# Synthesis of and Complexation Studies with Polyaminopolycarboxylic Acid Crown Ethers

A Thesis

Submitted for the Degree of

**Doctor of Philosophy**

**By**

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July 1996

*Dedicated to*
*my father B. Devasahayam,*
*my mother B. Danamma*
*and to my sister Chanti*

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## DECLARATION

*I hereby declare that the matter embodied in this thesis* ***is*** *the* ***result of investigations*** *carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad under the supervision of Professor M. Nagarajan.*

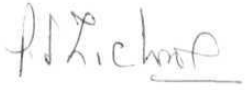
*In keeping with the general practice of reporting* ***scientific*** *observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.*

B. L. A. Prabhavathi Devi.

## CERTIFICATE

*This is to certify that the work described in this thesis entitled* **SYNTHESIS OF AND COMPLEXATION STUDIES WITH POLYAMINOPOLYCARBOXYLIC ACID CROWN ETHERS** ***has*** *been carried out by Ms. B. L. A. Prabhavathi Devi, under my supervision and the same has not been submitted elsewhere for any degree.*

M NAGARAJAN
(THESIS SUPERVISOR)



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## ACKNOWLEDGEMENTS

*I wish to express my deep sense of gratitude to my research supervisor, Professor M. Nagarajan, for his excellent and inspiring guidance through out my research career. I am indebted to him for his openmindedness in our stimulating discussions, for the freedom he rendered me to perform reactions of my interest and also to his moral support during this tenure. 1 have learnt many things from him along with chemistry. I sincerly thank him for all his help.*

*I wish to thank Professor Goverdhan Mehta, Vice-Chancellor and Professor P. S. Zacharias, Dean for providing me lot of inspiration, confidence and encouragement throughout my slay.*

*1 am very much grateful to Dr. M. Durga Prasad for his discussions and help in programming the software for the calculations. I thank Dr. M. V. Rajashekaran for his help and expert comments. I am grateful to Professor E. D. Jemmis, Dr. Bhasker G. Maiya, Dr. D. Basavaiah, Dr. K. C. Kumara Swamy and Dr. M. J. Swamy for extending their computer facility for my thesis work. My due respects to all other faculty members of the school for their inspiring lectures and encouragement throughout.*

*I am very much appreciative of the pleasant and co-operative atmosphere my labmates Drs. R. Murali, K. Narkunan, P. K. Vasudeva, K. Rajender Reddy, B. Lakshman Raju, Ms. A. Manjula, Mr. C. V. Ramana,*

*Ms. A. V. R. L. Sudha and Mr. K. R Lakshmi Kanthan have furthered throughout my research tenure and also Manjula and Ramana have been very helpful in my thesis preparation.*

*I specially thank Narkunan, Prasad and Nachimuthu for their keen interest and timely help during my thesis preparation.*

*My thanks are due to all my friends Prasuna, Padma, Aparna, Suguna, Anuradha, Ajitha, Vidhya, Raghu, Srinivas, Takhi, Murali and Bramhananda for making my stay a pleasant and memorable one.*

*I thank Dr P. Bheema Rao, Chandrakala, Madhavi, Padmaja, T & H. Anithas, Vijjulatha, Ramalakshmi, Sindhu, Prasad, Kir an, Kumar, Venkat, Giri Babu, Arunagiri, srinivas, Srinivas Reddy, Ravi, Nagasrinivas and all other friends for their help and co-operation.*

*I am very much indebted to my parents and sister, but for their staunch support I would not have come upto this stage. I am also grateful to all my cousins Kiran, Vardhan, Vijay Kumar, Vijay Prasad and Bujji for their encouragement.*

*I would like to extend my sincere thanks and express my respects to Mrs. Manikarnika Nagarajan for her constant moral support, affection and hospitality. My little friend Putty is expressly acknowledged for her love and friendliness.*

*Thanks are also due to the non-teaching staff of the School of Chemistry, especially to Mr. Shetty, Mr. R. Venkat Rao, Mr. Satyanarayana, Mr. Bhaskar Rao, Mrs. Vijayalakshmi, Mrs. Ayesha Begum, Mrs. Sharada and Mr. Prasad for their assistance during the course of my research period.*

*My thanks are also due to the University authorities for providing infrastructure, SAP and UGC for the financial assistance.*

*B. L. A. Prabhavathi Devi.*

## ABBREVIATIONS

| | |
|---|---|
| aq | aqueous |
| Bn | benzyl |
| Bu | butyl |
| Bz | benzoyl |
| CDTA | 1,2-diaminocyclohexanetetraacetic acid |
| cyclam | 1,4,7,10-tetraazacyclotetradecane |
| DBU | l,8-diazabicyclo[5 4 0]undec-7-ene |
| DBN | l,5-Diazabicyclo[4.3.0]non-5-ene |
| DCC | 1,3-dicyclohexylcarbodiimide |
| DCTA | 1,2-diaminocyclohexanetetraacetic acid |
| dien | diethylenetriamine |
| DOTA | 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid |
| DTPA | diethylenetriaminepentaacetic acid |
| DTPA-BAM | N,N''-bis[(methylcarbamoyl)methyl]-N,N',N''-tris(carboxymethyl)diethylenetriamine |
| DMAP | 4-dimethylaminopyridine |
| DMF | dimethylformamide |
| EDTA | ethylenediaminetetraacetic acid |
| EGTA | ethylene glycol(2-aminoethyl ether)tetraacetic acid |
| Et | ethyl |
| g | gram |
| HEHA | 1,4,7,13,16-hexaazacyclohexadecane-N,N' ,N'' ,N ''' ,N " ", N""'-hexaacetic acid |

| | |
|---|---|
| LAH | lithium aluminium hydride |
| Me | methyl |
| min | minute(s) |
| ml | millilitre(s) |
| mmol | millimole(s) |
| Ms | methanesulfonyl (mesyl) |
| NOTA | 1,4,7-triazacyclononane-N,N',N''-triacetic acid |
| PCC | pyridiniumchlorochromate |
| PDC | pyridiniumdichromate |
| PEPA | 1,4,7,10,13-pentaazacyclopentadecane-N,N',N'',N''',N''''-pentaacetic acid |
| Ph | phenyl |
| Pr | propyl |
| Py | pyridine |
| $R_1$ | longitudinal relaxivity |
| TAAHA | tris-(2-aminoethyl)aminohexaacetic acid |
| rt | room temperature |
| TEA | triethylamine |
| TETA | 1,4,8,11-tetraazacyclotetradecane-N,N',N'', N'''-tetraacetic acid |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl (tosyl) |

# ABSTRACT

This thesis deals with the synthesis of and complexation studies with polyaminopolycarboxylic acid crown ethers, the crown diamine 71, the crown tetraamine 78, the crown diaminetetraacetic acid 79 and the crown tetraaminehexaacetic acid 82. The thesis consists of three sections, namely, introduction, results and discussion and experimental The results and discussion is divided into two parts Part-1 deals with the synthesis of the ligands 71, 78, 79 and 82. Part-2 deals with the determination of the dissociation constants of 71, 79 and 82 and the stability constants of these ligands with different metal ions.

The introductory chapter is divided into two sections. The first section presents a brief survey of some of the salient features of crown ether chemistry. In the second section the synthesis of polyaminopolycarboxylic acid chelating agents of medicinal interest, both diagnostic and therapeutic, are covered. A brief survey of their utility in medicine is also included

Multidentate polyamino crown ethers 71 and 78 were synthesized in high yields starting from easily available pentaerythritol 2. Utilising the compounds 71 and 78, we prepared the target crown diaminetetraacetic acid 79 and the crown tetraaminehexaacetic acid 82. The general methods of N-alkylation of 71 and 78 with bromoacetic acid as well as with ethyl bromoacetate followed by hydrolysis of the respective ethyl esters 80 and 83 to obtain 79 and 82 in pure form were unsuccessful Finally, the

x

polyaminopolycarboxylic acid crown ethers 79 and 82 were obtained in pure form, by alkylating 71 and 78 with benzyl bromoacetate followed by hydrogenolysis of the respective benzyl esters 81 and 84. Attempts at the synthesis of multiloop spiro crown ethers 85, 87 and 89 were however unsuccessful.

In order to examine the chelating abilities of the ligands 71 and 79, we prepared some solid metal complexes such as the crown diamine-copper (II) complex 92, the crown salicylaldimine nickel (II) complex 94 and the crown diaminetetraacetic acid-gadolinium complex **95**

Using the potentiometric titration method, the dissociation constants of 71, 79 and 82 were evaluated employing the computer program SCOGS 2. The same technique was adapted to determine the stability constants of the complexes formed from 71, 79 and 82 with different metal ions.

From our results, it is evident that the first acid dissociation constant ($pK_1$ = 2.86) of the crown diamine 71 is very low when compared with that of 1,3-propanediamine ($pK_1$ = 8.36). This indicates that the diprotonated species of crown diamine 71 is more acidic than that of 1,3-propanediamine. The large difference in $pK_1$'s may be due to the effect of the crown ether moiety that is present in the crown diamine 71. The monoprotonated species of the crown diamine formed from the diprotonated species by loss of one proton, is stabilised by intramolecular complexation of the crown with the primary ammonium ion, thus shifting the equilibrium towards the

monoprotonated species and resulting in a low value for $pK_1$ This type of large differences in acid dissociation constants are not observed in the case of crown diaminetetraacetic acid 79 as well as in crown tetraminehexaacetic acid 82, when compared to trimethylenediamine tetraacetic acid ($H_4L$) and triethylenetetraamine hexaacetic acid ($H_6L$), because in these cases intramolecular complexation with the crown is not a factor

It was also found that the crown diamine 71 forms 1 : 1 and 2 : 1 complexes with nickel and copper, whereas with cobalt and lanthanides it forms 3 : 1 complexes. The stability constants (log $K_1$ and log $K_2$) of the crown diamine 71 with $Cu^{2+}$ are 4 80 and 9.95, respectively and log $K_N$ is 14.75. Among the lanthanides, crown diamine 71 was found to complex best with $Gd^{3+}$ ion (log K = 15.40). We also studied the synergistic effect of sodium ions on the complexation ability of the crown diamine 71 with transition and lanthanide ions. It was found that in the presence of sodium ions, the stability constants of crown diamine 71 with transition and lanthanide metal ions were reduced For example, the stability constant of $Cu^{2+}$ with crown diamine 71 in the absence of sodium ion was found to be 14.75, whereas in the presence of sodium ion it was 10.05. This effect is attributed to the participation of the amine group in the stabilization of sodium-crown complexation In the case of the tetraacid 79, this kind of effect was not significant, where the stability constants with $Cu^{2+}$ in the absence of sodium ion was found to be 12.81, whereas in the presence of sodium ion it was 12.67. This is perhaps due to the greater role played by the carboxylate groups in metal ion complexation in the crown tetraacid 79 than

the amino groups in the crown diamine 71. It was also found that the crown tetraaminehexaacetic acid 82 is a better ligand than the crown diaminetetraacetic acid 79 and the crown diamine 71 with transition and lanthanide metal ions The stability constant (log K) of 82 with $Gd^{3+}$ was 19.75 and with $Cu^{2+}$ was 21.76, whereas for 79 and 71 the corresponding values with $Gd^{3+}$ are 10.77 and 15.40 and with $Cu^{2+}$ are 12.67 and 15.04.

In the experimental section, full details regarding the synthesis of the compounds as well as the measurements made with them are presented. A bibliography of all the relevant references concludes the thesis.

We have accomplished a novel and facile synthesis of crowns with pendant amino groups (71 and 78) and polyaminopolycarboxylic acid arms (79 and 82). The results obtained indicate that these ligands are good metal chelating agents with transition and lanthanide metal ions These complexes have potential use as MRI agents and as NMR shift reagents for NMR active alkali metal ions.

*Intrdoduction*

# INTRODUCTION

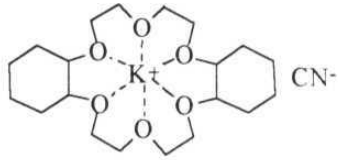
The discovery of dibenzo-18-crown-6 by Charles J Pedersen[1] in 1967 is one of the landmarks in the history of chemistry and also marks the beginning of synthetic host-guest chemistry In 1987, the Noble prize in chemistry was shared by Pedersen, Cram and Lehn for their contributions to the field of supramolecular chemistry and host-guest chemistry "Supramolecular chemistry" has been defined by Lehn[2] as "chemistry beyond the covalent bond or the chemistry of associates with well defined structure" The gross structure of the associates is governed by relatively weak forces such as hydrogen bonds, ion-dipole and dipole-dipole interactions and van der Waals interactions Although supramolecular chemistry has rapidly expanded into a burgeoing research area encompassing a multitude of disciplines,[3] in this introduction the attention is specifically on crown ethers

This thesis, as the title itself indicates, deals with the synthesis of polyaminopolycarboxylic acid crown ethers and a study of their complexing abilities, especially towards rare earth metal ions The potential utility of such complexes as contrast agents for magnetic resonance imaging (MRI) provided the impetus for undertaking the present work In keeping with this objective, the introductry chapter is divided into two sections The first section presents a brief survey of some of the salient features of crown ether chemistry. Due to the exhaustive nature of the subject, the coverage, as might be expected, is very selective and is restricted to crown ethers with multiple cation binding sites and their role in metal ion transport. Synthesis

of polyaminopolycarboxylic acids of medicinal interest, both diagnostic and therapeutic, are covered in the second section along with their applications. These include the use of metal complexes of polyaminopolycarboxylic acids as contrast reagents for MRI, in radioimmunotherapy, in tumour targeting, as models for calcium binding proteins and as antiviral agents against the viruses HIV-1 and 2

Most of the initial work on crown ethers was concentrated on the design of selective receptors for either alkali and alkaline earth cations[4] and very little is known even today about receptors (host molecules) which can simultaneously and selectively complex with several different types of alkali, alkaline earth and heavy metal ions Among the many applications of selective complexation of cations by crown ethers are chemical sensors,[5] selective removal of poisonous or radioactive metal cations from waste streams,[6] membrane transport,[7] immobilisation of radioisotopes[8] and as phase-transfer catalysts [9]

Crown ethers have found much use in organic synthesis as phase-transfer catalysts for nucleophilic substitutions.[10] In a nucleophilic substitution reaction, the organic substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is soluble in water but not in the substrate or other organic solvents. When these kinds of reactions are carried out in the presence of crown ethers, the rate of the reaction is accelerated. Thus, for example, a salt like KCN is converted by

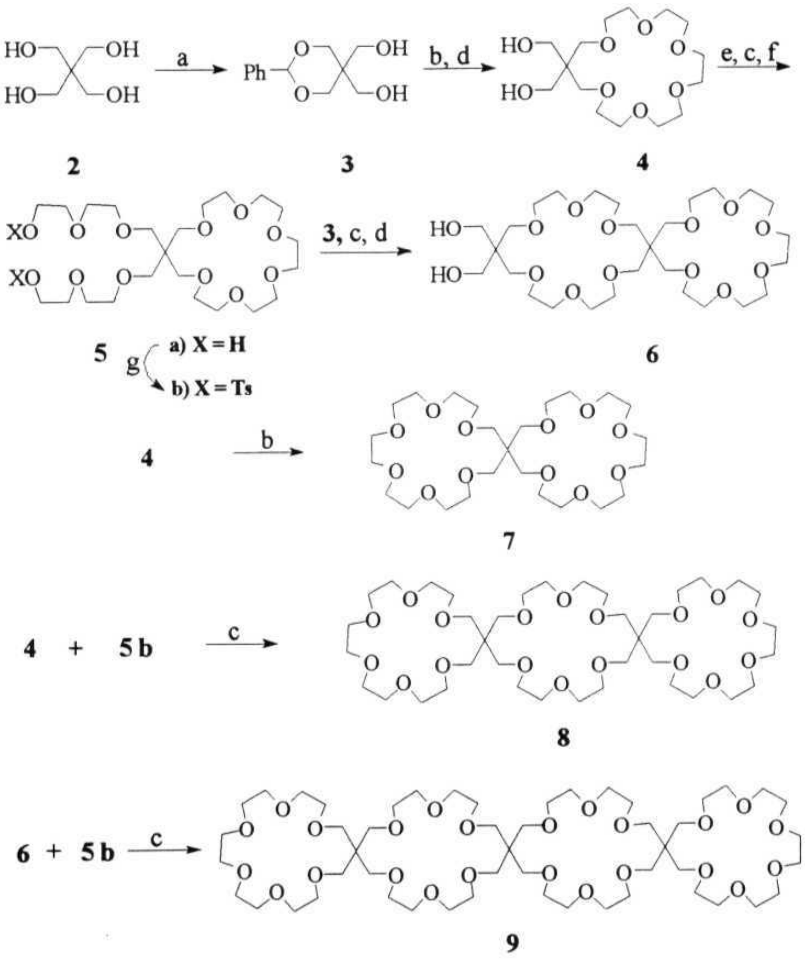



**1**

Figure 1

dicyclohexano-18-crown-6 into a new salt 1 (Fig 1) whose anion is the same, but whose cation is now a much larger species with the positive charge spread over a larger volume, and hence much less concentrated This larger cation is much less soluble in water than $K^+$ and more soluble in organic solvents, thus bringing the anion, by an ion-pairing mechanism, to the organic media Also, the anion is not solvated by the organic solvent unlike in water and is therefore a "free" species which is more reactive Any reaction that needs an insoluble anion to be solubilized in organic solvents can be accelerated by an appropriate phase-transfer catalyst

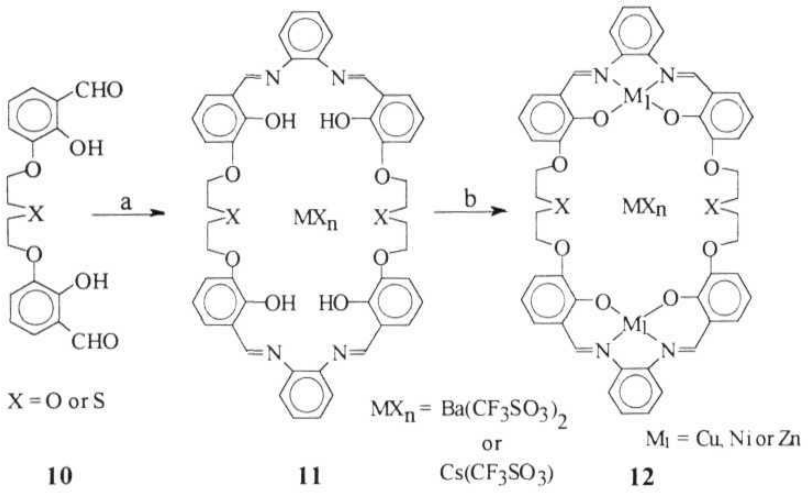
Most studies on complexation phenomena with crown ethers involve a single host and a single guest but molecular receptors with multiple interacting binding sites are of current interest In 1982, Weber[11] reported the synthesis and selective complex formation of spiro-linked multiloop crown compounds 7, 8 and 9. These compounds were prepared by stepwise cyclisation, making use of blocking/deblocking and high-dilution techniques,


HO
OH
HO
OH
a
Ph
O
O
OH
OH
b, d
HO
HO
O
O
O
O
O
O
e, c, f
2
3
4
XO
XO
O
O
O
O
O
O
O
O
3, c, d
HO
HO
5
g
a) X = H
b) X = Ts
6
4
b
7
4 + 5b
c
8
6 + 5b
c
9

**Scheme 1.** *Reagents and conditions:* a) PhCHO, HC1, b) pentaethylene glycol ditosylate, NaH, THF, c) NaH, THF, d) $H_2$, Pd/C, EtOH, 3 atm, e) $ClCH_2CH_2OCH_2CH_2OTHP$, f) HC1, EtOH, g) *p*-TsCl, Py

starting from pentaerythritol (2) as the basic building block as shown in Scheme 1 It was found that the symmetrically looped molecules can incorporate two or three identical metal cations and asymmetrical loop molecules allow the simultaneous uptake of different metal ions of the alkali and alkaline earth families.

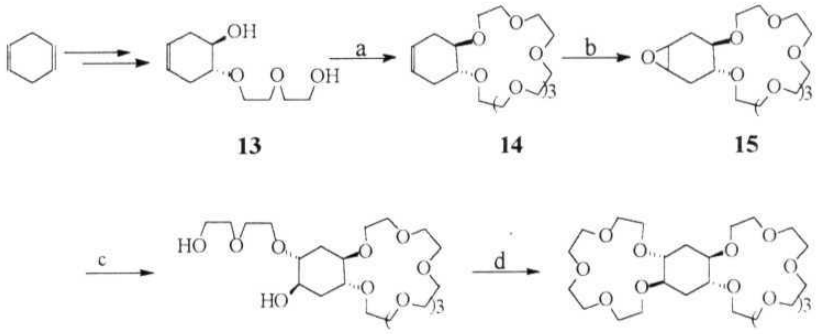
The propensity for complex formation in transition metal ions has prompted the synthesis of ligands with suitable donor atoms in the macrocycle In 1991, Reinhoudt[12] synthesised macrocyclic hetero-trinucleating ligands that have one compartment for complexation of alkali or alkaline earth cations and two compartments for transition metal cations The hetero-trinucleating ligands were prepared by (2+2) macrocyclisation of




**Scheme 2.** *Reagents and conditions:* a) *o*-phenylenediamine, 1/2 $MX_n$, MeOH, heat, b) $M_1(OAc)_2$, MeOH

a salicylaldehyde derivative 10 and o-phenylenediamine in the presence of $Ba(CF_3SO_3)_2$ or $Cs(CF_3SO_3)$ as the template salt in methanol as shown in Scheme 2 The complexes 11 were converted into the hetero-trinuclear complexes 12 by reacting **11** with 2 equiv. of copper, nickel or zinc acetate in methanol. Dinuclear copper complexes without a bridging ligand are interesting as models for copper proteins.[13]

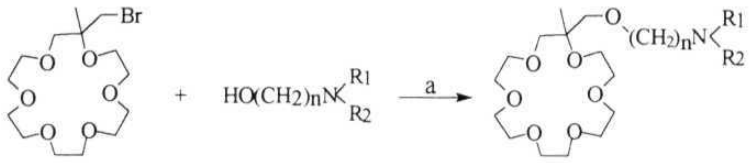
Bis-macrocyclic ethers with positive and negative allosteric cooperativity were developed by Costero [14] A system in which binding at one site increases binding elsewhere displays positive cooperativity and the opposite result, negative cooperativity The bis-macrocyclic ether 17 was synthesized by converting 1,4-cyclohexadiene to its monoepoxide by treatment with hydrogen peroxide and ethyl chloroformate The monoepoxide was opened with diethylene glycol to the trans hydroxy ether 13, from which the first ethereal cavity was constructed by condensation with the appropriate glycol ditosylate as depicted in Scheme 3 Repetition of the sequence leads to trans diaxial opening of the epoxide 15 to the second diol **16**, necessary for the construction of second cavity as exemplified by **17**




**Scheme 3.** *Reagents and conditions:* a) $TsOCH_2(CH_2OCH_2)_3CH_2OTs$, NaH, THF; b) $H_2O_2$, ethyl chloroformate, c) $HOCH_2CH_2OCH_2CH_2OH$; d) $TsOCH_2CH_2OCH_2CH_2OTs$ , NaH, THF.

It was shown that the bis-macrocyclic ether 17 was able to transport double the amount of $Na^+$ and $K^+$ cations when compared to the corresponding monocyclic systems because of the negative allosteric cooperativity

In ion transport systems, macrocyclic polyethers are excellent candidates for the recognition of the binding sites of carriers towards specific cations because of their selective complexation properties Okahara[15] and co-workers reported the synthesis, complexation and application in ion transport of a new series of 18-crown-6 ethers containing an amino group Thus, the ionophores **20a-d** were prepared by the reaction of 2-(bromomethyl)-2-methyl-18-crown-6 (18) with the sodium alkoxide of the appropriate amino alcohols **19a-d** for 4 h at 100-120° (Scheme 4) These ionophores display better transport of $K^+$ than $Na^+$. The foregoing brief




**18** **19** **20**

a) n = 5, $R_1 = R_2 = H$
b) n = 2, $R_1 = R_2 = H$
**C)** n = **2,** $R_1 = H, R_2 = C_2H_5$
d) n = 2, $R_1 = R_2 = C_2H_5$

**Scheme 4.** *Reagents and conditions:* a) Na, 100-120°, 4 h

account underlines the importance of crown ethers in multi-cation complexation and metal ion transport

In recent times, rapid advances have occurred in medical diagnostics, amongst which, perhaps, MRI occupies the pride of place. MR1 permits the study of different types of tissues and enables the identification of diseased tissues For this purpose, nuclear magnetic resonance (NMR) imaging contrast agents are used in cancer and tumour treatment to detect the infected tissue Complexes of paramagnetic transition metal and lanthanide ions, which can decrease the relaxation times of adjacent nuclei via dipolar interactions, have received most attention as potential contrast agents in magnetic resonance imaging (MRI) Paramagnetic contrast agents are unique amongst diagnostic agents as in the tissues these agents are not visualized directly on the NMR image, but are detected indirectly by virtue of changes in proton relaxation behaviour in their vicinity The development of these agents offers an intriguing challenge for the investigators in the fields of chemical, physical and biological sciences These include the design and synthesis of stable, non-toxic and tissue specific metal complexes and the quantitative understanding of their effect on the nuclear relaxation behaviour in solution and in tissue

The need for NMR contrast agents and the interesting research problem associated with their development has produced an active research area. Bloch[16] first described the use of a paramagnetic salt, ferric nitrate, to enhance the relaxation rates of water protons The first human NMR imaging

study involving a paramagnetic agent was performed by Young.[17] The diagnostic potential of paramagnetic agents was first demonstrated in patients by Carr[18] Gadolinium (III) diethylenetriaminepentaacetate [[Gd(DTPA) $(H_2O)]^{2-}$] was administered intravenously to patients with cerebral tumours, providing enhancement of the lesion in the region of cerebral capillary breakdown. This is the only MRI agent currently in clinical use.

One of our objectives in the course of this research was to synthesize suitable ligands for use as complexing agents of metal ions, especially $Gd^{3+}$, so as to investigate their utility as MRI agents. Therefore, the requirements that a metal complex should possess for use as an MRI agent are briefly discussed

**General requirements for metal complexes to function as NMR contrast agents:**

NMR imaging contrast agents must be biocompatible Pharmaceuticals in addition to being nuclear relaxation probes. Besides the standard pharmaceutical features such as water solubility and shelf stability, the requirements relevant for metal complex based agents can be classified into three general categories 1) Relaxivity 2) Specificity in vivo distribution and 3) Non toxicity, in vivo stability and excretability. Each of these is now discussed in greater detail.

**1). Relaxivity:** The efficiency with which the complex enhances the proton relaxation rates of water, referred to as relaxivity, must be sufficient to significantly increase the relaxation rates of the target tissue This directly contributes to the sensitivity of the observation In the specific case of Gd , the hydrated ion has a logitudinal relaxivity of 9.1 $mM^{-1}$ $s^{-1}$ at 20 MHz and 35°, whereas the corresponding values for $Gd(EDTA)^{-}$ and $Gd(DTPA)^{2-}$ are 6 6 and 4 1 $mM^{-1}$ $s^{-1}$, respectively, under the same conditions [19]

**2). Specific in vivo distribution:** Ideally, to be of diagnostic value, the complex should localise for a period of time in the target tissue or tissue compartment in preference to nontarget regions, and thus enhance relaxation rates This is not only a function of the concentration of the agent in the desired tissue, but more importantly, also of the difference in relaxivities of the desired tissue over the others The choice of suitable MRI agent in this case is largely governed by the type of tissue to be studied.

**3). Non-toxicity, in vivo stability and excretability:** At the dosage required for MRI studies, lanthanide metal ions are known to be toxic The toxicity is reduced by complexation with ligands which form stable and kinetically inert complexes with the metal ion This forms the basis for detoxification of metal ion poisoning by chelation therapy While the high thermodynamic stability reduces the degree of complex dissociation, the kinetic inertness precludes loss of metal ion due to substitution processes Finally, the MRI agent should be excreted rapidly from the system

In medical sciences, chelating agents are used in both diagnostic and therapeutic applications.[21] Among the chelating compounds used either for chemical or medicinal purposes, polyaminopolycarboxylic acids stand out as archetypical metal binding agents. Some of the linear polyaminopolycarboxylic acid chelating agents (Fig. 2) arc ethylenediaminetetraacetic acid (EDTA, **21**), 1,2-diaminocyclohexanetetraacetic acid (DCTA, 22), tris-(2-aminoethyl) aminehexaacetic acid (TAAHA, 23) and diethylenetriaminepentaacetic acid (DTPA, **24).**

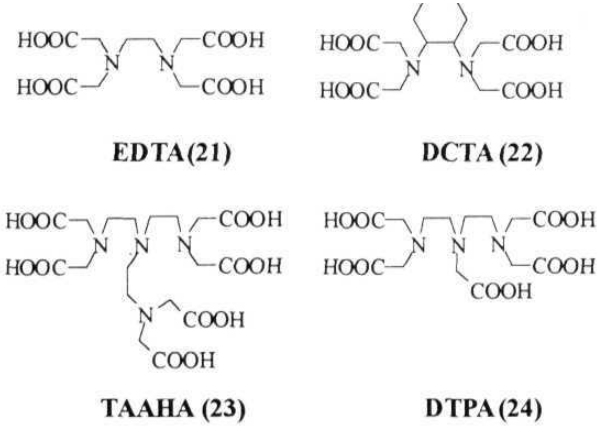
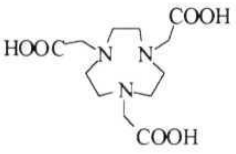



**Figure 2**

EDTA forms stable complexes with a number of physiologically important cations such as $Ca^{2+}$, $Mn^{2+}$, $Cu^{24}$, $Zn^{2+}$, $Fe^{2+}$ and $Fe^{3+}$ and is used to protect against toxic elements in cationic forms DTPA is superior to EDTA for polyvalent cations such as lanthanides and actinides because of its octadenticity

Amongst the metal ions, $Gd^{3+}$ ion appears to be the most useful paramagnetic[24] species because of its high magnetic moment and efficent relaxation However, this ion is too toxic to be used in vivo and it must be reacted with a chelating agent before being injected into the blood stream in order to facilitate its rapid excretion through the kidneys Safe and effective contrast agents containing gadolinium should not dissociate in the body, and thus should be highly stable and kinetically inert towards metal ion release High stability is achieved with the $Gd^{3+}$ complex of DTPA, and $Gd(DTPA)^{2-}$ is the most commonly used MRI contrast agent today.

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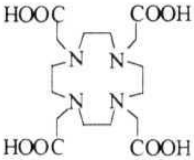
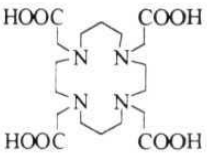



DOTA(26)

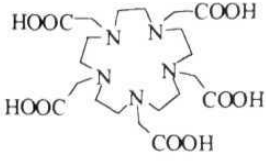



TETA(27)

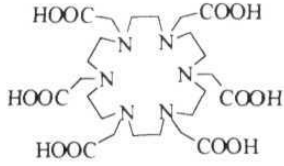
Figure 3

Chelating agents based on azacrown ethers bearing acetic acid moieties such as 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA, 25), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA, 26) and 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA, 27, Fig 3) have attracted considerable interest in the design of NMR contrast agents because of their multidentate ligating sites.[25] Stetter and Frank[26] reported that DOTA 26 forms the most stable $Ca^{2+}$ complex known, with a log K value of 16.5.[27] Kinetic investigation of the lanthanide DOTA chelates by Desreux[28] has shown that $Gd(DOTA)^-$ dissociates more slowly than $Gd(DTPA)^{2-}$ even in acidic media. $Gd(DOTA)^-$ is kinetically remarkably inert and also the complexes of lanthanides with DOTA have formation constants that are several orders of magnitude higher than both the EDTA and TETA. The stability constant for the formation of $Gd(DOTA)^-$, for example, was found to be $10^{27}$.

However, one of the drawbacks of these macrocyclic ligands is their slow complexation rate. The larger the ring size, the slower is the encapsulation rate.[28] In an attempt to design new ligand systems which could give a faster rate of complexation, Kodama[29a] synthesized the macrocyclic pentaazapentacarboxylic acid ligand (PEPA, 28) and hexaazahexacarboxylic acid ligand (HEHA, 29, Fig. 4) and studied their complexation with lanthanides ($La^{3+}$-$Lu^{3+}$, except $Pr^{3+}$). The stabilities of these complexes are almost parallel to those of DTPA and DOTA. In contrast to DOTA and TETA, PEPA and HEHA interact much faster with lanthanides. A comparison of the stability constants of the lanthanide




PEPA(28)




**HEHA(29)**

Figure 4

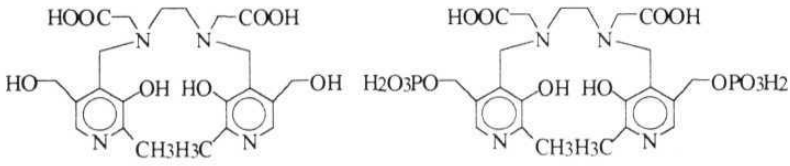
complexes of these macrocycles indicates that as the nitrogen atoms in the macrocycle increase, the 1 : 1 complex becomes more stable The stability constants of these macrocycles are presented in Table 1 [29b]

**Table 1**

**Stability Constants (log $K_{ML}$) of Macrocyclic Complexes of Lanthanides at 25° and μ=0.2 M $NaNO_3$.**

| Metal ion | **TETA** | PEPA | HEHA | **DTPA** | DOTA |
|---|---|---|---|---|---|
| $La^{3+}$ | 12.74 | 13.57 | 19.11 | **19.50** | – |
| $Ce^{3+}$ | 13.12 | 14 16 | **19.59** | 20.30 | 23.00 |
| $Nd^{3+}$ | 13.76 | 14.85 | 20.36 | 21.60 | – |
| $Sm^{3+}$ | 14.47 | 15 35 | 21.24 | 22.30 | - |
| $Eu^{3+}$ | 14.66 | 15.59 | 22.68 | 22.40 | 28.20 |
| $Gd^{3+}$ | 1473 | **15.88** | 22.95 | 22.50 | 24.60 |

Martell[30] prepared a multidentate ligand containing hydroxypyridyl donor groups (Fig.5), namely, N,N'-bispyridoxylethylenediamine-N,N'-diacetic acid (PLED, 30). This hexadentate ligand was found to have high affinity for trivalent metal ions [Ga(III) and Fe(III)], low ligand protonation constants and high water solubility Rocklage[31] synthesized the 5,5'-

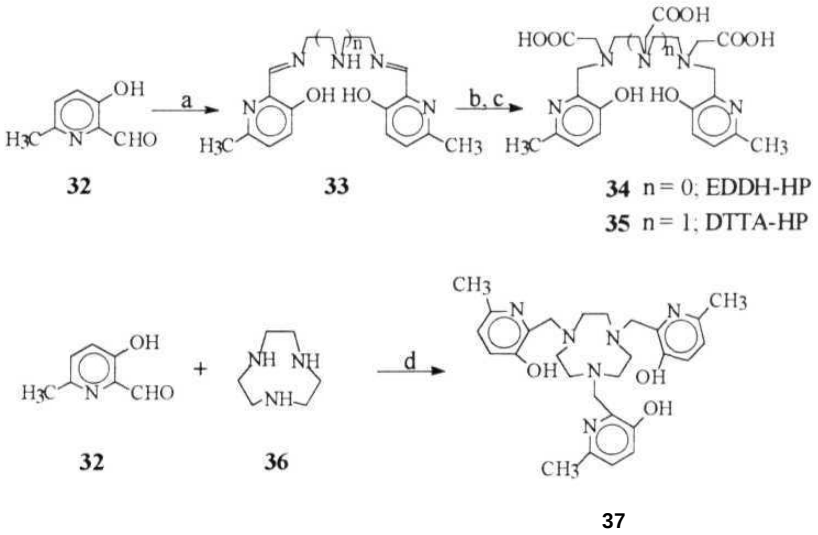



**PLED (30)** **DPDP(31)**

**Figure** 5

bisphosphate analogue of PLED, N,N'-dipyridoxylethylenediamine-N,N'-diacetic acid 5,5'-bisphosphate (DPDP, 31), and studied its divalent metal ion complexes for NMR imaging contrast enhancement. The disadvantage of these ligands is that they contain sterically demanding methyl groups and the pyridine nitrogens lower the pKa's of the ligands, making them more acidic. To overcome these problems, Martell[32] prepared septadentate ligands 34 and 35 and one octadentate ligand 37 (Scheme 5) and studied their complexation properties with Ga(III), Fe(III) and In(III) The ligands 34 and

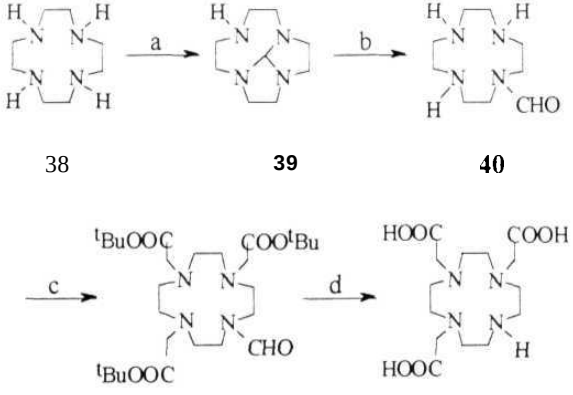
35 were prepared starting from a simple aldehyde, 3-hydroxy-6-methyl-2-pyridinecarboxaldehyde (32), by a modified Schiff s base formation, followed by reduction and alkylation with bromoacetate The ligand 37 was prepared from triazacyclononane (36), formaldehyde and 3-hydroxy-6-methylpyridine (32) by the Mannich reaction as shown in Scheme 5. Preliminary investigations showed that Ga(III) and Fe(III) complexes of 37 are extremely stable when compared to those derived from **34** and **35.**




**Scheme 5.** *Reagents and conditions:* a) diethylenetriamine, MeOH, b) $NaBH_4$; c) $BrCH_2COONa$, 6 N **HCl;** d) $CH_2O$, EtOH

Gadolinium complexes of DTPA, DOTA and EDTA ligands are charged under physiological conditions, and the requirement *of* nonparamagnetic cationic counterions increases the osmolality of the solution Minimum osmolality is predicted for a neutral complex, which behaves in aqueous solution as one species and this aspect has been addressed by several workers

Tweedle[33] prepared a new synthetically useful ligand, 1,4,7-tris (carboxymethyl)-1,4,7,10-tetraazacyclododecane, D03A 42, by several methods. One amongst them was by carboxymethylation of 40 with chloroacetic acid or tert-butyl bromoacetate followed by removal of the



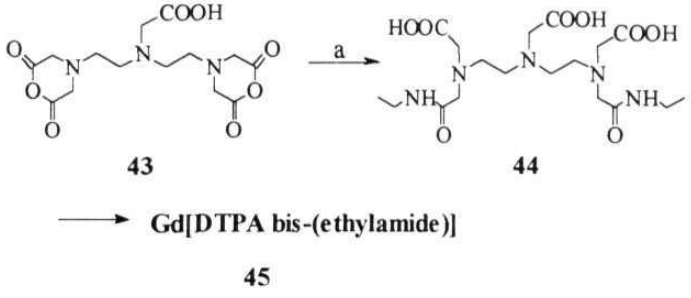

38 **39** **40**

41 42

**Scheme 6.** *Reagents and conditions:* a) $(CH_3)_2NCH(OCH_3)_2$, cyclohexane, b) $H_2O$, c) $BrCH_2CO_2{}^tBu$, toluene, NaOH, $H_2O$, d) $H_2SO_4$

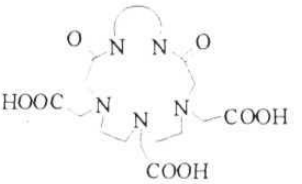
protecting groups as shown in Scheme 6 The ligand DO3A 42 is heptadentate and can be easily derivatized on the unique nitrogen of the macrocyclic ring, providing potentially octadentate ligands, which, upon reaction with gadolinium, form neutral Gd(III) complexes that are highly water soluble, inert to dissociation and substitution for Gd(III), and effective as proton relaxation agents.

In order to prepare a neutral gadolinium complex that retains high water solubility and relaxivity, DTPA-bis(ethylamide) 44 was prepared by Raymond[34] by treatment of DTPA-bis(anhydride) 43 with 70% ethylamine (Scheme 7). On reacting the ligand 44 with $Gd_2O_3$ in $H_2O$, the gadolinium complex 45 was obtained, whose crystal structure showed that the amide carbonyl oxygens play a prominent role in metal ion coordination.

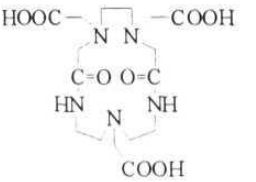



**Scheme** 7. *Reagents and conditions:* a) ethylamine, $H_2O$; b) $Gd_2O_3$, $H_2O$, heat

In order to understand the ligand selectivity in greater detail and to design newer generation of MRI contrast agents, several macrocyclic bis



DTPA . bis (amide) (46)



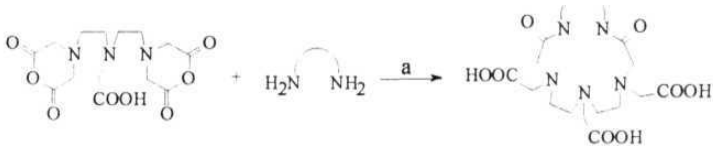
EDTA . DAM (47)

| macrocycle | N N |
|---|---|
| a) DTPA-EAM | HN NH |
| b) DTPA-PAM | HN NH |
| c) DTPA-BAM | HN NH |
| d) DTPA-cis$^{c=c}$BAM | HN NH |
| e) DTPA-Pen AM | HN NH |
| f) DTPA-XAM | HN NH |
| g) DTPA-OAM | HN O O NH |

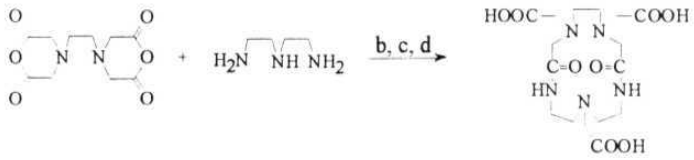
**Figure 6**

(amide) derivatives of DTPA and EDTA (Fig 6) were prepared by Carvalho[35] as illustrated in Scheme 8 Macrocyclic ligands have several advantages over acyclic ones as they are "preorganized" for metal complexation[36] and have the ability to structurally discriminate in binding various metal ions.[37]

It was found that the stability of the $Gd^{3+}$ complexes increases with increasing size of the DTPA-bis(amide) macrocycle series, because of the enhanced participation of the amide carbonyl oxygens in metal ion




**DTPA . bis (amide) macrocycle (46)**




**EDTA . DAM (47)**

Scheme 8. *Reagents and conditions:* a) DMSO, DMF, DBN; b) DBN, DMSO, c) $BrCH_2COO^tBu$, i-$Pr_2EtN$, MeOH; d) Trifluoroacetic acid

**Table 2**

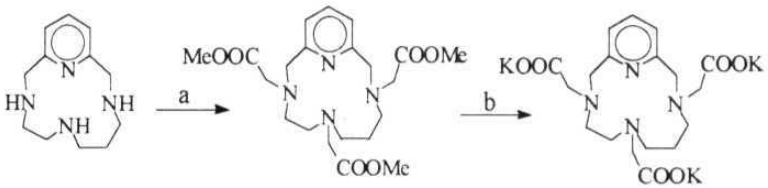
**Metal Chelate Stability Constants [log K, 25°, μ=0.10 M (KCl)j.**

| metal ion | DTPA -EAM | DTPA -PAM | DTPA-BAM[a] | DTPA-cis$^{c=c}$BAM | DTPA-PenAM | DTPA -XAM | DTPA -0 AM | EDTA -DAM |
|---|---|---|---|---|---|---|---|---|
| $Gd^{3+}$ | 11.15 | 14.49 | 1685 | 15 56 | 15.94 | 12.34 | 1744 | **15.14** |
| $Zn^{2+}$ | 12.08 | 11.74 | 1204 | 12 19 | 11 46 | 1065 | 12.19 | 9.03 |
| ($Gd^{3+}$ /$Zn^{2+}$) | -0.94 | 2.75 | 4.81 | 3.38 | 448 | 1.69 | 5.25 | 6.12 |

[a]Ref 38

coordination (Table 2) The greater the thermodynamic stability, the lesser the degree of complex dissociation which can potentially lead to toxicity However, a metal complex in vivo may also undergo other types of reactions including ligand displacement and transmetallation Thus, for example, endogenously available metal ions such as $Cu^{2+}$ and $Zn^{2+}$ can potentially compete for the ligand of a contrast agent and promote the release of $Gd^{3+}$ Gd(DTPA-BAM), the bis(methylamide) derivative of DTPA was the first nonionic MRI contrast agent developed for clinical application and its logarithmic selectivity constant for $Gd^{3+}$ over $Zn^{2+}$ is 4 81.[38] EDTA-DAM ligand was found to have highest selectivity for $Gd^{3+}$ over $Zn^{2+}$, presumably through a more favourable structural discrimination by this Iigand, and the structural isomer DTPA-EAM showed less favourable selectivity for $Gd^{3+}$ over $Zn^{2+}$.

Recently, Aime reported the synthesis of a novel heptadentate chelating ligand 50 and its lanthanide complexes with improved relaxation efficiencies.[39] The ligand 50 was prepared by reacting 48 with methyl bromoacetate in the presence of silver (I) carbonate followed by hydrolysis

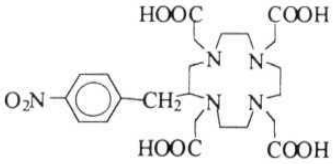



48 49 50

Scheme 9. *Reagents and conditions:* a) $BrCH_2CO_2Me$, $Ag_2CO_3$, DMF, b) KOH, MeOH

with KOH as in Scheme 14. $Ln^{3+}$ complexes of ligand 50 were prepared by mixing stoichiometric amounts of the ligand and the lanthanoid (III) chloride at neutral pH Thermodynamic formation constant (Kf) for the $Eu^{3+}$ complex was estimated through competitive NMR experiments between the ligand 50 and $Eu^{3+}$-1,2-diaminocyclohexane- N,N,N',N'-tetraacetic acid (22), and was found to be $3 \pm 2 \times 10^{18}$ and the relaxivity of $Gd^{3+}$-50 complex was 6.3 $m\ M^{-1}\ s^{-1}$ (20 MHz, 25°), about 35% higher than for Gd-DOTA and similar to that of Gd-DO3A

Complexes of polyazamacrocycles (bearing a C-substituted functional group for antibody attachment) exhibit remarkable kinetic inertness and have found applications in radioimmunotherapy For example, Mears[40] showed that the copper complex of 2-(*p*-nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (nitrobenzyl-TETA 52, Fig. 7) is very stable in human serum under physiological conditions. The conjugate of this complex with a monoclonal antibody has been tested as well in tumour bearing mice. These types of macrocyclic polyamines are the key precursors to macrocyclic bifunctional chelating agents conjugated to monoclonal antibodies Chelators that can hold radiometals such as $^{90}Y$ or

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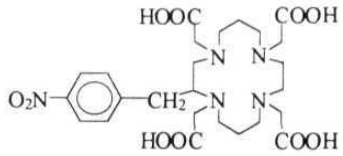


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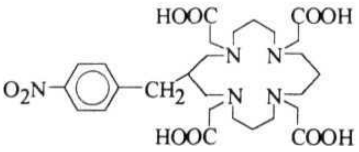
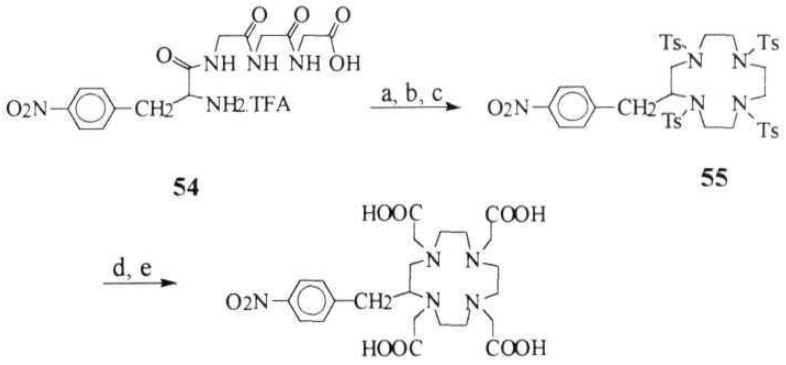



53

**Figure 7**

$^{67}Cu$ with high stability under physiological conditions are essential to avoid excessive radiation damage to nontarget cells in radioimmunotherapy

In this connection, Mears[41] prepared in good yields, polyazamacrocyclic bifunctional chelating agents such as the 12-memberd 2-(*p*-nitrobenzyl)-1,4,7,10-tetraazacyclotetradecane-N,N',N",N'"-tetraacetic acid (nitrobenzyl-DOTA, 51) via peptide synthesis and intramolecular tosylamide ring closure as shown in Scheme 10 The $^{88}Y(III)$ complex of this octadentate ligand (nitrobenzyl-DOTA, 51) forms in a few hours at




**51**

**Scheme 10.** *Reagents and conditions:* a) $BH_3$ THF, reflux, 3h, b) *p*-TsCl, $CH_3CN$, $Et_3N$, rt, 8h; c) $Cs_2CO_3$, DMF, 60°, 5h, d) 96% $H_2SO_4$, $C_6H_5OH$, 100°, 48h, e) $BrCH_2COOH$, pH 10, 70°, 3h

room temperature in 0.1 M ammonium acetate at pH 5 and is quite stable, whereas under the same conditions nitrobenzyl-TETA 52 or nitrobenzyl-HETA 53 do not form $^{88}Y(III)$ complexes in significant yields.

Derivatives of EDTA and DTPA are also used as bifunctional chelating agents with applications in tumour targeting via monoclonal antibody conjugates. In 1974 Mears[42] synthesized an EDTA derivative bearing a *p*-aminophenyl substituent **56a** (Fig. 8) that may be coupled to proteins under mild conditions. Benzyl **(56b, 56c),** phenethyl **(56d)** and 2-carboxyethyl (57) analogues have subsequently been described. Recently, Gansow[43] reported the preparation of the DTPA analogue *p*-SCN-Bz-DTPA 60 according to Scheme 11

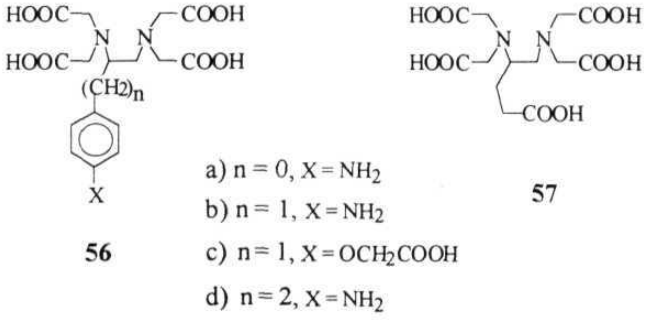
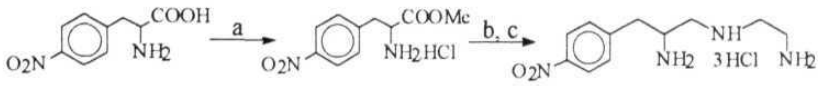
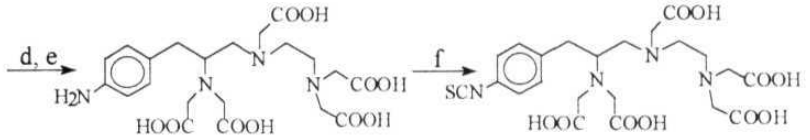



**Figure 8**



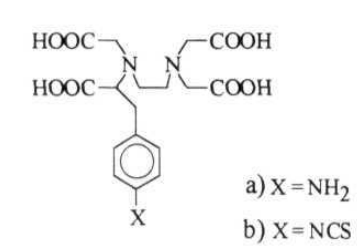

**58**



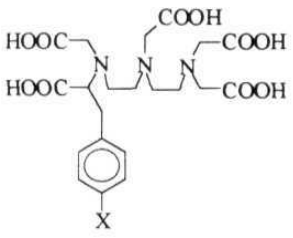

59 **60**

Scheme **11.** *Reagents and conditions:* a) HC1, MeOH; b) ethylenediamine, TEA, c) $BH_3$ THF, HC1, d) $BrCH_2COOH$, KOH; e) $H_2$, Pd/C, pH 10, f) $C(S)Cl_2$, pH 8.5.

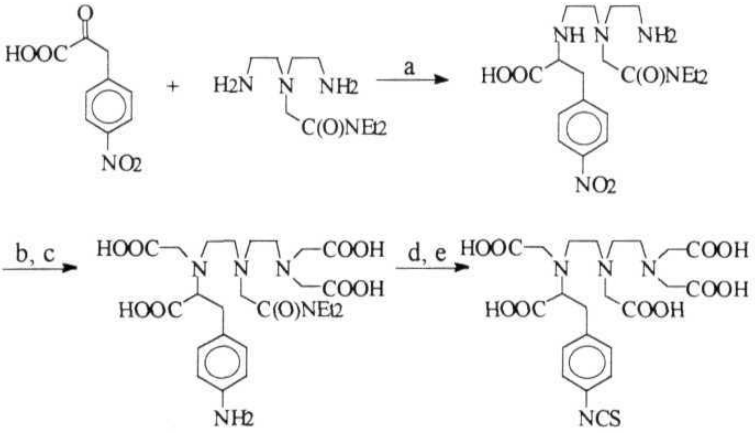
A common feature in all these structures is the attachment of the protein reactive function at a methylene carbon away from the polyamine backbone In seeking a more flexible, generic route for introducing a protein reactive moiety into a wide variety of polyaminopolycarboxylate frameworks, Johnson[44] synthesized another class of bifunctional chelating agents of the types 61 and 62, in which the protein reactive site is incorporated at a position common to, and accessible in all such chelators, namely, on one of the carboxymethyl arms, as shown in Scheme 12 All these




**61**




**62**




62a 62b

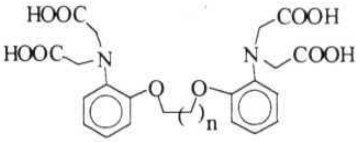
Scheme 12. *Reagents and conditions:* a) NaOH, $NaBH_3CN/HCl$; b) $BrCH_2COONa$; c) $H_2$, Pd/C, $H_2O/HCOOH$; d) NaOH, e) $C(S)Cl_2/HCl$, $CCl_4$.

bifunctional chelators are used in preparing monoclonal antibody conjugates for tumour targeting

Polyaminopolycarboxylate type chelators exert interesting patterns in selectivity for binding a series of alkaline earth metal ions from $Mg^{2+}$ to $Ba^{2+}$ Interest has been focussed on $Ca^{2+}$ because of its importance in physiological activities such as muscle contraction, neurotransmitter release, hormonal response and blood clotting Calcium binding proteins, such as troponin C[45] and calmodulin,[46] have high affinity for $Ca^{2+}$ over $Mg^{2+}$ and other alkaline earth metal ions because of their polycarboxylate binding sites In 1980, Schauer and Anderson[47] synthesized 3,6-dioxaoctane-l,8-diamine-N,N,N',N'- tetraacetic acid ($H_4$ egta, 63, Fig.9) and showed it to be an useful model for the $Ca^{2+}$ binding site of proteins


**$H_4$ egta**

**63**




**64**

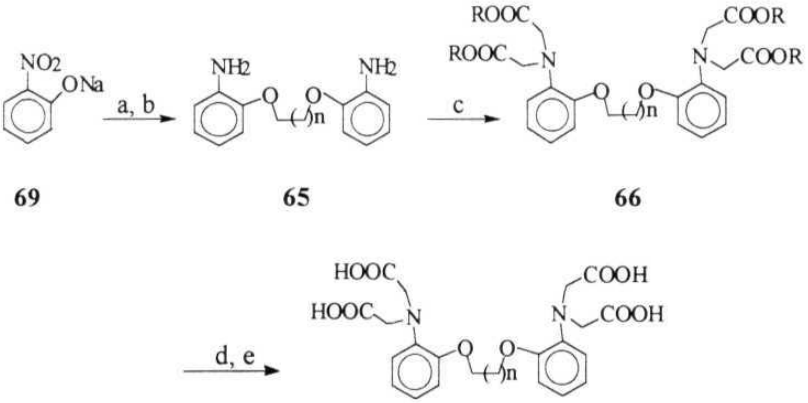
**a) n = l,** $H_4$ bapta

b) n = 2, $H_4$ bappta

c) n = 3, $H_4$ bapbta

**Figure 9**

Tsien[48] synthesized 1,2-bis(*o*-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (H4 bapta, 64a), an $H_4$ egta like chelator in which the 1,2-disubstituted benzene rings hold the amino nitrogens in the vicinity of the ethereal oxygens (Scheme 13). In addtion, $H_4$ bapta has some useful properties The existence of two phenyl groups in the molecule endows $H_4$ bapta with an appropriate absorption maximum in its UV spectrum. Thus,



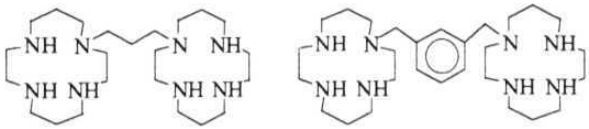

64a-c n = 1 - 3

Scheme 13. *Reagents and conditions:* a) $Br(CH_2)_nBr$, DMF, 100°; b) Sn, con.HCl, EtOH, reflux; c) 1,8-bis(diethylamino)naphthalene, $BrCH_2CO_2R$ (R = Me or Et), $CH_3CN$, reflux, d) KOH, $EtOH/H_2O$, 60°, e) Dowex 50wX8, $H_2O$

the chelated and free states of $H_4$ bapta can be followed quite conveniently by UV spectroscopy In addtion, $H_4$ bapta complexes faster with $Ca^{2+}$ than does $H_4$ egta, with about the same selectivity for $Ca^{2+}$ over $Mg^{2+}$ as $H_4$ egta

In order to study the structural interaction relationships on selective chelation towards metal ions, Ohno[49] prepared 1,3-bis(*o*-aminophenoxy) propane-N,N,N',N'-tetraacetic acid ($H_4$ bappta, **64b)** and 1,4-bis(*o*-aminophenoxy)butane-N,N,N',N'-tetraacetic acid ($H_4$ bapbta, **64c)** following the procedure reported by Tsien as depicted in Scheme 13 and showed that the $Ca^{2+}/Mg^{2+}$ selectivity of $bappta^{4-}$ resembles that of the $Ca^{2+}$-transporting protein, calmodulin

A series of bis-tetraazamacrocycles such as the bicyclam JM2763 (65) and JM3100 (66, Fig 10), are a novel class of antiviral agents that exhibit potent inhibitory effects on HIV-1 and HIV-2 replication with high selectivity These have been reported by De Clercq.[50]



8 HCl

**JM2763(65)**

8 HCl or 8 HBr

**JM3100 (66)**

**Figure 10**

As mentioned above, polyaminopolycarboxylic acid chelating agents such as EDTA, DTPA, DOTA and TETA and their derivatives form stable complexes with a number of transition and lanthanide metal ions which are useful in MRI studies and cancer treatment, whereas the crown ether complexes with alkali and alkaline earth metal ions are important from the physiological viewpoint Pendant macrocyclic compounds containing both crown ether and polyaminopolycarboxylic acid moieties are unknown Such compounds may exhibit some interesting properties which may be useful in biological systems Thus, we planned to prepare some polyaminopolycarboxylic acid crown ethers and study their complexation abilities with transition and lanthanide metal ions The synthesis *of* these compounds, and the results *of* their complexation studies, are discussed in the next chapter

# *RESULTS AND DISCUSSION*

## Results and discussion

As mentioned in the introductory chapter, the potential utility of chelating agents containing pendant polyaminopolycarboxylic acid arms in magnetic resonance imaging, cancer diagnosis and therapy prompted us to prepare some compounds containing both crown ether and polyaminopolycarboxylic acid units Two prototype structural units A and B incorporating both crown ether and polyaminopolycarboxylic acid moieties shown in Fig. 11 were initially identified for further analysis. The presence of two a-amino ether units in structure A suggests that it would be susceptible to acid catalysed hydrolysis and hence attention was focussed on structure B A straightforward retrosynthetic analysis of B led to the conclusion that pentaerythritol would be a convenient starting material

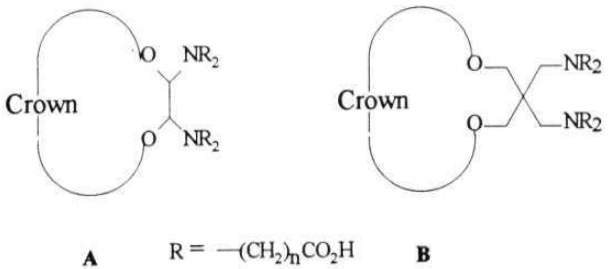
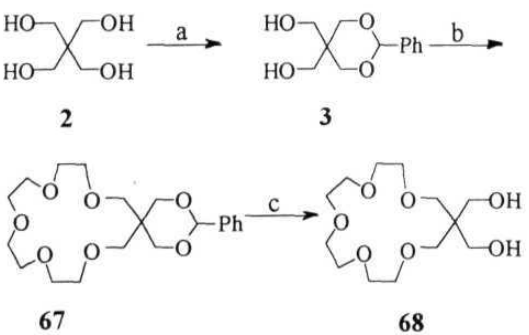



**Figure 11**

Weber has reported the synthesis of multi-loop spiro crowns 7, 8 and 9 containing the crown diol moiety 4 . We realized the utility of 4 and related structures in the synthesis of our polyaminopolycarboxylic acid crown ethers since they provide a crown ether cavity as well as the hydroxyl functionality which can further be transformed into the polyaminopolycarboxylic acid unit.

Thus, the crown diol 68 was prepared starting from the easily available pentaerythritol [2, Scheme 14]. Treatment of pentaerythritol (2) with benzaldehyde in the presence of conc. HC1 furnished monobenzalpentaerythritol 3 which on treatment with tetraethylene glycol ditosylate in the presence of sodium hydride in THF at reflux temperature

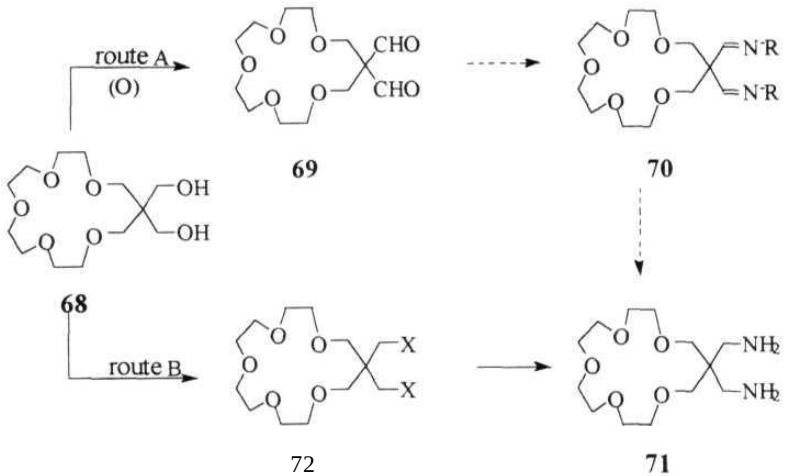



**Scheme 14.** *Reagents and conditions:* a) PhCHO, HC1; b) tetraethylene glycol ditosylate, NaH, THF, reflux, 12 h; c) 0.1 N $H_2SO_4$, heat, 12 h

afforded the 3-phenyl-2,4,8,11,14,17,20-heptaoxaspiro[5.15]heneicosane (67). This upon acid hydrolysis afforded the required crown diol 68. The physical and spectral properties of 68 were in agreement with those reported in the literature.

At this point, starting from the crown diol 68 several options were considered to prepare the crown diamine 71, which could serve as the starting material for the synthesis of the target polyaminopolycarboxylic acid crown ethers. In the first approach, synthesis of the crown dialdehyde 69 was envisaged to be followed by its condensation with a suitable amine to provide the Schiffs base 70 (Scheme 15). Subsequent removal of the R group would then lead to the crown diamine 71. This route was planned so as to avoid a nucleophilic substitution of the hydroxyl group of 68, a neopentyl type substrate, by a nitrogen nucleophile An alternate method for the synthesis of 71 involves a nucleophilic substitution as the key step, although it suffers from the drawback mentioned earlier (route B).

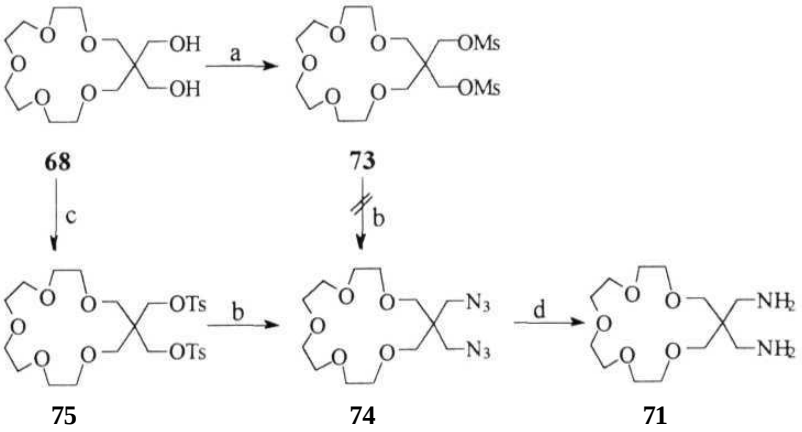
Oxidation of the crown diol 68 with several oxidising agents such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), chromic acid in pyridine and N-chlorosuccinimide/dimethyl sulfide, all lead to complex mixtures. Examination of the IR spectra of these mixtures revealed the presence of the carbonyl group. However, no separations of the mixtures could be achieved.




**Scheme 15.**

As oxidation of 68 did not provide the required dialdehyde 69 in pure form, the second approach was adopted Thus, as shown in Scheme 16, the crown diol 68 on treatment with methanesulfonyl chloride provided the crown dimesylate 73 which, without further purification, was reacted with sodium azide to afford a mixture of products from which the required crown diazide 74 was not separable in pure form by column chromatography. The IR spectrum of the mixture showed the characteristic azide absorption at 2100 $cm^{-1}$ and mesylate bands at 1370 and 1190 $cm^{-1}$, indicating the presence of both product and starting material. This incomplete reaction is

probably due to the sluggish nucleophilic displacement of the mesylate group In order to make the nucleophilic displacement more facile, we planned to use the crown ditosylate 75 instead of the dimesylate An initial attempt at tosylation of 68 was by treating it with p-toluenesulfonyl chloride in pyridine The reaction gave a mixture and the required product could not be obtained in a pure form Under the conditions employed by Ouchi, we were able to tosylate the crown diol 68 in good yield (80%) and the desired product 75 was obtained as a white crystalline solid ` The product was characterized by its spectral as well as by its analytical data The IR spectrum




**Scheme 16.** *Reagents and conditions:* a) methylenesulfonyl chloride, DMAP, pyridine, b) $NaN_3$, DMF, 120°, 72 h, c) *p*-toluenesulfonyl chloride, NaOH, $THF/H_2O$, 5°, 1 h; d) LAH, THF, reflux, 12 h.

of the compound showed sulfonate bands at 1353 and 1187 cm"[1] and no band corresponding to the -OH groups, substantiating the ditosylation of the crown diol 68. The $^{1}H$ and $^{13}C$ NMR spectra were also fully in consonance with the assigned structure.

Nucleophilic displacement of the crown ditosylate 75 with azide was performed by refluxing it with 6 eq. of sodium azide in DMF for 3 days. Under these conditions, the crown diazide 74 was obtained in almost quantitative yield. The IR spectrum of crown diazide 74 clearly showed the azide absorption at 2100 cm'[1].

Our intial attempts at reducing the diazide 74 to diamine 71 with 2.5 eq. of LAH at rt or at reflux were unsuccessful. Subsequently, other methods of reduction of the crown diazide 74 such as catalytic transfer hydrogenation using 10% Pd/C in cyclohexene[52] or triphenylphosphine/hydrobromic acid/acetic acid[53] were found to be of no avail.

Suprisingly, when the reduction of 74 was carried out with 6 fold excess of LAH in THF under reflux, the required crown diamine 71 was obtained in quantitative yield. The diamine 71 was completely characterized by its spectral and analytical data. Its IR spectrum showed amine absorptions at 3315, 939 and 879 cm"[1] and the absence of the azide band at 2100 $cm^{-1}$, indicating the complete reduction. The $^{1}H$ NMR spectrum contained a singlet at 2.89 ppm corresponding to the methylene protons adjacent to the amino group, as well as signals at 3.46 and 3 60-3.65 ppm that of the crown

protons Finally the $^{13}C$ NMR specrtum displayed resonance at 72 24, 70 77, 64.59, 44 59 and 35 59 ppm, conforming the assigned structure

The reactions of two other nitrogen nucleophiles, ethyl urethane and benzyl amine on the crown ditosylate 75 were both unsuccessful Only the unreacted starting material could be recovered in each case

At this stage, our attention was focussed on the synthesis of polyaminopolycarboxylic acid crown ethers starting from the crown diamine **71** The crown diamine 71, at the most, can only lead to a crown diaminetetraacetic acid with 6 binding sites. In order to obtain compounds with more ligating sites (lanthanides are known to form complexes with higher coordination numbers like 8-12),[24] synthesis of the crown tetraamine 78 was planned, which in turn can be transformed to a crown tetraaminehexaaacetic acid having 10 binding sites

Synthesis of the crown tetraamine 78 can be conceived of in two possible ways (Fig 12). The first approach consists of the nucleophilic displacement of the crown dihalide 72 with ethylenediamine The second route involves incorporation of two more nitrogens into the crown diamine moiety The former suffers from the drawback that it can yield more than one product leading to problems in purification Therefore. the latter approach was adopted since the formation of a mixture of products can be avoided by selecting suitable reagents

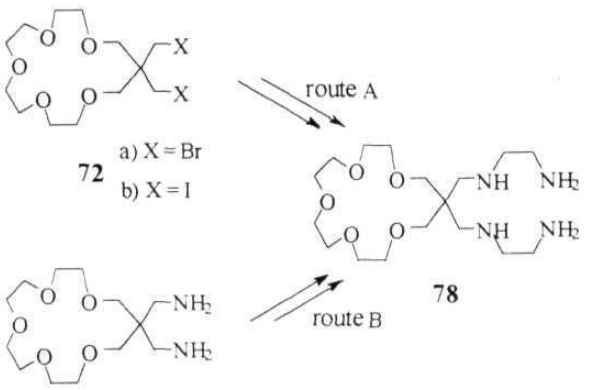
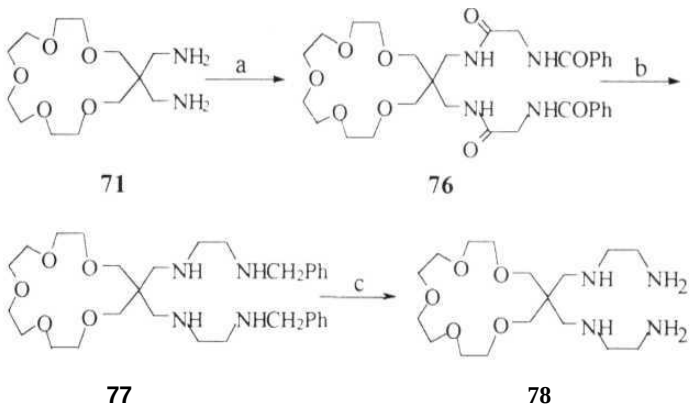



**Figure 12**

Thus, according to Scheme 17, the crown diamine 71 was condensed with hippuric acid in the presence of DCC to afford the diamide 76 in 75% yield Compound 76 was fully characterised by elemental and spectral data The IR spectrum of 76 contains the characteristic amide absorption bands at 1650 and 1550 $cm^{-1}$ and the $^1H$ NMR spectrum showed a doublet at **4.12-**4 15 ppm corresponding to methylene protons adjacent to the carbonyl group ($COCH_2NH$). **The** $^{13}C$ NMR spectrum indicates the presence of two types of carbonyl carbons at 170 19 **ppm** ($NHCOCH_2$) and 167 50 ppm ($NHCOPh$).




71 76 77 78

Scheme 17. *Reagents and Conditions:* a) hippuric acid, DCC, dichloromethane, 5°; b) LAH, THF. reflux, 12 h, c) $H_2$, 20% $Pd(OH)_2/C$, EtOH, 65 psi, 5 h

Diamide 76 on reduction with 6 eq of LAH in THF at reflux afforded the crown N,N'-dibenzyltetraamine 77 in quantitative yield as a brown coloured syrup An excess of LAH was needed for the complete reduction of 76 to 77. The IR spectrum of 77 showed the absence of amide and carbonyl bands, indicating the complete reduction of **76** The FAB mass spectrum contains the $(M + H)^+$ peak at m/z = 559 Inadequate purification of 77 due to its high polar nature precluded its elemental analysis Hence its hydrochloride salt was prepared by passing dry HC1 gas into a dichloromethane solution *of* 77 The salt, however, was highly sensitive to

moisture Finally, 77 was characterized as its (tetrakis)hexafluorophosphate salt, a white solid prepared by treating the hydrochloride salt of 77 with 4 eq of ammonium hexafluorophosphate

Removal of the N-benzyl groups of 77 was attempted next No cleavage occurred when 77 was treated with: 1) 4 4% formic acid in methanol and 10% Pd/C[54] (quantitative amount), 2) sodium in liq ammonia,[55] 3) ammonium formate and 10% Pd/C[56], 4) hydrogenation with 10% Pd/C in the presence of acetic acid[57] and 5) hydrogenation with 10% Pd/C in ethanolic HC1 [58] Finally, cleavage of the N-benzyl group was attained using 20% $Pd(OH)_2/C$ (Pearlman **catalyst).**[59] Thus, when the N,N'-dibenzyltetraamine 77 was hydrogenated in ethanol using 2 eq of 20% $Pd(OH)_2/C$ (by weight) at 65 psi for 4 h, the desired crown tetraamine 78 was obtained in good yield as a hygroscopic foamy material During the course of this reaction, it was observed that the amount of 20% $Pd(OH)_2/C$ used was a decisive factor When catalytic or 1 eq of 20% $Pd(OH)_2/C$ was used, cleavage of the N-benzyl group was not effected This is attributed to the complexation of the crown tetraamine 78 with palladium, thus poisoning the catalyst for further reaction

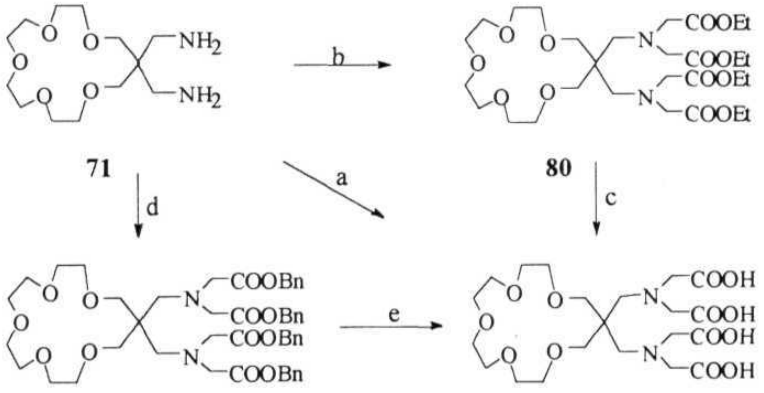
The hygroscopic nature of 78 precluded direct elemental analysis For the complete characterization of 78, preparation of its hexafluorophosphate salt was attempted, but without success However, the bis(tetraphenylborate) salt of 78 could be prepared by treating 78 in 0 1 M HC1 solution with an aq solution of sodium tetraphenylborate This was

identified by its elemental and spectral data The $^{1}H$ NMR spectrum showed no signals due to the benzyl groups, indicating complete cleavage

Having the crown diamine 71 and the crown tetraamine 78 in hand we endeavoured to prepare the corresponding tetra- and hexaacetic acids as depicted in Schemes 18 and 19 Initially, direct N-alkylation using bromoacetic acid was attempted [43] Thus, when the crown diamine 71 and the crown tetraamine 78 were subjected to N-alkylation with bromoacetic acid in the presence of potassium hydroxide at 5°, the crude crown diaminetetraacetic acid 79 and the crown tetraaminehexaacetic acid 82 were obtained The IR spectra of 79 and 82 clearly indicate the acid hydroxyl and carbonyl absorptions at 3408 and 1734 $cm^{-1}$ Purification of 79 and 82 by either chromatography or ion exchange techniques was, however, unsuccessful.

An alternate method, also reported in the literature, involves the use of ethyl bromoacetate as the alkylating reagent, followed by hydrolysis to afford the free acid[60]. Accordingly, the crown ethyl esters 80 and 83 were obtained by N-alkylation of the corresponding amines 71 and 78 with ethyl bromoacetate in the presence of potassium carbonate These compounds 80 and 83 were characterized by their spectral and analytical data The IR spectrum of 80 showed the ester carbonyl band at 1734 $cm^{-1}$ and the $^{1}H$ NMR spectrum indicated the presence of ethyl ester signals as a quartet at 4.09-4.19 ppm and a triplet at 1 22-1.25 ppm, along with crown proton signals at 3.48-3.64 ppm as a multiplet. The $^{13}C$ NMR spectrum showed the

ester carbonyl carbon at 172 ppm and finally the FAB mass spectrum displayed the $(M + H)^+$ peak at m/z = 637 In the IR spectrum of 83, a strong ester carbonyl absorption at 1732 $cm^{-1}$ was seen The $^1H$ NMR spectrum showed signals at

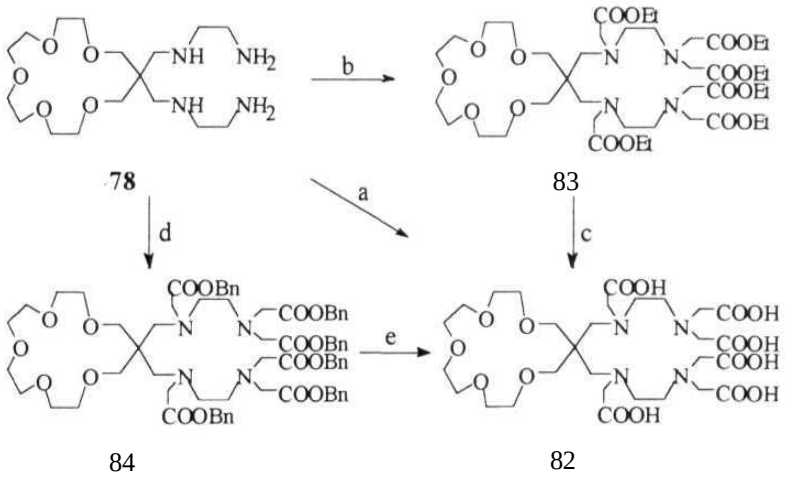



81

**Scheme 18.** *Reagents and conditions:* a) $BrCH_2COOH$, KOH, $H_2O$; b) $BrCH_2COOEt$, $K_2CO_3$, DMF, 100°, 48 h, c) KOH, $H_2O$, reflux, 12 h, d) $BrCH_2COOBn$, $K_2CO_3$, DMF, 120°, 72 h, e) $H_2$, 20% $Pd(OH)_2/C$, EtOH, 65 psi, 3 h.

4.13-4.20 and at 1.22-1 29 ppm corresponding to the ethyl ester protons and the crown protons at 3.53-3.63 ppm as a multiplet. The $^{13}C$ NMR spectrum

contains two carbonyl carbon peaks at 172 and 171 ppm and the FAB mass spectrum gave the $(M + H)^+$ peak at m/z = 895




Scheme 19. *Reagents and conditions:* a) $BrCH_2COOH$, KOH, $H_2O$; b) $BrCH_2COOEt$, $K_2CO_3$, DMF, 100°, 72 h, c) KOH, $H_2O$, reflux, 12 h, d) $BrCH_2COOBn$, $K_2CO_3$, DMF, 120°, 72 h; e) $H_2$, 20% $Pd(OH)_2/C$, EtOH, 65 psi, 5 h.

Basic hydrolysis of 80 and 83 yielded the crude crown diaminetetraacetic acid 79 and the crown tetraaminehexaacetic acid 82, respectively. In this case also purification of 79 and 82 was unsuccessful either by chromatography or ion-exchange techniques. This difficulty

perhaps arises due to the use of strongly basic and acidic conditions in the course of hydrolysis and workup. In order to avoid acidic and basic conditions in the preparation and purification of 79 and 82, either in reaction or in the workup procedure, we adopted a new method for their synthesis This method comprises the preparation of benzyl esters of 79 and 82, followed by hydrogenolysis. Accordingly, 71 and 78 were reacted with benzyl bromoacetate in the presence of potassium carbonate to obtain the corresponding benzyl esters 81 and 84 in 54% and 12-15% yields, respectively. Attempts to improve the yield of 84 by treating 78 with benzyl iodoacetate/potassium carbonate or cesium carbonate in DMF as well as in acetonitrile under reflux conditions for 3 days were of no avail. These benzyl esters 81 and 84 were identified by their elemental and spectral data. The IR spectra of 81 and 84 showed the carbonyl absorption at 1743 cm" and H NMR spectrum clearly indicated the benzyl methylene protons at 5.10 ppm as a singlet. In the C NMR spectrum of 81, the carbonyl signal was observed at 171.76 ppm whereas in 84 two carbonyl signals at 171 14 and 170.60 ppm were observed.

Finally, synthesis of the desired crown diaminetetraacetic acid 79 and the crown tetraaminehexaacetic acid 82 were accomplished by hydrogenolysis of 81 and 84, respectively, using 2 eq. of 20% $Pd(OH)_2/C$ (by weight) in ethanol at 65 psi. These compounds 79 and 84 were fully characterised by their elemental and spectral data. The IR spectrum of 79 showed the acid OH and carbonyl absorption bands at 3422 and 1739 $cm^{-1}$, respectively. In the $^1H$ NMR spectrum, the benzyl ester signals of 81 were

absent and the $^{13}C$ NMR spectrum clearly displayed the acid carbonyl carbon at 170 ppm The IR spectrum of 82 showed acid OH and carbonyl absorption bands at 3429 and 1736 $cm^{-1}$, respectively. The $^{1}H$ NMR spectrum showed the absence of benzyl ester signals of 84, indicating complete benzyl group cleavage.

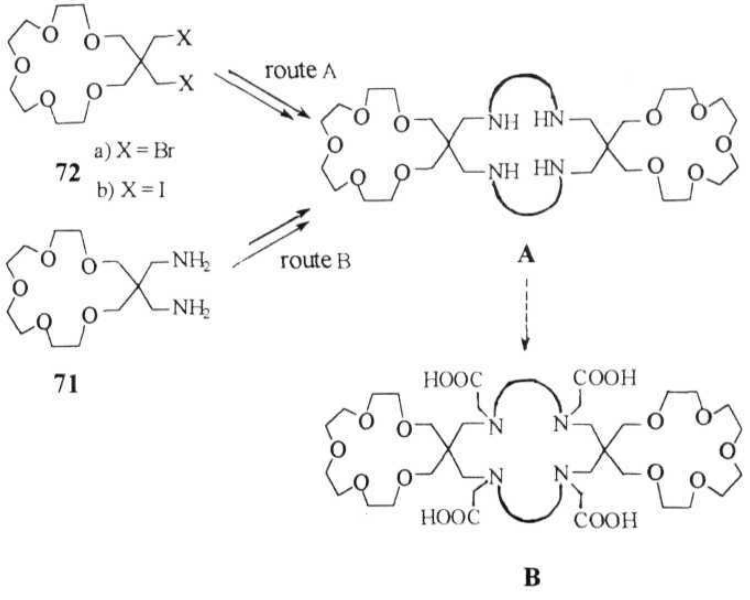
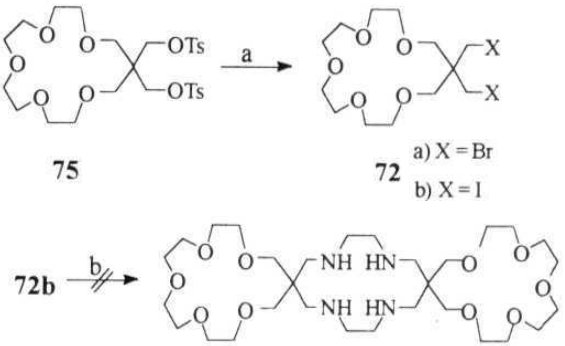



**Figure 13**

The successful realization of the synthesis of 79 and 82 prompted us to take up the synthesis of multiloop aza crown ethers of the type A (Fig 13). These compounds could then serve as precursors to the polyaminopolycarboxylic acids B, analogous to the tetraazamacrocyclic compounds DOT A 26 and TETA 27. As depicted in Fig. 13, this was sought to be achieved from either the crown dihalides 72a, b or the crown diamine 71. Accordingly, the dibromide 72a and the crown diiodide 72b were prepared from the crown ditosylate 75 (Scheme 20). Thus, the crown ditosylate 75 was reacted with sodium bromide or sodium iodide in diethylene glycol at 150° to furnish the crown dibromide 72a or the crown diiodide 72b in good yields. The products were characterized by elemental analysis and spectral data. In the $^{1}H$ NMR and $^{13}C$ NMR spectra, the tosylate signals of 75 were absent 72a & b showed the bromomethyl carbon at 35.9 ppm and iodomethyl carbon at 13.58 ppm, respectively, in the $^{13}C$ NMR spectra.

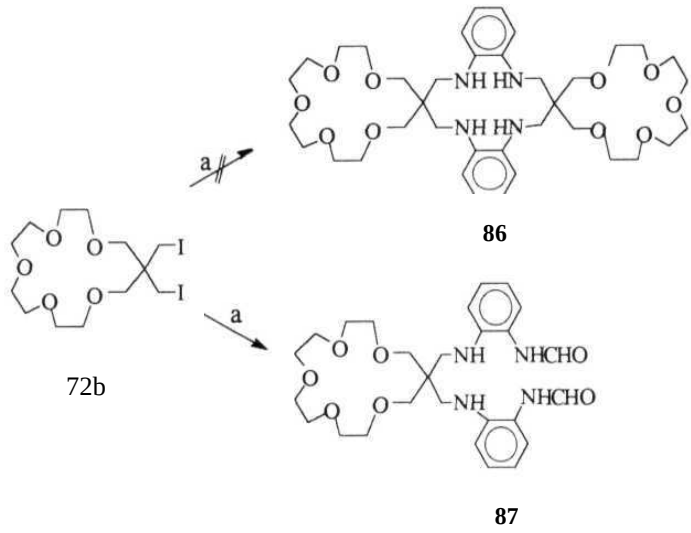
With the halides 72a and 72b in hand, the linking process to generate a tetraazamacrocycle was attempted. On reaction with ethylenediamine, 72b gave a complex, inseparable mixture. When nickel (II) sulphate was added to act as a template in the above reaction, a more polar, complex mixture resulted. Once again, no separation could be achieved. Examination of the crude IR and $^{1}H$ NMR spectra of these products indicated the presence of crown ether protons. No further structural information could be obtained




85

Scheme 20. *Reagents and conditions:* a) NaBr or NaI, diethylene glycol, 50°, 12 h, b) ethylenediamine, 100°, 12 h.

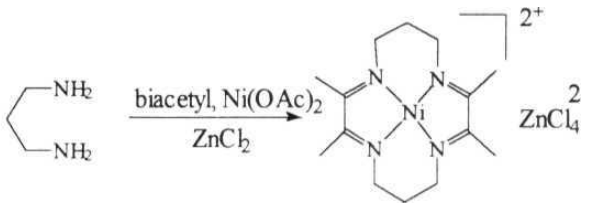
The crown diiodide **72b** on heating with o-phenylenediamine in DMF furnished a complex mixture (Scheme 21). This mixture was partially separated by successive extraction with dichloromethane and methanol. The IR and $^1H$ NMR spectra of both dichloromethane and methanol soluble fractions showed signals corresponding to aromatic and crown ether protons. It was observed that the $^1H$ NMR spectra of these products contain a signal at 8.13 ppm corresponding to a formyl proton From this it was deduced that the reaction resulted only in the formylated product 87 and that none of the desired product 86 was formed Further purification and characterization of 87 was not attempted.




**Scheme 21.** *Reagents and conditions:* a) *o*-phenylenediamine, DMF, 120°, 72 h.

In order to avoid the formation of a mixture of products, the second approach was adopted starting from crown diamine 71. It is known in the literature that 1,3-diamines on reaction with biacetyl in the presence of nickel (II) sulphate and zinc (II) chloride form the nickel (II) complexes of [14]-cyclam 88 [61] (Fig. 14). Accordingly, when the crown diamine 71 was treated with one eq. of biacetyl, under the same conditions (Scheme 22), a buff

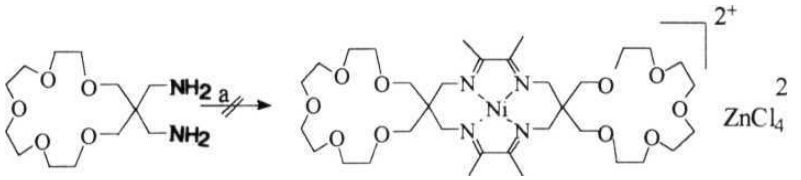
coloured solid was obtained. However, its elemental analysis and spectral data did not correspond to the expected nickel complex of the spiro crown




88

**Figure 14**

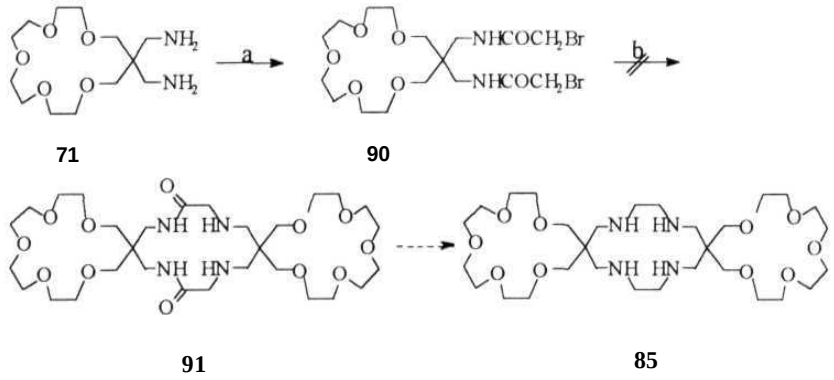
compound 89. The IR spectrum of the product mixture has absorption bands at 3134, 3047 and 1610 $cm^{-1}$ and a strong ether band at 1093 $cm^{-1}$. The $^{1}H$ and $^{13}C$ NMR spectra do not display the signals corresponding to methyl protons of **89.**




71 89

**Scheme 22.** *Reagents and conditions:* a) biacetyl, HC1, **MeOH,** $NiSO_4$, $ZnCl_2$.

In another method, condensation of the crown diamine 71 with bromoacetic acid in the presence of DCC in dichloromethane afforded the crown bis(bromoacetamide) 90 in 60% yield (Scheme 23). The IR spectrum of 90 showed a strong absorption band at 3400 and 1760 $cm^{-1}$, indicating the presence of a secondary amide and the $^{13}C$ NMR spectrum had signals from the amide carbonyl carbon at 168 6 ppm and halocarbon at 29 12 ppm When the crown bis(bromoacetamide) 90 was treated with the crown diamine 71 in ethanol at reflux temperature a complex resulted mixture from which the required product was not isolable. The IR spectrum of the crude mixture showed the carbonyl band at 1660 and the crown ether band at 1100 $cm^{-1}$.

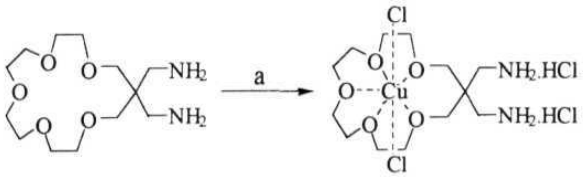



**Scheme 23.** *Reagents and conditions:* a) $BrCH_2COOH$, DCC, dichloromethane, 5°, 12 h; b) 71, EtOH, reflux, 12 h

Finally, in order to obtain the spiro crown system present in 85, the crown diamine 71 was treated with oxalyl chloride in dichloromethane as well as with diethyl oxalate in ethanol at reflux temperature Both reactions, however, resulted in complex mixtures and their separation was not attempted

At this stage we did not pursue further the synthesis of spiro crowns in the light of all these failures

In order to investigate the complexation ability of the crown diamine 71, preparation of some of its metal complexes were attempted. When a 1 : 1 mixture of the crown diamine 71 and cupric chloride in ethanol was heated, a light yellow coloured crystalline material of the crown diamine-copper complex 92 was obtained (Scheme 24) The IR spectrum of 92 showed the crown ether bands at 1100 $cm^{-1}$ along with primary ammonium bands at 3100-3000 $cm^{-1}$. In the UV spectrum of 92, recorded in methanol,

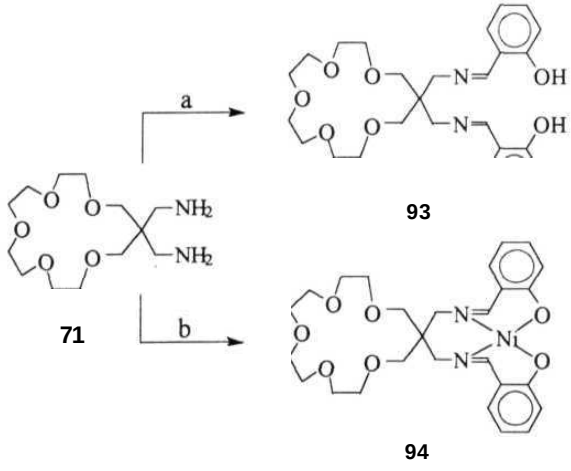



71 **92**

**Scheme 24.** *Reagents and conditions:* a) $CuCl_2\ 2H_2O$, EtOH, heat

an absorption maximum at 899 nm was seen. The complex analysed for $C_{13}H_{30}N_2O_5CuCl_4$, suggesting that both amine nitrogens are protonated. A plausible structure, with the copper (II) ion in the middle of the cavity, is shown in **92.**

When the crown diamine 71 was treated with salicylaldehyde in ethanol at reflux temperature for 24 h, the crown salicylaldimine 93 was obtained as a brown coloured syrup, found to be unstable on long standing (Scheme 25). The structure of 93 was confirmed by the presence of a strong phenolic OH absorption band at 3300 $cm^{-1}$ in the IR spectrum and also by



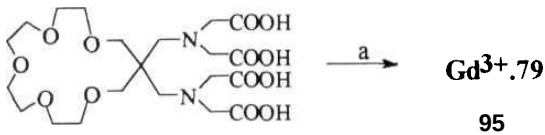

**Scheme 25.** *Reagents and conditions:* a) salicylaldehyde, EtOH, heat, 12 h; b) salicylaldehyde, $NiSO_4$, EtOH, heat, 48 h.

the presence of phenolic OH protons, aromatic proton and imine proton signals at 8.38 , at 7.27-7.35 and at 6.84-6.97 ppm, respectively, along with the crown proton signals in the $^1H$ NMR spectrum

It is known in the literature that nickel (II) complexes of Schiff s bases can be prepared using nickel (II) sulfate or nickel (II) acetate as a template [62] Thus, the crown salicylaldiimine nickel (II) complex 94 was prepared by refluxing the crown diamine 71 and salicylaldehyde in ethanol, followed by the addition of nickel (II) sulfate The resulting dark green complex was purified by column chromatography. Identification of the product rests on its spectral data. The UV spectrum of the complex 94 in methanol showed an absorption maximum at 585.4 nm (e = 68), typical of a d-d transition [62] The $^1H$ NMR spectrum contains signals at 6.99-7.22 ppm corresponding to the aromatic protons, the imine protons as a triplet at 6.50 ppm along with the crown proton signals at 3.41-3.64 ppm. It was also observed that in the $^1H$ NMR spectrum of 94, a signal at 8.38 ppm corresponding to the phenolic OH proton of the free crown salicylaldimine 93 was absent, indicating the participation of the phenolic oxygen in complexation.

The crown diaminetetraacetic acid-$Gd^{3+}$ complex 95 was prepared by treating 79 with gadolinium oxide (Scheme 26). The light pink coloured solid $Gd^{3+}$ complex 95 was identified by the presence of a carboxylate absorption band at 1600 $cm^{-1}$ in the IR spectrum Broadening of signals in the $^1H$ NMR spectrum, because of paramagnetic nature of the $Gd^{3+}$ ion, was

observed The ESR spectrum of 95 also showed a broad symmetric signal with a g value of 2.06, close to the reported $Gd^{3+}$ g value of 1 991 for gadolinium trichloride doped in lanthanum trichloride.[63]




79 95

**Scheme 26.** *Reagents and conditions:* a) $Gd_2O_3$, $H_2O$, heat.

**Determination of Acid Dissociation and Stability Constants.**

Due to **the** importance of gadolinium complexes of polyaminopolycarboxylic acid chelating agents like DTPA 24, DOTA 25 and TETA 26 in MRI studies, we synthesized novel chelating ligands containing both crown and polyaminopolycarboxylic acid functionalities, such as the crown diamine 71, the crown diaminetetraacetic acid 79, the crown tetraamine 78 and the crown tetraaminehexaacetic acid 82 and studied their complexation abilities with different metal ions in solution. Crown ethers are known to form stable complexes with lanthanide metal ions with different stoichiometries[64]. Our attention in the study of the complexation abilities of 71, 79 and 84 was also focussed mainly on the lanthanides. The acid dissociation and chelate stability constants were measured by the

potentiometric titration method All the constants were determined by using the computer program SCOGS 2 [65]

Initially, the acid dissociation constants were calculated and were used for determining the stability constants The dissociation constants were calculated using the methods of Jonassen[66] and Martell[69] and were used as rough estimates for the input data in the program SCOGS 2 The measurements and calculations are discussed in the following paragraphs

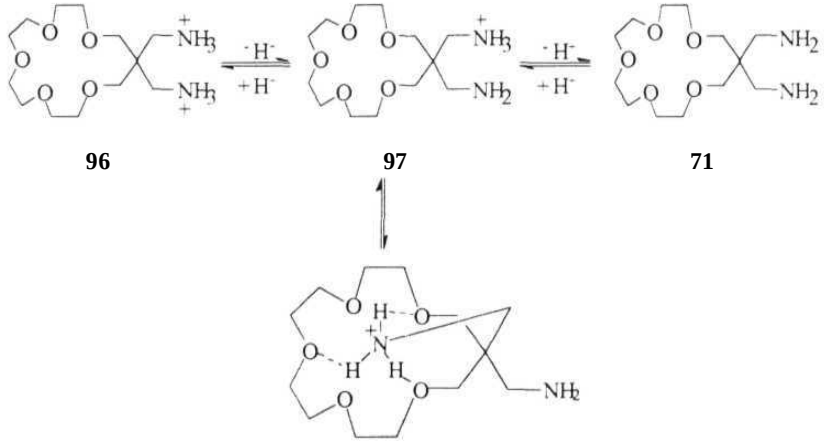
### 1. Crown Diamine 71.

**a) Determination of acid dissociation constants:**

Using the potentiometric data (please see experimental for details) the acid dissociation constants of the protonated form of 71 were calculated by Jonassen's method[66] and $pK_1$ was obtained as 3.31 and $pK_2$ as 8.76. These values were used as input in the program, and after refinement, the acid dissociation constants obtained were $pK_1$ = 2.86 and $pK_2$ = 8.79.

From our results, it is evident that the first acid dissociation constant ($pK_1$ = 2.86) of the crown diamine 71 is very low when compared with that of 1,3-propanediamine ($pK_1$ = 8.36 and $pK_2$ = 10.52).[68] This indicates that the diprotonated species of crown diamine 71 is more acidic than that of 1,3-propanediamine The large difference in $pK_1$'s may be due to the effect of the crown ether moiety that is present in 71 It is known in the literature that in the case of 18-crown-6 ethers containing a pendant primary ammonium

group, hydrogen bonding is possible between the ammonium moiety and the crown cavity [15] A similar phenomenon is likely with the crown diamine 71 also. The monoprotonated species of the crown diamine 97 formed from the diprotonated species 96 by loss of one proton is stabilised by intramolecular complexation of the crown with the primary ammonium ion as shown in 98 (Fig. 15 ), thus shifting the equilibrium towards 97 and resulting in a low value for $pK_1$



**96** **97** **71**

**98**

**Figure 15**

**b) Determination of stability constants:**

The potentimetric titrations of the ligand solution were performed in the presence of metal ions and the stability constants were determined by processing the potentiometric data using the SCOGS 2 program and the results obtained are listed in Table 3.

Table 3

Stability constants of the crown **diamine** 71 [25°, $\mu$ = 0.10 **M** **($Et_4NClO_4$)]**

| | $Co^{2+}$ | $Ni^{2+}$ | $Cu^{2+}$ | $La^{3+}$ | | $Nd^{3+}$ | $Sm^{3+}$ | $Eu^{3+}$ | $Gd^{3+}$ |
|---|---|---|---|---|---|---|---|---|---|
| log $K_1$ | 9.74 | 838 | 9 95 | 3.01 | 5.97 | 3.48 | 3.55 | 3.85 | 3 62 |
| log $K_2$ | 3.95 | 3.64 | 4.80 | 4.51 | 4.05 | 2.34 | 601 | 445 | 641 |
| log $K_3$ | 1 35 | – | · | **3.60** | **4.60** | 5.90 | 5.21 | 4.90 | 5 37 |
| log $K_N$ | 15.04 | 12.02 | 14.75 | 11.12 | 1462 | 11.80 | 14.77 | 13.42 | 1540 |

It was found that the crown diamine 71 forms 1 : 1 and 2 : 1 complexes with nickel and copper, whereas with cobalt and lanthanides it forms 3 : 1 complexes. It was also observed that the stability constants of the crown diamine 71 decreased when the titration was carried out using sodium perchlorate to maintain the ionic strength instead of tetraethylammonium perchlorate (Table 4) This effect of sodium may be attributed to the participation of the amino group in stabilisation of the sodium-crown complex

**Table 4**
**Stability constants of the crown diamine 71 at 25°**

| Metal ion | log K | |
|---|---|---|
| | $\mu$ = 0.10 M $Et_4NClO_4$ | $\mu$ = 0.10 M $NaClO_4$ |
| $Cu^{2+}$ | 14.75 | 10.05 |
| $Sm^{3+}$ | 14.77 | 12.91 |
| $Gd^{3+}$ | 15.40 | 12.94 |

**2) Crown diaminetetraacetic acid 79.**

**a) Determination of acid dissociation constants:**

The titration curve of the crown diaminetetraacetic acid 79 (pH vs a, where a is the number of moles of base added per mole of 79) showed the saturation point at a = 6 instead of 4, as might be expected for a tetrabasic acid The reason for this behaviour is not clear. Therefore, 79 was first neutralised with 6 molar eq of sodium hydroxide and then titrated with perchloric acid. The acid dissociation constants were calculated according **to** Martell's and Schwarzenbach's graphical method[69] and the values obtained are $pK_1$ = 1.60, $pK_2$ = 2.82, $pK_3$ = 6.20 and $pK_4$ = 9.43. These values were used as input in the computer program SCOGS 2 and after refinement the values obtained are listed in Table 5

**Table 5**

**Stability constants of crown diaminetetraacetic acid 79 |25°, μ = 0.10 M ($NaClO_4$)]**

| | |
|---|---|
| $pK_1$ | 2 12 |
| $pK_2$ | 2.80 |
| $pK_3$ | 6.07 |
| | 9.35 |

The acid dissociation constants of the crown diaminetetraacetic acid 79 are comparable with that reported for trimethylenediaminetetraacetic acid

**b) Determination of stability constants:**

Processing the potentiometric titration data for the complexation of 79 with $Cu^{2+}$ gave the value of log K as 12.67. Similarly, the stability constants of the crown diaminetetraacetic acid 79 with other metal ions were obtained and are listed in Table.6

**Table 6**

**Stability constants of the crown diaminetetraacetic acid 79 (25°, μ = 0.10 M ($NaClO_4$)]**

| No. of displaceable protons | log K | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | metal ion | | | | | | | |
| | $Ni^{2+}$ | $Cu^{2+}$ | $La^{3+}$ | $Ce^{3+}$ | $Nd^{3+}$ | $Sm^{3+}$ | $Eu^{3+}$ | $Gd^{3+}$ |
| 3 | – | – | 11 05 | 11 20 | 11 45 | 10.80 | 10.70 | 11 84 |
| 4 | 12.25 | 12.67 | 9 96 | 9 80 | 10.44 | 9 82 | 9.56 | 10 77 |

When the crown diaminetetraacetic acid 79 was titrated in the presence of cobalt perchlorate at pH 7.90, the metal ion started precipitating out and hence its stability constant was not processed. It was found that when the number of displaceable protons were given as 3 or 4 in the input to the SCOGS 2 program, the log K values obtained were different as shown in Table 6 However, it should be noted that with $Ni^{2+}$ and $Cu^{2+}$, convergencies were obtained only when the number of displaceable protons was taken as 4 Since DTPA 24 and DOT A 25 form charged complexes with lanthanides, it is more appropriate to use the data for log K corresponding to 4 displaceable protons for the acid 79 as well It was also observed that in the case of the crown diaminetetraacetic acid 79, the effect of sodium ions was not significant (Table 7 ) This is perhaps due to the greater role played

by the carboxylate groups in metal ion complexation in 79 than the amino groups in **71.**

**Table 7**

**Stability constants of the crown diaminetetraacetic acid 79 at 25°**

| Metal ion | log K (No of displaceable protons 4) | |
|---|---|---|
| | $\mu$ = 0.10 M ($NaClO_4$) | $\mu$ = 0.10 M ($Et_4NClO_4$) |
| $Cu^{2+}$ | 12.67 | 1281 |
| $Sm^{3+}$ | 982 | 10 40 |
| $Eu^{3+}$ | 9.56 | 9.83 |
| $Gd^{3+}$ | 10.77 | 10.38 |

### 3. Crown tetraaminehexaacetic acid 82.

**a) Determination of acid dissociation constants:**

When the titration data was processed with the computer program SCOGS 2, the last protonation constant $pK_6$ was found not to converge and hence $pK_6$ was calculated according to Martell's method.[69] The results obtained are listed in Table 8 The acid dissociation constants of the crown tetraaminehexaacetic acid 82 are also comparable with the reported data for triethylenetetraaminehexaacetic acid ($H_6L$) [70]

**Table 8**

**Acid dissociation constants of the crown tetraaminehexaacetic acid 82 [25°, μ = 0.10 M ($NaClO_4$)]**

| | |
|---|---|
| $pK_1$ | 2.14 |
| $pK_2$ | 3.16 |
| $pK_3$ | 4 54 |
| $pK_4$ | 706 |
| $pK_5$ | 9.51 |
| $pK_6$ | 10.85 |

**b) Determination of stability constants:**

The titrations were done in the presence of metal ions and the data was processed with the computer program and the stability constants thus obtained are tabulated in Table 9.

**Table 9**

**Stability constants of the crown tetraaminehexaacetic acid 82 |25°, μ = 0.10 M ($NaClO_4$)]**

| Metal ion | log K (No of displaceable protons) | | | |
|---|---|---|---|---|
| | 6 | 5 | 4 | 3 |
| $Cu^{2+}$ | 6.97 | 13.10 | 21.76 | 22.40 |
| | 444 | **11.33** | 1960 | 21.32 |
| $Ce^{3+}$ | 5.30 | 9 01 | 1891 | 21.06 |
| $Nd^{3+}$ | 5.48 | 10.00 | 1970 | 21.46 |
| $Sm^{3+}$ | 6.30 | 11.14 | 19.35 | **21.25** |
| $Eu^{3+}$ | 6 64 | 10.48 | 19.75 | 21.53 |
| $Gd^{3+}$ | 6.56 | 1087 | 1975 | 21.65 |

From these results, it is observed that the crown tetraaminehexaacetic acid 82 has better ligating ability with transition and lanthanide metal ions than the tetraacid 79 when the number of displaceable protons are 4. However, it was found that the chelate stability constants of the crown tetraaminehexaacetic acid 82, when calculated according to Mart ell's method,[67] were close to those of the stability constants obtained from the SCOGS 2 program when the number of displaceable protons are 4. However, since we did not prepare and isolate any of the metal complexes with the ligand 82, the stoichiometry of the complexes is not clear at this point

In conclusion, from our results, it is clear that the ligands 71, 79 and 82 have good ligating abilities. Additionally, they are highly soluble in water It was observed that the crown diamine 71 forms 1 : 1 and 2 : 1 complexes with $Ni^{2+}$ and $Cu^{2+}$, whereas with $Co^{2+}$ and lanthanides it forms 3 : 1 complexes also The stability constants of the crown diamine 71 with transition and lanthanide metal ions were found to be better than that of those with 1,3-propanediamine. In the presence of sodium ions, the stability constants were significantly reduced This is attributed to the involvement of the amino groups in stabilizing the sodium complex with the crown ether moiety The stability constants of the ligand 82 with lanthanides were close to those of DTPA (24) and HEHA (29). As expected, the crown tetraaminehexaacetic acid 82 is a better chelator than the crown diaaminetetraacetic acid 79.

Our preliminary results indicate that the lanthanide complexes of 71, 79 and 82 meet the basic requirements to function as MRI agents Proton relaxation studies are needed before their suitability as MRI agents can be properly assessed Toxicity tests of these compounds may also be required as crown ethers have been reported to be mildly toxic.[74]

A second potential application of these complexes is as NMR shirt reagents for NMR active alkali metal ions.[29b] Since the crown ether moiety offers a ready site for alkali metal ion complexation, these complexes should act as efficient shift reagents. Their charge and side chains are added points in their favour.

Work on these lines is being currently pursued in our laboratory

*EXPERIMENTAL*

## Experimental

All moisture sensitive reactions were carried out under nitrogen atmosphere Reagents were transferred using standard septa-syringe techniques All solvents were distilled from appropriate drying agents prior to use All reagents were purified by appropriate methods before use. All organic extracts were dried using anhydrous $MgSO_4$

Solvents used for column chromatography were of commercial grade and were fractionally distilled Column chromatography was performed using ACME 100-200 mesh silica gel and ACME alumina. Analytical thin layer chromatography (TLC) was performed on home made plates using ACME silica gel GF 254 grade containing 13% calcium sulphate as binder and were developed by shining ultraviolet light and/or by exposure to iodine vapours.

Melting points were determined by using a SUPERF1T melting point apparatus and are uncorrected IR spectra were recorded on a Perkin-Elmer model 1310 spectrophotometer or JASCO FT-IR 5300 instrument Solid samples were prepared as KBr wafers and liquid samples as a film between NaCl plates. $^{1}H$ NMR (100 and 200 MHz) and $^{13}C$ NMR (25 and 50 MHz) spectra were obtained with JEOL FX-100 and Bruker AF 200 instruments. All spectra were recorded using chloroform-d as solvent, unless otherwise mentioned Chemical shifts are reported as 6 values in parts per million relative to tetramethylsilane (0.0 ppm) as internal standard ($^{1}H$ and $^{13}C$).

Data are reported as follows: chemical shifts (multiplicity, integrated intensity, assignment). Elemental analyses were performed using a Perkin-Elmer 240C CHN analyser. The FAB mass spectra were obtained from CDRI Lucknow.

**Preparation of Monobenzalpentaerythritol 3:**

In an open 1 L three necked round bottomed flask pentaerythritol (80.0 g, 0.587 mole) and water (600 ml) were taken and the flask was equipped with an efficient mechanical stirrer and a dropping funnel containing benzaldehyde (67.0 g, 0 62 mole). The flask was heated until all the solid dissolved and was then allowed to cool undisturbed. When the solution was at rt, stirring was started and 4 5 ml of concentrated hydrochloric acid was added through the open neck of the flask, followed by 10 ml of benzaldehyde from the dropping funnel. When the precipitate of monobenzalpentaerythritol started forming, benzaldehyde was added dropwise. After the addition of benzaldehyde was complete, the mixture was stirred for an additional 2 h. The precipitate was collected on a Buchner funnel and washed with ice-cold water, made slightly alkaline with sodium carbonate. The solid was transferred to 1 L round bottomed flask, 350 ml water, slightly alkaline with sodium carbonate, was added and the mixture was heated to 100°. After about 10 min at this temperature, the hot mixture was filtered quickly through a fluted filter paper. The solid remaining on the paper was washed with 50 ml of hot water (made slightly alkaline with sodium carbonate). The combined aq. filtrates were cooled in an ice bath for several hours, and the crystals were collected on a Buchner funnel and dried

The dry product was heated under reflux for 15 min in an Erlenmeyer flask with 95 ml of toluene, and the hot mixture was allowed to cool to rt with continuous agitation to prevent formation of hard lumps Finally, the mixture was cooled in an ice bath for 5 h, and the solid product was collected on a Buchner funnel and dried.

Yield: 23.0 g.

Solid, mp: 132-134°, (lit 134)[11]

**3-Phenyl-2,4,8,11,14,17,20,-heptaoxaspiro [5.15] heneicosane (67):**[11]

Monobenzalpentaerythritol 3 (11.2 g, 50 mmol) and tetraethylene glycol ditosylate (25.1 g, 50 mmol) in separate 250 ml portions of THF were simultaneously added over a period of 8 h to a vigorously stirred, refluxing suspension of sodium hydride (3.0 g, 125 mmol) in 1 L of THF (high dilution conditions). After refluxing for an additional 12 h, the mixture was allowed to cool to rt and then quenched with methanol. The solvent was removed under reduced pressure, and the resulting residue was extracted with chloroform (3 x 250 ml). The combined extracts were evaporated and the residue was purified by chromatography on a silica gel column First, 1 L of hexane was passed through the column to remove the mineral oil (NaH suspension). The product was then eluted with ethyl acetate.

Yield: 16.25 g (85%)

IR (neat): 3020, 2860, 1460, 1360, 1100, 750, 700 $cm^{-1}$.

$^1H$ NMR (100 MHz):

6 7.18-7.50 (m, 5H, Ar*H*), 5.38 (s, 1H, PhC*H*), 3.43-3.78 (m, 24H, $OCH_2CH_2O$ and dioxane $CH_2$)

$^{13}C$ NMR (25 MHz):

138.07, 128.83, 128.18, 12606, 101.65, 71 30, 71.00, 70.35, 69 94,69.18,38.71 ppm.

**15,15-Bis (hydroxymethyl)-l,4,7,10,13-pentaoxacyclohexadecane (68):** [11]

A mixture of 67 (19.94 g, 0.052 mol) and 100 ml of aq. 0 1 N $H_2SO_4$ was refluxed for 12 h. The solution then was neutralised with aq barium hydroxide, filtered and evaporated to dryness. The crude product was extracted with chloroform and then purified by column chromatography using acetone as eluent to obtain the crown diol 68 as a colourless, viscous oil.

Yield: 14.5 g (95%).

IR (neat): 3360, 2870, 1110 $cm^{-1}$.

$^1H$ NMR (100 MHz):

5 3.68 (m, 24H, $OCH_2CH_2O$), 2 84 (br, 2H, $OH$)

$^{13}C$ NMR (25 MHz):

72.90, 71.90, 65.20, 46.50 ppm

**Attempted oxidation of the crown diol 68 to crown dialdehyde 69:**

**1. Pyridinium chlorochromate (PCC) Oxidation:**

To a stirred suspension of PCC (220 mg, 1.02 mmol) in dichloromethane (1 ml) at rt was added the crown diol 68 (100 mg, 0.34 mmol) in dichloromethane (1 ml) and the contents stirred for 3 h. The resulting reaction mixture was passed through a fluorosil column and eluted with dichloromethane and the solvent was evaporated. The IR spectrum of

the residue obtained showed a strong O-H band (3350 $cm^{-1}$) and a weak carbonyl band (1740 $cm^{-1}$). However, tlc showed a complex mixture and further purification was not attempted.

When pyridinium dichromate (PDC) was used as the oxidising agent in dichloromethane, a complex mixture resulted. Chromic acid oxidation of the above crown diol 68 in pyridine/dichloromethane also did not give the required product

**2. Oxidation of the crown diol 68 using *N*-chlorosuccinimide/dimethyl sulphide:**

A solution of *N*-chlorosuccinimide (34 mg, 0 255 mmol) and dimethyl sulphide (0 025 ml, 0.425 mmol) in toluene (0 10 ml) was cooled to -25°. To this, a solution of crown diol 68 (50 mg, 0.17 mmol) in toluene (0.20 ml) was added and cooling was continued for a further 30 min Triethylamine (25 mg, 2.50 mmol) in toluene (0.10 ml) was then added and the cooling bath was removed After 5 min, diethyl ether (2 ml) was added and the organic layer was washed with 0.40 ml of 1% HCl followed by water and then dried, filtered and concentrated. The IR spectrum of the resulting residue showed both O-H and carbonyl bands and its further purification was not attempted.

IR (neat): 3350, 2950, 1720, 1470, 1110 $cm^{-1}$.

**Preparation of crown dimesylate** 73:

To a stirred, ice cold solution of crown diol 68 (1.25 g, 4.25 mmol) in pyridine (30 ml) were added a few crystals of 4-(N,N-dimethylamino) pyridine followed by methanesulfonyl (III) chloride (1.95 g, 0.017 mol) The reaction mixture was stirred overnight and then poured into a mixture of dil HCl/ice-water mixture and extracted with dichloromethane. The organic layer was washed with dil. HC1 solution, followed by saturated sodium bicarbonate solution and then dried, filtered and concentrated. The residue thus obtained was chromatographed to obtain the required crown dimesylate 73 as a syrup.

Yield: 1.13 g (60%).

IR(neat): 2900, 1470, 1360, 1180, 1110, 960, 850 $cm^{-1}$.

**Reaction of crown dimesylate 73 with sodium azide 74:**

To a solution of the crown dimesylate 73 (1.13 g, 2.50 mmol) in dimethylformamide (10 ml) was added sodium azide (490 mg, 7.53 mmol) and maintained at 60° overnight. The resulting reaction mixture was poured into water and extracted with diethyl ether. The organic layer was dried, filtered and concentrated The IR spectrum of the resultant residue showed both azide and mesylate bands and further purification was not attempted

IR (neat): 2900, 2100, 1470, 1370, 1190, 1115 $cm^{-1}$.

**Preparation of crown ditosylate** 75:

Sodium hydroxide (1 20 g, 30.0 mmol) dissolved in water (6 ml) and crown diol 68 (3 0 g, 10 2 mmol) in THF (12 ml) were placed in a flask and

the mixture was cooled in an ice bath with magnetic stirring After 0.5 h of cooling, *p*-toluenesulfonyl chloride (4 08 g, 21.4 mmol) was added in small portions and the reaction mixture was stirred for 1 h at 5°. The reaction mixture was then poured into ice water and the white solid thus formed was filtered and dried. The product was recrystallised by dissolving it in minimum amount of ethyl acetate and a few drops of hexane were added till the solution became turbid. The contents were allowed to stand at rt to obtain the crown ditosylate 75 as a white crystaline solid

Yield: 4.90 g (80%).

Solid, mp: 124-126°.

IR(KBr): 3050,2900, 1600, 1353, 1187, 1119 $cm^{-1}$.

$^1H$ NMR:

6 7.14-7.55 (AA'BB' system, $J$ = 8 Hz, 8H, Ar*H*), 3.78 (s, 4H, TsOC$H_2$), 3.23-3.35 (m, 20H, OC$H_2$C$H_2$O), 2.24 (s, 6H, TsC$H_3$)

$^{13}C$ NMR:

144.0, 132.0, 129.0, 128.0, 70.80, 70.50, 70.20, 68.50, 68.20, 44 0, 21.0 ppm.

Analysis:

Calcd for $C_{27}H_{38}O_{11}S_2$: C, 53.80; H, 6.35

Found: C, 53.71; H, 6.35.

**Reaction of the ditosylate 75 with ethyl urethane:**

To a solution of the crown ditosylate 75 (50 mg, 0.08 mmol) in dimethylformamide (2 ml) was added ethyl urethane (287 mg, 0.33 mmol)

and stirred at 60° overnight. The resulting reaction mixture was extracted with diethyl ether, dried and evaporated. The IR and NMR spectra of the crude product mixture showed that the starting material was recovered unchanged.

**Reaction of the ditosylate 75 with benzylamine:**

To a stirred solution of benzylamine (20 mg, 0 186 mmol) in dioxane (1 ml) was added ditosylate 75 (50 mg, 0 08 mmol) and refluxed overnight To this 20% sodium hydroxide solution (5 ml) was added and the contents were extracted with ethyl acetate. The organic layer was dried and concentrated to give back unreacted starting material, as established by its IR spectrum

**Preparation of the Crown diazide 74:**

A mixture of the crown ditosylate 75 (3.0 g, 4.977 mmol) and sodium azide (1.95 g, 29.9 mmol) in dry dimethylformamide (15 ml) was heated to 120° for 3 days. The reaction mixture was cooled to rt, diluted with water and extracted with dichloromethane. The organic layer was dried and evaporated to give the product which was further purified by column chromatography using 50% ethyl acetate-hexane mixture as eluent.

Yield: 1 68 g (98%) as **a** colourless **oil.**

IR(neat): 2870, 2102, 1454, 1356, 1249, 1118 $cm^{-1}$.

$^1H$ NMR:

6 3.40 (s, 4H, $CH_2N_3$), 3 46 (s, 4H, $OCH_2CCH_2O$), 3 64 (m, 16H, $OCH_2CH_2O$)

$^{13}C$ NMR:

70.24, 51.71, 45.0 ppm.

Analysis:

Calcd for $C_{13}H_{24}N_6O_5$: C, 45.34, H, 7.02, N, 24.40

Found: **C, 45.70; H, 7.24; N, 22.35.**

(lower value for nitrogen may be because of thermal instability of the azide)

When the reaction was carried out for 3 days using **2.5** equivalents of sodium azide in dimethylformamide at rt as well as at 120°, the reaction was incomplete and yields were, thus lesser.

**Attempted reductions of the crown diazide 74 to crown diamine 71:**

**1. Catalytic transfer hydrogenation:**[52]

A mixture of the crown diazide 74 (100 mg, 0.3 mmol) and 10% palladium on carbon in cyclohexene (10 ml) was stirred overnight at rt. The catalyst was filtered and the solvent was removed to obtain a residue The residue did not contain any of the required product by IR and $^1H$ NMR analysis. No starting material was recovered as well

IR (neat): 2900, 1460, 1280, 1120 $cm^{-1}$.

Hydrogenolysis the crown diazide 74 with 10% Pd/C in ethyl acetate also did not afford the required product

**2. Attempted reduction of the crown azide 74 using triphenylphosphine:**[53]

To a solution of the crown diazide 74 (100 mg, 0.3 mmol) in toluene (3 ml) was added a solution of triphenylphosphine (156 mg, 0.58 mmol) in

toluene (3 ml) and refluxed for 1 h The solvent was removed and the residue was hydrolysed by heating for 1 h with a mixture of equal volumes of acetic acid (3 ml) and 40% hydrobromic acid (3 ml). The reaction mixture was diluted with water, neutralised with aq. ammonia, filtered and extracted with dichloromethane. The organic layer was dried and evaporated. The IR spectrum and tlc of the crude material showed the presence of the starting material only.

IR (neat): 2850, 2100, 1650, 1440, 1110 $cm^{-1}$

When the reaction was carried out using triphenylphosphine and 10% HC1 in THF, the required product was not obtained

**3. Reduction of the crown diazide 74 using LAH; Preparation of the crown diamine 71:**

To a stirred suspension of LAH (1.12 g, 29.5 mmol) in dry THF (10 ml), the crown diazide 74 (1.7 g, 4.91 mmol) in dry THF (10 ml) was added dropwise at rt. After the addition was complete, the reaction mixture was refluxed overnight. The contents were cooled to rt and the reaction mixture was quenched by adding saturated sodium sulphate solution dropwise. A granular precipitate that formed was filtered off and washed with acetone The filtrate was evaporated to obtain the product which was further purified by chromatography on a neutral alumina column using 50% ethyl acetate-acetone mixture as eluent to obtain the crown diamine 71 as a light yellow coloured syrup.

Yield: 1.40 g (98%).

**IR(neat):** 3315,2866, 1662, 1450, 1359, 1120, 939, 879 $cm^{-1}$

$^1H$ NMR:

8 3.60-3.65 (m, 16H, $OCH_2CH_2O$), 3 46 (s, 4H, $OCH_2CCH_2O$), 2.89 (s, 4H, $CH_2NH_2$)

$^{13}C$ NMR

72.24, 70.77, 64.59, 44 59, 35.59 ppm

Analysis:

Calcd for $C_{13}H_{28}N_2O_5$ C, 53.40; H, 9 65, N, 9.58.

Found: **C, 53.56; H, 9.64; N, 9.65.**

When the crown azide 74 was treated with LAH in diethyl ether at rt as well as at reflux temperature and in THF at rt, no product was obtained

**Reaction of the crown diamine 71 with hippuric acid: Preparation of the crown diamide** 76:

To a stirred and ice cooled solution of hippuric acid (250 mg, 0.86 mmol) in dry dichloromethane (8 ml), DCC (445 mg, **2.15 mmol)** was added and allowed to stir for 30 min at 5°. To this, the crown diamine 71 (385 mg, 2 15 mmol) in dry dichloromethane (8 ml) was added and stirred for 3 h under ice cooling and then at rt overnight. Water was added, the contents stirred for some time and the white solid thus formed was filtered off. The dichloromethane layer was separated from the aq. layer, dried and evaporated and the residue thus obtained was chromatographed using ethyl acetate as eluent to obtain the product 76 as a white coloured hygroscopic foamy solid.

Yield: 400 mg (76%).

IR (neat): 3300, 3050, 2850, 1650, 1530, 1300, 1110 $cm^{-1}$.

$^1H$ NMR:

5 7.91-7.94 (d, 4H, Ar*H*), 7.40-7.44 (d, 6H, Ar*H*), 4 12-4.15 (d, 4H, $COCH_2NH$), 3.35-3.53 (m, 24H, $OCH_2CH_2O$)

$^{13}C$ NMR

170 19, 167.50, 133 58, 13169, 128.47, 127 28, 127 10, 74.24, **71.42,** 70.50, 70.32, 69 72, 43.94 ppm

Analysis:

Calcd for $C_{31}H_{42}N_4O_9$: C, 60.56; H, 6.88; N, 9.11.

Found: C, 60.38; H, 6.95; N, 9.28.

**Preparation of the crown N,N'-dibenzyldiamine** 77:

To a stirred suspension of LAH (148 mg, 3.90 mmol) in dry THF (8 ml) was added dropwise the crown diamide 76 (400 mg, 0.65 mmol), in dry THF and the reaction mixture was refluxed overnight under nitrogen atmosphere. The reaction mixture was cooled to rt and then quenched by adding saturated sodium sulphate The solid precipitate formed was filtered off and the cake was washed thoroughly with acetone The combined organic layer was dried, concentrated and the residue was chromatographed to yield the pure product 77 as a brown coloured syrup.

Yield: 360 mg (96%).

IR(neat): 3317, 3028, 2868, 1454, 1358, 1120, 738, 700 $cm^{-1}$.

$^1$H NMR

8 7.29 (m, 10H, Ar*H*), 3.76 (s, 4H, C$H_2$Ar) 3.59-3.63 (m, 20H, OC$H_2$C$H_2$O), 2 55-2 68 (m, 12H, C$H_2$NC$H_2$C$H_2$).

$^{13}$C NMR

140 40, 128.20, 128 0, 126 00, 70.60, 70.20, 53.50, 51.80, **49.0, 47.0, 42.80** ppm.

Analysis:

Calcd for $C_{31}H_{15}N_4O_5$ C, 66.63; H, 9.02; N, 10.02

Found: C, 63.99; H, 8.77; N, 9.13

FAB mass:

m/z = 559 $(M + H)^+$, 466, 345, 317, 285, 105, 91.

**Preparation of hydrochloride salt of the crown dibenzyldiamine** 77:

The crown N,N'-dibenzyldiamine 77 was dissolved in dichloromethane and HCl gas was passed till the solution became turbid The solvent was evaporated to yield the salt as a white hygroscopic solid Due to its high sensitivity to moisture, its characterization could not be carried out and hence the hexafluorophosphate salt was prepared.

$^1$H NMR ($D_2O$)

8 **7.31-7.34** (m, 10H, Ar*H*), 4.14 (s, 4H, C$H_2$Ar), 3 15-3.53 (br, 32H, OC$H_2$C$H_2$O and C$H_2$NC$H_2$C$H_2$N)

**Preparation of tetrakis(hexafluorophosphate) salt of the crown dibenzyldiamine** 77:

To a solution of the hydrochloride salt of the crown dibenzyldiamine 77 in methanol, 4 eq. of ammonium hexafluorophosphate dissolved in methanol was added and to this solution, few drops of acetone were added until the solution becomes turbid and then allowed to stand at rt The white solid thus formed was filtered, washed with methanol-acetone mixture and dried.

Solid, mp: Decomposes at 200°.

IR(KBr): 3337,3038,2430, 1624, 1431, 1271, 1186, 1132, 721 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

5 7.36 (s, 10H, Ar*H*), 4.19 (s, 4H, $CH_2$Ar), 3.18-3.56 (m, 32H, $OCH_2CH_2O$and $CH_2NCH_2CH_2N$).

Analysis:

Calcd for $C_{31}H_{54}N_4O_5P_4F_{24}$: C, 32.58, H, 4.76; N, 4.90

Found: C, 32.45; H, 4 72: N, 4.85.

**Attempted reactions for the cleavage of *N*-benzyl group of 77: Preparation of the crown tetraamine 78:**

**1. With formic acid:**[54]

To the crown N,N'-dibenzyldiamine 77 (100 mg, 0.12 mmol) dissolved in 4.4% formic acid in methanol (10 ml) was added 10% Pd/C (200 mg) and stirred for 10 h. The catalyst was filtered and washed with methanol The residue that was obtained after removal of solvent was found

to be the starting material from its IR spectrum When the reaction was carried out using ammonium formate[56] and 10% Pd/C, sodium and liquid ammonia,[55] hydrogenation with 10% Pd/C in the presence of acetic acid[57] as well as with ethanolic HC1,[58] no cleavage of the TV-benzyl group occurred

**Preparation of Pearlman's catalyst (20% $Pd(OH)_2/C$):**[59]

Palladium chloride (1.0 g), carbon (2.40 g) and deionised water (20 ml) were mixed and stirred rapidly while being heated to 80°. To this, lithium hydroxide (LiOH $H_2O$, 50 mg) dissolved in water (2 ml) was added all at once and the heating stopped The reaction mixture was stirred overnight at rt, filtered and the catalyst washed with 0 5% aq. acetic acid (20 ml). The cake was sucked as dry as possible and then dried in vacuum at 60°.

**2. Cleavage of the crown N,N'-dibenzyldiamine 77 using Pearlman catalyst (20% $Pd(OH)_2/C$):**

The crown N,N'-dibenzyldiamine 77 (90 mg, 0.161 mmol) in ethanol (5 ml) was hydrogenated using 20% $Pd(OH)_2/C$ (200 mg) in a Parr apparatus at 65 psi for 4 h. The catalyst was filtered and the cake washed with methanol The product, crown tetraamine 78 was obtained after evaporation of the solvent as a hygroscopic foamy solid.

Yield: 58 mg (95%).

IR (KBr): 3290, 2866, 1574, 1454, 1116, 943 $cm^{-1}$.

5 5.50 (br, N*H*), 3.35-3.51 (m, $OCH_2CH_2O$ and $NCH_2$).

$^{13}C$ NMR

73.69, 70.63, 70.45, 62.50, 59.23, 39.73 ppm.

The hygroscopic nature of the material precluded elemental analysis When a catalytic amount or one equivalent (by weight) of 20% $Pd(OH)_2/C$ was used, the cleavage was not effected

**Preparation of bis (tetraphenyiborate) salt of the crown tetraamine 78:**

To a solution of the crown tetraamine 78 (30 mg, 0.07 mmol) in 0.1M HC1 was added an aq. solution of sodium tetraphenyiborate (180 mg, 0.52 mmol). During the addition, a white solid was formed. After complete addition, the solid formed was filtered and dried. The product was recrystallised by dissolving it in minimum amount of ethyl acetate followed by adding ether till the solution became turbid. On cooling in the refrigerator a white solid was obtained which on drying became granular.

Yield: 60 mg (74%).

Solid, mp: 78-80°.

IR(KBr): 3425,3055, 1579, 1479, 1427, 1109, 736, 707, 611 $cm^{-1}$

$^1H$ NMR

5 7.80-7.06 (m, Ar*H*), 3.61 (br, s).

Analysis:

Calcd for $C_{65}H_{80}N_4O_5B_2$: C, 76 61; H, **7.91;** N, 5.49

Found: C, 76.19; H, 7.64; N, 5.18.

**Preparation of the crown diaminetetraacetic acid 79:**

**Reaction of the crown diamine 71 with bromoacetic acid:**[43]

A solution of bromoacetic acid (238 mg, 1 71 mmol) in water (2.8 ml) was brought to pH 10 with 7 M KOH, maintaining the temperature below 5°. To this, a solution of the crown diamine 71 (100 mg, 0.34 mmol) in ethanol (5 ml) was added and the reaction mixture was heated to 70° for 4h The pH of the mixture was maintained at 10 with 7 M KOH After cooling to rt, the reaction mixture was acidified to pH 2 with 47% aq. HBr and was then evaporated. The resulting residue was dissolved in water (1 ml) and was loaded on a column of Amberlite 120 cation-exchange resin (washed with dil HC1). The column was eluted with water (500 ml) followed by 2% aq. $NH_3$ (500 ml). Both the water and aq. $NH_3$ fractions were concentrated to afford the product as a hygroscopic white, foamy solid Further purification either by column chromatography or by preparative tlc was unsuccessful and hence a thorough characterization was not posible.

Yield 115 mg (64%, crude).

IR (KBr): 3408, 2922, 1743, 1439, 1249, 1109, 945 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

8 3.68-4.08 (m).

$^{13}C$ NMR:

172.59, 74.00, 73.87, 72 47, 62.65, 62.35, 62 00, 60.35, 60.24, 55.94, 45.88 ppm

**Preparation of the crown tetraethyl ester 80:**[61]

A mixture of the crown diamine 71 (100 mg, 0.34 mmol), ethyl bromoacetate (1.20 g, 7.18 mmol) and potassium carbonate was heated to 100° for 48 h. The reaction mixture was cooled to rt and the volatiles removed under vacuum. The residue thus obtained was extracted with dichloromethane and this organic layer was washed with bicarbonate solution, dried and concentrated to obtain the crude product which was further purified by column chromatography using ethyl acetate as the eluent.

Yield: 140 mg (64%).

IR(neat): 2872, 1734, 1662, 1464, 1371, 1186, 1116, 1032 $cm^{-1}$.

$^1H$ NMR:

$\delta$ 4.09-4.19 (q, 8H, $CH_2CH_3$), 3.48-3.64 (m, 28H, $OCH_2CH_2O$and $NCH_2CO_2$), 2.80 (s, 4H, $CH_2N$), 1 22-1 25 (t, 12H, $CH_2CH_3$)

$^{13}C$ NMR:

172.08, 70.60, 70.30, 60 30, 57 10, 56.80, 47.40 ppm.

Analysis:

Calcd for $C_{29}H_{52}N_2O_{13}$: C, 54.70, H, 8.23, N, 4.40.

Found: C, 53.63, H, 8.19, N, 3.40.

FAB mass

m/z = 637 $(M + H)^+$, 307, 202, 130, 116.

**Hydrolysis of the crown tetraethyl ester 80:**[60]

A mixture of the crown tetraethyl ester 80 (200 mg, 0.31 mmol) and KOH (350 mg, 6 24 mmol) in aq methanol (8 ml) was heated to 100°

overnight The reaction mixture was neutralised with conc HC1 to pH 7, the solvent was removed under vacuum and the residue thus obtained was dissolved in methanol and filtered Concentration of the solvent gave a hygroscopic foamy solid which was not amenable to further purification.

Yield: 145 mg (crude).

IR (KBr): 3410, 2191, 1734, 1635, 1402, 1248, 1107, 945 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

8 3 50-3.80 (br).

**Preparation of the crown tetrabenzyl ester 81:**

A mixture of the crown diamine 71 (100 mg, 0.34 mmol), benzyl bromoacetate[71] (470 mg, 2.05 mmol) and anhydrous potassium carbonate (285 mg, 2.05 mmol) in dry dimethylformamide (5 ml) was heated to 100° for 3 days The mixture was concentrated under vacuum and the residue thus obtained was extracted with dichloromethane The dichloromethane layer was dried and evaporated and the residue was chromatographed using ethyl acetate as eluent to obtain the product 81 as a brown coloured syrup with a fruity smell

Yield: 165 mg (54%).

IR(neat): 3034,2876, 1743, 1170, 1114, 736, 698 $cm^{-1}$.

$^1H$ NMR:

δ 7.32 (s, 20H, Ar*H*), 5.10 (s, 8H, $CH_2$Ar), 3.43-3.60 (m, 28H, $OCH_2CH_2O$ and $NCH_2CO$), 2 81 (s, 4H, $CCH_2N$).

$^{13}C$ NMR:

171.76, 135.92, 128.56, 128.23, 77.80, 77.17, 76.53, 66.10, 57.27, 56.89, 47.43 ppm.

Analysis:

Calcd for $C_{49}H_{60}N_2O_{13}$: C, 66 49, H, 6.83, N, 3.16.

Found: C, 66.62; H, 6.88; N, 3.25.

When the reaction was carried out using benzyl iodoacetate in dimethylformamide under reflux conditions, the same product was obtained in 64% yield.

**Hydrogenolysis of the crown ether tetrabenzyl ester 81:**

The crown tetra-benzyl ester 81 (60 mg, 0.07 mmol) was hydrogenated with 20% $Pd(OH)_2/C$ (100 mg) in dry ethanol (8 ml) at 65 psi in a Parr apparatus for 3 h. The catalyst was filtered off and washed with methanol. Upon evaporation of the solvent, the pure crown diaminetetraacetic acid 79 was obtained as a hygroscopic white solid.

Yield: 35 mg (95%).

**IR (KBr):** 3422, 2926, 1739, 1249, 1113 $cm^{-1}$

$^1H$ NMR ($D_2O$):

6 3.20-3.80 (br, m).

$^{13}C$ NMR.

170.45, 69.13, 71.22, 59.72, 57.90, 43 06 ppm.

Analysis:

Calcd for $C_{21}H_{36}N_2O_{13}$: C, 48.08; H, 6.91; N, 5.34.

Found: C, 48.15, H, 6.88; N, 5.31.

**Preparation of the crown tetraaminehexaacetic acid 82 by direct alkylation with bromoacetic acid:**[43]

A solution of bromoacetic acid (850 mg, 6.12 mmol) in water (3 ml) was brought to pH 10 with 7 M KOH solution at 5° and then a solution of the tetraamine 78 (115 mg, 0.30 mmol) in ethanol (3 ml) was added. The reaction mixture was stirred at 70° for 12 h and during this time the pH of the reaction mixture was maintained at 10 by adding 7 M KOH solution The reaction mixture was cooled to rt and acidified to pH 2 with 47% aq. HBr solution and then extracted with ether to remove the organic impurities. The resulting aq layer was concentrated loaded on a column of cation exchange resin (IR 120, $H^+$ form) and the column was eluted first with water (100 ml) followed by 2% ammonia solution (100 ml). Both the fractions were combined and concentrated to yield the crude product 82, which once again was not amenable to further purification.

Yield: 140 mg (64%, crude)

IR(KBr): 3408, 2926, 1745, 1651, 1454, 1248, 1091, 945 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

$\delta$ 3.20-3.70 (br).

**Preparation of the crown tetraaminehexaacetic acid hexaethyl ester 83:**[60]

A mixture of the crown tetraamine 78 (75 mg, 0 20 mmol), ethyl bromoacetate (1.5 g, 9.00 mmol) and potassium carbonate (620 mg, 4 50 mmol) in dry dimethylformamide was heated to 100° for 3 days. DMF was removed in vacuum and the residue was extracted with dichloromethane The dichloromethane extract was filtered, dried and concentrated and the residue was chromatographed using ethyl acetate as eluent to obtain the hexaester 83 as a dark brown syrup.

Yield: 100 mg (56.4%).

IR(neat): 2982, 1732, 1192, 1116, 1032, 733 $cm^{-1}$.

$^1H$ NMR

5 4.20-4.13 (q, 12H, $CH_2CH_3$), 3.63-3.53 (m, 32H, $OCH_2CH_2O$ & $NCH_2CO_2$), 2.80-275 (m, 12H, $CH_2NCH_2CH_2N$), 1.29-1.22 (t, 18H, $CH_2CH_3$)

$^{13}C$ NMR:

172.10, 171.20, 70.40, 70.0, 60.45, 60.16, 56.63, 55 23, 54.61, 52.94,46.90, 14.31 ppm.

Analysis:

Calcd for $C_{41}H_{74}N_4O_{17}$: C, 55.01; H, 8.33, N, 6 26.

Found: C, 53.71; H, 7.62; N, 5.29.

FAB mass: m/z = 895 $(M + H)^+$

**Saponification of the hexaethyl ester 83:**[60]

A mixture of the hexaethyl ester 83 (150 mg, 0 17 mmol) and KOH (500 mg) in aq. methanol (8 ml) was heated at 100° overnight The reaction mixture was concentrated and loaded on a column of ion exchange resin (IR 120, $H^+$ form) The column was eluted with water and then with 2% aq ammonia solution. These fractions were combined and concentrated in vacuum to afford the crude product, the crown tetraaminehexaacetic acid 82 as an yellow coloured hygroscopic solid. Its further purification was not successful for adequate characterization

Yield: 90 mg (73% crude).

IR(KBr): 3423,2935, 1728, 1614, 1462, 1390, 1116, 1030 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

6 3.00-3.90 **(br).**

**Preparation of the crown tetraaminehexaacetic acid hexabenzyl ester 84:**

A mixture of the crown tetraamine 78 (100 mg, 0.26 mmol), benzyl bromoacetate (545 mg, 4.75 mmol) and anhydrous $K_2CO_3$ (330 mg, 2.38 mmol) in dry dimethylformamide (5 ml) was heated to 120° for 3 days. The solvent was removed in vacuum and the resulting residue was extracted with dichloromethane. The organic layer was dried, filtered and concentrated. The residue thus obtained was purified by column chromatograph using ethyl acetate as the eluent to obtain the pure product 84 as a brown coloured syrup

Yield: 40 mg (12%).

IR (neat): 3034, 2922, 1743, 1498, 1172, 736, 698 $cm^{-1}$.

$^1H$ NMR:

6 7.28-7.36 (m, 30H, Ar*H*), 5.09 (s, 12H, $CH_2Ar$), 3 45-3 55 (m, 32H, $OCH_2CH_2O$ & $NCH_2CO_2$), 2 78 (m, 12H, $CH_2NCH_2CH_2$).

$^{13}C$ NMR

171.40, 170.60, 135.36, 128.90, 128.30, 128.0, 126 20, 70.50, 68 80, 66.30, 66.0, 55.0, 46 20 ppm.

Analysis:

Calcd for $C_{71}H_{86}N_4O_{17}$: C, 67.27; H, 6.83; N, 4.42

Found: C, 66 98, H, 6 62; N, 4.01.

When the reaction was carried out using benzyl iodoacetate in acetonitrile under reflux conditions and in the presence of cesium carbonate in DMF under reflux conditions, the yield of the product 84 was similar.

**Hydrogenolysis of the crown tetraaminehexaacetic acid hexabenzyl ester 84:**

Crown hexaester 84 (70 mg, 0.05 mmol) was hydrogenated using 20% $Pd(OH)_2/C$ (150 mg) in ethanol (5 ml) at 65 psi for 5 h in a Parr apparatus. The catalyst was filtered off and washed with methanol The methanol was evaporated to dryness to obtain the crown tetraaminehexaacetic acid 82 as an hygroscopic foamy material Due to its hygroscopicity, its melting point could not be determined.

Yield: 30 mg (75%).

IR (KBr): 3429,2926, 1736, 1651, 1385, 1249, 1109 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

δ 3.12-3.69 (br), 2.45-2 76 (br).

Analysis

Calcd for $C_{29}H_{50}N_4O_{17}$: C, 47.92, H, 6.93, N, **7.71.**

Found: C, 48.15; H, 6 98; N, 7.78

**Attempted reactions to prepare spiro crown compounds:**

**Preparation of the crown dibromide 72a:**

A mixture of the crown ditosylate 75 (1.0 g, 1.66 mmol) and sodium bromide (1.02 g, 9.95 mmol) in diethylene glycol (5 ml) was maintained at 150° overnight. The reaction mixture was cooled to 90° by adding ice slowly and then to 10° and finally poured into water and extracted with dichloromethane. The organic layer was washed with water, sodium bicarbonate solution and dried and evaporated to obtain the product **72a** as a pale yellow oil which was purified by column chromatography using ethyl acetate as eluent.

Yield: 670 mg (96%).

IR(neat): 2850, 1345, 1245, 1110 $cm^{-1}$.

$^1H$ NMR:

5 3.35-3.75 (m).

$^{13}C$ NMR:

70.65, 70.47, 70.18, 69.77, 44.94, 35.90 ppm.

Analysis:

Calcd for $C_{13}H_{24}O_5Br_2$: C, 37.16; H, 5.75.

Found: C, 37.87, H, 5.93.

**Preparation of the crown diiodide 72b:**

A mixture of the crown ditosylate 75 (500 mg, 0.83 mmol) and sodium iodide (750 mg, 4.98 mmol) in diethylene glycol (5 ml) was heated to 150° for 12 h. The reaction mixture was cooled to rt, diluted with water and extracted with dichloromethane. The dichloromethane layer was washed with saturated sodium thiosulfate and with brine solution. The organic extract was dried, filtered and evaporated to obtain the product which was further purified by column chromatography using 50% ethyl acetate-hexane mixture as eluent to obtain the crown diiode 72b as a light yellow coloured liquid.

Yield: 365 mg (85%).

IR (neat): 2845, 1440, 1340, 1230, 1110 $cm^{-1}$.

$^1H$ NMR:

5 3 72 (br, s, 18H, $OCH_2CH_2O$), 3 60 (s, 4H, $OCH_2CCH_2O$),3.38 (s, 4H, $CH_2I$).

$^{13}C$ NMR:

71.0, 70.65, 41.52, 13.58 ppm.

**Reaction of the crown diiodide 72b with ethylenediamine:**

a) A mixture of the crown diiodide 72b (90 mg, 0.21 mmol) and ethylenediamine (2 ml) was heated to 100° overnight Excess

ethylenediamine was removed under vacuum to yield a complex mixture The residue was dissolved in dichloromethane and the residue material was extracted with methanol.

Yield: 154 mg (crude)

Dichloromethane soluble product: 98 mg (syrup)

IR (neat): 3200, 2850, 1614, 1440, 1350, 1100 $cm^{-1}$.

$^1H$ NMR:

8 3 65-3.76 (m), 3.20 (s, br), 2.80 (s).

The above dichloromethane soluble product after neutralisation with ion exchange resin (IR 400, OH" form) gave a syrup whose homogenity could not be established

Yield: 45 mg.

$^1H$ NMR

δ 3.61-3.70 (m), 3.06 (s), 2.47-2.66 (m), 2.30 (s, br).

$^{13}C$ NMR:

77.35, 73.58, 70.67, 70.48, 62.24, 59 28, 39.82, 39.59 ppm

Methanol soluble product: 56 mg (solid).

IR (KBr): 3350, 2900, 1640, 1100 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

δ 3.50-3.70 (m).

b) The reaction when carried out with the crown diiodide **72b** (115 mg, 0 26 mmol) and ethylenediamine (1 ml) in the presence of nickel (II) sulphate (35 mg, 0.13 mmol) yielded a complex mixture containing five

different products. The residue after removal of volatiles was taken up in different solvents to separate the products.

1 Hexane soluble product: 8 mg (syrup).

$^1$H NMR:

5 3.64-3.66 (m, crown-H), 3.20 (s), 3.55-3 75 (m).

After passing through ion exchange resin (IR 400, OH" form), $^1$HNMR was recorded again.

$^1$H NMR:

5 3.64-3.68 (m, crown-H), 3.07-3.08 (d), 2.50-2.70 (tt).

2 Dichloromethane soluble product: 25 mg (syrup).

IR(neat): 3398, 2868, 1668, 1454, 1114, 912, 731 cm"$^1$.

$^1$H NMR:

6 3.64-3.67 (m, crown-*H*), 3.30-3.40 (d), 2.80-2.90 (m), 2.50 (s, br).

3. Acetone soluble product: 30 mg (solid)

IR(KBr): 3445, 2967, 1664, 1381 cm"$^1$.

4. Methanol soluble product: 30 mg (solid).

IR (KBr): 2918, 1599, 1510, 1084, 1035 cm$^{-1}$

5. Pink coloured solid (insoluble in the above four solvents): 30 mg

IR(KBr): 3294,2926, 1593, 1116, 1026,704,613 cm$^{-1}$.

**Reaction of the crown diiodide** 72b **with *o*-phenylenediamine:**

A mixture of the crown diiodide **72b** (100 mg, 0 19 mmol) and *o*-phenylenediamine (21 mg, 0.19 mmol) in dimethylformamide (5 ml) was heated to 120° for three days. The DMF was removed from the reaction

mixture under vacuum The residue obtained was taken in dichloromethane and undissolved material was extracted with methanol IR and NMR spectra of both the fractions showed only formylated product 87 no other tractable material.

Yield: 60 mg (crude).

Dichloromethane soluble: 12 mg (syrup)

IR(neat): 3300, 1650, 1100 $cm^{-1}$

$^1H$ NMR

8 8.13 (s, 2H, C*H*O), 7 64-7.70 (m, 4H, Ar*H*), 7.25-7.33 (m, 4H, Ar*H*), 4.86 (s, 4H, $CH_2N$), 3.26-3.64 (m, 20H, $OCH_2CH_2O$)

Methanol soluble: 10 mg (white solid).

IR(KBr): 3300, 1650, 1100 $cm^{-1}$

$^1H$ NMR:

5 8.00-8.10 (m), 7.70-7.80 (m), 7 50-7.60 (m), 7.20-7.30 (m), 3.56-3.65 (m).

**Reaction of the crown diamine 71 with biacetyl:**[61]

To a solution of the crown diamine 71 (500 mg, 1.71 mmol) in methanol (10 ml) was added conc. HC1 (0.15 ml) and the reaction mixture was cooled to 5°. Biacetyl (200 mg, 2.32 mmol) was added and stirred for 30 min and then the reaction mixture was maintained at rt for 20 min followed by the addition of nickel (II) acetate (425 mg, 1.71 mmol). After 4 h, conc. HC1 (0.15 ml) followed by $ZnCl_2$ (235 mg, 1.72 mmol) was added 10 min later, 3 ml of ether was added and the reaction mixture was kept at

rt. The solid thus formed was filtered and washed with methanol-ether mixture

Yield: 260 mg.

IR(KBr): 3134, 3047, 2926, 1610, 1498, 1354, 1093 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

5 3.51-3.57 (m, ), 2.96 (s).

$^{13}C$ NMR:

71.07, 69.60, 69.16, 68.99, 42 36, 40.25 ppm.

**Reaction of the crown diamine 71 with bromoacetic acid: Preparation of the bis(bromoacetamide) 90:**

To a stirred and ice cooled solution of the crown diamine 71 (200 mg, 0.68 mmol) in dichloromethane (10 ml) was added bromoacetic acid (240 mg, 1.72 mmol) followed by DCC (356 mg, 1.72 mmol) and this reaction mixture was stirred at 5° overnight. Water (10 ml) was added and after 15 min, the solid dicyclohexyl urea formed was filtered. The organic layer was separated, dried and evaporated to furnish a residue which was subjected to column chromatography using 50% acetone in ethyl acetate to afford the required product 90 as a foamy material.

Yield: 220 mg (60%).

IR (neat): 3200, 3050, 2900, 1160, 1560, 1100, 940, 740 $cm^{-1}$

$^1H$ NMR

6 3.88 (s, 4H, $CH_2COCH_2$), 3.57-3.64 (m, 20H, $OCH_2CH_2O$),3 35-3 38 (d, 4H, $CH_2Br$).

$^{13}C$ NMR

168.60, 74.77, 71.06, 69 18, 68.47, 45.18, 38.76, 29.12 ppm

**Reaction of the crown bis(bromoacetamide) 90 with the crown diamine 71:**

A mixture of the bromoacetamide 90 (110 mg, 0.2 mmol) and the crown diamine 71 (50 mg, 0.17 mmol) in ethanol (10 ml) was refluxed overnight Evaporation of the solvent afforded a brown coloured residue TLC and IR spectrum of the residue showed a complex mixture whose purification was not attempted.

Yield: 80 mg (crude).

IR (neat): 3400, 3050, 2900, 1660, 1100 $cm^{-1}$.

$^{1}H$ NMR

5 3.66(br, s).

$^{13}C$ NMR:

70.00-70 41 (m), 69.41-69.71 (m).

**Reaction of the crown diamine 71 with oxalyl chloride:**

To a stirred and ice cooled solution of the crown diamine 71 (50 mg, 0.17 mmol) in dichloromethane (5 ml) was added oxalyl chloride (48 mg, 0.37 mmol) and stirred at 5° for 1 h and then at rt overnight Excess oxalyl chloride was removed from the reaction mixture and the residue was taken in dichloromethane and filtered The undissolved material was dissolved in methanol IR and NMR spectra of both fractions did not lead to any characterisable products

Yield: 45 mg (crude).

Dichloromethane soluble product: 12 mg (syrup).

IR (neat): 3300, 2850, 1660, 1100 $cm^{-1}$.

$^1H$ NMR:

$\delta$ 4.40 (br), 3.62 (s).

Methanol soluble product: 35 mg.

$^1H$ NMR ($D_2O$):

5 3.50(br, m).

**Reaction of the crown diamine 71 with diethyl oxalate:**

A mixture of the diamine 71 (50 mg, 0.17 mmol) and diethyl oxalate (0.1 ml) in ethanol (2 ml) was refluxed overnight. The solvent was removed from the reaction mixture and the residue obtained was chromatographed eluting with 10% methanol in dichloromethane to afford a complex mixture, whose separation was not attempted.

Yield: 35 mg.

IR (neat): 2850, 1680, 1200, 1100, 920 $cm^{-1}$.

$^1H$ NMR:

5 4.20-4.40 (t), 3.60 (br, s), 1.20-1 40 (m).

**Preparation of the Copper (II) complex of the crown diamine92:**

To the crown diamine 71 (175 mg, 0 60 mmol) in ethanol (3 ml), cupric chloride (306 mg, 1.80 mmol) in ethanol (2 ml) was added and the mixture was heated on a water bath The undissolved cupric chloride was filtered off. To the filtrate, a small amount of ether was added and allowed to

stand at rt. The light yellow coloured crystals thus formed were filtered and dried

IR (KBr): 3450,3200, 3100, 2850, 1607, 1100, 940 $cm^{-1}$.

Analysis:

Calcd for $C_{13}H_{30}N_2O_5CuCl_4$:

C, 31.24, H, 6.05; N, **5.61;** Cu, 12 71; Cl, 28.38.

Found: C, 30.52, H, **5.93;** N, **5.52;** Cu, **12.71;** Cl, 28.00.

The amounts of copper and chloride present in the complex 92 were estimated by gravimetry. UV spectra of the complex in methanol showed an absorption maxima at 893 nm.

**Reaction of the crown diamine 71 with salicylaldehyde: Preparation of the crown salicylaldimine 93:**

A mixture of the diamine 71 (175 mg, 0.60 mmol) and salicylaldehyde (0 14 ml, **1.31** mmol) in ethanol (10 ml) was refluxed for 24h. The solvent removed and the residue thus obtained was subjected to column chromatography. Eluting with ethyl acetate yielded the required product **93**

Yield: 139 mg (65%), starting material recovered is 50 mg.

IR (neat): 3300, 2850, 1600, 1340, 1100, 740 $cm^{-1}$.

$^1H$ NMR

8 8.38 (s, br, 2H, Ar-O*H*), **7.27-7.35** (m, 6H, Ar*H*), 6.84-6.97 (m, 4H, Ar*H* and N=C*H*), 3.63-3.70 (m, 24H, $OCH_2CH_2O$)

**Preparation of the crown salicylaldimine nickel (II) complex 94:** [62]

To the crown diamine 71 (200 mg, 0 68 mmol) in ethanol (10 ml) salicylaldehyde (250 mg, 2.05 mmol) was added and refluxed for 2 days. To this reaction mixture, nickel (II) sulphate (100 mg) was added and refluxed for 30 min. The solvent was evaporated, the residue thus obtained was dissolved in dichloromethane and filtered The residue obtained was chromatographed on basic alumina using ethyl acetate and acetone as eluent to afford the product 94 as a dark green coloured solid.

Yield: 80 mg.

IR(neat): 3350, 2850, 1610, 1540 $cm^{-1}$.

$^1H$ NMR:

5 6.99-7.25 (m, 6H, Ar*H*), 6.50 (t, 2H, Ar*H*), 3.41-3.64 (m, 24H, $OCH_2CH_2O$).

UV (methanol): The UV spectrum of 94 shows an absorption maxima at 585.4 nm. The extinction coefficient (e = 68) is small, typical of a d-d transition.

**Preparation of the gadolinium complex of the crown diaminetetraacetic acid 95:** [73]

A mixture of the crown diaminetetraacetic acid 79 (33 mg, 0 06 mmol) and gadolinium oxide (11.4 mg, 0.03 mmol) in water was refluxed overnight. Initially, gadolinium oxide was not soluble completely but on heating, it dissolved. The reaction mixture was cooled to rt and filtered and the water was removed under reduced pressure to dryness. The light pink

coloured solid thus obtained could not be satisfactorily recrystallised from various solvents.

Yield: 37 mg

IR (KBr): 3400, 2920, 1600, 1410, 1107 $cm^{-1}$.

$^1H$ NMR ($D_2O$):

5 4.70(br), 3 59 (br), 3 22(br)

The ESR spectrum was recorded at room temperature. The g value obtained was 2.06. Literature[63] g value for $Gd^{3+}$ (gadolinium trichloride doped in lanthanum trichloride) is 1.991.[63]

**Determination of Acid Dissociation and Stability Constants.**

The dissociation constants of the crown diamine 71, the crown diaminetetraacetic acid 79 and the crown tetraaminehexaacetic acid 82 and the stability constants of these ligands with metal ions were obtained from potentiometric titration experiments. Potentiometric measurements of the ligands in the presence and in the absence of the metal ions were carried out with a pH meter equipped with glass and calomel reference electrodes and calibrated with standard pH 7 and pH 4 solutions The readings are correct to ± 0.01 units. The temperature was maintained at 25.00 ± 0.05°, and the ionic strength was adjusted to 0.10 by using tetraethylammonium perchlorate or sodium perchlorate as the supporting electrolyte. Anhydrous lanthanide metal chlorides were prepared according to the literature.[73] The concentrations of the experimental solutions were 2 - 5 x $10^{-3}$ M in metal ions and ligands. Standard perchloric acid and carbonate and carbon dioxide free standard sodium hydroxide solutions were used for titrations. All the metal ion solutions were standardised by titrating against standard EDTA All the experimental solutions were prepared using double distilled water.

Potentiometric titrations were performed in a nitrogen atmosphere by taking a known volume of ligand solution and the pH was measured after each addtion of the titer base or acid in the presence as well as in the absence of the metal ions. All the experimental titrations were checked for consistency The pH meter was calibrated for pH 7 and pH 4 before each titration.

All the calculations were performed using the computer program SCOGS 2 reported by Perrin and Stunzi.[65] All the calculations were carried out in two steps. First, the dissociation constants of the ligands were determined and in the second step, these constants were used for the determination of the stability constants In all the computer calculations the standard deviations were of the order of $2 \times 10^{-2}$ All the dissociation and stability constants are correct to $\pm 0.01$ log units. Initially all the dissociation constants were calculated according to Jonassen[66] Schwarzenbach and Martell[69] and were used as input data in the SCOGS 2 program.

The experiments were performed first with the crown diamine 71 followed by crown diaminetetraacetic acid 79 and crown tetraaminehexaacetic acid 82 and the data obtained are given below.

### 1. Crown Diamine 71.

**1. Determination of acid dissociation constants ($\mu$ = 0.10 M, $Et_4NClO_4$):**

5 ml of $5 \times 10^{-3}$ M crown diamine 71 solution was titrated with 0.0953 M perchloric acid. The ionic strength of the solution was maintained with tetraethylammonium perchlorate at $\mu = 0.10$. The titration data consists of two rows in which the first row gives the amount of titrant acid or base added (in ml) and the second row is the pH measured after each addtion of the titrant.

| acid added | PH | 0.15 | 8.51 | 038 | 4.06 |
|---|---|---|---|---|---|
| 000 | 10.22 | 0.16 | 8.39 | 0.39 | 3.62 |
| 001 | 10.13 | 0.17 | 8.27 | 0.40 | 3.39 |
| 0.02 | 10.03 | 0 18 | 8.15 | 0 41 | 3.24 |
| 0.03 | 9.93 | 0.19 | 8.04 | 0.42 | 3 13 |
| 0.04 | 9.82 | 020 | 7.94 | 0.43 | 3.04 |
| 0.05 | 9.72 | 0.22 | 7.73 | 0.44 | 2.97 |
| 006 | 9.60 | 024 | 7.57 | 0.45 | 290 |
| 0.07 | 9.48 | 0.25 | 7.50 | 0.46 | 2.85 |
| 0.08 | 9.36 | 0 26 | 7.41 | 0.47 | 280 |
| 0.09 | 9.23 | 0.28 | 720 | 0.48 | 2.76 |
| 0.10 | 9.10 | 0.30 | 698 | 0.49 | 2.72 |
| 0.11 | 898 | 032 | 6 68 | 0.50 | 269 |
| 0.12 | 8.87 | 0.34 | 628 | 0.51 | 2.65 |
| 0.13 | 8.75 | 036 | 563 | 0.52 | 2.62 |

Initially the dissociation constants were determined by Jonassen's method[66] as $pK_1 = 3.31$ and $pK_2 = 8.76$. These pK's values were given as rough estimates in the input to the SCOGS 2 program and after refinement the values were obtained as

$$pK_1 = 2.86$$
$$pK_2 = 8.79$$

**2. Determination of stability constants ($\mu$ = 0.10 M, $Et_4NClO_4$):**

**a) With $Cu^{2+}$:**

To 5 ml of 5 x $10^{-3}$ M diamine 71 solution, 0 04 ml of 0.1613 M copper (II) perchlorate solution was added and then titrated with 0.0953 M perchloric acid

| acid added | pl I |
|---|---|
| 0.00 | 8.70 |
| 001 | 8.50 |
| 0.02 | 8.30 |
| 0.03 | 808 |
| 004 | 7.87 |
| 0.05 | 7.69 |
| 0.06 | 7.54 |
| 0.07 | 7.41 |
| **0.08** | 7.30 |
| 0 09 | 7.20 |
| 0.10 | 7.10 |
| 0.11 | 7.02 |

| 0.12 | 6.94 |
|---|---|
| 013 | 6 86 |
| 0 14 | 6.77 |
| 0.15 | 6.69 |
| 0.16 | 6.60 |
| 0.17 | 6 50 |
| 0 18 | 6.40 |
| 0.19 | 6.30 |
| 0.21 | 6.08 |
| 0.23 | 5.90 |
| 0.25 | 5.74 |
| 0.27 | 5.59 |
| 0.29 | 5.43 |

| **0.31** | 5.24 |
|---|---|
| 0.33 | 4.97 |
| 0.35 | 4.37 |
| 0.37 | 3.55 |
| 0.39 | 3.20 |
| 0.41 | 3.01 |
| 0.43 | 2.87 |
| 0.45 | 2 77 |
| 0.47 | 2.69 |
| 0.49 | 2.63 |
| 0.51 | 2.57 |
| 0.53 | 2.53 |

When this data was processed it was observed that the crown diamine 71 forms 1 : 1 and 2 : 1 complexes with $Cu^{2+}$ and the values obtained are log $K_1$ - 9.95, log $K_2$ = 4.80 and log $K_N$ = **14.75.**

**b) With $Co^{2+}$:**

To 4 ml of 5 x 10 $^{-3}$ M diamine 71 solution, 0.40 ml of 0.0159 M cobalt (II) perchlorate solution was added and then titrated with 0.0953 M perchloric acid solution.

| acid added | PH | 0.14 | 725 | 0.26 | 3.39 |
|---|---|---|---|---|---|
| 000 | 8.05 | 0.15 | 7.19 | 0.27 | 3.23 |
| 0.01 | 7.97 | 0.17 | 7.06 | 0.28 | 3.11 |
| 0.02 | 7.90 | 0.18 | 6.90 | 0.29 | 3.02 |
| 0.04 | 7.76 | 0.20 | 6.68 | 0 30 | 2.94 |
| 0.06 | 7.63 | 0.21 | 6.39 | 0.31 | 2.87 |
| 0.08 | 7.52 | 0.22 | 599 | 032 | 2.82 |
| 0.10 | 7.46 | 023 | 5.48 | 033 | 2.77 |
| 0.12 | 7.35 | 0.24 | 4 18 | 0.34 | 2.72 |
| 0.13 | 7.30 | 0.25 | 3.65 | 0.35 | 268 |

The stability constants obtained are log $K_1$ = 9.74, log $K_2$ = 3.95, log $K_3$ = 1.35 and log $K_N$ = 15.04. It was observed that the crown diamine 71 forms 1:1, 2:1 and 3 : 1 complexes with $Co^{2+}$.

**c) With $Ni^{2+}$:**

To 4 ml of 5 x $10^{-3}$ M diamine 71 solution, 0.30 ml of 0.0193 M nickel (II) perchlorate solution was added and titrated with 0 095 M perchloric acid solution

| acid added | PH | 0.10 | 7.65 | 0.24 | 6.44 |
|---|---|---|---|---|---|
| 0.00 | 9.16 | 0.11 | 7.55 | 0.26 | 6.00 |
| 0.01 | 8.99 | 0 12 | 7.45 | 0.28 | 478 |
| 0.02 | 882 | 0.13 | 7.37 | 0.30 | 3 41 |
| 0.03 | 8.65 | 0.14 | 7.30 | 0.31 | 3.21 |
| 0.04 | 8.48 | 0.15 | 7.23 | 0.32 | 3.09 |
| 0.05 | 8.32 | 0.16 | 7.16 | 0.33 | 2.99 |
| 0.06 | 8.15 | 0.17 | 7.10 | 0.34 | 2.92 |
| 0.07 | 8.00 | 0.18 | 7.02 | 0.35 | 285 |
| 0.08 | 7.87 | 0 20 | 687 | 0.36 | 2.79 |
| 0.09 | 7.75 | 0.22 | 6.69 | 0.37 | 2.74 |

The stability constants obtained are log $K_1$ = 8.38, log $K_2$ = 3.64 and the log $K_N$ = 12.02. It is seen that the crown diamine 71 forms 1 : 1 and 2 : 1 complexes with $Ni^{2+}$.

**d) With $La^{3+}$:**

To 4 ml of 5 x $10^{-3}$ M diamine 71 solution, 0.20 ml of 0.0262 M lanthanum (III) chloride solution was added and titrated with 0 0953 M perchloric acid solution. The pH data is summarized below

| acid added | PH | 0.16 | 7 16 | 0.29 | 3.47 |
|---|---|---|---|---|---|
| 0.00 | 8.89 | 0.18 | 6 86 | 0.30 | 3.26 |
| 0.01 | 8.80 | 020 | 6.58 | 0.31 | 3.12 |
| 0.02 | 8.70 | 021 | 638 | 0.32 | 301 |
| 0.03 | 861 | 0.22 | 626 | 0.33 | 2.93 |
| 0.05 | 8.43 | 0.23 | 6.14 | 0.35 | 2.80 |
| 0.07 | 8.26 | 0.24 | 6.00 | 037 | 2 70 |
| 0.08 | 8.12 | 0.25 | 5.94 | 0.38 | 2.66 |
| 0.10 | 7.91 | 0 26 | 5.73 | 0.40 | 2.59 |
| 0.12 | 7.67 | 0.27 | 5.09 | 0.41 | 2.56 |
| 0.14 | 7.43 | 0.28 | 388 | 0.42 | 2.53 |

The stability constants obtained show that the crown diamine 71 forms 1 : 1,2: 1 and 3 : 1 complexes with $La^{3+}$ and the values obtained are $\log K_1 = 3.01$, $\log K_2 = 4.51$, $\log K_3 = 3.60$ and $\log K_N = 11.12$.

**e) With $Ce^{3+}$:**

To 5 ml of 5 x $10^{-3}$ M diamine 71 solution, 0.20 ml of 0.04015 M cerium (III) chloride solution was added and titrated with 0.0953 M perchloric acid solution.

| acid added | pH | 0.09 | 6.77 | 0.19 | 3.58 |
|---|---|---|---|---|---|
| **0 00** | 7.80 | 0.10 | 662 | 0.20 | 3.37 |
| 0.01 | 7.68 | 0.11 | 643 | **0.21** | 3.23 |
| 0.02 | 7.57 | 0 12 | 6.22 | 0.22 | 3.13 |
| 0.03 | 7.47 | 0.13 | 5.97 | 0.23 | 3.04 |
| 0.04 | 7.37 | 0 14 | 5.70 | 0.24 | 2.98 |
| 0.05 | 7.26 | 0.15 | 5.34 | 0.25 | 292 |
| 006 | 7.16 | 0.16 | 5.04 | 0.26 | 2.87 |
| 0.07 | 7.02 | 0.17 | 4 70 | 0.27 | 2.82 |
| 0.08 | 6.91 | 0.18 | 4.06 | 0.28 | 2.78 |

The stability constants obtained are log $K_1$ = 5.97, log $K_2$ = 4.05, log $K_3$ 4.60 and log $K_N$ = 14.62.

**0 With $Nd^{3+}$:**

To 5 ml of 5 x $10^{-3}$ M diamine 71 solution, 0.20 ml of 0.0415 M neodymium (III) chloride solution was added and titrated with 0 0953 M perchloric acid solution

| acid added | pH | 0.16 | 7.49 | 0.32 | 581 |
|---|---|---|---|---|---|
| 000 | 8.10 | 0.18 | 7.39 | 0.34 | 4.85 |
| 0 02 | 8.00 | 0.20 | 7.29 | 0.36 | 3.62 |
| 004 | 7.92 | 0.22 | 715 | 0.38 | 326 |
| 0.06 | 7.84 | 0.24 | 6 96 | 0.40 | 3.07 |
| 0.08 | 7.76 | 0.26 | 6.70 | 0.42 | 2.94 |
| 0.10 | 7.70 | 0.28 | 6.40 | 0.44 | 284 |
| 0.12 | 7.63 | 0.30 | 6.01 | 0.46 | 276 |

The stability constants obtained are

$$\log K_1 = 3\ 48$$
$$\log K_2 = \mathbf{2.34}$$
$$\log K_3 = 5\ 90$$
$$\log K_N = 11\ 80.$$

g) **With $Sm^{3+}$:**

To 4 ml 5 x $10^{-3}$ M diamine 71 solution, 0.20 ml of 0.0241 M samarium (III) chloride solution was added and titrated with 0 0953 M perchloric acid solution

| acid added | pH |
|---|---|
| 0.00 | **8.18** |
| 0.01 | 8.02 |
| 0 02 | 786 |
| 0.03 | 7.77 |
| 0.04 | 7.60 |
| 0.05 | 7.47 |
| 0.06 | 7.34 |
| 0.07 | 7.22 |
| 0.08 | 7.09 |
| 0.10 | 678 |
| 0.11 | 6.60 |
| 0.12 | 6.44 |
| 0.14 | 6.24 |
| 0.15 | 6.19 |
| 0.17 | 6.12 |
| 0.19 | 6.00 |
| 0.20 | 5.91 |
| 0.21 | 5.85 |
| 0.23 | 5.71 |
| 0.24 | 5.54 |
| 0.25 | 5.10 |
| 0.26 | 4.07 |
| 0.27 | 3.62 |
| 0.28 | 3.35 |
| 0.30 | 3.09 |
| 0.32 | 2.93 |
| 0.33 | 2.87 |
| 0.34 | 281 |
| 0.35 | 2.76 |
| 0.36 | 2 72 |
| 0.37 | 268 |
| 0.38 | 265 |

The stability constants obtained are

$$\log K_1 = 3.55$$

$$\log K_2 = 6.01$$

$$\log K_3 = 5.21$$

$$\log K_N = 14.77.$$

**h) With $Eu^{3+}$:**

To 4 ml of 5 x $10^{-3}$ M diamine 71 solution, 0.30 ml of 0.02275 M europium (III) chloride solution was added and titrated with 0.0953 M perchloric acid solution.

| acid added | pH | 0.12 | **6.94** | 0.24 | 5.59 |
|---|---|---|---|---|---|
| 000 | 7.83 | 0.13 | 6 85 | 0.25 | 5.29 |
| 001 | 7.73 | 0.14 | 6.73 | 0.26 | 5 13 |
| 0.02 | 7.65 | 0.15 | 6.60 | 0.27 | 4.25 |
| **0.03** | 7.56 | 0.16 | 6.47 | 0.28 | 3.68 |
| 0.04 | 7.48 | 0.17 | 6 34 | 0.29 | 3.41 |
| 0.05 | 7.41 | **0.18** | 6.20 | 0.30 | 3 24 |
| 006 | 7.35 | 0 19 | **6.09** | 0.31 | 3.12 |
| 007 | 7.30 | 0.20 | **6.00** | 0.32 | 303 |
| 0.09 | 7.14 | 0.21 | 586 | 0.33 | 2 95 |
| 0 10 | 709 | 022 | 5.72 | 0.34 | 2.88 |
| 0 11 | 7.03 | 0.23 | 5.62 | 035 | 2.83 |

The stability constants obtained are

$$\log K_1 = 3\ 85$$
$$\log K_2 = 4.45$$
$$\log K_3 = 4\ 90$$
$$\log K_N = 13.42.$$

**i) With $Gd^{3+}$:**

To 4 ml of 5 x $10^{-3}$ M diamine 71 solution, 0.20 ml of 0.02677 M gadolinium (III) chloride solution was added and titrated with 0.0953 M perchloric acid solution

| acid added | pH | 0.12 | 6 18 | 0.26 | 428 |
|---|---|---|---|---|---|
| 0.00 | 7.72 | 0.14 | (..02 | 0.27 | 3.66 |
| 0.01 | 7.52 | 0.15 | 5.94 | 0.28 | 3.39 |
| 0 02 | 7.34 | 0.16 | 589 | 029 | 3.25 |
| 0.03 | 7 27 | 0.17 | 5.85 | 0.30 | 3.14 |
| 0.04 | 7.15 | 0.18 | 5.80 | 031 | 3.06 |
| 0.05 | 7.00 | 0.19 | 5.77 | 0.32 | 2.98 |
| 0.06 | 6.93 | 0.20 | 5.72 | 033 | 2.92 |
| 0.07 | 6.79 | 0.21 | 568 | 0.34 | 2.87 |
| 0.08 | 669 | 0.22 | 562 | 0.35 | 2.81 |
| 0.09 | 6.59 | 0.23 | 5.52 | 0.36 | 2.77 |
| 0.10 | 6.48 | 0.24 | 5.37 | 0.37 | 2.73 |
| 011 | 6.31 | 0.25 | 5.16 | 0.38 | **2.69** |

The stability constants obtained are log $K_1$ = 3.62, log $K_2$ = 6.41, log $K_3$ = 5.37 and log $K_N$ = 15.40.

**2. Determination of stability constants of the crown diamine 71 ($\mu$ = 0.10 M, $NaClO_4$):**

**a) With $Cu^{2+}$:**

5 x $10^{-3}$ M crown diamine 71 solution was prepared using sodium perchlorate as the supporting electrolyte with $\mu$ = 0.10 M. To 4 ml of this diamine solution, 0.05 ml of 0.1613 M copper (II) perchlorate solution was added and titrated with 0.0953 M perchloric acid solution.

| acid added | pH |
|---|---|
| 0.00 | 7.37 |
| 0.02 | 7.16 |
| 0.04 | 6.97 |
| 0.05 | 688 |
| 0.06 | 6.79 |
| 007 | 6.71 |
| 0.08 | 6.62 |
| 0.09 | 6.54 |
| 0.10 | 6.46 |
| 0.11 | 639 |
| 0.12 | 6.30 |
| 0.14 | 6.15 |
| 0 15 | 6.08 |

| 0.16 | 6.01 |
|---|---|
| 0.17 | 5.95 |
| 0.18 | **5.90** |
| 020 | 5 83 |
| **0.21** | 5.77 |
| 022 | **5.71** |
| 0.23 | 5 64 |
| 0.24 | 5.57 |
| 0.25 | 5.50 |
| 0 26 | 5.43 |
| 027 | 533 |
| 0.28 | 5.24 |
| 029 | 5.11 |
| 0.30 | 4 94 |

| 031 | 465 |
|---|---|
| 0.32 | 4.16 |
| 033 | 3.71 |
| 0.34 | 3.44 |
| 0.35 | 3.27 |
| 0.36 | 3.14 |
| 0.37 | 3.04 |
| 038 | 2.97 |
| 039 | 2.90 |
| 040 | 2.84 |
| 0.41 | 2.79 |
| 0.42 | 2.74 |

The stability constant obtained is log K = 10.05 and the stoichiometry corresponds to a ligand to metal ratio of 2 1

**b) With $Sm^{3+}$:**

To 4 ml of 4 x $10^{-3}$ M diamine 71 solution, 0.20 ml of 0.0241 M samarium (III) chloride solution was added and titrated with 0 0953 M perchloric acid solution.

| acid added | pH | 0.10 | 7.20 | 0.24 | 3.38 |
|---|---|---|---|---|---|
| 0.00 | 8.16 | **0.12** | 7.05 | 0.25 | 3.19 |
| 0.01 | 802 | 0.14 | 6.82 | 026 | 3.05 |
| 0.02 | 7.89 | 0.16 | 6.46 | 0.28 | 2.84 |
| 003 | 7.78 | 0.18 | 6.12 | 0 30 | 2.70 |
| 0.04 | 7.68 | 020 | 5.72 | 0.32 | 2.60 |
| 0.05 | 7.58 | 0.21 | 5.25 | 0.34 | 2.52 |
| 0.06 | 7.50 | 0.22 | 4.34 | 0.36 | 2.45 |
| 0.08 | 7.34 | 0.23 | 3.70 | 0.38 | 2.39 |

The stability constant obtained is log K = 12.91 and the stoichiometry corresponds to a ligand to metal ratio of 3 : 1.

**c) With $Gd^{3+}$:**

To 4 ml of 4 x $10^{-3}$ M diamine 71 solution, 0.16 ml of 0.02677 M gadolinium (III) chloride solution was added and titrated with 0 0953 M perchloric acid solution.

| acid added | PH | 0.08 | 7.33 | 0.24 | 4.32 |
|---|---|---|---|---|---|
| 000 | 8.52 | 0.09 | 722 | 026 | 3.29 |
| 0.01 | 8.30 | 0.10 | 7.10 | 028 | 3.00 |
| 0.02 | 8.10 | 0.12 | 6 84 | 0 30 | 2.81 |
| 003 | 7.93 | 0 14 | **6.50** | 0.32 | 2.69 |
| 0.04 | 7.79 | 0.16 | 6.55 | 0.34 | 2.59 |
| 0.05 | 7.65 | **0.18** | **6.28** | 0.36 | 2.50 |
| 0.06 | 7.53 | 0.20 | 6 10 | 0.38 | 2.43 |
| 0.07 | 7.42 | 0.22 | 5.82 | 0.40 | 2.37 |

The stability constant obtained is log **K** = 12 94 and the stoichiometry corresponds to a ligand to metal ratio of 3 : 1

## 2. Crown diaminetetraacetic acid 79.

**1. Determination of the dissociation constants of crown diaminetetraacetic acid** 79 **($\mu$ = 0.10 M, $NaClO_4$):**

4 ml of 1.8645 x $10^{-3}$ M crown diaminetetraacetic acid solution 79 was titrated with 0.3125 M sodium hydroxide solution and pH measured is given below.

| base added | **pH** |
|---|---|
| **0.000** | 2.55 |
| 0.010 | 2.62 |
| 0.020 | 2.71 |
| 0.030 | 2.80 |
| 0 040 | 2.93 |
| 0.045 | 2.99 |
| 0.050 | 3.07 |
| 0.055 | 3.17 |
| 0.060 | 3.28 |
| 0065 | 3.42 |

| 0.070 | 360 |
|---|---|
| 0.075 | 3 86 |
| 0.080 | 4.22 |
| 0.085 | 4.73 |
| 0.090 | 5.38 |
| 0095 | 5.91 |
| **0.100** | 6.30 |
| 0.105 | 6.61 |
| 0 110 | 691 |
| 0.115 | 7.32 |
| 0.120 | 8 17 |

| **0.125** | 9.12 |
|---|---|
| 0.130 | 9.54 |
| **0.140** | 9.98 |
| 0 150 | 10.26 |
| 0.160 | 10.47 |
| 0.170 | 1062 |
| **0.180** | 1073 |
| 0.190 | 1081 |
| 0.200 | 1087 |
| 0.220 | 10.97 |
| 0.240 | 11 05 |

The titration curve (pH vs a where a = number of moles of base added per mole of the ligand 79) showed the saturation point at a = 6 instead of 4 (see results and discussion) Hence, initially the crown diaminetetraacetic acid 79 solution was neutralised with 6 **eq** of 0.125 M

sodium hydroxide solution and then titrated with perchloric acid solution. The titration data was used for calculating the acid dissociation constants

4 ml of 1.8645 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution was neutralised by adding 0.39 ml of 0.125 M NaOH and titrated with 0.0953 M perchloric acid solution.

| acid added | pH |
|---|---|
| 000 | 10 18 |
| 0.01 | 10.03 |
| 0 02 | 985 |
| 0.03 | 9.62 |
| 0.04 | 9.35 |
| 0.05 | 8.90 |
| 0.06 | 8.14 |
| 0.07 | 7.39 |
| 0.08 | 7.01 |
| 0.09 | 673 |

| | |
|---|---|
| 0.10 | 6.46 |
| 0 11 | 6.19 |
| 0.12 | 584 |
| 0.13 | 5.36 |
| 0 14 | 4.83 |
| 0.15 | 4.40 |
| 0.16 | 4.06 |
| 0.17 | 3.79 |
| 0.18 | 3 59 |
| 0.19 | 3.43 |
| 0.20 | 3 31 |

| | |
|---|---|
| 0.21 | 3 20 |
| 0.22 | 3.12 |
| 0.23 | 3.05 |
| 0.24 | 298 |
| 0.25 | 2.93 |
| 0.26 | 288 |
| 0.27 | 283 |
| 0.28 | 2.79 |
| 0.29 | 2.75 |
| 0.30 | 2.72 |

Initially, the acid dissociation constants of 79 were calculated using Schwarzenbach's and Martell's methods[69] and the values obtained are $pK_1$ = 1.60, $pK_2$ = 2.82, $pK_3$ = 6.20 and $pK_4$ = 9.43. These numbers were used as rough estimates in the program and after refinement, the values obtained are $pK_1$ =2.12, $pK_2$ = 2.80, $pK_3$ = 6.07 and $pK_4$ = 9 35.

**2. Determination of the stability constants of the crown diaminetetraacetic acid 79 ($\mu$ = 0.10 M, $NaClO_4$):**

**a) With $Cu^{2+}$:**

To 4 ml of 1.8645 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0 046 ml of 0.1613 M copper (II) perchlorate solution was added and then titrated with 0.3125 M sodium hydroxide solution

| base added | pH |
|---|---|
| 0.00 | 2.27 |
| 0.01 | 2.31 |
| 0.02 | 2.35 |
| 0.04 | 2.44 |
| 0.06 | 2 56 |
| 0.08 | 2.72 |
| 0.10 | 2.95 |
| 0.11 | 3.11 |
| 0.12 | 3.31 |
| 0.13 | 3.61 |
| 0.140 | 4.09 |
| 0.150 | 5.16 |
| 0.160 | 7.46 |
| 0 165 | 9.24 |
| 0.170 | 9.89 |
| 0.175 | 10.17 |
| 0.180 | 10.35 |
| **0.185** | **10.45** |
| 0.195 | 1063 |
| 0.205 | **10.73** |
| 0.215 | 1082 |
| 0.225 | 10.88 |
| 0.235 | 10.93 |
| 0.245 | 1098 |
| 0.255 | 11.01 |

The stability constant obtained is log K = 12.67 and the stoichiometry corresponds to a ligand-metal ratio of 1 : 1.

**b) With $Ni^{2+}$:**

To 4 ml of 1 8645 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.4 ml of 0.01927 M nickel (II) perchlorate solution was added and titrated with 0.3125 M sodium hydroxide solution and pH measured is listed below.

| base added | PH |
|---|---|
| 0.000 | 2.33 |
| **0.020** | 2.41 |
| 0.040 | 2.51 |
| 0.060 | 2.63 |
| 0.080 | 2.79 |
| **0.100** | 3.06 |
| 0.120 | 3.60 |
| 0.125 | 3.83 |
| 0.130 | 4.14 |

| | |
|---|---|
| 0.12 | 3.31 |
| 0.135 | 4.66 |
| **0.140** | 5.55 |
| 0.145 | 7.60 |
| 0.150 | 8.55 |
| 0.155 | 9.21 |
| 0.160 | 9.70 |
| **0.165** | 10.04 |
| 0.170 | 10.21 |
| 0.175 | 10.33 |

| | |
|---|---|
| 0.185 | 10.45 |
| 0 180 | 10.43 |
| 0.190 | 10.59 |
| 0.200 | 10.70 |
| 0.210 | 10.77 |
| 0.230 | **10.84** |
| 0.250 | **10.94** |
| 0.270 | 11.01 |
| 0.280 | 11.04 |

The stability constant obtained is log K = 12 25 and the stoichiometry corresponds to a ligand-metal ratio of 1 1

**c) With $La^{3+}$:**

To 4 ml of 1.5538 x $10^{-3}$ **M crown** diaminetetraacetic **acid 79** solution, 0.25 ml of 0.02623 M lanthanum (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | PH |
|---|---|
| 0.000 | 2.64 |
| 0.025 | 286 |
| 0.050 | 3.28 |
| 0.065 | 3.90 |
| 0.075 | 4.48 |
| 0.085 | 4.80 |
| 0.095 | 5.09 |
| 0.100 | 5.25 |

| | |
|---|---|
| 0.110 | 5.75 |
| **0.115** | 6.59 |
| 0 120 | 7.83 |
| 0.125 | 8 50 |
| 0.130 | 886 |
| 0.135 | 9.50 |
| 0.140 | 9.91 |
| 0.145 | 10.18 |
| **0.150** | 10 33 |

| | |
|---|---|
| 0.160 | 10.56 |
| 0.170 | **10.45** |
| 0.180 | 10 43 |
| 0.190 | 10.59 |
| 0.200 | 10.70 |
| 0.210 | 1077 |
| 0.230 | 1084 |
| 0.240 | 10 94 |
| 0.260 | 11 01 |

The stability constants obtained are
with 4 displaceable protons, log K = 9.96
with 3 displaceable protons, log K = 11.05.

**d) With $Ce^{3+}$:**

To 4 ml of 1.5538 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.15 ml of 0.04015 M cerium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | pH | 0.085 | 4.54 | 0.140 | 10.03 |
|---|---|---|---|---|---|
| 0 000 | 2.64 | 0.090 | 4.68 | 0.145 | 10.22 |
| 0.020 | 282 | 0.095 | 482 | 0.150 | **10.33** |
| 0.040 | 3.11 | **0.100** | **4.99** | 0.160 | 10.53 |
| 0.050 | 3.35 | 0.105 | 5.23 | 0.170 | 10.65 |
| 0.055 | 3.52 | 0.110 | 5.70 | 0.180 | 10.74 |
| 0.060 | 3.73 | 0.115 | 6.76 | 0.200 | 10.88 |
| 0.065 | 3.96 | 0.120 | 7.75 | 0.220 | 10.97 |
| 0.070 | 4.14 | 0.125 | 841 | 0.240 | 11 03 |
| 0.075 | 4.29 | 0.130 | 9.12 | 0260 | 11 10 |
| 0.080 | 4.42 | 0.135 | 9.71 | 0.280 | 11 15 |

The stability constants obtained are

with 4 displaceable protons, log K = 9 80

with 3 displaceable protons, log K = 11.20.

**e) With $Nd^{3+}$:**

To **4** ml of 1 5538 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.15 ml of 0.04149 M neodymium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | pH |
|---|---|
| 0.000 | 2.57 |
| **0.020** | 2.73 |
| 0.040 | 2.99 |
| 0.060 | 3.46 |
| **0.065** | 3.62 |
| 0.070 | 3.77 |
| 0.075 | 391 |
| 0.080 | 4.03 |
| **0.085** | 4.14 |
| 0090 | 4.26 |

| | |
|---|---|
| 0.100 | 4 50 |
| **0.105** | **4.66** |
| 0.110 | 4.87 |
| 0.115 | 5.19 |
| 0.120 | 591 |
| 0.125 | 7 06 |
| 0.130 | 7.69 |
| 0.135 | 8.25 |
| 0.140 | 9.06 |
| 0.145 | 9.64 |
| 0.150 | 993 |

| | |
|---|---|
| **0.155** | 10.15 |
| **0.160** | **10.31** |
| 0.170 | 10.51 |
| 0.180 | 10 (.3 |
| 0.190 | 10.71 |
| 0.200 | 1078 |
| 0.220 | 10.83 |
| 0.240 | 10.93 |
| 0.260 | 11.00 |
| 0.280 | 11.06 |
| 0.300 | 11.11 |

The stability constants obtained are
with 4 displaceable protons, log K = 10.44
with 3 displaceable protons, log K = 11.45.

**f) With $Sm^{3+}$:**

To 4 ml of 1.5538 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.26 ml of 0.0241 M samarium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | pH | 0.100 | 4.46 | 0.155 | 10.21 |
|---|---|---|---|---|---|
| 0.000 | 2.61 | 0.105 | 4.69 | 0.160 | 10.32 |
| 0.020 | 2.78 | **0.110** | 5.07 | 0.170 | 10.48 |
| 0.040 | 3.06 | 0.115 | 5.75 | 0.180 | 10.59 |
| 0.060 | 3.51 | 0.120 | 6.67 | 0.200 | 10.74 |
| 0.070 | 3.75 | 0.125 | 7.26 | 0.220 | **10.84** |
| 0075 | 385 | 0.130 | **7.99** | **0.240** | 10.92 |
| 0.080 | 396 | 0.135 | 885 | 0.260 | 1098 |
| 0.085 | **4.07** | 0.140 | 9.46 | **0.280** | 11.04 |
| 0090 | 4.17 | 0.145 | 982 | 0 300 | 11.09 |
| 0.095 | 4.30 | 0 150 | 10.04 | | |

The stability constants obtained are
with 4 displaceable protons, log **K** = 9.82
with 3 displaceable protons, log **K** = 10.80.

**g) With $Eu^{3+}$:**

To 4 ml of 1.5538 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.28 ml of 0.02275 M europium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | pH | 0.100 | 4.44 | 0.155 | 1027 |
|---|---|---|---|---|---|
| **0.000** | 262 | 0.105 | 4.68 | 0.160 | 10.37 |
| 0.020 | 2.79 | 0.110 | 5.10 | 0.170 | 1052 |
| 0.040 | 3.05 | 0.115 | 5.87 | 0.180 | 10 62 |
| 0 060 | 3.48 | 0 120 | 7 00 | 0.190 | 10.70 |
| 0.070 | 3 71 | 0.125 | 7.55 | 0.200 | 10.77 |
| 0.075 | 3.81 | 0.130 | 8.38 | 0.220 | 10.87 |
| 0.080 | 3.92 | 0.135 | 9 04 | 0.240 | 10.95 |
| 0.085 | 402 | 0.140 | 9.60 | 0.260 | 11.02 |
| 0.090 | 4.13 | 0.145 | 9.92 | 0.280 | **11.08** |
| 0.095 | 4.27 | **0.150** | 10.13 | 0.300 | 11.13 |

The stability constants obtained are
with 4 displaceable protons, log K = 9.56
with 3 displaceable protons, log K = 10.70.

**h) With $Gd^{3+}$:**

To 4 ml of 1.5538 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.23 ml of 0.02677 M gadolinium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution

| base added | pH |
|---|---|
| 0.00 | 2.50 |
| 0.02 | 2.68 |
| 0.04 | 2.92 |
| 0.06 | 3.34 |
| 0.07 | 356 |
| 0.08 | 3.77 |
| 0.09 | 4.00 |

| | |
|---|---|
| 0.10 | 4.28 |
| 0.11 | 4.78 |
| 0.12 | **6.36** |
| 0.13 | 7.91 |
| 0.14 | 9.37 |
| 0.15 | 10 07 |
| 0.16 | **10.43** |
| **0.17** | 10.64 |

| | |
|---|---|
| 0.18 | 10.76 |
| 0.19 | 10.84 |
| 0.20 | 10.91 |
| 0.21 | 10.97 |
| 0.22 | 11.00 |
| 0.24 | 11.10 |
| 026 | 1 1 14 |

The stability constants obtained are

with 4 displaceable protons, log K = 10 77

with 3 displaceable protons, log K = 11 84

**2. Determination of the stability constants of the crown diaminetetraacetic acid 79 ($\mu$ = 0.10 M, $Et_4NClO_4$):**

**a) With $Cu^{2+}$:**

To 4 ml of 1.8645 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.05 ml of 0 1613 M copper (II) perchlorate solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | pH I |
|---|---|
| 0.00 | 2.26 |
| 0.02 | 2.35 |
| 0.04 | 2.46 |
| 0.06 | 2.61 |
| **0.07** | 2.70 |
| **0.08** | 282 |
| 0.09 | 2.97 |

| 0.10 | **3.16** |
|---|---|
| 0 11 | **3.44** |
| 0.12 | **3.88** |
| **0.13** | 4.84 |
| 0 14 | **6.23** |
| 0.15 | 8.07 |
| 0 16 | 9 84 |
| 0.17 | **10.40** |

| **0 18** | **10.63** |
|---|---|
| 0.19 | 10.77 |
| 0.20 | 10.87 |
| 0.21 | 10.96 |
| 0.22 | 11.02 |
| 0.23 | 11.07 |

The stability constant obtained is log K = 12.81.

**b) With $Sm^{3+}$:**

To 4 ml of 2 175 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.40 ml of 0.0241 M samarium (III) chloride solution was added and then titrated with 0.3125 M sodium hydroxide solution.

| base added | pH |
|---|---|
| 0.00 | 2.49 |
| 0.02 | 2.59 |
| 0.04 | 2.70 |
| 0.06 | 2.87 |
| 008 | 3.09 |
| 0 10 | 3.37 |
| 0.11 | 3.51 |
| 0.12 | 3.65 |
| 0.13 | 3.77 |
| 0.14 | **3.89** |
| 0.15 | 4.05 |
| **0.16** | 4.20 |
| 0.17 | 4.44 |
| **0.18** | 487 |
| 0.19 | 4.74 |
| 0.20 | 7.12 |
| 0.21 | 8.36 |
| 0.22 | 9.25 |
| 023 | 9.87 |
| 0.24 | 1026 |
| 0.25 | 10.50 |
| 0.26 | 1065 |
| 0.27 | 10.74 |
| 0.28 | **10.80** |
| 0.29 | 1085 |
| 0.30 | 10.91 |
| 0.31 | 1096 |

The stability constants obtained are
with 4 displaceable protons, log K = 10 40
with 3 displaceable protons, log K = 11.30

**c) With $Eu^{3+}$:**

To 4 ml of I 8645 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.30 ml of 0.02275 M europium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | PH |
|---|---|
| 0.00 | 2.58 |
| 0 02 | 2.72 |
| 0.04 | 2.90 |
| 0.06 | 3.19 |
| 0.07 | 338 |
| 008 | 3.55 |
| 0 10 | 3.90 |

| | |
|---|---|
| 0.11 | 4.10 |
| 0.12 | 4.38 |
| 0 13 | 4 92 |
| 0.14 | **6.30** |
| 0.15 | 8.20 |
| 016 | 9 34 |
| 0.17 | 993 |
| 0.18 | 10 26 |

| | |
|---|---|
| 0.19 | 1046 |
| 0.20 | 10.59 |
| 0.21 | 1067 |
| 0.22 | **10.71** |
| 0.23 | 10.77 |
| 0.24 | 1084 |
| 0.25 | 10.87 |
| 0.26 | 1093 |

The stability constants obtained are
with 4 displaceable protons, log K = 9.83
with 3 displaceable protons, log K = 11.04.

**d) With $Gd^{3+}$:**

To 4 ml of 2.175 x $10^{-3}$ M crown diaminetetraacetic acid 79 solution, 0.30 ml of 0.02677 M gadolinium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution

| base added | pH |
|---|---|
| 0.00 | 2.55 |
| 0.02 | 2.62 |
| 0.04 | 2.75 |
| 0.06 | 2.90 |
| 0.07 | 3.00 |
| **0.08** | 3 11 |
| 0.09 | 3.25 |
| 0.10 | 339 |
| 0 11 | 3.52 |

| | |
|---|---|
| 0.12 | 3.64 |
| 0.13 | 3 77 |
| 0 14 | 3.92 |
| 0.15 | 4.07 |
| 0.16 | 4.26 |
| 0.17 | 4.54 |
| **0.18** | 5.03 |
| 0 19 | 6.34 |
| 0.20 | 8.58 |
| 0.21 | 9.47 |

| | |
|---|---|
| 0.22 | 996 |
| 0.23 | 1023 |
| 0.24 | 10 40 |
| 0.25 | 10.52 |
| 0.26 | 10.61 |
| 0.27 | 10.65 |
| 0.28 | 1070 |
| 0.29 | 10 76 |
| 0.30 | **10.80** |
| 0.31 | **10.83** |

The stability constants obtained are

with 4 displaceable protons, log K = 10.38

with 3 displaceable protons, log K = 11.20.

## 3. Crown tetraaminehexaacetic acid 82.

### 1. Determination of acid dissociation constants of the crown tetraamine-hexaacetic acid 82 ($\mu$ = 0.10 M, $NaClO_4$):

**4** ml of 1.8989 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 was titrated with 0 3125 M sodium hydroxide solution.

| base added | PH |
|---|---|
| 0,00 | 2.76 |
| 0.01 | 2.88 |
| 0,02 | 3.02 |
| 0.03 | 3.25 |
| 004 | 3.55 |
| 005 | 3.96 |
| 006 | 4.52 |
| 0.07 | 5.30 |

| 0080 | 640 |
|---|---|
| 0 090 | 7.86 |
| 0.100 | 891 |
| 0.110 | 9.56 |
| 0.120 | 10 04 |
| 0.130 | 10.33 |
| 0.135 | 10.42 |
| 0.140 | 1049 |
| 0.145 | 1055 |

| 0.150 | 1059 |
|---|---|
| 0.160 | 10.70 |
| 0.170 | 1078 |
| 0.180 | 10.85 |
| 0 190 | 10.91 |
| 0.200 | 1095 |
| 0.210 | 10.99 |
| 0.220 | 11.03 |

When the data was processed in the program SCOGS 2 it was found that the last acid dissociation constant did not converge and hence the $pK_6$ was calculated according to Martell.[69] Thus, the pK's obtained are $pK_1$ = **2.14,** $pK_2$ = 3.16, $pK_3$ = 4.53, $pK_3$ = 7.06, $pK_5$ = 9.51 and $pK_6$ = 10.85. These acid dissociation constants were used in the determination of the stability constants.

**2. Determination of the stability constants of the crown tetraaminehexaacetic acid 82 (μ = 0.10 M, $NaClO_4$):**

**a) With $Cu^{2+}$:**

To 3 ml of 1.8383 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 solution, 0.035 ml of 0.1613 M copper (II) perchlorate solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | pH |
|---|---|
| 0.00 | 2.64 |
| 0.01 | 2.77 |
| 0.02 | 2.95 |
| 0.03 | 3.20 |
| 0.04 | 3.58 |
| 0.05 | 4.14 |
| 0.06 | 484 |
| 0.07 | 5.38 |
| 0.08 | 5 98 |
| 0.09 | **7.00** |
| 0.10 | 8.36 |
| **0.11** | 9.22 |
| 0.12 | 9.84 |
| 0.13 | 10.25 |
| 0.14 | **10.51** |
| 0.15 | 1066 |
| **0.16** | 1078 |
| 0.17 | 1086 |
| **0.18** | 1094 |
| 0.19 | 11.00 |
| 0.20 | 11.05 |

The stability constants obtained are listed below.

| log K (No. of displaceable protons) | | | |
|---|---|---|---|
| 6 | 5 | 4 | 3 |
| 6.97 | 13. 10 | 21.76 | 2240 |

**b) With $La^{3+}$:**

To 4 ml of 1.8989 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 solution, 0 30 ml of 0 02623 M lanthanum (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution

| base added | **pH** |
|---|---|
| 0.00 | 2.77 |
| 0.01 | **2.90** |
| 0.02 | 3.05 |
| 0.03 | 3.24 |
| 0.04 | 3.48 |
| 005 | 3.76 |
| 0 06 | 405 |

| 007 | 4.47 |
|---|---|
| 0.08 | **5.13** |
| 0.09 | 633 |
| 0.10 | 7.24 |
| 0.11 | 7.71 |
| 0 12 | 8 02 |
| 0.13 | 822 |
| 0 14 | 8 50 |

| 0.15 | **8.83** |
|---|---|
| 0 16 | 9.26 |
| 0.17 | 9.78 |
| 0.18 | 10.20 |
| 0.19 | 10.48 |
| 0.20 | 10.67 |
| 0.21 | 10 80 |
| 0.22 | 10.90 |

The stability constants obtained are

| log K (No of displaceable protons) | | | |
|---|---|---|---|
| 6 | 5 | 4 | 3 |
| 4.44 | 11.33 | 19.60 | 21.32 |

**c) With $Ce^{3+}$:**

To 3 ml of 1 8383 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 solution, 0.14 ml of 0.04015 M cerium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | PH | 0.06 | 6 12 | 0.13 | **10.33** |
|---|---|---|---|---|---|
| 0.00 | 2.85 | 0.07 | 689 | 0.14 | 10.57 |
| 0.01 | 3.04 | 0.08 | 7.39 | 0 15 | 10.77 |
| 0.02 | 3.30 | 009 | 7.76 | 0 16 | 10.91 |
| 0.03 | 3.62 | 0.10 | **8,30** | 0.17 | **11.01** |
| 0.04 | 4.08 | 0.11 | ) 10 | 0.18 | 11.09 |
| 0.05 | 4.91 | 0.12 | 9.79 | 0.19 | 11.17 |

The stability constants obtained are

| log K (No. of displaceable protons) | | | |
|---|---|---|---|
| 6 | 5 | 4 | 3 |
| 5.30 | 9.01 | 1891 | 21 06 |

**d) With $Nd^{3+}$:**

To 3 5 ml of 1 8383 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 solution, 0.15 ml of 0.014149 M neodymium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution

| base added | pH |
|---|---|
| 0.00 | 2.78 |
| 0.01 | 2.94 |
| 0 02 | 3 14 |
| 0.03 | 3 38 |
| 0.04 | 3.68 |
| 0.05 | 4.10 |
| 0.06 | 4.76 |

| | |
|---|---|
| 0.07 | 580 |
| 0.08 | 6 62 |
| 0.09 | 7.16 |
| 0 10 | 7.53 |
| 0 11 | 7.90 |
| 0.12 | 8.53 |
| 0.13 | 9.30 |
| 0.14 | 9.89 |

| | |
|---|---|
| 0.15 | 10.35 |
| 0.16 | 10 65 |
| 0.17 | 10.83 |
| 0.18 | 1096 |
| 0 19 | 11 06 |
| 0.20 | 11 15 |

The stability constants obtained are

| log K (No of displaceable protons) | | | |
|---|---|---|---|
| 6 | 5 | 4 | 3 |
| 5.48 | 10.00 | 19 70 | 21 46 |

**e) With $Sm^{3+}$:**

To 4 ml of 1 8989 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 solution, 0.30 ml of 0.0241 M samarium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | PH |
|---|---|
| 0 00 | 2.78 |
| 0.01 | 291 |
| 0.02 | 3.07 |
| 0.03 | 3.25 |
| 0.04 | 3.43 |
| 0.05 | 3.69 |
| 0.06 | 4.07 |

| | |
|---|---|
| 0.07 | 4.63 |
| 0.08 | 5.43 |
| 0.09 | 623 |
| 0 10 | **6.68** |
| 0.11 | 7.02 |
| 0.12 | 7.32 |
| 0.13 | 7.68 |
| 0.14 | 8.25 |

| | |
|---|---|
| 0.15 | 8.93 |
| 0.16 | 9.49 |
| 0.17 | 9.95 |
| 0.18 | **10.28** |
| 0.19 | **10.50** |
| 0.20 | 1066 |
| 0.21 | 10.80 |
| 0.22 | 10.90 |

The stability constants obtained are

| log K (No. of displaceable protons) | | | |
|---|---|---|---|
| 6 | 5 | 4 | 3 |
| 6.30 | 11. 14 | 19.35 | 21 .25 |

**0 With $Eu^{3+}$:**

To 3.5 ml of 1.8383 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 solution, 0.30 ml of 0 02275 M europium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

| base added | pH |
|---|---|
| 0.00 | 2.74 |
| 0.01 | 2.90 |
| 0.02 | 3.10 |
| 0.03 | 3.31 |
| 0.04 | 3.59 |
| 0.05 | 402 |
| 0.06 | 4.67 |
| 007 | 5.61 |
| 0.08 | **6.40** |
| 0.09 | 683 |
| 0.10 | 7.18 |
| 0 11 | 7.50 |
| **0.12** | 808 |
| 0.13 | **884** |
| 0.14 | **9.51** |
| 0.15 | **10.04** |
| 0.16 | 10 44 |
| 0.17 | **10.69** |
| 0.18 | 10.83 |
| 0.19 | **10.97** |
| 0.20 | 11.07 |

The stability constants obtained are

| log K (No of displaceable protons) | | | |
|---|---|---|---|
| 6 | 5 | 4 | **3** |
| 6.64 | 10.48 | 19.75 | 21 53 |

g) **With $Gd^{3+}$:**

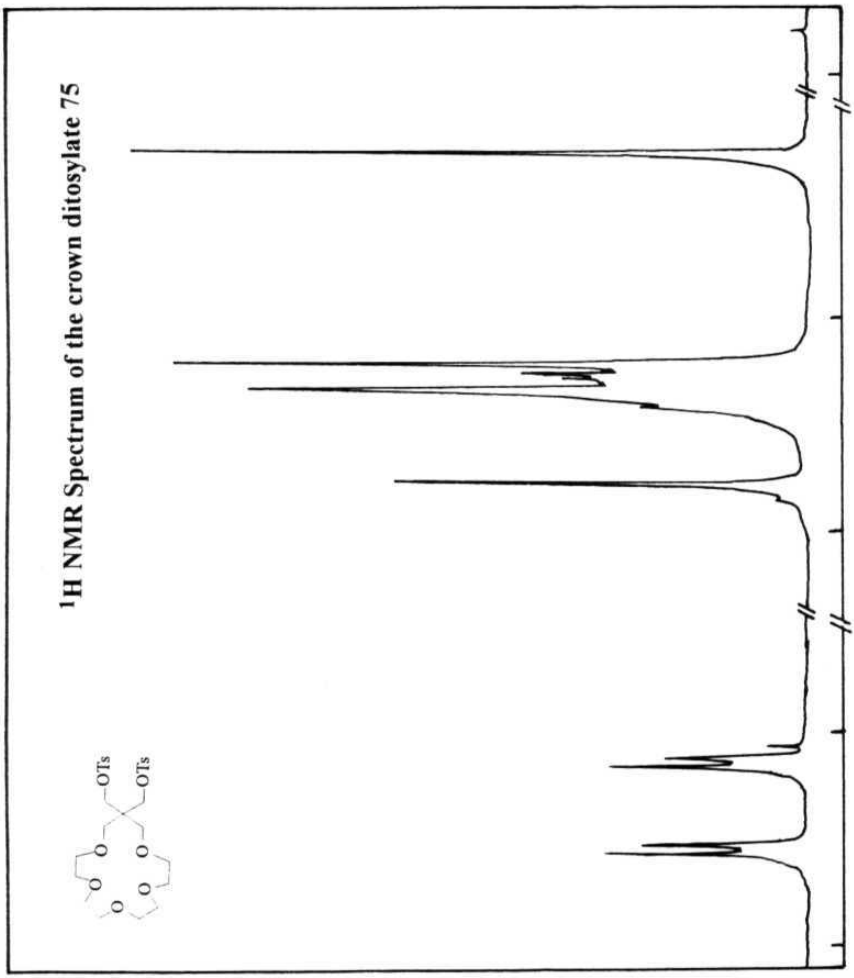
To 3 ml of 1.8383 x $10^{-3}$ M crown tetraaminehexaacetic acid 82 solution, 0 20 ml of 0 04015 M gadolinium (III) chloride solution was added and titrated with 0.3125 M sodium hydroxide solution.

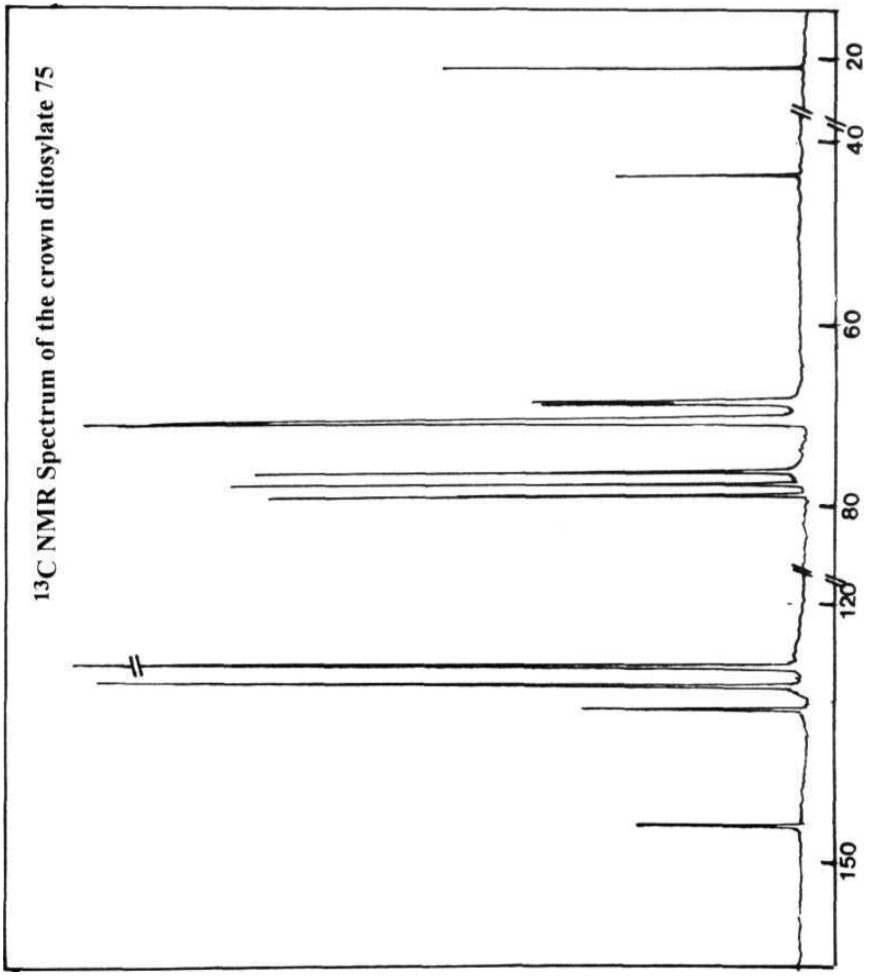
| base added | PH |
|---|---|
| 0.00 | 2.76 |
| 0.01 | 2.94 |
| 0.02 | 3.18 |
| 003 | 3.48 |
| 0.04 | 3.86 |
| 0.05 | 4.50 |
| 0.06 | 552 |
| 0.07 | 6.42 |
| 0.08 | 6 94 |
| 009 | 7.33 |
| **0.10** | 7.91 |
| 0.11 | 8.85 |
| **0.12** | **9.59** |
| 0.13 | **10.18** |
| 0.14 | 1054 |
| 0.15 | 10.77 |
| 0.16 | 10 93 |
| 0.17 | **11.03** |
| **0.18** | 11 13 |

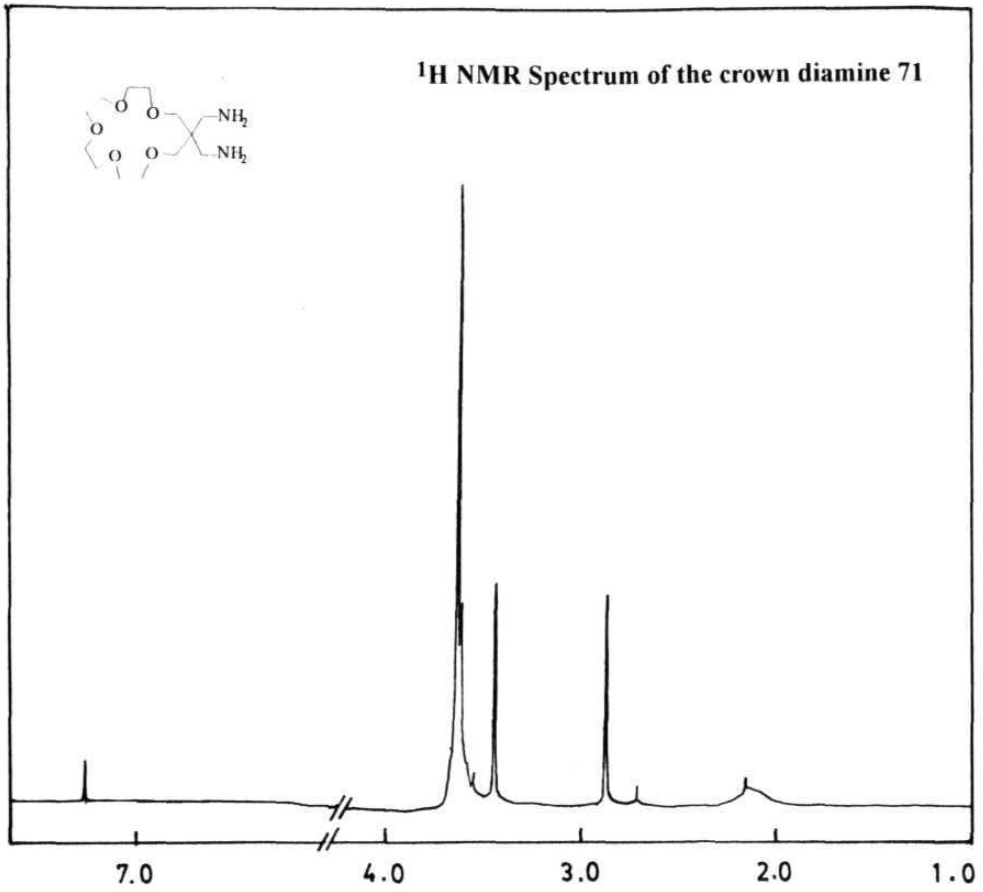
The stability constants obtained are

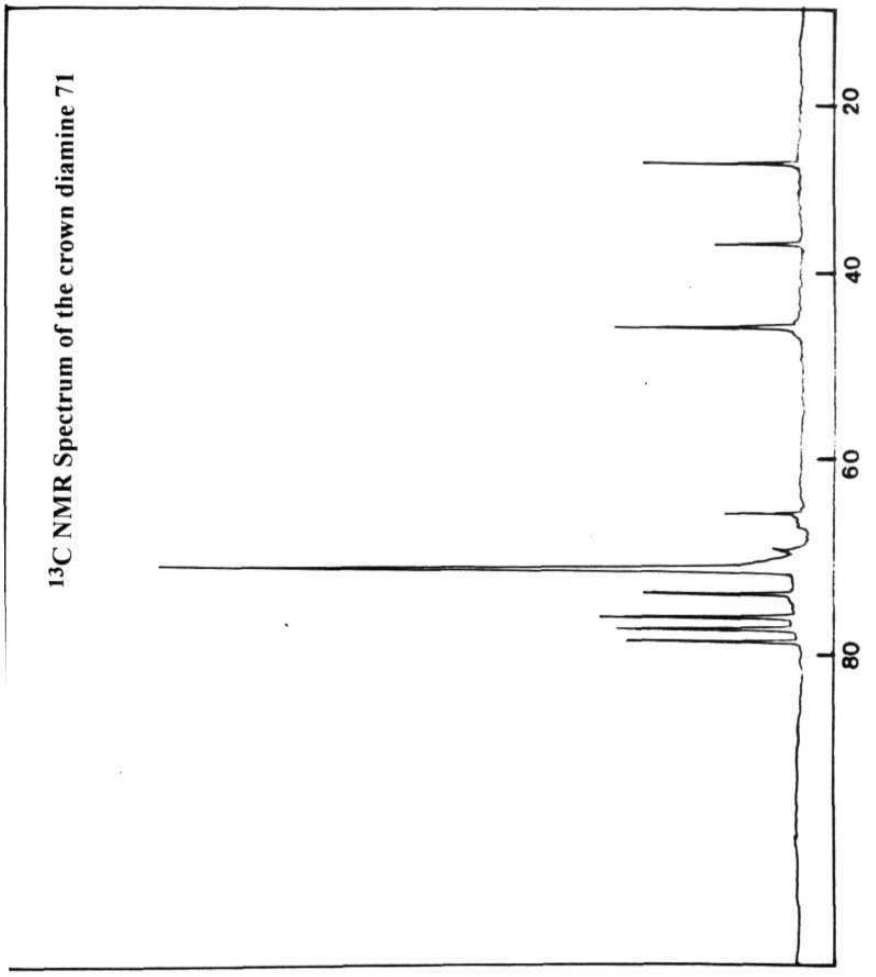
| log K (No. of displaceable protons) | | | |
|---|---|---|---|
| 6 | 5 | 4 | 3 |
| 6.56 | 10.87 | 19.75 | 21.65 |

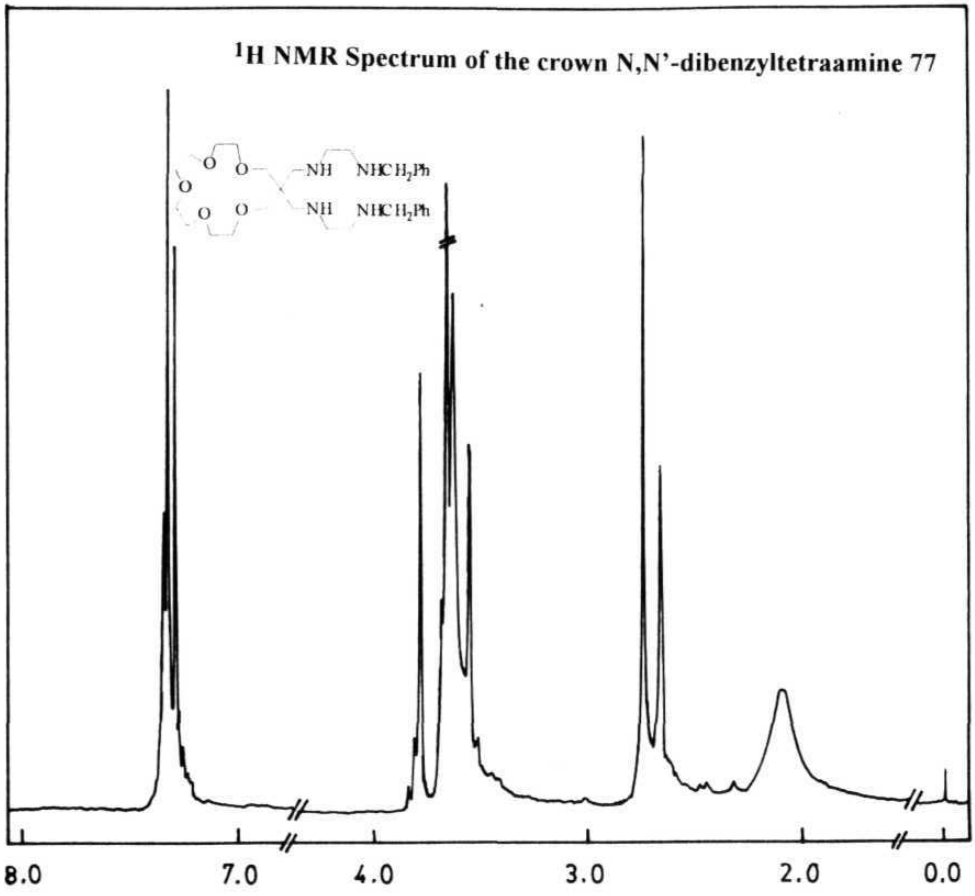
*SPECTRA*

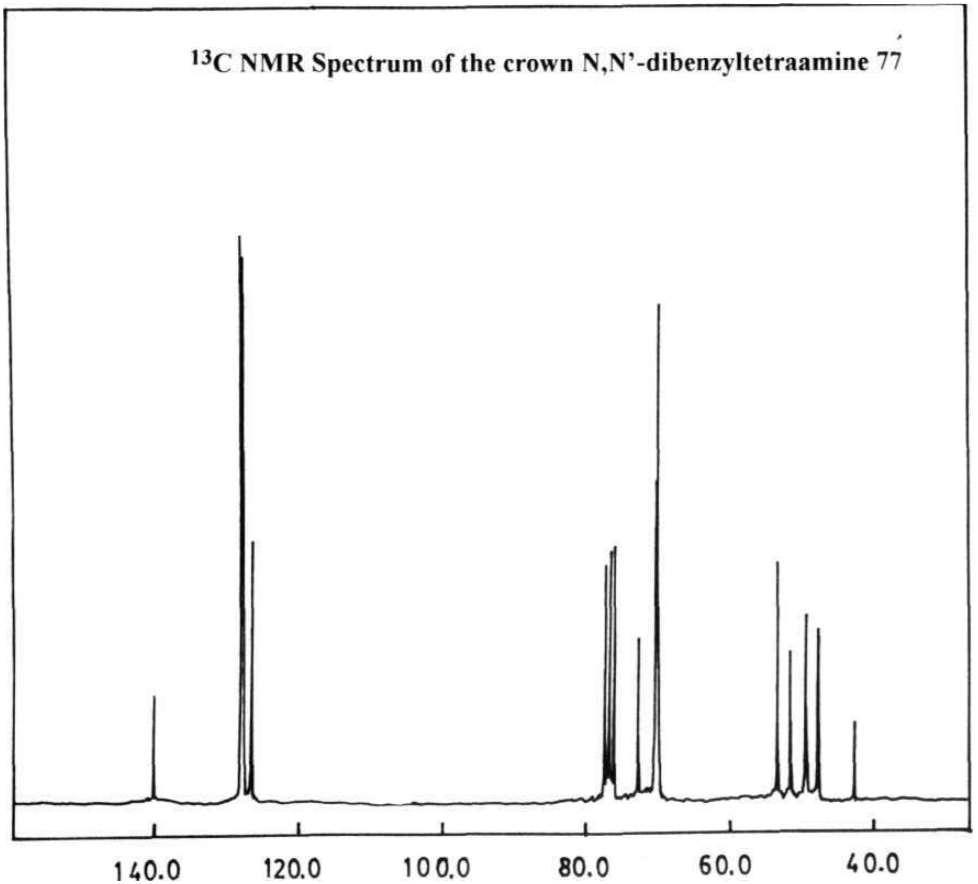

$^1$H NMR Spectrum of the crown ditosylate 75
OTs
OTs
8.0
7.0
4.0
3.0
0.0

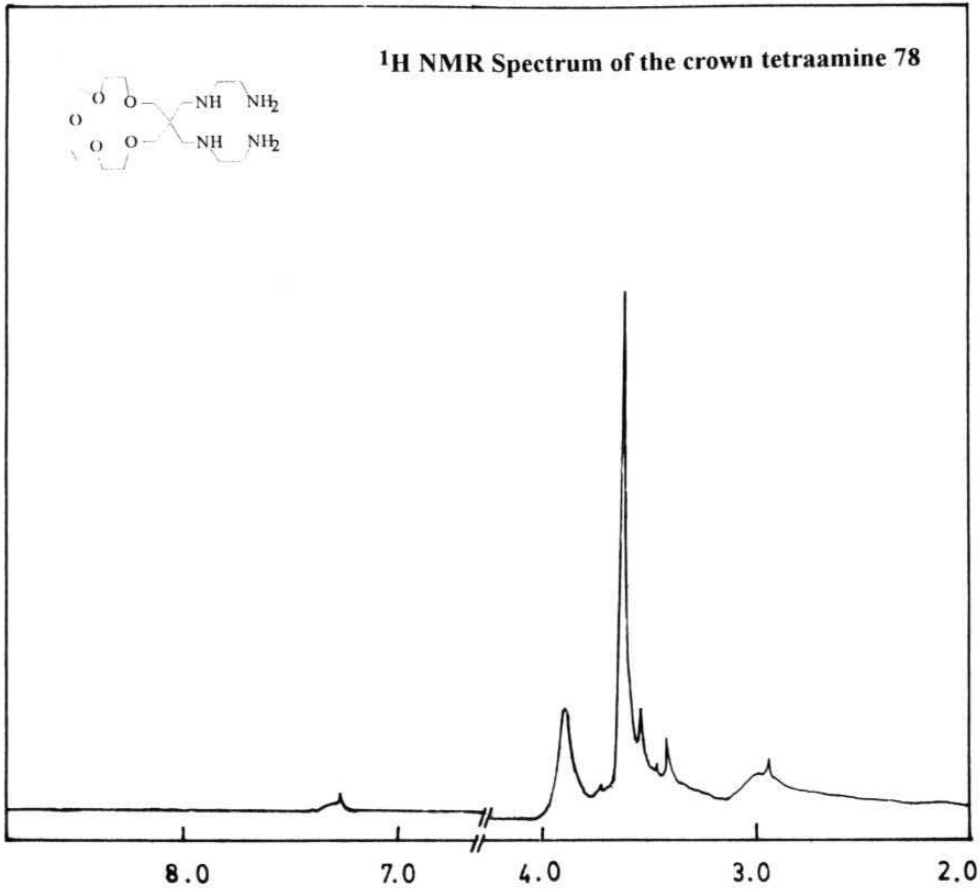

$^{13}$C NMR Spectrum of the crown ditosylate 75
150
120
80
60
40
20

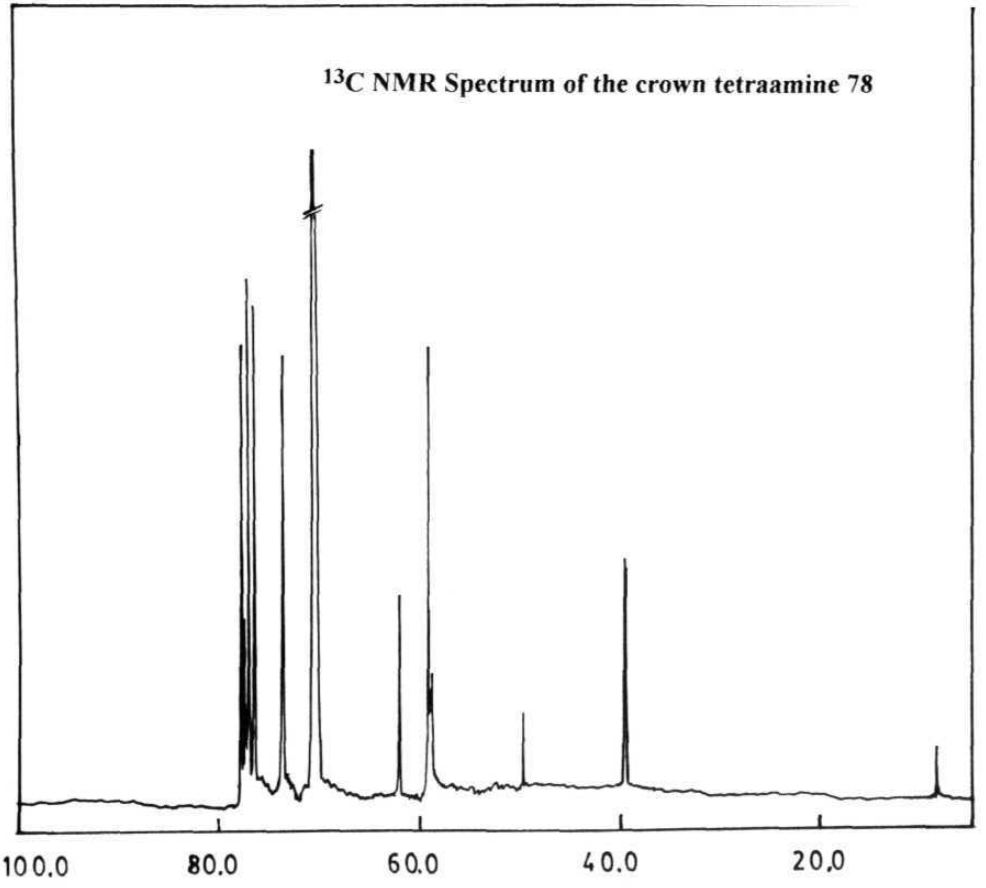

$^1$H NMR Spectrum of the crown diamine 71
O
O
O
O
O
O
NH$_2$
NH$_2$
7.0
4.0
3.0
2.0
1.0

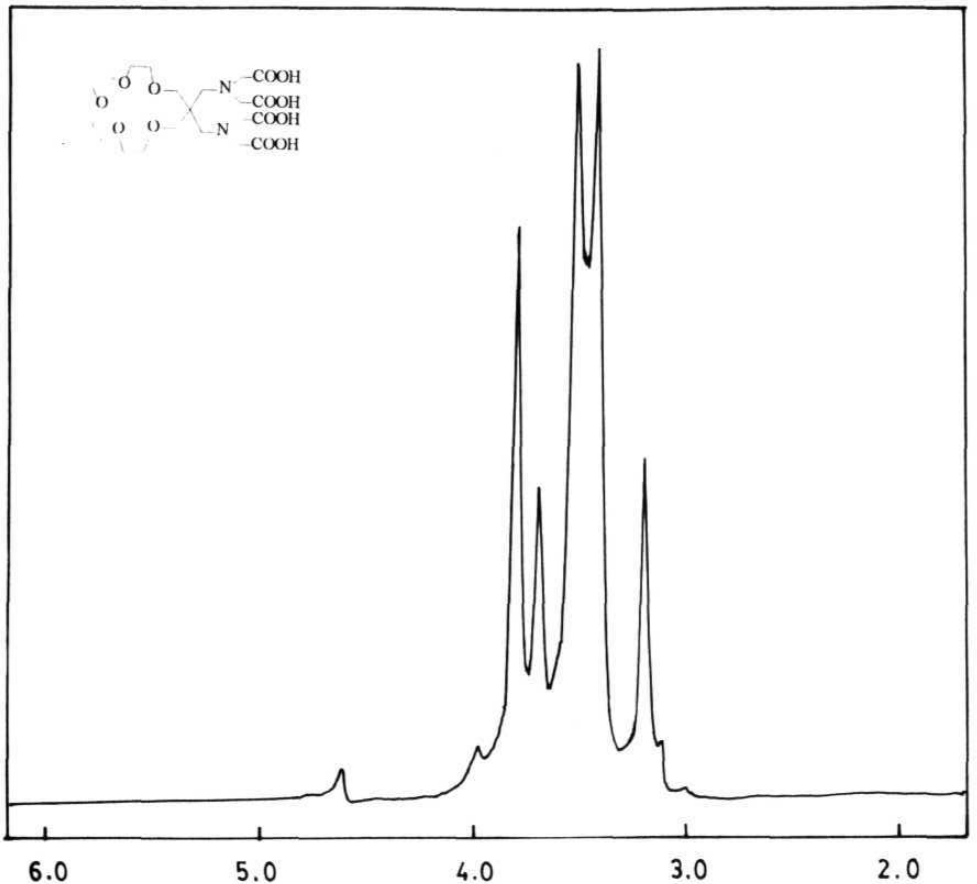

$^{13}$C NMR Spectrum of the crown diamine 71
80
60
40
20


$^1$H NMR Spectrum of the crown N,N'-dibenzyltetraamine 77
O
O
O
O
NH
NHCH$_2$Ph
NH
NHCH$_2$Ph
8.0
7.0
4.0
3.0
2.0
0.0

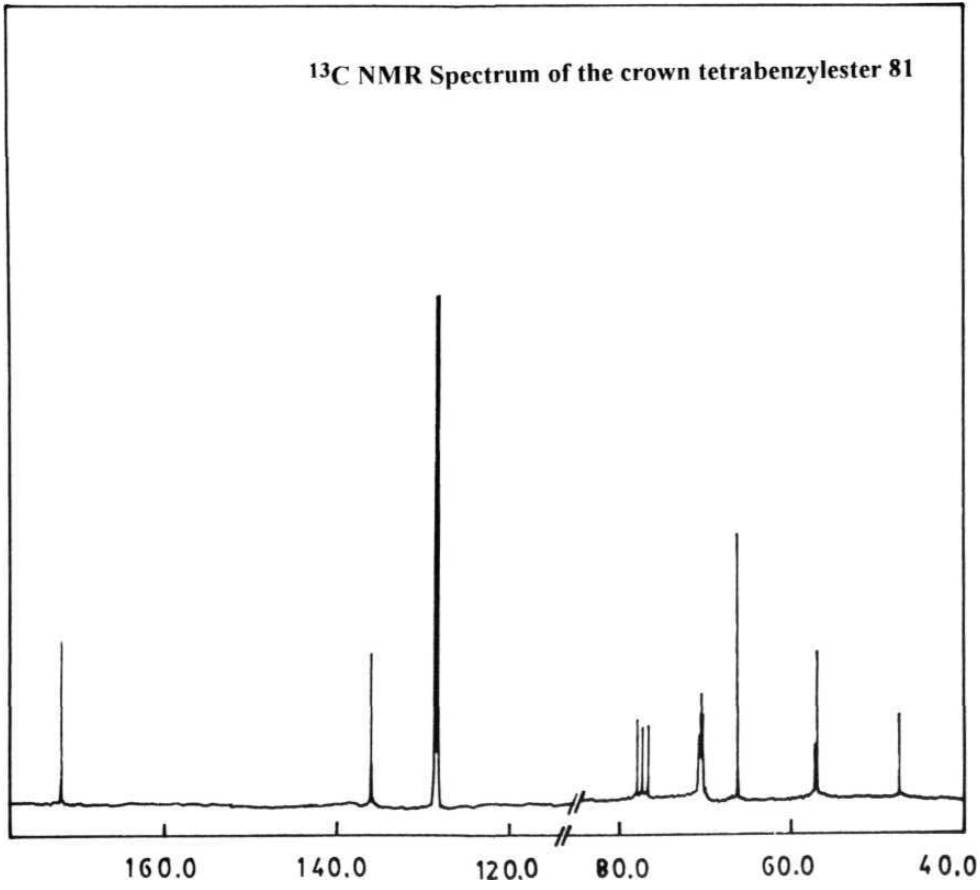

$^{13}$C NMR Spectrum of the crown N,N'-dibenzyltetraamine 77
140.0
120.0
100.0
80.0
60.0
40.0

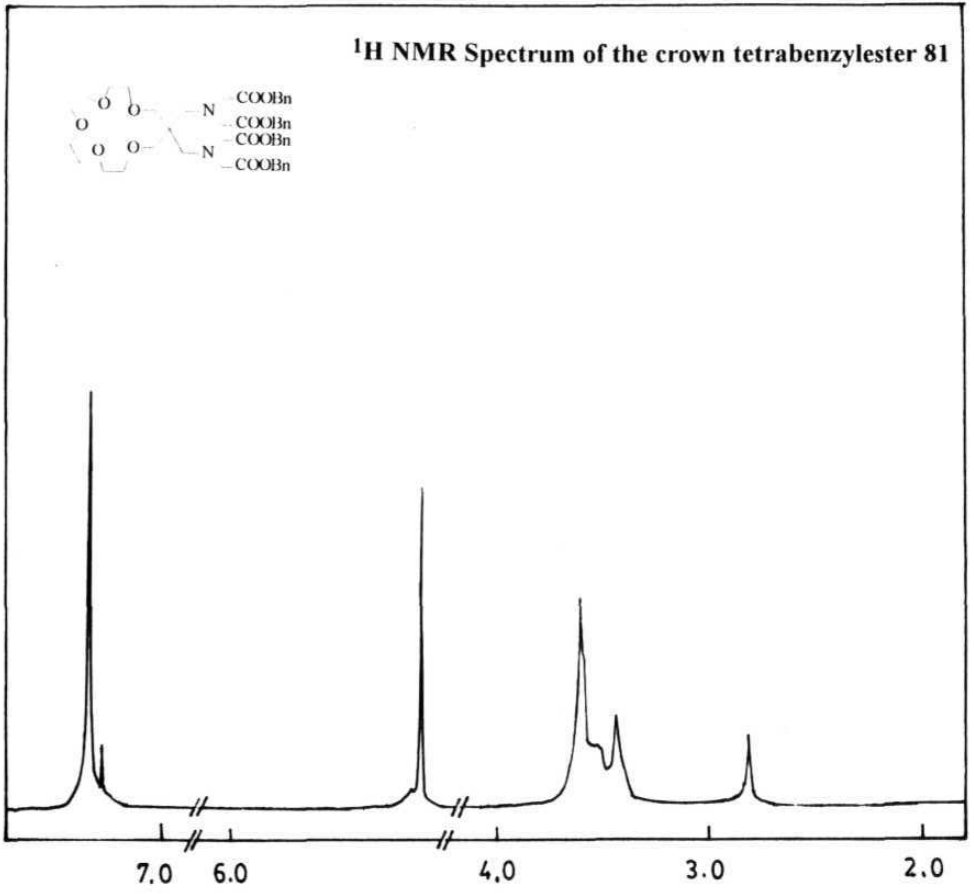

$^1$H NMR Spectrum of the crown tetraamine 78
O
O
O
O
NH
NH$_2$
NH
NH$_2$
8.0
7.0
4.0
3.0
2.0

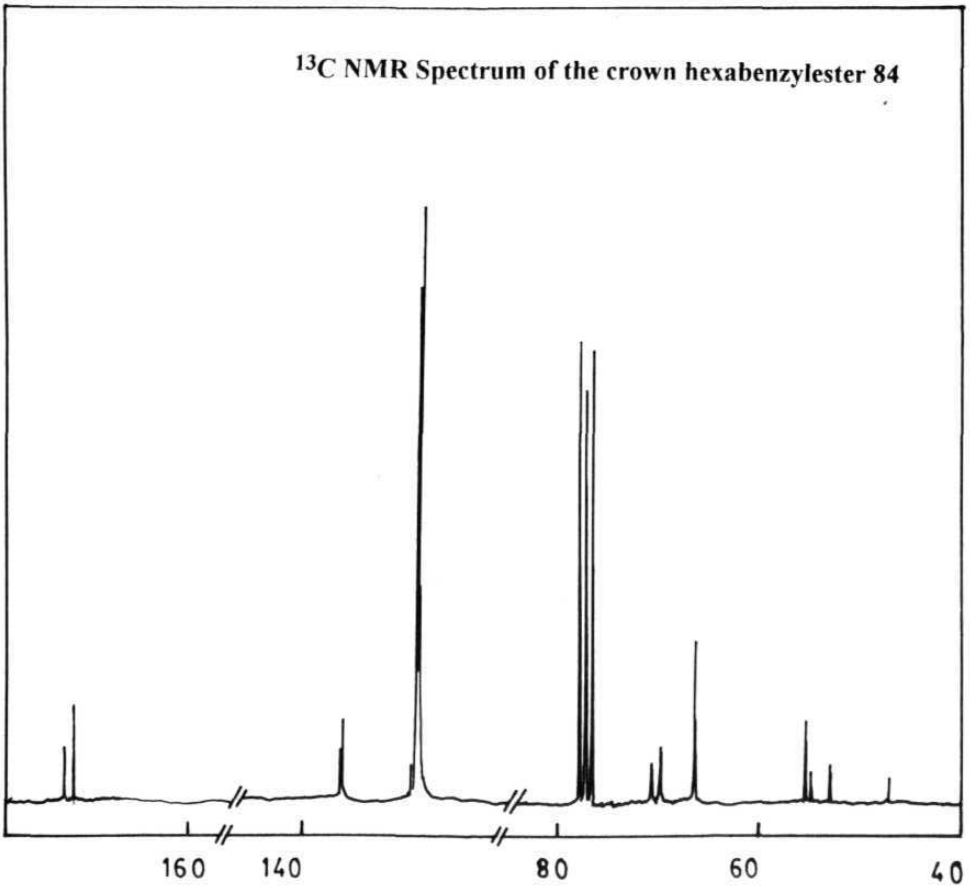

$^{13}$C NMR Spectrum of the crown tetraamine 78
100.0
80.0
60.0
40.0
20.0

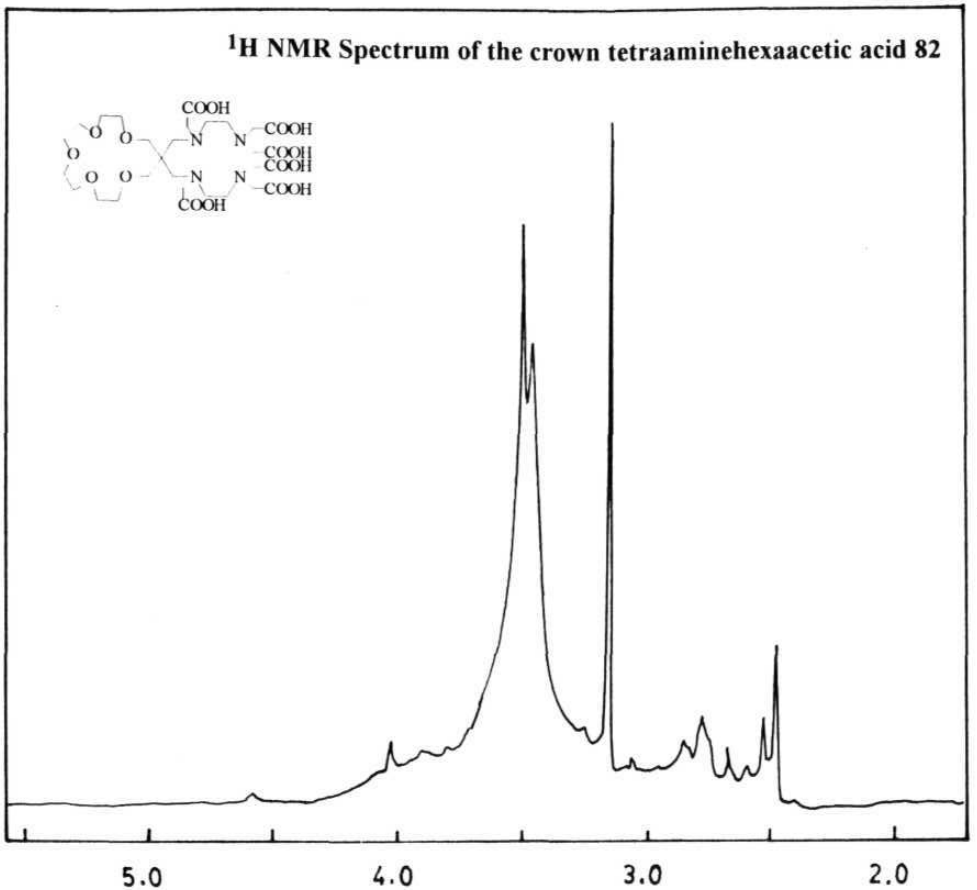


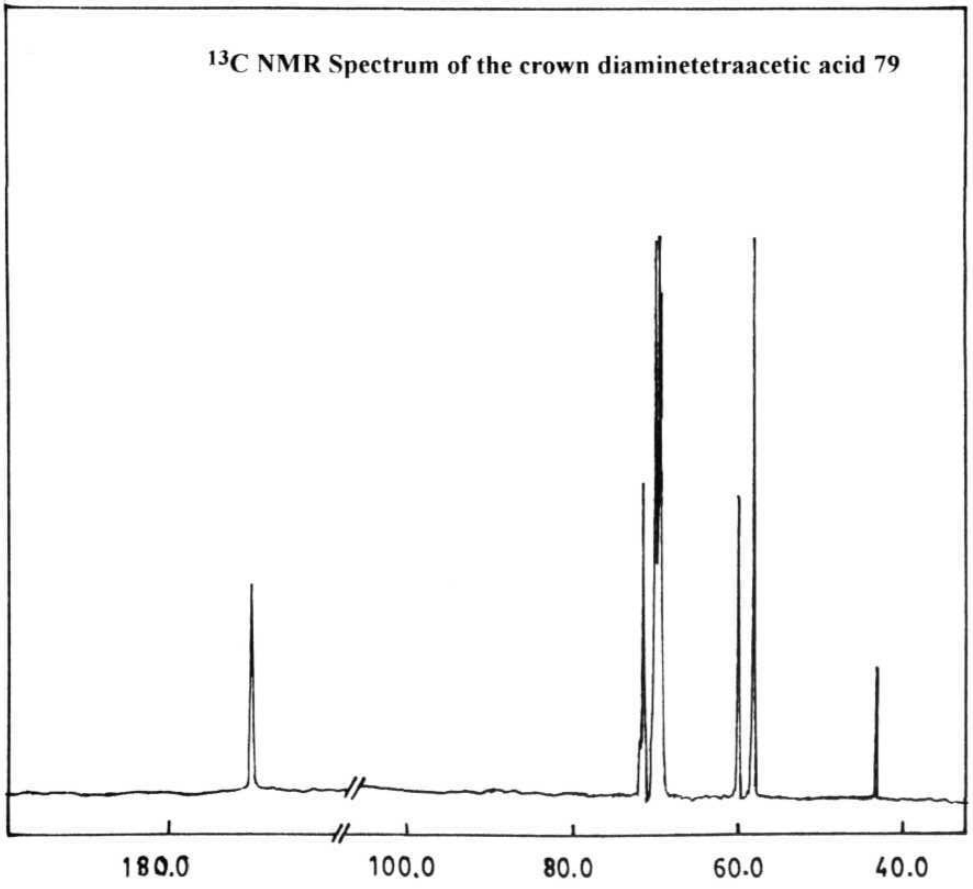

**$^{1}$H NMR Spectrum of the crown diaminetetraacetic acid 79**


$^{13}$C NMR Spectrum of the crown tetrabenzylester 81
160.0
140.0
120.0
80.0
60.0
40.0


$^1$H NMR Spectrum of the crown tetrabenzylester 81
O
O
O
O
O
O
N
N
COOBn
COOBn
COOBn
COOBn
7.0
6.0
4.0
3.0
2.0

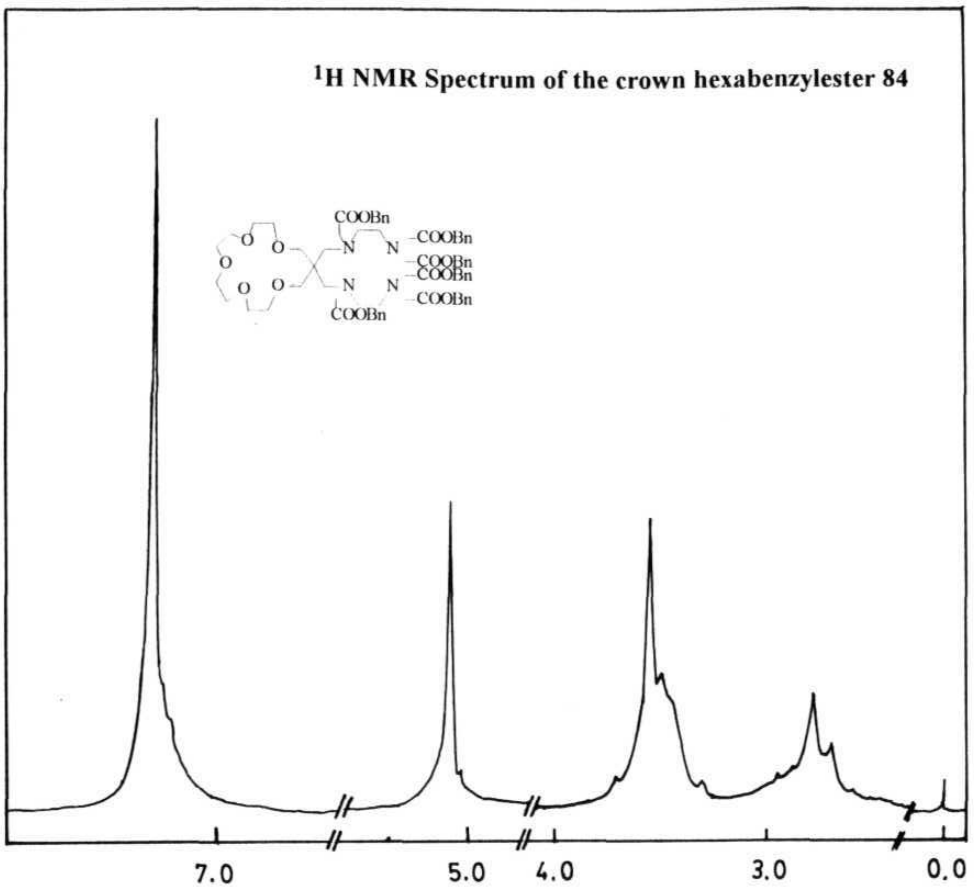

$^{13}$C NMR Spectrum of the crown hexabenzylester 84
160
140
80
60
40


$^1$H NMR Spectrum of the crown tetraaminehexaacetic acid 82
COOH
COOH
COOH
COOH
COOH
COOH
5.0
4.0
3.0
2.0




$^{13}C$ NMR Spectrum of the crown diaminetetraacetic acid 79

**$^1$H NMR Spectrum of the crown hexabenzylester 84**



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