The synthesis and behaviour of novel Ionophores

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THE SYNTHESIS AND BEHAVIOUR OF NOVEL IONOPHORES

by

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MEMORANDUM

The work for the thesis has been carried out in the Department of Chemistry at the Univeristy of Durham between October 1993 and September 1996. It is the work solely of the author unless stated otherwise. None of the work has been submitted for any other degree.

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Finally, I would like to thank all the people in labs 27 and 29 for helping me keep my sense of humour when things weren't going well.

ABSTRACT

Two series of oxa-amide ionophores based on 2-phenylglycerol and cis-cis-1,3,5-cyclohexanetriol with ligand coordination numbers of 4, 5 and 6 have been synthesised and studied. Complexation of the ligands with group Ia and IIa metal ions was studied using IR, ^{13}C NMR and electrospray mass spectroscopy. Potentiometric membrane electrodes have been prepared and their performance evaluated using a fixed interference method. Ionophores based on the hexadentate cyclohexyl triamide show excellent Na^+/K^+ selectivity ($-\log K^{pot}_{Na,K} = 3.1$), and the pentadentate analogue shows good Li^+/Na^+ selectivity ($-\log K^{pot}_{Li,Na} = 2.2$). Ligands based on 2-phenylglycerol exhibited good Ca^{2+} selectivity which was highest for the hexadentate triamide.

The attempted synthesis of two 14-crown-4 fluorophores is reported as well as the synthesis and evaluation of an 18-crown-6 based fluorophore. The 18-crown-6 fluorophore shows a bathochromic fluorescent shift in the presence of potassium ions.

Additionally a fluorophore was prepared based on a tri (napthylmethyl oxaamide) derivative of cis-cis-1,3,5-cyclohexane and its fluorescence characteristics assessed. A reduction in fluorescence intensity was observed with increasing concentrations of calcium and sodium ions.

Abbreviations.

Ac	acetyl.
Bu	butyl.
^{i}Bu	iso-butyl.
^{t}Bu	tert-butyl.
DCM	dichloromethane.
DMF	dimethyl formamide.
DMSO	dimethyl sulfoxide.
Et	ethyl.
ESMS	electrospray mass spectrum.
fig.	figure.
h	hour(s).
IR	infra-red.
K_S	stability constant.
Me	methyl.
min	minute(s).
NMR	nuclear magnetic resonance.
Np	naphthyl.
Ph	phenyl.
THF	tetrahydrofuran
tosic	p-toluene sulfonic.
Ts	p-toluene sulfonyl.
UV	ultra-violet.

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CHAPTER 1.

INTRODUCTION.

1. Introduction

1.1 Supramolecular and Host-Guest Chemistry.

Supramolecular chemistry[1] may be defined as the chemistry resulting from the association of two or more chemical species, held together by intermolecular forces to form a new complex or adduct. These intermolecular forces include hydrogen-bonding, ion pairing, van der Waal's forces, π-acid to π-base interactions and metal-ligand bonding.

Host-guest chemistry is a more specific form of supramolecular chemistry. A highly structured molecular complex is composed of at least one host and one guest.[2] The host and guest have a relationship involving a complementary stereoelectronic arrangement of binding sites. The host is defined as an organic molecule or ion whose binding sites converge in the complex and the guest is defined as any molecule or ion whose binding sites diverge in the complex. The association of host and guest leads to a host-guest complex (Fig. 1.01).

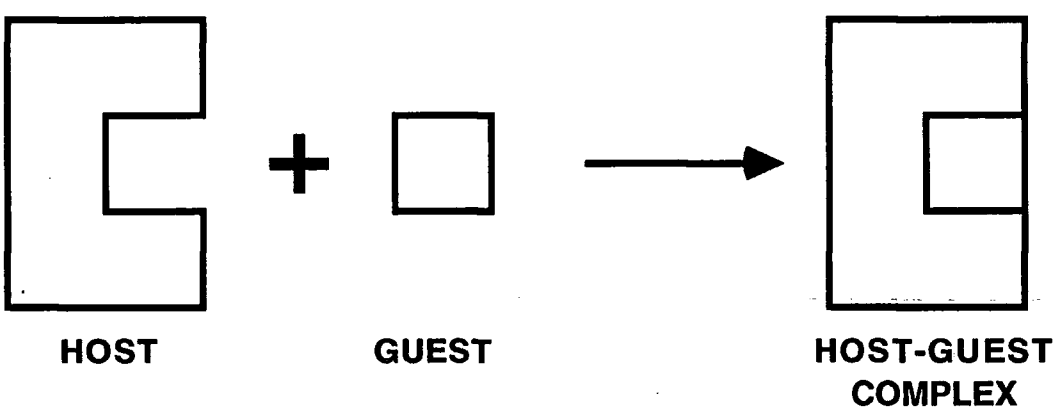


Figure 1.01 Formation of a Host-Guest Complex.

1.2. Molecular Recognition.

An intrinsic requirement of a host is that it should not only exhibit binding of the guest but also do so selectively. For this to be achieved the host needs a degree of molecular recognition.

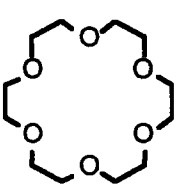
Molecular recognition has been defined as a process involving both binding and selection of a guest by a given host[3]. The binding energy of a single contact between guest and host is at most a few kilojoules per mole. Several such contacts are required for the formation of a host-guest complex. For binding to occur a complementarity needs to exist between host and guest so that these contacts can occur. This complementarity between the host and guest may exist in two forms:

(a) Steric Complimentarity: where the shape and size of the host's cavity fits that of the guest.

(b) Binding Site Complimentarity: where the number, spatial arrangement and chemical nature of the host's binding sites matches those of the guest.

A good complementarity will result in recognition of a specific guest by the host and lead to selective complexation.

Hosts that possess a rigid structure, such as spherands, calixarenes and some small cryptands, have a well defined cavity that does not alter significantly on binding and therefore they exhibit size selectivity[4]. The host's readiness for complexation is known as preorganisation. A difficulty inherent in such rigid structures is that while they may posses a well defined structure they have poor complexation kinetics. Ideally a host will have good structural preorganisation but also sufficient flexibility of structure to facilitate rapid complexation.



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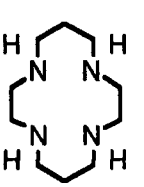

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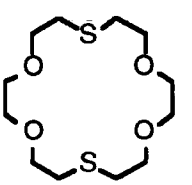


3.

The nature and number of the host's donor atoms is also critical in determining the selectivity of the host. Oxygen atoms favour binding of alkali and alkaline earth metal cations as demonstrated by the potassium selectivity of 18 crown 6 (**1**)[5,6]. Nitrogen donor atoms favour transition metals, for example, the aza crown 14-N-4 (**2**) complexes strongly to nickel (II), copper (II) and cobalt (II), amongst other cations[7]. Silver, lead and mercury are preferentially bound by sulfur donors, dithia

18 crown 6 (**3**) has no affinity for potassium but binds silver (I) strongly[8]. The number of donors is also important as different guests favour different co-ordination numbers (see section 1.4.2).

A host that shows some selective binding of free ions from a solution is known as an ionophore. A wide variety of synthetic ionophore classes have been developed since Pederson accidentally synthesized the first crown ethers in 1962[9].

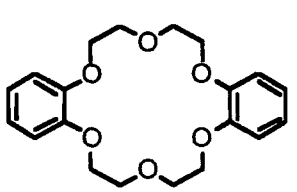
1.3 Ionophore Hosts for Cations.

This thesis details the synthesis and behaviour of ionophores which are to be used as sensors to determine metal cation concentrations. Not all ionophore types are suitable for use in sensors as they may not be sufficiently selective resulting in inaccurate measurements, or they may have slow complexation kinetics and so do not give an accurate measurement within a reasonable time scale. The method by which an ionophore is to be used as a sensor also determines some of the properties required. (A more detailed discussion of the methods used to study complexation kinetics and complex stabilities and measure ion concentrations is given in section 1.5).

1.3.1 Crown ethers.

Supramolecular chemistry is considered to have originated with the discovery of crown ethers in 1962[9]. Whilst Pederson was trying to synthesize bis[2-(o-hydroxyphenoxy) ethyl] ether from 2-(o-hydroxyphenoxy) tetrahydropyran using vanadium as a catalyst he isolated a small amount of a white crystalline product.

Later 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 (**4**).



4.

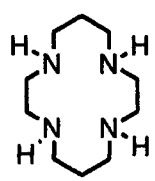
This compound was found to be only sparingly soluble in protic solvents. However upon addition of sodium the solubility of the crown was found to increase

dramatically. Pederson proposed that an electrostatic interaction between the positively charged sodium cation and the negatively charged dipole on the six oxygen atoms was causing the cation to enter the cavity of the crown and so increase the solubility.

Following this observation, Pederson synthesized a wide range of macrocyclic polyethers containing four to ten oxygen atoms and demonstrated that the selectivity for a particular cation was controlled by the size of the macrocycle's ring[10]. For example, 18-crown-6 exhibits potassium selectivity over other ions[5,11] whereas smaller crowns show sodium[12,13] and lithium selectivity[14-24]. This is an over-simplification and a more detailed discussion of the factors affecting ionophore selectivity is given in section 1.4.

Since their initial discovery many hundreds of papers detailing crown ethers and their analogues have been published placing them amongst the most important and well documented molecules in supramolecular chemistry. Crown ethers have been prepared with varying chain length between adjacent oxygens, with alkyl and aryl substituents and with varying numbers of ethereal oxygens[25-35].

1.3.2 Crown ethers with heteroatoms other than oxygen.



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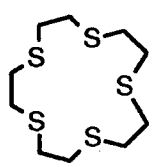
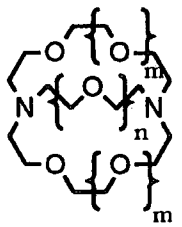


5.

In an effort to vary the binding properties of crown ethers a wide variety have been synthesized with heteroatoms (other than oxygen) partly or fully replacing the oxygens[36-46]. Principally nitrogen[36-42], for example the aza crown (**2**), and sulfur[43-46], for example the thia crown (**5**), have been used, with phosphorus in a limited number of cases[47,48]. The nature, size and number of the donor atoms affect the selectivities of complexation of the macrocycles (see section 1.4).

1.3.3 Cryptands.



6.

n = 1, m = 0, [1,1,1] cryptand
n = 1, m = 1, [2,2,1] cryptand
n = 2, m = 1, [2,2,2] cryptand.

Cryptands (**6**) are macrobicyclic ligands which were first designed and synthesized by Lehn and co-workers in order to improve upon the selectivities offered by crown ethers[49-51] . The basic structure consists of three polyether chains, which maybe of variable or similar length, linking together two bridgehead nitrogen atoms to produce a "3D" cavity lined with oxygen and nitrogen donors.

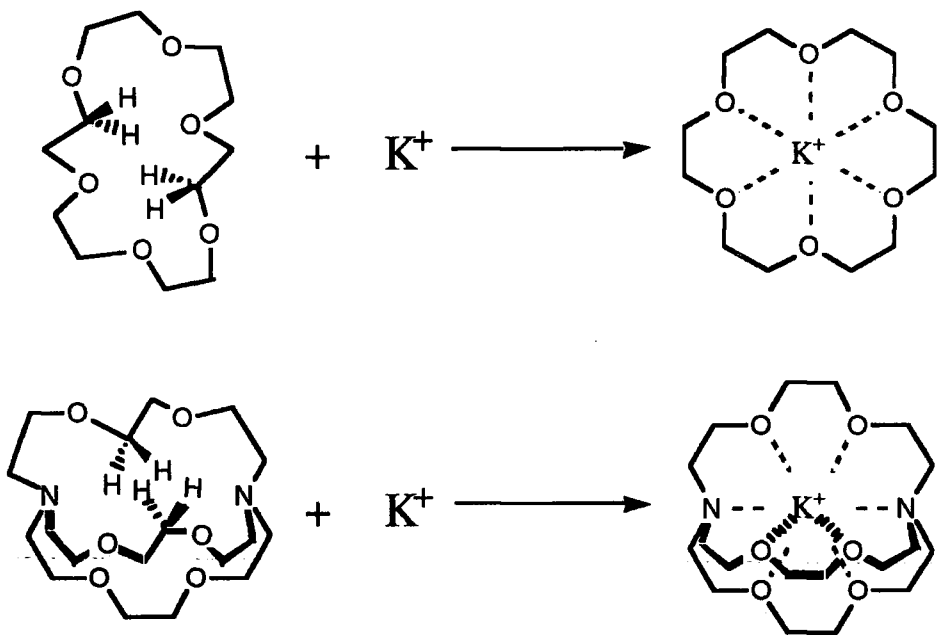
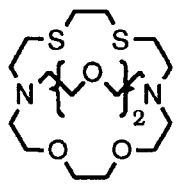


Figure 1.02 Illustration of the relatively poorly defined nature of the cavity in both crowns and cryptands prior to complexation.

Cryptands have an enhanced selectivity and complex stability over comparably sized macrocyclic analogues, for example the potassium ion [2,2,2] cryptate is 10^4 times more stable in methanol than the potassium ion complex of 18-crown-6[52] . The enhanced stability is enthalpic in origin and due to the cryptate effect (see section 1.4.5). However, even in cryptands the cavity is still relatively poorly defined prior to complexation (Fig. 1.02).

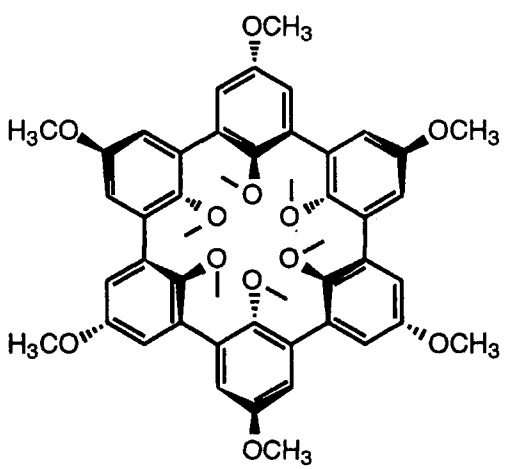
Although cryptands have been shown to exhibit high levels of selectivity they are not generally usable as ionophores in ion selective membranes or membrane transport since their complex stabilities are so large that ions are not decomplexed at a sufficient rate for acceptable ion transport rates. Furthermore they are sensitive to pH, being strongly basic.



7.

Cryptands, like crown ethers, may also contain non-oxygen heteroatoms designed to alter the selectivity for different guests, for example the dithia derivative (**7**). Similarly to crown ethers, alkyl or aromatic groups have been incorporated to alter both the stereochemistry and lipophilicity of the cryptand[53-56].

1.3.4. Spherands.



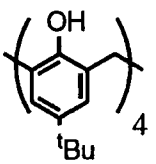
8.

Unlike cryptands and crown ethers, Cram designed spherands (**8**) to possess a well defined cavity which is occupied upon complexation. Oxygen lone pairs are focussed into the centre of the cavity in an octahedral arrangement giving 12 pairs of electrons lining the inside[57-59].

The cavity rigidity is maintained by the benzene rings and the spatial requirements of the methoxy groups. Very little rotation can occur around the aryl-aryl bond and the methyl groups prevent rotation around the aryl-oxygen bonds. Hence,

little reorganisation is required prior to complexation. These molecules exhibit some of the highest stability constants known for alkali and alkaline earth metals. However, the use of these ligands is limited as they exhibit very slow kinetics of complexation. In fact, the complexation kinetics can be so slow it is often difficult to measure the stability constants of spherands, the slow dissociation constants preventing the process reaching equilibrium.

1.3.5 Calixarenes.



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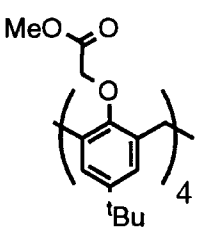

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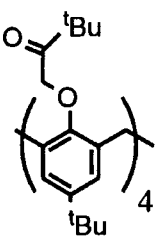

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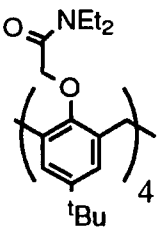
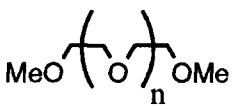


12.

Gutsche introduced the term calixarenes to describe a homologous series of macrocyclic phenol formaldehyde condensates typically involving four to six aryl rings. The term's origin lies in the chalice like appearance of the smallest member of the series[60] . The simplest calixarenes (**9**) have a central cavity around which several hydroxyl groups are arranged. However, the hydroxyl groups have been functionalised by addition of several functionalities, including esters[61-67] (**10**), ketones[67-69] (**11**) and amides[70] (**12**), to try to adjust the preference of the host for various metal cations. The size of the cavity also has a bearing on the selectivity of the calixarene. Typically calix[4]arenes demonstrate selectivity for sodium ions over potassium and other metal ions. Where as calix[6]arenes show the opposite selectivity, favouring potassium cations over sodium cations.

1.3.6. Podands.



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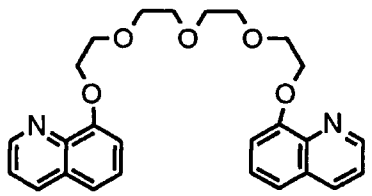
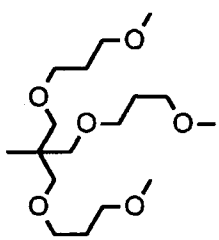


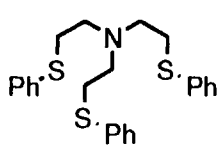
14.

Podands, in contrast to other ionophores, lack any ring or bridge systems. This type of system has been known for a long time in the guise of polyethylene glycols (**13**) (n=3 to 8). Most work on podands has been stimulated by studies on their macrocyclic analogues. Podands with two arms, such as "Kryptofix"[71] (**14**), mimic crown ethers[71-76] . The rigid terminal groups of Kryptofix function as anchorage points with locally fixed donors onto which the cation can take hold. Three or four armed podands form analogues of cryptands[77-81], eg. podand (**15**)[78].



15.

Podands do not generally show any significant preorganisation because of the conformational freedom inherent in their acyclic component chains[58]. This freedom disfavours binding both entropically and enthalpically because effective binding conformations are few in number and high in energy. However, this freedom does allow fast complexation kinetics and thus podands are ideal for use in sensors if selectivity can be achieved.



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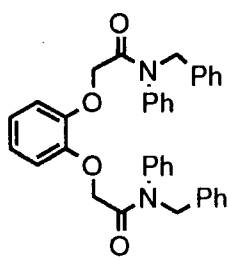
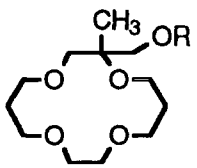


17.

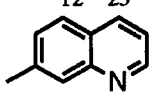
Many different functionalities have been incorporated into podands with the aim of achieving selectivity. For example, ethers[71,78,82-87], thioethers[88-90], amides [77,79,80,91-95], and esters[80,96] have all been included in podands depending on the

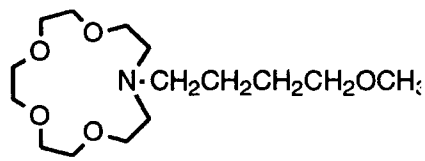
selectivity required. As with other ionophores the type and number of donors determines selectivity. Soft donor atoms favour soft Lewis acids, for example podand (**16**) binds silver preferentially over mercury, lead and other metal cations[88], and hard donors favour hard Lewis acids, the amide donor groups of podand (**17**) favouring sodium over other softer metal cations[77].

1.3.7. Lariat ethers.



18. R= $CH_2CH_2OCH_3$
19. R=$C_{12}H_{25}$
20.





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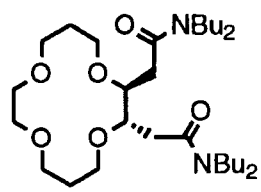


22.

In an effort to enhance the selectivity of simple macrocycles, whilst maintaining their rapid reaction kinetics, sidearms were attached[97-104]. A monocyclic ligand possessing pivoting ligating side-arms should offer both rapid exchange kinetics and the high selectivity and stability associated with the bicyclic equivalent. The side-arm also has the ability to prevent the formation of 2:1 complexes by blocking the bound guest from another host.

The 14-crown-4 macrocycles (**18-20**) prepared by Okahara demonstrated that the electron donating side chains attached to the carbon increased the lithium selectivity and the transport of the cation across a membrane[97]. Electron donating groups have also been connected via a nitrogen atom[98,99], for example the aza-15-crown-5 containing an ethereal oxygen side-arm (**21**) synthesized by Gokel and co-workers[99].

This technique of incorporating sidearms into simple macrocycles has led to the creation of highly selective ionophores which still possess rapid complexation kinetics typified by the 14-crown-4 (**22**) developed by Parker and co-workers[102,103]. This lariat ether has a selectivity for lithium over sodium of 1000 to 1.

1.4. Factors Affecting the Selectivity of Binding in Ionophores.

1.4.1. Thermodynamic parameters of complexation.

The binding of an ion to ionophore can be thought of as an electrostatic interaction and may be represented by the equilibrium shown in equation (1.1):-

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

where M^{n+} = metal cation
L = ligand
(s) = solvent
ML^{n+} = the complex

The equilibrium stability constant, K_S, can be defined as :-

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

and this is related to the free energy of change associated with complexation, ΔG°, by :-

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

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

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

From these equations it can be seen that a stable complex results from $\Delta G^\circ < 0$ and this can result from four possible situations :-

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 examples the complexation is enthalpy driven, whereas in the second two examples, (c) and (d), the complexation is entropy driven.

Many factors contribute to the complexation enthalpy [105]:-

i. part / complete cation de-solvation.

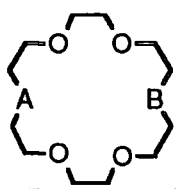
ii. change of ligand solvation.
iii. interaction between the cation and some or all of the host's donors.
iv. repulsion between (neighbouring) donor atoms.
v. influence of complex formation on solvent molecules outside the first solvation sphere.
vi. steric deformation of the host due to the cation.

The following contribute to the complexation entropy :-
i. solvation entropy of the cation.
ii. solvation entropy of the host.
iii. changes in the ligand's internal entropy due to orientation, rigidification and conformational changes upon binding.
iv. variation of the number of particles during reaction.
v. changes in translational entropy.

Many aspects of an ionophore's structure affect these factors and these will be discussed in the following sections.

1.4.2. The nature and number of ionophore donor atoms.

Alkali and alkaline earth metal cations can be classified as hard Lewis acids and interact most favourably with hard Lewis bases, such as oxygen.

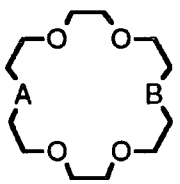


Ligand		Cation			
A	B	Na^+	K^+	Ag^+	Pb^{2+}
O	O	4.38	6.10	4.58	6.99
NH	O	2.69	3.90	-	9.11
NH	NH	1.0	2.04	10.02	9.48
S	S	-	1.15	10.33	4.76

Table 1.01 Stability constants for complexes with varying donor groups of metal cations, in methanol.

Replacement of the oxygen donors in 18-crown-6 with nitrogen and thio-ether donors leads to a large reduction of the stability constants for the potassium and sodium

complexes[106-109] (Table 1.01). This is partly due to the less favourable enthalpic changes upon complexation, (Table 1.02), indicating that nitrogen and sulfur interact poorly with the hard potassium and sodium cations[110-113]. Soft cations, such as silver and lead, favour binding with the softer amino and thio donors.



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

Table 1.02 Effects of varying donor groups in 18-crown-6 upon enthalpy of complexation with potassium in methanol at 25 °C.

The ability of the binding site to interact with the coordinating cation is dependent upon the electron density of the donor atom. The replacement of an ethylene

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	>5.50	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	4.04	-	3.55	4.28

Table 1.03 Stability constants of metal ion complexes with 18-crown-6 (18C6), benzo 18-crown-6 (B18C6) and dibenzo 18-crown-6 ($B_2$18C6)in methanol[113].

group by a benzo group in 18-crown-6 results in a delocalisation of electron density at the adjacent oxygen donors and a corresponding reduction in the stability of the complex formed[113].

Sodium does not follow this trend as it is too small for an optimal fit in the cavity of 18-crown-6. The slight reduction in cavity size, resulting from the inclusion of the benzo groups, allows sodium to interact more favourably with the donors causing an increase in complex stability.

Functional groups act similarly to individual donor atoms, the higher the electron density of the functional group the better it is at stabilising complexes with

small cations. For example, studies of tripodal oxa-amides and tripodal oxa-esters have shown that the higher dipole moment amides are more selective for the high charge density sodium ion than are the esters[80]. Similarly with lariat 14-crown-4 an amide pendent arm donor binds the small lithium ion more selectively than a similar ester function[102].

The number of binding sites in an ionophore needs to match the co-ordination number of the cation in order to replace all the bound solvent molecules and so optimise binding. A clear illustration of the effect of decreasing the number of donor atoms whilst maintaining the structure of the ionophore is shown by the 10^5 reduction in complex stability seen when a pair of oxygens in [2,2,2] is replaced with carbon atoms[51] (Table 1.04).

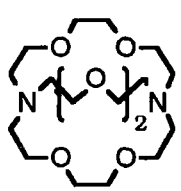
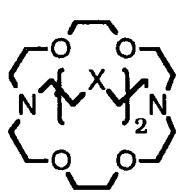
Ligand	Na^+	K^+	Rb^+	Cs^+
	7.9	10.4	9.0	4.4
 X=CH_2	3.5	5.2	3.4	2.7

Table 1.04 Stability constants (log K_S) of [2,2,2] and related bicyclic ligand in methanol at 25 °C.

Small metal ions of high charge are more sensitive to variations in binding site numbers than mono-valent cations. Notably, Mg^{2+}, Be^{3+}, Al^{3+}, and Ga^{3+}, which have large solvation numbers and high solvation energies, display a reluctance to form complexes with macrocycles compared with larger ions of lower charge density. This may be attributed to these small ions' high nuclear charge requiring anionic donors[114].

1.4.3 The influence of cation and ligand solvation upon complexation.

Ion solvation:-

The solvation of cations is very important in determining complex stability and kinetics. The solvation energies involved are very large, several hundred to several thousand kilojoules per mole, and strongly dependent upon the ion's size and charge. Even though the variations in ionic solvation energies between different solvents is small (approx 60 kJ mol^{-1}) when compared to absolute values, they are sufficient to exert a considerable influence upon complexation strengths.

Ligand solvation:-

When compared to cation solvation ligand solvation is small, but it still exerts a significant influence on the strength of complexation. As with cations the extent of ligand solvation is solvent dependent. The complexation process results in the displacement of solvent molecules from the ligand and this is energetically "expensive". An unfavourable enthalpy term results which is only partially compensated for by a favourable entropy term.

The enthalpy term is highly solvent dependent, the higher the dielectric constant the solvent possesses the greater the energy required on desolvation[104,115]. Hence, the enthalpies of complexation are much lower when recorded in water than in less polar solvents such as methanol. The enthalpies of complexation of potassium and sodium with dibenzo 18-crown-6 are much lower when recorded in water than in methanol.

solvent	Na^+	K^+
water	1.08[a]	1.6[a]
methanol	4.36[b]	5.00[b]

[a] ref 115, [b] ref 104.

Table 1.05 Complexation enthalpies of dibenzo 18-crown-6 with sodium and potassium in water and methanol.

1.4.4 The anion effect.

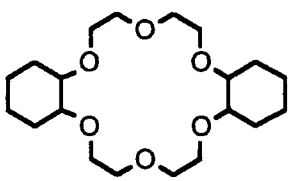
The nature of the anion and the solvent controls the extent to which anions influence the complexation process. The cation-anion association is determined by the

size, shape and polarizability of the anion. Small anions tend to associate more strongly with the cation than larger anions as a result of the shorter complex-anion distances. In high polarity solvents both the anion and complex are highly solvated and little interaction occurs between the two, but in low polarity solvents solvation is poor and the ion-pairing and/or aggregation can occur. Cation-anion associations lead to the formation of a new complex, with a new stability constant (equation 1.5). For example, the stability of the 1:1 sodium complex of benzo 15-crown-5 in methanol decreases as the counter-ion is changed from 2, 4, 6-trinitrophenolate (log K = 5.49) to 2 ,4-dinitrophenolate (log K = 4.36) to 2-nitrophenolate (log K = 3.52)[116].

$$ML + X \rightleftharpoons MLX \qquad (1.5).$$

ML = metal-ligand complex.
X = counter-ion.
MLX = association complex.

The counter ion can also influence the solvation properties of the complex. The solubility of dicyclohexano 18-crown-6 (**23**) in various solvents decreases when the counter-ion is changed from Cl^- to Br^- to I^- [5].

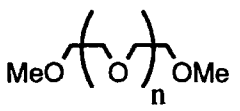


23.

1.4.5 Structural effects in podands.

There are many effects in podand structures, many of which conflict, and it is very difficult to predict what effect a structural change will have. The dominant effect is usually the nature and number of donors. However, the structure on which these groups are arranged is also important.

Vögtle showed that rigid terminal groups in simple oligoethers (**14**) enhanced the stability of their alkali and alkaline earth cation complexes when compared to methoxy groups (**13**)[71]. The terminal groups are thought to act as anchor points for initial binding.



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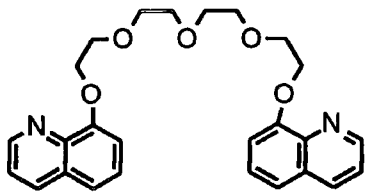
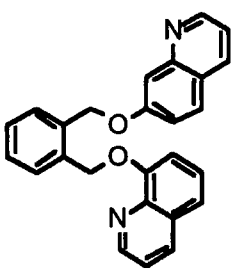


14.

A rigid spine may also help selectivity as it limits the number of conformations available to the podand and reduces the unfavourable enthalpy and entropy terms inherent in flexible ligands (see Chapter 2 for a more detailed discussion). However, an increase in spine rigidity can also reduce selectivity by limiting the ability of the podand to interact with the cation. The increase in spine rigidity of podand (**24**) when compared to podand (**25**) leads to a reduction in selectivity of lithium over sodium[117].



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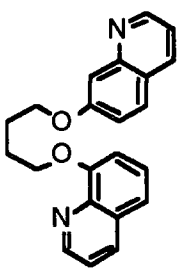

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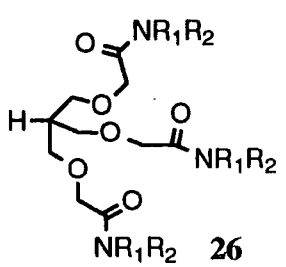
The number of arms a podand possesses also affects their binding and selectivity. Tripodal systems, such as (**26**), allow the binding groups to arrange around the cation forming a cavity[92]. This cannot occur as easily in linear podands, the podand requiring more energy to arrange the donor groups in a binding orientation. Four armed podands (**27**) generally bind less strongly than their three armed analogues (**28**) as the arms cause more severe steric hindrance on complexation[118].



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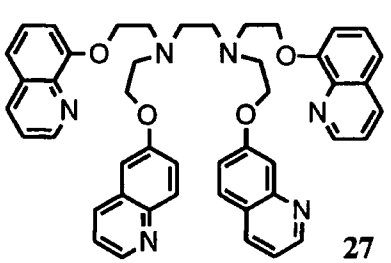

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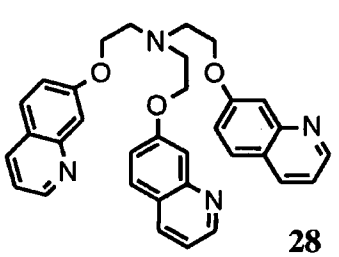


28

R_1 = Me, $R_2 = C_7H_{15}$.

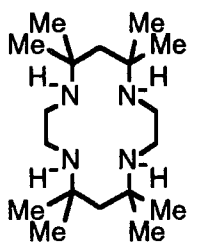
1.4.6. The macrocyclic and chelate effect

The stability of metal cation - host complexes increases in the order:-

monodentate < acyclic < cyclic < bicyclic.

These increases in stability have been explained in terms of the chelate effect (monodentate to acyclic)[119], macrocyclic effect and the cryptate effect.

The increase in stability constant of the complex when an acyclic ligand is replaced by a cyclic ligand was first noted by Cabbiness and Margerum[120] and termed the macrocyclic effect. They noticed the stability constant of the copper (II) complex of the cyclic tetraaza ligand (**29**) was 10^4 greater than that of the complex with the non-cyclic ligand (**30**) (Table 1.06).



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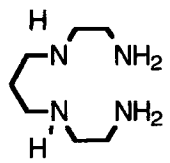

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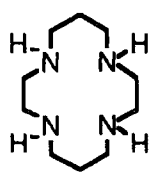
			Macrocyclic Effect
Log Ks	22.2	15.3	Δ=6.9
ΔH° / kJ mol^{-1}	-130	-70.3	Δ=-59.7
ΔS° / kJ mol^{-1}	-8.4	57.7	Δ=-66.1

Table 1.06 Influence of macrocyclic effect on stabilities, in water (298 K).

Further studies to ascertain the origin of the enhanced stability of the macrocycle were carried out. The thermodynamic study of the nickel (II) complex of 14-N-4 (**2**) and the non-cyclic tetra amine (**30**) showed the effect to be enthalpic in nature[121]. In fact entropy favours the binding of the acyclic ligand but the macrocycle's lower degree of solvation prior to complexation produces a controlling enthalpic effect.



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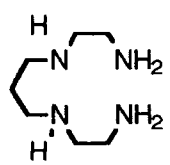

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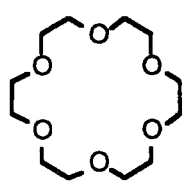
However, further studies of tetra amine - copper (II) complexes indicated that ring size played an important part in determining the source of the macrocycle's increased stabilities[122]. For small ring sizes, where a large conformational change is required to accommodate the ion, entropic factors dominate. Transition metal ions place a high degree of stereo chemical demands on their binding ligands. The stereo-chemical factors associated with this type of ligand make it difficult to determine if the stability enhancements are due to the macrocyclic effect, the differences between cyclic and acyclic ligands not allowing reliable comparisons.

Studies of alkali and alkaline earth cation complexes are preferable because they impose less demanding stereo chemical constraints. Haymore et al[123] studied the complexation thermodynamics of 18-crown-6 (**1**) and its acyclic analogue, the polyether pentaglyme, (**31**) with a range of cations (Table 1.07). The results indicate that the major contribution to enhanced stability is enthalpic, although for potassium and barium entropy also favours macrocyclic complexation.



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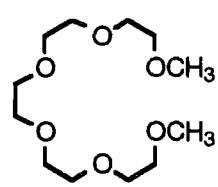
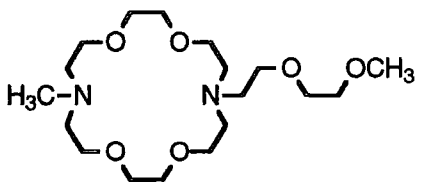


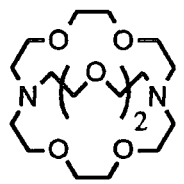
31

cation	ligand	Log K_s	ΔH° (kJ mol^{-1})	ΔS° (kJ mol^{-1})
Na^+	**1**	4.36	-35.0	-33.8
	31	1.44	-16.8	-28.9
Macrocyclic effect		Δ=2.92	Δ=-18.2	Δ=-4.9
K^+	**1**	6.06	-56.2	-72.1
	31	2.1	-36.4	-81.4
Macrocyclic effect		Δ=4.0	Δ=-19.7	Δ=9.3
Ba^{2+}	**1**	7.04	-43.6	-11.2
	31	2.3	-23.2	-33.7
Macrocyclic effect		Δ=4.7	Δ=-20.4	Δ=22.5

Table 1.07 Influence of macrocyclic effect upon the stabilities, enthalpies and entropies of complexation of 18-crown-6 in comparison with pentaglyme (methanol at 298 K)

The cryptate effect[50] is similar to the macrocyclic effect, with a rise in complex stabilities when monocyclic and bicyclic analogues are compared. When the alkali and alkaline earth cation complexes of macrocycle (**32**) and [2,2,2] cryptand (**33**) are compared an increase in stability of between 10^4 and 10^5 is observed (Table 1.08). Thermodynamic studies have shown this to be predominantly an enthalpy effect. The cryptand has lower solvation before binding and requires less energy to reorganise into a conformation suitable for binding.





Cation	**29**	**30**
Na+	3.26	7.21
K+	4.38	9.75

Table 1.08 Stability constant values in 95:5 methanol : water for sodium and potassium complexes of monocyclic and bicyclic ligands at 25 °C.

1.4.7 The effect of macrocyclic ring size.

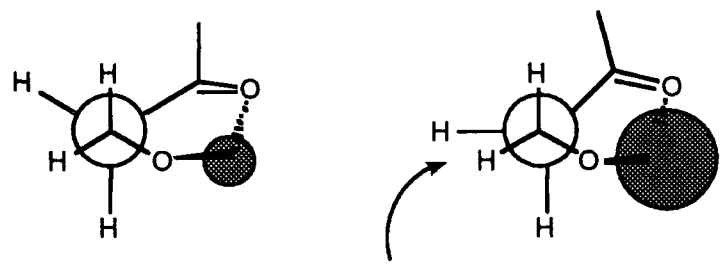
Monocyclic ionophores show peak selectivities in log K_S and the cations that form the most stable complexes have been used to estimate the cavity radii. These estimates appear to be reliable as can be seen from Table 1.09. The table shows that the cavity radii derived from CPK models for some simple crown ethers matches the cation size with maximum K_S[9,124]. However, an obvious flaw in this argument is that the variation of donor number with cavity size is not considered.

Gokel *et al*[125] examined the binding constants for a series of crown ethers with a range of cations, Na^+, K^+, NH_4^+, and Ca^{2+}, showing that K^+ binds the strongest with all crowns, and all cations exhibit their highest binding constants with 18-crown-6. Hence, it can be seen that the cavity size - cation size relationship is not of prime importance. It can be surmised that the highest binding constants are observed for 18-crown-6 due to the fact that the optimum number of donors for the cations is six.

Ligand	Cavity radius (Å) CPK model	ion of maximum log K_s 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 1.09 Cavity radii of crown ethers.

The high conformational flexibility of crown ethers results in the existence of up to four groups of complexes for a given crown ether depending on the relative size of the cation and of the formal ligand cavity. The first group is where the cation fits the ligand cavity without inducing any strain. The second is where the cation is too large for the cavity and either lies above the plane of a 1:1 complex or sits between two ligands. The third group consists of cations which are too small for the ligand cavity and the ligand either wraps around the cation, or two cations are bound simultaneously. The final group is where a solvent or, more commonly, an anion replaces one or more of the ligand's binding groups. This occurs particularly for transition metals and mixed donor ligands.



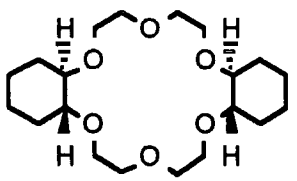
Small ions favour 6 ring chelation

Steric interactions. Large ions disfavour 6 ring chelation.

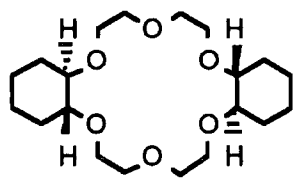
Figure 1.03 Preference of small cations to form six-membered chelate rings upon complexation.

The size of the ring does become important when the size of the chelate rings formed upon complexation are considered. Hancock[126,127] has performed molecular mechanics calculations which indicate that the chelate ring size formed upon

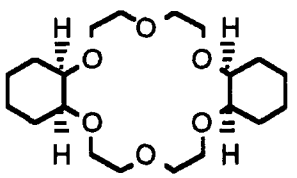
complexation plays an important part in determining the strain in the complex and thus its stability. Binding of small cations is favoured by the formation of six-membered chelate rings because the hydrogens can adopt a staggered configuration (fig. 1.03). Large cations held in six-membered chelate rings cause eclipsing strain between the hydrogens.



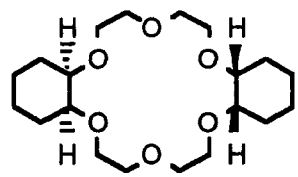
trans-syn-trans



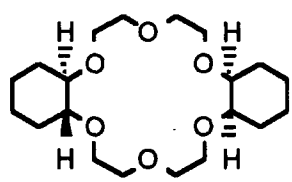
trans-anti-trans



cis-syn-cis



cis-anti-cis



trans-cis

Figure 1.04 The configurations of dicyclohexano 18-crown-6.

Complexation can also be affected by the configurations of the macrocycle prior to complexation. Stoddart et al[128] studied the different stereoisomeric variations of dicyclohexano 18-crown-6 on metal complex stabilities. Dicyclohexyl 18-crown-6 can exist in five different stable configurations and the complex stabilities of four of them and 18-crown-6 with a variety of ions are shown in Table 1.10.

Ligand	Na+	K+	Rb+	Cs+
18-crown-6	4.32	6.10	5.35	4.71
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	2.52	3.26	2.73	2.27

Table 1.10 Stability constant (log Ks) values for complexation with alkali metals in methanol at 25 °C.

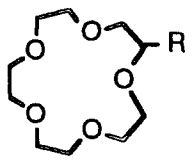
The stabilities indicate that trans isomers form weaker complexes with alkali metal cations than cis isomers. Also, the syn isomers are more stable than the anti. These differences originate in the orientation of the oxygen donors in the free ligand. The trans isomer requires greater structural reorganisation prior to complexation resulting in an unfavourable enthalpy term. X-ray crystallographic studies show that the cis-syn-cis isomer has all six oxygens directed into the cavity whereas, the trans-anti-trans isomer has only one[129].

1.4.8 The effect of ligating sidearms in lariat crown ethers.

Sidearms, containing binding functional groups, can be incorporated into crown ethers achieving greater binding strengths and selectivities provided the functional groups are situated at an appropriate distance from the metal centre to allow binding.

C-pivot Lariat ethers.

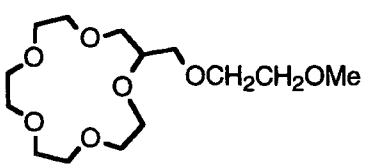
Gokel[130] synthesized and studied a 15-crown-5 based system incorporating a series of flexible binding sidearms (**34-39**) in order to determine the effect of various donor groups upon cation binding. Extraction studies were performed in a dichloromethane / water system at 25 °C using both sodium and potassium picrate salts (Table 1.11).



Ligand	Na^+	K^+
(**34**) R = H	7.6	5.7
(**35**) R = CH_2OMe	5.1	3.3
(**36**) R = $CH_2O(CH_2)_2OMe$	18.0	13.7
(**37**) R =$CH_2(OCH_2CH_2)_2OMe$	15.7	24.4
(**38**) R = $CH_2OC_6H_4OMe$ (para)	6.4	--
(**39**) R = $CH_2OC_6H_4OMe$ (ortho)	15.7	--

Table 1.11 Extraction co-efficients for a series of C-pivot lariat ethers with sodium and potassium picrates at 25 °C in dichloromethane / water.

The study showed that the position of the donor atom in the sidearm was critical. In the short chain ether donor (**35**) the oxygen is sterically prevented from binding to the cation and, also, restricts the cation's access to the ring resulting in weaker binding compared to the unsubstituted derivative (**34**). Comparison of the ortho and para methoxyphenoxymethyl side armed derivatives (**38** and **39**) further demonstrates the importance of donor orientation. The ortho derivative has a greatly enhanced extraction coefficient compared to the para derivative. CPK models of the para derivative indicated the methoxy group was unable to bind to the cation held in the ring whereas the ortho derivative was well positioned to do so.



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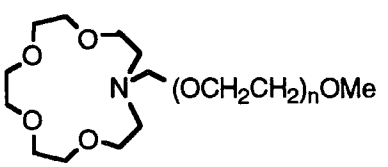
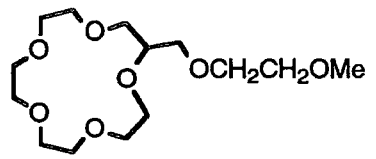


40 n=1

41 n=2

A comparison of the ^{13}C NMR relaxation times of similar C-pivot and N-pivot crown ethers (**36** and **40, 41**) showed a much smaller reduction in T_1, the relaxation time, for the N-pivot crown ether than for the C-pivot[131-133] . The relaxation time reflects the change in mobility of the ligand upon complexation. The smaller T_1 changes seen in **40** and **41** indicate a much smaller change in ring flexibility upon complexation.

The exchange rates of cation binding with N- and C- pivot crowns were also studied by ^{23}Na NMR. Gokel compared the line widths as a variant of temperature of **36** and **40** (Table 1.12).



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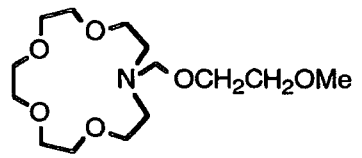
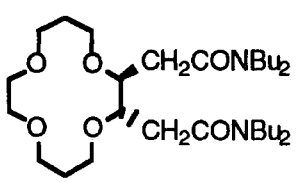


40

Temperature	Line widths ($\omega_{1/2}$, Hz)	
°C	**36**	**37**
25	96	58
0	202	87
-25	587	190
-50	~2500	490
-75	>2500	~1300

Table 1.12 ^{23}Na relaxation times of sodium complexes recorded in methanol : D_2O.

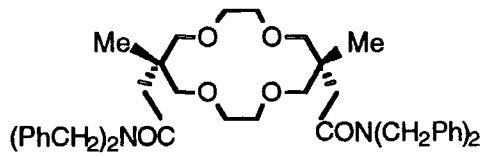
Rapid exchange is indicated by sharp lines being retained at low temperature, slow exchange by considerable line broadening. The data listed above clearly indicates that N-pivot lariats undergo faster exchange kinetics compared to C-pivot as considerably less line broadening is observed at low temperature.



22

The low flexibility of C-pivot ligands was avoided by Parker *et al*[102,103] by designing lithium selective crown ethers incorporating chiral sub-units (**22**). The chiral sub-units offer the desired stereochemistry for binding without the problem of ring flexibility as the sidearms are already orientated suitably. The cation can bind to the ring easily as the sidearms can simply flip out of the way by rotation around the CH_2-CO bond. However the position of the chiral substituents is still critical. In ligands **42** and **43** the amide side-arms are not thought to be involved in binding. The selectivities for lithium over sodium are very similar to those of the alkyl substituted 14-crown reported by Shono[134] indicating that only the ring oxygens are involved in binding. It

is thought the sidearms adopt an equatorial position in the complex and therefore are unable to become involved in binding[135].



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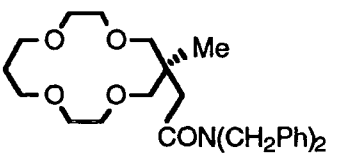


43

N-pivot lariat ethers.

Gokel[136-137] studied the stability constants with sodium in methanol of a series of 12, 15 and 18 membered ring N-pivot lariat ethers having a polyether side arm, $(CH_2CH_2O)_nCH3$. The peak binding for sodium where six oxygens are present in the ligand indicates that these ligands have the flexibility to allow them to adopt conformations where the optimum oxygen-sodium distance is achieved (Fig. 1.05).

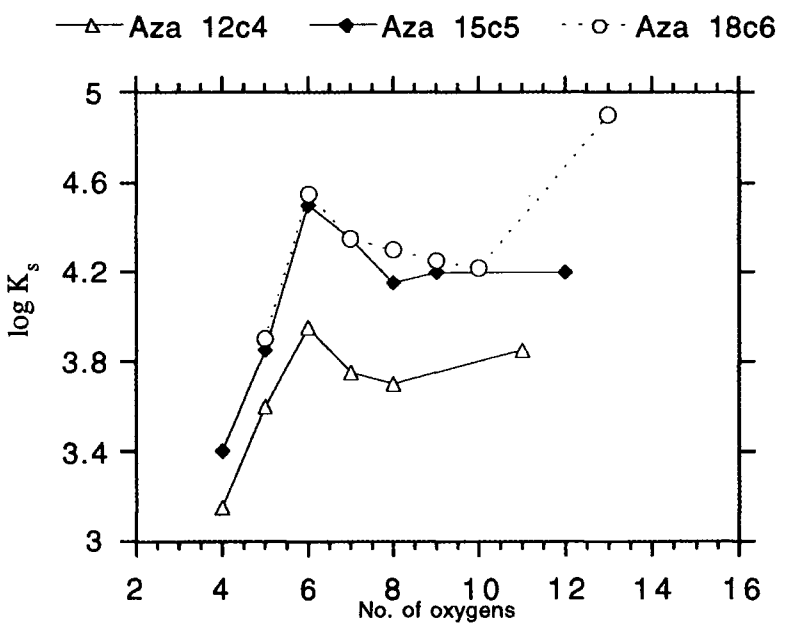
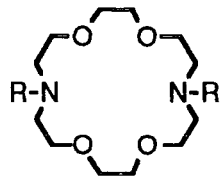


Figure 1.05 Plot of log K_S for Na^+ in MeOH at 25 °C against total number of oxygens in the ligand.

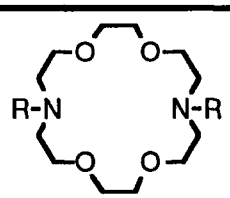
Two armed lariat systems possessing different secondary donor groups in the arms, referred to as bibrachial lariat ethers (from the Latin term bracchium meaning arm) have been investigated. Gokel[138] synthesized several such "BIBLE's" (**44-47**) and showed the side arm had a considerable beneficial effect upon binding strengths (Table 1.13). The nature of the sidearm effects the binding, as discussed earlier (see section 1.4.2). High charge dense cations, such as calcium, exhibit stronger binding to the substituent possessing ester groups.



Ligand	Log K_S Na	K	Ca
(**44**) R = H	1.5	1.8	--
(**45**) R = CH_2CH_2OMe	4.75	5.46	4.48
(**46**) R = CH_2CH_2OH	4.87	5.08	6.02
(**47**) R = CH_2CO_2Et	5.51	5.78	6.78

Table 1.13 Stability constants for a series of N-pivot BIBLE's with sodium, potassium and calcium ions in methanol at 25 °C.

The complexation entropies and enthalpies were determined for a series of N-pivot BIBLE's in complexation with sodium and potassium to ascertain the thermodynamic basis for their enhanced stability. The data in table 1.14 clearly shows the enhanced stability is enthalpic in origin.



	Cation	Log K_S	ΔH (kcal mol^{-1})	ΔS kcal mol^{-1})
(**48**) R = $(CH_2)_3$	Na^+	2.86	-2.82	1.08
	K^+	3.77	-6.28	-1.14
(**46**) R = CH_2CH_2OH	Na^+	4.83	-5.82	0.76
	K^+	5.07	-8.80	-1.89
(**47**) R = CH_2CO_2Et	Na^+	4.77	-7.24	-0.73
	K^+	5.52	-8.81	-1.28

Table 1.14 Thermodynamic parameters for the complexation of a series of N-pivot BIBLE's with sodium and potassium in methanol.

1.5 Techniques used to determine the stability and selectivity of complexation.

A wide range of techniques is available for the determination of stability and selectivity constants between cations and ligands. The following section will outline the most common techniques and discuss the limitations of each. Direct comparison of stability and selectivity constants determined by one technique cannot be made with those derived from other techniques unless the following strict criteria are adhered to :-

i) constant temperature.

ii) ensuring the solvent system is the same

iii) the same counter-ion is used (where possible).

1.5.1 ^{13}C and ^{1}H NMR

NMR experiments can be used to determine the stoichiometry of complexation, to give a semi-quantitative assessment of binding strengths and to gain insight into the dynamics of the complexation procedure. ^{13}C and ^{1}H NMR are predominantly used but the chemical shift of nuclei bound in the cavity of a ligand can be examined. However, not all ions are NMR active and those that are often pose the problem of low natural abundance and sensitivity making it difficult to acquire data.

^{13}C NMR is useful for assessing both the stoichiometry and sometimes the actual stability constants associated with complexation. The technique involves the addition of stoichiometric quantities of solid alkali or alkaline earth metal salts to a deuterated solution of ligand. Complexation is accompanied by a change in the observed chemical shift of the ligand carbons.

Where the stability constant is greater than 10^5 two discrete lines are observed for each carbon signal for intermediate stoichiometries, one line corresponding to the free ligand and the other to the bound state. The stability constant equals the rate of complexation over the rate of decomplexation and when the stability constant exceeds 10^5 the complexation kinetics are too fast to be observed by NMR (rate of complexation is approximately 125 Hz for the experiments carried out in chapter 2). An accurate judgement of stability constants of complexation exceeding 10^5 cannot be made using this method. However, the stoichiometry of complexation can be determined by measuring the mole ratio of metal to ligand at which the free ligand signals disappear.

Weaker complexation leads to time averaged signals, indicative of fast exchange kinetics on the NMR time scale. It is possible to determine the stoicheometry

of complexation by plotting the ^{13}C NMR chemical shift displacement for a particular carbon atom against the ratio of salt to ligand, the stoicheometry derived from the curve bend position (fig. 1.06). If the stoichiometry is known then the stability constant can be calculated by detailed analysis of a specific resonance[139,140]

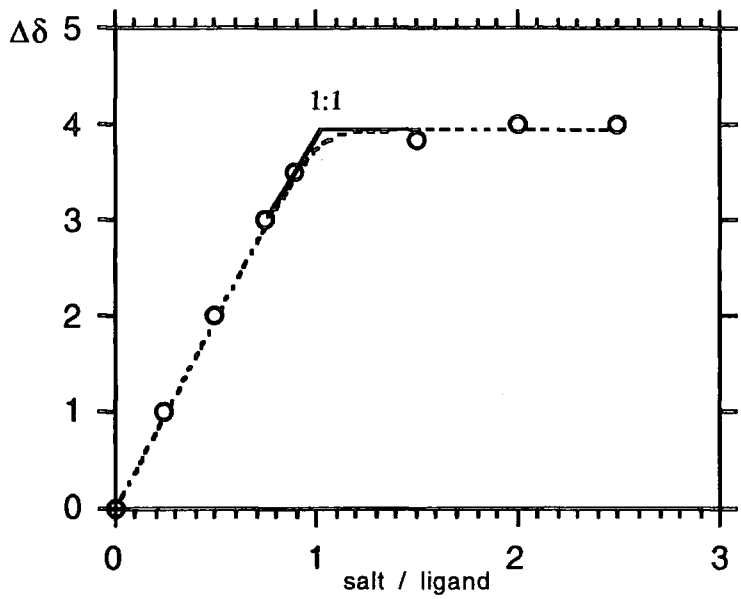


Figure 1.06 Plot of ^{13}C NMR chemical shift displacement against ratio of metal salt to ligand.

Free energies of activation can be calculated for strongly bound complexes. The technique involves recording the chemical shift difference between the free and bound ligand at various temperatures until the lines coalesce[141-143]. The dissociation rate constants at a series of temperatures are calculated by a line shape analysis. From these the free energy of activation at the coalescence temperature can be determined.

NMR can also be used to qualitatively study the dynamics of complexation by comparison of relaxation times (see Section 1.4.7).

1.5.2 Calorimetry.

Calorimetry is one of the most common techniques used to determine thermodynamic parameters[144]. Measurement of the variation of temperature during addition of metal salt solution to a ligand solution allows the determination of the enthalpy of complexation and the equilibrium constant. From these the entropy of complexation can be determined (eqn. 1.3 and 1.4).

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

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

As the titration of ligand solution against metal solution proceeds a thermogram of the reaction is plotted, and from this log K_S and ΔH° are deduced.The non-chemical effects seen prior to and after the reaction result from several factors and are compensated for in the calculation.

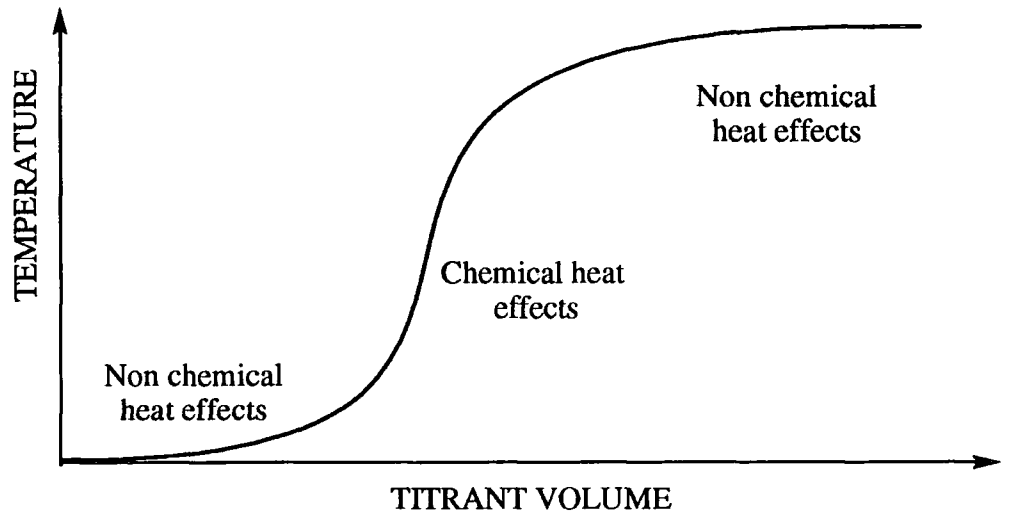


Figure 1.07 A typical thermogram

Four steps are involved in the determination of K_S by this method[145]:-

i) The total heat evolved in the reaction vessel is determined as a function of titrant volume added.

ii) The data is corrected for non-chemical heat effects.

iii) Corrections are made for the heat arising from reactions other than those of interest.

iv) The corrected value for total heat evolved is used to determine K_S.

Again the limitation of this technique is that the maximum stability constant that can be determined is 10^5. However, Buschmann[146] has developed a technique involving competitive titration that allows an indirect method of gaining semi-quantitative values for higher complexation stabilities.

1.5.3 Extraction techniques.

Extraction techniques are used widely to determine the selectivity of a ligand. The technique was originally developed by Pederson[9,10] and involves the extraction of cations from an aqueous phase into an organic phase. The counter-ion to the cation is

usually coloured, typically the picrate anion. The cation salt is dissolved in water and shaken with an organic solvent, no extraction occurs and therefore the organic layer remains colourless. When a ligand is dissolved in the organic layer extraction occurs and some of the ion pairs are transported into the organic layer colouring it. Ultra-violet spectrophotometry can then be used to determine the concentrations of the picrate ion using Beer's Law:-

$$A = \varepsilon.c.l \qquad (1.6)$$

where ε = Molar absorptivity (L cm^{-1} mol^{-1})

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

l = path length.

Beer's law is applicable to dilute solutions only.

There are many variables involved in this technique which have to be kept as constant as possible if various measurements can be compared. These variables include cation and anion concentration, temperature, volumes of aqueous and organic phases, ionic strengths, salt to ligand ratio, and even the nature of the mixing process.

A problem with extraction coefficients is that they may not accurately reflect the equilibrium binding constants. Extraction data[130] suggests (Table 1.15) that the ortho ligand (**39**) binds sodium more strongly than both the para (**38**) and the parent macrocycle (**34**). However, the stability constants determined potentiometrically indicate that **39** and the parent macrocycle (**34**) have similar stability constants.

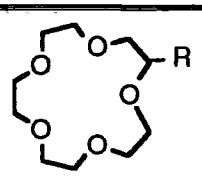
	Extraction coefficient (in CH_2Cl_2 / H_2O)	Stability constant (Log K_s) 90% MeOH
(**34**) R = H	7.6%	2.97
(**39**) R = $OCH_2C_6H_4OMe$ (ortho)	15.7%	2.97
(**38**) R = $OCH_2C_6H_4OMe$ (para)	6.4%	2.56

Table 1.15 Comparison of extraction coefficients and stability constants.

1.5.4 Fast atom bombardment mass spectometry (FAB-MS) techniques.

This technique is a quick and easy method of assessing competitive selectivities[147]. The species to be examined are placed in a glycerol matrix and bombarded by a beam of high energy, fast atoms, usually argon or xenon. FAB-MS allows the detection of molecular ions with little fragmentation as there is no heating of the sample, unlike techniques such as EI or CI, and therefore heat labile samples do not fragment. The relative abundance of the m/e peaks reflects the selectivity of the ligand.

Johnstone and Rose[148] have reported that complex formation between several macrocyclic ligands and a range of alkali metal cations could be observed. However, the data obtained from this technique are not directly comparable to selectivity coefficients determined potentiometrically since no selectivity coefficients have been determined using the glycerol / water solvent system. Therefore, it is difficult to judge the accuracy of the readings obtained from this technique

1.5.5 Potentiometric methods.

A) pH metric titration.

This method is a quick and easy route to gaining a precise value for the stability constant of a complex between basic ligands and metal cations. A great many ligands have been examined by this method and therefore a comparison can readily be made between old and new ligands.

A solution of the protonated ligand is titrated against tetramethylammonium hydroxide and the acid dissociation constants determined. Once these are known the titration is repeated in the presence of metal cations and from the resulting graph the stability constants can be determined[149-151].

Tetramethylammonium hydroxide is used as a base as it does not interact with the ligand, unlike more conventional metal bases. Metal complexation by the ligand results in exchange between the metal ion and the labile proton resulting in a decrease in the pH. The resulting titration data is processed using a least square regression analysis, for example either with Superquad[152] or SCOGS[153].

The disadvantages of this method are relatively minor. The ligand needs to be soluble in methanolic or aqueous media, possess basic sites and undergo rapid

protonation / deprotonation kinetics. The accuracy of the stability constants gained depends on having well conditioned electrodes and the liquid junction potential remaining constant throughout the determination.

B) Ion selective electrodes.

The metal ion activity, in aqueous or methanolic solution, can be determined using ion selective electrodes The ion selective electrode is either a glass or membrane electrode. The membrane electrode is made by the incorporation of an organic sensor into a polymeric matrix, this is then attached to the electrode body and a cell constructed[154] (Fig 1.08). An internal silver / silver chloride reference electrode is used for all measurements. The electrode is conditioned and then calibrated by a constant dilution technique[155]. The selectivity of the ligand incorporated in the electrode is assessed by a fixed interference method (see section 2.4 for the exact procedure).

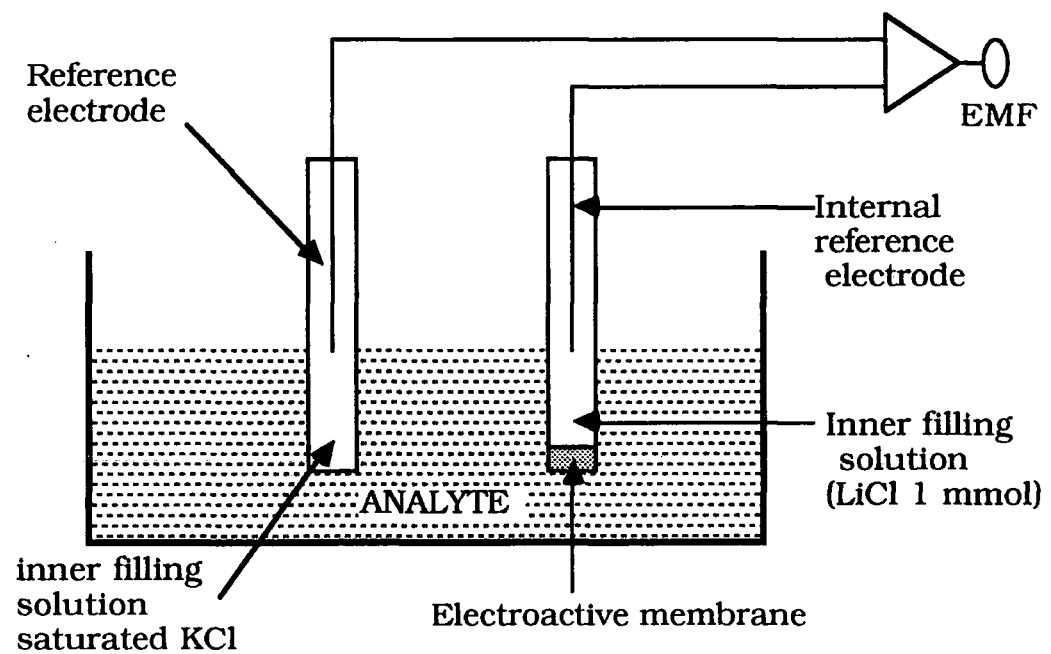


Figure 1.08 A typical cell construction.

Frensdorff[156] developed a technique which allowed ion selective electrodes to be used to determine stability constants and thermodynamic parameters of complexation. The e.m.f. response of the electrode is directly proportional to the free metal cation concentration (eqn. 1.7). The constant, k, is determined during

calibration of the electrode. Hence the free metal concentration can be determined and from this the stability constant for the complex.

$$E = E_o + k \log[M^+] \qquad (1.7)$$

where
- E = electrode potential
- E_o = standard electrode potential
- k = constant
- $[M^+]$ = concentration of free metal cations.

Enthalpy, ΔH, and entropy, ΔS, of complexation can be evaluated by determining the stability constant, K_S, at various temperatures, T, and plotting log K_S against 1/T. The gradient of the graph corresponds to $-\Delta H/T$ and the intercept $\Delta S/R$ (where R is the gas constant). As the electrode is not specific to the ion of interest, but only selective, the electrode response for these uses has to be maintained in its linear region.

The main disadvantages of ion selective electrodes stem from the specifications needed for the incorporation of the ligand into the electrode membrane. The ligand has to be lipophilic so that it remains in the membrane during use and is not leeched out by the aqueous ionic phase. It has to have fast kinetics so that the response time is quick enough to gain a value within a reasonable time scale. The ligand also has to be relatively robust so that several readings can be made and compared without the need to make a new membrane.

Several other techniques have been used to study complexation phenomenon such as u.v. spectroscopy[9,157, 158], cyclic voltammetry[159], polarography[160] and electrical conductivity[161].

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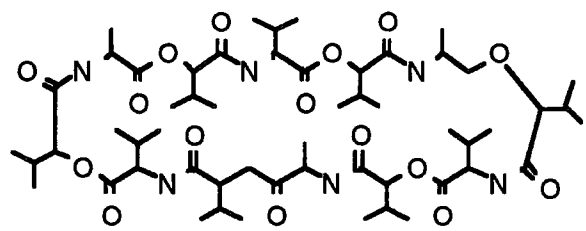
CHAPTER 2.

SYNTHESIS AND STUDY OF TRIPODAL IONOPHORES FOR GROUP I AND II METAL CATIONS.

2. Synthesis and Study of Tripodal Ionophores for Group I and II Metal Cations.

2.1 Introduction.

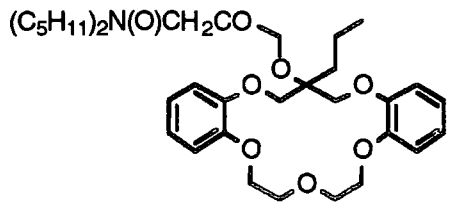
2.1.1 Developments in sodium selective ionophores for use in ion selective electrodes.



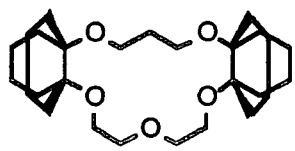
49.

Sodium and potassium ions have very important roles in the regulation of many important biological events Therefore, measurement of the concentration of these ions is useful in controlling human health conditions and diagnosing sickness. To selectively recognise potassium for medical use, naturally occurring valinomycin is more than sufficient for medical use (**49**) having a selectivity of 10^5 for potassium over sodium[1]. Sodium selective electrodes are routinely used in hospitals for clinical measurement of Na^+ concentrations. Analytical instruments can rapidly and easily measure the sodium ion concentration in human serum. Sodium ion concentrations are relatively high, at approx. 140 mM, in human serum (extracellular fluid), thus an ion selective electrode only needs a selectivity coefficient for sodium over potassium of log $K_S < -0.6$. However, for intracellular fluid the sodium concentration is much lower compared with potassium levels (Na^+ ~ 10 mM, K^+ ~ 120 mM). Ion selective electrodes require a selectivity for sodium over potassium of 4000 for a sodium determination with less than a 1% error in measurement. Hence a highly selective ionophore is required for use in the electrode.

Early work on sodium selective ionophores focussed on crown ether derivatives[2]. For example, Bartsch[3] devised a Na^+ selective ionophore based on a dibenzo-16-crown-5 (**50**) which showed a $10^{2.1}$ Na^+ / K^+ selectivity. A recent modification of the 16-crown-5 system has led to a 10^3 ration of selectivity, Suzuki[4] used two decalino blocking groups (**51**) to prevent competitive 2:1 complexation and allow the cavity size to control selectivity.

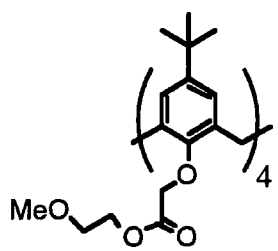


50.

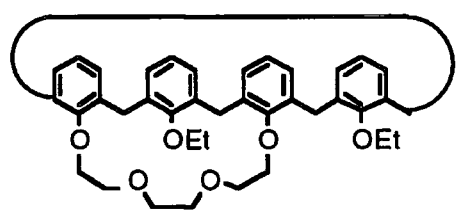


51.

Calixarenes offer an alternative cavity based system to crown ethers. Amide and ester derivatives of calixarenes have been synthesized and studied as ionophores[5]. For example, the methoxyethylester calix[4]arene (**52**) developed by McKervey et al[6] demonstrates a selectivity coefficient of $10^{2.5}$ for sodium over potassium. A remarkable selectivity has been reported by Shinkai[7] for a calix[4]arene based ionophore (**53**) which aparently showed a selectivity of $10^{5.3}$ for sodium over potassium. However, this value has been questioned by Suzuki[4] who has attempted to repeat the results obtained by Shinkai but has been unable to do so, only achieving selectivities of $10^{2.7}$. Suzuki believes the method used to determine the selectivity coefficients was flawed, because equilibrium had not been established prior to the critical measurement.

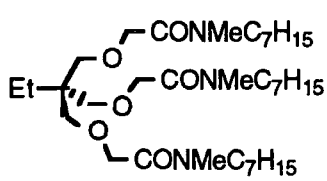


52.

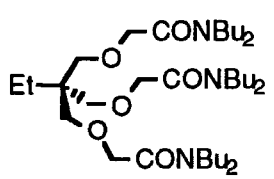


53.

Acyclic neutral ionophores have also been used in ion selective electrodes. Simon et al[8] developed a tripodal trioxaamide (**54**) which has found widespread application. However this still has insufficient sodium selectivity over potassium for intracellular use. Further studies of acyclic ionophores by Parker[9] based on the structure of (**54**) produced a slightly more sodium selective ionophore (**55**), $10^{2.64}$ Na^+ / K^+ selectivity. The study also showed that the use of amide groups in ionophores of this type give superior linearity of response, limits of detection and selectivity for sodium over potassium.



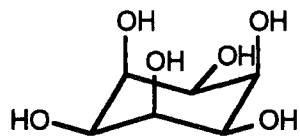
54.



55.

2.1.2 *Cation binding by cyclohexane based systems.*

Metal ions are frequently found in the same physiological media as sugars . Interest was aroused as to whether there was any association between the two. Mills[10] discovered the first reliable evidence of an association while studying the acidity of sugars by paper electrophoresis. He hoped to be able to separate sugars at a certain pH on the basis of their acidity. However, he found that even at pH 7 some sugars migrated towards the cathode. The only explanation for this behaviour was that the sugars were associated with the metal cations, the strength of the association controlling the distance they migrated. The greatest migration occurred with cis-inositol (**56**) a synthetic sugar.



56.

Cis-inositol is unique in that it has three syn-axial hydroxyls in each conformation. It seems reasonable that the syn-axial hydroxyls could bind to a metal cation. However, NMR studies[11] showed that the three syn-axial hydroxyls do bind but the major contribution to binding is through the three hydroxyls in closest proximity, the axial-equatorial-axial arrangement (fig. 2.01).

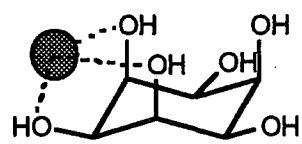


Figure 2.01 Binding mode of cis-inositol.

Hegetschweiler[12] studied the chelating properties of 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-cis-inositol (tdci). He showed that tdci favoured binding to small highly charged metal ions through the three oxygens in an axial arrangement forming a 2:1 complex, aluminium binding particulary stongly. The metal ion binds preferably to the three hard oxygen donors rather than the weaker nitrogen donor.

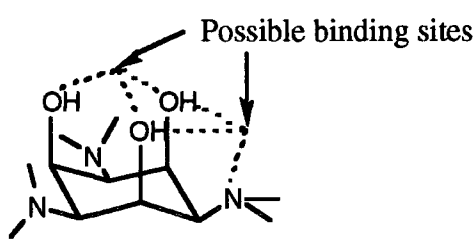
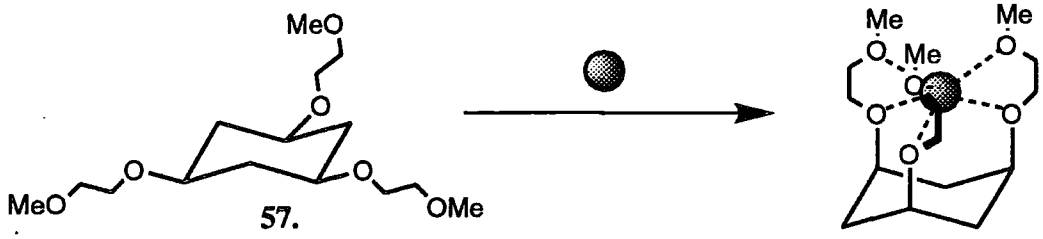


Figure 2.02 Possible binding sites of 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-cis-inositol (tdci)

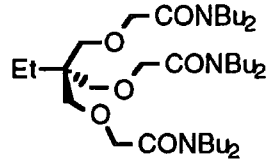
Weisman[13] synthesized the first tripodal systems based on cis, cis 1,3,5-trioxa-cyclohexane (**57**). This structure undergoes a switch in conformation on binding from a tri-equatorial to a tri-axial system in the presence of a cation (fig. 2.02). The ligand (**57**) displays some Na^+ over K^+ selectivity even with its weakly defined cavity and lack of functional group assistance in determining preference.



57.

Figure 2.02 Conformational change promoted by cation binding.

2.2 Aims and Objectives.



55.

The aim of this work was to continue the study of trioxaamide systems synthesized by Teasdale[9]. The complexation chemistry of sodium and other early group I ions indicate certain requirements for selective binding. As seen in the study by Teasdale, amide carbonyl oxygens are more suited than esters to binding the more highly charge dense early group I ions. In most cases the smaller ions favour six ring chelates compared to their five ring analogues[14]. However, their might possibly be strain in the three six ring chelates involving the ether oxygens in the 1:1 complexes of (**55**) (fig. 2.03), the C-CH_2-O bond angle becoming distorted from tetrahedral bond angles on complexation.

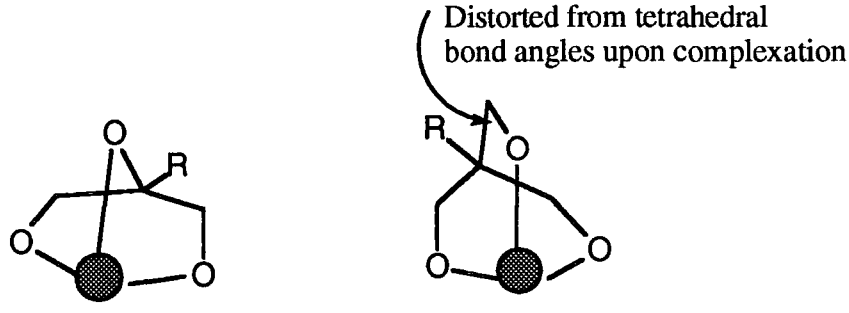
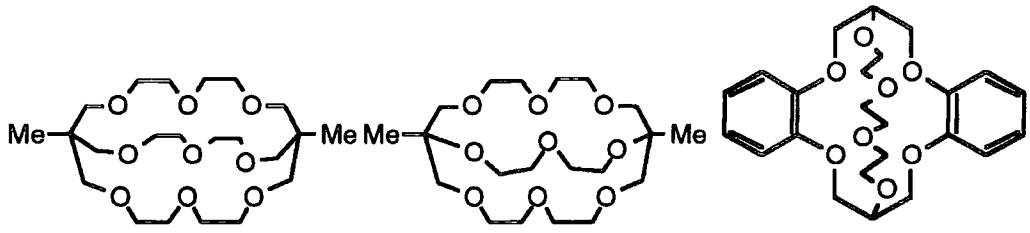


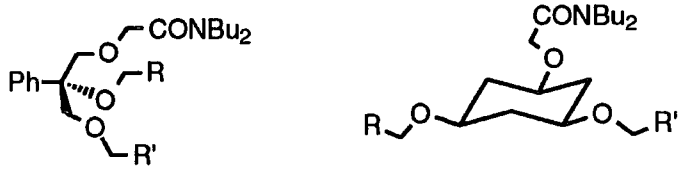
Figure 2.03 Strain induced in six membered chelate ring around three carbon bridgehead.

Also, work involving structurally analogous cryptands showed that in systems with three carbons around the bridgehead separating two successive oxygen atoms[15], eg. (**58**), sodium and potassium complex stabilities and selectivities were much lower



58. **59.** **60.**

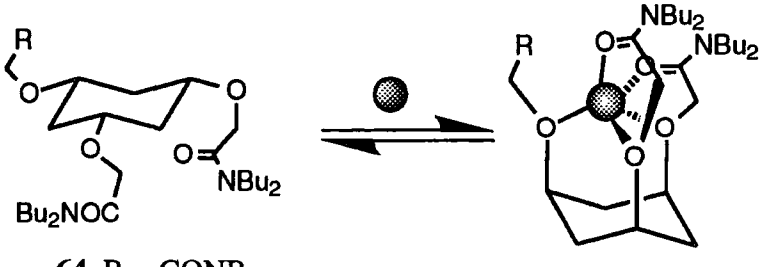
than related cryptands based on the 2-phenylglycerol sub-unit (**59** and **60**)[16,17]. Accordingly, podands (**61-63**) were synthesized from 2-phenylglycerol varying the co-ordination number from 6 to 4 by replacing the amide groups with butyl chains. It was thought that a reduction in the coordination number may disfavour ions, such as calcium, which favour coordination numbers of six and greater compared to ions, such as lithium, which favour coordination numbers of six or less.



61. R = $CONBu_2$ = R'
62. R = $CONBu_2$; R' = nPr
63. R = nPr = R'

64. R = $CONBu_2$ = R'
65. R = $CONBu_2$; R' = nPr
66. R = nPr = R'

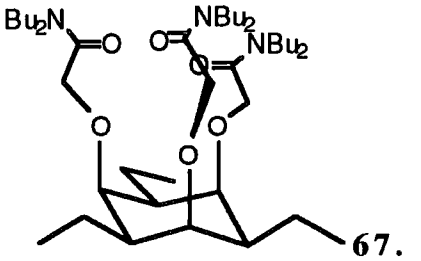
Ligands (**64-66**), based on the cis - cis trioxacyclohexane sub-unit, were also examined. The ligands will normally adopt a chair conformation with the arms in equatorial positions. Inter-conversion between conformations will be rapid (fig. 2.04) and promoted by the presence of ions. The pseudo-adamantyl array formed on binding may favour the binding of small ions since cooperative binding of the ether oxygens forms three six membered chelate rings. Again a study of the effects of varying the potential coordination number of the ligand was made.



64 R = $CONBu_2$
65 R = Pr

Figure 2.04 Pseudo-adamantyl structure adopted on binding by cyclohexane system.

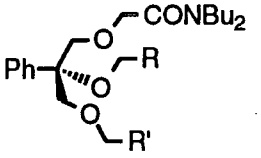
The re-organisation of ligands' **64-66** equatorial arms to an axial position is energetically expensive. Incorporation of ethyl groups on the alternate ring carbons (**67**) should force the binding arms into an axial position prior to binding and hence increase complex stability and may possibly alter the selectivity. Pre-organisation is well known to enhance the ion binding selectivities in spherands and related molecules[18].



67.

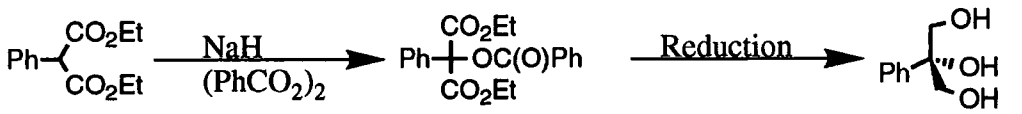
2.3 Synthesis of Ligands

2.3.1 Synthesis of 2-Phenylglycerol derivatives.



61. R = $CONBu_2$ = R'
62. R = $CONBu_2$; R' = nPr
63. R = nPr = R'

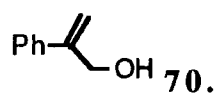
Initially the synthesis of the three derivatives was considered *via* a common intermediate, 2-phenylglycerol (**68**). The first approach to the synthesis of **68** is illustrated below (fig. 2.05). The triester (**69**) was synthesized following Lawesson's literature method[19]. The acidic methine proton was readily abstracted from phenyl diethyl malonate with sodium hydride and subsequent nucleophilic substitution with benzoyl peroxide gave the desired triester.



69. **68.**

Figure 2.05 Proposed route of 2-phenylglycerol synthesis.

Subsequent reduction of the triester proved to be difficult. When lithium aluminium hydride was used as the reducing agent small quantities of the desired product were isolated (5 to 14%). The product was believed to be strongly chelated to the aluminium salt side products as infra-red (IR) analysis of the crude product gave no indication of an ester stretch (even allowing for a shift resulting from metal chelation). Attempts to remove the product from the salts by addition of hydrochloric acid (0.1 to 2 molar) failed to increase the yield. The major product was later identified as the elimination product (**70**) formed when 2-phenylglycerol loses water. Acid was not used in subsequent product isolation steps for the reaction in an attempt to avoid this elimination problem . An alternative method to release the complexed product involved boiling the aluminium salts with a 10% solution of methanol in chloroform. This gave the highest recovered yield (14%) of the reduction methods examined but attempts to increase the yield above this proved fruitless.



70.

It was then thought that the use of lithium borohydride as the reducing agent might allow easier removal of the salts produced during the reaction. The boric acid borate ester products could be removed as the volatile trimethoxy borane after boiling the boron salts with methanol. However, only starting material was recovered, indicating that lithium borohydride was not sufficiently reactive to reduce all of the ester groups.

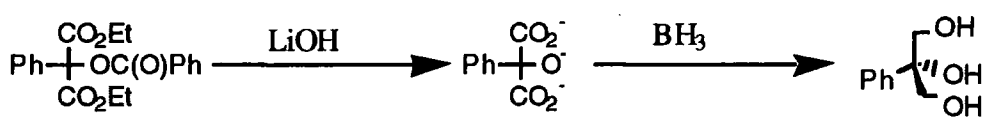


Figure 2.06 Proposed route using Yoon's reduction.

Yoon[20] has reported that carboxylate salts may be reduced rapidly by two equivalents of the borane-THF complex (fig. 2.06). The triester was hydrolysed with lithium hydroxide and after IR had indicated that complete hydrolysis had occurred, the pH was adjusted to 8 and reduction of the carboxylate salt was attempted. Again the borate ester side products were removed by entrainment with methanol. Although the product was isolated in low yields (8%), the major product was again the elimination product of 2-phenylglycerol, and after several failed attempts to improve the yield of desired product by variation of the reaction temperature (from -40 °C to 20 °C) and the pH before reduction (7 to 14), this route was abandoned.

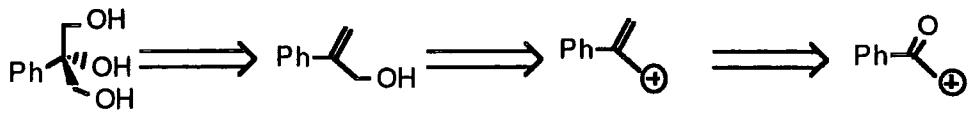


Figure 2.07 Disconnection analysis of 2-phenylglycerol.

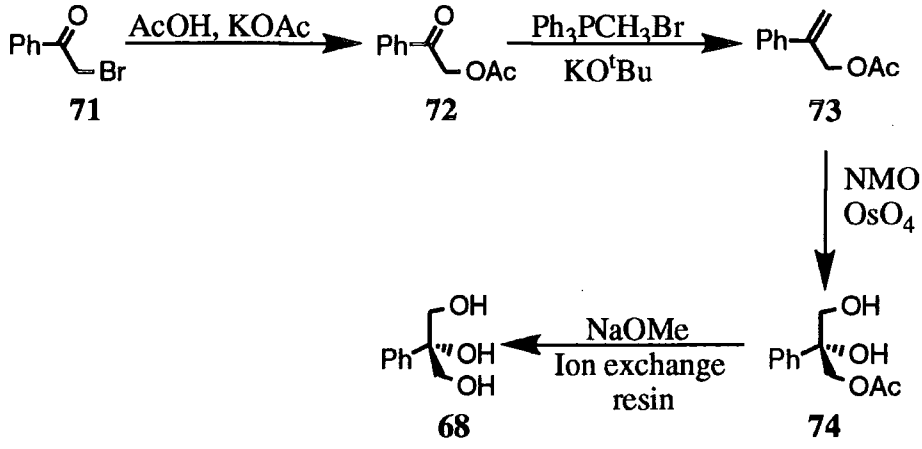


Figure 2.08 Synthetic route to 2-phenylglycerol.

Application of disconnection theory to 2-phenylglycerol indicated the product could be synthesized from the commercially available phenacyl bromide (**71**). In a modification of Parker's synthesis, 2-acetoxy acetophenone (**72**) was made by boiling phenacyl bromide in acetic acid in the presence of potassium acetate[21]. 2-Acetoxy acetophenone was reacted with the Wittig reagent methyltriphenylphosphonium bromide, with potassium tert-butoxide as the base, and readily converted to the analogous alkene, 3-acetoxy 2-phenylpropene (**73**). For a good yield to be obtained from this reaction it was found that the methyltriphenylphosphonium bromide had to be dried extensively. The Wittig reagent was first suspended in toluene and the toluene then removed under reduced pressure (1 mm Hg) to remove azeotropically any water present.

Oxidation of the 3-acetoxy 2-phenylpropene to the corresponding alkene (**74**) was achieved using N-methylmorpholine-N-oxide under osmium tetroxide catalysis. Traces (up to 10%) of 2-acetoxy acetophenone (**72**) were also obtained from this reaction. It is thought that osmium tetroxide catalyses the loss of formaldehyde during the reaction to give the side product (fig. 2.09).

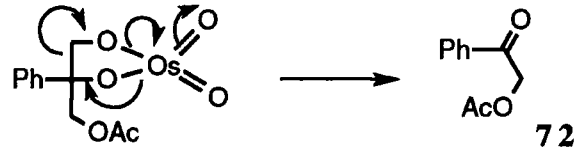
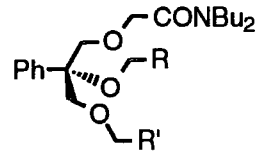


Figure 2.09 Proposed mechanism of formation of side product (**72**) by OsO_4 catalysis.

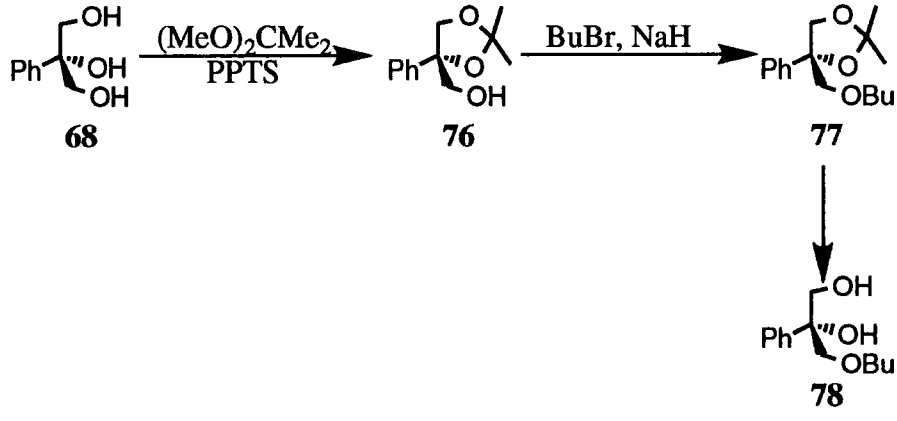
2-Phenylglycerol was obtained from the oxidation product by catalytic hydrolysis of the acetate functionality using sodium methoxide in methanol. The alkoxide formed was reprotonated using Dowex® 50 W cation exchange resin (H^+ form) to avoid the use of aqueos acid and hence elimination.



61. R = $CONBu_2$ = R'
62. R = $CONBu_2$; R' = nPr
63. R = nPr = R'

Alkylation of the triol with N,N-dibutyl 2-chloroethanamide using sodium hydride as the base gave the trioxa amide (**61**) in modest yields after purification on neutral alumina.

In the synthesis of the mono and dibutyl ethers (**62** and **63** respectively), the corresponding mono-butyl ether and mono-amide were prepared by a rather different route.



68 **76** **77** **78**

Figure 2.10 Initial synthetic route to 1-bromo-2-phenylpropan-2,3-diol.

Protection of the triol (**68**) with 2,2-dimethoxy propane under p-toluene sulfonic acid catalysis gave very poor yields of the ketal (**76**), the major product formed being the elimination product (**70**). It was found necessary to use a weaker acid, pyridinium p-toluene sulfonate (PPTS), to catalyse the reaction. Reasonable yields were achieved using PPTS with far less elimination product resulting. Alkylation with 1-bromobutane using sodium hydride as the base gave good yields of the butyl ether (**77**) after excess 1-bromobutane was removed under reduced pressure (1 mm Hg, 20 °C). However, de-protection of the diol functionality led to competitive elimination under a variety of conditions (0.1 M hydrochloric acid,

aqueous oxalic acid, p-toluene sulfonic acid and pyridinium p-toluene sulfonate) and little of the desired product was isolated. With hindsight a non-protic method of de-protecting the diol (eg. use of CBr_4 / PPh_3[22]) may have avoided the competitive elimination.

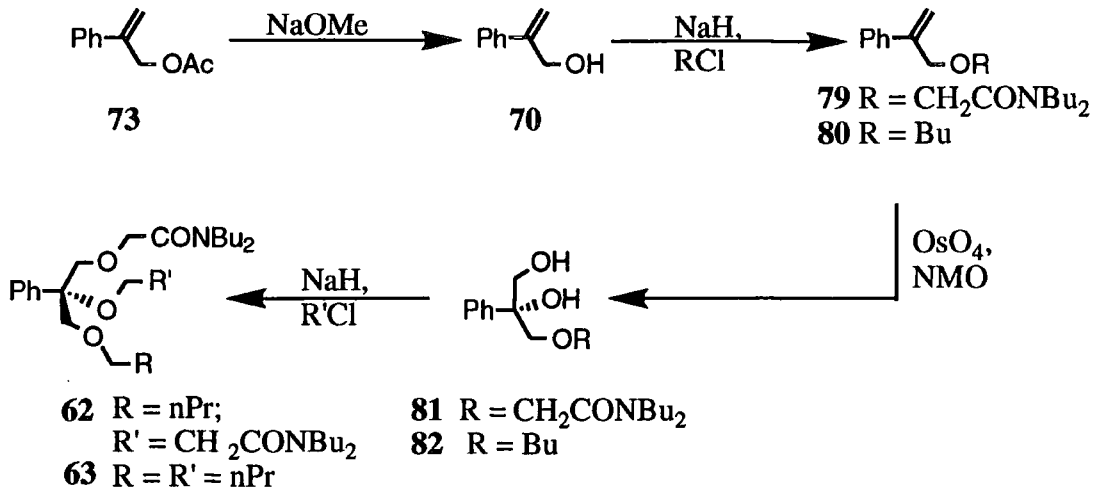


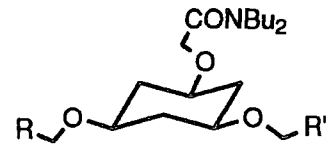
Figure 2.11 Reaction scheme for the mono and dibutyl target ligands.

2-Phenylpropenol (**70**) was used as the intermediate in the synthesis of the mono and dibutyl ethers (**62** and **63**). This was obtained by hydrolysis of 3-acetoxy 2-phenylpropene using catalytic amounts of sodium methoxide. Alkylation of this alcohol with 1-bromobutane or N,N-dibutyl 2-chloroethanamide gave the intermediate ethers (**80** and **79** respectively). The oxa-ethanamide (**79**) was found to be light sensitive in air decomposing to multiple products over a few hours. Hence it was stored in the dark under argon and used soon after preparation.

Oxidation of the appropriate alkene using N-methyl morpholine-N-oxide and osmium tetroxide as the catalyst gave the desired 1,2 diols (**81** and **82**). In both cases the formaldehyde elimination product was again obtained in small amounts. Reaction of these diols with the the relevant electrophile (1-bromobutane for the oxa-ethanamide and N,N-dibutyl 2-chloroethanamide for the butyl ether) using sodium hydride as the base gave the target ligands (**62** and **63**).

2.3.2 Synthesis of Cyclohexane based ligands.

The C_3-symmetric triamide (**64**) was prepared by direct alkylation of anhydrous cis-cis-1,3,5-cyclohexanetriol with N,N-dibutyl 2-chloroethanamide and sodium hydride. It was found that the reaction required potassium iodide as a catalyst (10% mole equivalent) to facilitate reaction.



64. R = $CONBu_2$ = R'
65. R = $CONBu_2$; R' = nPr
66. R = nPr = R'

Attempts to protect two of the alcohol groups of the cyclohexanetriol to allow addition of only one butyl or ethanamide group failed. The poor solubility of the cyclohexanetriol prevented it from being protected . A number of methods and conditions were tried:-

i) 2,2-dimethoxy propane (as solvent), p-toluene sulfonic acid, boiled under reflux.

ii) 2,2-dimethoxy propane (as solvent), 0.1 molar hydrochloric acid, boiled under reflux.

iii) 2,2-dimethoxy propane, DMF (as solvent), 0.1 molar hydrochloric acid, 80 °C.

iv) Dimethyl sulfoxide (as solvent), benzaldehyde, zinc (II) chloride, 100 °C / room temperature[23].

v) Cyclohexanone (as solvent), conc. sulfuric acid, boiled under reflux / room temperature.

vi) Dimethyl acetal benzaldehyde, DMF (as solvent), p-toluene sulfonic acid, 80 °C[24].

The inability to protect the cyclohexanetriol led to a statistical approach to the synthesis of the products being adopted. One equivalent of 1-bromobutane was reacted with cyclohexanetriol and the monoalkylated product isolated by chromatography on neutral alumina to give a reasonable yield (considering the nature of the reaction) of the desired monobutyl ether (**83**). Similarly, one equivalent of N,N-dibutyl chloroethanamide, in the presence of potassium iodide, was reacted with cyclohexanetriol and the monoalkylated product isolated (**84**). The monoalkylated products were then reacted with the appropriate electrophile using sodium hydride as the base to give the required ligands (**65** and **66**).

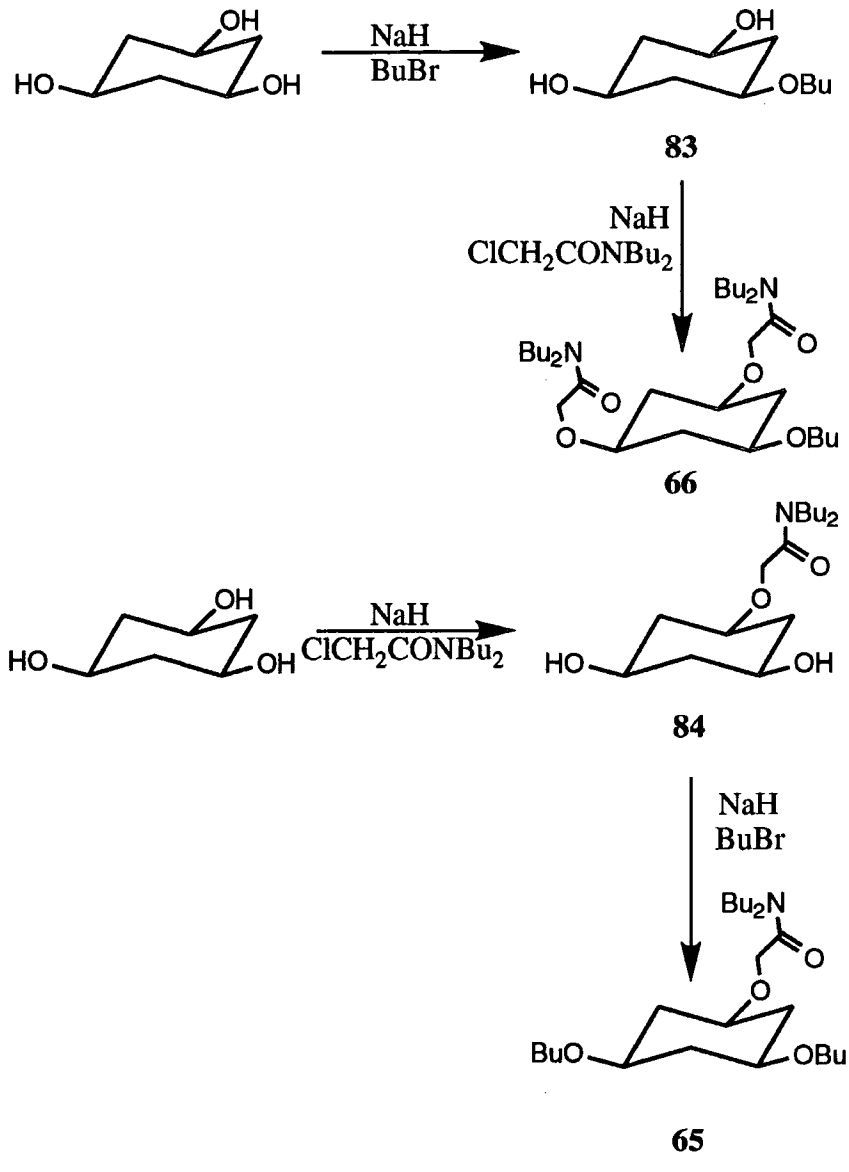
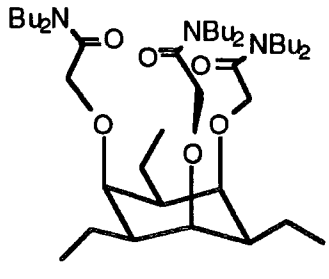


Figure 2.12 Reaction schemes for the synthesis of mono-butyl and dibutyl ether ligands.

2.3.3 Synthesis of biased cyclohexane ligand.

Application of disconnection theory to the biased C_3 symmetric ligand (**67**) shows it can be derived from a substituted 1,3,5-trihydroxy benzene (**87**). The scheme outlined below (fig. 2.13) details the proposed method of synthesis.



67.

Acylation of the hydroxyl groups using acetic anhydride proved straight forward giving 1,3,5-triacetoxy benzene (**86**). This was converted to 1,3,5-triacetyl 2,4,6-trihydroxybenzene (**87**) by a Fries reaction, following Desai's method[25], in good yields (70%). Attempts to hydrogenate **87** using a mixed rhodium and palladium catalyst, which was pre-reduced at pressure of 3 atmospheres of hydrogen prior to use, in acidified wet ethanol failed. It was thought the large number of moeities requiring hydrogentation may have prevented successful reaction.

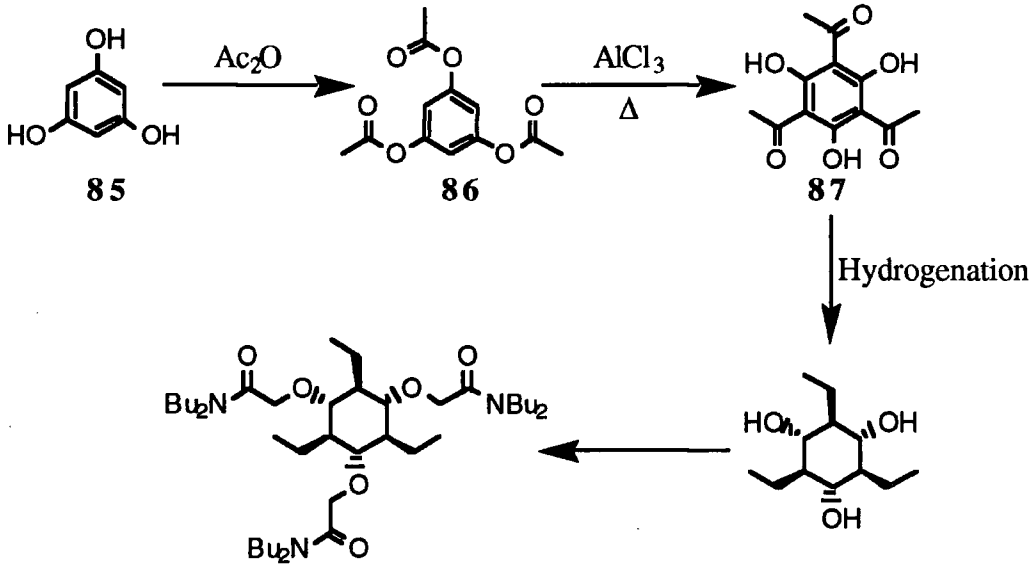
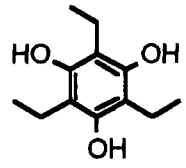


Figure 2.13 Proposed route of synthesis for ligand **67**.

A Clemmensen reduction of 1,3,5-triacetyl 2,4,6-trihydroxybenzene was performed to reduce the number of functionalities requiring hydrogenation. This was carried out in a mixed phase system of toluene / aqueous hydrochloric acid with a zinc-mercury amalgam to give the triethyl derivative (**88**). However, again attempts to hydrogenate this proved impossible. Table 2.01 shows the various conditions that were used in attempts to hydrogenate the triethyl derivative (**88**). In all cases the catalyst was pre-reduced at a pressure of 3 atmospheres of hydrogen for 1 hour before use.

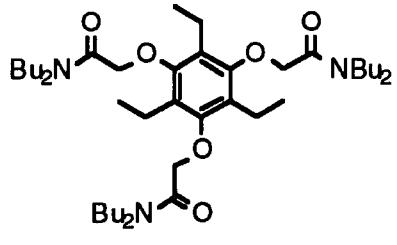


88.

Solvent	Catalyst	Pressure H_2 (atm)	Acid
Ethanol	20 % Rh/Pd on C	3	4 M H_2SO_4
Ethanol	20 % Rh/Pd on C	3	0.4 M H_2SO_4
Ethanol	20 % Rh/Pd on C	3	---
Ethanol	20 % Rh on Al	3	---
Ethanol	20 % Rh on Al	3	10 % Acetic acid
Ethanol	20 % Rh/Pd on C	3	10 % Acetic acid
90 % Acetic acid	20 % Rh/Pd on C	3	---
Ethanol	20 % Rh/Pd on C	300	0.4 M H_2SO_4
Ethanol	20 % Rh/Pd on C	300	---
90 % Acetic Acid	20 % Rh/Pd on C	300	---

Table 2.01 Conditions used in attempts to hydrogenate **88.**

The hydrogenation method was checked, 1,3,5-trihydroxy benzene being successfully hydrogenated in ethanol with the rhodium / palladium mixed catalyst allowing isolation of cis-cis-1,3,5-cyclohexanetriol (identified by comparison with commercially available material). As all attempts to hydrogenate the alcohol failed, the alcohol (**88**) was alkylated using N,N-dibutyl 2-chloroethanamide and sodium hydride to give the trioxa-amide (**89**).



89

Attempts to hydrogenate the trioxa-amide in ethanol using the mixed catalyst also failed. It is thought the bulky substituents on **87**, **88** and **89** prevented the catalyst interacting with the aromatic ring thus preventing hydrogenation. As no alternative route to the target ligand could be determined the synthesis was abandoned.

2.4 Potentiometric Studies.

The behaviour of ligands **61-66** as ionophores for the detection of selected Ia/IIa cations was compared in standard polymeric membrane ion-selective electrodes (ISEs). The membranes were prepared by dissolving 1.3% ionophore, 65.6% o-nitrophenyl octyl ether (NPOE), 32.8% polyvinyl chloride (PVC) (high molecular weight) and 0.5% sodium tetrakis [3,5-bis(trifluormethyl) phenyl] borate in distilled tetrahydrofuran and casting the solution in a glass ring.

The purpose of the plasticizer is to provide a non-volatile solvent in which to incorporate the ionophore. The added lipophilic anion reduces interference from other anions and reduces the resistance of the membrane.

2.4.1. Electrode calibration.

The ion selective electrodes were calibrated using a constant dilution technique which in basic terms involves the monitoring of electrode output as the ion concentration is continuously reduced. The experimental apparatus used in these determinations is illustrated in Fig 2.14 below.

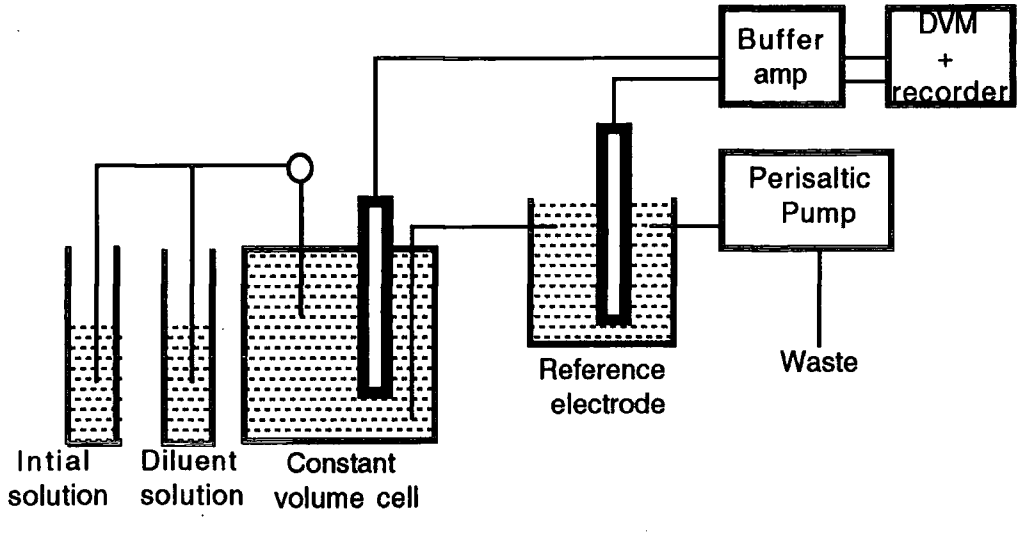


Figure 2.14 Apparatus used for ion selective electrode evaluation.

Prior to examination, all the electrodes were conditioned for 24 hours in 10^{-2} mole dm^{-3} solution of analyte at 25 °C. Thereafter they were rinsed thoroughly and immersed in a constant volume cell, which initially contained a 10^{-1} mole dm^{-3} solution of the analyte, maintained at 25 °C for ligands **61-63** and 37 °C for ligands **64-66**. This solution was then diluted constantly with de-ionised water, pumped into the constant volume cell at a fixed rate. As the analyte concentration decreased the electrode response was plotted on a Y/t chart recorder.

When an electrode behaves ideally it is said to exhibit a Nernstian response to variations in specific ion concentrations. This behaviour is defined by the Nernst equation:-

$$E = E^\circ + \frac{RT}{nF} \ln [M_i^+.a_i] \qquad \text{Eqn. 2.1}$$

where R = the gas constant; E = emf; F = Faraday constant; E° = standard emf; T = temperature; $[M_i^+]$ = concentration of ion, i.; n = number electrons transferred.; a_i = activity coefficient of ion, i.

Inserting the relevant values for the constants at 37 °C, gives the equation:-

$$E = E^\circ + \frac{0.06154}{n} \log_{10} [M_i^+.a_i] \qquad \text{Eqn. 2.2}$$

Hence, for a monovalent ion a decade change in ion activity results in a change in e.m.f. of 61.54 mV. Similarly, at 25 °C the electrode response to a monovalent ion should exhibit a slope of 59.15mV / decade change in ion concentration.

Limits of detection were measured according to IUPAC recommendations. The limit of detection being when the electrode response deviates from the linear portion of the calibration graph by 18.5 mV at 37 °C and 17.8 mV at 25 °C (see below for the origin of these values).

2.4.2 Selectivity coefficients.

Measurements of selectivity are made against a fixed interferent background of 10^{-1} mole dm^{-3} of interferent ion (as the chloride salt) using the constant dilution method. The technique used is almost identical to that used to calibrate the electrode but

instead of the analyte solution being diluted with de-ionised water the solution of interferent ion is used.

The electrode response is not exclusive to one ion. At low concentrations of the ion to be detected interferent ions can influence the output of the electrode. A plot of electrode output against primary ion concentration, $[M^+]$, in the presence of a fixed concentration of interferent ion, consists of three regions. Region AB is where the electrode is responding to the primary ion and exhibiting a Nernstian response. In region BC, as the primary ion concentration decreases the electrode output becomes increasingly influenced by the interferent ion. Finally, in the third region the electrode output responds solely to the interferent ion.

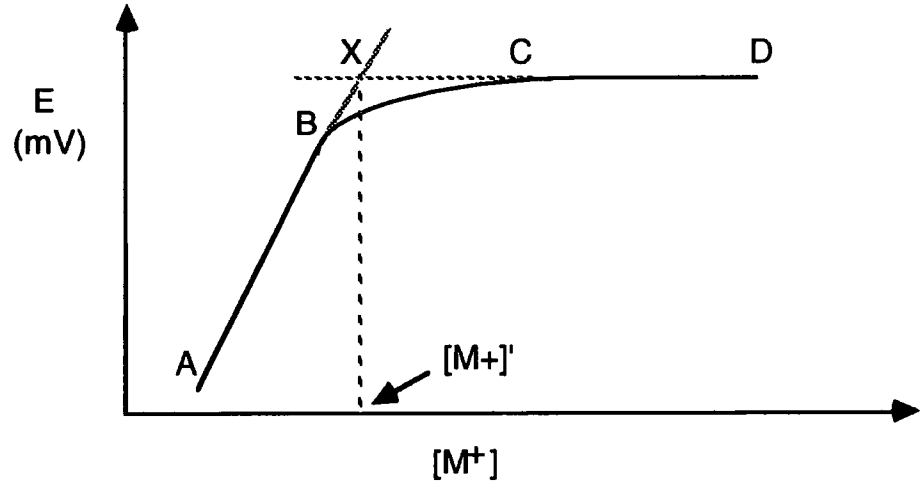


Figure 2.15 Plot of electrode potential against primary ion concentration with a fixed interferent background.

The selectivity coefficient, $K^{pot}_{m,i}$, defines the selectivity of the electrode. The coefficient is defined by the Nicolsky - Eisenmann equation (at 37 °C), under dilute conditions (thus activity = concentration):-

$$E = E^\circ + 0.06154 \log \{[M^+] + \Sigma K^{pot}_{m,i}.[I^+]^{z_m/z_i}\} \quad \text{Eqn. 2.3}$$

where $[I+]$ = interferent ion concentration
z = ion charge.

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

$$[M^+] = K^{pot}_{m,i}.[I^+]^{z_m/z_i}$$

If the concentration M at which this occurs is $[M^+]'$ and the concentration of I at which this occurs is $[I^+]'$ then :-

$$E = E^\circ + 0.06154 \log \{[M^+]' + K^{pot}_{m,i}.[I^+]'^{\,z_m/z_i}\}$$

$$= E^\circ + 0.06154 \log \{2.[M^+]'\}$$

The difference between this and the point where no interference is present at concentration $[M^+]'$ can be expressed as:-

$$\Delta E = 0.06154 \log \{2.[M^+]'-[M^+]\}$$

$$\Delta E = 0.06154 \log \{2\}$$

$\Delta E = 18.5$ mV (at 37 °C for a monovalent ion).

Thus from the graph the point at which the experimental line BC differs from the extrapolation of AB by 18.5 mV gives the concentration, $[M^+]'$. Hence :-

$K^{pot}_{m,i} = [M^+]'^{\,z_i} / [I^+]^{\,z_m}$ NB: $[I^+]$ is a constant.

This is also the variation from linearity that is used to determine the limts of detection.

*2.4.3 Calibration and Selectivity measurements on ionophores **61-66.***

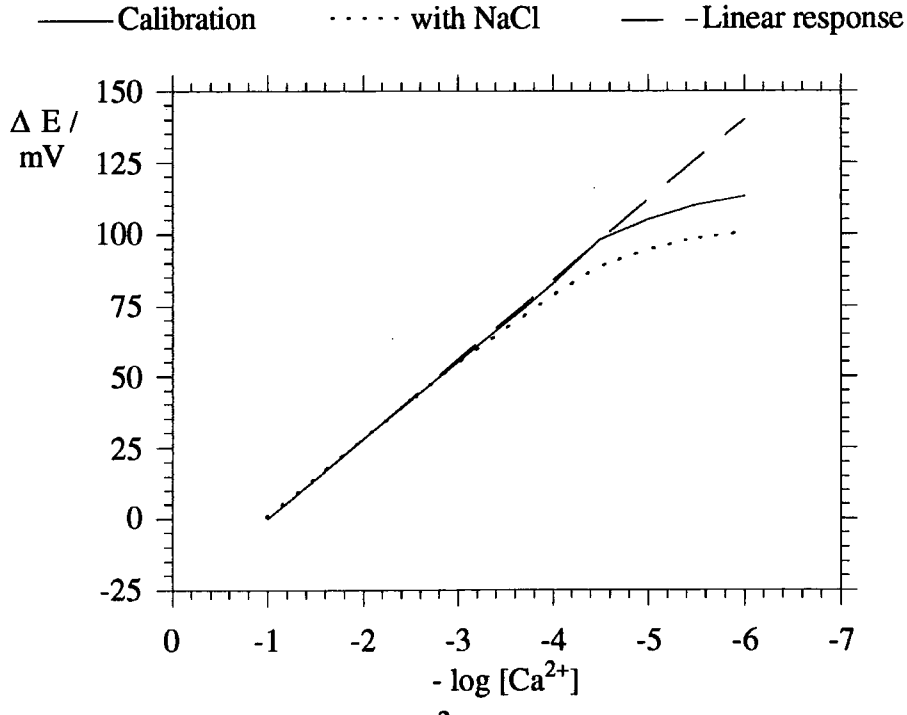
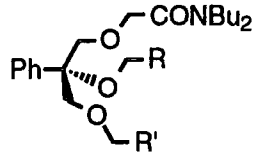
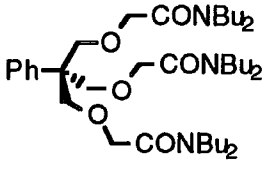


Figure 2.16 Plot of ΔE against $[Ca^{2+}]$ for ligand **61** with a fixed interferent background of 0.1 M NaCl at 37 °C

The triamide (**61**) and diamide (**62**) demonstrated good selectivity and sensitivity for Ca^{2+}. A nernstian response with a limit of detection of 10^{-6} mole dm^{-3} was found and selectivities over Li^+, Na^+, K^+, and Mg^{2+} were good, particularly for the diamide (Table 2.02). The similarity in responses of ligand **61** and **90**[9] show the loss of a methylene group has not altered the selectivity in ion binding as had been postulated (section 2.2).



61. R = $CONBu_2$ = R'
62. R = $CONBu_2$; R' = nPr
63. R = nPr = R'

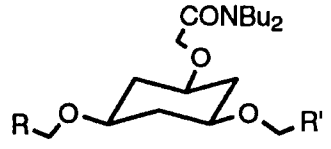


90.

Ligand	Primary ion	Calibration		Selectivity: $pK_{i,j}^{pot}$				
		Slope (mV)	limit of detection (mol dm^{-3})	Na	K	Mg	Ca	Li
monoamide **63**	Li	59.1	$10^{-4.5}$	0.19	0.2	1.8	0.7	-
	Mg	25.5	$10^{-4.3}$	-0.9	-0.8	-	0.1	-
	Ca	27.5	$10^{-4.7}$	-0.7	-0.7	2.9	-	-
diamide **62**	Na	61.5	$10^{-5.1}$	-	0.8	1.4	0.5	-
	Ca	30.8	$10^{-6.0}$	3.1	3.7	4.5	-	3.4
triamide **61**	Na	56.0	$10^{-4.4}$	-	0.9	1.3	0.5	-
	Ca	30.0	$10^{-5.1}$	2.4	3.3	4.7	-	2.1
90[9]	Ca	30.0	$10^{-5.2}$	2.3	3.2	4.8	-	2.0

Table 2.02 Selectivity coefficients and electrode response parameters for ISEs based on ionophores **61**, **62**, **63** and **90** (310K).

The effect of reducing the ligand co-ordination number only had a pronounced effect on ion selectivity in the transition from a potential ligand donor number of five to four. A large deterioration of selectivity for Ca^{2+} was seen. The reduction in the number of dipolar amide donors, which are able to stabilise the relatively charge dense calcium ion, and the loss of steric hinderance allowing larger deformations on binding, reduces the distinguishing ability of the ligand. The increase in selectivity seen for lithium in ligand **63** is probably due to the change in co-ordination number to four. A co-ordination number of four is still favoured by lithium but not the interferent ions which favour a co-ordination number of six.



64. R = $CONBu_2$ = R'
65. R = $CONBu_2$; R' = nPr
66. R = nPr = R'

All of the cyclohexane based ligands (**64-66**) gave fast responses times (less than 10 s) and displayed good selectivities for lithium. This is not unexpected; the three focused ether oxygen lone pairs form three six-membered chelate rings on

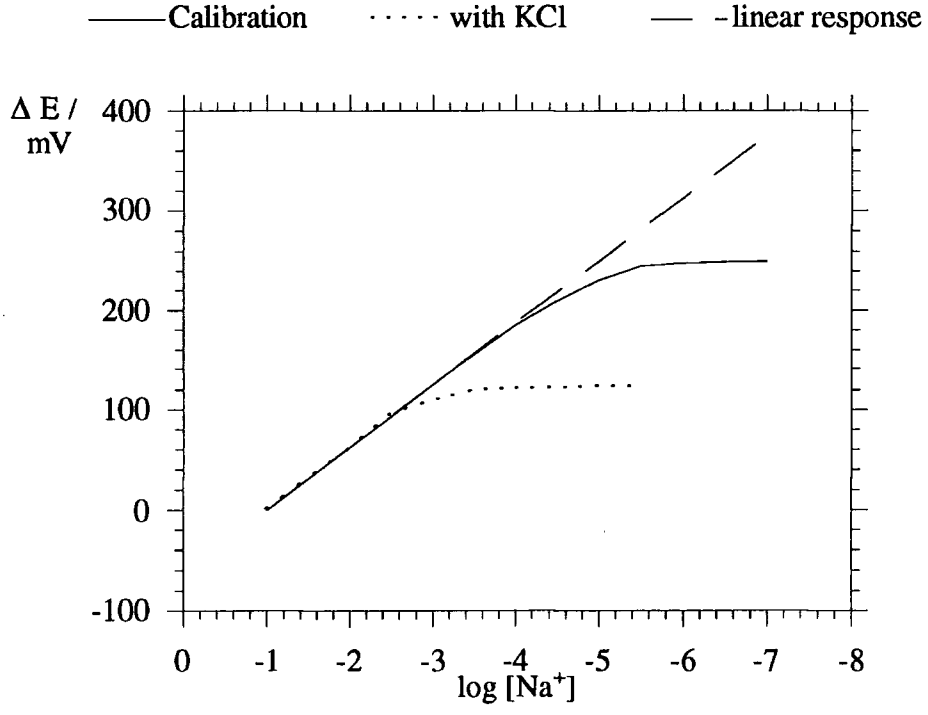


Figure 2.17 Plot of ΔE against [Na^+] for ligand **64** with a fixed interferent background of 0.1 M KCl at 37 °C

cooperative binding and combined with the strongly dipolar amide donors, favour a small relatively high charged ion such as lithium. The five co-ordinate ligand (**65**) exhibits selectivities for lithium over potassium, magnesium and calcium ($10^{3.8}$, $10^{3.6}$ and $10^{2.1}$ respectively) that demonstrate this effect clearly Of particular interest is the ligand's lithium selectivity in the presence of a 0.1 mole dm^{-3} solution of sodium ions. The measured value of $10^{2.2}$ is one of the highest found for a non-macrocyclic ionophore (cf. $10^{3.25}$ for the most selective Li^+ sensor based on a diamide substituted 14-crown-4 ionophore)[26] .

Ligand	Primary ion	Calibration		Selectivity: $pK_{i,j}^{pot}$					
		Slope (mV)	limit of detection (mol dm^{-3})	Na	K	Mg	Ca	Li	NH_4^+
monoamide	Na	60.0	$10^{-4.8}$	-	0.6	1.3	0.8	0.1	0.5
66	Li	56.0	$10^{-5.1}$	0.7	1.2	2.1	1.3	-	1.1
diamide	Na	57.2	$10^{-4.8}$	-	1.7	1.9	0.5	0	1.5
65	Li	57.0	$10^{-5.6}$	2.2	3.8	3.6	2.1	-	3.6
	Ca	27.4	$10^{-5.2}$	0.6	3.6	4.2	-	-0.9	3.3
triamide	Na	55.5	$10^{-5.9}$	-	3.1	2.7	0.8	0.1	3.0
64	Li	58.4	$10^{-5.8}$	0.8	3.4	3.2	1.3	-	3.4
	Ca	27.7	$10^{-6.6}$	-0.6	3.9	4.0	-	-0.9	3.6

Table 2.03 Selectivity coefficients and electrode response parameters for ISEs based on **64**, **65** and **66** (298K)

The six co-ordinate ionophore (**64**) has marked selectivity for sodium over potassium. This is attributable to the donor type and number preferences of the smaller, more charge dense sodium ion. The measured selectivity of $10^{3.1}$ is the highest reported value obtained for membrane based potentiometric sodium sensors. All other sodium selective sensors, including those based on monensin[27], crown ethers[3,4], calixarenes[5-7] and podands[8,9], have Na^+/K^+ selectivities of less than 10^3. This ionophore may be useful for intracellular sodium concentration measurements given that lithium is not a biologically significant ion (except in cases where patients are

being treated for depression with Li_2CO_3) and intracellular calcium levels are low (typically less than 0.1 mM).

Using an electrode incorporating ionophore (**64**) the response curve for sodium has been measured in the presence of a simulated intracellular background of interfering ions. The electrode is able to measure the typical intracellular Na^+ concentration of between 5 and 18 mM with a nernstian response.

As was the case with the four co-ordinate ligand based on 2-phenylglycerol, ligand (**66**) showed relatively poor selectivities and therefore was not examined any further.

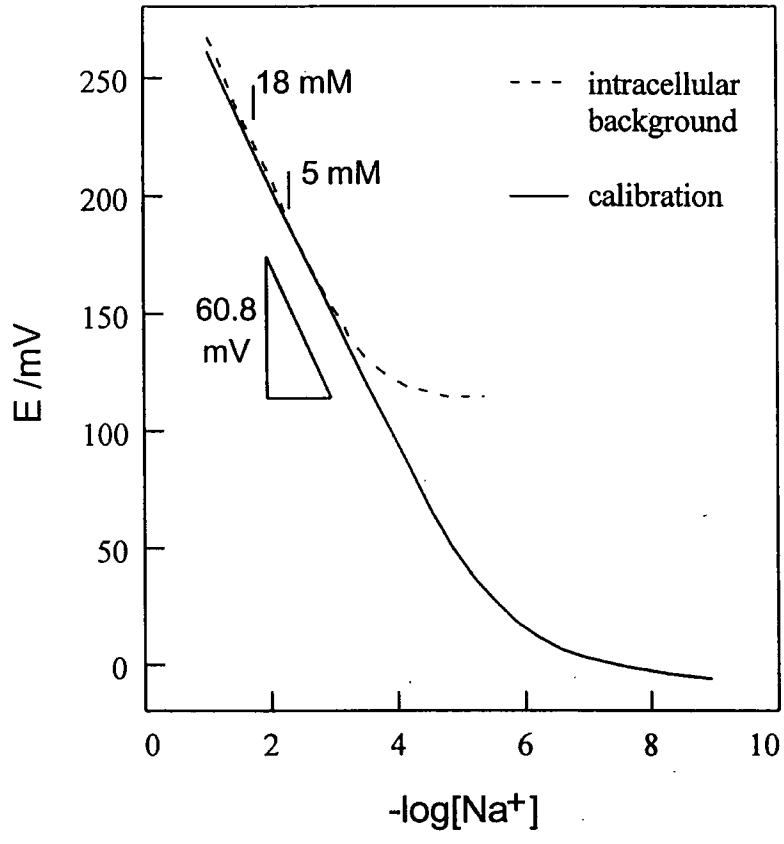


Figure 2.18 Response curve for Na^+ obtained with the electrode based on **64** in the presence of interfering ions, of concentrations similar to those found in intracellular fluids (310K; 120 mM K^+, 3 mM Mg^{2+}, 0.4 μM Ca^{2+}).

2.5 ^{13}C NMR and Infra-red Complexation Studies.

All ^{13}C NMR (62.90 MHz) studies were carried out in deuterated methanol with addition of calcium perchlorate, lithium perchlorate or sodium trifluoromethane-sulfonate as appropriate at 25 °C. Infra-red studies were carried out in methanolic

solutions in calcium fluoride cells at 25 °C (5 x 10^{-2} mol dm^{-3} ligand, 25 x 10^{-2} mol dm^{-3} metal salt).

*2.5.1 Complexation with Ligand **61**.*

A sharp end point was observed after the addition of one equivalent of calcium ions indicative of the formation of a relatively strong 1:1 complex. The observation of time averaged signals for the the free and complexed ligand at intermediate stoichiometries indicated a stability constant of less than $10^{5.5}$. Analysis[28] of the titration curve obtained by plotting $\Delta\delta$ versus Ca^{2+}/ligand ratio gave $K_S = 4500$. Also,

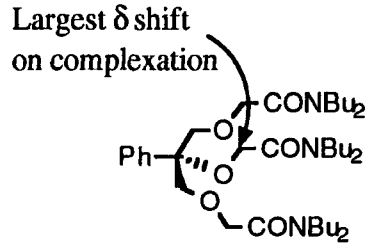


Figure 2.19 Largest NMR coordiantion shift, $\Delta\delta$, of ligand **61**.

the carbon chemical shifts changed very little between free and complexed ligand (all less than 1 ppm) suggesting there is relatively little change in the ligand's conformation. The largest coordination shift was seen for the methylene carbon on the shortest arm ($\Delta\delta$ = 0.98 ppm).

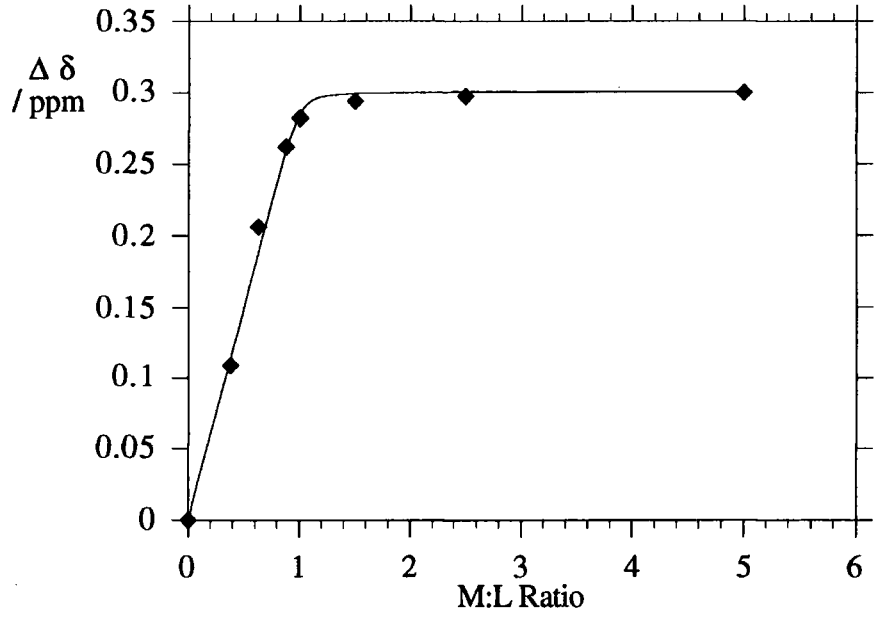


Figure 2.20 Plot of $\Delta\delta$ versus Ca^{2+} : ligand for ligand **61** at 298 °C in deuteriated methanol.

Complexation was also accompanied by a drop in the amide carbonyl IR stretching frequency of 18 cm^{-1}. This is consistent with a strong interaction between the amide carbonyls and the ion in the complex. Carbonyl stretching frequencies of the complexes formed with sodium and potassium showed no shift within the experimental error (shifts of 3 cm^{-1} and 1 cm^{-1} were observed respectively with an error of 4 cm^{-1} in peak position).

2.5.2 *Complexation with Ligand 62*

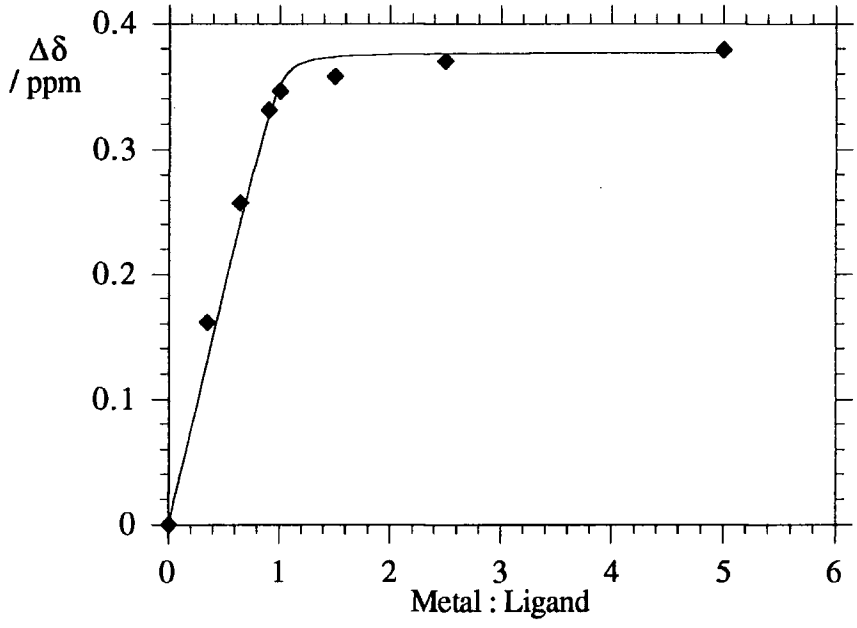


Figure 2.22 Plot of $\Delta\delta$ versus Ca^{2+} : ligand for ligand **61** at 298 °C in deuteriated methanol.

As with ligand **60** a time averaged signal was observed with a sharp end point following addition of more than one equivalent of calcium salt. Again this was indicative of the formation of a 1:1 complex between the ligand and cation with $K_S < 10^{5.5}$. Analysis of the graph gave a stability constant, $K_S = 2500$.

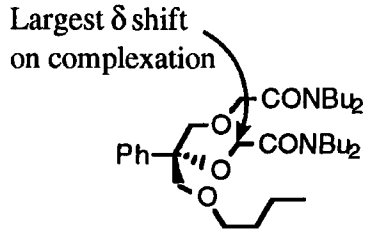


Figure 2.21 Largest NMR coordiantion shift, $\Delta\delta$, in ligand **62**.

The carbon ^{13}C NMR coordination shifts were similar to those for ligand **61**, the methylene carbon on the shortest chain again undergoing the largest coordination

shift ($\Delta\delta$ = 0.98 ppm), indicating a similar degree of conformational rearrangement to ligand **61** is required for this ligand to bind.

Again, an accompanying decrease in the amide carbonyl infra-red stretching frequency of 24 cm^{-1} indicated strong participation of the carbonyl groups in cation complexation.

2.5.3 Complexation with Ligand 63.

The infra-red amide carbonyl stretch of the ligand in the presence of a five fold excess of metal salt (lithium, sodium, potassium and calcium salts) showed little shift; the maximum shift of 6 cm^{-1} was seen with lithium ions. This, combined with the lack of selectivity shown in ion selective electrode measurements, suggested that there was relatively little interaction between the various cations and the ligand and that any interactions occurring were not worth studying further by NMR.

2.5.4 Complexation with Ligand 64.

Upon addition of Ca^{2+} to a solution of **64** in deuteriated methanol, the ^{13}C NMR showed peaks for both free and complexed ligands at intermediate stoichiometries indicating that relatively strong complexation was occurring between the calcium ions and ligand, $K_S > 10^{5.5}$. Only one set of ligand resonances were observed when one equivalent of calcium had been added indicating the formation of a 1:1 complex. The ring methylene group underwent the largest coordination shift (9.0 ppm) as the ring underwent a flip to arrange the pendent arms axial instead of equatorial. A shift of the amide carbonyl stretching frequency (12 cm^{-1}) was also observed again indicating participation of the amide carbonyls in binding.

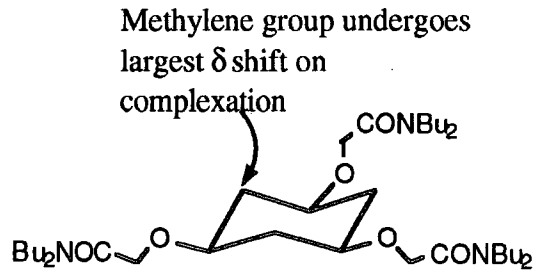


Figure 2.23 Indication of largest NMR coordination shift, $\Delta\delta$, in ligand **64** following complexation with calcium ions.

^{13}C NMR titration with sodium trifluoromethane sulfonate presented a different picture. No discernible titration end point was observed following addition of sodium cations to the ligand solution suggesting weak complexation. The largest coordination shift was seen for the methylene carbon on the pendent arm (0.2 ppm) not the ring methylene carbon as seen in the complex with calcium. The coordination shift was similar to that observed for the pendent arm methylene carbon of the calcium complex suggesting that the pendent arms are still involved in binding but sodium ion is perhaps not bound above the cyclohexane ring. This is supported by an accompanying change in the carbonyl stretching frequency of 12 cm^{-1} on binding indicating that, although complexation is weak, the carbonyls are still interacting with the ion relatively strongly.

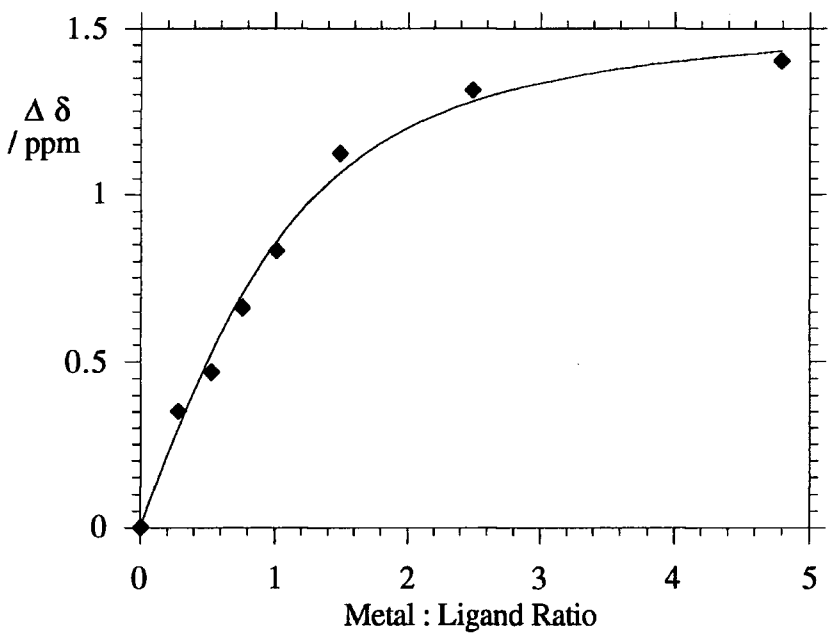


Figure 2.24 ^{13}C NMR titration of $\Delta\delta_c$ versus sodium : ligand showing weak complexation of ligand **64** with sodium ions (293 K, CD_3OD).

In the presence of an excess of lithium perchlorate (5 equivalents) the carbonyl amide stretch moved downwards by 19 cm^{-1} indicating lithium ion ligation to the amide carbonyls. No NMR titration was performed with lithium ions.

2.5.5 Complexation with Ligand 65.

Complexation with calcium gave a time averaged ^{13}C NMR signal. Analysis of the graph of $\Delta\delta$ versus metal / ligand ratio gave a $K_s = 10^{3.6}$. The largest δ shifts were observed for the methylenes of the cyclohexane ring, similarly to the triamide ligand.

Again, amide participation in binding was demonstrated by a downward amide carbonyl shift in the infra-red spectrum of 14 cm^{-1}.

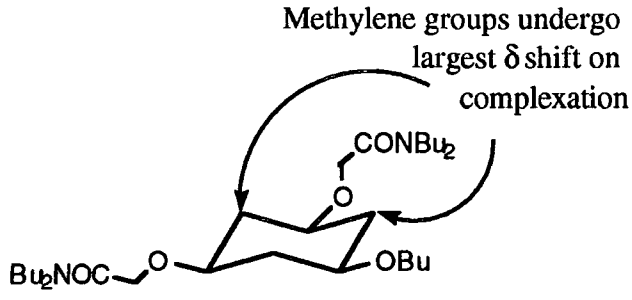


Figure 2.25 Largest coordiantion shift, $\Delta\delta$, on ligand **65** complexation with calcium.

Lithium NMR titration indicated weak complexation with no complex stoichiometry identifiable. The largest coordination shift, of 3.6 ppm, was also seen for the methylene carbon of the cyclohexane ring, but the shift is significantly smaller than that found for the complex with calcium. As was the case with the weak sodium complexation of ligand **64**, amide participation in the complexation is observed. A downward shift of 14 cm^{-1} occurs in the amide carbonyl infra-red stretching frequency. These observations suggest that the lithium may not be fully bound by the three arms above the cyclohexane ring as is the case with calcium . The lithium may be bound by two or more ligands, with preferential amide coordination.

2.6. Electrospray Mass Spectroscopic Studies.

2.6.1 Experimental parameters and considerations.

Use of electrospray mass spectroscopy (ESMS) in complexation and supramolecular chemistry is becoming commonplace[29,30,31], since it offers information about the distribution of molecular and ionic species in solution If fast kinetics of exchange exist, the atmospheric pressure inlet allows information about the equilibrium distribution of solution species to be obtained provided that no distortion of the species distribution occurs on ionisation, de-solvation, transfer through the electrospray interface or in the mass analyser and detector. The effect the latter two may have can be studied experimentally and conditions established to minimise fragmentation and inhibition of any discrimination[32]. However, a detailed understanding of the electrospray ionisation and de-solvation processes is lacking[33].

The triamide ligand **63** and diamide **64** were studied using this technique. ^{13}C NMR and IR studies indicate that the sodium complex of **63** and the potassium

complex of **63** have very different solution structures. The potassium complex shows no evidence of amide binding whereas the sodium complex involves the cooperative binding of the three amide carbonyls (single IR band at 1633 cm^{-1} and a coordination shift of 0.9 ppm for the carbonyl in ^{13}C NMR spectrum.) It is likely that in solution the potassium ion is bound by at least three methanol solvent molecules, whereas the sodium complex may have none. This leads to differences in the energies of de-solvation which is an important determinant in ESMS response factors[23].

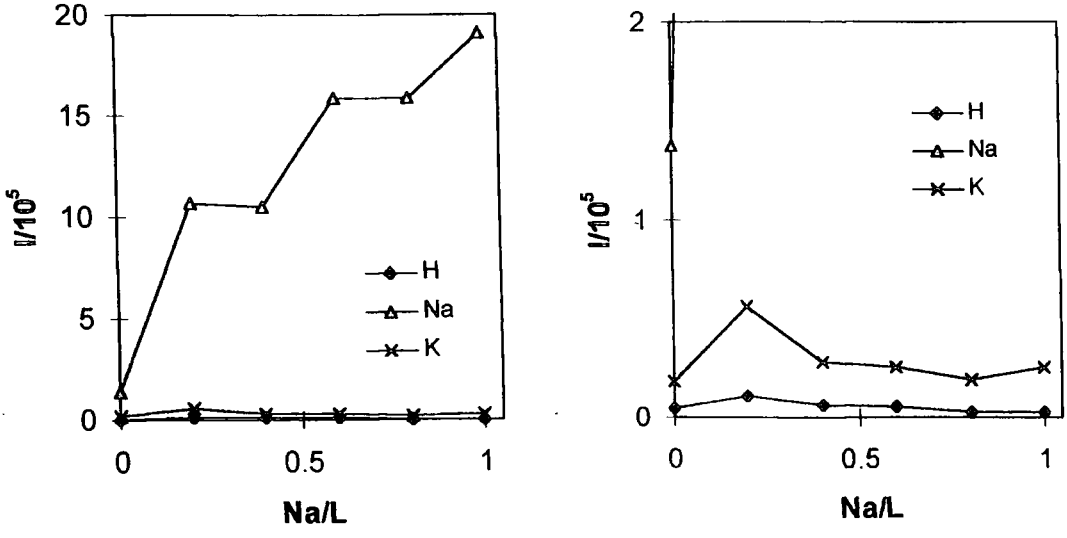


Figure 2.24 Variation of complex peak intensities in ESMS as a function of Na^+/**63** ratio (Analar MeOH, [**63**] = 10^{-4} M).

Preliminary experiments compared the peak heights of the sodium complex of **63** to the protonated and potassium impurity complexes. The concentration of sodium was varied (10^{-5} to 10^{-4} mol dm^{-3}) with a fixed concentration of **63** (10^{-4} mol dm^{-3}) at a cone voltage of 30 V. The comparison of the intensity of the sodium complex compared to the protonated complex and the sodium complex compared to the potassium, fig. 2.24, reveals a general increase in the sodium complex signal accompanied by a diminution of the other peaks. Previous workers have suggested that in similar experiments involving FABMS, the ionisation efficiencies can be estimated by comparing the intensity ratio of the sodium vs. potassium complex against the protonated ligand vs potassium complex[34]. It was assumed in this work that as the sodium concentration increased protons would be displaced and the peak intensity for the protonated complex would diminish. However, the effective proton concentration was uncontrolled and the potassium impurity concentration, while constant for one set

of data, was also uncontrolled. Also, protons and potassium ions are competing for the ligand even when the ligand is present in excess.

Rather than use the potassium impurity as an internal reference experiments were carried out using the tetra-alkylammonium ions $^{+}N(C_8H_{17})_4$ and $^{+}N(C_{10}H_{21})_4$, varying the Na^+ and K^+ concentration with a fixed ligand concentration (10^{-5} mol dm^{-3}). These alkylammonium ions were chosen as they are likely to be poorly solvated and give a similar $^{m}/_{z}$ value to the complexes being examined in this work.

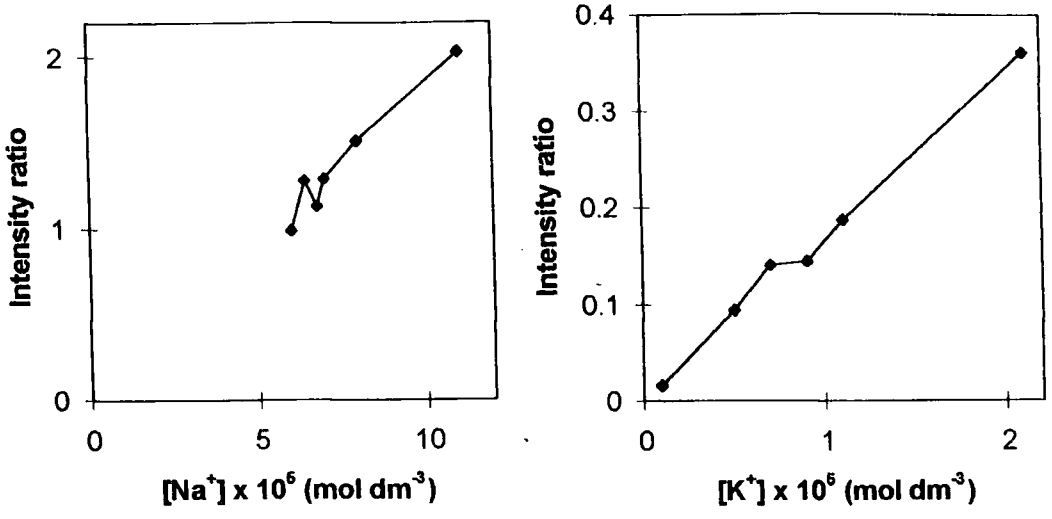


Figure 2.27 Relative peak intensity for [Na.**63**]$^+$ and [K.**63**]$^+$ compared to $^{+}N(C_8H_{17})_4$ as a function of Na^+/K^+ concentration [Aristar MeOH, [**63**] = 10^{-5} mol dm^{-3}].

Fig 2.27 shows the results, corrected for background sodium ion (6 x 10^{-5} mol dm^{-3}) and potassium ion (10^{-6} mol dm^{-3}) concentrations, which suggest in comparison to the $^{+}N(C_8H_{17})_4$ 'internal reference' that the peak intensities of the sodium and potassium complexes change as a function of the sodium and potassium ion concentration. However, the mass spectrum peak heights show that as sodium (or potassium) concentrations were increased the intensity of the $^{+}NR_4$ reference did not remain constant invalidating its use as a standard. Similar observations have also been noted by Kebarle[31d] in ESMS undermining the use of a non-competitive ion as a standard.

However the two experiments suggest to a first approximation that the potassium and sodium complexes of ligand **63**, notwithstanding their different solvation states in methanol, have similar ionisation efficiencies.

2.6.2 *Ion selectivity measurements.*

When the concentrations of ligand **64** were relatively high in solution ($\geq 10^{-4}$ mol dm^{-3}) many more impurity peaks were evident. Reducing the ligand concentration had the effect of lowering or removing the trace metal peaks and also reducing the appearance of cluster ions, eg. L_nCa (n = 2 - 6, evident at cone voltage = 30 V, ligand concentration of 10^{-4}.) At a ligand concentration of 10^{-5} mol dm^{-3} there was no evidence of cluster formation. Maximal peak intensities were obtained with a cone voltage of 110 V and little fragmentation was visible.

M^+	I_{Na^+}[a]	I_{M^+}	I_{Na^+}/I_{M^+}[b]
K^+	28.0	3.03	9.3 (1.1)
Rb^+	28.5	1.17	24.6 (1.5)
Li^+	12.0	26.1	0.46 (0.03)

(a) each figure given is the mean for 3 sets of experiments, for each of which the given peak intensity represents the mean of ~80 scans in the plateau region of the ion-current.

(b) e.s.d. in parenthesis.

Table 2.04 ESMS Determined Selectivity Parameters for Ligand **64** (110V cone voltage, 4kV capillary voltage, [**64**] = 10^{-5} M, 100 μdm^3 injection loop)

Competition experiments were carried out between pairs of ions with ligand concentrations of 10^{-5} mol dm^{-3} and ion concentrations of 10^{-4} mol dm^{-3} allowing an equimolar concentration of ions to compete for a deficiency of ligand, a procedure used in earlier work[35]. The results for ligand **64** showed the expected order of selectivities deduced from potentiometric measurements, Table 2.04. The selectivity ratios obtained by ESMS while in qualitative agreement with the selectivity coefficients obtained by potentiometry cannot be linked quantitatively (ESMS method, $^{Li}/_{Na}$ = 2.2, $^{Na}/_{K}$= 9.3, potentiometry -log $K^{pot}_{Li,Na}$ = 0.8, -log $K^{pot}_{Na,K}$ = 3.1).

For ligand **65** a similar experiment was carried out and the selectivities again followed the pattern expected from potentiometric measurements, Table 2.05, with the cone voltage = 90 V for maximum peak intensities.

M^{+a}	$I_{Li}{}^b$	I_M	I_{Li}/I_M
Na^+	13.3	3.22	4.1
K^+	11.1	0.41	27
Rb^+	13.1	0.22	58
M^+	I_{Na}	I_M	I_{Na}/I_M
Li	3.14	13.1	0.24
K	9.05	1.47	6.2
Rb	11.7	0.70	16.6

(a) $[M^+] = 10^{-4}$ M.

(b) peak intensities are the mean of ~80 scans on the ion-current plateau region.

Table 2.05 ESMS Determined Selectivity Parameters for **65** (90V cone voltage, **[65]** = 10^{-5} M, 4kV capillary voltage, Aristar MeOH, 100 μdm^3 injection loop)

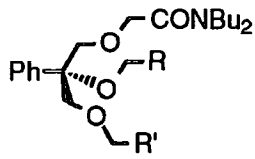
2.6.3 Summary of electrospray mass spectrum studies.

The precise details of the physical processes involved in ESMS are still ill-defined. It is doubtful that the spectrum obtained from ESMS measurements is a direct representation of the solution equilibrium. Counter-ions dissociate, droplets gain vibrational and translational energy and solvent molecules are removed concentrating the various species in the droplet. It has not been established whether the formation of the ion observed is a result of a droplet 'explosion' or 'evaporation' of solvent molecules from the droplet surface. The different processes will favour ion formation in different ways depending on the charge density, solvation energy, polarity and m/z ratio of the species involved. Notwithstanding these complications the experiments show that a reliable *qualitative* order of complex selectivity may be obtained.

2.7. Conclusions.

In potentiometric and electrospray mass spectrum studies, the hexa- and penta-coordinate ligands **64** and **65** demonstrate lithium selectivity over sodium, potassium, calcium and magnesium ions. As postulated the combination of six membered chelate rings which form on binding and the amide donor groups, which favour binding of

ions with a high charge density, produced ligands which bind preferentially to small ions. Where the coordination number of the ligand is optimised in the penta coordinate ligand **65**, the lithium over sodium selectivity is one of the highest Li^+/Na^+ selectivities ($10^{2.2}$) for a non-macrocyclic ligand reported to date.



61. R = $CONBu_2$ = R'
62. R = $CONBu_2$; R' = nPr
63. R = nPr = R'

64. R = $CONBu_2$ = R'
65. R = $CONBu_2$; R' = nPr
66. R = nPr = R'

The favouring of small ions when six-membered chelate rings form on complexation is clearly shown in ligand **64.** It exhibits exceptional Na^+/K^+ selectivity, the measured value of $10^{3.1}$ representing the highest reported value for a neutral ionophore used in ion-selective electrodes. Another example of this effect can be seen on comparison of the 2-phenyl glycerol based ligands to the cyclohexane based ligands. The small lithium ion is favoured by the cyclohexane based ligands, which only form three contiguous six-membered chelate rings, whereas the 2-phenyl glycerol derivatives, which form a five membered chelate ring and two six-membered chelate rings on complexation, favour the larger calcium ion.

The stability of the complexes formed with these ligands is higher for the more preorganised cyclohexane based ligands compared to the 2-phenyl glycerol based ligands. For example, the calcium complex of ligand **64** has a far higher stability constant than that of the less pre-organised ligand **61** ($K_S > 10^{5.5}$ vs. $K_S = 10^{3.65}$).

The other major influence on all the ionophores' binding characteristics is the degree of participation of the amide donor groups. Even where weak binding is indicated by ^{13}C NMR studies, such as the lithium complex of ligand **65**, amide bonding is still evident from infra-red analysis of the complexes. It is the main difference between binding and non-binding ions for a given ligand. For example, in ligand **65** relatively strong amide carbonyl coordination has been measured in the lithium complex, whereas the sodium complex shows no such binding.

2.8 References

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CHAPTER 3.

TOWARDS FLUORESCENT IONOPHORES FOR LITHIUM.

3. Towards Fluorescent Ionophores for Lithium.

3.1 Medical Application of Lithium.

3.1.1 Anti-Depressant Uses.

Lithium carbonate is used as a mood stabiliser 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.

The mode of action of lithium is not entirely understood. However, lithium is known to alter the chemical balance of the body and it is believed that lithium influences the chemical systems which regulate emotional states[1].

Lithium is generally well tolerated at its therapeutic levels (0.5 - 1.0 mmol dm^{-3}) but can have some adverse effects (see fig. 3.01) in higher concentrations, toxic effects occurring at concentrations greater than 1.5 mmol dm^{-3}. There is a great deal of individual variation and this necessitates careful monitoring of lithium concentrations in blood plasma. It is therefore highly desirable to develop lithium selective ionophores which can be used to determine lithium concentrations in blood.

Plasma contains several ions which may interfere with the measurement of lithium levels. Sodium levels in plasma are very high compared to the expected lithium levels (Table 3.01). For an accurate potentiometric measurement of lithium concentrations, with less than 1% interference from interferent cations, a lithium ionophore must possess a Li^+/Na^+ selectivity of 30,000 in a serum background. At present the best neutral ionophore for lithium has a Li^+/Na^+ selectivity in a serum background of 1700[2].

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

Table 3.01 Interferent cation concentrations in human plasma.

ADVERSE EFFECTS

Gastrointestinal	Nausea, vomiting, diarrhorea.
Haematological	Leukocytosis.
Thyroid	Hypothyroidism.
Renal	Polyurea, polydypsia, nephrogenic diabetes insipidus, kidney damage.
Skin	Acne, worsening of psoriasis.
Cardiovascular	EKG changes.
Reproduction	Tetratogenic
Neurological	Tremor, EEG changes.

TOXIC EFFECTS

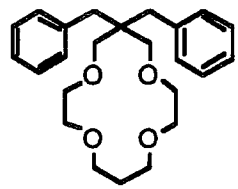
Moderate	**Severe**
Persistent nausea and/or diarrhoea.	Arrhythmias.
Lethargy.	Anuria.
Muscle weakness.	Shock.
Ataxia.	Siezures.
Muscle irritability.	Incontinence.
Coarse tremor.	Confusion.
	Stupor.
	Coma.
	Death.

Figure 3.01 Illustration of the possible side effects of lithium therapy[1].

3.1.2 Cardiac Output Monitoring.

As lithium is not naturally present in the body it has found a use in cardiac output monitoring[3]. A lithium sensor incorporated in an ion selective electrode is attached to an arterial blood flow and washed until a steady output is obtained. A solution of lithium chloride (2 ml of 0.3 mol dm^{-3} solution) is injected into the superior vena cava and the response of the lithium electrode recorded. The dilution curve that results is then used to calculate the blood flow rate.

This method of cardiac blood flow measurement has several advantages over techniques that are used. It is accurate, quick, simple and avoids the risks associated with pulmonary artery catheterization. Non-invasive methods, such as Doppler ultrasound monitoring, which allow continuous measurement are difficult and inaccurate, especially in patients recovering from heart or aortic surgery.



93.

At present 6,6-dibenzyl-1,4,8,11-tetraoxa-cyclotetradecane (**91**) is used in the ion selective membrane to monitor the lithium levels. The selectivity of this ionophore is relatively low for lithium over sodium ($\log^{pot}_{Li,Na} = -2.36$) and an improvement in the selectivity of the ionophore used for the measurement would allow smaller doses of lithium chloride to be used hence reducing the risks to the patient. However, not all ionophores are suitable for use in this technique as many are prone to protein binding to the ionophore producing severe interference.

3.2 Fluorescence Ionophores as Sensors.

Although it is possible to use absorption or electrical changes as a signal of binding occurring to an ionophore a fluorescence change offers real advantages. As fluorescent emission occurs at a different wavelength to excitation the background signal can be made very low. Hence, fluorescence offers a high sensitivity. Electrochemical signalling offers the potential of a very large signal range but at a cost of having to stick electrodes into the medium to be examined. Also, to gain spatial information sensors need to be located in every region of the media simultaneously. Clearly 'molecular sized' sensors signalling complexation by fluorescence solve these problems.

3.2.1 The origin of fluorescence.

Molecules or ions in excited states lose absorbed energy in one of the following ways:-

a) radiationless - by internal conversion or intersystem crossing (macroscopically seen as heat).

b) radiation emission.

c) photochemical reaction.

Processes (a) and (b) are shown on the Jablonski diagram below.

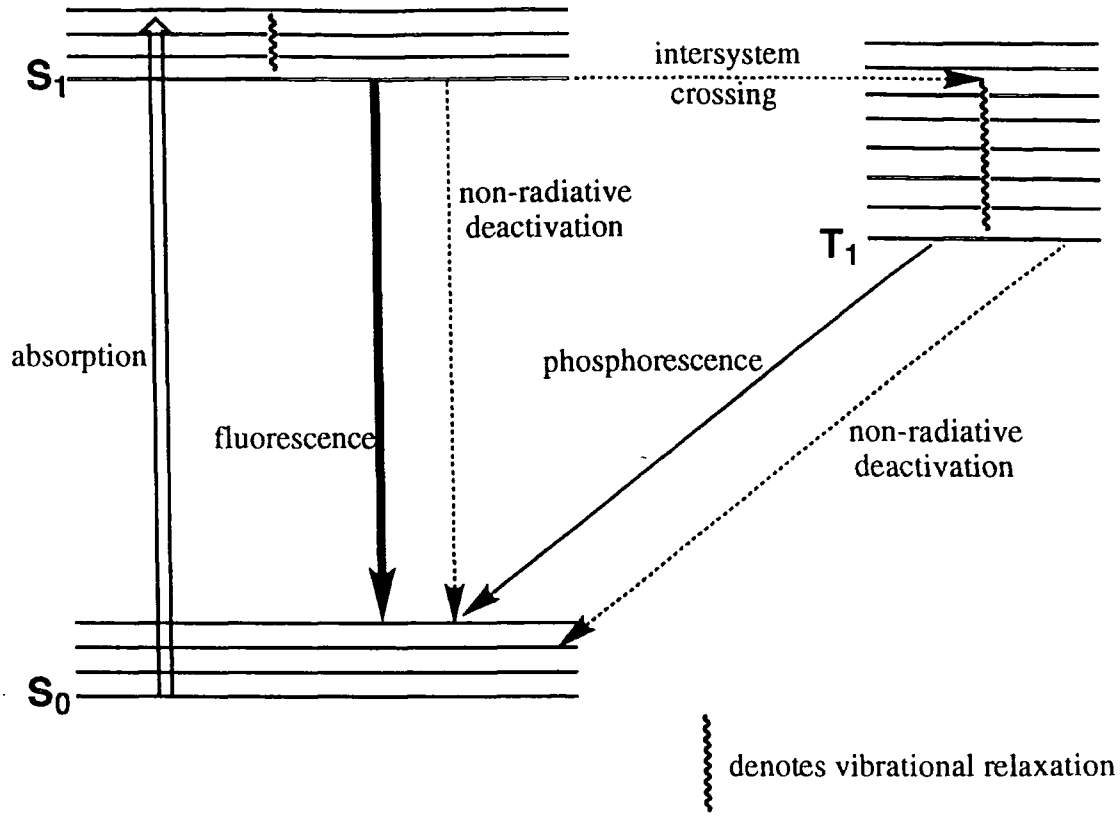


Figure 3.02 Jablonski diagram showing the routes of absorbed energy loss.

A molecule in the ground state, S_0, can be excited to the singlet state, S_1, by absorption of light. Vibrational de-activation (vertical dotted line on the Jablonski diagram) leads to the lowest vibrational state of the singlet excited state or to a lower singlet state. Intersystem crossing (horizontal dotted line) leads to triplet states. Emission from the lowest vibrational level of S_1 to any vibrational level of the ground state is fluorescence. Emission from the lowest vibrational level of the triplet state T_1 to any vibrational level of the ground state is phosphorescence.

Fluorescence takes place from the lowest vibrational level of the first excited state, S_1, and results in an electron dropping to one of the vibrational ground state levels. As the electron can drop to any of the vibrational levels of the ground state a

broad peak results. The fluorescence spectrum is , in ideal cases, a mirror image of the absorption spectrum but shifted to a higher wavelength (Stokes rule).

In order to display phosphorescence molecules in the S_1 excited state need to intersystem cross to the triplet state, T_1. From T_1 slow emission of radiation occurs (phosphorescence) or return to the S_0 ground state by another intersystem crossing resulting in no emission. Phosphorescence is bathochromically shifted compared to the absorbance spectrum, more so than for the fluorescence spectrum, as usually the T_1 energy level is lower than the S_1 and therefore phosphorescence occurs at higher wavelengths.

3.2.2 Requirements of a Molecule for use as a Fluorescent Sensor.

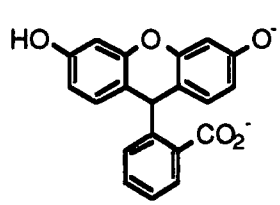
For a molecule to be a useful as a fluorescent sensor it requires:-

a) A rigid extended conjugation system connected to a binding site.

b) A change of fluorescence characteristics on binding.

c) Fluorescence emission in the region of 550 to 700 nm for clinical applications.

A rigid conjugation system is needed to absorb light. This system creates a molecular orbital of lower energy than a similar unconjugated system due to stabilisation by p orbital overlap. A lower S_1 level results and hence a reduction of the energy needed to promote an electron from the ground state to the excited state occurs bringing the wavelength of the energy into the visible or UV region. This produces a number of electrons in the S_1 level which may lead to fluorescence as the electrons return to the ground state. However, having electrons in the S_1 state does not guarantee fluorescence as the energy may be lost in several ways.



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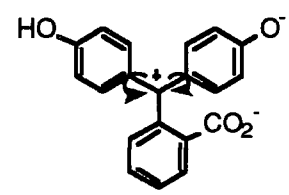


93

A rigid structure is required to prevent the energy of the excited states being lost by torsional vibration of the molecule. This can be seen in the strongly fluorescent molecule fluorescein (**92**) as against the non-fluorescent phenolphthalein (**93**).

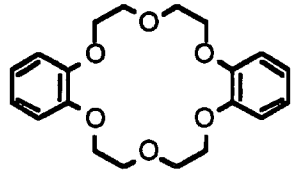
Phenolphthalein loses energy from the excited state by internal conversion (vibration of the benzene rings) whereas this cannot occur in fluorescein because of the ether bridge.

Alteration of the UV / visible spectrum occurs due to the charge on the cation affecting the charge density on the donor atom (either oxygen or nitrogen) in the fluorophore. The conjugated system is affected to differing degrees in the ground and the excited states thus altering the transitional energy of the photon that is absorbed/released by the molecule and hence changing the wavelength of the fluorescence maximum. Perturbation in the ground state and excited state of the molecule also effects the probability of excitation of the molecule and thus the extinction coefficients.

Ideally fluorescence should occur in the 550 to 700 nm region as this is the region in vivo applications can be considered. Below 550 nm natural absorption (eg. by protein molecules) and fluorescence (eg. by tryptophan) would hide or absorb the fluorescence. Above 700 nm water absorbs strongly so no signal would be visible.

3.2.3 Developments in Fluorescent ionophores.

Fluorescence of aromatic hydrocarbons is normally quenched by inorganic salts[4,5]. However, in the 1980's several authors detailed enhancements in the fluorescence of dibenzo 18-crown-6 (**94**) and 1,8-naptho 18-crown-6 (**95**) in the presence of metal cations[5,6,7,8].



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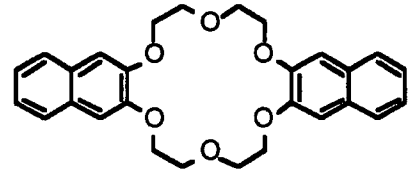
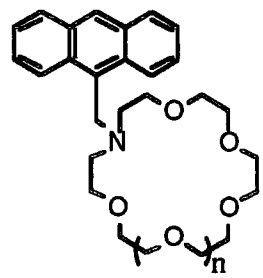
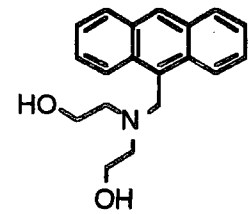


95.

DeSilva[9] investigated this phenomenon using the anthracene based systems anthraceno monoaza-18-crown-6 (**96**) and 21-crown-7 (**97**). Both gave increased quantum yields of a factor of 47 in the presence of sodium and potassium ions, although no such increase was seen with lithium. The analogous system (**98**), without a macrocycle, gave no such effect.

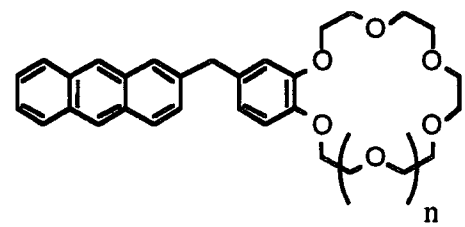


96. n = 1
97. n = 2



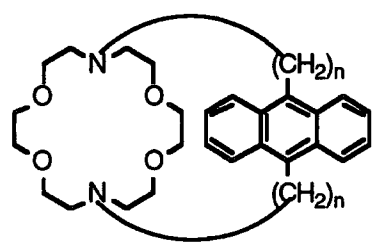
98.

DeSilva also synthesized analogous compounds with benzo crown ethers[10]. Again selective complexation of sodium and potassium gave increased quantum yields of fluorescence for (**99**) and (**100**).

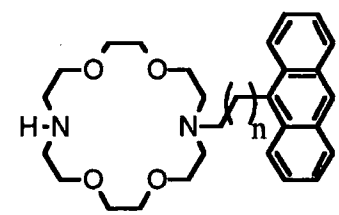


99. n = 1
100. n = 2

Lehn *et al*[11] used anthracene in bridged diaza 18-crown-6 (**101**) and also as a sidearm (**102**). The bridged diaza crown exhibits dual fluorescence whereas the sidearmed system only shows single fluorescence. The dual fluorescence results from



101. n = 2 or 3

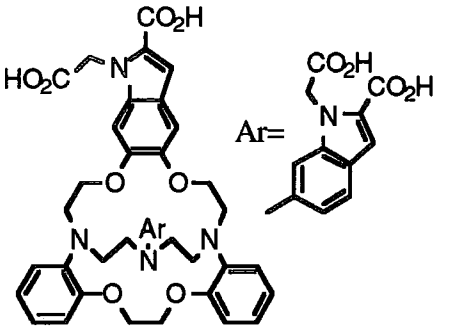


102.

an exciplex between the Π electron system of the fluorophore and the nitrogen lone pairs. Metal cations (Li, Na, K, Ag, and Tl) increased fluorescence quantum yields but quenched the excimer component. Quenching of the exciplex occurs as the nitrogen lone pairs interact with the ions and are therefore no longer able to interact with the Π system.

Smith *et al*[12] produced fluorescent cryptands (**103**) which exhibited a hypsochromic shift (460 to 395 nm) on complexation with sodium. This shift was not present with other alkali metals demonstrating the possible use of the cryptand as a

sodium sensor, although the slow kinetics of complexation raise doubts as to the accuracy of the values that could be obtained with the system. Also the pH dependence of cryptands may limit the applications of the fluorophore.



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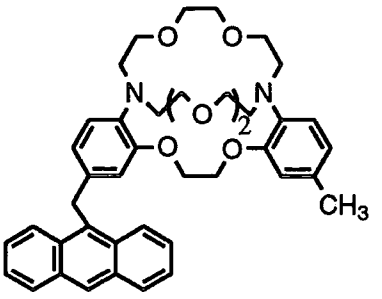
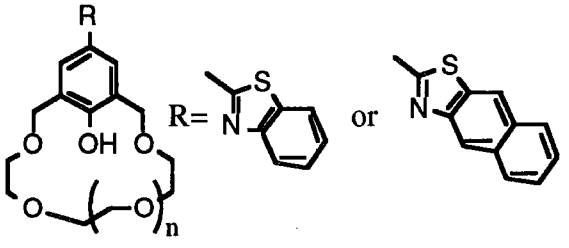


104.

DeSilva[13] later synthesized the cryptand (**104**) replacing the aryl nitrogen in (**103**) with a two oxygen bridge thus increasing the association constant of the complex. Various metal ions on complexation increased the quantum yields by a factor of around 10 due to de-conjugation of the nitrogen lone pairs and fast photoinduced electron transfer. However the ion selectivity of the system was significantly lower than that of (**103**) and therefore reduced the potential applications of this molecule.

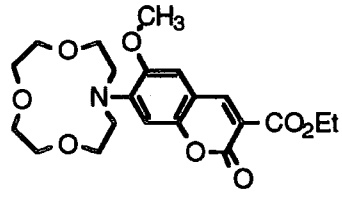
Lithium selective fluorescence has been demonstrated by coupling an ionisable phenolic crown with benzo- and naptho- thiazoylphenols (**105**)[14]. The smaller ring



105.

sizes, with n = 1 and n = 2, showed lithium selective emission relative to other alkali metal salts, while the larger sizes complex sodium (n = 3) and potassium (n = 4) selectively. A strong blue violet fluorescence is shown by these macrocycles due to two cooperative effects, the enhanced dissociation of the phenolic proton and the electrostatic interaction of the bound cation with the fluorescent anion.

A coumarin based monoaza 12-crown-4 (**106**) has been shown to have a hypsochromic shift in the presence of lithium ions[15]. The emission maximum shifts to shorter wavelengths with an increase in intensity on addition of lithium ions eventually reaching saturation.



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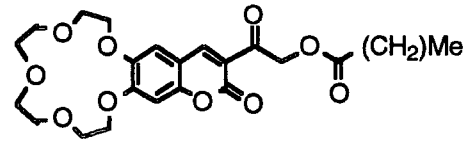
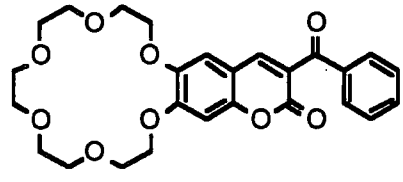


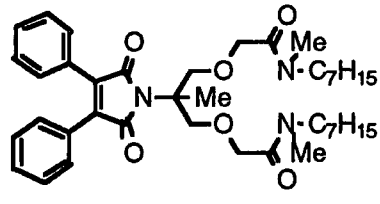
107.

The crowned-coumarin[16] (**107**) prepared by Takadate shows the perturbation of fluorescence when a metal cation interacts with the oxygens of the crown ether ring. An intensity drop is seen in the fluorescence in the presence of metal ions, the greatest drop occurring with sodium and potassium. Sodium and potassium both complex well with the benzo 15-crown-5, sodium forming a 1:1 complex and potassium a 2:1 complex. Similarly, the 3-aroylcoumarin crown ether (**108**) synthesized by Rodríguez-Ubis *et al* exhibits a fluorescence intensity drop with alkali and alkaline earth metals[17].



108.

The acyclic fluorophore (**109**), synthesized by Simon *et al* [18], demonstrated ion selectivity , with a $K^{pot}_{Li/Na} = -1.08$, transport behaviour in membranes and was shown to be a carrier for Li^+ in PVC membranes. It also demonstrated a hypsochromic shift (525 nm to 500 nm) with increasing lithium concentration (upto 20 equivalents).



109.

3.2.4 Excimer Emission.

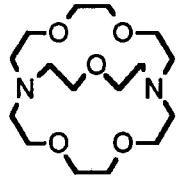
The first reported emission from an excited dimer (excimer) was made by Forster and Kaspar in 1954[19]. They found that as the concentration of pyrene in cyclohexane was increased the usual structured fluorescence band at 395 nm gave way to a strutureless emission with λ_{max} = 480 nm. This resulted from the formation of a complex of two pyrene molecules, one in the ground state and the other in the excited state[20].

As two ground state molecules are brought together they experience a mutual repulsion at smaller separations.. However, as an excited state molecule and a ground state molecule are brought together a net stabilisation results at small distances.and a weakly bound dimer is formed. The emission from the dimer is of lower energy than that from an isolated excited state monomer. Also, after emission the molecules fly apart as both are now in the ground state and repel each other. Hence, no vibratonal structure is seen.

The stabilisation of the excimer depends strongly on the overlap of the orbitals of the aryl groups. Theoretical calculations have led to the conclusion that the two chromophores are ideally 3.5 Å apart and in a parallel plane orientation for an excimer to be formed[21].

3.3 Lithum Ionophores.

Rapid complexation kinetics is essential for ionophores which are to be used as sensors, ensuring measurements can be made in a reasonable time scale. Hence, although the largest lithium selectivities are seen for spherand[22] (**9**) and [2,2,1] cryptand (**7**)[23] these are not used as they possess complexation kinetics which are too slow. Furthermore cryptands are pH sensitive Hence more flexible ligands, which demonstrate faster complexation kinetics, have been developed.



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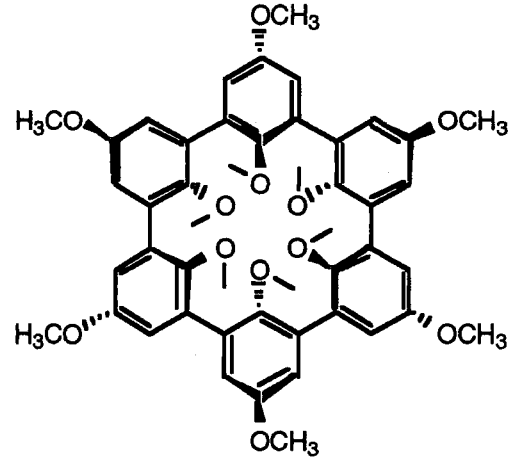
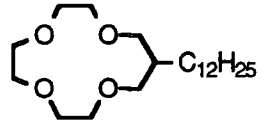


9.

3.3.1 Crown ether lithium ionophores.

A study of the effects of cavity size in 13 to 16-membered lipophilic tetraoxa crowns (**110-113**) showed that the 13-membered had a much lower selectivity for

lithium over other metal cations than the 14 and 15-membered rings (Table 3.02)[24]. The enhanced selectivity was not due to a size fit effect but due to the formation of two and three six-membered chelate rings on complexation with **111** and **112** respectively. As stated earlier (section 1.4.6) six-membered chelate rings favour small cations, such as lithium, as they allow the hydrogens to form a staggered conformation in the linking methylene groups. However, the pattern is reversed for the sixteen membered ring, steric crowding inhibits the formation of four six-membered chelate rings on complexation.



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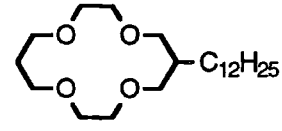

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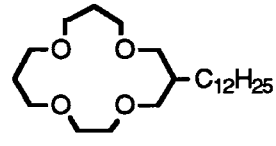

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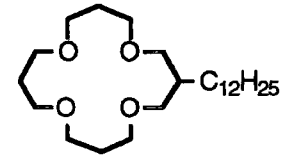
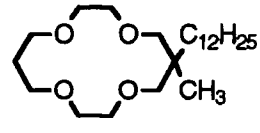


113

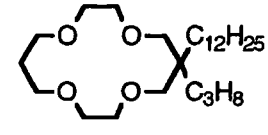
Ligand	**110**	**111**	**112**	**113**
$K^{pot}_{Li/Na}$	1.7	1.6×10^{-2}	3.2×10^{-2}	0.17

Table 3.02 Selectivity coefficients measured by potentiometry for ligands **110-113** (fixed interferent method, 5×10^{-2} mol dm^{-3} Na+ at 298 K).

Lithium selectivity was also affected by the existence and nature of geminal substituents to the dodecyl group[25]. A geminal methyl group (**114**) improved the lithium selectivity over sodium as did a geminal propyl group (**115**). The geminal groups inhibit the formation of 2:1 complexes for sodium and potassium.

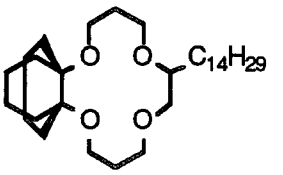


114.



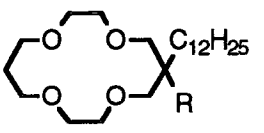
115.

Suzuki *et al* [26] prevented 2:1 complex formation by incorporating a decalino subunit into the ethanato bridge of 14-crown-4 (**116**). This crown has the highest lithium over sodium selectivity reported for a potentiometric ion selective electrode (-log $K^{pot}_{Li/Na}$ = 3.3). However, the Li^+/Na^+ selectivity of the ligand has not yet been tested in a serum background.



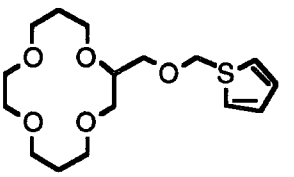
116.

Although high selectivity can be achieved using sterically hindered four co-ordinate systems crystallographic studies indicate lithium favours a co-ordination number of five or six[27,28]. The selectivity and complex stability of 14-crown-4 ligands may be modified by attaching sidearms to the macrocycle ring. The orientation of the donors must be such that they allow them to bind to the centrally held lithium.



117 R = $(CH_2)_2OCH_3$
118.R = $C_{12}H_{25}$
119.R = $(CH_2)_2OCH_2Ph$
120.R = $CH_2CO_2CH_3$
121.R = $(CH_2)_2CO_2CH_3$
122.R = CH_2CONEt_2
123.R = $CH_2OP(O)(OEt)_2$

Kitizawa *et al* [25] synthesized a number of 14-crown-4 derivatives (**117-123**) and assessed them potentiometrically using a fixed interference method. Of the derivatives examined only the amide (**122**) and phosphonate (**123**) functionalities enhanced the selectivity relative to the parent macrocycle. The amide and the phosphonate groups have high ground state dipole moments and thus favour binding of the small charged lithium ion over sodium and potassium.



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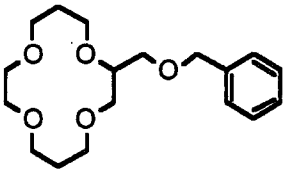

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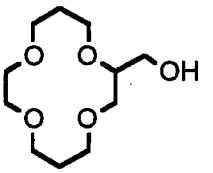

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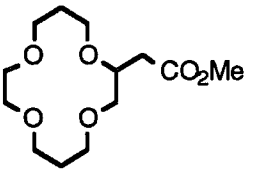

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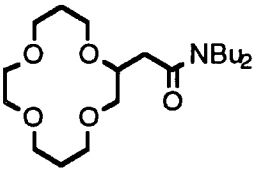

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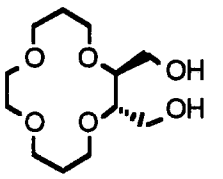

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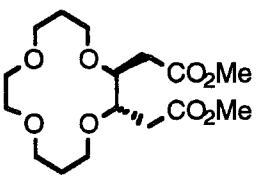

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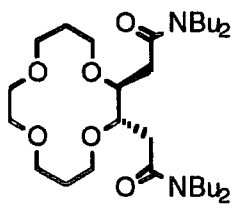

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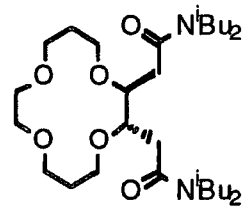

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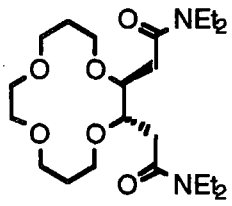

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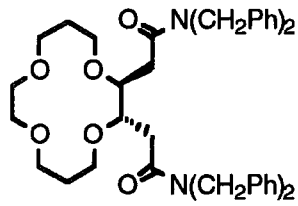

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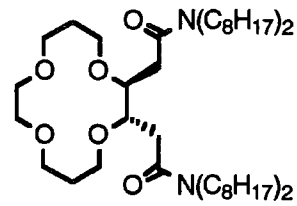
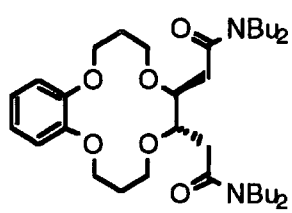


135.

Parker et al also studied the incorporation of sidearms into 14-crown-4. A series of 14-crown-4 derivatives were prepared varying the nature and number of donors (**124-135**)[29,30]. As lithium can exhibit octahedral co-ordination two additional "axial" donors can enhance the 1:1 complex and sterically inhibit the formation of 2:1 complexes with sodium and potassium. The length of the donor arm was such that six-membered chelate rings formed upon complexation. Amides again proved to be the most selective for lithium over sodium and potassium. A study of the nature of the amide varying the N-alkyl groups showed that n-butyl gave the highest selectivity in serum (-log $K^{pot}_{Li/m}$ = 2.92) and also gave fast response times (10 - 15 s)[31].

3.4 Aims and Objectives.



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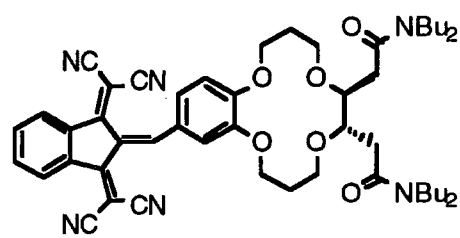


137.

a) At the outset of the project, the aim of this work was to synthesize the benzo 14-crown-4 (**136**) based on the crown (**131**) that gave the best performance in serum. If this proved to be lithium selective then it would be developed into a fluorescent sensor by connection of the benzene ring to an extended conjugation system, such as ligand **137**. Binding of an ion to the macrocycle ring's aryl oxygens will lead to a perturbation in the conjugation system leading to a change in the fluorescent characteristics of the ligand (fig. 3.03).

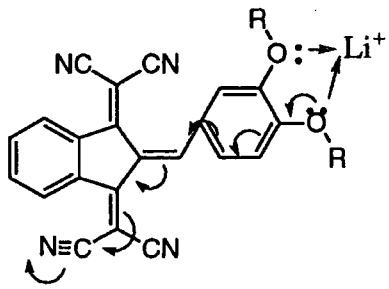
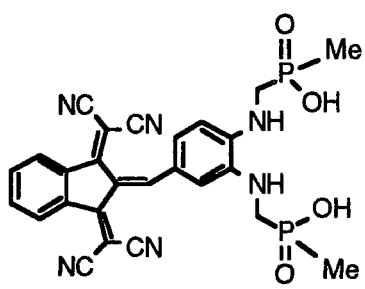
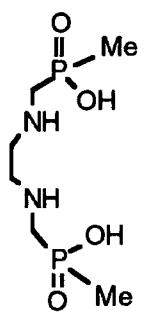


Figure 3.03 Peturbation of conjugation system when macrocyclic oxygens bind to an ion.

b) However, the synthesis of the benzo 14-crown-4 (**136**) proved very difficult and was not achieved. To establish the principle behind the idea it was proposed that a phenylene diamine based derivative (**138**) was synthesized and its fluorescence properties examined. The initial stimulus for this work was the podand **139** developed by Bates[32]. The podand exhibited strong complexation with small charged doubly charged ions, such as magnesium, calcium, nickel and zinc. It was proposed that the ligand could be synthesized using a substituted phenylene diamine.

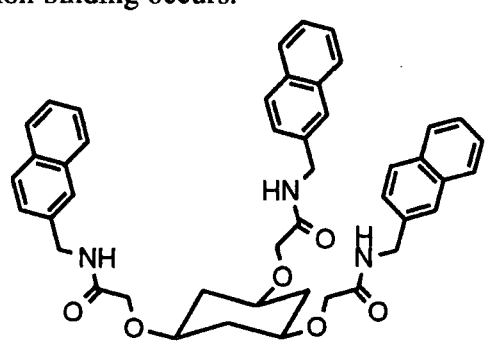


138.



139.

c) The ligand (**140**) was synthesized based on the sodium over potassium selective cyclohexane ligand (**63**). On binding it was thought that the naphthyl groups would be brought together causing the formation of an excimer which is not present in the unbound ligand. Hence, fluorescence at approximately 410 nm would be "switched on" when ion binding occurs.



140.

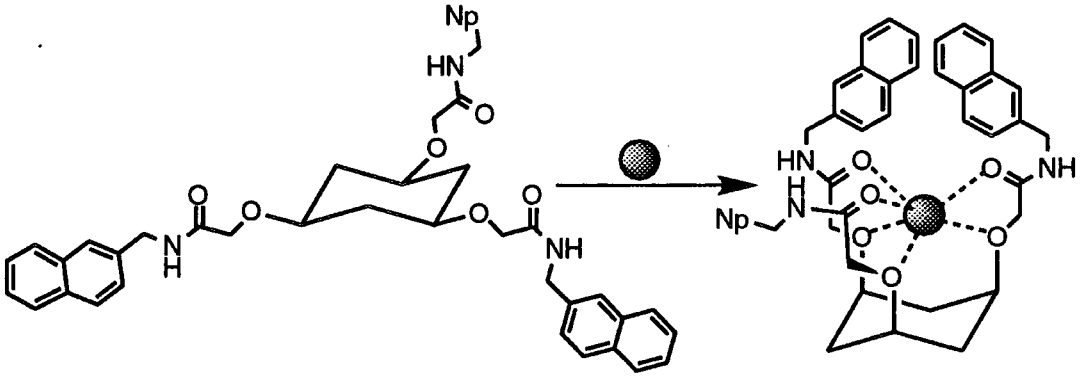
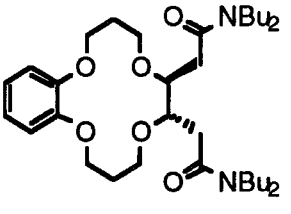


Figure 3.04 Switching on of excimer luminescence by ion binding.

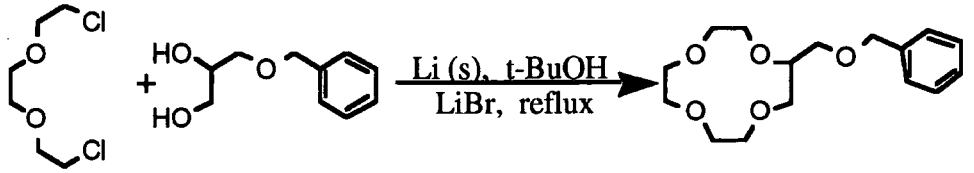
3.5 Synthesis of Ligands.

3.5.1 Synthesis of benzo 14-crown-4 derivative.



136.

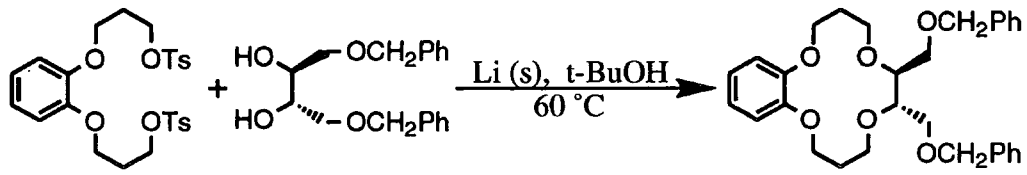
The ligand **136** was to be synthesized in a procedure analogous to that devised by Parker *et al* [26]. The cyclisation was performed using a modified procedure of that developed by Okahara et al (fig. 3.05)[33]. The success of the procedure is attributed to the heterogenous nature of the reaction. The lithium salt of the diol (**142**) is insoluble in the reaction solvent, tert-butanol, and thus the reaction occurs heterogenously under the template action of the lithium ion.



141. **142.** **143**

Figure 3.05 Okahara cyclisation procedure.

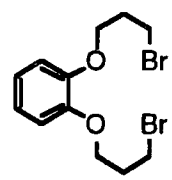
The actual procedure involved using a tosyl leaving group instead of the halide and is detailed below (fig. 3.06). The tosyl group is a better leaving group relative to the halide, reducing the reaction time required.



144. **145.** **146.**

Figure 3.06 Cyclisation procedure used.

Another change to the procedure was that lithium bromide was not added. Initial attempts at cyclisation included lithium bromide and lead to the isolation of the side product (**147**) and little of the desired product. After cyclisation the solvent was removed under reduced pressure and the residue dissolved in dichloromethane. At first the dichloromethane was washed with 0.1 molar hydrochloric acid to remove residual base and allow recovery of unreacted diol but purification of the product after washing always led to a reduced yield of the cyclised product. It is believed the electron rich ring system is prone to electrophilic attack and the acid causes ring opening. Hence, although this led to the solvent running very slowly, the crude oil was purified directly after removal of the tert-butanol by column chromatography.



147.

The reaction also occurs much more slowly than the analogous non-benzenoid cyclisation, taking around 14 days compared to the 3 days of the non-benzenoid reaction. The reduced flexibility of **144** reduces the probability of it adopting a conformation allowing cyclisation hence lengthening the reaction time. This increase in reaction time led to a difficulty in keeping the reaction completely dry and on several occasions benzo 11-crown-3 was isolated (fig. 3.07). The product results from nucleophilic attack by an hydroxide ion on one of the tosylate groups and then internal cyclisation occurring. To increase the speed of reaction mesylate leaving groups were used instead of the tosylate groups. However, this did not increase the reaction yield.

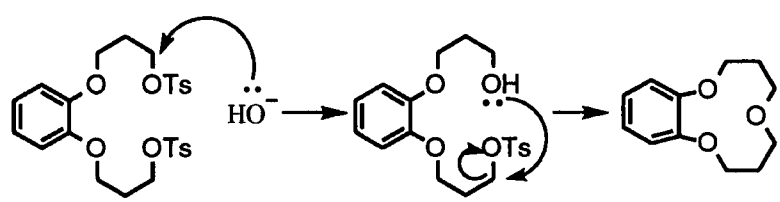
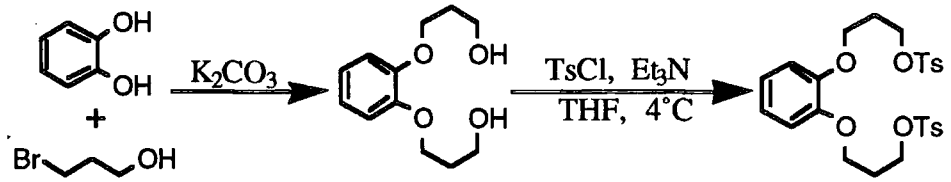


Figure 3.07 Mechanism of internal cyclisation.

Attempts to produce gram quantities of the cyclised product proved impossible the reaction becoming very difficult to stir, even with an over-head mechanical stirrer, as the reaction mixture became very viscous.

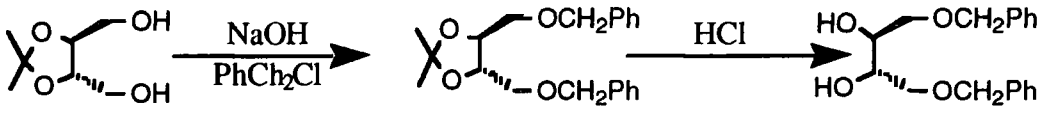


147. 144.

Figure 3.08 Synthesis of the ditosylate, **144**.

The ditosylate was synthesized by the procedure outlined above (fig 3.08). The diol (**147**) was readily prepared by alkylation of catechol using 1-bromopropanol and potassium carbonate. Initially tosylation was performed in pyridine at -20 °C but obtaining the product (**148**) from the pyridine once reaction had occurred led to difficulties. The tosylate (**148**) did not crystalise out on addition to ice and complete removal of the pyridine proved impossible without decomposition of the product. Therefore tosylation was carried out in dry tetrahydrofuran using triethylamine as a base. The reaction in both pyridine and in tetrahydrofuran proved to be slow, taking between 7 and 14 days, slow enough for the mono-tosylate to be observed during the reaction. The solvent and triethylamine salts could be readily removed and the product was obtained in 76% yield by column chromatography on silica.

Synthesis of the dibenzylated diol (**145**) was carried out using literature methods[34]. The benzylation of the diol was carried out in a slightly modified procedure, instead of using tetrapropylammonium bromide as a phase transfer catalyst tetrabutylammonium hydrogen sulfate was used. This was found to improve both the rate of reaction and the yield. The ketal protection was removed by hydrolysis, again using a slight modification of the reported synthesis with methanol and six molar hydrochloric being used.

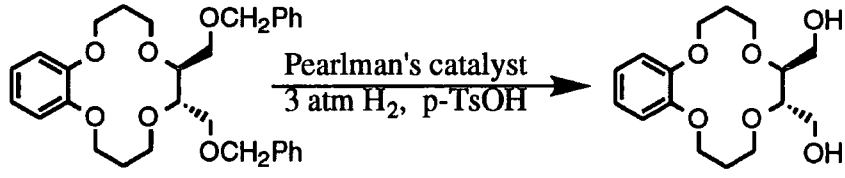


149. 145.

Figure 3.09 Synthesis of diol (**145**).

After cyclisation, the protecting benzyl groups were removed by catalytic hydrogenation using Pearlman's catalyst ($Pd[OH]_2$ on carbon, 30 % v/v water) with a

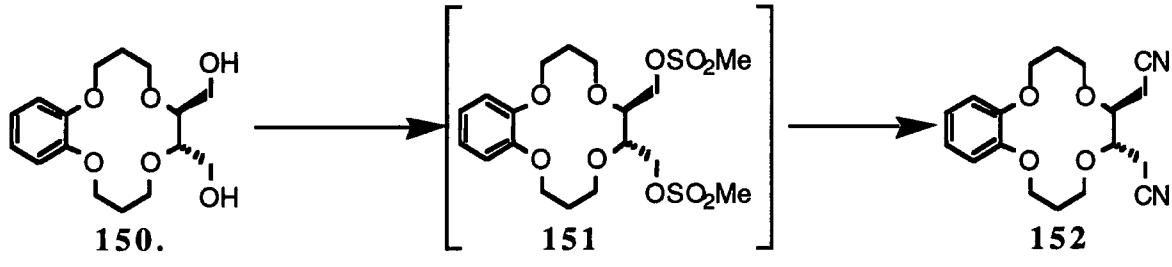
catalytic amount of p-toluene sulfonic acid in ethanol under a hydrogen pressure of 3 atm at room temperature. The purification of the product after hydrogenation was initially attempted by column chromatography on alumina. However, the chromatography process led to decomposition of most of the product and attempts to purify the product by chromatography on silica also resulted in the same decomposition. It was therefore necessary to simply wash the product with weak base, saturated sodium hydrogensulfate, to remove the p-toluene sulfonic acid and use the product as it was (purity was estimated at 95% by NMR examination).



146. **150.**

Figure 3.10 Deprotection of 14-crown-4.

In order to extend the length of the axial substituents by one carbon atom (fig 3.11) it was necessary to convert the diol to a good leaving group. Attempts to tosylate the diol (**150**) failed in both pyridine and tetrahydrofuran at -4 °C. Variation of the temperature from -20 °C to 25 °C had little affect, only the mono-tosylate being isolated at any stage. It is thought the steric bulk of the tosylate group combined with that of the benzo crown prevented a second tosyl group attacking the hydroxyl group. To circumvent this problem of steric inhibition the smaller mesyl leaving group was used. However, the high reactivity of the dimesylate prevents isolation of the intermediate (**151**), thus the product was given a minimal amount of purification, and then used immediately in the reaction with potassium cyanide.

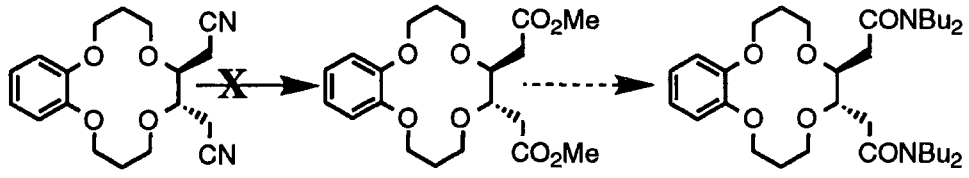


150. **151** **152**

Figure 3.11 Extension of the pendent arms by one carbon.

The dinitrile (**152**) was isolated by column chromatography. Ethanolysis of the dinitrile was then attempted to convert it to the ester (**153**) using an ethanol solution saturated with hydrochloric gas. However, the ester could not be isolated by this method and no sign of its formation was visible during the reaction (TLC, NMR or IR). A multitude of products was obtained from the reaction and it is believed, as stated earlier, the acidic conditions lead to ring opening of the macrocycle. A variety of

temperatures (-78 °C, -20 °C, 25 °C and boiling) were used in attempts to limit this, but with no success.

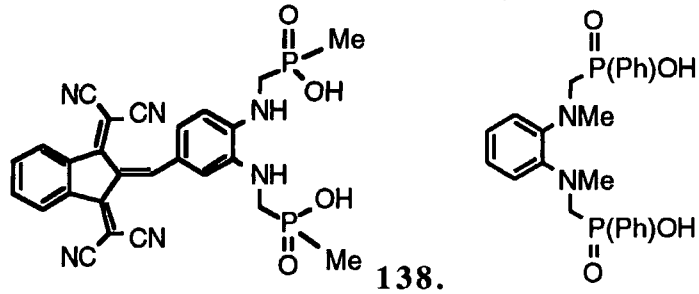


152 **153.**

Figure 3.12 Remaining steps in synthesis of target benzo 14-crown-4 derivative.

As no quick alternative to this route was available, the synthesis of the benzo 14-crown-4 derivative was abandoned at this stage.

3.5.2 Synthesis of phenylene diamine derivative.



138. **154.**

The ligand (**154**) was synthesized to test the binding characteristics of the parent ligand without the donor-acceptor system incorporated. In an analogous reaction to that carried out by Bates *et al* [29] on ethane-1,2-diamine (fig. 3.13), phenylene-1,2-diamine was reacted with paraformaldehyde and dimethoxy phenyl phosphine.

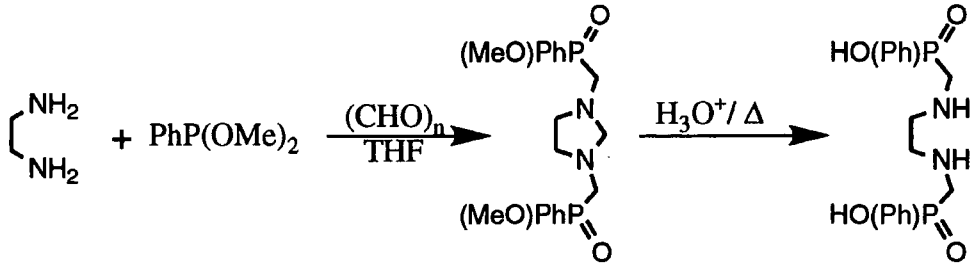
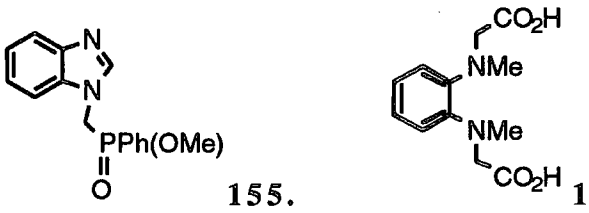


Figure 3.13 Alkylation and hydrolysis of ethane-1,2-diamine.

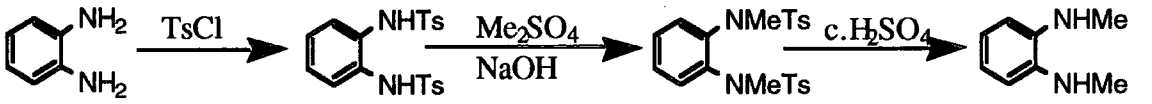
However, attempts to alkylate the phenylene diamine in the presence of formaldehyde only led to the formation of a benzaldehye derivative (**155**). The system becoming aromatic after reaction with formaldehyde had bridged the two nitrogens. After several attempts all resulted in formation of the benzimidazole derivative it became apparent that an alternative functionality had to be used. The binding characteristics of

carboxylates are similar to those of phosphonates thus a similar ligand to (**154**) was prepared (**156**).



155. **156.**

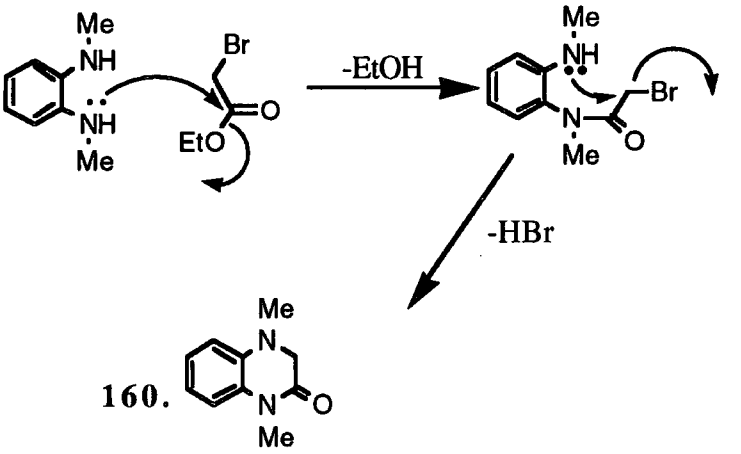
To avoid tetra-alkylation of the amines of phenylene-1,2-diamine one binding site of the nitrogens was converted to a methyl group. The synthesis of N,N'-dimethyl phenylene-1,2-diamine was achieved by Cheeseman's literature methods[35] (fig. 3.14). The tosylation of phenylene-1,2-diamine was carried out in pyridine the temperature being maintained below 60 °C. The product readily crystallised on addition of the reaction mixture to ice. Methylation using dimethyl sulfate gave good yields (96%) of the N-methyltosylamide (**158**). Heating of this with 9:1 concentrated sulfuric acid : water, addition to basic ice, and extraction gave a black oil which on distillation gave colourless crystals of the product (**159**). These rapidly decompose on exposure to air.



157. **158.** **159.**

Figure 3.14 Synthesis of N,N'-dimethyl o-phenylenediamine.

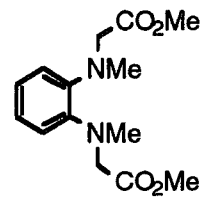
The N,N'-dimethyl o-phenylenediamine was used immediately in alkylation attempts. Initially, alkylation was attempted by using ethyl 2-bromoethanoate and potassium carbonate in acetonitrile. However, none of the desired product was obtained only the bridged amide (**160**) product being isolated (fig. 3.15).



160.

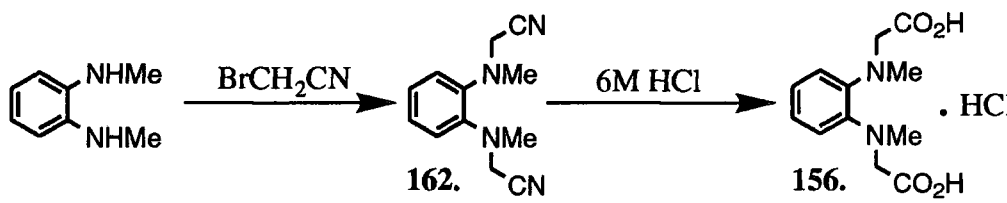
Figure 3.15 Lactamisation of N,N'-dimethyl o-phenylenediamine with ethyl 2-bromoethanoate.

To avoid the cyclisation a buffered reaction with 2-bromo-ethanoic acid was attempted. The pH was maintained at 9, sufficiently basic to ensure deprotonation of the acid, and thus prevent nucleophilic attack on the carbonyl, but not basic enough to produce hydroxide ions which would give an S_N2 reaction. The diamine was dissolved in 1:1 methanol : water and the pH maintained at 9 during addition of the bromoethanoic acid. After several attempts to obtain the diacid by crystallisation had failed, the crude reaction mixture was boiled under reflux with methanol and purification by column chromatography gave the diester (**161**) in a poor yield (7%).



161.

However, again the major product was the cyclised amide (**160**) (75% yield). It appeared that the rate of this favourable 6-exo tetrahedral cyclisation was very high and it proved impossible to adjust the pH sufficiently quickly. Use of a solution of potassium bromoacetate, made by reacting one equivalent of bromoacetic acid and one equivalent of potassium carbonate, and maintaing the pH = 9 with 0.1 molar sodium hydroxide solution still led to the cyclised product. Attempts to increase the yield of either the diacid or the diester by this method failed, so this route was abandoned and an alternative used.



162. **156.**

Figure 3.16 Synthetic route to amino acid (**156**).

Reaction of N,N'-dimethyl o-phenylenediamine with bromoacetonitrile and potassium carbonate gave the dicyanomethyl derivative (**162**). This was again air sensitive, colouring on exposure to air. Hydrolysis of the nitrile groups in degassed hydrochloric acid was slow, taking 4 days. The impurities were removed by recrystallisation from hot acetone to give purple crystals of the amino acid (**156**).

To facilitate attachment of the donor - acceptor group a similar synthetic route was used starting with 4-bromo-phenylene-1,2-diamine. 4-bromo-2-nitrophenylamine was prepared by literature methods[36], and the nitro group reduced using tin (II) chloride and hydrochloric acid to give the diamine (**163**). Following a similar route to that used before, tosylation and methylation of **163** gave **165**.

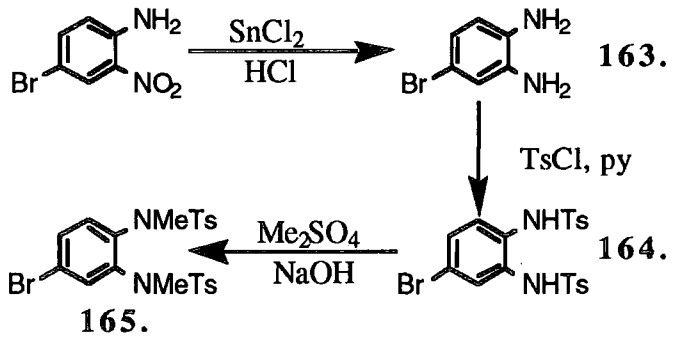


Figure 3.17 Synthesis of the brominated derivative (**165**).

Lithiation followed by reaction with carbon dioxide was attempted at this stage as the protected amines would facilitate the addition of the electron donor - acceptor system. However, intial attempts to lithiate the compound failed and scope for future work exists. With the benefit of hindsight, it may have been better to form a Grignard reagent and react this with carbon dioxide to give the acid.

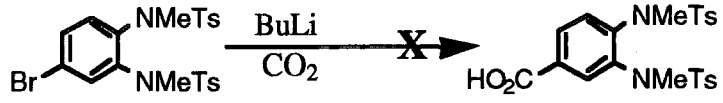
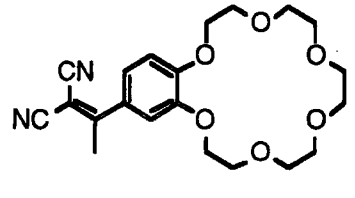


Figure 3.18 Attempted method of convertion of bromide to carboxylate.

3.5.3 Synthesis of malononitrile derivative of benzo 18-crown-6



In an effort to show the perturbation of fluorescence when an ion interacts with the conjugation of an electron donor - acceptor system, the benzo 18-crown-6 derivative (**166**) was synthesised.

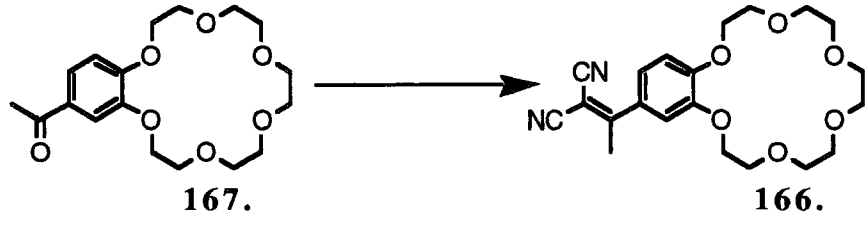
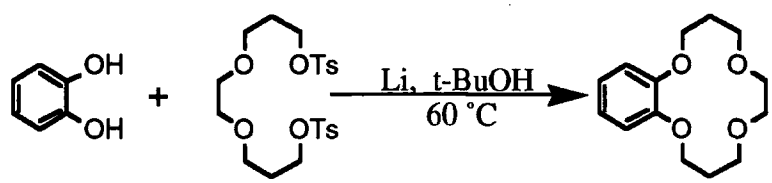


Figure 3.19 Malononitrile addition to acetyl benzo 18-crown-6.

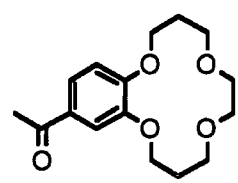
Benzo 18-crown-6 was acetylated following literature procedures[37]. This monoacetyl benzo-crown (**167**) was then reacted with malononitrile in ethanol in the presence of piperidine. After reaction was judged to be complete as indicated by IR analysis of a sample, the reaction mixture was cooled and the product isolated by filtration. Purification was attempted by column chromatography on alumina, however only starting material was isolated, the product hydrolysing during purification. Instead of purification by column chromatography the product was recrystallised. Initial attempts to recrystallise the product from wet ethanol only yielded the starting material. Recrystallisation from freshly distilled dry anhydrous ethanol gave the desired product (**166**) in poor yield (6%) with further attempts to gain more product from the ethanol only resulting in the hydrolysis of the product.



169. **168.**

Figure 3.20 Cyclisation to produce benzo-14-crown-4.

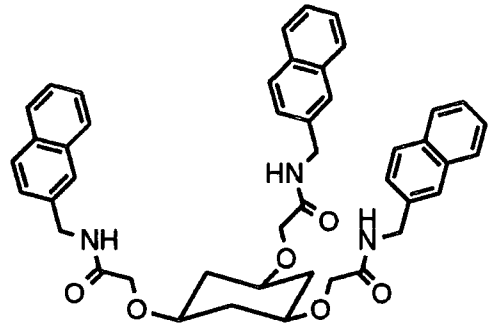
A similar reaction scheme was carried out on benzo-14-crown-4. The benzo 14-crown-4 (**168**) was synthesised following an analogous reaction to the cyclisations carried out earlier (section 3.5.1). Catechol was reacted with the ditosylate (**169**), which was prepared by literature methods[27], and the product purified by column chromatography. Acetylation of the benzo 14-crown-4 was carried out in an identical manner to the reaction of the benzo 18-crown-6. Polyphosphoric acid was warmed to 80 °C and a solution of the benzo 14-crown-4 in acetic acid added. After reaction the mixture was poured into ice, the product extracted, and purified by column chromatography on alumina to give 3'-acetyl benzo 14-crown-4 (**170**).



170.

Attempts to form the malononitrile derivative failed, isolation of the product proving impossible. The product could not be recrystallised and purification by column chromatography led to hydrolysis giving the starting material.

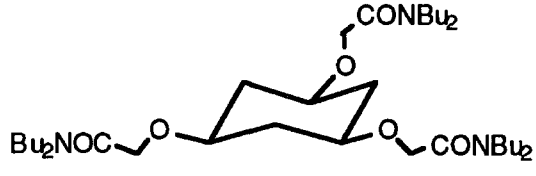
3.5.4 Synthesis of a cyclohexane trioxa-napthylmethyl amide.



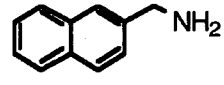
140.

171.

Hydrolysis of the triaoxa amide (**63**) was carried out using 1:1 methanol 6 molar hydrochloric acid. It was hoped that the acid could be isolated by a base wash of the products, reacidification of the aqueous layer and extraction of the acid. However, no product was obtained from the basic layer. Extraction of the acid layer gave the triester product (**171**) instead. Hydrolysis of the ester using 1 molar hydrochloric acid, removal of the solvent, and reaction with thionyl chloride at -20 °C in dichloromethane gave an intermediate acid chloride which was not isolated. Immediate addition of 2-napthyl methylamine (**172**) and triethylamine followed by purification by column chromatography gave the desired product (**140**).



63.



172.

3.6. Fluorescence characteristics of ligands 140 and 166.

3.6.1 Ligand 140.

The maximum ultra-violet / visible absorption band, $\lambda_{max,abs}$, was observed at 275 nm corresponding to the absorption of the naphthyl groups. The absorption maximum was determined in a variety of solvents (acetonitrile, dichloromethane, ethanol, isopropyl alcohol, methanol and tetrahydrofuran) but showed no significant solvent nor concentration dependence.

The ligand concentration used for fluorescence studies was 0.1 mmol dm^{-3}, and the excitation wavelength was 275 nm. The free ligand was examined in methanol and gave a spectrum corresponding to typical naphthyl group fluorescence. There was no eximer fluorescence observed with the free ligand, under any conditions.

The ligand is known to have a binding affinity for calcium ions of greater than $10^{5.5}$ in solutions and thus, in an attempt to study the fluorescence behaviour of the ligand, calcium ions were added to a methanolic solution of the ligand.

Over a wide range of calcium perchlorate concentrations the position of the maximum in the fluorescence spectrum did not change, nor did a new fluorescence band appear corresponding to the formation of an exciplex. However, a reduction in the intensity of the fluorescence maximum was observed. As the concentration of calcium increased relative to the concentration of ligand, the peak intensity decreased, suggesting that binding of the ion causes some quenching of the fluorescence. Similarly, on addition of between 1 to 20 mole equivalents of sodium trifluoromethanesulfonate the fluorescence intensity was reduced, again suggesting fluorescence was being quenched (ligand concentration = 0.1 mmol dm^{-3}).

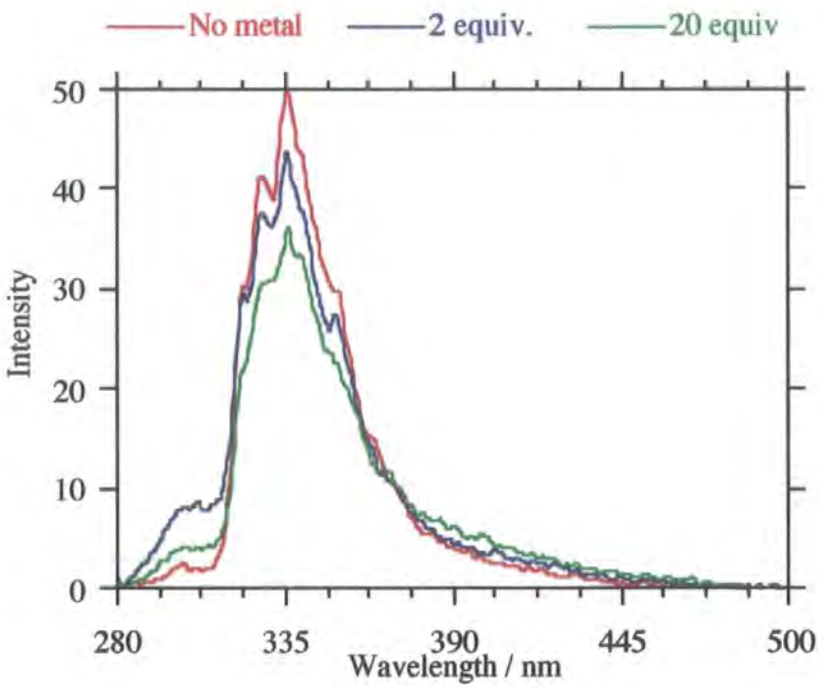


Figure 3.21 Fluorescence spectrum of ligand **140** on addition of calcium perchlorate (ligand concentration = 0.1 mmol dm^{-3}, 298 K, in MeOH).

The lack of the formation of a new fluorescence band on addition of metal ions would suggest that there is no interaction between the napthyl groups in the complex. CPK modelling indicated the distance between the nathyl groups in the complexed ligand should have been small enough to allow an interaction (3.5 Å) and formation of an excimer. However, the most stable conformation of the complex is not known and it appears that in this conformation the napthyl groups are not close enough to interact.

Infra-red studies of the complexes showed that the amide carbonyl groups in **140** were involved in binding of both the calcium and sodium ions (shifts of -14 cm^{-1} and -12 cm^{-1} respectively, with 5 equivalents of metal ion in methanol), as had been observed with the tris (N,N-dibutyl) analogue (Chapter 2 Section 2.5.4)

*3.6.2 Ligand **166**.*

The ultra-violet / visible absorption spectrum of **166** (concentration = 2.5 x 10^{-5} mol dm^{-3}) showed variation with solvent, ie. solvatochroism. The more polar the solvent, the lower the absorption maximum, corresponding to a hypsochromic shift. The interaction of the solvent with the ligand changes the charges and dipole moment of the ligand resulting in a perturbation of the ground state or excited state energy levels. The solvent will either stabilise the ground state or excited state energy levels, whichever is the more polar. The stabilisation of one level will cause a change in the energy gap between the ground and excited state and thus a change in the energy absorbed to promote an electron between the two levels. An hypsochromic shift results from the ground state being stabilised, lowering its energy and increasing the energy gap between the two levels, causing an increase in the transitional energy and hence decreasing the wavelength of the absorption maximum.

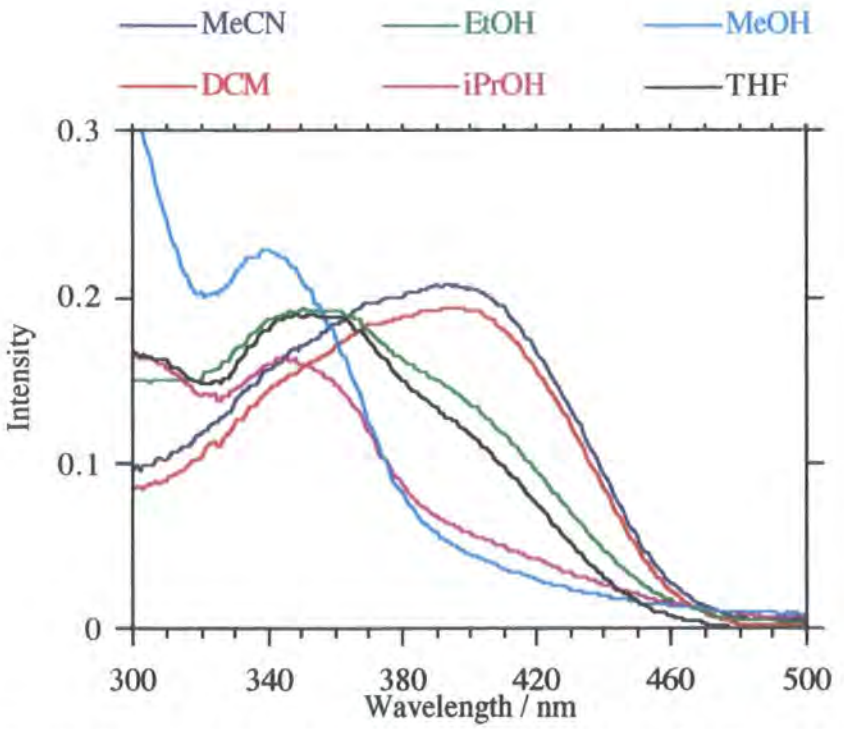


Figure 3.22 Variation of ultra-violet response with solvent for ligand **166** (293 K, ligand concentration = 2.5 x 10^{-5} mol dm^{-3})

The ultra-violet / visible spectrum did not change when excess (50 equivalents) potassium iodide was added to a solution of the ligand in methanol. However, in the fluorescence spectrum an effect was seen. With no metal present, the fluorescence maximum was at 411 nm in a methanol solution (concentration = 2.5 x 10^{-5} mol dm^{-3}). As potassium ions were added the emission band shifted to higher wavelengths, a bathochromic shift, reaching a maximum wavelength of 458 nm when two equivalents of potassium iodide had been added.

The shift in the peak to higher wavelength on addition of potassium ions is a result of the bound cation decreasing the energy gap between the ground and excited states. The cation removes electron density from the conjugated system resulting in a stabilisation of the excited state and thus decreasing the transitional energy required to promote an electron from the ground state to the excited state.

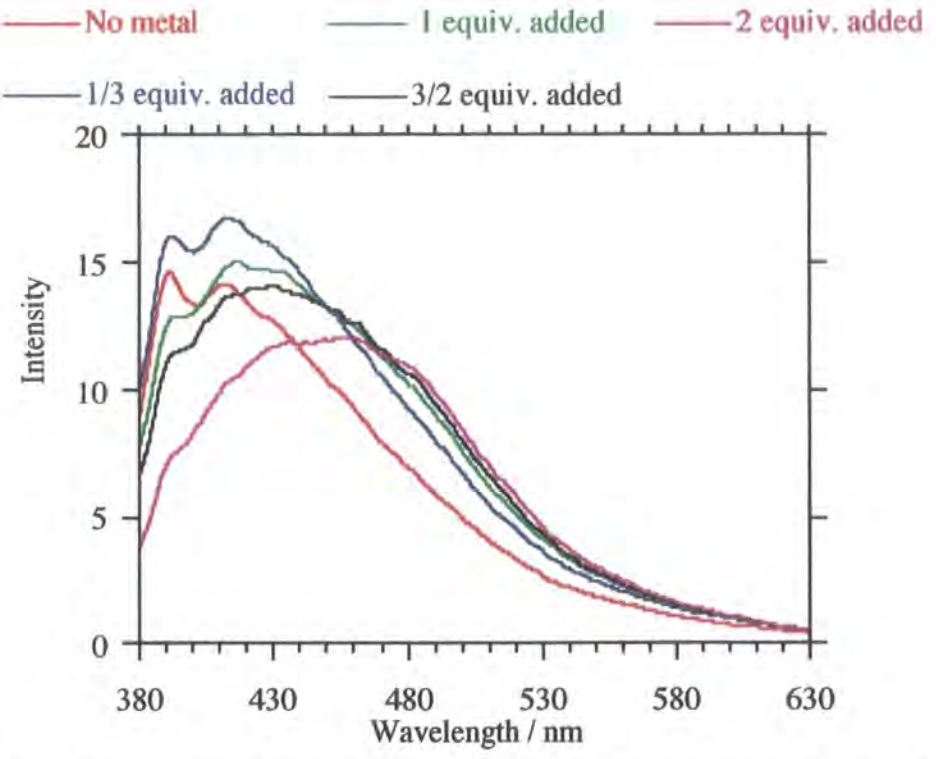


Figure 3.23 Fluorescence of ligand **166** on addition of potassium iodide (methanol, 298 K, λ_{em} = 350 nm, ligand concentration = 2.5 x 10^{-5} mol dm^{-3})

Further studies of the ligand's fluorescence were hampered by its tendency to leech sodium out of glassware and / or bind sodium from background sources. Even the crystalline product when used immediately in a freshly distilled Aristar grade methanol solution gave the fluorescence spectrum of the fully complexed ligand.

3.7 Conclusions

The fluorescent benzo 18-crown-6 (**166**) demonstrates the principle of cation perturbed fluorescence in benzo crowns. The ligand shows a shift on full binding of 44 nm. A larger donor - acceptor system would allow the wavelength of fluorescence to be increased to more suitable values for biological use. The results indicate it would be worth pursuing the route of using a benzo crown attached to a donor - acceptor conjugation system to produce a lithium selective fluorophore.

The failure of the napthylmethyl trioxa amide (**140**) to form an exciplex is probably because the naphthyl groups do not come close enough together in the bound state to interact. The ligand may well be sterically crowded upon binding causing the napthyl groups to swing away from each other thus preventing any interaction. Alternatively the two napthalene groups may be unable to line up parallel and so again no interaction occurs. A more rigid system involving a napthyl-amide, ie. a system without the methylene group between the nitrogen and the napthalene ring, may prevent the rings from swinging away. However, the rings may not be able to lie parrallel to each other. The synthesis of this type of ligand was not attempted as it involves the use the highly toxic and carcinogenic 2-chloronapthalene (and similar halides).

3.8 References.

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CHAPTER 4.

EXPERIMENTAL.

4. Experimental.

4.1 Potentiometric Studies

The membranes were prepared by dissolving 1.3% ionophore, 65.6% NPOE (Fluka), 32.8% PVC (high molecular weight, Fluka) and 0.5% sodium tetra kis[3,5-bis(trifluoromethyl)phenyl]borate in distilled tetrahydrofuran and casting the solution in a glass ring resting on a sheet of plate glass. Slow evaporation was achieved by weighting down a pad of filter papers on top of the ring. Discs 7 mm in diameter were cut from these master membranes and mounted in standard electrode bodies supplied by Fluka. The inner filling solution was a 10^{-3} mol dm^{-3} solution of the analyte. The electrodes were conditioned in 10^{-2} mol dm^{-3} analyte solution. Calibrations and selectivity measurements were performed using a constant volume dilution technique in a thermostatted small volume cell (~2.3 cm^3). A T-shaped thermostatted liquid junction configuration was used in which the analyte solution flowed over a capillary containing a saturated KCl bridge solution in contact with a saturated calomel reference electrode (Russell pH Ltd). Measurements were recorded by a buffer amplifier interfaced to a Keithley 197 multimeter and a chart recorder (Kipp and Zonen).

Selectivity coefficients were determined by the fixed interferent method. Solutions were made up in deionized water. Analar NaCl, KCl, LiCl, $MgCl_2.6H_2O$ and $CaCl_2$ (1 mol dm^{-3} volumetric solution) were obtained from BDH, Microselect NH_4Cl from Fluka and RbCl (99.99%) from Aldrich.

4.2 Electrospray Mass Spectrometry

Spectra were recorded with a VG Platform II (Fisons Instruments) employing Mass Lynx software. Samples were presented as solutions in methanol (Aristar Grade, BDH unless otherwise stated) at a flow rate of 0.01 cm^3 min^{-1}.

Solutions were made up in glassware or PMP volumetric flasks. Samples were prepared using Gilson Pipetman micropipettes, in polypropylene Eppendorf tubes. Glassware was washed with hot nitric acid, thoroughly rinsed with deionized water and dried. Plastics were washed with methanol or propanol followed by deionized water and then dried at 35 °C in air. The spectrometer was operated in positive ion mode, with a capillary voltage of 4 kV and source temperature of 60°C. Mass scale calibration employed NaI. (HPLC grade

methanol (Fisons) was used as the background (carrier) solvent into which the samples were 'injected'). Cone voltages and analyte concentrations were varied according to the nature of the experiment (see text) and ranged from 30 to 110 V, and from 10^{-4} mol dm^{-3} to 10^{-7} mol dm^{-3}.

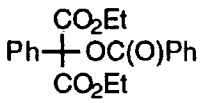
The solvent flow was maintained using a Hewlett Packard HPLC instrument that was directly linked to the ES mass spectrometer. The sample was inserted into the flow using an injection value with a 10 μl or 100 μl steel loop and transported to the electrospray capillary through a silica tube. The injection valve and tubing were flushed through with a variety of solvents from dichloromethane to deionized water prior to experiments being performed.

4.3 Syntheses

All reactions were carried out in apparatus which had been oven-dried and cooled under argon. All solvents were dried from an appropriate drying agent and water was purified from the 'Purite' system. Alumina refers to Merck Alumina activity II-III that was soaked in ethyl acetate for at least 24 hours prior to use. Silica refers to Merck silica gel F60 (230-400 mesh). ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC 250 operating at 250.13 and 62.90 MHz respectively, Varian Gemini 200 operating at 200 and 50.1 MHz respectively, Varian XL 200 operating at 200.1 MHz, and a Varian VXR 400S operating at 400.1 MHz. All chemical shifts are given in ppm relative to the residual solvent resonance and coupling constants are in Hz.

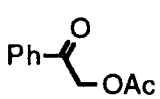
Mass spectra were recorded on a VG 7070E, operating in EI^{+} or DCI ionization modes as stated. Electrospray mass spectra were recorded using a VG Platform (Fisons instruments) operating in ES^{+} mode or were performed by the EPSRC Mass Spectrometry service at Swansea. Accurate mass spectrometry was performed by the EPSRC Mass Spectrometry service. Infra-red spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer as a thin film or KBr disc, or as a solution in MeOH using CaF_2 cells, as stated. Ultra-violet spectra were recorded on a UVIKON 930 spectrometer. Combustion analysis was performed using an Exeter Analytical Inc CE440 elemental analyser. Metal concentrations were determined by atomic absorption spectroscopy using a Perkin Elmer 5000 atomic absorption spectrophotometer. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.

Diethyl-2-benzoyl-2-phenylmalonate (69):[1]



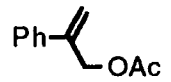
Sodium hydride (0.72 g, 0.03 mol) was suspended in toluene (30 ml) under N_2 and diethyl phenylmalonate (7.08 g, 0.03 mol) added dropwise over 45 min. The mixture was stirred for 2 h before being cooled to 0 °C and benzoyl peroxide (4.82 g, 0.02 mol) added over 40 min. The mixture was stirred for 28 h, poured into water (75 ml), the toluene layer separated, and the water layer extracted with diethyl ether (3x50 ml). The diethyl ether extracts were combined with the toluene, washed with water until neutral, dried ($MgSO_4$), and the solvent removed. The excess diethyl phenylmalonate was distilled off under reduced pressure (125 °C, 2mm Hg) to leave a yellow oil. Recrystallisation from hexane gave a pale yellow crystalline solid, 5.20 g (74%). mp = 79-81 °C (lit. 80-81 °C). δ_H ($CDCl_3$) 1.22 (t, 6H, $C\underline{H}_3CH_2$, *J* 7.1), 4.27 (q, 4H, $CH_3C\underline{H}_2$, *J* 7.1), 7.58 (m, 8H, Arom.), 8.22 (m, 2H, Arom.). δ_C ($CDCl_3$) 13.74 ($\underline{C}H_3$), 62.43 ($\underline{C}H_2$), 82.74 ($\underline{C}$), 125.82, 128.45, 128.51, 128.99, 129.04, 129.94, 133.61, and 133.99 (Arom.), 165.18 ($\underline{C}O_2Et$), 165.60 ($\underline{C}OPh$). $m/_z$ (CI, dichloromethane) 357 (MH^+, 24%), 252 (M^+-OCPh, 100%). Found C = 67.61, H = 5.70, $C_{20}H_{20}O_6$ requires C = 67.42, H = 5.62.

2-Acetoxy-acetophenone (72):



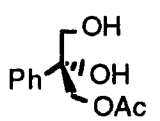
2-Bromo-acetophenone (10 g, 0.05 mol) and potassium ethanoate (6 g, 0.06 mol) was heated under reflux in ethanoic acid (50 ml) for 14 h. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (75 ml), filtered, washed with water (3 x 25 ml), and dried (K_2CO_3). The solvent was removed to yield orange crystals, 8.06 g (91%). mp = 45-47 °C. δ_H ($CDCl_3$) 2.22 (s, 3H, $C\underline{H}_3$), 5.24 (s, 2H, $C\underline{H}_2$), 7.54 (dt, 3H, Arom.), 7.90 (dd, 2H, Arom.). δ_C ($CDCl_3$) 20.90 ($\underline{C}H_3$), 66.51 ($\underline{C}H_2$), 128.15 (meta Arom. $\underline{C}H$), 129.26 (ortho Arom. $\underline{C}H$), 134.28 (para Arom. $\underline{C}H$), 134.57 (Arom. $\underline{C}$), 170.75 ($\underline{C}O_2$), 192.66 ($\underline{C}OPh$). υ_{max} (KBr disc) (cm^{-1}) 1226 (CO), 1742 (CO_2). $m/_z$ (CI, dichloromethane) 179 (M^+, 43%), 105 (PhCO, 100%). Found C = 66.95, H = 5.70, $C_{10}H_{10}O_3$ requires C = 67.03, H = 5.63.

3-Acetoxy-2-phenylpropene (73):[2]



Methyltriphenylphosphonium bromide (10.1 g, 0.283 mol) and potassium tert-butoxide (3.17 g, 0.283 mol) were suspended in THF (150 ml) and stirred under N_2 at 40 °C for 1 h. 2-acetoxy-acetophenone (4.85 g, 0.270 mol) was added and the mixture heated under reflux for 46 h under N_2, evaporated to dryness, and extracted with hexane (3 x 75 ml). The solvent was removed and the residue purified by column chromatography on silica, eluting with 3:1 dichloromethane : hexane (R_f = 0.65), to give a yellow oil, 3.85 g (79%). δ_H ($CDCl_3$) 2.08 (s, 3H, $C\underline{H}_3$), 4.99 (s, 2H, $C\underline{H}_2$), 5.37 (d, 1H, $=C\underline{H}_E$, *J* 1), 5.57 (d, 1H, $=C\underline{H}_Z$, *J* 1), 7.39 (m, 5H, Arom.) (lit. ($CDCl_3$) 2.04, 4.97, 5.35, 5.52, 7.35). δ_C ($CDCl_3$) 21.43 ($\underline{C}H_3$), 66.25 ($\underline{C}H_2$), 115.72 ($=\underline{C}H_2$), 126.56 (ortho Arom. $\underline{C}H$), 128.61 (para Arom. $\underline{C}H$), 129.04 (meta Arom. $\underline{C}H$), 138.55 (=C), 143.09 (Arom. $\underline{C}$), 171.27 ($\underline{C}O$) (lit. (CD_2Cl_2) 21.1, 66.0, 115.2, 126.4, 127.9, 128.5, 128.9, 143.3, 170.8). υ_{max} (thin film) (cm^{-1}) 1740 (C=O), 1228 (CO). $^m/_z$ (CI, dichloromethane) 177 (MH^+, 100%), 194 (MNH_4^+, 29%).

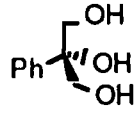
3-Acetoxy-1,2-dihydroxy-2-phenylpropane (74):



3-acetoxy-2-phenylpropene (3.17 g, 18.0 mmol) and N-methylmorpholine N-oxide (NMO) (2.22 g, 19.0 mmol) were dissolved in tert-butanol (20 ml) and 2.5% w/v solution of osmium tetroxide in tert-butanol (0.6 ml) was added. The solution was stirred for 5 days and further NMO (0.5 g, 4.3 mmol) and 2.5% w/v osmium tetroxide solution (0.6 ml) added. After another 2 days sodium sulfite (2.0 g) was added, the mixture stirred for 1 h and methanol (50 ml) was added. The mixture was filtered through celite, the solvent removed under reduced pressure, water (10 ml) added, and the pH reduced to 2 using 1M hydrochloric acid. The product was extracted with dichloromethane (2 x 50 ml), dried (K_2CO_3), and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica, eluting with 3:1 dichloromethane : hexane to remove fast running impurities and the product removed with ethyl

acetate (R_f = 0.8), to give a colourless oil, 1.26 g (46%). δ_H (CD_3OD) 2.03 (s, 3H, $C\underline{H}_3$), 3.77 (d, 2H, $C\underline{H}_2OH$), 4.41 (d, 2H, $C\underline{H}_2O$), 7.35 (m, 3H, Arom. C<u>H</u>), 7.55 (m, 2H, Arom. C<u>H</u>). δ_C (CD_3OD) 21.29 ($\underline{C}H_3$), 68.37 ($\underline{C}H_2OH$), 69.52 ($\underline{C}H_2O$), 77.02 (<u>C</u>), 127.37 (ortho Arom. <u>C</u>H), 128.78 (para Arom. <u>C</u>H), 129.56 (meta Arom. <u>C</u>H), 143.67 (Arom. <u>C</u>), 173.25 (<u>C</u>O). υ_{max} (thin film) (cm^{-1}) 1731 (CO_2), 1247 (CO). m/z (CI, methanol) 193 ($[M\text{-}OH]^+$, 100%), 228 (MNH_4^+, 11%). Found C = 67.79, H = 7.26, $C_{11}H_{14}O_4$ requires C = 68.04, H = 7.22.

2-Phenyl-1,2,3-trihydroxypropane (68):



Method 1:

Lithium aluminium hydride (5.6 g, 0.15 mol) was suspended in dry diethyl ether (100 ml) under argon and cooled to -20 °C. Diethyl-2-benzoyl-2-phenylmalonate (4.85 g, 13.7 mmol) was dissolved in dry diethyl ether (100 ml) and added dropwise over 1 h. The reaction was then heated under reflux for 96 h, and the lithium aluminium hydride quenched with water (10 ml), 20% w/v sodium hydroxide solution (10 ml), and water (10 ml). The aluminium salts were filtered off and the solvent removed to yield a small quantity of crude product. The aluminium salts were suspended in 9:1 chloroform : methanol and heated under reflux for 6 h. The suspension was filtered and the solvent removed under reduced pressure to yield more crude product. The product was purified by column chromatography on silica eluting with ethyl acetate (R_f = 0.2) to yield a white solid, 219 mg (10%).

Method 2:

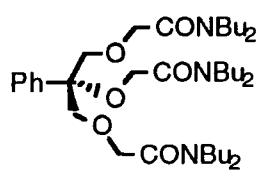
Diethyl-2-benzoyl-2-phenylmalonate (1.10 g, 3 mmol) was suspended in 1:1 ethanol : water (60ml) and lithium hydoxide monohydrate (0.46 g, 11 mmol) added. The reaction was stirred for 28 h, the pH reduced to 8 using 0.1M hydrochloric acid and the solvent removed under vacuum at room temperature to give a white powder. The powder was suspended in dry THF (30 ml), cooled to -40 °C under N_2 and 1M borane-THF complex (20 ml) added over 20 min. The mixture was allowed to warm to room temperature, stirred for 14 h, 1M borane-

THF complex (20 ml) added and stirred for a further 4 days. The reaction was quenched with methanol and the solvent removed under reduced pressure. Methanol (100 ml) was added to the residue and the mixture heated under reflux for 3 h to remove residual borane salts. The solvent was removed and the oily residue purified by column chromatography on silica eluting with ethyl acetate (R_f = 0.2) to give a white solid, 40 mg (8%).

Method 3:

Sodium (5 mg) was dissolved in methanol (30 ml) and 3-acetoxy-1,2-dihydroxy-2-phenylpropane (1.16 g, 5.52 mmol) added. The solution was stirred for 14 h, and passed through acidic cation exchange resin eluting with methanol. The solvent was removed and the residue purified by column chromatography on silica eluting with ethyl acetate (R_f = 0.2) to give a white solid, 0.77 g (83%). mp = 44-46 °C. δ_H ($CDCl_3$) 3.62 (br s, 2H, $CH_2O\underline{H}$), 3.80 (d, 2H, $C\underline{H}_2OH$, *J* 11.5), 3.98 (d, 2H, $C\underline{H}_2OH$, *J* 11.5), 4.35 (s, 1H, CO<u>H</u>), 7.48 (m, 5H, Arom.). δ_C(CD_3OD) 68.23 ($\underline{C}H_2OH$), 78.17 ($C\underline{C}H_2$), 127.39 (ortho Arom. <u>C</u>H), 128.30 (para Arom. <u>C</u>H), 129.32 (meta Arom. <u>C</u>H), 144.52 (Arom. <u>C</u>). υ_{max} (KBr disc) (cm^{-1}) 3262 (OH), 696 (Ar-H). $m/_z$ (CI, methanol) 186 (MNH_4^+, 100%), 168 (M^+, 16%). Found C = 64.56, H = 7.82, $C_9H_{12}O_3$ requires C = 64.25, H = 7.20.

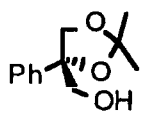
2-Phenyl-1,2,3-tri(N,N-dibutyl-carbamoylmethyloxa)-propane (61):



2-Phenyl-1,2,3-trihydoxypropane (550 mg, 3.27 mmol) and potassium iodide (1.08 g, 6.54 mmol) were dissolved in THF (25 ml) under argon. Sodium hydride (0.15 g, 6.25 mmol) and then N,N dibutyl-chloroethanamide (0.80 g, 3.9 mmol) were added. The mixture was heated under reflux for 6 days, after 2 and 4 days additional sodium hydride (0.15 g, 6.25 mmol) and N,N dibutyl-chloroethanamide (0.80 g, 3.9 mmol) were added. Additional THF (50 ml) was added, the reaction filtered through celite and the residue purified by column chromatography on alumina eluting with hexane : ethyl acetate (3:1 to 5:2) (R_f = 0.2 in 3:2 hexane : ethyl acetate) to yield a brown oil, 608 mg (28%). δ_H 0.93

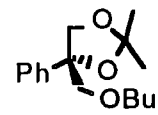
(m, 18H, $C\underline{H}_3$); 1.28 (m, 12H, $CH_3C\underline{H}_2$); 1.48 (m, 12H, $CH_3CH_2\underline{C}H_2$); 3.05 (t, 4H, $NC\underline{H}_2$); 3.27 (m, 8H, $NC\underline{H}_2$); 3.94 (d, 2H, $CC\underline{H}_2O$, *J* 10); 4.07 (d, 2H, $CC\underline{H}_2O$, *J* 10); 4.18 (s, 2H, $C\underline{H}_2CO$); 4.21 (s, 2H, $C\underline{H}_2CO$); 4.31 (s, 2H, $C\underline{H}_2CO$); 7.31 (m, 3H, Arom. C<u>H</u>); 7.55 (m, 2H, Arom. C<u>H</u>, J). δ_C 14.17, 14.26 and 14.31 ($\underline{C}H_3$, rotamer); 20.34, 20.48 and 20.67 ($\underline{C}H_2CH_3$, rotamer); 30.12, 31.28 and 31.46 ($CH_2\underline{C}H_2CH_2$, rotamer); 45.96, 46.09, 46.92, and 46.98 ($N\underline{C}H_2$, rotamer); 63.47 ($CO\underline{C}H_2CO$); 69.47 and 70.02 ($C\underline{C}H_2O$); 74.85 ($CH_2CO\underline{C}H_2CO$); 81.92 (Ph<u>C</u>); 127.69, 128.29 and 128.85 (Arom. <u>C</u>H); 139.06 (Arom. <u>C</u>); 168.94, 169.08 and 169.73 (<u>C</u>=O, rotamer). υ_{max} (thin film) (cm^{-1}) 1648 (NC=O), 1119 (C-O). $^m/_z$ (CI, dichloromethane) 677 (MH^+, 26%), 128 (NBu_2, 100%). $^m/_z$ (MH^+) found 676.527 $C_{39}H_{70}N_3O_6$ requires 676.526

2,2-Dimethy-4-hydroxymethyl-4-phenyl-dioxalane (76):



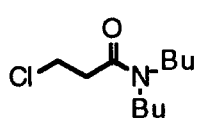
Under argon 2-phenyl-1,2,3-trihydoxypropane (500 mg, 3.0 mmol), 2,2-dimethoxypropane (1.5 ml, 10.4 mmol), and pyridinium paratoluenesulfonate (10 mg, 0.04 mmol) were dissolved in acetone (30 ml). The reaction was heated under reflux through 4Å molecular sieves for 8 h. The solvent and excess dimethoxypropane were removed under reduced pressure and the residue purified by column chromatography on silica eluting with 4:1 hexane:ethyl acetate (R_f = 0.25) to yield a coulourless oil, 410 mg (75%). δ_H ($CDCl_3$) 1.37 (s, 3H, $C\underline{H}_3$); 1.58 (s, 3H, $C\underline{H}_3$); 3.76 (m, 2H, $C\underline{H}_2OH$); 4.16 (d, 1H, $C\underline{H}_2O$, *J* 9); 4.41 (d, 1H, $C\underline{H}_2O$, *J* 9); 7.36 (m, 5H, Arom. C<u>H</u>). δ_C ($CDCl_3$) 26.40 ($\underline{C}H_3$); 27.54 ($\underline{C}H_3$); 68.85 ($\underline{C}H_2OH$); 71.87 ($\underline{C}H_2O$); 85.87 (Ph<u>C</u>); 110.78 ($\underline{C}Me_2$); 125.80, 128.01, 128.84 (Arom. <u>C</u>H); 142.90 (Arom. <u>C</u>). υ_{max} (thin film) (cm^{-1}) 1060 (C-H, Arom.), 3448 (OH). $^m/_z$ (CI, Dichloromethane) 208 (M^+, 13%), 177 (M-CH_2OH, 100%). Found C = 69.41, H = 7.88, $C_{12}H_{16}O_3$ requires C = 69.19, H = 7.75.

4-Butoxymethyl-2,2-dimethyl-4-phenyl-dioxalane (77):



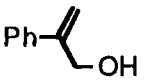
2,2-Dimethyl-4-hydroxymethyl-4-phenyl-dioxalane (180 mg, 0.86 mmol) was dissolved in THF (10ml) under argon and sodium hydride (25 mg, 1.04 mmol) and 1-bromobutane (0.141 g, 1.03 mmol) added. The mixture was heated under reflux for 24 h, additional sodium hydride (25 mg, 1.04 mmol) and 1-bromobutane (70 mg, 0.51 mmol) was added, and the reaction heated under reflux for another 24 h. THF (25 ml) was added and the reaction filtered through celite, the solvent and excess 1-bromobutane removed under vacuum to yield an oil, 228 mg (88%). δ_H ($CDCl_3$) 0.89 (t, 3H, $CH_2C\underline{H}_3$, 7Hz); 1.26-1.39 (m, 5H, $C\underline{H}_3$+$C\underline{H}_2CH_3$); 1.48-1.61 (m, 5H, $C\underline{H}_3$+$CH_2C\underline{H}_2CH_2$); 3.44 (m, 2H, $OC\underline{H}_2CH_2$); 3.54 (q, 2H, $CC\underline{H}_2O$, *J* 12); 4.12 (d, 1H, $COC\underline{H}_2C$, *J* 8); 4.46 (d, 1H, $COC\underline{H}_2C$, *J* 8); 7.39 (m, 5H, Arom. C<u>H</u>). δ_C ($CDCl_3$) 14.39 ($CH_2\underline{C}H_3$); 19.76 ($\underline{C}H_2CH_3$); 26.73 ($C\underline{C}H_3$); 27.42 ($C\underline{C}H_3$); 32.13 ($\underline{C}H_2CH_2CH_3$); 72.12, 72.23 and 76.40 ($\underline{C}H_2O$); 84.79 (Ph<u>C</u>); 110.61 ($\underline{C}CH_3$); 126.11, 127.63 and 128.42 (Arom. <u>C</u>H); 143.84 (Arom.<u>C</u>). υ_{max} (thin film) (cm^{-1}) 2932 (C-H stretch), 1114 (Arom. C-H). $^m/_z$ (CI, dichloromethane) 264 (M^+, 100%). Found C = 72.53, H = 9.32, $C_{16}H_{24}O_3$ requires C = 72.69, H = 9.15.

N,N-Dibutyl chloroethanamide :



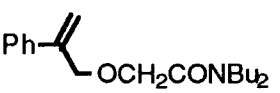
Chloroacetyl chloride (5.98 g, 53 mmol) was dissolved in diethyl ether (50 ml) under argon and cooled to -70 °C. Dibutylamine (15 g, 116 mmol) was dissolved in diethyl ether (50 ml) and added slowly over 30 min at lower than -40 °C. The reaction was allowed to warm to room temperature, filtered, the filtrate washed with 1M hydrochloric acid (2 x 25 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure to yield a colourless oil, 10.21 g (95%). δ_H ($CDCl_3$) 0.96 (m, 6H, $C\underline{H}_3CH2$), 1.27-1.63 (m, 8H, $C\underline{H}_2$), 3.30 (m, 4H, $C\underline{H}_2N$), 4.08 (2H, s, $C\underline{H}_2Cl$). δ_C ($CDCl_3$) 13.44 ($\underline{C}H_3$), 19.72, 29.09 and 30.83 ($\underline{C}H_2$), 41.04 ($\underline{C}H_2CO$), 45.58 and 47.67 ($\underline{C}H_2N$), 165.61 (<u>C</u>O). $^m/_z$ (CI, dichloromethane) 206 (MH^+).

3-Hydroxy-2-phenyl-prop-1-ene (70):



Sodium (20 mg) was dissolved in dry methanol (100 ml) under argon and 3-acetoxy-2-phenyl-prop-1-ene (13.0 g, 97 mmol) was added. The mixture was stirred for 48 h and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (100 ml), washed with water (50 ml), dried (K_2CO_3), and purified by column chromatography on silica, eluting with 3:1 dichloromethane : hexane (R_f = 0.25), to give a yellow oil, 8.0 g (81%). δ_H ($CDCl_3$) 4.55 (d, 2H, $C\underline{H}_2O$, *J* 5); 5.36 (d, 1H, =$C\underline{H}_E$), *J* 1); 5.47 (d, 1H, =$C\underline{H}_Z$, *J* 1); 7.40 (m, 5H, Arom. C$\underline{H}$). δ_C ($CDCl_3$) 64.9 ($\underline{C}H_2OH$); 112.9 (=$\underline{C}H_2$); 126.7, 128.5 and 129.1 (Arom. $\underline{C}$H): 139.4 ($\underline{C}$=); 147.8 (Arom. $\underline{C}$). υ_{max} (thin film) (cm^{-1}) 3346 (O-H), 1025 (O-C). $^m/_z$ (EI, dichloromethane) 312 (M^+, 100%). Found C = 80.70, H = 7.36, $C_9H_{10}O$ requires C = 80.56, H = 7.51.

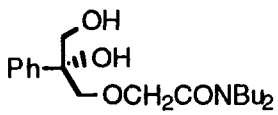
3-(N,N-Dibutylcarbamoyl-methyloxa)-2-phenyl-prop-1-ene (79):



3-Hydroxy-2-phenyl-prop-1-ene (1.34 g, 10 mmol) and potassium iodide (20 mg) were dissolved in dry THF (50 ml) under argon. Sodium hydride (300 mg, 12.5 mmol) and N,N dibutyl chloroethanamide (2.47 g, 12 mmol) were added and the reaction heated under reflux. After 24 h additional sodium hydride (100 mg, 4.2 mmol) and chloroethanamide (0.25 g, 4.2 mmol) were added and the reaction heated under reflux for a further 12 h. The reaction mixture was filtered, the solvent removed under reduced pressure and the product purified by column chromatography on silica, eluting with 4:1 hexane : ethyl acetate (R_f = 0.4 in 3:1 hexane : ethyl acetate), to yield a yellow oil, 2.20 g (73%). δ_H ($CDCl_3$) 0.79 (q, 6H, $CH_2C\underline{H}_3$, *J* 7); 1.14 (m, 4H, $C\underline{H}_2CH_3$, *J* 7); 1.36 (m, 4H, $C\underline{H}_2CH_2$, *J* 6); 3.01 (t, 2H, $NC\underline{H}_2$, *J* 7.8); 3.19 (t, 2H, $NC\underline{H}_2$, *J* 7.8); 4.03 (s, 2H, $C\underline{H}_2O$); 4.37 (s, 2H, $C\underline{H}_2O$); 5.24 (d, 1H, =C$\underline{H}$, *J* 1); 5.43 (d, 1H, =C$\underline{H}$, *J* 1z); 7.17 (m, 3H, Arom. C$\underline{H}$); 7.37 (m, 2H, Arom. C$\underline{H}$). δ_C ($CDCl_3$) 14.2 and 14.3 ($\underline{C}H_3$, rotamer); 20.4 and 20.6 ($\underline{C}H_2CH_3$, rotamer); 30.1 and 31.4 ($\underline{C}H_2CH_2$, rotamer); 45.8 and 47.1 ($N\underline{C}H_2$, rotamer); 69.2 and 73.3 ($\underline{C}H_2O$);

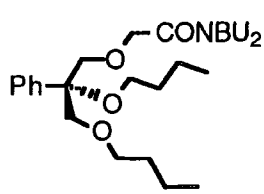
115.3 (=$\underline{C}H_2$); 126.4, 128.2 and 128.7 (Arom. $\underline{C}H$); 138.8 (=$\underline{C}$); 144.1 (Arom. $\underline{C}$); 168.9 ($\underline{C}$=O). υ_{max} (thin film) (cm^{-1}) 1645 (C=O). $^m/_z$ (CI, dichloromethane) 304 (MH^+, 100%). Found C = 75.27, H = 9.59, $C_{19}H_{29}NO_2$ requires C = 75.31, H = 9.65.

3-(N,N-Dibutylcarbamoyl-methyloxa)-1,2-dihydroxy-2-phenyl-propane (81):



3-(N,N-Dibutylcarbamoyl-methyloxa)-2-phenyl-prop-1-ene (320 mg, 1.05 mmol), N-methyl-morpholine-N-oxide (128 mg, 1.10 mmol) and 2.5% w/v osmium tetroxide in tert butanol (0.5 ml) were dissolved in tert-butanol (20 ml) under argon and stirred for 6 days. Dichloromethane (45 ml) and sodium bisulfite (1 g) were added and the suspension stirred for 30 min. The mixture was filtered, the solvent removed under reduced pressure and the product purified by column chromatography on silica using a gradient elution of 2:1 to 1:1 hexane : ethyl acetate (R_f = 0.4 in 1:1 in hexane : ethyl acetate) to give a yellow oil, 190 mg (54%). δ_H ($CDCl_3$) 0.84 (t, 6H, $CH_2\underline{C}H_3$, *J* 6); 1.18 (m, 4H, $C\underline{H}_2CH_3$); 1.40 (m, 4H, $C\underline{H}_2CH_2$); 2.95 (t, 2H, $NC\underline{H}_2$, *J* 8); 3.24 (t, 2H, $NC\underline{H}_2$, *J* 8); 3.53 (d, 1H, $OC\underline{H}_2$, *J* 11.4); 3.74 (dd, 2H, $OC\underline{H}_2$, *J* 9.4 and 20.4); 3.86 (d, 1H, $OC\underline{H}_2$, *J* 11.4); 4.11 (s, 2H, $OC\underline{H}_2$); 7.22 (m, 3H, Arom. $C\underline{H}$); 7.48 (dd, 2H, Arom. $C\underline{H}$, *J* 8 and 1.2). υ_{max} (thin film) (cm^{-1}) 3360 (O-H), 1640 (C=O). $^m/_z$ (EI) 338 (MH^+, 100%). Found C = 67.65, H = 9.11, N = 4.31, $C_{27}H_{47}NO$ requires C = 67.63, H = 9.27, N = 4.15.

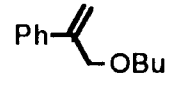
1,2-Dibutoxy-3-(N,N-dibutylcarbamoyl-methyloxa)-2-phenyl-propane (63):



3-(N,N-Dibutylcarbamoyl-methyloxa)-1,2-dihydroxy-2-phenyl-propane (120 mg, 0.36 mmol) was dissolved in dry THF (20 ml) under argon and sodium hydride (20 mg, 0.80 mmol) and 1-bromobutane (109 mg, 0.78 mmol) added. The

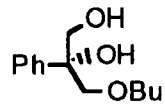
mixture was heated under reflux for 48 h. After 24 h additional sodium hydride (10 mg, 0.42 mmol) and 1-bromobutane (54 mg, 0.39 mmol) were added. The reaction was allowed to cool to room temperature, dichloromethane (35 ml) added, filtered through celite, and the solvent and excess 1-bromobutane removed under reduced pressure to yield a yellow oil, 120 mg (69%). δ_H ($C\underline{D}Cl_3$) 0.89 (m, 2H, $C\underline{H}_3$); 1.26 (m, 8H, $C\underline{H}_2CH_3$); 1.48 (m, 8H, $C\underline{H}_2CH_2$); 3.08 (t, 2H, $OC\underline{H}_2CH_2$); 3.25-3.48 (m, 6H, $OC\underline{H}_2CH_2$+$NC\underline{H}_2$); 3.72 (d, 1H, $OC\underline{H}_2C$, *J* 7.5); 3.83 (d, 2H, $OC\underline{H}_2C$, *J* 6.0); 3.91 (d, 1H, $OC\underline{H}_2C$, *J* 7.5); 4.12 (s, 2H, $OC\underline{H}_2CO$); 7.28 (m, 3H, Arom. C<u>H</u>); 7.43 (m, 2H, Arom. C<u>H</u>). δ_C ($CDCl_3$) 14.3, 14.4, and 14.5 ($\underline{C}H_3$); 19.8, 20.5 and 20.7 ($\underline{C}H_2CH_3$); 30.1, 30.4, 32.1 and 33.0 ($CH_2\underline{C}H_2CH_2$); 45.8 and 46.9 ($N\underline{C}H_2$); 63.4 ($O\underline{C}H_2CO$); 71.5, 71.9, 73.3 and 74.4 ($O\underline{C}H_2$); 80.6 ($CH_2\underline{C}CH_2$); 127.4, 127.7 and 128.4 (Arom. <u>C</u>H); 141.3 (Arom. <u>C</u>); 169.2 (<u>C</u>O). υ_{max} (thin film) (cm^{-1}) 1648 (C=O), 1112 (C-O). $^m/_z$ (CI, dichlromethane) 450 (MH^+, 100%). m/z (MH^+) Found 450.3583, $C_{27}H_{48}NO_4$ requires 450.3583.

3-Butoxy-2-phenyl-propene (80):



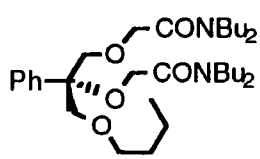
3-Hydroxy-2-phenyl-prop-1-ene (1.34 g, 10 mmol) was dissolved in dry THF (30 ml) under argon and sodium hydride (0.30 g, 12.5 mmol) and 1-bromobutane (1.51 g, 11.0 mmol) were added. After heating under reflux for 24 h additional sodium hydride (0.10 g, 4.2 mmol) and 1-bromobutane (0.50 g, 3.6 mmol) were added and the reaction heated under reflux for a further 36 h. The solvent was removed, the residue dissolved in dry dichloromethane (30 ml), filtered through celite, and the volatiles removed under vacuum to yield a yellow oil, 1.4 g (74%). δ_H ($CDCl_3$) 0.91 (t, 3H, $C\underline{H}_3CH_2$, *J* 7.3); 1.36 (m, 2H, $C\underline{H}_2CH_3$, *J* 6.9); 1.59 (m, 2H, $OCH_2C\underline{H}_2$, *J* 8.0); 3.50 (t, 2H, $OC\underline{H}_2CH_2$, *J* 6.4); 4.37 (s, 2H, $OC\underline{H}_2$); 5.35 (s, 1H, $=C\underline{H}_2$); 5.53 (s, 1H, $=C\underline{H}_2$); 7.32 (m, 3H, Arom. C<u>H</u>); 7.51(m, 2H, Arom. C<u>H</u>). δ_C ($CDCl_3$) 14.50 ($\underline{C}H_3$); 19.99 ($\underline{C}H_2$); 32.43 ($\underline{C}H_2$); 70.58 ($O\underline{C}H_2$); 73.32 ($O\underline{C}H_2$); 114.37 ($=\underline{C}H_2$); 126.63, 128.25 and 128.85 (Arom. <u>C</u>H); 139.52 (=<u>C</u>); 145.14 (Arom. <u>C</u>). υ_{max} (thin film) (cm^{-1}) 1094 (C-O). $^m/_z$ (CI, dichloromethane) 189 (M^+, 100%). Found C = 82.52, H = 9.81, $C_{13}H_{18}O$ requires C = 82.61, H = 9.60.

3-Butoxy-1,2-dihydroxy-2-phenyl-propane (82):



N-Methyl morpholine N-oxide (0.35 g, 3.0 mmol) and 3-butoxy-2-phenyl-prop-1-ene (0.57 g, 3.0 mmol) were dissolved in tert-butanol (10 ml) under argon , 2.5% w/v OsO_4 in tert-butanol (0.5 ml) was added and the reaction was stirred for 7 days. Sodium metabisulfite (1 g) was added and after stirring for 1h the reaction was filtered through celite, the solvent removed, and the product purified by column chromatography on silica, eluting with 3:1 hexane : ethyl acetate (R_f = 0.25), yielding a yellow oil, 0.34 g (58%). δ_H ($CDCl_3$) 0.92 (t, 3H, $C\underline{H}_3$, *J* 7); 1.37 (m, 2H, $C\underline{H}_2CH_3$); 1.44 (m, 2H, $C\underline{H}_2CH_2CH_3$); 3.49 (t, 2H, $OC\underline{H}_2CH_2$, *J* 6.5); 3.64 (d, 1H, $OC\underline{H}_2$, *J* 9.1); 3.69 (d, 1H, $OC\underline{H}_2$, *J* 6.5); 3.85 (d, 1H, $OC\underline{H}_2$, *J* 9.1); 3.95 (d, 1H, $OC\underline{H}_2$, *J* 11.5); 7.35 (m, 3H, Arom. C<u>H</u>); 7.49 (m, 2H, Arom. C<u>H</u>). δ_C ($CDCl_3$) 14.36 ($\underline{C}H_3$); 19.74 ($CH_2\underline{C}H_2$); 32.01 ($\underline{C}H_2CH_2CH_2$); 69.20 ($O\underline{C}H_2CH_2$); 72.28 ($C\underline{C}H_2O$); 76.13 (<u>C</u>OH); 77.24 ($\underline{C}H_2OH$); 125.74, 127.93 and 128.78 (Arom. <u>C</u>H); 142.09 (Arom. <u>C</u>). υ_{max} (thin film) (cm^{-1}) 3416 (OH), 1098 (C-O). $^m/_z$ (CI, dichloromethane) 242 (MNH_4^+, 21%), 207 ($[M\text{-}OH]^+$, 100%). Found C = 69.92, H = 8.67, $C_{13}H_{20}O_3$ requires C = 69.61, H = 8.99.

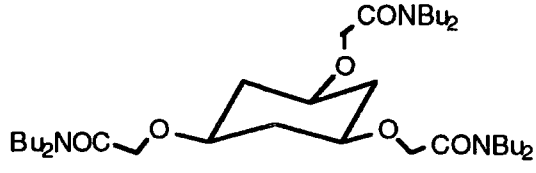
1-Butoxy-2,3-di(N,N-dibutylcarbamoyl-methyloxa)-2-phenyl-propane (62):



3-Butoxy-1,2-dihydroxy-2-phenyl-propane (160 mg, 0.70 mmol) and potassium iodide (20 mg) were dissolved in dry THF (20 ml) under argon and sodium hydride (40 mg, 1.67 mmol) and N,N dibutyl chloroethanamide (345 mg, 1.67 mmol) were added. The mixture was heated under reflux for 24 h and then additional sodium hydride (20 mg, 1.36 mmol) and chloroethanamide (100 mg, 0.49 mmol) were added. After heating under reflux for a further 6 days the reaction was filtered through celite, the solvent removed under reduced pressure and the product purified by column chromatography on silica eluting with 6:1 hexane : ethyl acetate (R_f = 0.25 in 3:1 hexane : ethyl acetate) to give a pale yellow

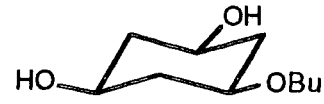
oil, 90 mg (23%). δ_H ($CDCl_3$) 0.86 (m, 15H, $C\underline{H}_3$); 1.28 (m, 10H, $C\underline{H}_2CH_3$); 1.46 (m, 10H, $C\underline{H}_2CH_2$); 2.98-3.45 (br m, 10H, $NC\underline{H}_2$+$OC\underline{H}_2$); 3.83 (d, 1H, $OC\underline{H}_2$, 10.3 Hz); 3.84 (d, 1H, $OC\underline{H}_2$, 10.0Hz); 3.97 (d, 1H, $OC\underline{H}_2$, 10.3Hz); 4.03 (d, 1H, $OC\underline{H}_2$, 10.0Hz); 4.13 (s, 2H, $OC\underline{H}_2$); 4.18 (d, 2H, $OC\underline{H}_2$, 2.6Hz); 7.35 (br m, 3H, Arom. C$\underline{H}$); 7.50 (m, 2H, Arom. C$\underline{H}$). δ_C ($CDCl_3$) 14.3 and 14.4 ($\underline{C}H_3$); 19.8, 20.5, and 20.7 ($\underline{C}H_2CH_3$); 30.2, 31.4 and 32.2 ($\underline{C}H_2CH_2$); 45.9, 46.0, 46.9 and 47.2 ($N\underline{C}H_2$, rotamer); 64.2 ($O\underline{C}H_2$); 70.8, 71.9, 73.8, and 75.0 ($O\underline{C}H_2$); 82.1 ($CH_2\underline{C}CH_2$); 127.1, 128.0 and 128.6 (Arom. $\underline{C}$H); 140.1 (Arom. $\underline{C}$); 169.0 and 169.5 ($\underline{C}$=O). υ_{max} (thin film) (cm^{-1}) 1648 (C-O). $^m/_z$ (CI, dichloromethane) 563 (MH^+, 100%). $^m/_z$ (MH^+) Found 450.3583, $C_{33}H_{59}N_2O_5$ requires 450.3583.

Cis,cis-1,3,5-tri(N,N-dibutyl-carbamoylmethyloxa)-cylcohexane (64):



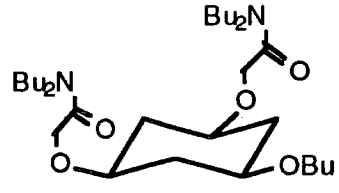
Anhydrous *cis,cis* 1,3,5 cyclohexanetriol (0.5 g, 3.8 mmol) was dissolved in dry DMF (20 ml) under argon . Sodium hydride (0.3 g, 12.5 mmol), potassium iodide (40 mg, 0.32 mmol) and N,N-dibutyl chloroethanamide (2.4 g, 11.7 mmol) was added and the reaction heated at 60 °C for 6 days. Every 2 days further sodium hydride (0.3 g, 12.5 mmol), potassium iodide (2.0 g, 16.0 mmol) and N,N-dibutyl chloroethanamide (2.4g, 11.7 mmol) was added. The excess sodium hydride was quenched with water (1 ml) and the mixture filtered. The volatiles were removed under vacuum (160 °C, 0.1 mm Hg) and the residue purified by column chromatography on alumina, using a gradient elution of 2:1 to 4:1 ethyl acetate : hexane (R_f = 0.3, 4:1 ethyl acetate : hexane), yielding a brown oil, 0.49 g (20%). δH ($CDCl_3$) 0.94 (m, 18H, $C\underline{H}_3C$); 1.24-1.35 (m, 15H, $C\underline{H}_2$+$C\underline{H}_{eq}$); 1.47-1.57 (m, 12H, $C\underline{H}_2$); 2.54 (m, 3H, $C\underline{H}_{ax}$); 3.16-3.31 (dt, 12H, $C\underline{H}_2N$); 3.38 (m, 3H, C$\underline{H}$O); 4.17 (s, 6H, $C\underline{H}_2O$). δC ($CDCl_3$) 13.83 ($\underline{C}H_3$); 20.08, and 22.22 ($\underline{C}H_2CH_3$, rotamer); 29.60, and 30.97 ($N\underline{C}H_2CH_2$, rotamer); 37.54 ($\underline{C}H_2$); 45.56, and 46.78 (NCH_2, rotamer); 66.97 (CHO); 73.36 (CH_2O); 168.70 (C=O). υ_{max} (thin film) (cm^{-1}) 1645 (NC=O), 1102 (C-O). $^m/_z$ (CI, dichloromethane) 640 (MH^+, 100%), 188 (OCH_2CONBu_2, 95%). $^m/_z$ (MH^+) Found 640.527, $C_{36}H_{70}N_3O_6$ requires 640.526.

***Cis,cis*-1-butoxy-3,5-dihydroxy-cyclohexane (83):**



Anhydrous *cis,cis*-1,3,5-cyclohexanetriol (250 mg, 1.89 mmol) was dissolved in DMF (5 ml) under argon, sodium hydride (45 mg, 1.89 mmol) and 1-bromobutane (285 mg, 2.08 mmol) were added and the reaction heated at 80 °C for 5 days. The volatiles were removed under vacuum (60 °C, 0.1 mm Hg) and the product purified by column chromatography on alumina using a gradient elution of ethyl acetate to 95:5 ethyl acetate : methanol (R_f = 0.8 in 90:10 ethyl acetate : methanol) to give a colourless, 0.13 g (37%). δ_H ($CDCl_3$) 0.88 (t, 3H, $C\underline{H}_3$); 1.18-1.58 (m, 7H, $C\underline{H}_2CH_3$ + $C\underline{H}_2CH_2$ + $C\underline{H}_{ax}$); 2.21 (m, 3H, $C\underline{H}_{eq}$); 3.26 (m, 1H, C<u>H</u>OBu); 3.43 (t, 2H, $OC\underline{H}_2$); 3.58 (m, 2H, C<u>H</u>OH). δ_C ($CDCl_3$) 13.84 ($\underline{C}H_3$); 19.23 ($\underline{C}H_2CH_3$); 31.95 ($\underline{C}H_2CH_2$); 40.11 and 43.26 (ring $\underline{C}H_2$); 65.78 (<u>C</u>HOH); 68.44 (<u>C</u>HOCH$_2$); 73.24 ($O\underline{C}H_2$). υ_{max} (thin film) (cm^{-1}) 3372 (OH), 1024 (C-O). $^m/_z$ (CI, dichloromethane) 189 (MH^+, 100%). $^m/_z$ (MH^+) Found 189.1491, $C_{10}H_{21}O_3$ requires 189.1491.

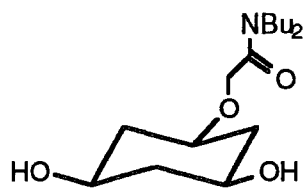
***Cis,cis*-1,3-dibutoxy-5-(N,N-dibutyl-carbamoylmethyloxa)-cyclohexane (65):**



Cis,cis-1-(N,N-dibutyl-carbamoylmethyloxa)-3,5-dihydroxy-cylcohexane (80 mg, 0.26 mmol) was dissolved in anhydrous DMF (5 ml) under argon and sodium hydride (20 mg, 0.83 mmol) and 1-bromobutane (0.114 g, 0.83 mmol) added. The reaction was stirred at 60 °C for 2 days after which additional sodium hydride (20 mg, 0.83 mmol) and 1-bromobutane (0.114 g, 0.83 mmol) were added. After a further 2 days of stirring at 60 °C the solvent and excess 1-bromobutane were removed under vacuum (120 °C, 0.1 mm Hg), the residue dissolved in dichloromethane (25 ml), washed with water (2 x 10 ml), dried (K_2CO_3), filtered and the solvent removed under reduced pressure. The product was purified by column chromatography on alumina eluting with dichloromethane (R_f = 0.3) to yield a colourless oil, 67 mg (62%). δ_H ($CDCl_3$) 0.90 (m, 12H,

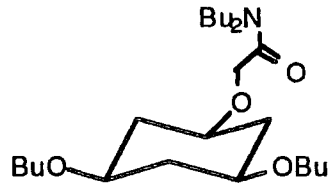
$C\underline{H}_3$); 1.27 (m, 11H, $C\underline{H}_2CH_3$+$C\underline{H}_{ax}$); 1.48 (m, 8H, $C\underline{H}_2CH_2$); 2.31 (m, 3H, $C\underline{H}_{eq}$); 3.32 (m, 6H, ring $C\underline{H}_2$+ $CC\underline{H}OCH_2$); 3.43 (t, 2H, $NC\underline{H}_2$); 3.59 (m, 1H, $C\underline{H}OCH_2$); 4.14 (s, 2H, $C\underline{H}_2CO$). δ_C ($CDCl_3$) 13.85 and 19.30 ($\underline{C}H_3$); 20.06 and 20.21 ($\underline{C}H_2CH_3$); 29.56 and 30.99 ($NCH_2\underline{C}H_2$, rotamer); 32.09 ($O\underline{C}H_2CH_2$); 37.99 and 38.32 (ring $\underline{C}H_2$) 45.45 and 46.84 ($N\underline{C}H_2$, rotamer); 67.38 and 68.25 ($\underline{C}HO$); 73.04 and 73.68 ($O\underline{C}H_2$); 168.94 (CO). υ_{max} (thin film) (cm^{-1}) 1643 (CON), 1093 (C-O). $^m/_z$ (CI, dichloromethane) 414 (MH^+, 9%); 358 ($[M\text{-}Bu]^+$, 100%). m/z (MH^+) Found 414.3583, $C_{24}H_{48}NO_4$ requires 414.3583.

Cis,cis-1-(N,N-dibutyl-carbamoylmethyloxa)-3,5-dihydroxy-cylcohexane (84):



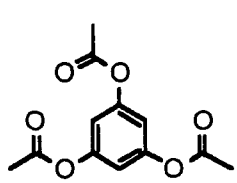
Anhydrous *cis,cis*-1,3,5-cyclohexanetriol (250 mg, 1.89 mmol) and potassium iodide (31 mg, 0.19 mmol) were dissolved in DMF (5 ml) under argon , sodium hydride (45 mg, 1.89 mmol) and N,N dibutyl chloroethanamide (389 mg, 1.89 mmol) were added and the reaction heated at 80 °C for 2 days. The volatiles were removed by distillation (120 °C, 0.05 mm Hg), the residue dissolved in ethyl acetate, filtered through celite, the solvent removed and the product purified by column chromatography on alumina by gradient elution with ethyl acetate to 5:95 methanol : ethyl acetate (R_f = 0.25 in 5:95 methanol : ethyl acetate) to yield a pale yellow oil, 122 mg (22%). δ_H ($CDCl_3$) 0.87 (m, 6H, $C\underline{H}_3$); 1.26 (m, 4H, $C\underline{H}_2CH_3$); 1.46 (m, 7H, $C\underline{H}_2CH_2$ + $C\underline{H}_{ax}$); 2.13 (m, 3H, $C\underline{H}_{eq}$); 3.14 (br t, 2H, $NC\underline{H}_2$); 3.44 (m, 1H, $C\underline{H}O$); 3.65 (m, 2H, $C\underline{H}OH$); 4.13 (s, 2H, $OC\underline{H}_2$); 4.21 (br s, 2H, $O\underline{H}$). δ_C ($CDCl_3$) 13.73 ($\underline{C}H_3$); 19.99 and 20.11 ($\underline{C}H_2CH_3$, rotamer); 29.48 and 30.85 ($\underline{C}H_2CH_2$, rotamer); 39.14 and 42.34 (ring $\underline{C}H_2$); 45.61 and 46.72 ($N\underline{C}H_2$, rotamer); 65.58 and 67.48 ($\underline{C}HO$); 74.62 ($O\underline{C}H_2CO$); 169.25 ($\underline{C}O$). υ_{max} (thin film) (cm^{-1}) 1634 (CON), 3386 (OH). $^m/_z$ (CI, dichloromethane) 302 (MH^+, 100%). $^m/_z$ (MH^+) Found 302.2331, $C_{16}H_{32}NO_4$ requires 302.2331.

Cis,cis-1-butoxy-3,5-di(N,N-dibutyl-carbamoylmethyloxa)-cylcohexane (66):



Cis,cis-1-butoxy-3,5-dihydroxy-cyclohexane (100 mg, 0.51 mmol) was dissolved in dry THF (10 ml) under argon , sodium hydride (30 mg, 1.25 mmol) and N,N dibutyl chloroethanamide (0.231 g, 1.25 mmol) were added and the reaction heated under reflux for 2 days. Additional sodium hydride (30 mg, 1.25 mmol) and N,N dibutyl chloroethanamide (0.231 g, 1.25 mmol) were added and the reaction heated under reflux for a further 6 days. The solvent was removed under reduced pressure and the excess chloroethanamide distilled off under educed pressure (0.1 mm Hg, 150 °C). The residue was dissolved in dichloromethane (10 ml), filtered through celite and the solvent removed under reduced pressure. The product was purified by column chromatograhy on alumina eluting with 3:1 hexane : ethyl acetate (R_f = 0.3 in 2:1 hexane : ethyl acetate) to yield a colourless oil, 90 mg (32%). δ_H ($CDCl_3$) 0.87 (m, 15H, $C\underline{H}_3$); 1.23 (m, 13H, $CH_2C\underline{H}_2$+$C\underline{H}_{ax}$); 1.47 (m, 10H, $CH_2C\underline{H}_2$); 2.42 (m, 3H, $C\underline{H}_{eq}$); 3.11-3.28 (m, 3H, $NC\underline{H}_2$+C<u>H</u>O); 3.29-3.42 (m, 3H, $OC\underline{H}_2$+C<u>H</u>O); 4.11 (s, 4H, $C\underline{H}_2CO$). δ_C ($CDCl_3$) 13.72 and 19.18 ($\underline{C}H_3$); 19.96 and 20.09 ($\underline{C}H_2CH_3$); 29.47 and 30.86 ($NCH_2\underline{C}H_2$, rotamer); 31.96 ($OCH_2\underline{C}H_2$); 37.46 and 37.83 (ring $\underline{C}H_2$); 45.38 and 48.69 ($N\underline{C}H_2$); 67.09 and 68.22 (<u>C</u>HO); 72.71 and 73.41 ($O\underline{C}H_2$); 168.73 (CO). υ_{max} (thin film) (cm^{-1}) 1646 (NCO), 1093 (C-O). $^m/_z$ (CI, dichloromethane) 528 (MH^+, 100%). $^m/_z$ (MH^+) Found 527.443, $C_{30}H_{59}N_2O_5$= requires 527.442.

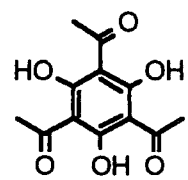
1,3,5-Triacetoxybenzene (86):



1,3,5-Trihydroxybenzene (10 g, 79 mmol) was heated under reflux in acetyl chloride (50 ml) for 12 h under N_2. The solvent was removed under reduced

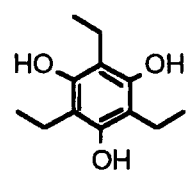
pressure and the solid residue washed with water (20 ml) and recrystallised from hot ethanol to give yellow crystals, 11.7 g (62%). mp = 106-108 °C (lit. 105-106 °C)[3]. δ_H ($CDCl_3$) 2.28 (s, 9H, $C\underline{H}_3$), 6.48 (s, 3H, Arom.). δ_C ($CDCl_3$) 21.58 ($\underline{C}H_3$), 113.26 ($\underline{C}H$, Arom.), 151.57 ($\underline{C}O$, Arom.), 169.09 ($\underline{C}$=O). υ_{max} (KBr disc) (cm^{-1}) 1763 (C=O), 1602 (C=C, Arom.). $m/_z$ (CI, dichloromethane) 270 (MNH_4^+, 100%). Found C = 56.87, H = 4.94, $C_{12}H_{12}O_6$ requires C = 57.14, H = 4.80.

1,3,5-Triacetyl-2,4,6-trihydroxybenzene (87):[4]



1,3,5-Triacetoxybenzene (4.10 g, 16.2 mmol) was mixed intimately with aluminium chloride (10 g, 71.1 mmol) and heated at 180 °C for 2 h under N_2. The residue was dissolved in 1M hydrochloric acid (50 ml) and extracted into diethyl ether (3x50 ml). The solvent was dried ($MgSO_4$), removed under reduced pressure and the product recrystallised from hot ethanol to give white crystals, 2.98 g (70%). mp = 157-158 °C (lit. 158-159 °C). δ_H ($CDCl_3$) 2.74 (s, 9H, $C\underline{H}_3$). δ_C ($CDCl_3$) 33.34 ($\underline{C}H_3$), 103.60 ($\underline{C}$, Arom.), 176.21 ($\underline{C}O$, Arom.), 205.46 ($\underline{C}$=O). υ_{max} (KBr disc) (cm^{-1}) 1580 (C=C, Arom.), 1626 (C=O). $m/_z$ (EI) 252 (M^+, 75%), 237 ($[M-CH_3]^+$), 100%). Found C = 57.45, H = 4.49, $C_{12}H_{12}O_6$ requires C = 57.14, H = 4.80.

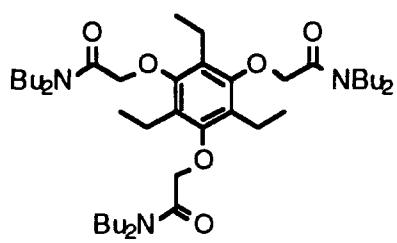
1,3,5-Triethyl-2,4,6-trihydoxybenzene (88):



Zinc (3.6 g, 55 mmol) and mercury (II) chloride (0.36 g, 1.3 mmol) were mixed with water (10 ml) and conc. hydrochloric acid (0.2 ml) for 5 min. The aqueous layer was decanted off and water (10 ml), conc. hydrochloric acid (2 ml), toluene (15 ml), and 1, 3, 5-triacetoxy-2, 3, 5-trihydroxybenzene (0.71 g, 2.8 mmol)

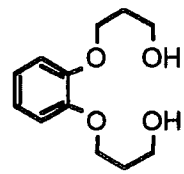
added. The reaction was heated under reflux for 5 days with conc. hydrochloric acid (1 ml) added every 12 h. The organic layer was separated, the aqueous layer extracted with dichloromethane (3 x 25 ml), the organics combined and the solvent removed under reduced pressure to give a yellow solid. The product was recrystallised from benzene to give white crystals, 0.46g (79%). mp = 104-105 °C (lit. 105 °C)[5] δ_H ($CDCl_3$) 1.16 (t, 9H, $C\underline{H}_3$, *J* 7); 2.60 (q, 6H, $C\underline{H}_2$, *J* 7.6); 4.63 (s, 3H, O<u>H</u>). δ_C ($CDCl_3$) 14.48 ($\underline{C}H_3$); 17.27 ($\underline{C}H_2$); 108.84 ($\underline{C}CH_2$); 150.38 ($\underline{C}OH$). υ_{max} (KBr disc) (cm^{-1}) 3490 (br, OH), 1605 (C=C). $^m/_z$ (CI, dichlromethane) 211 (MH^+, 100%). Found C = 68.51, H = 8.97, $C_{12}H_{18}O_3$ requires C = 68.55, H = 8.63.

1,3,5-Tris(N,N-dibutyl-carbamoylmethyloxa)-2,4,6-triethyl-benzene (89):



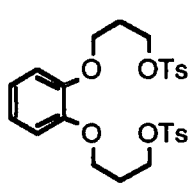
1,3,5-Triethyl-2,4,6-trihydroxy benzene (0.5 g, 2.4 mmol) was dissolved under argon in anhydrous THF (10 ml). Sodium hydride (0.19 g, 8.0 mmol) and N-dibutyl chloroethanamide (1.6 g, 8.0 mmol) were added and the reaction stirred at r.t. for 72 h. The reaction was quenched with water (2 ml), the solvent removed under reduced pressure, and the residue dissolved in dichloromethane (40 ml). The organics were washed with water (2 x 25 ml), dried (K_2CO_3), and the solvent removed under reduced pressure. The excess N-dibutyl chloroethannamide was distilled off at 115 °C and 0.1 mm Hg to leave a pale yellow oil, 0.33 g (20%). δ_H ($CDCl_3$) 0.80 (t, 18H, $CH_2C\underline{H}_3$); 1.08 (t, 9H, $C\underline{H}_3$); 1.18 (m, 12H, $C\underline{H}_2CH_3$); 1.44 (m, 12H, $CH_2C\underline{H}_2$); 2.52 (q, 6H, $CC\underline{H}_2CH_3$); 3.21 (m, 12H, $NC\underline{H}_2$); 4.31 (s, 6H, $OC\underline{H}_2$). δ_C ($CDCl_3$) 13.72, 13.76 ($N(CH_2)_3\underline{C}H_3$ rotamer); 15.08 ($\underline{C}H_3$); 18.38 ($\underline{C}H_2CH_3$); 20.01, 20.10 ($N(CH_2)_2\underline{C}H_2$ rotamer); 29.17, 31.05 ($NCH_2\underline{C}H_2$ rotamer); 45.42, 46.93 ($N\underline{C}H_2$ rotamer); 72.92 ($O\underline{C}H_2$); 127.65 ($\underline{C}CH_2$); 154.72 (<u>C</u>-O); 167.13 (<u>C</u>=O). υ_{max} (thin film) (cm^{-1}) 1649 (NC=O). $^m/_z$ (CI, dichloromethane) 719 (MH^+, 35%), 172 (CH_2CONBu_2, 100%). Found C = 70.27, H = 10.50, N = 5.87, $C_{42}H_{75}O_6N_3$ requires C = 70.25, H = 10.53, N = 5.85.

1,2-Bis (3-hydroxypropxy)benzene (147):



Catechol (10.8 g, 98 mmol) and potassium carbonate (37.4 g, 918 mmol) were suspended under N_2 in N,N-dimethyl formamide (250 ml) for 3 h at 60°C. 3-Bromopropan-1-ol (30.0 g, 215 mmol) was added dropwise over 45 min. The mixture was stirred under N_2 at 60 °C for 4 days. The suspension was filtered and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (50 ml) and washed with 0.1 M HCl (3 x 100 ml), dried ($MgSO_4$) and the solvent removed to yield the product. Recrystallisation from ethyl ethanoate : hexane gave a pale brown crystalline solid, 15.41 g (91%). mp = 55-56 °C. δ_H ($CDCl_3$) 2.06 (p, 4H, $CH_2C\underline{H}_2CH_2$, *J* 5.7), 3.85 (t, 4H, $C\underline{H}_2OH$, *J* 5.7), 4.17 (t, 4H, $OC\underline{H}_2$, *J* 5.7), 6.91 (s, 4H, Arom.). δ_C ($CDCl_3$) 32.26 ($CH_2\underline{C}H_2CH_2$), 61.31 ($\underline{C}H_2OH$), 68.04 ($O\underline{C}H_2CH_2$), 113.46 and 121.77 (Arom. $\underline{C}H$), and 148.84 (Arom. $\underline{C}$). υ_{max} (KBr disc) (cm^{-1}) 1258 (Arom. C-H). $m/_z$ (EI) 226 (M^+, 100%), 168 (M^+-C_3H_6O, 18%), 110 (M^+-2xC_3H_6O, 59.5%). Found C = 63.94, H = 8.15, $C_{12}H_{18}O_4$ requires C = 63.72, H = 8.03.

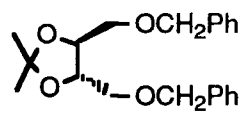
1,2-Bis (3-(p-toluenesulfanato)-propoxy)benzene (144):



To a solution of 1,2-bis (3-hydroxypropxy)benzene (10.0 g, 44.2 mmol) and triethylamine (18.2 g, 180 mmol) in dry THF (150 ml) under N_2 at -20 °C was added p-toluene sulfonyl chloride (20.5 g, 108 mmol). The solution was then held at 4 °C under N_2 for 12 days. After filtration and removal of the solvent the residue was purified by column chromatography on silica eluting with a gradient 1:1 dichloromethane : hexane to dichloromethane (R_f = 0.5, dichloromethane) to yield a white solid, 18 g (76%). mp = 61-63 °C. δ_H ($CDCl_3$) 2.00 (p, 4H, $CH_2C\underline{H}_2CH_2$, *J* 5.8), 2.26 (s, 6H, $C\underline{H}_3$), 3.80 (t, 4H, $OC\underline{H}_2CH_2$, *J* 5.8), 4.12 (t, 4H, $CH_2C\underline{H}_2O$, *J* 5.8), 6.62-6.79 (dm, 4H, Arom.), 7.13 (d, 4H,

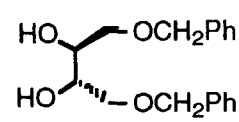
Arom., *J* 8.0), 7.63 (d, 4H, Arom., *J* 8.0). δ_C ($CDCl_3$) 21.61 ($CH_2\underline{C}H_2CH_2$), 29.04 ($\underline{C}H_3$), 64.48 ($\underline{C}H_2O$), 67.26 ($\underline{C}H_2O$), 114.18, 121.57, 127.79, and 127.80 (Arom.), 132.90 (Arom. $\underline{C}CH_3$), 144.74 (Arom. $\underline{C}O$), 148.49 (Arom. $\underline{C}O$). υ_{max} (KBr disc) (cm^{-1}) 1175 (Arom. C-H). $^m/_z$ (CI, dichloromethane) 552 (MNH_4^+, 100%). Found C = 58.64, H = 5.73, $C_{26}H_{26}S_2O_8$ requires C = 58.43, H = 5.62.

4S,5S-(-)-Bis-(dibenzoyloxymethyl)-2,2-dimethyl-1,3-dioxalane (149)[6]:



Trans-(4S,5S)-(+)-4,5-bis (hydroxymethyl)-2,2-dimethyl-1,3-dioxalane (2.5 g, 15.4 mmol) was heated under reflux under N_2 in dry THF (40 ml) with sodium hydroxide (1.9 g, 47.5 mmol) for 3 h. Tert-butylammonium hydrogensulfate (0.2 g) and benzyl chloride (3.96 g, 31 mmol) was added and the mixture heated under reflux under N_2 for 48 h. The solvent was removed under reduced pressure and the residue treated with water (25 ml) and extracted with diethyl ether (3x25 ml). The combined extracts were dried (K_2CO_3), filtered and the solvent removed under reduced pressure to produce a residue which was distilled (115 °C, 0.1 mm Hg) to yield a colourless oil , 4.65 g (88%). δ_H ($CDCl_3$) 1.44 (s, 6H, $C\underline{H}_3$), 3.61 (d, 4H, $C\underline{H}_2O$, *J* 2.7), 4.05 (t, 2H, $C\underline{H}_2CHO$, *J* 2.7), 4.57 (s, 4H, $C\underline{H}_2Ph$), 7.32 (br s, 10H, Arom.). δ_C ($CDCl_3$) 27.63 ($\underline{C}H_3C$), 71.23 ($\underline{C}H_2O$), 74.04 ($Ph\underline{C}H_2$), 78.06 ($\underline{C}HO$), 110.17 ($\underline{C}$), 128.18 and 128.93 (Arom. $\underline{C}H$), 138.56 (Arom. $\underline{C}$). υ_{max} (thin film) (cm^{-1}) 1087 (CO), 1214 (CO). $^m/_z$ (CI, dichloromethane) 343 (MH^+, 100%).

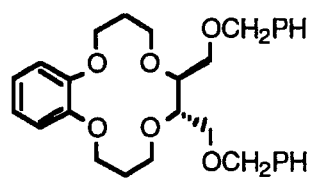
2S,3S-(-)-1,4-Bis (dibenzyloxymethyl)butane-2,3-diol (145):[1]



To a solution of 4S,5S-(-)-bis (dibenzoyloxymethyl)-2,2-dimethyl-1,3-dioxalane (4.65 g, 13.5 mmol) in methanol (25 ml) was added 1M hydrochloric acid (2.5 ml) and the mixture was heated under reflux. After 8 h further 1M hydrochloric

acid (2.5 ml) was added and the mixture heated under reflux for a further 8 h. The solvent was removed under reduced pressure to leave a residue which was treated with saturated aq. sodium hydrogen carbonate until alkaline and then extracted with dichloromethane (3x25 ml). The solvent was removed under reduced pressure and the residue purified by column chromatography on silica, eluting with dichloromethane : 5% methanol to give a white waxy solid, 3.67 g (90%). mp = 51-52 °C (lit. 51-52 °C). δ_H ($CDCl_3$) 2.76 (d, 2H, O<u>H</u>), 3.60 (m, 4H, C<u>H</u>$_2$O), 3.87 (m, 2H, C<u>H</u>O), 4.54 (s, 4H, OC<u>H</u>$_2$Ph), 7.32 (br s, 10H, Arom.). $^m/_z$ (CI, dichloromethane) 320 (MNH_4^+, 100%), 303 (MH^+, 11%).

Trans (2S,3S)-(-)-2,3-bis (benzyloxymethyl)-2,3-benzo-1,4,8,11-tetra-oxa-cyclotetradecane (146):



Method 1.

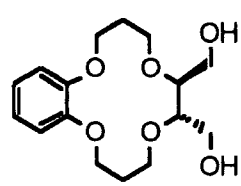
To a solution of 1,2-bis (3-hydroxypropxy) benzene (0.25 g, 1.11 mmol) and triethylamine (0.27 g, 2.7 mmol) in dry THF (20 ml) under N_2 at -20 °C was added mesityl chloride (0.32 g, 2.7 mmol) dropwise. The mixture was allowed to warm to room temperature over 6 h. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (20 ml), washed with 1mM hydrochloric acid (20 ml) and then saturated aq. sodium hydrogen carbonate (20 ml), and dried (K_2CO_3). The solvent was removed under reduced pressure to yield a crude product (170 mg, 75% pure as assessed by NMR) which was used immediately. δ_H ($CDCl_3$) 2.24 (p, 4H, $CH_2C\underline{H}_2CH_2$, 6.1Hz), 3.00 (s, 6H, C<u>H</u>$_3$), 4.12 (t, 4H, $CH_2C\underline{H}_2O$, 5.8Hz), 4.48 (t, 4H, $CH_2C\underline{H}_2OSO_2$, 6.1Hz), 6.92 (s, 4H, Arom.). $^m/_z$ (CI, dichloromethane) 400 (MNH_4^+, 100%), 382 (M^+, 29%). Lithium metal (0.11 g, 15.8 mmol) was added to tert-butanol (30 ml) under N_2 and the mixture stirred until the lithium had dissolved. To this solution was added 2S,3S-(-)-1,4-bis (dibenzyloxymethyl) butane-2,3-diol (0.75 g, 2.5 mmol) and the mesylate (0.95 g, 2.5 mmol) and the mixture stirred at 60 °C for 3 days under N_2. After cooling the solvent was removed under educed pressure, and the residue treated with 1M hydrochloric acid until the pH = 2. The solution was extracted with dichloromethane (2 x 25 ml) and chloroform (25 ml), washed with water (25 ml), dried (K_2CO_3), filtered and the solvent

removed under reduced pressure. The residue was purified by column chromatography on alumina eluting with hexane : ethyl acetate (5:1) ($R_f = 0.7$, 3:1 hexane : ethyl acetate, alumina) to yield a colourless oil, 70 mg (6%).

Method 2:

Lithium metal (0.11 g, 15.8 mmol) was added to tert-butanol (50 ml) under N_2 and the mixture stirred until the lithium had dissolved. To this solution was added 2S,3S-(-)-1,4-bis (dibenzyloxymethyl) butane-2,3-diol: (1.55 g, 5.13 mmol) and 1,2-bis (3-(p-toluenesulfanato)-propoxy) benzene (2.74 g, 5.13 mmol) and the reaction mixture stirred at 60 °C for 8 days under N_2. After cooling the solvent was removed, and the residue treated with 1M hydrochloric acid until the pH = 2. The solution was extracted with dichloromethane (2 x 25 ml) and chloroform (25 ml), washed with water (25 ml), dried (K_2CO_3), filtered and the solvent removed. The residue was purified by column chromatography on alumina eluting with hexane : ethyl acetate (5:1) ($R_f = 0.7$, 3:1 hexane : ethyl acetate, alumina) to yield a colourless oil, 250 mg (10%). δ_H ($CDCl_3$) 2.06 (m, 4H, $CH_2C\underline{H}_2CH_2$), 3.46-4.38 (m, 16H, $C\underline{H}_2O$ + $C\underline{H}O$), 4.46 (m, 4H, $C\underline{H}_2OPh$), 6.97 (m, 4H, Arom.), 7.31 (m, 10H, Arom.). δ_C ($CDCl_3$) 31.00 ($CH_2\underline{C}H_2CH_2$), 67.56 ($CH_2\underline{C}H_2O$), 70.08 ($CH\underline{C}H_2O$), 73.82 ($O\underline{C}H_2Ph$), 80.76 ($\underline{C}HO$), 118.14, 122.87, 128.07, 128.26, and 128.83 (Arom.), 138.75 ($\underline{C}CH_2$, Arom.), 150.60 ($\underline{C}$-O, Arom.). υ_{max} (thin film) (cm^{-1}) 1498 (C=C, Arom.), 1256 (C-O). $^m/_z$ (CI, dichloromethane) 492 (M^+, 17.6%), 91 ($PhCH_2^+$, 100%). Found C = 73.02, H = 7.41, $C_{26}H_{36}O_6$ requires C = 70.25, H = 8.16.

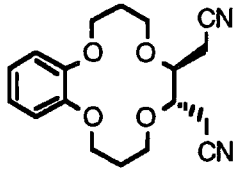
Trans-(2S,3S)-(-)-2,3-bis(hydroxyoxymethyl)-2,3-benzo-1,4,8,11-tetraoxa-cyclotetradecane (150):



Trans (2S, 3S)-(-)-2, 3-bis-(benzyloxymethyl)-2,3-benzo-1,4,8,11-tetraoxa-cyclotetra-decane (0.5 g, 1.0 mmol) was dissolved in ethanol (10 ml) and Pearlman's catalyst (100 mg) and p-toluene sulfonic acid (25 mg) added. The reaction mixture was shaken at room temperature under 3 atmospheres of hydrogen gas for 48 h. The reaction mixture was filtered and the solvent removed

under reduced pressure. The residue was dissolved in dichloromethane (25 ml), washed with saturated sodium hydrogensulfate (2 x 10 ml), dried (K_2CO_3), and the solvent removed under reduced pressure. The oil was purified by colum chromatography on alumina eluting with 4% methanol in dichloromethane (R_f = 0.4) to give colourless crystals, 180 mg (57%). δ_H ($CDCl_3$) 2.03 (m, 4H, $CH_2\underline{CH_2}CH_2$); 3.52 (d, 2H, $\underline{CH_2}OH$); 3.57 (d, 2H, $\underline{CH_2}OH$); 3.71 (m, 4H, $OCH_2\underline{CH_2}$); 4.26 (td, 2H, $\underline{CH}$); 6.93 (br s, 4H, Arom. $\underline{CH}$). δ_C ($CDCl_3$) 30.8 ($CH_2\underline{CH_2}CH_2$); 61.9 ($\underline{CH_2}OH$); 67.7 and 67.8 ($CH_2\underline{CH_2}O$); 81.8 ($\underline{CH}$); 117.9 and 122.9 (Arom. $\underline{CH}$); 150.3 (Arom. $\underline{C}$). υ_{max} (thin film) (cm^{-1}) 3384 (O-H), 2923 (C-H). $^m/_z$ (EI) 312 (M^+, 100%). Found C = 61.47, H = 7.91, $C_{16}H_{24}O_6$ requires C = 61.52, H = 7.74.

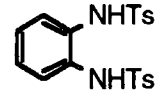
Trans-(2S,3S)-(-)-2,3-bis(cyanomethyl)-2,3-benzo-1,4,8,11-tetraoxa-cyclotetradecane (152):



Trans-(2S,3S)-(-)-2,3-bis(hydroxyoxymethyl)-2,3-benzo-1,4,8,11-tetraoxa-cyclo-tetradecane (0.156 g, 0.5 mmol) was dissolved in tetrahydrofuran (10 ml) and triethylamine (0.5 ml). The solution was cooled to -40 °C and methane sulfonyl chloride (0.26 g, 2.25 mmol) added. The reaction mixture was stirred and allowed to warm to room temperature. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (10 ml), washed with water (2 x 5 ml), dried (K_2CO_3), and the solvent removed to give the crude mesylate. δ_H ($CDCl_3$) 2.05 (m, 4H, $CH_2\underline{CH_2}CH_2$); 3.01 (s, 6H, $SO_2\underline{CH_3}$); 3.76-4.28 (m, 12H, OCH_2); 4.47 (m, 2H, OCH); 6.95 (s, 4H, Arom. $\underline{CH}$). $^m/_z$ (CI, dichloromethane) 486 (MNH_4^+, 100%). The crude mesylate was dissolved in DMSO (5 ml) and potassium cyanide (100 mg, 1.5 mmol) and 18-crown-6 (5 mg) added under argon. The reaction mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure, the residue heated under reflux in dichloromethane for 30 min and the potassium salts filtered off. The solvent was removed under reduced pressure and the residue purified by column chromatography on alumina eluting with hexane : ethyl acetate (3:1 to 2:1, R_f = 0.6 in 2:1 hexane : ethyl acetate) to give a colourless oil, 96 mg (60%). δ_H ($CDCl_3$) 2.06 (m, 4H, $CH_2\underline{CH_2}CH_2$); 2.40-2.72 (m, 4H, $\underline{CH_2}CN$); 3.80-4.22

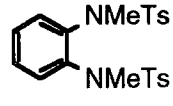
(m, 10H, $OC\underline{H}_2$ + $OC\underline{H}$); 6.93 (s, 4H, Arom. $C\underline{H}$). δ_C ($CDCl_3$) 18.22 ($CH_2\underline{C}H_2CH_2$); 28.70 ($\underline{C}H_2CN$); 65.48 and 66.83 ($\underline{C}H_2O$); 74.40 ($\underline{C}H$); 114.11 ($\underline{C}N$); 116.25 and 120.87 (Arom. $\underline{C}H$); 147.85 (Arom.$\underline{C}$). υ_{max} (thin film) (cm^{-1}) 2213 (CN), 1494 (Arom. C=C). $^m/_z$ (CI, dichloromethane) 348 (MNH_4^+, 100%). Found C = 65.83 H = 7.39, N = 8.54, $C_{18}H_{24}N_2O_4$ requires C = 65.45, H = 7.27, N = 8.48.

N, N' Di (p-toluene sulfonyl)benzene-1,2-diamine (157)[7]:



o-Phenylenediamine (10.8 g, 0.1 mol) was dissolved in dry pyridine (25 ml) under argon, cooled to 0 °C and p-toluene sulfonyl chloride (38.0 g, 0.4 mol) dissolved in dry pyridine (50 ml) added slowly over 30 min, the temperature not being allowed to exceed 60 °C. The reaction mixture was stirred for 12 h and then poured into 15% v/v hydrochloric acid (250 ml) and stirred until the product precipitated out. The solid was filtered off and recrystallised from hot ethanol (300 ml) to give pale brown crystals, 35.8 g (86%). mp = 204-205 °C (lit. 204-5 °C). δ_H ($CDCl_3$) 2.39 (6H, s, $C\underline{H}_3$); 6.98 (4H, m, Ar$\underline{H}$); 7.21 (4H, d, tosyl $C\underline{H}$, *J* 8); 7.57 (4H, d, tosyl $C\underline{H}$, *J* 8). δ_C ($CDCl_3$) 21.59 ($\underline{C}H_3$); 126.06, 127.29, 127.51, 129.60, 130.76, 135.36 and 144.17 (Arom. $\underline{C}$). υ_{max} (thin film) (cm^{-1}) 3414 (N-H), 1323 (S=O). $^m/_z$ (CI, dichloromethane) 434 (MNH_4^+, 10%); 263 ([M- $CH_3C_6H_4SO_2$]$^+$, 100%).

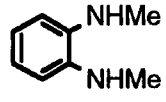
N,N'-Dimethyl N,N'-di-(p-toluene sulfonyl)benzene-1,2-diamine (158):[7]



N, N' di-(p-toluene sulfonyl) benzene-1,2-diamine (33.2 g, 0.08 mol) was heated with 2M sodium hydroxide (100 ml) and water (100 ml), cooled to room temperature and methyl sulfate (15 ml, 164 mmol) added. The mixture was heated under reflux for 5 min, the solids in the reaction crushed and further 2M sodium hydroxide (100 ml) and methyl sulfate (15 ml, 164 mmol) added. This was repeated until a total of 60 ml methyl sulfate and 400 ml 2M sodium

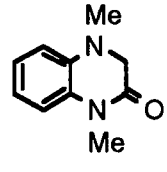
hydroxide solution had been added. The reaction was cooled to room temperature and the brown crystalline product filtered off and recrystallised from ethanol, 34.0 g (96%). mp = 176-78 °C (lit. 178-79 °C). δ_H ($CDCl_3$) 2.43 (6H, s, $C\underline{H}_3$); 3.20 (6H, s, $NC\underline{H}_3$); 6.86 (2H, m, Arom. H); 7.22 (2H, m, Arom. H); 7.32 (4H, d, Tosyl H, *J* 8); 7.69 (4H, d, Tosyl H, *J* 8). δ_C ($CDCl_3$) 21.49 ($\underline{C}H_3$); 38.63 ($N\underline{C}H_3$); 128.19, 128.23, 128.83 and 129.46 (Arom. CH); 134.66, 141.00 and 143.61 (Arom C). υ_{max} (thin film) (cm^{-1}) 1346 (S=O). $^m/_z$ (CI, dichloromethane) 445 (MH^+, 100%).

N,N' Dimethylbenzene-1,2-diamine (159):[7]



N,N'-Dimethyl N,N'-di-(p-toluene sulfonyl)benzene-1,2-diamine (10.0 g, 24 mmol) was heated at 100 °C in c. H_2SO_4 (10 ml) and water (1 ml) for 4 h. The reaction was poured into ice (100 g) and basified with solid sodium hydroxide. The product was extracted with dichloromethane (2 x 25 ml), dried (K_2CO_3) and the solvent removed under reduced pressure. The crude product was distilled at 1mm Hg and 93 °C to yield a colourless crystalline solid that colours in air, 2.6 g (81%). mp = 29-30 °C (lit. 30.5-31 °C). δ_H ($CDCl_3$) 2.90 (s, 6H, $NC\underline{H}_3$); 6.73 (m, 2H, Arom. H); 6.92 (m, 2H, Arom. H). δ_C ($CDCl_3$) 30.89 ($N\underline{C}H_3$); 110.27 and 118.87 (Arom. CH); 138.17 (Arom. CN). υ_{max} (thin film) (cm^{-1}) 3346 (NH) 1513 (C=C).

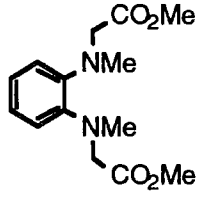
3-H-N,N'-Dimethyl-benzopyrazinone (160):



N,N'-dimethyl o-phenylenediamine (2.0 g, 15 mmol) was dissolved in methanol (10 ml) and the pH maintained at 9 by addition of sodium hydroxide solution (0.1 mol dm^{-3}) during the addition of a solution of chloroacetic acid (3.05 g, 32 mmol) in water (10 ml). After complete addition of the chloroacetic acid the reaction was bolied under reflux for 16 h. The solvent was removed under reduced pressure

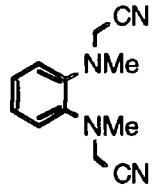
and the oil purified by column chromatography eluting with dichloromethane (R_f = 0.3)to give a pale brown solid, 1.94 g (75%). mp = 73-74 °C. δ_H ($CDCl_3$) 2.84 (s, 3H, $CH_2NC\underline{H}_3$); 3.37 (s, 3H, $CONC\underline{H}_3$); 3.74 (s, 2H, $NC\underline{H}_2$); 6.71 (dd, 1H, Arom. C<u>H</u>, *J* 1 and 8); 6.85-7.09 (m, 3H, Arom. C<u>H</u>). δ_C ($CDCl_3$) 28.61 ($NC\underline{H}_3$); 37.37 ($NC\underline{H}_3$); 55.17 ($NC\underline{H}_2$); 111.49, 114.29, 119.10 and 123.72 (Arom. <u>C</u>H); 129.81 and 137.76 (Arom. <u>C</u>); 165.99 (<u>C</u>=O). υ_{max} (thin film) (cm^{-1}) 1673 (NC=O). $^m/_z$ (CI, dichloromethane) 177 (MH^+, 100%). Found C = 68.31, H = 6.77, N = 16.06, $C_{10}H_{12}N_2O$ requires C = 68.16, H = 6.86, N = 15.90.

N,N'-Dimethyl-N,N'-di(methylethanoate)-o-phenylenediamine (161):



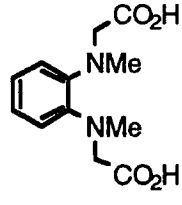
N,N'-Dimethylphenylenediamine (2.46 g, 18 mmol) was disssolved in 1:1 methanol : water (50 ml). The pH was maintained at 9 by addition of 0.5 M sodium hydroxide solution during the slow addition of bromoacetic acid (5.9 g, 48 mmol) over 3 h. The reaction mixture was stirred for 14 h, and the solvent then removed under reduced pressure. The residue was dissolved in methanol (50 ml), c. hydrochloric acid (3 drops) addded and the reaction mixture heated under reflux for 4 h. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (100 ml), washed with water (2 x 50 ml), dried (K_2CO_3) and the dichloromethane evaporated. The resulting brown oil was purified by column chromatography eluting with 1:1 dichloromethane : hexane (R_f = 0.5) to give a white crystalline product (colours in air), 0.35 g (7%). mp = 75-77 °C. δ_H ($CDCl_3$) 2.87 (s, 6H, $NC\underline{H}_3$); 3.66 (s, 6H, $OC\underline{H}_3$); 4.10 (s, 4H, $NC\underline{H}_2$); 7.00 (m, 4H, Arom. <u>H</u>). δ_C ($CDCl_3$) 39.46 ($NC\underline{H}_3$); 51.31 ($OC\underline{H}_3$); 53.66 ($NC\underline{H}_2$); 119.68 and 122.39 (Arom. <u>C</u>H); 142.62 (Arom. <u>C</u>); 171.73 (<u>C</u>=O). υ_{max} (thin film) (cm^{-1}) 1748 (C=O). $^m/_z$ (CI, dichloromethane) 281 (MH^+, 100%).

N,N'-Di(cyanomethyl)-N,N'-dimethyl-o-phenylenediamine (162):



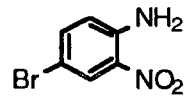
N,N'-Dimethyl o-phenylenediamine (2.3 g, 17 mmol), bromoacetonitrile (6.09 g, 51 mmol) and potassium carbonate (10 g) were stirred in anhydrous THF (5 ml) under argon at room temperature for 6 days. The potassium carbonate was filtered off and the solvent removed under reduced pressure. The black oil was purified by column chromatography on alumina eluting with 4:1 hexane : dichloromethane (R_f = 0.2, 1:1 dichloromethane : hexane) to yield a white crystalline solid which colours in air, 0.6 g (17%). mp = 88-89 °C. δ_H ($CDCl_3$) 2.91 (s, 6H, $NC\underline{H}_3$); 4.22 (s, 4H, $NC\underline{H}_2$); 7.12 (m, 4H, Arom. $\underline{H}$). δ_C ($CDCl_3$) 39.31 ($N\underline{C}H_3$); 42.50 ($N\underline{C}H_2$); 115.44 ($\underline{C}N$); 120.40 and 124.95 (Arom $\underline{C}H$); 141.49 (Arom. $\underline{C}$). υ_{max} (thin film) (cm^{-1}) 2228 (CN). $^m/_z$ (CI, dichloromethane) 215 (MH^+, 100%).

N,N'-Di(carboxymethyl)-N,N'-dimethyl-o-phenylenediamine (156):



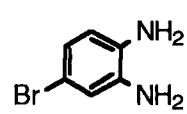
N,N'-di(cyanomethyl)-N,N'-dimethyl-o-phenylenediamine (0.6 g, 2.8 mmol) was dissolved in degassed hydrochloric acid (6 M, 20 ml) under argon and stirred for 4 days. The solvent was removed unde reduced pressure and the purple solid recrystallised from hot acetone to give purple crystals, 330 mg (41%). mp = 110-111 °C. δ_H (D_2O) 2.17 (s, 6H, $NC\underline{H}_3$); 3.36 (s, 4H, $NC\underline{H}_2$); 6.67 (m, 2H, Arom. $C\underline{H}$); 6.82 (m, 2H, Arom. $C\underline{H}$). δ_C (D_2O) 49.95 ($N\underline{C}H_3$); 62.92 ($N\underline{C}H_2$); 127.26 and 134.74 (Arom. $\underline{C}H$); 145.65 (Arom. $\underline{C}$); 175.82 ($\underline{C}$=O). υ_{max} (thin film) (cm^{-1}) 1734 (C=O). Found C = 49.82, H = 5.90, N = 9.65, $C_{12}H_{16}N_2O_4$.HCl requires C = 49.91, H = 5.89, N = 9.71.

4-Bromo-2-nitro-phenylamine :[8]



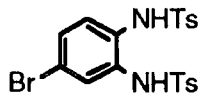
4-Bromo-acetanilide (4.28 g, 0.02 mol) was dissolved in c. sulfuric acid (60 ml) and cooled to 0 °C. c. Sulfuric acid (6 ml) and c. nitric acid (3.6 ml) were mixed and cooled to 0 °C before being added dropwise to the 4-bromo-acetanilide solution over 15 min. The reaction mixture was stirred for a further 15 min. at room temperature and then poured into ice cold water (400 ml). The yellow precipitate was filtered off and partially dried under reduced pressure. The precipitate was dissolved in c. hydrochloric acid (30 ml) and water (20 ml), heated under reflux for 20 min, poured into ice water (100 ml) and then made basic with c. ammonia (approx. 50 ml). The yellow product was filtered off and recrystallised from 50% ethanol, 2.3 g (50%). mp = 108-9 °C (lit. 109-110 °C). δC ($CDCl_3$) 107.75 ($\underline{C}NH_2$); 120.28 and 128.22 ($\underline{C}H$); 132.36 ($\underline{C}Br$); 138.41 ($\underline{C}H$); 143.52 ($\underline{C}NO_2$).

4-Bromo-phenylenediamine (163):



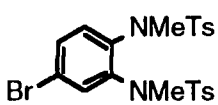
4-Bromo-2-nitro-phenylamine (1.30 g, 5.99 mmol) was dissolved in c. hydrochloric acid (10 ml) and tin (II) chloride added (8.0 g). The reaction mixture was stirred at 100 °C for 90 min, poured onto ice (100 ml) and made basic with potassium hydroxide. The product was extracted with diethyl ether (3x25 ml), dried (K_2CO_3), filtered and the solvent removed under reduced pressure to yield a pale brown solid which was recrystallised from ethanol, 1.0 g (90%). mp = 61-2 °C (lit. 61-2 °C)[9]. δH ($CDCl_3$) 3.34 (s, 4H, $N\underline{H}_2$); 6.55 (m, 1H, Arom. C$\underline{H}$); 6.81 (m, 2H, Arom. C$\underline{H}$).

1-Bromo-4,5-di(p-toluenesulfonamide)-benzene (164):



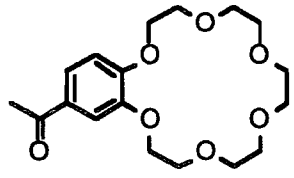
4-Bromo phenylenediamine (2.4 g, 13.4 mmol) was dissolved in dry pyridine (5 ml), cooled to 0 °C under argon and p-toluene sulfonyl chlodide (4.4 g, 26.8 mmol) dissolved in pyridine (5 ml) was added slowly. The reaction mixture was stirred at room temperature for 16 h, poured into 15% hydrochloric acid and stirred until the product precipitated. The product was filtered off and recrystallised from ethanol to give pale brown crystals, 6.27 g (94%). mp = 212-14 °C (lit. 213-14 °C)[10]. δ_H ($CDCl_3$) 2.39 (s, 6H, $C\underline{H}_3$); 6.72 (d, 1H, Arom. H, *J* 9); 7.11 (dd, 1H, Arom. H, *J* 3 and 9); 7.24 (m, 5H, Arom. H); 7.55 (d, 2H, Tos. H, *J* 9); 7.62 (d, 2H, Tos. H, *J* 9). υ_{max} (thin film) (cm^{-1}) 3250 (NH).

1-Bromo-4,5-di(N-methyl-p-toluenesulfonamide)-benzene (165):



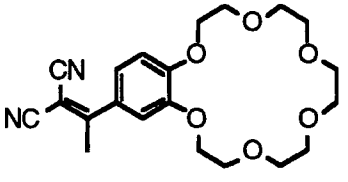
1-Bromo-4, 5-di(p-toluenesulfonamide)-benzene (1.0 g, 2.0 mmol) was dissolved in 4 molar sodium hydroxide solution (5 ml) and dimethyl sulfate (0.25 g) added. The reaction was heated to 100 °C for 5 min and additional 4 molar sodium hydroxide solution (5 ml) and dimethyl sulfate (0.25 g) added. This was repeated four times. The reaction mixture was stirred at 100 °C for a further 30 min, allowed to cool to room temperature, the product was then filtered off and recrystallised from ethanol to give pale brown crystals, 0.73 g (70%). mp = 171-2 °C. δ_H ($CDCl_3$) 2.46 (s, 3H, $C\underline{H}_3$); 2.48 (s, 3H, $C\underline{H}_3$); 3.17 (s, 3H, $NC\underline{H}_3$); 3.18 (s, 3H, $NC\underline{H}_3$); 6.74 (d, 1H, Arom. H, *J* 8); 7.00 (d, 1H, Arom. H, *J* 2); 7.36 (m, 5H, Arom. H); 7.69 (d, 2H, Tos. H, *J* 8); 7.43 (d, 2H, Tos. H, *J* 8). δ_C ($CDCl_3$) 21.55 ($\underline{C}H_3$); 38.53 ($N\underline{C}H_3$); 121.72 ($\underline{C}Br$); 129.44, 129.61, 131.75, 132.01 (Arom. CH); 134.16 and 134.40 ($\underline{C}CH_3$); 140.37 and 142.40 (C-N); 143.88 and 144.06 ($\underline{C}SO_2$). υ_{max} (thin film) (cm^{-1}) 1490 (C=C arom.). $^m/_z$ (CI, dichloromethane) 525 (MH^+, 100%). Found C = 50.19, H = 4.68, N = 5.39, $C_{22}H_{23}N_2O_4S_2Br$ requires C = 50.48, H = 4.43, N = 5.35.

3'-Acetyl-2,3-benzo-1,4,7,10,13,16-hexaoxa-octadecane (167)[11]:



Polyphosphoric acid (1 g) was warmed to 80 °C and 2,3-benzo-1,4,7,10,13,16-hexaoxa-octadecane (0.48 g, 1.54 mmol) dissolved in acetic acid (4 ml) was added. The reaction mixture was stirred at 80 °C for 30 min and then poured into ice (100 ml). The product was extracted with chloroform (3x20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure to yield a yellow oil. The product was purified by column chromatography on alumina eluting with 4:1 dichloromethane : ethyl acetate (R_f = 0.5) to yield a colourless crystalline solid, 0.51 g (93%). mp = 76-7 °C (lit 76-7 °C). δ_H ($CDCl_3$) 2.54 (s, 3H, $C\underline{H}_3$); 3.67 (s, 4H, $OC\underline{H}_2$); 3.74 (m, 8H, $OC\underline{H}_2$); 3.93 (m, 4H, $OC\underline{H}_2$); 4.20 (m, 4H, $OC\underline{H}_2$); 6.84 (d, 1H, Arom. H); 7.54 (m, 2H, Arom. H). δ_C ($CDCl_3$) 26.12 ($\underline{C}H_3$); 68.75, 68.87, 69.17, 69.30, 70.48, 70.53, 70.58, 70.66, 70.77 and 70.78 ($O\underline{C}H_2$); 111.59, 112.32 and 123.35 (Arom. CH); 130.42, 148.48 and 153.13 (Arom. C); 196.66 ($\underline{C}$=O). υ_{max} (thin film) (cm^{-1}) 1667 (C=O); 1593 (Arom. C=C).

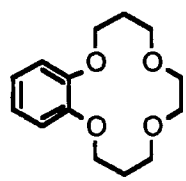
4'-(2'',2''-Dicyano-1''-methylethenyl)-2,3-benzo-1,4,7,10,13,16-hexaoxa octadecane (166):



4'-Acetyl-2,3-benzo-1,4,7,10,13,16-hexaoxa-octadecane (0.25 g, 0.71 mmol) was dissolved in ethanol (5 ml) and malononitrile (50 mg, 0.76 mmol) and 3 dops piperidine added. The reaction mixture was heated under reflux through 4 Å sieves for 18 h. The reaction mixture was cooled in ice and the precipitate filtered off, dissolved in dichloromethane (10 ml), washed with hydrochloric acid (0.1 M, 2 x 5 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting yellow solid was recrystallised from ethanol to give yellow crystals, 17mg (6%). mp = 91-92 °C. δ_H ($CDCl_3$) 2.12 (br s, 3H, $C\underline{H}_3$); 3.79 (br m, 12H, $OC\underline{H}_2$); 4.02 (br m, 4H, $OC\underline{H}_2$); 4.28 (br m, 4H, $OC\underline{H}_2$); 6.64 (br m,

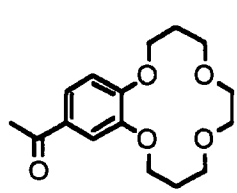
1H, Arom C<u>H</u>); 7.86-7.20 (br m, 2H, Arom. C<u>H</u>). υ_{max} (thin film) (cm^{-1}) 2212 and 2192 (CN). Found C = 62.42, H = 7.18, N = 6.73, $C_{21}H_{26}N_2O_6$ requires C = 62.69, H = 6.99, N = 6.97. Mass spectrum only gave acetyl benzo 18-crown-6, the mass analysis conditions leading to hydrolysis of the product. This occured for EI, CI and ESMS. The ^{13}C spectrum was not obtainable as the peaks were extremely broad due to charge transfer in the molecule.

2,3-Benzo-1,4,8,11-tetraoxacyclotetradecane (168):



Lithium (49 mg, 7.0 mmol) was dissolved, under argon, in anhydrous tert-butanol (25 ml). Di-(p-toluene sulfonyl)-1, 5, 8, 12-tetraoxa-dodecane (0.68 g, 1.58 mmol) and catechol (0.19 g, 1.73 mmol) were added and the reaction mixture stirred at 60 °C for 8 days. The solvent was removed under reduced pressure, the residue dissolved in water (20 ml) and the product extracted with dichloromethane (3x15 ml). The dichloromethane was dried (K_2CO_3), the solvent removed under reduced pressure and the product purified by column chromatography on alumina eluting with 1:1 hexane : dichloromethane (R_f = 0.5, 2:1 dichloromethane : hexane) to give a colourless oil, 0.125 g (32%). δ_H ($CDCl_3$) 2.01 (p, 4H, C<u>H</u>$_2$); 3.68 (s, 4H, OC<u>H</u>$_2$); 3.80 (t, 4H, OC<u>H</u>$_2$CH$_2$); 4.16 (t, 4H, OC<u>H</u>$_2$CH$_2$); 6.95 (m, 4H, Arom. <u>H</u>). δ_C ($CDCl_3$) 29.75 (<u>C</u>H$_2$); 67.27, 67.30 and 70.71 (O<u>C</u>H$_2$); 117.24 and 122.19 (Arom. <u>C</u>H); 149.79 (Arom. <u>C</u>). υ_{max} (thin film) (cm^{-1}) 1498 (Arom. C=C). $^m/_z$ (CI, dichloromethane) 270 (MNH_4^+, 100%). $^m/_z$ (MNH_4^+) Found 270.1705, $C_{14}H_{24}O_4N$ requires 270.1705.

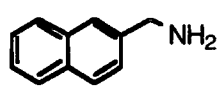
3'-Acetyl-2,3-benzo-1,4,8,11-tetraoxacyclotetradecane (170):



Polyphosphoric acid (1 g) was warmed to 80 °C and 2,3-benzo-1,4,8,11-tetraoxacyclotetradecane (125 mg, 0.50 mmol) dissolved in ethanoic acid (1 ml)

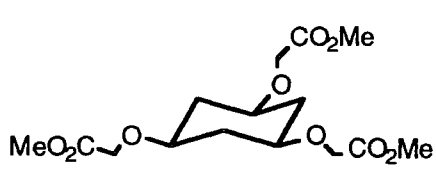
was added. The reaction mixture was stirred at 80 °C for 30 min and then poured into ice (50 ml). The product was extracted with chloroform (2 x 25 ml) and the solvent removedunder reduced pressure. The residue was purified by column chromatography on alumina eluting with 2:1 dichloromethane : hexane ($R_f = 0.6$) to yield a colourless oil, 45mg (34%).δ_H ($CDCl_3$) 2.02 (m, 4H, $CH_2\underline{CH_2}CH_2$); 2.52 (s, 3H, $\underline{CH_3}$); 3.64 (s, 2H, $O\underline{CH_2}$); 3.65 (s, 2H, $O\underline{CH_2}$); 3.77 (m, 4H, $O\underline{CH_2}$); 4.20 (m, 4H, $O\underline{CH_2}$); 6.92 (d, 1H, Arom. $\underline{H}$); 7.58 (m, 2H, Arom. $\underline{H}$). δ_C ($CDCl_3$) 26.25 ($\underline{C}H_3$); 29.21, 29.54, 66.91, 67.63, 67.64, 68.13, 70.30 and 70.99 ($O\underline{C}H_2$); 114.11, 116.77 and 124.05 (Arom. $\underline{C}H$); 130.97, 149.11 and 154.35 (Arom. $\underline{C}$); 196.72 ($\underline{C}$=O). υ_{max} (thin film) (cm^{-1}) 1675 (C=O); 1595 (Arom. C=C). $^m/_z$ (CI, dichloromethane) 295 (MH^+, 100%). $^m/_z$ (MH^+) Found 295.1545, $C_{16}H_{23}O_5$ requires 295.1545.

2-Naphthylmethylamine (172):



Borane-THF (1.0 M, 80 ml) was added to a solution of 2-cyano naphthalene (2.5 g, 16 mmol) in THF (5 ml) under argon and the mixture heated under reflux for 48 h. Excess borane was destroyed with methanol after which the solvent was removed under reduced pressure and the residue heated under reflux in 6 M hydrochloric acid (50 ml) for 4 h. The water was removed, aqueous potassium hydroxide added (20% solution, 30 ml), and the product extracted into dichloromethane (2x40 ml). The extracts were dried (K_2CO_3) and the solvent removed under reduced pressure to give a yellow brown solid, 2.1 g (84%). mp = 58-60 °C (lit. 59-60 °C)[12]. $^m/_z$ (CI, dichloromethane) 158 (MH^+, 100%).

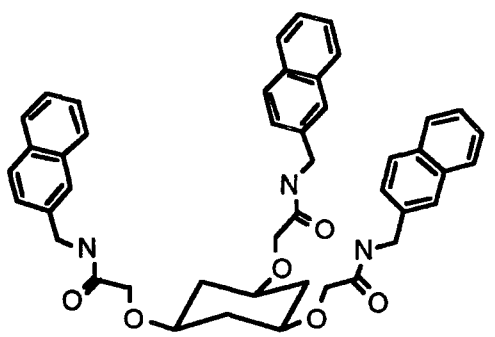
***Cis,cis*-1, 3, 5-tris(methoxycarbonylmethyloxa) cyclohexane (171):**



Cis,cis-1,3,5-tris(N,N-dibutyl-carbamoylmethyloxa)-cylcohexane (0.64 g, 1 mmol) was dissolved in methanol (5 ml) and 6 M hydrochloric acid (5 ml) added. The reaction mixture was heated under reflux for 48 h, the solvent removed under

reduced pressure, the residue dissolved in 2 M sodium hydroxide (10 ml) and the amine side product extracted with diethyl ether (2x25 ml). The aqueous layer was reacidified to pH 2 with 6 M hydrochloric acid, the solvent removed under reduced pressure and the residue dissolved in methanol (25 ml). The methanol solution was stirred with weakly acidic cation exchange resin (Amberlite® CG 50), filtered and the solvent removed under reduced pressure to yield a colourless oil, 74 mg (50%). δ_H (CD_3OD) 0.58-0.82 (br m, 3H, C<u>H</u>$_{ax}$); 1.57-1.78 (br d, 3H, C<u>H</u>$_{eq}$); 2.71-2.89 (br m, 3H, OC<u>H</u>); 3.06 (s, 9H, C<u>H</u>$_3$); 3.53 (s, 6H, OC<u>H</u>$_2$C=O). δ_C (CD_3OD) 37.50 (<u>C</u>H_2 ring); 52.77 (<u>C</u>H_3); 67.18 (O<u>C</u>H); 75.17 (O<u>C</u>H_2C=O); 173.52 (<u>C</u>=O). υ_{max} (thin film) (cm^{-1}) 1748 (OC=O). $^m/_z$ (CI, dichloromethane) 366 ($M+NH_4^+$, 100%). Found C = 51.47, H = 6.73, $C_{15}H_{24}O_9$ requires C = 51.72, H = 6.94.

Cis,cis-1,3,5-tris(N-(2-napthylmethyl)carbamoylmethyloxa)-cylcohexane (140):



Cis, cis-1,3,5-tri(methoxycarbonylmethyloxa) cyclohexane (174 mg, 0.5 mmol) was dissolved in methanol (1 ml) and hydrochloric acid (1 M, 10 ml) and heated under reflux for 4 h. The solvent was removed under reduced pressure and the solid residue suspended in dichloromethane (10 ml), cooled to - 20 °C and thionyl chlroide (195 mg, 1.65 mmol) added. The reaction mixture was allowed to warm to room temperature, the solvent and volatile materials removed under reduced pressure. The crude acid chloride was dissoled in tetrahydrofuran (10 ml) and triethylamine (1 ml) and 2-napthyl methyl amine (0.25 g, 1.6 mmol) added. The reaction heated under reflux for 20 h, the solvent removed under reduced pressure, the residue dissolved in dichloromethane (20 ml), washed with hydrochloric acid (1 M, 2 x 10 ml), dried (K_2CO_3), and the solvent removed under reduced pressure. The product was purified by column chromatography eluting with ethyl acetate to 5% methanol in ethyl acetate (R_f = 0.5 in 5% methanol in ethyl acetate) to give a pale brown solid, 45 mg (13%). mp = 53-54 °C. δ_H ($CDCl_3$) 1.22 (m, 3H, C<u>H</u>); 2.31 (m, 3H, C<u>H</u>); 3.21 (m, 3H, C<u>H</u>O); 3.99

(s, 6H, $OC\underline{H}_2$); 4.61 (d, 6H, $NC\underline{H}_2$); 6.85 (t, 3H, N<u>H</u>); 7.36-7.49 (m, 9H, Napthyl C<u>H</u>); 7.59 (s, 3H, Napthyl C<u>H</u>); 7.78 (m, 9H, Napthyl C<u>H</u>). δ_C ($CDCl_3$) 37.51 ($\underline{C}H_2$); 42.92 ($N\underline{C}H_2$); 67.94 ($O\underline{C}H$); 73.53 ($O\underline{C}H_2$); 125.77, 126.00, 126.32, 126.40, 127.61, 127.63 and 128.54 (Napthyl <u>C</u>H); 132.67, 133.20 and 135.26 (Napthyl <u>C</u>); 169.12 (<u>C</u>=O). υ_{max} (thin film) (cm^{-1}) 1669 (NC=O). $^{m}/_{z}$ (CI, dichloromethane) 724 (MNH_4^+, 35%). Found C = 74.51, H = 6.11, N = 5.77, $C_{45}H_{45}N_3O_6$ requires C = 74.676, H = 6.27, N = 5.80.

4.4 References.

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APPENDIX.

Colloquia, Lectures and Seminars from Invited Speakers.

1993

October 4

Prof. F.J. Feher, University of California, Irvine, USA
Bridging the Gap between Surfaces and Solution with Sessilquioxanes

October 14

Dr. P. Hubberstey, University of Nottingham
Alkali Metals: Alchemist's Nightmare, Biochemist's Puzzle and Technologist's Dream

October 20

Dr. P. Quayle, University of Manchester
Aspects of Aqueous ROMP Chemistry

October 21

Prof. R. Adams, University of South Carolina, USA
Chemistry of Metal Carbonyl Cluster Complexes : Development of Cluster Based Alkyne Hydrogenation Catalysts

October 27

Dr. R.A.L. Jones, Cavendish Laboratory, Cambridge
Perambulating Polymers

November 10

Prof. M.N.R. Ashfold, University of Bristol
High Resolution Photofragment Translational Spectroscopy : A New Way to Watch Photodissociation

November 17

Dr. A. Parker, Rutherford Appleton Laboratory, Didcot
Applications of Time Resolved Resonance Raman Spectroscopy to Chemical and Biochemical Problems

November 24

Dr. P.G. Bruce, University of St. Andrews
Structure and Properties of Inorganic Solids and Polymers

November 25

Dr. R.P. Wayne, University of Oxford
The Origin and Evolution of the Atmosphere

December 1*

Prof. M.A. McKervey, Queen's University, Belfast
Synthesis and Applications of Chemically Modified Calixarenes

December 8*

Prof. O. Meth-Cohn, University of Sunderland
Friedel's Folly Revisited - A Super Way to Fused Pyridines

December 16

Prof. R.F. Hudson, University of Kent
Close Encounters of the Second Kind

1994

January 26*

Prof. J. Evans, University of Southampton
Shining Light on Catalysts

February 2

Dr. A. Masters, University of Manchester
Modelling Water Without Using Pair Potentials

February 9*

Prof. D. Young, University of Sussex
Chemical and Biological Studies on the Coenzyme Tetrahydrofolic Acid

February 16

Prof. K.H. Theopold, University of Delaware, USA
Paramagnetic Chromium Alkyls : Synthesis and Reactivity

February 23

Prof. P.M. Maitlis, University of Sheffield
Across the Border : From Homogeneous to Heterogeneous Catalysis

March 2*

Dr. C. Hunter, University of Sheffield
Noncovalent Interactions between Aromatic Molecules

March 9

Prof. F. Wilkinson, Loughborough University of Technology
Nanosecond and Picosecond Laser Flash Photolysis

March 10*

Prof. S.V. Ley, University of Cambridge
New Methods for Organic Synthesis

March 25

Dr. J. Dilworth, University of Essex
Technetium and Rhenium Compounds with Applications as Imaging Agents

April 28

Prof. R. J. Gillespie, McMaster University, Canada
The Molecular Structure of some Metal Fluorides and Oxofluorides: Apparent Exceptions to the VSEPR Model.

May 12

Prof. D. A. Humphreys, McMaster University, Canada
Bringing Knowledge to Life

October 5

Prof. N. L. Owen, Brigham Young University, Utah, USA
Determining Molecular Structure - the INADEQUATE NMR way

October 19

Prof. N. Bartlett, University of California
Some Aspects of Ag(II) and Ag(III) Chemistry

November 2

Dr P. G. Edwards, University of Wales, Cardiff
The Manipulation of Electronic and Structural Diversity in Metal Complexes - New Ligands

November 3

Prof. B. F. G. Johnson, Edinburgh University
Arene-metal Clusters

November 9

Dr G. Hogarth, University College, London
New Vistas in Metal-imido Chemistry

November 10

Dr M. Block, Zeneca Pharmaceuticals, Macclesfield
Large-scale Manufacture of ZD 1542, a Thromboxane Antagonist Synthase Inhibitor

November 16*

Prof. M. Page, University of Huddersfield
Four-membered Rings and β-Lactamase

November 23*

Dr J. M. J. Williams, University of Loughborough
New Approaches to Asymmetric Catalysis

December 7

Prof. D. Briggs, ICI and University of Durham
Surface Mass Spectrometry

1995

January 11*

Prof. P. Parsons, University of Reading
Applications of Tandem Reactions in Organic Synthesis

January 18

Dr G. Rumbles, Imperial College, London
Real or Imaginary Third Order Non-linear Optical Materials

January 25*

Dr D. A. Roberts, Zeneca Pharmaceuticals
The Design and Synthesis of Inhibitors of the Renin-angiotensin System

February 1

Dr T. Cosgrove, Bristol University
Polymers do it at Interfaces

February 8

Dr D. O'Hare, Oxford University
Synthesis and Solid-state Properties of Poly-, Oligo- and Multidecker Metallocenes

February 22*

Prof. E. Schaumann, University of Clausthal
Silicon- and Sulphur-mediated Ring-opening Reactions of Epoxide

March 1

Dr M. Rosseinsky, Oxford University
Fullerene Intercalation Chemistry

March 22

Dr M. Taylor, University of Auckland, New Zealand
Structural Methods in Main-group Chemistry

April 26*

Dr M. Schroder, University of Edinburgh
Redox-active Macrocyclic Complexes : Rings, Stacks and Liquid Crystals

May 4*

Prof. A. J. Kresge, University of Toronto
The Ingold Lecture Reactive Intermediates : Carboxylic-acid Enols and Other Unstable Species

October 11

Prof. P. Lugar, Frei Univ Berlin, FRG
Low Temperature Crystallography

October 13*

Prof. R. Schmultzer, Univ Braunschweig, FRG.
Calixarene-Phosphorus Chemistry: A New Dimension in Phosphorus Chemistry

October 18

Prof. A. Alexakis, Univ. Pierre et Marie Curie, Paris,
Synthetic and Analytical Uses of Chiral Diamines

October 25

Dr.D.Martin Davies, University of Northumbria
Chemical reactions in organised systems.

November 1*

Prof. W. Motherwell, UCL London
New Reactions for Organic Synthesis

November 3

Dr B. Langlois, University Claude Bernard-Lyon
Radical Anionic and Psuedo Cationic Trifluoromethylation

November 8*

Dr. D. Craig, Imperial College, London
New Stategies for the Assembly of Heterocyclic Systems

November 15

Dr Andrea Sella, UCL, London
Chemistry of Lanthanides with Polypyrazoylborate Ligands

November 17

Prof. David Bergbreiter, Texas A&M, USA
Design of Smart Catalysts, Substrates and Surfaces from Simple Polymers

November 22

Prof. I Soutar, Lancaster University
A Water of Glass? Luminescence Studies of Water-Soluble Polymers.

November 29

Prof. Dennis Tuck, University of Windsor, Ontario, Canada
New Indium Coordination Chemistry

December 8

Professor M.T. Reetz, Max Planck Institut, Mulheim
Perkin Regional Meeting

1996

January 10

Dr Bill Henderson, Waikato University, NZ
Electrospray Mass Spectrometry - a new sporting technique

January 17

Prof. J. W. Emsley , Southampton University
Liquid Crystals: More than Meets the Eye

January 24*

Dr Alan Armstrong, Nottingham Univesity
Alkene Oxidation and Natural Product Synthesis

January 31

Dr J. Penfold, Rutherford Appleton Laboratory,
Soft Soap and Surfaces

February 7

Dr R.B. Moody, Exeter University
Nitrosations, Nitrations and Oxidations with Nitrous Acid

February 12

Dr Paul Pringle, University of Bristol
Catalytic Self-Replication of Phosphines on Platinum(O)

February 14

Dr J. Rohr, Univ Gottingen, FRG
Goals and Aspects of Biosynthetic Studies on Low Molecular Weight Natural Products

February 21

Dr C R Pulham , Univ. Edinburgh
Heavy Metal Hydrides - an exploration of the chemistry of stannanes and plumbanes

February 28

Prof. E. W. Randall, Queen Mary & Westfield College
New Perspectives in NMR Imaging

March 6*

Dr Richard Whitby, Univ of Southampton
New approaches to chiral catalysts: Induction of planar and metal centred asymmetry

March 7

Dr D.S. Wright, University of Cambridge
Synthetic Applications of Me_2N-p-Block Metal Reagents

March 12*

RSC Endowed Lecture - Prof. V. Balzani, Univ of Bologna
Supramolecular Photochemistry

March 13

Prof. Dave Garner, Manchester University
Mushrooming in Chemistry

April 30*

Dr L.D.Pettit, Chairman, IUPAC Commission of Equilibrium Data
pH-metric studies using very small quantities of uncertain purity

* Indicates attended by the author.

Research Conferences.

RSC UK Macrocyclic's Group,
University of Warwick, 5 - 6th January 1994.

RSC UK Macrocyslic's Group,
University of Newcastle, 4 - 5th January 1995.

RSC UK Macrocyclic's Group,
University of Sheffield, 4 - 5th January 1996.

European Conference on Electroanalysis*,
University of Durham, 25th - 29th March 1996

* Poster presented.

Publications.

Selective Cation Binding with cis-cis-1,3,4-Trioxacyclohexyl Based Ligands: Aplications to Ion Transport and Electrochemical Detection and Assessment of Complexation by Electrospray Mass Spectrometry.

M.Goodall, P.M.Kelly, D.Parker, K.Gloe, H.Stephan.

Journal of the Chemical Society, Perkin Transactions II, In Press.