NEW LOWER RIM CALIX[4]ARENE DERIVATIVES CONTAINING MIXED DONOR ATOMS. SYNTHESIS, CHARACTERISATION AND BINDING PROPERTIES.

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

by

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ABSTRACT

Novel $p$-tert-butylcalix[4]arene derivatives (L-3-10) containing mixed donor atoms (O, N, S) have been synthesised in a two stage reaction, the first part of which involves the preparation of L-2 using 18-crown-6 as a phase transfer catalyst and $\text{K}_2\text{CO}_3$ as a weak base. These conditions lead to the removal of two distal protons from the lower rim, allowing the 1, 3-bis-methylethylthio ether derivative (L-2) to be synthesised in a reduced reaction time with greater yield and purity than previously published. The final two protons were removed using NaH, sites to which a variety of amine, amide and thiophene moieties were introduced. This thesis reports investigations on these new compounds detailed as follows,

i) $^1\text{H}$ and $^{13}\text{C}$ NMR characterisation of these derivatives. In two cases, X-ray crystallographic structures have been determined, showing distortions from the symmetrical cone conformation of $p$-tert-butylcalix[4]arene caused by steric interactions of the lower rim substituents.

ii) Solubility and derived Gibbs energies of these ligands in various solvents at 298.15 K. Using acetonitrile and methanol as reference solvents, Gibbs energy of transfer are calculated.

iii) The acid-base properties of ligands L-3,4,6-8 were investigated by potentiometry. Equilibrium constants for the dissociation processes reveal relative proton affinities in methanol at 298.15 K. Data of individual species present as a function of pH are presented in diagrams.

iv) Conductimetric measurements. These data are used to derive the stoichiometry of metal cation complexes of L-4 in methanol.

v) $^1\text{H}$ NMR studies of the complexation of L-4 with metal cations in $\text{CD}_3\text{OD}$ at 298 K. These reveal conformational change in the macrocycle cyclic structure as the substituents' arrangements are altered to accommodate the guests cations.

vi) Determination of Gibbs energy of complexation for ligand L-4 and $\text{Ag}^+$, $\text{Pb}^{2+}$, $\text{Cd}^{2+}$ and $\text{Cu}^{2+}$ metal cations in methanol at 298.15 K, using a competitive potentiometric method. Cation selectivities are discussed.
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# Contents

1. **Introduction** .............................................................................................................. 1

1.1. **Host-Guest Chemistry** .......................................................................................... 1

1.2 **Calixarenes. A New Macrocycle** .......................................................................... 2

1.2.1. **History of calixarenes** ......................................................................................... 2

1.2.2. **Nomenclature** ......................................................................................................... 4

1.2.3. **Synthesis of calixarenes** ...................................................................................... 5

1.2.4. **Mechanism of the calixarene forming reaction** .................................................... 7

1.2.5. **Physical properties of calixarenes** ....................................................................... 13

1.2.5.1. Melting Points ...................................................................................................... 14

1.2.5.2 Solubility ................................................................................................................. 15

1.2.5.3 NMR Spectra ......................................................................................................... 17

1.2.5.4 Infrared spectra ..................................................................................................... 19

1.2.5.5 Ultraviolet spectra ............................................................................................... 19

1.3 **Synthesis of Calixarene Derivatives** ..................................................................... 21

1.3.1. **Calixarenes containing soft donor atoms** ............................................................ 22

1.3.2. **Calixarenes with hard-soft metal cation binding properties** ................................ 28

1.3.3. **Phosphorous donor calixarenes** ......................................................................... 29

1.3.4. **Recent synthetic developments in calixarene chemistry** .................................... 30

1.4 **The Study of Host-Guest Interactions in Calixarene Chemistry** ......................... 34

1.4.1. **Calixarene interactions with groups I and II metal cations** ................................ 37

in solution

1.4.2. **Calixarene interactions with transition and heavy metal ions** ............................... 43

1.4.3 Interactions with neutral molecules ........................................................................ 46

1.4.4. **The selective complexation of anions** .................................................................. 48

1.4.5. **Proton interactions with parent and derivatised calixarenes** ............................. 50

1.4.6. **The solution thermodynamics relating to calixarene derivatives** ...................... 52

1.5 **Applications** ............................................................................................................ 56

1.5.1. **Therapeutic and biologically active calixarene derivatives** ................................. 56
1.5.2. Ion sequestration ................................................................. 57
1.5.3. Separation and purification of neutral molecules ............... 60
1.5.4. Calixarenes used as sensors ............................................. 61
1.5.5. Miscellaneous applications .............................................. 63

1.6. AIMS OF WORK ................................................................. 65

2. EXPERIMENTAL PROCEDURES ....................................... 66

2.1. LIST OF CHEMICALS, SOLVENTS AND THEIR ................. 66
ABBREVIATIONS

2.2. PURIFICATION OF SOLVENTS ........................................ 69

2.3. SYNTHESIS OF LOWER RIM CALIX[4]ARENE ..................... 70
DERIVATIVES CONTAINING SOFT DONOR ATOMS

2.3.1. Preparation of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)..... 71
-25, 26, 27, 28-tetakis-[2-(thiophenemethoxy]
calix[4]arene (L-1)

2.3.2. Preparation of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)..... 73
-25, 27-dihydroxy-26, 28-bis[2-(methylthio)ethoxy]
calix[4]arene (L-2)

2.3.3. Preparation of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)..... 75
-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-dimethylamine)
ethoxy]calix[4]arene (L-3)

2.3.4. Preparation of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)..... 76
-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]
calix[4]arene (L-4)

2.3.5. Preparation of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)..... 77
-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diisopropylamine)
ethoxy]calix[4]arene (L-5)

2.3.6. Preparation of 5, 11, 17, 23-tetrakis-(1, 1 dimethylethyl)..... 79
-25, 27-bis(methylthioethoxy)-26, 28-bis[1-(morpholinyI)ethoxy]
calix[4]arene (L-6)

2.3.7. Preparation of 5, 11, 17, 23-tetrakis-(1, 1 dimethylethyl)..... 80
-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(1-piperidinyI)ethoxy]
calix[4]arene (L-7)
2.3.8. Preparation of 5, 11, 17, 23-tetrais-(1, 1-dimethylethyl)..............81
-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(1-pyrrolidine)

2.3.9. Preparation of 5, 11, 17, 23-tetrais-(1, 1-dimethylethyl)..............82
-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[1-(2-methylthiophene)
oxy]calix[4]arene (L-9)

2.3.10. Preparation of 5, 11, 17, 23-tetrais-(1, 1-dimethylethyl)............84
-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diisopropylacetamide)
oxy]calix[4]arene (L-10)

2.4. NUCLEAR MAGNETIC RESONANCE MEASUREMENTS..................86
2.4.1. \(^1\)H NMR measurements ..............................................86
2.4.2. \(^13\)C NMR measurements..............................................86

2.5. X-RAY CRYSTALLOGRAPHY................................................87

2.6. SOLUBILITY MEASUREMENTS..............................................88

2.7. UV-SPECTROPHOTOMETRIC MEASUREMENTS:..........................89
INTERACTION OF 5, 11, 17, 23-TETRAKIS-
(1, 1-DIMETHYLETHYL)-25, 27-BIS[2-(METHYLTHIO)ETHOXY]
WITH PERCHLORIC ACID IN METHANOL AT 298 K
2.7.1. Spectrophotometric determination of the interaction of...........89
5, 11, 17, 23-tetrais-(1, 1-dimethylethyl)-25, 27-bis(methylthio
with perchloric acid in methanol at 298 K

2.8. DETERMINATION OF DISSOCIATION CONSTANTS OF ...............90
THIOAMINE CALIX[4]ARENE DERIVATIVES (L-3-8) IN
METHANOL AND ETHANOL AT 298.15 K
2.8.1. Preparation of standard solutions..................................90
2.8.2. Apparatus.................................................................91
2.8.3. Electrode calibration....................................................91
2.8.4. Measurements of the dissociation constants in methanol........91
and ethanol at 298.15 K
2.8.5. Calculation of dissociation constants at 298.15 K.............92
2.9. CONDUCTANCE MEASUREMENTS ..................................................... 92

2.9.1. Apparatus .................................................................................. 93
2.9.2. Platinisation of electrodes used in the conductivity cell ................. 94
2.9.3. Determination of the cell constant at 298.15 K............................ 94
2.9.4. Conductimetric titrations in non-aqueous media at 298.15 K......... 96

2.10. 'H NMR COMPLEXATION EXPERIMENTS .................................. 96

2.11. DETERMINATION OF STABILITY CONSTANTS OF METAL...... 97

CATIONS WITH 5, 11, 17, 23-TETRAKIS-(1, 1-DIMETHYL-
ETHYL)-25, 27-BIS[2-(METHYLTHIO)ETHOXY]-26, 28-BIS[2-
(DIETHYLAMINE)ETHOXY]CALIX[4]ARENE (L-4) IN
METHANOL AT 298.15 K BY POTENSIOMETRY USING
SILVER ELECTRODES

2.11.1. Apparatus .................................................................................. 98
2.11.2. Competitive potentiometry procedure ....................................... 99
2.11.3. Treatment of results ................................................................. 102

3. RESULTS AND DISCUSSION .......................................................... 103

3.1. SYNTHESIS AND CHARACTERISATION OF LOWER .................... 103

RIM CALIX[4]ARENE DERIVATIVES CONTAINING SOFT
DONOR ATOMS

3.1.1. Use of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl) ...................... 103
-25, 27-dihydroxy-26, 28-bis[2-(methylthio)ethoxy]
calix[4]arene (L-2)

3.1.2. Use of sodium hydride as a deprotonating base ....................... 105
3.1.3. 'H and 'C spectral characterisation of lower rim ....................... 110
calix[4]arene derivatives (L-1-10)

3.1.4. X-ray crystallographic studies ................................................. 127
3.1.4.1. Crystallographic data for 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 26, 27, 28-tetakis-[2-
(thiophene)methoxy]calix[4]arene (L-1) ........................................ 127
3.1.4.2. Crystallographic data for 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-methylthio)ethoxy]-26, 28-bis[2-
(dimethylamine)ethoxy]-calix[4]arene (L-3) .............................. 133
3.2. SOLUBILITY MEASUREMENTS AND DERIVED .............................138
GIBBS ENERGIES OF SOLUTION. TRANSFER GIBBS
ENERGIES FROM ACETONITRILE TO VARIOUS SOLVENTS

3.3. UV-SPECTROPHOTOMETRIC MEASUREMENTS : .................148
INTERACTION OF 5, 11, 17, 23-TETRAKIS-(1, 1-
DIMETHYLETHYL)-25, 27-BIS[2-(METHYLTHIO)ETHOXY]
WITH PROTONS IN METHANOL AT 298 K

3.4. DETERMINATION OF DISSOCIATION CONSTANTS ..............150
OF DI-SUBSTITUTED DIETHYLAMINE CALIX[4]ARENE
DERIVATIVES IN METHANOL AND ETHANOL AT 298.15 K

3.4.1. Electrode calibration..................................................150
3.4.2. Potentiometric titrations to determine dissociation constants....151

3.5. CONDUCTANCE MEASUREMENTS ............................................161
3.5.1. Determination of the cell constant at 298.15 K ..........162
3.5.2. Conductimetric titration of 5, 11, 17, 23-tetras-
(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-
bis(diethylamine)ethoxy]calix[4]arene (L-4) with metal ion
salts in methanol at 298.15 K

3.5.2.1. Conductimetric titration of 5, 11, 17, 23-tetra-
(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-
bis(diethylamine)ethoxy]calix[4]arene (L-4) with cadmium
nitrate in methanol at 298.15 K
3.5.2.2. Conductimetric titration of 5, 11, 17, 23-tetra-
(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-
bis(diethylamine)ethoxy]calix[4]arene (L-4) with lead
nitrate in methanol at 298.15 K
3.5.2.3. Conductimetric titration of 5, 11, 17, 23-tetra-
(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-
bis(diethylamine)ethoxy]calix[4]arene (L-4) with silver
nitrate in methanol at 298.15 K

3.6. \textsuperscript{1}H NMR COMPLEXATION EXPERIMENTS

3.6.1. \textsuperscript{1}H NMR titration of cadmium and lead nitrate with 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-diethylamine)ethoxy]calix[4]arene (L-4) in deuterated methanol at 298 K

3.6.2. \textsuperscript{1}H NMR titration of silver nitrate with 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-diethylamine)ethoxy]calix[4]arene (L-4) in deuterated methanol at 298 K


3.6.4. Mixed complexation NMR measurements


3.7.1. Determination of standard electrode potential, E\textdegree of the cell


3.7.3. Determination of stability constants of various metal cations in methanol at 298.15 K
4. CONCLUSIONS ................................................................. 193
5. SUGGESTIONS FOR FURTHER WORK .......................... 195
6. APPENDIX ................................................................. 197
7. REFERENCES .............................................................. 207
1. INTRODUCTION

1.1. HOST-GUEST CHEMISTRY

The huge expansion in the field of macrocyclic chemistry in the last two decades has been accelerated by the potential of these compounds to take part in host-guest interactions. A general property of these interesting compounds is to selectively offer greater stability to guests than equivalent linear analogues. This stability enhancement is known as the 'macrocyclic effect' or for three-dimensional ligands, the term 'macrobicyclic effect' is used.

The capability of derivatised calixarenes to selectively extract metal cations and neutral molecules has, over the past decade, become commercially viable. By derivatising calixarenes, changing ligand parameters such as conformation, cavity size, number, arrangement and flexibility of binding sites and most importantly, the type of donor atoms, it has become possible to target specific metal cations.

Environmental issues in many areas of modern life are becoming increasingly important. The toxic effects of heavy metals are well documented and the implications of their removal from contaminated sources are without doubt of great significance. Calixarenes are now being tailored to selectively extract heavy metal cations.

The study and quantification of the host-guest interactions via solution and complexation processes is therefore vital chemistry in order to understand the targeting of particular metal cations. These interactions, studied in different solvents, can best be investigated by measuring thermodynamic parameters such as the Gibbs energy, the enthalpy and the entropy associated with these processes.

One factor (which is often forgotten) is the effect of different solvents upon the strength of the complexation processes. The relative strength of the solvent-solvent
bonds and the solvation of the host, the guest and the complex largely determine the strength of complexation. However, the magnitude of the stability constant (hence Gibbs energy of complexation) depends on enthalpy and entropic changes and it is important to obtain this information.

The following introduction reviews calixarene chemistry in terms of synthesis, derivatisation, thermodynamic properties and applications.

1.2. CALIXARENES. A NEW CLASS OF MACROCYCLES

1.2.1. History of calixarenes

Towards the end of the nineteenth century Baeyer\textsuperscript{7} investigated reactions between phenols and aldehydes, publishing results in 1872. Unfortunately, some of the products he obtained remained uncharacterised for almost 70 years. In 1940, Neiderl and Vogel\textsuperscript{8} reported their conclusions regarding the structure of a crystalline product from an acid catalysed condensation reaction between acetaldehyde and resorcinol, which had eluded several other investigators\textsuperscript{9-11}. The compound was thought to have carbon linkages between the resorcinol units, since it was found to be resistant to acid hydrolysis and had a high melting point.
Only a cyclic structure (Fig. 1.1) could satisfy all the physical and chemical behaviour which had been detailed.

In 1944 Zinke and Ziegler\textsuperscript{12} obtained a white crystalline product from a base-induced reaction of para-substituted phenol with formaldehyde. A cyclic tetrameric structure was then proposed (Fig. 1.2).

In the 1950's the Petrolite Company manufactured demulsifiers for crude oil which consisted of p-alkylphenol with formaldehyde, followed by treatment of the condensate with ethylene oxide, to produce an oxy-alkylate. Customers complained of sludges precipitating from their oils. Company research scientist, John Munch, investigated the problem and simulated the experiment in the laboratory, reproducing the formation of a colourless, high melting and very insoluble material. This procedure is now referred to as the 'Munch' or 'Petrolite' Procedure and modified versions of this technique are now used to prepare the other two main parent calixarenes; hexamer\textsuperscript{13} and octamer\textsuperscript{14}.

Generally, macrocyclic chemistry developed slowly until 1964 when Pressmann\textsuperscript{15} discovered that natural antibiotics, such as valinomycin, were responsible for the selective transport of sodium and potassium across biological membranes. Within a few years, Pederson\textsuperscript{16}, Lehn\textsuperscript{17} and Cram\textsuperscript{18} had published their discoveries of three new macrocycles - crown ethers, cryptands and spherands respectively.
Research into host-guest chemistry was dramatically stimulated. Thus, Patrick and Egan\textsuperscript{19} improved the experimental method for producing phenolic [\textsuperscript{III}]-
metacyclophanes, a nomenclature which was discarded by Gutsche\textsuperscript{20} in 1978 (who introduced the term ‘calixarenes’).

Now calixarenes have developed from being a ‘by-product of phenoplasts manufacture’\textsuperscript{21} to extremely versatile macrocycles.

1.2.2. Nomenclature

In 1978 Gutsche\textsuperscript{20} proposed naming the cyclic oligomers formed from the condensation of phenol with formaldehyde in basic conditions, ‘calixarenes’. ‘Calix’ means ‘beaker’ in Latin and Greek and was chosen as it describes the conformation which the cyclic tetramer generally adopts. The number of benzene or ‘arene’ units is indicated by a bracketed number which is inserted between ‘calix’ and ‘arene’. Complicated derivatised structures are then systematically named according to normal IUPAC nomenclature rules (Fig. 1.3) with the basic calix[n]arene term retained and the \textit{para} substituent from which the product was derived indicated.

Abbreviated name and structure,

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{p-tert-butylcalix4arene.png}
\caption{Structure and numbering system of parent calix[4]arenes}
\end{figure}

Full structure and numbering,

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{calix4arene.png}
\caption{Structure and numbering system of parent calix[4]arenes}
\end{figure}
Parent calix[n]arenes in the cone (beaker) conformation are said to have a ‘lower’ and ‘upper’ rim. The ‘lower’ rim is already functionalised with hydroxy groups, while the ‘upper’ rim consists of t-butyl groups, which create a hydrophobic cavity.

1.2.3. Synthesis of calixarenes

Many reviewers often describe the synthesis of calixarenes as a ‘single step’ reaction or as a ‘simple one-pot’ procedure. However, difficulties in reproducing Gutsche’s experimental methods were often encountered and noted by various researchers, including myself, especially for the synthesis of p-tert-butylcalix[4]arene. A later revised procedure has become the accepted method for producing calix[4]arene in high yield and purity. This method will be further discussed in this section.

Hayes and Hunters initially developed a stepwise procedure which was later modified by Kämmerer et al., consisting of the sequential addition of methylene and aryl groups to p-substituted phenols, with one of the ortho positions blocked by a halogen atom. Other similar methods introduced by Gutsche and Böhmer further revealed the flexibility in producing tailored calixarene derivatives (unfortunately all these methods give rise to low yields).

Calixarenes are formed in condensation reactions between para-substituted phenols and formaldehyde. The original ‘one-pot’ Zinke and Ziegler procedure had limitations, producing p-tert-butylcalix[4]arene as a minor product and involving several long tedious steps. Cornforth and then Gutsche improved upon the original method, resulting in pure p-tert-butylcalix[4]arene as a major product. Gutsche’s ‘modified Zinke-Cornforth’ method still involved several long steps detailed as follows,

i) The reaction mixture consisting of p-tert-butylphenol, formaldehyde 37% (aq) and sodium hydroxide is heated for 45 hours at = 55 °C.

ii) Heating is then increased to ≈ 120 °C for 2 hours, in order to drive off water.

iii) The solid formed is then neutralised with hydrochloric acid and dried.

5
iv) Finally cyclisation is completed by a high temperature reflux for 2 hours at \( \approx 230 \, ^\circ C \).

In an attempt to study the reaction, Gutsche and other co-workers\(^{25}\) modified the above procedure by fully neutralising the yellow precursor formed after Stage ii) with dilute hydrochloric acid. The addition of sodium hydroxide was then varied. It was found that if the precursor had been fully neutralised, then the experiment failed to produce calixarene upon heating, indicating the necessity of base to induce cyclisation. These results clearly reveal that other researchers had been too thorough in the following of Gutsche's method and had neutralised the precursor totally, which is why they had experienced difficulties in reproducing what appeared to be a simple method.

The optimum base addition was found to be 0.03-0.04 mol-equivalents with respect to the phenol concentration. Lower base concentrations lead to low yields but a pure calix[4]arene product, while higher concentrations give rise to high yields but with calix[6]arene impurities. The introduction of sodium hydroxide at this intermediate stage, to a base concentration of 0.037 mol-equivalent was found to give the best results.

Knowing that the reaction required a certain amount of the base to catalyse the cyclisation reaction, Gutsche changed his 'modified Zinke-Comforth' procedure, omitting the neutralising step and using the correct amount of base from the initial stage of the experiment. This 'one-pot' procedure consists of two shorter steps:

i) The preparation of precursor. The reaction mixture of \( p \)-tert-butylphenol, formaldehyde 37\% (aq) and 0.045 mol-equivalents of sodium hydroxide is heated for \( \approx 2 \) hours at 120 \(^\circ C \).

ii) The pyrolysis of precursor. The resinous material is then dissolved in diphenyl ether, heated to \( \approx 150 \, ^\circ C \) with a high flow rate of \( N_2 \) (g) passing over the reaction mixture in order to drive off water. This is followed by a high temperature reflux for two hours.
Attempts to further streamline the experiment by the simpler Munch or Petrolite procedure\textsuperscript{22} were unsuccessful. Even after the correct reactants were heated in the diphenyl ether for several hours, little or no cyclic product was obtained.

Parent calix[n]arenes, \(n = [6]\) and \([8]\), can be synthesised \textit{via} 'modified'-Petrolite procedures\textsuperscript{13,14}. \textit{p-tert-Butylcalix[6]} arene is formed by refluxing a mixture of \textit{p-tert}-butylphenol, formaldehyde and potassium hydroxide (potassium ions act as large template ions compared with sodium ions) and water is removed by a Dean-Stark trap. Lower temperatures are required to form the hexamer, therefore xylene is used as the reaction medium. The octamer is prepared by the same 'modified'-Petrolite method used to synthesise the hexamer, however paraformaldehyde is used as a reagent.

Ninagawa\textsuperscript{33} and Nakamoto\textsuperscript{34} have reported the preparation of the pentamer and heptamer parent calixarenes respectively. These methods give low yields and produce a mixture of oligomers which requires separation by column chromatography.

\textit{p-tert-Butylcalix[3]} arene has now been tentatively reported twice. There is some doubt surrounding Moshfegh's \textit{et al}\textsuperscript{35} procedure as this has failed to be reproduced. However, HPLC analysis of the crude product produced using Hayes and Hunter's\textsuperscript{37} procedure (which yields calix[6] arene as the major product) shows weak signals which could possibly be due to the trimer polymer.

Reports for calixarenes with up to 16 phenol units have been detected by HPLC analysis, but many of these larger rings have not been isolated and characterised\textsuperscript{36}.

\textbf{1.2.4. Mechanism of the calixarene forming reaction}

The various mechanisms proposed for the base catalysed condensation reaction between \textit{p-tert}-butylphenol and formaldehyde forming calixarenes have not been fully validated. Gutsche and co-workers\textsuperscript{25,37} intensely investigated the mechanism splitting the reaction into two stages :-

\begin{itemize}
  \item Stage 1: Condensation reaction between \textit{p-tert}-butylphenol and formaldehyde to form a dimer.
  \item Stage 2: Hydrolysis of the dimer to form the calixarene.
\end{itemize}
i) Formation of linear oligomers
ii) Cyclisation of oligomers

In order to investigate these two stages, the product distribution of the parent calixarenes was studied while reaction parameters, which can be grouped in the following way, were changed:

(a) Fixing the starting oligomer (e.g. monomer, dimer etc.).
(b) Changing the \(p\)-alkyl group of the starting material.
(c) Altering reaction conditions (e.g. ratio of reactants, the base cation, entrainment effects, solvent and temperature of reflux).

Some of Gutsche's results are discussed further in this section.

The first stage is thought to be well understood. The phenol is deprotonated by the base catalyst forming the 2-hydroxymethylphenol (Fig. 1.4, 1) and 2,6-bis(hydroxymethyl)phenol (Fig. 1.4, 2).

![Fig. 1.4 Hydroxymethylation of \(p\)-substituted phenols](image)

Arylation through an \(O\)-quinonemethide intermediate starts the formation of linear oligomers (Fig. 1.5).
As dehydration occurs between pairs of hydroxymethyl compounds, dibenzyl ethers are formed. These oligomers account for the formation of impurities such as dihomooxacalix[4]arene (Fig. 1.6), often found in the reaction mixture.
Gutsche's group proceeded in their investigation of the mechanism by fixing the oligomer for the first stage, then systematically studying the reactions of the mono and bis-hydroxymethylated monomers, dimers, trimers and tetramers, using the three main calixarene forming reactions - 'standard'-Petrolite (involves refluxing a suspension of phenol, formaldehyde and base in xylene for 4 hours), the 'modified'-Petrolite (follows the Petrolite procedure which employs a larger amount of base) and the 'modified' Zinke-Cornforth procedures (previously described, p.6). These reactions were monitored by T.L.C. and in some cases HPLC analysis. Estimations of yields were made by visual comparisons of the size and intensities of spots, giving low accuracy to an already erratic reaction. This patient research revealed that the starting monomer seemed to be unimportant in determining the final product mixture, e.g. the cyclic octamer can be formed from linear trimers, and the cyclic hexamer can form in good yield from linear tetramers, clearly indicating the reaction's complexity.

After linear oligomers have started to form, the mechanism for the second stage of calixarene forming reactions is still open to some conjecture. The formation of the cyclic tetramer has two main proposed pathways. The first follows the loss of water from a di-hydroxymethylated tetramer to form dihomooxacalix[4]arene (Figs. 1.6 and 1.7). This compound appears in the early stages of the reaction, reducing in concentration as the reaction proceeds to completion, although it is not viewed as a direct precursor to the tetramer, but as a storage depot that provides calixarene forming entities (Fig. 1.7).
Fig. 1.7  Postulated pictorial mechanism for cyclization of oligomers

The second proposed mechanism involves intermolecular association, through hydrogen bonding of a pair of zig-zag conformers to form hemicalix[8]arene (Fig. 1.7). This proposal requires no conformational change, unlike the mechanism for a pair of the zig-zag conformers intramolecularly hydrogen bonded - a structure which has been reported by X-ray crystallography. The hemicalix[8]arene's structure has a circular array of hydrogen bonds which are virtually identical to the octamer. The two ends of the linear tetramer clip together, two molecules of formaldehyde and water are eliminated and the octamer is formed (Fig. 1.7).

If the reaction conditions are sufficiently strenuous, e.g. boiling in diphenyl ether at 220 °C, the octamer is thought to be transformed to the cyclic tetramer by a process called molecular mitosis (Figs. 1.7 and 1.8), where the cyclic tetramer 'pinches' together at two points across its ring and splits into a pair of tetramers. The view that the tetramer is produced by a chemical mitosis from the octamer under Zincke-Cornforth conditions is further substantiated by the analysis of the precipitate which forms shortly after the precursor stage, but long before reflux temperature is reached.
This precipitate is found to be the pure octamer. As the reaction mixture reaches reflux temperature, the precipitate re-dissolves and precipitates back out when the diphenyl ether is cooled as the tetramer. Therefore, it has been proposed that the tetramer is formed via the octamer and/or the hexamer and not via the linear tetramer.

![Diagram of molecular mitosis](image)

**Fig. 1.8 Conversion of calix[8]arene to calix[4]arene, 'molecular mitosis'**

Therefore, the octamer is formed if the reaction conditions are less strenuous. The formation of the hexamer however is even more conjectural, the problem being that the octamer can be converted as a major product to either the tetramer or hexamer, depending on the amount of base. Furthermore, larger cations give rise to the hexamer (template effect) and the hemicalix[6]arene can be formed via a pair of linear trimers. An X-ray structure has not been obtained for the cyclic hexamer, but space filling models indicate that instead of a pleated loop conformation, a winged or hinged conformation exists. To adopt a pleated loop conformation two phenolic hydrogens must be removed, forming a dianion.
Using the three established methods for producing calixarenes in high yields available at the time ('modified'-Zinke-Cornforth, 'standard'-Petrolite and the 'modified' Petrolite procedure) Gutsche's work was unable to determine the identity of the starting compounds and intermediates; the major reason for this failure was that extensive reorganisation occurred in the starting material.

To summarise, it is postulated that the octamer is a product of kinetic control as a pair of hydroxymethylated linear tetramers, intermolecularly associated. The hexamer formation is believed to be controlled by template effects, while the tetramer formation is thermodynamically controlled, as ring contractions occur in the octamer and hexamer structures.

1.2.5. Physical properties of calixarenes

In the solid state, $p$-tert-butylcalix[4]arene exists exclusively in a rigid cone conformation. All four $p$-tert-butyl pendant arms, which form the hydrophobic cavity or the upper rim, lie in the same atomic plane. The lower rim consists of four interacting hydroxy groups which create a 'circular hydrogen bonding' pattern. These very strong intramolecular hydrogen bonds are often responsible for many of the properties shown by parent calixarenes. FTIR measurements have revealed that these intramolecular hydrogen bonds are strongest for the cyclic tetramer and weakest for the cyclic pentamer.

Larger parent calixarenes have more conformational freedom. Surprisingly, calix[8]arene shows dynamic $^1$H NMR characteristics that are almost identical to those of calix[4]arenes in solvents whose molecules do not interact by H-bonding. In these conditions the solvent does not interfere with the intramolecular H-bonding, and therefore, the calix[8]arene which exists in a pleated loop conformation can adopt the same intramolecular H-bonds as calix[4]arene. Calix[5]arene (which exists in a cone conformation) with the weakest intramolecular H-bond interaction, shows a considerable amount of conformational freedom as reflected by the low coalescence temperature, $T_c$, of its bridging methylene signals, measured by $^1$H NMR.
In contrast to the solid state, four calix[4]arenes conformations are observed in solution:

![Conformations of p-tert-butylcalix[4]arene in solution](image)

The transformation between the different conformations is accomplished by the aryl group rotating through the centre (annulus) of the macrocycle. By selective functionalisation of the upper and the lower rims, conformational mobility can be permanently frozen forming 'changeless calixarenes'.

### 1.2.5.1. Melting points

High melting points are a characteristic property of calixarene compounds (Table 1.1). The strong hydrogen bonds formed between the lower rim's hydroxy groups are responsible for this property.

However, Böhmert, van-Loon and Asfari have shown that small synthetic changes to calixarene structures produce derivatives with melting points lower than 100 °C.
Chapter One Introduction

Oligomer Melting point

<table>
<thead>
<tr>
<th>Oligomer</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>p</em>-tert butylcalix[4]arene</td>
<td>342-344 °C</td>
</tr>
<tr>
<td><em>p</em>-tert butylcalix[5]arene</td>
<td>310 °C</td>
</tr>
<tr>
<td><em>p</em>-tert butylcalix[6]arene</td>
<td>381-381 °C</td>
</tr>
<tr>
<td><em>p</em>-tert butylcalix[7]arene</td>
<td>331 °C</td>
</tr>
<tr>
<td><em>p</em>-tert butylcalix[8]arene</td>
<td>411-412 °C</td>
</tr>
</tbody>
</table>

Table 1.1 Melting points of parent calixarenes

1.2.5.2. Solubility

The low solubilities of parent calixarenes in many common solvents is a distinctive feature of their chemistry.

Parent calixarenes’ insolubility in water was one property which drew the attention of many of the original researchers. Even this characteristic has been overcome through derivatisation - sulfonate[^6], acid-soluble amino[^7], and base-soluble carboxyl[^8,^9] calixarene derivatives have all been synthesised. Table 1.2 displays the low solubility (mol dm[^3]) determined for *p*-tert-butylcalix[n]arenes (n = 4, 8) in various solvents at 298.15 K.
<table>
<thead>
<tr>
<th>Solvent</th>
<th>[4]</th>
<th>[8]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$5.90 \times 10^{-4}$</td>
<td>$&lt;10^{-5}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$3.30 \times 10^{-4}$</td>
<td>$&lt;10^{-5}$</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>$1.10 \times 10^{2}$</td>
<td>$2.20 \times 10^{3}$</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>$4.73 \times 10^{-5}$</td>
<td>$1.68 \times 10^{-5}$</td>
</tr>
<tr>
<td>n-Hexane</td>
<td>$2.12 \times 10^{-4}$</td>
<td>$2.51 \times 10^{-5}$</td>
</tr>
<tr>
<td>Chloroform</td>
<td>$4.34 \times 10^{-3}$</td>
<td>$6.23 \times 10^{-3}$</td>
</tr>
<tr>
<td>Benzonitirile</td>
<td>$9.47 \times 10^{-4}$</td>
<td>$1.14 \times 10^{2}$</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>$1.83 \times 10^{-2}$</td>
<td>$2.57 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

Table 1.2 Solubilities of $p$-tert-butylcalix[n]arene ($n = 4, 8$) in various solvents at 298.15 K (mol dm$^{-3}$)$^{50,51}$
1.2.5.3. NMR Spectra

The $^{13}$C and $^1$H NMR spectra for $p$-tert-butylcalix[n]arenes ($n = [4], [6], \text{ and } [8]$) are simple and almost identical.

![NMR Spectrum](image)

**Fig. 1.10 $^1$H NMR spectrum for $p$-tert-butylcalix[4]arenes in CDCl$_3$ at 298.15 K**

The *cone* conformation can be verified by the position of the bridging methylene $^{13}$C NMR shift signal in deuterated chloroform, which appears around 31 ppm$^{52}$. For the 1, 3- *alternate* conformation, steric effects are believed to cause this methylene signal to shift downfield to ca. 8 37 ppm. Likewise the pair of doublets from the bridging methylene group in the $^1$H NMR spectrum for $p$-tert-butylcalix[4]arenes (Fig. 1.10) also indicates a *cone* conformation, while other spectral patterns indicate different conformations (Table 1.3).
Chapter One: Introduction

Conformation Bridging methylene

<table>
<thead>
<tr>
<th>Conformation</th>
<th>Bridging methylene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone</td>
<td>One pair of doublets ($J = 12$ Hz)</td>
</tr>
<tr>
<td>Partial Cone</td>
<td>Two pairs of doublets ($J = 12$ Hz) (ratio 1:1) or one pair of doublets ($J = 12$ Hz) and one singlet (ratio 1:1)</td>
</tr>
<tr>
<td>1,2-Alternate</td>
<td>One singlet and two doublets ($J = 12$ Hz) (ratio 1:1)</td>
</tr>
<tr>
<td>1,3-Alternate</td>
<td>One singlet</td>
</tr>
</tbody>
</table>

Table 1.3 $^1$H NMR spectral patterns for the conformations of $p$-tert-butylealix[4]arenes$^{42}$

At 298 K, several dynamic $^1$H NMR studies$^{51,53,54}$ have shown the cone conformation preferentially existing with an interconversion rate of ca. 100 sec$^{-1}$.

The singlet arising from the hydroxy groups (Fig. 1.10) does not vary with ring size. However, differentiation between calix[4]arene and calix[8]arene can be achieved by studying the signal from the bridging methylene groups. These methylenes consist of non-equivalent hydrogen atoms, whose geminal coupling (coupling constant ca. 12-14 Hz) forms a pair of doublets. The axial methylene protons, which are nearer to the hydroxy groups, are found downfield with respect to the equatorial methylene protons. The coalescence temperature, $T_c$, for the pair doublets in various solvents have been measured$^{41}$. In deuterated chloroform (which does not interfere with the intramolecular hydrogen-bonding) the coalescence temperature was found to be approximately 48 °C for both calix[n]arenes (n = 4 and 8). However, in a solvent like pyridine, $T_c$, for calix[4]arene falls to ca. 15 °C, while for calix[8]arene, $T_c$, is even lower than -90 °C as the intramolecular hydrogen bonding is disrupted$^{41}$.

Calix[n]arenes (n = 4, 5, 8) display a pair of doublets for the bridging methylene protons in non polar solvents at 298 K. However, calix[n]arenes (n = 4, 5) have a
cone conformation, while \( p\text{-}\text{tert}-\text{butyl} \) calix[8]arene has a pleated loop conformation. At low temperatures calix[6]arene has a more rigid conformation than the tetramer and pentamer, as three pairs of doublets are observed, but at 298 K a broad singlet is recorded. Calix[7]arene has a complicated spectra corresponding to a macrocycle with even less symmetry than calix[6]arene.

1.2.5.4. Infrared spectra

The very strong circular array of intramolecular hydrogen bonds found in parent calixarenes leads to unusually low frequency for the OH stretch vibrations. These bonds are at their strongest for calix[4]arene, lowest for the pentamer, with the remaining cyclic oligomers found in between. By studying the related infrared spectra the varying strength of these intramolecular bonds was clearly demonstrated\(^\text{40}\). For the tetramer and pentamer, the OH stretch vibrations were found around 3150 cm\(^{-1}\) and 3300 cm\(^{-1}\) respectively. Again the other oligomers fall between these limits.

Characterisation using the ‘fingerprint’ region (1500 - 900 cm\(^{-1}\)) and lower wave-numbers has only limited possibilities, since a similar spectra for all the oligomers is recorded.

1.2.5.5. Ultraviolet spectra

Calixarenes give rise to a pair of absorption maxima near 280 and 288 nm. The ratio of the intensity at these two wavelengths is a function of the ring size, ranging from 1.3 for calix[4]arene to 0.75 for calix[8]arene (Table 1.4)\(^\text{55,57}\). 
<table>
<thead>
<tr>
<th>Ring Size</th>
<th>280 ± 1 nm</th>
<th>288 ± 1 nm</th>
<th>Solvent</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>9,800</td>
<td>7,700</td>
<td>CHCl₃</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>14,030</td>
<td>14,380</td>
<td>Dioxane</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>15,500</td>
<td>17,040</td>
<td>CHCl₃</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>17,210</td>
<td>17,800</td>
<td>Dioxane</td>
<td>41,58</td>
</tr>
<tr>
<td>7</td>
<td>18,200</td>
<td>20,600</td>
<td>CHCl₃</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>19,800</td>
<td>20,900</td>
<td>Dioxane</td>
<td>41,58</td>
</tr>
<tr>
<td>8</td>
<td>23,100</td>
<td>32,000</td>
<td>CHCl₃</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 1.4 Absorptivities ($e_{max}$, mol$^1$.dm$^3$.cm$^{-1}$) of $p$-tert-butylcalix[n]arenes ($n = 4, 5, 6, 7, 8$) in CHCl₃ and dioxane at 280 and 288 nm
1.3. SYNTHESIS OF CALIXARENE DERIVATIVES

When synthesising new derivatives, it is important to consider the factors which determine the stability and selectivity of complex formation. Cox and Schneider, have reviewed these factors in the field of macrocyclic chemistry under the following headings:

i) Cavity sizes of macrocycles
ii) Donor atoms
iii) Functional groups as binding sites
iv) Electron density of binding sites
v) Cavity shapes and conformations

The macrocyclic and cryptate effects, as well as the role of the solvent and counterion were also discussed.

Considering the factors above, parent calixarenes (whose synthesis has been previously described in this chapter) are macrocycles which can be further functionalised through two possible routes. The first follows the removal of the lower rim protons from the phenolic groups, which then allows a variety of nucleophilic substitutions.

The second route involves the introduction of substituents at the upper rim once the t-butyl groups are removed. Several pathways are then available to functionalise the macrocycles:

i) Electrophillic substitution route
ii) p-Claisen rearrangement route
iii) p-Quinonemethide route
iv) p-Chloromethylation route

A review of the early synthetic routes used for derivatisation of calixarenes has been documented. The following section describes the more recent synthetic progress.
reported on calixarenes containing soft donor atoms as well as more unusual calixarene derivatives.

1.3.1. Calixarenes containing soft donor atoms

Investigating the factors underlying heavy-metal ion recognition by macrocycles has, until recently, produced few publications. By contrast, calixarene derivatives with functionalities binding via their oxygen or nitrogen metal cations from groups I and II have been widely developed.

Lindoy has led research into investigating and developing strategies which determine the factors leading to the discrimination between heavy and transition metal cations. Selectivity was discussed by comparing stability constants of related macrocycles, forming a matrix of data in order to look for stability maxima. Although Lindoy's research does not involve calixarene chemistry, polydentate macrocycles (having various substituted donor atoms and therefore different binding properties and cavity size) were investigated. These concepts also apply to calixarene chemistry.

One such calorimetric investigation revealed a marked preference for Ag$^+$ when a thioether replaces an ether donor polydentate macrocyclic ring. Similar stability enhancements do not occur for complexes of Pb$^{2+}$. This study was then developed by the gradual replacement of the oxygen donor atoms with sulphur donor atoms in the ligand framework, in order to see how Ag$^+$ discrimination proceeds. A suggestion for the high selectivity for silver(1) focuses on molecular model views that the ion 'triggers' a major ligand conformational change to produce a sterically locked conformation.

Cobben et al. has specifically substituted sulphur and nitrogen donor atoms to the lower rim of calix[4]arenes in order to selectively complex silver, copper, cadmium and lead metal cations. Soft donor calix[4]arene derivatives, shown in Fig. 1.11, were incorporated into membranes and then integrated on a chemically modified field effect transistor (C.H.E.M.F.E.T.) which discriminates between metal ions, transducing an
electrical signal. Ion sensitive field effect transistors (I.S.F.E.T.) have the potential to transfer molecular recognition into an electrical signal. Unfortunately these are not generally mechanically stable; CO$_2$ interferes with the electrical signal and they are not sufficiently hydrophobic to avoid being leached in aqueous solutions. However, when novel calixarene ionophores were incorporated into these membranes these problems were overcome, forming highly selective metal cation complexes which respond electrically in a linear fashion to the activity of metal ions.

C.H.E.M.F.E.T.s with incorporated calixarenes (containing thioethers, thioamides and thiocarbonyl functionalities, see Fig 1.11) have been found to be selective towards silver, cadmium and copper metal ions respectively.
### Chapter One Introduction

<table>
<thead>
<tr>
<th>Ion</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag⁺</td>
<td>$R_1 = R_3 = \text{OCH}_2\text{CH}_2\text{SCH}_3$, $R_2 = R_4 = \text{OH}$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 = R_2 = R_3 = R_4 = \text{OCH}_2\text{CH}_2\text{SCH}_3$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 = R_3 = \text{OCH}_2\text{CH}_2\text{SCH}_3$, $R_2 = R_4 = \text{On-Pr}$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 = R_3 = \text{OCH}_2\text{CH}_2\text{SCH}_3$, $R_2 = R_4 = R_5 = \text{H}$</td>
</tr>
<tr>
<td>Pb²⁺</td>
<td>$R_1 = R_3 = \text{OCH}_2\text{CH}_2\text{OCH}_2\text{C(O)N(CH}_3)_2$, $R_2 = R_4 = \text{On-Pr}$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 = R_3 = \text{OCH}_2\text{C(O)N(CH}_3)_2$, $R_2 = R_4 = \text{On-Pr}$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td>Cu²⁺</td>
<td>$R_1 - R_4 = \text{OCH}_2\text{CH}_2\text{SC(S)N(CH}_3)_2$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 = R_3 = \text{OCH}_2\text{CH}_2\text{SC(S)N(CH}_3)_2$, $R_2 = R_4 = \text{On-Pr}$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td>Cd²⁺</td>
<td>$R_1 = R_3 = \text{OCH}_2\text{C(S)N(CH}_3)_2$, $R_2 = R_4 = \text{OH}$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 = R_3 = \text{OCH}_2\text{C(S)N(CH}_3)_2$, $R_2 = R_4 = \text{OH}$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 - R_4 = \text{OCH}_2\text{CH}_2\text{OCH}_2\text{C(S)N(CH}_3)_2$, $R_5 = \text{t-butyl}$</td>
</tr>
<tr>
<td></td>
<td>$R_1 = R_3 = \text{OCH}_2\text{CH}_2\text{OCH}_2\text{C(S)N(CH}_3)_2$, $R_2 = R_4 = \text{On-Pr}$, $R_5 = \text{t-butyl}$</td>
</tr>
</tbody>
</table>

**Fig. 1.11** Ion selective soft donor functionalities used in chemically modified field effect transistors
Yordanov\(^6\) has published a series of heavy metal selective calixarene derivatives containing sulphur functionalities appended to the lower rim. A full range of sulphur donor calixarene tetramers was prepared from a flexible bromide derivative (Fig. 1.12, 3) via the 2-hydroxyethoxy functional groups (Fig. 1.12, 1), rather than using tosylate as the starting compound (Fig. 1.12, 2).

![Chemical structures](image)

*Fig. 1.12 Sulphur containing lower-rim functionalities*

Reported extraction data for the water-chloroform system at 298 K for Pb\(^{2+}\), Cd\(^{2+}\), Hg\(^{2+}\), Hg\(^{2+}\), MeHg\(^+\), with ligand 4d containing the SC(S)NMe\(_2\) functionality (Fig. 1.12) show high selectivity for mercury over lead and cadmium cations. As can be seen from Table 1.5, this ligand does not extract the latter two cations.
<table>
<thead>
<tr>
<th>Ion</th>
<th>Before Extraction</th>
<th>After Extraction</th>
<th>Extraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb$^{2+}$</td>
<td>30.5</td>
<td>30.9</td>
<td>0</td>
</tr>
<tr>
<td>Cd$^{2+}$</td>
<td>24.2</td>
<td>24.2</td>
<td>0</td>
</tr>
<tr>
<td>Hg$^{2+}$</td>
<td>51.4</td>
<td>9.6</td>
<td>81</td>
</tr>
<tr>
<td>Hg$_2$$^{2+}$</td>
<td>244.0</td>
<td>52.0</td>
<td>78</td>
</tr>
<tr>
<td>MeHg$^{+}$</td>
<td>37.5</td>
<td>23.4</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 1.5 Extraction results for Pb$^{2+}$, Cd$^{2+}$, Hg$^{2+}$, Hg$_2$$^{2+}$, MeHg$^{+}$ by ligand 4d shown in (Fig. 1.13)
Interestingly the reference also examines the extraction of methylmercury. In the 1960's there was a surprising discovery that a large fraction of the mercury in fish was methylmercury, despite some fish being taken from lakes and rivers where no methylmercury had been discharged. Eventually it was revealed that biological cycles were responsible for the transformation of mercury to methylmercury. Obviously, from the environmental point of view the removal of such toxic species is of huge importance.

The preparation of \( p\text{-}\text{tert-butyl} \text{tetramercapto} \text{calix}[4] \text{arene} \) (Fig. 1.13, 4) in a 1, 2-alternate conformation has been accomplished. Initially the condensation of \( p\text{-}\text{tert-butyl} \text{calix}[4] \text{arene} \) [Fig. 1.13, (1)] with \( \text{N, N-dirnethyltricarbamoyl chloride} \) led to a mixture of various conformers and partially substituted analogues. In a reaction based on the Newman-Kwart method for converting phenols to thiophenols, strenuous heating of the reaction mixture gave rise to the 1, 2-alternate conformation (Fig. 1.13, 3) which on reduction with lithium aluminium hydride forms the tetramercapto derivative. This derivative has the ability to bind two soft metal \( \text{Hg}^{2+} \) cations per ligand.
Fig. 1.13 Preparation of \( p \)-\( \text{tert} \)-butyltetramercaptopcalix[4]arene

Finally a range of sulphur and/or nitrogen containing calixarene derivatives has been developed as ion-selective membrane electrodes\(^{56-69}\). Generally, the prepared ionophores are incorporated into PVC membranes and have shown selective responses towards transition and heavy metal ions.

1.3.2. Calixarenes with hard-soft metal cation binding properties

Novel calixarenes with ditopic 'hard' - 'soft' metal binding sites have attracted interest as catalytic sites in both enzymatic and artificial systems\(^7^0\). The preferred ligands have been found to have substituent chain lengths comprised of six atoms \( (n = 6) \) (Fig. 1.14). Sufficiently long chain lengths on the lower rim can allow two metal ions in different coordination sites to be complexed. In the example shown below, when the first metal is complexed by the hard donor sites, unique conformational changes occur. Thus the four carbonyl groups turn inwards to complex. This behaviour is unusual as
electrostatic effects would often make the carbonyl groups to adopt positions which are as far apart as possible. The second binding site is now more accessible to soft metal cations, but only if the chain length is long enough (e.g. \( n = 6 \)). Too short chains lead to the formation of 1:1 complexes. This kind of mutual communication or allosteric effect between two metal binding sites is commonly seen in enzymatic systems.

Fig. 1.14 A ditopic hard-soft metal cation binding calix[4]arene derivative

More complicated ‘hard’-‘soft’ donor calixarenes have tetraamide lower rim functionalities which have been systematically capped with a tetraphenylporphyrin\(^7\). Upon complexation with potassium and zinc(II) ions, this new ligand is also able to capture iodide anions.

1.3.3. Phosphorus donor calixarenes

Phosphorus is another type of donor atom which is now being extensively researched to selectively complex transition\(^7\), heavy, lanthanide and actinides metal ions\(^22\). New phosphorus upper and lower rim functionalities are in a tri-coordinate form, where the heteroatom can act as a two electron donor atom to a metal cation.
1.3.4. Recent synthetic developments in calixarenes chemistry

The construction of more sophisticated calixarenes is constantly being developed in order to fashion molecular scaffolds for the building of artificial enzymes. Böhmer and Vicens\textsuperscript{21} have written a fairly extensive review into some of the more obscure calixarene derivatives. An account on the more recent synthetic work on calixarenes is now given. These are :-.

i) Furan-based calixarenes (Fig. 1.16)

![Fig. 1.15 Macrocycle containing furan sub-units](image)

Where $n = 1, 2, 3, 5$

Macrocycles containing furans are relatively rare; Musau and Whiting\textsuperscript{76} derived furans calixarenes (Fig. 1.15) which have so far received little attention. The lack of availability of starting materials has lead to only a few structures being reported, although the basic ring structures can be modified by reduction or by ring opening reactions.
ii) Thiocalixarenes

**Fig. 1.16 Thiocalix[n]arenes \( n = 0, 1, 2, 3 \)**

These novel supramolecular hosts, prepared by Tsuge et al\(^7\), have heteroatoms introduced to the bridges (Fig. 1.16), providing greater conformational flexibility and the availability of lone pairs, which can participate in hydrogen bonding. The hydrogen bonds are crucial to many of the sequestering properties and conformational features seen in calixarene chemistry as described in this chapter.

iii) Calixarene-based 'Carcerand'

**Fig. 1.17 Calixarene-based 'carcerand'**

Shinkai et al\(^8\) has prepared macrocycles where two calixarenes are joined at their upper rims through an 'adhesive' functional group (Fig. 1.17). A non-collapsible molecular cell structure is formed in which neutral species such as N-methylformanilide
are trapped non-covalently as a guest. Calixarene-based macrocycles which can selectively trap neutral molecules are already being used in industry (see applications, p. 56)

iv) Bicyclocalix[4]arene

Fig. 1.18 Bicyclocalix[4]arene

Bicyclocalix[4]arenes (Fig. 1.18) have two opposite para positions linked by a methylene-1, 3-(2-hydroxyphenylene)-methylene bridge. These novel calixarene structures, prepared by Berger et al. have a fixed cone conformation. Theoretically, conversion to the partial cone or a 1, 3- alternate conformation is still possible, however in the temperature dependant $^1$H NMR spectra no such conversions are detected.

Host-guest applications are obviously the driving force for the investigation of these new calixarene derivatives; to date their properties have not been fully investigated.
v) Polythiophenes functionalised with calix[4]arene-based ion receptors

![Polythiophene functionalised calixarene derivative](image)

**Fig. 1.19 Polythiophene functionalised calixarene derivative**

The optical and electrochemical properties of substituted polythiophene calix[4]arenes (Fig. 1.19) showing ion selective voltammetric, chromic, fluorescent and resistive responses, have been demonstrated by Marsella *et al.* These conducting polymers (CPs) which are involved in reversible binding processes, show an increased effective conjugation length of the polymer backbone leading to an ionochromic response. Complexed sodium ions induce a large positive shift in the potential at which the polymer is oxidised; balanced with a decrease in conductivity.

The idea of this work is to design new sensory materials capable of selectively binding specific analytes to receptor sites covalently attached to the polymer. Reversible recognition allows a complete reversible response - the sensory material then returns to its original unperturbed state once de-complexed.
1.4. THE STUDY OF HOST-GUEST INTERACTIONS IN CALIXARENE CHEMISTRY

In order to study host-guest interactions two basic processes must be studied:

i) Complexation or 'binding' processes

Stability constants can be determined through a variety of techniques. These can be classified into methods which measure effects proportional to concentration and those measuring properties which are dependant upon the logarithm of concentration. The latter techniques are generally regarded as far more sensitive to changes when the reaction is near to completion and therefore high stability constants can be measured. These methods are summarised as follows:

Techniques where effects are dependant upon the logarithm of ion concentration.

a) Potentiometry

This is one of the most accurate techniques for determination of metal ion concentrations, or strictly activities. Very low metal-ion concentrations can be measured and as a result stability constants of very stable complexes can be determined. Potentiometry requires the availability of a suitable electrode which undergoes a reversible reaction with the metal ion under investigation.

b) Polarography

This is an electrochemical technique involving the dropping mercury electrode. During a polarography experiment the current is measured as the potential difference between the two electrodes is changed. The current climbs with the potential difference until the limiting value is reached, the value being characteristic of the ion present. If several ions are present the current rises to a series of characteristic values, and they
are identified by measuring their half-wave potentials. The magnitude of the limiting current density is used to calculate the concentration of the ions.

c) Cyclic voltammetry

'Cyclic Stationary Electrode Voltammetry', involves a back and forth scanning of the electrode potential, with a higher speed than polarography. Each redox process is characterised by two current peaks, one for the reduction and the other for the oxidation potential scan. This technique is less accurate than polarography for the determination of stability constants.

Techniques where effects are proportional to concentration.

a) Titration calorimetry

After potentiometry the versatility of this technique means that it is regularly employed to study thermodynamic properties of complexation. Measurements of the variations in temperature or heat change during the titration of a metal ion with a ligand are recorded as a thermogram. Depending on the magnitude of the stability constant, titration calorimetry can be used for the determination of log $K$, and $\Delta_{r}H^{\circ}$ (enthalpy of complexation) values in a given solvent. Consequently, the standard Gibbs energy, $\Delta_{s}G^{\circ}$, the enthalpy, $\Delta_{r}H^{\circ}$, and entropy $\Delta_{s}S^{\circ}$ of complexation, can be calculated.

b) Ultraviolet-Visible spectrophotometry

These techniques can be used to determine coordination and complex stabilities. However they are restricted to hosts which absorb in the UV and visible regions. Generally, the greatest change is exhibited by the most stable complexes, but the absence of an effect does not necessarily mean a small or negligible interaction between the metal ion and ligand.
c) N.M.R. spectroscopy

$^1$H and $^{13}$C NMR spectra deliver the most detailed information about the conformational changes as a result of ligand and metal ion interactions. However, by studying chemical shifts and the relationship between the time-scale of chemical exchanges and that of the NMR experiment, these techniques can also determine stoichiometry and stability constants of the complexes. In stable complexes where exchange between the free and complexed species is slow compared to the NMR time-scale, two separate groups of lines are seen (one set for the free and the other for the complexed species). The ratio of complexed to free species is given directly by the relative integrals of the sets of signals, allowing stoichiometry of the complex to be determined, but high stability constants cannot be measured by this technique. For less stable complexes, rapid exchange between the free and complexed species occurs resulting in a time averaged spectra. In this instance chemical shifts of the metal ion are measured at constant total metal ion concentration but increasing ligand concentration. The two straight lines corresponding to limiting behaviour intersect at the stoichiometry of the complex, and the deviation of the actual shifts provides a measure of the stability constant.

d) Conductimetry

Variation of the electrical conductance with the concentration of the salt and ligand allows, in principle to determine, the stoichiometry and the stability constant of a metal ion complex. Ionic mobilities and ionic interactions are the underlying factors which control conductance measurements. For stable complexes, the presence of a sharp break in a plot of equivalent conductance against ligand:metal ($C_L/C_M$) concentration ratios (neglecting ion pair formation) is noted, while less stable complexes give rise to a more continuous curve. Only by extrapolation of the slopes at high and low $C_L/C_M$ ratios is it possible to obtain a point of intersection corresponding to the composition of the complex.
ii) Thermodynamic parameters of solution

Often thermodynamic studies have been restricted to stability constant measurements, with no significant explanation as to the role of the reaction media (solvent) in the binding process. Using solution calorimetry and by determining the solubility of the solute (host, guest and host-guest complex), solution thermodynamic parameters \(\Delta G^\circ, \Delta H^\circ\) and \(\Delta S^\circ\) can be calculated. Solvation of the solute plays an essential role in the binding process, differences in solvation between two solvents are reflected in the transfer thermodynamic parameters \(\Delta G^\circ, \Delta H^\circ\) and \(\Delta S^\circ\) from one solvent to another.

The following section briefly reviews recent thermodynamic reports relating to calixarenes.

1.4.1. Calixarene interactions with group I and II metal cations in solution

The host-guest interactions involving Group I (alkali series) and II (alkaline-earth series) metal ions and calixarene derivatives have been studied by many authors.\(^{31-34}\) However, these data are usually only confined to stability constant measurements. Publications which discuss the role of the reaction media in the host-guest interactions are rare.

Danil de Namor et al.\(^{35}\) has recently published thermodynamic parameters for the interactions of calixarene ester derivatives and alkali-metal cations in acetonitrile and benzonitrile at 298.15 K. A new potentiometry technique (double competitive potentiometric method) and titration calorimetry to derive stability constants (log \(K_a\)) for highly stable complexes with the former method and thermodynamic parameters of complexation (log \(K_a\) and derived Gibbs energies, \(\Delta G^\circ\) and enthalpies, \(\Delta H^\circ\)) with the latter technique were used.
As far as the double competitive potentiometric method is concerned, previous results published for the complexation of silver, lithium and sodium by cryptands 222 and 22 in acetonitrile and benzonitrile at 298.15 K, using silver-silver ion electrodes in potentiometric titrations, spectrophotometry, calorimetry and conductimetry, compared favourably with results derived from this new versatile technique. Considerable differences were only noted where stability constant measurements for these metal cations were determined at the limits of the techniques employed above.

The advantages of double competition potentiometry are that the technique utilises the sensitivity of the silver-silver ion electrode system to accurately investigate (outside the scope of other techniques) highly stable complexes which do not form complexes with silver ions. Therefore the method applies where the first ligand has a high affinity for silver while the second ligand has a low or no affinity for this cation. In conclusion, this new method is the most suitable for determining stability constants of highly stable metal cation complexes of calix[4]arene esters. The following equations describe the technique:

i) The complexation of silver and cryptand (Cry).

\[ \text{Ag}^+ (s) + \text{Cry} (s) \leftrightarrow \text{K} \rightarrow \text{Ag}^+\text{Cry} (s) \]  

(1.1)

ii) The competition of silver cryptate and the relevant cation M\(^{+}\) in a given solvent (s).

\[ \text{Ag}^+\text{Cry} (s) + \text{M}^+ (s) \leftrightarrow \text{K} \rightarrow \text{M}^+\text{Cry} (s) + \text{Ag}^+ (s) \]  

(1.2)

iii) Second competition reaction involving calixarene ester (RCalix) a ligand which is a poor complexing agent for silver.

\[ \text{M}^+\text{Cry} (s) + \text{RCalix} (s) \leftrightarrow \text{K} \rightarrow \text{M}^+\text{RCalix} (s) + \text{Cry} (s) \]  

(1.3)
iv) Combination of the three equations above leads to the stability constant of the metal cation with the calixarene derivative

\[ M^+ (s) + R\text{Calix} (s) \rightleftharpoons K^+ M'R\text{Calix} (s) \]

(1.4)

Results for the calixarene esters determined using this new technique were discussed in terms of the ligand, the solvent and the cation.

In terms of the ligand, as the electron donating effect of the alkyl group increases (when moving from the methyl to the ethyl and onto the n-butyl derivatives) making the carbonyl oxygen of the ester functionality more electronegative, their interaction with metal cations increases.

Stability constant results (expressed by the Gibbs energy) relating to the solvent, showed the same selectivity pattern \((Na^+ > Li^+ > K^+ > Rb^+)\) in both solvents, with a stability maxima for sodium and a decrease from sodium to rubidium in acetonitrile and to potassium in benzonitrile. In most cases, it was shown that the complexation process is enthalpy stabilised. The greatest entropy losses were found for the most stable complexes, with higher stabilities found for complexes in acetonitrile than benzonitrile. Previously published thermodynamic studies by Danil de Namor et al. in which the interactions of cryptands with most of these cations in benzonitrile and acetonitrile were measured, showed that the interaction with most highly solvated alkali metal cation leads to the lowest stability. Thus, benzonitrile, a poorer solvator of these cations than acetonitrile, offers a better complexation medium for these cations than the latter solvent. Clearly, these results differed significantly with similar studies carried out with calixarene ester derivatives.

In an attempt to explain these results for the calixarene esters, the solvation changes of the cation upon complexation, best reflected by the entropy term \((A_{solv} S^o)\), were discussed. During complexation, solvent molecules in the coordination sphere of the cation are replaced by the binding sites of the ligand reversing the trend in the entropy
effects of complexation relative to that of solvation. The trend is only observed for lithium and sodium in acetonitrile, while potassium and rubidium follow the same trend. All the cations in benzonitrile as regards ΔS° and Δ_{solv}S° results follow the same trend. These results seem to indicate that for the larger cations in acetonitrile and for most cations in benzonitrile, either the cation is not fully desolvated upon complexation with calixarene esters or even more likely, that in the metal-ion complexes the cations are able to enter direct interaction with the solvent.

In summary calixarene esters are unable to totally shield the complexed cation unlike cryptands which is why considerable differences in the entropy of calixarenate formation, Δ_{cal}S°, were found, compared with the constant value determined for the entropy of cryptate formation.

Arnaud-Neu et al have published a number of papers investigating the interactions of calixarenes with alkali and alkaline-earth cations. Two recent publications compare the interactions of these cations with calixarene amide and bis-crown calixarene derivatives in acetonitrile and in methanol (Fig. 1.20). Thermodynamic parameters were determined, using UV spectrophotometry (for less stable complexes) and competitive silver electrode potentiometry (for stable complexes). Enthalpy of complexation measurements were derived from titration calorimetry.
The results determined for the interactions of the tetraamide calix[4]arene derivatives with alkali metal ions in methanol and acetonitrile were discussed by addressing three questions:

i) Why are $\Delta_{\text{c}}H$ and $\Delta_{\text{c}}S$, respectively, higher and lower in acetonitrile than in methanol?

Enthalpies of complexation are a measure of the changes in energy of the bonds between the cation and either the ligand or the solvent and the solvent with the ligand. Acetonitrile would be expected to solvate the ligand and cation to a lesser extent compared with methanol. Solvent interactions are therefore lower, which results in higher cation-ligand interactions and lower cation-solvent and ligand-solvent interactions, leading to more favourable enthalpies of complexation. This fact is also reflected in the entropy results, which mainly relate to conformational and solvation effects. The negative entropic effects of complexation are far less important than the release of solvent molecules during the process. The sum of the solvation of the cation and ligand is less in acetonitrile therefore lower entropy values are recorded upon
complexation. However, not all the alkali cations are better solvated in methanol than acetonitrile (a fact which should increase ligand-cation interactions in the former solvent). Despite this there is an increase in stability for Rb$^+$ and Cs$^+$ metal ions (which are less solvated in methanol than acetonitrile) going from methanol to acetonitrile. Therefore it is suggested that the higher solvation of the ligand in methanol is the predominant factor to explain the higher stability constants of these cations in acetonitrile.

Molecular dynamics simulations\(^{92}\) of tetraamide calix[4]arene derivatives and their complexes (alkali and Eu$^{3+}$ metal cations), suggest that in acetonitrile the carbonyl groups of the amide functionalities are not solvated as much as in methanol. Therefore the complexes are able to adopt a ‘closed type’ structure where the cation is shielded from the solvent. No simulations have been made in methanol, but the properties were considered to be very close to those of water, whose results are thought reasonable to apply to methanol. These results suggest conformational changes as a result of the different solvation properties of the solvent which are thought to be responsible for changes in stability constant data.

ii) What explains the variation of $\Delta H$ and $\Delta S$ for a given ligand?

As the size of the cation increases (decrease in charge density), a reduction in their interaction with the donor sites of the ligand results in a decrease in the enthalpy of complexation.

It would be expected that as the size of cation increases, the conformation of the complex adopts different orientations, with the structure becoming more open, allowing greater solvent interactions at both rims. Hence a loss of entropy is expected as size increases. Experimentally, this is not seen. NMR studies have shown the possibility of the inclusion of one molecule of solvent (methanol or acetonitrile) in all complex structures, in order that (with the exception of the lithium complex) the entropic contributions will remain constant in both solvents along the series of alkali
metal ions. One possibility is that the larger complexes can exist in more conformations, accounting for the increase in entropy after Li⁺.

iii) What is the origin of the high stability of Li⁺ complexes in acetonitrile?

Complexation processes involving the lithium ion seem to show exceptional behaviour, whatever the ligand and the solvent. Entropic contributions control stability of complexes which is mainly related to the importance of solvation of this smallest cation.

1.4.2. Calixarene interactions with transition and heavy metal ions

The number of publications in the literature regarding calixarene derivatives with the potential to selectively extract transition and heavy metals has increased dramatically. The interaction of uranyl ions (UO₂^{2+}) with calix[6]arene derivatives, containing p-sulphonato substituents (Fig. 1.26) was studied as long ago as 1987 (first publication). This work, whose commercial application is explained later in this chapter, was initiated by Shinkai^{94-96}, although other groups are now involved^{97,98}.

Table 1.6 shows a selection of publications where calixarene derivatives have been synthesised to selectively target transition metal ions. Most of these references only show the synthesis and characterisation results of free and complexed ligands. Initial studies for many of these derivatives involve extraction experiments and their use as selective membranes. Determination of stability constants has been scarcely reported for this group of metal ions and the calculation of thermodynamic parameters and solvent effects are practically absent from the literature.
<table>
<thead>
<tr>
<th>Metal Cation</th>
<th>Parent calix[n]arene - chemical formula of cation interacting functionality</th>
<th>Research</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am³⁺</td>
<td>calix[4] - (CH₂)₃P(=O)Ph₂</td>
<td>Extraction</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>calix[4] - NH[C(=O)]CH₂P(=O)Ph₂</td>
<td>Extraction</td>
<td>75</td>
</tr>
<tr>
<td>As³⁺</td>
<td>calix[4] - P(NMe₂)₃</td>
<td>Preparation of complexes</td>
<td>98</td>
</tr>
<tr>
<td>Cd²⁺</td>
<td>calix[4] - CH₂C(=O)NH(OH)</td>
<td>Extraction</td>
<td>99</td>
</tr>
<tr>
<td>Ce³⁺</td>
<td>calix[4] - SO₃Na</td>
<td>Stability constants determ. by UV</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>calix[4] - CH₂C(=O)NEt₂</td>
<td>Characterisation of complex</td>
<td>101</td>
</tr>
<tr>
<td>Co²⁺</td>
<td>calix[4] - CH₂C(=O)NH(OH)</td>
<td>Extraction</td>
<td>99</td>
</tr>
<tr>
<td>Cu²⁺</td>
<td>calix[4] - CH₂C(=O)NEt₂</td>
<td>Characterisation of complex</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>calix[4] - CH₂C(=O)NH(OH)</td>
<td>Extraction</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>calix[4] - CH₂COOCH₂CH₃</td>
<td>Extraction</td>
<td>104</td>
</tr>
<tr>
<td>Eu³⁺</td>
<td>calix[8]</td>
<td>Characterisation of complex</td>
<td>105</td>
</tr>
<tr>
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<td>calix[4] - (CH₂)₃P(=O)Ph₂</td>
<td>Extraction</td>
<td>73</td>
</tr>
<tr>
<td>Au⁺</td>
<td>calix[4] - (CH₂)₂SH</td>
<td>Characterisation of complex</td>
<td>106</td>
</tr>
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<td>Au⁺</td>
<td>calix[4] - CH₂CH₂SH</td>
<td>Extraction</td>
<td>106</td>
</tr>
<tr>
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<td>calix[4] - CH₂CH₂SC=S(NMe₂)</td>
<td>Characterisation of complex</td>
<td>107</td>
</tr>
<tr>
<td>Fe³⁺</td>
<td>calix[4] - CH₂C(=O)NH(OH)</td>
<td>Extraction</td>
<td>69, 108</td>
</tr>
<tr>
<td></td>
<td>calix[4] - CH₂C(=O)NEt₂</td>
<td>Characterisation of complex</td>
<td>102</td>
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<td>calix[4] - CH₂C(=O)NEt₂</td>
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<td>Extraction</td>
<td>6, 106</td>
</tr>
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<td>110</td>
</tr>
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<td>6, 111</td>
</tr>
<tr>
<td></td>
<td>calix[4] - N=N(C₆H₆)</td>
<td>UV study of stability constants</td>
<td>112</td>
</tr>
<tr>
<td>Ni²⁺</td>
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<td>Characterisation of complex</td>
<td>102</td>
</tr>
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<td>calix[4] - CH₂C(=O)NH(OH)</td>
<td>Extraction</td>
<td>113</td>
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<td>Pu⁺⁺</td>
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<td>73</td>
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<td>Pr²⁺</td>
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<td>101</td>
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<td>Ag⁺</td>
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<td>Extraction</td>
<td>67, 108</td>
</tr>
<tr>
<td></td>
<td>calix[4] - CH₂CH₂SCH₃</td>
<td>Ion selective electrode</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>calix[4] - CH₂C(=S)N(C₆H₅)₂</td>
<td>Ion selective electrode</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>calix[5] - CH₂C(=O)OC₆H₅</td>
<td>Extraction/stability constant study</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>calix[4] - N=N(C₆H₆)</td>
<td>UV study of stability constants</td>
<td>112</td>
</tr>
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<td>Characterisation of complex</td>
<td>102</td>
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</table>

Table 1.6 Calixarene derivatives synthetically tailored to interact with specific metal ions
Environmental issues have clearly focused research into developing calixarene derivatives able to interact with Hg$^{2+}$, Pb$^{2+}$ and Cd$^{2+}$ metal ions. Incorporation of functional groups containing soft sulphur donor atoms has led to several publications where mercury ions have been selectively targeted. Mercury cations have the ability to be linearly coordinated, therefore at least two sulphur donor sites are necessary. Delaigue$^{11}$ has synthesised a 1, 3-alternate disulfanyl calixarene derivative (Fig. 1.21), for which an X-ray crystal structure clearly shows that metal ion is coordinated in linear fashion. The author suggests that the ligand offers mercury(II) the possibility of having its secondary coordination requirements satisfied via the two phenyl rings, by polyhapto($\pi$)-interactions.

![Fig. 1.21 A diagramatic representation of X-ray crystallography results of $p$-tert-butyl-1, 3-dihydroxy-2, 4-disulfanylcalix[4]arene, in 1, 3-alternate conformation, linearly co-ordinating a mercury(II) cation](image)

Extraction studies carried out by Yordanov $et\ al^{106}$ using various thiocarbamoyl and mercapto calixarene derivatives (Fig. 1.22) show that they are effective extractants for Hg$^{2+}$, Hg$^{+}$, Ag$^+$ and Au$^{3+}$, while being virtually ineffective for other heavy metals such as Pb$^{2+}$, Cd$^{2+}$, Ni$^{2+}$ and Pt$^{2+}$. Their conclusions for this high degree of selectivity are unclear, although their results compared favourably with previously prepared macrocycles with similar functional groups$^{115}$. 

45
Fig. 1.22 (a) 5, 11, 17, 23-tetra-tert-butyl-25, 26, 27, 28-tetra-(2-N, N-dimethylthiocarbamoylethoxy)calix[4]arene and (b) 5, 11, 17, 23-tetra-tert-butyl-25, 26, 27, 28-tetra-(2-mercaptoethoxy)calix[4]arene

Lead<sup>69</sup>, cadmium<sup>109</sup> and silver<sup>66,68</sup> selective electrodes and chemically modified field effect transistors (C.H.E.M.F.I.T.s)<sup>5</sup> are now being designed using calixarene sensors incorporated into plastic membranes. Like the mercury selective calixarene ligands discussed above, they contain sulphur donor atoms in the form of thioamides, thiocarbamoyl and mercapto functional groups.

1.4.3. Interactions with neutral molecules

The capacity of calixarenes to act as structural platforms for the inclusion of neutral guests was foreseen by Gutsche<sup>116</sup>. Acetone<sup>117</sup>, acetonitrile<sup>118</sup>, anisole<sup>119</sup>, toluene<sup>120</sup> and water<sup>121</sup> are just some of the calixarene clathrates which have been reported in the literature (clathrates are calixarene-neutral guest aggregates in which the guests are retained by steric barriers formed by the host lattices).

Gutsche <i>et al</i><sup>122</sup> reported association constants for toluene by comparing the difference in chemical shift, in the <sup>1</sup>H NMR spectrum, between the calixarene in the complexed form (i.e., in pure toluene) and the uncomplexed form (i.e., in pure chloroform). The potential of amines (tert-butylamine) was also tested as a guest molecule. These
studies revealed interactions between tert-butylamine and calixarenes, and the behaviour of the hydroxyl and amine groups resonances suggested that proton transfer was occurring. These conclusions were reinforced by the observations that when the amine was protonated with picric acid, the degree of downfield shift of the tert-butyl protons was almost the same as for the calixarene-amine solution. Likewise, a mixture of calixarene in an excess of NaOH shows the same $^1$H NMR spectrum as the calixarene in the calixarene-amine solution. Association constants$^{123}$ were then determined for the formation of the endo amine-calixarene complexes, which had formed from two charged species resulting from the initial proton transfer (eqn. 1.5).

$$ArO^- + R_N^+ \rightarrow ArO^- + R_N^+ \leftrightarrow HNR_3$$

Equation (1.5) describes the formation of endo amine-calixarene complex (where $K_1$ and $K_2$ are the proton transfer step and ‘association’ step respectively).

Further UV spectrophotometric studies calculating association constants for amine interactions with calixarenes have been carried out by Böhmer and Vicens$^{21}$ and by Görmar et al.$^{24}$

Danil de Namor et al.$^{125,126}$ has extensively studied the electrochemical and thermodynamic interactions of amines with parent $p$-tert-butylcalix[n]arenes in nitrobenzene and benzonitrile at 298.15 K. These solvents were chosen as they gave good phase separation with water, therefore allowing direct partitioning. Potentiometric and conductance measurements (which were seen as the most suitable method to quantify a reaction consisting of two neutral species (non-conducting) to give an electrolyte after a proton transfer reaction) were used to quantify the interactions in conjunction with solution and titration calorimetry experiments.

Recent publications describing amine interactions with calixarene derivatives of rather complex structures$^{127-129}$, have reported association constants using UV spectroscopy.
Water soluble calixarenes are now being developed to interact with neutral organic molecules\textsuperscript{130-132}, with much research targeted at the removal of aromatic hydrocarbons. Association constants through a variety of techniques have been determined.

UV spectroscopy has been used to study the association constants of C\textsubscript{60} fullerenes\textsuperscript{133} and pyrene\textsuperscript{134} with calixarene based hosts. Sugars, like glucose and fructose, are now being complexed at neutral pH. Association constants have been calculated using fluorescence spectroscopy\textsuperscript{135}.

1.4.4. The selective complexation of anions

Research into the selective complexation of anions by calixarene derivatives is a relatively new area of host-guest chemistry. Therefore, the thermodynamics of these processes have not generally received a great deal of attention. Recent research has divided the subject into two classes of anionic complexing agents based on calixarene derivatives. The first class consists of positively charged ligands, where anion complexation only occurs when a metal complex has formed.

Beer \textit{et al}\textsuperscript{136} has synthesised the ligand shown in Fig. 1.23 which is only able to complex with anions after being precomplexed with a cation. It is believed that the complexation rigidifies the hydrogen-bonding arrangement of the amides and hydroxy groups, creating a pseudo-tetrahedral cavity shaped perfectly for anionic species. \textsuperscript{1}H NMR titration experiments and subsequent plots of signal shifts have shown 1:1 stoichiometry for the complexed anions. Stability constants were also determined by \textsuperscript{1}H NMR titration experiments in deuterated acetonitrile at 298.15 K (Table 1.7). Highest selectivities were reported for \textit{H}\textsubscript{2}PO\textsuperscript{4-} and HSO\textsubscript{4-} anions which are believed to be extremely shape selective.
<table>
<thead>
<tr>
<th>Complexa</th>
<th>Anion</th>
<th>log $K_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[KL]PF$_6$</td>
<td>Cl$^-$</td>
<td>3.54</td>
</tr>
<tr>
<td>[KL]PF$_5$</td>
<td>NO$_3^-$</td>
<td>3.11</td>
</tr>
<tr>
<td>[NH$_4$L]PF$_6$</td>
<td>NO$_3^-$</td>
<td>3.25</td>
</tr>
<tr>
<td>[KL]PF$_6$</td>
<td>HSO$_4^-$</td>
<td>3.75</td>
</tr>
<tr>
<td>[NH$_4$L]PF$_6$</td>
<td>HSO$_4^-$</td>
<td>3.81</td>
</tr>
<tr>
<td>[KL]PF$_6$</td>
<td>H$_2$PO$_4^-$</td>
<td>$&gt;4$</td>
</tr>
<tr>
<td>[NH$_4$L]PF$_6$</td>
<td>H$_2$PO$_4^-$</td>
<td>$&gt;4$</td>
</tr>
</tbody>
</table>

a L notation represents the ligand displayed in Fig. 1.23

Table 1.7 Stability constants for anion and ligand shown in Fig. 1.23 determined by $^1$H NMR spectroscopy in CD$_3$CN at 298 K

![Figure 1.23](image-url)

Fig. 1.23 New lower rim di-substituted calixarene derivative showing an anion complexed by hydrogen bonding from the amide and hydroxy groups, while a cation is bound by two crown appendages.

Wróblewski *et al* has developed anion selective membranes based on Hg$^{2+}$ calixarene derivative complexes. Potentiometric titration experiments have shown membranes which are selective for iodide over a wide variety of anions.
Neutral calixarene derivatives form the second class of anion selective ligands. Recently urea-derivatised ligands\textsuperscript{137-138} (Fig. 1.24) have shown anion complexation through hydrogen bond formation. However where the derivative contains aromatic substituents, CH\textsubscript{3} / \pi and \pi / \pi interactions are believed to operate in stabilising the complexes. The \textsuperscript{1}H NMR technique was used to determine stability constants and complex compositions. Stability constants were found to be relatively low when compared to values calculated for the first class of these ligands.

![Fig. 1.24](image)

Fig. 1.24 5, 17-bis[(N'-phenylureido)methyl]-25, 26, 27, 28-tetrakis(1-propyloxy)calix[4]arene

1.4.5. Proton interactions with parent and derivatised calixarenes

The properties of parent calixarenes are largely influenced by the circular array of intramolecular hydrogen bonds present at the lower rim of the macrocycle. Böhmer\textsuperscript{139} calculated the first dissociation constant of calix[4]arene derivatives with four hydroxy groups at the lower rim. UV absorption measurements, at different pH's, were compared between the cyclic compounds and their linear analogues. The pK\textsubscript{a} values calculated represent the difference in Gibbs energy between the undissociated molecule and the mono-anion. Large differences in the pK\textsubscript{a} values were explained by slight changes in the preferred conformation caused by the different upper rim substituents, of the macrocycle which in turn, change the cyclic array of intramolecular hydrogen bonds at the lower rim of the calixarene derivative.
Araki et al.\(^{140}\) estimated apparent pK\(_a\)'s of parent calixarenes and partially methylated structures in THF at 298.15 K, using IR and \(^1\)H NMR techniques. The frequency and chemical shift (\(\delta_{	ext{CH}}\)) of the hydroxy groups were measured to quantify the strength of hydrogen bonding and to calculate the pK\(_a\) values. The stronger the hydrogen bonding the higher the pK\(_a\) values. The sequence found for the pK\(_a\) values was, calix[4] > calix[8] > calix[6]. These findings reflect the degree of hydrogen bonding. These results were used to understand conformation isomerism and ring inversion rates.

Using potentiometry Danil de Namor et al.\(^{126}\) determined the pK\(_a\) values for p-tert-butylcalix[n]arene (n = 4, 8) in benzonitrile at 298.15 K. Benzonitrile has a lower permittivity than acetonitrile, therefore electrolytes will have a greater tendency to undergo ion-pair formation allowing amine-calixarene interactions to be studied. In addition, parent calixarenes are more soluble in benzonitrile than in acetonitrile\(^{50}\).

<table>
<thead>
<tr>
<th>Calix[n]arene</th>
<th>pK(_{d1})</th>
<th>pK(_{d2})</th>
<th>pK(_{d3})</th>
<th>pK(_{d4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>[4]</td>
<td>19.33</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[8]</td>
<td>17.42</td>
<td>20.01</td>
<td>27.0</td>
<td>30.4</td>
</tr>
</tbody>
</table>

Table 1.8 Dissociation constants of p-tert-butylcalix[n]arene (n = 4, 8) in benzonitrile at 298.15 K

The corresponding titration curves for the calculated pK\(_a\) values shown in Table 1.8 clearly show that calix[4]arene has one inflection point, while two and four inflection points were found for p-tert-butylcalix[4]arene and p-tert-butylcalix[6]arene respectively.

One of the main characteristics of calixarenes is their poor solubility in many solvents, especially water. In order to develop calixarene derivatives capable of acting as catalysts and selective ionophores in aqueous solutions, Shinkai has initiated research into p-sulfonato\(^{141}\), p-nitro\(^{142}\) and lower rim substituted derivatives with carboxylates\(^{143}\).
groups. Dissociation constants were determined by NMR, potentiometric and spectrophotometric techniques. Recently, similar work has been reported by Arena, Scharff, Atwood, Arnaud-Neu and Steed.

Acid-base properties of lower rim calix[4]arene amine derivatives synthesised at the University of Surrey have been characterised by Danil de Namor. Equilibrium constants were determined using potentiometric techniques. The pKₐ values of a series of tetraamine calix[4]arene derivatives reveal the percentage of individual species as a function of pH, information of fundamental importance for investigating the use of these ligands as cation and anion binders.

1.4.6. Solution thermodynamics of calixarene derivatives

Often, host-guest interactions in terms of complexation processes are studied. However the role of the solvent is often overlooked. The Thermochemistry Laboratory at the University of Surrey has made important contributions to the solution thermodynamics of many host-guest systems. Solution and transfer enthalpy data for host (H), guest (G) and the resulting complex (G-H) in different solvent systems (s) can be described using a thermodynamic cycle which was introduced by Abraham and Danil de Namor in 1977.

\[
\begin{align*}
G(s_1) + H(s_1) & \xrightarrow{\Delta_c H^\circ(s_1)} G-H(s_1) \quad (1) \\
\Delta_c H^\circ(3) & \Delta_c H^\circ(4) \Delta_c H^\circ(5) \\
G(s_2) + H(s_2) & \xrightarrow{\Delta_c H^\circ(s_2)} G-H(s_2) \quad (2)
\end{align*}
\]

In eqn. 1.6, \(\Delta_c H^\circ\) (1 and 2) denotes the enthalpy of complexation of the guest (G) and the host (H) in the appropriate solvents (s₁ and s₂) and \(\Delta_c H^\circ\) denotes the enthalpy of
transfer of the guest (3), the host (4) and the resulting complex (G-H) (5) from a reference solvent $s_1$ to another $s_2$.

Standard enthalpies of transfer, $\Delta H^\circ$, of a solute from a reference solvent ($s_1$) to another solvent ($s_2$) can be obtained from standard enthalpies of solution, $\Delta s H^\circ$, of this solute in the two solvents. Thus process (3) is calculated in the following way:

$$\Delta H^\circ(G)(s_1 \rightarrow s_2) = \Delta s H^\circ(G)(s_2) - \Delta s H^\circ(G)(s_1) \quad (1.7)$$

The same applies to processes (4) and (5).

Initially solution thermodynamics for host-guest interactions involving cryptands, crowns and cyclodextrins were investigated. More recent research has centred on calixarene derivatives. An example of this work is an interpretation of the solution thermodynamics of ester calix[4]arene derivatives' interactions with lithium and sodium cations in acetonitrile, benzonitrile and methanol, including solubilities and derived Gibbs energies.

Standard enthalpies of solution are the result of two processes, the breakage of the crystal lattice (endothermic) and the solvation (exothermic) process. In Table 1.9 where the electrolytes contain the same anion, it is expected that as the size of the cation increases from the free salt to the metal cation complex, the energetic requirement to overcome the crystal lattice will be lower and therefore the dissolution process is expected to be enthalpically more favoured (more negative) for the complex than for the free salt.

Transfer enthalpies from acetonitrile to benzonitrile for the complexed and free ligand are very similar. It was concluded that the difference in the $\Delta H^\circ$ values in benzonitrile relative to acetonitrile reflects the changes in solvation of the lithium cation in these media.
The enthalpy of coordination, $\Delta_{\text{coord}}H^\circ$ (see Table 9), was calculated by referring to the process where reactants and product are in the solid state (eqn. 1.1).

$$MX({\text{solid}}) + L({\text{solid}}) \xrightleftharpoons[\Delta_{\text{coord}}H^\circ]{\text{solid}} MLX({\text{solid}}) \quad (1.8)$$

If solution and complexation data are known, enthalpy of coordination data can be calculated. Coordination results provide a suitable indicator of specific interactions in the solid state, information usually only derived from X-ray crystallographic studies. The availability of coordination data together with solution data allows the calculation regarding binding processes in low dielectric media, as attempts to directly determine the thermodynamics of the complexation process in these solvents are likely to be misleading as extensive ion-pair formation occurs between free and complexed cation with the anion (eqns. 1.2 & 1.3).

$$M^+ (s) + X^- (s) \leftrightarrow MX(s) \quad (1.9)$$

$$ML^+(s) + X^- (s) \leftrightarrow MLX(s) \quad (1.10)$$


<table>
<thead>
<tr>
<th></th>
<th>( \Delta H^o )</th>
<th>( \Delta_{\text{coord}} H^o )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiClO₄</td>
<td>EtCalix(4)</td>
<td>[Li⁺Calix(4)]ClO₄⁻</td>
</tr>
<tr>
<td>MeCN</td>
<td>-43.26</td>
<td>+22.64</td>
</tr>
<tr>
<td>PhCN</td>
<td>-27.32</td>
<td>+14.03</td>
</tr>
</tbody>
</table>

Table 1.9  Enthalpies of coordination (kJ.mol⁻¹) for ethyl \( p \)-tert-butyl calix[4]arene and lithium perchlorate at 298.15K\(^\circ\)

\(^{161}\)
1.5. APPLICATIONS

A good account of the industrial applications of calixarenes prior to 1990 has been written by Perrin and Harris\textsuperscript{33}. In the last six years more than 30 internationally significant patents have been published. These patents centre on the potential of calixarenes to sequester metal ions and neutral species, although their ultimate use is fairly broad. Calixarene based compounds, like many other macrocycles, have been found to have biological activity, while being low in toxicity. A general review of more recent published potential uses of calixarenes follows.

1.5.1. Therapeutic and biologically active calixarene derivatives

Calixarene based compounds have shown anti-bacterial, anti-fungal, anti-cancer, anti-viral and particularly anti-HIV activity\textsuperscript{162}. AZT (3'-Azido-2',3' dideoxythymidine) is probably the most widely used compound to combat the HIV virus by inhibiting an enzyme which is responsible for its replication. Unfortunately, several factors limits its use. Thus, physical properties such as low water solubility for drug absorption, compound stability, toxicity and the virus' ability to become drug resistant, have led to much research work into simpler and cheaper alternatives without the problems mentioned. Fig. 1.25 shows a representative example of calixarene derivatives which have been patented.
Fig. 1.25 Calixarene based compounds which have shown anti-HIV activity

Other derivatives have also been shown to envelop viruses, such as Herpes Simplex viruses (HSV), which are able to elude a host's immune system. The virus is highlighted to the body's immune system upon complexation with the calixarene derivative. Calixarene derivatives demonstrating thrombus inhibition and anti-tuberculosis activity have also been investigated.

1.5.2 Ion sequestration

Recent patents for the recovery of sodium, caesium and the actinides have been published, but the recovery of heavy metals has not yielded many internationally significant publications in recent years.

i) Recovery of caesium from nuclear waste materials

Metal sequestration is probably the most obvious and ultimately important industrial application involving calixarenes. The patent by Izatt et al. regarding caesium recovery from nuclear waste materials is the oldest patent concerning calixarenes. It involves $p$-tert-butylcalix[8]arene dissolved in a mixture of carbon tetrachloride and dichloromethane, forming a liquid membrane. The ligand (in an anionic form) then behaves as a cation carrier between phases, transporting caesium selectively from a basic aqueous phase to a pure water phase. Transport rates are shown in Table 1.10.
Table 1.10 Ion transport rate of metal hydroxides through a liquid membrane using \( p\text{-tert-butylexilx[8]arene} \)

<table>
<thead>
<tr>
<th>Source phase</th>
<th>Transport rate ( \times 10^7 ) (moles / 24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOH</td>
<td>0.9</td>
</tr>
<tr>
<td>NaOH</td>
<td>1.5</td>
</tr>
<tr>
<td>KOH</td>
<td>1.7</td>
</tr>
<tr>
<td>RbOH</td>
<td>22</td>
</tr>
<tr>
<td>CsOH</td>
<td>130</td>
</tr>
<tr>
<td>Ca(OH)(_2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Sr(OH)(_2)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

\( ii) \) Recovery of uranium from sea water

Shinkai's group\(^9\) is still researching the selective extraction of the uranyl ion \( \left( \text{UO}_2^{2+} \right) \) from sea water and nuclear waste. These calixarene based uranophiles have high stability constants \( \left( \log K_s = 18.4-19.2 \right) \) and selectivity factors \( \left( \log K_{s_{\text{UO}_2^{2+}}} / \log K_{s_M^{2+}} = 10^{12-17} \right) \) \( \left( M^{2+} = \text{Ni}^{2+}, \text{Cu}^{2+}, \text{Zn}^{2+} \right) \).

Shinkai's functionalised calixarenes (Fig. 1.26) contain a polymerisable moiety forming hydrophillic gels. The sulfonate groups of calix[6]arene-\( p\)-hexasulfonate are converted to chlorosulfonyl groups which, when reacted with poly(ethyl-encimine), result in hexamer derivatives being immobilised in a polymeric framework.

However, doubts remain as to whether the resin could be recycled cost effectively since the metal cation is strongly bound.
iii) Ion selective membranes

Functionalised calixarenes are increasingly used for the development of ion-selective membrane electrodes.

Sodium\textsuperscript{169}, potassium\textsuperscript{170} and caesium\textsuperscript{171} require hard oxygen donor atoms - esters and ethers are generally used, whereas softer donor substituents such as thioether\textsuperscript{68} and thioamides\textsuperscript{69} have led to silver and lead selective membranes respectively.

Wroblewski\textsuperscript{110} \textit{et al} have published a mercury complex based polymeric membrane which shows anionic selectivity.
1.5.3. Separation and purification of neutral molecules

i) Selective purification of fullerite

Two recent patents\textsuperscript{172,173} concern the use of calixarenes on a large scale to efficiently purify fullerenes. Currently, fullerenes are formed from soot obtained by the laser vaporisation or arc discharging of carbon material such as graphite. The soot or fullerite contains mainly C\textsubscript{60} and some bigger fullerenes such as C\textsubscript{70}. Methods of separation such as chromatography are expensive and cannot practically be scaled up.

In these patents, parent and derivatised calix[n]arenes (where n = 6, 8) are used to form fullerene complexes. Recrystallisation of these complexes yields the pure fullerene. \textit{p-tert-Butylcalix[8]}arenes seem suitable for C\textsubscript{60} molecules - a purity greater than 99.5\% was achieved - while the hexamers select C\textsubscript{70} fullerenes with a purity greater than 87.5\%.

ii) Removal of aromatics and/or alkenes from gaseous hydrocarbon mixtures

Calixarenes (Fig. 1.27) have shown properties for the separation of aromatic and/or alkenes from gaseous hydrocarbon mixtures\textsuperscript{174} (in particular the removal of benzene, which can be modified by altering the temperature and the pressure of the gaseous hydrocarbon feeds) to the extent that up to six benzene units per molecule of calixarene can be selectively removed.
**Fig. 1.27 Derivatised calixarenes used to separate aromatics and/or alkenes**

iii) Improving the solubility of s-triazine in diesel fuels

S-triazine and similar compounds are responsible for producing isocyanic acid (HNCO) which reduces the NOx pollutants in diesel fuels. By encapsulating s-triazine within a non-rigid calixarene matrix, its solubility within diesel fuels is increased. As a result, the exhaust emissions responsible for acid rain, photochemical smog, acute respiratory disease and high incidence of chronic bronchitis are economically reduced.

**1.5.4. Calixarenes used as sensors**

i) Detection of toxic chemicals

Beer et al. has published a patent whereby calixarene derivatives are used to detect the presence of neutral molecules. The upper rim contains one or more redox active substituents, while the lower rim is functionalised with a polymerisable moiety capable of forming a conductive polymer. In this way a membrane type electrode can be constructed to measure the amount of particular chemical agents in solutions (Fig. 1.28) by detecting changes in electrical behaviour, during and after exposure (starting from a reference condition).
Interest in this work centres around the ability to detect highly toxic compounds such as those found in chemical warfare agents.

ii) Optical amine sensor

Another more complicated chromogenic calixarene derivative is a lithium complex which is used to detect amines, particularly trimethylamine (TMA). As a result, a potential to detect fish spoilage has been patented\(^\text{177}\) (fish degrade after death and TMA is produced as a by-product of bacterial reactions). The change in the colour of the optical sensors when in contact with these amines, serves as an indication of the fish freshness.

iii) Calcium sensor in physiological fluids

Optical sensors based on calixarene derivatives immobilised in hydrophilic polymeric membranes, capable of interacting with calcium, have been developed. These derivatives are used as calcium sensors for physiological fluids\(^\text{178}\). The membranes are analysed by UV spectroscopy after contact with a fluid.
1.5.5. Miscellaneous applications

i) Heat resistant and tough films

Fig. 1.29 Film forming novel calixarene derivative

Novel calixarene derivatives (Fig. 1.29) which have high solubilities in organic solvents are formed into films by conventional spin coating methods. These solidified films are hard and very resistant to heat though still soluble in organic solvents. The films can be selectively irradiated with high-energy X-ray, thereby polymerising and rendering selective regions insoluble. The rest of the film can be removed by organic solvents. Their practical application in industry is to provide tough, heat resistant films.

ii) Overbased calixarene metal salts

Compounds generally employed to neutralise acidic materials and disperse sludge within lubricating oil are overbased alkaline-earth metal sulphurised hydrocarbyl-substituted phenates, salicylates and sulphonates. The term ‘overbased’ describes the ratio of alkaline-earth metal moieties to the number of equivalent acid moieties - this must be greater than 1.2.

Due to environmental pressures, sulphur containing lubricant additives, which release sulphur dioxide emissions, are being phased out by sulphur free overbased alkaline-earth metal salts.
Therefore, overbased calixarene metal salts are now being developed for industrial application\textsuperscript{180}. Sulphur-free calixarene derivatives which have hydroxy group(s) substituent available are reacted with a metal base or a linear phenol / formaldehyde resin. The derivative comprises two metallic components, the first of which is at least one alkaline-earth metal and the second, at least one of either (i) an alkali metal or (ii) a metal from groups IIIa, IVa, Va, VIA, VIIa and VIII of either the first or the second transition series.

iii) Charge control agents and toners for developing electrostatic images

Most toners currently available have complex structures and low stability. They are liable to decompose or deteriorate and lose their charge control performance due to mechanical friction and impact, changes in humidity, electric shocks, light irradiation \textit{etc}. Furthermore they are densely coloured, thus lacking versatility for use in colour toners. Some contain heavy metals and have insufficient dispersibility properties.

The new calixarene derivatives overcome many of the problems above and are non-toxic\textsuperscript{181}. They form no more than 5 % of the resin’s weight.

iv) Non linear optical waveguiding materials

Calixarene derivatives are being used as optical non-linear dopants in transparent polymers which have optical non-linear active waveguiding properties\textsuperscript{182}. The purpose of these materials is to act as optical switches and frequency doublers, utilising phenomena such as frequency doubling and pockets effect.

The calixarenes are substituted at the upper rim with an acceptor group and on the lower rim with donor groups. These compounds have excellent hyperpolarisability and when under the influence of an external electric field non-linear polarisation occurs.
1.6. AIMS OF WORK

Derivatisation through the lower rim has been a widely used avenue to develop new calixarenes capable of selective binding with specific neutral and ionic species. As indicated in the introduction, the synthesis of mixed soft donor calixarenes is becoming important in order to target soft metal cations of environmental interest.

The aims of this thesis are:

i) The synthesis of new derivatives containing soft donor atoms by the introduction of methylethylthio substituents followed by further substitutions of various amines, amides and thiophene moieties.

ii) The full characterisation of the novel ligands, including $^1$H, $^{13}$C, DEPT-135, $^1$H/$^{13}$C correlations and homonuclear decoupling NMR experiments and whenever possible the isolation of suitable crystals for X-ray diffraction studies.

iii) The investigation of acid-base dissociation equilibria of the new derivative containing groups.

iv) The investigation of the solution properties of these ligands in a variety of solvents. This data will be used to calculate the standard Gibbs energies of solution. The difference in solvent of a ligand between two solvents will be assessed from the calculation of the transfer Gibbs energies from a reference solvent to another.

v) The study of the interactions of these ligands with metal cations including mercury(II), silver(I), cadmium(II) and lead(II) by conductimetry (complex stoichiometry) and $^1$H NMR (stoichiometry and site of interaction) titrations.

vi) The determination of stability constants of a representative ligand with metal cations in a given solvent.
Chapter Two Experimental Procedures

2. EXPERIMENTAL PROCEDURES

2.1. LIST OF CHEMICALS, SOLVENTS AND THEIR ABBREVIATIONS

This section deals with chemicals, solvents and their abbreviations used throughout this thesis. Duplication of chemicals used in different sections are not listed unless a different grade or manufacturer was used.


- Thiophene (Thio), 99+ %, Aldrich Chemical Company.
- Concentrated hydrogen chloride (HCl), Fisher UK Scientific International.
- Concentrated sulphuric acid (H₂SO₄), Fisher UK Scientific International.
- Sodium chloride (NaCl), Fisher UK Scientific International.
- Formaldehyde (HCHO), 37 %, Fisher UK Scientific International.
- Diethyl ether, SLR grade, Fisher UK Scientific International.
- Sodium hydrogen carbonate (NaHCO₃), 99 %, BDH.
- Calcium chloride (CaCl₂), 99 %, BDH.

2.3.1-10. Synthesis of lower rim calix[4]arene derivatives (L-2-10)

- Acetonitrile (MeCN), HPLC grade, Fisher UK Scientific International.
- Dichloromethane (DCM), SLC grade, Fisher UK Scientific International.
- Dimethylformamide (DMF), AR grade, Fisher UK Scientific International (dried with 4A molecular sieves).
Chapter Two Experimental Procedures

- Diethylether, SLC grade, Fisher UK Scientific International.
- Ethanol, 96 %, Hayman.
- Ethylacetate (EA), SLC grade, Fisher UK Scientific International.
- Tetrahydrofuran (THF), 99+ %, Aldrich Chemical Company.
- Sodium hydride (NaH), dry 95 %, Aldrich Chemical Company.
- 18-crown-6, 99 %, Aldrich Chemical Company.
- 2-Chloroethylmethyl sulphide, 97 %, Aldrich Chemical Company.
- 2-Dimethylaminoethylchloride hydrochloride, 99 %, Aldrich Chemical Company.
- 2-Diethylaminoethylchloride hydrochloride, 99 %, Aldrich Chemical Company.
- 2-Diisopropylaminoethylchloride hydrochloride, 97 %, Aldrich Chemical Company.
- 4-(2-Chloroethyl)morpholine hydrochloride, 99 %, Aldrich Chemical Company.
- 1-(2-Chloroethyl)piperidine hydrochloride, 98 %, Aldrich Chemical Company.
- 1-(2-Chloroethyl)pyrrolidine hydrochloride, 98 %, Aldrich Chemical Company.
- Bromoacetyl bromide, 98+ %, Aldrich Chemical Company.
- Diisopropylamine, 99+ %, Aldrich Chemical Company.

2.4. Nuclear magnetic resonance measurements

- Deuterated Methanol (CD$_3$OD), Aldrich Chemical Company.
- Deuterated Chloroform (CDCl$_3$), Aldrich Chemical Company.
- Tetramethysilane (TMS), Aldrich Chemical Company.
- Trifluoroacetic acid (TFAA), Aldrich Chemical Company.
2.8. Determination of dissociation constants of thioamine calix[4]arene derivatives (L-3-8) in methanol and ethanol at 298.15 K

2.8.1. Preparation of standardised solutions

- Benzoic acid, 99 %, Aldrich Chemical Company.
- Tetra-n-butylammonium hydroxide (TBAH), Fluka Chemical Company.
- Tetra-n-butylammonium perchlorate (TBAP), 99 % electrochemical grade, Fluka.
- Perchloric acid (HClO₄), 70 %, redistilled 99.99 % grade, Aldrich Chemical Company.

2.9. Conductance measurements

2.9.2. Platinisation of the electrodes used in the conductivity cell

- Platinising solution, Greypoint Laboratories.

2.9.3. Determination of the cell constant at 298.15 K

- Potassium chloride (KCl), Fisher UK Scientific International.

2.10. ¹H NMR Complexation experiments

- Cadmium (II) nitrate tetrahydrate Cd(NO₃)₂.4H₂O, 99.99 %, Aldrich Chemical Company.
- Lead (II) nitrate Pb(NO₃)₂, AnalaR, BDH.
- Mercury (II) nitrate Hg(NO₃)₂.H₂O, 98 %, Aldrich Chemical Company.
- Silver nitrate AgNO₃, 99.8 %, Rose Chemicals.
2.2. **PURIFICATION OF SOLVENTS**

**Acetonitrile.** HPLC grade acetonitrile was refluxed in a nitrogen atmosphere and distilled over calcium hydride. The middle fraction of distilled solvent was used. The water content of the solvent, verified by Karl Fischer titration, was not more than 0.02%.

**Benzonitrile.** Benzonitrile was charged with calcium chloride; the solvent was siphoned into a distillation unit, refluxed and vacuum distilled over phosphorous pentoxide. The middle fraction was redistilled from a flask containing bumping stones, thereby removing any phosphorous pentoxide present after the first distillation. The amount of water in solvent did not exceed 0.01%.

**Dimethylformamide.** HPLC grade dimethylformamide was further dried using 4A molecular sieves (which had been dried in an oven at 300 °C for several hours). The amount of water was less than 0.02%.

**Nitrobenzene.** Nitrobenzene was dried over calcium chloride for 24 hours. The solvent was then carefully decanted into a clean, dry flask, refluxed and vacuum distilled over calcium chloride, with the middle fraction being used. The amount of water was less than 0.2%.

**Tetrahydrofuran.** Tetrahydrofuran was dried for 24 hours by adding potassium hydroxide pellets. To remove peroxides, the solvent was passed through a column of activated alumina. The solvent was carefully decanted into a clean distillation unit, whereupon benzophenone and sodium metal were added, which in dry conditions created a deep blue potassium / benzophenone ketyl complex. The middle fraction of solvent distilled in an inert atmosphere was used. The water content of the solvent, verified by Karl Fischer titration, was not more than 0.02%.
2.3. SYNTHESIS AND CHARACTERISATION OF LOWER RIM CALIX[4]ARENE DERIVATIVES CONTAINING SOFT DONOR ATOMS


The synthesis of this tetra-thiophene calix[4]arene derivative (L-1) is described in two parts. The first involves the preparation of the 2-chloromethylthiophene adduct, while the second part involves the addition of this adduct to p-tert-butylcalix[4]arene.

Part 1  Preparation of 2-chloromethylthiophene

\[
\text{S} + \text{CH}_2\text{O} + \text{HCl} \rightarrow \text{S} + \text{CH}_2\text{Cl} + \text{H}_2\text{O}
\]

Blicke and Burckhalter\(^{184}\) first reported this reaction (eqn. 2.1) in 1942; later entries in the literature are essentially based on their method with improvements in yields\(^{185,186}\).

Thiophene (100 g) and concentrated hydrochloric acid (48 ml) were placed in a flange flask with five necks (500 ml), surrounded by a salted ice or dry-ice bath. The solution was stirred vigorously while hydrogen chloride gas (prepared by allowing concentrated sulphuric acid to drip into a round bottom flask containing solid sodium chloride\(^{187}\))
was passed rapidly over the mixture, until the fitted thermometer temperature read
0 °C. Through a dropping funnel fitted to the flask, formaldehyde (119 ml of 37 %)
was introduced at a rate such that the temperature did not rise above 5 °C
(approximately four hours were required to complete the addition).

The mixture was then extracted with three portions of diethylether. The extracts were
combined, washed initially with water and subsequently with an aqueous saturated
solution of sodium hydrogen carbonate. Finally the organic layer was dried over
calcium chloride.

Dried organic extracts were then distilled under reduced pressure.
Chloromethylthiophene boils at 0.1 torr / 73 °C (note: chloromethylthiophene should
not be stored for any length of time in sealed containers, as it can decompose,
producing HCl gas and may cause an explosion). The clear, viscous, pungent liquid
was stored in a loosely bunged round bottom flask in a cold and dark freezer.

The afforded product (≈ 45 ml, 0.37 mol, 31 % yield) was characterised by elemental
analysis and $^1$H NMR spectroscopy.

Microanalysis found: C, 52.31, H, 3.52 %. Calculated for C$_5$H$_5$ClS: C, 45.29, H,
3.80 %.

$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.29 (m, 1H, ArH), 7.06 (m, 1H, ArH), 6.94 (m, 1H,
ArH), 4.79 (s, 2H, CH$_2$Cl)
Part 2  Substitution of 2-chloromethylthiophene, at the lower rim of \( p\text{-}tert\text{-}butylicalix[4]arene \)

\[ \text{OCH}_2 \]

\( p\text{-}tert\text{-}butylicalix[4]arene \) (2.7 g) was stirred under a nitrogen atmosphere in a DMF / THF (10:70) solvent mixture for 15 minutes. Dry NaH (2 g) was added to the suspension, followed by 2-chloromethylthiophene (5.25 ml). The reaction mixture was then refluxed for a period of 12 hours at 50 °C. The course of the reaction was monitored by T.L.C. using a hexane : ethylacetate (4:1) mixture as the developing solvent. The mixture was cooled and the solvent was removed under reduced pressure using a rotary evaporator. The residue was dissolved in \( \text{CH}_2\text{Cl}_2 \) and extracted with HCl (2 mol.dm\(^{-3}\)), NaHCO\(_3\) (aqueous saturated solution) and distilled water. The organic phase was dried with CaCl\(_2\) and again the solvent was removed under reduced pressure. The remaining oil was recrystallised from hot acetonitrile and dichloromethane. The resulting crystals were dried under vacuum at 100 °C.

The afforded product (2.1 g, 2.03 mmol, 53 %) was characterised by elemental analysis, \(^1\)H and \(^{13}\)C NMR spectroscopy.

T.L.C. - \( R_f \) 0.74 using a hexane : ethylacetate (4:1) solvent mixture;
m.p. 255-257 °C

Microanalysis found: C, 74.34, H, 7.05 %. Calculated for \( \text{C}_{64}\text{H}_{72}\text{O}_4\text{S}_4 \): C, 74.39, H, 7.02 %.

72
Chapter Two Experimental Procedures

\[ ^1H \text{NMR (CDCl}_3\text{): } \delta \text{ (ppm) 7.25 (m, 1H, ThioH1), 6.94 (m, 1H, ThioH2), 6.69 (m, 1H, ThioH3), 6.69 (s, 2H, ArH), 5.10 (s, 2H, OCH}\textsubscript{2}, 4.14 (d, J = 12.8 Hz, 1H, ArCH}_2\text{Ar), 2.89 (d, J = 12.8 Hz, 1H, ArCH}_2\text{Ar), 1.06 (s, 9H, (CH}_3\textsubscript{3})} \]

\[ ^13C \text{NMR (CDCl}_3\text{): } \delta \text{ (ppm) 152.3 (Cl), 144.7 (C4), 140.5 (Cp), 134.1 (Co), 128.1 (CJ), 126.5 (C2), 125.9 (C3), 124.8 (Cm), 69.3 (OCH}_2\text{), 33.8 (C(CH}_3\textsubscript{3}), 31.9 (ArCH}_2\text{Ar), 31.4 (C(CH}_3\textsubscript{3})} \]

The crystal structure for this ligand was determined at the Institute of Material Science in the Autonoma University of Barcelona. These results confirmed the structure indicated by the NMR results (see 2.5., 3.1.4., for experimental method and X-ray crystallographic results respectively).


\[ \text{Ligand L-2 was prepared by adding p-tert-butylcalix[4]arene (8 g), potassium carbonate (6.9 g), and 18-crown-6 (0.6 g) to freshly distilled acetonitrile (dried over CaH}_2\text{). The mixture was stirred for 15 minutes and then, 2-chloroethylmethyl sulphide (5 g) was introduced. The reaction mixture was refluxed at 90 °C for 12 hours. The reaction was monitored by T.L.C. using hexane : ethyl acetate (4:1) as the developing solvent.} \]

On cooling, the solvent was removed under reduced pressure by rotary evaporation. The residue was dissolved in dichloromethane and extracted with HCl (2 mol.dm\(^{-3}\)), NaHCO\(_3\), (saturated solution) and distilled water. The organic phase was dried with
CaCl₂ and again the solvent was removed under pressure. The remaining oil was twice recrystallised from a hot ethanol : dichloromethane solvent mixture. The solid was dried under vacuum at 100 °C.

The afforded product (6.4 g, 8.03 mmol, 65 %) was characterised by elemental analysis, \(^1\)H and \(^13\)C NMR spectroscopy.

T.L.C. - \(R_f.0.75\) using a hexane : ethylacetate (4:1) solvent mixture, m.p. 226.0-227.5 °C

Microanalysis found: C, 75.29, H, 8.89 %. Calculated for C\(_{50}\)H\(_{38}\)O\(_4\)S\(_2\): C, 75.33, H, 8.60 %.

\(^1\)H NMR (CDCl₃): \(\delta\) (ppm) 7.06, 6.75 (s, 4H, ArH), 7.00 (s, 1H, OH), 4.31 (d, \(J = 13.0\) Hz, 2H, ArCH₂Ar), 4.13 (t, \(J = 7.0\) Hz, 2H, OCH₂), 3.32 (d, \(J = 13.0\) Hz, 2H, ArCH₂Ar), 3.06 (t, \(J = 7.0\) Hz, 2H, SCH₂), 2.29 (s, 3H, SCH₃), 1.29, 0.96 (s, 18H, C(CH₃)₃)

\(^13\)C NMR (CDCl₃): \(\delta\) (ppm) 150.5, 149.9 (Ct), 146.9, 141.5 (Cp), 132.3, 127.8 (Co), 125.5, 125.0 (Cm), 75.4 (OCH₂), 33.5 (SCH₂), 33.9, 33.7 (C(CH₃)₃), 31.6 (ArCH₂Ar), 31.7, 31.0 (C(CH₃)₂), 16.4 (SCH₃)

Ligand L-3 was prepared by adding L-2 (0.75 g) and dry NaH (0.23 g) to freshly distilled THF (70 ml dried over potassium / benzophenone ketal) and DMF (20 ml, HPLC grade). The resulting suspension was stirred for ten minutes whereupon 2-dimethylaminoethylchloride hydrochloride (0.81 g, dried under vacuum over CaCl₂) was added slowly. The reaction mixture was then refluxed at 90 °C under a nitrogen atmosphere for 12 hours. The reaction was monitored by T.L.C., using a methanol : dichloromethane (1:9) mixture as the developing solvent. After cooling, the solvent mixture was removed under pressure by rotary evaporation, the residue was dissolved in dichloromethane and extracted with NaHCO₃ (saturated aqueous solution) and distilled water. The organic phase was dried with CaCl₂ and the solvent was removed under reduced pressure. The remaining oil was recrystallised from a hot methanol / dichloromethane mixture. The resulting crystals were dried under vacuum at 100 °C.

The afforded product (0.44 g, 0.47 mmol, 50 %) was characterised by elemental analysis, ¹H and ¹³C NMR spectroscopy.

T.L.C. - Rₖ 0.56 using a methanol : dichloromethane (1:9) solvent mixture; m.p. 207-210 °C

Microanalysis found: C, 74.15, N, 3.05, H, 9.62 %. Calculated for C₈₅H₆₅O₄S₂N₂: C, 74.15, N 2.98, H, 9.23 %.
Chapter Two Experimental Procedures

$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.06, 6.50 (s, 4H, ArH), 4.39 (d, $J = 12.5$ Hz, 2H, ArCH$_2$Ar), 4.17 (t, $J = 8.3$ Hz, 2H, OCH$_2$CH$_2$), 3.85 (t, $J = 6.8$ Hz, 2H, OCH$_2$CH$_2$N), 3.23 (t, $J = 6.4$ Hz, 2H, OCH$_2$CH$_2$S), 3.14 (d, $J = 12.6$ Hz, 2H, ArCH$_2$Ar), 2.82 (t, $J = 6.8$ Hz, 2H, OCH$_2$CH$_2$N), 2.33 (s, 6H, N(CH$_3$)$_2$), 2.22 (s, 3H, SCH$_3$), 1.29, 0.84 (s, 18H, C(CH$_3$)$_3$)

$^{13}$C NMR (CDCl$_3$): $\delta$ (ppm) 152.8, 149.9 (Cr), 144.1, 143.3 (Cp), 134.2, 131.1 (Co), 124.4, 123.6 (Cm), 72.3 (OCH$_2$CH$_2$S), 72.1 (OCH$_2$CH$_2$N), 58.2 (OCH$_2$CH$_2$N), 45.0 (N(CH$_3$)$_2$), 33.0, 32.6 (C(CH$_3$)$_3$), 31.6 (OCH$_2$CH$_2$S), 30.0 (ArCH$_2$Ar), 30.6, 30.1 (C(CH$_3$)$_3$), 16.7 (SCH$_3$)

The crystal structure for this ligand was determined at the Institute of Material Science in the Autònoma University of Barcelona. These results confirmed the structure indicated by the NMR results (see 2.5., 3.1.4., for experimental method and X-ray crystallographic results respectively).


![Diagram of L-4 ligand]

Ligand L-4 was prepared according to the procedure described for L-3 using 2-diethylamineethoxymethylene chloride hydrochloride (5.83 g). The final product was recrystallised from a methanol / dichloromethane solvent mixture. The reaction was monitored by T.L.C., using a methanol : dichloromethane (1:9) mixture as the developing solvent.
The afforded product (3.65 g, 3.7 mmol, 65%) was characterised by elemental analysis, $^1$H and $^{13}$C NMR spectroscopy.

T.L.C. - Rf. 0.56 using a methanol : dichloromethane (1:9) solvent mixture; m.p. 192-198 °C

Microanalysis found: C, 74.79, N, 2.77, H, 9.92%. Calculated for C$_{62}$H$_{94}$O$_4$S$_2$N$_2$: C, 74.80, N 2.81, H, 9.52%.

$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.09, 6.47 (s, 4H, ArH), 4.36 (d, J = 12.5 Hz, 2H, ArCH$_2$Ar), 4.17 (m, 2H, OCH$_2$CH$_2$S), 3.85 (t, J = 7.4 Hz, 2H, OCH$_2$CH$_2$N), 3.20 (m, 2H, OCH$_2$CH$_2$S), 3.14 (d, J = 12.3 Hz, 2H, ArCH$_2$Ar), 3.02 (t, J = 7.4 Hz, 2H, OCH$_2$CH$_2$N), 2.61 (q, J = 7.1 Hz, 4H, N(CH$_2$CH$_3$)$_2$), 2.22 (s, 3H, SCH$_3$), 1.07 (t, J = 7.2 Hz, 3H, N(CH$_2$CH$_3$)$_2$), 1.31, 0.84 (s, 18H, C(CH$_3$)$_3$)

$^{13}$C NMR (CDCl$_3$): $\delta$ (ppm) 153.6, 152.2 (Ct), 145.2, 144.3 (Cp), 135.3, 131.9 (Co), 125.5, 124.5 (Cm), 73.5 (OCH$_2$CH$_2$S), 73.3 (OCH$_2$CH$_2$N), 52.8 (OCH$_2$CH$_2$N), 47.6 (N(CH$_2$CH$_3$)$_2$), 34.1, 33.6 (C(CH$_3$)$_3$), 32.7 (OCH$_2$CH$_2$S), 30.1 (ArCH$_2$Ar), 31.7, 31.1 (C(CH$_3$)$_3$), 15.7 (SCH$_3$), 11.7 (N(CH$_2$CH$_3$)$_2$)


Ligand L-5 was prepared by adding the adduct 2-diisopropylaminoethylchloride hydrochloride (1.51 g) to L-2, using the same method of preparation as L-3. The final
product was recrystallised from a methanol : dichloromethane solvent mixture. The reaction was monitored by T.L.C., using a methanol : dichloromethane (1:9) mixture as the developing solvent.

The afforded product (0.73 g, 0.7 mmol, 55 %) was characterised by elemental analysis, $^1$H and $^{13}$C NMR spectroscopy.

T.L.C. - Rf 0.62 using a methanol : dichloromethane (1:9) solvent mixture; m.p. 234-236 °C

Microanalysis found: C, 75.42, N, 2.69, H, 9.69 %. Calculated for C$_{66}$H$_{102}$O$_4$S$_2$N$_2$: C, 75.38, N, 2.66, H, 9.78 %.

$^1$H NMR (CDCl$_3$): δ (ppm) 7.12, 6.44 (s, 4H, ArH), 4.35 (d, J = 12.5 Hz, 2H, ArCH$_2$Ar), 4.22 (t, J = 8.4 Hz, 2H, OCH$_2$CH$_2$S), 3.67 (t, J = 8.0 Hz, 2H, OCH$_2$CH$_2$N), 3.25 (m, 2H, OCH$_2$CH$_2$S), 3.16 (d, J = 12.6 Hz, 2H, ArCH$_2$Ar), ≈ 3.0 (m, 2H, OCH$_2$CH$_2$N), ≈ 3.0 (m, 4H, N(CH(CH$_3$)$_2$)$_2$), 2.22 (s, 3H, SCH$_3$), 1.33, 0.81 (s, 18H, C(CH$_3$)$_3$), 1.04 (d, J = 6.5 Hz, 12H, (N(CH(CH$_3$)$_2$)$_2$)

$^{13}$C NMR (CDCl$_3$): δ (ppm) 154.0, 152.0 (C=), 145.3, 144.1 (Cp), 135.6, 131.7 (Ca), 125.5, 124.5 (Cm), 76.9 (OCH$_2$CH$_2$N), 73.3 (OCH$_2$CH$_2$S), 49.9 (N(CH(CH$_3$)$_2$)$_2$), 45.1 (OCH$_2$CH$_2$N), 34.1, 33.6 (C(CH$_3$)$_3$), 32.8 (OCH$_2$CH$_2$S), 30.1 (ArCH$_2$Ar), 31.7, 31.1 (C(CH$_3$)$_3$), 20.8 (N(CH(CH$_3$)$_2$)$_2$), 15.7 (SCH$_3$)

Ligand L-6 was prepared by adding the adduct 4-(2-chloroethyl)morpholine hydrochloride (1.05 g) to L-2, using the procedure described for the preparation of L-3. The final product was recrystallised from a methanol: dichloromethane solvent mixture. The reaction was monitored by T.L.C., using a methanol: dichloromethane (1:9) mixture as the developing solvent.

The afforded product (0.64 g, 0.6 mmol, 50 %) was characterised by elemental analysis, $^1$H and $^{13}$C NMR spectroscopy.

T.L.C. - R$_6$ 0.80 using a methanol: dichloromethane (1:9) solvent mixture; m.p. 173-177 °C

Microanalysis found: C, 72.56, N, 2.85, H, 9.21 %. Calculated for C$_{62}$H$_{90}$O$_5$S$_2$N$_2$: C, 72.76, N 2.74, H, 8.86 %.

$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.06, 6.50 (s, 4H, ArH), 4.41 (d, J = 12.5 Hz, 2H, ArCH$_2$Ar), 4.18 (t, J = 8.1 Hz, 2H, OCH$_2$CH$_2$S), 3.90 (t, J = 6.4 Hz, 2H, OCH$_2$CH$_2$N), 3.75 (m, 4H, OCH$_2$(2)), 3.20 (t, J = 8.5 Hz, 2H, OCH$_2$CH$_2$S), 3.13 (d, J = 12.6 Hz, 2H, ArCH$_2$Ar), 2.84 (t, J = 6.4 Hz, 2H, OCH$_2$CH$_2$N), 2.54 (m, 4H, NCH$_2$(1)), 2.20 (s, 3H, SCH$_3$), 1.29, 0.86 (s, 18H, C(CH$_3$)$_3$)

Ligand L-7 was prepared by adding the adduct 1-(2-chloroethyl)piperidine hydrochloride (1.40 g) to L-2, using the procedure described for the preparation of L-3. The final product was recrystallised from a methanol : dichloromethane solvent mixture. The reaction was monitored by T.L.C., using a methanol : dichloromethane (1:9) mixture as the developing solvent.

The afforded product (0.78 g, 0.8 mmol, 61 %) was characterised by elemental analysis, $^1$H and $^{13}$C NMR spectroscopy.

T.L.C. - Rf. 0.72 using a methanol : dichloromethane (1:9) solvent mixture; m.p. 239-241 °C

Microanalysis found: C, 75.50, N, 2.77, H, 9.67 %. Calculated for C$_{44}$H$_{94}$O$_4$S$_2$N$_2$: C, 75.39, N 2.75, H, 9.29 %.
Chapter Two Experimental Procedures

$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.06, 6.49 (s, 4H, ArH), 4.39 (d, $J = 12.5$ Hz, 2H, ArCH$_2$Ar), 4.17 (t, $J = 8.2$ Hz, 2H, OCH$_2$CH$_2$S), 3.89 (t, $J = 7.0$ Hz, 2H, OCH$_2$CH$_2$N), 3.22 (m, 2H, OCH$_2$CH$_2$S), 3.13 (d, $J = 12.6$ Hz, 2H, ArCH$_2$Ar), 2.86 (t, $J = 7.0$ Hz, 2H, OCH$_2$CH$_2$N), 2.47 (m, 4H, NCH$_2$(1)), 2.22 (s, 3H, SCH$_3$), 1.61 (m, 4H, NCH$_2$(2)), 1.44 (m, 2H, NCH$_2$(3)), 1.30, 0.85 (s, 18H, C(CH$_3$)$_3$)

$^{13}$C NMR (CDCl$_3$): $\delta$ (ppm) 153.8, 152.3 (Ci), 145.0, 144.2 (Cp), 135.3, 132.0 (Co), 125.4, 124.5 (Cm), 73.2 (OCH$_2$CH$_2$S), 72.6 (OCH$_2$CH$_2$N), 58.8 (OCH$_2$CH$_2$N), 55.2 (NCH$_2$(1)), 34.0, 33.5 (C(CH$_3$)$_3$), 32.8 (OCH$_2$CH$_2$S), 31.1 (ArCH$_2$Ar), 31.6, 31.1 (C(CH$_3$)$_3$), 26.0 (NCH$_2$(2)), 24.3 (NCH$_2$(3)), 15.8 (SCH$_3$)


Ligand L-8 was prepared by adding the adduct 1-(2-chloroethyl)pyrrolidine (1.28 g) to L-2, using the procedure described for the preparation of L-3. The final product was recrystallised from a methanol : dichloromethane solvent mixture. The reaction was monitored by T.L.C., using a methanol : dichloromethane (1:9) mixture as the developing solvent.

The afforded product (0.66 g, 0.7 mmol, 53 %) was characterised by elemental analysis, $^1$H and $^{13}$C NMR spectroscopy.
T.L.C. - Rf 0.55 using a methanol : dichloromethane (1:9) solvent mixture; m.p. 185-
188 °C

Microanalysis found: C, 75.07, N, 2.86, H, 9.52 %. Calculated for C₆₂H₅₀O₄S₂N₂: C,
75.10, N 2.83, H, 9.15 %.

¹H NMR (CDCl₃): δ (ppm) 7.07, 6.50 (s, 4H, ArH), 4.40 (d, J = 12.5 Hz, 2H,
ArCH₂Ar), 4.16 (m, 2H, OCH₂CH₂S), 3.90 (t, J = 7.0 Hz, 2H, OCH₂CH₂N), 3.21 (m,
2H, OCH₂CH₂S), 3.14 (d, J = 12.6 Hz, 2H, ArCH₂Ar), 3.00 (t, J = 7.2 Hz, 2H,
OCH₂CH₂N), 2.60 (m, 4H, NCH₂(1)), 2.22 (s, 3H, SCH₃), 1.81 (m, 4H, NCH₂(2)),
1.30, 0.85 (s, 18H, C(CH₃)₃)

¹³C NMR (CDCl₃): δ (ppm) 153.9, 152.3 (Ci), 145.1, 144.3 (Cp), 135.3, 132.2 (Co),
125.4, 124.5 (Cm), 74.0 (OCH₂CH₂S), 73.3 (OCH₂CH₂N), 56.0 (OCH₂CH₂N), 54.6
(NCH₂(1)), 34.1, 33.6 (C(CH₃)₃), 32.7 (OCH₂CH₂S), 31.1 (ArCH₂Ar), 31.7, 31.2
(C(CH₃)₃), 23.6 (NCH₂(2)), 15.8 (SCH₃)

2.3.9. Preparation of 5, 11, 17, 23-tetrakis-(1, 1 dimethylethyl)-25, 27-

Ligand L-9 was prepared by adding the adduct 2-chloromethylthiophene (0.5 ml) to L-2, using the procedure described for the preparation of L-3. The product was recrystallised from a methanol : dichloromethane solvent mixture. The reaction was
monitored by T.L.C., using hexane : ethylacetate (4:1) mixture as the developing solvent.

The afforded product (0.30 g, 0.30 mmol, 48 %) was characterised by elemental analysis, $^1$H and $^{13}$C NMR spectroscopy.

T.L.C. - Rf. 0.80 using a hexane : ethylacetate (4:1) solvent mixture;
m.p. 249-259 °C

Microanalysis found: C, 72.86, H, 7.96 %. Calculated for C$_{60}$H$_{76}$O$_4$S$_4$: C, 72.83, H, 7.74 %.

$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.34 (d, 1H, J = 5.0 Hz, SCH), 7.07 (d, J = 3.3 Hz, 1H, SCHCHCH), 7.02 (m, 1H, SCHCH)b 7.10, 6.47 (s, 4H, ArH), 4.86 (s, 2H, OCH$_2$C(O)), 4.35 (d, J = 12.5 Hz, 2H, ArCH$_2$Ar), 4.02 (m, 2H, OCH$_2$CH$_2$S), 3.11 (d, J = 12.6 Hz, 2H, ArCH$_2$Ar), 2.88 (m, 2H, OCH$_2$CH$_2$S), 1.95 (s, 3H, SCH$_3$), 1.32, 0.83 (s, 18H, C(CH$_3$)$_3$)

$^{13}$C NMR (CDCl$_3$): $\delta$ (ppm) 154.0, 151.6 (Cl), 145.2, 144.9 (Cp), 139.7 (SC), 135.4, 132.1 (Co), 127.9 (SCH), 126.9 (SCHCH), 126.4 (SCHCHCH), 125.5, 124.8 (Cm), 73.3 (OCH$_2$CH$_2$S), 71.0 (OCH$_2$), 34.1, 33.6 (C(CH$_3$)$_3$), 32.5 (OCH$_2$CH$_2$S), 31.1 (ArCH$_2$Ar), 31.7, 31.2 (C(CH$_3$)$_3$), 15.4 (SCH$_3$)

Ligand L-10 was prepared by adding the adduct 2-N, N-diisopropylbromoacetamide (0.75 ml) to L-2, using the procedure described for the preparation of L-3. Bromoacetyl bromide was added to diisopropylamine in chloroform at 0 °C, to produce the diisopropylacetamide adduct. Recrystallisation from a methanol / dichloromethane solvent mixture yielded fine needle crystals. The reaction was monitored by T.L.C., using a methanol : dichloromethane (1:9) mixture as the developing solvent.

The afforded product (0.17 g, 0.2 mmol, 17 %) was characterised by elemental analysis, $^1$H and $^{13}$C NMR spectroscopy.

T.L.C. - R$_f$ 0.51 using a methanol : dichloromethane (1:9) solvent mixture; m.p. 274-282 °C

Microanalysis found: C, 73.49, N, 2.45, H, 9.73 %. Calculated for C$_{66}$H$_{98}$O$_6$S$_2$N$_2$: C, 73.43, N 2.59, H, 9.15 %.

$^1$H NMR (CDCl$_3$): 8 (ppm) 7.11, 6.46 (s, 4H, ArH), 4.49 (d, J = 12.5 Hz, 2H, ArCH$_2$Ar), 4.35 (s, 2H, OCH$_2$C(O)), 4.30 (m, 2H, OCH$_2$CH$_2$S), $\sim$ 3.7 (brm, 2H, OCH$_2$CH$_2$O, OCH$_2$CH$_2$N(iPr)$_2$).
N(CH(CH₃)₂)₂, 3.35 (m, 2H, OCH₂CH₂S), 3.15 (d, J = 12.6 Hz, 2H, ArCH₂Ar), 2.31 (s, 3H, SCH₃), 1.42, 1.17 (brm, 12H, N(CH(CH₃)₂)₂), 1.34, 0.82 (s, 18H, C(CH₃)₃)

¹³C NMR (CDCl₃): δ (ppm) 166.4 C=O, 154.3, 152.2 (Cf), 144.9, 144.5 (Cp), 135.6, 131.8 (Co), 125.5, 124.7 (Cm), ≈ 73.8 (OCH₂CH₂S), ≈ 73.8 OCH₂C(O), 34.1, 33.6 (C(CH₃)₃), 32.0 (OCH₂CH₂S), 31.3 (ArCH₂Ar), 31.7, 31.1 (C(CH₃)₃), 29.7 CH(CH₃)₂), 21.0 (br,CH(CH₃)₂) (two carbon signals were resolved when ¹³C NMR was carried out at 273 K, 21.1, 20.6 CH(CH₃)₂), 15.3 (SCH₃)
2.4. NUCLEAR MAGNETIC RESONANCE MEASUREMENTS

2.4.1. $^1$$H$ NMR measurements

$^1$$H$ NMR measurements were carried out at the University of Surrey using a Brucker AC-300E pulsed Fourier transform NMR spectrometer. Typical operating conditions for routine proton measurement involved:

- 'Pulse' or Flip angle: 30°
- Sweep Width: 15 ppm ($^14$ - $^1$ppm)
- Spectral Frequency (SF): 300.135 MHz
- Delay Time: 1.6 seconds
- Acquisition Time (AQ): 1.819 seconds
- Line Broadening: 0.55 Hz

Spectra were collected into 16 K data points and zero-filled to 32 K points.

$^1$$H$ NMR measurements characterising the novel ligands (L-1-10) consisted of samples ($\approx$ 5 mg) prepared using 0.5 ml of deuterated chloroform (CD$_2$Cl). All measurements were conducted at 298 K.

Directly coupled protons were revealed using homonuclear decoupling experiments (one dimensional). Complicated couplings are resolved by Lorentzian / Gaussian resolution enhancement techniques.

2.4.2. $^{13}$C NMR measurements

$^{13}$C measurements were made on the same instrument as the proton experiments. Typical carbon experiments were carried out under the following routine conditions and usually accompanied by a DEPT-135 multi-pulse spectral editing experiment:

- 'Pulse' or Flip angle: 60°
Sweep Width | 250 (°230 - 20) ppm
---|---
Spectral Frequency (SF) | 75.47 MHz
Delay Time | 0.3 seconds
Acquisition Time (AQ) | 0.7 seconds
Line Broadening | 1.4 Hz

Originally, samples of novel ligands (L-1-10) (~30 mg) were dissolved in deuterated chloroform (2 ml) and introduced into a 10 mm broad-band probe. However, more recently a 5 mm proton / carbon dual probe was used, therefore less sample (~15 mg) and deuterated solvent (0.5 ml) were needed to record spectra.

In cases where the frequency of exchange corresponded to the frequency of chemical shift, line broadening in the carbon spectrum was recorded (e.g. L-10). In order to resolve these broad peaks the \(^{13}\text{C}\) measurements were made at a reduced temperature, resulting in a reduction in the frequency of exchange, while the chemical shifts remain the same, thereby resolving the peaks.

Assignment and connections between the carbon and proton spectral peaks were improved by simple (magnitude calculation) proton / carbon correlation, two dimensional experiments.

### 2.5. X-RAY CRYSTALLOGRAPHY

X-ray crystallographic structures were determined at the Institute of Material Science in the Autonoma University of Barcelona. Crystals were prepared by recrystallising the ligands in ethanol-dichloromethane solutions, allowing slow evaporation to take place.

Suitable single crystal were mounted on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo-Kα radiation. The cell parameters were obtained by a least-squares fit of 25 well-centred reflections, intensity data was collected using the α
/ 2θ scan mode in the range 2° < 2θ < 50°. Intensities were corrected for Lorentz and polarization effects. No absorption correction was applied.

The structures were solved by direct methods using the SHELXS-86 program. The refinement was performed by full least-square method using the SHELXL-93 program.

2.6. SOLUBILITY MEASUREMENTS

The solubility of ligands was determined in several solvents at 298.15 K. Saturated solutions of these ligands were prepared by adding an excess amount of the solid to the solvent. The mixtures were left to equilibrate for at least five days in a thermostatically controlled bath. The final solubility results were calculated from three analysis carried out on the same sample of different equilibria experiments. Two different analytical techniques were then used to determine the concentration of the ligand in the saturated solution. These are described as follows.

i) Gravimetric analysis: aliquots of the solution were placed into pre-weighed porcelain crucibles. The solvent was left to evaporate and the solid was weighed until constant weight. Separate blank experiments were carried out in order to assess whether or not any involatile material was found in the pure solvent.

ii) UV spectroscopic analysis: This was conducted on a Pye-Unicam PU8720 UV/Vis scanning spectrophotometer. For this purpose, a standard solution of the ligand in the chosen solvent was used to describe the calibration curve. The intensity of the saturated solution (dilutions were necessary in some cases) was measured at the same wavelength at which the standard curve was constructed, allowing the solubility to be calculated. Where solubilities were too low to prepare standard solutions, a spike consisting of a standard solution of the ligand in another miscible solvent was titrated into the saturated solution.
Solvate formation was tested by placing small quantities of the solid in open vessels over the appropriate solvent placed at the bottom of a closed desiccator. In this way a saturated atmosphere of solvent was ensured. Uptake of the solvent was checked by weighing the samples from time to time.

2.7. UV-SPECTROPHOTOMETRIC MEASUREMENTS:

Measurements were made on a Pye Unicam PU8720 UV/Vis scanning spectrophotometer using a 4 cm quartz cell with fused silica windows, fitted with a ground glass stopper to prevent the loss of solvent. Circulating water from a thermostatically controlled water bath maintained the cell at 298 K.


For these measurements a solution of L-4 in methanol (≈ 1.1 x 10⁻⁴ mol.dm⁻³) was injected into the 4cm cell (using a calibrated automatic pipette). Using methanol as the background solution, an absorption spectrum of the free ligand was measured at the wavelength range between 260 and 300 nm. A standardised perchloric acid solution in methanol (≈ 8.8 x 10⁻³ mol.dm⁻³), was titrated into the cell (≈ 30 μL injections). The mixture was homogenised by vigorous shaking followed by another spectrum. This process was repeated until no absorbance differences could be observed. From a plot
of absorbances against proton : calixarene mole ratios, the stoichiometry of the complex was determined.

2.8. DETERMINATION OF DISSOCIATION CONSTANTS OF THIOAMINE CALIX[4]ARENE DERIVATIVES (L-3-8) IN METHANOL AND ETHANOL AT 298.15 K

2.8.1. Preparation of standard solutions

i) Preparation and standardisation of tetrabutylammonium hydroxide (TBAH)

A stock solution of tetrabutylammonium hydroxide (1 litre, \( \approx 0.02 \text{ mol.dm}^{-3} \)) was prepared in methanol and stored in a dark place (TBAH was dried at 298 K for 24 hours before use). This solution was standardised by accurately weighing and dissolving benzoic acid in methanol into a thermostatically controlled titration cup at 298.15 K. Constant ionic strength (I) was maintained using a solution of tetrabutylammonium perchlorate in methanol (TBAP [0.05 mol.dm\(^{-3}\)] an inert salt that does not interfere with the ligand or ions involved in this reaction). The concentration of TBAP was such that the mean ionic activity coefficients of the species under investigation could be considered to remain constant.

ii) Preparation and standardisation of perchloric acid (HClO\(_4\))

A stock solution of perchloric acid (1 litre) was prepared by diluting a weighed amount (\( \approx 3 \text{ g} \)) in methanol (see section 2.2, purification of solvents). The solution was homogenised by vigorous shaking. The stock solution was then standardised with the previously standardised solution of TBAH. Constant ionic strength (I) was maintained using a solution of TBAP in methanol (0.05 mol.dm\(^{-3}\)).
2.8.2. Apparatus

An Aldrich glass electrode, with a calomel reference electrode (which was responsive over a wide pH range (0-14) and had a low sodium error) was used.

A digital micro-processor pH / mV-meter HANNA model HI 8417 (accurate to ± mV) was used to measure the potential changes during the course of the titration. The volume of titrant added was measured by an automatic Radiometer ABU 12 burette (piston burette), which delivered the solutions to the indicator electrode, at a calibrated rate of 0.0033 ml unit⁻¹ recorded by the burette meter.

2.8.3. Electrode calibration

For the determination of dissociation constants (pK⁻ = -log K_e) of the ligands (L-3-8) in methanol and ethanol at 298.15 K, a glass electrode containing a calomel reference electrode was used. The internal aqueous solution of KCl was replaced by solutions containing KCl in methanol and ethanol (1 mol dm⁻³). The electrode was then allowed to equilibrate for several days. Calibration of the electrode was carried out by titrating a standard stock solution of perchloric acid into the reaction vessel, in a nitrogen atmosphere. Constant ionic strength (I) was maintained using a solution of TBAP in methanol (0.05 mol dm⁻³). The electrode potential was evaluated from the slope of a straight line, when potential was plotted against -log [H⁺].

2.8.4. Measurements of the dissociation constants in methanol and in ethanol at 298.15 K

The reaction vessel was filled with methanol (40 ml) containing the ligand (≈ 20 mg), at constant ionic strength (TBAP, I = 0.05). After an equilibration period (≈ 15 minutes), the ligand was then fully protonated using the standardised stock perchloric acid solution. Once protonated, the ligand was then deprotonated using the standardised base solution, until a sharp reduction or inflection in the millivolt reading was recorded.
2.8.5. Calculation of dissociation constants at 298.15 K

Dissociation constants were derived using a general computer program called Miniquad\textsuperscript{88}. The program can calculate constants for systems containing many reactant species and potentiometric electrodes. To use the program, the system i.e. the number and type of equilibrium involved, must be understood, including the self-ionisation or protonation constant of solvent.

2.9. CONDUCTANCE MEASUREMENTS

Conductance measurements provide a valuable tool for the investigation of ion-ion and ion-solvent interactions in electrolyte solutions. Information regarding ion mobility and the extent of ion-pair formation in solution can be obtained. Conductance measurements can be used for the determination of stability constants of complexes formed between macrocycles and cations in solution\textsuperscript{59}.

In this thesis conductivity measurements are used to determine the complex stoichiometry. Depending on the magnitude of the stability constant, a plot of molar conductance ($\Lambda_m$) against ligand : free metal ion concentration ratio, $C_L / C_{M}^{m+}$, can provide information regarding the stoichiometry of the complex. Vis-a-vis strong complexes, a clear break in the conductance is observed at the point where the ligand : cation ratio equals the complex stoichiometry. For less stable complexes a more continuous variation of conductivity with concentration ratio, is observed and it is not always possible to accurately determine the complex stoichiometry. Some of the principles are now studied.
2.9.1. **Apparatus**

Conductivity measurements were carried out using two meters:

i) The Wayne-Kerr B642 autobalance universal bridge

ii) The Orion research conductivity meter model 101

The former is an autobalance transformer ratio arm bridge which measures resistance or conductance, while the latter measures conductivity, since the cell constant is known.

The Wayne-Kerr meter was connected to a conductivity cell consisting of two platinum black electrodes contained within two glass arms filled with mercury. The electrodes housed in a 50 ml capacity cylindrical glass vessel, with two wholes on its sides, where samples were injected. Nitrogen gas was passed through the cell prior to measurements. During the conductance measurements, the magnitude of the capacitance and the conductance were monitored on the two meters. Each of these meters has four decades which can be operated in succession. Small signal lamps are placed between the decade control knobs to indicate the decimal points. The control knobs are selected automatically by operation of the range switch. The sensitivity of the meter can be switched to one of these normal positions to adjust the apparatus manually. The accuracy of the bridge, determined by its internal sources, was found to be 0.1% for all the decades in use. Calibration of the bridge was effected by the use of different standard resistances.

The Orion conductivity meter is a simpler instrument. The cell constant was entered and a suitable scale for the conductance (siemens) chosen. A compact Orion research specific ion electrode system, consisting of two platinum square plates bound to the inside of a glass support tube, was connected to the meter. Results were displayed on a digital display.
2.9.2 Platinisation of electrodes used in the conductivity cell

The conductivity cell was prepared by placing the electrode system in a platinising solution (≈ 25 ml), equilibrated at 298.15 K in a thermostatic bath for a few hours. An electrical current (≈ 0.001 A) was passed through the electrodes and polarities reversed every ten seconds for a total of ten minutes in order to cover all electrode surfaces with a thin layer of platinum black. Small amounts of hydrogen gas were evolved during this process. The preparation was complete when the electrodes were turned to a dull black colour.

2.9.3 Determination of cell constant at 298.15 K

An aqueous solution of potassium chloride was used to determine the cell constant. Initially, the conductance of freshly de-ionised water at 298.15 K was measured. Subsequent conductance changes after each injection of a KCl solution (≈ 1 ml, 0.1 mol.dm⁻³, KCl recrystallised from water and dried for 3 days at 120°C) were recorded. A computer program derived the cell constant (L/a or θ) by calculating the molar conductance, \( \Lambda_m \) (mol⁻¹.cm².Ω⁻¹), using the equation of Lind, Zwolenik and Fuoss (eqn. 2.2) from the KCl concentration (a solution of known specific conductance, \( \kappa \)):

\[
\Lambda_m = 149.43 - 96.45 \cdot c^{1/2} + 58.74 \cdot c \cdot \log c + 198.4 \cdot c
\]  

(eqn. 2.2)

where \( c \) (mol.dm⁻³) was the molar concentration of the KCl solution. By substituting the molar conductance into the equation below the cell constant (θ, cm⁻¹) was calculated:

\[
\theta = \frac{\Lambda_m \cdot c}{1000 \cdot S}
\]

where \( S \) (Ω⁻¹, siemens) is the reciprocal of the resistance.
The formula used to calculate the cell constant, $\theta$, is derived from the need to express conductivity in terms of concentration. This process is initiated by defining the resistance, $R$:

$$R = \rho \cdot \frac{L}{a} \quad (2.4)$$

where, $\rho$, denotes resistivity and $L/a$, is the cell constant ($\theta$, cm$^{-1}$).

Therefore,

$$R = \rho \cdot \theta \quad (2.5)$$

the reciprocal of the resistivity gives the specific conductance or conductivity, $\kappa$. The reciprocal of the resistance, conductance, is represented by the letter, $S$ (the accepted notation of conductance, siemen).

$$\frac{1}{R} = \frac{1}{\rho} \cdot \frac{1}{\theta} \quad (2.6)$$

Therefore,

$$S = \kappa / \theta \quad \text{and} \quad \kappa = S \cdot \theta \quad (\text{units, } \Omega^{-1} \cdot \text{cm}^1) \quad (2.7)$$

Although it is necessary to express conductance, $S$, in terms of concentrations, $c$, giving the molar conductance, $\Lambda_m$:

$$\Lambda_m = (S \cdot 0 \cdot 1000) / c \quad (2.8)$$

Rearrangement of eqn. 2.8 leads to the expression used to calculate the cell constant (eqn. 2.9):

$$\theta = \frac{\Lambda_m \cdot c}{1000 \cdot S} \quad (2.9)$$

The cell constant was entered into the Orion instrument before the start of the titration experiment. This was accomplished by preparing a standard KCl solution (aq, 0.1
mol.dm$^3$), which was equilibrated in a 25 ml vessel at 298.15 K. The cell constant was then changed until the digital display recorded the standard conductivity value (0.13 $\Omega^{-1}.cm^{1}$) for this standard solution at 298.15 K$^{192}$.

2.9.4. Conductimetric titrations in non-aqueous media at 298.15 K

In order to determine the stoichiometry of the complex, conductimetric titrations were carried out in the appropriate solvent in which the metal-ion containing salt was titrated with a standard solution of the ligand.

In a typical experiment, the reaction vessel accurately weighed was filled with a methanolic solution of the metal-ion salt (Pb$^{2+}$, Cd$^{2+}$, Hg$^{2+}$ and Ag$^{+}$ nitrate solutions, $\approx 6 \times 10^{-3}$ mol.dm$^3$). The vessel was then sealed, placed in a thermostatic bath at 298.15 K for $\approx 20$ minutes while nitrogen was passed through the solution. The titrant (L-4, $\approx 5 \times 10^{-3}$ mol.dm$^3$) was added using a hypodermic syringe. Conductance readings were made after each addition and the amounts added were weighed accurately.

2.10. $^1$H NMR COMPLEXATION EXPERIMENTS

$^1$H NMR techniques were used to investigate the interactions of the novel ligands (L-1-10) with protons and metal cations in CD$_3$OD. Proton chemical shifts of the free and complexed ligands were noted. Single frequency homo nuclear decoupling experiments to establish which of the methylenes at the lower rim were directly coupled to each other were carried out. Expansion and enhancement experiments also revealed the fine structure of the methylene signals.

Qualitative protonation experiments, using trifluoroacetic acid, were performed on the novel ligands whose lower rim moieties contained a nitrogen donor atom (L-3-8), in order to assign the methylene signals.
Chapter Two Experimental Procedures

\[^1\text{H} \text{NMR complexation experiments were performed by injecting a solution of known concentration of the metal-ion salt (} \approx 0.01 \text{ mol.dm}^{-3} \) (Pb\(^{2+}\), Cd\(^{2+}\), Hg\(^{2+}\) and Ag\(^+\) nitrates) into a solution of known concentration of L-4 (} \approx 0.006 \text{ mol.dm}^{-3} \) pre-dissolved in deuterated methanol. Step-wise titrations were undertaken until shift changes ceased; spectrums were viewed using stack plots.


Potentiometry is one of the most accurate techniques to determine metal ion concentrations or more strictly ‘activities’. Very low concentrations can be measured, thereby allowing the study of highly stable complexes. The reversible silver cation selective electrode, with a silver / silver chloride reference electrode described by the cell diagram (Fig. 2.1) and by the Nernst equation (eqn. 2.10), was used in a competitive reaction to determine the stability constant of the various metal cations with the calix[4]arene derivative (L-4) in methanol at 298.15 K.

\[E_{Ag^+/Ag} = E^\circ_{Ag^+/Ag} + \left(\frac{RT}{zF}\right) \ln a_{Ag^+} \]  

(2.10)

\(z\) the number of electrons in the redox process \((z = 1 \text{ for } Ag^+)\)

\(R, \ T, \ \text{and} \ F\) are the gas constant, temperature and Faraday constant \((9.648 \times 10^4 \text{ C.mol}^{-1})\) respectively.
Schneider and Cox\textsuperscript{59} lists four pre-requisites for the stability constant measurements using this technique:–

i) The stability constant of \(ML^{n+}\) should preferably be lower than that of \(AgL^{+}\) and must not be more than one or two orders of magnitude larger. Therefore, the free silver concentration is not measurably different from the stoichiometric silver concentration.

ii) Competitive metal cation should be titrated into the reaction vessel containing the silver and ligand especially when the \(ML^{n+}\) forms a stable complex, otherwise long equilibrium times will be required because of the slow dissociation rate of \(ML^{n+}\) complexes.

iii) Titrations should be performed in the presence of an inert salt to maintain a constant ionic strength.

iv) For processes in which extensive ion-pair formation takes place in solution corrections should be applied.

2.11.1. Apparatus

The indicator and reference electrodes were kept at a constant temperature by two thermostated glass vessels, maintained at 25.00 ± 0.05 °C. The reference electrode was an Ag/Ag\(^+\) electrode, formed by immersing a silver wire into a methanolic silver nitrate solution (0.01 mol.dm\(^{-3}\)). The indicator electrode, where the activity of the free silver was measured, was equipped with a magnetic stirrer. Constant ionic strength was maintained by using TEAP (0.05 mol.dm\(^{-3}\)) in all solutions, including the filling solution for the salt bridge.

A digital micro-processor pH / mV-meter HANNA model H18417 (accurate to ± mV) was used to measure the potential changes during the course of the titration. The
volume of titrant added was measured by an automatic Radiometer ABU12 burette (piston burette).

Salt Bridge, TBAP 0.05 mol.dm\(^{-3}\)

\[
\begin{align*}
\text{Ag}^+ & \rightarrow \text{Methanol} \text{ Ligand} \left\{ \begin{array}{c} \text{C}_{\text{Ag}^+} \text{Methanol} \text{ 0.05M TBAP} \\ \text{Sample} \end{array} \right. \\
\text{Ag}^+ & \rightarrow \text{Methanol} \text{ 0.05M TBAP} \\
\text{Reference} & \rightarrow \text{Ag}^+ \text{ 0.05M TBAP}
\end{align*}
\]

Fig. 2.1 Potentiometer apparatus and electrochemical cell used for titration experiments

2.11.2. Competitive potentiometry procedure

Initially, the indicator electrode vessel was filled with solution TBAP (25 ml, I = 0.05). Allowing a short time for the experiment to attain thermal equilibrium (~10 minutes), the method consisted of three steps (all solutions were prepared and measurements were carried out on the same day).

i) Determination of the standard potential (\(E^0\)) of the reference cell. A methanolic solution of silver nitrate was titrated into the indicator electrode vessel containing TBAP (0.05 mol.dm\(^{-3}\), this inert salt was used to maintain constant ionic strength throughout the experiment); at least twelve additions were performed. The
Chapter Two Experimental Procedures

electrochemical cell's response, evaluated from the slope (Nernst constant value) and the standard potential (E° intercept) of the cell in use, were determined by plotting potential against -log [Ag⁺].

ii) Determination of the stability constant of the silver-calixarene complex. The calixarene derivative, 5, 11, 17, 23-tetrakis-(1, 1-dimethyl)ethy1)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4), was titrated to excess of the silver concentration into the indicator electrode, allowing the formation of a stable silver calixarene complex. During the titration experiment the potential, which is proportional to the activity of the free silver ions (Ag⁺) (eqn. 3.56) reduces, with an end point at the stoichiometric ratio of 1:1 (silver ion : calixarene). The following equations describe the complexation process and the mathematical calculation leading to the determination of Kᵣ (the stability constant for the silver complex):

\[
\text{Calix}(s) + Ag^+(s) \xrightarrow{K_r} Ag\text{Calix}^+(s)
\]  

(2.11)

from the Nernst equation

\[
\log a_{Ag^+} = \frac{E^o - E}{0.059}
\]  

(2.12)

The total concentration of silver ions, [Ag⁺],

\[
[Ag^+] = Ag^+_r + [Ag\text{Calix}^+]
\]  

(2.13)

rearranging,

\[
[Ag\text{Calix}^+] = [Ag^+] - Ag^+_r
\]  

(2.14)

The total concentration of calixarene, [Calix],

\[
[Calix] = [Calix] + [Ag\text{Calix}^+]
\]  

(2.15)

rearranging,
The stability constant of the silver ion calixarene complex is calculated by the following equation:

\[ K_i = \frac{[AgCalix^+]}{[Ag^+]_t[Calix]} \]  

(2.17)

iii) Competition of a second metal ion with the silver-calixarenate complex. A solution of the metal was titrated in excess of the total silver-calixarenate complex. The formation of an equilibrium between the silver calixarene complex and the free metal ions is set up. An increase in the activity of free silver ions is recorded as the competitive metal ions are introduced into the system and silver ions are displaced (eqn.2.18).

\[ AgCalix^+(s) + M^+(s) \xrightleftharpoons{K_2} MCalix^+(s) + Ag^+(s) \]  

(2.18)

The equilibrium constant, \( K_2 \), is calculated by first establishing the total concentrations for the three species in the reaction mixture,

\[ [Ag]_t = [Ag^+]_t + [AgCalix^+] \]  

(2.19)

\[ [Calix]_t = [Calix] + [AgCalix^+] + [MCalix^+] \]  

(2.20)

\[ [M]_t = [M^+] + [MCalix^+] \]  

(2.21)

The free silver concentration was calculated using the Nernst equation (eqn. 2.10). Using equations 2.19 and 2.22, the concentration of the silver calixarene complex and the concentration of the free calixarene are calculated.

\[ [Calix] = \frac{[AgCalix^+]}{K_i, Ag^+_t} \]  

(2.22)
Finally, $K_{M}$ is determined from eqn. 2.23, once the concentration of the metal complex and the free metal ion concentration is calculated from eqns. 2.20 and 2.21 respectively.

$$K_M = \frac{[MCalix^+]}{[M^+][Calix]} \quad (2.23)$$

### 2.11.3. Treatment of results

The simulation program SIMCXNA2.BAS$^{193}$, was used to select appropriate concentrations of ligand and metal-ion salt to be used in these measurements. A computation simulation program developed at the University of Surrey (POTK123B$^{193}$) was used to determine equilibrium constants from the titration points.
3. RESULTS AND DISCUSSION

3.1. SYNTHESIS AND CHARACTERISATION OF LOWER RIM CALIX[4]ARENE DERIVATIVES CONTAINING SOFT DONOR ATOMS

In the following section, the use of phase transfer catalysts in the synthesis of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-dihydroxy-26, 28-bis[2-(methylthio)ethoxy] calix[4]arene (L-2) is first discussed.


The title compound was previously synthesised in the absence of 18-crown-6 almost simultaneously by Cobben et al. and by Beer et al. in 1992.

In the procedure used by Beer et al., the initial 53% yield of an impure product (which contained the mono-alkylated derivative) was reduced after further purification by column chromatography, to 22% yield of L-2. The reaction involved a refluxing period of 48 hours, using the alkylating reagent 2-chloroethylmethyl sulphide in excess of p-tert-butylcalix[4]arene (2:1). The final product was recrystallised from chloroform and ethanol. The synthetic procedure used by Cobben requires a shorter refluxing period (20 hours) but a larger excess of the alkylating agent relative to p-tert-butylcalix[4]arene (3:1) than that involved in this work. The method afforded 67% of L-2 and no further purification by column chromatography was necessary. The product was recrystallised from methanol.

Solid-liquid phase transfer catalysts were previously used at the Thermochemistry laboratory for the synthesis of p-tert-butylcalix[n]arene (n = 4, 6, 8) esters and the
advantages of this method relative to others were described. In doing so, the reaction medium and the selectivity of the crown ether for the cation component of the salt were carefully considered. Thus, acetonitrile was used as the reaction medium because it offers a higher dielectric medium \((\varepsilon = 37.5)\) than tetrahydrofuran \((\varepsilon = 7.6)\)^{196}. Therefore, the former solvent is a more suitable medium for the formation of the naked anions of \(p\text{-}\text{tert}-\text{butylcalix}[4]\)arene than the latter, in which ion-pairs are likely to be the predominant species in solution. Since the selectivity of 18-crown-6 for potassium in acetonitrile at 298.15 K is higher than that for sodium by a factor of ten^{197}, the potassium salt was used.

As far as ‘alternate alkylation’ of \(p\text{-}\text{tert}-\text{butylcalix}[4]\)arene is concerned, regioselective reactions used for the removal of specific hydroxyl groups from the lower rim of parent calixarenes are of particular importance for the construction of larger molecules using calixarenes as building blocks. ‘Alternate alkylation’ reactions of \(p\text{-}\text{tert}-\text{butylcalix}[8]\)arene in the presence of weak bases have been investigated by Neri^{198,199} and the formation of direct mono and di-alkylation reactions have been summarised by Böhmer^{22}. The outcome of these studies is that under certain conditions, weak bases are able to deprotonate only one of the hydroxyl groups at the lower rim of the parent calix[n]arene (Fig.3.1(a)), while the anion formed is stabilised by intramolecular hydrogen bond formation as shown in Fig. 3.1.

![Fig. 3.1 Mechanism for the formation of 1, 3-alternately derivatised calix[4]arenes](image-url)
In the formation of calixarene derivatives in 1, 3-alternate conformations, the first deprotonation step produces preferentially the most stable anion (two intramolecular hydrogen bonds stabilising the structure, Fig. 3.1). After alkylation of this monoanion (Fig. 3.1(b)), a second proton opposite to the site of the first substitution is removed from the lower rim, forming an anion, with two stabilising hydrogen bonds.

The proposed ‘alternate alkylation’ mechanism seems to explain the substitution pattern found for the 1, 3-bis-methylthioether calix[4]arene (L-2). However, this mechanism does not fully explain all the regioselective results seen for the alkylation of hexamer and octamer parent calixarenes in the presence of weak bases. Neri’s current research recognises that apart from the basic strength and the stability of the mono- or polyanions, other factors such as metal template effects, conformational behaviour and difference in solubility of intermediates, may be involved in the substitution of these higher oligomers.

3.1.2. Use of sodium hydride as a deprotonating base

Gutsche\(^{200}\) has successfully extended the method based on the use of sodium hydride in tetrahydrofuran for the alkylation of phenols and alcohols\(^{291}\), to derivatise the lower rim of parent calix[n]arenes. The efficient deprotonation reagent has now been used by many researchers to develop new derivatives. The alkylation reactions described below proceed in a direct and smooth fashion affording derivatives in good yields, high purity and in a fixed cone conformation.

For the preparation of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 26, 27, 28-tetrakis-[2-(thiophene)methoxy]calix[4]arene (L-1) (Fig. 3.2), the four of the lower rim’s hydroxyl protons need to be removed. Sodium hydride (a strong base) was used initially in an oil dispersed form (60 %). However, before its use the base was washed with hexane to remove the oil, an awkward procedure which often led to difficult recrystallisations, sometimes producing a ‘sticky’ crystalline product. The use of dry sodium hydride led to no pre-washing and gave rise to a trouble free recrystallisation.
Fig. 3.3 Reaction scheme and table showing the introduction of aliphatic and alicyclic amine moieties to 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-dihydroxy-26, 28-bis[2-(methylthio)ethoxy]calix[4]arene (L-2)

The various substituted amine moieties (Fig. 3.3) at the lower rim of calixarenes confer to these macrocycles' different acid-base properties which are reflected in their pKₐ values (see section 3.4.).
The alkylating reagents were purchased as hydrochloride salts, therefore sodium hydride neutralised the salts in order to free the amine for the alkylation reaction. As a result, sodium hydride was used five times in excess of the phenol concentration.

The preparation of 5, 11, 17, 23-tetrais-(1, 1 dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[1-(2-methylthiophene)oxy]calix[4]arene (L-9) and of 5, 11, 17, 23-tetrais-(1, 1 dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diisopropylacetamide)oxy]calix[4]arene (L-10) (Fig. 3.4) was derivatised by the same procedure used for the preparation of the 2, 4-disubstituted aliphatic and alicyclic tertiary amines (L-3-8) (Fig. 3.3).

![Reaction scheme and table showing the introduction of thiophene and diisopropylacetamide moieties to 5, 11, 17, 23-tetrais-(1, 1 dimethylethyl)-25, 27-dihydroxy-26, 28-bis[2-(methylthio)ethoxy]calix[4]arene (L-2)](image)

<table>
<thead>
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</tr>
<tr>
<td>L-10</td>
<td><img src="image" alt="Diisopropylacetamide" /></td>
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</tbody>
</table>

Fig. 3.4 Reaction scheme and table showing the introduction of thiophene and diisopropylacetamide moieties to 5, 11, 17, 23-tetrais-(1, 1 dimethylethyl)-25, 27-dihydroxy-26, 28-bis[2-(methylthio)ethoxy]calix[4]arene (L-2)

Table 3.1 summarises the analytical and physical data for ligands L-1-10.
### Table 3.1 Summary of analytical and physical data for mixed donor derivatives (L-1-10)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Formula</th>
<th>FW(^a)</th>
<th>% yield</th>
<th>m.p. (°C)</th>
<th>% calculated</th>
<th>% found</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-1</td>
<td>C(<em>{64})H(</em>{72})O(_4)S(_4)</td>
<td>1033.51</td>
<td>53</td>
<td>255-257</td>
<td>74.39</td>
<td>7.02</td>
</tr>
<tr>
<td>L-2</td>
<td>C(<em>{52})H(</em>{66})O(_4)S(_2)</td>
<td>797.21</td>
<td>65</td>
<td>226-227.5</td>
<td>75.33</td>
<td>8.60</td>
</tr>
<tr>
<td>L-3</td>
<td>C(<em>{53})H(</em>{66})O(_4)S(_2)N(_2)</td>
<td>939.45</td>
<td>50</td>
<td>207-210</td>
<td>74.15</td>
<td>9.23</td>
</tr>
<tr>
<td>L-4</td>
<td>C(<em>{62})H(</em>{94})O(_4)S(_2)N(_2)</td>
<td>995.56</td>
<td>65</td>
<td>192-198</td>
<td>74.80</td>
<td>9.52</td>
</tr>
<tr>
<td>L-5</td>
<td>C(<em>{66})H(</em>{102})O(_4)S(_2)N(_2)</td>
<td>1051.67</td>
<td>55</td>
<td>234-236</td>
<td>75.38</td>
<td>9.78</td>
</tr>
<tr>
<td>L-6</td>
<td>C(<em>{52})H(</em>{90})O(_6)S(_2)N(_2)</td>
<td>1023.53</td>
<td>50</td>
<td>273-277</td>
<td>72.76</td>
<td>8.86</td>
</tr>
<tr>
<td>L-7</td>
<td>C(<em>{64})H(</em>{94})O(_4)S(_2)N(_2)</td>
<td>1019.58</td>
<td>61</td>
<td>239-241</td>
<td>75.39</td>
<td>9.29</td>
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<tr>
<td>L-8</td>
<td>C(<em>{62})H(</em>{90})O(_4)S(_2)N(_2)</td>
<td>991.53</td>
<td>53</td>
<td>185-188</td>
<td>75.10</td>
<td>9.15</td>
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<tr>
<td>L-9</td>
<td>C(<em>{60})H(</em>{76})O(_4)S(_4)</td>
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<td>249-259</td>
<td>72.83</td>
<td>7.74</td>
</tr>
<tr>
<td>L-10</td>
<td>C(<em>{62})H(</em>{86})O(_6)S(_2)N(_2)</td>
<td>1079.63</td>
<td>17</td>
<td>274-282</td>
<td>73.43</td>
<td>9.15</td>
</tr>
</tbody>
</table>

\(^a\)FW in g mol\(^{-1}\)
3.1.3. $^1$H and $^{13}$C spectral characterisation of lower rim calix[4]arene derivatives (L-1-10)

The $^1$H NMR spectral data in CDCl$_3$ at 298 K for all derivatives (L-1-10) are listed in Table 3.2 and shown in Figs. 3.5-15. Similar spectral patterns for all the novel derivatives are found with major differences arising from the residual amino terminal groups. A typical proton spectra for these derivatives consists of:

a) two singlets in the aryl region corresponding to the aromatic protons
b) a pair of doublets (ArCH$_2$Ar)
c) a pair of triplets for the amine substituent (OCH$_2$CH$_2$N)
d) a pair of triplets for the methylethylthio substituent (OCH$_2$CH$_2$S)
e) two singlets representing the t-butyl groups.

The $^{13}$C NMR spectra (Table 3.4 and Figs. 3.5-15) show that derivatives L-2-10 are characterised by eight peaks which appear at a lower magnetic field between 154 and 124 ppm, corresponding to the aromatic carbons (Ci, Cp, Co and Cm) in the ring. The remaining aliphatic peaks are observed between 76 and 15 ppm.

The t-butyl groups produce the most intense peak in this region ($\approx$ 30 ppm), the rest of the peaks are further distinguished by DEPT-135 and $^1$H/$^{13}$C correlation experiments.

The proton and carbon spectra for all the derivatives (L-1-10) follows :-
Chapter Three Results and Discussion

Fig. 3.5 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 26, 27, 28-tetrakis-[2-(thiophene)methoxy]calix[4]arene (L-1) in CDCl$_3$ at 298 K

Fig. 3.6 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-dihydroxy-26, 28-bis[2-(methylthio)ethoxy]calix[4]arene (L-2) in CDCl$_3$ at 298 K
Fig. 3.7 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(dimethylamine)ethoxy]calix[4]arene (L-3) in CDCl$_3$ at 298 K

Fig. 3.8 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4) in CDCl$_3$ at 298 K
Fig. 3.9  $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(1-diisopropylamine)ethoxy]calix[4]arene (L-5) in CDCl$_3$ at 298 K

Fig. 3.10  $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[1-(morpholinyl)ethoxy]calix[4]arene (L-6) in CDCl$_3$ at 298 K
Fig. 3.11 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetraš-(1, 1 dimethylethyl)-
25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(1-piperidinyl)ethoxy]
calix[4]arene (L-7) in CDCl$_3$ at 298 K

Fig. 3.12 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetraš-(1, 1 dimethylethyl)-
25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(1-pyrrolidine)ethoxy]
calix[4]arene (L-8) in CDCl$_3$ at 298 K
Fig. 3.13 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1 dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[1-(2-methylthiophene)oxy] calix[4]arene (L-9) in CDCl$_3$ at 298 K

Fig. 3.14 $^1$H and $^{13}$C NMR spectra of 5, 11, 17, 23-tetrakis-(1, 1 dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diisopropylacetamide)oxy] calix[4]arene (L-10) in CDCl$_3$ at 298 K
Fig. 3.15 $^{13}$C NMR spectrum of 5, 11, 17, 23-tetrakis-(1, 1-dimethyl)ethyl]-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diisopropyl acetamide)oxy] calix[4]arene (L-10) in CDCl$_3$ at 278 K, showing the resolved methyl signal of the diisopropylacetamide moiety.

NMR techniques were used extensively to characterise the new derivatives (see Experimental Procedures 2.3.). These studies were carried out in deuterated chloroform, a solvent in which all the new compounds were found to be very soluble. The following discussion concentrates on derivative, 5, 11, 17, 23-tetrakis-(1, 1-dimethyl)ethyl]-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy] calix[4]arene (L-4).

The conformation of calix[4]arenes can be confirmed from the $^1$H NMR splitting pattern of the methylene groups (ArCH$_2$Ar) bridging each of the aromatic rings, which appear in the proton spectrum as a pair of doublets when the macrocycle is in the cone conformation. The calix[4]arene derivatives (L-1-10) are all in the cone conformation as a pair of doublets are recorded for each $^1$H NMR spectrum (Figs. 3.5-3.14). Each methylene proton exists in a different environment; the downfield doublet (closest to the phenolic oxygen) corresponds to the axial or endo proton, while the upfield doublet is the exo or equatorial methylene proton. For derivative L-4, these doublets can be seen at 4.36 and 3.15 ppm (Figs. 3.8, 3.16)$^{32}$ respectively.

As far as the $^{13}$C NMR spectra is concerned, the phenol rings beside each methylene are in a syn orientation; the methylene signal in the carbon spectra appears around 31 ppm$^{32}$. This is the case for all the new derivatives (L-1-10) synthesised in this...
thesis. If the phenol rings are anti-orientated (i.e., in 1, 3-alternate conformation) the methylene signal registers around 37 ppm; steric effects are believed to cause these large shift differences.

For the other three conformations - partial cone, 1, 2-alternate, 1,3-alternate - different spectral patterns in the proton spectrum are observed.

The difference in shift values between $H_{\text{exo}}$ and $H_{\text{endo}}$ protons gives an indication of the symmetry of the cone conformation. In the parent calixarene, $p$-tert-butylcalix[4]arene, $\Delta \delta \approx 0.75$ ppm, while for derivative L-4, $\Delta \delta \approx 1.20$ ppm. Shift differences indicate conformational changes from the symmetrical parent calix[4]arene. In the distorted cone conformation of derivative L-4, new ring current effects on the methylene protons cause greater shielding to the $H_{\text{exo}}$ protons (moving the signal upfield) and less shielding to the $H_{\text{endo}}$ protons (moving the signal downfield), resulting in a greater $\Delta \delta$ value as the two doublets move further apart.

Steric crowding between the lower rim substituents is responsible for the distorted cone conformation of L-4. X-ray crystallographic results (Results and Discussion 3.1.4.) clearly show the distortion of the cone conformation and parallel nature of the amine substituted aromatic rings in derivative L-3. The conformation of L-4 is believed to be very close to L-3, as only an extra methylene group distinguishes them. Tetraester derivatives show extreme steric hindrance between the lower rim substituents with $\Delta \delta$ values for the bridging methylene greater than 1.7 ppm. On complexation with sodium ions, $\Delta \delta$, is significantly reduced ($\Delta \delta \approx 1.00$ ppm) to a value resembling a symmetrical cone conformation. It is believed that steric crowding forces are responsible for the uncomplexed tetraester derivative to adopt a conformation where the aromatic rings are more parallel, thus allowing the ester substituents to move as far as possible from each other in order to reduce steric effects at the lower rim. As complexation with metal cations draws the substituents closer, the aromatic rings now adopt a flatter more parent cone-like conformation. Gutsche et al. has also noted that the shift difference ($\Delta \delta$) between axial and equatorial protons serves as a measure of the flattened conformation.
Tables 3.2 and 3.3 clearly show that the $\Delta \delta ((H_{ax}-H_{eq}) / \text{ppm})$ value increases as the steric effect of the lower rim substituents increases with a movement of the aromatic rings to a relatively more parallel position in relation to that found for the parent $p$-tert-butylcalix[4]arene as shown in the $^1H$ NMR spectra of these compounds in CDCl$_3$.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$\Delta \delta (H_{ax}-H_{eq}) / \text{ppm}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$-tert-butylcalix[4]arene</td>
<td>0.75</td>
</tr>
<tr>
<td>L-2</td>
<td>0.99</td>
</tr>
<tr>
<td>L-3-9</td>
<td>1.19-1.28</td>
</tr>
<tr>
<td>L-10</td>
<td>1.34</td>
</tr>
</tbody>
</table>

Table 3.2 Difference between the bridging methylene splitting patterns of the protons in $p$-tert-butylcalix[4]arene and derivatives (L-1-10) in CDCl$_3$ at 298.15 K

The results for L-4 indicate:

i) steric crowding between the lower rim substituents
ii) a distorted cone conformation with aromatic rings in a more parallel orientation compared to $p$-tert-butylcalix[4]arene

Derivatives L-2 to L-10 have a 1, 3 and 2, 4 substitution pattern on the lower rim. The shift difference ($\Delta \delta$) between the two $t$-butyl and two meta-aromatic signals of compound L-4 are 0.47 ppm and 0.62 ppm respectively. Electronic effects of substitution are unlikely to be responsible for these shift differences. The difference of substituted moieties containing nitrogen or sulphur donor atoms cannot produce the observed shift changes as the donor atoms are too far away from the aromatic and $t$-butyl protons. Similar calix[4]arene derivatives previously synthesised by other researchers show the same pattern of signals, although no attempts have been made to assign particular signals to lower rim substituents$^{5,194}$. Studies to assign each signal to either the nitrogen or sulphur donor substituent are currently underway. These consist
of measuring the effect of different ring currents which are present as a result of irregular symmetry of the cone conformation. X-ray crystallographic results (Results and Discussion 3.1.4.) of derivative L-3 indicate the two aromatic rings containing amine substituents are parallel, while those involving the methylethylthio substituents' aromatic rings are flatter.

The two singlet signals for both, the t-butyl and aromatic protons in the proton spectrum, are a distinctive feature for these mixed donor ligands.

$^1$H NMR measurements on derivative L-4 (Table 3.3) were also performed in d$_6$-DMSO, enabling the rigidity of the ligand at higher temperatures to be studied. At 100 °C no change in the proton spectrum was recorded, clearly indicating the existence of a rigid cone conformation in solution.

Derivatives L-3-10 have ethylene groups between two different heteroatoms in each of the lower rims' pendant arms. In the proton spectrum of derivative L-4 (Fig. 3.8), four 'triplets' can be seen between 4.3 and 2.9 ppm (Fig. 3.16).

![NMR spectrum](image)

**Fig. 3.16** Expansion of the $^1$H NMR spectrum between 4.3 and 2.9 ppm for the 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis(2-(diethylamine)ethoxy)calix[4]arene (L-4) derivative in CDCl$_3$ at 298 K

A closer inspection of the 'triplets' show that more complicated structures are involved. Lorentzian / Gaussian resolution enhancement techniques were used to
study their fine structures (Fig. 3.18). Restricted rotation (due to steric crowding) around the C-C bond between two heteroatoms (OCH$_2$CH$_2$N or S [of different electronegatives]) on each of the lower rim substituents leads to non-equivalent protons on each methylene group. AA'BB' coupling systems$^{203}$ are formed, resulting in the four multiplet structures (Fig. 3.16) being observed for derivatives L-3-8, the individual proton couplings are summarised as follows (Fig. 3.17),

\[ \begin{align*}
\text{Gauche Configurations} & \quad \text{Trans Configuration} \\
\text{(Mirror Images, NMR Equivalent)} & \\
\end{align*} \]

i. Trans couplings between 2/4 or 1/3 protons (give rise to large coupling constants).

ii. Gauche couplings between 1/4 or 2/3 protons of the trans configuration (give rise to medium coupling constants).

iii. Geminal coupling between 1/2 or 3/4 of the trans configuration (give rise to small coupling constants).

Fig. 3.17. Newman projections describing all proton couplings

The AA'BB' coupling systems, part of which is displayed in Fig. 3.18, contain a theoretical maximum fifty six lines. For derivative L-4 at 298 K, only twenty four lines can be resolved.

Compound L-2 is effectively the starting material for other derivatives. In this dithio-substituted compound, there are two unsubstituted hydroxy groups in the 2, 4-positions. As a result of a less crowded lower rim, the methylethylthio moieties freely rotate around the C-C bond of the two methylenes between the two heteroatoms. The protons on each methylene are equivalent. No AA'BB' system of coupling is formed and two triplets with a 1:2:1 intensity pattern are observed (Fig. 3.19).
In the proton spectra of derivatives L-3-8 four multiplet signals which arise from the eight methylene groups between the heteroatoms in the lower rim are found. Acid titrations, in conjunction with selective single frequency homo decoupling experiments, were performed in order to assign these multiplets to either the amine or methylethylthio substituent pendant arms.

As far as derivative L-4 is concerned, decoupling experiments were initially conducted on the free ligand in deuterated methanol. These experiments showed that multiplets at 4.15 and 3.28 ppm were coupled (Figs. 3.8, 3.16). When the decoupling frequency and power were set to 4.15 ppm the multiplet completely collapses to the base line, while the signal at 3.20 ppm collapses to a more intense singlet.

If the decoupling frequency is set to the highest upfield methylene at 3.1 ppm (Fig. 3.8) the methylene is clearly coupled to the multiplet at 3.88 ppm. Again this multiplet collapses to a more intense singlet.
Fig. 3.18 Restricted rotation of lower rim substituents of derivative L-4. Resolution enhancement of methylene at 4.15 ppm in CDCl$_3$ at 298 K

Fig. 3.19 Free rotation of lower rim substituents of derivative L-2. Resolution enhancement of methylene at 3.06 ppm in CDCl$_3$ at 298 K
In order to determine which proton signals belong to the amine (OCH$_3$CH$_2$N) or to the methylethylthio (OCH$_3$CH$_2$S) substituents, stepwise acid titrations using deuterated trifluoroacetic or perchloric acid were conducted. Only the nitrogen donor atoms on the lower rim can be protonated, as can be seen from the deshielding of the methylene and methyl protons of the substituent. One set of coupled pairs move downfield, showing that these correspond to the amine moiety.

The methylene protons of the methylethylthio substituted which are not deshielded due to the lack of protonation, moved slightly upfield due to the field effects. Because of the larger than expected downfield shift seen by the methylene protons next to the oxygen of the amine substituent (Table 3.20), a five membered ring hydrogen bonded to the oxygen donor atom is believed to have been established.

![Fig. 3.20. Protonated derivative L-4, showing possible formation of five membered ring, with an oxygen donor atom](image)

Another feature of the protonation experiment of derivative L-4 is that the two methylenes of the sulphur substituent now show free rotation. The methylene’s AA’BB’ coupling system collapses to a normal 1:2:1 triplet. The spectrum now looks like the di-substituted methylethylthio starting material, L-2 (Fig. 3.19) previously described, where a low degree of steric hindrance or crowding at the lower rim is present.
Structural changes born out by the coalescence of the two sets of signals for each of the $t$-butyl and aromatic protons, seem to indicate that the distorted cone conformation is becoming more symmetrical. Ring current effects must now be acting equally in the protonated form when compared to the free ligand. For this conformational change to take place, the methylthio substituted aromatic rings must become more parallel, moving these moieties away from the sterically crowded lower rim, while the amine moieties become closer as their substituted rings become flatter.
<table>
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<tr>
<th>Ligand</th>
<th>$H_m$</th>
<th>$H_{ax}$</th>
<th>OCH$_2$CH$_2$S</th>
<th>OCH$_2$CH$_2$N</th>
<th>$H_{eq}$</th>
<th>CH$_2$SCH$_3$</th>
<th>OCH$_2$CH$_2$NR$_2$</th>
<th>C(CH$_3$)$_3$</th>
<th>$J_{AB}$/Hz</th>
<th>$\Delta\delta(H_{ax}-H_{eq})$/ppm</th>
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<td>L-1</td>
<td>6.69</td>
<td>4.14</td>
<td>-</td>
<td>-</td>
<td>2.89</td>
<td>-</td>
<td>-</td>
<td>1.06</td>
<td>12.76</td>
<td>1.25</td>
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<td>7.06, 6.75</td>
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<td>4.13</td>
<td>-</td>
<td>3.32</td>
<td>3.06</td>
<td>-</td>
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<td>13.02</td>
<td>0.99</td>
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<tr>
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<td>7.06, 6.50</td>
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<td>4.17</td>
<td>3.85</td>
<td>3.14</td>
<td>3.23</td>
<td>2.82</td>
<td>1.29, 0.84</td>
<td>12.50</td>
<td>1.25</td>
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<tr>
<td>L-4</td>
<td>7.09, 6.47</td>
<td>4.36</td>
<td>4.17</td>
<td>3.85</td>
<td>3.14</td>
<td>3.20</td>
<td>3.02</td>
<td>1.31, 0.84</td>
<td>12.52</td>
<td>1.22</td>
</tr>
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<td>4.35</td>
<td>4.22</td>
<td>3.67</td>
<td>3.16</td>
<td>3.25</td>
<td>$\approx$3.0</td>
<td>1.33, 0.81</td>
<td>12.49</td>
<td>1.19</td>
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<td>4.18</td>
<td>3.90</td>
<td>3.13</td>
<td>3.20</td>
<td>2.84</td>
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<td>1.28</td>
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<td>4.17</td>
<td>3.89</td>
<td>3.13</td>
<td>3.22</td>
<td>2.86</td>
<td>1.30, 0.85</td>
<td>12.53</td>
<td>1.26</td>
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<td>L-8</td>
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<td>4.40</td>
<td>4.16</td>
<td>3.90</td>
<td>3.14</td>
<td>3.21</td>
<td>3.00</td>
<td>1.30, 0.85</td>
<td>12.52</td>
<td>1.26</td>
</tr>
<tr>
<td>L-9</td>
<td>7.10, 6.47</td>
<td>4.35</td>
<td>4.02</td>
<td>-</td>
<td>3.11</td>
<td>2.88</td>
<td>-</td>
<td>1.32, 0.83</td>
<td>12.52</td>
<td>1.24</td>
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<td>7.11, 6.46</td>
<td>4.49</td>
<td>4.30</td>
<td>-</td>
<td>3.15</td>
<td>3.35</td>
<td>-</td>
<td>1.34, 0.82</td>
<td>12.53</td>
<td>1.34</td>
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</table>

Table 3.3 Summary of $^1$H NMR data for mixed donor derivatives (L-1-10) in CDCl$_3$ at 298 K ($\delta$ ppm with respect to TMS)
<table>
<thead>
<tr>
<th>Ligand</th>
<th>C₁</th>
<th>C₂</th>
<th>C₃</th>
<th>C₄</th>
<th>OCH₂CH₂S</th>
<th>OCH₂CH₂N</th>
<th>OCH₂CH₂S</th>
<th>OCH₂CH₂N</th>
<th>C(CH₃)₃</th>
<th>C(CH₂)₃</th>
<th>ArCH₂Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-1</td>
<td>152.3</td>
<td>140.5</td>
<td>134.1</td>
<td>124.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>33.8</td>
<td>31.4</td>
<td>31.9</td>
</tr>
<tr>
<td>L-2</td>
<td>150.5, 149.9</td>
<td>146.9, 141.5</td>
<td>132.3, 127.8</td>
<td>125.5, 125.0</td>
<td>75.4</td>
<td>-</td>
<td>33.5</td>
<td>-</td>
<td>33.9, 33.7</td>
<td>31.7, 31.0</td>
<td>31.6</td>
</tr>
<tr>
<td>L-3</td>
<td>152.8, 149.9</td>
<td>144.1, 143.3</td>
<td>134.2, 131.1</td>
<td>124.4, 123.6</td>
<td>72.3</td>
<td>72.1</td>
<td>31.6</td>
<td>58.2</td>
<td>33.0, 32.6</td>
<td>30.6, 30.1</td>
<td>30.0</td>
</tr>
<tr>
<td>L-4</td>
<td>153.6, 152.2</td>
<td>145.2, 144.3</td>
<td>135.3, 131.9</td>
<td>125.5, 124.5</td>
<td>73.5</td>
<td>73.3</td>
<td>32.7</td>
<td>47.6</td>
<td>34.1, 33.6</td>
<td>31.7, 31.1</td>
<td>30.1</td>
</tr>
<tr>
<td>L-5</td>
<td>154.0, 152.0</td>
<td>145.3, 144.1</td>
<td>135.6, 131.7</td>
<td>125.5, 124.5</td>
<td>73.3</td>
<td>76.9</td>
<td>32.8</td>
<td>45.1</td>
<td>34.1, 33.6</td>
<td>31.7, 31.1</td>
<td>30.1</td>
</tr>
<tr>
<td>L-6</td>
<td>153.6, 152.3</td>
<td>145.2, 144.5</td>
<td>135.2, 134.1</td>
<td>125.5, 124.6</td>
<td>73.3</td>
<td>71.7</td>
<td>33.0</td>
<td>58.7</td>
<td>34.1, 33.6</td>
<td>31.6, 31.1</td>
<td>31.1</td>
</tr>
<tr>
<td>L-7</td>
<td>153.8, 152.3</td>
<td>145.0, 144.2</td>
<td>135.3, 132.0</td>
<td>125.4, 124.5</td>
<td>73.2</td>
<td>73.6</td>
<td>32.8</td>
<td>58.8</td>
<td>34.0, 33.5</td>
<td>31.6, 31.1</td>
<td>31.1</td>
</tr>
<tr>
<td>L-8</td>
<td>153.9, 152.3</td>
<td>145.1, 144.3</td>
<td>135.3, 132.2</td>
<td>125.4, 124.5</td>
<td>74.0</td>
<td>73.3</td>
<td>32.7</td>
<td>56.0</td>
<td>34.1, 33.6</td>
<td>31.7, 31.2</td>
<td>31.1</td>
</tr>
<tr>
<td>L-9</td>
<td>154.0, 151.6</td>
<td>145.2, 144.9</td>
<td>135.4, 132.1</td>
<td>125.5, 124.8</td>
<td>73.3</td>
<td>-</td>
<td>32.5</td>
<td>-</td>
<td>34.1, 33.6</td>
<td>31.7, 31.2</td>
<td>31.1</td>
</tr>
<tr>
<td>L-10</td>
<td>154.3, 152.2</td>
<td>144.9, 144.5</td>
<td>135.6, 131.8</td>
<td>125.5, 124.7</td>
<td>≈ 73.8</td>
<td>-</td>
<td>32.0</td>
<td>-</td>
<td>34.1, 33.6</td>
<td>31.7, 31.1</td>
<td>31.3</td>
</tr>
</tbody>
</table>

Table 3.4 Summary of $^{13}$C NMR data for mixed donor derivatives (L-1-10) in CDCl$_3$ at 298 K ($\delta$ ppm with respect to TMS)
3.1.4. X-ray crystallography results

The single crystal X-ray structure determinations for both, the L-1 and the L-3 derivatives were carried out by Prof. J. L. Briansó and Dr. A. Alvarez at the Department of Geology, Autònoma University of Barcelona. All refinement calculations were carried out using the computer program, SHELXL-93.

X-ray crystallographic results confirmed the structures of the synthesised ligands and were used in the discussion of the $^1$H NMR complexation results (\textit{\textsuperscript{1}H NMR complexation results 3.1.2}).

3.1.4.1. Crystallographic data for 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 26, 27, 28-tetrakis-[2-(thiophene)methoxy]calix[4]arene (L-1) (Fig. 3.21)

![Figure 3.21](image)

Fig. 3.21 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 26, 27, 28-tetrakis-[2-(thiophene)methoxy]calix[4]arene (L-1)

Crystallographic parameters for this tetra-thiophene substituted calix[4]arene derivative are given in Table 3.5. The structure of the molecule and the atom numbering system are depicted in Figs. 3.23 and 3.24 respectively. Selected bond lengths and angles are given in Table 3.6.

The symmetrical nature of the molecule (space group $C_{2v}$) can be appreciated as only half of the ligand is needed to describe the full structure. Unfortunately, disorder in the thiophene rings gave rise to inaccuracies in the determination of ring bond lengths and
angles. Consequently, values for these rings have been ‘fixed’ to standard lengths and angles which were used to create the molecular structures seen in Figs. 3.23 and 3.24. The molecular disorder is not reflected in these diagrams. This disorder does not invalidate the essential features of the determined structure.

The standard proximal sulphur-sulphur non-bonded contact is 6.022 Å. These sulphur atoms form a square shaped donor pattern at the lower rim (Fig. 3.22); the symmetrical nature of the macrocycle is emphasised by the whole molecule being represented by only half the full structure with a two carbon chain length distance between the oxygen and sulphur heteroatoms, since the methylene bridging unit is connected to the 2-position of the thiophene moiety (Fig. 3.23). Many ion selective substituted calixarene ionophores have been developed with this common heteroatom arrangement for example amides\textsuperscript{82}, amines\textsuperscript{354} and esters\textsuperscript{202}.

![Fig. 3.22 Square shaped sulphur donor pattern at the lower rim of L-1. The average S(1)-S(32) bond length of 6.022 Å is labelled](image-url)
<table>
<thead>
<tr>
<th>Crystal parameters</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>C_{64}H_{72}O_{4}S_{4}</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.90 x 0.58 x 0.40</td>
</tr>
<tr>
<td>Colour</td>
<td>Colourless</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>C_{2}</td>
</tr>
<tr>
<td>a (Å)</td>
<td>11.973 (5)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>23.640 (6)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>20.974 (4)</td>
</tr>
<tr>
<td>β (°)</td>
<td>93.26 (2)</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>5927 (3)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>D_c (g.cm⁻³)</td>
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</tr>
<tr>
<td>F(000)</td>
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</tr>
<tr>
<td>μ (MoKα) (mm⁻¹)</td>
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</tr>
<tr>
<td>Temperature (K)</td>
<td>293 (2)</td>
</tr>
<tr>
<td>Wavelength (Å)</td>
<td>0.71069</td>
</tr>
<tr>
<td>θ Angular range (°)</td>
<td>1-25</td>
</tr>
<tr>
<td>Index range</td>
<td>14/14, 0/28, 0/24</td>
</tr>
<tr>
<td>Unique reflections</td>
<td>5213</td>
</tr>
<tr>
<td>No. refined parameters</td>
<td>343</td>
</tr>
<tr>
<td>R_w(F²) (all data)</td>
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<td>R(F) (I &gt; 2σ(I))</td>
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</tr>
<tr>
<td>R (F) (all data)</td>
<td>0.080</td>
</tr>
<tr>
<td>w = [σ²(F_o²) + (0.1177P)² + 0.696P]¹, where P = (Max. (F_o², 0) + 2F_c²) / 3</td>
<td></td>
</tr>
<tr>
<td>Max. / Min. electron density (e / Å³)</td>
<td>0.34 / 0.29</td>
</tr>
</tbody>
</table>

Table 3.5 Crystal data and refinement details for L-1
Fig. 3.23 Side views of L-1, showing the cone conformation
Fig. 3.24 Atom numbering scheme for L-1
Selected atoms

<table>
<thead>
<tr>
<th>Bond lengths and contacts (Å)</th>
<th>Angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)-S(32) 6.022 (4)</td>
<td>-</td>
</tr>
<tr>
<td>O(7)-O(29) 3.149 (2) / 3.244(3)</td>
<td>-</td>
</tr>
<tr>
<td>O(7)-S(1) 3.454 (3)</td>
<td>-</td>
</tr>
<tr>
<td>O(29)-S(32) 3.357 (3)</td>
<td>-</td>
</tr>
<tr>
<td>O(7)-C(6) 1.439 (3)</td>
<td>-</td>
</tr>
<tr>
<td>C(8)-O(7) 1.370 (2)</td>
<td>-</td>
</tr>
<tr>
<td>C(6)-O(7)-C(8) -</td>
<td>115.6 (2)</td>
</tr>
<tr>
<td>O(29)-C(30) 1.442 (3)</td>
<td>-</td>
</tr>
<tr>
<td>C(20)-O(29) 1.385 (2)</td>
<td>-</td>
</tr>
<tr>
<td>C(20)-O(29)-C(30) -</td>
<td>114.8 (2)</td>
</tr>
</tbody>
</table>

Table 3.6 Selected bond lengths and contacts (Å) and angles (°) L-1 with e.s.d.s in parentheses

Figs. 3.23 and 3.24 clearly depict the cone conformation present in this calix[4]arene. However, these two side views [which are at 90° to each other] show a distortion from a symmetrical cone conformation which is present in the parent p-tert-butylcalix[4]arene. Crystal structures show this distortion of molecule in the solid state, while $^1$H NMR measurements in solution show the i-butyl and aromatic protons to be equivalent. In solution, significant conformational movements may be responsible for the averaging of the distorted cone conformation seen in the X-ray crystal structure.
3.1.4.2. Crystallographic structure of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(dimethylamine)ethoxy]-calix[4]arene (L-3) (Fig. 3.25)

![Diagram](image)

Fig. 3.25 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(dimethylamine)ethoxy]-calix[4]arene (L-4)

The X-ray crystal structure confirms the synthesis of a mixed donor calix[4]arene where the nitrogen and sulphur donor atom substituents are alternately arranged.

Crystallographic parameters for this nitrogen-sulphur mixed donor calix[4]arene derivative are given in Table 3.7. The structure of the molecule and the atom numbering are depicted in Figs. 3.26 and 3.27 respectively. Important bond lengths and angles are given in Table 3.8.

Unlike the X-ray crystal structure for L-1 where a considerable disorder is present, the crystal structure of L-4 was found to be well defined and therefore bond lengths and angles are relevant and precise to the molecular structures. A distorted cone conformation can clearly be seen in Fig. 3.26, where two views, which are at 90° in rotation to each other are shown. However, the two nitrogen atoms are 8.678 Å apart, while the two sulphur atoms are separated by 5.231 Å. Therefore, these heteroatoms do not form a square shaped donor pattern found in L-1. The $^1$H NMR measurements in solution for this free ligand show two signals for both the $t$-butyl and aromatic protons. Therefore it is presumed that the solid state structure shown by the X-ray crystallography result is not averaged in solution. Proton shifts of these signals on complexation with metal ions demonstrate the nitrogen and sulphur atoms interacting.
independently. It is hoped that future crystal structures of the metal ion complexes will show that significant conformational movements must have taken place in order for complexation to occur, as the \(^1\)H NMR titration results indicate (see 3.1.2. \(^1\)H NMR complexation measurements).

<table>
<thead>
<tr>
<th>Crystal parameters</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>C(<em>{38})H(</em>{60})O(_4)S(_2)N(_2)</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
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</tr>
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<td>Colour</td>
<td>Colourless</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P(_{21}/n)</td>
</tr>
<tr>
<td>a (Å)</td>
<td>15.473 (4)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>19.752 (6)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>19.987 (17)</td>
</tr>
<tr>
<td>β (°)</td>
<td>107.51 (5)</td>
</tr>
<tr>
<td>V (Å(^3))</td>
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</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>D(_c) (g.cm(^{-3}))</td>
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<tr>
<td>F (000)</td>
<td>2048</td>
</tr>
<tr>
<td>μ (MoKα) (mm(^{-1}))</td>
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</tr>
<tr>
<td>Temperature (K)</td>
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</tr>
<tr>
<td>Wavelength (Å)</td>
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</tr>
<tr>
<td>θ Angular range (°)</td>
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</tr>
<tr>
<td>Index range</td>
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</tr>
<tr>
<td>R (F) (all data)</td>
<td>0.304</td>
</tr>
<tr>
<td>w = [σ(^2)(F(_o))^2 + (0.1177P)^2 + 0.696P]^1, where P = (Max. (F(_o)^2, 0) + 2F(_o)^2) / 3.</td>
<td></td>
</tr>
<tr>
<td>Max. / Min. electron density (e / Å(^3))</td>
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</table>

Table 3.7 Crystal data and refinement details for L-4
Fig. 3.26 Side views of L-4, showing the cone conformation
Fig. 3.27 Atom numbering scheme for L-4
<table>
<thead>
<tr>
<th>Selected atoms</th>
<th>Bond lengths (Å)</th>
<th>Angles (°)</th>
</tr>
</thead>
<tbody>
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<td>N(42)-N(48)</td>
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<td>5.231 (4)</td>
<td>-</td>
</tr>
<tr>
<td>O(29)-O(34)</td>
<td>3.603 (5)</td>
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<tr>
<td>O(39)-O(45)</td>
<td>5.445 (6)</td>
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<tr>
<td>O(29)-S(32)</td>
<td>3.987 (5)</td>
<td>-</td>
</tr>
<tr>
<td>O(34)-S(37)</td>
<td>3.952 (5)</td>
<td>-</td>
</tr>
<tr>
<td>O(39)-N(42)</td>
<td>3.662 (9)</td>
<td>-</td>
</tr>
<tr>
<td>O(45)-N(48)</td>
<td>2.950 (9)</td>
<td>-</td>
</tr>
<tr>
<td>S(32)-C(33)</td>
<td>1.722 (10)</td>
<td>-</td>
</tr>
<tr>
<td>C(31)-S(32)</td>
<td>1.824 (9)</td>
<td>-</td>
</tr>
<tr>
<td>C(31)-S(32)-C(33)</td>
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<td>97.0 (0.5)</td>
</tr>
<tr>
<td>O(29)-C(25)</td>
<td>1.379 (6)</td>
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<td>C(30)-O(29)</td>
<td>1.447 (9)</td>
<td>-</td>
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<tr>
<td>C(25)-O(29)-C(30)</td>
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<td>116.5 (0.4)</td>
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<td>N(42)-C(43)</td>
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</tr>
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<td>N(42)-C(44)</td>
<td>1.291 (13)</td>
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<td>-</td>
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<td>112.3 (0.8)</td>
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<td>108.0 (0.8)</td>
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<td>O(39)-C(40)</td>
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</tr>
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<td>C(26)-O(39)</td>
<td>1.391 (6)</td>
<td>-</td>
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<tr>
<td>C(26)-O(39)-C(40)</td>
<td>-</td>
<td>113.1 (0.4)</td>
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<td>S(37)-C(38)</td>
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<td>C(36)-S(37)</td>
<td>1.808 (7)</td>
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<td>101.9 (0.4)</td>
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<td>O(34)-C(35)</td>
<td>1.418 (8)</td>
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<tr>
<td>C(27)-O(34)</td>
<td>1.364 (6)</td>
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<tr>
<td>C(27)-O(34)-C(35)</td>
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<td>112.4 (0.4)</td>
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<tr>
<td>C(47)-N(48)-C(50)</td>
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<td>114.4 (0.8)</td>
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<td>C(49)-N(48)-C(50)</td>
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<td>104.0 (0.7)</td>
</tr>
<tr>
<td>O(45)-C(46)</td>
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<td>-</td>
</tr>
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<td>C(28)-O(45)</td>
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</tr>
<tr>
<td>C(28)-O(45)-C(46)</td>
<td>-</td>
<td>113.9 (0.4)</td>
</tr>
</tbody>
</table>

Table 3.8 Selected bond lengths (Å) and angles (°) in L-4 with e.s.d.s. in parentheses.
3.2. SOLUBILITY MEASUREMENTS AND DERIVED GIBBS ENERGIES OF SOLUTION. TRANSFER GIBBS ENERGIES FROM ACETONITRILE TO VARIOUS SOLVENTS

In order to determine the acid-base properties of these ligands and their complexation abilities, it is important to have knowledge of their solubility in various solvents at the standard temperature of 298.15 K. However, this information can also be used to calculate solution and transfer Gibbs energies as described below. Thus for a given ligand, L, the equilibrium between the solid (sol.) and a saturated solution (s) of the solute is given by eqn. 3.1.

\[ L(\text{sol.}) \rightarrow L(s) \quad (3.1) \]

The thermodynamic equilibrium constant, \( K^\circ \), may be defined as,

\[ K^\circ = \frac{a_{L(s)}}{a_{L(\text{sol.})}} = \frac{[L]}{a_{\text{sol.}}} \quad (3.2) \]

By convention, the activity of the solid is equal to unity. For very dilute solutions, the activity coefficient (\( \gamma \)) of the neutral ligand (non-electrolyte) can be equalled to unity. Thus, \( K^\circ \) may be written as,

\[ K^\circ \equiv [L] \quad (3.3) \]

where the concentration of L on the molar scale (mol dm\(^{-3}\)) is referred to the standard state of 1 mol dm\(^{-3}\) (units are cancelled).

The standard Gibbs energy of solution, \( \Delta_{s}G^\circ \) is thus given by the following relationship,
Chapter Three Results and Discussion

\[ \Delta G^o = -RT \ln K^o \]  

(3.4)

However, \( \Delta G^o \) is made of two components, the lattice Gibbs energy, \( \Delta_{\text{lat}} G^o \) and the solvation Gibbs energy, \( \Delta_{\text{solv}} G^o \) (eqn. 3.5).

\[ \Delta G^o = \Delta_{\text{lat}} G^o + \Delta_{\text{solv}} G^o \]  

(3.5)

In order to remove the contribution of the lattice Gibbs energy and in this way obtain information regarding the differences in solvation of a solute in two solvents, the standard transfer Gibbs energy, \( \Delta_t G^o \) is calculated. Thus, for the process,

\[ L(s_1) \rightarrow L(s_2) \]  

(3.6)

the equilibrium constant for the transfer process, \( K_t \), can be calculated from,

\[ K_t = \frac{[L](s_2)}{[L](s_1)} \]  

(3.7)

It therefore follows that the transfer Gibbs energy of a solute from a reference solvent to another is given by,

\[ \Delta_t G^o = \Delta_{\text{alt}} G^o(s_2) - \Delta_{\text{alt}} G^o(s_1) \]  

(3.8)


<table>
<thead>
<tr>
<th>Derivative</th>
<th>L-1</th>
<th>L-2</th>
<th>L-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>3.0 x 10^{-5} $^a$</td>
<td>8.4 x 10^{-3} $^a$</td>
<td>$3.3 \pm 0.4 \times 10^{-3}$</td>
</tr>
<tr>
<td>Methanol</td>
<td>3.0 x 10^{-5} $^a$</td>
<td>4.7 x 10^{-3} $^a$</td>
<td>$1.16 \pm 0.03 \times 10^{-2}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>6.0 x 10^{-5} $^a$</td>
<td>5.9 x 10^{-3} $^a$</td>
<td>$2.05 \pm 0.36 \times 10^{-2}$</td>
</tr>
<tr>
<td>Butan-1-ol</td>
<td>1.2 x 10^{-4} $^a$</td>
<td>$3.7 \pm 0.01 \times 10^{-3}$</td>
<td>$1.36 \pm 0.04 \times 10^{-1}$</td>
</tr>
<tr>
<td>N, N-dimethylformamide</td>
<td>2.0 $\pm 0.02 \times 10^{-3}$</td>
<td>9.9 $\pm 0.13 \times 10^{-3}$</td>
<td>$1.63 \pm 0.01 \times 10^{-2}$</td>
</tr>
<tr>
<td>Propylene carbonate</td>
<td>$&lt;10^{-5} \ ^a$</td>
<td>-</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>Benzonitrile</td>
<td>$5.8 \pm 0.04 \times 10^{-3}$</td>
<td>$5.87 \pm 0.22 \times 10^{-2}$</td>
<td>VS</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>$2.5 \pm 0.01 \times 10^{-3}$</td>
<td>$2.31 \pm 0.86 \times 10^{-2}$</td>
<td>VS</td>
</tr>
<tr>
<td>Ethylacetate</td>
<td>$1.43 \times 10^{-2} \ ^a$</td>
<td>$1.03 \times 10^{-1} \ ^a$</td>
<td>VS</td>
</tr>
<tr>
<td>Hexane</td>
<td>$7.4 \times 10^{-4} \ ^a$</td>
<td>$3.81 \times 10^{-2} \ ^a$</td>
<td>VS</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>$2.35 \pm 0.19 \times 10^{-1}$</td>
<td>$2.59 \pm 0.25 \times 10^{-1}$</td>
<td>VS</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>$2.21 \pm 0.09 \times 10^{-1}$</td>
<td>$4.82 \pm 0.78 \times 10^{-2}$</td>
<td>VS</td>
</tr>
<tr>
<td>Chloroform</td>
<td>-</td>
<td>-</td>
<td>VS</td>
</tr>
<tr>
<td>1, 2-dichloromethane</td>
<td>-</td>
<td>-</td>
<td>VS</td>
</tr>
</tbody>
</table>

* Solubility determined by spectrophotometry, all other reported values were determined by gravimetric analysis

VS - Very soluble
Quite clearly the results show that as far as the L-1 derivative is concerned in ionising solvents such as acetonitrile, methanol, propylene carbonate and to a lesser extent, N, N-dimethylformamide this ligand is not soluble enough to proceed with the determination of pK_a values or indeed to study the complexing abilities for metal cations.

Although in low dielectric media (dichloromethane, tetrahydrofuran), solubility is not a limitation, there are other factors which need to be considered, such as the ion-pair formation of the free MX (eqn. 3.9) and complexed electrolyte MLX (eqn. 3.10) in these solvents,

\[
\text{M}^+ (s) + X^- (s) \rightarrow \text{M}^+X^- (s) \quad \text{eqn. 3.9}
\]

\[
\text{ML}^+ (s) + X^- (s) \rightarrow \text{MLX} (s) \quad \text{eqn. 3.10}
\]

which make it difficult to evaluate the stability constant of the complexation process (eqn. 3.11)

\[
\text{M}^+ (s) + \text{L} (s) \rightarrow \text{M}^+\text{L} (s) \quad \text{eqn. 3.11}
\]

It is clear from Table 3.9 that there is a solubility enhancement in moving from L-1 to L-2. However, the introduction of tertiary amino groups (although these structures are not strictly comparable) leads to a ligand with moderate solubility in protic, dipolar aprotic and inert solvents. The use of this ligand offers a series of advantages from the solubility viewpoint, since not only its solution behaviour can be studied but it can be used as an extracting agent for the removal of cations from the aqueous phase, as its solubility in solvents which are water immiscible is relatively high. Solubility data are now used to calculate the solution Gibbs energies (eqn. 3.4) and the data are reported in Table 3.10. For the reasons stated above, the differences in the solvation of the ligand in the various solvents are best assessed from the standard transfer Gibbs energies, $\Delta G^\circ$ (eqn. 3.8).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\Delta G^\circ / \text{kJ mol}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>+25.8</td>
</tr>
<tr>
<td>Methanol</td>
<td>+25.8</td>
</tr>
<tr>
<td>Ethanol</td>
<td>+24.1</td>
</tr>
<tr>
<td>Butan-1-ol</td>
<td>+22.4</td>
</tr>
<tr>
<td>N, N-dimethylformamide</td>
<td>+15.4</td>
</tr>
<tr>
<td>Propylene carbonate</td>
<td>-</td>
</tr>
<tr>
<td>Benzonitrile</td>
<td>+12.8</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>+14.9</td>
</tr>
<tr>
<td>Ethylacetate</td>
<td>+10.5</td>
</tr>
<tr>
<td>Hexane</td>
<td>+12.2</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>+3.6</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>+3.7</td>
</tr>
<tr>
<td>Chloroform</td>
<td>-</td>
</tr>
</tbody>
</table>

Thus, $\Delta G^\circ$ values for these ligands are calculated taking acetonitrile as the reference solvent. Details are given in Table 3.11.

The $\Delta G^\circ$ values reported in this table reflect that these ligands undergo selective solvation in the various solvents since the transfer from acetonitrile to other solvents shifts the equilibrium position to favour the solvent in which the ligand is better solvated. For L-1, the observed $\Delta G^\circ$ values reflect the following sequence in terms of solvation,

$$\text{DCM} \approx \text{THF} > \text{EtAc} > \text{Hex} > \text{PhCN} > \text{PhNO}_2 > \text{DMF} > \text{BuOH} > \text{EtOH} > \text{MeOH} = \text{MeCN}$$

This sequence is altered for L-2 where $\Delta G^\circ$ values are as follows,

$$\text{DCM} > \text{EtAc} > \text{PhCN} > \text{THF} > \text{Hex} > \text{PhNO}_2 > \text{DMF} > \text{MeCN} > \text{EtOH} > \text{MeCN} > \text{BuOH}$$

For L-4, $\Delta G^\circ$ values for the transfer to only a few solvents are available. Thus, the order followed is,

$$\text{BuOH} > \text{EtOH} > \text{DMF} > \text{MeCN}$$

It is interesting to note that changes of up to 22 kJ mol$^{-1}$ are observed in the transfer to L-2 from acetonitrile. This clearly shows the various degrees of solvation that the ligand undergoes in the various solvents. The favourable transfer Gibbs energies (negative values) are indicative that these ligands are better solvated in the receiving solvent than in the reference solvent. Consequently, the stabilities of the complexes formed with metal cations may be altered. Undoubtedly the introduction of amino functional groups in the structure of these compounds favours considerably the transfer from acetonitrile to the alcohols probably due to the ability of the latter to enter hydrogen bond formation. It is interesting to compare these data with those of the
tetra amino derivative. Solubility data for this ligand, solution Gibbs energies and derived $\Delta_G^\circ$ values are reported in Table 3.11.
### Table 3.11


<table>
<thead>
<tr>
<th>Solvent</th>
<th>L-1 ΔG° (MeCN→s) / kJ mol⁻¹</th>
<th>L-2 ΔG° (MeCN→s) / kJ mol⁻¹</th>
<th>L-4 ΔG° (MeCN→s) / kJ mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Methanol</td>
<td>0</td>
<td>1.5</td>
<td>-3.2</td>
</tr>
<tr>
<td>Ethanol</td>
<td>-1.7</td>
<td>0.9</td>
<td>-4.6</td>
</tr>
<tr>
<td>Butan-1-ol</td>
<td>-3.4</td>
<td>2.1</td>
<td>-9.2</td>
</tr>
<tr>
<td>N, N-dimethylformamide</td>
<td>-10.4</td>
<td>-0.4</td>
<td>-4.0</td>
</tr>
<tr>
<td>Benzonitrile</td>
<td>-13.0</td>
<td>-4.8</td>
<td>-</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>-10.9</td>
<td>-2.5</td>
<td>-</td>
</tr>
<tr>
<td>Ethylacetate</td>
<td>-15.3</td>
<td>-6.2</td>
<td>-</td>
</tr>
<tr>
<td>Hexane</td>
<td>-13.6</td>
<td>-3.7</td>
<td>-</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>-22.2</td>
<td>-8.5</td>
<td>-</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>-22.1</td>
<td>-4.3</td>
<td>-</td>
</tr>
</tbody>
</table>

![Diagram of Derivatives]

L-1: CH₂-CH₂-S-CH₂-CH₂-OH
L-2: CH₂-CH₂-N(CH₃)₂
L-4: CH₂-CH₂-S-CH₂-CH₂-OH

Chapter Three Results and Discussion
<table>
<thead>
<tr>
<th>Substance</th>
<th>Solubility / mol dm(^{-3})</th>
<th>(\Delta G^\circ / \text{kJ.mol}^{-1})</th>
<th>(\Delta G^\circ / \text{kJ.mol}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>288.15 K (MeOH→s)</td>
<td>298.15 K (MeCN→s)</td>
</tr>
<tr>
<td>Benzonitrile</td>
<td>8.45 ± 0.62 \times 10^2</td>
<td>+5.9</td>
<td>-0.2</td>
</tr>
<tr>
<td>Butanol</td>
<td>1.78 ± 0.11 \times 10^{-1}</td>
<td>+4.1</td>
<td>-2.0</td>
</tr>
<tr>
<td>Ethanol</td>
<td>7.38 ± 0.19 \times 10^2</td>
<td>+6.2</td>
<td>+0.1</td>
</tr>
<tr>
<td>Methanol</td>
<td>7.77 ± 1.07 \times 10^2</td>
<td>+6.1</td>
<td>-</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>4.79 ± 0.90 \times 10^2</td>
<td>+7.3</td>
<td>+1.2</td>
</tr>
<tr>
<td>Toluene</td>
<td>solvate formation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benzonitrile</td>
<td>1.81 ± 0.18 \times 10^{1}</td>
<td>+4.2</td>
<td>-10.0</td>
</tr>
<tr>
<td>Butanol</td>
<td>2.25 ± 0.20 \times 10^{1}</td>
<td>+3.7</td>
<td>-10.5</td>
</tr>
<tr>
<td>Ethanol</td>
<td>8.94 ± 0.35 \times 10^2</td>
<td>+6.0</td>
<td>-8.2</td>
</tr>
<tr>
<td>Methanol</td>
<td>9.85 ± 0.57 \times 10^2</td>
<td>+5.8</td>
<td>-8.4</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>9.36 ± 0.60 \times 10^2</td>
<td>+5.9</td>
<td>-8.3</td>
</tr>
<tr>
<td>Toluene</td>
<td>solvate formation</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.12 Solubility, derived Gibbs energy of solution of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 26, 27, 28-tetrakis-[2-diethylamine (ethoxy)]calix[4]arene in various solvents at three temperatures determined by gravimetric analysis. Transfer Gibbs energies from methanol (288.15 K and 315.15 K) and from acetonitrile (298.15 K) to other solvents.
Table 3.11 displays calculated Gibbs energy of transfer results at 298.15 K, using the Gibbs energy of solution data for L-4 (Table 3.10) in acetonitrile at the same temperature as the reference solvent. These transfer results compare the degree of solvation in various solvents. The high solubility of the tetraamine derivative gives rise to more favourable transfer Gibbs energies; this ligand clearly interacts to a greater extent with the solvents in Table 3.12 than ligands L-1,2,4 in the same solvents (Table 3.11). The further introduction of amino functionalities from the di to the tetra derivative increases the prospect for further solvent hydrogen bond formation with regard to the alcohols.

The reduction in Gibbs energy of solution data as temperature increases (less positive) for the tetraamine (Table 3.12), indicates increased solubility and therefore, ligand-solvent interactions.

In order to investigate the acid-base properties of these ligands, UV spectrophotometric and potentiometric studies were carried out in methanol at 298.15 K. The former technique was used to determine the stoichiometry of the process involving L and the proton in methanol while the latter method was used for the determination of the pKₐ values of these ligands in the same solvent. The results obtained from UV measurements are now discussed.
3.3. UV-SPECTROPHOTOMETRIC MEASUREMENTS:
INTERACTION OF 5, 11, 17, 23-TETRAKIS-(1, 1-
DIMETHYLETHYL)-25, 27-BIS[2-(METHYLTHIO)
ETHOXY]-26, 28-BIS[2-(DIETHYLAMINE)ETHOXY]
CALIX[4]ARENE (L-4) WITH PROTONS IN METHANOL
AT 298 K

Information about the composition of the complex formed as a result of the interaction
between 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-
26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4) and the proton was obtained
from UV spectrophotometry. Thus, Fig. 3.28 shows a representative
spectrophotometric titration curve for the L-4 (Calix[4]) and the proton in methanol at
298.15 K. Readings were taken at the wavelengths of maximum absorption (272.1 and
281.3 nm).

As the titration experiment proceeded, the absorption intensity decreased. This could
be attributed to possible interactions between the protonated nitrogen atom and the
phenol oxygen. The titration experiment produces a shallow curve with no abrupt
changes (Fig. 3.28). By extrapolation of the slopes at low and high mole ratios, the
stoichiometry of the fully protonated ligand was found to give a 2:1 complex described
by the following equation:-

\[ N_2S_2Calix[4](MeOH) + 2H^+(MeOH) \rightarrow H_2N_2S_2Calix[4]^{2+}(MeOH) \quad (3.12) \]
Fig. 3.28 UV spectrophotometric titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4) with perchloric acid in methanol at 298 K

Fig. 3.29 Plot of absorbance against mole ratio, showing the stoichiometric interaction of perchloric acid with 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4) in methanol at 298 K
Potentiometric techniques were used to determine the dissociation constants for five di-substituted amine calix[4]arene derivatives (L-3-4,6-8). The electrochemical cell (eqn. 3.13) was constructed and initial calibration experiments were characterised using the Nernst equation (eqn. 3.14) from which the standard potential (\(E^0\)) and Nernst constant (\(RT/F\), where \(R\) is the gas constant, \(T\) the temperature and \(F\) the Faraday constant) were calculated.

\[
glass\ electrode \ | \ S\ || \ KCl\ (MeOH) \ | AgCl \ | Ag
\]

The electrochemical cell consisted of a combined glass electrode containing the mercury, mercury chloride reference electrode (calomel electrode), placed in the thermostatically controlled sample solution(s). The original saturated aqueous potassium chloride solution in the external reference electrode was replaced by a potassium chloride methanolic solution (~1 mol.dm\(^{-3}\)).

Calibration and protonation experiments were conducted according to the method documented in the experimental procedures (see chapter 2.8.).

**3.4.1. Electrode calibration**

Section 2.8.1. describes how the standard perchloric acid solution was prepared and standardised. A typical plot of \(E(v)\) against \(-\log[H^+]\) led to a linear relationship which can be described by the Nernst equation (3.14).

\[
E = E^0 + (RT/nF)\ln(a_{H^+})
\]
The slope \((59.59 \pm 0.64 \text{ mV})\) indicates that a Nernstian behaviour is obeyed. Therefore, the relationship between cell potential readings and the activity of the protons \(a_{\text{H}^+}\) could now be described by the following equation:

\[
E = 574.3 + 59.59 \log a_{\text{H}^+}
\]  

(3.15)

3.4.2. Potentiometric titrations for the determination of the dissociation constants of thioamine calix[4]arene derivatives (L-3-8)

Fig. 3.30 shows the potentiometric titration curve for a representative ligand (L-6) where two inflection points are observed. The first one corresponds to the neutralisation of the excess of acid used to protonate the ligand, while the second indicates the formation of a fully deprotonated ligand.

Experimental data demonstrates that the proton complex stoichiometry is 2:1 (proton : ligand ratio). This can be clearly seen by observing the ratio difference between the peaks of the derivative curve (Fig. 3.30). The two individual (eqn. 3.16 and 3.17) and the overall equilibria (eqn. 3.18) involved during the titration are described:

\[
(H_2N_2S_Calix[4])^{2+} \leftrightarrow \text{pK}_a \rightarrow HN_2S_Calix[4])^+ + H^+
\]  

(3.16)

\[
(HN_2S_Calix[4])^+ \leftrightarrow \text{pK}_a \rightarrow N_2S_Calix[4]) + H^+
\]  

(3.17)

Overall equilibria

\[
(H_2N_2S_Calix[4])^{2+} \leftrightarrow \text{pK}_a \rightarrow N_2S_Calix[4]) + 2H^+
\]  

(3.18)

After the excess acid is neutralised, only one inflection point is observed (Fig. 3.30), suggesting that the nitrogen atoms (two) are likely to behave independently from each other in their interaction with the proton. Danil de N amor et al.\(^{154}\) has stated that it is reasonable to assume that the most stable conformation (lowest energy) for lower rim aminocalix[4]arene derivatives is antiperiplanar, where the bulky substituents move to extreme positions with respect to each other. The X-ray crystal structure of L-3 (3.1.4.2.) clearly shows that the nitrogen donor atoms of the more bulky dimethylamine
Fig. 3.30 Potentiometric titration curve of a fully protonated L-6 and TBAOH in methanol at 298.15 K

substituents are approximately 3 Å further apart than those involving the methylthioethyl substituents.

Individual dissociation constants pKₐ₁ and pKₐ₂ for these calix[4]arene thioamino derivatives (L-3-8) in methanol (Table 3.13) and ethanol (Table 3.14) at 298.15 K were calculated using the MINIQUAD computer programme.

Dissociation constants, Kₐ, expressed in terms of pKₐ values (pKₐ = -log Kₐ), in methanol at 298.15 K are listed in Table 3.13. These are compared with corresponding data for lower rim tetraamine calix[4]arene derivatives in methanol at 298.15 K (values between parentheses).
<table>
<thead>
<tr>
<th>Derivative</th>
<th>pK&lt;sub&gt;a1&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>pK&lt;sub&gt;a2&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ(pK&lt;sub&gt;a2&lt;/sub&gt;−pK&lt;sub&gt;a1&lt;/sub&gt;)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-3</td>
<td>7.95 (8.44)</td>
<td>9.06 (9.40)</td>
<td>1.11 (0.96)</td>
</tr>
<tr>
<td>L-4</td>
<td>8.39 (8.96)</td>
<td>9.25 (9.48)</td>
<td>0.86 (0.52)</td>
</tr>
<tr>
<td>L-5</td>
<td>8.88 (9.37)</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>L-6</td>
<td>6.42 (6.93)</td>
<td>7.11 (7.49)</td>
<td>0.69 (0.56)</td>
</tr>
<tr>
<td>L-7</td>
<td>8.56 (9.01)</td>
<td>9.20 (9.35)</td>
<td>0.64 (0.34)</td>
</tr>
<tr>
<td>L-8</td>
<td>8.59 (9.11)</td>
<td>9.60 (9.68)</td>
<td>1.01 (0.57)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated error in pK<sub>a</sub> values is <i>ca.</i> 0.02 log units (L-3-8).

<sup>b</sup> Solubility of derivative was found too low to conduct the experiment.

<sup>c</sup> Parentheses indicate dissociation constants for the equivalent tetraamine calix[4]arene derivatives<sup>154</sup>, maximum difference found between the values of the third and fourth dissociation constants Δ(pK<sub>a3</sub>_pK<sub>a4</sub>). Estimated error in pK<sub>a</sub> values is <i>ca.</i> 0.1 log unit.

Table 3.13 Dissociation constants (pK<sub>a</sub>) of fully protonated thioamino and tetraamine calix[4]arene derivatives in methanol at 298.15 K
Table 3.13 displays the individual dissociation constants (eqn. 3.13-14) contributing to the overall process (eqn. 3.15) for ligands L-3-8 in methanol at 298.15 K. The largest pKₐ values correspond to the weakest acids and strongest conjugate bases. For all the derivatives (L-3-8), the neutral ligand is the strongest base, while the di-protonated ligand shows the strongest acid behaviour in this solvent. The neutral macrocycles can be ordered in terms of strongest base, in the following the sequence (the most basic derivative first):-

\[ L-8 > L-7 \equiv L-4 > L-3 > L-6 \]

The electron withdrawing properties of the oxygen atom in the 4-position of L-6 creates the most acidic nitrogen, reflected in the pKₐ values which are \( \approx \) 2.5 log units lower than L-8. The greater electron donating characteristic of the ethyl moiety also explains the derivative’s position in the series before the methyl derivative (L-3).

The significant difference between the two pKₐ values expressed in Table 3.13 for the di-substituted amine calix[4]arene derivatives (L-3-8) suggests that the nitrogens behave independently and adopt an antiperiplanar conformation, where the bulky substituents point outwards with respect to the macrocycle cone.

Table 3.13 displays the results for the tetraamino derivatives (values between brackets). These pKₐ values follow the same trends as those of the disubstituted amino derivatives (L-3-8) however, the protonated forms of the tetraamine are weaker acids, as their pKₐ values are higher. When the \( \Delta(pK_{a2} - pK_{a1}) \) values for L-3-8 are compared with the analogous results from the tetraamine derivatives \( (\Delta(pK_{a4} - pK_{a3})) \), the differences between the pKₐ values are found to be smaller for the tetraamine derivatives. Therefore, the nitrogen atoms of the diamine derivatives behave more independently compared to the tetraamine derivatives.

pKₐ's of the di-substituted amine derivatives (Table 3.13) determined in ethanol follow the same trend as in methanol, but in all cases the neutral and di-protonated species are seen to have a less basic and acidic character respectively.
<table>
<thead>
<tr>
<th>Derivative</th>
<th>pK$_{a1}$</th>
<th>pK$_{a2}$</th>
<th>Δ(pK$<em>{a2}$-pK$</em>{a1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-3</td>
<td>7.61</td>
<td>8.54</td>
<td>0.93</td>
</tr>
<tr>
<td>L-4</td>
<td>8.06</td>
<td>8.86</td>
<td>0.80</td>
</tr>
<tr>
<td>L-5</td>
<td>b</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>L-6</td>
<td>5.91</td>
<td>6.51</td>
<td>0.60</td>
</tr>
<tr>
<td>L-7</td>
<td>8.17</td>
<td>8.68</td>
<td>0.51</td>
</tr>
<tr>
<td>L-8</td>
<td>8.41</td>
<td>8.93</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Estimated error in pK$_a$ values is ca. 0.02 log unit
b Solubility of ligand was found too low to conduct the experiment

Table 3.14 Dissociation constants (pK$_a$) of fully protonated thioamine calix[4]arene derivatives in ethanol at 298.15 K
The dissociation process, $pK_{a2}$, describes the first protonation constant, $log K_{p1}$. Table 3.15 indicates the proton affinity for each ligand with the overall protonation constant, $K_{ov} (K_{ov} = K_{p1} \times K_{p2})$. These results clearly indicate that these derivatives have a high proton affinity; $L-8$ has the highest $log Kp$ value.
### Table 3.15 Protonation constants of thioamine and tetraamine calix[4]arene derivatives in methanol at 298.15 K

<table>
<thead>
<tr>
<th>Ligand</th>
<th>( K_{p1} )</th>
<th>( K_{p2} )</th>
<th>( K_{ov} )</th>
<th>( K_{ov} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-3</td>
<td>1.1 x 10^9</td>
<td>8.9 x 10^7</td>
<td>1.0 x 10^17</td>
<td>5.4 x 10^22</td>
</tr>
<tr>
<td>L-4</td>
<td>1.8 x 10^9</td>
<td>2.5 x 10^8</td>
<td>4.4 x 10^17</td>
<td>1.6 x 10^35</td>
</tr>
<tr>
<td>L-5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.9 x 10^26</td>
</tr>
<tr>
<td>L-6</td>
<td>1.3 x 10^8</td>
<td>2.6 x 10^6</td>
<td>4.4 x 10^13</td>
<td>2.1 x 10^27</td>
</tr>
<tr>
<td>L-7</td>
<td>1.6 x 10^9</td>
<td>3.6 x 10^8</td>
<td>5.8 x 10^17</td>
<td>2.0 x 10^36</td>
</tr>
<tr>
<td>L-8</td>
<td>4.0 x 10^9</td>
<td>3.9 x 10^8</td>
<td>1.54 x 10^18</td>
<td>2.1 x 10^27</td>
</tr>
</tbody>
</table>
In ethanol (Table 3.16) all the ligands have a lower proton affinity as reflected in the data for this solvent relative to methanol. Table 3.9 lists the solubility data for L-4 in various solvents at 298.15 K. This derivative is more soluble in ethanol than in methanol. Therefore the ligand is better solvated in the former relative to the latter solvent.

Finally, species distribution plots for each of the thioamine calix[4]arene derivatives are shown in Fig. 3.31. This information is of great value since for each ligand the predominant species in solution at a given pH can be quantitatively evaluated and therefore, the optimum conditions for cation complexation without the competitive effect of the proton can be selected.
Chapter Three Results and Discussion

Table 3.16 Protonation constants of thioamine calix[4]arene derivatives (L-3-8) in ethanol at 298.15 K

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$K_{p1}$</th>
<th>$K_{p2}$</th>
<th>$K_{ov}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-3</td>
<td>$3.5 \times 10^8$</td>
<td>$4.1 \times 10^7$</td>
<td>$1.4 \times 10^{16}$</td>
</tr>
<tr>
<td>L-4</td>
<td>$7.2 \times 10^8$</td>
<td>$1.1 \times 10^8$</td>
<td>$8.3 \times 10^{16}$</td>
</tr>
<tr>
<td>L-5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L-6</td>
<td>$3.2 \times 10^6$</td>
<td>$8.1 \times 10^5$</td>
<td>$2.6 \times 10^{12}$</td>
</tr>
<tr>
<td>L-7</td>
<td>$4.8 \times 10^8$</td>
<td>$1.5 \times 10^6$</td>
<td>$7.1 \times 10^{16}$</td>
</tr>
<tr>
<td>L-8</td>
<td>$8.5 \times 10^8$</td>
<td>$2.6 \times 10^9$</td>
<td>$2.2 \times 10^{17}$</td>
</tr>
</tbody>
</table>
Fig. 3.31 Species distribution (%) for the protonation process of ligands L-3, 4, 6, 7, 8 using perchloric acid in methanol at 298.15 K
3.5. CONDUCTANCE MEASUREMENTS

Conductance studies are used to investigate the mobility of charged species (electrolytes) between the electrodes. The shape of the conductance curve depends upon the reaction taking place in solution.

The theory used to derive the data from conductivity measurements is based on Ohm's law, which states that the current, $I$ (amperes), flowing through a conductor of resistance, $R$ (ohms), is related to the potential difference, $V$ (volts), by:

$$V = I \cdot R \quad (3.19)$$

where,

$$R = \rho \cdot \frac{L}{A} \quad (3.20)$$

$\rho$, denotes resistivity (ohm.cm), $L$ (cm) and $A$ (cm$^2$) are the length and the cross-sectional area of the conductor, respectively.

The conductivity or specific conductance, $\kappa$ (ohm$^{-1}$.cm$^{-1}$), is the inverse of the resistivity.

$$R = \frac{1}{\kappa} \cdot \frac{L}{A} \quad (3.21)$$

therefore,

$$\kappa = \frac{1}{R} \cdot \frac{L}{A} \quad (3.22)$$

Once the cell constant is determined, the specific conductance for an unknown solution can be evaluated from a measured value of the resistance, $R$. The reciprocal of the ohm is referred to as mho, but the recommended notation is now the siemen, S.
The molar conductivity, $\Lambda_m$, is defined by:

$$\Lambda_m = \frac{1000A}{c}$$  \hspace{1cm} (3.23)

In eqn. 3.23, $c$ is the molar concentration of the solution (mol.dm$^{-3}$) and the units of $\Lambda_m$ are S.cm$^2$.mol$^{-1}$.

3.5.1. **Determination of the cell constant at 298.15 K**

The method used to calculate the cell constant is fully explained in the Experimental Section (2.9.3.). A computer program (KCLCON.BAS$^{193}$) was used to calculate the conductance after each addition of potassium chloride. Data required by the program includes, the initial conductance of the deionised water, the concentration of the potassium chloride solution (mol.dm$^{-3}$), the initial weight of deionised water in the cell, the weight of each injection of the salt solution, as well as the initial and step-wise titration conductance data. Table 3.17 shows the calculated specific conductance data for potassium chloride in water, at various concentrations, as well as the cell constant ($\theta$) values at these concentrations at 298.15 K.
<table>
<thead>
<tr>
<th>Weight of solution g</th>
<th>Conductance (Ω⁻¹)</th>
<th>[KCl] mol.dm⁻³</th>
<th>( \theta ) cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.533</td>
<td>30.68 \times 10⁻³</td>
<td>3.031 \times 10⁻²</td>
<td>0.138</td>
</tr>
<tr>
<td>1.476</td>
<td>33.78 \times 10⁻³</td>
<td>3.361 \times 10⁻²</td>
<td>0.136</td>
</tr>
<tr>
<td>1.355</td>
<td>36.40 \times 10⁻³</td>
<td>3.612 \times 10⁻²</td>
<td>0.136</td>
</tr>
<tr>
<td>1.495</td>
<td>39.08 \times 10⁻³</td>
<td>3.869 \times 10⁻²</td>
<td>0.135</td>
</tr>
<tr>
<td>1.193</td>
<td>41.09 \times 10⁻³</td>
<td>4.061 \times 10⁻²</td>
<td>0.135</td>
</tr>
<tr>
<td>1.210</td>
<td>43.00 \times 10⁻³</td>
<td>4.243 \times 10⁻²</td>
<td>0.134</td>
</tr>
<tr>
<td>1.411</td>
<td>45.02 \times 10⁻³</td>
<td>4.444 \times 10⁻²</td>
<td>0.134</td>
</tr>
</tbody>
</table>

Initial conductance of freshly boiled deionised water 218.85 \times 10⁻⁶ \, Ω⁻¹.

Table 3.17 Conductance data for aqueous solutions of potassium chloride at 298.15 K used for the determination of the cell constant

The average value for the cell constant was found to be 0.135 ± 0.001 cm⁻¹

The conductimetric curves obtained for the titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy] calix[4]arene (L-4) with metal cations (Cd²⁺, Pb²⁺, Ag⁺, Hg²⁺) in methanol at 298.15 K are now discussed.

Molar conductance data were calculated with the aid of a computer program (CONCW1\textsuperscript{192}). This program requires the input of the following experimental details: cell constant, weight, concentrations of the metal and ligand solutions. The complexation experiments were carried out in methanol, the following properties\textsuperscript{196} of this solvent were also entered into the program:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>0.7914 g.mL(^{-1}) (at 298.15 K)</td>
</tr>
<tr>
<td>Dielectric constant</td>
<td>32.63 (at 298.15 K)</td>
</tr>
<tr>
<td>Viscosity</td>
<td>0.547 cP (at 298.15 K)</td>
</tr>
</tbody>
</table>

The initial conductivity of the metal cation solution was measured; further measurements were made after each addition of the ligand solution (L-4).
3.5.2.1. Conductimetric titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-
25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]
calix[4]arene (L-4) with cadmium nitrate in methanol at 298.15 K

Table 3.18 details the conductimetric data for the interaction of L-4 with cadmium cations.

<table>
<thead>
<tr>
<th>[L-4] (mol.dm(^{-3}))</th>
<th>[Cd(^{2+})] (mol.dm(^{-3}))</th>
<th>[L-4 / Cd(^{2+})]</th>
<th>(A_m) S. cm(^2).mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.68 \times 10^{-4}</td>
<td>3.74 \times 10^{-4}</td>
<td>0.183</td>
<td>200.70</td>
</tr>
<tr>
<td>1.74 \times 10^{-4}</td>
<td>3.67 \times 10^{-4}</td>
<td>0.475</td>
<td>202.05</td>
</tr>
<tr>
<td>2.81 \times 10^{-4}</td>
<td>3.59 \times 10^{-4}</td>
<td>0.781</td>
<td>202.08</td>
</tr>
<tr>
<td>3.47 \times 10^{-4}</td>
<td>3.55 \times 10^{-4}</td>
<td>0.979</td>
<td>204.18</td>
</tr>
<tr>
<td>4.39 \times 10^{-4}</td>
<td>3.48 \times 10^{-4}</td>
<td>1.260</td>
<td>205.38</td>
</tr>
<tr>
<td>5.33 \times 10^{-4}</td>
<td>3.42 \times 10^{-4}</td>
<td>1.559</td>
<td>206.42</td>
</tr>
<tr>
<td>6.19 \times 10^{-4}</td>
<td>3.36 \times 10^{-4}</td>
<td>1.844</td>
<td>208.97</td>
</tr>
<tr>
<td>7.08 \times 10^{-4}</td>
<td>3.29 \times 10^{-4}</td>
<td>2.150</td>
<td>208.99</td>
</tr>
<tr>
<td>7.90 \times 10^{-4}</td>
<td>3.24 \times 10^{-4}</td>
<td>2.442</td>
<td>210.87</td>
</tr>
<tr>
<td>8.82 \times 10^{-4}</td>
<td>3.17 \times 10^{-4}</td>
<td>2.781</td>
<td>211.69</td>
</tr>
<tr>
<td>9.64 \times 10^{-4}</td>
<td>3.11 \times 10^{-4}</td>
<td>3.096</td>
<td>212.72</td>
</tr>
<tr>
<td>10.24 \times 10^{-4}</td>
<td>3.07 \times 10^{-4}</td>
<td>3.334</td>
<td>213.38</td>
</tr>
<tr>
<td>11.19 \times 10^{-4}</td>
<td>3.00 \times 10^{-4}</td>
<td>3.725</td>
<td>213.46</td>
</tr>
<tr>
<td>11.96 \times 10^{-4}</td>
<td>2.95 \times 10^{-4}</td>
<td>4.053</td>
<td>213.30</td>
</tr>
</tbody>
</table>

Table 3.18 Conductimetric data for the titration of 5, 11, 17, 23-tetrakis-(1, 1-
Fig. 3.32 shows that the molar conductance increases within a very narrow range as the cadmium cations are titrated into the conductivity vessel. No significant breaks in the complexation titration curve are seen, indicating the formation of a low stability constant cadmium complex. The molar conductance increases, possibly due to the equilibrium shifting towards the complex formation as more ligand is added into the reaction vessel. Increasing conductance readings may indicate that the complexes are less well solvated than the free salt (their mobility and therefore, their conductance increases).

Fig. 3.32  Conductimetric titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4) and cadmium nitrate in methanol at 298.15 K

Table 3.19 details the conductimetric data for the interaction of L-4 with lead cations.

<table>
<thead>
<tr>
<th>[L-4] (mol.dm⁻³)</th>
<th>[Pb²⁺] (mol.dm⁻³)</th>
<th>[L-4 / Pb²⁺]</th>
<th>A_m S. cm².mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.45 x 10⁻⁴</td>
<td>6.59 x 10⁻⁴</td>
<td>0.372</td>
<td>137.39</td>
</tr>
<tr>
<td>2.92 x 10⁻⁴</td>
<td>6.52 x 10⁻⁴</td>
<td>0.448</td>
<td>140.74</td>
</tr>
<tr>
<td>3.43 x 10⁻⁴</td>
<td>6.45 x 10⁻⁴</td>
<td>0.532</td>
<td>144.12</td>
</tr>
<tr>
<td>3.77 x 10⁻⁴</td>
<td>6.41 x 10⁻⁴</td>
<td>0.588</td>
<td>146.12</td>
</tr>
<tr>
<td>4.32 x 10⁻⁴</td>
<td>6.33 x 10⁻⁴</td>
<td>0.683</td>
<td>149.73</td>
</tr>
<tr>
<td>4.75 x 10⁻⁴</td>
<td>6.27 x 10⁻⁴</td>
<td>0.757</td>
<td>152.08</td>
</tr>
<tr>
<td>5.47 x 10⁻⁴</td>
<td>6.17 x 10⁻⁴</td>
<td>0.886</td>
<td>155.47</td>
</tr>
<tr>
<td>5.84 x 10⁻⁴</td>
<td>6.12 x 10⁻⁴</td>
<td>0.953</td>
<td>157.40</td>
</tr>
<tr>
<td>6.31 x 10⁻⁴</td>
<td>6.01 x 10⁻⁴</td>
<td>1.041</td>
<td>159.40</td>
</tr>
<tr>
<td>6.73 x 10⁻⁴</td>
<td>6.00 x 10⁻⁴</td>
<td>1.122</td>
<td>161.27</td>
</tr>
<tr>
<td>7.13 x 10⁻⁴</td>
<td>5.95 x 10⁻⁴</td>
<td>1.198</td>
<td>163.08</td>
</tr>
<tr>
<td>7.56 x 10⁻⁴</td>
<td>5.89 x 10⁻⁴</td>
<td>1.284</td>
<td>164.89</td>
</tr>
<tr>
<td>7.88 x 10⁻⁴</td>
<td>5.85 x 10⁻⁴</td>
<td>1.347</td>
<td>165.92</td>
</tr>
<tr>
<td>8.24 x 10⁻⁴</td>
<td>5.80 x 10⁻⁴</td>
<td>1.423</td>
<td>167.20</td>
</tr>
<tr>
<td>8.77 x 10⁻⁴</td>
<td>5.72 x 10⁻⁴</td>
<td>1.533</td>
<td>168.79</td>
</tr>
<tr>
<td>9.06 x 10⁻⁴</td>
<td>5.68 x 10⁻⁴</td>
<td>1.595</td>
<td>169.61</td>
</tr>
<tr>
<td>9.34 x 10⁻⁴</td>
<td>5.65 x 10⁻⁴</td>
<td>1.655</td>
<td>170.40</td>
</tr>
<tr>
<td>9.83 x 10⁻⁴</td>
<td>5.58 x 10⁻⁴</td>
<td>1.763</td>
<td>171.72</td>
</tr>
<tr>
<td>10.16 x 10⁻⁴</td>
<td>5.53 x 10⁻⁴</td>
<td>1.837</td>
<td>172.41</td>
</tr>
<tr>
<td>10.61 x 10⁻⁴</td>
<td>5.47 x 10⁻⁴</td>
<td>1.939</td>
<td>173.96</td>
</tr>
<tr>
<td>11.08 x 10⁻⁴</td>
<td>5.41 x 10⁻⁴</td>
<td>2.050</td>
<td>174.93</td>
</tr>
<tr>
<td>11.83 x 10⁻⁴</td>
<td>5.30 x 10⁻⁴</td>
<td>2.232</td>
<td>176.64</td>
</tr>
</tbody>
</table>

Table 3.19 Conductimetric data for the titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy] calix[4]arene (L-4) with lead nitrate in methanol at 298.15 K
The conductimetric titration curve (Fig. 3.33) for lead and L-4 in methanol at 298.15 K displays a more continuous variation of conductivities with concentration ratios and it is only by extrapolating the slopes at high and low ligand / metal cation ratios that the point of intersection which corresponds to a 1:1 complex stoichiometry can be determined (Fig. 3.33). This behaviour, typical of less stable complexes, is much more pronounced than that found for cadmium. For this system, it is difficult to establish the complex stoichiometry from the conductance measurements.

This rise in molar conductance during the experiment may be due to lower solvation of the complex compared to the free salt.

![Graph showing conductimetric titration curve](image)

**Fig. 3.33** Conductimetric titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene(L-4) and lead nitrate in methanol at 298.15 K
### Table 3.20


<table>
<thead>
<tr>
<th>[L-4] (mol.dm(^{-3}))</th>
<th>[Ag(^+)] (mol.dm(^{-3}))</th>
<th>[L-4 / Ag(^+)]</th>
<th>(\Lambda_m) S. cm(^2).mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.67 x 10(^{-4})</td>
<td>6.70 x 10(^{-4})</td>
<td>0.099</td>
<td>103.33</td>
</tr>
<tr>
<td>1.41 x 10(^{-4})</td>
<td>6.61 x 10(^{-4})</td>
<td>0.213</td>
<td>98.88</td>
</tr>
<tr>
<td>2.13 x 10(^{-4})</td>
<td>6.51 x 10(^{-4})</td>
<td>0.326</td>
<td>96.72</td>
</tr>
<tr>
<td>2.98 x 10(^{-4})</td>
<td>6.41 x 10(^{-4})</td>
<td>0.465</td>
<td>92.25</td>
</tr>
<tr>
<td>3.86 x 10(^{-4})</td>
<td>6.30 x 10(^{-4})</td>
<td>0.613</td>
<td>88.31</td>
</tr>
<tr>
<td>4.68 x 10(^{-4})</td>
<td>6.20 x 10(^{-4})</td>
<td>0.755</td>
<td>84.92</td>
</tr>
<tr>
<td>5.34 x 10(^{-4})</td>
<td>6.12 x 10(^{-4})</td>
<td>0.873</td>
<td>82.63</td>
</tr>
<tr>
<td>6.27 x 10(^{-4})</td>
<td>6.00 x 10(^{-4})</td>
<td>1.045</td>
<td>81.24</td>
</tr>
<tr>
<td>7.08 x 10(^{-4})</td>
<td>5.90 x 10(^{-4})</td>
<td>1.200</td>
<td>81.45</td>
</tr>
<tr>
<td>7.87 x 10(^{-4})</td>
<td>5.80 x 10(^{-4})</td>
<td>1.356</td>
<td>81.80</td>
</tr>
<tr>
<td>8.62 x 10(^{-4})</td>
<td>5.70 x 10(^{-4})</td>
<td>1.511</td>
<td>82.00</td>
</tr>
<tr>
<td>9.63 x 10(^{-4})</td>
<td>5.58 x 10(^{-4})</td>
<td>1.727</td>
<td>82.35</td>
</tr>
<tr>
<td>10.51 x 10(^{-4})</td>
<td>5.47 x 10(^{-4})</td>
<td>1.921</td>
<td>82.72</td>
</tr>
<tr>
<td>11.38 x 10(^{-4})</td>
<td>5.36 x 10(^{-4})</td>
<td>2.123</td>
<td>83.09</td>
</tr>
<tr>
<td>12.26 x 10(^{-4})</td>
<td>5.25 x 10(^{-4})</td>
<td>2.335</td>
<td>83.50</td>
</tr>
</tbody>
</table>
The interesting curve resulting from the conductimetric titration of silver(I) nitrate with L-4 in methanol shows a sharp break point when the ligand : metal ratio reaches unity; the slope of the titration point indicates the formation of a highly stable complex. In Fig. 3.34 the molar conductance decreases as the metal-ion complex is formed which may indicate that the mobility of the latter is lower than that for the free metal-ion salt.

![Molar conductance vs. [L-4]/[Ag+]](image-url)

**Fig. 3.34** Conductimetric titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethyamine)ethoxy]calix[4]arene (L-4) and silver nitrate in methanol at 298.15 K

Table 3.21 details the conductimetric data for the interaction of L-4 with mercury cations.

<table>
<thead>
<tr>
<th>[L-4] (mol dm⁻³)</th>
<th>[Hg²⁺] (mol dm⁻³)</th>
<th>[L-4 / Hg²⁺]</th>
<th>Aₑ⁹ S. cm² mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.62 x 10⁻⁴</td>
<td>6.04 x 10⁻⁴</td>
<td>0.102</td>
<td>105.74</td>
</tr>
<tr>
<td>1.56 x 10⁻⁴</td>
<td>5.93 x 10⁻⁴</td>
<td>0.263</td>
<td>104.18</td>
</tr>
<tr>
<td>2.59 x 10⁻⁴</td>
<td>5.81 x 10⁻⁴</td>
<td>0.447</td>
<td>102.93</td>
</tr>
<tr>
<td>3.32 x 10⁻⁴</td>
<td>5.72 x 10⁻⁴</td>
<td>0.580</td>
<td>115.12</td>
</tr>
<tr>
<td>4.15 x 10⁻⁴</td>
<td>5.62 x 10⁻⁴</td>
<td>0.738</td>
<td>129.58</td>
</tr>
<tr>
<td>4.98 x 10⁻⁴</td>
<td>5.52 x 10⁻⁴</td>
<td>0.901</td>
<td>141.47</td>
</tr>
<tr>
<td>5.80 x 10⁻⁴</td>
<td>5.43 x 10⁻⁴</td>
<td>1.069</td>
<td>150.27</td>
</tr>
<tr>
<td>6.88 x 10⁻⁴</td>
<td>5.30 x 10⁻⁴</td>
<td>1.291</td>
<td>157.82</td>
</tr>
<tr>
<td>8.15 x 10⁻⁴</td>
<td>5.15 x 10⁻⁴</td>
<td>1.582</td>
<td>162.81</td>
</tr>
<tr>
<td>8.71 x 10⁻⁴</td>
<td>5.08 x 10⁻⁴</td>
<td>1.714</td>
<td>164.16</td>
</tr>
<tr>
<td>9.31 x 10⁻⁴</td>
<td>5.01 x 10⁻⁴</td>
<td>1.857</td>
<td>166.65</td>
</tr>
<tr>
<td>10.12 x 10⁻⁴</td>
<td>4.92 x 10⁻⁴</td>
<td>2.059</td>
<td>168.28</td>
</tr>
<tr>
<td>11.18 x 10⁻⁴</td>
<td>4.79 x 10⁻⁴</td>
<td>2.334</td>
<td>168.50</td>
</tr>
<tr>
<td>12.00 x 10⁻⁴</td>
<td>4.70 x 10⁻⁴</td>
<td>2.554</td>
<td>168.10</td>
</tr>
</tbody>
</table>

Table 3.21 Conductimetric data for the titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4) with mercury nitrate with in methanol at 298.15 K
Chapter Three Results and Discussion

The conductimetric titration curve for Hg$^{2+}$ and L-4 is rather striking (Fig. 3.35). Thus, the addition of the ligand to a solution containing an excess of the metal-ion salt slightly lowers the conductivity of the solution and the minimum found at a ligand:metal cation ratio of 0.5 unambiguously demonstrates that L-4 hosts two mercury cations per unit of ligand (eqn. 3.24).

\[ 2\text{Hg}^{2+} (\text{MeOH}) + \text{L-4} (\text{MeOH}) \rightarrow \text{Hg}_2\text{L-4}^{4+} (\text{MeOH}) \] (3.24)

However, the rise in conductance observed at a ratio higher than 0.5 indicates that the presence of an excess of ligand induces a metal cation transfer from the [Hg$_2$L-4]$^{4+}$ complex to the ligand with the formation of a 1:1 complex stoichiometry as indicated in the change in conductance observed when the ligand:metal cation ratio reaches unity (eqn. 3.25).

\[ [\text{Hg}_2\text{L-4}]^{4+} (\text{MeOH}) + \text{L-4} (\text{MeOH}) \rightarrow 2[\text{HgL-4}]^{2+} (\text{MeOH}) \] (3.25)

Quite clearly, the stability constant corresponding to the process,

\[ [\text{Hg}_2\text{L-4}]^{2+} (\text{MeOH}) + \text{Hg}^{2+} (\text{MeOH}) \rightarrow [\text{Hg}_2\text{L-4}]^{4+} (\text{MeOH}) \] (3.26)

must be relatively low since the presence of an excess of ligand leads to the formation of the 1:1 complex (eqn.3.26).
Fig. 3.35  Conductimetric titration of 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-dimethylamino)ethoxy]calix[4]arene (L-4) and mercury nitrate in methanol at 298.15 K

Conductance results clearly demonstrate interactions between 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-dimethylamino)ethoxy]calix[4]arene (L-4) and metal cations (Hg^{2+}, Ag^+, Pb^{2+}, Cd^{2+}). In two cases where strong interactions are indicated by sharp breaks in conductance curves, information regarding complex composition can be studied. Silver cations form a 1:1 complex (Fig. 3.34) while mercury cations interact to form a 2:1 metal ion : ligand complex with L-4 (Fig. 3.35).

However, the conductance results do not give information concerning the site of complexation. L-4 has three different donor atoms and therefore three possible sites of complexation. ^1H NMR complexation experiments will indicate the site of cation interactions with L-4 and will also provide information regarding the complex composition. Conformational information resulting from metal cation interactions with L-4 can also be attained and are described in the following section.
3.6. \(^{1}\text{H} \text{NMR COMPLEXATION EXPERIMENTS}\)

The following \(^{1}\text{H} \text{NMR complexation discussion is centred on derivative 5, 11, 17, 23-}\)
\(\text{tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-(diethyl}\)
\(\text{amine)ethoxy]calix[4]arene (L-4). All measurements were performed in deuterated}\)
\(\text{methanol at 298 K. The complexation titration experiments were performed using the}\)
\(\text{method described in the experimental section of this thesis (see 2.10.). Titration}\)
\(\text{experiments were necessary to monitor several similar proton signals which could be}\)
\(\text{seen within} \approx 1 \text{ ppm of each other. The site of complexation, stoichiometry and}\)
\(\text{conformational information were attained.}\)

\(^{1}\text{H} \text{NMR measurements failed to detect complexation between derivative L-4 and}\)
\(\text{alkali and alkaline-earth metal cations. These results are expected since these metal}\)
\(\text{cations are generally complexed with oxygen or other hard donors atoms.}\)

\(^{1}\text{H} \text{NMR complexation studies involving Pb}^{2+}, \text{Cd}^{2+}, \text{Hg}^{2+} \text{and Ag}^{+} \text{cations were carried}\)
\(\text{out in deuterated methanol at 298 K. The}^{1}\text{H NMR titration experiments for four}\)
\(\text{metal cations and L-4 in CD}_{3}\text{OD at 298 K are discussed separately.}\)
3.6.1. \(^1\text{H} \) NMR titration of cadmium and lead nitrate with \(5, 11, 17, 23\)-tetrakis-(1, 1-dimethylethyl)-25, 27-bis[2-(methylthio)ethoxy]-26, 28-bis[2-diethyl amine)ethoxy]calix[4]arene (L-4) in deuterated methanol at 298 K

The interaction of \(\text{Pb}^{2+}\) and \(\text{Cd}^{2+}\) metal ions with derivative L-4 (Tables 3.22-23, see appendix 1 for \(\text{Pb}^{2+}\) titration \(^1\text{H} \) NMR stack plots) gives rise to precisely the same proton signal shift sequence from the free ligand as those observed in the protonation experiment (Table 3.26). Only the nitrogen donor atoms of the amine substituents are involved in the protonation process. Therefore, these pendant arms are the site of complexation with the metal cations as similar significant downfield shifts for the methyl and methylene groups are recorded in both experiments. There is no evidence that the methylethylthio substituents are involved in the complexation process. Observed shift changes are greater for lead than for cadmium, indicating a larger interaction of L-4 with the former cation (for comparison of selected signal shifts between lead and cadmium see Table 3.26).

A result of the complexation of L-4 with lead or cadmium, or during the protonation process, the two aromatic and \(\tau\)-butyl signals begin to coalesce as the titration experiments proceeded (Tables 3.22-23, 26). If the signals move to a similar resonance position, the protons must be occupying the same position within the structure (ring currents equally affecting all the aromatic protons to produce the same signal shift). Therefore, these proton shifts must indicate the formation of a symmetric cone structure. Further conformational changes are also observed in the bridging methylene protons as complexation with lead (and to a much lesser extent cadmium) takes place. The axial protons are shielded while the equatorial protons become less shielded due to ring current effects\(^{204}\). As a result, the shift difference (\(\Delta\delta\)) between the pair of doublets decreases from the free to the complexed ligand. The X-ray crystallographic results for L-3 (free ligand) (see 3.1.4.), clearly demonstrate that the aromatic rings form an asymmetrical cone conformation. In solution during a \(^1\text{H} \) NMR experiment this irregular conformation, caused by steric interactions of the lower rim substituents, is not averaged producing the two sets of aromatic and \(\tau\)-butyl proton signals.
However, the X-ray crystallographic results for L-1 (free ligand) (see 3.1.4.), also display an asymmetric cone conformation, but in solution considerable conformational freedom must be present (low degree of steric interaction between lower rim substituents), as only one proton signal is present for the aromatic and \( \tau \)-butyl groups.

Furthermore, the X-ray crystallographic results (see 3.1.5.) of derivative L-3, show the distance between the nitrogen donor atoms to be approximately 8\( \AA \), some 3\( \AA \) further apart than the sulphur donor atoms of the methylethylthio substituents. From the \(^1\)H NMR results (Table 3.26) it seems likely that for the ligand to complex with lead and cadmium metal ions, the amine containing pendant arms have to move closer, while the sulphur containing pendant arms move to a more extreme antiperiplanar position (Table 3.23, 26) and this is reflected in the shift changes observed in the aromatic and \( \tau \)-butyl protons. Consequently, the C-C bond between the two heteroatoms is able to rotate freely, the AA'BB' coupling system collapses and a 1:2:1 triplet forms as the multiplet signal collapses.
Table 3.22 $^1$H NMR titration of L-4 with cadmium nitrate in deuterated methanol at 298 K (proton chemical shifts of free ligand in the same solvent indicated)
### Table 3.23 $^1$H NMR titration of L-4 with lead nitrate in deuterated methanol at 298 K (proton chemical shifts of free ligand in the same solvent indicated)

<table>
<thead>
<tr>
<th>mole ratio</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free</td>
<td>7.11</td>
<td>1.29</td>
<td>4.37</td>
<td>7.11</td>
<td>1.29</td>
<td>4.37</td>
<td>7.11</td>
<td>1.29</td>
<td>4.37</td>
<td>7.11</td>
</tr>
<tr>
<td>Ligand</td>
<td>1.12</td>
<td>2.67</td>
<td>3.11</td>
<td>3.89</td>
<td>6.59</td>
<td>0.89</td>
<td>3.20</td>
<td>4.15</td>
<td>3.20</td>
<td>2.22</td>
</tr>
<tr>
<td>0.452</td>
<td>+0.07</td>
<td>+0.18</td>
<td>+0.14</td>
<td>+0.14</td>
<td>-0.11</td>
<td>-0.08</td>
<td>0</td>
<td>-0.02</td>
<td>-0.07</td>
<td>0</td>
</tr>
<tr>
<td>0.678</td>
<td>+0.10</td>
<td>+0.27</td>
<td>+0.23</td>
<td>+0.19</td>
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<td>-0.11</td>
<td>0</td>
<td>-0.03</td>
<td>-0.09</td>
<td>0</td>
</tr>
<tr>
<td>0.904</td>
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<td>+0.28</td>
<td>+0.23</td>
<td>-0.16</td>
<td>-0.13</td>
<td>0</td>
<td>-0.03</td>
<td>-0.11</td>
<td>0</td>
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<tr>
<td>1.120</td>
<td>+0.16</td>
<td>+0.42</td>
<td>+0.37</td>
<td>+0.28</td>
<td>-0.18</td>
<td>-0.14</td>
<td>0</td>
<td>-0.03</td>
<td>-0.12</td>
<td>0</td>
</tr>
<tr>
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<td>+0.46</td>
<td>+0.41</td>
<td>+0.31</td>
<td>-0.18</td>
<td>-0.15</td>
<td>0</td>
<td>-0.03</td>
<td>-0.12</td>
<td>0</td>
</tr>
<tr>
<td>1.582</td>
<td>+0.19</td>
<td>+0.51</td>
<td>+0.45</td>
<td>+0.33</td>
<td>-0.18</td>
<td>-0.15</td>
<td>0</td>
<td>-0.03</td>
<td>-0.12</td>
<td>0</td>
</tr>
<tr>
<td>1.808</td>
<td>+0.20</td>
<td>+0.55</td>
<td>+0.49</td>
<td>+0.35</td>
<td>-0.18</td>
<td>-0.15</td>
<td>-0.01</td>
<td>-0.02</td>
<td>-0.13</td>
<td>+0.01</td>
</tr>
<tr>
<td>2.034</td>
<td>+0.21</td>
<td>+0.59</td>
<td>+0.51</td>
<td>+0.37</td>
<td>-0.18</td>
<td>-0.15</td>
<td>-0.01</td>
<td>-0.02</td>
<td>-0.13</td>
<td>+0.01</td>
</tr>
<tr>
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<td>-0.16</td>
<td>-0.01</td>
<td>-0.02</td>
<td>-0.13</td>
<td>+0.01</td>
</tr>
</tbody>
</table>

As far as the $^1$H NMR complexation studies of L-4 and Ag$^+$ (Tables 3.24, see appendix 2 for Ag$^+$ titration $^1$H NMR stack plots) are concerned, large shifts changes in the proton signals relative to those for the free ligand are recorded. Both donor atoms appear to be involved in the complexation. During the silver complexation titration experiment, all the protons on the amine and methylthiolthio lower rim substituents are deshielded (Table 3.24,26). Conformation changes described in the protonation, lead and cadmium complexation experiments do not take place as the two aromatic and two $t$-butyl signals remain stationary, only a minimum amount of conformational movement of the ligand appears to be required to complex this cation. The sulphur donor atoms seem to bind more strongly since the adjacent protons are deshielded to a greater extent than those for the nitrogens. The latter, although deshielded, may also experience field effects which accounts for the lower than expected shift changes. This is particularly true for the methylene protons adjacent to the nitrogen, which show a lower downfield change in shift than the complexed methylene protons next to the oxygen, suggesting that the oxygen atoms are also involved in the complexation process.
Table 3.24  
\( ^1H \) NMR titration of L-4 with silver nitrate in deuterated methanol at 298 K (proton chemical shifts of free ligand in the same solvent indicated)

<table>
<thead>
<tr>
<th>mole ratio</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.11</td>
<td>1.29</td>
<td>4.37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ligand</td>
<td>1.12</td>
<td>2.67</td>
<td>3.11</td>
<td>3.89</td>
<td>6.59</td>
<td>0.89</td>
<td>3.20</td>
<td>4.15</td>
<td>3.20</td>
<td>2.22</td>
</tr>
<tr>
<td>0.251</td>
<td>+0.02</td>
<td>+0.03</td>
<td>+0.04</td>
<td>+0.01</td>
<td>0</td>
<td>-0.01</td>
<td>0</td>
<td>+0.10</td>
<td>+0.02</td>
<td>+0.05</td>
</tr>
<tr>
<td>0.502</td>
<td>+0.03</td>
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<td>+0.02</td>
<td>-0.01</td>
<td>-0.02</td>
<td>0</td>
<td>+0.15</td>
<td>+0.07</td>
<td>+0.12</td>
</tr>
<tr>
<td>0.753</td>
<td>+0.04</td>
<td>+0.10</td>
<td>+0.10</td>
<td>+0.02</td>
<td>-0.01</td>
<td>-0.02</td>
<td>0</td>
<td>+0.21</td>
<td>+0.10</td>
<td>+0.17</td>
</tr>
<tr>
<td>1.004</td>
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<td>-0.02</td>
<td>-0.01</td>
<td>+0.23</td>
<td>+0.15</td>
<td>+0.24</td>
</tr>
<tr>
<td>1.255</td>
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<td>+0.14</td>
<td>+0.15</td>
<td>+0.02</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
<td>+0.27</td>
<td>+0.19</td>
<td>+0.30</td>
</tr>
<tr>
<td>1.506</td>
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<td>+0.14</td>
<td>+0.16</td>
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<td>-0.01</td>
<td>-0.01</td>
<td>+0.28</td>
<td>+0.19</td>
<td>+0.30</td>
</tr>
<tr>
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<td>+0.15</td>
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<td>-0.01</td>
<td>+0.29</td>
<td>+0.20</td>
<td>+0.31</td>
</tr>
<tr>
<td>2.510</td>
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<td>+0.18</td>
<td>+0.23</td>
<td>+0.04</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
<td>+0.29</td>
<td>+0.21</td>
<td>+0.33</td>
</tr>
<tr>
<td>3.012</td>
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<td>+0.19</td>
<td>+0.25</td>
<td>+0.05</td>
<td>-0.02</td>
<td>-0.04</td>
<td>0</td>
<td>+0.30</td>
<td>+0.21</td>
<td>+0.33</td>
</tr>
</tbody>
</table>

Note: Due to the nature of the table, the chemical shifts are indicated as changes from the free ligand state. The proton chemical shifts of the free ligand in the same solvent are indicated for reference.

By far the most interesting $^1$H NMR titration experiment was that involving the interaction of L-4 with mercury(II) ions (Table 3.25 and Appendix 3). As the titration experiment proceeded to the formation of the 1:1 metal cation / ligand complex, the changes in the spectra were found to be similar to those observed for the protonation as well as those involving the interaction of this ligand with lead and to a lesser extent, cadmium. Indeed, the first mercury ion is solely complexed by the two nitrogen containing arms. However, after the formation of the 1:1 ligand : metal cation complex, further addition of Hg$^{2+}$ ions, resulted in the resonance positions of the methyl and methylene protons, of the methylethylthio substituents, moving downfield from their original free ligand shift positions. The free rotation observed for the methylenes between the heteroatoms of the methylethylthio substituents (1:2:1 triplets) display a more restricted movement and complex multiplets were observed.

As far as the nitrogen containing pendant arms are concerned, at the 2:1 cation : ligand complex ratio, the most significant changes are observed in the methylene protons next to the oxygen which are now more deshielded than the methylene protons next to the nitrogen as seen in Tables 3.25,26. The most intriguing question is how the ligand is preorganised to host a second cation in the hydrophilic cavity? Interaction with sulphur atoms, as suggested from the $^1$H NMR titration studies, must involve a rearrangement of the active sites of complexation of the ligand in such a way that the first cation is well shielded through its donor atoms, in order to minimise the electrostatic repulsion resulting from the introduction of a second cation. In doing so, the mercury cation initially seated close to the nitrogens in the amino ligating arms penetrates further into the cavity by increasing its proximity to the oxygen, as shown by the significant downfield shifts observed in the methylene protons adjacent to the oxygens when the 2:1 mercury-ligand complex is formed ($\Delta\delta = 0.51$ ppm). Under these conditions, the soft sulphur donor atoms are able to provide the active sites of complexation for the second cation.
The movement in the signals representing the \( t \)-butyl and aromatic protons seen in the complexation of the first mercury ion (coalescence of signals) is seemingly reversed as the second mercury ion is complexed. The shift difference \((\Delta\delta)\), between the two sets of signals, first increases to a value equalling the \( \Delta\delta \) for the free ligand and then to a greater value when the ligand is fully complexed with two mercury ions. However, from the titration experiment it is difficult to decide whether the signals coalesce and move apart again or whether they coalesce and cross (Table 3.25). When the titration experiment was conducted in reverse (L-4 titrated into the solution \( \text{Hg}^{2+} \) cations, Appendix 3) the two \( t \)-butyl and aromatic signals are seen to coalesce, clearly indicating the possibility that the signals cross. If the the \( t \)-butyl and aromatic signals reveal conformational information, what structure could possibly form as a result of the complexation of the second mercury cation? In order to shield the first \( \text{Hg}^{2+} \) cation it has already been suggested that the amine pendant arms wrap around the cation as simultaneous conformational changes occur with the amine substituent rings moving from a parallel position (X-ray crystallographic results of \( L-3, 3.1.5 \)) to a flatter aspect as the methylethylthio substituent aromatic rings move in the reverse fashion. The formation of a symmetrical cone conformation is observed as the signals coalesce. The second cation is then complexed by the sulphur donor atoms and in response, the further conformational changes allow the first cation to increase its proximity to the oxygen atoms and further into the macrocyclic ring. If the signals cross and end in an extreme position with respect to the appropriate signals of the free ligand, the macrocyclic ring must also exist in an extreme conformation. An explanation is that the amine substituents' aromatic rings have adopted a flatter position than that of the methylethylthio substituents' aromatic rings in the free ligand. The methylethylthio substituents' aromatic rings adopt a more extreme position relative to the amine substituents' aromatic rings of the free ligand as depicted by the Fig. 3.36.
Chapter Three Results and Discussion

Fig. 3.36 Possible cone conformations formed as a result of the 2:1 mercury ion :
ligand complex of L-4. Conformations responsible for the 'cross-over'
of t-butyl and aromatic proton signals

The Δδ value between the pair of doublets of the bridging methylene protons decreases
throughout the mercury titration experiment, possibly confirming the ligand
conformation is constantly changing throughout.

Published ion-responsive conformation changes similar to the proposed ring and lower
rim substituent movements reported in this section, which allow 2:1 mercury ion
complexes to form, have been reported. Shinkai\textsuperscript{225} has designed a calixarene whose
receptor site (pyridyl group) was activated from a 'closed' form to an 'open' form by
first binding Na\textsuperscript{+} ions to an acetamide group on the same substituent as the receptor
site. The receptor site can therefore be switched 'on' and 'off', an allosteric effect
frequently seen in biological systems. Unfortunately, no NMR data for the
complexation experiment was reported and therefore, no comparison can be made.
<table>
<thead>
<tr>
<th>mole ratio</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.11</td>
<td>1.29</td>
<td>4.37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ligand</td>
<td>1.12</td>
<td>2.67</td>
<td>3.11</td>
<td>3.89</td>
<td>6.59</td>
<td>0.89</td>
<td>3.20</td>
<td>4.15</td>
<td>3.20</td>
<td>2.22</td>
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<td>0.136</td>
<td>+0.05</td>
<td>+0.12</td>
<td>+0.12</td>
<td>+0.09</td>
<td>-0.07</td>
<td>-0.06</td>
<td>0</td>
<td>-0.01</td>
<td>-0.04</td>
<td>0</td>
</tr>
<tr>
<td>0.272</td>
<td>+0.08</td>
<td>+0.20</td>
<td>+0.16</td>
<td>+0.15</td>
<td>-0.11</td>
<td>-0.09</td>
<td>0</td>
<td>-0.02</td>
<td>-0.07</td>
<td>0</td>
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<td>+0.21</td>
<td>-0.14</td>
<td>-0.12</td>
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<td>-0.02</td>
<td>-0.08</td>
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<td>0.545</td>
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<td>+0.36</td>
<td>+0.33</td>
<td>+0.26</td>
<td>-0.16</td>
<td>-0.13</td>
<td>0</td>
<td>-0.03</td>
<td>-0.09</td>
<td>+0.02</td>
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<tr>
<td>0.681</td>
<td>+0.16</td>
<td>+0.43</td>
<td>+0.38</td>
<td>+0.27</td>
<td>-0.16</td>
<td>-0.14</td>
<td>0</td>
<td>-0.02</td>
<td>-0.10</td>
<td>+0.03</td>
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<td>0.817</td>
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<td>+0.52</td>
<td>+0.47</td>
<td>+0.33</td>
<td>-0.16</td>
<td>-0.15</td>
<td>-0.01</td>
<td>-0.08</td>
<td>+0.06</td>
<td></td>
</tr>
<tr>
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<td>+0.55</td>
<td>+0.48</td>
<td>+0.36</td>
<td>-0.15</td>
<td>-0.15</td>
<td>-0.01</td>
<td>+0.01</td>
<td>-0.05</td>
<td>+0.07</td>
</tr>
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<td>+0.38</td>
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<td>-0.14</td>
<td>-0.02</td>
<td>+0.03</td>
<td>-0.02</td>
<td>+0.11</td>
</tr>
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<td>+0.56</td>
<td>+0.41</td>
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<td>-0.08</td>
<td>-0.02</td>
<td>+0.08</td>
<td>+0.10</td>
<td>+0.26</td>
</tr>
<tr>
<td>1.634</td>
<td>+0.17</td>
<td>+0.63</td>
<td>+0.50</td>
<td>+0.41</td>
<td>+0.02</td>
<td>-0.01</td>
<td>-0.03</td>
<td>+0.15</td>
<td>+0.32</td>
<td>+0.42</td>
</tr>
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<td>1.906</td>
<td>+0.16</td>
<td>+0.61</td>
<td>+0.46</td>
<td>+0.45</td>
<td>+0.10</td>
<td>+0.01</td>
<td>-0.05</td>
<td>+0.19</td>
<td>+0.53</td>
<td>+0.59</td>
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<td>+0.11</td>
<td>+0.58</td>
<td>+0.41</td>
<td>+0.51</td>
<td>+0.15</td>
<td>+0.05</td>
<td>-0.07</td>
<td>+0.25</td>
<td>+0.67</td>
<td>+0.70</td>
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<td>+0.09</td>
<td>+0.57</td>
<td>+0.39</td>
<td>+0.51</td>
<td>+0.17</td>
<td>+0.06</td>
<td>-0.08</td>
<td>+0.30</td>
<td>+0.71</td>
<td>+0.77</td>
</tr>
</tbody>
</table>

Table 3.25 $^1$H NMR titration of L-4 with mercury nitrate in deuterated methanol at 298 K (proton chemical shifts of free ligand in the same solvent indicated)
<table>
<thead>
<tr>
<th>Protons</th>
<th>(\text{Cd}^{2+}) (HClO(_4))</th>
<th>(\text{H}^+)</th>
<th>(\text{Pb}^{2+})</th>
<th>(\text{Hg}^{2+}(1:1))</th>
<th>(\text{Hg}^{2+}(2:1))</th>
<th>(\text{Ag}^+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArH</td>
<td>+0.04, -0.04</td>
<td>+0.23, -0.17</td>
<td>+0.23, -0.15</td>
<td>+0.23, -0.15</td>
<td>+0.03, -0.01</td>
<td></td>
</tr>
<tr>
<td>H(_{ax})</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.08</td>
<td>-0.01</td>
</tr>
<tr>
<td>H(_{eq})</td>
<td>0.0</td>
<td>+0.08</td>
<td>+0.07</td>
<td>+0.08</td>
<td>+0.16</td>
<td>+0.07</td>
</tr>
<tr>
<td>O-CH(_2)CH(_2)S</td>
<td>-0.01</td>
<td>-0.03</td>
<td>-0.02</td>
<td>+0.01</td>
<td>+0.30</td>
<td>+0.27</td>
</tr>
<tr>
<td>O-CH(_2)CH(_2)N</td>
<td>+0.05</td>
<td>+0.36</td>
<td>+0.37</td>
<td>+0.36</td>
<td>+0.51</td>
<td>+0.16</td>
</tr>
<tr>
<td>O-CH(_2)CH(_2)S</td>
<td>-0.05</td>
<td>-0.14</td>
<td>-0.13</td>
<td>-0.05</td>
<td>+0.71</td>
<td>-0.19</td>
</tr>
<tr>
<td>O-CH(_2)CH(_2)N</td>
<td>+0.06</td>
<td>+0.48</td>
<td>+0.51</td>
<td>+0.48</td>
<td>+0.39</td>
<td>-0.02</td>
</tr>
<tr>
<td>NCH(_2)CH(_3)</td>
<td>+0.08</td>
<td>+0.54</td>
<td>+0.59</td>
<td>+0.55</td>
<td>+0.57</td>
<td>-0.15</td>
</tr>
<tr>
<td>SCH(_3)</td>
<td>0.0</td>
<td>+0.01</td>
<td>+0.01</td>
<td>+0.07</td>
<td>+0.77</td>
<td>+0.30</td>
</tr>
<tr>
<td>NCH(_2)CH(_3)</td>
<td>+0.03</td>
<td>+0.19</td>
<td>+0.21</td>
<td>+0.22</td>
<td>+0.09</td>
<td>+0.05</td>
</tr>
<tr>
<td>t-butyl</td>
<td>+0.03, -0.03</td>
<td>+0.17, -0.15</td>
<td>+0.17, -0.15</td>
<td>+0.15, -0.15</td>
<td>-0.06, +0.05</td>
<td>-0.03, -0.01</td>
</tr>
</tbody>
</table>

L-4 (free ligand), \(^1\text{H NMR}\) (300 MHz) (CD\(_3\)OD) \(\delta\) (ppm), 6.59, 7.11 (ArH), 4.37 (H\(_{ax}\)), 4.15 (O-CH\(_2\)CH\(_2\)S), 3.89 (O-CH\(_2\)CH\(_2\)N), 3.20 (O-CH\(_2\)CH\(_2\)S), 3.20 (H\(_{eq}\)), 3.11 (O-CH\(_2\)CH\(_2\)N), 2.67 (N(CH\(_2\)CH\(_3\))\(_2\)), 2.22 (SCH\(_3\)), 1.12 (N(CH\(_2\)CH\(_3\))\(_2\)), 0.89, 1.29 (t-butyI).

Table 3.26 Summary of Selected \(^1\text{H NMR}\) chemical shifts (ppm) for 5, 11, 17, 23-tetrakis-(1, 1-dimethylethyl)-25, 27-bis(methylthioethoxy)-26, 28-bis[2-(diethylamine)ethoxy]calix[4]arene (L-4) metal-ion complexes in CD\(_3\)OD at 298 K.
From the above discussion it is concluded that:

(i) Lead, silver and cadmium cations interact with L-4 in methanol forming 1:1 complexes, while for mercury, two cations are taken up per unit of ligand.

(ii) The active sites of complexation vary with the cation. Thus, the greatest chemical shift changes for cadmium and lead are found in the methylene protons corresponding to the amino pendant arms, particularly those close to the nitrogen atoms. The $^1H$ NMR spectra does not give any indication that the methylethylthio substituted pendant arms participate in the complexation of this ligand and these cations.

For silver, chemical shift changes are found in the protons attached to all donor atoms (O, N, S), although these changes appear to be more pronounced for the thiosubstituted pendant arms. As far as mercury is concerned, the amino substituted arms provides the sites of interaction for the formation of the 1:1 complex. The formation of a 2:1 complex requires a rearrangement of the 1:1 complex followed by the participation of the methylethylthio substituted pendant arms in hosting a second cation, in order to minimise the electrostatic interaction caused by the entrance of a second cation.

(iii) The $^1H$ NMR suggest that the strength of complexation follows the sequence:

$$Hg^{2+} > Ag^{+} > Pb^{2+} > Cd^{2+}$$
3.6.4. Mixed complexation NMR measurements

Several semi-quantitative mixed metal ion complexation experiments were also undertaken with L-4. It was clearly demonstrated that once the ligand had been pre-complexed with lead, cadmium metal ions or protons, the complex was still able to form a 2:1 mixed complex with mercury. This showed that after the formation of the 1:1 complex, the methylethylthio substituents’ sulphur atoms were clearly free to act as donor atoms to mercury cations.

The formation of a 1:1 mercury complex followed by the addition of a silver metal ion, gives a shift sequence mimicking the addition of two mercury ions. It is unclear whether the mercury ions are displaced for silver ions and then the methylethylthio substituents bind the free mercury, but since silver ions can be partially complexed by the sulphur donor atoms, it is presumed that the silver ion sits in the second complexation site, whereas the addition of protons to a 1:1 mercury ion complex, must clearly involve another mechanism. Again the spectrum for a 2:1 complex is observed, but in this example the sulphur donor atoms of the methylethylthio moieties are unable to complex the protons, indicating the transfer of the mercury ion to the second complexation site, while the nitrogen donor atoms of the amine substituents are protonated.

In order to obtain quantitative information regarding the strength of complexation, the stability of complex formation for L-4 in methanol at 298.15 K, was determined. This is described in the following section.

3.7.1. Determination of standard electrode potential, $E^\circ$ of the cell

The data in Table 3.27 and Fig. 3.37 show the typical response of a silver electrode during a calibration experiment as described in the experimental section (2.11).

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<thead>
<tr>
<th>mV</th>
<th>-log[Ag$^+$]</th>
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<td>4.85</td>
</tr>
<tr>
<td>-149.4</td>
<td>4.55</td>
</tr>
<tr>
<td>-138.0</td>
<td>4.38</td>
</tr>
<tr>
<td>-130.3</td>
<td>4.25</td>
</tr>
<tr>
<td>-124.7</td>
<td>4.16</td>
</tr>
<tr>
<td>-120.2</td>
<td>4.08</td>
</tr>
<tr>
<td>-116.0</td>
<td>4.01</td>
</tr>
<tr>
<td>-112.2</td>
<td>3.95</td>
</tr>
<tr>
<td>-109.5</td>
<td>3.91</td>
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<tr>
<td>-106.8</td>
<td>3.86</td>
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<tr>
<td>-104.6</td>
<td>3.82</td>
</tr>
<tr>
<td>-102.2</td>
<td>3.78</td>
</tr>
</tbody>
</table>

Table 3.27 Data points used to determine standard electrode potential, $E^\circ$ of the cell at 298.15 K

Interactions between the silver cations and L-4 will lead to a reduction in the potential as activity of the free silver cations decreases. The theory of this reaction is described in experimental procedures (2.11). Table 3.28 and Fig. 3.38 show typical experimental data as L-4 was titrated to excess of the free silver ions.

Fig. 3.37 Potentiometric curve for the determination of the standard potential and Nernst constant of the cell in methanol at 298.15 K

\[ y = -59.638x + 123.34 \]

\[ R^2 = 0.9998 \]
Chapter Three Results and Discussion

Table 3.28 Data points used to determine the stability constant of silver-(L-4) complex, $K_1$

<table>
<thead>
<tr>
<th>mV</th>
<th>mole ratio</th>
<th>mV</th>
<th>mole ratio</th>
<th>mV</th>
<th>mole ratio</th>
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<tr>
<td>-114.2</td>
<td>0.340</td>
<td>-157.5</td>
<td>0.893</td>
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<td>-117.5</td>
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<td>0.920</td>
<td>-202.4</td>
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<td>-120.4</td>
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<td>-206.9</td>
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<td>-124.4</td>
<td>0.533</td>
<td>-169.6</td>
<td>0.967</td>
<td>-211.9</td>
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<td>-129.4</td>
<td>0.600</td>
<td>-173.1</td>
<td>1.000</td>
<td>-215.9</td>
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<td>-134.3</td>
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<td>-177.4</td>
<td>1.067</td>
<td>-218.9</td>
<td>1.666</td>
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<td>0.800</td>
<td>-184.8</td>
<td>1.333</td>
<td>-222.4</td>
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<td>-147.5</td>
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<td>-191.7</td>
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<td>-225</td>
<td>1.833</td>
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Fig. 3.38 Potentiometric titration curve showing the formation of a silver calixarene complex (L-4) in methanol at 298.15 K.
### 3.7.3. Determination of stability constants of various metal cations with L-4 in methanol at 298.15 K


<table>
<thead>
<tr>
<th>Metal-ion</th>
<th>Silver-ion stability constant log $K_{st}$</th>
<th>Metal-ion competition stability log $K_{s2}$</th>
<th>Mean stability constant log $K_{s2}$</th>
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<tr>
<td>Ag$^{+}$</td>
<td>5.89</td>
<td>-</td>
<td>$5.92 \pm 0.09^{(24)*}$</td>
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<tr>
<td></td>
<td>5.88</td>
<td>-</td>
<td></td>
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<tr>
<td>Cd$^{2+}$</td>
<td>6.07</td>
<td>2.26</td>
<td>$2.37 \pm 0.08^{(0)*}$</td>
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<tr>
<td></td>
<td>5.91</td>
<td>2.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.86</td>
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<tr>
<td></td>
<td>5.79</td>
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</tr>
<tr>
<td></td>
<td>6.04</td>
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<td>$&lt; 2$</td>
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<td>3.58</td>
<td></td>
</tr>
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<td></td>
<td>5.83</td>
<td>3.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.89</td>
<td>3.43</td>
<td></td>
</tr>
<tr>
<td>Ni$^{2+}$</td>
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<td>$&lt; 2$</td>
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<tr>
<td>Pb$^{2+}$</td>
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<td>3.58</td>
<td>$3.47 \pm 0.06^{(0)*}$</td>
</tr>
<tr>
<td></td>
<td>6.00</td>
<td>3.44</td>
<td></td>
</tr>
<tr>
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<td>5.80</td>
<td>3.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.93</td>
<td>3.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.96</td>
<td>3.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.15</td>
<td>3.48</td>
<td></td>
</tr>
<tr>
<td>Zn$^{2+}$</td>
<td>5.89</td>
<td>$&lt; 2$</td>
<td>$&lt; 2$</td>
</tr>
<tr>
<td></td>
<td>5.99</td>
<td>$&lt; 2$</td>
<td></td>
</tr>
</tbody>
</table>

* parenthesis in final column denotes the number of measurements

Table 3.29 Stability constants determined by the competitive potentiometric technique in methanol at 298.15 K

191
Standard deviations of log $K_{\text{st,2}}$ are calculated from:

$$S = \left[ \frac{\sum (x_i - \bar{x})^2}{(n-1)} \right]^{1/2}$$  \hspace{2cm} (3.27)

Table 3.30 displays the calculated Gibbs energy of complexation results derived from stability constant data. The selectivity factor of L-4 for silver with respect to other metal cations can be calculated from eqn. 3.27. These data are shown in Table 3.30.

$$S'_{\text{Ag}^+,\text{M}^+} = \frac{K_{\text{L-4Ag}^+}}{K_{\text{L-4M}^+}}$$  \hspace{2cm} (3.28)

<table>
<thead>
<tr>
<th>Cation</th>
<th>log $K_i$</th>
<th>$\Delta G^0 / \text{kJ mol}^{-1}$</th>
<th>Selectivity Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag$^+$</td>
<td>5.92</td>
<td>-33.79 ± 0.51</td>
<td>1</td>
</tr>
<tr>
<td>Cd$^{2+}$</td>
<td>2.37</td>
<td>-13.53 ± 0.46</td>
<td>3548</td>
</tr>
<tr>
<td>Co$^{2+}$</td>
<td>&lt; 2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cu$^{2+}$</td>
<td>3.49</td>
<td>-19.92 ± 0.34</td>
<td>269</td>
</tr>
<tr>
<td>Ni$^{2+}$</td>
<td>&lt; 2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pb$^{2+}$</td>
<td>3.47</td>
<td>-19.81 ± 0.34</td>
<td>282</td>
</tr>
<tr>
<td>Zn$^{2+}$</td>
<td>&lt; 2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.30  Standard Gibbs energies of complexation of L-4 and metal cations in methanol at 298.15 K

From the data displayed in Table 3.30, ligand L-4 clearly discriminates in favour of silver over other metal cations.
4. CONCLUSIONS

From chapter 3 (Results and Discussion) the following conclusions are drawn;

a) The introduction of 18-crown-6, as a phase transfer catalyst for the synthesis of L-2, leads to a shorter reflux period, producing the pure ligand in high yields.

Nine novel calix[4]arene derivatives have been successfully synthesised and characterised by NMR spectroscopy. The tetra thiophene derivative L-1, aliphatic (methyl, ethyl, isopropyl, diisopropylacetamide) and alicyclic (piperidine, pyrrolidine, morpholine, thiophene) moieties have been introduced to the lower rim of L-2. In all cases the derivatives were found to be disubstituted and in the cone conformation. Subsequent X-ray crystal structures of L-1 and L-3 confirmed structures and showed their cone conformations to be distorted.

b) Derivatisation of calixarenes can produce hydrophilic and hydrophobic regions. As a result, specific solute-solvent interactions often occur. Results obtained for L-1, L-2 and L-4 complement this statement showing no correlation between solvent properties, such as Gutman’s donor number, and the degree of solvation.

c) Acid-base properties of ligands (L-3 to L-8) have been investigated in methanol and ethanol at 298.15 K. Potentiometric measurements indicate the formation of diprotonated species $(\text{H}_2\text{N}_2\text{Calix}[4])^{2+}$. The presence of only one inflection point from the titration curve suggests that the two nitrogen atoms act independently from each other in their interaction with the protons.

d) Conductance measurements clearly revealed complex formation of L-4 with silver and mercury cations in methanol at 298.15 K, where the two titration curves displayed sharp breaks, indicating strong interactions between these cations and this ligand. Conductance titration curves for lead and cadmium are indicative of complexes of low stability. The striking curve for mercury cations clearly reveals a complex
stoichiometry of two mercury cations per unit ligand and this is also confirmed by \(^1\)H NMR titrations in deuterated methanol at 298 K.

e) \(^1\)H NMR complexation experiments not only confirmed interactions but they revealed the sites of complexation of the ligand (L-4) and Ag\(^+\), Cd\(^{2+}\), Pb\(^{2+}\) and Hg\(^{2+}\) cations. The most striking result of these experiments was the confirmation that the first mercury cation was complexed by the nitrogen donor atoms of the amine substituents, while the second cation was bound by the sulphur donor atoms of the methylethylthio substituents. In order to establish a 2:1 cation:ligand complex, L-4 undergoes considerable conformation changes as indicated by the significant signal shifts of the \(t\)-butyl and aromatic protons.

f) Stability constants of L-4 with various cations (Ag\(^+\), Cd\(^{2+}\), Pb\(^{2+}\), Cu\(^{2+}\)) in methanol at 298.15 K were measured. The results obtained reveal that this ligand selectively interacts with metal cations following the sequence,

\[
\text{Ag}^+ > \text{Cu}^{2+} > \text{Pb}^{2+} > \text{Cd}^{2+}
\]
5. SUGGESTIONS FOR FURTHER WORK

The synthetic work outlined in this thesis demonstrates the flexibility of calixarenes to act as building blocks in order to construct new ligands capable of selectively interacting with neutral and ionic species. The successful use of a phase transfer catalyst in the alternate alkylation of \( p\text{-}\text{tert-} \)butylcalix[4]arene, forming L-2, leaves the possibility of further substitutions at two sites at the lower rim. The subsequent introduction of substituents containing different donor atom arrangements is a possible avenue for the synthesis of new ionophores. Recent work carried out in the Thermochemistry Laboratory has resulted in the introduction of pyridine moieties to L-2.


i) Assignment of the \( t\)-butyl and the aromatic signals from the \( ^1H \) and \( ^13C \) NMR spectra would also aid the discussion of the \( ^1H \) NMR complexation results. If the influence of the ring currents on the \( t\)-butyl and aromatic protons can be measured then not only can each individual signal be assigned, but signal shifts can then be interpreted in terms of conformational movements. Molecular Dynamics calculations may assist in the interpretation of the complexation process in solution.

ii) X-ray diffraction studies of the metal cation complexes, particularly that with mercury cations are required in order to obtain a clear picture of the interactions of L-4 with this metal cation.

iii) A comprehensive thermodynamic study on the solution process involving these ligands and their metal-ion complexes in a variety of solvents would seek to elucidate more effectively the role of the solvent in the binding process of these ligands with metal cations.
(iv) Thermodynamic parameters of complexation (Gibbs energies, $\Delta G^\circ$, enthalpies, $\Delta H^\circ$ and entropies, $\Delta S^\circ$) in various solvents coupled with solution thermodynamic data ($\Delta G^\circ$, $\Delta S^\circ$, $\Delta H^\circ$) for the free and the complexed salts containing different anions and the ligand in the appropriate solvent would lead to the calculation of corresponding data for the coordination process, where the reactants and the product are in the solid state. These results are useful as a means of (i) checking the reliability of thermodynamic data (ii) assessing the anion effect and (iii) obtaining complexation data in low dielectric media where direct measurements are difficult to perform. As far as the interaction of L-4 with mercury ($\text{Hg}$) is concerned, a new model for the derivatisation of thermodynamic data taking into account possible rearrangements taking place in the 1:1 complex to allow the introduction of a second cation may be considered.

Work in this area is now in progress.
6. APPENDIX


<table>
<thead>
<tr>
<th>Titration No.</th>
<th>mole ratio ($M^+/L$)</th>
<th>Free ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>0.452</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>0.678</td>
<td></td>
</tr>
</tbody>
</table>

197

<table>
<thead>
<tr>
<th>Titration No.</th>
<th>mole ratio (M$^{4+}$/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Free ligand</td>
</tr>
<tr>
<td>2.</td>
<td>0.251</td>
</tr>
<tr>
<td>3.</td>
<td>0.502</td>
</tr>
</tbody>
</table>

Titration No.                              mole ratio ($L/M^{\text{m+}}$)

1.                                      0.081

2.                                      0.162

3.                                      0.242
7. REFERENCES


References

References


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Majesty’s Government of the United Kingdom of Great Britain and Northern Ireland.

177. S. J. Harris, D. Diamond, M. A. McKervey, International patent, WO 95/04483, 3rd March (1994), assigned to S. J. Harris, D. Diamond, M. A. McKervey.


193. Program developed in the Thermochemistry Laboratory at the University of Surrey.