency of

10 cm^{-1} upon calcium complexation. This is clearly indicative of the simultaneous ligation of both types



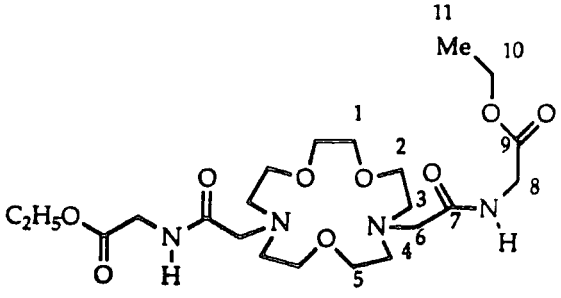
116

carbon atom	Δδ(Ca) (ppm)	Δδ(Na) (ppm)
1	0.82	1.57
2	1.13	1.62
3	0.82	1.27
4	1.95	0.28
5	0.15	1.20
6	0.10	1.11



117

carbon atom	Δδ(Ca) (ppm)
1	0.77
2	0.96
3	0.35
4	3.38
5	0.55
6	0.08
7	0.35
8	0.53
9	0.06



119

carbon atom	Δδ(Ca) (ppm)	Δδ(Na) (ppm)
1	0.29	0.71
2	0.89	1.03
3	1.65	1.57
4	3.63	2.26
5	0.58	0.76
6	0.08	0.61
7	0.76	1.21
8	0.00	0.49
9	0.34	0.51
10	0.26	0.71
11	0.03	0.09

Figure 3.04 Representative ^{13}C NMR Coordination Shifts (Δδ) following 1:1 complexation with $CaCl_2$ or NaOAc (293 K, CD_3OD).

of carbonyl group upon calcium complexation. However the sodium complex of (117) showed no ester ligation, suggesting no ester participation in complexation.This is in accord with the findings of Gokel *et al*, whereby crystallographic analysis [6] of the sodium complex of the closely related methyl ester of (117) showed no participation of the ester carbonyls in the complex (Figure 3.05). Another interesting feature of this crystal structure is the fact that the ring adopts a twist boat conformation with both the side arms on the same side of the complex. This represents a large change in ligand conformation in order to complex sodium since the free ligand has been shown to adopt a conformation in which the side arms are in an anti relationship [6]. Thus energy must be expended in substantially altering the conformation to effect complexation. In the [15] ring series, the amide, ester derivative (119) showed only a very small reduction in the ester stretching frequency upon calcium complexation, indicating very weak or no ester carbonyl ligation.

Thus it appears that only with (117) is the ligand able to adopt a conformer in which the carbonyl group can be located close enough to the calcium ion to allow ligation to occur. It is also likely that two of the ring ether oxygens are not bound to calcium, eight coordination being more likely than ten.

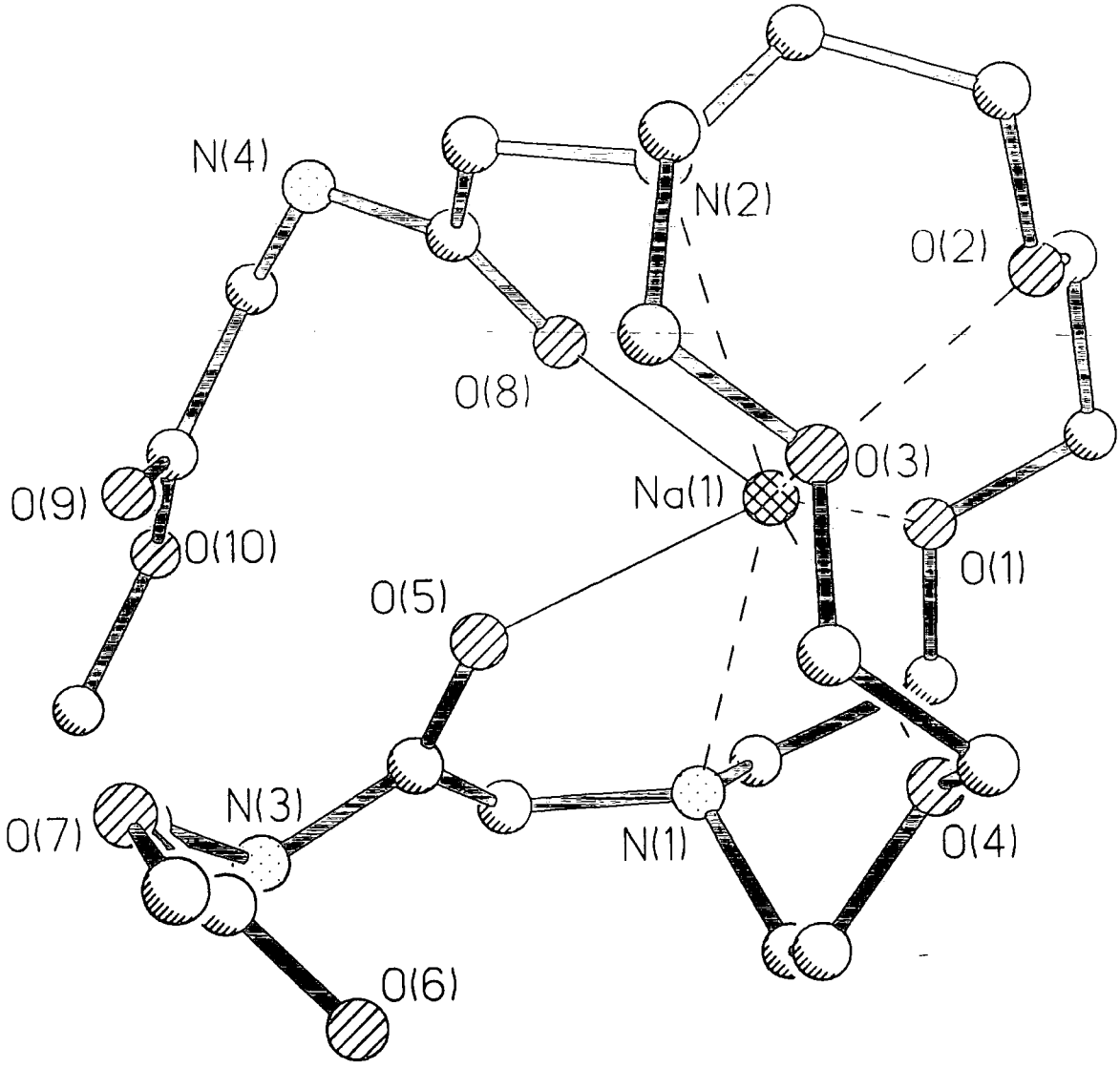


Figure 3.05: Sodium Complex of 18 N_2O_4 $(CH_2CONHCH_2CO_2Me)_2$

3.4 AQUEOUS POTENTIOMETRIC MEASUREMENTS OF ACID DISSOCIATION CONSTANTS AND STABILITY CONSTANTS.

The acid dissociation constants of ligands (116) to (122) were determined by pH-metric titration[4] the data collected being evaluated using SCOGS[7] and SUPERQUAD[8] (Table 3.01). The values recorded show good correlation and are comparable with the values measured for the primary diamide (123)[9]. The values are somewhat lower than those recorded for both the parent macrocycle diaza-18-crown-6 and its N-methylated derivative[10, 11] The slightly more acidic nature of derivatives (116) to (122) can be explained in terms of the reduction in basicity brought about by the electron withdrawing effect of the β carbonyl group.

Ligand	pK_{a1}	pK_{a2}
116	6.49	4.82
117	6.42	4.79
118	6.48	5.43
119	6.24	5.23
120	6.73	4.84
121	7.19	3.98
122	6.98	4.50
123[a]	6.68	5.40
4,13-diaza-18-crown-6[a]	8.94	7.81
Me_2-4,13-18-crown-6[b]	9.58	7.61

a) from reference 9. b) from reference 10.

Table 3.01 Dissociation Constants for protonation of ligands **(116)** to **(122)** (298K, I=0.1 mol dm^{-3} NM_4 NO_3, $^+/_-$ 0.03)

Crystallographic studies of a [12]N_2O_2 derivative bearing $CH_2CH_2CONMe_2$ side-chains [4] and the methyl ester analogue of (117) [5] have shown that prior to protonation the N-lone pairs point into the cavity [12], thus inversion must occur before protonation is achieved. However this is unlikely to affect the acid dissociation constant.

Once the acid dissociation constants (pKa's) had been calculated, metal complexation constants for all the ligands (116) to (122) with sodium, potassium and calcium were determined, using the same potentiometric titration methods followed by iterative data analysis.(Table 3.02)

ligand	Na^+	K^+	Ca^{2+}
116	2.48	2.36	4.99
117	2.36	2.45	5.97
118	2.55	2.24	4.93
119	2.67	2.51	4.46
120	2.65	2.51	4.74
121	2.57	2.56	5.11
122	2.48	2.50	4.52
123 [a]	<2	<2	5.65

a) data from reference 9 (0.5 M $LiClO_4$).

Table 3.02 Stability Constants for complexation of ligands **(116)** to **(123)** with cations [298K, I = 0.1 moldm^{-3} (+/- 0.05)].

The values obtained correlate well with the preliminary findings from the ^{13}C complexation study. The stability constants for 1:1 complexation with calcium for all ligands were around log K = 5, this confirms the postulation made from the ^{13}C data that stability constants were of the order of log K > 4 for calcium complexation. Again the stability

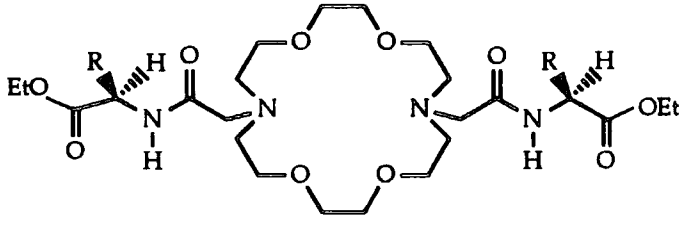
constants for sodium and potassium are in agreement with the ^{13}C study, weak complexation being observed, all values below log K = 3.

The highest stability constant recorded was for the calcium complex of ligand (117), (log K = 5.97). This higher value would seem to confirm simultaneous amide ester ligation as indicated by IR spectroscopy, resulting in the formation of a stronger complex than amide participation alone would produce. The conformation of the complex must be such that the side arms are able to wrap around the calcium cation encapsulting it with simultaneous amide and ester ligation. For the smaller and more conformationally rigid [15]N_2O_3 it may be that such a conformation is not sterically possible.

Ligand (117) also exhibited the highest selectivity for Ca^{2+}/ Na^+ ($10^{3.61}$), however in general this selectivity was of the order of $10^{2.5}$. No Na^+/K^+ selectivity was noted.

The stability constants determined for Ca^{2+} were somewhat lower than those quoted in a related study [3], (see Table 3.03). However, the values reported previously are thought to be artifically high as a result of a systematic error in the determination of calcium concentrations, resulting from the attempt to measure calcium concentrations beyond that of the linear operating range of the calcium I.S.E. used.

Although the absolute values quoted in the related study are questionable, the enhanced Ca^{2+} selectivity observed for ligand **(124)-(126)** compared to the closely related analogue **(117)** is a valid observation.



124 R = CH_3
125 R = iPr
126 R = iBu

LIGAND	SOLVENT	LOG Ks	
		Ca^{2+}	Na^{+}
117	H_2O	6.7	2.2
124	H_2O	7.8	2.2
125	H_2O	7.7	2.2
126	H_2O	7.8	2.2

Table 3.03:- Stability constants (log K) determined for a series of $18N_2O_4$ derivatives in water. [3]

It may be that the isopropyl groups sterically influence the orientation of the ester carbonyl groups such that the conformation prior to binding is closer to the required binding conformation than that displayed by (117).

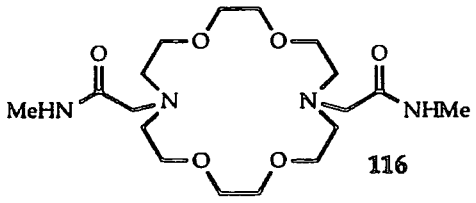
Interestingly the [12]N_2O_2 tertiary amide derivative (121) exhibited a slightly higher stability constant than the structurally related secondary amide derivative (120) , log K = 5.11, compared to log K = 4.74. The increase in the binding strength may result from a more favourable enthalpy term. It is possible that hydrogen bonding between the N-H present in the secondary amide and H_2O results in a reduction in the enthalpy of complexation because energy needs to be expended prior to complexation in order to desolvate the ligand. However this will in part be compensated for by a more favourable entropy of ligand desolvation resulting from this process. This topic will be studied more closely in the next section.

3.5. CALORIMETRIC EXPERIMENTS

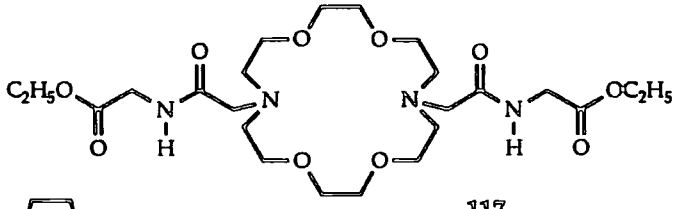
Enthalpies of complexation were recorded for the complexation of ligands (116) to (122) to a range of Ia and IIa cations in methanolic solution. The complexation enthalpies were predominantly exothermic, only with

lithium was an endothermic complexation observed (Table 3.04). It is thought that endothermic complexation occurs with lithium as a result of the highly solvated nature of the lithium cation in methanol and desolvation is energetically expensive, although this is in part balanced by a favourable entropy term.

Another interesting point to note from the data collated is the systematic reduction seen in enthalpy of complexation of the calcium ion as the ring size increases from [12] to [18]. This may reflect the greater conformational rigidity of the smaller [12] N_2O_2 ring, which adopts a similar quadrangular [3,3,3,3] conformation in the free ligand and in its complexes. Thus less energy is expended on ligand reorganisation prior to complexation.



116



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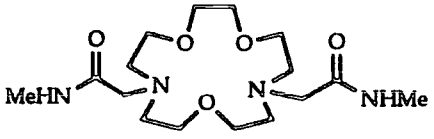

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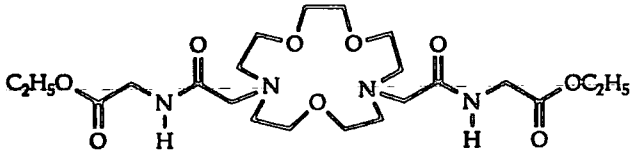

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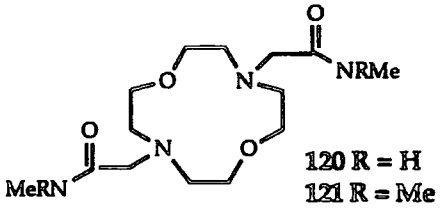
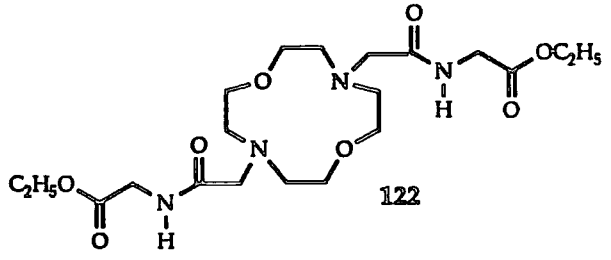


120 R = H
121 R = Me



122

Ligand	Li^+	Na^+	K^+	Rb^+	Cs^+	Ag^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
116	-3.0	11.1	16.2	10.4	0.6	50.5	15.7	17.4	19.5
117	-1.2	5.0[a]	13.5	13.5	3.7	31.9	18.6	20.1	23.9
118	-1.9	12.4	23.8	23.3	12.7	40.9	25.0	21.8	30.2
119	-3.3	12.2	18.5	12.5	-1.3	48.3	19.0	22.5	23.7
120	-	9.8	2.0	0.6	0.8	43.3	29.6	15.3	16.6
121 [b]	12.7	26.0	25.7	22.7	-	59.1	46.6	35.8	33.0
122	-	14.5	5.2	3.2	2.8	45.6	34.9	24.8	24.4

a) A value of 5.8 for the related methyl ester is reported in reference 6.

b) data from reference 4.

Table 3.04 Enthalpies of complexation ($-\Delta H$, kJ mol^{-1}, 298K, CH_3OH) for ligands **(116)** to **(122)** with a range of Ia and IIa cations.

It is interesting to compare the enthalpy of calcium complexation for the [12] N_2O_2 secondary amide derivative (120) with that of the tertiary amide analogue (121); -46.6KJ mol^{-1} for (120) compared to -29.6 KJ mol^{-1} for (121). The enhanced enthalpic term displayed by the tertiary amide derivative is almost certainly due to the lesser extent of ligand solvation seen with tertiary amides compared to that associated with secondary amides which possess a potentially H-bonding N-H group. In the secondary amide the N-H group probably H-bonds to the oxygen atom of methanol and thus prior to complexation, energy is expended in breaking this bonding in order to effect desolvation.

If the data presented in figure 3.09 is studied carefully it becomes apparent that the difference in enthalpy of complexation of (120) and (121) with various cations is fairly constant and averages -18.8 $KJmol^{-1}$ (Figure 3.06)

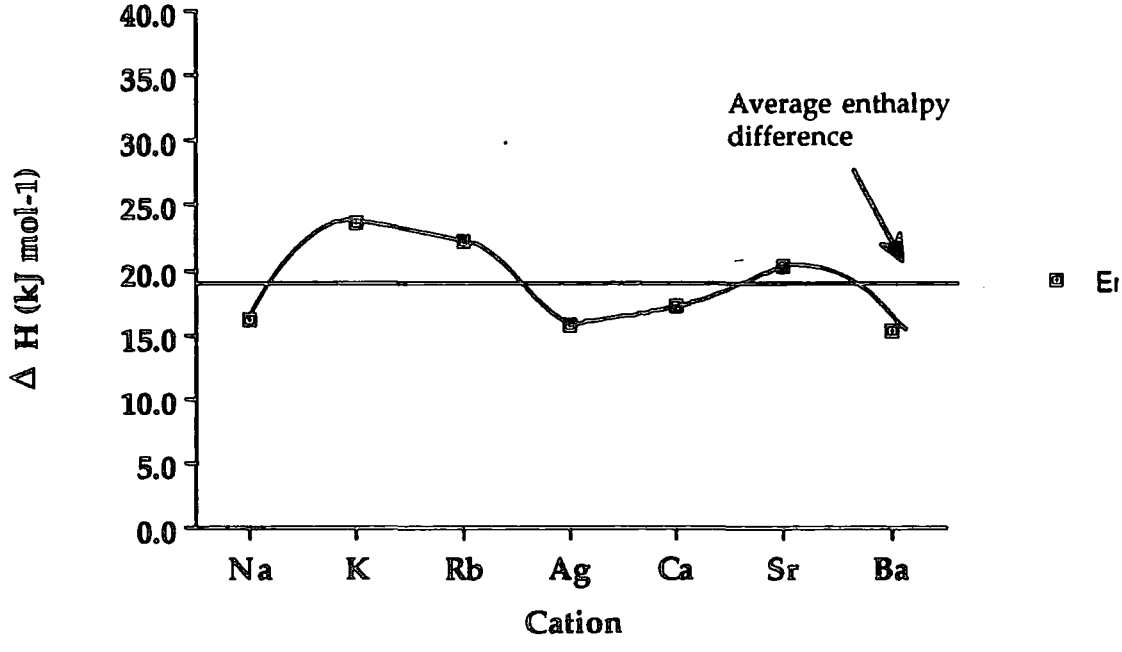


Figure 3.06 Plot illustrating the enthalpy of complexation difference seen between ligands (120) and (121) for complexation to a range of cations.

This value may approximate to the difference, in terms of enthalpy of solvation, between the free ligand and the complex, and is associated with the differing degree of hydrogen bonding in the free and bound states (figure 3.07)

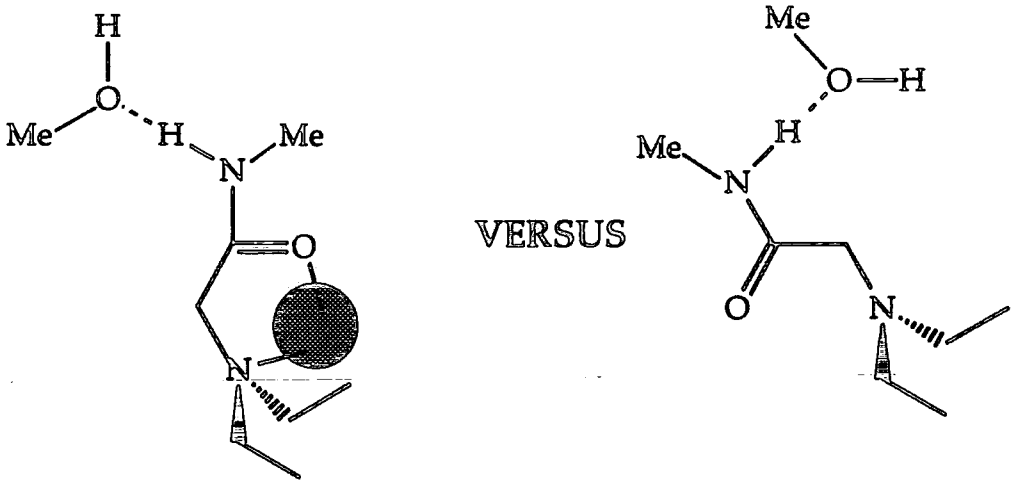


Figure 3.07 Possible partial solvation models for free ligand and complex in MeOH.

If it is also assumed that the σ binding ability of the carbonyl oxygen in CONHMe and $CONMe_2$ are virtually identical then an estimate of the enthalpy of H-bonding between methanol and a secondary amide can be made (-9.4 kJ mol^{-1})[13]. This value is probably an underestimate since it represents the difference in solvation between the free and complexed state, the ligand still forming H-bonds to some extent in the complexed state.

The tertiary amide does not possess the potential to form such H-bonds. It does, potentially form CO----HOMe H-bonds, however this type of H-bonding will probably occur to the same extent in both secondary and tertiary amide systems and can therefore be discounted.

Thus it was decided to further investigate this phenomenon by determining stability constants calorimetrically in methanol. With the group Ia ions (Table. 3.05) the stability constants were all found to be 10^2 to 10^3 higher than the values recorded in water. This is in line with

expectations since cation solvation is considerably greater in water than in methanol. Lithium was found to be the most strongly bound by both ligands **(120)** and **(121)**, with moderate selectivity for lithium over sodium being exhibited.

In order to determine stability constants for the complexation of group IIa cations a modified procedure had to be used. This is because stability constants greater than five cannot be determined directly by calorimetry. Instead competitive titrations were performed‡ with ligand **(120)** in the presence of either 18-crown-6, [2,2,2]-cryptand or 1,10-diaza-18-crown-6, for which stability constants and enthalpies have been established[14]. Stability constants were then calculated using these known values. For ligand **(121)**, a slightly different approach was used in order to determine stability constants for the complexation of calcium and strontium. A solution of free Ca^{2+} (or Sr^{2+}) was added to a solution containing the ligand of interest and sodium (or lithium) ions. Thus the thermogram recorded is related to the difference in stability beteen the calcium (or strontium) complex and the sodium (or lithium) complex.

The entropies and enthalpies associated with these complexation were also determined and are illustrated overleaf. (Table 3.06)

The correlation between the data collected indirectly and that determined directly is quite good. For example ΔH for the complexation of ligand **(121)** with calcium was determined directly as being -46.0 kJ mol^{-1}, whereas a value of -49.5 kJ mol^{-1} was determined by the competitive titration of calcium with the sodium complex.

‡ These measurements were carried out by Dr. H.J. Buschmann (Krefield, Germany), on samples provided by the author.

Ligand	Li^+	Na^+	K^+	Rb^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
120	4.41	4.07	n/d	n/d	11.2[a] (>8.87)[b]	8.17[c]	7.49[c]
121	5.38	4.72	3.85	3.08	7.68[e]	7.12[d]	4.94

a) This value was obtained by competitive titration against [2,2,2]-cryptand, for which ΔH and ΔG values are accurately known.

b) Competitive titration against 18-crown-6 allowed only a limit to be set.

c) Competitive titration with 1,10-diaza-18-crown-6.

d) Competitive titration of Sr^{2+} with $[121.Na]^+$.

e) Competitive titration of Ca^{2+} with $[121.Na]^+$

Table 3.06 Stability Constants (log K) determined for the complexation of ligands **(120)** and **(121)** with a range of Ia and IIa cations in methanol.

Surprisingly the secondary amide derivative **(120)** displayed a significantly higher stability constant for Ca^{2+} complexation than that exhibited by the tertiary amide **(121)**, (11.2 compared to 7.68). This greater stability must be entropic in origin since the enthalpy of complexation associated with **(120)** is lower than **(121)** as a result of the greater energy expended in order to desolvate it. This hypothesis proved to be correct when the enthalpy and entropy data was analysed (Table. 3.07). With the secondary amide derivative **(120)**, enthalpy values were lower than those associated with **(121)** (averaging 18.8KJ mol^{-1} i.e. 8.9 kJ mol^{-1} per amide N-H, see earlier discussion pages 120-122). However the trend in entropy values were seen to be the reverse.

Ligand		Li^+	Na^+	K^+	Rb^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
120	$-\Delta H$	2.4	9.2	2.0	0.65	30.4	16.4	17.0
	$T\Delta S$	22.8	14.0	n/d	n/d	33.5	30.2	25.7
121	$-\Delta H$	12.7	26.0	25.7	22.7	46.0[a]	35.8[b]	33.0
	$T\Delta S$	18.0	0.8	-3.8	-5.2	-2.2	4.8	-4.8

a) A value of 49.5 KJ mol^{-1} was obtained from the competitive titration of Ca^{2+} with the sodium complex of (121), for which log K = 2.96 and ΔH = -23.5 KJ mol^{-1}.

b) A value of 36.6 KJ mol^{-1} was obtained for the competitive titration of Sr^{2+} with the sodium complex of (121) was obtained.

c) Salts used were $SrBr_2$, $LiClO_4$, $NaClO_4$ or $NaNO_3$, $Ca(NO_3)_2$, KI and RbI. No allowance has been made for specific anion complexation.

Table 3.07 Enthalpies and Entropies of Complexation for reaction of **(120)** and **(121)** with Cations in methanol.

The idea of a "compensating effect" involving ΔH and ΔS, being associated with the binding of cations by macrocycles, is a well defined phenomenom.[15] However, in this case, the large positive $T\Delta S$ term associated with the complexation of ligand **(120)** to various cations must be made up largely of a ligand desolvation contribution. The large differences displayed in terms of entropy by ligands **(120)** and **(121)**, can be rationalised in terms of the changes in the degree of solvent ordering around the ligand. The secondary amide **(120)**, is thought to induce considerable ordering of solvent around the ligand (in both primary and secondary solvation spheres), in a manner which is not possible with a tertiary amide. A possible

model for this ordering is given in figure 3.08. The NH groups allow the selective inclusion of methanol giving an ordered "solvate".

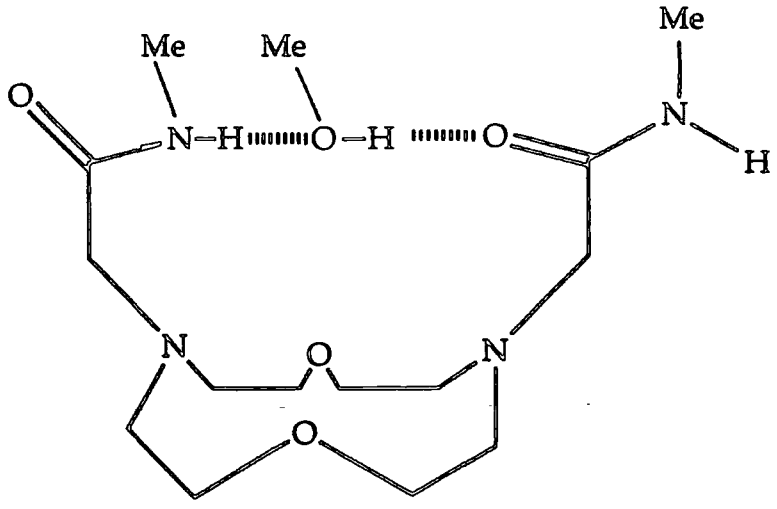


Figure 3.08 Proposed ligand ordering by solvent inclusion involving H-bonding

The effect of this ordering is to align the side-arms in a syn conformation, whereas ligand (121) is more likely to adopt an anti conformation prior to complexation. Previous crystallographic studies[6] had indicated that with related $18N_2O_4$ ligands, the cryptate-like syn conformation was usually the preferred geometry for potassium and calcium complexes. It is resonable to presume that for 12 N_2O_2 systems a similar geometry is adopted and therefore the ordering of side-arms prior to complexation postulated for ligand (120) would have the effect of aligning the side-arms in the preferred conformation prior to complexation.

3.6 REFERENCES

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CHAPTER IV:

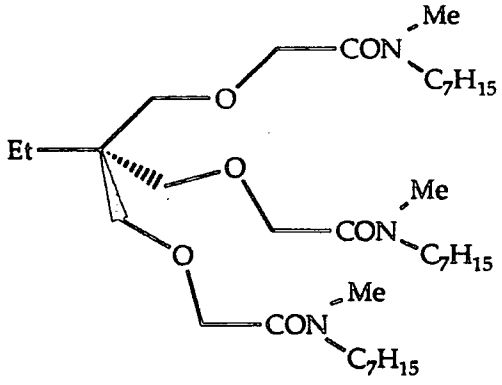
COMPARATIVE STUDY OF TRI-PODAL OXA-AMIDES AND OXA-ESTERS AS IONOPHORES IN POTENTIOMETRIC ION-SELECTIVE ELECTRODES FOR ALKALI AND ALKALINE EARTH METAL CATIONS

4.1 INTRODUCTION

The development of acyclic neutral ionophores for incorporation into potentiometric ion-selective electrodes and the subsequent measurement of intracellular or extracellular cation concentrations has received considerable attention.[1,2,3] Of particular interest to us was the tripodal ionophore N,N',N"- trimethyl-4,4',4"-propylidine tris (3-oxabutyramide) (127 , or ETH 227). This was developed by Simon *et al* [3] and has found widespread application as a sodium ionophore for the measurement of sodium concentrations in intracellular fluids, where high discrimination over potassium is required (intracellular sodium levels are around 10mM, whereas potassium levels are around 200mM).

Using this acyclic structure as a skeleton, a study was undertaken to define the effect that altering both ligand structure and the nature of the donor groups has upon the properties of the resultant ion-selective electrodes towards alkali and alkaline earth metal cations [4].

Compounds (128) to (132) were prepared in order to study both, dibutylamide versus carbutoxy as σ-donors and the effect of chelate ring size i.e. five membered ring (128)-(130) versus (131) and (132). It was hoped that the extended ionophores would exhibit selectivity for small cations over larger cations in line with the findings of previous studies.[5]



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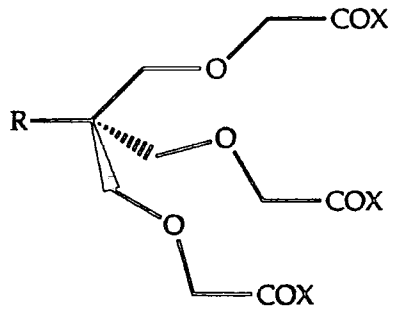
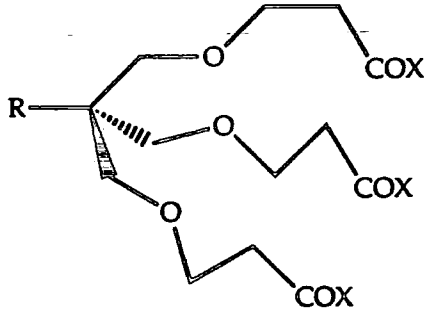


128 R = Et, X = NBu_2
129 R = Ph X = NBu_2
130 R = Et X = OBu



131 X = NBu_2
132 X = OBu

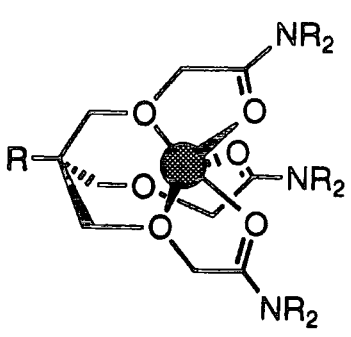
Figure 4.01

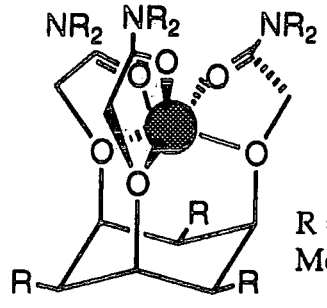
Additionally two different plasticizers were used in the electrode fabrication and the properties of the subsequent electrodes compared. The two plasticizers used were the relatively polar o-nitrophenyl octyl ether (oNPOE) and the more lipophilic plasticizer bis(butylpentyl) adipate (BBPA), which possess a significantly lower dielectric constant. It was presumed that the more lipophilic BBPA would favour the transport of ions of low charge density.

The nature of the anchor group positioned on the quaternary carbon was also examined, the flexible ethyl group being replaced by a phenyl group (129). It was thought that the more rigid, bulky aromatic ring would inhibit

flexability in the donor arms particularly in the CH_2-O bonds immediately attached to the quaternary pivot carbon.

The major drawback of such tripodal systems is the relatively strained 2,2,2-bicyclo-octane conformation adopted upon complexation (figure 4.02) and the lack of donor atom convergency prior to complexation. In order to try to overcome these problems it was decided to study a series of ionophores based upon a 1,3,5 cyclohexane triol skeleton. The advantage of such systems lies in the less strained "adamantyl like" conformation adopted upon complexation (figure 4.02). Thus, in theory, these may form stronger complexes and also exhibit more size selectivity.





bicyclo [222] framework — **adamantyl - like**

more strained — **convergent O_3 donor set**

unfavourable ΔS term — **more favourable ΔS, ΔH ?**

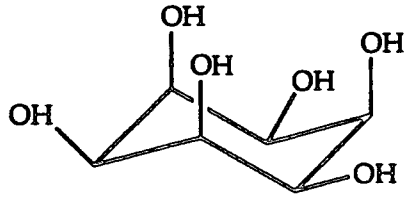
Figure 4.02:-

4.1.1. Historical overview of cation binding by cyclohexane triols

Historically it is well known that under physiological conditions metal cations occur in the same media as various sugars. Thus interest was aroused as to whether any association existed between these two species. There was considerable circumstantial evidence to suggest such an

association, however the first reliable evidence to confirm this was found by chance. Mills was studying the acidity of sugars by paper electrophoresis. [6] He hoped that at a certain pH it would be possible to separate sugars on the basis of their acid strength. Somewhat to his surprise he discovered that, even at pH 7, some sugars migrated towards the cathode.

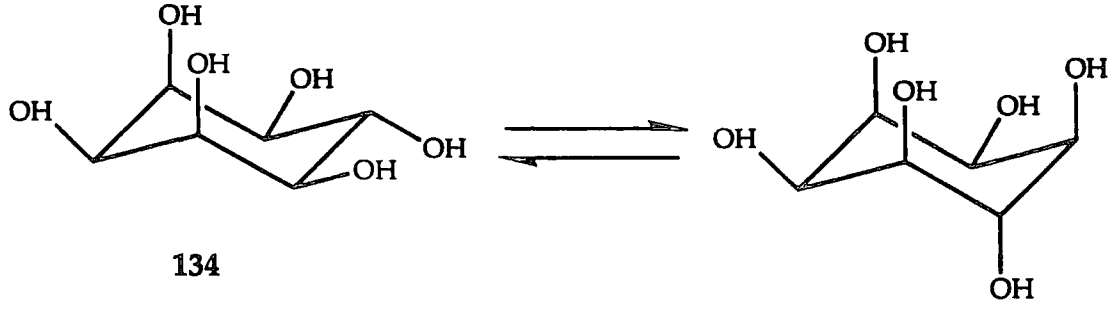
The only explanation for this phenomenon was that the sugars had associated with the metal cations and migrated towards the cathode as a result of the association complex bearing a positive charge. Of the sugars studied the greatest mobility and hence the strongest sugar-cation interaction was displayed by CIS-INOSITOL (133) a synthetic sugar first synthesised in 1957. [7]



133

This sugar analogue is structurally unique in that it possesses three syn-axial hydroxyls in each of its two equivalent chair forms.

Closely related to cis-inositol is epi-inositol (134) which can provide three syn hydroxyl groups by flipping into its less stable chair form.



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It would appear feasible that in both cases the metal would complex with the three axial hydroxyl groups. However NMR studies [8] have

revealed that whilst complexation of the cation by the three axial hydroxyl's does occur, the predominant complex formed is between the cation and the three hydroxyl's in closest proximity (figure 4.03) i.e. the complexation site consists of three hydroxyl groups in an axial-equatorial-axial sequence.

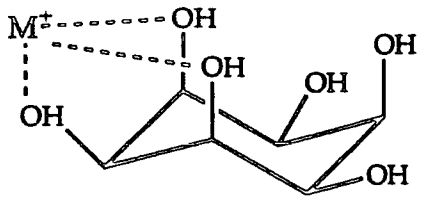


Figure 4.03:- Predominant mode of cation complexation in inositol sugars.

The participation of equatorial hydroxyl groups in complexation is not ideal. The tri-axial arrangement offers a more favourable arrangement upon which to design suitable ionophores, although little progress has been achieved to date. The first such tripodal structures based upon 1,3,5-cyclohexane triol were developed by Weisman[9], The synthesis was straightfoward, simply alkylation to give structures such as (135). Complexation was found to be accompanied by a switch in conformation of the ligand from a tri-equatorial conformation to a tri-axial arrangement.

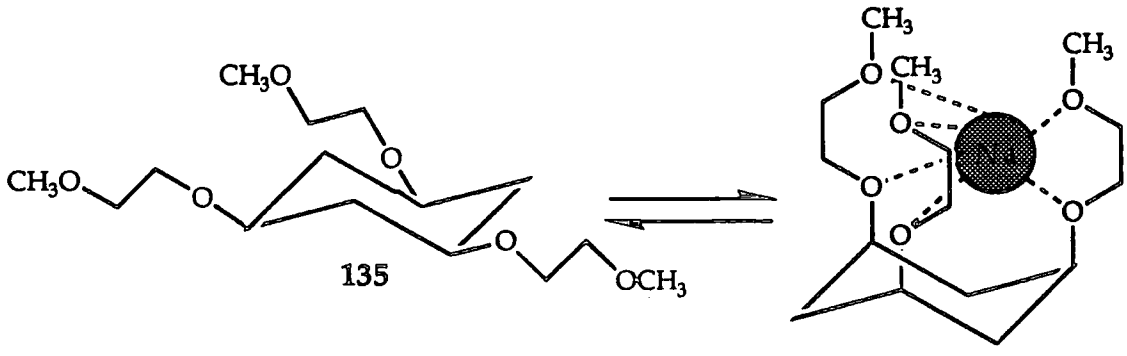


Figure 4.04:- Conformational reorientation accompanying complexation.

Ligand was found to display some Na^+/K^+ selectivity, however the problem of divergency, prior to complexation, of the donor sites still remains. Energy is expended prior to complexation in re-organising the ligand in order to align the three donor arms in a tri-axial array, thus the enthalpy of complexation is reduced.

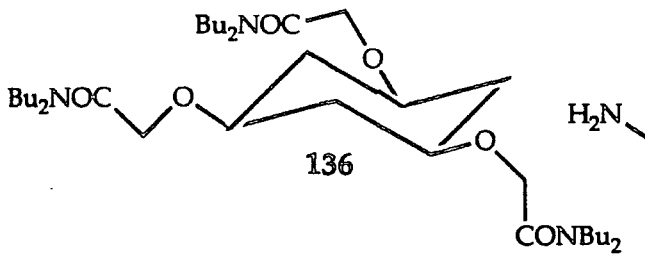
The aim therefore is to develop ligands based upon a 1,3,5-triaxial cyclohexane triol sub-unit in which the donor arms are effectively locked in a tri-axial array. The approaches which were persued in order to achieve this are detailed below.

Firstly a simple tripodal derivative of 1,3,5 cyclohexane triol **(136)** was prepared by alkylation. This was prepared so as allow a means of comparison for subsequent, more rigid, derivatives. Two ionophores **(137)**, and **(138)** , based upon 1,3,5 triamino-2,4,6 trihydroxy cis inositol (TACI) **(139)** were studied and the synthesis of a tripodand based upon 1,3,5-trihydroxy-1,2,2,3,4,4,5,6,6-nonamethyl cyclohexane was attempted **(140)**.

4.2 SYNTHESIS OF LIGANDS

4.2.1. Dendritic tripodal oxa-amide and oxa-ester ionophores

The short chain oxa-amide ligand **(128)** was simply prepared by alkylation of the parent triol, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol under basic conditions (NaH, THF) using N,N'-dibutyl-2-chloroethanamide (see Figure 4.06)



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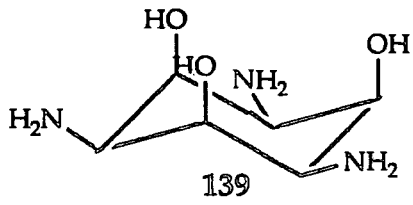

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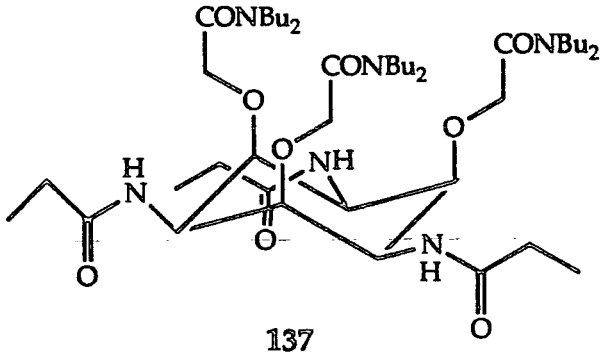

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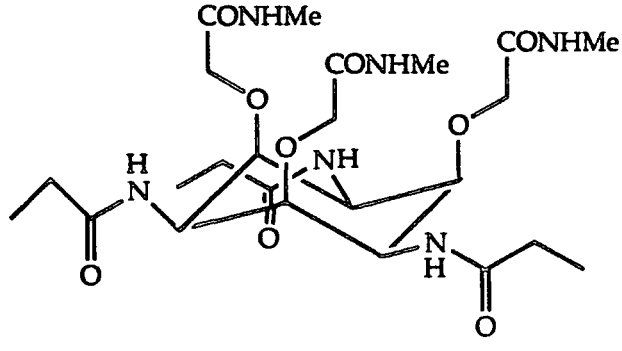

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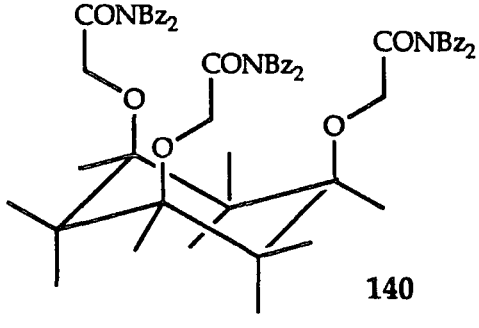

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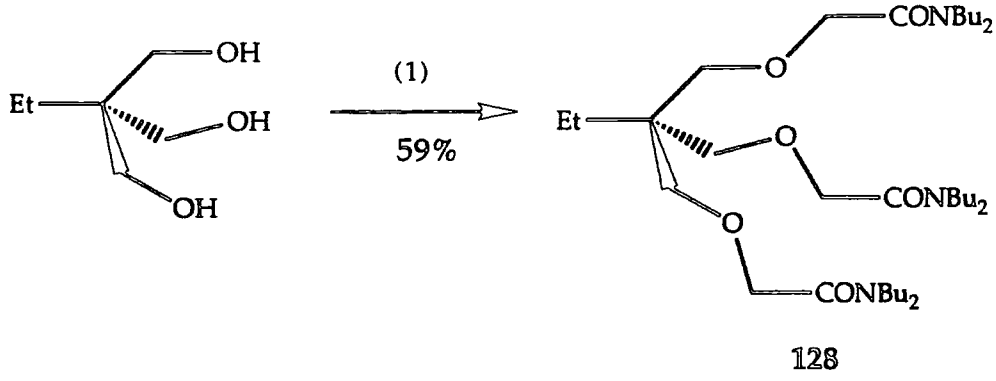
Figure 4.05:- Target Ligands.



128

Figure 4.06:- (1) N,N'-dibuty-2-chloroethanamide, NaH, NaI, THF.

The synthesis of the related phenyl analogue (129), was not so straight forward. Unlike 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, 2-phenyl-2-(hydroxymethyl)-1,3-propanediol (141), is not commercially available and therefore had to synthesised.

The first approach to the synthesis is illustrated below (figure 4.07). The first step involved the abstraction of the acidic proton present in phenyl diethyl malonate, followed by subsequent alkylation, using benzyl chloromethyl ether.

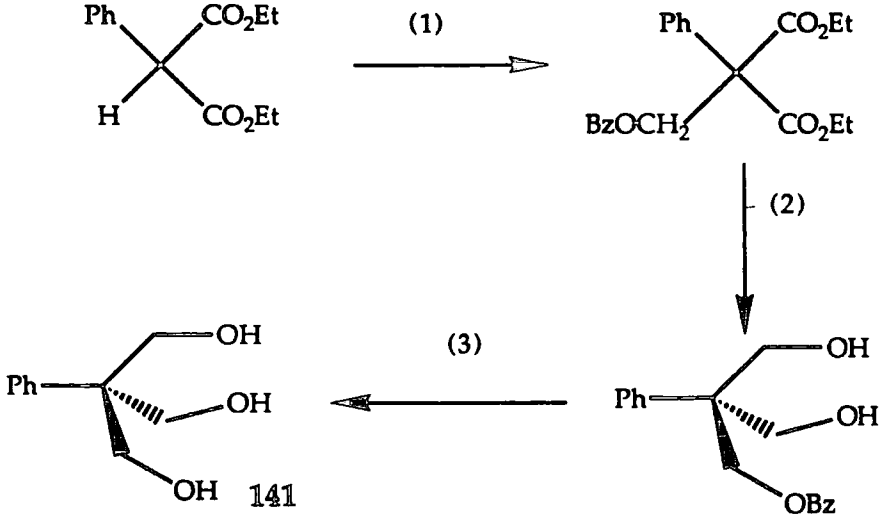


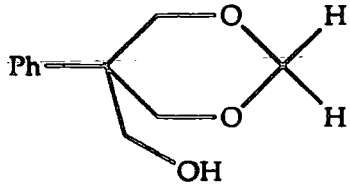
Figure 4.07:- (1) Base, benzyl chloromethyl ether, (2) $LiAlH_4$. ether, (3) H_2, Pearlman's Catalyst, EtOH.

Several bases tried, including sodium and magnesium ethoxides, LDA and sodium amide, in order to abstract the proton. However, in all

cases, following addition of benzyl chloromethyl ether and subsequent work-up, only starting material was recovered. The same occured when benzyl chloromethyl ether was replaced by chloroacetate. It thus became apparent that the problem lay not in the base used or the alkylating agent but with the reactivity of the anion itself. A literature survey revealed that 2-phenyl-2-(hydroxymethyl)-1,3-propanediol (141) had apparently been synthesised from phenyl diethyl malonate [10], using NaH and chloro-acetate, yielding a tri-ester, which was subsequently reduced. However, when the first step of this procedure was attempted, instead of the required tri-ester being isolated, several alcoholic species were recovered. Thus rather than removing the acidic proton, sodium hydride in fact partially reduced the ester functionality present in the two starting materials resulting in a complex mixture of products, none of which was found to be the required tri-ester.

Further, extensive literature surveying, revealed only one other reference to 2-phenyl-2-(hydroxymethyl)-1,3-propanediol **(141)**. It was claimed that **(141)** could be prepared in low yields by the reaction of phenylacetaldehyde and formaldehyde under basic conditions (CaO, H_2O), a procedure referred to as a Tollen's condensation. [11] This procedure was attempted, however work-up of the residue proved difficult. It was claimed that the required triol **(141)** could isolated by recrystallising from chloroform, however the residue proved to be insoluble in hot chloroform and although different solvent systems were experimented with, no product could be isolated. Mass spectrometry did however confirm the presence of **(141)** in the matrix and therefore it was decided to modify the reaction conditions in order to effect a more satisfactory synthetic procedure. Rather than simply using water as a solvent a mixed solvent system was used, comprising of a mixture of dioxan:water (4:1). Calcium oxide was replaced with calcium hydroxide and paraformaldehyde used in place of

formaldehyde solution. The work-up procedure was also modified. After cooling the solution was acidified and the precipitated calcium chloride filtered off. The filtrate residue was concentrated and partitioned between water and diethyl ether. The water layer was again concentrated and the presence of the product required (141) confirmed by mass spectrometry. The residue was then distilled under vacuum, unfortunately rather than recovering the required triol (141), instead the acetal (142) was recovered.



142

It would appear that at the high temperature required for distillation, the triol reacted with residual paraformaldehyde also present to form a ketal (142). Thus hydrolysis was required in order to reform the triol. The triol was further purified by recrystallisation from chloroform.

During the course of this work a procedure was published which descibes the synthesis of (141) in high yields. The procedure again utilises a Tollens condensation, the only difference between it and the procedure described above is that it is performed in a sealed Carius tube and that the solvent used is THF. Yields of around 65% are claimed, [12] and were reproduced when attempted

Once isolated, the triol (141), was simply alkylated in the manner used to alkylate 2-ethyl-2-(hydroxymethyl)-1,3-propanediol. i.e. basic conditions (NaH, THF) using N,N'-dibutyl-2-chloroethanamide as the alkylating agent (Figure 4.08).

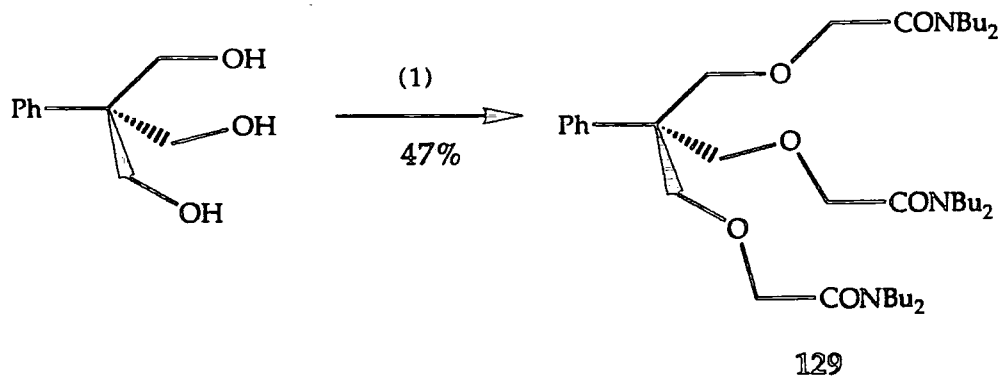


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Figure 4.08:- (1) N,N'-dibuty-2-chloroethanamide, NaH, NaI, THF.

The ester derivative (130) was again synthesised from 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (see figure 4.09). The first step involved treatment of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol with ethyl diazo-acetate. The ethyl ester was then simply converted to the butyl ester (130) , by ester exchange.

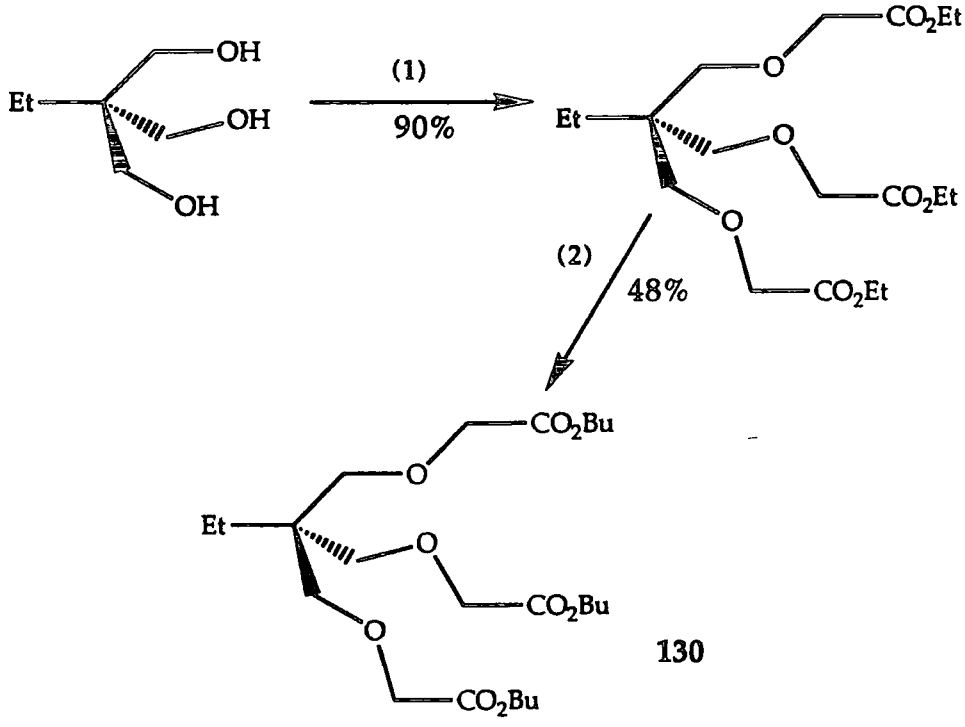

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Figure 4.09:- (1) Ethyl Diazoacetate, BF_3-Ethereate, CH_2Cl_2, (2) ^{n}Butanol, H_2SO_4.

The extended chain derivatives (131) and (132) were again prepared using 2-ethyl-2-(hydroxymethyl)-1,3-propanediol as a starting material. Synthesis of (131) was first attempted by treatment of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol with N,N'-Di-butyl acrylamide (143) under basic conditions (Figure 4.10)

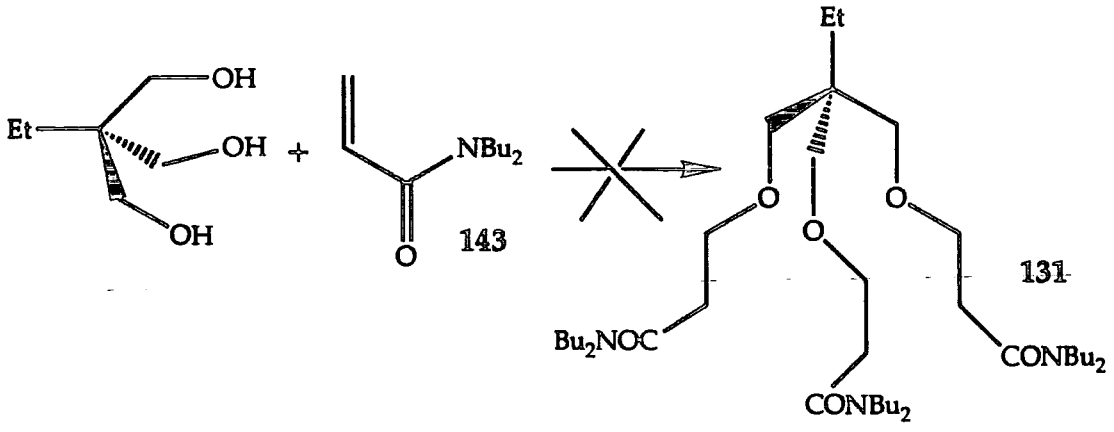


Figure 4.10: NaH, THF.

However this procedure was unsuccessful possibly because the double bond was not sufficiently electrophilic. An alternative scheme was sought: instead of using N,N'-Di-butyl acrylamide (143), acrylonitrile was used as the electrophile.[13] The trinitrile podand (144), was then hydrolysed to form the tricarboxylic acid which was subsequently converted to the required tri-amide (131) via the acid chloride (see figure 4.11). Synthesis of the tri-ester (132) was simply effected by performing butanolysis upon the tri-nitrile podand (144).

In addition to using 2-ethyl-2-(hydroxymethyl)-1,3-propanediol and 2-phenyl-2-(hydroxymethyl)-1,3-propanediol (141), an attempt was made to prepare a triol precursor (146) with a mesitylene group present in place of ethyl or phenyl. It was hoped that the bulky nature of such a group would help to restrict rotation in any subsequent tripodal structure.

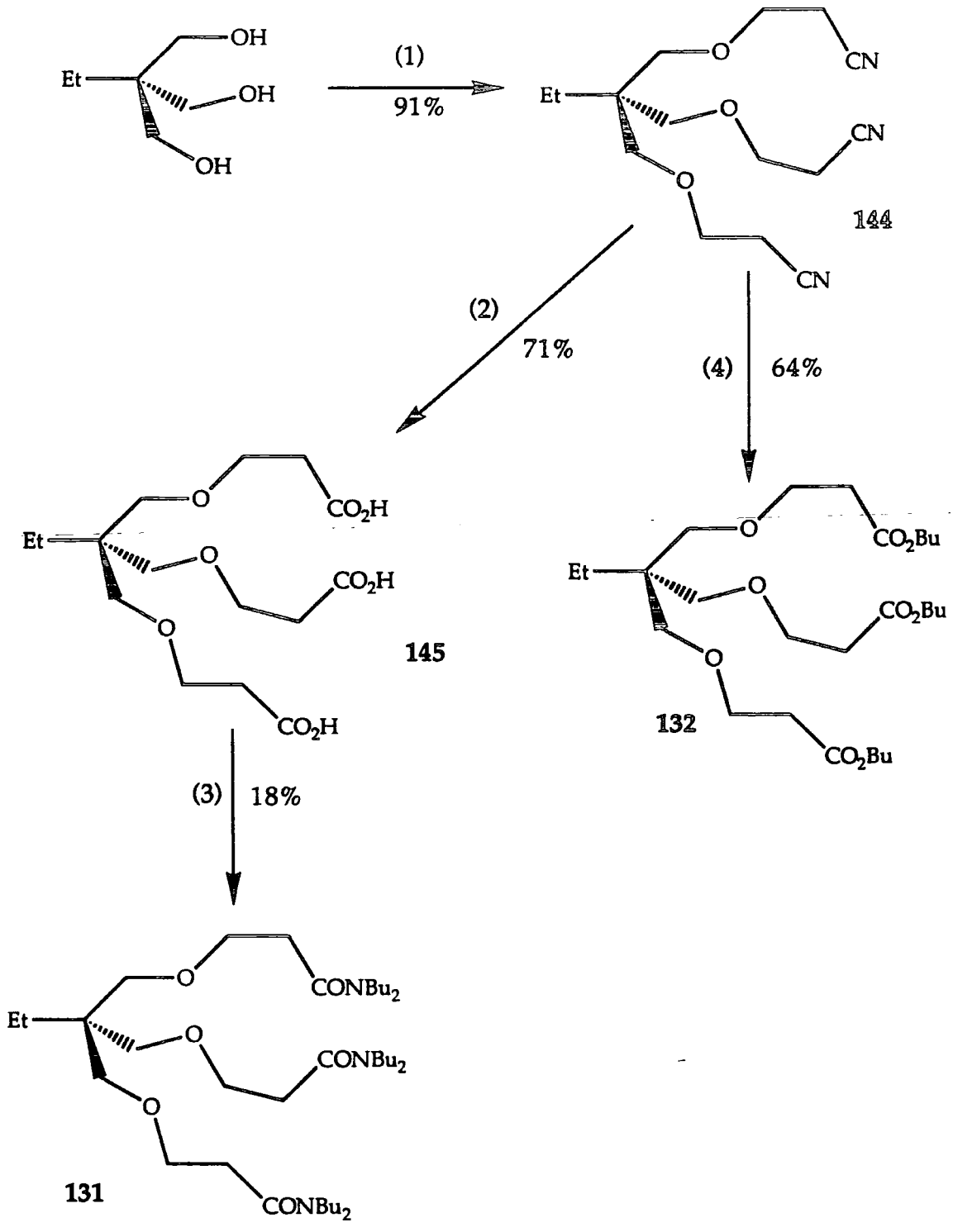


Figure 4.11:- (1) NaOH, acrylonitrile, (2) 6H HCl, (3) a) Oxalyl chloride, CH_2Cl_2, b) dibutylamine, triethylamine, CH_2Cl_2. (4) BuOH, $HCl_{(g)}$.

Synthesis of (146) was attempted using the same procedure developed to synthesise 2-phenyl-2-(hydroxymethyl)-1,3-propanediol (141), starting with mesitylacetaldehyde, (147) which itself was prepared by Swern Oxidation[14] of 2-mesitylethanol (Figure 4.12).

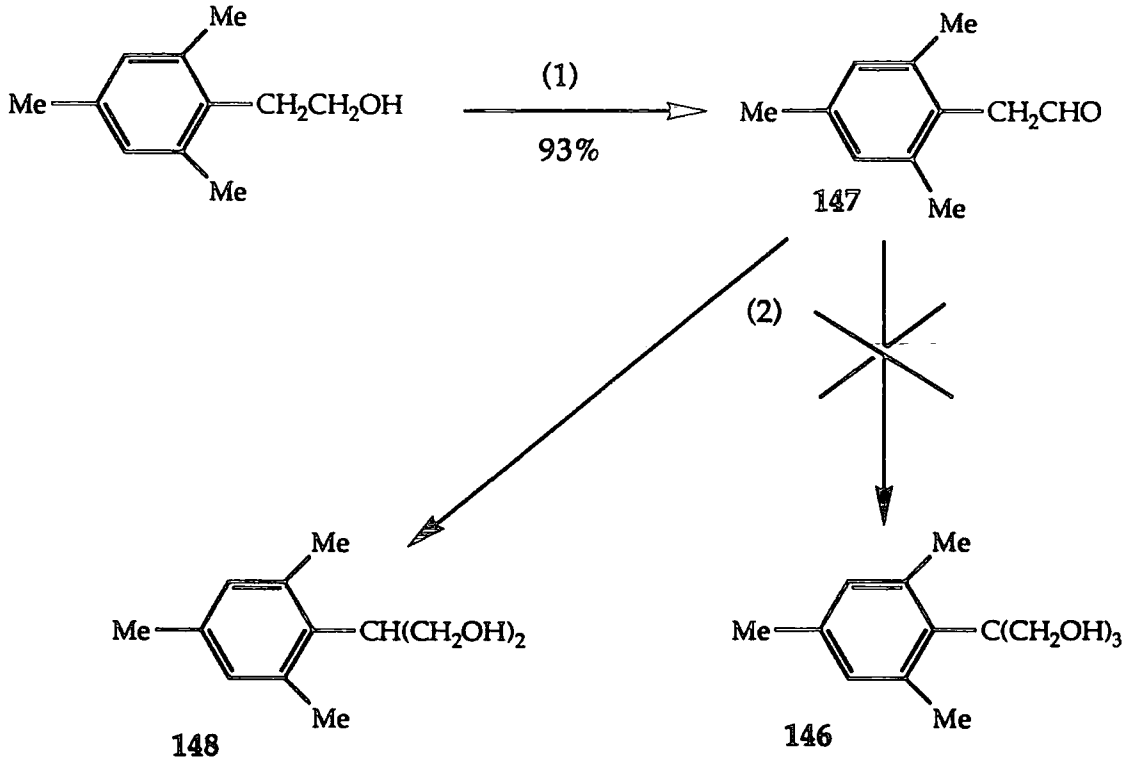
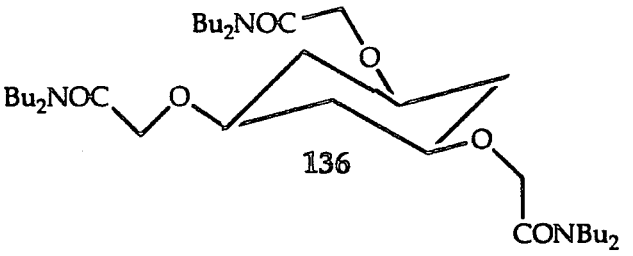


Figure 4.12:- (1) DMSO-Oxalyl chloride, (2) Paraformaldehyde, $Ca(OH)_2$, dioxan: water.

However instead of the required triol being produced, only a diol was isolated **(148)**. It appears that the steric bulk of the mesityl group prevents a second aldol condensation from occurring and therefore only one hydroxymethyl group is incorporated.

4.2.2 Preparation of tripodal ligands based upon a cyclohexane triol skeleton

The first target ligand was a simple tripodal structure **(136)** based upon cyclohexane triol itself. Synthesis was achieved by alkylating the triol with N,N'-dibuty-2-chloroethanamide under basic conditions (NaH, DMF). The presence of sodium iodide, as a catalyst, was found to be necessary in order to facilitate reaction.



This ligand was prepared in order to allow a comparison with the tri-axial ligands it was later hoped to develop. The first target ligand devised was (149), 1,3,5 tris hydroxy-2,4,6-tris propyl cyclohexane. It was postulated that in such a ligand structure the less bulky hydroxyl groups would occupy the axial positions, with the alkyl chains preferring it adopt equatorial positions. Thus any ligand based upon such a skeleton would be, in effect, fixed in the required binding conformation, prior to complexation. Figure 4.13 illustrates the scheme originally devised for the synthesis of (149).

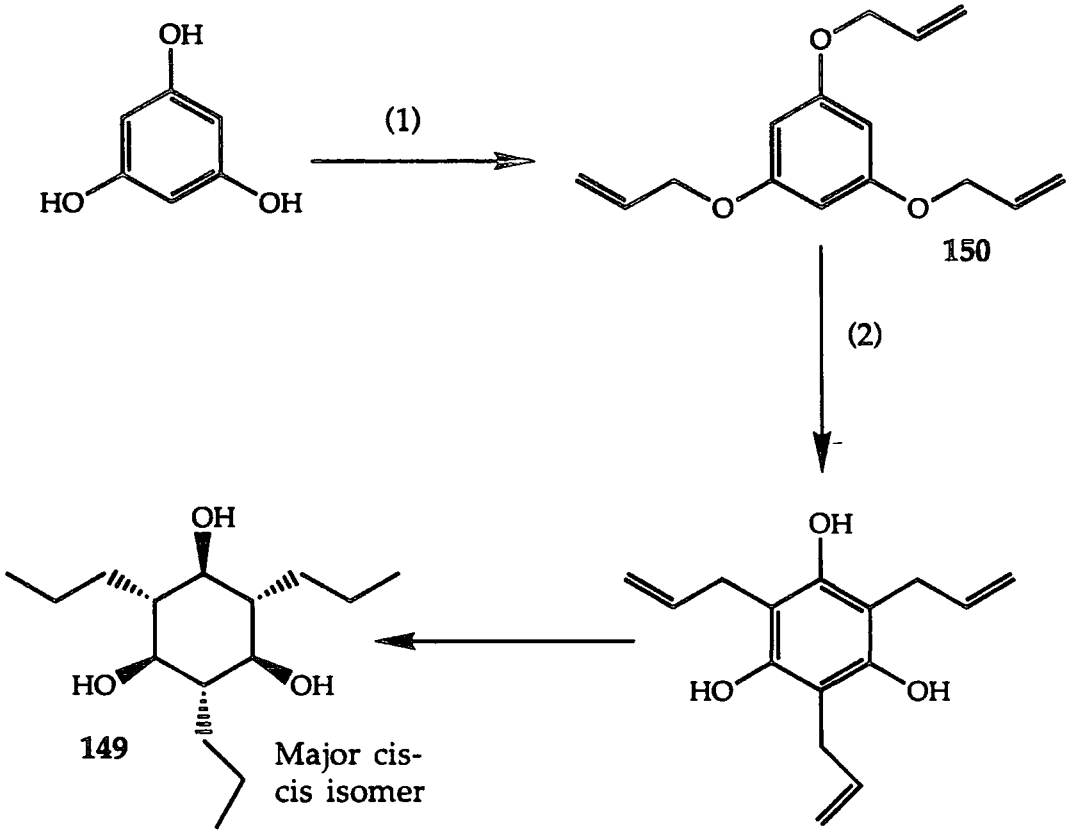


Figure 4.13:- Proposed synthetic route for the synthesis of **(149)**. (2) Δ or CF_3CO_2H / Δ. (3) Raney Nickel / H_2

Unfortunately all attempts to achieve alkylation at the three phenolic oxygens only failed, despite experimenting with a wide range of experimental conditions:-

a) K_2CO_3, acetone, RT.

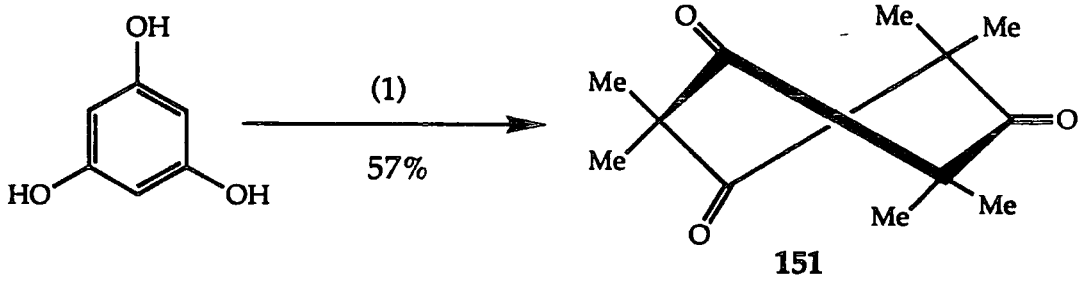
b) K_2CO_3, acetone, reflux, 8 hours.

c) K_2CO_3, DMF, 60°C, 8 hours.

d) NaOH, THF, $Bu_4N^+HSO_4^-$, reflux.

Under all conditions listed above a multitude of products were isolated as a result of both O and C alkylation and although GC-MS indicated the presence of the required product, preparative isolation was not possible.

Therefore an alternative approach to developing a tri-axial tri-hydroxyl cyclohexyl skeleton was considered. In 1965, Dale [15] reported the synthesis of hexamethylcyclohexane-1,3,5-trione from phlorglucinol (see Figure 4.14). This was found to adopt a twist-boat conformation (151) in order to alleviate steric strain.



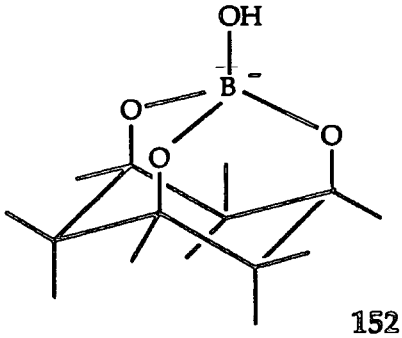
151

Figure 4.14:- (1) NaOH, MeI, H_2O, autoclave 130°C.

Treatment of the trione, with methyl magnesium bromide, was reported [16], to yield a stereoisomeric mixture of nonamethylcyclohexane-1,3,5-triols. Furthermore isolation of the tri-axial cis,cis isomer was reported to be achieved by treating the mixture of stereoisomers with sodium

metaborate, the cis, cis isomer forming a stable complex (152), which could be isolated and the triol regenerated by hydrolysing with aqueous H_2SO_4. The insoluble triol precipitated out of solution.

However, when the procedure was attempted, none of the required product was obtained. Instead of the required triol (153), a stereoisomeric mixture of mono-olefin diol (154), and di-olefin mono-ol (155) were isolated. It was apparent that the product had undergone partial dehydration, during work-up.



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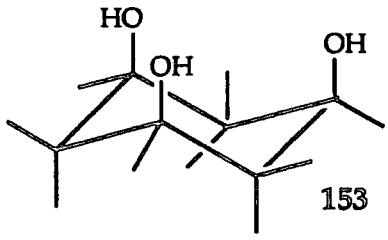

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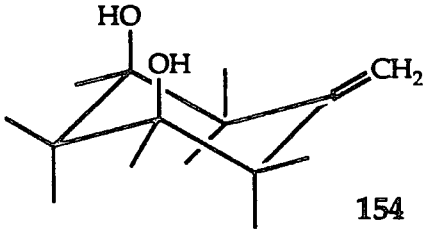

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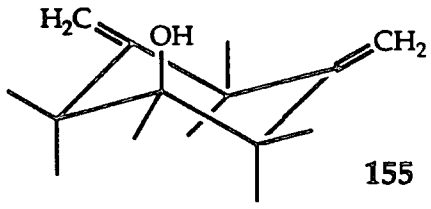


155

The problem with the procedure woud appear to occur upon the addition of ammonium chloride solution to facilitiate the breakdown of any residual Grignard reagent. Addition was accompanied by rapid discolouration and evolution of heat, even when addition was made slowly at -20°C. Undoubtably the acidic nature of the ammonium chloride solution catalyses the dehydration of the tertiary alcohol groups present, thus leading to the products described above.

Therefore an alternative work-up procedure was devised, substituting basic potassium carbonate solution for ammonium chloride.

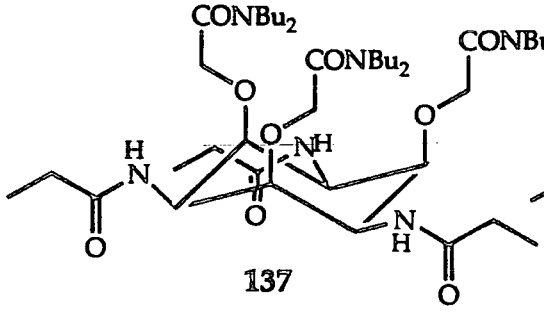
The crude product was recrystallised from benzene to yield a white crystalline product which was identified as the required product. Furthermore NMR studies, (^{1}H and ^{13}C), suggested that the major fraction of the product was the required cis-cis isomer (the ^{13}C NMR spectrum consisting predominantly of three resonances at shifts that the symmetrical cis,cis isomer could be expected to possess). Attempts made to isolate the cis isomer by the formation of the borate complex (**152**), proved unsuccessful as did attempts to separate the stereoisomers chromatographically.

Thus the synthesis of (**140**) was attempted using the crude mixture of isomers. As with (**136**) the synthesis of (**140**) was attempted by alkylating the parent triol (**153**) under basic conditions (NaH, NaI, THF) using N,N'-dibenzyl-2-chloroethanamide (**156**) as the alkylating agent (see Figure 4.14). The dibenzyl analogue of N,N'-dibutyl-2-chloroethanamide was used in order to produce a product which would be detectable under UV light, since this would allow possible separation of the stereoisomers to be achieved by preparative HPLC. However even after 7 days no alkylation had occured. It would appear that the tertiary alcohols are too hindered sterically to react with the alkylating agent. Thus steric factors seem to preclude the use of tertiary alcoholic species such as (**153**), for the synthesis of tri-podal ligands.

4.2.3 Development of ligands based upon a 1,3,5 triamino-2,4,6 trihydroxy cis inositol (TACI) skeleton

As discussed in section 4.1, inositol and related sugars exhibit enhanced affinities for metal ions due to the unique tri-axial hydroxl conformation they can adopt. A similar conformation of either three hydroxyl groups or three amino groups can be found in 1,3,5 triamino-2,4,6 trihydroxy cis inositol (TACI). This ligand facilitates metal binding at either amino or hydroxyl sites depending upon the nature of the cationic species involved [17].

It was hoped that the TACI skeleton could be used to develop ionophores which would possess a tri-axial donor array prior to cation complexation. In order to achieve this it was postulated that the amine groups could be converted to amides and that these groups would adopt a triequatorial conformation thus forcing the trihydroxl groups into a tri-axial conformation. The hydroxyl groups could, in turn, be alkylated to synthesise potential 6 coordinate ligands such as (137) and (138).



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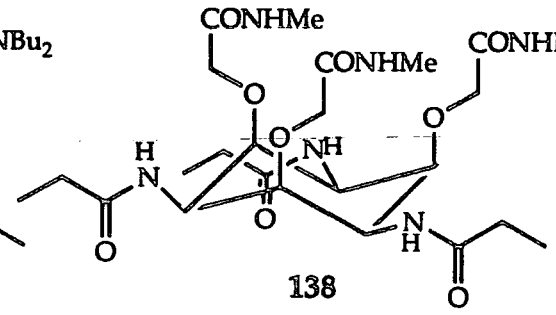


138

The synthetic scheme is illustrated below (Figure 4.15). Step one involved the per-acetylation of both amino and hydroxyl site under basic conditions (pyridine) with propionic anhydride to yield tris 1,3,5 (propanoata), 2,4,6 tris (propanamido) cyclohexane (157). The hydroxyl groups were then simply deprotected, using sodium ethoxide to yield tris (hydroxy), tris 2,4,6 (propanamido) cyclohexane (158). The triol (158) was then simply alkylated, under basic conditions (NaH, NaI, DMF) with N,N'-dibutyl-2-chloroethanamide to yield tris 1,3,5 (N,N'-dibutylcarbomylmethyloxy), 2,4,6 tris (propanamido) cyclohexane (137) or N-methyl-2-bromoethanamide to yield (138).

Figure 4.15:- (1) Propionic anhydride, pyridine. (2) Sodium ethoxide, ethanol. (3) a) N,N'-dibutyl-2-chloroethanamide, NaH, NaI, DMF. b) N,N'-dibutyl-2-chloroethanamide, NaH, NaI, DMF.

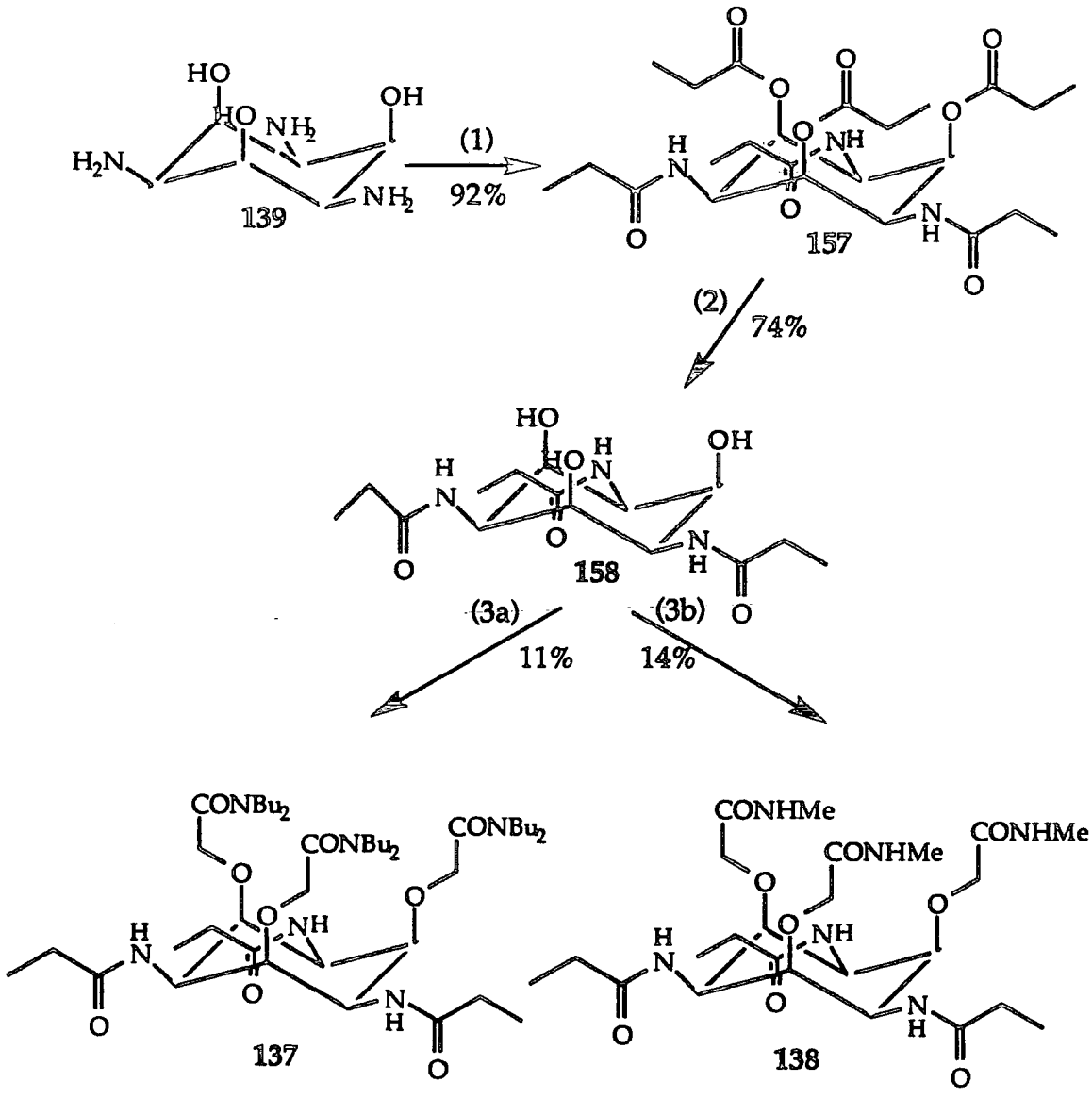


Figure 4.15:- (1) Propionic anhydride, pyridine. (2) Sodium ethoxide, ethanol. (3) a) N,N'-dibutyl-2-chloroethanamide, NaH, NaI, DMF. b) N,N'-dibutyl-2-chloroethanamide, NaH, NaI, DMF.

The more lipophilic derivative **(137)**, was prepared in order to assess the potential of this ligand system as an ionophore for alkali and alkaline earth metal cations. The N-methyl derivative **(138)**, was prepared in order to possibly obtain crystallographic data for complexes involving **(138)** and metal cations such as sodium. It was believed that the H-bonding potential of the N-H groups present in the ligand would facilitate the crystallisation of the cationic species.

4.3 ^{13}C NMR COMPLEXATION STUDIES

4.3.1. LIGAND:METAL COMPLEXATION STUDIES

Ligand (128)

Carbon	Δδ (Ca)
1	1.29
2	3.57
3	2.45
4	0.69
5	7.01
6	0.57
7	0.31 &0.27
8	0.27 & 0.72
9	0.10 & 0.10
10	0.05

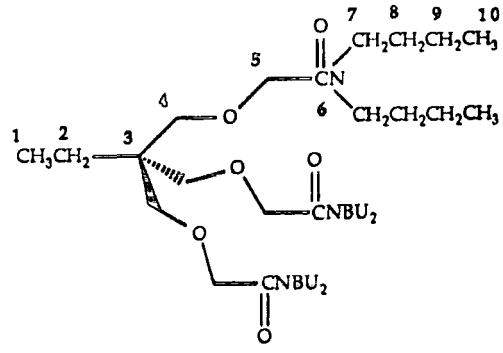


Table 4. 01 :- ^{13}C NMR Coordination Shifts (Δδ) following 1:1 complexation of ligand **(128)** with $CaCl_2$

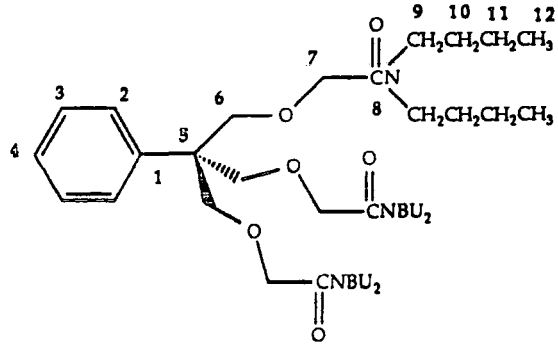
A sharp end point was observed after the addition of 1 equivalent of calcium ions (in the form of the chloride salt). This was indicative of relatively strong 1:1 complexation between **(128)** and calcium. However the observation of time averaged signals for the free and complexed ligand at intermediate stoichiometries indicated that the stability constant (Log K) for complexation was less than 4.

It was interesting to note the large change in chemical shift observed for methylene carbon (5) upon complexation (Δδ = 7.01 ppm). This suggested that a considerable change in the conformation of the ligand might have occurred upon complexation. This was a somewhat expected result bearing in mind the lack of convergent functionality possessed by the ligand prior to complexation.

Complexation was also accompanied by a drop in the carbonyl stretching frequency of 21 cm^{-1}, which indicated strong participation of the amide carbonyl in the ligation of the calcium cation.

Ligand (129)

carbon	Δδ (Ca)	Δδ (Na)*
1	2.94	0.32
2	2.15	0.24
3	1.66	0.28
4	1.62	0.04
5	---	---
6	6.05	0.95
7	0.81	0.37
8	0.63	0.20
9	---	---
10	0.27,0.64	0.11,0.03
11	0.11,0.12	0.04
12	0.01	0.03



* stoichiometric ratio 5:1 sodium : **(129)**

Table 4. 02 :- ^{13}C NMR Coordination Shifts (Δδ) following 1:1 complexation of ligand **(129)** with $CaCl_2$ and NaCl.

As with ligand **(128)** a sharp end-point was observed when one equivalent of calcium (in the form of the chloride salt) had been added. Again this was indicative of relatively strong complexation although the appearence of time averaged signals for free and complexed ligand at intermediate stoichiometries again indicated a stability constant for the complex of less than 4.

As with ligand **(128)** a large change in the chemical shift observed for the methylene carbon (7) upon complexation (6.05ppm). Again this was sugestive of a considerable change in ligand conformation upon

complexation. Furthermore a large downward shift was observed for the carbonyl stretching upon complexation (-21 cm^{-1}). Again this is showing strong participation of carbonyl groups in cation complexation.

However when the complexation characteristics of (129) were examined substituting sodium (in the form of its acetate salt) for calcium, the results were considerably different. Instead of observing a well defined end point at 1:1 stoichiometry the chemical shift difference induced by complexation was observed to increase as the stoichiometric ratio increased, up to and possibly beyond 5:1 sodium: (129) ratio. (see figure 4.19). Also the shifts induced are small in comparison to those induced by calcium complexation.

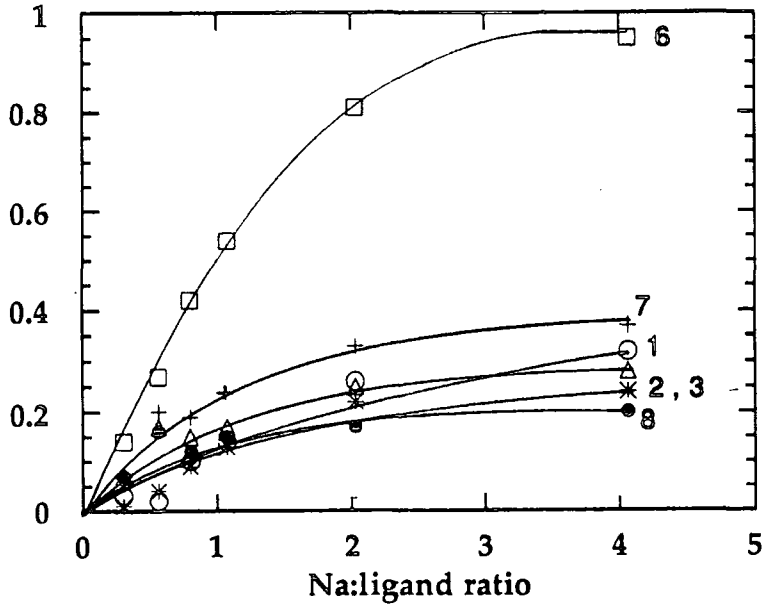


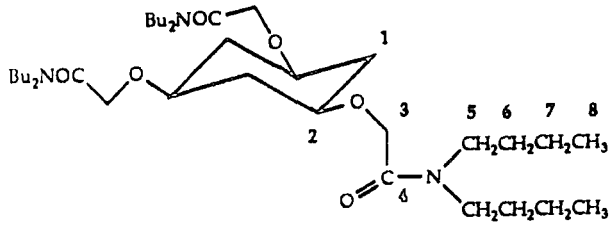
Figure 4.19:- ^{13}C NMR coordination shifts for the carbon atoms of ligand **(129)** following incremental addition of solid NaOAc (298K, d^4MeOH).

This is indicative of very weak complexation. Furthermore little change in the carbonyl stretching frequency was observed upon

complexation (-6 cm^{-1}) suggesting only weak carbonyl ligation of the sodium cation.

Ligand (136)

Carbon	Δδ (Ca)	Δδ (Na)*
1	7.29	---
2	0.22	1.20
3	2.40	0.28
4	0.70	0.29
5	0.35 & 0.31	0.07 &0.02
6	0.20 & 0.59	0.03 &0.17
7	0.06 & 0.15	0.07 & 0.02
8	0.02	0.06



* stoichiometric ratio 5:1 sodium : (136)

Table 4. 03 :- ^{13}C NMR Coordination Shifts (Δδ) following complexation of ligand (136) with $CaCl_2$ and NaCl.

Again as with previous studies the ligand was seen to display one to one complexation with calcium, accompanied by a downward shift in the carbonyl stretching frequency of 17 cm^{-1}. However sodium complexation was weak with no discernible stoichiometric ratio for ligand:sodium. Again complexation was accompanied by only a very small change in the carbonyl stretching frequency of 3cm^{-1}, clearly indicating little involvment of the amide carbonyls in cation ligation.

Ligand (137)

Carbon	Δδ (Ca)
1	0.37
2	4.27
3	0.55
4	0.19 &0.30
5	0.29 & 0.52
6	0.15 & 0.10
7	0.01
8	2.20
9	0.50
10	0.39
11	0.25

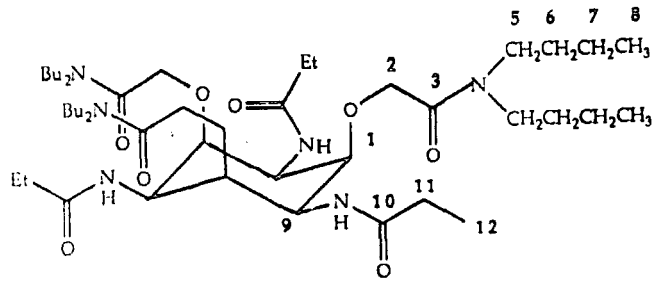


Table 4. 04 :- ^{13}C NMR Coordination Shifts (Δδ) following 1:1 complexation of ligand **(137)** with $CaCl_2$

The major point to note from this data is the chemical shift difference induced upon complexation in both forms of amide carbonyls. This is indicative of the participation of both forms of carbonyl (CH_2CONBu_2) and (NHCONHEt) in cation complexation.Thus rather than forming a complex with calcium utilising only the triaxial donor arms, the ligand is seen to form complexes incorporating equatorial donors and thus little selectivity is observed.

4.3.2 Relaxation Time Studies

T_1 ^{13}C relaxation times were measured for both the free ligands **(128)** and **(129)** and their respective calcium complexes. The relevant data is summarised in Tables 4.05 and 4.06.

Ligand (128)

Carbon	T_1 (Free) (s)	T_1(s) (complexed)
1	0.44 (±0.04)	0.26 (±0.08)
2	0.27 (±0.04)	0.28 (±0.06)
3	6.6 (±0.3)	3.6 (±0.5)

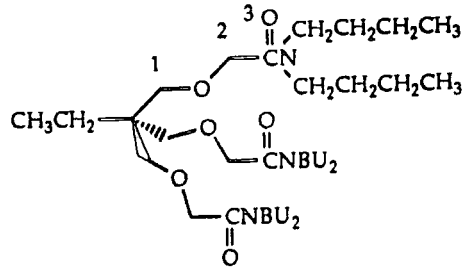


Table 4.05 Relaxation times for selected carbons of ligand (128) both in the free ligand and the calcium complex.

Ligand (129)

Carbon	T_1 (Free) (s)	T_1(s) (complexed)
1	0.21 (±0.03)	0.11 (±0.06)
2	0.34 (± 0.04)	0.16 (±0.08)
3	5.3 (±0.4)	2.4 (±0.5)

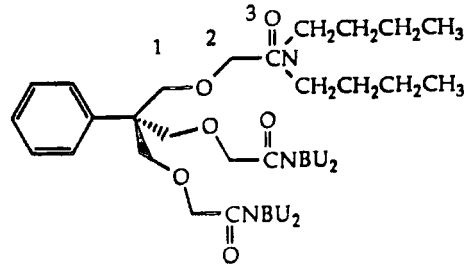


Table 4.06 Relaxation times for selected carbons of ligand (129) both in the free ligand and the calcium complex.

From the data it is apparent that complexation results, as expected, in a decrease in the conformational 'freedom' of the ligand which is associated with a reduction in the relaxation time. Also, the data would tend to suggest that ligand (129) possessed greater rigidity than (128), since the relaxation times of the carbons of interest in (129) are lower than the corresponding carbons in (128). It would appear, therefore, that the phenyl group, as was hoped, helped to restrict the conformational 'freedom' of the ligand prior to complexation.

4.4 CALIBRATION AND SELECTIVITY MEASUREMENTS

Membranes were fabricated from a mixture of 1.3% ionophore, 65.4 % plasticiser (oNPOE unless stated otherwise), 32.8 % PVC and 0.5 % KTpClPB dissolved in THF and cast according to published procedures. [18]

Calibration and selectivity measurements were performed by a constant dilution technique described in chapter 2. Calibration graphs (Figures 4.19 - Figures 4.27) illustrate the response of electrodes fabricated from ionophores **(128)-(132)** and **(136)-(137)** to a variety of alkali and alkaline earth metal cations. The calibration data for these electrodes is collated in Table 4.05)

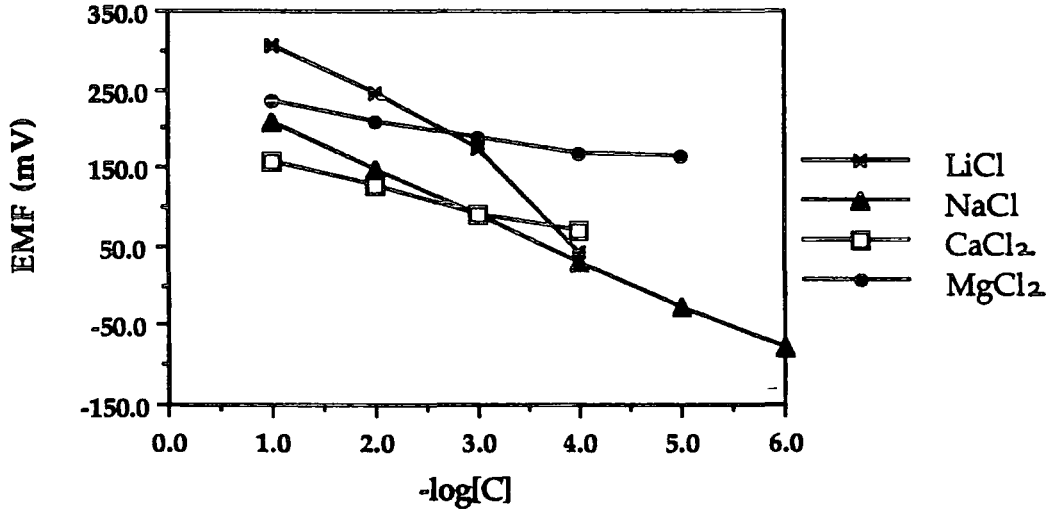


Figure 4.19:- Response of electrode based upon **128**/ oNPOE for different cations (37°C).

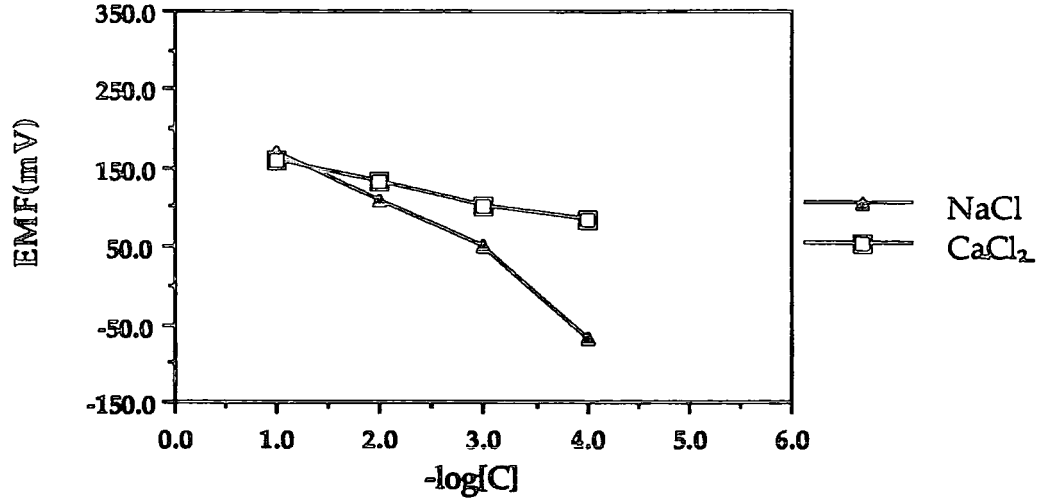


Figure 4.20:- Response of electrode based upon 128/ BBPA for different cations (37°C).

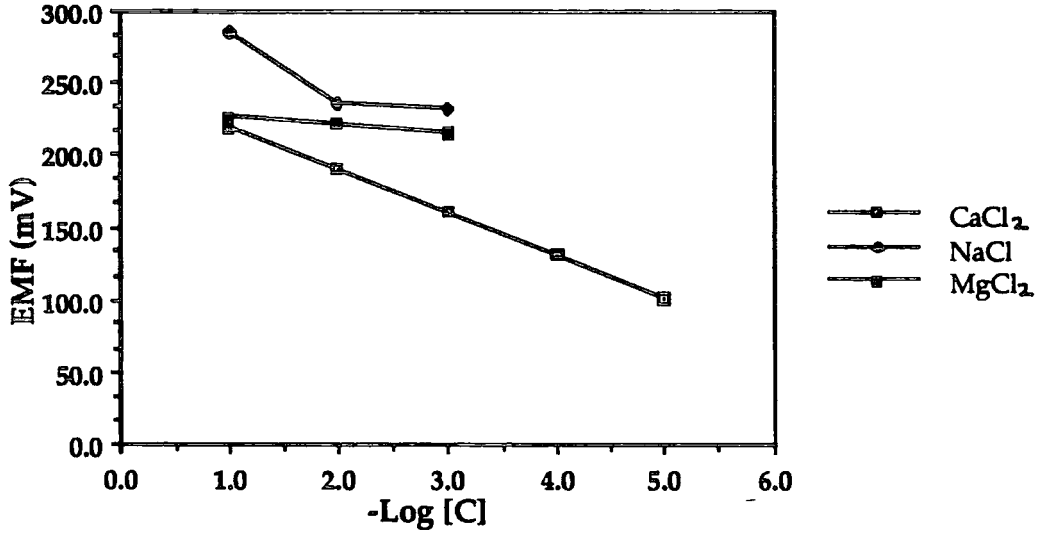


Figure 4.21:- Response of electrode based upon **129**/ oNPOE for different cations (37°C).

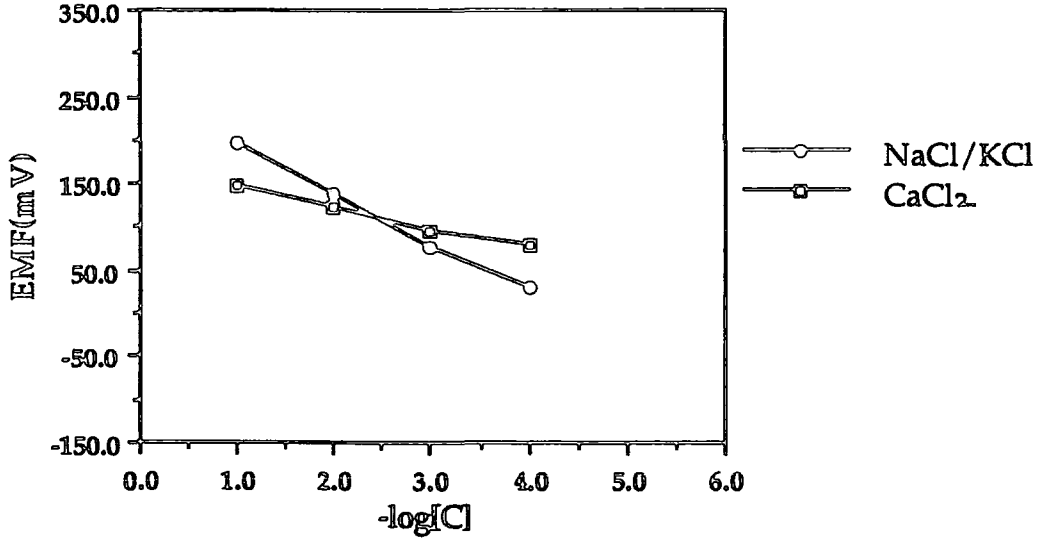


Figure 4.22:- Response of electrode based upon 130/ oNPOE for different cations (37°C).

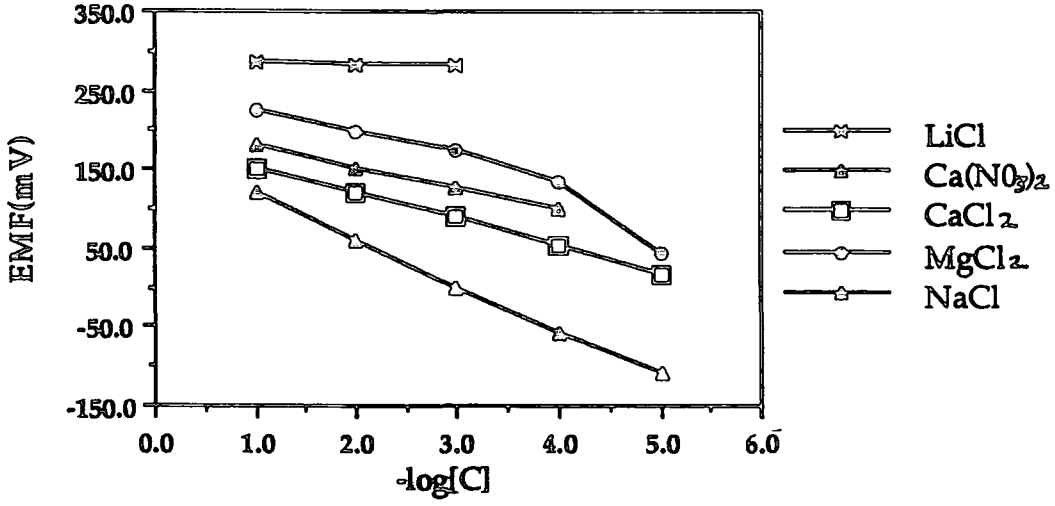


Figure 4.23:- Response of electrode based upon 131/ oNPOE for different cations (37°C).

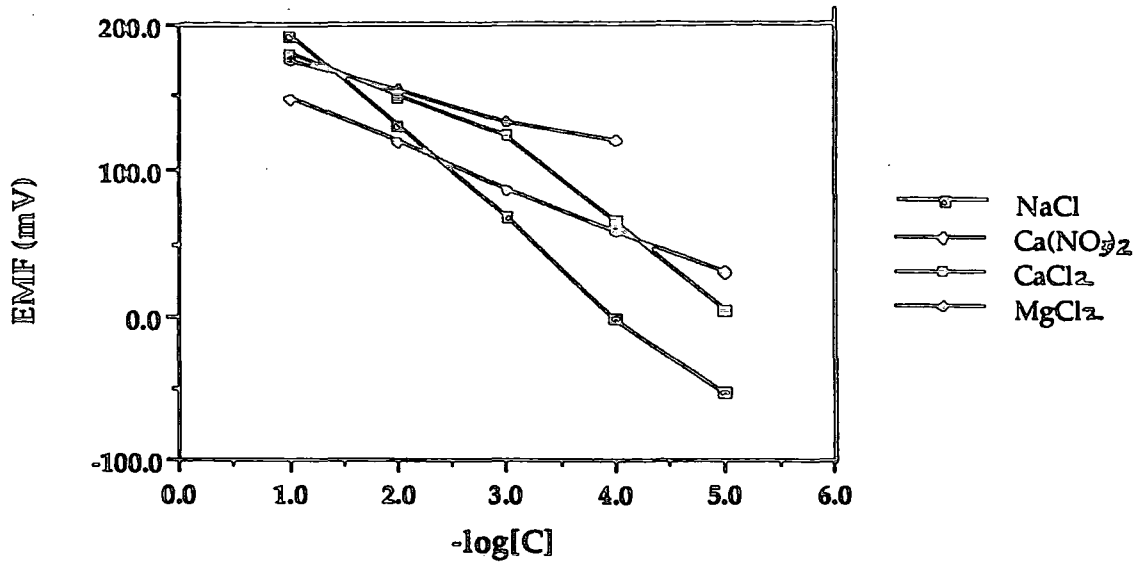


Figure 4.24:- Response of electrode based upon 132/oNPOE for different cations (37°C).

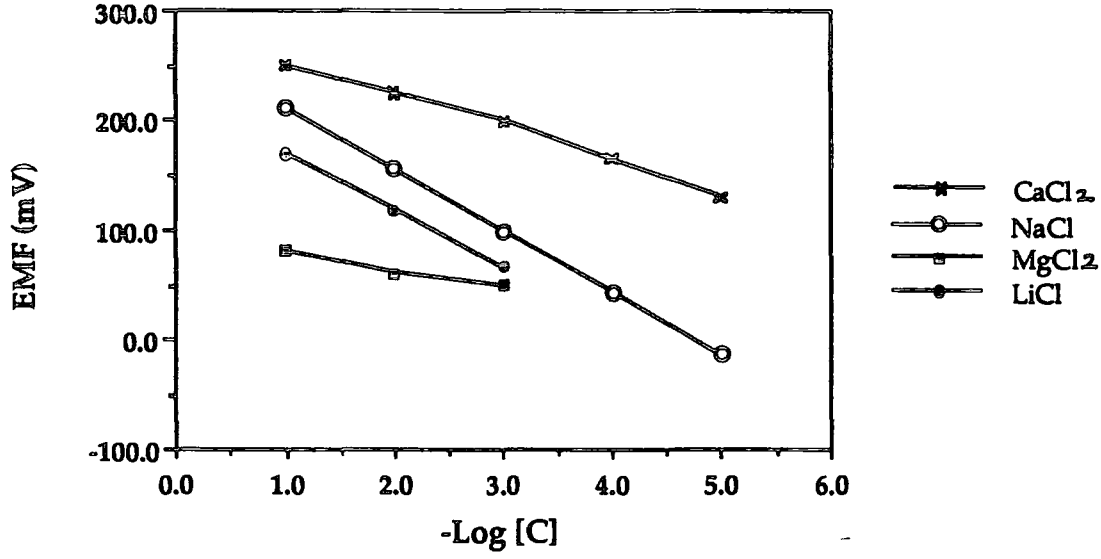


Figure 4.25:- Response of electrode based upon 136/oNPOE for different cations (37°C).

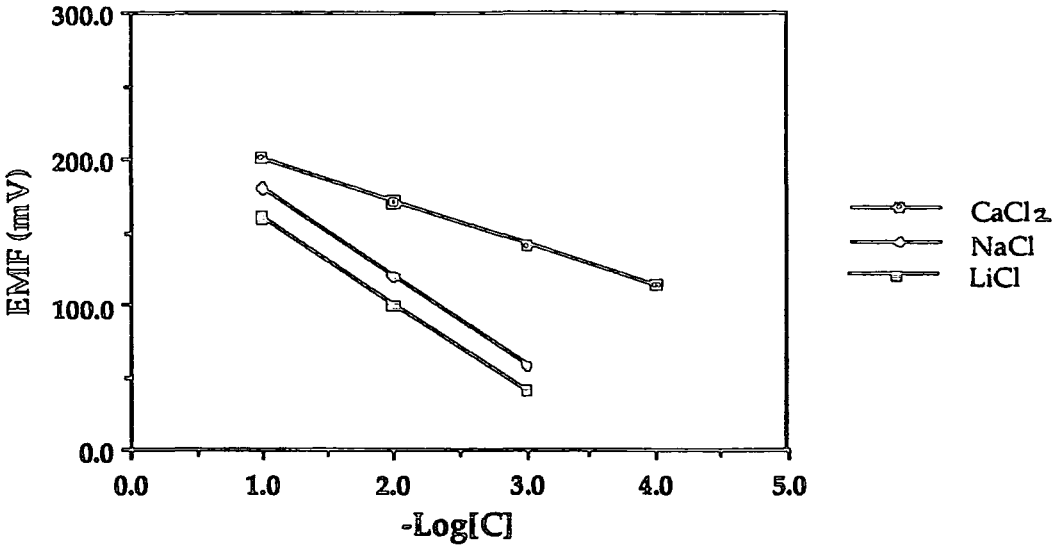
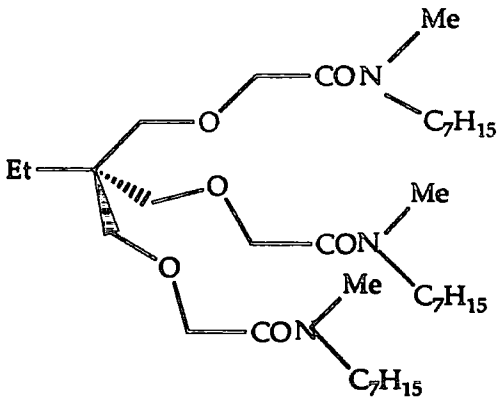
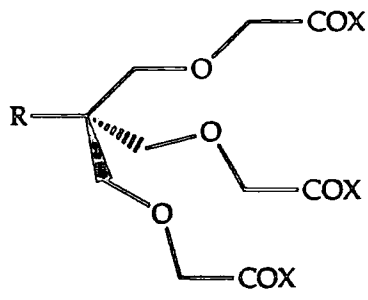


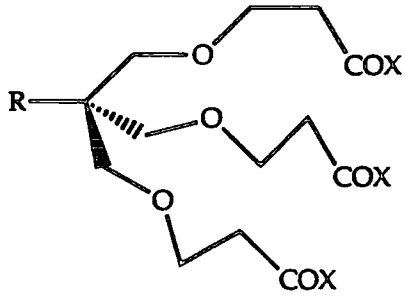
Figure 4.26:- Response of electrode based upon 137/oNPOE for different cations (37°C).



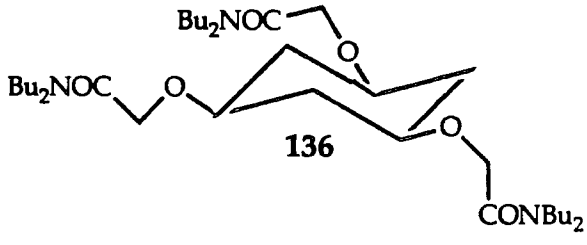
127



128 R = Et, X = NBu_2
129 R = Ph X = NBu_2
130 R = Et X = OBu



131 X = NBu_2
132 X = OBu



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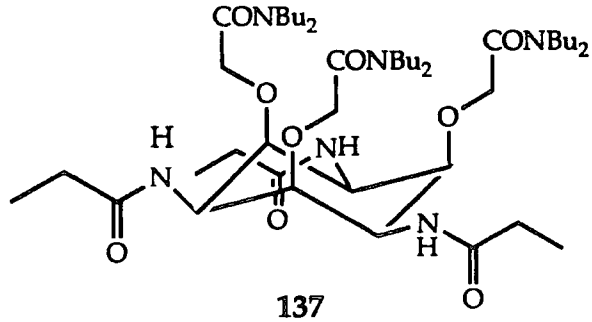

137

IONOPHORE	CATION	SLOPE (mV/dec) (±2mv)	LIMIT of DET (±0.05)
128	Na^+	60.5[a]	$10^{-6.0}$
		61.0[b,c]	—
	Ca^{2+}	31.0[a]	$10^{-3.9}$
		30.0[b]	$10^{-4.0}$
	Li^+	61.0[c]	—
	Mg^{2+}	30.0	$10^{-4.4}$
129	Na^+	50.0	$10^{-2.0}$
	Ca^{2+}	29.0[d]	$10^{-5.8}$
130	Na^+	61.0	$10^{-3.5}$
	K^+	61.0	$10^{-3.7}$
131	Na^+	61.5	$10^{-4.3}$
	Ca^{2+}	30.0, (36.0)[e]	—
		30.0[f]	$10^{-3.3}$
132	Na^+	61.0	$10^{-4.3}$
	Ca^{2+}	25.0 (35.0)[e]	—
		25.0[f]	$10^{-5.0}$
136	Na^+	56.0	$10^{-4.4}$
	Ca^{2+}	25.0 (33.0)[e]	---
	Li^+	52.0	$10^{-3.1}$
	Mg^{2+}	21.0	---
137	Li^+	60.0	$10^{-3.0}$
	Na^+	61.0	$10^{-3.0}$
	Ca^{2+}	29.0	$10^{-3.7}$

a) oNPOE used as the plasticiser. b) BBPA used as the plasticiser.

c) Nernstian response observed with concentrations above 10^{-3} mol dm^{-3}. Below 10^{-3} super Nernstian response exhibited

d) In the presence of a background of 0.1 mol dm^{-3} $MgCl_2$.

e) Nernstein response observed with concentrations above 10^{-3} mol dm^{-3}. Below 10^{-3} super Nernstian response exhibited, when $CaCl_2$ used (values in brackets).

f) Super Nernstian response not observed when $Ca(NO_3)_2$ used as the counter-ion.

Table 4.07:- Calibration data for electrodes based upon ionophores (128)-(132) and (136) - (137)

Selectivity coefficients were obtained using a fixed interference method, the electrodes being immersed in a solution comprising of 1.0 mol dm^{-3} analyte and 0.1 mol dm^{-3} interferent, diluted continuously with 0.1 mol dm^{-3} interferent. Selectivity coefficients for all electrodes are defined in terms of sodium and calcium as the primary ion (Tables 4.08 and 4.09)

ION	Electrode	-log K (±0.05)				
	Eth 227	128	130	131	132	136
K^+	2.36	2.63	0.1	1.5	0.2	3.4
Ca^{2+}	0.54	0.1	3.1	0[a]	0.8	0[a]
Mg^{2+}	3.0	3.0	3.0	0[a]	---	---

a) Severe interference, prevents determination.

(---) Value not determined.

Table 4.08:- Selectivity coefficients of sodium electrodes determined by a fixed interference method (Expressed as -Log $K^{POT}_{Na,M}$ in the presence of 0.1mol dm^{-3} solution of interferent).

ION	Electrode		-log K (±0.05)			
	128[a]	128[b]	129	130	131	132
Mg^{2+}	3.1	3.3	4.8	3.4	1.5	3.8
K^+	3.5	2.7	3.2	0.1	2.1	0.1
Na^+	3.5	2.8	2.3	0.1	1.2	0.1

a) oNPOE used as the plastiser in membrane fabrication.

b) BBPA used as the plastiser in membrane fabrication.

Table 4.09:- Selectivity coefficients of calcium electrodes determined by a fixed interference method (Expressed as -Log $K^{POT}_{Ca,M}$ in the presence of 0.1mol dm^{-3} solution of interferent).

Amide ionophores (128) (129) ,(131) (136) and (137)

Ligand (127) was originally reported as a sensor for sodium, however as the data in Table 4.06 illustrates it suffers from strong calcium interference ($-\text{Log}\,K^{POT}_{Na,Ca} = 0.54$), although it does exhibit good selectivity over potassium and magnesium ($-\text{Log}K^{POT}_{Na,K} = 2.36$) and ($-\text{Log}K^{POT}_{Na,Mg} = 3.0$).[3]

When the structurally related ionophore (128) was examined as a sodium sensor, usiing oNPOE as a plastisiser it showed both a good limit of detection ($10^{-6.0}$) and a near Nernstian response (60.5mV/ decade, 37°C) in the absence of interferents.(Figure 4.19). As with (127), (128) suffered from severe calcium interference (in the presence of 0.1mol dm^{-3} $CaCl_2$ solution the response to sodium was very poor with a slope of less than 5mV/decade). It did however exhibit slightly better selectivity over potassium ($-\text{Log}K^{POT}_{Na,K} = 2.63$).

When the membrane was fabricated using the less polar plasticiser BBPA, the electrode response to sodium was found to super-Nernstian behaviour for sodium concentrations less than 10^{-3} mol dm^{-3} (Figure 4.20). The origin of this effect will be discussed in detail later.

Because considerable interference from calcium ions was encountered when a membrane impregnated with **(128)** was examined as a sodium electrode it was decided to evaluate the use of this system as a calcium electrode. When the membrane prepared using oNPOE as the plasticiser was examined it showed a Nernstian response to calcium ions with a moderate limit of detection ($10^{-3.9}$ mol dm^{-3}) (Figure 4.19 and 4.20) in the absence of interferents. Good selectivity was observed over sodium, potassium and magnesium ($-\log K^{POT}_{Ca,Mg} = 3.1$, $-\log K^{POT}_{Ca,Na} = 3.5$, and $-\log K^{POT}_{Ca,K} = 3.5$,).

Using BBPA as the plasticiser was found to result in a marginal improvement in the detection limit. Additionally selectivity over magnesium was seen to increase, although a slight decrease in sodium selectivity was also observed. ($-\log K^{POT}_{Ca,Mg} = 3.3$, $-\log K^{POT}_{Ca,Na} = 2.8$).

The behaviour of the electrode based upon (128) and oNPOE was also studied with respect to lithium and magnesium. For magnesium a Nernstian response was observed with a moderate limit of detection ($10^{-4.4}$ mol dm^{-3}) in the absence of interferents. However severe interference from sodium, calcium and potassium was observed. For lithium a super-Nernstian response was observed for concentrations below 10^{-3} mol dm^{-3}.

An electrode fabricated from (129) and oNPOE was examined as a sensor for calcium, sodium and magnesium. Somewhat surprisingly the electrode performed very poorly as a sodium sensor with a slope of 50 mV/decade and a limit of detection of 10^{-2} mol dm^{-3}. However this mirrors the earlier findings from the ^{13}C NMR complexation study which indicated weak complexation. As a calcium sensor the electrode response was almost Nernstian down to 10^{-4} mol dm^{-3} in the absence of interferents. However in with a background of 0.1 mol dm^{-3} Mg^{2+} present the performance of the electrode was considerably improved, displaying a slope of 29 mV/decade and a limit of detection of $10^{-5.8}$ (Figure 4.21)

The selectivity of this electrode system for calcium was also impressive, $-\log^{POT}_{Ca,Mg} = 4.8$, $-\log^{POT}_{Ca,Na} = 2.3$, $-\log^{POT}_{Ca,K} = 3.2$. respectively. As a magnesium sensor not surprisingly, the electrode performed very poorly, with a slope of only 5 mV/ decade and limit of detection of 10^{-2} mol dm^{-3}.

The extended amide (131) differs from (128) only in terms of the chelate ring size formed upon cooperative cation complexation by the ether oxygen and the amide carbonyl of the podand. As stated earlier in the thesis (see introduction), the formation of 6-ring chelates favours the

(see introduction), the formation of 6-ring chelates favours the complexation of cations with a small ionic radius. It may also be anticipated that the binding constants for 1:1 complexation involving the extended amide would be lower. An electrode based upon (131) / oNPOE responded very poorly to both potassium and lithium. The response to sodium ions was Nernstian (61.5mV/ decade) with a moderate limit of detection ($10^{-4.3}$), but as with its analogue (128) calcium interference was severe. When studied as a calcium sensor the electrode response was counter-ion dependant. When Calcium chloride was used as the analyte for concentrations below $10^{-3.0}$ a super Nernstian response was observed (i.e the slope changed from (30.0 mV/decade to 36.0 mV/decade). This effect was not observed when calcium nitrate was used as the analyte. (Figure 4.23). The selectivity for calcium over Mg^{2+}, Na^{+} and K^{+} was found to be poorer than that observed using the unextended amide (128), $-\text{Log}\ {}^{POT}_{Ca,Mg} = 1.5$,

$-\log {}^{POT}_{Ca,Na} = 1.2$, $-\log {}^{POT}_{Ca,K} = 2.1$.

An electrode fabricated using the simple cyclohexane triol analogue (136) and oNPOE, gave a Nernstian response when examined as a sodium sensor (slope 56 mV/decade, limit of detection $10^{-4.4}$). As a sodium sensor selectivity over potassium was very good $-\log {}^{POT}_{Na,K} = 3.4$.

However interference from calcium ions was severe.

When studied as a calcium sensor the electrode response was counter-ion dependant. When Calcium chloride was used as the analyte for concentrations below $10^{-3.0}$ a super Nernstian response was observed (i.e the slope changed from (25.0 mV/decade to 35.0 mV/decade).

The mixed amide ionophore (137) was found to show little preference for any cation.

Ester Ionophores (130) and (132)

The incorporation of ester groups would, it was believed, favour the binding of cations with lower charge density, although the overall binding constants would be lower.

An electrode fabricated from (130) / oNPOE was shown to exhibit an almost identical response to sodium and potassium ions with Nernstian slopes and limits of detection of $10^{-3.5}$ (Na^+) and $10^{-3.7}$ (K^+) respectively (Figure 4.22). As expected when examined as a sodium sensor, severe potassium interference was observed, although good selectivity over calcium was observed ($-\text{Log}\,^{POT}_{Na,Ca} = 3.1$).

When the electrode was examined as a calcium sensor severe interference from both potassium and sodium was observed, however good selectivity over magnesium was observed ($-\log^{POT}_{Ca,Mg} = 3.4$).

With an electrode based upon the extended ester (132) and oNPOE as the plasticiser, the response to sodium ions was Nernstian with a moderate limit of detection ($10^{-4.3}$ mol dm^{-3}). Again severe potassium interference was observed when the electrode was examined as a sodium sensor and selectivity over calcium was considerably reduced when compared to that achieved with the unextended triester (130), ($-\log^{POT}_{Na,Ca} = 0.8$).

The electrode was also examined as a calcium sensor. The studies again revealed a super Nernstian response to calcium ions when $CaCl_2$ concentrations were below 10^{-3} mol dm^{-3}. This effect was not observed when nitrate was used as the counter-ion. As expected sodium interference was severe, although selectivity over magnesium was maintained ($-\log^{POT}_{Ca,Mg} = 3.8$).

Origin of super-Nernstian behaviour

As stated above in several cases, involving both singly and doubly charged ions, where the cation concentration fell below 10^{-3} mol dm^{-3} a super-Nernstian response was observed. For divalent cations the effect was only observed when the counter-ion was chloride. The origin of the effect is thought to involve the formation of $[LM\text{-}Cl]^+$ species, according to:-

$$L + M^{2+} \rightleftharpoons LM^{2+} \quad (1)$$

$$LM^{2+} + Cl^- \rightleftharpoons LMCl^- \quad (2)$$

where L is the ionophore and M is the metal.

At higher ionic strengths the more charge dense species is favoured and therefore the equilibrium in equation 2, will lie to the left favouring dissociation. However as the solution is diluted the formation of the $LMCl^+$ species becomes more favoured and therefore the slope of the electrode will tend towards 61.5 mV/decade (37°C). This formation of the LMX species does not occur with the nitrate ion due to the low nucleophilicity of this species. The observation of such behaviour has been reported previously, for example with magnesium and complexes of bis-crown ethers [19] and in the response of some thio-amides to cadmium ions.[20]

Obviously the origin of the effect for singly charged species must be different to that postulated for divalent cations. A possible explanation is that the charged aquatic species $[ML.\ nH_2O]^+$ may be in equilibrium with the neutral conjugate base $[ML\ .\ (n\text{-}1)H_2O(OH)]$ thus the effective overall charge is less than unity. The equilibrium between these two species will favour the formation of the uncharged species at low ionic strength, in accordance

with the observed super-Nernstian response observed when the ion concentration is below 10^{-3} mol dm^{-3}.

4.5 CONCLUSIONS:-

An electrode based upon (128) and oNPOE may be used to the determine sodium concentrations in intracellular fluid, where the relative concentration of interferent ions leads to a requirement for good Na^+/K^+ and Na^+/Mg^{2+} selectivity (intracellular background: 200mM K^+, 2.0mM Mg^{2+}, <0.01mM Ca^{2+}; log Na ca. -2.5). Furthermore it may offer a slight improvement in terms of Na^+/K^+ selectivity over ETH 227.

Both (128) /oNPOEand (129) /oNPOE can be used to determine calcium concentrations in the range 10^{-3} - 10^{-6} mol dm^{-3} range with good selectivity over sodium and magnesium being observed. The former displaying greater selectivity over sodium, $-\log K^{POT}_{Ca,Na} = 3.5$, the latter, greater selectivity over magnesium, $-\log K^{POT}_{Ca,Mg} = 4.8$.

The other electrodes examined performed less well in terms of their selectivities and slopes. It is possible that their poor behaviour may be linked to a relatively weak 1:1 L-M formation constant. In the case of the ester ionophores this weakness is likely to result from the weak σ donor ability of the ester carbonyl oxygens. For the chain extended derivatives, weak complexation is likely to be a result of a *lack* of functional group convergency prior to complexation.

In order to enhance binding strengths and hopefully increase cation selectivity, ionophores based upon a more rigid framework are required (without of course losing fast kinetics of cation exchange). Preliminary studies have been attempted based upon a cyclohexane triol framework in

order to achieve the development of such systems. However this preliminary study has shown that the development of ionophores based upon a cyclohexane framework possessing a 1,3,5 triaxial array of tertiary hydroxyls (1,2,2,3,4,4,5,6,6-nonamethyl cyclohexane-1,3,5-triol) is not feasible. The reasons are the low nucleophilicity of the tertiary alcohol, its sterically hindered nature and its propensity to eliminate. Thus a means of achieving a 1,3,5 triaxial array of 2° hydroxyls remains to be established.

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CHAPTER V

ANION COMPLEXATION

5.1 INTRODUCTION

The complexation of anions has recieved comparatively little attention in comparison to the studies involving the complexation of cationic counterparts. Yet in nature, anions play an important role in a number of biological processes. For example, many enzymes possess a guanidinium sub-unit which have been shown to be responsible for the binding of many physiological anions.[1] The ammonium ions of lysine residues have also been shown to behave as anionic binding sites [2]

The fact that little progress has been made in developing effective anionic receptors is somewhat suprising until you consider the characteristics associated with anionic species:-

(1) Anions , in comparison to cations, have much larger ionic radii.[3] This effect is shown in Table 5.01, for a range of cations and anions and highlights the fact that the smallest anion F^- has an ionic radius comparable to that of potassium. Therefore the size of the cavity or arrangement of binding sites in any potential receptor must be such that the larger anions can be incorporated.

Cation	r/Å	ΔG	Anion	r/Å	ΔG
Li^+	0.73	122.1	F^-	1.36	103.8
Na^+	1.02	98.2	Cl^-	1.81	75.8
K^+	1.38	80.6	Br^-	1.95	72.5
Cs^+	1.86	68.6	I^-	2.16	61.4

Table 5.01 Ionic radii and hydration energies (ΔG) (Kcal/mol) for selected cationic and anionic species.

(2) Unlike cations, anions can exist in several geometric forms [4] other than spherical. This is illustrated in Table 5.02.

Spherical	Linear	Tetrahedral	Planar	Octagonal
F^-	N_3^-	PO_4^{3-}	NO_3^-	$Co(CN)_6^{4-}$
Cl^-	CN^-	SO_4^{2-}	CO_3^{2-}	
Br^-	SCN^-	ClO_4^-	RCO_2^-	
I^-		MnO_4^-		

Table 5.02:- Illustration of possible anionic geometries

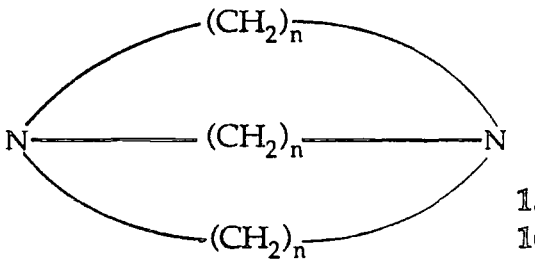
(3) The hydration energies associated with anions are much greater than those associated with cations of a similar ionic radii. As a result complexation is disfavoured enthalpically as a significant amount of energy is required to desolvate the anion prior to complexation.

(4) The majority of anions only exist within a narrow pH range, thus any receptor must be able to operate in the pH range imposed by the anionic species for whose detection it was designed.

5.2 DESIGN OF POTENTIAL ANIONIC RECEPTORS

5.2.1 RECEPTORS BASED UPON PROTONATED POLYAMMONIUM CENTRES

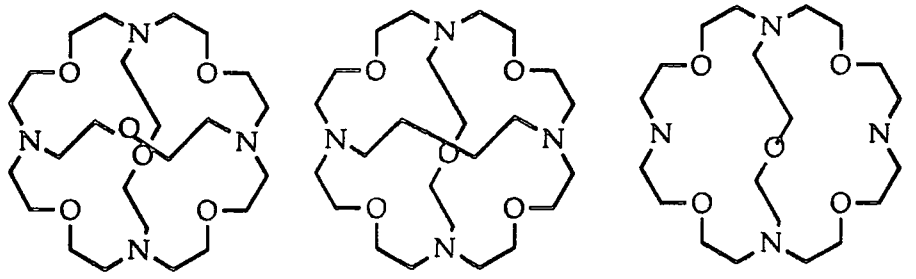
Polyammonium macrocycles and macropolycycles have been extensively studied as potential receptors for anions. The first example of such receptors being reported in 1968 by Simmons and Park. [5] (Figure 5.01). At low pH's these ligands are fully protonated and have been found to bind halides to differing extents depending upon the size correlation between the cavity size and the anionic radius of the guest halide



159 n=9
160 n=10

Figure 5.01:- Schematic representation of diazamacrocyclic halide receptors.

Following on from this work Lehn prepared a series of macro-bicyclic polyammonium receptors **(161)** to **(163)** which, in their protonated forms, were found to form stable complexes with spherical halide anions. [6] As with the structures examined by Simmons and Park, Lehn found that these ligands exhibit size-selectivity. Ligands **(162)** and **(163)** demonstrated a marked selectivity for Cl^- over Br^- ($>10^3$).



(161) **(162)** **(163)**

An X-ray crystal structure of one such complex (Figure 5.02) is illustrated below. This shows the anion to be held within a tetrahedral array of N^+-H---Cl^- bonding interactions. [7]

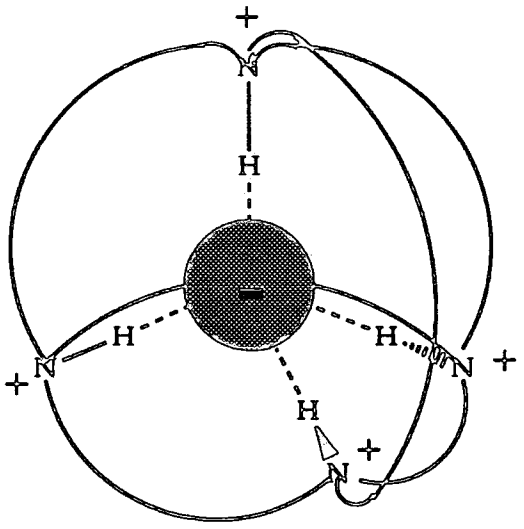
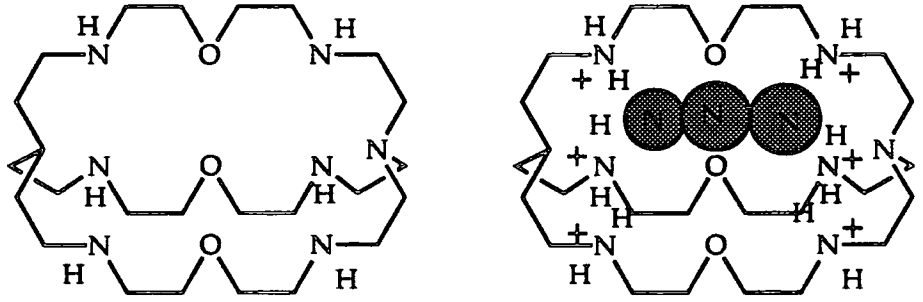


Figure 5.02:- Schematic representation of the chloride complex of (161)-4H+

These bicyclic structures were somewhat limited in that they would only bind spherical anions such as halides. Therefore in order to effect complexation of anions with an alternative geometry Lehn [8,9] designed the "BISTREN" ligand. (Figure 5.03). In the hexaprotonated form Bistren forms a complex with linear anions such as the azide anion. The azide anion shows size and shape complementarity with the cavity of (164)-6H+ and is held by a pyramidal array of 3 H-bonds at each terminal nitrogen.



164

Figure 5.03:- Schematic rpesentation of Bistren (164) and the azide complex of (164)-6H+.

Bistren however only forms very weak complexes with halide ions. Spherical halide ions are not complementary to the elipsodial receptor and

distort the ligand structure, F^- being found in a tetrahedral array whereas Cl^- and Br^- exhibit octahedral coordination [10].

A similar approach was adopted by Schmidtchen, who synthesised a series of symmetrical macro-tricyclic receptors incorporating quaternary ammonium ions. [11,12,13,14] (Figure 5.04)

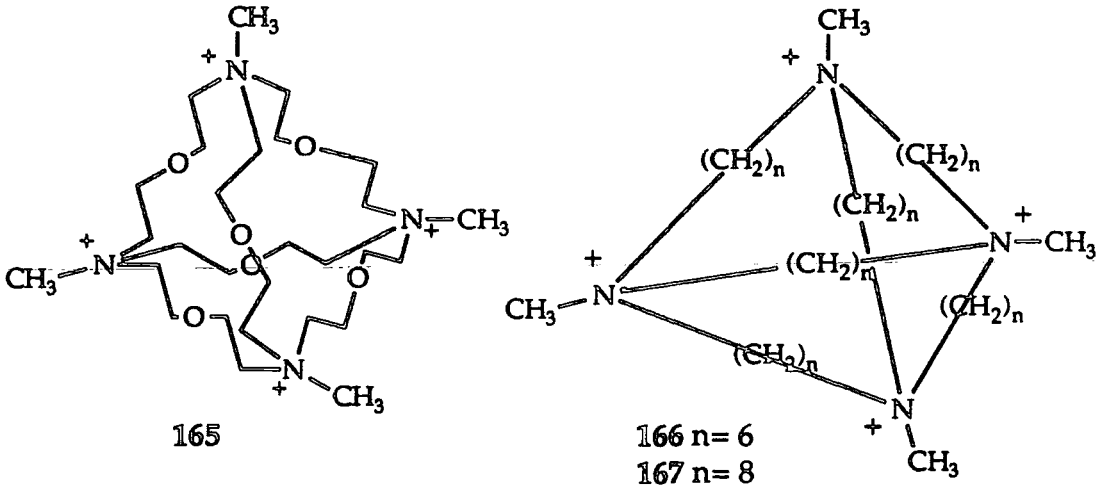


Figure 5.04:- Schematic representation of macrotricyclic receptors

As a result of the replusive forces between the four positive charges at the corners of a tetrahedron, a well defined cavity is formed. The cavity is so well defined that inclusion is dependent upon the size of the anion. Ligands **(166)** and **(167)** differ only in terms of cation diameter, the smaller having a cavity diameter of 4.5Å and the larger 7.5Å.

Anion complexation was observed with 1:1 host:guest stoichiometries in aqueous solution and binding constants were recorded (Table 5.03). The results showed that host **(166)** appears to prefer more 'polarisable' 'soft' anions. It may be that in such cases complexation is enhanced by hydrophobic forces.

	(165)	(166)	(167)
Cl^-	1.0	1.3	<0.5
Br^-	1.8	2.45	2.45
I^-	-	2.2	2.4

Table 5.03:- Stability constants (log K) for a series of halide complexes of **(165)** -**(167)**.

Isolation of a crystalline iodide salt of **(166)** allowed the structure to be elucidated by X-ray crystallography. [15] This showed that one of the four iodide counter-ions occupies the central cavity.

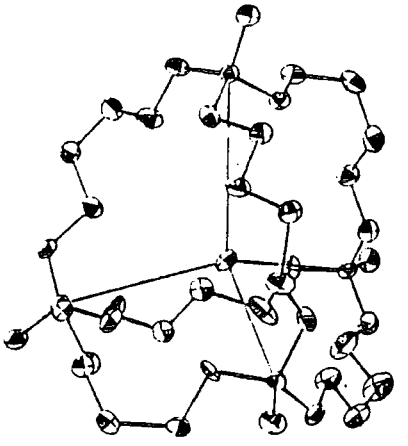
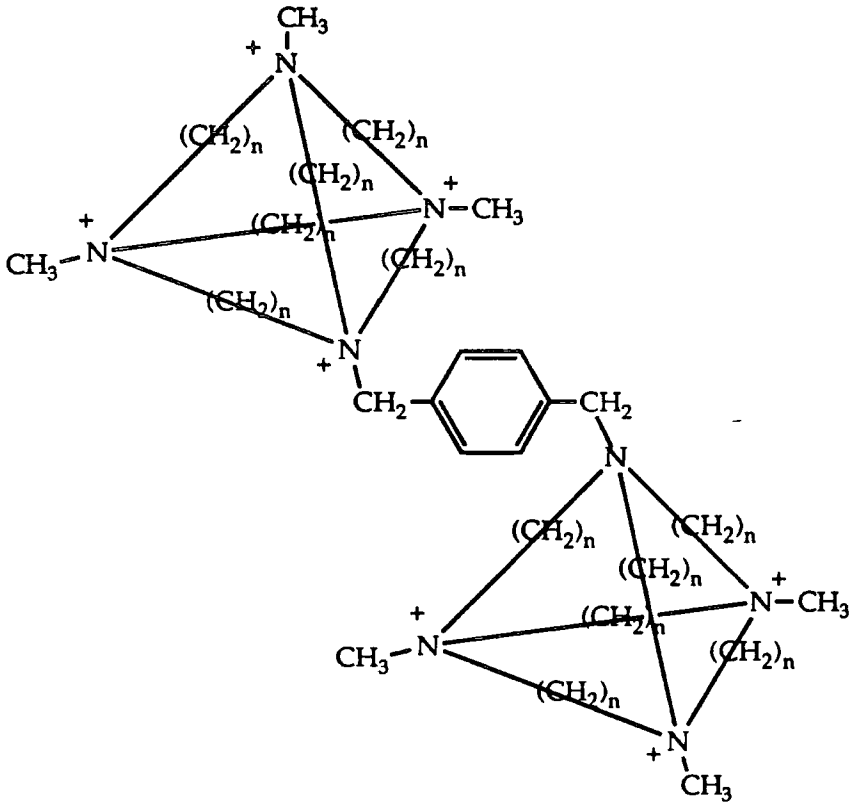


Figure 5.05:- X-ray crystal structure of the iodide inclusion complex of **(166)**.

The stability constants of the halide complexes of **(166)** and **(167)** are somewhat lower than those displayed by the tetraprotonated forms of **(161)** and **(162)**. This would appear to be due to the absence of H-bonding interactions which occur between quaternary ammonium protons and the anion in complexes formed by **(161)** and **(162)**. Thus complexation occurs only as a result of electrostatic interactions.

Many anionic species are large and structurally complex, often consisting of several sub-structures, one of which is the anionic moiety. It may therefore be possible to construct molecular hosts which contain anchor sites for the anionic moiety within a rigid molecular framework. However such systems may prove to be synthetically difficult to prepare and exhibit slow complexation kinetics.

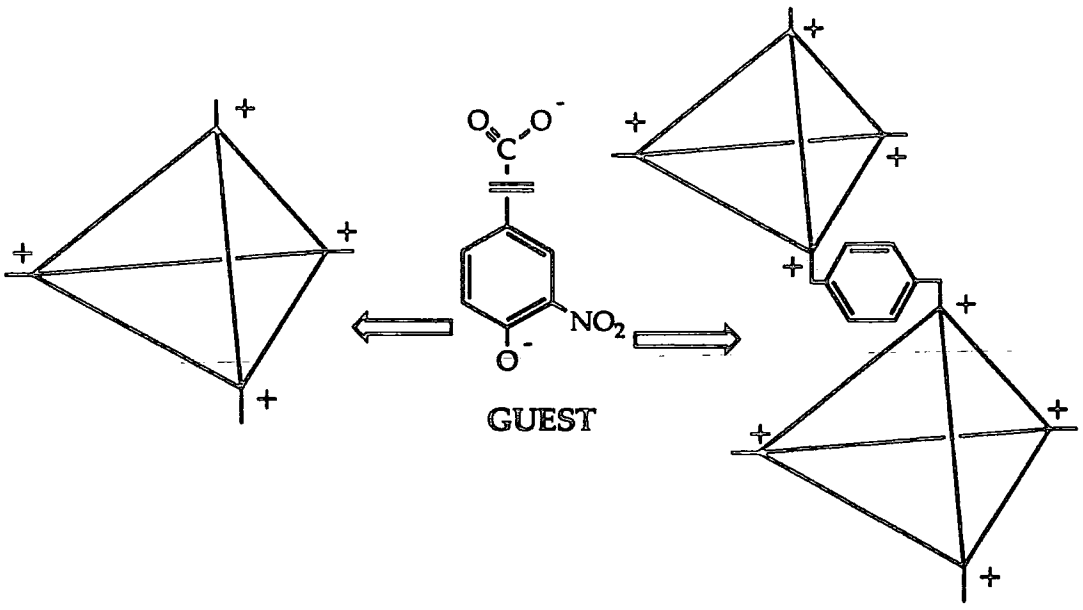
An alternative approach was adopted by Schmidtchen. [16,17] He linked two anchor sites via a linear chain and was able to selectively complex linear ditopic molecules. He linked one large **(167)** and one small **(166)** quaternary ammonium sub-structures via a p-xylene bridge,which facilitated free rotation of the ligand, to produce a ditopic receptor **(168)** .



(168)

Figure 5.06:- Proposed host for linear ditopic anions.

This ditopic receptor was examined using a series of probes containing two anionic sites at a fixed but adjustable distance. Association constants were determined and compared to those exhibited by **(166)**, such that Q was defined as (Figure 5.07):-



$$Q = \frac{\text{Kass (guest c (168))}}{\text{Kass (guest c (166))}}$$

Figure 5.07

The study showed that all the probes were more strongly bound by the ditopic ligand than by **(166)**. Optimum binding was observed when the anionic sites were separated by a C_4 spacer, i.e. the cinnamic acid salt [18]. (Figure 5.08)

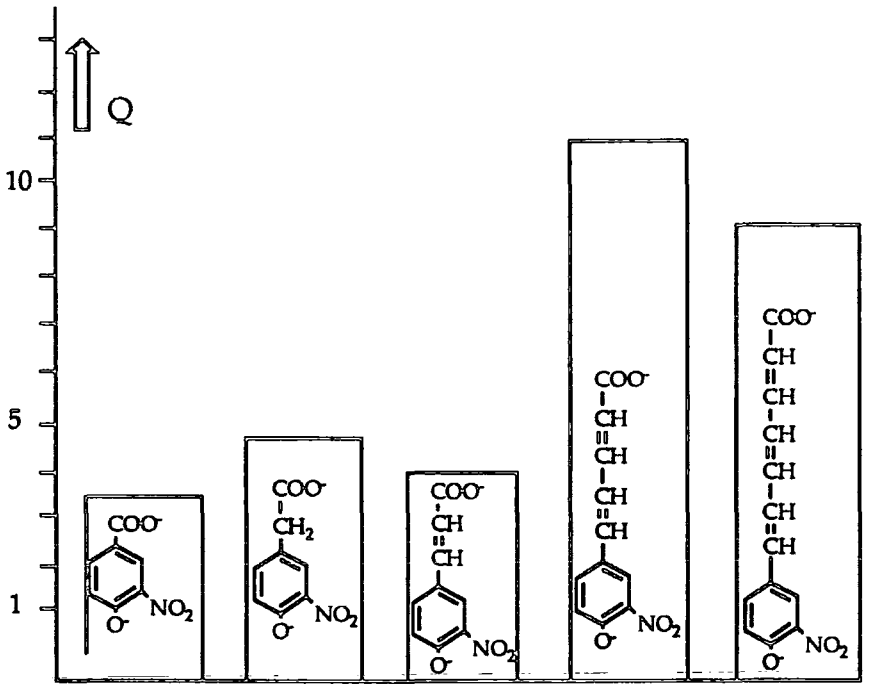


Figure 5.08:- Illustration of the relative association constants for **(168)** for a range of linear diatopic anions.

In addition to macropolycycles the binding properties of partially or fully protonated polyazamacrocycles have received considerable attention. Zompa *et al* [19,20,21] found that simple polyazamacrocycles **(169)** - **(171)** (Figure 5.09) underwent electrostatic and H-bonding interactions with a large number of anions

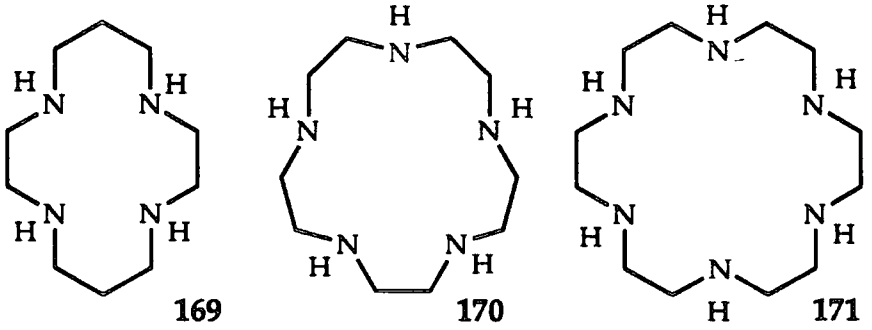


Figure 5.09:- Polyazamacrocycles studied as potential anion receptors.

Such polyazamacrocycles have one major drawback in that full protonation only occurs at very low pH when the nitrogen atoms are separated by ethylene groups and at such low pH's the anion itself is often protonated. Therefore many studies performed using such macrocycles have

been performed on partially protonated species.[20,21,22,23] Often 1:1 stoichiometry was observed, however in many cases interaction occured with the anion located outside of the macrocyclic cavity.

The reason for the difficulty in achieving full protonation in such systems lies in electrostatic replusion arising from the close proximetry of the nitrogen centres. In order to alleviate this macrocycles with three or more atoms separating the nitrogen centres were prepared (172) to (176).[24,25,26,27] (Figure 5.10).

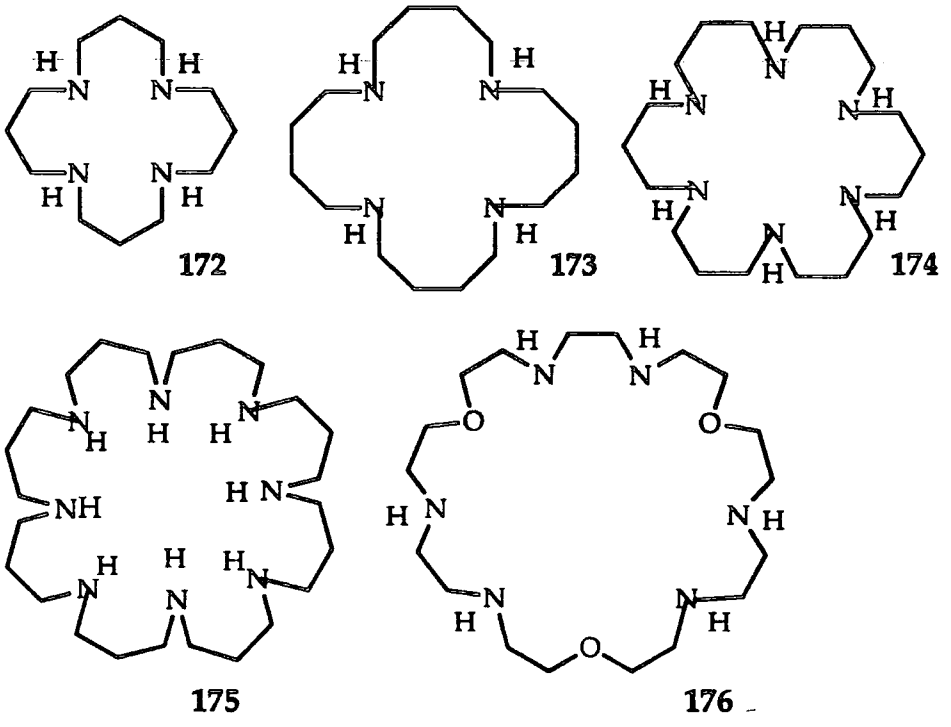


Figure 5.10:- Polyazamacrocycles designed to facilitate full protonation at pH's close to 7.

Of these ligands **(172)** and **(173)** are fully protonated at pH 4 and pH 5 respectively. Ligands **(174)** and **(175)** are usually fully protonated at neutral pH and have been shown to form strong association complexes with a wide range of anions, such as Adenosine monophopshate (AMP^{2-}), ADP^{3-}, $ATP.^{4-}$

5.2.2. RECEPTORS BASED UPON THE GUANIDINIUM CATION

The naturally occuring guanidinium group has been shown to play a role in the binding of a variety of oxo-anions. [28] It possesses several features which facilitate its use as an anion binding site:-

(1) The pKa of the guanidinium cation is 13.5 [29] thus it remains protonated over a much wider pH range than that of the ammonium cation.

(2) The primary interaction which occurs between the guanidinium sub-unit and the carboxylate anion is an electro-static ion-pairing interaction. Additionally the orientation of the guanidinium sub-unit is such that bidentate H-bonding can occur.

(3) The interaction between a guanidinium sub-unit and a carboxylate anion is stronger than that seen between an ammonium ion and a carboxylate anion by approximately 25 $KJmol^{-1}$ [30].

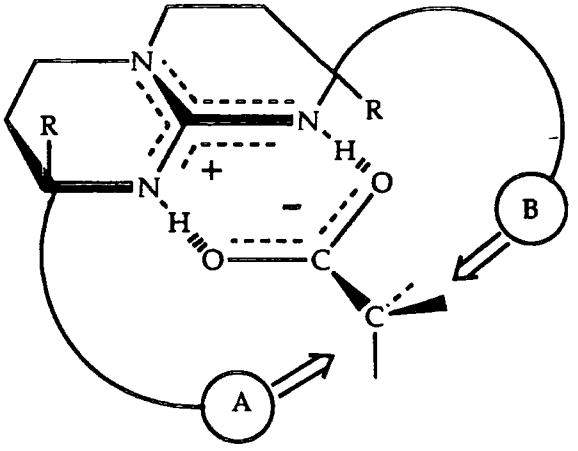
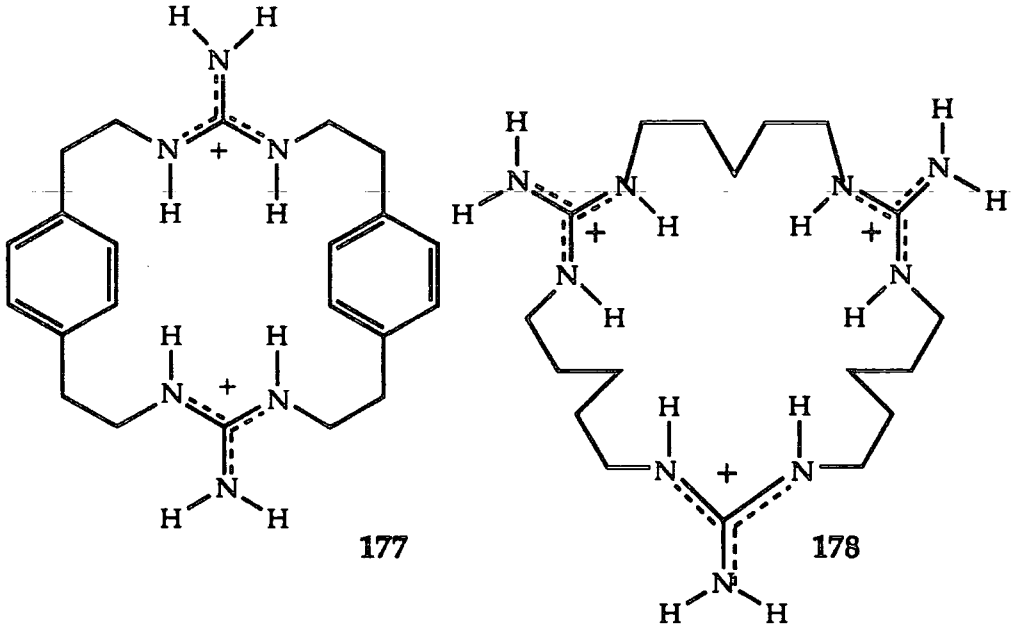


Figure 5.11:- Proposed mode of binding of carboxylate anions by a bicyclic guanidinium receptor.

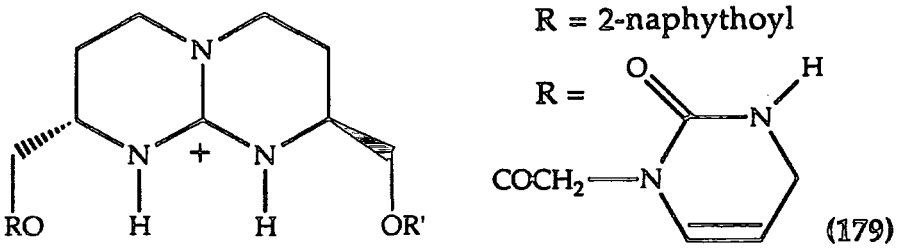
Early work involved the incorporation of guanidinium sub-units into macrocyclic structures (Figure 5.12). However although the receptors (177) and (178) were shown to coordinate anions, no significant macrocyclic effect was seen when comparing binding strengths with those of acyclic analogues. [31]



177 178

Figure 5.12:- Guanidine functionalised macrocyclic ligands.

As a result of these findings the majority of subsequent work has focussed upon the development of acyclic guanidinium based receptors [32]. Schmidtchen *et al* [18] studied the binding of such acyclic receptors and was able to demonstrate 1:1 complexation with several anions using NMR spectroscopy. Following on from this Schmidtchen set about developing chiral guanidinium receptors such as **(179)** and was able to demonstrate that binding of anionic species such as AMP^{3-} resulted from a three point interaction involving ion-pairing, hydrogen bonding and aromatic $\pi-\pi$ stacking (Figure 5.13).



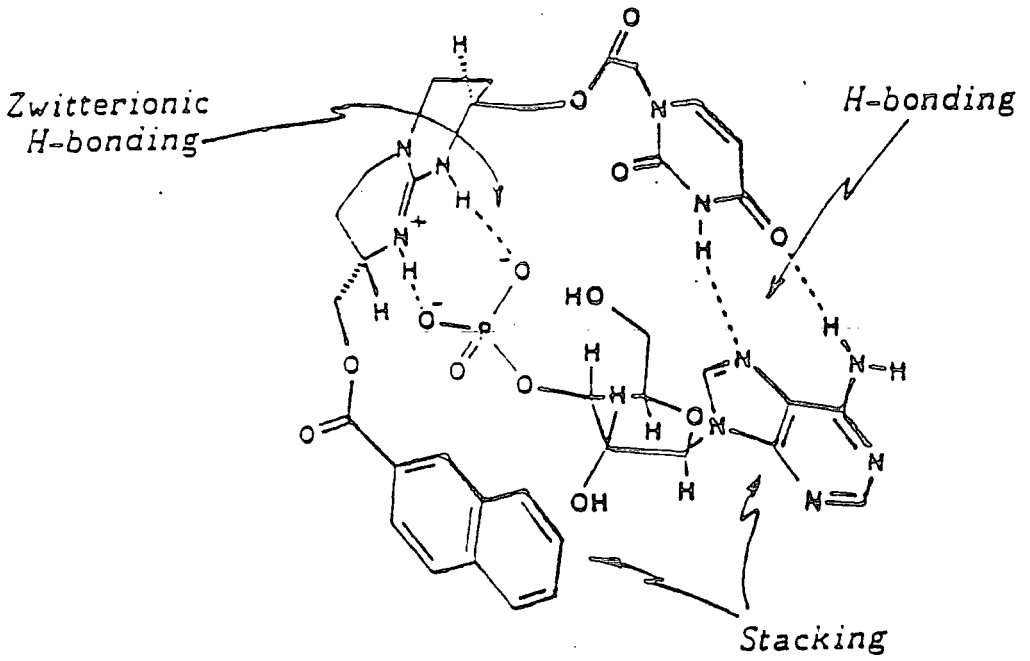


Figure 5.13:- Schematic representation of the 3-point interaction between **(179)** and AMP^{3-} .

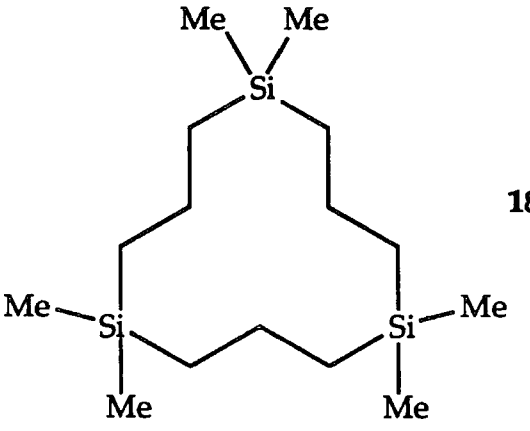
The bulky side-chains adjacent to the anion binding site result in the formation of diastereomeric complexes when bound to racemic N-acetyl amino acids or α-Hydroxy carboxylic acids. The diastereomers are easily distinguishable by NMR and thus receptors such as **(179)** can be used to determine enantiomeric purity. Further work has concentrated upon the development of diatopic guanidinium receptors, the geometry of which is ideally set up to bind tetrahedral anions. [33,34]

5.2.3. ANION RECEPTORS BASED UPON LEWIS ACID BINDING SITES

Only recently has anion complexation by compounds containing electron deficient atoms such as silicon[35], tin [36] mercury [37,38], and boron [39,40] been extensively studied. A brief summary of the development of such anionic receptors is given below.

5.2.3.1 Receptors Based upon silicon

Considerable evidence [41] is available to suggest that silicon can expand its valence shell and produce pentavalent (monanionic) or hexavalent (dianionic) species. Therefore M.E. Jung and H. Xia [35] examined the possible use of silicon monocyclics such as **(180)** as possible anion sensors.

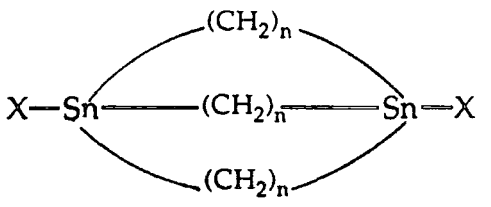


180

This has been shown to bind halide anions such as Cl^- and Br^-

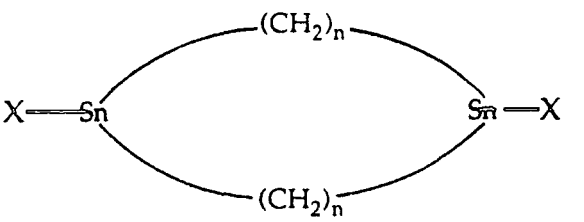
5.2.3.2 Receptors Based upon Tin

A large series of macrocyclic and macrobicyclic structures incorporating tin Lewis acidic centres were prepared by Newcomb [42] and evaluated as possible anion sensors. These structures were demonstrated to show selectivity for spherical halide anions based upon a anion diameter/cavity size ratio.



n = 5,6,7,8,9,10,12

X= Cl or Ph 181

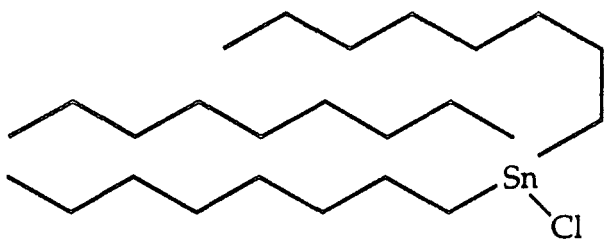


n= 4,5,6,8,10,12 R = Ph_2

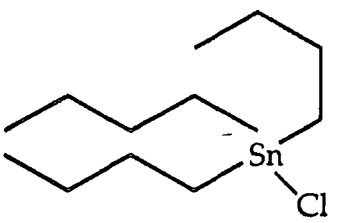
n= 8,10,12 R = Cl_2 182

Figure 5.14:- Series of macrocycles and macrotricycles based upon tin.

Simon *et al* [36] also studied a number of organotin compounds as possible electrically neutral carriers in anion-selective electrodes. When trioctyltin chloride (TOTCl 183) tributyltin chloride (TBTCl 184) and tetraoctyltin (TOT 185) were embedded in a membrane, differences in induced selectivity were observed. Tetracoctyltin (TOT 185) was found to exhibit no selectivity for anions. This is expected since tetraorgano-tin complexes are relatively stable even in the presence of a large quantities of nucleophiles.



TOTCl 183



TBTCl 184

Trioctyltin (TOTCl) and tributyltin (TBTCl) chlorides were both found to induce anion selectivity in membranes. For this type of tin complex i.e. R_3SnY, where R is an alkyl substituent and Y is an electronegative substituent, the mode of action may either involve dissociation into the trialkyltin cation or association with another anion. The two modes

correspond to electrically charged and electrically neutral carrier mechanisms respectively.

Thus in order to attempt to determine the mechanism involved NMR was used [43] . ^{119}Sn NMR is ideally suited because ^{119}Sn shifts are very sensitive to changes in the chemical environment surrounding the Sn atom. An increase in coordination number from 4 (tetrahedral) to 5 (trigonal bipyramid) would cause a significant high field shift [44]. Furthermore ^{119}Sn - ^{13}C coupling constants are a good indicator of the hybridisation of the Sn atom [45]

Several trialkyltin compounds were titrated with Bu_3NCl. In all cases the ^{119}Sn chemical shift moved to a higher field, ~ 180ppm to ~ -40ppm. The ^{119}Sn - ^{13}C coupling constant changed from 330 to ~ 475Hz, and the ^{13}C resonance of the carbon atom bonded directly to the Sn changed from 17.5ppm to ~ 25.0ppm.

The marked increase in the shielding of the Sn centre together with the increase in the ^{119}Sn - ^{13}C coupling constant clearly indicated that a change from 4-coordinate to 5-coordinate geometry had occured. The confirmation of a 5-coordinate adduct supports a neutral carrier transport mechanism (Figure 5.15)

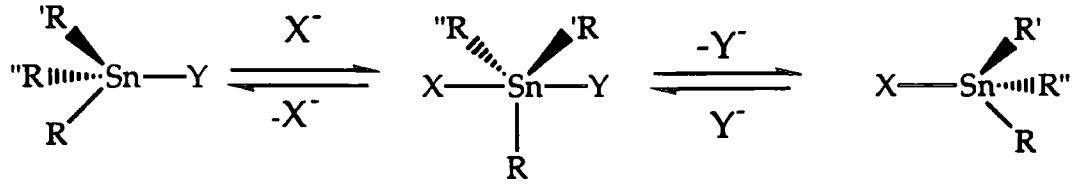
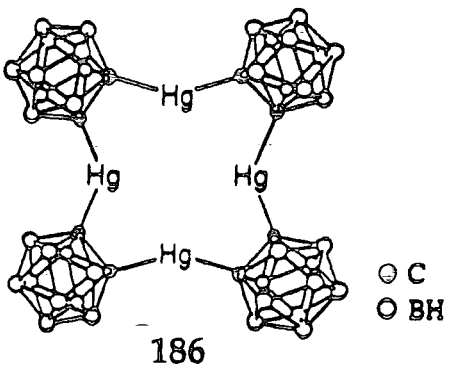


Figure 5.15 :- Postulated mechanism for the interaction between tri-alkyl tin compounds and an anion X^-.

In fact an ISE based upon (TBTCl 184) displays sufficient Cl^- selectivity for it to used in clinical applications when buffered solutions are used.

5.2.3.3 Receptors based upon Mercury

Recently Hawthorne *et al* [46] developed a carborane-supported cyclic mercuric structure (186) and have demonstrated that it forms a very stable complexes with halide ions.

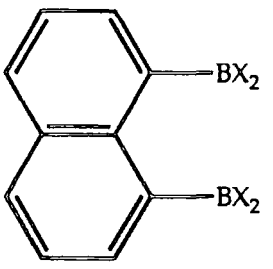


186

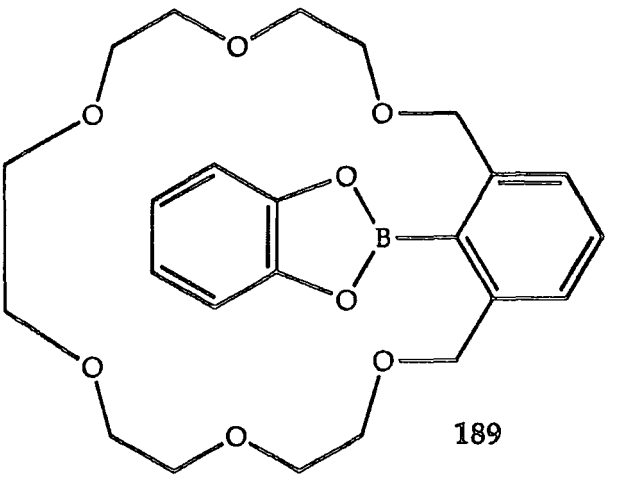
5.2.3.4 Receptors based upon boron

Until comparitively recently little work has been undertaken to develop anion receptors based upon boron. The first example of such receptors were two bidentate structures (187) and (188), developed by Katz *et al* [39]. The dimethyl derivative (187) was shown to form a very stable 2:1 Ligand : Hydride ion complex, whereas the chloride derivative (188) was found to bind the chloride ion in a similar manner.

Recently Reetz *et al* [40] designed an anion selective receptor (189) based upon a conventional crown ether moiety containing a σ-bonded Lewis acidic boron centre. The complexation properties of this ligand, following the addition of dry KF to a solution (dichloromethane) were studied using both ^{13}C and ^{11}B NMR techniques.



(187) X= Me
(188) X= Cl



189

The ^{11}B spectrum, with BF_3-etherate as an external standard, showed peak at δ=10ppm, a shift of approximately 20ppm to a higher field compared to the signal of the host compound (δ=30 ppm). Furthermore complexation of the potassium cation by the ring was confirmed by ^{13}C NMR spectroscopy. The spectrum showed discrete lines corresponding to both free and complexed ligand at intermediate stoichiometries. The fact that sharp signals were observed is indicative of strong complexation as rapid exchange does not occur on the NMR timescale. X-ray analysis confirmed that both the cation and the anion were included in the complex.

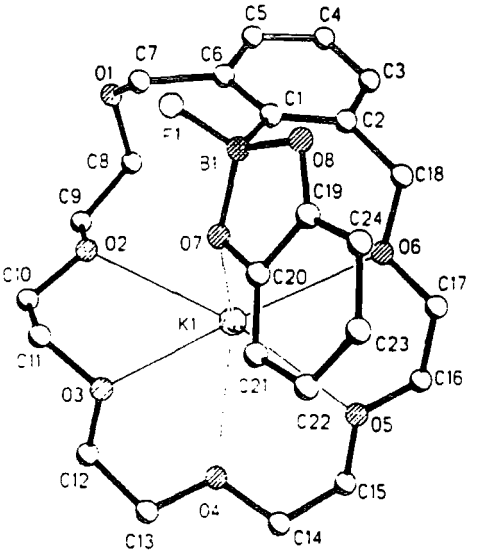
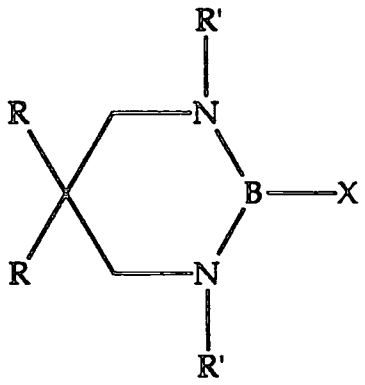


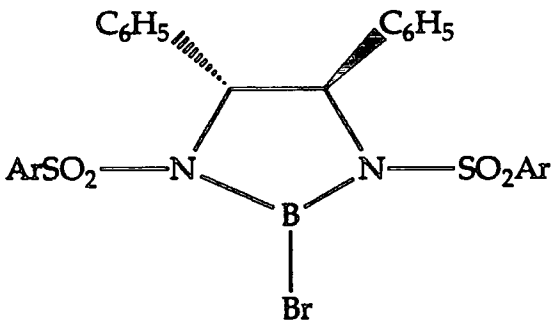
Fig 5.16:- Asymmetric view of (189)-KF complex, illustrating inclusion of both cation and anion.

5.3 AIMS AND OBJECTIVES

The aim of this work was to develop a series of 6 membered ring boron-nitrogen heterocycles (190) to (194). It was hoped that the electron deficient boron centres would be sufficiently Lewis acidic to facilitate the binding of electron rich anionic species.

Similar boron-nitrogen structures (195)-(197) have been demonstrated to promote enantioselective aldol reactions involving achiral aldehydes to give syn or anti aldol products with excellent diastereo- and enantioselectivity [47]. The mechanism is thought to involve the formation of a bond between the electron deficient boron atom and a lone pair present on the aldehyde carbonyl.





(190) R = H, R' = ^{i}But, X = Br
(191) R = H, R' = ^{i}But, X = Cl
(192) R = But, R' = ^{i}But, X= Br
(193) R= H, R' = Tosyl, X = Br
(194) R= H, R' = Tosyl, X = Cl

(195) Ar = p-CH_3-C_6H_4
(196) Ar = p-NO_2-C_6H_4
(197) Ar = 3,5 $(CF_3)_2$-C_6H_3

In order to prepare the required boron-nitrogen heterocycles a series of amine derivatives were prepared. The first step in the development of the simple isobutylamine derivative involved heating diethyl malonate in neat isobutylamine, to yield a diamide **(198)**. This in turn was converted to the required amine **(199)** by performing a borane reduction. The synthesis of the more lipophilic amide derivative **(200)**, could not be prepared simply by heating di-butyl diethyl malonate in neat isobutylamine. The reaction was

too slow and thus preparation of the required amine (202) was to be achieved by performing a borane reduction upon the diamide. However because of the lack of success achieved in preparing the boron-nitrogen heterocycles (190) and (191), the actual synthesis was not attempted. The tosylamide analogue (203), was simply prepared by tosylating 1,3-diaminopropane.

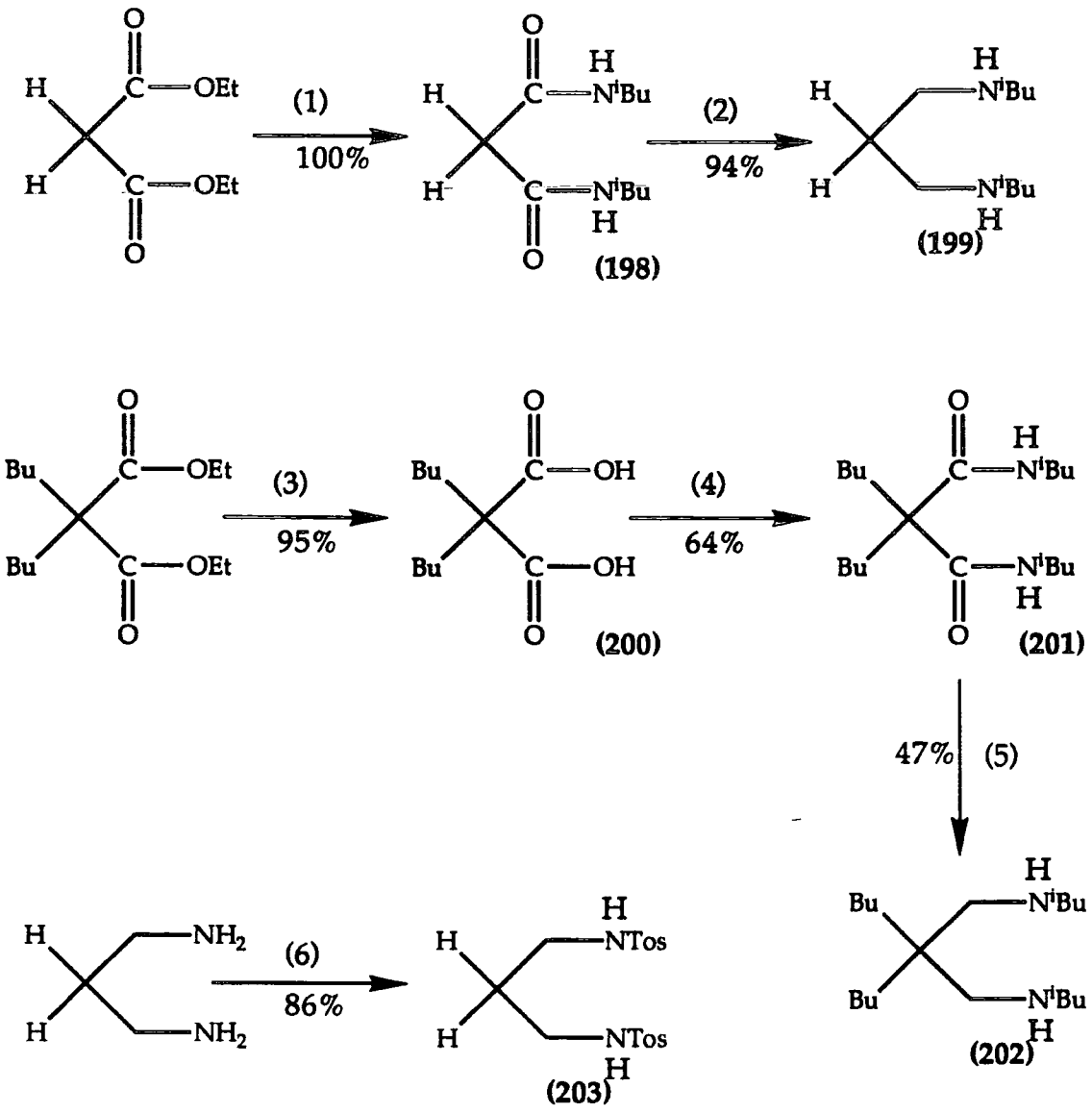


Figure 5.17 :- (1) isobutylamine, 60°C. (2) a) BH_3-THF, b) $HCl_{(aq)}$ 6N. (3) NaOH, MeOH/H_2O. (4) a) oxalyl chloride, CH_2Cl_2. b) isobutylamine, CH_2Cl_2. (5) a) BH_3-THF, b) $HCl_{(aq)}$. (6) Tosyl chloride, K_2CO_3, THF/H_2O.

Conversion of (199) to the required boron-nitrogen heterocycle (191) was first attempted by simple addition of BCl_3 (soln. in CH_2Cl_2) to a solution of the diamine (199) at low temperatures (-10°C, under nitrogen). Addition was accompanied by precipitation of a white solid. This was removed by filtration and dried. Analysis of the solid identified it as the dihydrochloride salt of (199). The filtrate was also examined and found to contain only the diamine (199). No evidence was found to suggest that synthesis of the required heterocycle had been achieved. The procedure was also attempted using BBr_3, in addition to varying the ratio of diamine (199) to boron trihalide. In all cases studying the ^{11}B NMR spectrum gave no indication of formation of (190) or (191).

The problem with the procedure would appear to be that the HCl evolved as the boron trichloride reacts with the amine, displaces the boron inserted into the ring resulting in the formation of the diamine hydrochloride. In order to prevent the formation of the hydrochloride salt an excess of potassium carbonate was added in order to remove the HCl evolved as the reaction proceeds.

This procedure was attempted using (199) and BBr_3 both at room temperature and with refluxing (dichloromethane, 3 hours). After filtration and concentration *in vacuo* , both residues were analysed. Mass spectral analysis revealed the presence of the required heterocycle in both samples. However neither procedure resulted in clean conversion and purification proved not to be possible. Distillation simply resulted in decomposition whereas chromatography also proved to be inapplicable. It was a matter of conjecture whether the diamine (199) present after the reaction resulted from residual starting material or that the heterocycle rapidly underwent decomposition.

One further method was attempted to effect synthesis of (190). This utilised a procedure developed by Richman *et al* [48], originally used in the preparation of tris amino boranes. This involved silylation of the diamine followed by treatment with boron tribromide (Figure 5.18)

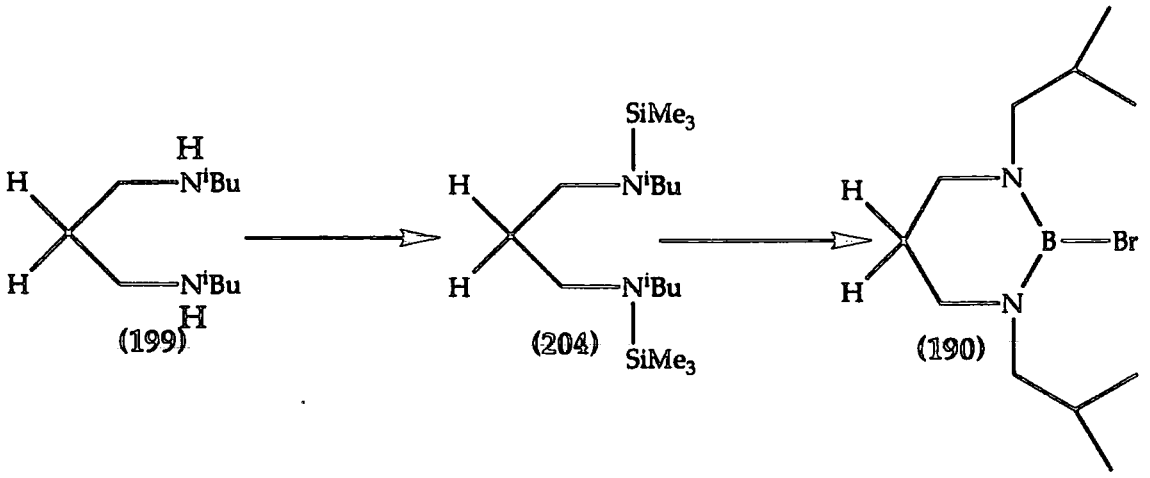


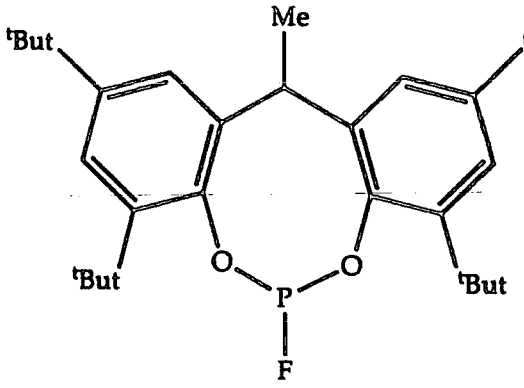
Figure 5.18:- (1)a) Butyl-lithium, THF, -78°C, b) Trimethylchlorosilane. (2) BBr_3, dichloromethane.

Again despite ensuring complete conversion of the diamine to the silylated amine (204), upon addition of BBr_3 clean conversion to the boron-nitrogen heterocycle was not achieved. Again purification of (190) was not carried out.

Therefore attention was switched to the synthesis of (193) and (194). Synthesis was simply achieved by addition of a solution of the boron trihalide to a cooled solution (-10°C) of the ditosylamide (203) and then allowing the temperature to slowly rise to room temperature. The solvent was then removed to yield a residue. ^1H NMR analysis indicated that the residue was the required product e.g. no N-H resonance was seen in the spectrum. Further purification was not attempted.

In addition to the boron-nitrogen heterocycles listed above an attempt was also made to prepare an anionic receptor based upon a boron-oxygen heterocycle. 2,2' Ethylidene-Bis (4,6-di-tert-butyl-phenol) was already known

to form a stable complex (205) when reacted with phosphorus trihalides and thus it was decided to attempt formation of a boron analogue (206) in similar fashion. Synthesis of (206) was simply achieved by the addition BBr_3 to a solution of 2,2' Ethylidene-Bis (4,6-di-tert-butyl-phenol), under nitrogen. The required product precipitated out of solution.



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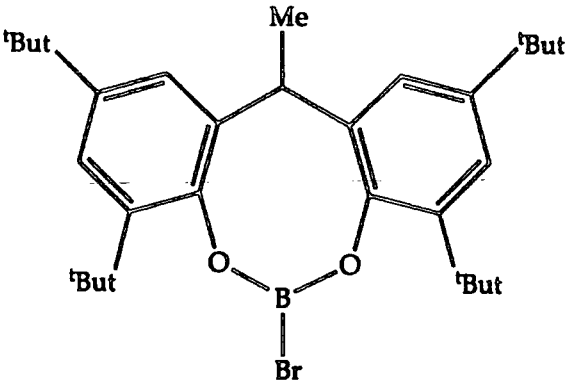

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5.4 ^{11}B NMR STUDIES

The response of (193), (194) and (206) to the addition of halide anions (in the form of quaternary ammonium salts) was monitored using ^{11}B NMR. Any anionic response would be accompanied by a change in the ^{11}B spectrum of the ligand.

Ligand (193) :-

The boron spectrum of (193) appeared as a single peak at 2.11 ppm (Figure 5.19a). This almost certainly corresponds to the neutral trivalent species illustrated above. Upon the addition of one equivalent of tetrahexyl ammonium chloride a significant alteration in the spectrum was observed. Instead of one peak at 2.11 ppm, three new species were observed at -24.97, -15.33 and -6.91 (Fig 5.19b).

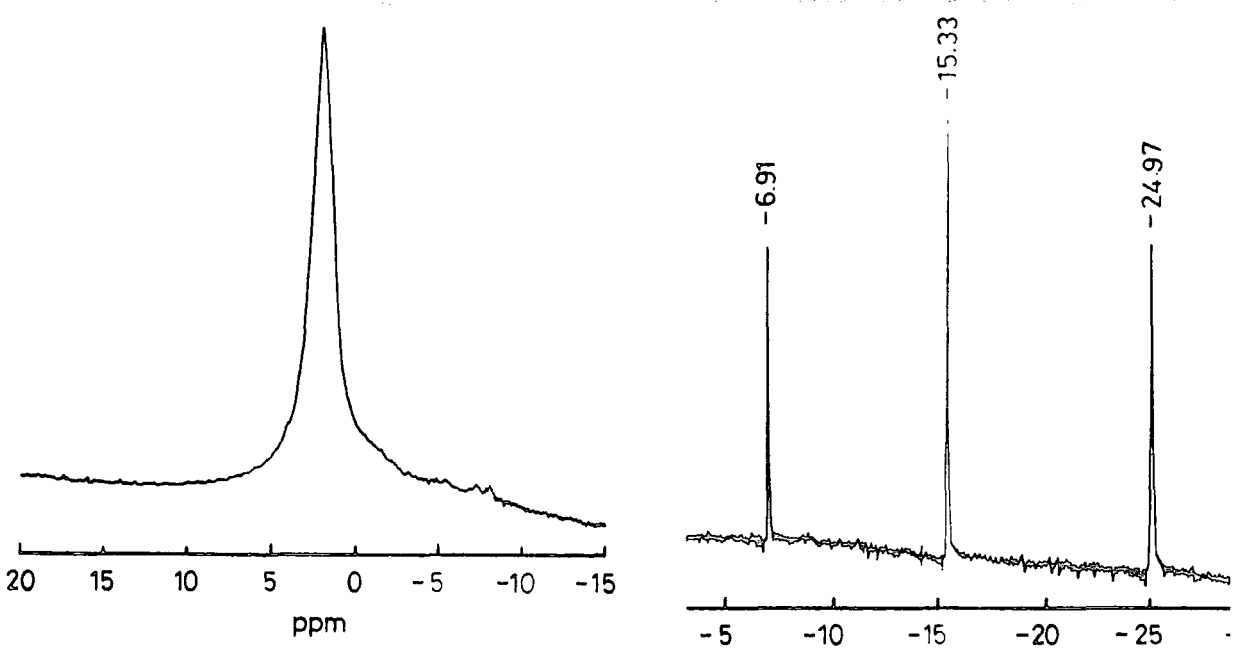


Figure 5.19:- ^{11}B NMR Spectrum of Ligand **(193)** a) before and b) after the addition of Cl^- ions.

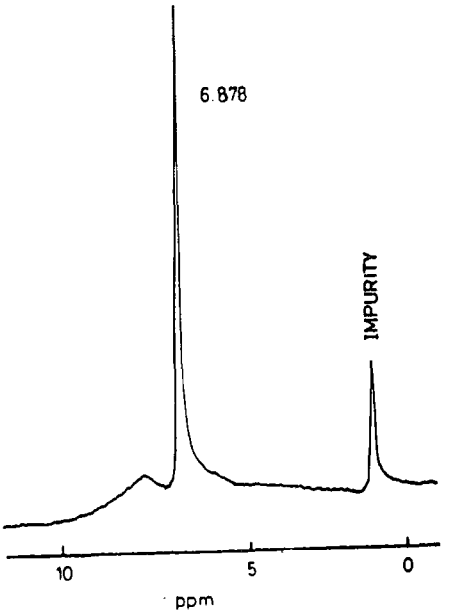


Figure 5.20:- ^{11}B NMR Spectrum of Ligand **(194)**

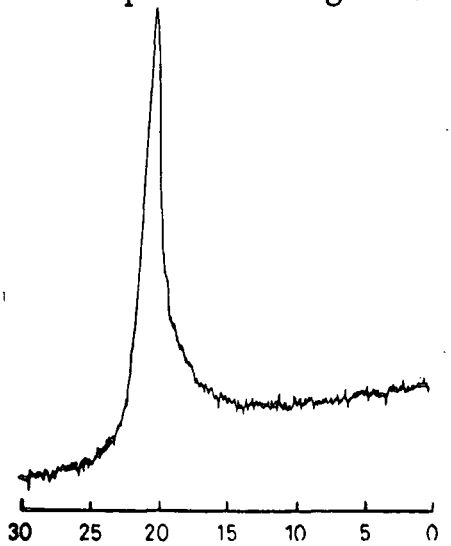
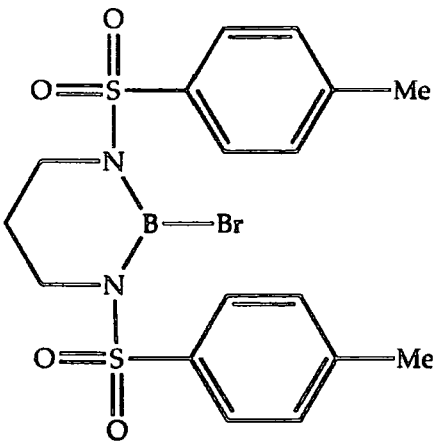
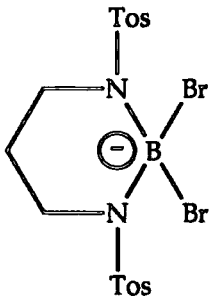


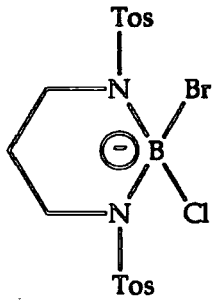
Figure 5.21:- ^{11}B NMR Spectrum of Ligand **(206)**



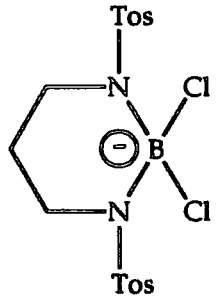
The negative chemical shifts suggested that the species obtained were anionic, in accord with the findings of previous studies into the ^{11}B chemical shifts of tetrahaloborate anions. [49] Thus it was postulated that the species observed were:-



207



208



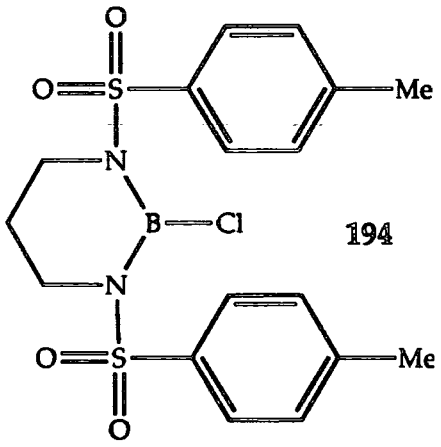
209

In addition to the change seen in the appearance of the spectrum, the line widths of the peaks seen after the addition of Cl^- ions are significantly narrower than the line widths of the neutral species. The fact that separate sharp peaks were observed is indicative of slow exchange on an NMR timescale.

The identity of the species observed at -24.97 ppm was later confirmed as the four coordinate di-bromo anion (207) by the addition of Br^- ions (in the form of tetrabutyl ammonium bromide). After addition, one peak was observed in the ^{11}B spectrum at -24.97 as expected.

Ligand (194)

The response of (194) to halide anions was also studied. The ^{11}B NMR spectrum of the ligand alone appeared as a singlet at 6.87 ppm (fig 5.20). Again this almost certainly corresponds to the neutral tri-valent species. Upon the addition of Br^- (in the form of tetrabutyl ammonium bromide) no change was observed in the spectrum. Similarly the addition of Cl^- ions resulted in no observable change.

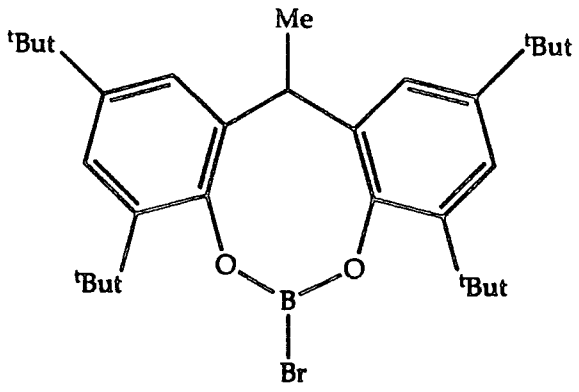


194

Unlike the bromide analogue (193) which undergoes association with halide ions, Br^- and Cl^-, (194) does not appear to. This is somewhat surprising since it is expected that the chloride analogue (194) would be more Lewis acidic than the bromide (193). It would therefore seem most likely that the lack of response was kinetic in origin i.e. halogen exchange rates for the chloride analogue (194) are considerably slower than those observed with the bromide (193).

Ligand 206:-

The ^{11}B spectrum of ligand (206) appeared as single peak at 20.58, (Figure 5.21) again consistent with the value expected for a tri-valent di-aryloxide boron species. However no change in the appearance of the spectrum was seen upon the addition of either Br^- or Cl^- ions, even after warming the solution.



206

It would appear therefore that either the Lewis acidity of the boron atom is too low for it to show any association with anionic species, or that as with the chloride analogue (194) detailed above, the rates of halogen exchange are very slow.

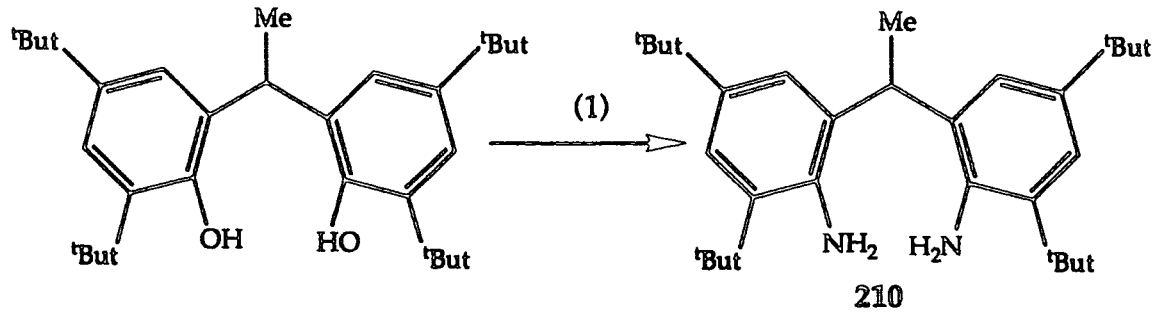
This "catechol-like" boron compound was however, significantly more stable in air than the boron-nitrogen heterocycles (193) and (194), no appreciable diminution in the ^{11}B response was observed after standing for 24 hours.

5.6 FUTURE WORK

Although a response to Cl^- ions has been observed with the boron-nitrogen heterocycle (193) the stability of the ligand and its chloride analogue (194) was poor. Both are very hygroscopic and despite the use of anhydrous solvents and salts, after only a matter of hours the ^{11}B signal virtually disappears and the ^1H spectrum displays a resonance corresponding to N-H, indicating hydrolytic ring opening. This lack of stability obviously precludes their use as anion receptors in an aqueous environment.

It may be possible to combine some of the Lewis acidity of the B-N heterocycles with the greater stability seen with the B-O derivative (206)

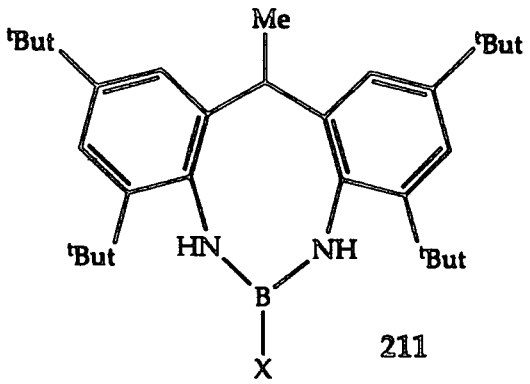
converting 2,2' Ethylidene-Bis (4,6-di-tert-butyl-phenol) to its di-aniline analogue (210) (Figure 5.22)



210

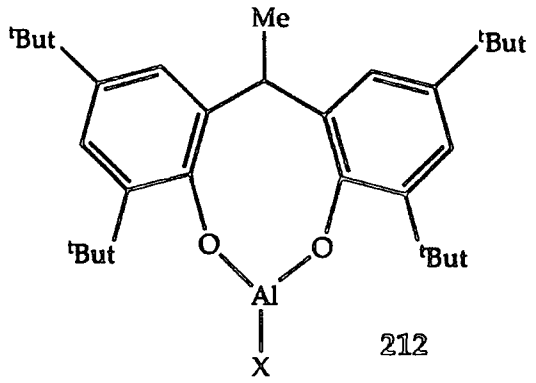
Figure 5.22:- (1) NH_4OH, SO_2

This dianiline analogue (210) could then be treated with a boron-trihalide in the presence of a base to yield the required heterocycle (211).

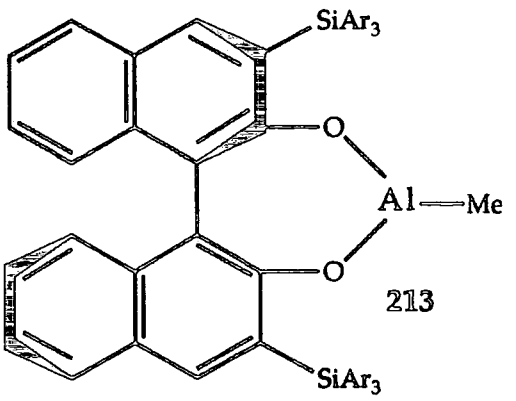


211

Alternatively instead of using boron as the Lewis acidic component, other elements such as aluminium could be experimented with. For instance, the aluminium analogue of (205) and (206) could be easily prepared (212) by treating 2,2' Ethylidene-Bis (4,6-di-tert-butyl-phenol) with a dialkyl aluminium halide.



212



213

Similar stable diaryloxide aluminium species (213) have recently been prepared [50].

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CHAPTER VI:

EXPERIMENTAL

6.1 INTRODUCTION

For all the reactions performed, temperatures are quoted in degrees centigrade. alumina refers to Merck Alumina (activity II - II) and silica refers to Merck silica gel F^{60} (230 - 400 mesh).

Proton and carbon-13 NMR spectra were recorded using either a Bruker AC250 or a Varian VXR 400 spectrometer. The Bruker AC250 was operated at 250.134 MHz (proton) and 62.896 MHz (C), whilst the Varian VXR 400 was operated at 399.952 MHz (proton) and 100.577 MHz (^{13}C). All chemical shifts are given in ppm (referenced to Me_4Si (TMS) at 0ppm).

Mass spectra were recorded on a VG 7070E mass spectrometer, operating in CI , EI or FAB modes as stated. Gas chromatography was performed on a Hewlett-Packard HP5890 using an SE30 capillary column. Infrared spectra were recorded on either a Perkin-Elmer 577 spectrometer as a thin film, KBr disc or Nujol mull as stated.

POTENTIOMETRIC STUDIES:- MEMBRANE PREPARATION. The membranes were made up by dissolving 1.2% sensor, 65.6% plasticizer (ONPOE or BBPA), 32.8% PVC (high molecular weight Fluka) and 0.4% lipophilic anion (KTpCIPB) , in $6cm^{-3}$ of spectroscopic grade tetrahydrofuran (THF) which was poured into a 33mm i.d. glass ring resting on a sheet of plate glass. A pad of filter papers was placed on top of the ring and kept in place by a heavy weight. The assembly was left for 48h to allow slow solvent evaporation. A small disc was cut from the membrane and affixed to a Philips Pye electrode body to form the ion-selective electrode.

Solutions were made up using anhydrous lithium chloride (BDH), sodium chloride (BDH), potassium chloride (BDH) and calcium chloride solution 1mol dm^{-3} (BDH) and deionised water (MilliQ).

FLOW SYSTEM . A constant-volume cell was used for the ion-selective electrodes. It was made from a water-jacketed glass tube with B19 ground glass joints. Drilled glass stoppers were used with a wax seal in order to fit the electrodes.

The ion selective and reference electrodes were connected to a digital multimeter (Keithley 197 Autoranging Microvolt DMM) via a buffer amplifier. The reference electrode was a porous plug, saturated calomel electrode (RE1 Petiacourt). A flat bed Linseis Yt chart recorder, provided with back off facilities, was used for monitoring potential difference changes. A suitable resistor was connected across the input of the chart recorder to smooth out residual noise. The peristaltic pump used was an RS330-812. The temperature of the system was maintained at 37° C using a Techne Tempette junior TE-85 Thermostat bath.

^{13}C *NMR Experiments*- Titration curves were obtained in CD_3OD solution of the ligand with subsequent admixture of LiCl (BDH). After each addition of the salt, the ^{13}C NMR chemical shift (relative to TMS) was measured at 298K using a Bruker AC250 instrument operating at 62.1MHz for the carbon nucleus.

6.2. SYNTHESIS

1,8 - Dicyano - 3,6 - dioxoctane (82) :- To a stirred solution of aqueous sodium hydroxide (40 ml , 2% $^{w}/_{v}$) and ethane 1,2,- diol (74.4g, 1.2 mol) at 0°C was added acrylonitrile (127.3g, 2.4mol) over 1hr. The mixture was then stirred at RT for 24hrs., then allowed to stand to aid separation of the two layers. The lower organic layer was then dried (K_2CO_3) and purified by distillation to yield a colourless oil (b.p. 90-95°C, 0.1mmHg); 170.5g (85%). δ_H ($CDCl_3$) 2.58 (4H, t, CH_2CN), 3.58 (4H, t, CH_2O) and 3.53 (4H , s, CH_2O). δ_C ($CDCl_3$) 17.9 (CH_2CN), 64.9 and 69.4 (CH_2O) and 117.7 (CH_2CN). υ_{max} (thin film)

(cm^{-1}) 2225 (CN). $^{m}/_{z}$ (CI) 169 ($M^+ + 1$, 100%) and 98 (M^+-CH_2CH_2CN, 15%).

Diethyl 4,7 - dioxadecane - 1,10 - dioate (83) :- To a solution of conc. sulphuric acid (60ml), distilled water (27ml) in ethanol (390ml) at 0°C was added **(82)** (168g, 1.0mol) and the mixture was boiled under reflux for 72hrs. After cooling K_2CO_3 (74g, 0.75mol) was added to neutralise the sulphuric acid. The solution was then filtered to remove excess K_2CO_3 and precipitated ammonium sulphate, and the solvent removed under reduced pressure. The residue was then treated with H_2O (150 ml) and extracted with dichloromethane (1 x 250ml, 2 x100ml). The combined extracts were dried (K_2CO_3), filtered and the solvent removed under reduced pressure to leave a residue which was distilled (70°C, 0.05mmHg) to give a colourless oil ; 203.1g (77%). δ_H ($CDCl_3$) 1.25 (6H, t, CH_3C), 2.60 (4H, t, CH_2CO), 3.75 (4H, t, CH_2O), 3.62 (4H, s, CH_2O) & 4.15 (4H, q, O-CH_2-CH_3). δ_C ($CDCl_3$) 13.9 (CH_3), 34.8 (CH_2CO), 60.2, 66.3 (CH_2O) and 171.3 (C=O). υ_{max} (thin film) (cm^{-1}) 1735 (C=O), 1110 (C-0-C). $^{m}/_{z}$ (CI, isobutane): Found ($M^+ + 1$) 263.148740. $C_{12}H_{22}O_6$ requires ($M^+ + 1$) 263.149463.

1,10 - Dihydroxy - 4,7 - dioxadecane (84) :- To a suspension of lithium aluminium hydride (24g, 0.63mol) in dry ether (150ml) at 0°C was added dropwise a solution of **(83)** (78.0g, 0.3mol) in dry ether (150ml). The mixture was then heated under reflux, under nitrogen, for 7 hours with vigorous stirring and then stirred for a further 7 hours at room temperature. The reaction mixture was then cooled to 0°C and H_2O (24ml), NaOH (15%, 48ml) and H_2O (24ml) were carefully added in turn. The aluminium salts were filtered off and the solvent removed under reduced pressure to yield a small amount of crude product. The aluminium salts were then boiled under reflux with chloroform : methanol (90:10) (250ml) for 3 hours to extract the product. The resultant suspension was then cooled to room temperature,

filtered to remove the aluminium salts and the solvent removed under reduced pressure to yield a residue. The two residues were combined and distilled (90°C, 0.05mmHg) to give a colourless oil, 24.8g (66%). δ_H ($CDCl_3$) 1.70 (4H, quint, CH_2C), 3.52 (4H, t, CH_2O), 3.49 (4H, s, CH_2O) & 3.60 (4H, t, CH_2OH). δ_C ($CDCl_3$) 31.8 (CH_2C), 59.1, 68.3, 69.5 (CH_2O). υ_{max} (thin film) (cm^{-1}) 3500-3100 (OH, br), 1105 & 845 (C-O-C). $^m/_z$ (CI) Found ($M^+ + 1$) 179.119410 : $C_8H_{18}O_4$ requires 179.120509.

1,10 - bis (p-toluenesulphanato) - 4,7 - dioxadecane (79) :- To a solution of **(84)** (20.8g, 0.12mol) in dry pyridine (250ml) at -10°C was slowly added toluene-p-sulphonyl chloride (69.0g, 0.36mol). The mixture was then held at -20°C for 72 hours, then poured onto 300 - 400g of crushed ice and stirred for 30 minutes. The crystallised crude product was filtered off and purified by recrystallisation from ethanol, 46.7g, (82%). δ_H ($CDCl_3$) 1.90 (4H, quint, CH_2C), 2.45 (6H, s, CH_3C), 3.46 (8H, m, CH_2O), 4.10 (4H, t, CH_2O), 7.33 - 7.77 (4H, dd, Ar). δ_C ($CDCl_3$) 21.47 (CH_2C), 29.10 (CH_3Ph), 66.42, 66.59, 70.0 (CH_2O), 127.73, 129.73, 132.90 & 144.64 (arom C). υ_{max} (nujol) (cm^{-1}) 1600 (C=C,arom), 1380 & 1170 (S=O). $^m/_z$ (CI) 504 ($M^+ + 18$, 100%), 213 (12%). Elemental Analysis: Found : C=54.0; H=6.20. $C_{22}H_{30}S_2O_8$ requires C=54.3; H=6.21.

Trans - (4R,5R) - (-) - 4,5 - bis (ethoxycarbonyl) - 2,2 - dimethyl - 1,3 - dioxalane(86) [1]:- (R,R) - (+) - dimethyl tartrate **(85)**, (35.6g, 0.2mol), 2,2-dimethoxypropane (23.0g, 0.22mol) and p-toluene sulphonic acid (200mg) were refluxed in dry chloroform (200ml) under nitrogen and through activated 4A molecular sieves (80g) for 3 hours. A further 8g (76mM) 2,2-dimethoxypropane in chloroform (40ml) was then added and the reaction refluxed for a further 1hour. Excess 2,2-dimethoxypropane and chloroform were removed under reduced pressure to yield a residue which was distilled (80-85°C, 0.3mmHg) to yield a colourless oil, 40.7g, (93%). δ_H

($CDCl_3$) 1.50 (6H, s, CH_3C), 3.83 (6H, s, CH_3O), 4.82 (2H, s, CHO). δ_C ($CDCl_3$) 26.69 (CH_3), 53.19 (CH_3O), 77.38 (CHO), 114.23 (C), 170.50 (C=O) υ_{max} (thin film) (cm^{-1}) 1760 (C=O). $^m/_z$ (DCI,

Trans - (4S,5S) - (+) - 4,5 - bis(hydroxymethyl) - 2,2 - dimethyl - 1,3-dioxalane (87) [1]:- To a suspension of lithium aluminium hydride (15g, 0.40mol) in dry ether (150ml) at 0°C was added dropwise a solution of (86) (40.0g, 0.18mol) in dry ether (150ml). The mixture was then refluxed under nitrogen for 12 hours, cooled to 0°C and H_2O (15ml), NaOH (15%, 30ml) and H_2O (15ml) added carefully in sequence. The aluminium salts were then filtered off and the solvent removed under reduced pressure to yield a small amount of crude product. The aluminium salts were then boiled under reflux with chloroform : methanol (90 : 10) (250ml) for 3 hours to extract the product. The suspension was then cooled to room temperature, filtered to remove the salts and the solvent removed under reduced pressure to yield a residue. The two residues were combined and distilled (78 - 81°C, 0.01mmHg) to yield a colourless oil, 18.3g (63%). δ_H ($CDCl_3$) 1.34 (6H, s, CH_3C), 3.65 (4H, s, CH_2OH), 3.87 (2H, s, CH_2OH), 3.87 (2H, s, CH). δ_C ($CDCl_3$) 26.5 (CH_3C), 61.9 (CH_2OH), 78.2 (CH) & 108.9 (C). υ_{max} (thin film) (cm^{-1}) 3600-3100 (OH, br), 1070 (C-O-C). $^m/_z$ (CI, isobutane): Found ($M^+ + 1$) 163.095057 . $C_7H_{14}O_4$ requires 163.097034.

4S,5S - (-) -4,5- bis(dibenzyloxymethyl) - 2,2- dimethyl - 1,3 - dioxalane (88):- A mixture of **(87)** (21.0g, 0.13mol), NaOH (16.0g, 0.4mol), benzyl chloride (46.0g, 0.4mol) and tetrabutylammonium hydrogen sulphate (2.0g) in dry THF (400ml) was refluxed under nitrogen for 48 hours. After cooling the solvent was removed to yield a residue. This was treated with H_2O (50ml) and extracted with diethyl ether (3 x 50ml). The combined extracts were dried (K_2CO_3), filtered and the solvent removed to yield a residue which was distilled (115°C, 0.1mmHg) to yield a colourless oil, 38.9g (88%). $[\alpha]^{20}_D$ = -8.5° (c1.0 in CH_2Cl_2). δ_H ($CDCl_3$) 1.44 (6H, s, CH_3C), 3.61 (4H, d,

CH_2O), 4.00 (2H, m, CHO), 4.57 (4H, s, $ArCH_2CO$), 7.32 (10H, br, s, Ar). δ_C ($CDCl_3$) 26.9 (CH_3C), 70.5 (CH_2O), 73.4 ($Ar\underline{C}H_2O$), 77.4 (CHO), 109.5 (C), 127.3, 128.3, 137.9 (Ar). υ_{max} (thin film) (cm^{-1}) 1600 (arom C=C), 1372 and 1081. m/z (CI) 343 ($M^+ + 1$, 100%), 342 (M^+, 34%).

(2S, 3S) - (-) - 1,4 - bis(dibenzyloxymethyl)butane - 2,3 - diol (80):- To a solution of **(88)** (38.9g, 0.11mol) in methanol (150ml) was added HCl (conc) (15ml) and the mixture was refluxed for 24 hours. The solvent was then removed under reduced pressure to leave a residue which was treated with saturated $NaHCO_3$ until alkaline, then extracted with dichloromethane (1 x 150ml; 2 x 100ml). The solvent was again removed under reduced pressure to yield a residue which was chromatographed on silica, eluting with dichloromethane : methanol (5%) to give a white waxy solid, 28.9g, (84%). Mpt 51 - 52^{0}C. $[\alpha]_D^{20}$ =-7.5 (c1.0 in CH_2Cl_2). δ_H ($CDCl_3$) 3.60 (4H, d, CH_2O), 3.87 (2H, m, CH), 4.54 (4H, s, $ArCH_2O$), 3.87 (2H, m, CH), 7.32 (10H, br, s, Ar). δ_C ($CDCl_3$) 70.4 (CH_2O), 73.4 ($Ar\underline{C}H_2O$), 71.7 (CHO), 127.6, 128.3, 137.6 (Ar). υ_{max} (nujol) 3500-3100 (OH,br), 1600 (arom C=C). $^m/_z$ Elemental Analysis Found, C=71.5; H=7.42. $C_{18}H_{22}O_4$ requires C=71.5; H=7.78.

Trans (2S, 3S) - (-) - 2,3 - bis(benzyloxymethyl) - 1,4,8,11 - tetraoxacyclotetradecane (63):- Lithium metal (0.62g, 0.09mol) was added to dry ^{t}BuOH (500ml) and the mixture was stirred until the lithium had dissolved. To this solution was added **(80)** (9.07g, 0.03mol), **(79)** (7.30g, 0.015mol) and LiBr (2.61g, 0.03mol) and the mixture was stirred at 60°C (under nitrogen) for 36 hours. Then another addition of **(79)** (7.30g, 0.015mol) was performed and again the mixture was stirred at 60^{0}C (under nitrogen) for 72 hours. After cooling the solvent was removed, under reduced pressure and the residue treated with HCl (6M) until the pH = 2. The solution was then extracted with dichloromethane (2 x 75ml) and chloroform (1 x 75ml), washed with H_2O (50ml), dried (K_2CO_3), filtered and

the solvent removed to yield a residue which was chromatographed on alumina, eluting with hexane :ethyl acetate (5 : 1) (Rf = 0.50) to yield a pale yellow oil, 8.6g (65%). $[\alpha]^{20}_D$ = -10.5° (c1.0 in CH_2Cl_2) .δ_H ($CDCl_3$) 1.77 (4H, m, CH_2C), 3.65 (18H, m, CH_2O + CHO), 4.44 (4H, s, CH_2Ph) & 7.26 (10H, s, br, Ar). δ_C ($CDCl_3$) 30.5 (CH_2C), 66.0, 66.3, 68.8, 69.9 (CH_2O), 72.4 (CH_2Ph), 79.7 (CHO), 127.0, 127.7 & 137.7 (arom). υ_{max} (thin film) (cm^{-1}) 1600 (arom C=C). $^m/_z$ (CI) 445 (M^+ + 1, 100%), 355 (M^+- Bz, 50%), 337 (M^+ - BzO, 80%) and 245 (M^+ - Bz - BzO, 70%).

Trans - (2S, 3S) - (-) - 2,3 - bis(hydroxmethyl) - 1,4,8,11-tetraoxacyclotetradecane (64):- A suspension of (63) (4.0g, 90mmol), Pearlman's catalyst [i.e. $Pd(OH)_2$ on C] (500mg) & toluene -p- sulphonic acid (20mg) in ethanol (50ml) was shaken under H_2 (3atm, 25°C) for 48 hours. After filtration and evaporation the residue was columned on silica eluting with dichloromethane : methanol (7%) (Rf =0.4) to give a viscous oil, 1.85g, (88%). $[\alpha]^{20}_D$ = -11.5° (c1.0 in CH_2Cl_2). δ_H ($CDCl_3$) 1.70 (4H, m, CH_2C), 2.85 (2H, s, OH) and 3.41 (18H, m CH_2O + CHO). δ_C ($CDCl_3$) 29.8 (CH_2C), 61.5 (CH_2OH), 66.1, 67.4, 70.0, 71.4 (CH_2O) and 78.5 (CHO). υ_{max} (thin film) (cm^{-1}) 3600 - 3100 (OH, br). $^m/_z$ (CI, isobutane) Found : (M^+ + 1) 265.156890. $C_{12}H_{25}O_6$ requires (M^++1) 265.154890.

Trans - (2S, 3S) - (-) - 2,3 - bis(toluene -p sulphonyloxymethyl) - 1,4,8,11 -tetraoxacyclotetradecane (89):- To a solution of **(64)** (3.60g, 13.6mmol) in dry pyridine (15ml) at -10°C was added, slowly, toluene-p-sulphonyl chloride (8.0g, 42mmol) and the mixture was held at -20°C for 96 hours. It was then poured onto crushed ice (50g) and stirred for 30 minutes. The crystallised crude product was filtered off and purified by recrystallisation from ethanol yielding a white crystalline solid 3.60g (46%), m.pt. 74 - 75°C. $[\alpha]^{20}_D$ = -15.0° (c 1.0 in CH_2Cl_2). δ_H ($CDCl_3$) 1.40-1.65 (4H, m, CH_2C), 2.36 (6H, s, CH_3), 3.20-3.77 (14H, m, CH_2O + CHO), 4.05 (4H, d, CH_2OTs), 7.27 (8H, dd, arom). δ_C ($CDCl_3$) 21.5 (CH_3), 30.5 (CH_2C), 66.5, 66.6, 68.6, 70.3 (CH_2O), 77.2 (CHO),

127.9,129.8, 132.6 & 144.9 (arom). υ_{max} (nujol) (cm^{-1}) 1600 (arom C=C). $^{m}/_{z}$ (CI) 590 ($M^+ + NH_4$, 100%), 573 (M^+, 37%), 229 (29%). Elemental analysis: found C=54.6; H=6.32; $C_{26}H_{36}S_2O_{10}$ requires C=54.5; H=6.29.

Trans - (2S, 3S) - (-) - 2,3 - bis(cyanomethyl) - 1,4,8,11 - tetraoxacyclotetradecane (90):- To a solution of **(89)** (3.5g, 6.11mmol) in dry DMSO (25ml) was added potassium cyanide (1.22g, 18.8mmol) and the mixture heated to 95°C for 3 hours under nitrogen. The solvent was then removed under reduced pressure leaving a residue. The residue was then refluxed with dichloromethane (40ml) for 30 minutes and filtered. This was then repeated, twice. The filtrates were combined and again the solvent removed under reduced pressure to yield a residue which was chromatographed on alumina using hexane : ethyl acetate (1 : 1) (Rf = 0.40) to yield a colourless solid 1.03g (59%). m.pt 77 - 78°C. $[\alpha]^{20}_D$ = -6.5° (c1.0 in CH_2Cl_2). δ_H ($CDCl_3$) 1.85 (4H, m, CH_2C), 2.37-2.73 (4H, m, CH_2CN), 3.59-3.90 (14H, m, CH_2CO + CHO). δ_C ($CDCl_3$) 18.9(CH_2C), 30.4 (CH_2C), 66.7, 67.4, 70.2 (CH_2O), 75.9 (CHO) & 117.3 (CN). υ_{max} (nujol) (cm^{-1}) 2250 (CN). $^{m}/_{z}$ (CI, CH_2Cl_2) 301 ($M^+ + NH_4$, 100%) 284 (M^++1, 100%), 215 (26%). Elemental analysis found C=59.3; H=7.85; N=9.82. $C_{14}H_{22}N_2O_4$ requires C=59.5; H=7.86; N=9.92.

Trans (2S, 3S) - (-) - 2,3 - bis(methyoxycarbonylmethyl) - 1,4,8,11 -tetraoxacylcotetradecane (66):- Through a solution of **(90)** (350mg, 1.24mmol), in dry methanol was bubbled dry HCl(g) for 1 hour. The mixture was then refluxed for 5 hours, cooled and the solvent removed to yield a residue. This was treated with H_2O (10ml) and extracted with dichloromethane (3 x 30ml), dried ($MgSO_4$) and the solvent removed to yield a residue which was chromatographed on alumina eluting with hexane : ethyl acetate (1:1) (Rf = 0.57) to yield a pale yellow oil, 302mg (70%). $[\alpha]^{20}_D$ = -39.5° (c1.0, CH_2Cl_2). δ_H ($CDCl_3$) 1.74 (4H, m, CH_2C), 2.48 (4H, m,

CH_2CO), 3.43-4.00 (20H, m, CH_3O, CH_2O + CHO). δ_C ($CDCl_3$) 30.8 (CH_2C), 35.9 (CH_2CO), 51.7 (CH_3O), 66.4, 66.6, 70.1 (CH_2O), 76.5 (CHO), 171.5 (C=O). υ_{max} (thin film) (cm^{-1}) 1742 (C=O). $^m/_z$ (CI, isobutane) 349 (M^+ + 1, 100%), 171 (80%).

Trans - (2S, 3S) - (-) - 2,3 - bis(carboxymethyl) - 1,4,8,11 -tetraoxacyclotetradecane (91):- To a solution of (66) (300mg, 0.86mmol) in aqueous methanol (10ml, 1 : 1, H_2O : MeOH)) was added tetrabutylammonium hydroxide (1g) and the mixture was refluxed for 2 hours. After the removal of the solvent under reduced pressure, the residue was treated with HCl (5ml, 6M) and extracted with diethyl ether (6 x20ml). The combined extracts were dried ($MgSO_4$), filtered and the solvent evaporated to yield an off-white waxy solid , 210mgs (77%). δ_H (D_2O) 1.83 (4H, m, CH_2C), 2.61 (4H, dd, CH_2CO) & 3.69-4.00 (14H, m, CH_2O + CHO). δ_C (D_2O) 29.9 (CH_2C), 35.6 (CH_2CO), 66.1, 67.0, 69.4 (CH_2O), 78.0 (CHO) & 174.8 (CO_2H). υ_{max} (nujol) (cm^{-1}) 3600-3100 (OH, br), 1710 (C=O).

Trans - (2S, 3S) - (-) - 2,3 - bis(N,N-dibutylcarbamoylmethyl) - 1,4,8,11 -tetraoxacyclotetradecane (68):- To a solution of (91) (500mg, 1.55mmol) in dichloromethane (10ml) was added phosphorus pentachloride (675mg, 3.24mmol) and the mixture was stirred at room temperature under nitrogen for 12 hours. After removing the solvent under reduced pressure an IR spectrum was recorded to confirm that the conversion to the acid chloride was complete. The residue was redissolved in dichloromethane (20ml) and this solution was slowly added to a solution of di-butylamine (805mg, 6.2mmol) and triethylamine (630mg, 6.2mmol) in dichloromethane (15ml) at 0°C. After 2 hours of stirring the solvent was removed under reduced pressure and the residue partitioned between hexane and water. The organic phase was washed with HCl (0.1M) (2 x 5ml), dried ($MgSO_4$) and the solvent evaporated to yield a residue which was chromatographed on neutral alumina eluting with hexane : ethyl acetate (1:1) (RF=0.45) to yield a

pale yellow oil, 512mg (61%). $[\alpha]^{20}_D$ = -33.7° (c1.0 in CH_2Cl_2). δ_H ($CDCl_3$) 0.85 (12H, m, CH_3), 1.30-1.45 (16H, m, CH_2C), 1.75 (4H, m, CH_2C ring), 2.31 (4H, dd, CH_2CO), 3.12 (8H, m, CH_2N), 3.50-3.89 (14H, m, CH_2O + CHO). δ_C ($CDCl_3$) 13.8 (CH_3C), 20.1 (CH_2C), 29.7, 31.1, ($NCH_2\underline{C}H_2$), 45.9, 47.9 (NCH_2), 35.3 (CH_2CO), 66.7, 67.6, 70.2 (CH_2O), 80.1 (CHO) & 170.6 (CO). υ_{max} (thin film) (cm^{-1}) 1638 (C=O). $^m/_z$ (CI, isobutane) 543 (M^++1, 55%), 231 (M^+ -2CONBu,).

Trans - (2S, 3S) - (-) - 2,3 - bis(N,N-di^{i}butylcarbamoylmethyl) - 1,4,8,11 -tetraoxacyclotetradecane (69):-This was prepared as described for **(68)** using **(91)** (100mg, 0.29mmol), dichloromethane (2ml), phosphorus pentachloride (130mg, 0.60mmol), isobutylamine (180mgs, 1.4mM) and triethylamine (120mgs, 1.2mM). Purification by column chromatography on alumina, eluting with hexane : ethyl acetate (1:1) (RF=0.45) to yield a pale yellow oil, (98mg, 62%). δ_H ($CDCl_3$) 0.89 (24H, m, CH_3C), 1.71 (4H, m, CH_2C), 1.95 (4H, m, $\underline{C}H(CH_3)_2$), 2.23-2.67 (4H, m, CH_2C=O), 3.04-3.98 (22H, m, CH_2O, CHO, CH_2N). δ_C ($CDCl_3$) 20.14 (CH_3C), 26.66 & 28.23 (CHC), 31.04 (CH_2C), 35.79 (CH_2C=O), 54.09 & 56.09 (CH_2N), 66.89, 67.80 & 70.38 (CH_2O). υ_{max} (thin film) (cm^{-1}) 1643 (C=O), 1087 (C-O). $^m/_z$ (CI, isobutane) 543 (M^+ + 1, 100%).

Trans - (2S, 3S) - (-) - 2,3 - bis(N,N-dioctylcarbamoylmethyl) - 1,4,8,11 - tetraoxacyclotetradecane (71):- This was prepared as described for **(68)** using **(91)** (100mg, 0.29mmol), dichloromethane (2ml), phosphorous pentachloride (130mg, 0.60mmol), dioctylamine (290mg, 1.2mmol) and triethylamine (120mg, 1.2mmol). Purification by column chromatography on alumina with ethyl acetate : hexane (1:1) (Rf=0.75) to yield a pale yellow oil, 189mg (77.1%). δ_H ($CDCl_3$) 0.85 (12H, q, CH_3), 1.28 (40H, broad s, CH_2C), 1.52 (8H, m, $\underline{C}H_2CH_2N$), 1.72 (4H, m, CH_2CN), 2.32 - 2.60 (4H, m, CH_2CO), 3.15 (4H, m, CH_2CN), 3.49 - 3.73 (12H, m, CH_2O), 3.93 (2H, m, CHO). δ_C ($CDCl_3$) 14.05 (CH_3), 26.60, 27.05,26.91, 27.76, 29.35, 31.1,31.78 (CH_2C),

35.51(CH_2CO), 46.43, 48.39 (CH_2CO), 66.92,67.81,70.41 (CH_2O), 80.36 (CHO), 170.78 (C=O).υ(max) (cm^{-1}) 1640 (C=O stretch). $^m/_z$ (CI) Found (M^+ + 1) 768.231876 $C_{46}H_{90}N_2O_6$ requires (M^++ 1) 768.231011.

Trans - (2S, 3S) - (-) - 2,3 - bis(N,N-dibenzylcarbomylmethyl) - 1,4,8,11 - tetraoxacyclotetradecane (72):- This was prepared as described for (68) using (91) (100mg, 0.29mmol), dichloromethane (2ml), phosphorous pentachloride (130mg, 0.60mmol), dibenzylamine (230mg, 1.2mmol) and triethylamine (120mg, 1.2mmol). Purification by column chromatography on alumina with ethyl acetate : hexane (1:1) (Rf = 0.44) yielded a colourless glassy solid. (157mg, 80%). δ_H ($CDCl_3$) 1.64 (4H, m, CH_2C), 2.37-2.66 (4H, m, CH_2CO), 3.49-3.66 (10H, m, CH_2O), 3.92 (2H, m, CHO), 4.04 (2H, dd, CH_2O), 4.33-4.83 (8H, m, CH_2N), 7.13-7.34 (20H, m, aromH). δ_C ($CDCl_3$) 30.98 ($\underline{C}H_2C$), 35.47($\underline{C}H_2CO$), 48.43 and 50.19 (CH_2N), 66.73, 67.89 and 70.27 (CH_2O), 80.06 (CHO), 126.42, 127.43, 127.54, 128.31, 128.47, 128.87, 136.55 and 137.30 (arom C). υ_{max} (thin film) (cm^{-1}) 1638 (C=O stretch), 1430 (C-N stretch), 730 and 697 (C-H bend). $^m/_z$ (DCI, chloroform) 678 (M^+, 11%), 593 (6%), 503 (13%), 196 (NBz_2, 11%), 179 (37%), and 106 (9%). $^m/_z$ found (M^+ +1) 679.880123 $C_{42}H_{50}N_2O_6$ +1 requires 679.8712.

Trans - (2S, 3S) - (-) - 2,3 - bis(N,N-diethylcarbamoylmethyl) - 1,4,8,11 - tetraoxacyclotetradecane (73):- This was prepared as described for **(68)** using **(91)** (70mg, 0.20mmol), dichloromethane (2ml), phosphorous pentachloride (85mg, 0.40mmol), diethylamine (excess). Purification by column chromatography on alumina with ethyl acetate : hexane (1:1) (Rf = 0.31) yielded a colourless oil (75mgs, 85%). δ_H ($CDCl_3$) 1.13 (12H, m, CH_3C), 1.72 (4H, m, CH_2C), 2.21-2.65 (4H, m, CH_2CO), 2.95-4.00 (22H, m, CH_2O, CH_2N and CHO). δ_C ($CDCl_3$) 13.05 and 14.40 (CH_3C), 31.11 (CH_2C), 35.51 (CH_2CO), 40.46 and 42.37 (CH_2N), 66.92, 67.86 and 70. 43 (CH_2O), 80.44 (CHO) and 170.49 (C=O). υ_{max} (thin film) (cm^{-1}) 1644 (C=O stretch), 1433 (C-N stretch). m/z

(DCI chloroform) 431 (M^+ + 1, 100%). $^m/_z$ found (M^+ +1) 431.568921 $C_{22}H_{42}N_2O_6$ +1 requires 431.5088.

2,2- Dimethyl - 5 - hydroxymethyl - 5 - methyl - 1,3 - dioxan (93) 1,1,1 Tris (hydroxymethyl) ethane (60g, 0.5mol), 2,2- dimethoxypropane (57.2g, 0.55mol), ρ-toluenesulphonic acid (460mg) were dissolved in dry chloroform (250ml) and placed in a 1 dm^3 flask which was fitted with a Soxhlet extraction apparatus containing 4A molecular sieves. The mixture was refluxed for 17 hours with one change of sieves and then cooled and stirred with moist sodium carbonate and filtered. The filtrate was then concentrated *in vacuo* to yield a colourless oil (77g, 96%). δ_H ($CDCl_3$) 0.83 (3H, s, CH_3C), 1.39 (3H, s, CH_3C), 1.44 (3H, s, CH_3C), 2.83 (1H, s, br, OH), 3.62 (2H, d, 11.6Hz, CH_2O), 3.67 (2H, s, CH_2OH), 3.70 (2H, d, 11.7Hz, CH_2C). δ_C ($CDCl_3$) 17.38 (CH_3C), 20.13 and 26.82 (CH_3C), 34.52 (CH_3-$\underline{C}$-CH_2), 65.00 (CH_2OH), 65.97 (CH_2O) and 97.72 ([CH_3]$_2$-$\underline{C}$-[OCH_2]$_2$). $\upsilon_{(max)}$ (cm^{-1}) (thin film) 3500-3100 (O-H stretch), 1115 (C-O stretch). $^m/_z$ (DCI, chloroform) 161 (M^+ +1, 100%), 145 (15%).

2,2 - Dimethyl -5 - benzyloxymethyl -5- methyl- 1,3 - dioxan (94) To a solution of **(93)** (77g, 0.48mol) in dry THF (250ml) was added ground sodium hydroxide (30g, 0.75mol) and tetrabutylammonium hydrogen sulphate (6.22g, 0.018mol) and the mixture stirred mechanically under nitrogen while a solution of benzyl chloride (64ml, 70.4g, 0.55mol) in THF (250ml) was added. The mixture was then refluxed for 48 hours, cooled and filtered to remove the precipitated salt. The filtrate was then concentrated *in vacuo* to give a yellow oil. This was distilled under vacuum through a 20mm vigreux column to yield a colourless oil (84.78g, 70%), b.p. 87-91° (0.002 mm Hg). δ_H ($CDCl_3$) 0.89 (3H, s, CH_3C), 1.37-1.42 (6H, d, CH_3C), 3.46 (2H,s, $\underline{C}H_2OBz$), 3.50 (2H, d, J = 11.6 Hz, CH_2O), 3.72 (2H, d, J = 11.6 Hz, CH_2O), 4.53 (2H, s, $\underline{C}H_2Ph$), 7.31 (5H, m, ArH). δ_C ($CDCl_3$) 18.17 (CH_3C), 20.98 (CH_3C), 26.23 (CH_3C), 34.22 (CH_2-$\underline{C}$-CH_3), 66.39 (CH_2O), 72.91 (CH_2O), 73.13 ($ArCH_2O$),

97.66 ([CH_3]$_2$-C-[OCH_2]$_2$), 127.21, 127.61, 128.11 and 138.51 (Ar). υ_{max} (thin film) (cm^{-1}) 1611 (arom C=C), 1088 (C-O stretch), 735 and 698 (=CH Arom OOP). $^m/_z$ (DCI, chloroform) 251 (M^+ + 1, 100%), 193 (43%), 158 (46%) and 91 (Bz, 43%).

2 - Benzyloxytmethyl - 2- methyl - propan - 1,3 - diol (95) The isopropylidine derivative (94) was refluxed with cHCL (45ml) in methanol (450ml) for 72 hours. The solvent was then removed *in vacuo* to yield a yellow oil which was then recrystallised from toluene / hexane (35.53g, 51%). m.pt. 44-45° C. δ_H ($CDCl_3$) 0.83 (3H, s, CH_3C), 2.45 (2H, s, br, OH), 3.47 (2H, s, CH_2OBz), 3.60 (2H, d, J = 10.8, CHHOH), 3.69 (2H, d, J = 10.8, CHHOH), 4.52 (2H, s, CH_2Ar), 7.25-7.45 (5H, m, ArH). δ_C ($CDCl_3$) 17.33 (CH_3C), 40.78 (CH_2-C-CH_3), 67.83, 73.60 & 75.60 (CH_2O), 127.51, 127.47, 127.78 & 137.85 (Ar). υ_{max} (cm^{-1}) (KBr disc) 3300 (O-H stretch), 1041 (C-O stretch), 738 and 697 (C-H bend). $^m/_z$ (DCI, MeOH), 228 (M^+ + 18, 36%), 211 (M^+ + 1, 100%), 108 (33%), 91 (CH_2Ar, 20%) and 86 (63%). Elemental analysis Found C = 68.3, H = 8.51 %, $C_{12}H_{10}O_3$ requires C = 68.6, H = 8.61%.

5 - Benzyloxytmethyl - 5- methyl - diethyl, 3,7, dioxanona- 1,9 - dioate (97):- To a solution of (95) (10.0g, 48mmol) and BF_3-etherate (20µl) in dry dichloromethane (120ml) was carefully added a solution of ethyl diazoacetate (10.86g, 96mmol) in dry dichloromethane (50ml), under nitrogen. The solution was then stirred at 40° C for 6 hours. After cooling the solvent was removed *in vacuo* to yield a yellow oil. This was purified by short path distillation (115° C, 0.05 mmHg), to yield a pale yellow oil (14.1g, 77%). G.C. analysis indicated that the compound was ≥ 99.5% chemically homogeneous. δ_H ($CDCl_3$) 1.05 (3H, s, CH_3C), 1.27 (6H, t, CH_3C), 3.42 (2H, s, CH_2O) 3.42 (2H, s, CH_2O), 3.48 (4H, s, CH_2O), 4.06 (4H, s, CH_2O), 4.18 (4H, q, O$\underline{CH_2}$-CH_3), 4.51 (2H, s, OCH_2Ar), 7.32 (5H, m, Ar). δ_H ($CDCl_3$) 14.11 (CH_3C), 17.17 ($\underline{CH_3}CH_2$), 40.95 (CH_3-C-CH_2), 60.54, 68.88, 72.46, 73.18 and 74.44 (CH_2O), 127.26, 128.14 and 138.75 (arom C), 170.58 (C=O). υ_{max} (cm^{-1})

1749 (C=O stretch), 1136 (C-O stretch), 740 and 700 (C-H OOP bend). $^{m}/_{z}$ (DCI, methanol) 400 (M^+ + 18, 59%), 383 (M^+ + 1, 100%), 308 (M^+ - CO_2Et, 21%), 291 (M^+ - Bz, 16%), 157 (23%), 108 (OBz +1, 43%), 91 (Bz, 26%).

5 - Benzyloxytmethyl - 5- methyl -3,7, dioxanona- 1,9 - dioate (98):- This was prepared using the same procedure as for the prepation of (84), using (97) (23.49g, 61.3mmol) , $LiAlH_4$ (7.0g, 184mmol) and ether (300ml). The product was purified by short path distillation (145°, 0.05mmHg) to yield a colourless oil (11.7g, 64%). G. C. analysis indicated that the compound was ≥ 95% chemically homogeneous. δ_H ($CDCl_3$) 0.97 (3H, s, CH_3C), 2.61 (2H, s, OH), 3.35 (2H, s, CH_2O), 3.40 (4H, d, CH_2O), 3.51-3.70 (8H, dt, CH_2O), 4.50 (2H, s, $ArCH_2O$), 7.32 (5H, m, Ar). δ_C ($CDCl_3$) 17.82 (CH_3C), 40.89 (CH_3-$\underline{C}$-CH_2), 61.57, 72.41, 73.19, 73.36 and 73.88 (CH_2O), 127.44, 127.50, 128.29 and 138.48 (arom C). υ_{max} (thin film) (cm^{-1}) 3380 (O-H stretch), 1107 (C-O stretch). $^{m}/_{z}$ (DCI) 299 (M^+ +1, 100%).

5 - Benzyloxytmethyl - 5- methyl -- 1,9 -bis (toluene -p- sulphonato) - 3,7, dioxanonane (99):- This was prepared using the same procedure as for the preparation of (79), using (98) (10.0g, 33.35mmol), tosyl chloride (19.2g, 100mmol) and dry pyridine (100ml). The product was purified by chromatographing on silica eluting with a gradient dichloromethane : methanol (100:0 to 97:3) to yield a viscous colourless oil (9.78g, 48%). δ_H ($CDCl_3$) 0.84 (3H, s, CH_3C), 2.43 (6H, s, CH_3-Ar), 3.21 (2H, s, CH_2O), 3.23 (4H, s, CH_2O), 3.55 (4H, t, CH_2O), 4.10 (4H, t, CH_2O), 4.44 (2H, s, $\underline{C}H_2Ar$), 7.29-7.80 (13H, M, Ar). δ_C ($CDCl_3$) 17.22 (CH_3C), 21.62 ($\underline{C}H_3$-Ar), 40.98 (CH_3-$\underline{C}$-CH_2), 68.76, 69.26, 72.71, 73.26, 73.64 (CH_2O), 127.34, 127.41, 127.93, 128.29, 129.84, 133.16, 138.83 and 144.75 (Ar). υ_{max} (thin film) (cm^{-1}) 1601 (arom C=C stretch). $^{m}/_{z}$ (DCI, chloroform) 624 (M^+ + 18, 100%), 607 (M^+ + 1, 10%), 437 (100%). Elemental analysis, found C = 59.27, H = 6.22, $C_{30}H_{38}S_2O_9$ requires C = 59.39 and H = 6.31.

3 - Benzyloxytmethyl - 3- methyl 1, 5,8, 12 - tetraoxacyclotetradecane (96):- This was prepared using the same procedure as for the preparation of **(63)**, using Li (870mg, 125mmol), LiBr (3.65g, 42mmol), **(95)** (8.72g, 42mmol), 1,9 di(toluene-p-sulphonato)-3,7-dioxanonane (19.87g, 42mmol), ^{t}Butanol (500ml). The residue was chromatographed on neutral alumina eluting with hexane: ethyl acetate (3:1, Rf = 0.44) to yield a pale yellow oil (7.21g, 53%). δ_H ($CDCl_3$) 0.98 (3H, s, CH_3C), 1.77 (2H, m, CH_2C), 3.32-3.66 (14H, m, CH_2O), 4.49 (2H, s, OCH_2Ar), 7.31 (5H, m, Ar). δ_C ($CDCl_3$) 16.67 (CH_3C), 29.57 (CH_2C), 39. 63 (CH_2-C-CH_3), 65.42, 66.63, 69.27, 71.64 & 72.24 (CH_2O), 127.27, 127.19 & 137.44 (arom C). υ_{max} (thin film) (cm^{-1}) 1132 (C-O stretch), 740 & 700 (CH OOP bend). $^{m}/_{z}$ (DCI, chloroform) 339 (M^+ +1, 100%).

3,10 Bis (Benzyloxytmethyl) 3,10-methyl 1,5,8,12 tetraoxacyclotetradecane (100):- This was prepared using the same procedure as for the preparation of **(63)**, using Li (1.04g,150mM), LiBr (4.34g, 50mM), **(95)** (10.3g, 49,5mM), **(99)** (30.0g, 49.5mM) and ^{t}Butanol (700ml). The residue was chromatographed on neutral alumina eluting with hexane: ethyl acetate (4:1, Rf =0.54) to yield a pale yellow oil (8.92g, 38%). δ_H ($CDCl_3$) 0.98 (6H, s, CH_3C), 3.23-3.57 (16H, m, CH_2O), 4.50 ($ArCH_2O$), 7.32 (Ar). δ_C ($CDCl_3$) 17.72,17.84(CH_3C), 40.56 (CH_2-C-CH_2), 70.27, 72.35, 73.25 (CH_2O), 73.95 ($ArCH_2O$), 127.22, 127.27, 128.24 and 138.93 (Ar). υ_{max} (thin film) (cm^{-1}) 1128 (C-O stretch), 738 & 699 (CH OOP bend) . $^{m}/_{z}$ (DCI, chloroform) 490 (M^+ +18, 42%), 473 (M^+ +1, 44%), 425 (70%), 423 (39%), 383 (M^+ -Bz, 100%).

3- hydroxymethyl -3- methyl- 1,5,8,12 tetraoxacyclotetradecane (101):- This was prepared using the same procedure as for the preparation of **(64)**, using **(96)** (7.0g, 20.7mmol), Pearlman's catalyst (500mg), tosic acid (20mg) and ethanol (50ml). After filtration and concentration *in vacuo* , a pale yellow oil (4.74g, 91%) was isolated. This was not purified further. δ_H ($CDCl_3$) 0.76 (3H, s, CH_3C), 1.77 (2H, m, CH_2C), 3.26 (1H, s, OH), 3.41-3.77 (18H, m, CH_2O). δ_C ($CDCl_3$) 17.55, 17.66 (CH_3C), 29.81 (CH_2C), 40.14 (CH_2-C-CH_3), 66.55, 70.24,

70.62, 70.65 & 74.49 (CH_2O). υ_{max} (thin film) (cm^{-1}) 3440 (O-H stretch), 1130 (C-O stretch). $^m/_z$ (DCI, chloroform) 249 (M^+ +1, 100%).

3,10- Bis (hydroxymethyl)-3,10-Bi (methyl)- 1,5,8,12 tetraoxacyclotetradecane (104):- This was prepared using the same procedure as for the preparation of (64), using (100) (8.5g, 18mM), Pearlman's Catalyst (750mg), tosic acid (30mgs) and ethanol (100ml). After filtration and concentration *in vacuo* a white solid was isolated (5.21g, 98%) The two diastereomers were separated by chromatographing on neutral alumina with a gradient elution system, CH_2Cl_2 : MeOH (100:0 to 98:2). The major diastereomer eluting with an Rf = 0.41, the minor, 0.34 (2% MeOH/CH_2Cl_2). δ_H (CD_3CN) 0.79 (6H, s, CH_3C), 2.76 (2H, s, OH), 3.32-3.55 (20H, m, CH_2O). δ_C ($CDCl_3$) 17.78 (CH_3C), 41.46 (CH_2-$\underline{C}$-CH_3), 67.89, 71.14 & 73. 74 (CH_2O). υ_{max} (KBr disc) (cm^{-1}) 3315 (O-H stretch), 1116 (C-O stretch). $^m/_z$ (DCI, acetonitrile) 293 (M^+ +1, 100%). Elemental analysis, found C=56.71 & H= 9.46 $C_{14}H_{28}O_6$ requires C=56.72 & H=9.64.

3- toluene -p- sulphonyloxymethyl-3-methyl -1,5,8,12 tetraoxacyclotetradecane (103):- This was prepared using the same procedure as for the preparation of (89), using (101) (2.1g, 8.47mmol), tosyl chloride (2.25g, 12.0mmol) and dry pyridine (30ml). The residue was chromatographed on silica eluting with dichloromethane:methanol (98:2) (Rf = 0.28) to yield a white solid (1.85g, 54%). m.pt. 64-66°C. δ_H ($CDCl_3$) 0.91 (3H, s, CH_3C), 1.73 (2H, p, CH_2C), 2.44 (3H, s, $\underline{C}H_3Ar$), 3.31 (4H, s, CH_2O), 3.49-3.59 (12H, m, CH_2O), 3.86 (2H, s, $\underline{C}H_2OTos$), 7.31-7.78 (4H, dd, Ar). δ_C ($CDCl_3$) 17.02 (CH_3C), 21.74 (CH_3C), 30.26 (CH_2C), 40.22 (CH_2-$\underline{C}$-CH_3), 66.55, 70.31, 70.77, 71.53 & 73.58 (CH_2O), 128.07, 129.84, 132.98 & 144.70 (Ar). υ_{max} (KBr disc) 1603 (C=C stretch), 1105 (C-O). $^m/_z$ (DCI, chloroform) 404 (M^+ +1, 100%). Elemental analysis, found C=56.96 & H=7.66 $C_{19}H_{30}SO_7$ requires C=56.69 and H=7.66.

3, 10 - Bis (toluene -p- sulphonyloxymethyl) -3,10- Bis methyl 1,5,8,12 tetraoxacyclotetradecane (104):- This was prepared using the same procedure as for the preparation of (89), using (102) (750mgs, 2.58mmol), tosyl chloride (1.5g, 7.74mmol) and dry pyridine (10ml). After pouring onto crushed ice (100g) the precipitated product was filtered off, dried and recrystallised from ethanol to yield a white crystalline solid (1.38g, 87%). m.pt 152-153°. δ_H ($CDCl_3$) 0.87 (6H, s, CH_3C), 2.44 (6H, s, $\underline{C}H_3Ar$), 3.23 (8H, s, CH_2O), 3.83 (4H, s, $\underline{C}H_2OTos$), 7.31-7.78 (8H, dd, Ar). δ_C ($CDCl_3$) 16.92 (CH_3C), 21.63 ($\underline{C}H_3Ar$), 40.00 (CH_2-$\underline{C}$-CH_3), 70.18, 71.18 & 73.47 (CH_2O), 127.73, 129. 93, 132.85 & 144.62 (Ar). υ_{max} (KBr Disc) 1604 (C=C stretch) 1110 (C-O stretch) . $^m/_z$ (DCI, chloroform) 618 (M^+ +18, 100%), 601 (M^+ +1, 68%), 429 (44%). Elemental analysis, found C=56.31 & H=6.91 $C_{28}H_{40}S_2O_{10}$ requires C=56.0 & H=6.71.

3 - cyanomethyl- 3-methyl - 1,5,8,12 tetraoxacyclotetradecane (105):- To a solution of (103) (1.26g, 3.13mmol) in dry DMSO (15ml) was added KCN (260mgs, 4.0mmol) and 18-crown-6 (10mgs) and the resultant solution heated at 150°C for 14 hours. After cooling the solvent was removed and the residue extracted with dichloromethane by refluxing for 1 hour. After filtration the filtrate was concentrated *in vacuo* again yielding a residue which was chromatographed on neutral alumina with 2:1 hexane:ethyl acetate (Rf = 0.67) to yield a white crystalline solid (735mgs, 91%). δ_H ($CDCl_3$) 1.05 (3H, s, CH_3C), 1.75 (2H, p, CH_2C), 2.33 (2H, s, CH_2CN), 3.40 (4H, s, CH_2O), 3.40 (4H, s, CH_2O), 3.56-3.64 (12H, m, CH_2O). δ_C ($CDCl_3$) 19.25 (CH_3C), 23.80 (CH_2C), 30.13 (CH_2CN), 38.25 (CH_2-$\underline{C}$-CH_3), 66.52, 70.31, 70.77 & 73.05 (CH_2O), 117.91 (CN). υ_{max} (KBr disc) (cm^{-1}) 2245 (CN stretch), 1105 (C-O stretch). $^m/_z$ (DCI, chloroform) 275 (M^+ +18, 85%), 258 (M^+ +1, 100%). Elemental analysis found C=60.56, H=8.88 & N=5.31 $C_{13}H_{23}NO_4$ requires C=60.68, H=9.01 & N=5.44.

3,10 - Bis (cyanomethyl), 3,10 bis-methyl - 1,5,8,12 - tetraoxacyclotetradecane (106):- This was prepared using the same procedure as for the preparation of

(105) using (104) (1.2g, 1.91mM), KCN (390mg, 3.6mmol), 18-crown-6 (10mg) and DMSO (10ml). The residue was chromatographed on neutral alumina eluting with 3:1 Hexane:Ethyl acetate (Rf =0.57) to yield a white crystalline solid (310mgs, 54%). δ_H ($CDCl_3$) 1.07 (6H, s, CH_3C), 2.34 (4H, s, CH_2CN), 3.39 (8H, m, CH_2O), 3.60 (8H, m, CH_2O). δ_C ($CDCl_3$) 19.34 (CH_3C), 23.91 (CH_2CN), 38.20 (CH_2-C-CH_3), 70.47 & 72.99 (CH_2O), 117.83 (CN). υ_{max} (KBr disc) (cm^{-1}) 2242 (CN stretch), 1105 (C-O stretch). $^m/_z$ (DCI, chloroform) 311 (M^+ +1, 100%). Elemental analysis found C= 61.56, H=8.23 & N=8.77 $C_{16}H_{26}N_2O_4$ requires C=61.91, H=8.44 & N=9.03.

3 - carboxymethyl -3- methyl 1,5,8,12 - tetraoxacyclotetradecane (107):- To a solution of (105) (180mgs 0.70mmol) in ethylene glycol (1.5ml) was added an aqueous solution of NaOH (1.0ml, 2M). The resultant solution was then heated at 150°C for 48 hours, cooled, acidified (6M HCl) and then extracted with diethyl ether (2 x 30ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield an off-white solid (90mgs, 47%). δ_H ($CDCl_3$) 0.95 (3H, s, CH_3C), 1.70 (2H, p, CH_2C), 2.28 (2H, s, CH_2C=O), 3.40 (4H, s, CH_2O), 3.58 (12H, m, CH_2O). δ_C ($CDCl_3$) 19.56 (CH_3C), 30.12 (CH_2C), 38.27 (CH_2-C-CH_3) 40.49 (CH_2C=O), 64.66, 70.23, 70.69 & 74.09 (CH_2O), 175.94 (C=O). υ_{max} (KBr disc) 3500-3100 (O-H stretch), 1710 (C=O stretch), 1090 (C-O stretch).

3,10 -Bis- (carboxymethyl) - 3,10 - bismethyl 1,5,8,12- tetraoxacyclotetradecane (108):- A solution of **(105)** (160mgs, 0.62mM) in 1:1 NaOH (aq, 2M) : Methoxyethanol (5ml) was refluxed for two days. After cooling the solvent was removed under reduced pressure to yield a residue which was redissolved in H_2O (3ml) and acidified with HCl (6M). After acidification the aqueous phase was extracted with diethyl ether (3 x 30ml), and the etherial layer dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield an off-white waxy solid (80mgs, 44%). δ_H ($CDCl_3$) 0.93 (6H, s, CH_3C), 2.20 (4H, s, CH_2CO), 3.33 (8H, s, CH_2O), 3.53 (8H, s, CH_2O). δ_C ($CDCl_3$) 19.11 and 19.43 (CH_3C),

38.00, 38.41 (CH_3-C-CH_2), 39.88, 40.23 (CH_2C=O). 70.06 and 73.71 (CH_2O) and 174.71 (C=O). υ_{max} (thin film) (cm^{-1}) 3100 (OH stretch), 1713 (C=O stretch).

3- dibenzylcarbamoylmethyl -3- methyl- 1,5,8,12- tetraoxacyclotetradecane (74):- To a solution of **(107)** (70mgs, 0.25mmol) in dry CH_2Cl_2 (2ml) was added dibenzylamine (100mgs, 0.51mmol) and DMAP (3mgs) and the solution cooled to -10°C. To this cooled solution was added DCC (51mgs, 0.25mmol). The temperature of the solution was then slowly allowed to rise to room temperature and stirred for 1 hour under argon. The precipitated DHU was filtered off and the filtrate concentrated *in vacuo* to yield a residue. This was chromatographed on neutral alumina eluting with 3:1 Hexane: ethyl acetate (Rf = 0.63) to yield a waxy solid (35mgs, 31%). δ_H ($CDCl_3$) 1.14 (3H, s, CH_3C), 1.74 (2H, p, CH_2C), 2.39 (2H, s, CH_2C=O), 3.46 (4H, d, CH_2O), 3.57 (12H, m, CH_2O), 4.57 (4H, d, CH_2N), 7.28 (10H, m, Ar). δ_C $(CDCl)_3$ 20.26 (CH_2C), 37.30 (CH_2C=O), 39.87 (CH_2-C-CH_3), 48.47 & 50.74 (CH_2N), 69.93, 70.84, 71.09 and 74.76 (CH_2O), 126.91, 127.44, 127.83, 127.90, 128.64, 128.71, 128.89, 129.02, 129.37, 137.46, 138.22 (arom C), 172.56 (C=O) υ_{max} (thin film) 1645 (C=O stretch). $^m/_z$ (DCI, chloroform) 456 (M^+ +1, 100%).

3,10 - Bis (dibenzylcarbamoylmethyl), 3,10 bis-methyl - 1,5,8,12 - tetraoxacyclotetradecane (75):- This was prepared using the same procedure as for the preparation of **(74)** using **(108)** (80mg, 0.23mmol), dibenzylamine (90mgs, 0.46mmol), DCC (95mgs, 0.46mmol) and DMAP (2mgs). This was chromatographed on neutral alumina eluting with 3:1 Hexane: ethyl acetate (Rf = 0.63) to yield a waxy solid (35mgs, 31%). δ_H ($CDCl_3$) 1.11 (6H, s, CH_3C), 2.36 (4H, s, CH_2C=O), 3.40 (8H, s, CH_2O), 3.50 (8H, s, CH_2O), 4.50-4.59 (8H, dd, CH_2N), 7.27 (20H, m, arom H). δ_C ($CDCl_3$) 19.69 and 19.78 (CH_3C), 36.89 (CH_2C=O), 39.30 (CH_2-C-CH_2), 47.99, 50.26 (CH_2N), 70.25, 74.04 (CH_2O), 126.41, 127.23, 127.45, 128.20, 128.47, 128.84, 137.14, 137.72 (arom C) 172.00 (C=O). υ_{max}

(thin film) 1645 (C=O stretch). $^{m}/_{z}$ (DCI, chloroform) 636 (M^+ +1, 58%), 440 (M^+ - NBz_2, 100%), 197 (Bz_2N^+ +1, 87%).

Trans - (2S, 3S) - (-) - 2,3 - bis(iodomethyl) - 1,4,8,11 - tetraoxacyclotetradecane (109):- To a solution of (89) (1.6g, 2.79mmol) in dry DMF (30ml) was placed potassium iodide (1.5g, 8.85mmol) and the mixture stirred for 12 hours at 60°C under nitrogen. The solvent was then removed under reduced pressure to yield a residue which was refluxed with dichloromethane (50ml) for 2hours, filtered and concentrated *in vacuo* to yield a residue. The residue was chromatographed on neutral alumina eluting as a pale yellow oil (870mg, 64%). δ_H ($CDCl_3$) 1.85 (4H, m, CH_2C), 3.05-3.95 (18H, m, CH_2O, CH_2I, CHO). δ_C ($CDCl_3$) 6.90 (CH_2I), 31.09 (CH_2C), 67.45, 67.61 and 71.41 (CH_2O) and 81.62 (CHO). υ_{max} (thin film) (cm^{-1}) C-H stretch 3000-2700. $^{m}/_{z}$ (DCI, methanol) found 485.10432, $C_{12}H_{22}I_2O_4$ requires (M^+ + 1) 485.10322.

Trans - (2S, 3S) - (-) - 2,3 - bis (butylcarbonylmethyl) - 1,4,8,11 - tetraoxacyclotetradecane (110) A solution of (66) (160mgs, 0.56mmol) in butanolic HCl (50ml) (produced by bubbling HCl gas through dry n-butanol for 1 hour) was refluxed for 5 hours. After cooling the solvent was removed *in vacuo* to yield a residue which was partitioned between H_2O (5ml) and dichloromethane (50ml). The organic portion was then concentrated *in vacuo* to yield a residue which was chromatographed on neutral alumina eluting with 4:1 hexane : ethyl acetate (Rf = 0.62) to yield a colourless oil (110mg, 45%). δ_H ($CDCl_3$) 0.93 (6H, t, CH_3C), 1.37-1.76 (12H, m, CH_2C), 2.50 (4H, m, $CH_2C{=}O$), 3.57-3.94 (14H, m, CH_2O and CHO), 4.10 (4H, t, CH_2O). δ_C ($CDCl_3$) 13.60 (CH_3C), 19.03, 30.56 and 30.86 (CH_2C), 35.33 ($CH_2C{=}O$), 64.38, 66.70 and 70.13 (CH_2O), 78.21 (CHO) and 171.61 (C=O). υ_{max} (thin film) (cm^{-1}) 1736 (C=O stretch) and 1120 (C-O). $^{m}/_{z}$ (DCI, chloroform) 450 (M^+ +18, 24%), 433 (M^+ + 1, 100%), 359 (M^+ -OBut, 25%), 255 (100%), 179 (35%).

2-[N,N'-dibutylcarbamoyl-2'-oxapropyl] - 1,4,8,11 tetraoxacyclotetradecane (112):- To a solution of 2-hydroxymethyl 1,4,8,11 tetraoxacyclotetradecane

(111) (250mg, 1.07mmol) in dry THF (30mls) was slowly added sodium hydride (60mgs, 2.4mmol) and the reaction refluxed for 1 hour. After cooling N,N-di-butyl-2-bromoethanamide () (500mgs, 2.4mmol) was added and refluxing recommenced for a further 24 hours. Again after cooling a further addition of NaH (30mgs, 1.2mmol) and N,N-di-butyl-2-bromoethanamide (250mg, 1.2mmol) was made and the reaction refluxed for 72 hours. After cooling the reaction was filtered and the filtrate concentrated *in vacuo* to yield a viscous oil. This was chromatographed on neutral alumina eluting with ethyl acetate:hexane (1:1, Rf = 0.34) to yield a clear viscous oil (330mgs, 76%). δ_H ($CDCl_3$) 0.90 (6H, q, CH_3), 1.25-1.33 (4H, m, CH_2C), 1.49-1.64 (4H, m, CH_2C), 1.70-1.84 (4H, m, CH_2C), 3.15-3.31 (4H, dt, CH_2N), 3.40-3.92 (15H, m, CH_2O & CHO), 4.16 (2H, s, $OCH_2C{=}O$). δ_C ($CDCl_3$) 13.83 & 13.79 (CH_3C), 20.06 & 20.20 (CH_2C), 29.64 & 30.99 (CH_2C), 30.36 & 30.50 (CH_2C), 45.41 & 46.64 (CH_2N), 65.83 66.72, 67.12, 69.88, 70.35, 71.01, 71.41 & 72.41 (CH_2O), 77.80 (CHO), 168.53 (C=O). υ_{max} (thin film) (cm^{-1}) 1647 (C=O stretch), 1126 (C-O stretch). $^{m}/_{z}$ (DCI, chloroform) 404 (M^+, 100%).

N-methyl-2-bromoethanamide (113):- A two phase system consisting of methylamine solution (25ml, 40%$^{w}/_{v}$), sodium hydroxide (20ml, 20%) and ethylene dichloride (100ml) was stirred at a temperature of -10°C. To this was slowly added bromo-acetyl-bromide (0.32M, 65g) in ethylene dichloride (50ml), maintaining the temperature below 0°C. After addition was complete the two layers were separated and the organic layer washed with $HCl_{(aq)}$ (0.1M, 2 x 50ml), and H_20 (50ml). It was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield a residue. The product was isolated as white crystals by sublimation (25°C, 0.05mmHg). This was found by GC analysis to be >98% one component. δ_H ($CDCl_3$) 2.87 (3H, d, CH_3N), 3.9 (2H, s, $BrCH_2$) and 6.6 (1H, broad s, NH). υ_{max} (KBr disc)

(cm^{-1}) 3293 (NH stretch), 1655 (C=O), 1558 (NH bend). $^{m}/_{z}$ (DCI, dichloromethane) 154(M^{+} +1) and 152 (M^{+} +1). Elemental analysis found C=23.6, H=4.0 and N=9.15 C_3H_6BrNO requires C=23.7, H=3.95 and N=9.21.

Ethyl N-(2-bromoethanoyl) glycinate (114):- To a solution of glycine ethyl ester hydrochloride (10g, 0.07 mol) in water (20ml) was added aqueous sodium carbonate until the pH was 10.0. The free amine was extracted using dichloromethane (5 x 40ml), the combined extracts were dried ($MgSO_4$) and the solvent reduced to a volume of *approx* . 80ml. Following sequential addition of sodium carbonate (8g, 75mmol) and a solution of bromoacetyl bromide (16g, 79mmol) in dichloromethane (30ml), the mixture was stirred for 1hour. After being filtered, washed with water (2 x 50ml) and dried ($MgSO_4$), the solvent was removed under reduced pressure to yield a residue which was recrystallised from propan-1-ol to yield a colourless solid (8.5g, 54%). m.pt. 68-69°C. δ_H ($CDCl_3$) 1.30 (3H, t, CH_3), 3.92 (2H, s, CH_2Br), 4.07 (2H, d, J = 5.2), 4.25 (2H, q, CH_2O) and 7.10 (1H, br, s, NHCO). δ_C ($CDCl_3$) 13.9 (CH_3), 28.21 (CH_2Br), 41.60 (CH_2N), 61.56 (CH_2O), 166.36 (NHC=O) and 169.22 (C=O ester). υ_{max} (KBr Disc) (cm^{-1}) 3267 (NH stretch), 1739 (C=O ester), 1651 (C=O amide), 1560 (NH bend), 1214 (C-O stretch). $^{m}/_{z}$ (DCI, dichloromethane) 243 & 241 (M^{+} +18, 100%), 226 & 224 (M^{+} +1, 26%). Elemental analysis found C=31.8, H=4.5%, N=6.10 $C_6H_{10}BrNO_3$ requires C=32.1, H=4.5 & N=6.24.

N,N-dimethyl-2-bromoethanamide (115):-A two phase system consisting of dimethylamine solution (23ml, 40%$^{w}/_{v}$), and ethylene dichloride (100ml) was stirred at a temperature of -10°C. To this was slowly added bromo-acetyl-bromide (0.1M, 20.2g) in ethylene dichloride (50ml), maintaining the temperature below 0°C. After addition was complete the two layers were separated and the organic layer washed with $HCl_{(aq)}$ (0.1M, 2 x 50ml), and H_20 (50ml). It was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield a residue. This was purified by

distillation (58-60°C, 0.4mmHg) to yield a colourless oil, 3.48g (21%). δ_H ($CDCl_3$) 2.99 (3H, s, CH_3N), 3.11(3H, s,CH_3N) & 3.87 (2H, s, CH_2Br). δ_C ($CDCl_3$) 26.87 (CH_2Br), 36.33 & 38.50 (CH_3N), 166.99 (C=O).

7,16-Bis(methylcarbamoylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (116):- To a solution of 4,7,10,13-tetraoxa-1,10-diazacyclooctadecane (0.65g, 2.48mmol) in dry acetonitrile was added potassium carbonate (0.76g, 5.20mmol) and N-methyl-2-bromoethanamide (113) (0.79g, 5.23mmol). The mixture was then heated under reflux for 72hours. The mixure was then filtered, the residue washed with dichloromethane (2 x 15ml) and the solvent removed under reduced pressure to yield a residue. Dichloromethane (20ml) was added to the residue and the mixture passed through a small bed of alumina under suction, washing with methanol (2 x 10ml). The solvent was removed under reduced pressure to yield a residue which was purified by chromatography on neutral alumina, eluting with dichloromethane-methanol (7%) (Rf = 0.52) to yield a yellow crystalline solid, 710 mg (71%). Mpt 118-122°C. δ_H ($CDCl_3$) 2.76-2.85 (14H, m, CH_2N, CH_3N), 3.15 (4H, s, CH_2CO), 3.48-3.65 (16H, m, CH_2O) and 7.95 (2H, broad s, NH). δ_C ($CDCl_3$) 25.7 (CH_3N), 56.2, 58.3 (CH_2N), 68.9 and 70.5 (CH_2O) and 172.1 (C=O). υ_{max} (KBr disc) (cm^{-1}) 3340-3040 (NH stretch), 1670 (C=O), 1540 (NH bend). $^m/_z$ (DCI, chloroform) 406 (M^+ + 1, 29%), 405 (M^+, 100%), 334 [M^+ -($CH_2CONHMe$ + 2), 23%] and 74 (31%). Elemental analysis found C=53.2, H=9.2, N=13.5 $C_{18}H_{36}N_4O_6$ requires C=53.4, H=9.0, N=13.8.

7,16-Bis(ethoxycarbonylmethylcarbamoylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (117):- This was synthesised using the same procedure as for **(116)**, except 4,7,10,13-tetraoxa-1,10-diazacyclooctadecane (0.42g, 1.60mmol), potassium carbonate (0.76g, 5.51mmol), potassium iodide (0.78g, 5.2mmol), ethyl N-(2-bromoethanoyl) glycinate **(114)** (0.79g, 5.23mmol) and acetonitrile (25ml). The residue was chromatographed on neutral alumina,

eluting with dichloromethane-methanol (5%) (Rf = 0.55) to yield a white crystalline solid, 600mgs (68%). m.pt. 108-111°C. δ_H ($CDCl_3$) 1.26 (6H, t, CH_3C), 2.81 (4H, m, CH_2N), 3.17 (4H, s, CH_2CO), 3.47 (16H, m, CH_2O), 4.08 (4H, d, CH_2CO), 4.16 (4H, q, CH_2CO arm) and 8.22 (2H, broad s, NH). δ_C ($CDCl_3$) 14.2 (CH_3C), 41.4 (CH_2NH), 56.5, 57.8 (CH_2N), 60.8, 68.8, 70.4 (CH_2O), 170.0 (amide C=O), 172.6 (ester C=O). υ_{max} (Nujol) (cm^{-1}) 3600-3100 (NH stretch), 1749 (ester C=O), 1670 (amide C=O) and 1540 (NH, bend). $^m/_z$ (DCI, chloroform) 549 (M^+ + 1, 29%), 548 (M^+, 100%), 406 [M^+ - ($CONHCH_2COOEt$ + 2), 28%), 146 (13%) and 133 (32%). Elemental Analysis found C=52.8, H=8.21 and N=9.90, $C_{24}H_{44}N_4O_{10}$ requires C=52.5, H=8.18 and N=10.2%.

7,13-Bis(methylcarbamoylmethyl)-1,4,10-trioxa-7,13-diaza-cyclopentadecane (118):-This was synthesised using the same procedure as for **(116)**, except 4,7,13,trioxa-1,10-diazacyclopentadecane (450mgs, 2.07mM), potassium carbonate (670mgs, 4.8mM), N-methyl-2-bromoethanamide **(113)** (730mgs, 4.8mM), potassium iodide (800mgs, 4.8mmol) and acetonitrile. The residue was chromatographed on neutral alumina, eluting with dichloromethane-methanol (7%) (Rf=0.47) yielding a pale brown oil 501mgs (67%). δ_H ($CDCl_3$) 2.73 (8H, t, CH_2N), 2.77 (6H, d, CH_3N), 3.10 (4H, s, CH_2CO), 3.77-3.93 (8H, m, CH_2O) and 8.03 (2H, broad s, NH). δ_C ($CDCl_3$) 26.4 (CH_3N), 57.1, 57.2 and 60.5 (CH_2N), 69.3, 70.1 (CH_2O) and 173.0 (C=O). υ_{max} (thin film) 3600-3100 (NH stretch), 1670 (C=O) and 1545 (NH bend). $^m/_z$ (DCI, chloroform) 361 (M^+ +1, 100%) and 290 (M^+ - $CCH_2CONHMe$ +1, 16%), (found 360.2379 $C_{16}H_{32}N_4O_5$ requires 360.2373).

7,13-Bis(ethoxycarbonylmethylcarbamoylmethyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (119):- This was synthesised using the same procedure as for **(116)**, except 4,7,13,trioxa-1,10-diazacyclopentadecane (440mgs, 2.02mmol), potassium carbonate (670mgs, 4.8mmol) ethyl N-(2-bromoethanoyl) glycinate **(114)** (1.07g, 4.8mmol), potassium iodide (720mgs, 4.8mmol) and acetonitrile. The residue was chromatographed on

neutral alumina, eluting with dichloromethane-methanol (5%) (Rf=0.64) to yield a pale yellow solid 702mgs (69%). m.pt. 85-86°C. δ_H ($CDCl_3$) 1.27 (6H, t, CH_3), 2.77 (8H, m, CH_2N), 3.20 (4H, s, NCH_2CON), 3.47-3.55 (12H, m, CH_2O), 4.04 (4H, d, NCH_2CO) and 8.32 (2H, t, NH). υ_{max} (Nujol) (cm^{-1}) 3350-3050 (NH stretch), 1746 (ester CO), 1670 (amide CO) and 1540 (NH bend). $^m/_z$ (DCI, chloroform) 505 (M^+ +1, 27%), 504 (M^+, 100%), 362 (M^+ - $CONHCH_2COOEt$ +2, 38%), 146 (12%) and 133 (32%). Elemental analysis C=53.1, H=8.05 and N=10.75 $C_{22}H_{40}N_4O_9$ C=52.4, H=8.0 and N=11.1.

4,10-Bis(methylcarbomylmethyl)-1,7-dioxa-4,10-diazacyclododecane (120):- This was synthesised using the same procedure as for (116), except 1,7-dioxa-4,10-diazacyclododecane (150mgs, 0.86mmol), potassium carbonate (290mgs, 2.1mmol), sodium iodide (315mgs, 2.1mmol), N-methyl-2-bromoethanamide (113) (320mgs, 2.1mmol) and acetonitrile (25ml). The residue was chromatographed on neutral alumina, eluting with dichloromethane-methanol (7%) (Rf=0.55) to yield a white solid 230mgs (84%). m.pt. 145-147°C. δ_H ($CDCl_3$) 2.69-2.76 (14H, m, CH_2N + CH_3N), 3.19 (4H, s, CH_2CO), 3.55 (8H, t, CH_2O) and 8.10 (2H, broad s, NH).δ_C ($CDCl_3$) 25.50 (CH_3N), 53.38 (CH_2N), 58.49 (CH_2N), 67.31 (CH_2O) and 170.2 (C=O).υ_{max} (nujol) (cm^{-1}) 3320 (NH stretch), 1670 (C=O) and 1540 (NH bend). $^m/_z$ (DCI, chloroform) 319 (M^+ +1, 100%), 318 (M^+, 98%), 258 (M^+ - CONHMe, 90%). Elemental analysis found C=53.5, H=9.00 and N=17.4 $C_{14}H_{28}N_4O_4$ requires C=53.1, H=8.92 and N=17.7.

4,10-Bis(dimethylcarbomylmethyl)-1,7-dioxa-4,10-diazacyclododecane (121):- This was synthesised using the same procedure as for **(116)**, except 1,7-dioxa-4,10-diazacyclododecane (140mgs, 0.81mmol), potassium carbonate (340mgs, 2.4mmol), sodium iodide (398mgs, 2.4mmol), N,N-dimethyl-2-bromoethanamide **(115)** (400mgs, 2.4mmol), acetonitrile (25ml). After filtering, the residue was dissolved in a minimum volume of $HCl_{(aq)}$ (2ml, 0.1M) and washed with dichloromethane (3 x 20ml), basified with $NaOH_{(aq)}$

and extracted with dichloromethane (3 x 30 ml). The organic layer was dried ($MgSO_4$),filtered and concentrated *in vacuo* to yield a white solid. The product was further purified by chromatographing on neutral alumina eluting with dichloromethane: methanol (methanol increasing from 0 to 2%) to yield a white solid 230mg (84%). m.pt. 135°C. δ_H ($CDCl_3$) 2.89 (8H, t, J=4.64 Hz, CH_2N), 2.93 (6H, s, CH_3N), 3.06 (6H, s, CH_3N), 3.45 (4H, s, $NCH_2C{=}O$) and 3.57 (8H, t, J=4.56 Hz, CH_2O). δ_C ($CDCl_3$) 35.6 (CH_3N), 36.42 (CH_3N), 54.69 (CH_2N), 57.41 ($NCH_2C{=}O$), 68.74 (CH_2O) and 179. 21 (C=O). υ_{max} (nujol) (cm^{-1}) 1641 (C=O). $^m/_z$ Found 344.243393 + 0.0002 $C_{16}H_{32}N_4O_4$ requires M^+ 344.242356. Elemental analysis found C=55.12, H=9.22, N=16.15 $C_{16}H_{32}N_4O_4$ requires C=55.24, H=9.37 and N=16.28.

4,10-Bis(ethoxycarbonylmethylcarbomylmethyl)-1,7-dioxa-4,10-diazacyclododecane (122):- This was synthesised using the same procedure as for **(116)**, except 1,7-dioxa-4,10-diazacyclododecane (150mg, 0.86mmol), potassium carbonate (340mgs, 2.4mmol), sodium iodide (398mgs, 2.4mmol), ethyl N-(2-bromoethanoyl) glycinate **(114)** (530mgs, 2.4mmol) and acetonitrile (25ml). After filtering, the residue was dissolved in a minimum volume of $HCl_{(aq)}$ (2ml, 0.1M) and washed with dichloromethane (3 x 20ml), basified with $NaOH_{(aq)}$ and extracted with dichloromethane (3 x 30 ml). The organic layer was dried ($MgSO_4$),filtered and concentrated *in vacuo* to yield a white solid. The product was further purified by chromatographing on neutral alumina eluting with dichloromethane: methanol (methanol increasing from 2to 7%) to yield a white solid 340mg (88%). m.pt. 173-175°C. δ_H ($CDCl_3$) 1.27 (6H, t, CH_3), 2.75 (8H, t, CH_2N), 3.24 (4H, s, $CH_2C{=}O$), 3.64 (8H, t, CH_2O), 4.00 (4H, d, NCH_2CO) 4.18 (4H, q, CH_2O) and 8.54 (2H, t, NH). δ_C ($CDCl_3$) 14.65 (CH_3), 41.42 (CH_2NH), 56.48 (CH_2N), 59.69 ($CH_2C{=}O$), 61.63 (CH_2O), 69.40 (CH_2O ring), 170.29 (amide C=O) and 172.63 (ester C=O). υ_{max} (nujol) (cm^{-1}) 3310 (NH stretch), 1750 (ester C=O), 1660 (amide C=O) and 1530 (NH bend). $^m/_z$ (DCI, chloroform) 461 (M^+ +1,

100%), 460 (M^+, 99%), 318 (M^+ - 143, 26%). Elemental analysis found C=51.9, H=7.95 and N=12.0. $C_{20}H_{36}N_4O_8$ requires C=52.2, H=7.83 and N=12.2.

Bis (N,N',N''-tributyl)-4,4',4''-propylidinetris(3-oxabutamide) (128):- To a solution of 2-ethyl-2-hydroxymethyl)-1,3-propanediol (100mg, 0.75mmol) in dry THF (40ml) was added sequentially sodium hydride (120mg, 5mmol) and N,N-dibutyl-bromoethanamide (1.25g, 5mmol) and the mixture refluxed for 48h. After cooling the reaction was filtered and the filtrate concentrated *in vacuo* to yield a brown oil. This was purified by chromatography on neutral alumina, eluting with a hexane: ethyl acetate (2:1) solvent system (Rf = 0.60) to yield a colourless oil 280mg, 59%. δ_H ($CDCl_3$) 0.93 (21H, m, $CH_3CH_2CH_2$ + CH_3CH_2), 1.32-1.51 (26H, m, CH_2C), 3.22 (6H, s, CH_2O), 4.11 (6H, s, CH_2O). δ_C ($CDCl_3$) 7.69 (CH_3), 13.81 (CH_3), 20.12 (CH_2C), 22.95 (CH_2C), 29.61, 30.98 (CH_2C), 43.33 (CH_2-C-CH_2), 45.34, 46.53 (CH_2N), 70.68, 72.02 (CH_2O), 168.73 (C=O). υ_{max} (thin film) 1647 (C=O stretch), 1088 (C-O). $^m/_z$ (DCI, THF) 643 (M^+ +1, 63%), 642 (M^+, 100%), 471 (11%), 172 (13%).

2-phenyl-2-(hydroxymethyl)-1,3-propanediol (141):- This was prepared using a modified Tollen's condensation.[2] To a solution of phenyl acetaldehyde (25g, 208mmol) in Dioxan:Water (500ml, 4:1) was added calcium hydroxide (23.4g, 312mmol) and paraformaldehyde (25g, 0.83moles) and the resultant suspension stirred for 48 hours at 60°C. After cooling the solution was acidified and then filtered. The filtrate was concentrated *in vacuo* to yield a viscous oil which was partitioned between water and ether, the water layer was then concentrated *in vacuo* to again yield a viscous oil. This was dissolved in hot chloroform and upon cooling, the required triol **(141)** was recovered as a white precipitate was formed. This was filtered off and dried, 3.51g (10%). m.pt. δ_H (CD_3OD) 4.14 (6H, s, CH_2OH), 5.06 (3H, s, OH), 7.40-7.66 (5H, m, Ar). δ_C (CD_3OD) 49.13 (Ar-C-CH_2), 64.50 (CH_2O), 126.25, 127.32, 128.14 and 141,25 (Ar). υ_{max} (KBr disc) (cm^{-1}) 3400-3100 (OH stretch, broad), 1032

(C-O stretch). $^{m}/_{z}$ (DCI, methanol), 200 (M^{+} +18, 100%), 183 (M^{+} +1, 8%), 147 (23%) and 129 (91%). Elemental analysis found C=65.5, H=7.90 $C_{10}H_{14}O_3$ requires C=65.9 and H=7.74.

Bis (N,N',N"-tributyl)-2,2',2"-phenylmethyllidinetris (3-oxabutanamide) (129):- To a solution of 2-phenyl-2-(hydroxymethyl)-1,3-propanediol (141) (500mg, 2.75mmol) in dry THF (50ml) was added sequentially sodium hydride (181mg, 8.25mmol) and N,N'-dibutyl-chloroethanamide (1.71g, 8.32mmol) and the mixture was heated to reflux for 72 hours. After cooling and filtering, the solvent was removed under reduced pressure and volatiles distilled off using a Kugelrohr apparatus. The residue was purified by chromatography on neutral alumina eluting with a hexane: ethyl acetate 5:1 solvent system (Rf = 0.34) to yield a colourless oil 894mg (47%). δ_H ($CDCl_3$) 0.87 (18H, t + t, CH_3C), 1.07-1.49 (24H, m, CH_2C), 3.01-3.27 (12H, dt, CH_2N), 3.89 (6H, s, CH_2O), 4.09 (6H, s, CH_2O), 7.15-7.53 (5H, m, Ar). δ_C ($CDCl_3$) 13.75 (CH_3C), 19.95, 20.14, 29.59, 30.83 (CH_2C), 45.28, 46.37 (CH_2N), 48.27 (CH_2-<u>C</u>-CH_2) 70.73, 73.39 (CH_2O), 126.28, 127.20, 127.93, 141.27 (Ar), 168.54 (C=O). υ_{max} (thin film) (cm^{-1}) 1647 (C=O), 1090 (C-O). $^{m}/_{z}$ (DCI, chloroform) 690 (M^{+} +1, 100%), 188 (20%), 172 (40%).

Tributyl-4,4',4"-propylidintris-(3-oxabutanoate) (130):- A solution of Triethyl-4,4',4"-propylidintris-(3-oxabutanoate) [3] (230mgs, 0.59mmol), was dissolved in n-butanol (100ml) and *p* -toluene sulphonic acid (0.2g) added and the mixture heated to reflux for 18h through molecular sieves (4Å). The solvent was then removed under reduced pressure to yield a residue which was redissolved in dichloromethane (50ml) and washed with aqueous hydrogen carbonate solution (3 x 20ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a residue which was chromatographed on neutral alumina using hexane: ethyl acetate 4:1 solvent system (Rf = 0.71) to yield a colourless oil 135mg (48%). δ_H ($CDCl_3$) 0.86 (12H, t + t, CH_3C) 1.29-1.59 (14H, m, CH_2C), 3.42 (6H, s, CH_2O), 4.00 (6H, s, CH_2O), 4.06 (6H, t,

CH_2O). δ_C ($CDCl_3$) 7.56 (CH_3C), 13.65 (CH_3C), 19.07, 22.84, 30.59 (CH_2O), 43.42 (CH_2-C-CH_2), 64.49, 68.94, 72.18 (CH_2O), 170.81 (C=O). υ_{max} (thin film) (cm^{-1}) 1735 (C=O). $^m/_z$ (DCI, chloroform) 494 (M^+ +18, 100%), 477 (M^+ +1, 29%), 275 (23%), 213 (32%), 199 (16%).

Bis (N,N',N"-tributyl)-5,5',5"-propylidintris-(4-oxa-pentanamide) (131):- To a solution of 5,5',5"-propylidintris-(4-oxa-pentanoic acid)[4] (500mgs, 1.43mmol) in dry dichloromethane (5ml) was added DMF (5µl) and oxalyl chloride (2ml) and the resultant solution stirred (under nitrogen) for 2 hours at room temperature. Conversion to the tri-acid chloride was confirmed by IR spectroscopy. The solvent was then removed under reduced pressure and the residue dissolved in dry ether (5ml). The solution was cooled to 0°C (under nitrogen) and a solution of butylamine (1.5g, 11mmol) in dry ether (5ml) added dropwise. The solution was then stirred for 2 hours at room temperature, filtered and the filtrate washed with $HCl_{(aq)}$ (2 x 10ml, 0.1M) and H_2O (20ml), dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo* to yield a residue. This was purified by chromatography on neutral alumina, eluting with hexane: ethyl acetate 2:1 (Rf =0.34) to yield a pale yellow oil 180mg (18%). δ_H ($CDCl_3$) 0.78 (3H, t, CH_3C), 0.94 (18H, m, CH_3C), 1.28-1.52 (26H, m, CH_2C), 2.54 (6H, t, CH_2C=O), 3.26 (18H, m, CH_2O + CH_2N), 3.68 (6H, t, CH_2O). δ_C ($CDCl_3$) 7.26 (CH_3C), 13.73 (CH_3C), 19.96, 29.8, 31.1, (CH_2C), 33.51 (CH_2C=O), 42.94 (CH_2-C-CH_2), 45.60 & 47.71 (CH_2N), 68.11, 71.45 (CH_2O), 170.60 (C=O). υ_{max} (thin film) (cm^{-1}) 1643 (C=O), 1110 (C-O). $^m/_z$ (DCI, chloroform) 684 (M^+, 29%), 200 (24%), 184 (92%).

Tributyl-5,5',5"-propylidintris-(4-oxa-pentanoate) (132):- This was prepared by butanolysis (Butanol, dry HCl) of the related trinitrile which was synthesised according to the published procedure.[3] δ_H ($CDCl_3$) 0.79 (3H, t, CH_3CH_2), 0.94 (9H, t, CH_3), 1.21-1.34 (14H, mult, CH_2C), 2.53 (6H, t, CH_2CO), 3.25 (6H, s, CH_2O), 3.64 (6H, t, CH_2O), 4.09 (6H, t, CH_2O). δ_C ($CDCl_3$) 7.49 (CH_3), 13.59 (CH_3C), 19.01, 22.74, 30.56 (CH_2C), 35.10 (CH_2CO), 42.94

(CH_2-C-CH_2), 64.13, 66.69, 71.01 (CH_2O) and 171.69 (C=O). υ_{max} (thin film) (cm^{-1}) 1743 (C=O stretch), 1101 (C-O stretch). $^m/_z$ (DCI, chloroform), 536 (M^+ +18, 48%), 519 (M^+ +1, 100%), 303 (35%), 227 (53%), 159 (48%) and 129 (48%).

Tris 1,3,5 (propanato),2,4,6 tris (propanamido) cyclohexane (157):- 1,3,5-Triamino- 1,3,5-trideoxy-cis-inositol (taci) (139) (1.0g, 4.7mmol) was placed in pyridine (40ml) and propionic anhydride (10ml) and the suspension stirred at 60^0 C for 24 hours, after which period the solution was clear. The solution was then concentrated in vacuo and the residue purified by recrystallising from chloroform/ether to yield a white crystalline solid (2.21g, 92%). Mpt 178-180^0 C. δ_H (CD_3OD) 1.09 (9H, t, CH_3C), 1.21 (9H, t, CH_3C), 2.50 (6H, q, CH_2CO), 2.78 (6H, q, CH_2CO), 4.50 (3H, m, CHN), 5.46 (3H, m, CHO) and 7.57 (3H, d, NH). δ_C (CD_3OD) 6.70 and 7.35 (CH_3C), 26.60 and 27.27 (CH_2CO), 48.42 (CHN), 67.93 (CHO), 173.93 and 174.76 (C=O). υ_{max} (cm^{-1}) (KBr disc) 3500 - 3100 N-H stretch, 1736 (C=O stretch, acetate), 1673 (C=O stretch, amide) and 1521 (C-N stretch). m/z (DCI, methanol), 531 ($M^+ + NH_4^+$, 100%), 514 ($M^+ + 1$, 38%), 475 ($M^+ -38$, 27%), 458 ($M^+ - C_2H_5CO$, 58%), 402 ($M^+ -2 \times C_2H_5CO$, 11%) and 367 ($M^+ -3 \times C_2H_5CO$, 23%). Found C = 55.61, H = 8.24, and N = 8.01. $C_{24}H_{39}N_3O_9$ requires C = 55.8, H= 8.20 and N = 8.13.

Tris 1,3,5 (hydroxy), tris 2,4,6 (propanamido) cyclohexane (158) A piece of clean dry sodium (20mgs) was added to dry methanol (30ml) and stirred (under nitrogen) until dissolution had occured and then **(157)** (1.0g, 1.94mM) was added and the resultant solution stirred for 2 hours at 20^0 C. Cation exchange resin (Dowex 50W) (100mg) was added and stirring continued for a further hour. The reaction was then filtered and the filtrate concentrated in vacuo to yield a white solid (495mgs, 74%). Mpt > 200^0 C. δ_H (CD_3OD) 1.31 (9H, t, CH_3C), 2.30 (6H, q, $CH_2C=O$), 3.93 (3H, m, CHN), 4.05 (3H, m, CHO). δ_C (CD_3OD) 10.29 (CH_3C), 30.10 ($CH_2C=O$), 52.36 (CHN), 72.15

(CHO) and 176.30 (C=O). υ_{max} (KBr disc) (cm^{-1}) 3340 (OH, NH stretch), 1650 (C=O stretch), 1530 (C=N stretch) and 1101 (C-O stretch). m/z (DCI, methanol) 346 (M^+ + 1, 100%), 328 (M^+ - OH, 71%), 223 (45%) and 165 (100%). Found C = 52.3, H = 7.67 and N = 12.01, $C_{15}H_{27}N_3O_6$ requires C = 52.2, H = 7.88 and N = 12.2.

Tris 1,3,5 (N,N'-dibutylcarbamoylmethyloxy) tris 2,4,6 (propanamido) cyclohexane (137):-

To a solution of (158) (400mg, 1.16mM) in dry DMF (20ml) was added NaH (80mg, 3.5mM) and the reaction stirred at 60° C for 2 hours. Then N,N' dibutyl- α- chloroethanamide (720mg, 3.5mM) was added, along with NaI (100mg). The reaction was stirred for 6 days at 60° C (under nitrogen), every 24 hours for 5 days NaH (40mg) and N,N' dibutyl- α- chloroethanamide (400mg), were added. After cooling the reaction was filtered through a celite bed and the filtrate concentrated in vacuo to yield a brown oil. The residue was chromatographed on silica with a solvent gradient 95 : 5 to 85 : 15 (CH_2Cl_2 : MeOH) and the required product recovered (Rf = 0.56, 15% MeOH). This was further purified by recrystallisation from chlorofrom / ether to give a white crystalline solid (110mg, 11%). Mpt > 240°C. δ_H ($CDCl_3$) 0.95 (18H, m, CH_3C), 1.18 - 1.61 (33H, m, CH_2 + CH_3), 2.37 (12H, m, CH_2C=O), 2.97 - 3.28 (12H, m, CH_2N), 3.86 (3H, m, CHN), 3.99(3H, m, CHO), 4.34 (6H, s, CH_2O), 10.17 (3H, bs, N-H). δ_C ($CDCl_3$) 10.41 (CH_3C), 13.70 & 13.78 (CH_3C), 20.14 (CH_2C), 29.34 & 29.64 (CH_2C), 30.68 (CH_2C=O), 45.84 & 46.13 (CH_2N), 51.64 (CHN), 70.29 (CH_2O), 79.19 (CHO), 170.74 & 174.81 (C=O). υ_{max} (KBr disc) (cm^{-1}) 3250 (N-H stretch), 1651 (C=O stretch), 1564 (C-N stretch) and 1122 (C-O stretch). Found C=51.27, H=8.14 and N=14.76 $C_{24}H_{44}N_6O_9$ requires C=51.41, H=7.91 and N=15.00.

Tris 1,3,5 (N,N'-Methylcarbamoylmethyloxy) tris 2,4,6 (propanamido) cyclohexane (138):- This compound was prepared using the same procedure as that used to produce (158), except N methyl bromoethanamide (1.06g,

6.96mmol), yielding an off white solid which was chromatographed on silica eluting with a solvent gradient (95:5 to 80:20 CH_2Cl_2 : MeOH) (Rf = 0.25, 20%). This was further purified by recrystallisation from chloroform: methanol: hexane, yielding a pale yellow solid (114mg, 0.203mM). Mpt > 240° C. δ_H ($CDCl_3/CD_3OD$ 90:10) 1.16 (9H, t, CH_3C), 2.32 (6H, q, CH_2C), 2.77 (9H, s, NCH_3), 3.81 (3H, t, CHN), 4.07 (3H, t, CHO), 4.12 (6H, s, CH_2O), 7.85 (3H, bs, NH). δ_C ($CDCl_3/CD_3OD$ 90:10) 9.86 (CH_3C), 25.77 (CH_2C), 29.23 (CH_3N), 50.76 (CHN), 73.05 (CH_2O), 80.01 (CHO), 171.83 & 175.05 (C=O). υ_{max} (KBr disc) (cm^{-1}) 3245 (N-H stretch), 1654 (C=O stretch), 1570 (C-N stretch) and 1120 (C-O stretch). Found C=52.3, H=7.67 and N=12.01 $C_{15}H_{27}N_3O_6$ requires C=52.2, H=7.88 and N=12.2.

N,N' -dibutylmalonamide (198):- Diethyl malonate (2.0g, 12.5mM) was dissolved in isobutylamine (25ml) and stirred at 60°C for 7 days. The solvent was then removed under reduced pressure to yield an off-white crystalline solid. This was purified by recrystallising from water/ethanol to yield a white crystalline solid, 2.18g (81%). δ_H (CD_3OD) 0.91 (12H, d, CH_3C), 1.72 (2H, sept, CHC), 2.93 (4H, d, CH_2C), 3.17 (2H, s, CH_2C). δ_C ($CDCl_3$) 20.10 (CH_3C), 28.37 (CH), 43.2 (CH_2CO), 47.0 (CH_2N), 167.81 (C=O). υ_{max} (KBr disc) (cm^{-1}) 3240, 3080 (NH-stretch), 1630 (C=O) & 1560 (NH-bend). m/z (CI, CH_2Cl_2) 215 ($M^+ + 1$, 100%), 116 (13%) & 74 (14%).

1,5 -bis -(N -butylamino)-propane (199):- N,N' -dibutylmalonamide (2.0g, 8.84mM) was placed in a flask under nitrogen. Then BH_3-THF solution (1M, 53ml) was added and the reaction refluxed under nitrogen for 72 hours. The reaction was then quenched with methanol and the solvent removed under reduced pressure to yield a residue. The residue was dissolved in $HCl_{(aq)}$ (6M, 90ml) and the reaction refluxed for 3 hours, cooled and the solvent removed under reduced pressure to yield a residue. The residue was treated with water (10ml), basified using $KOH_{(s)}$ and extracted with dichloromethane (3 x 50ml). The combined extracts were dried (K_2CO_3), filtered and the solvent removed under reduced pressure to yield a pale

yellow oil, 1.58g (90%). δ_H ($CDCl_3$) 0.84 (12H, d, CH_3C), 1.63 (4H, m, CHC), 2.31 - 2.61 (8H, m, CH_2N). δ_C ($CDCl_3$) 20.3 (CH_3C), 28.0, 30.0 (CH_2C + CHC), 48.5 & 57.9 (CH_2N). υ_{max} (thin film) (cm^{-1}) 3300 (NH-stretch), 1630 (NH -bend), 1120 (C-N stretch) & 750 (NH-wag). $^m/_z$ (CI) 187 (M^++ 1, 100%), 114 (M^+- ButNH, 36%), 74 (38%).

Dibutyl malonic acid (200)

To a solution of diethyl dibutyl malonate (15.0g, 5.5mmol) in methanol/water (4:1) (100ml) was added sodium hydroxide (20g). The solution was then refluxed for 3 hours. After cooling the solvent was removed under reduced pressure to yield a residue which was redissolved in water (50ml) and carefully acidified maintaining the temperature below 0°C. The free acid was then extracted with ether (2 x 200ml), dried ($MgSO_4$), filtered and the solvent removed to yield a white solid. 11.02g (92%). δ_H (CD_3OD) 0.89 (6H, t, CH_3C), 1.05-1.37 (8H, m, CH_2C), 1.89 (4H, m, CH_2C) and 5.40 (2H, s, br, OH). δ_C ($CDCl_3$) 13.51 (CH_3C), 22.58, 26.74 and 34.89 (CH_2C), 57.18 (CH_2-<u>C</u>-CO_2H), 176.13 (C=O). υ_{max} (KBr disc) (cm^{-1}) 3400-2900 (OH stretch), 1707 (C=O stretch), 1088 (C-O stretch).

N,N'-Bis (p-toluenesulponyl)-1,3-diaminopropane (203)

To a solution of 1,3 diaminopropane (10.0g, 0.14mmol) and K_2CO_3 (50g, 0.36mmol) in water (200ml) was added dropwise a solution of p-toluene sulphonyl chloride (69g, 0.36mmol) in THF (400ml). The resultant two phase system was stirred vigorously for 12 hours at 50°C. After cooling the upper (organic) layer was separated and slowly poured onto crushed ice. The precipitate was then filtered off, dried *in vacuo*, and then recrystallised from hot ethanol to yield a white crystalline solid, 42.30g (86%). M.pt 135-138°. δ_H ($CDCl_3$) 1.65 (2H, m, CH_2C), 2.43 (6H, s, Ar-<u>C</u>H_3), 3.00 (4H, m, CH_2N), 4.93 (2H, t, N-H), 7.29-7.74 (8H, dd, Ar). δ_C ($CDCl_3$) 20.96 (Ar-<u>C</u>H_3), 29.34 (CH_2C), 40.22 (CH_2N), 126. 50, 126.53, 137.46 and 142.57 (Ar). υ_{max} (KBr disc) (cm^{-1}) 3250 (N-H stretch), 1601 (C=C stretch). $^m/_z$ (DCI, chloroform) 400

(M^+ +18, 100%), 383 (M^+ +1, 100%), 229 (M^+ - $NHSO_2ArMe$, 100%). Found C=53.0, H=5.81 and N=7.13 $C_{17}H_{22}N_2O_4S_2$ requires C=53.4, H=5.76 and N=7.33.

N,N'-bis (p-toluenesulphonyl)-2-bromobora-1,3-diazine (193):- To a solution of (203) (1.0g, 2.62 mmol) in dry CH_2Cl_2 (5ml) stirred under argon at -10°C was added boron tribromide (651mg, 250µl, 2.62mmol) and the solution stirred for 2 hours. δ_H (CD_2Cl_2) 2.07 (2H, t, CH_2C), 2.33 (6H, s, CH_3Ph), 3.77 (4H, t, CH_2N), 7.21-8.11 (8H, m, Arom H). δ_B (CH_2Cl_2) 2.11ppm.

N,N'-bis (p-toluenesulphonyl)-2-chlorobora-1,3-diazine (194):- This was prepared as above except BCl_3 (1M solution) (2.65ml) was used in place of BBr_3. δ_H (CD_2Cl_2) 2.05 (2H, t, CH_2C), 2.31 (6H, s, CH_3Ph), 3.70 (4H, t, CH_2N), 7.29-7.93 (8H, m, Arom H). δ_B (CH_2Cl_2) 6.87 ppm.

2,2-Ethylidene-bis-(4,6-di-*tert* -butyl-phenyl) bromoborate (206):- To a solution of 2,2-Ethylidene-bis-(4,6-di-tert -butyl-phenol) (1.0g, 2.28mmol) in dry CH_2Cl_2 (5ml) stirred under argon, was added BBr_3 (220µl, 572mg, 2.28 mmol) and the reaction stirred for 2 hours at room temperature. The reaction was then filtered under argon and the precipitate dried. δ_B (CH_2Cl_2) 20.11 ppm.

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PUBLICATIONS, CONFERENCES & COLLOQUIA

COLLOQUIA, LECTURES AND SEMINARS GIVEN BY INVITED SPEAKERS 1ST AUGUST 1990 TO 31ST JULY 1991

ALDER, Dr. B.J. (Lawrence Livermore Labs., California) 15th January, 1991

Hydrogen in all its glory.

*BELL†, Prof. T. (SUNY, Stoney Brook, USA) 14th November, 1990

Functional Molecular Architecture and Molecular Recognition.

*BOCHMANN†, Dr. M (University of East Anglia) 24th October, 1990

Synthesis, Reactions and Catalytic Activity of Cationic Titanium Alkyls.

*BRIMBLE, Dr. M.A. (Massey University, New Zealand) 29th July, 1991

Synthetic Studies Towards the Anti-biotic Griseusin-A.

BROOKHART, Prof. M.S. (University of N. Carolina) 20th June, 1991

Olefin Polymerisations, Oligomerisations and Dimerisations Using Electrophilic Late Transition Metal Catalysts.

*BROWN, Dr. J. (Oxford University) 28th February, 1991

Can Chemistry Provide Catalysts Superior To Enzymes?

*BUSHBY†, Dr. R. (Leeds University) 6th February, 1991

Biradicals and Organic Magnets

COWLEY, Prof. A.H. (University of Texas) 13th December, 1990

New Organometallic Routes to Electronic Metals.

*CROUT, Prof. D. (Warwick University) 29th November, 1990

Enzymes in Organic Synthesis.

DOBSON†, Dr. C.M. (Oxford University) 6th March, 1991

NMR Studies of Dynamics in Molecular Crystals.

GERRARD†, Dr. D. (British Petroleum) 7th November, 1990

Raman Spectroscopy for Industrial Analysis.

*HUDLICKY, Prof. T. (Virginia Polytechnic Institute) 25th April, 1991

Biocatalysis and Symmetry Based Approaches to the Efficient Synthesis of Complex Natural Products.

*JACKSON†, Dr. R. (Newcastle University) 31st October, 1990

New Synthetic Methods: α Amino acids and Small Rings.

*KOCOVSKY†, Dr. P (Uppsala University) 6th November, 1990

Stereo-Controlled Reactions Mediated by Transition and Non-Transition Metals.

LACEY, Dr. D. (Hull University) 31st January, 1991

Liquid Crystals.

*LOGAN, Dr. N. (Nottingham University) 1st November, 1990

Rocket Propellents.

MACDONALD, Dr. W.A. (ICI Wilton) 11th October, 1990

Materials for the Space Age.

*MARKAM, Dr. J. (ICI Pharmaceuticals) 7th March, 1991

DNA Fingerprinting.

PETTY, Dr. M.C. (Durham University) 14th February, 1991

Molecular Electronics.

*PRINGLE†, Dr. P.G. (Bristol University) 5th December, 1990

Metal Complexes with Functionalised Phosphines.

PRITCHARD, Prof. J. (Queen Mary and Westfield College London University) 21st November, 1990

Copper Surfaces and Catalysts.

*SADLER, Dr. P.J. (Birkbeck College, London) 24th January, 1991

Design of Inorganic drugs: Hypertension + HIV.

SARRE, Dr. P (Nottingham University) 17th January, 1991

Comet Chemistry.

SCHROCK. Prof. R.R. (Masschusetts Institute of Technology) 24th April, 1991

Metal-Ligand Multiple Bonds and Metathesis Initiators.

SCOTT, Dr. S.K. (Leeds University) 8th November, 1990

Clocks, Oscillations and Chaos.

*SHAW,† Prof. B.L. (Leeds University) 20th February 1991

Synthesis with Coordinated, Unsaturated Phosphine Ligands.

SINN†, Prof. E. (Hull University) 30th January, 1991

Coupling of Little Electrons in Big Molecules.
Implications for the active sites of (Metalloproteins and other) Macromolecules.

SOULEN†, Prof. R. (South Western University, Texas) 26th October, 1990

Preparation and Reactions of Bicycloalkenes.

WHITAKER†, Dr. B.J. (Leeds University) 28th November, 1990

Two-dimensional Velocity Imaging of State-Selected Reaction Products.

DURING THE PERIOD: 1991-1992

*ANDERSON. Dr. M. (Shell Research, Sittingborne) 30th January, 1992
Recent Advances in the Safe and Selective Control of Insect Pests.

BILLINGHAM, Dr. N.C. (University of Sussex) 5th March, 1992
Degradable Plastics- Myth or magic?

*BUTLER, Dr. A.R. (St. Andrews University) 7th November, 1991
Traditional Chinese Herbal drugs: a different way of treating disease.

COOPER, Dr. W.D. (Shell Research) 11th December, 1991
Colloid Science: Theory and Practice.

*FENTON†, Dr. D.E. (Sheffield University) 12th February, 1992
Polynuclear Complexes of Molecular Clefts as Models for Copper Biosites.

GANI†, Prof. D. (St. Andrews University) 13th November, 1991
The chemistry of PLP-dependent Enzymes.

*GEHRET, Dr. J-C. (Ciba Geigy, Basel) 13th May, 1992
Some Aspects of Industrial Agrochemical Research.

GRIGG†, Prof. R. (Leeds University) 4th December, 1
Palladium-Catalysed Cyclisation and ion-capture process.

HANN, Dr.R.A. Hann, (ICI Imagedata) 12t

Electronic Photography - An Image of the Future.

HARRIS†, Dr. K.D.M. (St. Andrews University) 22th January 1992

Understanding the Properties of Solid

Inclusion Compounds.

HITCHMANN†, Prof. M.L. (Strathclyde University) 26th February 1992

Chemical Vapour deposition.

*HOLMES†, Dr. A. (Cambridge University) 29th January 1992

Cycloaddition Reactions in the service of the synthesis

of Piperidine and Indolizidine Natural Products.

JOHNSON†, Prof. B.F.G. (Edinburgh University) 6th November 1991

Cluster-Surface Analogues.

*KEELEY, Dr. R. (Metropolitan Police Forensic Science) 31st October 1991

Modern Forensic Science.

KNIGHT, Prof D.M. (Philosophy Department, 7th April 1992

University of Durham).

Interpreting Experiments: the beginning of Electrochemistry.

MASKELL†, Dr. H. (Newcastle University) 18th March 1992

Concerted or Stepwise Fragmentation in a Diamination

Type Reaction.

*MORE O' FERRALL†, Dr. M. 20th November 1991

(University College, Dublin)

Some Acid-Catalysed Rearrangements in Organic Chemistry.

NIXON, Prof. J.F. (University of Sussex) 25th February 1992

The Tilden Lecture: Phosphaalkynes: New Building

Blocks in Inorganic and Organometallic Chemistry.

*SALTHOUSE, Dr. J.A. (University of Manchester) 17th October 1991

Son et Lumiere - A demonstration Lecture.

*SAUNDERS, Dr. J. (Glaxo Group Research Limited) 13th February 1992

Molecular Modelling in Drug Discovery.

SMITH, Dr. A.L. (ex Unilever) 5th December 1991

Soap, Detergents and Black Puddings.

*THOMAS†, Prof. E.J. (Manchester University) 19th February 1992

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*THOMAS†, Dr. S.E. (Imperial College) 5th March 1992

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*VOGEL Prof. E. (University of Cologne) 20th February 1992

The Musgrave Lecture: Porphyrins: Moolecules

of Interdisciplinary Interest.

WARD Prof. I.M. (IRC in Polymer Science, 28th November 1991

University of Leeds)

The SCI Lecture: The Science and Technology of

Orientated Polymers.

DURING THE PERIOD: 1991-1992

AITKEN Prof. A.F. (University of St. Andrews) 2nd December 1992

The Versatile Cycloaddition Chemistry of $Bu_3P.CS_2$.

BAKER Dr. P.K. (University College of North 10th March 1993

Wales, Bangor)

Chemistry of Highly Versatile 7-Coordinate Complexes.

BRYNDZA Dr. H.E. (Du Pont Central Reasearch) 20th October 1992

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Reactive Prosessing of Composite Materials.

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NMR and Molecular Motion in Solution.

*GLAZER Dr. M and TARLING Dr. S — 15th October 1993

Oxford University and Birbeck College

It pays to be British-The Chemist's Role as an Expert Witness in Patent Litigation.

GRANT Prof. D.M. (University of Utah) — 22nd February 1993

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Oxatrimethylenemethane Metal Complexes.

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Development of the Pauson-Khand Annulation Reaction: Organocobalt Mediated Synthesis of Natural and Unnatural Products.

KNOX Prof. S (Bristol University) — 11th February 1993

The Tilden Lecture Organic Chemistry at Polynuclear Metal Centres.

*KONOPELSKI Prof. J.P. (University of California) 1st June 1993

Synthetic Adventures with Enantiomerically Pure Acetals.

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Explosions, A Demonstration Lecture.

MANN Prof. J. (University of Reading) 28th January 1993

Murder, Magic and Medicine.

NIELSEN Prof. O.F. (H.C. Ørsted Institute, University of Copenhagen). 17th June 1993

Low Frequency IR- and Raman Studies of Hydrogen Bonded Liquids.

NIX Dr. R. (Queen Mary College, London) 18th November 1992

Characterisation of Heterogeneous Catalysts.

POPLE Prof J.A. (Carnegie-Mellon University Pittsburgh, USA) 13th May 1993

The Boys-Rahman Lecture Applications of Molecular Orbital Theory.

QUIN Prof. L.D. (University of Massachusetts Armherst) 25th November 1992

Fragmentation of Phosphorus Heterocycles as a Route to Phosphoryl Species with Uncommon Bonding.

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Enzymes in Organic Synthesis.

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Chemistry on the Flat-Reactivity of Ordered Systems.

*SUTHERLAND Prof I.O. (University of Liverpool) 24th March 1993
Chromogenic Reagents for Cations.

*TAYLOR Dr. R.J.K. (University of East Anglia) 17th March 1993
Adventures in Natural Product Synthesis.

TRUTER Prof. M.R. (University College, London) 12th November 1992
Luck and Logic in Host-Guest Chemistry.

VALLEE Prof. Y (University of Caen) 25th November 1992
Reactive Thiocarbonyl Compounds.

WEBER Prof. L. (University of Bielfeld) 21st May 1993
Metallo-phospha Alkenes as Synthons in
Organometallic Chemistry.

* Indicates attended by Author.

† Indicates colloquia arranged as part of post-graduate training.

RESEARCH CONFERENCES

Uk Macrocyclics Group

University of Manchester, 4-5 January 1991.

Sixteenth International Symposium on Macrocyclic Chemistry

University of Sheffield, 1-6 September 1991.

North East Graduate Symposium

University of Durham, 3 April 1992.

International Symposium on Structure and Bonding

University of Durham, 2-4 September 1992.

PUBLICATIONS

1. *Binding properties of Amide and Amide-Ester N-Functionalised Polyaza Macrocycles.*
   R. Kataky, D. Parker, A. Teasdale and J.P. Hutchinson
   Journal of the Chemical Society Perkin Transactions II, (1992), 1347.

2. *Comparative Study of Tri-Podal Oxa-Amides and Oxa-Esters as Ionophores in Potentiometric Ion-Selective Electrodes for Alkali and Alkaline Earth metal cations.*
   R. Kataky, D. Parker and A.Teasdale
   Analytica. Chimica. Acta., (1993), 276, 353.

3. *Pronounced Calcium Binding Selectivity with Diamide Derivatives of 12-N_2 O_2 and the Importance of Desolvation.*
   D. Parker, A. Teasdale and H.J. Buschmann
   Supramolecular Chemistry. In Press

APPENDICES

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empiral Formula: $C_{16}H_{26}N_2O_4$

Color: Transparent.

Crystal Size (mm) 0.20 x 0.25 x 0.45.

Crystal System: Monoclinic.

Space Group: $P2_1$ / n.

Unit Cell Dimensions: a = 6.282 (2) Å.
b = 8.052 (2) Å.
c = 17.079 (3) Å.
β = 97.39 (3) °

Volume: 856.7 (4) $Å^3$

Z: 2

Formula Weight: 310.4

Density (calc): 1.203 Mg/m^3.

Absoption Coefficient: 0.086 mm^{-1}.

F(100): 336.

Data Collection

Diffractometer Used: Rigaku AFC6S/V.

Radiation: MoKα (λ = 0.71073 Å).

Temperature: 150K.

Monochromator: Highly orientated graphite crystal.

2θ Range: 4.0 to 60.0°.

Scan Type: 2θ - θ.

Scan Speed: Constant: 8.00° / min. in ω.

Scan Range (ω): 1.90° plus Kα separation.

Background Measurement: Stationary crystal and stationary counter at beginning and end of the scan, each for 25.0% of the total scan time.

Standard Reflections: 3 measured every 100 reflections.

Index Ranges: $0 \leq h \leq 8$, $0 \leq k \leq 10$. $-23 \leq l \leq 23$.

Reflections Collected: 2145.

Independent Reflections: 1999 (R_{int} = 0.00%).

Observed Reflections: 1415 ($F \geq 4.0\ \sigma(F)$).

Absorption Correction: N/A.

Solution and Refinement

System Used: Siemens SHELXTL PLUS (VMS).

Solution: Direct methods.

Refinement Method: Full matrix least squares.

Quantity Minimized: $\Sigma_w (F_o - F_c)^2$.

Absolute Structure: N/A.

Extinction Coefficient: $\chi = 0.0009(6)$, where

$$F^* = F [1 + 0.002\chi F^2 / \sin(2\theta)]^{-1/4}$$

Hydrogen Atoms: Refined isotropically.

Weighting Scheme: $w^{-1} = \sigma^2(F) + 0.0000F^2$.

Number of Parameters Refined: 161.

Final R Indices (obs. data): R = 10.53 %, wR = 10.26 %.

R Indices (all data): R = 14.53 %, wR = 14.36%.

Goodness of Fit: 4.69.

Largest and Mean Δ / σ 0.199, 0.027.

Data-to-parameter Ratio: 8.8 : 1.

Largest Difference Peak: 0.50 eÅ^{-3}.

Largest Difference Hole: -0.54 eÅ^{-3}.

	X	Y	Z	U (eq)
O (1)	819 (5)	1453 (4)	1034 (2)	28 (1)
O (2)	-3013 (5)	1760 (4)	-94 (2)	26 (1)
N (1)	7243 (7)	-3854 (6)	1748 (3)	57 (1)
C (1)	3565 (7)	-595 (5)	1407 (3)	26 (1)
C (2)	3076 (7)	1166 (6)	1094 (3)	28 (1)
C (3)	249 (7)	2985 (5)	643 (3)	28 (1)
C (4)	-2142 (7)	3052 (6)	440 (3)	30 (1)
C (5)	-2326 (7)	1874 (6)	-857 (3)	27 (1)
C (6)	6012 (7)	-810 (6)	1422 (3)	30 (1)
C (7)	6731 (7)	-2523 (7)	1609 (3)	37 (1)
C (8)	2885 (7)	-818 (6)	2225 (3)	32 (1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 1:- Atomic coordinates (x 10^4) and equivalent isotropic displacement coefficients (Å x 10^3).

O (1) - C (2)	1.427 (5)	O (1) - C (3)	1.425 (5)
O (2) - C (4)	1.444 (5)	O (2) - C (5)	1.427 (6)
N (1) - C (7)	1.135 (7)	C (1) - C (2)	1.532 (6)
C (1) - C (6)	1.544 (6)	C (1) - C (8)	1.524 (7)
C (1) - C (5A)	1.537 (6)	C (3) - C (4)	1.498 (6)
C (5) - C (1A)	1.537 (6)	C (6) - C (7)	1.474 (7)

Table 2:- Bond Lengths (Å)

C (2) - O (1) - C (3)	111.2 (3)	C (4) - O (2) - C (5)	113.3 (3)
C (2) - C (1) - C (6)	105.3 (4)	C (2) - C (1) - C (8)	111.2 (4)
C (6) - C (1) - C (8)	111.6 (4)	C (2) - C (1) - C (5A)	110.1 (3)
C (6) - C (1) - C (5A)	111.1 (4)	C (8) - C (2) - C (5A)	107.6 (4)
O (1) - C (2) - C (1)	109.1 (4)	O (1) - C (3) - C (4)	108.9 (4)
O (2) - C (4) - C (3)	114.0 (4)	O (2) - C (5) - C (1A)	109.0 (4)
C (1) - C (6) - C (7)	112.7 (4)	N (1) - C (7) - C (6)	178.5 (5)

Table 3 Bond Angles (°).

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O (1)	31(1)	25 (1)	27 (1)	-3 (1)	2 (1)	4 (1)
O (2)	32(1)	26 (1)	19 (1)	-5 (1)	-1 (1)	0 (1)
N (1)	65 (1)	51 (1)	53 (1)	17 (1)	-6 (1)	6 (1)
C (1)	33 (1)	29 (1)	15 (1)	-7 (1)	5 (1)	0 (1)
C (2)	37 (1)	29 (1)	16 (1)	-7 (1)	3 (1)	-3 (1)
C (3)	38 (1)	18 (1)	26 (1)	-4 (1)	-3 (1)	0 (1)
C (4)	35 (1)	25 (1)	29 (1)	-5 (1)	1 (1)	-4 (1)
C (5)	36 (1)	26 (1)	18 (1)	-3 (1)	- 6 (1)	3 (1)
C (6)	29 (1)	34 (1)	25 (1)	-2 (1)	2 (1)	-2 (1)
C (7)	31 (1)	51 (1)	26 (1)	7 (1)	-10 (1)	-4 (1)
C (8)	38 (1)	37 (1)	19 (1)	-3 (1)	1 (1)	3 (1)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 (h^2a^{*2}U_{11} + ...+ 2hka^*b^*U_{12})$

Table 4:- Anisotropic displacement coefficients ($Å^2 \times 10^3$).

	X	Y	Z	U
H (21)	3613 (13)	1252 (13)	608 (12)	41 (1)
H (22)	3737 (13)	2019 (13)	1427 (12)	48 (1)
H (31)	1321 (13)	3089 (13)	202 (12)	45 (1)
H (32)	631 (13)	3980 (13)	886 (12)	44 (1)
H (41)	-2906 (13)	2919 (13)	932 (12)	43 (1)
H (42)	-2656 (13)	4149 (13)	137 (12)	70 (1)
H (51)	865 (13)	1617 (13)	-911 (12)	51 (1)
H (52)	-2597 (13)	3007 (13)	-1052 (12)	42 (1)
H (61)	6592 (13)	-638 (13)	937 (12)	45 (1)
H (62)	6815 (13)	-19 (13)	1698 (12)	53 (1)
H (81)	3379 (13)	-1938 (13)	2423 (12)	48 (1)
H (82)	1230 (13)	-732 (13)	2285 (12)	53 (1)
H (83)	3519 (13)	-94 (13)	2540 (12)	50 (1)

Table 5:- H-atom coordinates (x 10^4) and isotropic displacement coefficients (Å ^{2} x 10^3).

Derivation of a 1:1 Binding Model

$$Li^+ + L \quad LiL \qquad \text{where } K = \frac{[ML]}{[L]\,[M^{n+}]}$$

δ_0 = ^{13}C chemical shift in the absence of M^{n+} and

δ_1 = ^{13}C chemical shift of the 1:1 complex.

but $[L] + [ML] = [L]_{int}$

where $[L]_{int}$ = the initial concentration of the ligand.

$$\delta_0 = \frac{\delta_0 [L]}{[L]_{int}} + \frac{\delta_1 [ML]}{[L]_{int}}$$

$$= \frac{\delta_0 [L]_{int} - [ML] + \delta_1 [ML]}{[L]_{int}}$$

$$= \frac{[ML] (\delta_1 - \delta_0) + [L]_{int} \delta_0}{[L]_{int}}$$

$$= \frac{[ML] (\delta_1 - \delta_0)}{[L]_{int}} + \delta_0$$

$$\Delta\delta_0 = \frac{[ML] (\delta_1 - \delta_0)}{[L]_{int}}$$

expressing [ML] in terms of known quantities:

$$K_1 = \frac{[ML]}{([L]_{int} - [ML])([L]_{int} A - [ML])}$$

where $A = [M]_{int} / [L]_{int}$ = quantity measured.

$$K_1 \{[L]^2_{int} A - [L]_{int} [ML] + [ML]^2\} = [ML]$$

$$K_1 [ML]^2 - (1 + K_1 [L]_{int} + K_1 [L]_{int} A) [ML] + K_1 [L]^2_{int} A = 0$$

Solving for a quadratic in [ML]:-

$$[ML] = (1 + \frac{K_l [L]_{int} + K_l [L]_{int} A}{2K_l})$$

$$= (1 + \frac{K_l [L]_{int} + K_l [L]_{int} A)^2 - 4 K^2_l [L]^2_{int} A}{2K_l}$$

$$\Delta\delta_0 = (\delta_1 - \delta_0) \left\{(1-K_l) [L]_{int} + K_l[L]_{int} A \pm (1+K.[L]_{int} + K_l[L]_{int}A)^2 - 4K^2_l[L]^2_{int} A\right\}$$

Points on the graphs are expermental values ($\Delta\delta_0$ verses A) are those calculated by a general curve fitting procedure to the above equation, giving values of the equilibrium constant K_l