Synthesis and complexation behaviour of substituted polyaza-macrocycles

James Chapman

SYNTHESIS AND COMPLEXATION BEHAVIOUR OF SUBSTITUTED POLYAZA-MACROCYCLES

by

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DECLARATION

The work described in this thesis was carried out in the Department of Chemistry at the University of Durham between October 1986 and September 1989. All the work is my own unless stated to the contrary and it has not been submitted previously for a degree at this or any other University.

To My Parents

ACKNOWLEDGEMENTS

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Finally, and by no means least, I would like to thank my parents for their love, encouragement and support, who have given so much for all the time I have been here.

ABBREVIATIONS

mac	Macrocycle
NTA	Nitrilo-triacetic acid
EDTA	Ethylenediamine-tetraacetic acid
DTPA	Diethylenetriamine-pentaacetic acid
TETA	1,4,8,11-tetraazacyclotetradecane-N,N′,N″,N‴-tetraacetic acid
DOTA	1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid
Cyclam	1,4,8,11-tetraazacyclotetradecane
en	ethylene diamine
TsCl	p-toluenesulphonyl chloride
TsOCl	p-methoxybenzene sulphonyl chloride
[9]N_3	1,4,7-triazacyclononane
[12]N_3	1,5,9-triazacyclododecane
TMS	Tetramethylsilane
THF	Tetrahydrofuran
DMF	Dimethylformamide
TLC	Thin Layer Chromatography
IR	Infra-red
UV	Ultra-violet
NMR	Nuclear Magnetic Resonance
CI	Chemical Ionisation
DCI	Desorption Chemical Ionisation
FAB	Fast Atom Bombardment
Py	Pyridine
ε	Extinction Coefficient
mass spec.	Mass Spectrometry
TCTA	1,4,7-triazacyclononane-N,N′,N″-triacetic acid

ABSTRACT

Macrocyclic ligands which bind to transition metal ions are known to form stable and kinetically inert metal complexes. They might be potentially used as soil micronutrients which have properties over and above their more commonly used NTA, EDTA and DTPA acyclic counterparts. Work has been directed to the synthesis of functionalised macrocyclic ligands to bind to copper and nickel and other transition metals. Macrocyclic ligands have been selected to bind to the respective transition metals, under mild conditions, to form kinetically stable complexes.

The stereoselective synthesis 1,8-disubstituted derivatives of 1,4,8,11-tetra-azacyclotetradecane (cyclam) has been achieved and copper and nickel complexes prepared. For the 1,8-dibutyl derivative, the square-planar nickel(II) complex exists as two diastereoisomers, as revealed by crystallographic analysis. The structure of the copper(II) complex of this ligand confirmed that a strong in-plane ligand field was conserved in square-planar complexes not withstanding the dialkylation at nitrogen. The structure of the copper(II) complexes of two 1,8-dicarboxymethyl derivatives of cyclam also reveal primary N_4 co-ordination with carbonyl oxygens occupying the elongated axial sites. The tricyclic ligand 1,5,8,12-tetraazatricyclo[10,2,2,$2^{5,8}$]octadecane is readily prepared from one of these diacids and the copper complex is kinetically stable in acidic solution.

The synthesis of [12]N_3 di- and tri-substituted triazacyclododecane ligands has also been effected through the intermediacy of monotosylamide derivatives. Copper(II) and nickel(II) complexes have been isolated as crystalline solids and have been characterised by spectrophotometric and FAB mass spectrometric methods.

CONTENTS

CHAPTER 1

INTRODUCTION

1.1 Synthesis of Lipophilic Complexes

1.1.1 Agricultural plant and crop requirements

Plant materials provide the main source of minerals to animals and humans, and the mineral concentration in plants is often controlled by the addition of fertilisers and micronutrients. Moreover the application of trace elements is widely practised as a means of raising herbage concentration from deficient to satisfactory levels for livestock.

It is known that plants and crops in general require various levels of particular metals to enhance their growth. There are in addition to the more usual growth stimulating elements such as phosphorus, nitrogen and potassium given in the commonly known NPK fertilisers, low level amounts of iron, manganese, copper and boron which are known to be amongst those elements required to sustain different biochemical pathways in plants, in much the same way as man requires small amounts of different metal elements in order to form health essential vitamins within the body. The low copper and manganese levels in plants grown on the humic soils of Europe have been demonstrated for example[1]. Relatively little is known of the chemical forms and availability to animals of trace elements in plants at different growth stages. There is also scant knowledge on the mechanism of uptake of trace elements by plants although it is strongly influenced by the acidity of the soil[2].

1.1.2 Essential trace elements uptake

Metal complexes of chelating agents are widely used as micronutrients in many different areas of agriculture and horticulture. Iron, manganese, zinc, copper, nickel and boron in a chelate form are by and large unaffected by soil

conditions or changes in pH value. Thus they are readily available to plant root systems.

1.1.3 Micronutrients

Iron is present in all living organisms in small quantities, e.g. haemoglobin in mammals and within agriculture it plays an important part in many enzyme systems notably oxidation and reduction reactions. It is also involved in chlorophyll formation along with manganese. Conditions leading to high iron deficiencies are those involving neutral to high soil pH or conditions that will precipitate iron such as high phosphate levels. Iron deficiency is manifested by interveinal chlorosis in plants particularly in the early stages of growth.

Manganese deficiencies, however, are clearly shown by small brown spots and streaks on many plants. Its symptoms are frequently quite similar to those of iron deficiency and again shows yellowing on the interveinal tissue. It is known to be involved in promotion and regulatory enzyme reactions in particular which are responsible for those reactions involving the metabolism of carbohydrates, organic acids and nitrogen. Manganese deficiencies are known to occur on neutral to alkaline soils and on poorly drained soils such as peats and mucks.

Zinc deficiencies within the soil affects many different crops throughout the world. Maize leaves, for example, become stunted and a broad white line appears down the centre of the leaf. Symptoms in many plants include a mottled chlorosis, rosetting and bronzing. Young corn plants also show broad whitish areas on each side of the mid rib of the leaf. Zinc deficiencies occur

both on calcareous soils naturally low in zinc as well as neutral to calcareous soils. High phosphate levels also often induce zinc deficiencies. It is known to be essential in plant cell oxidation reactions, carbohydrate metabolism and the formation of growth promoting hormone auxins. It is also essential for the production of genetic materials.

Many cereals particularly barley are affected by copper deficiencies and are shown by a browning and spiralling of the leaves. Because copper is not translocated in the plant, symptoms of deficiency usually show up in the youngest part of the leaves, usually as die-back at the leaf tips. Those deficiencies usually show up on high peat or muck soils as well as light coloured acid soils in high rainfall areas. Copper mainly functions as an enzyme activator and takes part in plant respiration. It is also involved in enzyme systems that are related to the use of proteins in the plant.

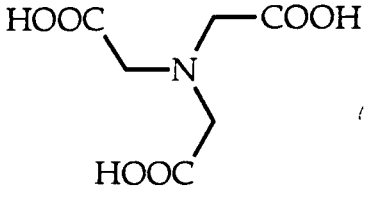
Although boron is essential for the propagation and growth of higher plants its role within plant metabolism has never been clearly elucidated, even though many theories have been put forward[3]. Recently it has become apparent, that its "primary role", if indeed there is one, may be associated with the biochemical effect of boron in enzymatic reactions and at the nucleic acid biosynthesis level similar to that of iron, manganese and copper. In both cases it was shown that a boron deficiency has a significant effect on plant enzymes reflected by a greater sugar distribution within the plant.

It has been shown by Dugger[3] that boron, by virtue of its complexing ability with sugars, facilitates the translocation of sugars in plants. It has been established that sugar levels are greater in the leaves of bean and tomato plants

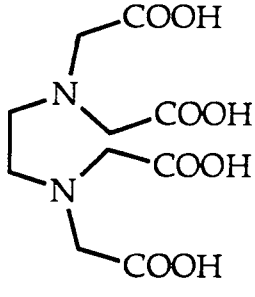
in the presence of 10 ppm of boron and that there is also a greater distribution of sugar throughout the plant. Enzyme activity appears to be inhibited by the inclusionment of 0.1 M boron solution from the inhibition of starch from glucose-1-phosphate in potatoes. This phenomena and similar ones have been reported elsewhere. Nucleic acid synthesis also seems to be stimulated by the increase in boron of some plants.

1.1.4 Uses of metal chelates

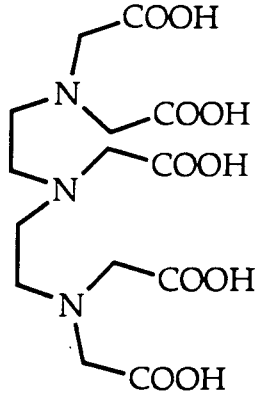
Normally these metal elements are applied to the soil as hydrophillic chelate complexes of NTA, EDTA or DTPA with copper, iron, manganese, zinc, cobalt, magnesium, molybdenum and boron and are used as micronutrients for plants and crops (e.g. Rexene, W. R. Grace Limited).



NTA



EDTA



DTPA

1.1.5 Macrocycles vs chelates

Why macrocycles instead of chelates? It is thought that this question may be answered by considering the following three points in which a range of functionalised macrocyclic ligands may possess the following advantages over chelates used now.

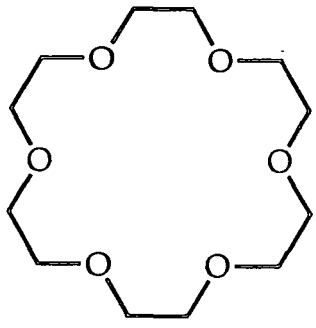
1. Enhanced lipophilicity - so that the applied metal complexes are more easily absorbed by the plants and less easily "drained away". This feature may markedly reduce the dosage required and promote the effectiveness of trace metal uptake.
2. Controlled metal release - macrocyclic metal complexes are generally more kinetically inert than chelate complexes, so that the metal release to the environment is slower. Dissociation of a metal is acid-catalysed, so soil acidity may be a determining factor controlling the rate of metal storage and release.
3. Selectivity in metal complexation - macrocyclic ligands with particular conformation and cavity sizes exhibit pronounced selectivity for binding given metal cations (unlike the more indiscriminate chelate complexes with EDTA and DTPA). Such behaviour could be used to advantage in selective removal of a given toxic metal cation.

The aim within this area of research is to develop a range of macrocyclic ligands which would bind selectively to those particular metals which should ideally have properties superior to those previously used chelates and ligands.

1.2 Macrocyclic Complexing Agents

1.2.1 Introduction

Since Pedersen[4] reported the synthesis and properties of crown ethers, e.g. 18-crown-6 1 and tribenzo-18-crown 6 2 and of the template reactions by Curtis[5], a vast amount of work has been given towards the synthesis and complexation properties of macrocyclic ligands. Pedersen's cyclic polyethers



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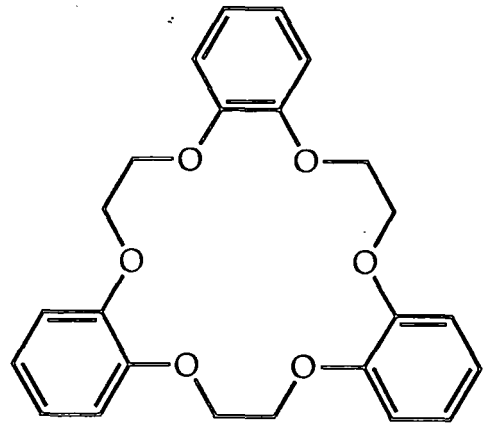

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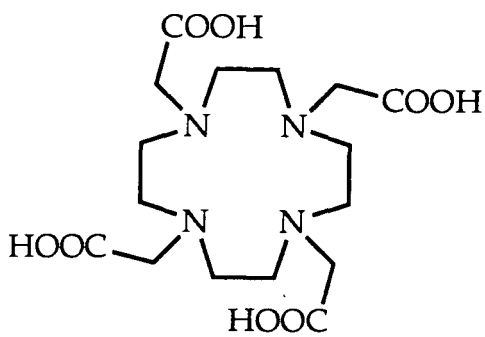
were observed to form stable 1:1 complexes with alkali and alkaline earth metals. The macrocyclic rings were considered initially to form molecular cavities, lined with oxygen donor atoms, which were able to bind metal ions through ion-dipole interactions, forming "host-guest" complexes. High stability constants were observed when there was a good correlation between the diameter of the macrocyclic "cavity" and that of the cation. Soon afterwards, the synthesis of macrocyclic diamines was reported[6] and since then a great variety of macrocycles with different donor atoms (usually O, N or S) have been reported.

Macrocycles being somewhat conformationally constrained can impose a specific co-ordination geometry to the metal ion, whereas open chain chelators will generally adapt themselves according to the geometrical requirements of the metal ion. In addition many "labile" metal ions will form kinetically stable complexes with macrocycles, thus allowing a study of their reactivity either in relatively strongly acidic or alkaline solutions.

1.2.2 Effects of modifying macrocycles and ligands

In the last few years efforts have been made to combine the properties of the macrocycles with those of the more flexible and kinetically labile open chain ligands. The reasons are various. By introducing additional ligating groups into a macrocycle, its properties can be modified so that more stable complexes are formed or its specificity in metal ion binding is increased or its solubility is changed. For example the 12-membered tetraazamacrocycle 3 to which four acetate groups have been attached gives thermodynamically stable alkali and alkaline earth complexes[7-9], whereas the unsubstituted ligand only



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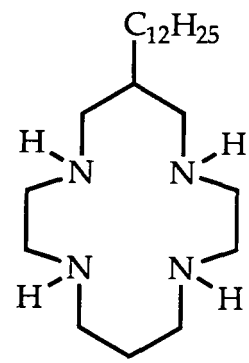

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binds to transition metal ions. Also the macrocycle 4 to which a long chain lipophilic side chain has been attached to make the ligand and its metal complexes soluble in organic solvents can be used to extract metal ions from aqueous solution into an organic phase[10].

1.2.3 Changes in redox potentials

Besides these aspects which are very important it is possible to study the effect of additional ligating groups on the properties of metal ions. It is

conceivable, for an example, that the redox potential of a co-ordinated metal ion may be changed and adjusted by introducing an additional ligand into its axial position. Also it is possible that selective binding of another ligand will depend on the nature of what is already co-ordinated in the axial position of the metal ion. For example, it is thought that the oxygen binding ability of iron in haemoglobin, and its reversibility, is a reflection of the axially co-ordinated imidazole of the distal histidine. This effect has been investigated by Traylor[11] by an iron porphyrin with a histidine terminal via a long chain and its reversible binding to oxygen at low temperatures.

1.2.4 Pendant side chain interactions

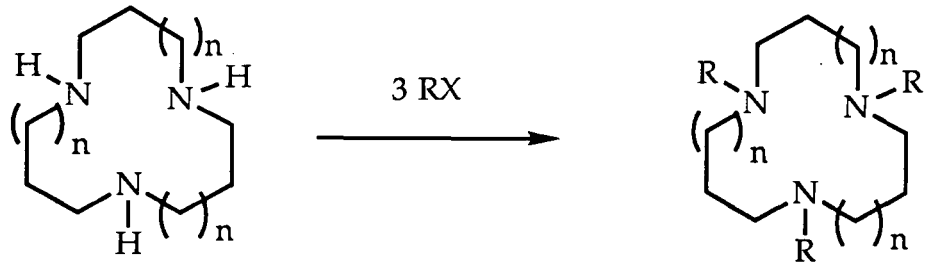
Another possible application of functionalised polyazamacrocycles may be to bring close together a metal ion and a weakly binding or even a non-co-ordinating organic group so that an interaction between the two can take place. Thereby the properties and reactivity of the organic group might be changed. Thus by covalent coupling of the organic group to the macrocycle which binds to the metal ion, metal ion promoted reactions can be studied. The metal ion can act as a Lewis acid or as a redox catalyst and the organic group as the substrate. This allows us to follow such processes on a molecular basis and to obtain information and insight into the mechanism of metal ion catalysed or promoted reactions.

1.3 Synthesis of Functionalised Polyazacycles

1.3.1 N-functionalised derivatives

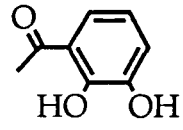
There are many examples of N-functionalised triazamacrocycles carrying pendant side chains. Their synthesis is quite simple and consists of the

alkylation or acylation of one or more of the amino nitrogen atoms in the ring, e.g.



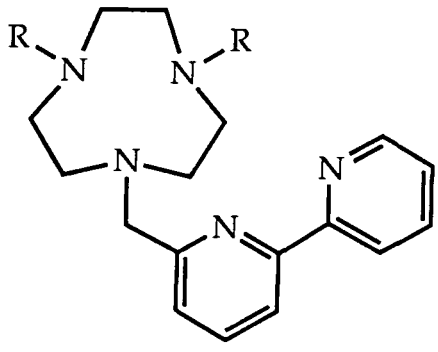
5 n = 0, R = CH_2CO_2H

6 n = 1, R =



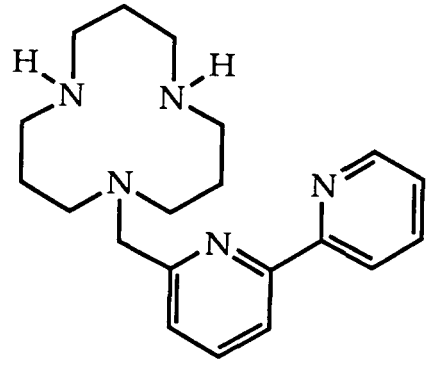
by 2,3 dioxomethylene benzoyl chloride[12] and chloroacetic acid[13] respectively, compound 6 being prepared by BCl_3 cleavage of an intermediate 1,3-dioxolan.

A recent example described by Moore[14] concerns the addition of a single pendant co-ordinating arm to 1,4,7-triazacyclononane and 1,5,8-triaza-



L_1, R = H

L_2, R = Me

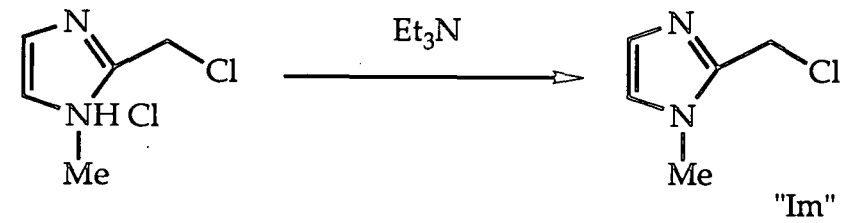


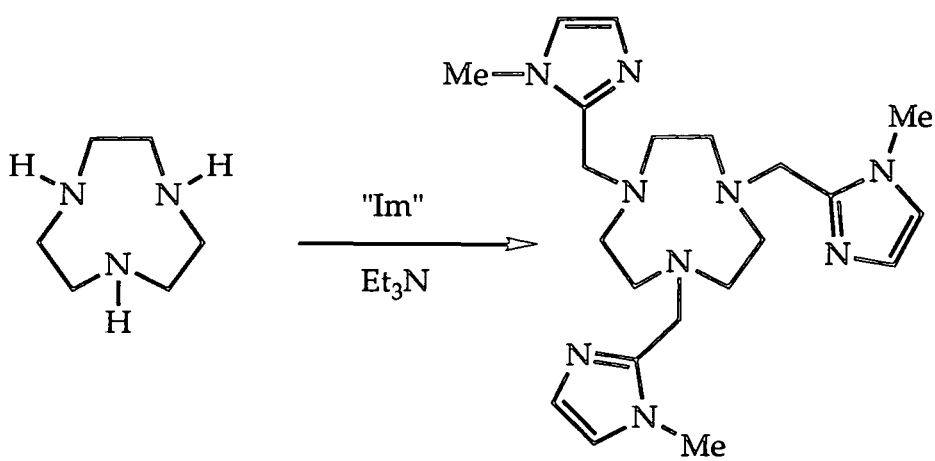
L_3

cyclododecane via reaction of the parent triamines with 6-(chloromethyl)-2,2′-bipyridine to produce the ligands L_1 and L_3. Methylation via the Eschweiler-Clarke method gives the ligand L_2. L_1 forms stable complexes with Ni^{2+}, Zn^{2+} and Pd^{2+}.

Vaira[15] has reported a new general synthetic route to polyaza-macrocyclic ligands with pendant biomimetic imidazole groups.

The free base of 1-methyl-2-chloromethyl imidazole hydrochloride was treated immediately with a stoichiometric amount of 1,4,7-triazacyclononane



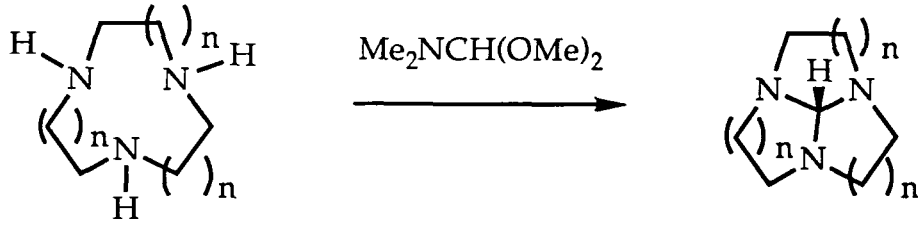


and stirred at room temperature in dry acetonitrile and in an inert atmosphere in the presence of triethylamine. This yielded the trisubstituted polyaza-macrocyclic ligand. The cobalt, nickel and iron complexes of these ligands were isolated, and the nickel complex showed an approximate octahedral

geometry. This synthetic route overcomes the quaternisation reactions normally associated by the reaction of nitrogen atoms and the chloroderivatives of heterocyclic bases.

1.3.2 Synthesis of selectively tri N-functionalised macrocycles

The synthesis of triazamacrocycles bearing pendant side chains often require N-protected azacoronands as their starting material. Weisman[16] has developed a short and efficient novel synthesis for the N-protected derivative of 1,4,7-triazacyclononane and 1,5,9-triazacyclododecane via their orthoamides. The general approach relies upon the introduction of a single N-formyl group masked as a tricyclic orthoamide and subsequent reaction of the orthoamide functional group. The cyclic triamines 7 and 8 reacted with $Me_2NCH(OMe)_2$ to

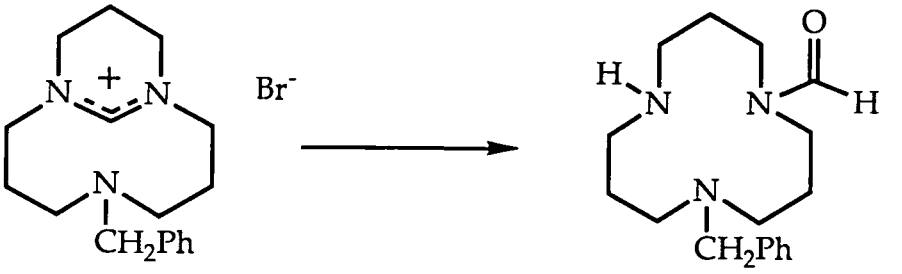


7 n = 1 9 n = 1

8 n = 2 10 n = 2

yield the corresponding orthoamides 9 and 10. Monoprotection of 7 was achieved by gentle hydrolysis of 9 after which the two secondary amino groups were protected by reaction with tosyl chloride in THF with Et_3N. More vigorous hydrolysis with excess boiling NaOH solution removed the formyl group to yield the vacant secondary ring amine. This scheme was found to be unsuccessful for 10.

Orthoamide 10 was cleanly monoalkylated with $PhCH_2Br$ in chloroform to give the stable salt 11 which in turn was hydrolysed under gentle basic conditions (0.34 M NaOH) to give the benzyl formyl derivative 12.



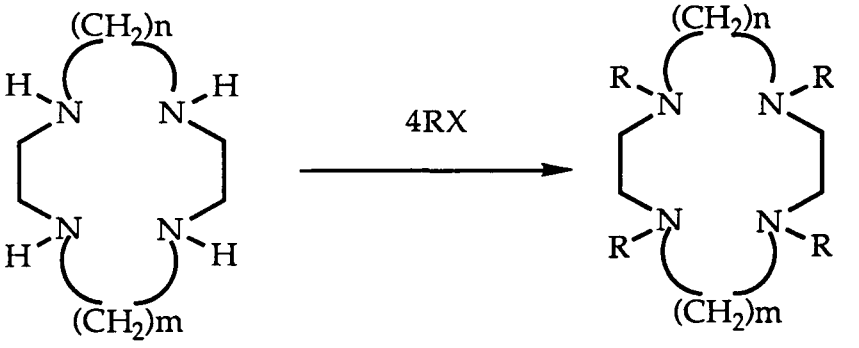
11 12

Tosylation with tosyl chloride in THF with Et_3N differentiates all three nitrogens of 6.

Similarly, the synthesis of tetra-N-substituted tetraazamacrocycles is relatively straightforward.

1.3.3 Tetra-N-substituted macrocycles

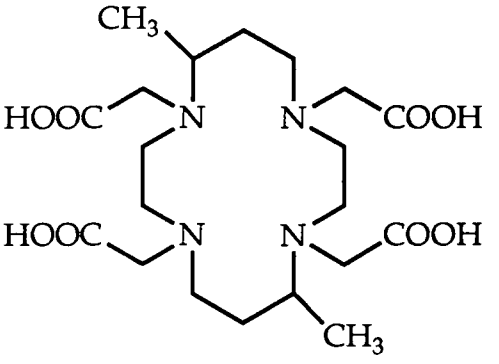
The unsubstituted macrocycle is reacted with an excess of an alkylating agent in the presence of a base to bind the acid formed to form a whole range of ligands.



Stetter[17] has exhibited this versatility by forming the ligands 13, 14 and 15 with different ring sizes (n, m = 2 or 3) using chloroacetic acid as the alkylating agent in alkaline solution. Following this Häfliger[18] has similarly

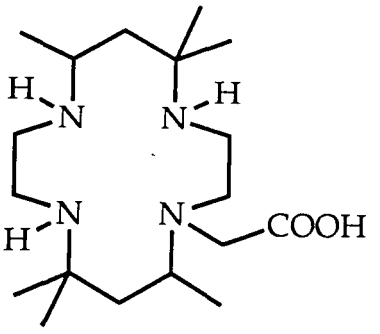
13	R = CH_2-COOH	n = m = 2
14	R = CH_2-COOH	n = 2, m = 3
15	R = CH_2-COOH	n = m = 3
16	R = CH_2-CH_2-OH	n = m = 3
17	R = CH_2-CH_2-CN	n = m = 3

treated the fourteen membered meso-5,13-dimethyl-1,4,8,11-tetraazacyclotetradecane with chloroacetic acid to obtain the corresponding tetraacetate 18.



18

Straightforward selective alkylation at the N′ positions was achieved by Yide[19] by the direct reaction of C-meso-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane with bromoacetic acid and the mono- and di-partially N-substituted tetraazamacrocycles were synthesised, HL^1 and H_2L^2. This selective alkylation is due to the steric hindrance caused by the increasing number of methyl substitutents around the unsubstituted amine groups. The Co^{III}, Ni^{II} and Cu^{II} salts with H_2L^2 were isolated and were given by a metal to

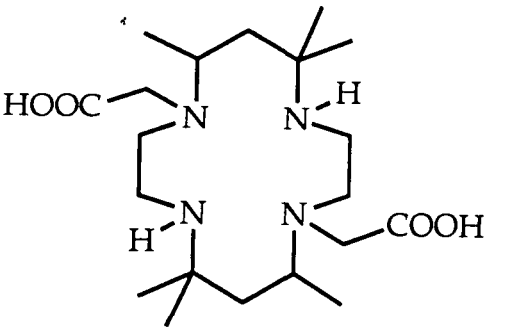


HL^1

5,5,7,12,12,14-hexamethyl-

1,4,8,11-tetraazacyclotetradecane

-N-acetic acid, HL^1



HL^2

5,5,7,12,12,14-hexamethyl-

1,4,8,11-tetraazacyclotetradecane

-N′,N‴-diacetic acid, H_2L^2

ligand ratio of 1:1. An interesting feature of the nickel complex is that it forms a cis-NiN_4O_2 structure in which the parent cyclic tetraamine is folded, Figure 1.1. The existence of another two stereoisomers is possible and would form the trans-enclosed six co-ordinated metal complexes.

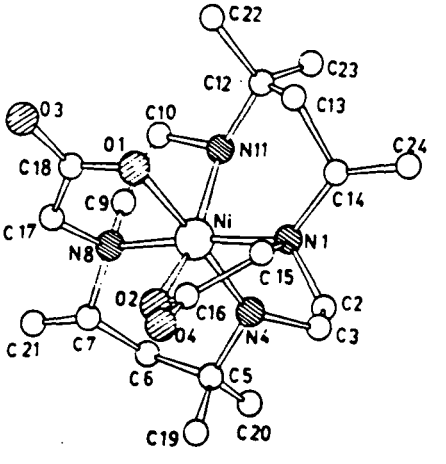


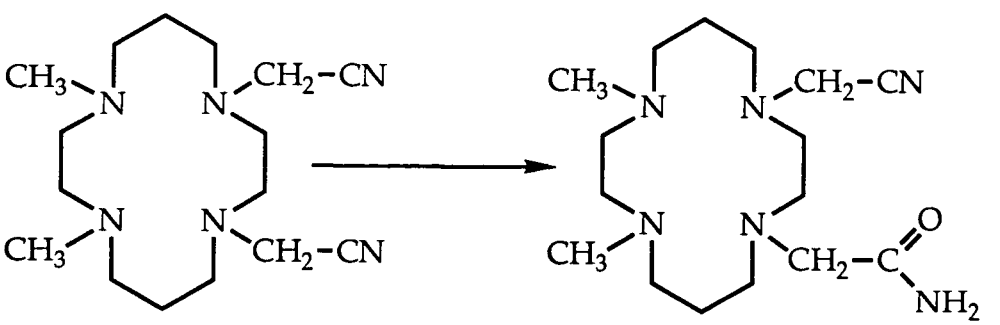
Figure 1.1

Dale[20] has produced compound 16 from the 12-membered ring where n=m=2 using ethylene oxide to produce a macrocycle containing four 2-hydroxyethyl side chains.

A versatile starting material has been prepared by Wainwright[21] where four 2-cyanoethyl groups have been introduced to 1,4,8,11-tetraazacyclo-tetradecane using acrylonitrile as an alkylating agent. This is a good starting material as the nitrile groups may be easily converted to their corresponding amides[21] and amines[22].

1.3.4 Selectivity functionalised tetraazamacrocycles

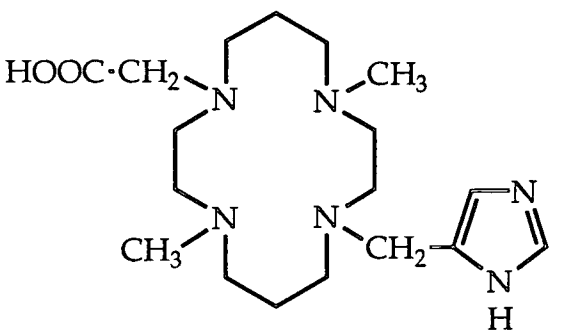
Only a few disubstituted tetraazamacrocycles have been prepared. Amongst these Schibler[23] describes the cyanomethylation of 1,4-dimethyl cyclam to give 19 which is selectively hydrolysed in the presence of Cu^{2+} to yield the monoamide monamine.



19

Selectively hydrolysed in the presence of Cu^{2+}.

Also Vitali[24] has prepared a trans-difunctional 16-membered macrocycle 20 containing an acetate and an imidazoyl methyl side chain and the uv/vis spectra of the Cu^{2+} complex indicates the possible co-ordination of all the ligating groups.



20

1.3.5 Mono substitution

The synthesis of mono substituted tetraazamacrocycles is somewhat different to those previously used and new routes to this end have been devised. They are shown in Figure 1.2 and are (a) selective alkylation, (b) cyclisation with a side chain, (c) modification of a side chain that is already present and (d) the alkylation of a selectively protected macrocycle.

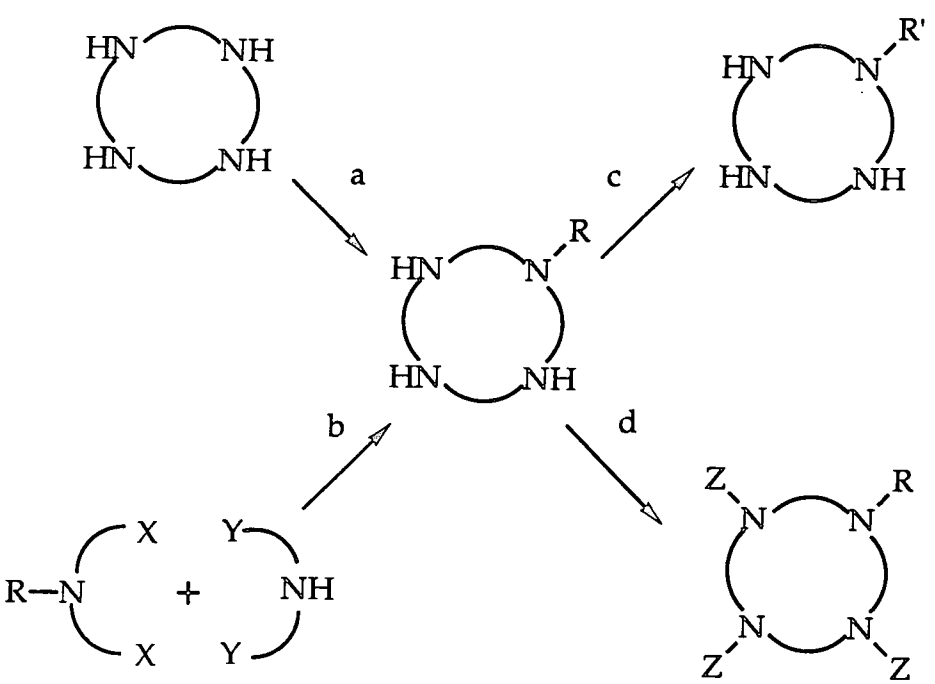
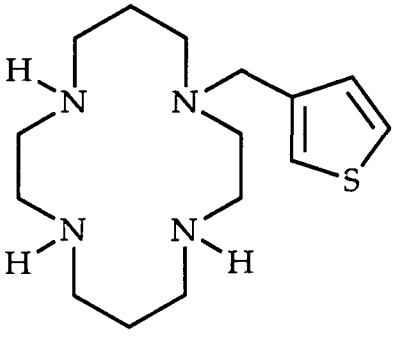


Figure 1.2

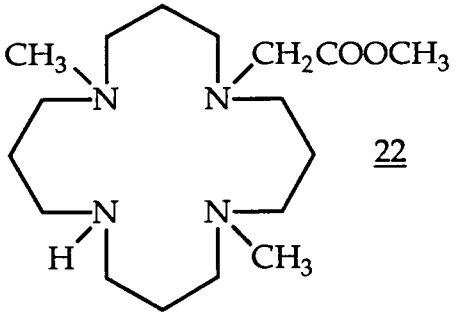
(a) The simplest and most elementary method of forming a mono substituted tetraazamacrocycle would be the reaction of an alkylating agent with a corresponding excess of macrocycle.

Wainwright[21] has shown in his preparation of the tetraacetate of cyclam that no mono product is formed as a by-product and claims that this is not a satisfactory route. Parker[25], however, successfully used this method of mono alkylation by reacting 3-bromoethyl thiophene with an excess of cyclam in the presence of chloroform and potassium carbonate to give the product N-(3-thienyl)-cyclam 21.

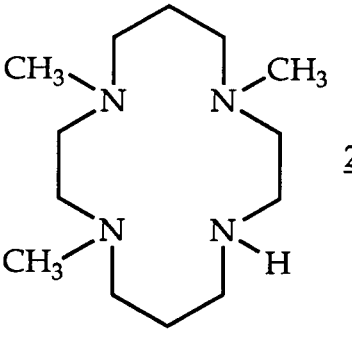


21

Selective monoalkylation of a disubstituted tetraazacycloalkane is possible to yield a trisubstituted material. Vitali[24] has demonstrated this by reacting 1,9-dimethyl-1,5,9,13-tetraazacyclohexadecane with bromomethyl acetate to give compound 22 in low yield.



22

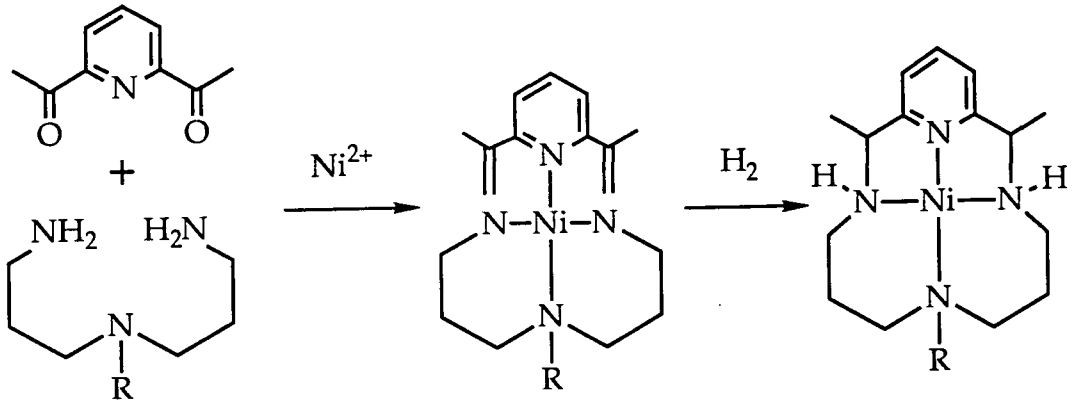


23

This type of pathway has also been demonstrated by Barefield[26] by the deprotonation and selective methylation of the Ni^{2+} complex of 1,8-dimethyl cyclam. Reaction in DMSO, with methyl iodide in the presence of strong base yielded the trimethyl derivative 23. This route gives good yields and shows that selective alkylation may be realistic and an effective path which has the advantage of being relatively simple.

(b) Another method of monoalkylating a tetraazacycloalkane is by the cyclisation of two components with a side chain or a precursor already attached using, for instance, either the template reaction[5,27] or the method used by Richman and Atkins[28].

An example of the template reaction is the condensation of 2,6-diacetyl pyridine with either 4-(2-dimethylaminoethyl)-1,7-diamino-4-azaheptane or 4-(2-hydroxyethyl)-1,7-diamino-4-azaheptane using Ni^{2+} as the template[29]. The Ni^{2+} complexes 24 and 25 are obtained respectively, with a 2-dimethylamino-ethyl or 2-hydroxyethyl pendant arm.

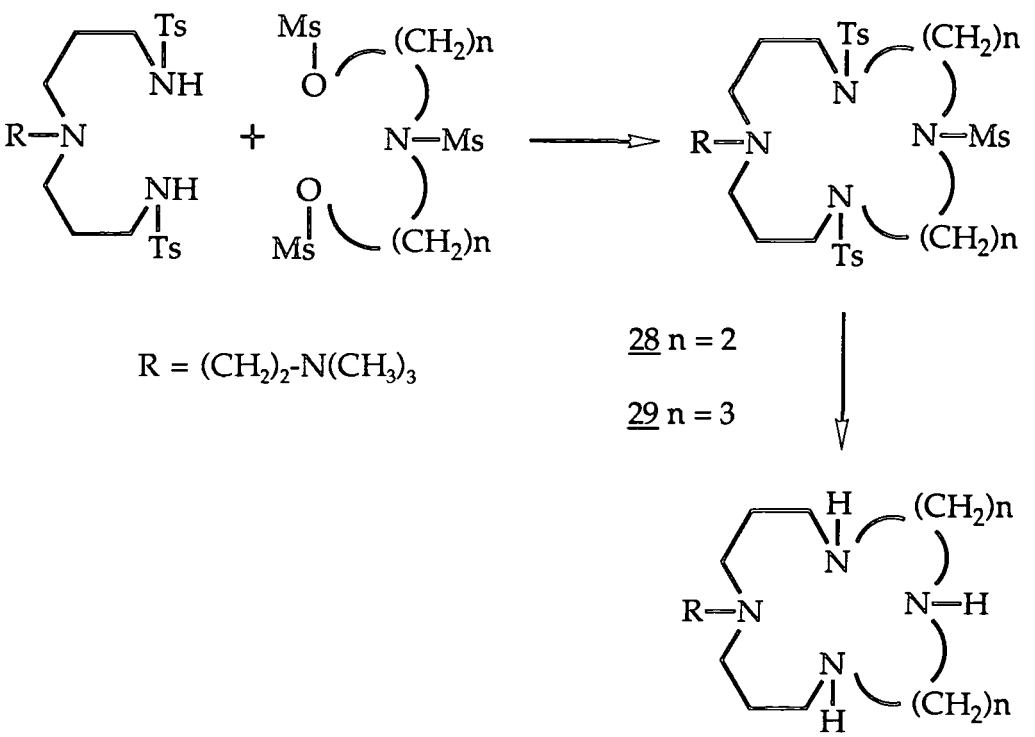


24 R = $(CH_2)_2NMe_2$ 26 R = $(CH_2)_2NMe_2$

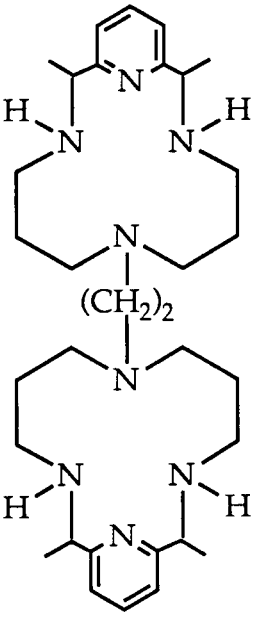
25 R = CH_2CH_2OH 27 R = CH_2CH_2OH

The Schiff's bases 24 and 25 can now be reduced to 26 and 27 using Pt/H_2 to give the saturated Ni^{2+} complexes. These are now treated with excess NaCN to liberate the free ligand from which other metal complexes of interest can now be formed.

Pierpoint[30] used the amine 4-(2-dimethylaminoethyl)-1,7-diamino-4-azaheptane also to form 14 and 16 membered macrocycles using the procedure of Richman and Atkins[28]. After subsequent deprotection the ligands 28 and 29 were made from which the Cu^{2+}, Ni^{2+} and Zn^{2+} complexes were readily formed.

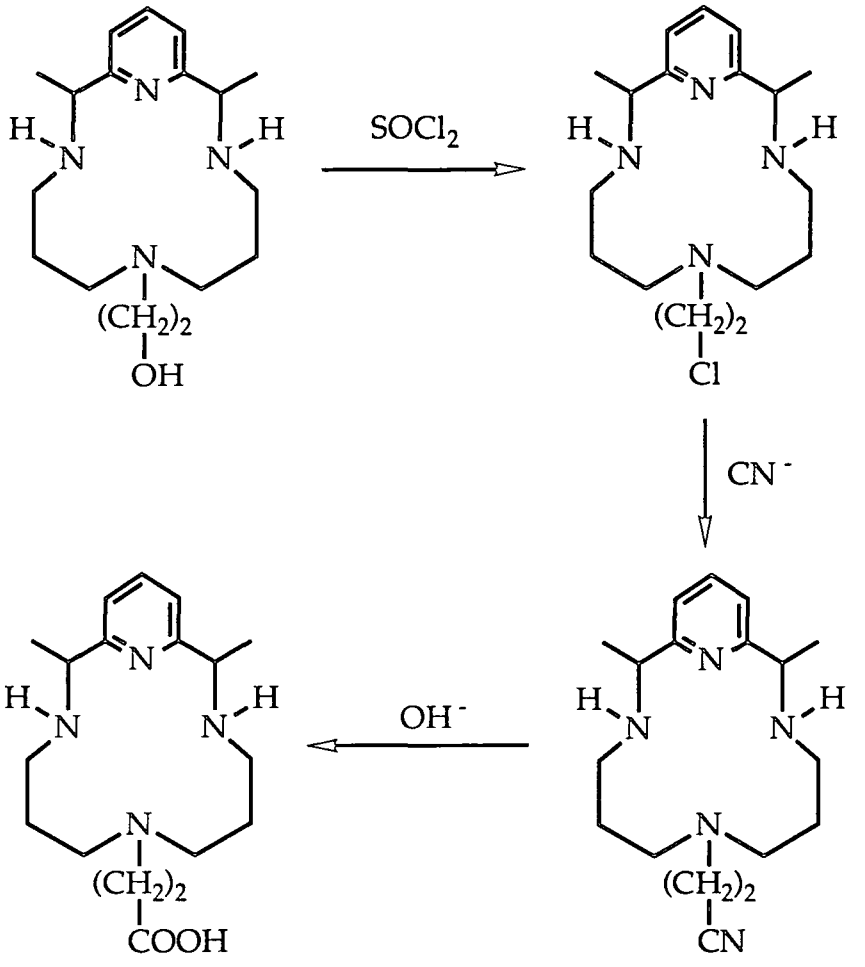


A binuclear Cu^{2+} complex containing two N_4 macrocyclic rings linked by an ethylene bridge is described by Murase[31]. This bis-macrocycle is formed following the above synthesis in figure 1.2 using two equivalents of 2,6-diacetyl-pyridine with one equivalent of N,N,N′,N′-tetrakis-(3-aminopropyl)-1,2-diaminoethane in the presence of Cu^{2+} as a template to give 30.



30

(c) Once a side chain has been introduced into a tetraazamacrocycle its modification into another derivative should, in theory, open a new range of possibilities, however, little work has been done in this area and what is required is an easily modifiable group. Furter[32] has pursued this avenue and has modified the side chain of 27 to produce its 2-chloroethyl, 2-cyanoethyl and 2-carboxyethyl derivative and also the corresponding Ni^{2+} complexes therein.



(d) This is one of the best ways of producing a monoalkylated tetraaza-macrocycle. The alkylation of a selectively protected macrocycle assumes that it is possible to have three protected nitrogens within the ring so they are blocked for further reactions leaving one available nitrogen for alkylation and then introduce a side chain robust enough to survive the deprotection stage. This has the advantage that cyclisation is only required at one stage and so allowing optimisation of the yield.

Hediger[33] describes two synthetic approaches which are a modification of the Richman and Atkins procedure[28]. Rather than use only tosyl groups for protecting and activating, he substituted either benzyl or trityl groups onto one

of the amine nitrogen atoms thus introducing selectivity into the synthesis. Both pathways, Figures 1.3 and 1.4, give, after cleavage of the benzyl or trityl group, a tritosylate leaving one ring nitrogen available for alkylation by a suitable electrophile. From the key products 31 and 32, a large range of derivatives is available, especially those with a functionalised side chain. To date the following pendant arms have been introduced 2-cyanoethyl[33], 2-carbamoylethyl[33], carbamoylmethyl[33], 2-tosylamidoethyl[33], 2-hydroxyethyl[34], 3-hydroxypropyl[34], 2-carbethoxyethyl[34] and carboxymethyl[34].

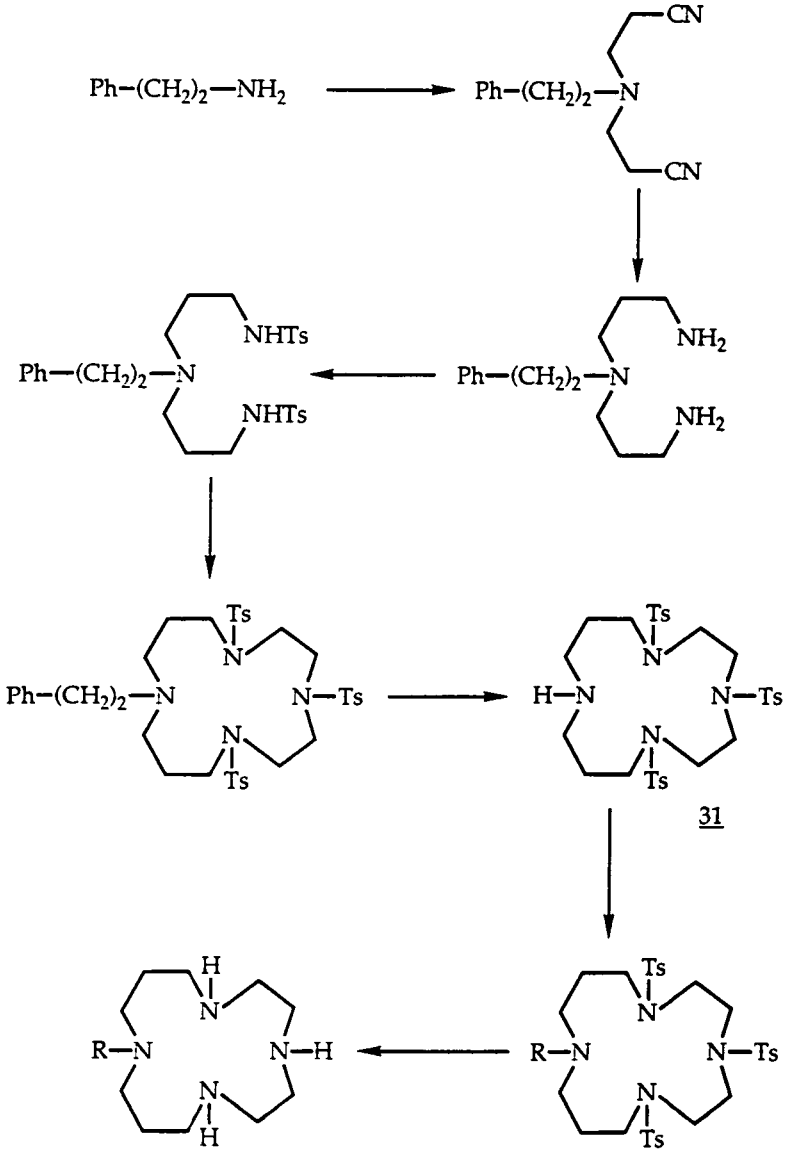


Figure 1.3

The last stage of the synthesis involves the removal of the tosyl groups. This deprotection stage should be carried out in as mild conditions as possible. Hydrogen bromide in glacial acetic acid in the presence of phenol or an electrochemical reduction according to Horner[35] have been used successfully[33]. Although the nitrile[34] and ester[34] functions were attacked the

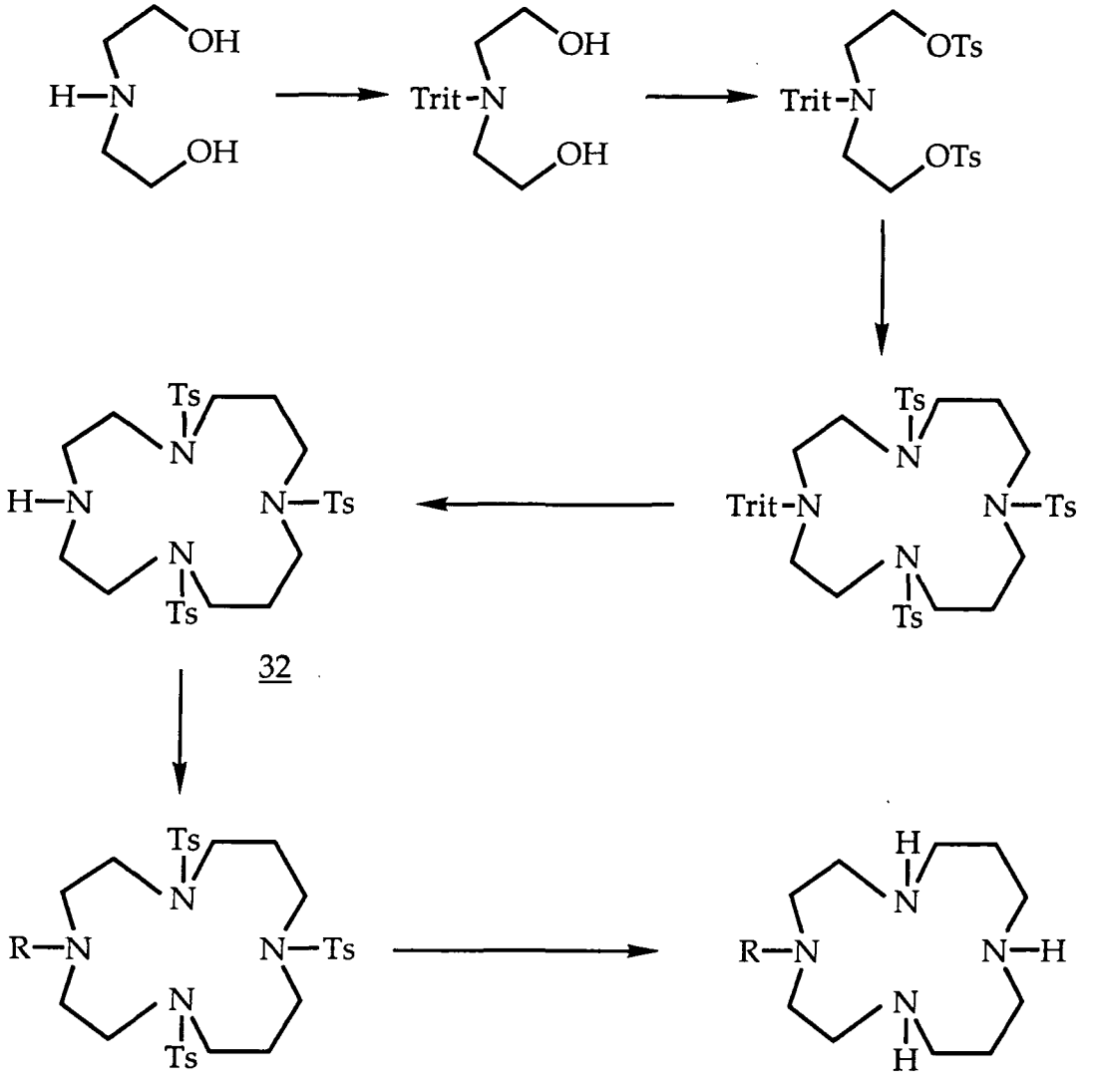
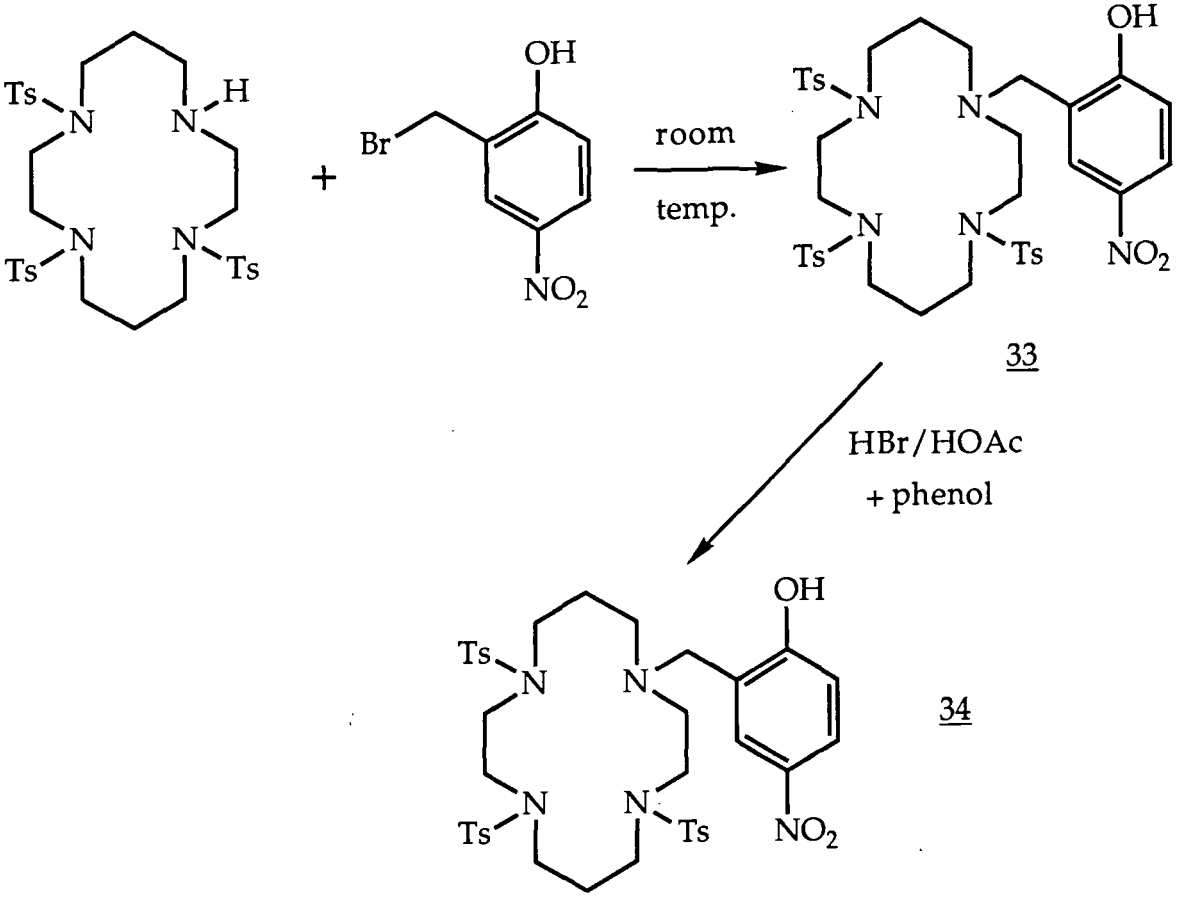


Figure 1.4

other groups remained intact. Parker[25] reacted the tritosylamide of cyclam with 2-hydroxy-5-nitrobenzylbromide in dichloromethane and triethylamine to give the intermediate 33. This was subsequently deprotected with 45% w/v

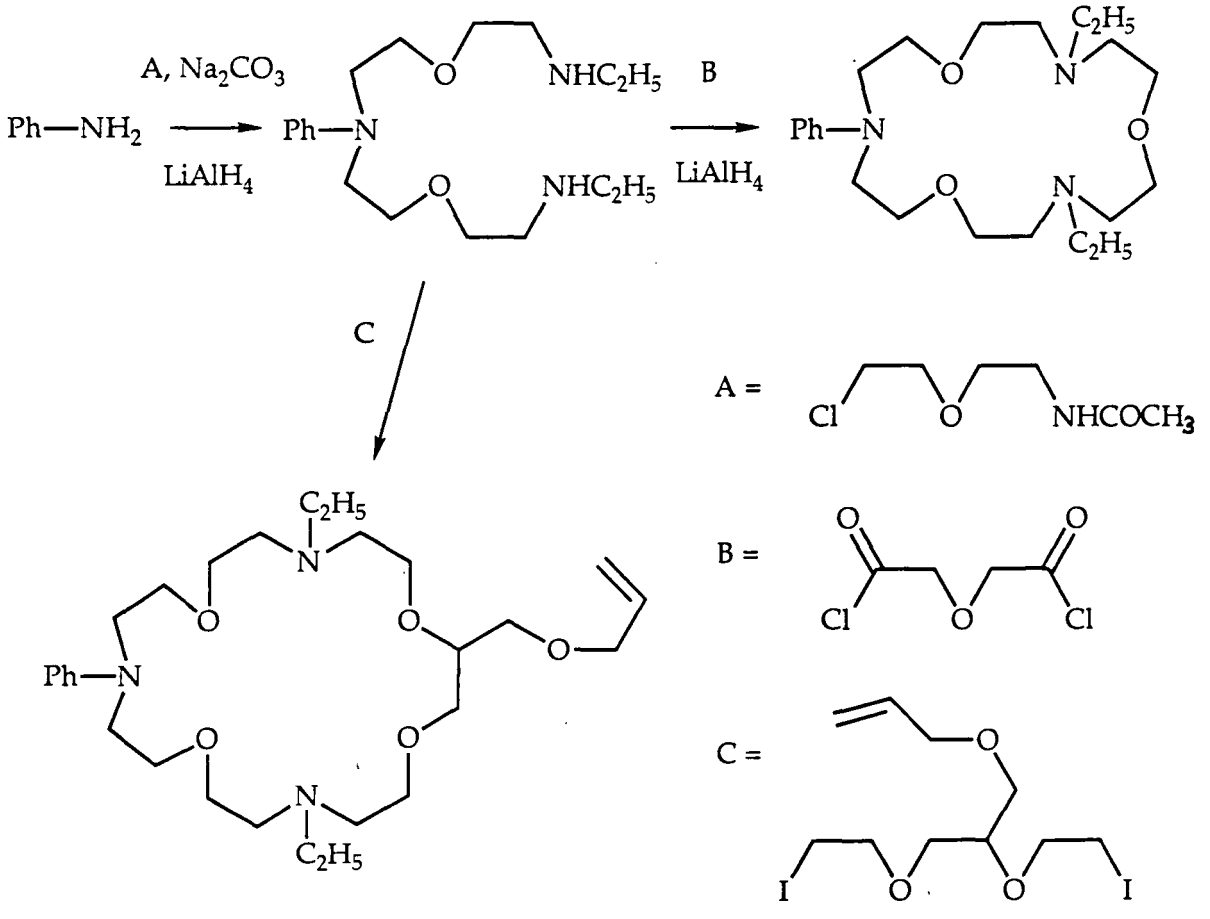
HBr/HOAc and phenol under reflux to yield the product N-(5-nitro-2-hydroxy-benzyl)-cyclam 34.



Although this route is a multistep synthesis, it seems most promising and versatile, especially if one wants to systematically vary the nature of the ligating group in the pendant arm.

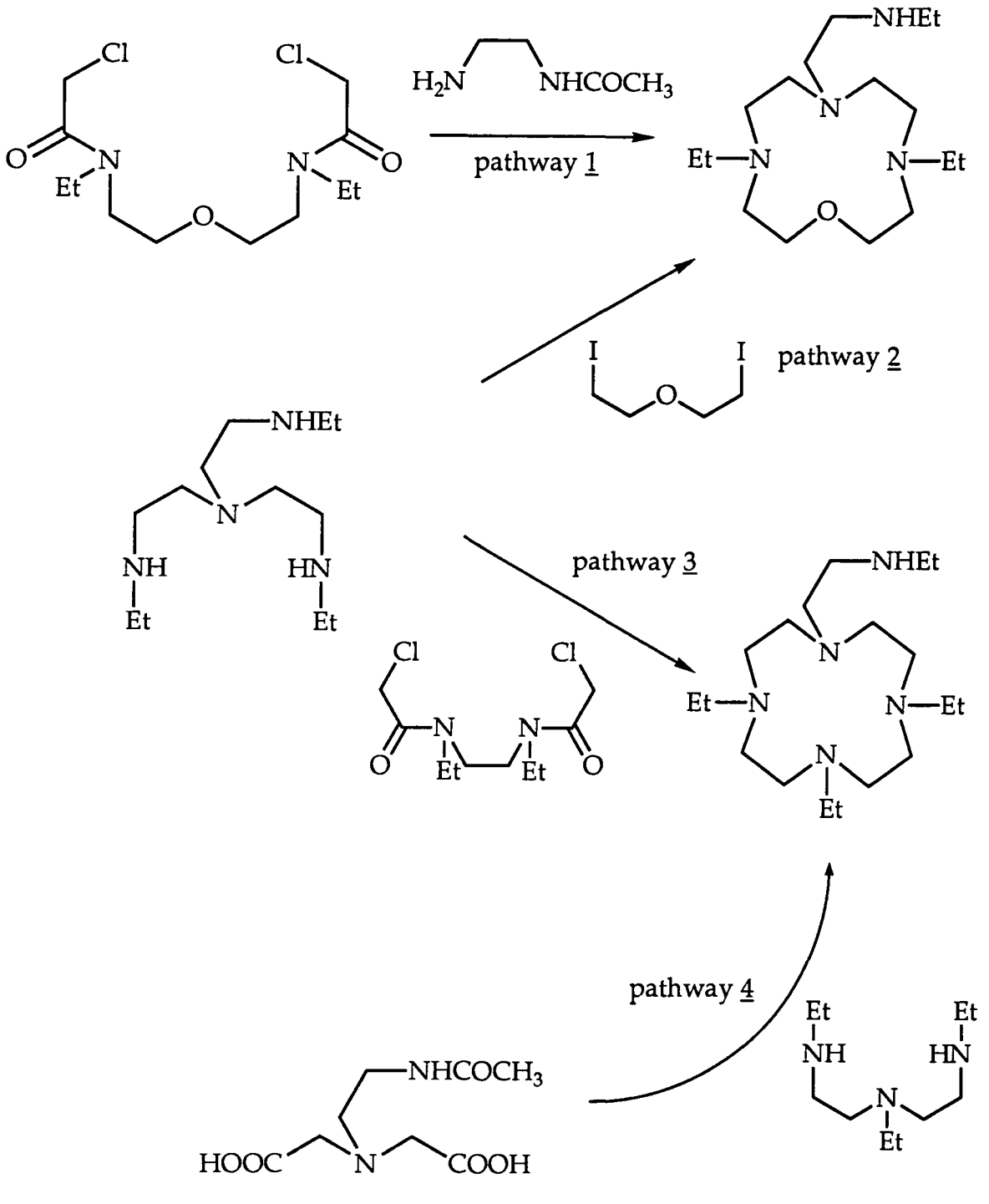
Izatt and Krakowiak[36] have reported a novel and convenient method of preparing N-alkyl substituted triaza-crown complexes using only a few steps.

The key material for this synthesis is N-[2-(chloroethoxy)ethyl] acetamide A to prepare the required structure for the target macrocycle. A typical synthesis is outlined in Scheme 1.1.



Scheme 1.1

Izatt and Krakowiak[37] have also reported a convenient method of preparing new mono-functionalised triaza-crowns and cyclams containing a secondary pendant amine group. It entails simple ring closure reactions of easily synthesised dihalides or a diacid and oligoethylene polyamines as shown in Scheme 1.2.



Scheme 1.2

Reaction Conditions

Pathway 1, 1 CH_3CN, 0° to 80°, Na_2CO_3; 2 BH_3.THF, THF.
Pathway 2, 1 CH_3CN, 0° to reflux, Na_2CO_3, NaI.
Pathway 3, 1 CH_3CN, -10° to 25°, Na_2CO_3; BH_3.THF, THF.
Pathway 4, 1 DMF, DCC, 1-hydroxybenzotriazole; 2 BH_3.THF, THF.

The X-ray crystal structure of the 4-silver perchlorate complex is shown in Figure 1.5. It is particularly interesting that the side chain of nitrogen (N73) is strongly associated with the silver ion. This crystal structure is the first one reported for a cyclam-15-metal complex with an interacting side chain. Similar metal ion complexes with a cyclam-14 containing a side chain have been reported[25,38].

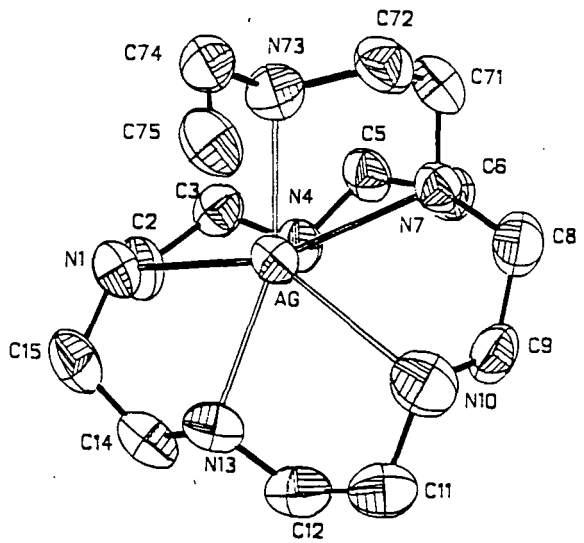


Figure 1.5

1.3.6 C-functionalised ligands

As well as being functionalised on the nitrogen atom tetraazamacrocycles have been functionalised by attaching a pendant side chain to one of the ring carbon atoms. Generally these type of compounds are made with the side chain already attached to one of the components and resembles path b for the corresponding N-substituted derivatives as in the method used by Richman and Atkins[28]. Richman and Atkins devised a simple method of producing

aza-crown ethers. This method enabled macrocycles of between 9 and 36 atoms to be made with yields of between 40 and 90%. By introducing substituents at one of the carbon atoms within the starting material a suitably C-functionalised macrocycle may be easily made. By following the method of Stetter and Roos[39] and using bisulphonamide sodium salts and sulphonate ester leaving groups in a dipolar aprotic solvent they found that yields and ring sizes of macrocycles were improved.

A typical reaction scheme is outlined in Figure 1.6. A stirred solution of the disodium salt 35 was treated with 1 equivalent of 36 in dimethylformamide at 100°C for 1→2 hours. The macrocycle 37 was isolated and detosylation by refluxing with HBr/HOAc and phenol or 97% sulphuric acid at 100°C for 48 hours afforded the substituted macrocyclic triamine 38.

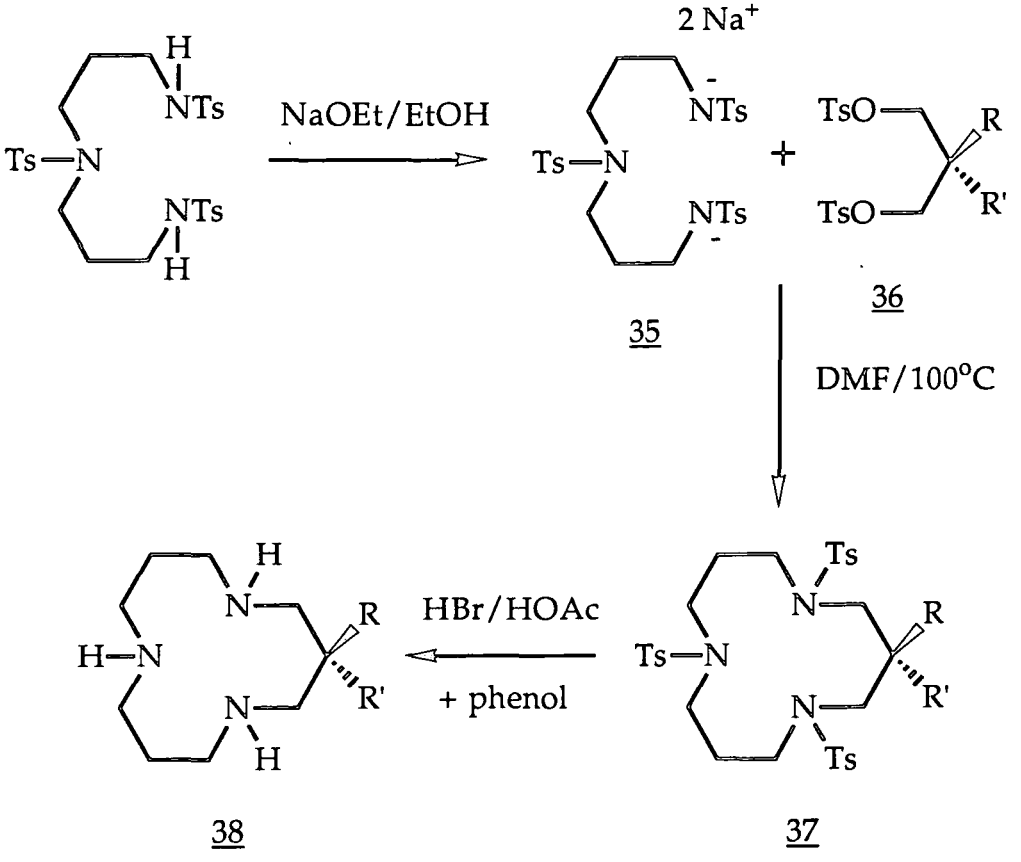
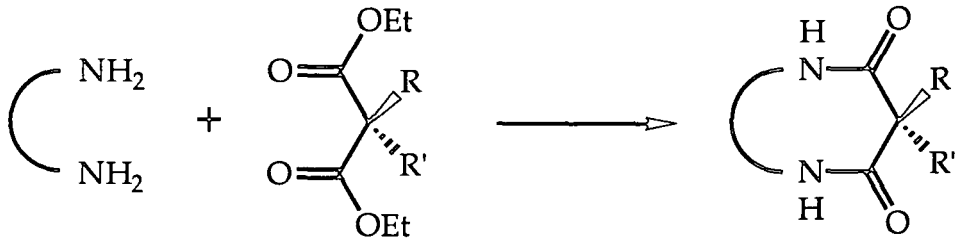
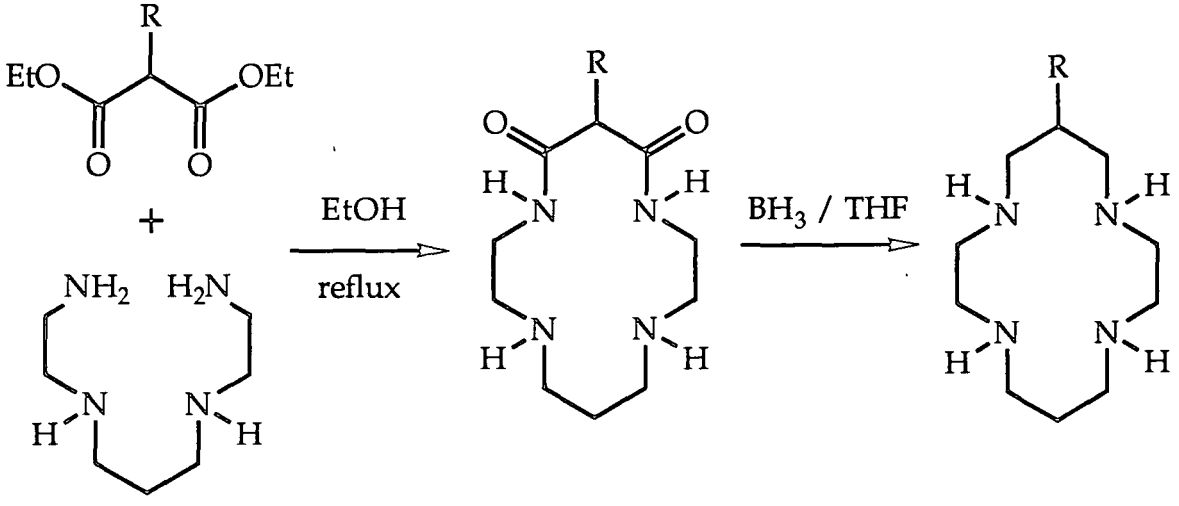


Figure 1.6

Tabushi[40] produced an interesting range of tetraazamacrocycles by the condensation of 1,9-diamino-3,7-diazanonane with different malonic esters that



were substituted at the α-carbon atom. This method was found to give good yields of the corresponding dioxocyclams and these resulting diamides may be reduced with diborane to give the corresponding tetraazamacrocycles 39 and 40.

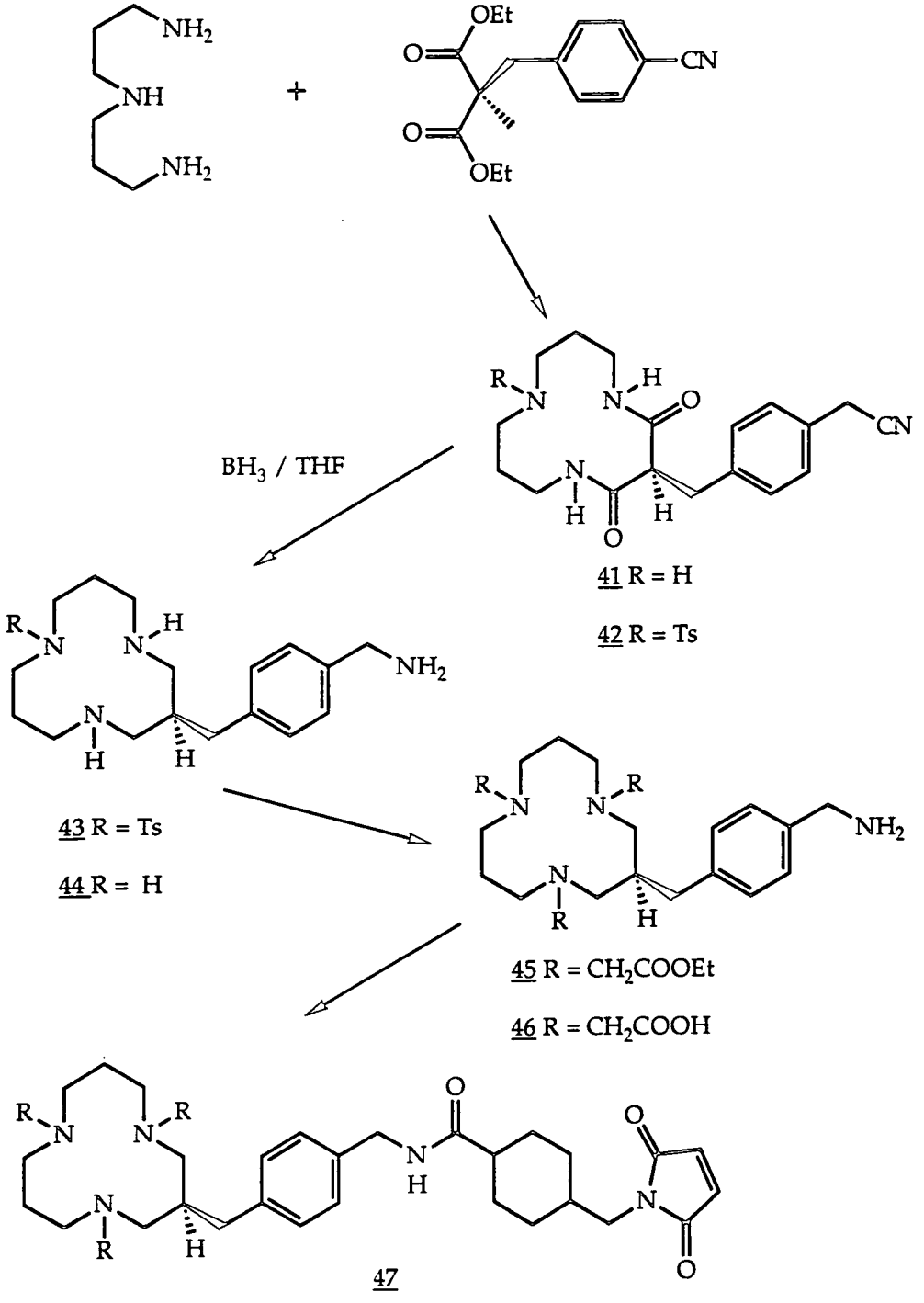


39 R = $-(CH_2)_2-OH$

40 R = $-(CH_2)_3-NH_2$

This diethyl malonate condensation reaction can be extended to C-substituted $[12]N_3$ ligands as shown by Helps and Parker[41]. For example a solution of 1,5,9-triazanonane in ethanol was refluxed with diethylcyanobenzyl

malonate for 15 days to give, after purification by column chromatography, the product 3-(p-cyanobenzyl)-1,5,9-triazacyclododecane-2,4-dione[31] in 18% yield. Tosylation of the ring nitrogen amine leads to the formation of 42 followed by reduction with diborane to give 43. Detosylation with hydrogen bromide in the presence of phenol yielded the tetraamine 44. The ring nitrogens are



41 R = H

42 R = Ts

43 R = Ts

44 R = H

45 R = CH_2COOEt

46 R = CH_2COOH

47

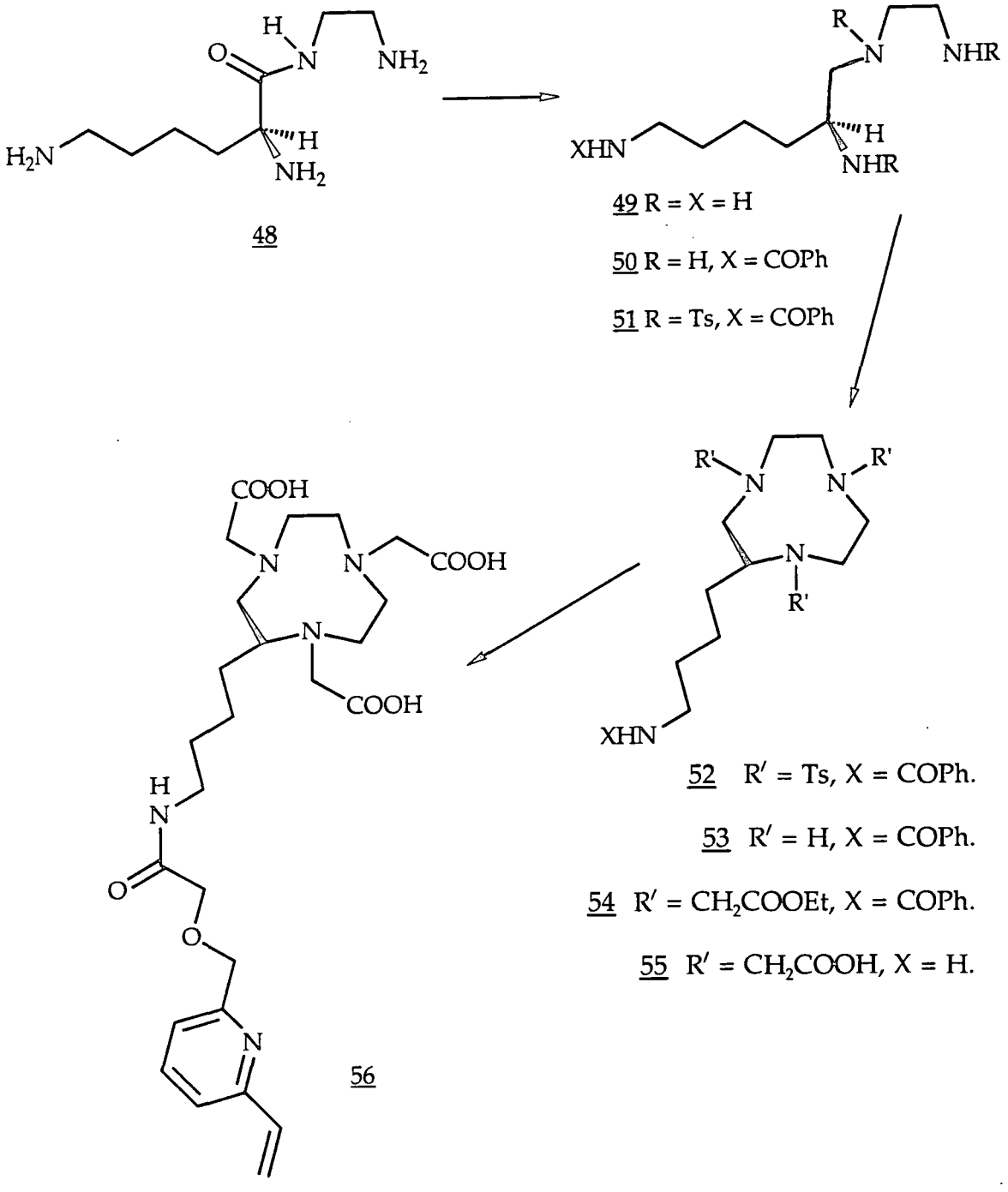
conveniently protected from electrophilic attack by protonation (pKa = 13.2 and 7.4 for the parent amine[42]) permitting selective alkylation of the exocyclic amine. Selective alkylation of the benzyl amine moiety gave the acetamide using p-nitrophenylacetate at pH 6.8 in aqueous dioxan 1:1. N-alkylation of the three ring nitrogen amines was effected using ethyl bromoacetate and caesium carbonate in ethanol to give the triester 45 which was hydrolysed with 6M HCl for 18 hours to yield the desired amino triacid 46. Functionalisation of the exocyclic amine group was affected using the N-hydroxysuccinimide ester of N-(4-carboxycyclohexylmethyl)maleimide at pH 6.8 in aqueous dioxan 1:1 to yield 47.

1.3.7 [9]N_3 and [12]N_4 macrocycles

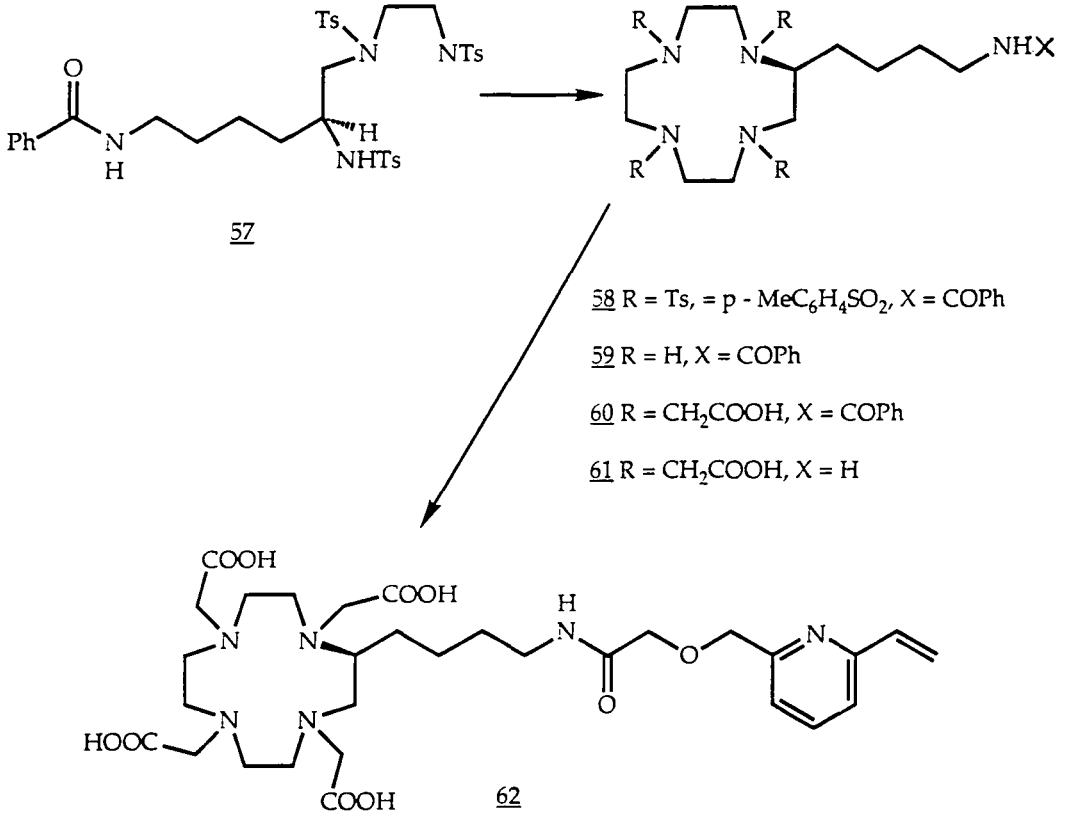
This idea has been used for other ring systems, namely [9]N_3[43] and [12]N_4[44] macrocycles.

Reaction of the methyl ester of (2S)-lysine with neat ethylene diamine gave the amide 48 in 96% yield, which was reduced with borane-THF in THF to form the tetraamine 49, yield 75%. This diethylene triamine sub-unit of 49 was protected by complexation with Cu^{II} in aqueous solution thus permitting the selective acylation of the remote primary amine group with PhCOCl. Copper was removed by treatment with H_2S to give the benzamide 50 (58%) which was next reacted with tosyl chloride in triethylamine and dichloromethane to give the tritosylamide 51. Condensation of 51 with ethylene glycol ditosylate and caesium carbonate in dimethylformamide at 65°C afforded the cyclic tritosylamide 52 in 71% yield. The tosyl groups were removed using either Li/NH_3/MeOH/THF or more simply with 98% H_2SO_4 to yield the triamine 53 in 64% yield. Alkylation of 53 with ethyl bromoacetate

and caesium carbonate in ethanol afforded the triester 54 (77%) and acid hydrolysis with 6M HCl for 18 hours yielded the amino functionalised triacid 55 quantitatively. Similarly to 47 antibody linkage was effected in a stepwise manner by reacting the p-nitrophenylester of 2-vinyl-6-(4′-carboxy-3′-oxa-butyl)pyridine with 55 in DMF to give 56.



A similar reactor pathway for the $[12]N_4$ system[44] starts with the condensation of 57 with 1,3,5-tris(p-toluenesulphonyl)-3-aza-1,5-pentanediamine in DMF in the presence of Cs_2CO_3 to give the macrocycle 58. This may then be converted through to the desired product 62, as defined for the $[9]N_3$ analogue.



1.3.8 Axial donors

As a large number of C-functionalised tetraazamacrocycles can be prepared by these methods, the possibility of attaching axial donors that can perturb the properties of the tetraamine complex has been studied. Critical roles of axial donors are known in nature, examples being in the haeme-iron systems of normal[45] and abnormal[46] haemoglobin and redox enzymes such as cytochrome P-450[47] and catalase[48].

Kimura[49] has described a one-step annelation procedure for obtaining a new phenol-appended tetraamine using coumarin or substituted coumarins as a source of the phenolic substituents. Coumarin 63 was refluxed with 1,9-diamino-3,7-diazanonane 64 in methanol for two weeks to give the dioxotetra-amine cyclam derivative 65 as its trihydrochloride in 20% yield. The diamide was reduced with diborane readily to give the cyclam derivative 66 in 50% yield.

A significant effect of the directly bonded aromatic ring in 65 and 66 is that the motion of the phenolic group is frozen with the phenol group hydrogen bonded to the protonated tetraamine. The ^{1}H NMR spectrum of 66 showed an unusually high chemical shift for OH (δ 0-1.5, brs, H-D exchangeable) and a well resolved doublet of doublets for the benzylic H_c signal (δ 3.7-4.0). An interesting feature of the phenolic ligand 66 is its ability to dissolve an equimolar amount of solid $Fe(OH)_3$ to form a 1:1 complex involving a phenolate iron bond. This behaviour is not normally associated with saturated polyamines, e.g. cyclam. The X-ray structure of the nickel complex of ligand 66 is shown in Figure 1.7.

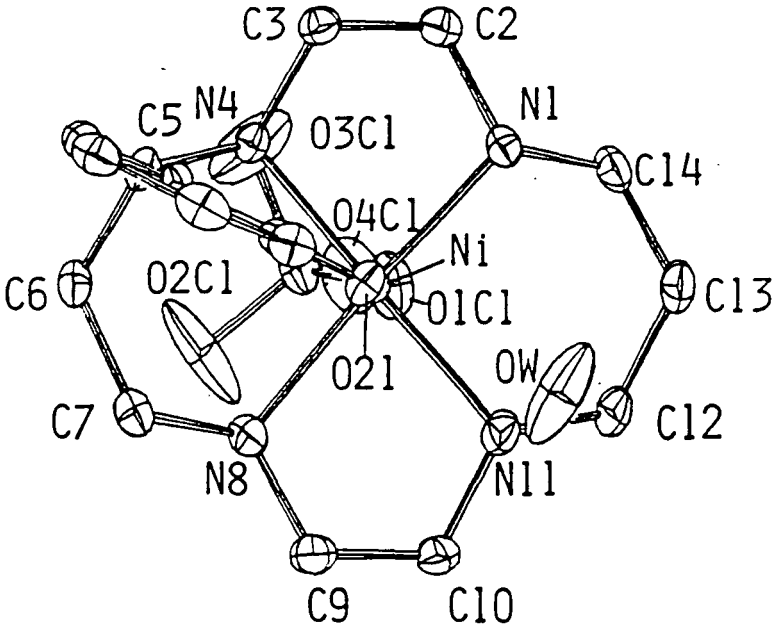
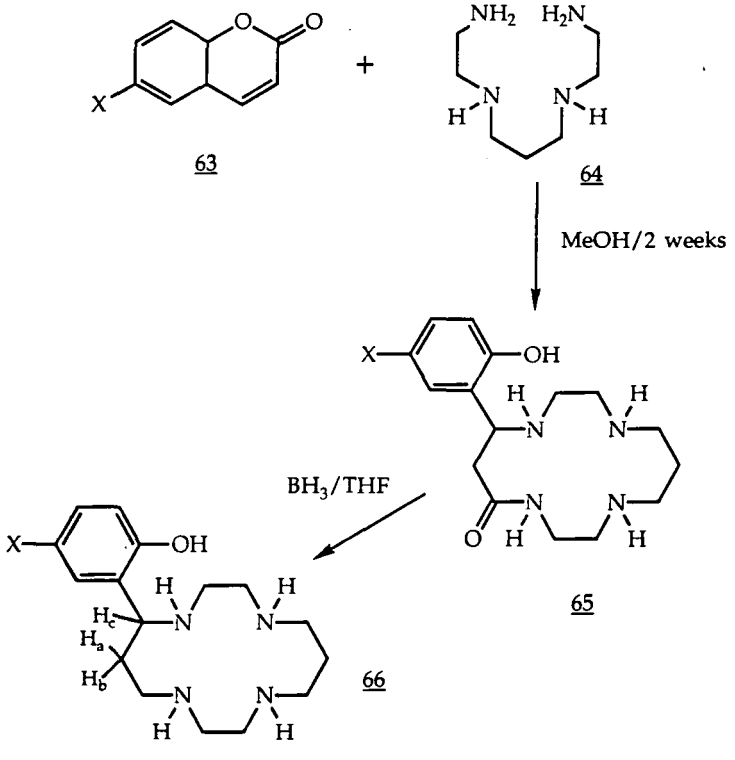


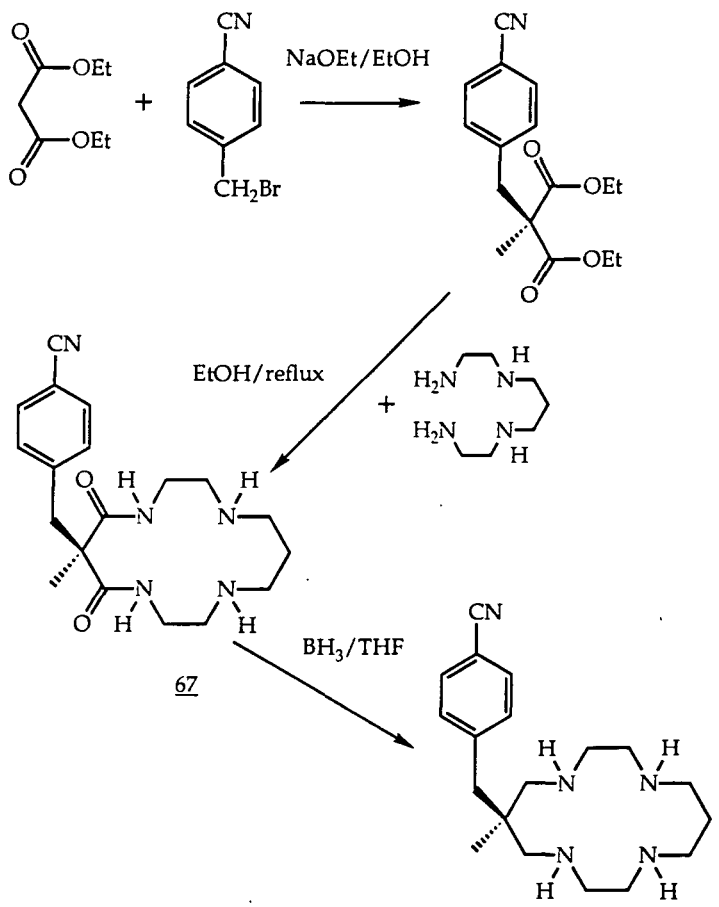
Figure 1.7

Kimura[50] also extended this annealation method to obtain a new 12-membered macrocyclic triamine ligand holding a C-functionalised pendant arm.



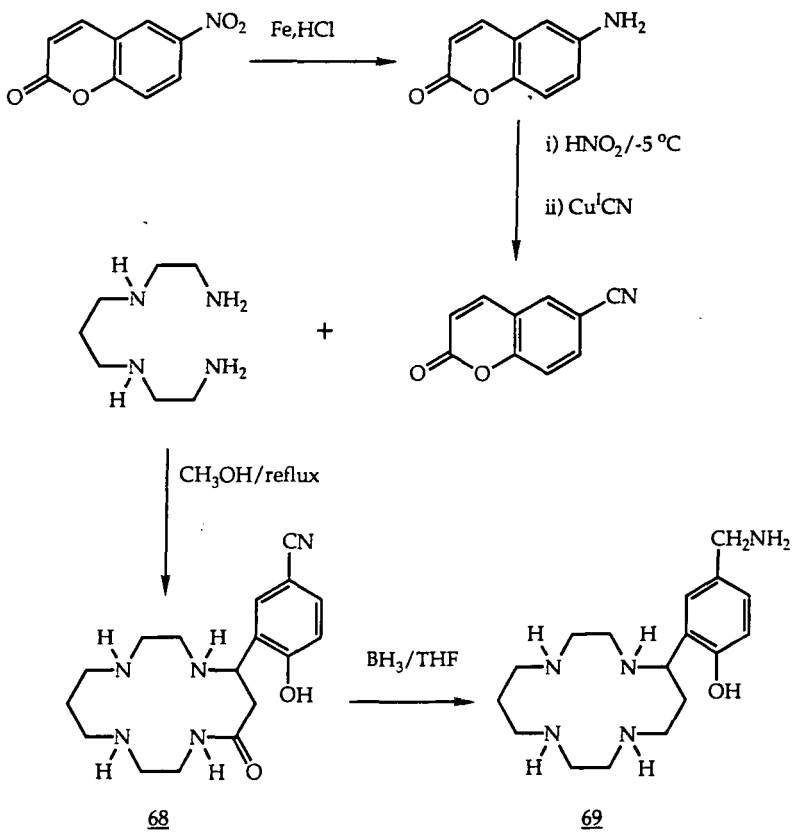
In general this phenol substituent was shown to have enhanced the binding of tetraazacycles with Cu^{II}, Ni^{II}, Zn^{II} and Co^{II}. This has been demonstrated by potentiometric measurement of complexation constants and by pH-metric methods.

Following the work of Tabushi[40] and Kimura[49], Morphy and Parker[51] prepared different macrocyclic ligands that were C-functionalised at different carbon atoms within the aliphatic cyclic chain. For instance, the non-phenolic tetraamine 67 was prepared.



67

The synthesis of the phenolic macrocycle 69, involved the condensation of 6-cyanocoumarin[51,52], with 1,4,8,11-tetraazaundecane. The resulting monoamide 68 was reduced with diborane in the usual fashion to give the target phenolic macrocycle 69.

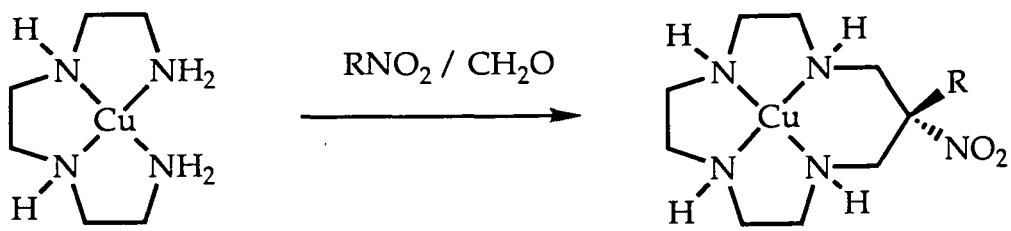


68 69

1.3.9 Template reactions

The template method used by Curtis[53] provides an alternative pathway to the synthesis of C-functionalised polyazamacrocycles. He employed a metal directed synthesis using either copper^{II} or nickel^{II} as a template with a tetra-amine ligand, formaldehyde and a nitroalkane.

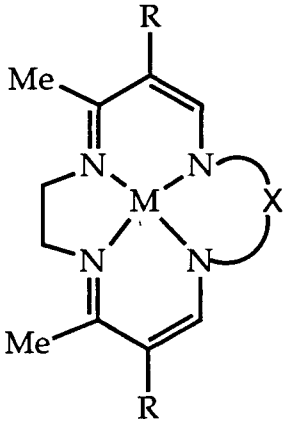
Typically 1,8-diamino-3,6-diazaoctane (triene) was condensed with a nitroalkane and formaldehyde in the presence of copper^{II} nitrate.



70 R = CH_3
71 R = C_2H_5

Hence the reaction of Cu^{II} (triene) and Ni^{II} (triene) in basic methanol with excess aqueous formaldehyde and either nitroethane or 1-nitropropane results in the ready formation of 12-methyl-12-nitro-1,4,7,10-tetraazacyclotridecane 70 or 12-ethyl-12-nitro-1,4,7,10-tetraazacyclotridecane 71 in good yields.

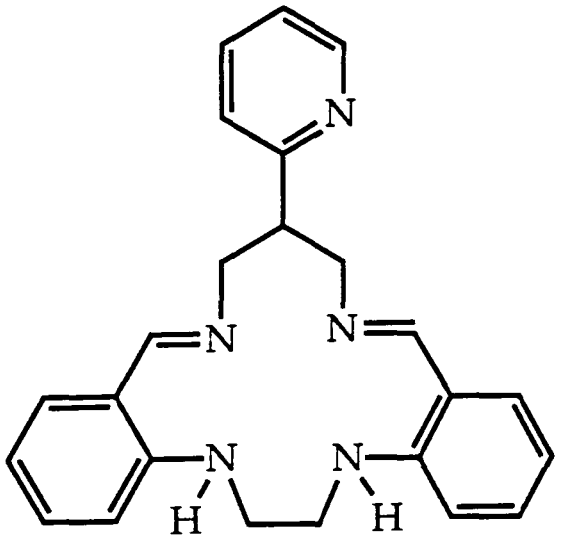
Jäger[54] made a large number of C-functionalised macrocycles in a similar way by reacting diamines such as ethylene diamine, 1,3-diamino propane or o-phenylene diamine with β-ketoimidato complexes in a template assisted cyclisation using Ni^{2+} ions. The acyclic precursors incorporated a carbonyl or an ester group. There was no evidence that these substituents co-ordinated to the bound metal ion.



X = $(CH_2)_2$, $(CH_2)_3$, o-C_6H_4

R = $COCH_3$, COC_6H_5, COOEt

Another C-substituted macrocycle has been prepared by Tasker[55]. The pyridyl group of 72, however, cannot co-ordinate to the metal ion since the chain is too short. The synthesis is based on a template reaction between a dialdehyde and 2-(2-pyridyl)-1,3-diamino propane in the presence of Ni^{2+} or Cu^{2+}.

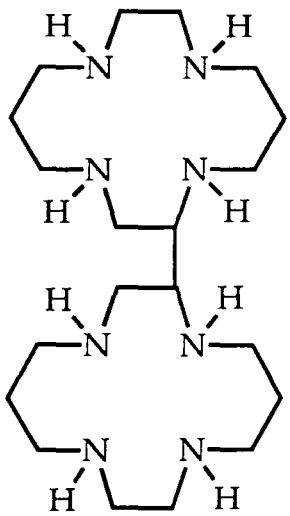


72

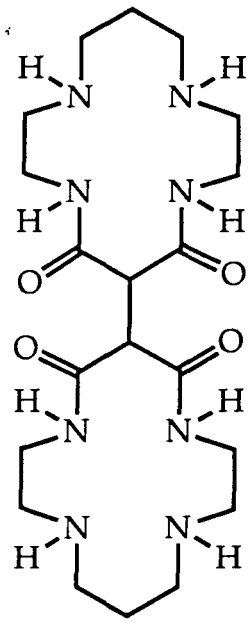
1.3.10 Bis-macrocycles

Finally, macrocycle 73 was obtained in low yields as a by-product of the synthesis of cyclam. This compound probably forms during the reduction by condensation of the active methylene group of the half reduced Schiff's base complex with the imine group of the second complex. The ligand forms binuclear Cu^{2+} and Ni^{2+} complexes.

Fabrizzi[56] has used the condensation of 1,9-diamino-3,7-diazanonane with tetraethyl-1,1,2,2-ethane tetracarboxylate to make the bis-macrocycle 74. The binuclear Cu^{2+} complex of this macrocycle has been made and these two Cu^{2+} ions can be oxidised to Cu^{3+} in two separate steps.



73



74

1.4 General Features of NiII and CuII Complexation Chemistry

1.4.1 Basic copper chemistry

The dipositive state is the most important one for copper[57]. The d^9 configuration makes Cu^{II} complexes subject to Jahn-Teller distortion* if placed in an environment of cubic or tetrahedral environments (i.e. regular octahedral or tetrahedral symmetry) and this has a profound effect on its co-ordination

* The Jahn-Teller theorem predicts that the unsymmetrical occupancy of a degenerate energy level will be unstable and the system will undergo distortion as to remove the degeneracy. The driving force for the distortion is a reduction in the overall energy of the occupied "d" orbitals.

geometry. When six co-ordinate, the "octahedron" is severely distorted. The typical distortion is an elongation along one 4-fold axis, such that there is a planar array of four short Cu-L bonds and two trans long ones. In the limit of course, the elongation leads to a situation indistinguishable from square co-ordination as found in CuO and many discrete complexes of Cu(II). This is the case of tetragonally distorted "octahedral" co-ordination and square co-ordination cannot be easily differentiated.

Six co-ordinate species are expected to be distorted from pure octahedral symmetry by the Jahn-Teller effect and this distortion is generally observed. A number of 5 co-ordinate species are known, both square pyramidal and trigonal bipyramidal. Four co-ordination is exemplified by square planar and tetrahedral species as well as intermediate configurations.

1.4.2 Stereochemical arrays of copper

There are a few tetrahedral complexes containing copper(II), examples being the chloro complex $CuCl_4^{2-}$ and the bis(salicylaldiminato) complex $((CH_3)_3C\text{-}N{=}CH(C_6H_4)\text{-}O\text{-})_2Cu$. Most copper(II) complexes have distorted "octahedral" or square planar symmetries. Again in the dipyrromethane

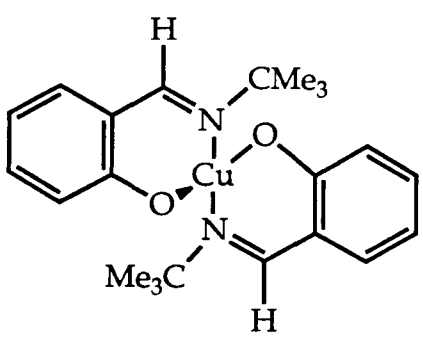


Figure 1.8

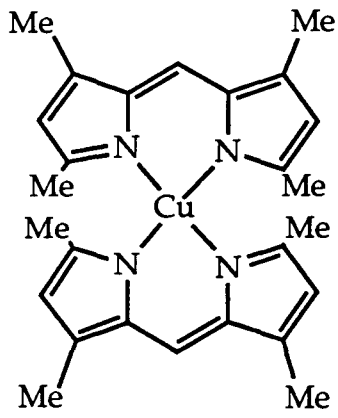
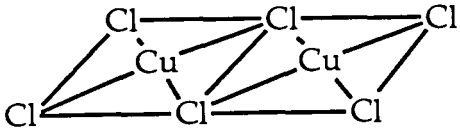
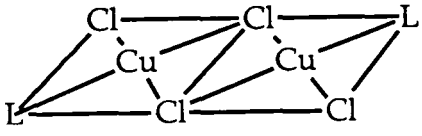


Figure 1.9

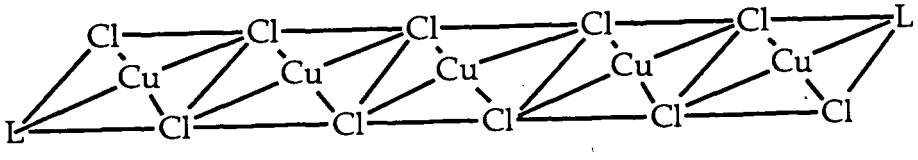
complex, steric interference of methyl groups renders a planar configuration impossible.

Numerous planar complexes are known. With a few exceptions such as salicylaldiminato (Figure 1.8) and dipyrromethane (Figure 1.9) complexes mentioned before, neutral four co-ordinate complexes containing chelating ligands have planar co-ordination. Examples of these include $Cu_2Cl_6^{2-}$, $Cu_2Cl_4(CH_2CN)_2$ and $Cu_5Cl_{10}(C_3H_7OH)_2$.





L = CH_3CN



L = C_3H_7OH

In aqueous solution, Cu(II) salts give the aquo ion $[Cu(H_2O)_6]^{2+}$ in which two of the water molecules are further from the metal ion than the other four. Addition of nitrogen containing ligands to aqueous solutions leads to successive displacement of water ligands since transition metal ions such as Cu^{2+} prefer "softer" nitrogen donors to "harder" oxygen donors. However, on

the addition of the fifth and sixth nitrogen donors are different due to the Jahn-Teller effect. For example $[Cu(NH_3)_6]^{2+}$ can only be made in liquid ammonia and $[Cu(en)_3]^{2+}$ is made only at very high concentrations of ethylene diamine. Amine complexes of CuII are much more intensely blue than the aqua ion because amines produce a stronger ligand field which causes a high frequency shift in the position of the "d-d" absorption band.

1.4.3 Basic nickel chemistry

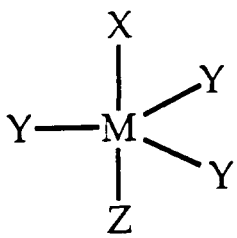
The chemistry of nickel is predominantly of its dipositive state Ni(II)[58]. In the divalent state nickel forms a very extensive series of compounds. This is the only oxidation state of importance in the aqueous chemistry of nickel, and with the exception of a few special complexes of nickel in other oxidation states, Ni(II) is also the most important oxidation level in its non-aqueous chemistry.

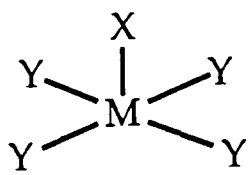
Nickel(II) forms a large number of complexes encompassing co-ordination numbers 4, 5 and 6 and all the main structural types, e.g. octahedral, trigonal bipyramidal, square pyramidal, tetrahedral and square.

The maximum co-ordination number is 6. A considerable number of neutral ligands, especially amines, displace some or all of the water molecules in the octahedral $[Ni(H_2O)_6]^{2+}$ ion to form complexes such as trans-$[Ni(H_2O)_2(NH_3)_4](NO_3)_2$, $[Ni(NH_3)_6](ClO_4)_2$ and $Ni(en)_3SO_4$ etc. Such amine complexes characteristically have blue or purple colours in contrast to the bright green colour of the hexaquo nickel ion.

1.4.4 Stereochemical arrays of nickel

A considerable number of both trigonal-bipyramidal and square pyramidal complexes are known.

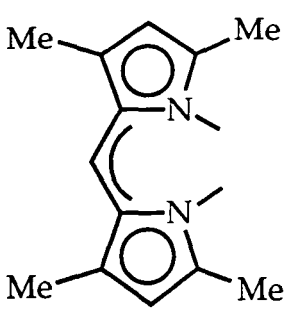


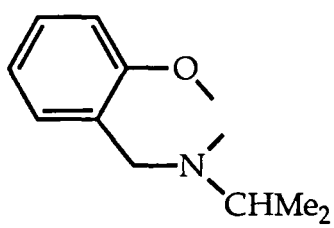


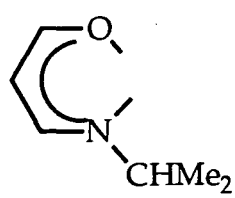
Trigonal-bipyramidal Square pyramidal

By far the commonest stereochemistry observed is trigonal-bipyramidal, or something approximately thereto, but this may be mainly due to the fact that in most cases a tripod ligand has been used.

Tetrahedral complexes are mainly of the following stoichiometric types, NiX_4^{2-}, NiX_3L^-, NiL_2X_2 and $Ni(L\text{-}L)_2$, where X represents a halogen and L a neutral ligand such as a phosphine, and L-L a bidentate ligand, e.g. A, B or C.





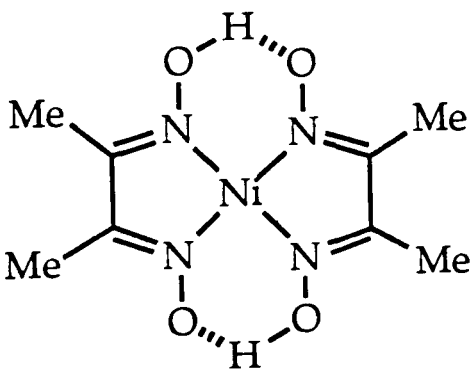


A B C

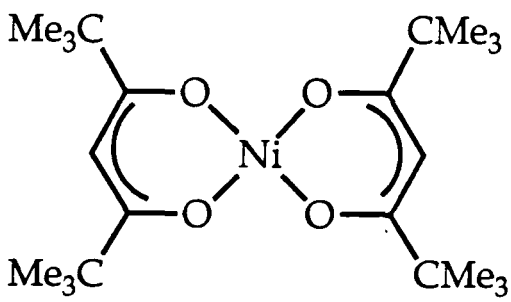
These three bidentate ligands render planarity of the $Ni(L\text{-}L)_2$ molecule sterically impossible and it should be stressed that except for the NiX_4^{2-} species a rigorously tetrahedral configuration cannot be expected.

For the vast majority of 4 co-ordinate nickel(II) complexes, planar geometry is preferred. This is a natural consequence of the d^8 configuration since the planar ligand set causes one of the d orbitals $d(x^2\text{-}y^2)$ to be uniquely high in energy and the eight electrons can occupy the other four orbitals but leave this strongly antibonding one vacant. In tetrahedral co-ordination on the other hand, occupation of antibonding orbitals is unavoidable.

Important examples of square complexes are yellow $Ni(CN)_4^{2-}$, red bis(dimethylglyoximato)nickel D and the red β-ketoenolate complex E.



D



E

Six co-ordinate Ni^{II} complexes may either have six identical ligands as in $[Ni(H_2O)_6]^{2+}$, $[Ni(NH_3)_6]^{2+}$ and $[Ni(en)_3]^{2+}$ or have the axial ligands different from the remaining four $[NiL_4L'_2]^{2+}$. The former form octahedral complexes

whilst the latter form as products of the reaction of square planar complexes with two additional ligands which may be solvent molecules.

1.5 Structural Features of Copper and Nickel Macrocyclic Complexes

1.5.1 Mononuclear copper species

The X-ray crystal structure[59] of the perchlorate salt of Cu(II) cyclam is shown in Figure 1.10. The four nitrogen donors lie in the same plane as the metal with all four Cu-N bonds of equal length (2.02 Å). A tetragonally distorted "octahedron" is completed by the oxygen atoms of perchlorate in the two axial positions (Cu-O = 2.57 Å). The ligand adopts an unstrained "trans III" configuration in which the six-membered chelate rings are in a stable chair form on opposite sides of the N_4 plane. The five-membered chelate rings adopt a stable gauche form.

In the crystal structure[60] of Cu(II) TETA Figure 1.11, the expected tetragonal distortion is also observed. However, in this case the equatorial positions are occupied by 2N and 2O donors, with Cu-donor bond lengths of 2.0 Å. The remaining two Cu-N bonds are elongated and occupy axial positions (2.428 and 2.367 Å). The strong interaction of the carboxylate oxygen is surprising in view of the usual preference of Cu^{2+} for N donors:

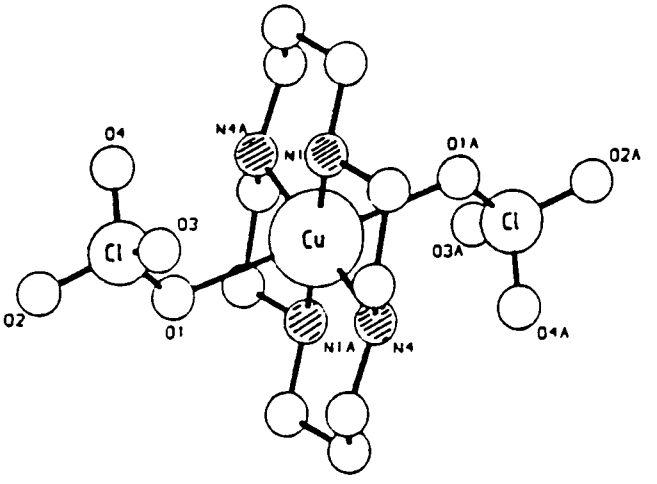


Figure 1.10

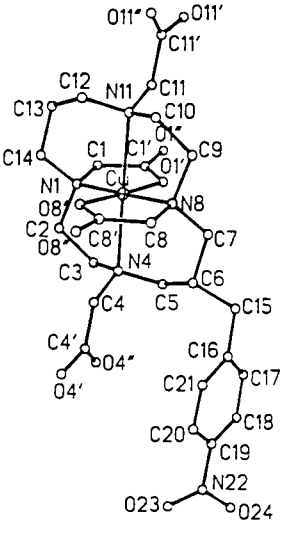


Figure 1.11

The X-ray structure[61] of the chloride salt of CuII[9]N_3 is shown in Figure 1.12 and the bromide salt[62] is given in Figure 1.13. Both contain discrete Cu(II) monomers with approximately square-pyramidal N_3Cl_2 ligand donor sets. The macrocyclic triamine is co-ordinated facially with N(2) and N(3) occupying equatorial positions and N(1) apically situated, chloride ions occupy the two remaining equatorial positions. The Cu atom is displaced 0.2 Å from the equatorial plane defined by N(2), N(3), Cl(1) and Cl(2) in the direction of N(1).

The most significant feature of this structure is the elongated Cu-N(1) bond, a feature which is not common to metal structures containing macrocyclic triamine ligands.

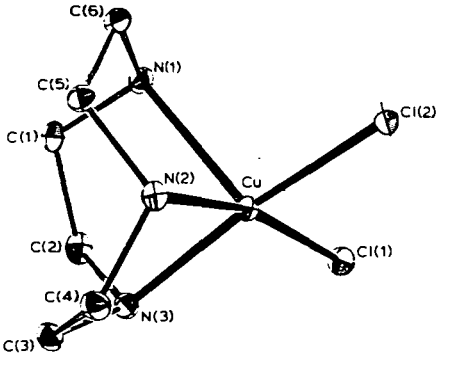


Figure 1.12

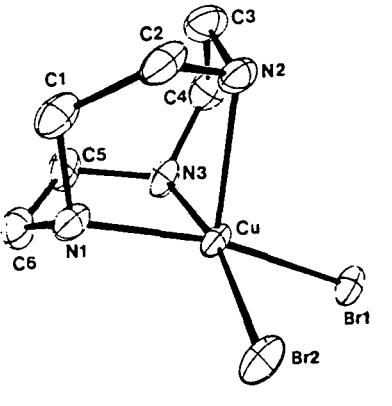


Figure 1.13

The structure of the [Cu(TCTA)]$^-$ anion is shown in Figure 1.14. The copper(II) ion is six-co-ordinated by three nitrogens and three oxygens of the chelate ligand. A distorted-pseudo-prismatic geometry of the CuN_3O_3 polyhedron is characterised by a twist angle of 13.3° within the structure.

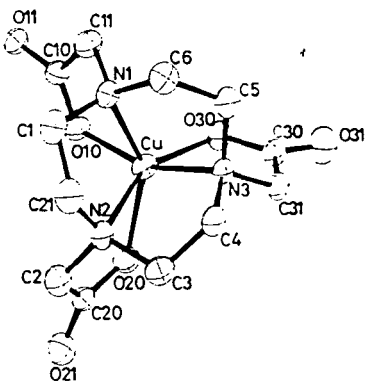
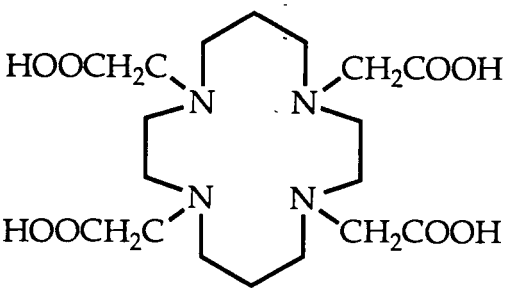


Figure 1.14

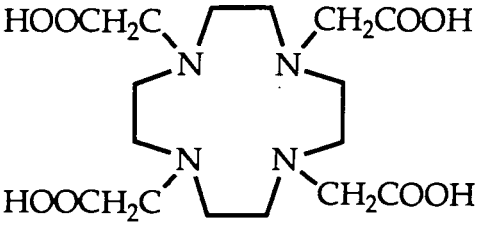
Bond distances within the $[9]N_3$ fragment of co-ordinated TCTA are very close to those reported for $(Cu[9]N_3)Cl_2$[61] and $(Cu[9]N_3)Br_2$[62], stressing again the rigidity of this structural unit. The Cu-N and Cu-O bond distances vary considerably showing that the CuN_3O_3 polyhedron is highly distorted.

1.5.2 Binuclear copper species

Kaden[63] has reported two interesting crystal structures of binuclear Cu^{2+} complexes. It is known that transition metals and tetraazacycloalkane tetra-acetic acids (H_4L) form species with different stoichiometry, e.g. $M(H_2L)$, $M(HL^-)$, $M(L)^{2-}$ or $M_2(L)$[9,18] and it is difficult to deduce the structure of these species from spectra alone. Although these binuclear species are not known in solution they can be easily prepared by mixing the ligand with a two-fold excess of the metal ion. The structures of the two binuclear Cu^{2+} complexes with 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-acetic acid (H_4DOTA) and with 1,4,8,11-tetraazacyclotetradecane-N,N′,N″,N‴-tetraacetic acid (H_4TETA) of the type Cu_2L have now been determined by X-ray crystallography.

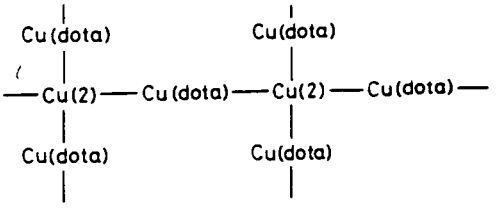


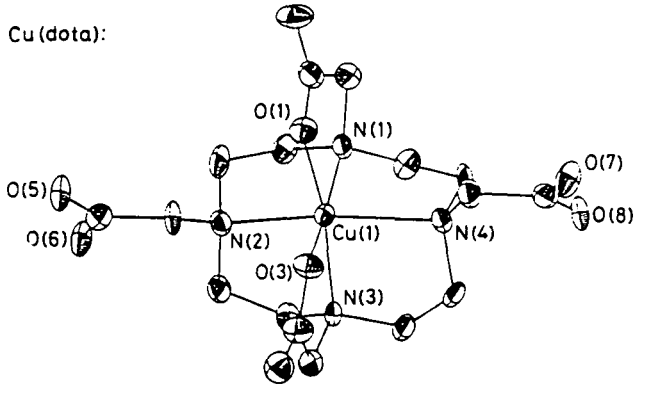
TETA



DOTA

The ligand DOTA gives a 2:1 Cu^{2+} complex in which the two Cu^{2+} ions are in completely different environments, Figure 1.15.





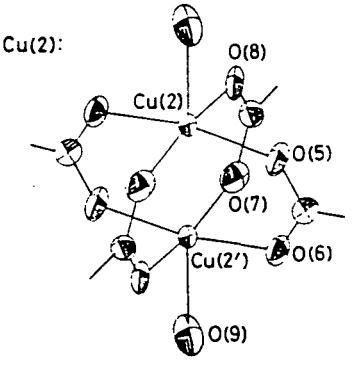


Figure 1.15

Cu(1) is co-ordinated by two carboxylate oxygen and four nitrogen atoms of the macrocycle which is folded to give a cis-octahedral geometry. The pseudo-octahedral geometry is distorted since the axial Cu(1)-N bonds (2.326 and 2.298 Å) are distinctly longer than the equatorial Cu-N bonds. This same geometry is also found in the mononuclear complex $Cu(H_2DOTA)$. The two carboxylates not bound to Cu(1) are used to co-ordinate to Cu(2). This resulting structural feature is the same as that found in many dicopper tetra carboxylates. Two Cu(2) ions are bridged by four carboxylate groups which come from four different macrocycles, and each Cu^{2+} additionally binds a water molecule. The Cu(2)-Cu(2′) distance of 2.652 Å is almost the same as in $Cu_2(acetate)_4$(2.65 Å). So the Cu(DOTA) complex is composed of two structural elements which have been found previously in other complexes.

For the binuclear complex of TETA the situation is very different (Figure 1.16). Both Cu(1) and Cu(2) are in similar environments, being co-ordinated by 2 amino nitrogens, 2 carboxylate oxygens and by an additional axial oxygen atom. It results in a square pyramidal geometry where Cu(1) and Cu(2) are out of the N_2O_2 plane by 0.17 Å and 0.22 Å respectively. Both Cu^{2+} ions are different in that one is bound to a water molecule O(9) and a carboxylate group O(5) respectively. The distances for the two Cu^{2+} ions co-ordinated in the same macrocycle are 4.78 Å and 4.88 Å respectively for Cu(1)-Cu(1′) and Cu(2)-Cu(2′) and for two Cu^{2+} ions in different macrocycles the distance is 5.53Å and hence some antiferromagnetic interaction is expected. These results show that a small change in ring size from a 12-DOTA to 14-TETA membered ring strongly influences the structure of the binuclear complexes of Cu^{2+}.

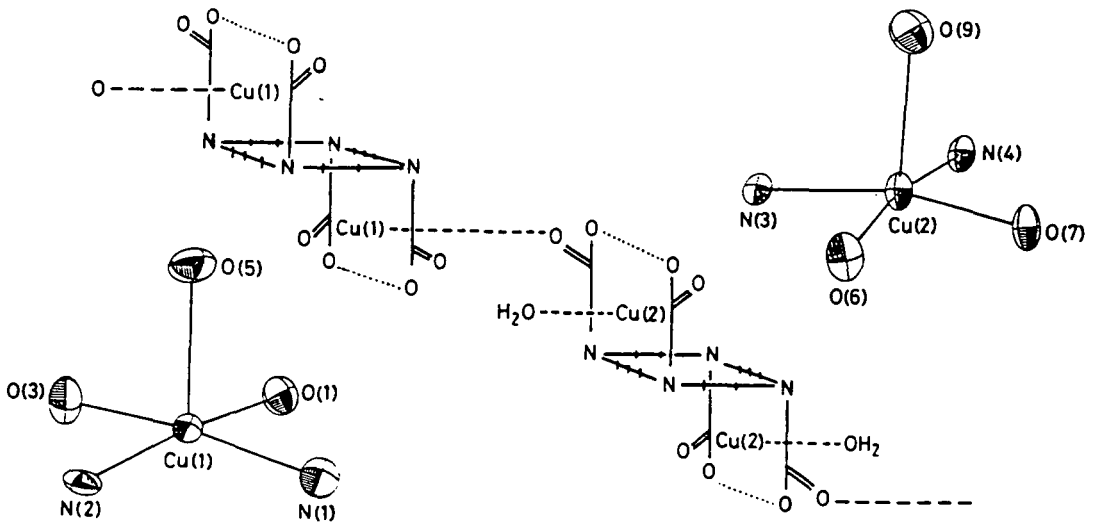


Figure 1.16

1.6 Factors Affecting the Binding Properties of Macrocycles

1.6.1 Introduction

The factors which determine the binding properties of macrocycles[64] include:

1. The type of binding site in the ring, e.g. O, N, S, carbonyl oxygen.
2. The number of binding sites in the ring.
3. The relative disposition of the binding sites.
4. The relative sizes of the ion and the macrocyclic "cavity".
5. Steric hindrance in the ring, including torsional strain, eclipsing or transannular interactions.
6. The solvent and the extent of solvation of the ion and the ligand.
7. The electrical charge of the ion.

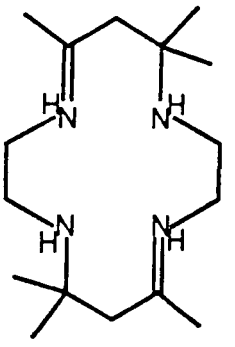
With so many variables there is considerable scope to design macrocycles which match the requirement of individual metal ions.

Cyclic polyethers bind readily to the alkali and alkaline earth metals to form relatively stable complexes but show little tendency to bind transition metal ions. However, when the oxygen donor atoms are replaced by softer nitrogen or sulphur atoms then more stable macrocyclic complexes with transition metal ions are readily formed.

The transition metal cations generally have larger and more polarisable valence shells. They are "softer" in nature and more readily bind with "softer" donor atoms forming dative bonds which show more covalent character in contrast to the ionic bonding found between the alkali and alkali earth metals and "hard" oxygen donor atoms.

Macrocyclic complexes of this type are found in nature, examples being the iron- and magnesium-porphyrins of haemoglobin and chlorophyll and the cobalt corrin complex of vitamin B_{12}. Some of the earliest synthetic macrocycles were the tetradentate nitrogen donor ligands of a similar type 75 and 76.

To fully encircle a first row transition metal ion, a macrocycle consisting of a thirteen to sixteen[65,66] membered ring is required, with spacing between the atoms such that five-, six- or seven-membered chelate rings are formed with the metal ion. Smaller rings, e.g. $12N_4$ can only be accommodated if the macrocycle folds and does not completely encircle the metal ion on co-ordination.



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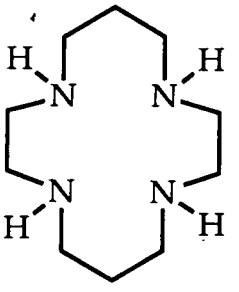
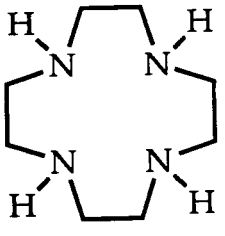
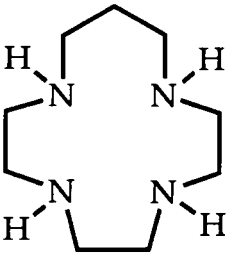


76 $14N_4$ "cyclam"

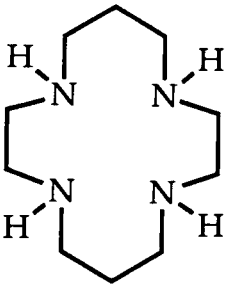
A list of common tetraazamacrocycles is given below 77 - 82.



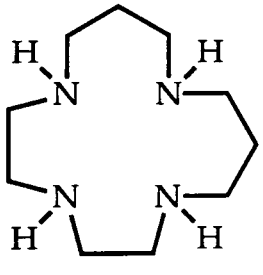
77 $12\text{-}N_4$



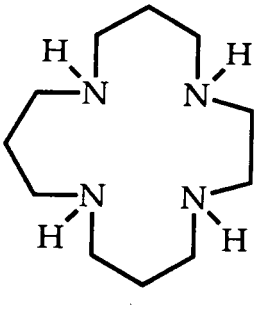
78 $13\text{-}N_4$



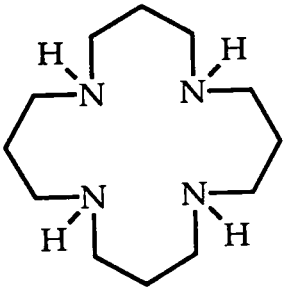
79 $14\text{-}N_4$



80 $14'\text{-}N_4$



81 $15\text{-}N_4$



82 $16\text{-}N_4$

The highest stability constants for these transition metal complexes are generally found when there is a good match between the size of the cation and the "cavity" imposed by the macrocycle, allowing optimum metal-donor bond length. A good example of this is where the stability constant of the copper(II) complex of tetraazamacrocyclic ligands which reaches a maximum at $[13]N_4$ and $[14]N_4$ and falls off rapidly with smaller and larger ring sizes.

1.6.2 Chelate and macrocyclic effect

The term chelate effect[67] refers to the enhanced thermodynamic stability of a complex system containing chelate rings compared to a similar system without such rings. An example of this is as follows:

$$Ni^{2+}(aq) + 6\ NH_3(aq) \longrightarrow Ni(NH_3)_6^{2+} + aq \quad \log K = 8.61$$

$$Ni^{2+}(aq) + 3\ en(aq) \longrightarrow Ni(en)_3^{2+} + aq \quad \log K = 18.28$$

The system $Ni(en)_3^{2+}$ in which the three chelate rings are formed is found to be nearly 10^{10} times more stable as that in which no such ring is formed. Although the chelate effect is not usually so pronounced as this, such an effect is very general.

An understanding of this is found when considering thermodynamic relationships:

$$\Delta G^\circ = -RT\ln K$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

As lnK increases so ΔG° becomes more negative. A more negative ΔG° can result from either making ΔH° more negative or making ΔS° more positive. This can be shown by a very simple case in Table 1.1 relating the addition of 4 x CH_3NH_2 against that of 2 x $NH_2CH_2CH_2NH_2$, e.g.

$$Cd^{2+}(aq) + 4CH_2NH_2(aq) \longrightarrow Cd(NH_2CH_3)_4^{2+}aq \quad logK = 6.52$$

$$Cd^{2+}(aq) + 2H_2NCH_2CH_2NH_2(aq) \longrightarrow Cd(en)_2^{2+} + aq \quad logK = 10.6$$

Ligand	ΔG(kJ mole^{-1})	ΔH(kJ mole^{-1})	ΔS(kJ mole^{-1} deg^{-1})
4 CH_3NH_2	-37.2	-57.3	-67.3
2 en	-60.7	-56.5	+14.1

Table 1.1

In this instance the enthalpies make a favourable contribution and are very similar, but the chelate effect here can be traced entirely to the differences in the entropies of complexation.

Another way to solve the problem is to visualise one end of a chelate ligand attached to the metal ion. The other end of it cannot move very far away, and the probability of it too, becoming attached to the metal ion is far greater than another independent molecule becoming attached to it having access to a much larger volume of the solution.

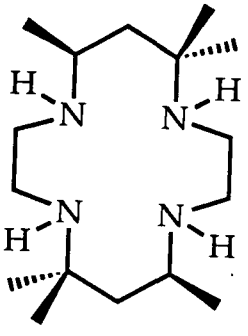
1.6.3 The macrocyclic effect

Macrocyclic complexes are, almost without exception, more stable thermodynamically and kinetically than their open-chain analogues. This is

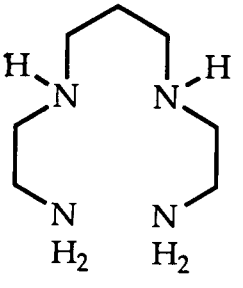
called the "macrocyclic effect" by its discoverers Margerum and Cabbiness[68], and is a more profound feature of macrocyclic complexes than simply an increased "chelate effect" arising from the presence of an additional chelate ring.

Much calorimetric and spectroscopic work has been done to investigate this phenomenon and it is thought that this enhanced stability is due to a favourable enthalpy or entropy or a combination of both.

For example, Margerum and Cabbiness[68] reported that the red copperII complex of 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane, or "tet-a", was 10^4 times more stable than the copperII complex of an open chain analogue "2,3,2-tet", which has a similar sequence of chelate rings.



"tet-a"



"2,3,2-tet"

Complex	log K
$Cu(2,3,3\text{-tet})^{2+}$	23.9
$Cu(\text{tet-a})^{2+}$ red*	28

Similarly, Margarum[68,69] found that the enthalpy term was dominant when the formation of the Ni(II) complex of the [14]-membered tetraamine macrocycle "cyclam" and its non-cyclic analogue are compared. However, for

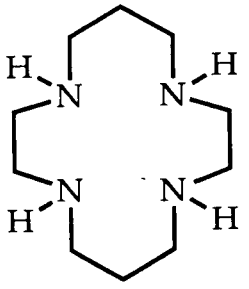
other complexes, the entropy term is primarily responsible for the increased thermodynamic stability, Table 1.2.

Complex	log K	ΔH/kcal mole^{-1}	ΔS cal K^{-1} mole^{-1}
Ni(2,3,2-tet)$^{2+}$	15.8	-13.0 $\pm$ 0.6	7.4
Ni(cyclam)$^{2+}$	22.2	-19.4 $\pm$ 0.1	-2

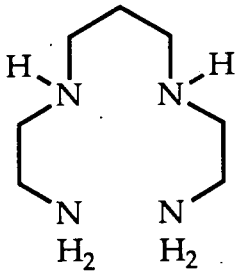
Table 1.2

This "macrocyclic effect" and its contributory effects of thermodynamic and kinetic stabilities is well illustrated by referring to the parent $14N_4$ cycle "cyclam" and its open-chain analogue 1,4,8,11-tetraazaundecane (2,3,2-tet) as examples. Kimura and Kodama[70] reported that the copper complex of cyclam was 2,000 times more stable than that of the linear tetraamine, Table 1.3.

* The blue copper(II) complex of CuII "tet-a" is not as stable thermodynamically or kinetically as red CuII "tet-a" and will rapidly convert to the red complex in aqueous solution.



cyclam



2,3,2-tet

Complex	log K	ΔH/kcal mole^{-1}	ΔS cal K^{-1} mole^{-1}
Cu(cyclam)$^{2+}$ *	27.2	-30.4	22.4
Cu(2,3,2-tet)$^{2+}$	23.9	-27.7	16.5

Table 1.3 (25°C, I = 0.2 mole dm^{-3})

They reported that the "macrocyclic effect" for Cu(II)-cyclam was due to a combination of favourable enthalpy (ca 60%) and entropy (ca 40%) contributions.

Hinz and Margerum[69] explained the enthalpy contribution for Cu(II) cyclam in terms of decreased free ligand solvation; less energy being required for desolvation prior to complexation. Fabrizzi and Paoletti[71,72] prefer to

* Cu^{II} cyclam is thought to be a mixture of two isomers, a blue isomer and a more thermodynamically more stable red isomer. The reported formation constant is a weighted average of the values for the individual isomers.

explain the effect in terms of the conformation of the free ligand being perfectly organised for copper complexation. In the acyclic system, energy must be expended for the required conformational change. Indeed this represents the popular notion of a relatively rigid macrocycle cavity (cyclam) accommodating a metal ion of "best-fit" with strong planar Cu-N bonds and a large heat of formation ($-\Delta H$).

The only conclusion to draw is the nature of the macrocyclic effect, i.e. the relative importance of the enthalpy and entropy of complexation, varies according to the type of cation and ligand involved. For example, the highly solvated "hard" alkali metal ions, e.g. Li^+ tend to have dominant entropic contributions associated with the loss of solvation molecules upon complexation, whereas larger softer cations tend to have dominant enthalpic contributions associated with metal donor atom bond energies.

1.6.4 Kinetic effect

Another feature of the "macrocyclic effect" is the kinetic inertness of macrocyclic complexes, particularly towards acid-catalysed dissociation. In fact it is so inert that decomplexation only occurs to an appreciable extent in very strong (5-6M) acid[73]. For instance, the dissociation of copper from tetraamines occurs in two steps for cyclam but one step for the linear tetraamine 1,5,8,12-tetraazadodecane (3,2,3-tet):

$$Cu(cyclam)^{2+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu(Hcyclam)^{3+} \xrightarrow{k_2} Cu(H_4cyclam)$$

$$Cu(3,2,3\text{-tet})^{2+} \xrightarrow{k_1} Cu^{2+}(H_4tet)^{4+}$$

For $Cu(cyclam)^{2+}$, the cleavage of the first Cu-N bond requires cleavage of two stable chelate rings (Figure 1.17A) and proceeds via a protonation pathway. Similar cleavage in $Cu(3,2,3\text{-tet})^{2+}$ requires distortion of a single chelate ring only (Figure 1.17B) and proceeds via a solvation pathway.

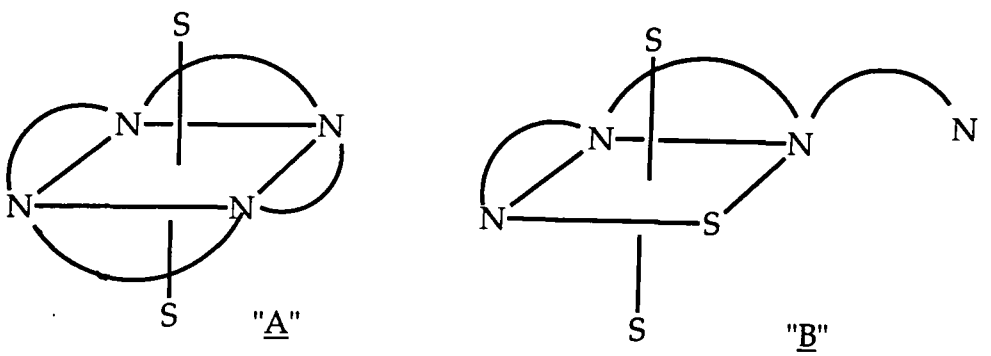


Figure 1.17 Species resulting from first Cu-N bond cleavage.

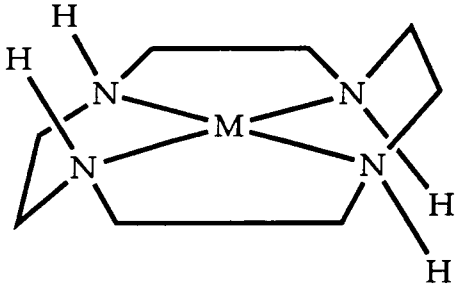
So the cleavage of the first Cu-N bond of $Cu(3,2,3\text{-tet})^{2+}$ is far more rapid (10^4-10^5 times) than for $Cu(cyclam)^{2+}$. As the solvation of A is hindered by the steric constraints of the macrocyclic ligand, k_{-1} is larger than k_2 and the cleavage of the second Cu-N bond is the rate determining step for $Cu(cyclam)^{2+}$.

1.6.5 "Cavity"-size correlations

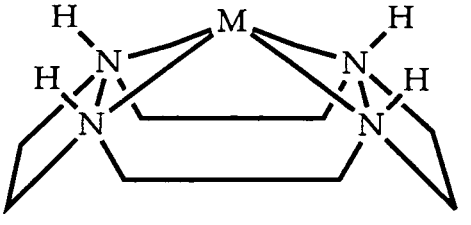
In previous sections, examples have been described where there has been reasonable correlation between "cavity"/cation size and the observed

stability constant of the complex. However, this is not always the case. Macrocyclic ligands, particularly the larger rings can be flexible and can adapt their conformations to accommodate cations of different size.

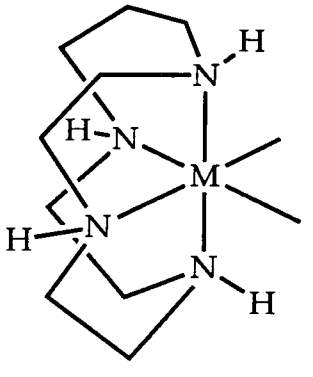
As discussed earlier, the copper(II) complexes of the tetraamine series 77-82 shows good cavity size correlation and maximum stability is achieved with $14N_4$ cyclam. However, studies by Hancock[74] have shown that the large cations Cd^{2+} and Pb^{2+} actually form more thermodynamically stable complexes with the smaller $12N_4$ ring. This is attributed to the fact that the macrocycle can adopt different conformations, Figure 1.18.



Trans-III



Trans-I

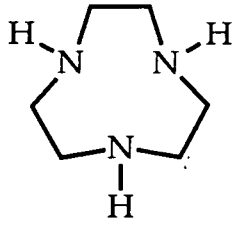


Cis-V

Figure 1.18 Conformers of the $12N_4$ macrocycle.

The trans-III isomer allows the metal to sit inside the ring with square planar co-ordination geometry. The trans-I isomer allows a slightly larger cation to sit above the plane of the ring and the cis-V isomer allows yet larger cations to co-ordinate facially (e.g. Cd^{2+} and Pb^{2+}). In this case the overall stability is determined by the relative stabilities of 5 and 6 membered chelate rings formed with the metal. For large cations the 5 membered chelate is preferred[74], so $12N_4$ gives the highest stability complex.

Smaller rings, e.g. 1,4,7-triazacyclononane 83 and 1,4,7-triazacyclododecane 84 have more rigid structures and the lone pairs are often exposed on one face of the cycle. Hence, many of the complexes are observed where the metal ion sits on top of the macrocycle, e.g. Cu-[9]N_2S^{2+} (Figure 1.19) or even sandwiched between two macrocycles, e.g. Ni-([10] $N_3)_2^{2+}$, (Figure 1.20).



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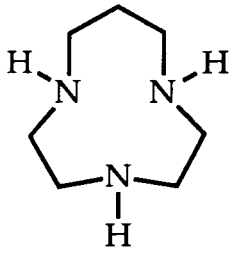

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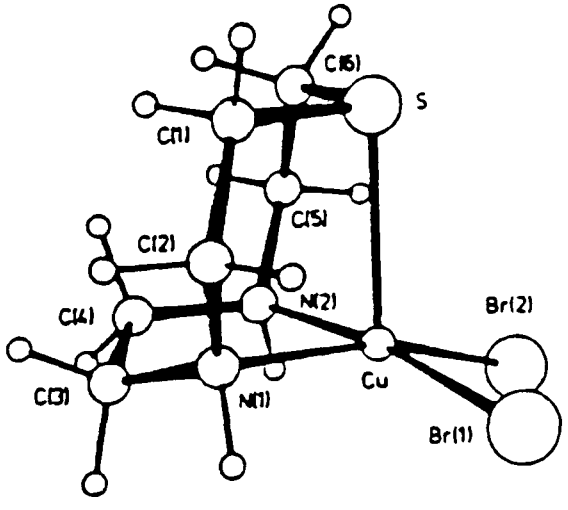


Figure 1.19 Crystal Structure of $(Cu\text{-}[9]N_3S)(Br)_2$

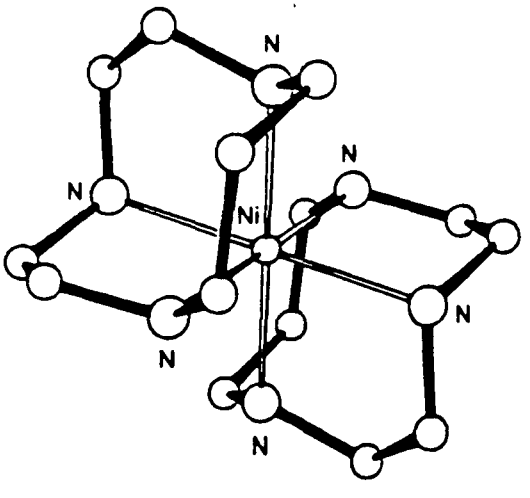


Figure 1.20 Crystal structure of Ni-$([10]N_3)_2^{2+}$

1.6.6 Thermodynamic stabilities of copper and nickel macrocyclic complexes

The stability constants of the copper complexes of a series of macrocyclic ligands is given in Table 1.4[70b].

With increasing ring size, the stability of copper-tetraamine complexes reaches a maximum value (29.1) for 1,4,7,10-tetraazacyclotridecane "$13N_4$" and then decreases again. It is noteworthy that the copper complex of iso-cyclam is significantly less than Cu(II) cyclam. The unsymmetrical arrangement of 5- and 6-membered rings introduces steric strain into the conformation of the bound ligand[72].

Ligand	log K
Cu - $12N_4$	24.8
Cu - $13N_4$	29.1
Cu - $15N_4$	24.4
Cu - cyclam	27.2
Cu - isocyclam	22.4

Table 1.4

The stabilities of the nickel complexes of (2,2,2-tet), (2,3,2-tet) and cyclam are shown in Table 1.5. There is a 10^6 fold increase in the stability of the nickel(II) complex of cyclam compared to the nickel(II) complex of "2,3,2-tet"[47], and both complexes are square planar.

Complex	log K	-ΔH/kcal mole^{-1}	ΔS cal K^{-1} mole^{-1}
Ni (2,2,2-tet)$^{2+}$	13.8	14.0	16.0
Ni (2,3,2-tet)$^{2+}$	15.8	13.0	7.4
Ni (cyclam)$^{2+}$	22.2	19.4	-2.0

Table 1.5

1.6.7 Structurally reinforced ligands

It is popular to ascribe the enhanced stability of macrocyclic complexes to the "fit" between the metal ion diameter and the size of a relatively rigid cavity in the centre of the macrocycle. Although this may be a valid concept for explaining the selectivity of crown-ether ligands for alkali metal ions[75], the correlation between stability and "fit" is less certain for tetramine macrocycles and is metal-dependant.

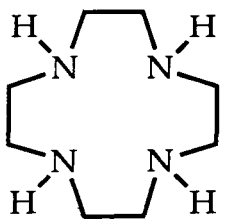
Previously[76], it has been shown that the formation constants of tetraazamacrocycles such as L_4 and L_6 do not support the idea of size-match selectivity.

In order to observe genuine size-metal selectivity, it is necessary to make the macrocycle ligand more rigid, so that the metal ion is forced to co-ordinate lying in the macrocyclic cavity. The synthesis and properties of the complexes of ligands L_4 to L_8 and a range of metal cations were reported by Hancock[77] to study this effect. The formation constants of complexes were determined for Cu^{II}, Ni^{II}, Zn^{II}, Cd^{II} and Pb^{II} with these ligands and are given in Table 1.6.

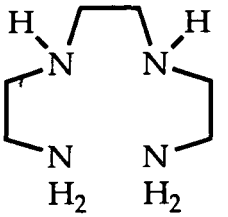
log K_1					
	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}
L_8	14.3	21.50	10.95	10.07	11.71
L_7	4.68	11.91	5.81	4.51	7.1
log K (mac) (L_7,L_8)	9.6	9.6	5.1	5.6	4.7
L_4	14.0	23.3	16.2	14.3	15.9
L_5	12.1	20.1	12.0	10.6	10.4
log K (mac) (L_4,L_5)	1.9	3.2	4.2	3.7	5.5
Ionic Radius Å	0.49	0.57	0.74	0.95	1.18

Table 1.6

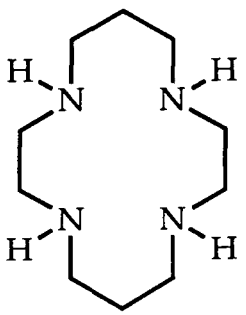
The thermodynamic property of the "macrocyclic effect", log K(mac), is given by the difference between log K_1 of the macrocycle complex and log K_1 of its acyclic analogue. From Table 1 log K(mac) for L_4 shows a tendency to increase with increasing size of metal ion. This is opposite to what is expected from size-match selectivity as the cavity in L_4 is too small for low-spin Ni^{II} which is the smallest metal ion used. This indicates possible out of plane co-ordination for the larger cation similar to the open-chain polyamines. However, log K(mac) for L_5 is largest for the very small metal ions, Cu^{II} and low spin Ni^{II} and smaller for the larger metal cations. This result is expected from the basis of size-match selectivity.



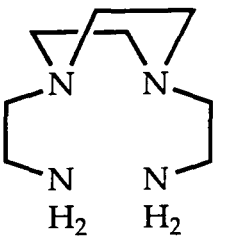
L4



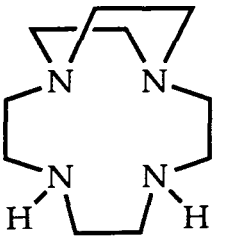
L5



L6



L7



L8

Ligands L4 - L8

1.6.8 Ligand rigidity and selectivity

Besides size-match selectivity, Hancock[78] also reports of a second idea, which appears to be widely accepted, that if a macrocycle is sufficiently rigid it will compress a too-large metal ion. This would account for some high ligand field strengths found in the complexes of N-donor macrocycles such as with Ni^{II} and Co^{III}. The ligand (1,4-C_2)-12-aneN_4, L_7, is of particular interest. Models show that there is very little space in the cavity of (1,4-C_2)-12-aneN_4 and it would be a good example of showing a compression induced increase in LF stength and its ligand rigidity would make out of plane metal ion co-ordination highly strained. This ligand should thus be able to show genuine size selectivity. Hancock[78] reported a formation study on the complexes of (1,4-C_2)-12aneN_4 with Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} providing a range of metal ion sizes from the very small low-spin Ni^{II} ion to the very large Pb^{II} ion, the results of which are shown in Table 1.7.

		L_7	L_8	log K (mac)	L_5	L_4	log K (mac)
log K_1	Ni^{2+}	4.68	14.3	9.6	12.1	14.4	2.3
	Cu^{2+}	11.91	21.50	9.6	20.1	23.3	3.2
	Zn^{2+}	5.81	10.95	5.1	12.0	16.2	4.2
	Cd^{2+}	4.51	10.07	5.6	10.6	14.3	3.7
	Pb^{2+}	~7.1	11.71	~4.7	10.4	15.9	5.5

Table 1.7

The formation constants for complexes of (1,4-C_2)-12-aneN_4 show very considerable stability especially so in comparison to the complex of its open-chain analogue L_7. The size of the macrocyclic effect, log K(mac), for Cu^{II} and Ni^{II} is 9.6 log units for complexes of L_8 relative to L_7, is by far the largest known value compared to typical values of 3-6 orders of magnitude for other complexes. An important aspect of the log K(mac) values in Table 1.7 is the way they vary with the metal ion size. For 12-aneN_4 the log K(mac) values tend to be smaller with small metal ions and larger with large metal ions showing that this ligand is not able to exert any selectivity in favour of small metal ions. On the other hand, log K(mac) for (1,4-C_2)-12-aneN_4 is very large for small metal ions but falls off rapidly as metal ion size increases. This indicates that the rigidity of a structurally reinforced ligand enables it to be more selective in its metal ion co-ordination.

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CHAPTER 2

MACROCYCLES TO BIND TO Cu(II) AND Ni(II)

2.1 Introduction

The fourteen membered tetraazamacrocycle 1,4,8,11-tetraazacyclotetradecane, cyclam, is a much studied and versatile ligand in inorganic co-ordination chemistry[1,2]. The basic ligand skeleton can be selectively functionalised at both carbon[2,3] and nitrogen[4,5] and permits the study of this system in catalysis and in metal ion discrimination. Although there were isolated examples of N-functionalised derivatives of cyclam 1, no general synthetic routes had been developed at the outset of this work other than the use of the tritosylamide 2 for the preparation of some mono-functionalised derivatives.

In this work, a set of straightforward syntheses, often from the parent 1, has been devised for the preparation of any given mono, di or tri-substituted derivative of cyclam.

2.2 Selective Functionalisation of Macrocyles

2.2.1 Regioselective tosylation of 1,4,8,11-tetraazacyclotetradecane

The main advantage of N-functionalised cyclam derivatives is their ease of synthesis from cyclam itself, which is commercially available. Reaction of cyclam with a two fold excess of p-toluene sulphonyl chloride in dichloromethane and in the presence of triethylamine, (using a method similar to that of Fabrizzi[5]) proceeds to give a mixture of mono, di and tri-substituted cyclam wherein the tri-substituted derivative is the major product. Column chromatography of the reaction mixture followed by recrystallisation proceeds cleanly to give the tri-N-tosylamide in reasonable yield.

The formation of "ditosyl cyclam" and other di-substituted derivatives of cyclam (such as di-N-alkylated derivatives of cyclam) is intrinsically more difficult as it requires the selective formation of one of the three constitutional isomers: the [1,4], [1,8] or [1,11] derivative. Reaction of cyclam with less tosyl chloride (1.5 equivalent) in dichloromethane and triethylamine at 0°C gives the two constitutional isomers 3 and 4 in reasonable yield in the ratio of 8:1. These isomers are separated from each other and the tritosylamide 2 formed concomitantly, by flash chromatography on silica gel. The constitution of these isomers was established spectroscopically using ^{1}H and ^{13}C NMR methods, and in the case of 3 following the crystallographic analysis of a derivative, (as shown on page 116).

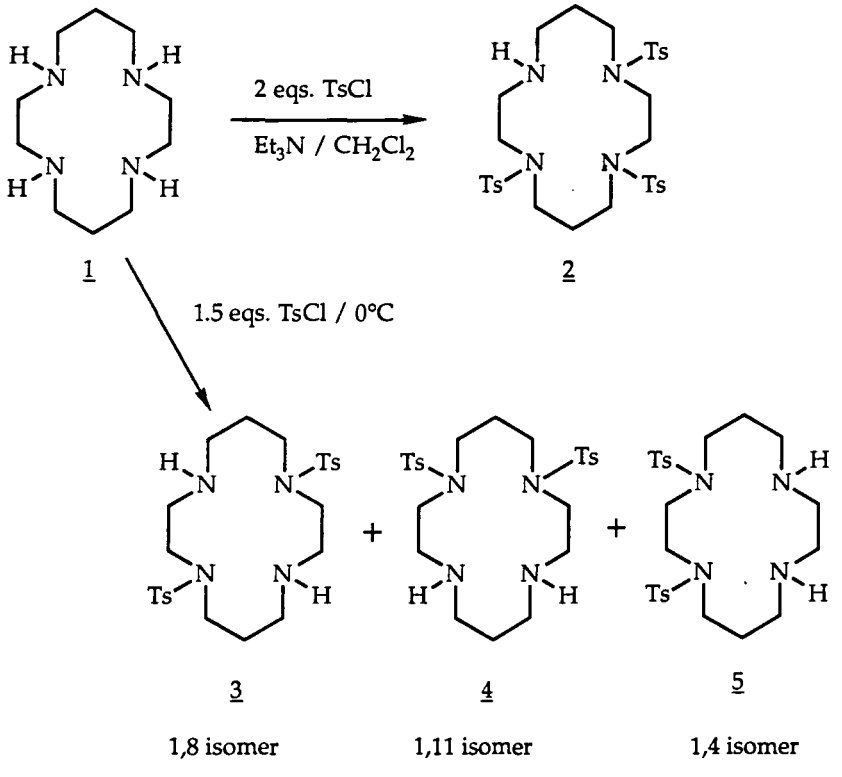
Using ^{13}C NMR the 1,11 derivative 4, may be distinguished from the 1,4 isomer 5 by virtue of its symmetry: for example the C-6 and C-13 methylene groups are homotopic and isochronous for 5 but are constitutionally heterotopic in 4 δ_C ($CDCl_3$) = 29.0, 28.4 ppm, δ_H ($CDCl_3$) = 1.96, 2.02 ppm). There was no success in attempts to isolate 5, the 1,4 derivative presumably as it is formed in very low yield (≤ 3.5%), under these reaction conditions because of steric inhibition of proximate sulphonylation.

The mono-tosylamide of cyclam appears to be formed as a by-product of these reactions as indicated by thin layer chromatography (R_f (SiO_2, 10% MeOH, 90% CH_2Cl_2): 0.25). However, the yield of it (< 5%) was too low to be of any significant synthetic use.

When using less tosyl chloride in relation to cyclam it appears that all three isomers of ditosyl cyclam are formed more readily, although their

separation is less than easy! Also at lower ratios of tosyl chloride to cyclam the formation of the monosubstituted compound appears to be more prominent, as expected.

Either slow addition of reactants or reaction at lower temperature (4°C) appears to encourage the formation of the 1,8 isomer. Using gradient elution with an increasing concentration of methanol in dichloromethane (2→5%) in the flash chromatography the separation of the three constitutional isomers was achieved to good effect, (Scheme 2.1).



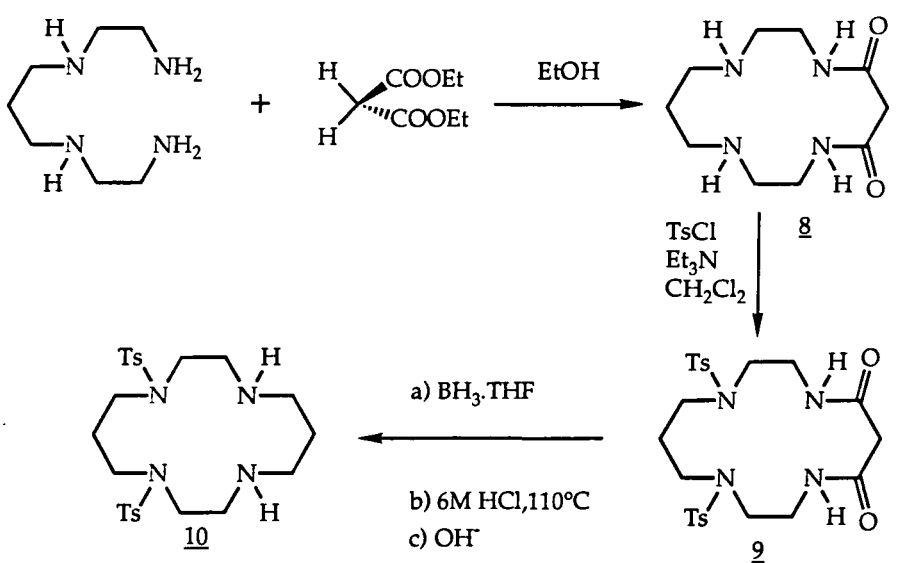
Scheme 2.1

The secondary amine group in 2 was now able to be mono-alkylated with a suitable electrophile, eg. chloroacetic acid. Subsequent removal of the tosyl group (HBr/HOAc and phenol) would yield a mono-functionalised cyclam derivative suitable for binding to metal ions.

The regioselective preparation and separation of the isomeric forms of tosylated cyclam is an important point as these compounds provide suitable building blocks for subsequent functionalisation and synthesis.

2.2.2 Alternative stereospecific routes

A simpler and higher yielding route to the 1,11 derivative 4 involves the intermediacy of the dioxocyclam 8, obtained by the condensation of diethyl malonate 6 with 1,4,8,11-tetraazaundecane 7 in dry ethanol under reflux for two weeks. The product which was formed as a precipitate was purified by chromatography on silica (usual conditions). A colourless solid was obtained in a typical low cyclisation yield of 20%. Tosylation of 8 via p-toluene sulphonyl chloride in methylene chloride and triethylamine was found to yield a white precipitate of the ditosylamide again being purified by column chromatography. Reduction with BH_3.THF afforded the ditosylamine, 10, in good yield as a clear oil. This ditosylamine may then be used for the synthesis of any 1,11-disubstituted derivative (Scheme 2.2).



Scheme 2.2

2.3 Synthesis of N-functionalised [14]N_4 Cyclam

2.3.1 Enhancing Macrocyclic Lipophilicity

As discussed earlier, the enhanced lipophilicity of a dialkylated macrocycle may well encourage its metal complexes to be more easily absorbed by roots in plants and hence less of the complex may be "drained away" by rainfall. Should this be so this feature should markedly reduce the required dose of the applied metal complexes and promote the effectiveness of trace metal uptake. To this effect the simplest lipophile to be introduced would be the methyl group.

2.3.2 Synthesis of dimethyl [14]N_4 cyclam 15

Reaction of 1,8-trans-ditosyl cyclam in acetonitrile in the presence of 2.1 equivalents of anhydrous sodium carbonate and 2.1 equivalents of methyl iodide led to formation of a white precipitate of sodium iodide over 18 hours.

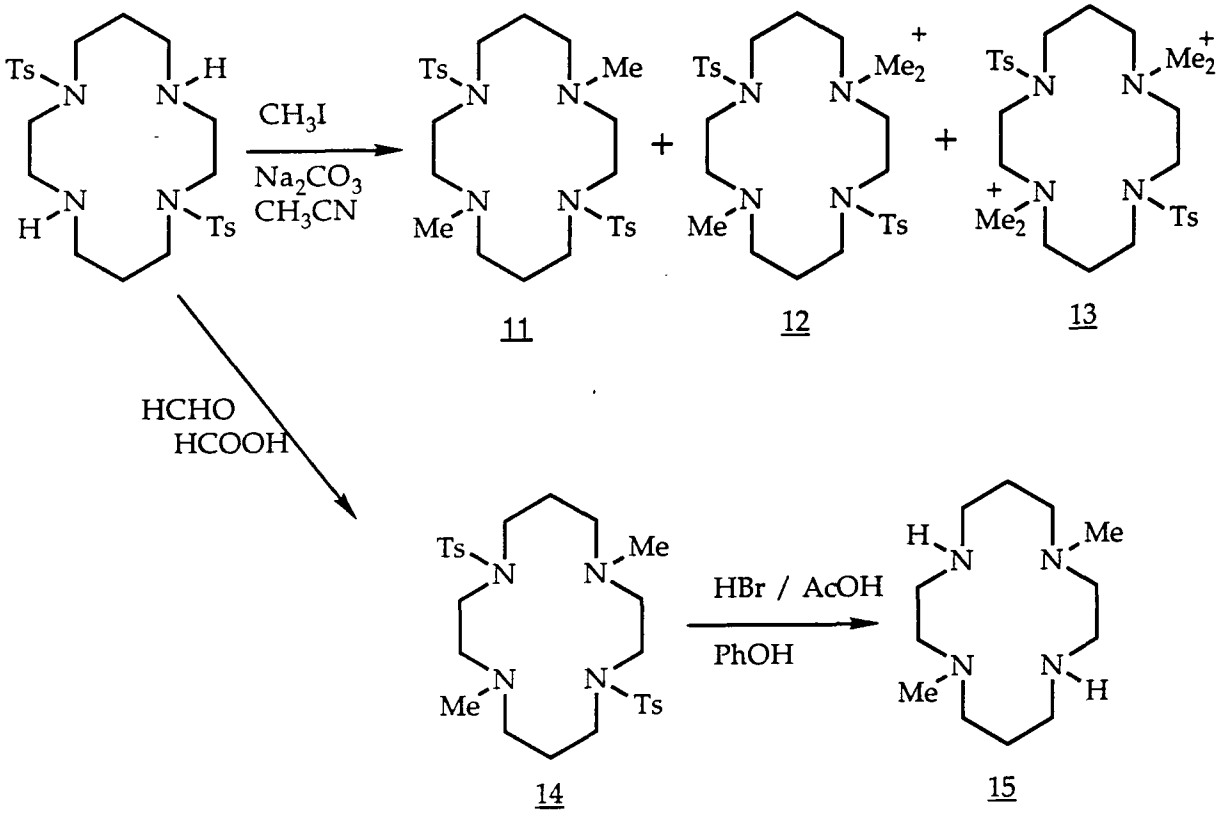
Subsequent analysis by t.l.c., ^{1}H NMR and DCI mass spectrometry indicated that a mixture of methylated products had been formed. It was apparent from mass spectroscopic measurements that quaternisation had occurred and the monomethyl ammonium (m/e 551) and dimethyl ammonium (m/e 566) salts had been formed along with the desired trans dimethyl analogue (m/e 536). The quaternary methyl ammonium salts were distinguished as a baseline spot by thin layer chromatographic analysis.

Demethylation was attempted with triphenyl phosphine in methanol under reflux for about 30 minutes which appeared, by t.l.c., to have given some degree of reaction. The yield was too low to be of synthetic value. Obviously the iodide ion is too good a leaving group and the reaction

conditions are too forcing and hence an alternative methylation method was sought.

The Eschweiler-Clarke[6] method uses formic acid and formaldehyde and has the advantage that after the reaction has been carried out the reagents can be very easily removed from the reaction mixture. The reaction proceeded in high yield to give the dimethyl amine 14, isolated as a clear oil, (Scheme 2.3).

This product was deemed sufficiently pure without recrystallisation as determined by tlc (single spot), 250 MHz ^{1}H NMR and DCI mass spectrometry. Attempted detosylation was now effected by refluxing 12 in 45% w/v HBr/HOAc in the presence of phenol to yield a light coloured precipitate. (Presumably the lipophilic methyl groups encourage dissolution of product).



Scheme 2.3

Further HBr/HOAc was added and after an additional 24 hours reflux the precipitate was filtered off. Proton and ^{13}C-NMR analysis confirmed the complete removal of tosyl groups.

2.3.3 Synthesis of methyl butyl [14]N_4 cyclam 18

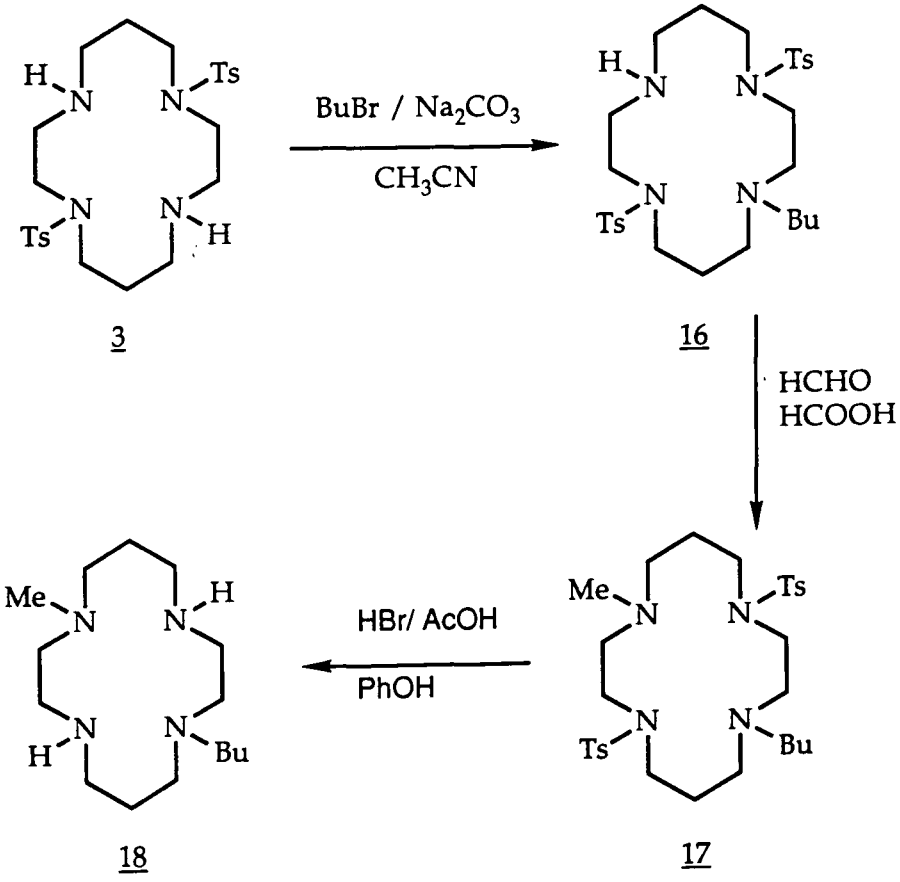
With the encouraging results of methylating ditosyl cyclam via the Eschweiler-Clarke method it was decided to enhance the lipophilicity of the macrocycle by attempting to form a longer chain analogue using butyl groups.

The synthesis of the N-functionalised derivative was accomplished by the careful and gradual addition of 2.1 equivalents of n-butyl bromide to a suspension of ditosyl cyclam and 2.1 equivalents of anhydrous sodium carbonate in acetonitrile. Overnight boiling under reflux indicated only partial reaction and after a further 24 hours t.l.c. analysis indicated that further reaction had occurred. Chromatographic purification on a flash silica gel column yielded a single component.

Subsequent analysis by ^{1}H, ^{13}C NMR and DCI mass spectrometry (m/e 565 [M^{+}+1]) showed that the monobutyl derivative, 16 had been formed and thus leaving a free secondary amine group within the macrocycle framework. This mono-substitution implies that alkylation of the remaining amino group is sterically hindered and occurs at a much slower rate than the first step.

Methylation of the other N-H group was achieved using the Eschweiler-Clarke method[6] and proceeded smoothly to give the mono-methyl mono-butyl ditosylamide in good yield, 17.

The trans-related tosyl protecting groups could now be removed using 45% w/v HBr/HOAc in the presence of phenol to yield a light coloured precipitate after 18 hours. Further HBr/HOAc was added to ensure an excess of the reagent and after an additional 48 hours refluxing, the precipitate was filtered off and washed with ether to give an almost white product which was soluble in D_2O . Analysis by ^1H and ^{13}C NMR and DCI mass spectrometry confirmed the smooth and complete removal of the tosyl groups. The macrocycle 18 was isolated as the tetrahydrobromide salt in 91% yield, compared to the dimethyl derivative 15 in 71% yield. Presumably the butyl group encourages dissolution of product and may be related to the higher yield that was found, (Scheme 2.4).



3 16 17 18

Scheme 2.4

2.3.4 Synthesis of dibutyl [14]N_4 cyclam 20

With these results in mind, the trans dibutyl derivative of cyclam was sought. Previously n-butyl bromide had been used as the alkylating agent and only mono butylation had been achieved. Alkylation with butyl iodide was attempted bearing in mind that the Br^- ion is usually a poorer leaving group than an iodide.

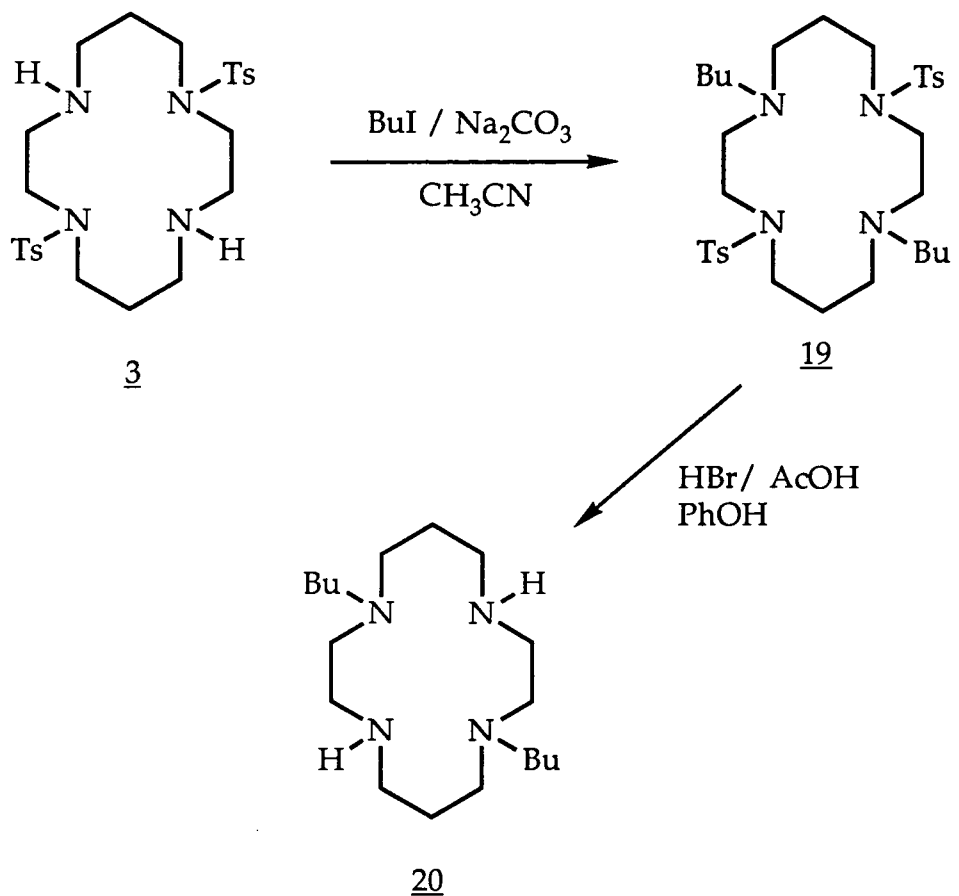
Hence, trans ditosyl cyclam in dry acetonitrile was stirred with 2.1 equivalents of anhydrous sodium carbonate to form a suspension. Gradual addition of 2.1 equivalents of n-butyl iodide to the suspension was effected and the mixture was boiled under reflux for 48 hours leading to the formation of a white precipitate of sodium iodide.

Initial analysis by t.l.c., after 24 hours, showed a predominant fast moving component (Rf (SiO_2 10% MeOH in CH_2Cl_2): 0.75) which was very comparable to the minor fast moving component from the predominantly mono-substitution reaction.

After refluxing for a further 48 hours the faster moving spot became more intense and was separated from the reaction mixture by using gradient elution column chromatography with an increasing concentration of methanol in dichloromethane (1→5%) on a flash silica gel column. A single component was obtained and dibutylation was confirmed by subsequent ^1H and ^{13}C NMR spectral analysis.

The next stage was the removal of the tosyl groups and was now carried out in the normal fashion by refluxing with 45%w/v HBr/HOAc in the presence of phenol. This detosylation was found to be easy and rapid and a white precipitate began to come out of solution after only half an hours boiling

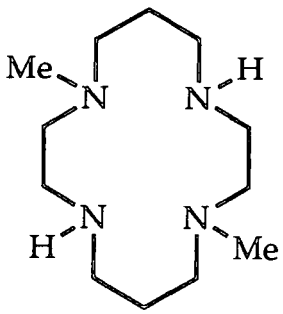
at reflux. After 18 hours a bulkier light coloured precipitate had come out of solution and excess of the reagent was added to ensure complete reaction. After a further 24 hours boiling under reflux the product was filtered off and was washed with ether to yield the hydrobromide salt as a whitish precipitate, 20 in a good yield of 93%, (Scheme 2.5).



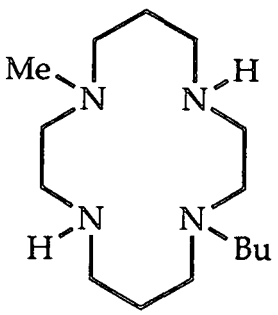
3 19 20

Scheme 2.5

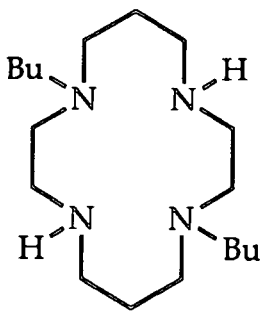
Thus three functionalised lipophilic tetraazamacrocycles derived from cyclam have been obtained, 15, 18 and 20, of progressively increasing chain length. These ligands should form stable metal complexes of varying lipophilicity and solubility.



15



18



20

2.4 Metal Complexes

Copper(II) and nickel(II) in complexes of ligands 15,18 and 20 were prepared and the structures of the 1,8-dibutyl derivatives (Cu-20)$^{2+}$ and (Ni-20)$^{2+}$ determined by X-ray crystallography.

2.4.1 Copper(II) complex of [14]N_4Me_2 15

The 1:1 copper complex of 1,8-dimethyl cyclam, 15, was formed by adding an approximately equimolar amount of copper perchlorate hexahydrate in water to an aqueous solution of the ligand hydrobromide at room temperature. After mixing, the solution was warmed gently and a colour change from brown to purple with an absorption at 545 nm was noted. The pH of the solution was adjusted to 6.5 with KOH. The volume of the solution was reduced by half and salt precipitated which was filtered off. The clear blue solution was evaporated to dryness and the complex redissolved in methanol and more potassium bromide filtered off. Through a solution of the complex in water was bubbled hydrogen sulphide gas and a small amount of precipitated copper sulphide was filtered off. The resulting blue solution had an absorption band at 546nm. It appears that this complex is stable with

respect to attack by sulphide. Attempts to isolate a crystalline product from this reaction mixture were not successful however.

The d-d absorption band was monitored over the pH range 1.5 to 14. In the pH range 1.5 to 7, no change in the absorption band (546 nm) was noted, although above pH 7 it shifted slightly to lower wavelength (pH 14, λ_{max}535) possibly due to formation of a weak $[CuLOH]^+$ species.

2.4.2 Nickel(II) complex of [14]N_4Me_2 15

The 1:1 dimethyl cyclam nickel(II) complex was prepared in similar fashion to give an orange complex (λ_{max} 456nm) which is characteristic of a square-planar d^8 nickel(II) complex i.e. a complex of nickel with a strong in-plane ligand field. Attempts to crystallise this complex for X-ray analysis were not successful.

2.4.3 Copper(II) complex of [14]N_4MeBu 18

Before forming the complex between trans methyl butyl cyclam, 18, and copper perchlorate, the ligand was converted to its free base form in an attempt to inhibit salt formation which may hinder crystallisation of the complex. The 1:1 copper(II) complex was obtained by the addition of an approximately equimolar amount of copper perchlorate hexahydrate in methanol, to a solution of the ligand in acetonitrile. After warming an indigo coloured solution was obtained. A solution of this complex in acetonitrile gave an absorption band at 521 nm. In methanol the band had shifted to a value of 536 nm, and after evaporating to dryness the complex was dissolved in water giving a solution with an absorption band at 536 nm. This complex was also stable with respect to attack by sulphide. The amount of complex obtained

was small precluding repetitive attempts at growing crystals for X-ray analysis purposes. A slightly different method of complex formation was used with 1,8-dibutyl cyclam.

2.4.4 Copper(II) complex of [14]N_4Bu_2 20

In order to form the complex between dibutyl cyclam and copper(II) perchlorate, the ligand was initially converted to the free amine in order that there should be no residual salt present which might interfere with crystallisation of the complex, as previously encountered with its 1,8-dimethyl analogue.

Thus trans-dibutyl cyclam, 20, was dissolved in the minimum amount of water and the pH adjusted to 1 with one drop of concentrated hydrochloric acid. The free base was now isolated in good yield as a white oily material by extracting a basic solution of this hydrobromide salt with chloroform.

An approximately equimolar amount of copper perchlorate hexahydrate in methanol was added to the free 1,8 dibutyl cyclam in tetrahydrofuran to give an immediate purple coloured solution with an absorption at 514 nm. Through this solution was bubbled hydrogen sulphide gas and the small amount of precipitated copper sulphide was filtered off. The absorption spectrum of the resulting purple solution again revealed a band at 514 nm. It appears that this complex is also stable with respect to attack by sulphide.

Crystallisation was attempted using a variety of different solvents. Initially acetonitrile and ice-cold methanol, and acetonitrile and ethanol were tried but the crystals obtained in both instances were too small for X-ray analysis. A solution of the complex in ethanol was allowed to slowly mix with

di-isopropyl ether to give irregular crystals and a 50 : 50 mixture of ethanol and acetonitrile with di-isopropyl ether also gave very small crystals. In an attempt to gain larger and more regular crystals, the counter ion was exchanged. The perchlorate anion was exchanged with hexafluorophosphate by adding a six-fold excess of ammonium hexafluorophosphate in methanol to the complex in acetonitrile. After warming and filtering the solution was left to crystallise overnight by slow evaporation. By the following morning the purple solution made was decanted from a large amount of excess ammonium salt. After evaporating to dryness the dibutyl cyclam copper(II) hexafluorophosphate complex was dissolved in ethanol plus 10% acetonitrile and di-isopropyl ether was added. Diffusion together of the layers yielded purple prismatic crystals suitable for X-ray crystallographic analysis.

2.4.5 Nickel(II) complex of [14]N_4Bu_2 20

In order to form the complex between dibutyl cyclam and nickel perchlorate, the ligand was converted to its free base. This was isolated as a colourless oil which was dissolved in methanol and to which an equimolar quantity of nickel perchlorate hexahydrate in methanol was added forming a yellow solution. The complex was re-dissolved in acetonitrile giving a solution with an absorption at 472 nm. Various different solvents were used in an attempt to grow crystals suitable for X-ray analysis but none was found.

The complex was then dissolved in water and reduced to about half of its volume and a small number of yellow prismatic crystals began to come out of solution. They were isolated by filtration and an absorption spectrum revealed a band at 461 nm. From the mother liquors needle crystals, of a

different crystalline form, were grown by further slow evaporation with an absorption at 473 nm. This is similar but distinct from that recorded in acetonitrile. This similarity suggested that perhaps the two complexes were stereoisomers.

2.5 Structural Analysis of Copper(II) and Nickel(II) Complexes

An ORTEP diagram of the X-ray crystal structure of the hexafluorophosphate salt of Bu_2cyclam-Cu(II) is shown in Figure 1. It reveals that each of the ring heteroatoms is bound equatorially to the central copper atom. The complex possesses a C_2-symmetry axis and there is a centre of inversion at copper, with two mirror planes, one about the N1-N1* direction and the other about the N4-N4* direction.

2.5.1 Analysis of copper(II) complex of [14]N_4Bu_2 20

Selected molecular dimensions are given in Table 2.1 and full positional and geometrical data are given in the Appendix. In this centrosymmetric structure the four nitrogen atoms lie in the same plane as the metal ion with the Cu-N1 and Cu-N1* bonds slightly longer 2.062(2) Å than the Cu-N4 and Cu-N4* bonds 2.005(2) Å (to NH) which is typical for copper complexes of this type, e.g. with Cu([14]aneN_4) (OCOMe)(ClO_4) the Cu-N bond length is between 2.010(6) to 2.032(6)Å[8]. The Cu-N bond lengths for Bu_2 cyclam Cu(PF_6)$_2$ are quite short, and may also be compared to values of 2.03 Å for a "strain-free" Cu-NH bond[9] and 2.02 Å observed in the copper complex of cyclam[10].

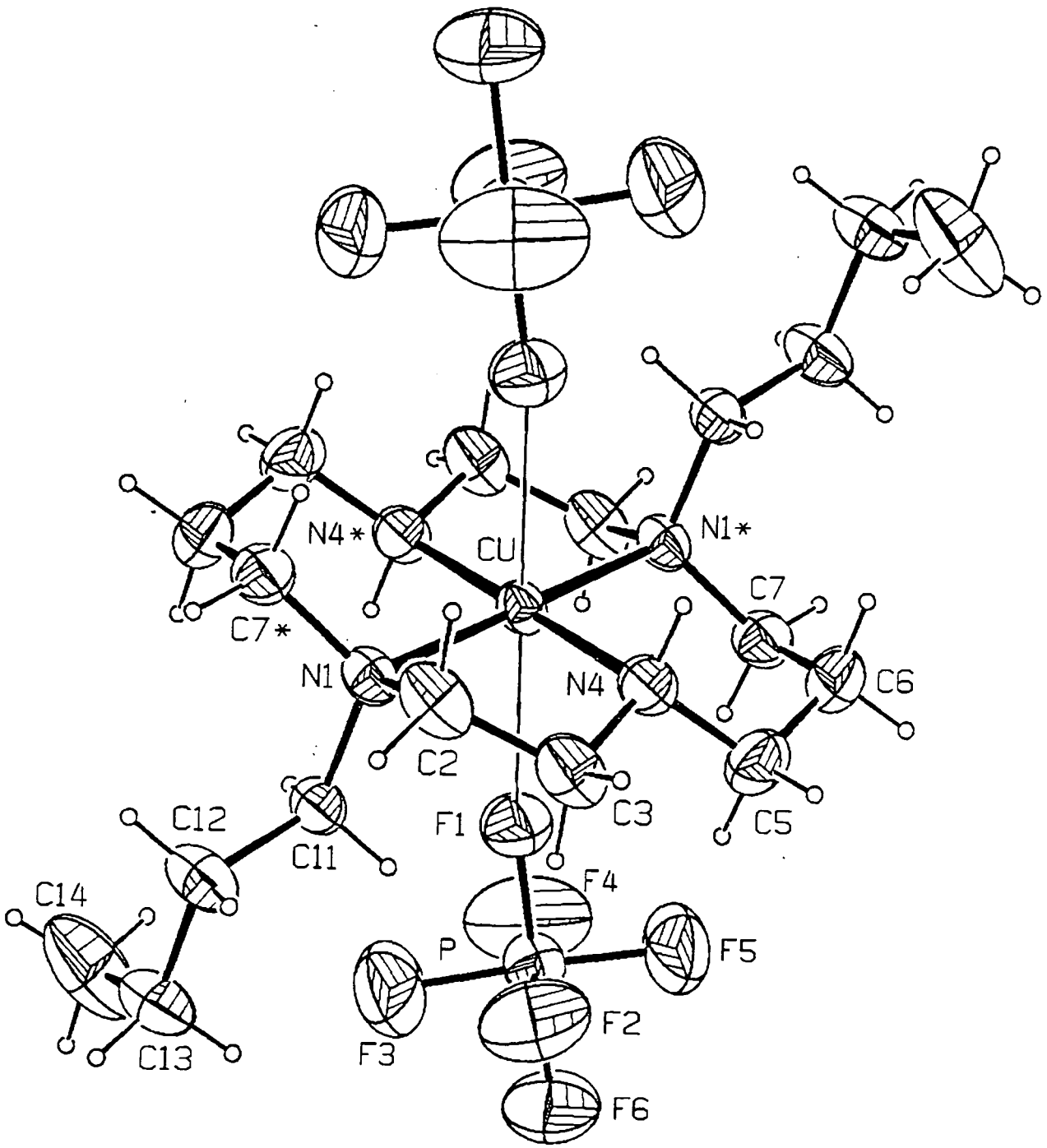


Figure 2.1 X-ray crystal structure of the copper(II) complex of [14]N_4Bu_2 20.

Table 2.1 Selected molecular dimensions (distances in Å, angles in °) for [Cu-20][PF_6]$_2$ with e.s.d.s in parentheses

Cu-N(1)	2.062(2)	N(1)-Cu-N(4)	86.61(8)
Cu-N(4)	2.005(2)	Cu-F(1)-P	158.48(9)
F(1)...Cu	2.840(2)	N(4)-H(4)-F(1^{I})	117.5
N(4)...F(1^{II})	3.303(4)	N(4)-H(4)-F(4^{II})	147.5
H(4)...F(1^{II})	2.76		
N(4)...F(4^{II})	3.221(4)		
H(4)...F(4^{II})	2.38		

Symmetry operations: I - x, -y, -z; IIx, y, -z

The structure appears to be a severely tetragonally distorted octahedron in which the elongated axial sites are occupied by fluorine atoms of the hexafluorophosphate counter ions. The complex is subject to a strong Jahn-Teller distortion[11] typical for a d^9 Cu(II) complex. The Cu-F bond lengths are 2.840(2)Å. In the related complex Cu([14]aneN$_4$)(OCOCH$_3$)(ClO$_4$)[8] the Cu-O counter ion bond length is 2.352(5) to 2.515(5) Å which is significantly shorter than for the Cu-F (counter ion) bond length. As the Cu-F bond length is quite long by comparison it implies that the Bu_2cyclam Cu(II) complex is very tetragonally distorted and is virtually square planar in structure coordination. Both of the butyl groups are situated in axial positions in the six-ring chelates (defined by NiN_2C_3). They are trans to each other on N1 and N1* thereby excluding any possible interaction between them. The ligand adopts a relatively unstrained "trans-III" conformation with the five and six membered chelate rings being in gauche and chair conformations respectively. From the X-ray crystallographic data the torsion angles for the [CuII-L][PF_6] complex are

shown in Figure 2.2. The torsion angles indicate corners at positions 2,6,2* and 6* thus giving a [3434] quadrangular type conformation for the cycle in the complex with an RSSR configuration at each nitrogen (Figure 2.2) and the two PF_6 counter ions occupying the axial sites.

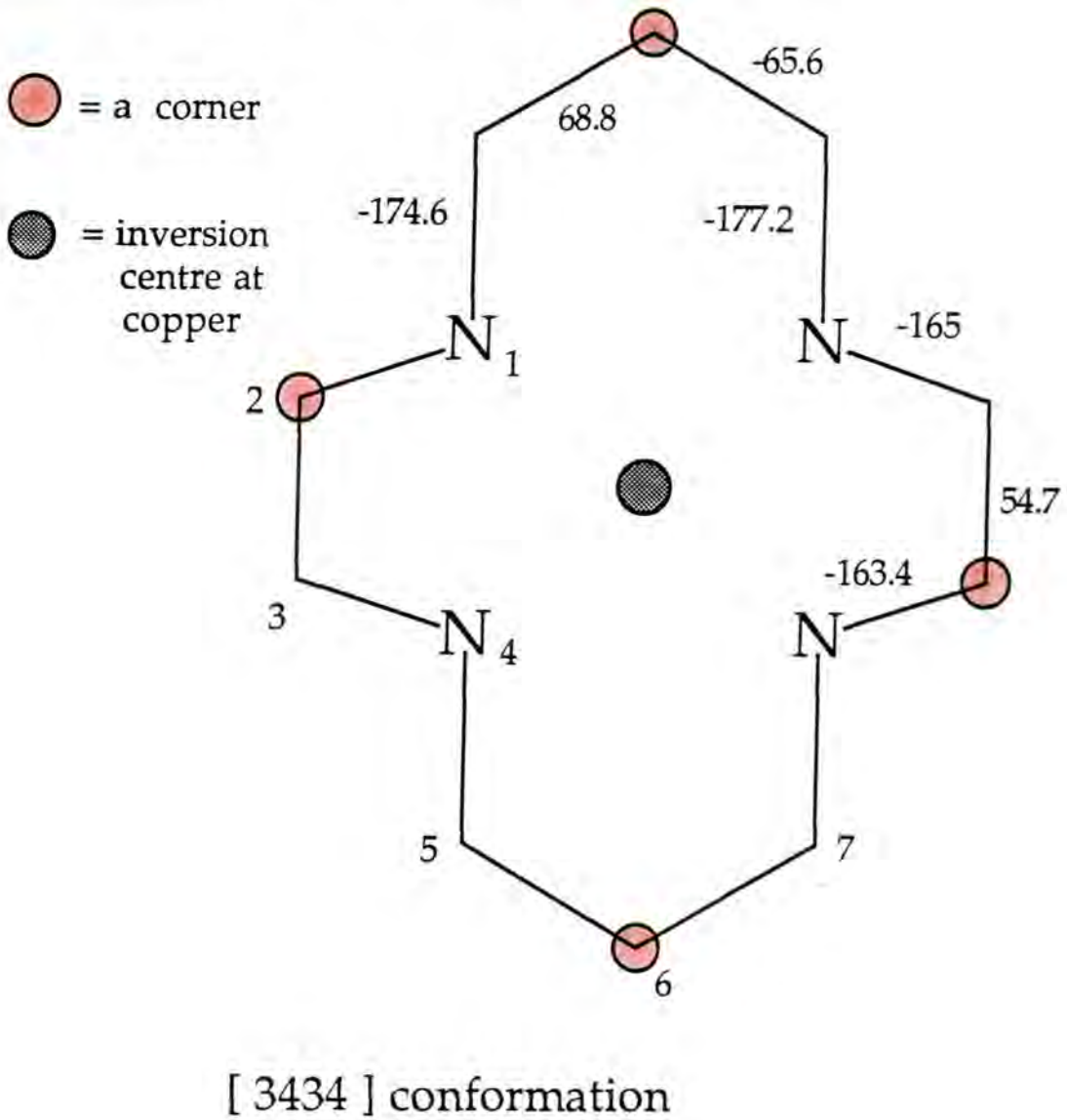
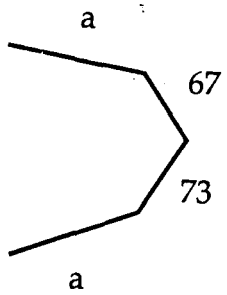
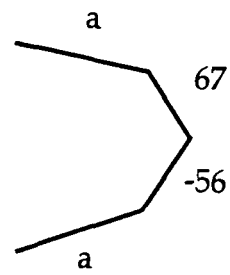


Figure 2.2 Torsion angles for the copper(II) complex of $[14]N_4Bu_2$ 20 indicating corners at 2,6,2* and 6*

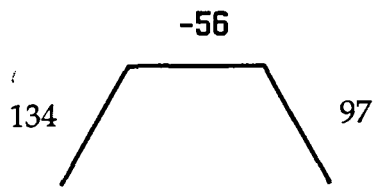
The designation of what constitutes a corner in macrocyclic structures follows the rules devised by Boeyens which are a modified version of the analysis originally put forward by Dale[12]. They may be summarised as

follows. A corner occurs at the junction of any two gauche bonds irrespective of sign e.g.

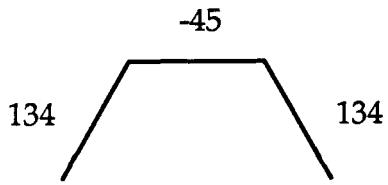




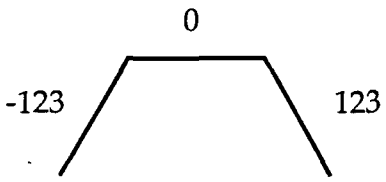
or where any torsion angle of $|\phi| > 90^0$ is considered non-gauche. This 90^0 discrimination between anti and gauche forms is consistent with IUPAC rules for describing the stereochemistry of conformational isomers rule E(23)[13]. A corner also exists at the junction of an isolated gauche bond of the adjacent bond with the smaller $|\phi|$.



When an isolated gauche bond contains a two-fold or pseudo two-fold axis it has a corner on either side.



A mirror or pseudo plane of this type, e.g.



is excluded on steric grounds.

2.5.2 Analysis of nickel(II) complex of trans-[14]N_4Bu_2 20

The X-ray crystal structure of the nickel perchlorate salt of Bu_2cyclam (prisms, λmax 461nm) is shown in Figure 2.3 and shows very similar structural features to those of the copper hexafluorophosphate complex. Again all the ring nitrogen atom atoms are bound to the central nickel cation (and to two oxygens of the two ClO_4 anions). There is a C_2-symmetry axis in the complex. The complex is a distorted octahedron with the metal ion lying in the same equatorial plane as the four nitrogen donors of the cyclam ring and the perchlorate counter ions situated in axial positions. Selected molecular dimensions are shown in Table 2.2 and full positional and geometrical parameters are given in the Appendix. The Ni-N1 and Ni-N1* bonds are again slightly longer 1.970(2)Å (to NBu) than the Ni-N4 and Ni-N4* bonds 1.939(2)Å (to NH) which is normal and comparable to reported values for other square planes co-ordinated nickel(II) complexes of this type[14]. For example, Hay[14] reports that an orange tetramethyl nickel derivative of cyclam contains discrete anions and centrosymmetric cations (Figure 2.4) and the Ni-O distance is 2.808(5)Å. The Ni-N bond lengths are 1.964(3) and 1.974(3)Å which is obviously similar to those found for the dibutyl complex. Octahedral nickel-cyclam

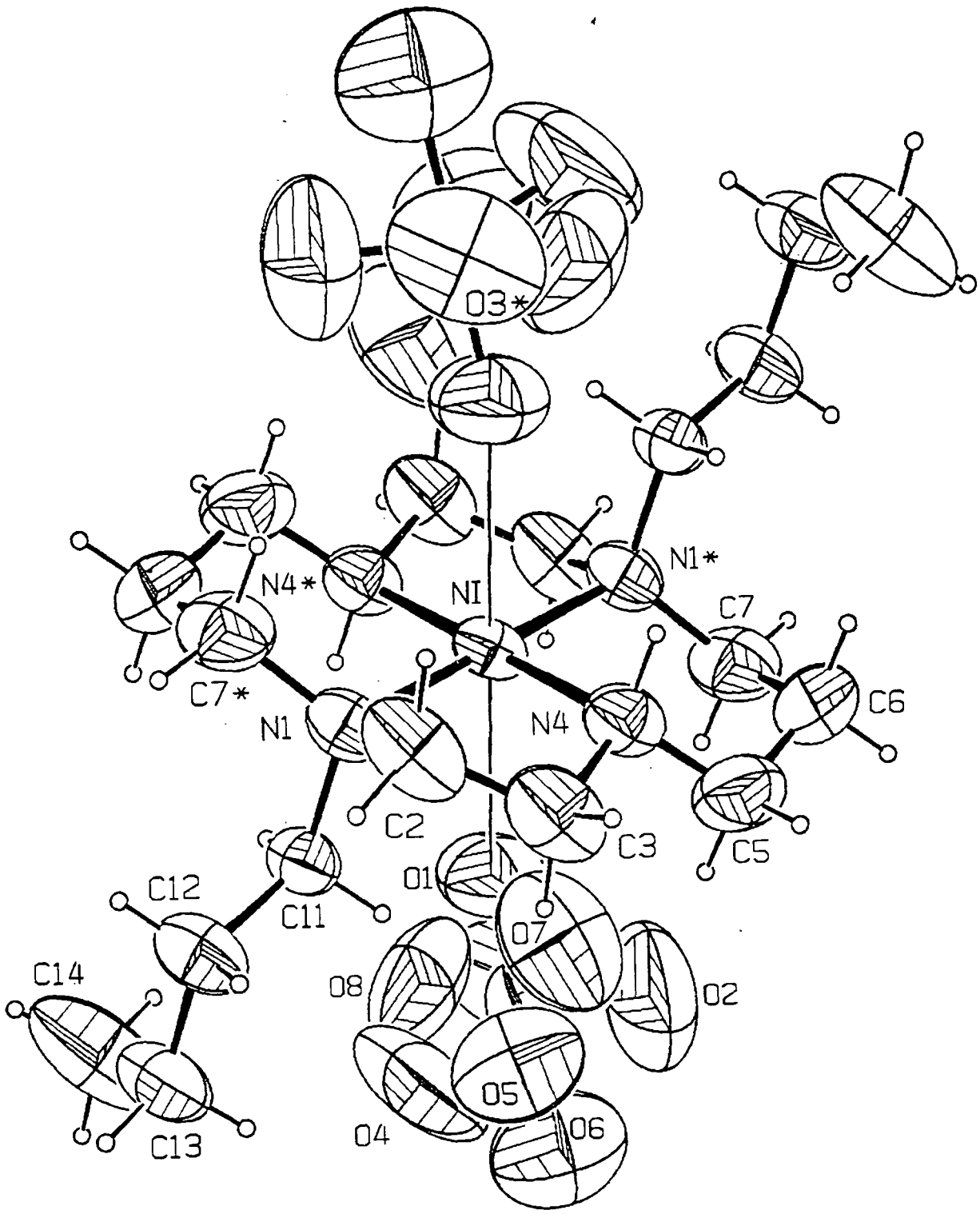


Figure 2.3 X-ray crystal structure of the nickel(II) complex of [14]N_4Bu_2 20. The perchlorate anions where disordered over two sites with equal occupancy.

Table 2 Selected molecular dimensions (distances in Å, angles in °) for [Ni-20][ClO]$_2$ with estimated standard deviations (e.s.d.s) in parentheses

Ni-N(1)	1.970(2)	N(1)-Ni-N(4)	87.45(9)
Ni-N(4)	1.939(2)	Ni-N(1)-C(2)	105.1(2)
O(1)...Ni	3.072(8)	Ni-N(1)-C(7^{I})	115.8(2)
N(4)...O(3^{II})	3.150(9)	Ni-O(1)-Cl	152.0(3)
N(4)...O(8^{II})	2.997(13)	N(4)-H(4)-O(3^{II})	139.4
H(4)...O(3^{II})	2.37	N(4)-H(4)-O(8^{II})	146.5
H(4)...O(8^{II})	2.16		

Symmetry operations: I - x, -y, -z; II x, y, -1 + z

complex. Octahedral nickel-cyclam complexes tend to be violet in colour and each centrosymmetric molecule has Ni-N distances of 2.063(2) to 2.16(1) Å, significantly longer than in the orange square planar structure of the dibutyl nickel complex (Figure 2.5).

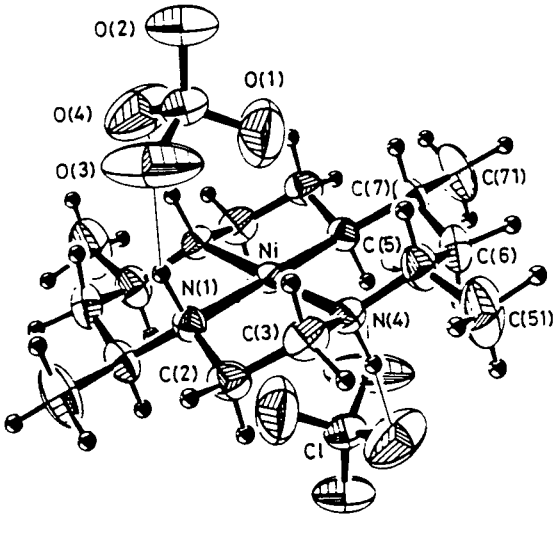


Figure 2.4

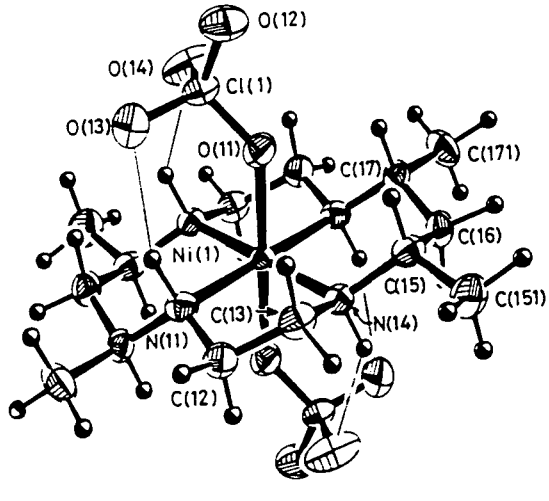
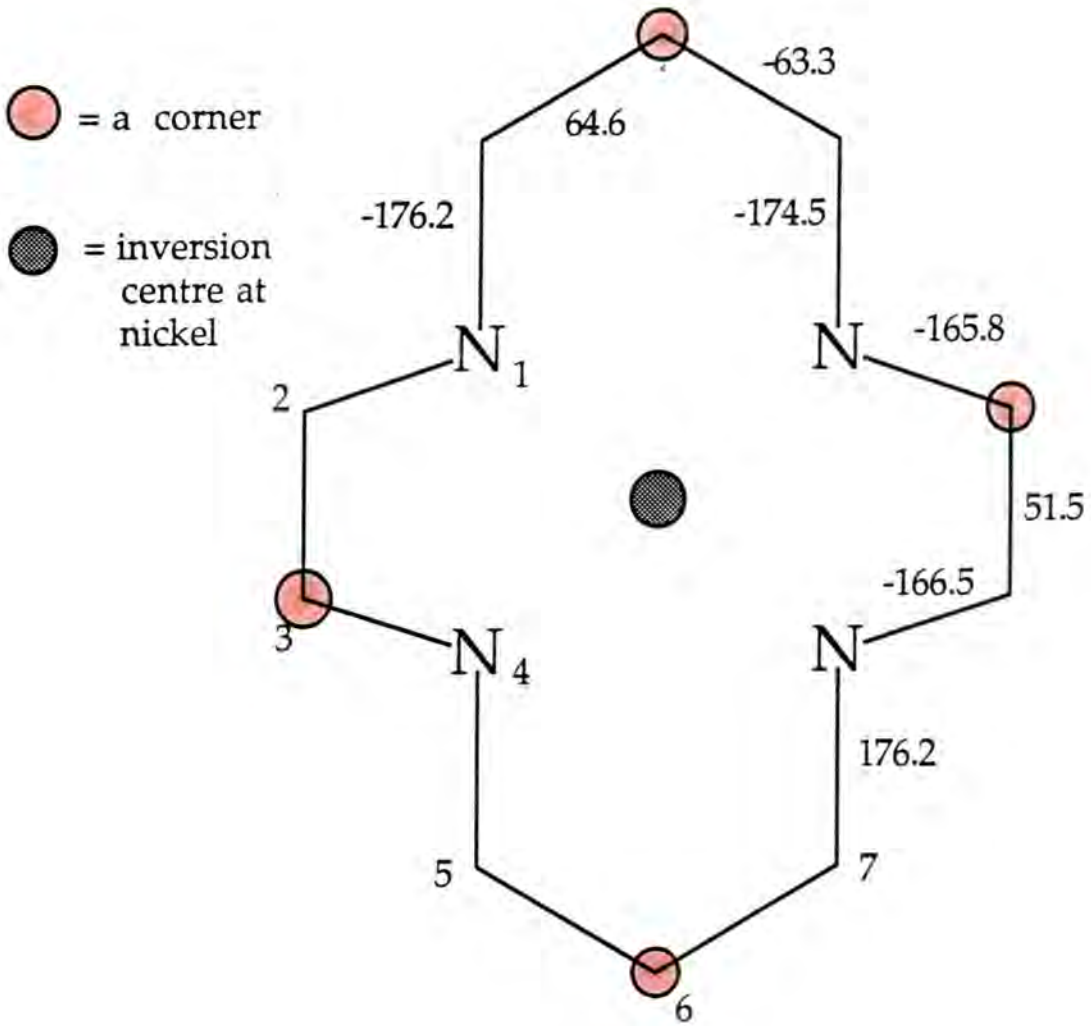


Figure 2.5

The Ni-O perchlorate counter ion bond length is 3.072(8)Å and is somewhat longer than observed for the Cu-F distance in the hexafluorophosphate copper complex. This is rather unusual given the enhanced propensity of copper(II) to form square planar complexes compared to nickel(II). Hay[14] reports for his violet tetramethyl cyclam nickel complex the Ni-O bond lengths are 2.221 and 2.235Å respectively which are regarded as normal for an octahedral complex. The Ni-O bond length for the dibutyl complex [Ni-L][ClO_4] complex is 3.072(8)Å and is quite long by comparison.

As with the [Cu-L][PF_6] complex both butyl groups are in axial positions and are trans to each other. The steric effect of the axial butyl groups interacting with 1,3-related axial hydrogens may result in the slight elongation of Ni-N1 and Ni-N1* in comparison to Ni-N4 and Ni-N4* producing a slight strain on the cyclam ring.

The torsion angles for the Bu_2cyclam Ni(II) perchlorate complex are given in Figure 2.6. The diagram highlights the centre of inversion about the central nickel atom and two mirror planes about N1-N1* direction and N4-N4*. Again the torsion angles indicate corners at positions 2,6,2* and 6* giving the expected quadrangular [3434] type conformation for the cycle in the complex with an RSSR configuration at the nitrogen stereogenic centres. Again for comparison in the nickel complex of 5,7,12,14-tetramethyl-1,4,8,11-tetraazacyclotetradecane, nickel nitrogen bond lengths of 1.964(3) and 1.974(3)Å were found[16] in the square planar complex with the perchlorate counterion somewhat closer at 2.808(5)Å from nickel.



[3434] conformation

Figure 2.6 Torsion angles for the nickel(II) complex of [14]N_4Bu_2 20 indicating corners at 2,6,2* and 6*.

2.5.3 Analysis of nickel(II) complex of cis-[14]N_4Bu_2 20

For the Bu_2cyclam Ni(II) complex, (needles, λ_{max} 473nm) X-ray analysis shows a high degree of disorder and although the data was collected at 293 and 173K the ratio of observed to the total number of reflections taken is still less then 50%. The electron density maps show that there are two independent cations in the unit cell each lying across mirror planes. In each case the Ni

atom and the two secondary nitrogen atoms that do not carry the butyl chains lie on the mirror plane. Electron density maps reveal only the position of the nitrogen atoms and of the first two carbon atoms of the butyl group in each case. Because of this mirror imposed disorder, instead of having five or six membered rings, what is seen is a composite of ill-defined density corresponding to a superposition of the 5- and 6- rings with no clearly defined maxima. This indicates that there is a high degree of disorder present. There are four chlorine atoms, each of which lies on the mirror plane, and each chlorine has a plethora of small maxima, corresponding to all the perchlorate oxygen atoms being scrambled making interpretation difficult. However, it is certain that the butyl groups are cis to each other, as the mirror plane through the two NH groups demand this. It is also likely that the hydrogens on the other two nitrogen atoms are cis to each other and probably trans to the butyl groups. In the diastereoisomer (prisms, λ_{max} 461 nm) the amine hydrogens and butyl groups are most definitely trans to each other as indicated in Figure 2.3. The analysis is certainly sufficient to pinpoint the differences from the structure of the isomeric complex. It is very likely that the needles are indeed a cis diastereoisomer with an RSRS configuration at nitrogen. Although the formation of two isomeric copper-cyclam cationic complexes has been known for sometime, the observation and structural determination of two diastereoisomeric square-planer nickel(II) complexes of a tetraazamacrocycle appears to be most uncommon.

2.6 Summary

The visible absorption spectra for the 1,8-dibutyl cyclam copper and nickel complexes are summarised in Table 2.3. In all of the nickel complexes the position of the observed visible absorption band suggested that the nickel atom was square planar with a relatively strong ligand field. This was confirmed by the crystallographic analysis of [Ni-20][ClO_4]$_2$ in which the Ni-N bond lengths were 1.939(2), (to NH) and 1.970 (2)Å (to NBu) Table 2.2. In this centro-symmetric structure (Figure 2.3) the perchlorate counterions were fairly remote from the nickel [O(1)-Ni 3.072(8)Å], and were disordered over two sites and bound axially. The ring adopted the expected quadrangular [3434] conformation with an RSSR configuration at the nitrogen stereogenic centres.

Table 2.3 Visible absorption spectra (H_2O, 293 K) for nickel and copper complexes

Complex cation	λ_{max}/cm^{-1}	$10D_{qxy}$[a]
[Ni-20]$^{2+}$	21 691	1971[b]
	21 141	1922[c]
[Ni-15]$^{2+}$	21 929	1993
[Ni-18]$^{2+}$	21 820	1984
[Ni-1]$^{2+d}$	22 473	2043
[Cu-1]$^{2+f}$	19 900	
[Cu-20]$^{2+}$	18 939	
[Cu-15]$^{2+}$	18 315	
[Cu-18]$^{2+}$	18 656	

[a] $10\ D_{qxy} = v_{d-d}/11.0$ (ref. 16). [b] trans Isomer. [c] cis Isomer.

The copper(II) complex of 20 was isolated as its hexafluorophosphate salt (from MeCN-MeOH-iPr_2O) and crystallised in the same space group as [Ni-20][ClO_4]$_2$. Again the 14-membered ring adopted a [3434] quadrangular

conformation with a RSSR configuration at each nitrogen (Figure 2.2) and the two PF_6 counterions occupied the axial sites. The nearest Cu-F distance was 2.840(2)Å (Table 2.1). The structural analysis of these nickel and copper complexes of 20 together with the observed ligand-field strength (Table 2.3), certainly supports the premise that the 1,8-disubstitution of 1,4,8,11-tetraazacyclotetradecane does not compromise complex stability as a result of unfavourable steric interactions. Indeed the only obvious poor non-bonding interactions in the structures of copper and nickel complexes are apparent in the six-membered chelate rings. There are unfavourable 1,3-synaxial interactions between the N-butyl group and an NH in each chair (Figure 2.1 and 2.3) which are expected.

2.7 References

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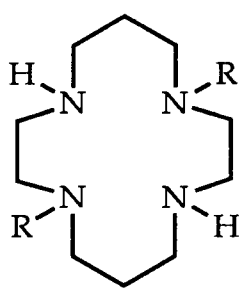
CHAPTER 3

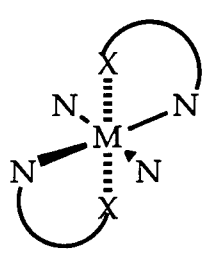
SYNTHESIS AND PROPERTIES OF FUNCTIONALISED [14]N_4 COPPER(II) AND NICKEL(II) COMPLEXES

3.1 Introduction

The elaboration of the co-ordination chemistry of 1,4,8,11-tetraazacyclotetradecane (cyclam) has been a pivotal feature in the development of macrocyclic complexation chemistry.[1] Less work has been reported for monosubstituted derivatives of cyclam[2], although the chemistry of both C- and N-substituted derivatives has been described in some detail[3,4]. Much less attention has been paid to the chemistry of the disubstituted derivatives although they are intrinsically very interesting. For example, the regioselective formation of 1,8-disubstituted derivatives,[5,6] A, in which the substituent may act as a donor to a metal allows the formation of octahedral complexes in which the two additional neutral or anionic donors X may adopt axial binding sites, B (X = COOH, $CONR_2$, COO^-). In such a complex destabilising steric interactions between the N-substitutents and other ligand atoms or torsional ring-strain effects are likely to be minimised, and a small divalent ion such as Cu^{2+} or Ni^{2+} may still experience a strong ligand field from the four



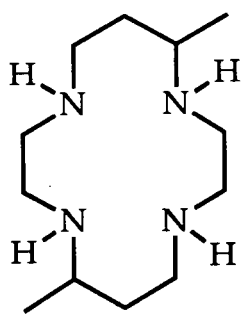
A R = alkyl or carboxyalkyl



B

"equatorial" ring nitrogens, comparable to that found in related complexes of cyclam itself. Such a situation may be compared with that found in the nickel(II) complex of 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane, where the low ligand field strength observed[7] has been attributed to a stretching of all the Ni-N bonds to relatively long values (1.98-1.99Å)[8]* due to Van der Waals' repulsions between N-methyl groups and proximate hydrogens.

An alternative and much better way of rendering a complex lipophilic and enhancing its solubility in organic solvents is to make the overall complex charge neutral. This is achieved where the donor X in B is ionisable and then the metal complexes formed with divalent ions will be charge neutral overall. These type of complexes are likely to be somewhat lipophilic and lipophilicity may be enhanced by alkylation at the 4,11 positions. The formation of such a 1,8-N,N-disubstituted derivative is also important as the ligand may then be hexadentate, whereby the four ring nitrogens are binding in the equatorial plane and the two ligating N-substituents occupying axial sites in an octahedral complex.



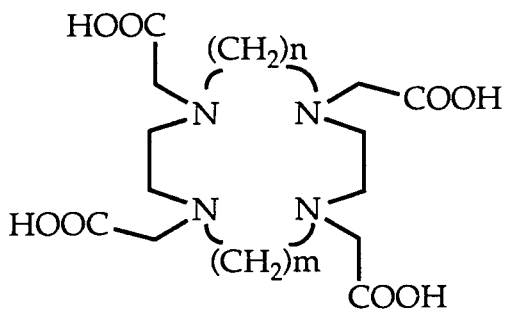
C

* These bond lengths may be compared with the Ni-N bonds lengths of 1.926 and 1.940(4) Å found [8b] in the structure of 5,12-dimethyl-1,4,8,11-tetraazacyclotetradecane C.

3.2 Synthesis of Functionalised Macrocycles

3.2.1 Simple functionalisation (with chloroacetic acid)

The synthesis of a tetra-N-substituted macrocycle is typically straightforward. Usually the unsubstituted macrocycle is reacted with an excess of the alkylating agent in the presence of a base to complex the protons thus liberated. Stetter[9] has described the preparation of macrocycles 1, 2 and 3 of different ring sizes where (n,m = 2 or 3) using chloroacetic acid as an alkylating agent in alkaline solution.

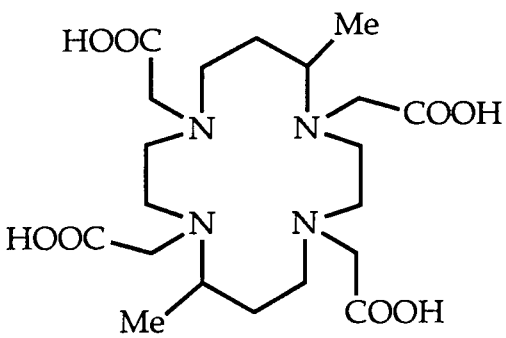


1 n = m = 2

2 n = 2, n = 3

3 n = m = 3

Similarly Häfliger[10] has reacted meso-5,13-dimethyl-1,4,8,11-tetraazacyclotetradecane with chloroacetic acid to obtain the tetra-N-substituted macrocycle 4 with four acetate groups. The selective 4,11-functionalisation of the



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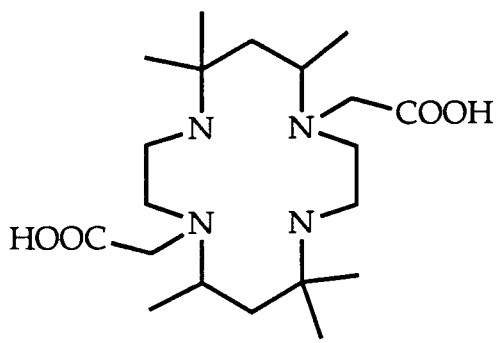


5

C-hexamethyl [14]-tetra-azamacrocycle 5, for instance, has been described[11] which relies upon the steric inhibition of alkylation at the nitrogens proximate to the 7,14-gem-dimethyl substituents.

3.2.2 Regioselective functionalisation of diacids

In order to make the complex of a divalent cation charge neutral, it is necessary to introduce two acidic groups. The synthesis of such a ligand system follows the previous strategy involving the intermediacy of the trans ditosylamide derivative of cyclam (Chapter 2, page 75).

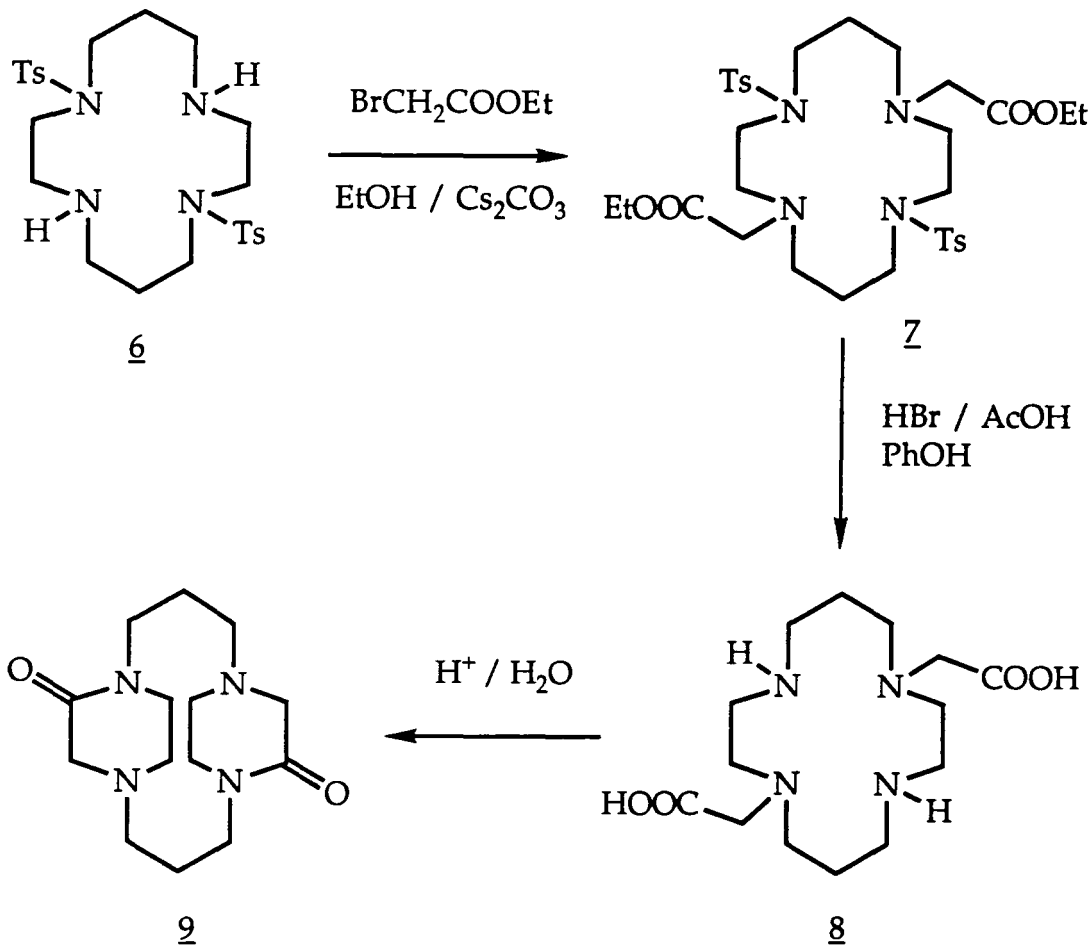
3.2.3 Synthesis of [14]N_4-diacid 8

The synthesis of the N-functionalised diester derivative of cyclam 7 (Scheme 3.1) was carried out by the careful and gradual addition of 2.1 equivalents of ethyl bromoacetate to a suspension of ditosyl cyclam in the presence of anhydrous sodium carbonate in acetonitrile. The diester was separated from the reaction mixture by flash chromatography.

Removal of these trans-related tosyl protecting groups to give the diacid was attempted in the usual fashion by refluxing at 110°C with 45%w/v HBr/ HOAc in the presence of excess phenol. After boiling under reflux for 18 hours, a white coloured precipitate began to come out of the solution and excess of the reagent was added to ensure complete reaction. After a further 24 hours reflux the diacid 8 was filtered off and washed with ether to yield the tetra-hydrobromide salt as a white solid, in reasonable yield of 60%. Analysis by ^{1}H, ^{13}C NMR and DCI mass spectrometry confirmed the complete removal of the tosyl groups.

This diacid 8 was found to be quite hygroscopic. In aqueous or alcoholic solution it quickly lactamised to give the tricyclic lactam 9 (m/e 282

M^++2). It was thought that the relatively slow detosylation step may encourage this lactamisation in-situ, lowering the yield of isolated product. In order to avoid this a more acid labile nitrogen protecting group was examined.



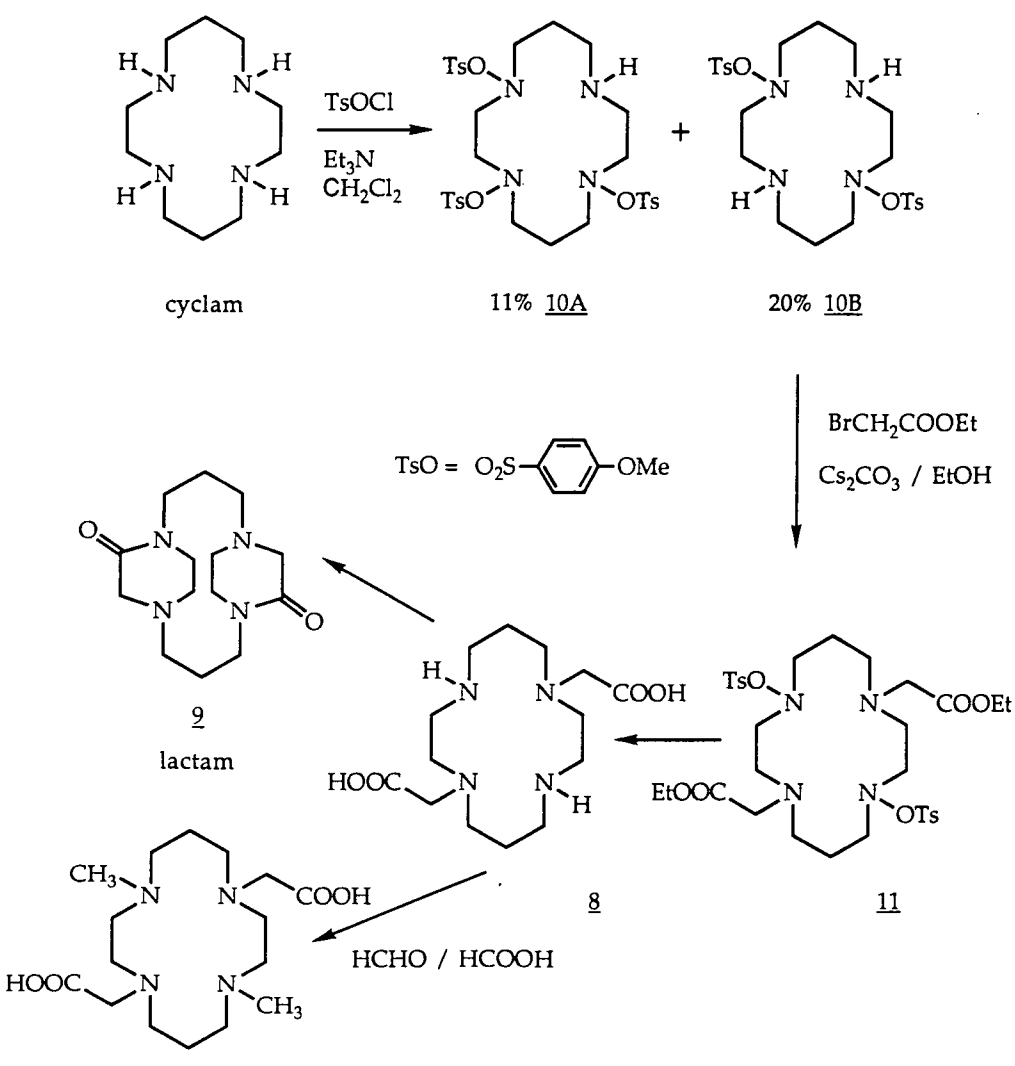
Scheme 3.1 Synthesis of $[14]N_4(COOH)_2$ 8

The p-methoxybenzenesulphonyl group is known to be more readily cleaved (under strongly acidic conditions) than the tosyl group.

3.2.4 Regioselective functionalisation using pMeO-TsCl

The synthesis of this N-functionalised derivative 12 is outlined in Scheme 3.2 and was achieved by the careful and gradual addition of 1.5

equivalents of p-methoxybenzenesulphonyl chloride to a stirred solution of cyclam in methylene chloride and triethylamine. Stirring for 48 hours at room temperature yielded a white precipitate which was filtered off and a yellow sticky solid resulted on evaporation of the reaction mixture.



Scheme 3.2

The disubstituted cycle 10B was purified by column chromatography on silica gel in moderate yield (20%). A reasonable amount of the trisubstituted ligand 10A (11%) was also separated during this isolation.

Subsequent ^{1}H and ^{13}C NMR spectral analysis revealed that the addition of the two p-methoxybenzenesulphonyl groups had proceeded in 1,8 fashion as noted previously for tosyl protection. Further alkylation involved the addition of two carbomethoxymethyl groups trans disposed available at the 4,11-positions to form the corresponding ester 11. This was carried out using ethyl bromoacetate in a suspension of caesium carbonate in acetonitrile and gave the diester 11 in 87% yield.

Deprotection was now effected in the normal fashion with 45% HBr/HOAc with excess phenol. After an initial 12 hours boiling under reflux a light grey precipitate began to come out of solution. Reaction was continued for another 12 hours after which this precipitate had grown significantly in bulk. It was next filtered off and washed with ether. Spectral analysis by ^{1}H and ^{13}C NMR indicated that reaction was complete and was confirmed by DCI mass spectrometry, m/e 313 $M^{+}+1$ giving the tetrahydrobromide salt of the 1,8-dicarboxymethyl ligand 8 in 69% yield. The general indication here was that this deprotection step was somewhat smoother and cleaner than for the ditosyl analogue.

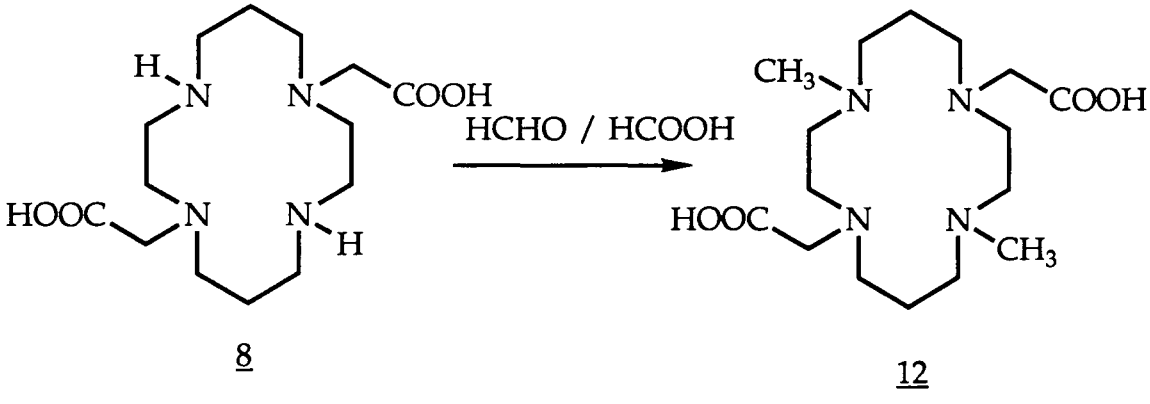
Lactamisation again was found to occur quite rapidly even under reasonably anhydrous conditions, and a molecular ion peak at 281 ($M^{+}+1$) for the lactam became a predominant feature within its mass spectrum.

3.2.5 Synthesis of [14]N_4Me_2-diacid 12

As lactamisation was found to be a kinetically favourable reaction producing a tricyclic lactam, protection (e.g. methylation) of the vacant secondary amine nitrogens was envisaged in order to eliminate this possibility.

This still leaves the lone pair of electrons on each nitrogen available for metal co-ordination.

Direct methylation via the Eschweiler-Clarke method, as discussed before for the preparation of dimethyl ditosyl cyclam in chapter 2 (30% HCHO, HCOOH, 1M HCl), proceeded readily - without significant lactamisation - easily to give the 4,11-dimethyl analogue amine diacid 12 as a light tan solid as its hydrochloride salt in a good yield of 91%, Scheme 3.3.



8 12

Scheme 3.3 Synthesis of $[14]N_4Me_2(COOH)_2$

Thus two functionalised diacid lipophilic tetraazamacrocycles derived from cyclam have been obtained 8 and 12. These ligands should form stable metal complexes of varying lipophilicity and solubility.

3.3 Copper(II), Nickel(II) and Manganese(II) Complexes

3.3.1 Copper(II) complex of $[14]N_4Me_2$-diacid 12

In order to form the 1:1 complex between the N,N′-dimethyl diacid 12 and copper perchlorate an approximately equimolar quantity of copper

perchlorate hexahydrate in water was added to the ligand hydrobromide in water at pH 1. This gave an immediate white precipitate and a pale blue solution. Upon warming and basification to pH 6 a royal blue solution was obtained. After filtering the visible absorption spectrum was recorded giving a strong maximum at 571 nm. Through this solution was bubbled hydrogen sulphide gas and the small amount of copper sulphide produced was filtered off. The absorption spectrum of the resultant royal blue solution revealed a smooth maxima again at 571 nm. Thus the complex is free from excess copper and is stable with respect to attack by sulphide. The complex was initially characterised by Fast Atom Bombardment (FAB) mass spectrometry. Molecular ions (M^+) of approximate intensity 2:1 were observed at m/e 407 and 409, consistent with the two isotopes of copper (^{63}Cu-L and ^{65}Cu-L). Molecular ions corresponding to copper-ligand complexes of other stoichiometry (1:2 or 2:1) were not observed.

Attempts to crystallise this complex from water by slow evaporation were successful and crystals were obtained quite easily after the early removal of excess sodium bromide. These crystals were suitable for X-ray crystallographic analysis.

3.3.2 Copper(II) complex of [14]N_4-diacid 8

The 1:1 complex between the trans-diacetate cyclam 8 and copper perchlorate was prepared in a similar manner. The copper complex was also stable to H_2S treatment. The position of the d-d absorption band for this complex was recorded in water at 565 nm. Crystals suitable for X-ray analysis were obtained by slow evaporation from water. The complex was

characterised by FAB mass spectrometry (molecular ions (M^+) at 379 and 381) consistent with the two isotopes of copper (^{63}Cu-L and ^{65}Cu-L).

3.3.3 Nickel(II) complex of [14]N_4-diacid 8

The nickel(II) complex of this ligand 8 was obtained by mixing equimolar quantities of nickel perchlorate hexahydrate and the ligand at pH 1 both in water. A white precipitate and a magenta coloured solution resulted by adjusting the pH to 6.5. After filtration the magenta complex gave a visible absorption band at 528 nm. This complex is not stable to attack by H_2S. Various different solvents were used in an attempt to grow crystals but none was found. Molecular ions (M^+) at m/e 374 and 376 (^{58}Ni-L and ^{60}Ni-L respectively) were observed in the FAB mass spectrum.

3.3.4 Nickel(II) complex of [14]N_4Me_2-diacid 12

Complex formation between the N-methyl ligand 12 and nickel perchlorate was achieved in an identical manner. The complex gave a d-d absorption maximum at 580 nm. Again this complex is not stable to attack by hydrogen sulphide and attempts to grow crystals suitable for X-ray analysis from various solvent systems were not successful. FAB mass spectrometry revealed molecular ions (M^+) at m/e 402 and 404 consistent with the [14] $N_4Me_2(COOH)_2$ cations $[^{58}Ni\text{-}L]^+$ and $[^{60}Ni\text{-}L]^+$.

3.3.5 Manganese(II) complex of [14]N_4Me_2-diacid 12

The manganese(II) 1:1 complex was formed by reaction between ligand 12 and aqueous manganese nitrate solution. Adjustment to pH 6 gave a light tan precipitate which when removed gave a pink solution of the manganese complex with a weak absorption band at 610 nm, typical of an octahedral

Mn(II) complex. FAB mass spectrometry revealed molecular ions at m/e 399 consistent with the formation of a 1:1 complex.

3.4 Structural Analyses of Copper Complexes of 8 and 12

3.4.1 Analysis of copper complex of [14]N_4Me_2-diacid 12

An ORTEP diagram of the X-ray molecular crystal structure of the perchlorate complex salt of Me_2cyclam dicarboxylate Cu(II) is illustrated in Figure 3.1 and reveals a centrosymmetric structure with each of the ring heteroatoms bound in equatorial positions to the central copper atom. The complex exhibits a C_2-symmetry axis and there is a centre of inversion about the central copper atom with two mirror planes one about the N1-N1* direction and the other about the N4-N4* direction. Salient molecular dimensions and parameters are given in Table 1 and full positional and geometrical parameters are listed in the Appendix. The four nitrogen atoms lie in the same plane as the central copper atom. The Cu-N1 and Cu-N1* bonds are slightly shorter (2.070(3)Å) than the Cu-N4 and Cu-N4* bonds (2.096(3)Å) which compares well with the dibutyl cyclam analogue and other complexes of this type.

The structure of the complex is distorted octahedral in which each of the carboxymethyl groups bind axially on opposite sides of the copper atom. The complex is subject to Jahn-Teller distortion[12] which is expected for a d^9 Cu(II) complex. The Cu-O carboxylate bond length is 2.369(3)Å which compares very well to the related complex (Cu[14]aneN_4)(O_2CCH_3)(ClO_4)[13] where the counterion bond length is 2.352(5) to 2.515(5)Å. The ligand is in a relatively

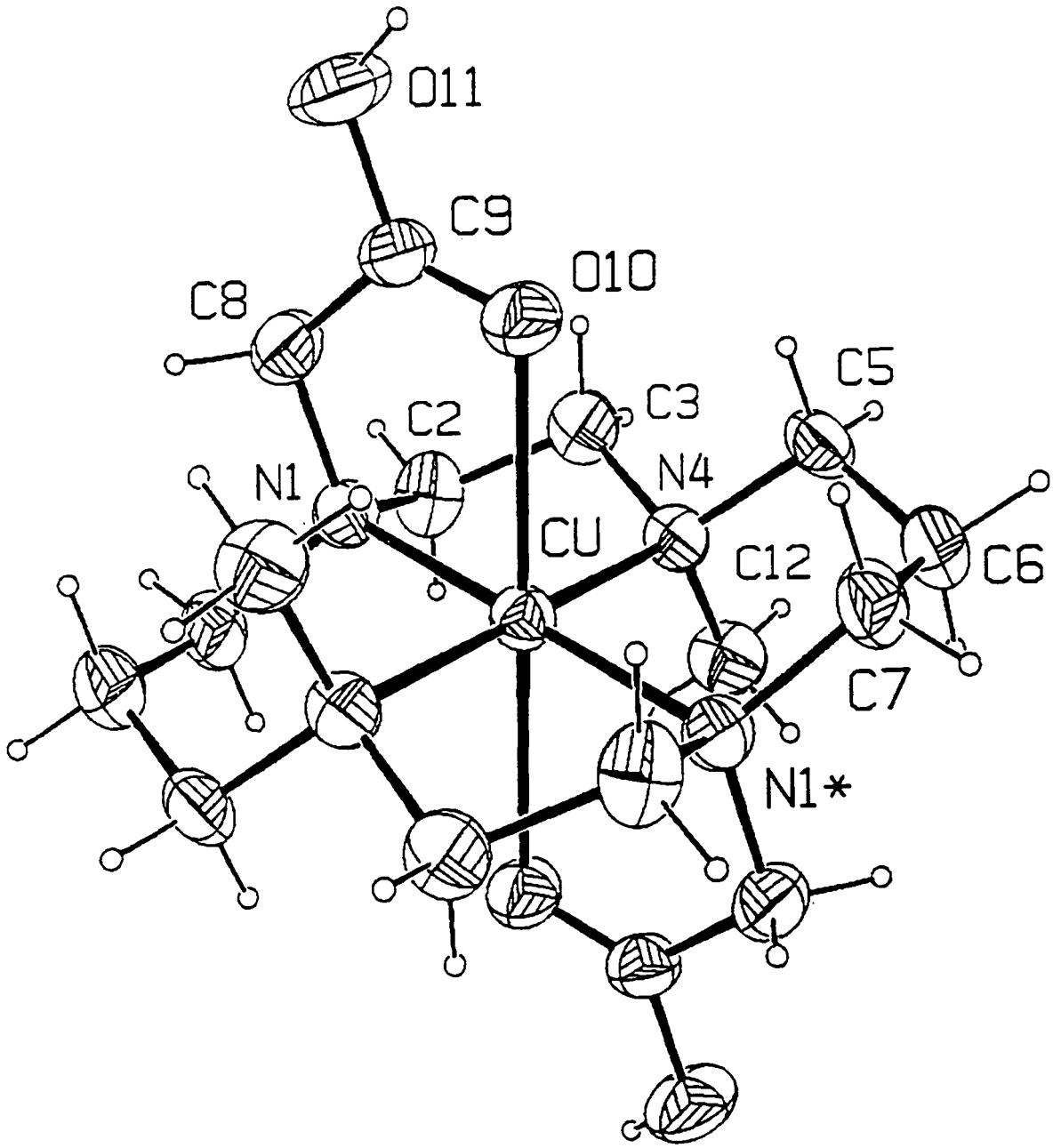


Figure 3.1 X-ray crystal structure of the copper(II) complex of [14]N_4Me_2-diacid 12

Table 1 Selected molecular dimensions (distances in Å, angles in °) for $[Cu(H_2L^9)][ClO_4]_2.2H_2$); with e.s.d.s. in parentheses.

Cu-N(1)	2.070(3)	N(1)-Cu-N(4)	87.1(1)
Cu-N(4)	2.096(3)	N(1*)-Cu-N(4)	92.9(1)
Cu-O(10)	2.369(3)	N(1)-Cu-O(10)	101.8(1)
		N(1*)-Cu-O(10)	78.2(1)
		N(4)-Cu-O(10)	91.9(1)

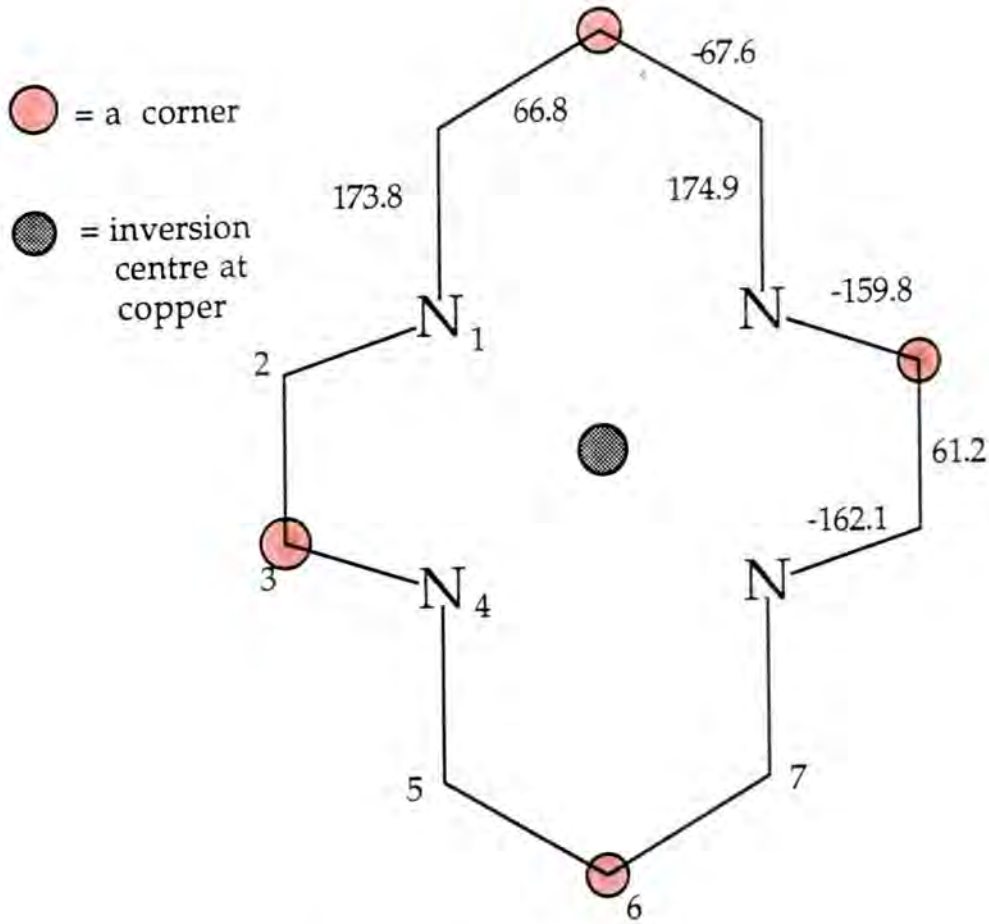


Figure 3.2 Torsion angles for copper(II) complex of [14]N_4Me_2-diacid 12 indicating corners at 2,6,2* and 6*.

unstrained trans III conformation with the five and six membered rings being in typically gauche and chair conformations. The torsion angles for this complex are given in Figure 3.2 and they indicate corners at positions 2,6,2* and 6* so giving a [3434] type conformation for the complex with the configuration at each nitrogen centre being RRSS.

3.4.2 Analysis of copper complex of [14]N_4-diacid 8

The molecular structure of the complex [8-Cu]$(ClO_4)_2$ is presented in Figure 3.3 and shows quite similar structural features to that of the copper

perchlorate salt of the N-methyl analogue. However, there are some notable differences. Again all the ring nitrogen atoms are bound to the central copper cation and the two carboxylate groups are situated axially. There is the expected C_2-symmetry axis in the complex. The complex has distorted octahedral geometry with the metal ion lying in the same equatorial plane and the two carboxymethyl groups situated on opposite axial sites. Again the complex is subject to a Jahn-Teller distortion[12] expected for a d^9 ion. Selected bond lengths and angles are given in Table 3.2 and full positional and geometrical parameters are listed in the Appendix. The Cu-N1 and Cu-N1* bonds are slightly longer (2.095(3)Å) than the Cu-N4 and Cu-N4* bonds (2.014(4)Å) which is expected and comparable to values reported for other similar copper(II) complexes of this type. The Cu-N1 and Cu-N1* bond lengths are very comparable for both complexes (2.095(3) N-H and 2.070(3)Å for N-Me) whilst the Cu-N4 and Cu-N4* bond lengths for the N-methyl

Table 3.2 Selected molecular dimensions (distances in Å, angles in °) for [Cu-8][ClO_4]$_2$.$H_2$9 with e.s.d.s. in parentheses.

Cu-N(1A)	2.095(3)	N(1A)-Cu-N(4A)	86.3(1)
Cu-N(4A)	2.014(4)	C(1A)-Cu-N(4A)	93.7(1)
Cu-O(10A)	2.263(3)	N(1A)-Cu-O(10A)	79.7(1)
N(4A)-O(1)	3.046(9)	N(4A)-Cu-O(10A)	90.0(1)
HN(4A)-O(1)	2.21		
HN(1B)-O(11A)	1.76	C(2B)-N(1B)-C(7B*)	111.2(4)
N(1B)-O(11A)	2.676(4)	C(2B)-N(1B)-C(8B)	106.5(4)
N(4B)-C(9B)	1.341(7)	N(1B)-C(2B)-C(3B)	111.6(3)
N(4B)-C(5B)	1.471(5)	C(2B)-C(3B)-N(4B)	113.3(5)
C(9B)-O(10B)	1.216(5)	C(3B)-N(4B)-C(5B)	117.0(4)
N(1B)-C(2B)	1.489(7)	C(3B)-N(4B)-C(9B)	124.2(4)
C(3B)-N(4B)	1.456(5)	N(4B)-C(9B)-O(10B)	123.7(4)

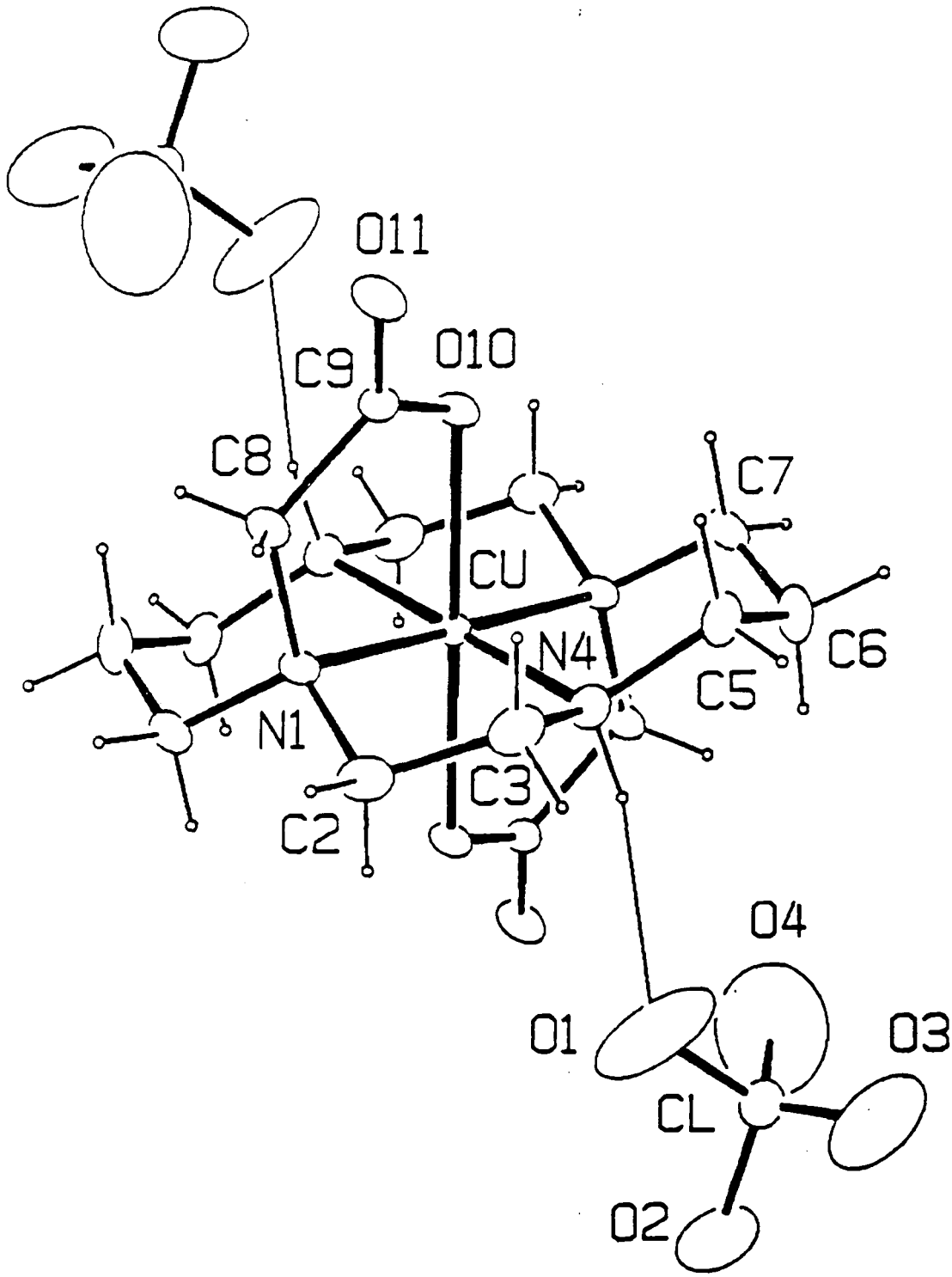


Figure 3.3 Structure of copper(II) complex of [14]N_4-diacid 8 showing the hydrogen bonding to the perchlorate anions of the protonated lactam H_2L^{2+}.

complex are slightly longer (2.096(3)) than its N-H counterpart (2.014(3)Å). A possible suggestion here is that the unfavourable 1,3-synaxial interactions between the N-Me group and N-H in each chair produces a slight Van der Waals' repulsion, causing a slight elongation of the Cu-N4 bonds. Numerous studies have demonstrated metal-nitrogen bond lengths are increased by N-alkyl substitution[7,14] due to Van der Waals' repulsion between alkyl hydrogens and those elsewhere in the complex. For example, in the CuII complex of bis (N,N'-diethyl ethylenediamine), values of 2.08 and 2.02Å were found for copper-tertiary and secondary nitrogen bonds respectively.

The copper is quite strongly co-ordinated to the four nitrogen atoms and more weakly bound to the axial carboxylate oxygen atoms where the Cu-O bond length is 2.263(3)Å and is slightly shorter compared to the N-methyl analogue copper complex. The structure resembles that of the copper complex of cyclam, in which the copper-nitrogen bonds are of equal length (2.02Å)[15] and the two perchlorate counter ions again occupy the Jahn-Teller elongated sites.

The torsion angles for the cyclam dicarboxylate Cu(II) perchlorate complex are given in Figure 3.4. The diagram highlights the centre of inversion about the N1-N1* direction and N4-N4*. Again the torsion angles reveal corners at positions 2,6,2* and 6* thus giving a [3434] type conformation for the cycle in the complex again with the configuration at each nitrogen centre being RRSS.

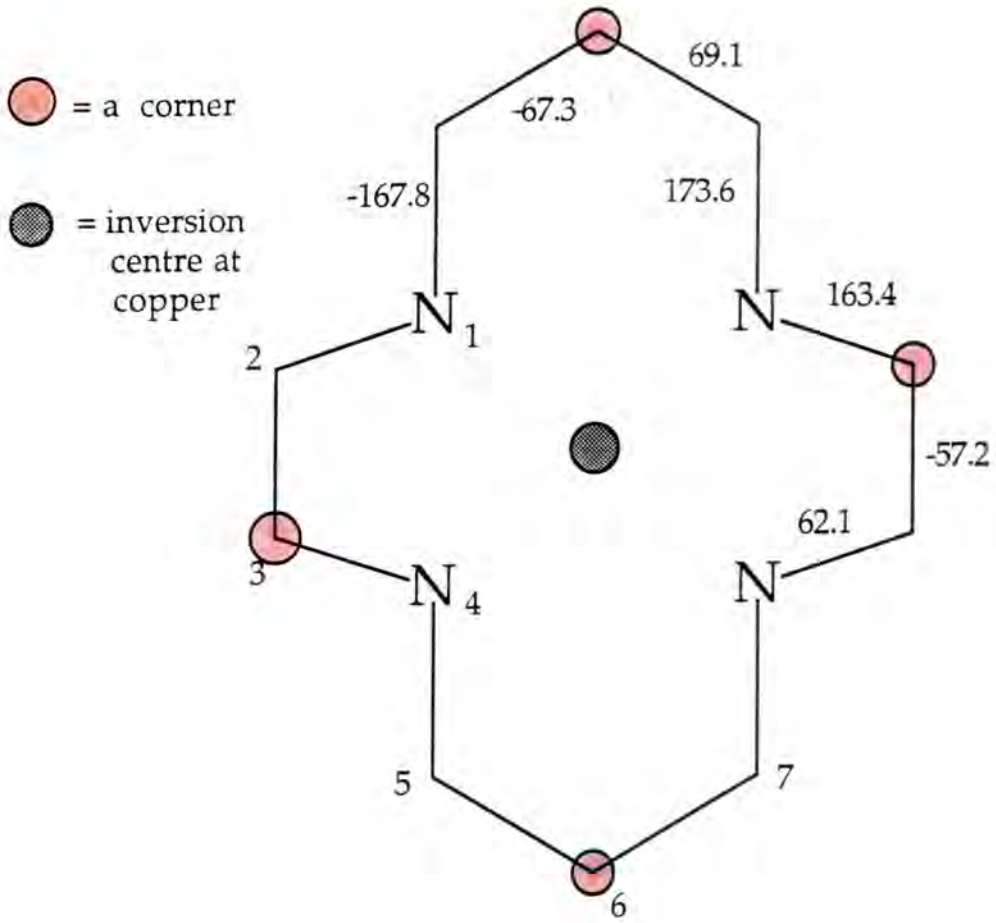


Figure 3.4 Torsion angles for the copper(II) complex of [14]N_4-diacid 8 indicating corners at 2,6,2* and 6*

In the crystal lattice of the complex [12-Cu]$(ClO_4)_2$ a hydrated proton was hydrogen bonded to each carbonyl oxygen and to a proximate perchlorate counter ion, Figure 3.5. This protonation on oxygen may account for the slight elongation of the Cu-O bonds notwithstanding the Jahn-Teller distortion and strong in-plane ligand field. Support for this idea comes from a comparison of the relative structures of (8-Cu) Figure 3.3 in which the Cu-O distance is shorter 2.263(4)Å (Table 3.2) and the copper-nitrogen bond lengths are similar 2.095(3) (to N-CH_2COO) and 2.014(4)Å to the secondary nitrogens. In contrast to this the crystal structure of [8-Cu]$^{II}(ClO_4)_2$ reveals quite clearly that the

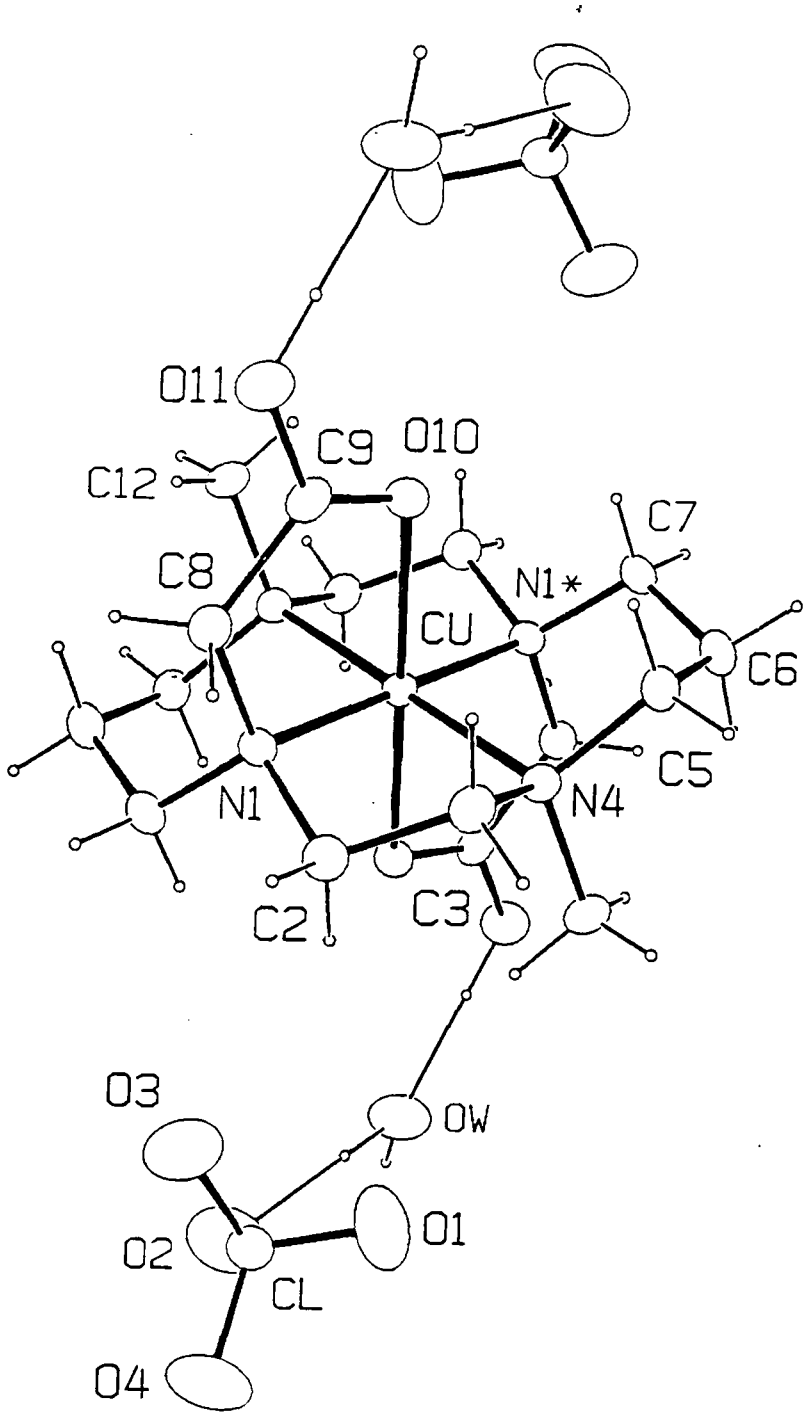


Figure 3.5 X-ray crystal structure of the copper(II) complexes of [14]N_4Me_2-diacid.$2H_2O$ 12 showing the pattern of hydrogen bonding.

perchlorate counter ions are hydrogen bonded to the secondary ring amine nitrogens N4 and N4* directly showing no bonding at all to the two axially disposed carboxyl methyl groups.

These copper complex structures with 8 and 12 may be contrasted with that reported 1,4,8,11-tetraazacyclotetradecane-tetraacetic acid (TETA) in which the primary co-ordination sphere involves N_2O_2 co-ordination and two nitrogen atoms occupy these elongated axial sites. In this case a strong N4- in plane ligand field cannot be attained without severe non-bonding interactions and the complex relaxes to the lower energy structure observed.

3.5 Structurally Reinforced Macrocycles

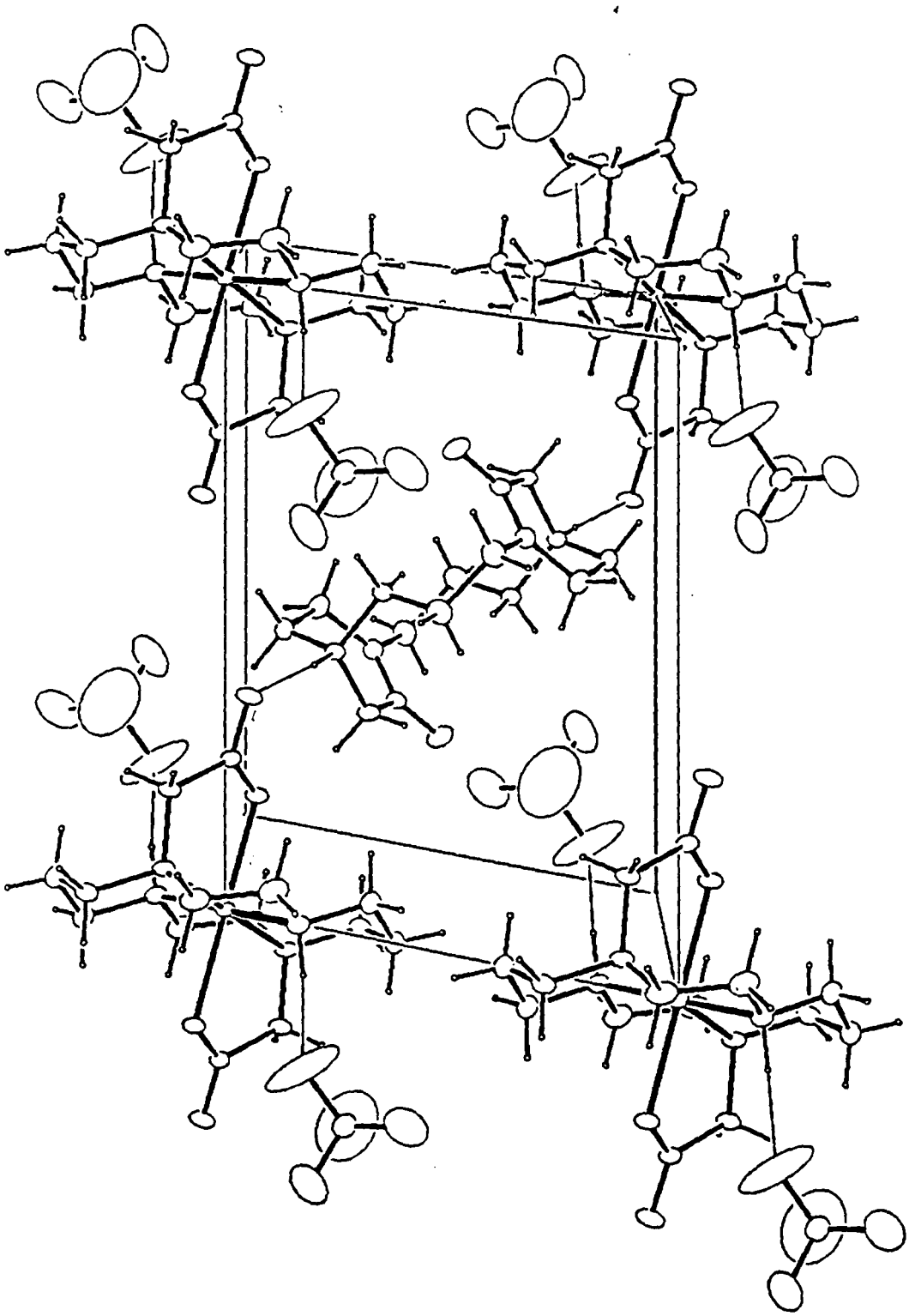
3.5.1 Synthesis of cyclam lactam 9

As mentioned before the 1,8 diacid macrocycle 8 readily lactamises via a 6-exo-trig. ring closure, to yield the lactam tricycle 9 and it does so readily at room temperature in aqueous solution. The lactam, which bears a topological similarity to a paracyclophane, is remarkably resistant to acid hydrolysis and may be recovered unchanged after boiling in 6M HCl overnight in the presence of methanol [ν 1660 cm^{-1} m/e (NH_3, chemical ionisation) 281 ($M^+ + 1$)]. Chromatographic separation on flash silica gel (5% MeOH and 95% CH_2Cl_2) separated two isomeric forms of the lactam. Although the crystallographic analysis Figure 3.7 revealed that the "E" stereoisomer was formed, lactamisation proceeds in solution to give an approximately 65:35 mixture of the "E" and "Z" diastereoisomers, as deduced by ^1H NMR integration of the resonances at 2.79-2.92 and 3.32-3.37 ppm. The resistance of the tricyclic lactam

9 to acid hydrolysis may be related to steric hindrance to the approach of a water molecule to the faces of the protonated amide carbonyl: attack at the Re face may be hindered by ring topology and the axial hydrogens in the half chair six membered rings may inhibit attack at the Si face.

3.5.2 Structural analysis of cyclam lactam 9

The constitution of the lactam was confirmed by X-ray crystallographic analysis and was located within the unit cell of the copper complex of the diacid macrocycle 8, shown in figure 3.6. In the case of the structure of the complex 8-Cu, the complex crystallised with the diprotonated lactam 9 in the crystal lattice. The lactam lay in the centre of the unit cell (at the inversion centre) with the copper complex at the four corners. The carbonyl oxygens of the copper complex O(11) were hydrogen bonded to the protonated tertiary amines N(1) of the lactam and the secondary N-H groups were hydrogen bonded to the perchlorate counter ions, Figure 3.6 and 3.7. A 2-D COSY ^{1}H NMR spectrum of the "E" (or "Z") lactam was recorded. This 2-D COSY plot is shown in Figure 3.8 and reveals the spin-spin coupling relation-ships between protons within the structure.



igure 3.6 View of the unit cell showing the protonated lactam H_2^{2+} at the inversion centre.

The structure of the diprotonated lactam 9 is shown in Figure 3.7.

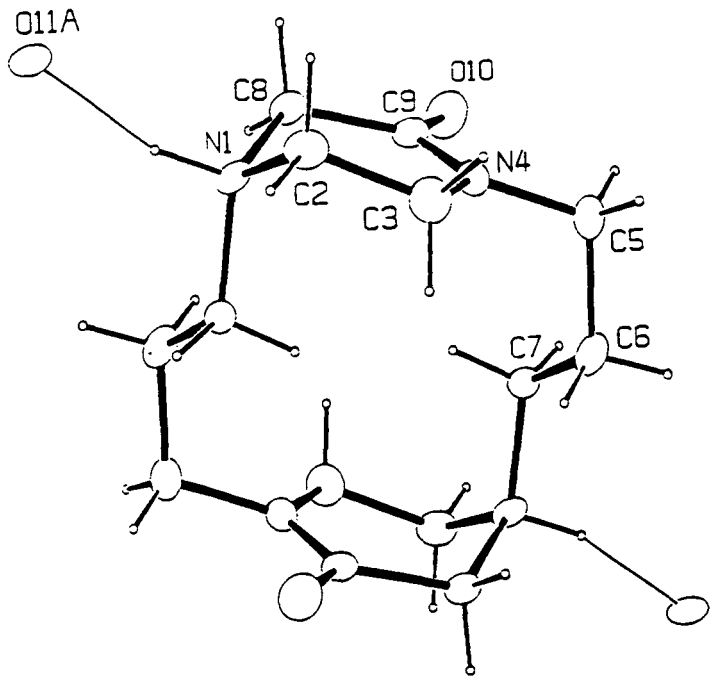


Figure 3.7

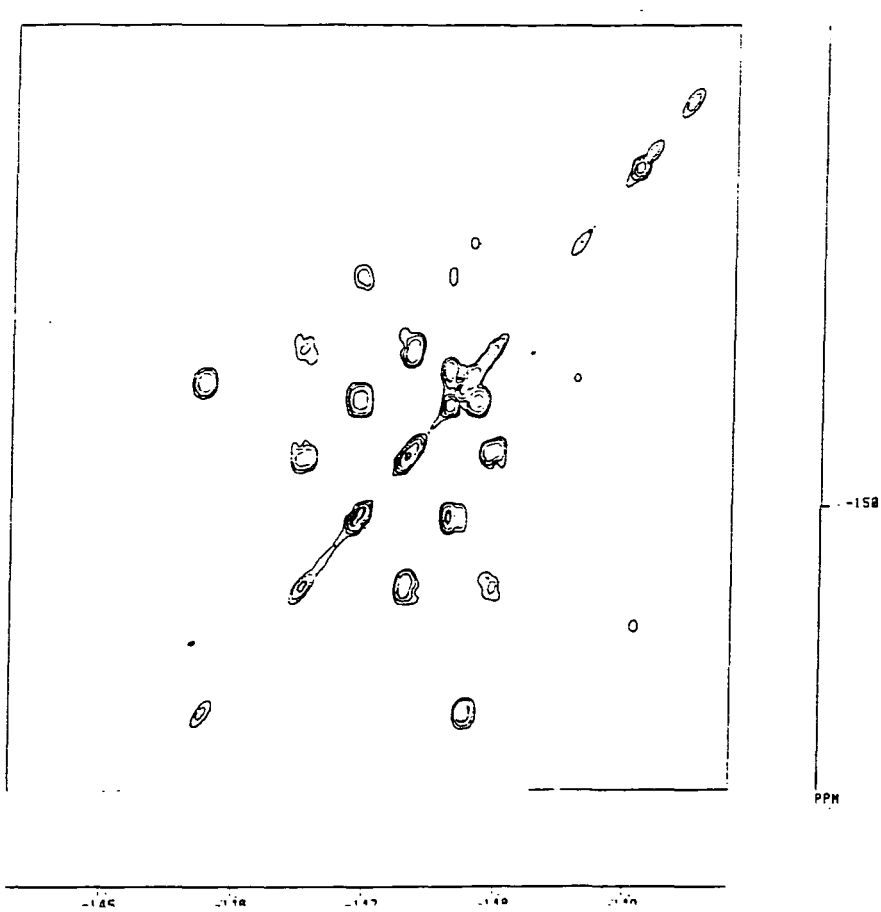


Figure 3.8

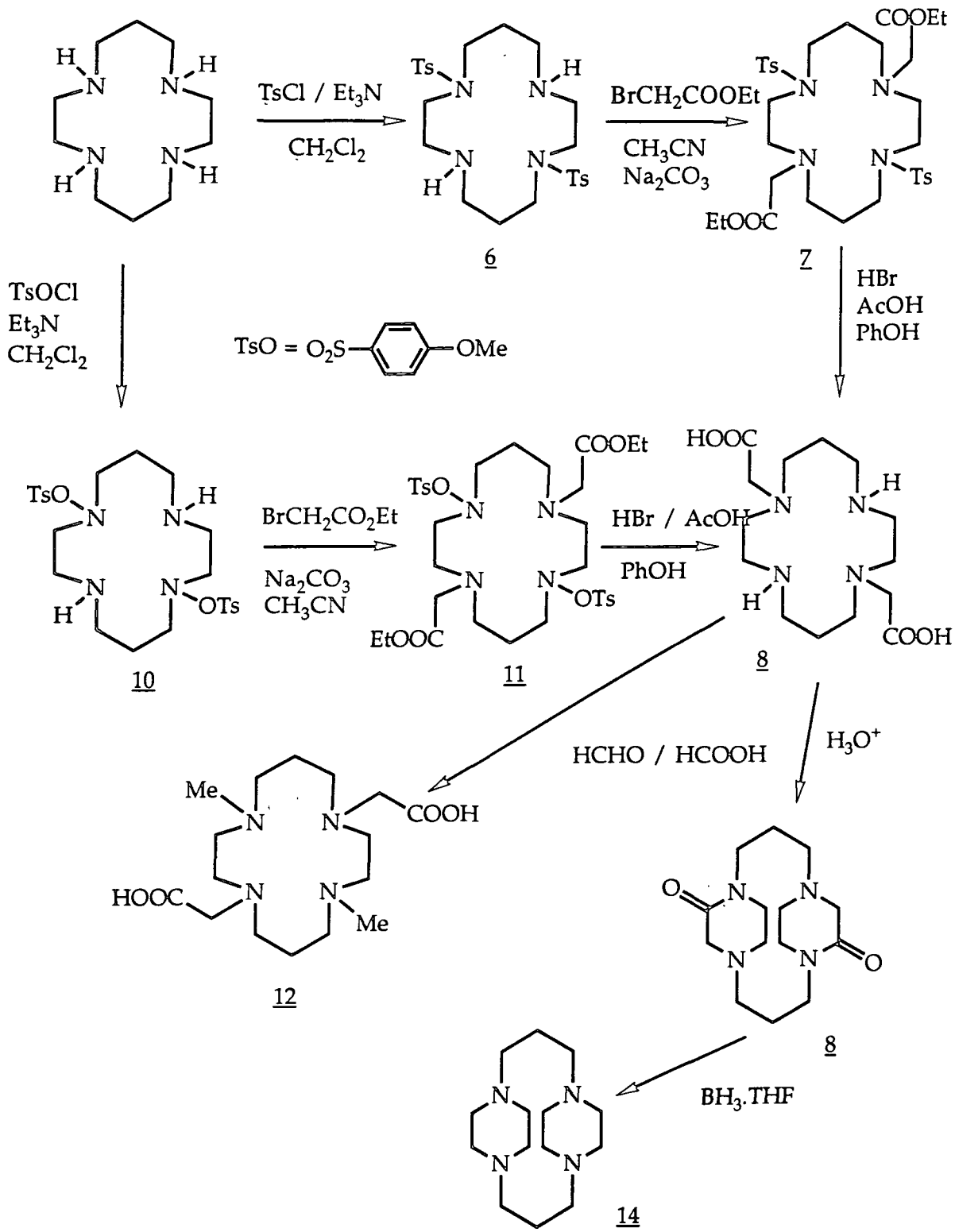
3.5.3 Synthesis of Tricyclam 15

Next, separate reduction of both isomeric forms of the lactam, or of a mixture of the two isomers proceeded readily by boiling in 1M BH_3.THF adduct under nitrogen. After 36 hours reaction, the disappearance of the amide peak at 1650 cm^{-1} confirmed the completion of the reaction. Subsequent hydrolysis of the amino-borane complex with 6M HCl (3 hours) yielded the cyclic tetra-amine 14 which was purified by extraction into dichloromethane in moderate yield, 60% (Scheme 3.4). Analysis by ^1H and ^{13}C NMR indicated that the target molecule had been obtained which was confirmed by DCI mass spectrometry, m/e 253 (M^+ + 1). This cyclic tetra-amine was considered as a possible lipophilic ligand to bind to copper and nickel.

This ligand - a cryptand - may also be regarded as a "structurally reinforced" macrocycle[16] in which the rigidity of the macrocyclic system enforces the metal ion to bind in the plane of the donor atoms. In binding in such a manner, each of the piperazine rings needs to adopt a boat conformation which is energetically unfavourable and will contribute an unfavourable term to the enthalpy of metal complexation. The unfavourable nature of the chair-boat interconversion and the structural rigidity of the ligand as a whole are reflected in the observed protonation constants for 14.

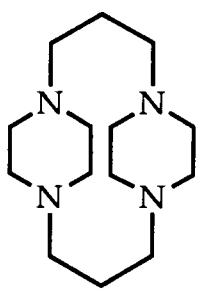
3.5.4 Measurement of acid dissociation constants

The acid dissociation constants, ie. its pKa values, for the tricyclic tetra-amine, tricyclam, were obtained by successive potentiometric titrations at 298K, in 0.1M dm^{-3} tetramethylammonium nitrate to ensure constant ionic strength in de-ionised water. The data analysis was performed with the aid of the least-



Scheme 3.4 Summary of synthetic routes to [14]N_4-diacid 8 and [14]N_4Me_2 diacid 12

squares programs SCOGS-2 and SUPERQUAD. Potentiometric titrations reveal successive pKa values of 8.33(3) and 3.02(2) for tricyclam. The first of these values is very similar to that found for other amines and piperazines or diazabicyclooctane[17] but the second protonation constant is rather low, Table 3.3 by comparison. The relatively high acidity of the diprotonated species



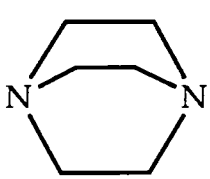
(298K, I = 0.1M Me_4NNO_3)

pK_1 8.33

pK_2 3.02

data analysis by SCOGS-2 and SUPERQUAD

compared to:-

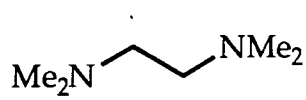


Diazabicyclooctane

pKa (25°C, I = 1)

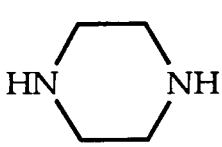
8.10

4.14



9.15

5.91

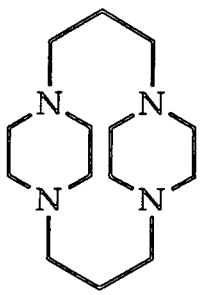


8.98

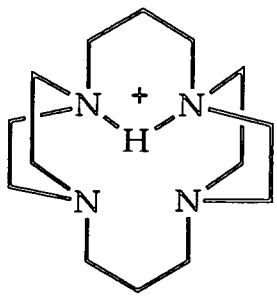
4.83

Table 3.3

$(\underline{15}H_2)^{2+}$ might be related to steric inhibition of protonation of the monoprotonated ligand. It seems likely that the monoprotonated species would suggest a structure 15b whereby a bridging proton would complete a six membered ring and this proton would lie above the plane of the ring system. A second protonation should produce a similar intermediate species whereby the second bridging proton would lie adjacent on the same side of the ring system thus producing a "flagpole"-type steric interaction, 15c.



15a



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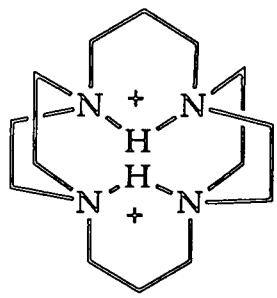

15c

3.5.5 Structural analysis by ^1H NMR as a function of pH

The ^1H NMR spectrum of the ligand was examined as a function of pH. At both high pH (greater than 11) and in $CDCl_3$ or CD_2Cl_2 resonances were observed that were consistent with time averaged D_2d symmetry: a single quintet and triplet for the two $NCH_2CH_2CH_2N$ moieties and a pair of symmetrical multiplets for the piperazine ring protons. The spectrum of the tetracation was shifted to higher frequency in 12M DCl/D_2O, but also had the same features, eg. a quintet for $NCH_2CH_2CH_2N$, suggesting that this species has similar high symmetry. At intermediate values of pH, broadened resonances were additionally observed and the spectra obtained were more

complex. In deutero acetate buffer at pH 5, two multiplets in a 1:1 ratio for the $NCH_2CH_2CH_2N$ resonances were observed suggesting structure 15b for the monocation while at pH 0 the broadened resonances of the 6-membered ring protons had shifted to higher frequency and at least four resonances for the $NCH_2\underline{CH_2}CH_2N$ protons were distinguished. Certainly the protonation behaviour of 15 is quite different from that of tetramethyl cyclam, 1,4,8,11-tetramethyl 1,4,8,11-tetraazacyclotetradecane and is not behaving like two independent piperazines.

3.5.6 Copper(II) complex of tricyclam 15

The 1:1 copper complex of the ligand tricyclam was prepared by the addition of approximately one equivalent of copper perchlorate hexahydrate in methanol, to a solution of tricyclam in methanol, at room temperature. Initially nothing happened but on warming gently a brown gelatinous precipitate was formed which was removed, with some difficulty, by filtering and centrifugation to yield a distinctively blue-red solution typical of a copper complex. Excess copper was removed by bubbling hydrogen sulphide through the solution and filtering off the residual precipitate, thus indicating that the complex is resistant to attack by sulphide, and the visible absorption spectra of the complex in methanol remained unchanged at 516 nm. The complex was initially characterised by Fast Atom Bombardment (FAB) mass spectroscopy and molecular ion peaks were observed at m/e 315 and 317 consistent with complexes of the two isotopes of copper ($^{63/65}$Cu-L). Molecular ions corresponding to copper ligand complexes of other stoichiometry (1:2 or 2:1) were not observed.

3.5.7 Nickel(II) complex of tricyclam 15

The nickel complex of tricyclam was prepared in a similar fashion to its copper analogue by the addition of an equimolar quantity of nickel perchlorate hexahydrate in methanol to the ligand tricyclam in methanol. Upon warming the solution colour changed from green to pale blue accompanied by a fine brown precipitate which was filtered off. The complex was not stable to attack by sulphide and did not appear to be particularly soluble in methanol, hence all spectroscopic measurements were made from water. The complex was characterised by FAB mass spectrometry to reveal molecular ions (M^+) at m/e 310 and 312. (^{58}Ni-L) and (^{60}Ni-L) respectively.

Attempts to crystallise both of these complexes was tried from different solvents but none were found that would give crystals suitable for X-ray analytical purposes.

The copper and nickel complexes of the tricyclic tetra-amine 15 in aqueous solution give visible absorption spectra, λ_{max} (H_2O) = 538 and 450 nm respectively, typical of square-planar complexes with a strong ligand field, Table 3.4. The copper complex is resistant to attack by hydrogen sulphide also in aqueous solution, which is consistent with high kinetic stability.
The visible absorption spectrum was invariant in the pH range 1.4 to 11.4 showing that the complex was resistant to protonation over this range. In comparison $[Cu\text{-cyclam}]^{2+}$ is also resistant to acid-catalysed decomplexation and dissociation may only be observed in 6M nitric acid[18]. In these square planar complexes with 15, the two piperazine rings must adopt boat conformations to produce the "least strain" conformation.

Table 3.4 Visible absorption spectra (H_2O, 293 K) for nickel and copper complexes.

Complex cation	λ_{max}/cm^{-1}	10 $D_{q_{xy}}$ [a]
[Ni-15]$^{2+}$	22 222	2020
[Ni-cylam]$^{2+}$	22 473	2043
[Ni-18]$^{2+}$	23 540	2140
[Cu-18]$^{2+}$	18 310	
[Cu-cyclam]$^{2+}$	19 900	
[Cu-15]$^{2+}$	18 587	

[a] 10 $D_{q_{xy}} = \nu_{d\text{-}d}/11.0$ (ref. 15). [d] Ref. 16.

[e] 18 = 1,4,7,10-tetraazacyclotridecane. [f] Ref. 7.

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CHAPTER 4

SYNTHESIS OF FUNCTIONALISED [9]N_3 AND [12]N_3 MACROCYCLES TO BIND TO COPPER(II) AND NICKEL(II)

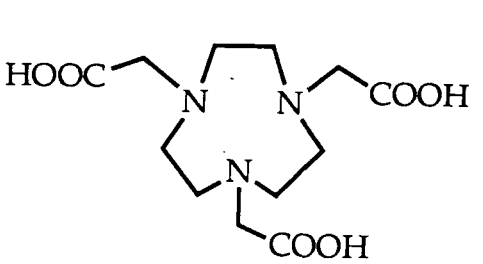
4.1 Introduction

The synthesis of functionalised azacoronands of variable ring size has been the subject of recent interest mainly because of their versatility and ability to selectivity bind a wide range of cationic species[1,2]. Tetra-azamacrocycles of varying ring sizes and degrees of unsaturation were among the first azamacrocycles synthesised and numerous complexes of the ligand 1,4,8,11-tetra-azacyclotetradecane and its analogues have been prepared.

Applications of these functionalised ligands in tumour targeting[3], ion selection[4], electrocatalysis[5] have been reported. Surprisingly, at the outset of this work much less work had been reported on the selective synthesis of functionalised triazacoronands, although the utility of derivatives of $[12]N_3$ systems as "proton-sponges" has been noted[6]. Recently reported syntheses of derivatives of the $[12]N_3$ ring system have involved either the selective protection of a ring precursor[7] prior to Richman-Atkins cyclisation[8], or the intermediacy of tricyclic orthoamides developed by Weisman[9] (Chapter 1, page 11). The work described in this chapter has concentrated on the synthesis of N-substituted derivatives of $[12]N_3$ systems.

A pentadentate dibasic ligand was sought, that would form charge neutral complexes with ions such as Cu^{II}, Ni^{II} and Zn^{II}, in order to promote complex lipophilicity and reduce the sensitivity of the complex to acid promoted dissociation.

Initially, the 12-N_3 triacid 4 was prepared in order to allow a comparison of its co-ordination chemistry with that of the more extensively studied [9]-N_3 analogue, 3.



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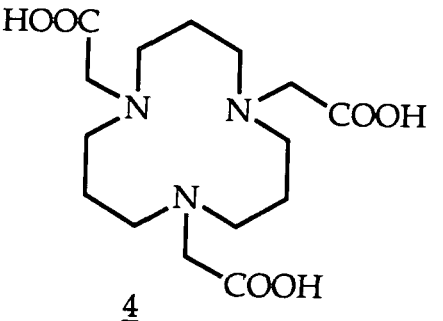


4

9 N_3-triacetate TCTA 12 N_3-triacetate

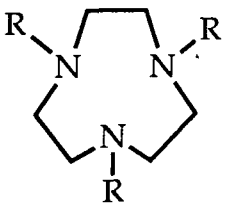
The synthesis of ligand 3 was first reported in 1973[10] and the formation of its neutral Fe(III), Cr(III) and Co(III) complexes reported later in 1977.[11] The anionic nickel(II) complex of ligand 3 $H_3O[Ni(TCTA)]$[12] was made by Hancock and he found that on standing it reverted in acid solution to the neutral nickel(III) complex Ni(TCTA).[13] Weighardt[14] has also reported the synthesis and spectral properties, uv-visible, infra-red of several transition metal complexes of TCTA and also reported the preparation of the group III metal complex of Al-TCTA.

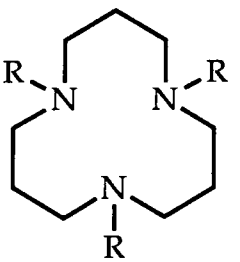
4.2 Synthesis of Macrocycles to Bind to Copper(II) and Nickel(II)

4.2.1 Synthesis of $[9]N_3$ and $[12]N_3$ tribasic hexaco-ordinating macrocyclic ligands

The target triazamacrocycle 3 and 4 were synthesised via the intermediate tosylamide and triester derivatives listed in Table 4.1.

The acyclic tosylates and tosylamides were readily prepared from their parent alcohols and amines according to the literature procedures,[15-17] using p-toluenesulphonyl chloride and pyridine.





R = Ts	5	6
R = H	1	2
R = CH_2COOEt	7	8
R = CH_2COOH	3	4

Table 4.1

The ring cyclisation reactions have been reported previously by a number of workers[18-21]. The method employed here was that of Richman and Atkins[19] using the sodium salt of a ditosylamide and refluxing it with a suitable acyclic tosylate in the presence of an aprotic solvent such as DMF. The sodium salt of the tosylamide was easily prepared by refluxing under anhydrous conditions with a solution of sodium ethoxide in ethanol in good yield (98%) giving a white crystalline solid. This was used directly and the ditosylate in DMF was added slowly to a well stirred solution of the sodium

salt of the ditosylamide in DMF, under anhydrous conditions. The tritosyl-amide cycles were obtained in good yield (80-84%) after purification by gravity silica gel chromatography.

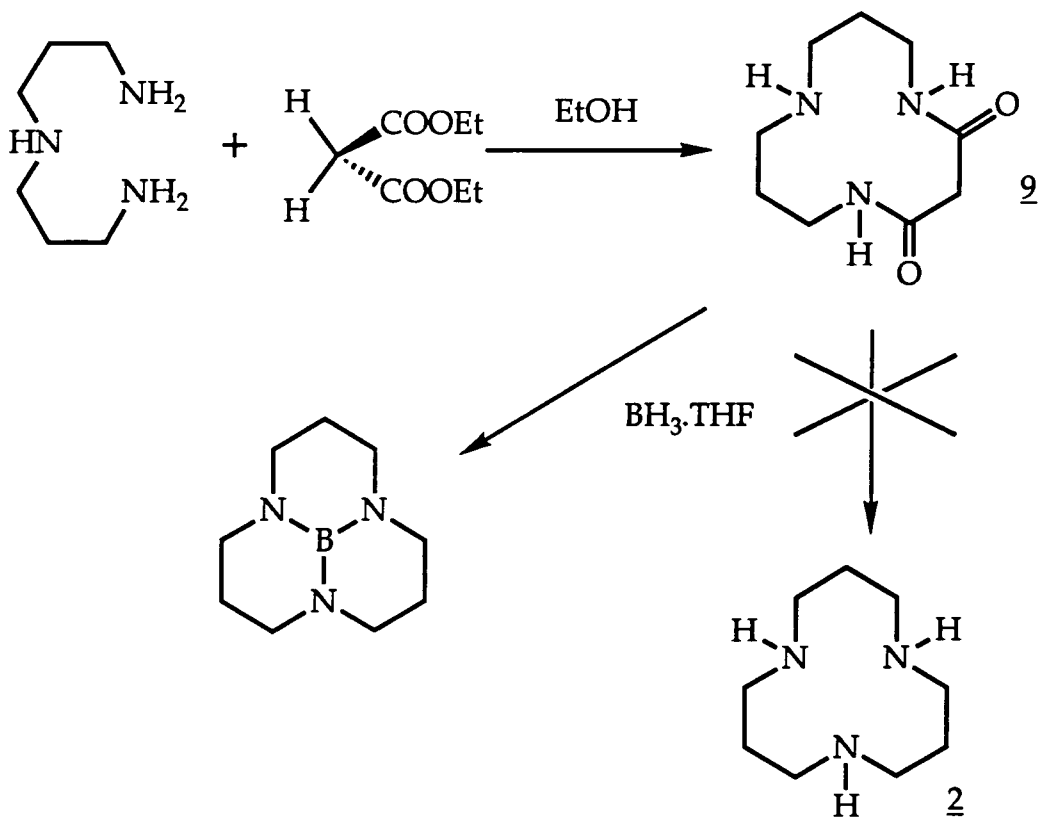
The next stage was the removal of the three tosyl groups and this was attempted using 45%w/v HBr/HOAc in the presence of phenol. ^{1}H NMR analysis indicated that detosylation was only partially complete. However, detosylation was more efficiently effected using concentrated sulphuric acid at 120°C followed by basification with 50% sodium hydroxide solution and extraction into chloroform[22] to yield the free amine. N-Alkylation was achieved by the reaction of these free amines with ethyl bromoacetate in the presence of caesium carbonate yielding the corresponding triesters which were purified by column chromatography on neutral alumina. Subsequent hydrolysis of the triester to the triacid was carried out by refluxing in 6M hydrochloric acid to yield the triacid as its hydrochloride salt as a colourless glassy solid.

4.2.2 Alternative route to the [12]N_3 ring system

An alternative route to produce the twelve-membered ring system is via the malonate condensation method. The main advantage is that it forms a cyclic diamide directly and hence omits the detosylation stage, which previously was found to be rather awkward. The main disadvantages are the moderate yield (11-19%) and the requirement for a further reduction step to produce the desired amine from the amide.

The starting materials, diisopropyl triamine and diethyl malonate are readily available. Equimolar quantities of these reagents were mixed together and heated to reflux in an excess of ethanol for 5 days, (Scheme 4.1).

Thin layer chromatographic analysis revealed three major components: a monomer R_f 0.60, a dimer R_f 0.30 and an oligomer R_f 0.10. The low yield of the desired monomer may be attributed to competitive dimer and polymer formation, although conditions of moderate dilution was used to try and



Scheme 4.1

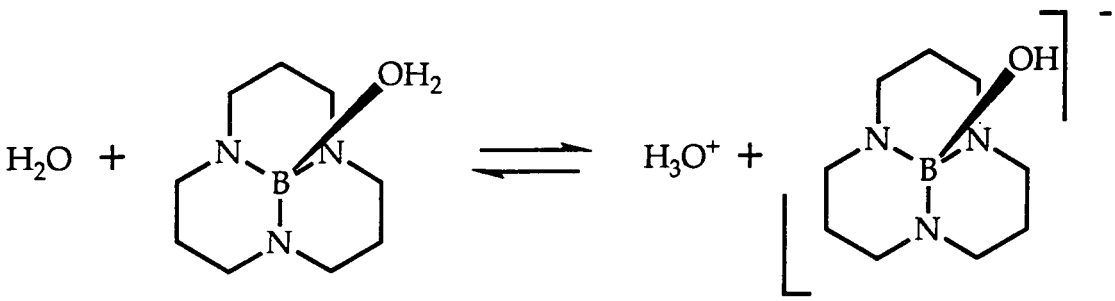
minimise this. The desired monomeric cyclic diamide 9 was separated by gravity silica gel column chromatography. This product was obtained as a homogeneous colourless solid.

Reduction of the amide to the amine was now attempted by refluxing with an excess of diborane-THF adduct under nitrogen for 24 hours. Surprisingly, reduction of the cyclic diamide 9 did not yield the expected triamine 2. Although the amide peak at 1650 cm^{-1} had disappeared, the product lacked the presence of N-H bonds (IR and ^{1}H NMR analysis). Microanalysis revealed that it contained 5.5% boron.

After further investigation, it was clear that the amide had been reduced, not to the free amine but to a very stable tris(amino)borane 13, in which the boron atom was bound to the three deprotonated nitrogens.

This obviously presented a synthetic problem, particularly as it was found that the tris(amino)borane was quite stable to acid hydrolysis and reformed on basification. A ^{11}B NMR analysis of the complex was effected monitoring the chemical shift as a function of solvent, and in aqueous solution as a function of pH. Over the pH range 0.1 to 15 (conc. acid to conc. alkali and buffers) the ^{11}B resonance shifted from -1.31 to +0.73 ppm. However, this minor variation may be explained by experimental error in shift measurement and referencing as results from similar samples in repeated experiments were not the same.

The only significant shift change occurred between non-aqueous and aqueous solvents. In acetone and deuterochloroform, values of 21.47 and 22.64 ppm respectively were recorded.



Structure A

The question posed is whether the variation in δ_B is a function of charge or of co-ordination number, or both. If it were a function of charge we would expect some change in chemical shift on going from pH 0.1 to 15. However, there is no such change and δ_B does not vary to any significant effect and hence a change in charge may not be occurring.

In aqueous solution the 4 co-ordinate structure A, is thought to be present which is independent of pH. In anhydrous non-aqueous solution, the boron atom remains 3 co-ordinate. Hence it would appear that δ_B is a function of boron co-ordination number. The boron complex of 1,5,9-triazacyclododecane has also been prepared following exhaustive reaction of the amine with $B(OMe)_3$[23]. We have shown that borane reduction of the diamide 9 affords an alternative route to this boron complex.

4.3 Synthesis of [12]N_3 Penta Co-ordinating Dibasic Macrocyclic Ligands

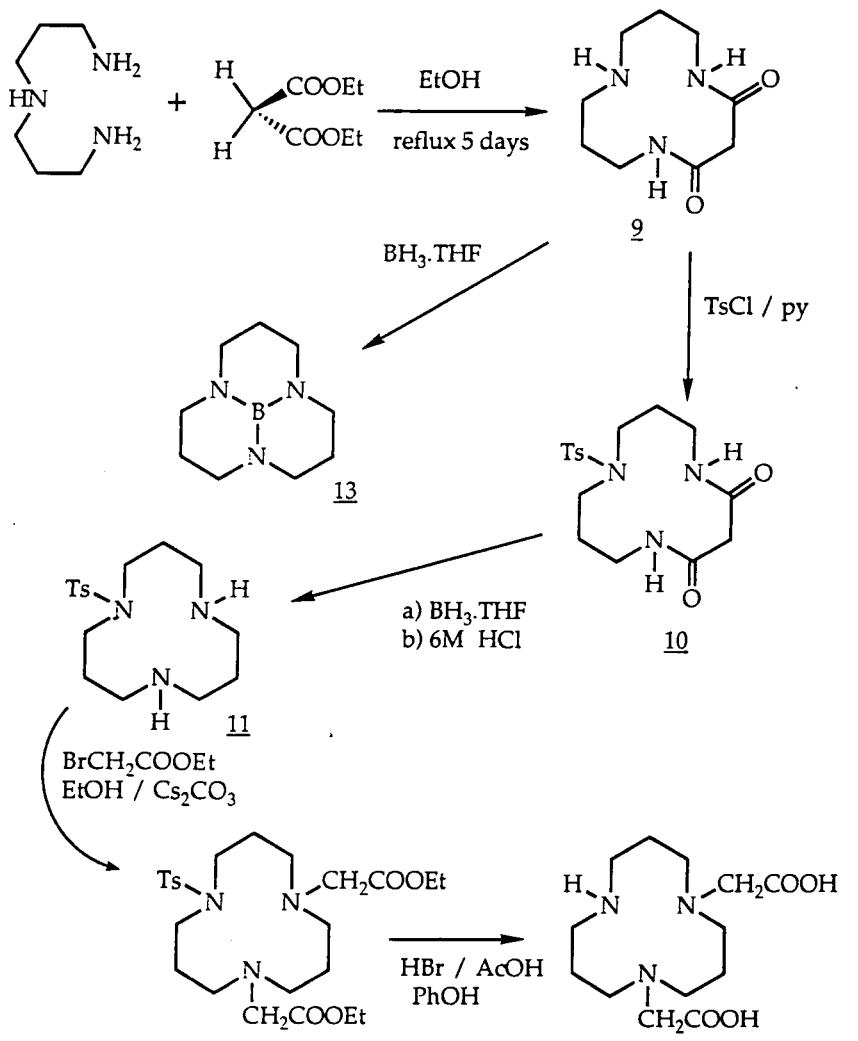
It was decided that if the free amine group of the cyclic amide was protected by a suitable protecting group, e.g. tosyl, this bridging boron complex could not be made. This route also effectively distinguished one

nitrogen from the other two. Tosylation of 9 prior to borane reduction would obviate the formation of this resilient boron complex, and lead to the formation of the N-tosylamide. Hence reduction of the protected amide would proceed as required.

This particular route should lead to the synthesis of a penta co-ordinating ligand with two ionisable groups. With this in mind the pentadentate diacid 14 was sought.

4.3.1 Synthesis of [12]N_3-diacid 14

The target triazamacrocycle 14 was synthesised according to the method outlined in scheme 4.2. The cyclisation to produce the diamide 9 was carried out in moderate yield.



Reaction of the diamide with a slight excess of tosyl chloride in pyridine at 4°C proceeded smoothly to yield the mono-substituted cycle according to a literature procedure[15-17]. Extraction into dichloromethane from the reaction mixture followed by recrystallisation from hot methanol gave the N-tosyl amide 10 in a reasonable yield of 53%.

Tosylation of this amide 9 was also found to be successfully effected with p-toluene sulphonyl chloride in methylene chloride and triethylamine as a base. This method proved to be a more efficient route and gave a better yield (53% vs. 85%).

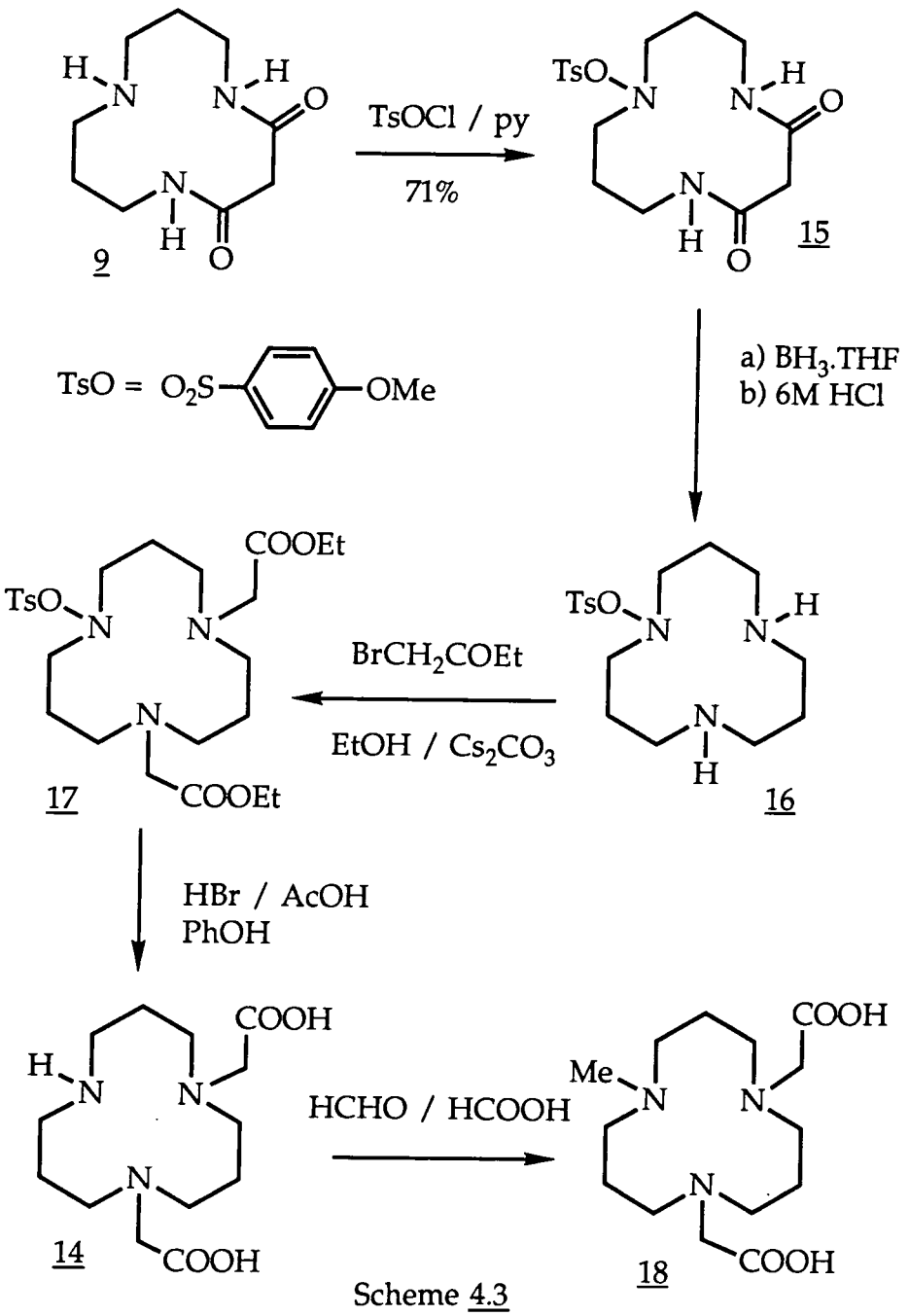
Next, reduction of this tosylamide, 10, proceeded readily by boiling in 1M BH_3.THF adduct under nitrogen. After refluxing for 24 hours, the disappearance of the amide peak at 1650cm^{-1} confirmed that reaction had gone to completion. Subsequent hydrolysis of the amino-borane complex with 6M HCl (3 hours) yielded the N-tosyl triamine 11 as a colourless glass by extracting into chloroform in a good yield of 90%, molecular ion peak at m/e 326 (M^+ + 1). Thus formation of the tris(amino)borane complex 13 had been avoided. This N-tosyl triamine may now be used for further N-functionalisation.

The triamine 11 in dry ethanol was alkylated with two equivalents of ethyl bromoacetate in the presence of caesium carbonate and initial analysis by thin layer chromatography indicated that a fast moving component had been formed, corresponding to the expected dialkylated product. The product was purified by flash chromatography to yield the diester 12 as a colourless oil in 74% yield.

The tosyl protecting group could now be removed in the usual fashion using 45%w/v HBr/HOAc in the presence of phenol to yield a light coloured precipitate. After a total of 100 hours reaction time a fine precipitate had formed which was isolated by filtration. The dihydrobromide salt was an off-white precipitate isolated in 73% yield. This diacid 14 was found to be slightly hygroscopic.

The formation of the cyclam diacid derivative 9 (Chapter 3) was found to proceed more cleanly and quickly with an improved yield by using a more acid labile nitrogen protecting group with respect to tosyl. With this in mind it was decided to repeat this synthesis of the [12]N_3-diacid 14 using the p-methoxybenzenesulphonyl group as it is known to be more readily cleaved (under strongly acidic conditions) than the tosyl group. The synthesis was repeated accordingly with the p-methoxybenzenesulphonyl group (scheme 4.3), in place of tosyl.

Formation of the sulphonamide 15 proceeded in 71% yield, and borane reduction gave the diamine 16, isolated as a crystalline solid, (73% yield). The diester 17 was obtained by the gradual addition of ethyl bromoacetate to a suspension of the triamine 16 in dry ethanol in the presence of caesium carbonate. The product was purified on a flash silica gel column to give the diester 17 as a colourless oil (83%). Deprotection of the benzenesulphonamide group with concomitant ester hydrolysis gave the diacid 14 as its dihydrobromide salt in high yield (94%). This would indicate that the p-methoxybenzenesulphonyl is a more appropriate protecting group as the deprotection step is higher yielding than for the tosyl analogue (73% vs. 94%).

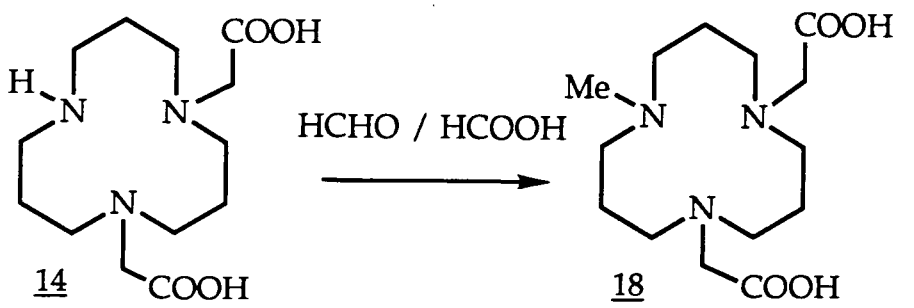


Scheme 4.3

4.3.2 Synthesis of [12]N_3Me-diacid 18

A simple way of further increasing the lipophilicity of a divalent metal complex is to alkylate the remaining secondary amine. Methylation of the pentadentate diacid 14 proceeded smoothly via the Eschweiler-Clarke method by refluxing with an equimolar amount of formic acid and 30% formaldehyde

for 18 hours outlined in Scheme 4.4. Addition of hydrochloric acid to the

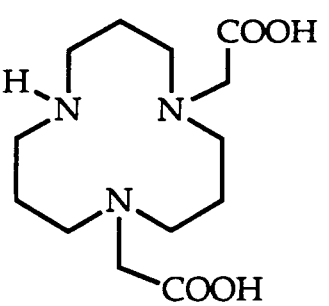


14 18

Scheme 4.4

reaction mixture gave the methylated diacid 18 as its hydrochloride salt which came out of solution as a white crystalline solid in a reasonable yield of 74%. This ligand was now available for any suitable metal complexation.

Thus two functionalised diacid triazamacrocycles 14 and 18 derived from 1,5,9-triazacyclododecane were obtained as their hydrobromide salts. These ligands should form stable transition metal complexes of different lipophilicity and solubility with respect to their non-functionalised azacoronand, 1,5,9-triazacyclododecane.



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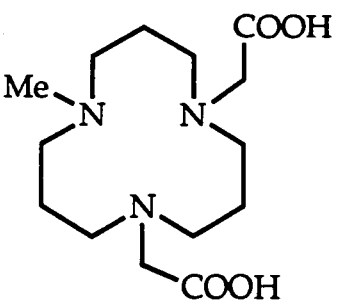

18

4.4 Copper(II) and Nickel(II) Complexes

4.4.1 Copper(II) complex of [12]N_3-diacid 14

In order to form the 1:1 complex between the [12]N_3-diacid 14 and copper perchlorate an approximately equimolar quantity of copper perchlorate hexahydrate in water was added to the ligand hydrochloride in water at pH 1. A pale green solution was obtained with an absorption maxima at 662 nm and 458 nm. Upon warming and basification to 6.5 with KOH the colourless precipitate of potassium salts grew in bulk and a royal blue solution was obtained, λ_{max} 675 nm (ε = 371 dm^3 $mole^{-1}$ cm^{-1}). Through an aqueous solution of the complex was bubbled hydrogen sulphide gas and a small amount of copper sulphide was filtered off. The absorption spectrum of the resultant royal blue solution revealed a smooth maximum at 675 nm. Thus the complex has been freed from excess aquo-copper(II) and is stable with respect to attack by sulphide. On adjusting the pH from 6.5 through to 14, a change in the positions and intersities of the $\lambda_{max's}$ was observed. At pH 8.5 a small amount of precipitate began to come out of solution with the appearance of an absorption peak at 528 nm. At pH 9.5 through to 14 this peak gradually grew in intensity while the peak at 675 nm shifted to 682 nm and decreased in intensity. The peak at 528 nm may possibly be due to the formation of a weak $[CuLOH]^+$ species. N.B. [CuL is neutral]. Crystallisation of the complex was attempted, (from aqueous and alcoholic solutions) but without success even after exchanging the counter ion for the hexafluorophosphate ion. The complex was characterised by Fast Atom Bombardment (FAB) mass spectrometry and molecular ion peaks were observed at m/e 350 and 352 consistent for the two isotopes of copper $(^{63/65}Cu\text{-}L)^+$.

4.4.2 Nickel(II) complex of [12]N_3-diacid 14

The 1:1 nickel(II) complex of this ligand 14 was obtained in a similar fashion to the copper analogue. At pH 1 a yellow coloured solution, (λ_{max} 459 nm) was obtained. After warming and adjusting the pH gradually to 4.5 a fine red precipitate formed accompanied by an orange-yellow solution, λ_{max} 453 nm. Further basification to pH 6.5 resulted in the formation of a thick red precipitate which was filtered off to give a yellow-red solution with a visible absorption band at 535 nm. This complex was resistant to attack by hydrogen sulphide, as was expected, although attempts to grow crystals suitable for X-ray analysis from various different solvent systems were not successful. The complex was characterised by Fast Atom Bombardment (FAB) mass spectrometry and molecular ion peaks were recorded at m/e 345 and 347 (^{58}Ni-L and ^{60}Ni-L).

4.4.3 Copper(II) complex of [12]N_3Me-diacid 18

Complexation of the N-methylated ligand, 18, with copper(II) and nickel(II) was examined in a similar manner. Reaction of equimolar quantities of copper perchlorate hexahydrate and 18 in methanol gave a plum-red to brown solution, which turned green on the addition of a few drops of water (λ_{max} 790 nm). Upon warming and basification to pH 6.5 a precipitate and a pale blue solution was given whose λ_{max} was recorded at 685 nm. Through a solution of the complex in methanol-water was bubbled hydrogen sulphide gas and a small amount of precipitated copper sulphide was filtered off and the resulting blue solution had an absorption band at 685 nm. It appears that this complex is also stable with respect to attack by sulphide and may be separated

from excess copper in this manner. In the pH range 1.5 to 4.0 a shift in the position of the absorption band from 620 nm to 686 nm was noted. This may correspond to protonation of the neutral copper(II) complex giving the cationic mono-protonated species. In the pH range 4.0 to 14 no further shift in the absorption maximum occurred suggesting that the complex is stable with respect to further ligation within this pH range.

Molecular ions (M^+) at m/e 364 and 366 for $^{63}Cu\text{-}L^+$ and $^{65}Cu\text{-}L^+$ respectively, approximately in the ratio 2:1, were observed in the FAB mass spectrum. Slow recrystallisation of the complex from a variety of different solvent systems was attempted, but none were found that yielded crystals of suitable quality for X-ray diffraction analysis purposes.

4.5 References

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CHAPTER 5

EXPERIMENTAL

5.1 Introduction

The synthetic procedures for the compounds used in this work are described in the proceeding section. Air sensitive reactions were carried out using standard Schlenk techniques. Reactions were carried out at room temperature unless otherwise stated. Rf values refer to silica gel TLC (Merck. Art. 5735, Kieselgel 60 F_{254}) or alumina TLC (Merck.Art. 5550, Kieselgel 60 F_{254}) with the eluent system specified. Column chromatography employed "gravity" silica (Merck. Art. 7734, Kieselgel 60, 0.063 - 0.200 mm) or "flash" silica (Merck. Art. 9385, Kieselgel 60, 0.040-0.063 mm) or neutral alumina (Merck Art. 1077, activity 1, 0.063-0.200 mm). Infra red spectra were recorded on a Perkin Elmer 577 spectrometer either as a thin film or Nujol mull on NaCl plates or as a KBr disc. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250 spectrometer, with spectral frequencies of 250.134 MHz and 62.896 MHz respectively. Chemical shifts are quoted in ppm to higher frequency of TMS at δ=0 and coupling constants (J) are given in Hz. Internal TMS reference was used for samples in $CDCl_3$, whereas samples in D_2O were referenced externally to TMS. ^{1}H NMR spectra recorded in CD_3OD were referenced to CD_2HOD at δ=3.35 ppm. Mass spectra were recorded on a VG 7070E mass spectrometer operating in the EI, CI, DCI or FAB mode.

Solvents were dried using the following reagents: Ethanol/Methanol/ $Mg(OR)_2$); Dichloromethane (CaH_2); Chloroform (P_2O_5); Tetrahydrofuran (Na)/ benzophenone and Toluene (Na). Anhydrous DMF (99+%) was purchased from Aldrich and water was pre-distilled. All other solvents were of reagent grade.

5.2 Synthetic Procedures

N,N',N''-tris(p-toluenesulphonyl)-1,4,8,11-tetraazacyclododecane

This was prepared by following a similar method to that of Fabbrizzi[1] by reaction of cyclam (1.0 gms, 5 mmol) with p-toluenesulphonyl chloride (2.0 gms, 10.4 mmol) in dichloromethane (100 cc) in the presence of triethylamine (1.1 gms, 11 mmol) and the mixture was stirred for 3 hours at 20°C. Solvent was removed under reduced pressure and the residue chromatographed on silica gel (1% MeOH, 99% CH_2Cl_2) to yield a colourless solid which was recrystallised from hot toluene (1.15 gms, 51%) mp 85-7°C. Found: C, 56.4; H, 6.40; N, 8.21; S, 15.0; $C_{31}H_{41}N_4O_6S_3$ requires C: 56.3; H, 6.20; N, 8.47; S, 14.5%; NMR (^1H, $CDCl_3$) δ_H ($CDCl_3$) 1.54 (2H quin, J = 7.4), 3.26 - 3.00 (10H, mult), 7.26 - 7.17 (6H, d+d+d), 7.65 - 7.55 (6H, d+d+d). ^{13}C ($CDCl_3$) δ_c 142.5, 135.7 (CH_2C), 20.4 (CH_3). m/e (CI-NH_3) 662 (M^++1), 661 (M^+).

1,8-N,N' Bis(toluenesulphonyl)-1,4,8,11-tetraazacyclododecane

This was prepared as for above but using only 1.5 equivalents of tosyl chloride and affecting the reaction at 5°C (18 hours). Separation of the ditosylated product from the tritosylate isomer was effected by flash chromatography on silica gel (R_f (SiO_2, 10% MeOH, 90% CH_2Cl_2): ditosyl cyclam, 0.45; tritosyl cyclam, 0.7), to yield a colourless solid (0.57gms, 30%) m.p. 256-7°C. NMR (^1H, $CDCl_3$) δ_H ($CDCl_3$) 2.19(4H, quint), 2.42 (6H, s) 3.15 - 3.10 (12H, mult), 3.30 (4H, mult), 7.33 (4H, d, J=7.1), 7.64 (4H, d), ^{13}C ($CDCl_3$) δ_C 143.1, 131.6, 128.8, 126.4; 48.6, 48.5, 47.5, 45.0 (CH_2N), 24.8 (CH_2), 20.3 (CH_3). m/e (DCI, NH_3) 509 (M^++1), 508 (M^+). Found C, 56.6; H, 6.92; N, 11.4; S, 12.2; $C_{24}H_{34}N_4O_4S_2$ requires: C, 56.7, H 6.69; N, 11.0; S, 12.6%.

A small quantity of the constitutional isomer 1,4-ditosyl cyclam was also produced in this reaction which could be separated by flash chromatography [R_f (SiO_2: 10% MeOH, 90% CH_2Cl_2) 0.4], to yield a glassy solid (66 mg, 3.5%) NMR (^1H, $CDCl_3$) δ_H 1.96 (2H, mult, J=5.1), 2.02 (2H, mult), 2.44 (6H, s), 3.06-2.96 (6H, mult), 3.15 (2H, mult), 3.26 (4H, t, J=5.6), 3.34 (4H, mult), 7.37 (4H, d, J=7.2), 7.67 (4H, d). $^{13}C(CDCl_3)$ $\delta_C(CDCl_3)$ 143.8, 134.5, 129.9, 127.4; 49.9, 49.4, 49.0, 48.6 (CH_2N); 29.0, 26.4 (CH_2), 2.15 (CH_3). A higher yielding route to this 1,11-ditosylamide is as follows:

1,11-N,N'-Bis(toluenesulphonyl)-1,4,8,11-tetraazacyclododecane

To dioxocyclam (912mg, 4 mmol) in dichloromethane (100 cc) was added p-toluene sulphonyl chloride (1.915 gms, 10 mmol) and triethylamine (1.01 gms) and the solution was stirred for 18 hours at 45°C. A white solid precipitated from solution and was filtered off, washed with ether and chloroform and dried to yield the diamide (1.67gms, 79%) m.p.>240°C. Found: C 53.4: H, 5.80; N, 9.61; S, 11.5, $C_{24}H_{32}N_4O_6S_2$ requires C, 53.7; H, 5.55; N, 9.72; S, 11.1%. IR (Nujol) 3300 (NH), 1663 (CO). m/e (C.I) 537 (M^++1), 536 (M^+) 447, 446, 381, 352. NMR (^1H, $CDCl_3$) δ_H ($CDCl_3$) 7.66 (4H, d, J=8.2), 7.36 (4H, d), 6.94 (2H, brt, NHCO), 3.59 (4H, mult), 3.25 (2H, s, CH_2CO) 3.13 (4H, brt, CH_2CN), 2.96 (4H, brt, CH_2N), 2.47 (6H, s, CH_3), 1.55 (2H, quint, CH_2C).

The diamide (536 mg, 1.0 mmol) was treated with a solution of borane in THF (20 cc, 1M solution) and boiled under nitrogen (42 hours). After cooling to 0°C, excess borane was destroyed by careful addition of methanol (2 cc) and volatiles removed under reduced pressure. The residue was treated with 6M hydrochloric acid (20 cc) and boiled under reflux (3 hours, bath temp. 110°C).

After evaporation of solvent, the residue was taken up in 2M KOH (10 cc) and extracted with dichloromethane (4 x 20 cc), dried (K_2CO_3) and evaporated to yield a colourless residue which was chromatographed on flash silica gel (10% MeOH and 90% CH_2Cl_2) to yield a glassy solid (300 mgs, 65%), identical to that obtained above.

1,8-Dimethyl-4,11-bis(toluene-p-sulphonyl)-1,4,8,11tetraazacyclotetradecane

1,8-N,N'-Bis(toluenesulphonyl)-1,4,8,11-tetraazacyclotetradecane. (0.51gms, 0.1 mmol) was heated at 90°C with formaldehyde (1 cc, 30% solution) and formic acid (1.2 cc) for 4 hours. Hydrochloric acid (6M, 10 cc) was added to the cooled solution to yield a cloudy solution later giving a crystalline precipitate, and the solution was evaporated to dryness under reduced pressure. The colourless solid residue was dissolved in water (5 cc) and the pH adjusted to 14 with KOH pellets. After extraction into dichloromethane (4x10 cc) and drying (K_2CO_3) solvent was removed to give a colourless residue and tlc analysis (SiO_2, 10% MeOH, 90% CH_2Cl_2) gave a single spot [R_f 0.7]; yield 0.48g (87%). δ_H ($CDCl_3$) 1.73 (4H, quin, CH_2C), 2.15 (6H, s, CH_3N), 2.35 (4H, trip, CH_2N), 2.40 (6H, s, Aryl-CH_3), 2.49 (4H, trip, CH_2N), 3.19 (8H, trip + trip. CH_2NTs), 7.25 (4H, d, J=7.7 H_z), 7.65 (4H, ortho aryl H, J=7.7 H_z), δc ($CHCl_3$) 143.1(s), 136.7(s), 129.5, 126.9(d); 55.7, 54.4(t), 47.6, 46.9 (CH_2N), 43.1 (CH_3N), 26.3 (CH_2C), 21.3 (CH_3-Aryl). m/e (DCI) 538 (M^++2), 537 (M^++1).

1,8-Dimethyl-1,4,8,11-tetraazacyclotetradecane

1,8-Dimethyl-4,11-bis(toluene-p-sulphonyl) 1,4,8,11-tetraazacyclo-tetradecane (0.46 gms) and phenol (0.5 gms) in HBr/HOAc (45% w/v, 20 cc)

were heated to reflux for 48 hours. After initial 12 hours reaction time a further HBr/HOAc (45% w/v, 20 cc) was added during which time a light coloured precipitate was forming. After two days reaction time a white coloured precipitate was removed by filtration, washed with ether and dried in vacuo. Yield 0.336 gms (87%) m.p. above 230°C (as fully protonated hydrobromide salt). $\delta_H(D_2O)$ 1.41 (4H, br. quin., CH_2C), 2.18 (4H, quin, NH), 3.03 (6H, s, CH_3-N), 3.49 (8H, mult, CH_2N), 3.73 (8H, brs, CH_2N); δc (D_20), 49.8, 45.8, 42.6, 40.8 (CH_2N), 36.5 (CH_3N) and 18.0 (CH_2C). m/e (DCI) 229 (M^++1). Found C, 25.9, H 5.95, N 9.99. $C_{12}H_{28}N_4.4HBr.\ H_2O$ requires: C 25.2; H, 5.95; N, 9.80%.

1,8-Dibutyl-4,11-bis(toluene-p-sulphonyl)-1,4,8,11-tetraazacyclotetradecane

To a solution of 1,8-N,N'-bis(toluene-p-sulphonyl)-1,4,8,11-tetraazacyclotetradecane (0.51gms, 0.1mmole) in acetonitrile (20 cc) was added anhydrous potassium carbonate (0.26 gms) and n-butyl iodide (0.39 gms, 2.12 mmol) and the mixture was heated to reflux under nitrogen for 48 hours. After filtration and removal of solvent, the colourless residue was chromatographed on flash silica gel (2% MeOH, 98% CH_2Cl_2) to yield a colourless oil which crystallised on standing m.p. 108-109°C. Yield 0.26 g (43%) Tlc analysis (SiO_2, 10% MeOH, 90% CH_2Cl_2) gave a single spot R_f 0.65. δ_H ($CDCl_3$) 0.89 (6H, t, CH_3CH_2), 1.28 (8H, mult, CH_2CH_2), 1,70 (4H, t), 2.31 (4H, t), 2.41 (6H, s, CH_3-Ar), 2.56 (4H, t), 3.12 (4H, t CH_2NTs), 3.22 (4H, t CH_2NTs), 7.30 (4H, d, J=8.1), 7.65 (4H, d) δ_C ($CDCl_3$) 143.0, 136.6(s), 129.5, 127.0 (d); 55.0, 53.2, 51.2, 47.9, 47.3, (CH_2N), 28.9, 26.3(CH_2C), 21.3 (CH_3Ar) and 13.9 (CH_3CH_2). m/e (DCI) 622 (M^++2), 621 (M^++1).

1,8-Dibutyl-1,4,8,11-tetraazacyclotetradecane

1,8-Dibutyl-4,11-bis(toluene-p-sulphonyl)1,4,8,11-tetraazacyclotetradecane, (0.34 gms 0.55 mmol) and phenol (0.40 gms) in HBr/HOAc (45% w/v, 20 cc) were heated to reflux 120°C for 48 hours. After initial 12 hours reaction time further HBr/HOAc (45% w/v, 20 cc) was added during which time a light coloured precipitate was forming. After two days reaction time a white coloured precipitate was formed of the tetrahydrobromide salt removed by filtration, washed with ether (3 x 10 cc) and dried in vacuo (0.1 mm Hg, ca 13.3 Pa). Yield 0.323 gms (93%) m.p.>250°C. δ_H ($CDCl_3$) 0.92 (6H, t, CH_3), 1.40 (4H, quint, CH_2C), 1.75 (4H, mult, $NH^+CH_2CH_3$), 2.16 (4H, mult, CH_2CH_2N), 3.31 (4H, mult CH_2N ring), 3.45 (4H, brt, CH_2N), 3.54 (4H, brt, CH_2N), 3.71 (8H, brt, CH_2N). Found: C, 31.4; H, 6.86; N, 7.65. $C_{18}H_{40}N_4.4HBr\ 3H_2O$ requires C, 31.3; H, 6.95; N, 8.10%. δ_C ($CDCl_3$) (D_2O) 54.5, 46.3, 42.9, 39.7, 35.2, (CH_2N); 24.8 (CH_2C), 17.9, 16.6 (CH_2C), 11.5 (CH_3). m/e (DCI) 315 $(M+3)^+$, 314 $(M+2)^+$ 313 $(M+1)^+$.

4-Butyl-1,8-bis(toluene-p-sulphonyl)-1,4,8,11-tetraazacyclotetradecane

To a solution of 1,8-N,N'-bis(toluenesulphonyl)-1,4,8,11-tetraazacyclotetradecane (0.25 gms, 0.05 mmol) in acetonitrile (10 cm^3) was added anhydrous sodium carbonate (0.11 gms, 2.1 mmol) and n-butyl bromide (0.142 gms, 2.1 mmol) and the mixture was heated to reflux under nitrogen for 48 hours. After filtering and removing solvent a colourless residue was obtained which was chromatographed on "flash" silica gel (5% MeOH, 95% CH_2Cl_2) to give a colourless hygroscopic gummy solid. Yield 0.11 gms (40%). T.l.c analysis (SiO_2, 10% MeOH, 90% CH_2Cl_2) gave a single spot: R_f 0.48. δ_H ($CDCl_3$)

0.92 (3H, t, CH_3CH_2) 1.28 (4H, mult, CH_2) 1.92 (4H, quint, CH_2C) 2.43 (6H, s, CH_3Aryl), 2.68 (4H, t, CH_2N), 2.71 (4H, t, CH_2N), 3.08 (4H, t, CH_2N), 3.23 (4H, t, CH_2N), 7.22 (4H, d+d, meta Aryl H, J=7.8), 7.63 (4H, d+d ortho ArylH). δ_C ($CDCl_3$) 143.5, 134.1(s), 129.5, 127.2(d), 53.7, 52.5, 50.7, 49.6, 49.1, 48.8, 47.3, 46.0, 45.1 (CH_2N), 27.2, 25.8 (CH_2), 21.3 (CH_3-Ar), 20.3 (CH_2C), 13.8 (CH_3CH_2). m/e (DCI) 566 (M^++2), 565 (M^++1), 564 (M^+).

1-Butyl-8-methyl-4,11-bis(toluenesulphonyl)-1,4,8,11-tetraazacyclotetradecane.

The 4-butyl-ditosylamide prepared above (0.11 gms) was heated to reflux with formaldehyde (2 cc, 30% solution) and formic acid (2.2 cc) for 4 hours. Hydrochloric acid (1M, 10 cc) was added to the cooled solution to yield a cloudy solution later giving a crystalline precipitate and the solution was evaporated to dryness under reduced pressure. The colourless solid residue was dissolved in water (4 cc) and the pH adjusted to 14 with KOH solution. After extraction into dichloromethane (3 x 20 cc) and drying (K_2CO_3) solvent was removed to give a colourless residue yield 0.10 gms (89%). NMR (^1H, $CDCl_3$) δ_H 0.90 (3H, t, CH_3), 1.28 (4H, mult, CH_2C), 1.73 (4H, quint, CH_2C), 2.15 (3H, s, CH_2N), 2.35 (4H, t, CH_2N), 2.42 (6H, s, CH_3Aryl), 2.49 (4H, t, CH_2N), 3.15 (4H, t, CH_2N), 3.24 (4H, t, CH_2N), 7.31 (4H, d, J=8.2 H_z), 7.65 (4H,d J=8.2 H_z) δ_C ($CDCl_3$); 142.9, 136.7, 136.0, 129.4, 126.9, 55.8, 55.0, 54.5, 52.4, 51.1, 48.0 (CH_2N), 47.4 (CH_3N), 47.1, 42.8 (CH_2N), 28.9, 26.3 (CH_2), 21.3 (CH_3-Ar), 20.3 (CH_2), 13.8 (CH_3). m/e (DCI) 580 (M^++2), 579 (M^++1), 578 (M^+).

1-Butyl-8-methyl-1,4,8,11-tetraazacyclotetradecane.

1-Butyl-8-methyl-4,11-bis(toluenesulphonyl)-1,4,8,11-tetraaza-cyclotetradecane (0.10 gms) and phenol (0.20 gms) in HBr/HOAc (45% w/v, 10 cc) were heated to reflux for 48 hours. After an initial 12 hours reaction time further HBr/HOAc (45% w/v, 10 cc) was added during which time a white coloured precipitate was forming. After two days reaction time a white coloured precipitate of the tetrahydrobromide was removed by filtration, washed with ether and dried in vacuo. Yield 0.041 gms (90%) m.p. above 240°C. NMR (^{1}H, $CDCl_3$) δ_H 0.94 (3H, t, CH_3) 1.42 (4H, mult, CH_2C), 2.30 (4H, quin, CH_2), 3.04 (5H, quin t+t, CH_3N+CH_2N), 3.32 (4H, mult, CH_2N), 3.44 (4H, mult, CH_2N), 3.71 (8H, mult, CH_2N). m/e (DCI) 271 (M^++1) and 270 (M^+). Found: C, 28.3; H, 6.80; N, 9.00. $C_{15}H_{34}N_4.4HBr.2H_2O$ requires C,28.6; H6.65; N,8.90%.

1,8-N,N'-bis(toluenesulphonyl)-4,11-bis(carboethoxymethyl)-1,4,8,11-tetraaza-cyclotetradecane.

To a solution of 1,8-N,N'-bis(toluenesulphonyl)-1,4,8,11-tetraaza-cyclotetradecane (0.508 gms, 1 mmol) in dry acetonitrile (10 cm^3) was added anhydrous sodium carbonate (0.23 gms, 2.1 mmol) and ethyl bromoacetate (0.35 gms, 2.1 mmol). After boiling (18 hours), the mixture was cooled, filtered and solvent removed under reduced pressure. The residue was chromatographed on "flash" silica gel (eluting 3% MeOH and 97% CH_2Cl_2) to yield a colourless solid (0.62 gms, 91%) m.p. 128-9°C. Found: C, 56.2; H, 7.35; N, 8.01; S, 9.80. $C_{32}H_{48}N_4O_8S_2$ requires: C, 56.5; H, 7.06; N, 8.23; S, 9.41%. δ_H

($CDCl_3$) 7.65 (4H, d), 7.27 (4H, d), 4.15 (4H, quart, CH_2O), 3.23 (4H, t), 3.15 (4H, t), 2,84 (4H, t), 2.64 (4H, t), 2.41 (6H, s, CH_3), 1.74 (4H, quin), 1.26 (6H, t, CH_3). δ_C($CDCl_3$) 171.0 ($\underline{C}O_2R$), 143.2, 136.3, 129.7, 127.2; 60.4, 55.7, 53.1, 51.6, 47.9, 47.8, (CH_2 N); 27.1 (CH_2C), 21.5 (CH_2-Ar) 14.3(CH_3). m/e (NH_3, DCI) 681 (M^++1), 680 (M^+).

1,8-N,N'-bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane

To a solution of 1,8-N,N'-bis (toluenesulphonyl)-4,11-bis (carboethoxymethyl)-1,4,8,11-tetraazacyclotetradecane (0.34 gms, 0.5 mmol) in HBr/HOAc (40%, 30 cc) was added phenol (0.2 gms) and the mixture heated to 110°C for 36 hours. After cooling to room temperature, a white precipitate formed which was collected by filtration, washed with ether (3 x 10 cc) and dried in vacuo to yield the dihydrobromide salt (143 mg, 60%). δ_C (D_2O) 178.6, (C=O), 59.1, 56.8, 51.8, 47.6, (CH_2N), 25.2 (CH_2C). δ_H (D_2O) 3.5-3.1 (12H, br mult, CH_2N + CH_2CO). m/e (fab, 3-nitrobenyl alcohol) 317 (M^+), 257, 199. The constitution of this diacid was confirmed by an X-ray crystallographic analysis of the copper(II) salt[2].

1,8,-N,N'-Bis(p-methoxybenzenesulphonyl)-1,4,8,11-tetraazacyclotetradecane

This was prepared as described for 1,8-N,N'-bis(toluenesulphonyl) 1,4,8,11-tetraazacyclododecane except that p-methoxybenzene sulphonyl chloride was substituted as the protecting group. To cyclam (2 gms, 0.01 mole) in dichloromethane (90 cc) was added p-methoxybenzene sulphonyl chloride (1.6 mgs, 0.021 mole) in the presence of triethylamine (1.06 gms, 0.022 mole)

and the mixture was stirred for 18 hours at 20°C. Solvent was removed under reduced pressure and the residue chromatographed on "flash" silica gel (R_f (SiO_2, 10% MeOH and 90% CH_2Cl_2) and two major isomeric products were isolated: a disubstituted cyclam (R_f 0.48) and a trisubstituted derivative, (R_f 0.75). The ditosylamide gave a colourless solid 0.993 gms (26%). NMR (^1H, $CDCl_3$) δ_H 2.10 (4H, quin, -CH_2-$\underline{CH_2}$-CH_2), 3.08 (12H, mult, CH_2N), 3.24 (4H, mult, CH_2N), 3.81 (6H, s, CH_3O-), 6.94 (4H, d, J=8.7), 7.67 (4H, d, J=8.7) ppm m/e (DCI) 542 (M^++2), 541 (M^++1), 540 (M^+).

The tritosylamide gave a yield of 0.58 gms (10.5%). δ_H ($CDCl_3$) 1.74 (2H, quin, CH_2), 2.0 (2H, quin, CH_2), 2.64 (2H, t, CH_2N), 2.78 (2H, t, CH_2N), 3.04-3.34 (12H, br, mult, CH_2N), 3.90 (9H, brs, CH_3O), 6.97-7.02 (6H, d+d+d) ppm m/e (DCI) 712 (M^++2), 711 (M^++1).

1,8-N,N'-bis(p-methoxybenzenesulphonyl)-4,11-bis(carboethoxymethyl)-1,4,8-11-tetrazacyclotetradecane

To a solution of 1,8-N,N'-bis(p-methoxybenzenesulphonyl)-1,4,8,11-tetraazacyclotetradecane (1 gms, 1 mol equiv.) in dry acetonitrile (20 cc) was added anhydrous sodium carbonate (0.41 gms, 2.1 mmol equiv) and ethyl bromoacetate (0.65 gms, 2.1 mmol equiv.). After boiling (18 hours), the mixture was cooled, filtered and solvent removed under reduced pressure. The residue was chromatographed on "flash" silica gel (eluting 5% MeOH and 95% CH_2Cl_2) to yield a glassy solid, 1.2 gms (86%). R_f (10% MeOH and 90% CH_2Cl_2) = 0.75. NMR (^1H, $CDCl_3$) δ_H ($CDCl_3$) 2.0 (6H, t, CH_3), 1.67 (4H, quint, $CH_2\underline{CH_2}CH_2$), 3.16 (4H, t, CH_2N), 3.26 (4H, s, CH_2N), 3.79 (6H, s, CH_3O), 4.09

(4H, quart, CH_2O), 6.92 (4H, d, J=8.6), 7.64 (4H, d) ppm. δ_C ($CDCl_3$) 170.6 (C=O); 52.6, 51.4, 47.5 (CH_2N); 26.8 (CH_2-$\underline{CH_2}$-CH_2), 14.1 (CH_3). m/e (DCI) 714 (M^++2), 713 (M^++1), 712 (M^+).

1,8-N,N'-Bis(carboxymethyl)-4,11-dimethyl-1,4,8,11-tetraazacyclotetradecane

1,8-N,N'-Bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane (0.1 gms, 0.32 mmol) was heated to reflux with formaldehyde (2 cc, 37% solution) and formic acid (2.2 cc) for 4 hours. Hydrochloric acid (1M, 20 cc) was added to the cooled solution and the mixture was heated for a further 10 minutes to yield a cloudy solution later giving a crystalline precipitate. The solution was evaporated to dryness under reduced pressure to give a white crystalline solid of the dihydrochloride salt. Yield 0.098 gms (90.8%) m.p. above 240°C. NMR (^1H, D_2O) δ_H (D_2O) 2.05 (4H, quint, -CH_2-$\underline{CH_2}$-CH_2), 2.89 (6H, s, CH_3N), 3.00 (4H, t, CH_2N), 3.23 (4H, t, CH_2N), 3.48 (8H, mult, CH_2N), 3.64 (4H, s, CH_2CO) ppm. m/e (DCI) 346 (M^++2), 345 (M^++1).

4,11-N'',N'''-Bis(acetylsalicyloyl)-1,8-N,N'-bis(toluenesulphonyl)-1,4,8,11-tetraazacyclotetradecane

To a solution of 1,8-N,N'-bis(toluenesulphonyl)-1,4,8,11-tetraaza cyclotetradecane (0.596 gms) and triethylamine (0.29 gms) in methylene chloride (25 cc) was added a solution of acetylsalicyloylchloride (0.45 gms) in methylene chloride (12 cc). After stirring for 18 hours (20°C) the temperature was raised to reflux for 4 hours. Solvent was removed under reduced pressure and the residue chromatographed on "flash" silica gel (eluent 2→4% MeOH

and 98→96% CH_2Cl_2) to yield a white solid (0.59 gm, 60%). R_f (5% MeOH and 95% CH_2Cl_2) = 0.40. Found: C, 60.0; H5.7; N6.1. Calculated for $C_{42}H_{48}N_4O_6$: C, 60.8; H5.8; N, 6.8%. NMR (^1H, $CDCl_3$) δ_H 1.79 (4H, vbr quin, $CH_2\underline{CH_2}CH_2$), 2.16 (6H, s, CH_3N), 7.07-7.61 (16H, overlapping mult, Ar). $\delta_C(CDCl_3)$ 168.7, 168.5, 168.1, 167.9 (C=O); 146.7, 143.6, 143.5, 133.9, 133.7, (Ar-$\underline{C}$); 130.2, 129.8, 129.5, 129.3, 129.0, 127.9, 127.2, 127.0, 126.8, 125.6, 122.7; (Ar,CH) 50.6, 49.9, 49.5, 49.1, 48.8, 48.3, 48.2, 47.5 (CH_2N), 43.2 (CH_2N) 27.7, 27.3, 25.4 (CH_2), 21.1 (CH_3-Ar), 20.6 (CH_3CO) ppm m/e 833 (DCI) (M^++1), 832 (M^+).

5,18-Dioxo-1,5,8,12-tetraazatricyclo[10.2.2.2^{5,8}]octadecane

A solution of the dihydrobromide salt of 1,8,-N,N'-bis (carboxymethyl)-1,4,8,11-tetraazacyclotetradecane (79 mgs, 0.25 mmol) in 6M hydrochloric acid (10 cc) was heated at 95°C (18 hours). On cooling to 0°C, ethanol was added (5 cc) and a white precipitate of the dihydrochloride salt formed which was collected by filtration, and dried in vacuo (30 mgs, 34%) m/e (NH_3, CI) 281 (M^++1), 280 (M^+). $\delta_H(D_2O)$ 4.46-4.13 (6H, mult), 3.91 - 3.83 (8H, mult, CH_2N), 3.57-3.44 (2H, mult), 3.20-3.12 (2H, dt+dt, J=4.0) 3.37-3.32 (0.7 H, mult, Z-isomer), 2.92-2.79 (1.3H, mult, E-isomer), 2.28-2.15 (4H, mult, CH_2C). One stereoisomer (E-isomer) was characterised by X-ray crystallography and permitted partial assignment of the ^1H spectrum. A mixture of 65% E and 35% Z diastereo isomers were formed therefore, which do not interconvert in solution (300°K, 250 MH_z). The lactam may also be isolated as the free base from solution as follows: removal of 6M HCl yielded a residue which was taken up in water (2 cc), washed with chloroform, basified to pH≥11 (NaOH) and extracted with dichloromethane (3 x 15 cc), dried (K_2CO_3) and evaporated

to yield a colourless residue. IR (KBr) 1660 cms^{-1} δ_C ($CDCl_3$) 168.8 (major), 168.4 (minor); (amide carbonyl), 57.6 (major), 55.3 (major), 54.8 (minor), 51.2 (major); 50.3, 49.8, 47.2, 4.67 (all minor peaks), 45.8, 45.7 (both major) 21.7, 21.5 (both major). m/e (NH_3, CI) 281 (M^++1), 280 (M^+).

1,5,8,12-Tetraazatricyclo[10.2.2.2^{5,8}]octadecane

6,13-Dioxo-1,5,8,12-tetreazatricyclo[10.2.2.2^{5,8}]octadecane (0.28 gms, 1.0 mmol) was treated with a solution of borane in THF (40 cc, 1.0 M solution) and boiled under nitrogen for 24 hours. After this further borane in THF (20 cc) was added and refluxing was continued for another 24 hours. After cooling to room temperature excess borane was quenched by the careful addition of methanol (2 cc) and solvents were removed under reduced pressure. The residue was treated with 6M hydrochloric acid (20 cc) and boiled for 3 hours, after water was removed under reduced pressure and the residue was taken up in 6M KOH (10 cc) to pH 14, and extracted with dichloromethane (4 x 20 cc), dried (K_2CO_3) and evaporated to yield a colourless solid. Yield 0.15 gms (62%); m.p. 80-82°C. NMR (^1H, CD_2Cl_2) δ_H 1.68 (4H, quin, $CH_2\underline{CH_2}CH_2$). 2.40-2.51 (8H, br mult, piperazine, CH_2N), 2.74-2.78 (8H, t, J=5.5H_z, CH_2CH_2N) 3.11-3.20 (8H, mult, CH_2N piperazine), δ_C ($CDCl_3$) 55.8 (CH_2N),. 49.4 ($CH_2\underline{CH_2}N$), 23.5 (CH_2C). m/e (DCI) 254 (M^++2), 253 (M^++1) 100%, 252 (M^+). Found: C, 66.5; H, 11.4; N, 22.0. $C_{19}H_{28}N_4$ requires, C, 66.7, H, 11.1; N, 22.2%.

9-(p-Methoxybenzenesulphonyl-1,5,9-triazacyclododecane-2,4-one

To a solution of 1,5,9-triazacyclododecane-2,4-dione (1 gms) in triethylamine (0.90 gms) and methylene chloride (25 cc) was added p-methoxy-

benzenesulphonyl chloride (1.45 gms) in methylene chloride (20 cc) and the solution was stirred at room temperature for 24 hours. A thick white precipitate was given which was filtered off, washed with dichloromethane and dried (0.560 gms). Solvent was removed from the filtrate and the residue chromatographed on "flash" silica gel (eluent 5% MeOH and 95% CH_2Cl_2) to yield a white solid (0.75 gms). R_f (10% MeOH and 90% CH_2Cl_2) = 0.45 which is identical to that of the white crystalline precipitate (co-spotted). Total yield (1.31 gms, 71%). Found C, 52.1; H, 6.32; N, 11.3. Calculated for $C_{16}H_{23}N_3SO_5$: C, 52.0; H, 6.23; N, 11.4%. m/e (DCI) 371 (M^++2), δ_H ($CDCl_3$) 8.44 (2H, d, J=8.4 H_z), 7.78 (2H, d), 4.58 (3H, s, CH_3O), 3.84 (8H, mult, CH_2N), 2.36 (4H, brs, CH_2,$\underline{CH_2}$,CH_2) 2.00 (2H, s, $COCH_2CO$).

1,2-Bis(p-toluenesulphanato)ethane

To a solution of ethylene glycol (12.4 gms, 0.2 mmol) in dry pyridine (200 cc) was added p-toluenesulphonyl chloride (96 gms, 0.5 mmol) and the solution was held at 4°C for 24 hours. It was then poured onto ice-water, stirred for 1 hour and the precipitate was filtered off and washed with water (3 x 50 cc). The residue was dissolved in dichloromethane (600 cc), washed successively with hydrochloric acid (1M 3 x 60 cc) and saturated sodium chloride solution (3 x 60 cc). The solution was dried ($MgSO_4$) filtered and evaporated under reduced pressure to yield an off-white solid which was recrystallised from hot acetone (60 gms, 92%). m.p. 125-6°C. NMR ^1H ($CDCl_3$) δ_H 7.46 (8H, mult, Ar), 4.13 (4H, s, CH_2), 2.43 (6H, s, CH_3) ppm.

1,3,5-Tris(p-toluenesulphonyl)-3-aza-1,5-pentane diamine

To a solution of diethylene triamine (16.8 gms, 0.15 mmol) in pyridine (35 cc) was added p-toluene sulphonyl chloride (96 gms, 0.5 mol) and the mixture was stirred at 45°C for 5 hours. After cooling to room temperature the mixture was poured onto ice (200 gms) and stirred mechanically for a further 2 hours. A yellowish solid was obtained by filtration and washed with ethanol (2 x 20 cc) to yield a yellowish solid which was recrystallised from hot ethanol (61.4 gms, 68%). m.p. 176-7°C (lit 175°C). NMR (^1H, $CDCl_3$) δ_H 7.43 (12H, mult, Ar), 3.1 (8H, s, CH_2), 2.4 (9H, s, CH_3-Ar) ppm.

1,4,7-Tris(p-toluenesulphonyl)-1,4,7-triazacyclononane

A solution of sodium ethoxide was made by carefully adding sodium metal (0.23 gms, 0.01 mol) to ethanol (45 cc) under nitrogen. To this cooled solution, 1,3,5-tris(p-toluenesulphonyl)-3-aza-1,5-pentane diamine (5.65 gms, 0.01 mol) was gradually added to give a clear solution. After refluxing for half an hour the cooled solution afforded a white crystalline precipitate which was isolated under nitrogen after the removal of solvent under reduced pressure.

Ethylene glycol ditosylate (3.7 gms, 0.01 mol) in anhydrous dimethylformamide (25 cc) was added dropwise over a period of 3 hours to a solution of 1,3,5-tris-(ptoluenesulphonyl)-3-aza-1,5-pentane diamine disodium salt (0.01 mole) in anhydrous dimethylformamide under nitrogen at 85°C. After complete addition over 2-3 hours refluxing was continued for a further half an hour. After cooling to room temperature water (90 cc) was added gradually to yield an oil which later solidified to white crystals. Cooling overnight at 4°C gave a solid which was filtered and washed with water (2 x

20 cc) and ethanol (2 x 20 cc) to yield a colourless solid 4.74 gms (80%). NMR (^1H, $CDCl_3$) δ_H 2.43 (9H, s, CH_3-Ar), 3.43 (12H, s, CH_2), 7.46 (12H, mult, Ar) ppm.

1,5,9-Tris(p-toluenesulphonyl)-1,5,9-triazacyclododecane

A solution of sodium ethoxide was made by the careful addition of sodium metal (0.23 gms, 0.01 mol) to ethanol (45 cc) under nitrogen. To this cooled solution 1,4,7-tris(p-toluenesulphonyl)-4-aza-1,7-heptane diamine (5.85 gms, 0.01 mole) was gradually added to give a clear solution. After refluxing for half an hour the cooled solution gave a white crystalline precipitate which was isolated under nitrogen after the removal of solvent under reduced pressure.

Propylene glycol-1,3-ditosylate (3.84 gms, 0.01 mole) in anhydrous dimethylformamide (25 cc) was added dropwise over a period of 3 hours to a solution of 1,4,7-tris(p-toluenesulphonyl)-4-aza-1,7-heptane diamine disodium salt (0.01 mole) in anhydrous dimethylformamide (90 cc) under nitrogen at 80-90°C. After complete addition over 2-3 hours refluxing was continued for a further half an hour. After cooling to room temperature, water (90 cc) was added gradually to yield a gum and a white precipitate which later solidified to give a white sticky solid. A less sticky solid was obtained by filtration and washing with water and ethanol. The solid was purified by column chromatography using "gravity" silica gel (eluent 2% MeOH and 98% CH_2Cl_2)=0.75. Crude yield 5.23 gms (83%) NMR (^1H, $CDCl_3$) δ_H 1.93 (6H, pentet, -CH_2-$\underline{CH_2}CH_2$), 2.4 (9H, s, CH_3-Ar), 3.2 (12H, t, CH_2N), 7.72 (6H, dd, J=8.1 ortho CH), 7.32 (8H, d, meta CH) ppm. Fully characterised previously.

1,4,7-Triazacyclononane

1,4,7-triazacyclononane tritosylamide (1 gms) and concentrated sulphuric acid (5 cc) were heated to 100°C for 72 hours. After cooling to room temperature the mixture was washed with diethyl ether (75 cc), water (2 cc) was carefully added to aid solution of product and excess ether was again decanted off. Sodium hydroxide solution (50%, 5 cc) was very carefully added and the mixture gently warmed and 3 cc of water were added to aid solution again. The mixture was filtered and extracted with chloroform (3 x 50 cc), dried over anhydrous potassium carbonate and solvent removed to yield an almost clear sticky solid which slowly solidified to yield white crystals. Yield 0.11 gms (51%). NMR (^{1}H, $CDCl_3$) δ_H 2.43 (3H, s, N-H), 2.7 (12H, s, CH_2) ppm. m.pt. 44-45°C.

1,5,9-Tris(ethoxycarbonylmethyl)-1,5,9-triazacyclododocane

To a solution of 1,5,9-triazacyclododecane (0.34 gms, 2 mmol) in ethanol (25 cc) was added caesium carbonate (2.0 gms, 6.2 mmol) and ethyl bromoacetate (1.05 gms, 6.2 mmol) and the mixture was heated to reflux (18 hours). It was then cooled, filtered and evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 cc) and the solution washed with water (2 x 10 cc) dried and evaporated to yield a residue which was purified by chromatography on neutral alumina (eluant 2% MeOH and 98% CH_2Cl_2) to yield a colourless oil (220 mgs, 28%); m/e (CI, iso-butane) 430 (M^++1), 429 (M^+), 344, 256 and 130 (Found: M^+ 429.283 696: $C_{21}H_{39}N_3O_6$ requires 429.283 886); υ_{max} (film) 1745 (CO), 1370, 1270, 1205, 1185, 1140s and 1035s cm^{-1}; δ_H ($CDCl_3$) 4.16 (6H, q, CH_2O), 3.23 (6H, s, CH_2CO), 2.65 (12H, t, CH_2N), 1.60

(6H, quint, CH_2C) and 1.26 (9H, t, CH_3); δ_C ($CDCl_3$) 59.4 (CH_2O); 55.0, 48.4 (CH_2N); 21.1 (CH_2C), 13.4 (CH_3).

1,5,9-Tris(carboxymethyl)-1,5,9-triazacyclododecane

A solution of 1,5,9-tris(ethoxycarbonylmethyl)-1,5,9-triazacyclododecane (200 mgs) in hydrochloric acid (6M, 10 cc) was heated to reflux for 6 hours and solvent removed to yield a colourless glassy solid; υ_{max} (KBr) 3600-2800br and 1740 (COOH) cm^{-1}; δ_H (D_2O) 4.08 (6H, s, CH_2CO), 3.48 (12H, t, CH_2N) and 2.31 (6H, quint, CH_2C); m/e (DCI) 346 (M^++1) and 345 (M^+).

1,5,9-Triazacyclododecane-2,4-dione

A solution of 1,5,9-triazanonane (13.1 gms, 0.1 mole) and diethyl malonate (16 gms, 0.1 mole) in ethanol (1.2 l) was boiled under reflux for 5 days. After removal of solvent, the residue was chromatographed on silica gel (NH_4OH - H_2O: 1 → 5%; MeOH 40%; CH_2Cl_2 59 → 55%) to yield a colourless solid mpt 152-154°C [R_f = 0.7 (1% NH_4OH, 59% CH_2Cl_2, 40% MeOH), 2.82 gms(14%). Found: C 49.0; H_1 8.75; N, 20.9 Calc for $C_9H_{17}N_3O_2$: C, 49.2; H, 8.55; N, 21.2%); m/e(NH_3, C.I.) 200 (M^++1) and 199 (M^+); NMR (^1H, $CDCl_3$) 8.56 (2H, brt, NHCO), 3.40 (4H, dt, CH_2NHCO), 3.13 (2H, s, CH_2CO), 2.76 (4H, t, $N\underline{CH_2}CH_2$), 1.85 (1H, brs, NH) and 1.66 (4H, quint, $CH_2\underline{CH_2}$ CH_2).

9-(p-Tolylsulphonyl)-1,5,9-triazacyclodecane-2,4-dione

To a solution of 1,5,9-triazacyclodecane-2,4-dione (0.5 gms, 2.5 mmole) in dry pyridine (20 cc) was added p-toluene-sulphonyl chloride (0.75 gms, 4 mmole) and the solution was held at 4°C for 24 hours. It was then poured on

to ice-water and the precipitate was filtered off. The residue was dissolved in dichloromethane (100 cc) and the solution dried (K_2CO_3) filtered, and evaporated to yield an off-white solid which was recrystallised from hot methanol (466 mgs, 53%), mpt > 260°C. (Found: C, 54.2; H, 6.2; N, 11.6. Calc for $C_{16}H_{23}N_3O_4S$: C, 54.4; N, 6.52; N, 11.9%); m/e (C.I.) 353 (M^+), 352 (M^+-1) and 198 (M^+-Ts); NMR (^1H, $CDCl_3$) δ_H 7.65 (2H, d, ArH), 7.27 (2H, d, ArH); 6.40 (2H, brs, NHCO), 3.29-3.14 (8H, m, CH_2NTsCH_2N), 2.43 (3H, s, CH_3), 1.75 (4H, quin, CH_2, $\underline{CH_2}$, CH_2), υ max (KBr) 3310w (NHCO) 1680, 1650s, 1620s, 1560 and 1160 cm^{-1}.

9-p-Tolylsulphonyl-1,5,9-triazacyclododecane

To a slurry of 9-p-tolylsulphonyl-1,5,9-triazacyclododecane-2,4-dione (0.5 gms, 1.41 mmol) in tetrahydrofuran (15 cc) was added borane. THF (50 cc, 1M) and the mixture was heated to reflux for 24 hours. Excess of borane was quenched with methanol, solvents were removed under reduced pressure and the residue was treated with hydrochloric acid (6M, 20 cc) and heated to 100°C (3 hours). After the solution had been cooled and basified to pH 14 (KOH), it was extracted with chloroform (3 x 30cc) and the extract dried (K_2CO_3), filtered and evaporated to yield a colourless glass (0.41 gms, 89%); NMR (^1H, $CDCl_3$) δ_H 7.65 (2H, d, ArH), 7.27 (2H, d, ArH); 3.21 (4H, t, CH_2 NTs), 2.76 (8H, t+t, CH_2C); 2.40 (3H, s, $ArCH_3$), 2.21 (2H, s, NH), 1.73 (6H, quin+quin, CH_2C); NMR (^{13}C, $CDCl_3$) δ_C 142.9(s), 139.5(s); 129.4, 127.3(d); 47.1, 45.5, 45.2 (t, CH_2N); 27.5, 26.9 (t, CH_2C); 21.4(quin); υ max (KBr) 3300 br (NH), 2920, 2810 (CH) and 1600w, 1160(w) cm^{-1}, m/e (CI) 326 (M^++1), 325 (M^+) and 170 (Found: 325.182689. $C_{16}H_{27}N_3SO_2$ requires 325.182399).

1,5-Bis(ethoxycarbonylmethyl)-9-(p-tolylsulphonyl)-1,5,9-triazacyclododecane

To a solution of 9-p-tolylsulphonyl-1,5,9-triazacyclododecane (0.3 gms, 0.92 mmol) in ethanol (10 cc) was added caesium carbonate (0.63 gms, 1.93 mmol) and ethyl bromoacetate (0.33 gms, 1.98 mmol), and the mixture was heated at reflux (18 hours). After removal of solvent the residue was chromatographed on silica gel (5% MeOH, 95% CH_2Cl_2) to yield a colourless oil (0.344 gms, 75%), R_f (10% MeOH, 90% CH_2Cl_2) 0.74; m/e (NH_3, CI) 499 (M^++2) 498 (M^++1) 410 and 342 (Found: M, 497.256248 $C_{24}H_{39}N_3SO_6$ requires 497.255958); NMR (^1H, $CDCl_3$) δ_H ($CDCl_3$) 7.70 (2H, d, J=8.2), 7.28 (2H, d), 4.11 (4H, q, CH_2O), 3.48 (4H, t, CH_2N), 3.16 (4H, s, CH_2CO), 2.59 (4H,brt), 2.52 (4H, brt), 2.41 (3H, s) 1.55 (4H, m, CH_2C), 1.49 (2H, m) and 1.24 (6H, t, CH_3CH_2); ^{13}C δ_C 171.5(s), 142.2(s), 138.5(s); 129.5, 126.9(d); 60.2 (CH_2O), 54.5, 52.6, 47.3, 42.2 (CH_2N); 24.1, 24.0 (CH_2C); 21.4 ($ArCH_3$), 14.2 (CH_3CH_2).

1,5-Bis(carboxymethyl)-1,5,9-triazacyclododecane

To a solution of 1,5-bis(ethoxycarbonylmethyl)-9-(p-tolysulphonyl)-1,5,9-triazacyclododecane (0.3 gms, 0.6 mmol) in HBr/HOAc (45% w/v, 25 cc) was added phenol (0.6 gms) and the mixture was heated at 110°C for 100 hours. A fine precipitate was removed by filtration on cooling, and was washed with diethyl ether (2 x 5 cc) and dried in vacuo, (0.23 gms, 76%). This was the dihydrobromide of the sought diacid; NMR (^1H, D_2O) δ_H (D_2O) 4.06 (4H, s, CH_2CO_2H), 3.51-3.19 (12H, m, CH_2N), and 2.35-2.01 (6H, m, CH_2C); $^{13}C(D_2O)$ $\delta_c(D_2O)$ 173.8(s); 57.2, 55.3, 54.5 (CH_3N); 47.2 (CH_2CO); 22.9, 22.7 (CH_2C); m/e (CI), 288 (M^++1), 287 (M^+), 244, 230 and 194.

9-p-Methoxybenzenesulphonyl-1,5,9-triazacyclododecane

To a slurry of 9-p-methoxybenzenesulphonyl-1,5,9-triazacyclododecane-2,4-one in tetrahydrofuran (15 cc) was added borane. THF (40 cc, 1M), and the mixture was heated to reflux for 24 hours. Further borane.THF (20 cc) was added and refluxing was continued for another 24 hours. Excess of borane was quenched with methanol after which the mixture was evaporated under reduced pressure and the residue heated to reflux in 6M HCl (40 cc) for 3 hours. After removal of water from the mixture, the residue was re-dissolved in aqueous base KOH (0.1M 10 cm^{-3}) and the pH adjusted to 14, it was extracted into chloroform (3 x 30 cc) and the extract dried (K_2CO_3), filtered and evaporated to yield a colourless solid (0.4420 gms, 73%), m.p. 135-136°C. Found: C, 54.3; H, 7.96; N, 11.60. Calculated for $C_{16}H_{27}N_3SO_32H_2O$; C, 56.4; H, 8.58; N, 11.63%. m/e (DCI) 342 (M^++1) δ_H ($CDCl_3$) 7.67 (2H, d, J=7.7), 6.92 (2H, d) 3.80 (3H, s, CH_3O), 3.18, (4H, t, CH_2N), 2.72 (4H, t, CH_2N), 2.64 (4H, t, CH_2N), 1.64 (4H, mult, CH_2), 1.49 (4H, mult, CH_2); δ_C ($CDCl_3$) 162.7, 130.3, 129.4, 114.0; 55.5 (CH_3O); 47.4, 46.0, 44.9 (CH_2N); 26.9 (CH_2).

1,5-Bis(ethoxycarbonylmethyl)-9-p(methoxybenzenesulphonyl)-1,5,9-triazacyclododecane

To a solution of 9-p-methoxybenzenesulphonyl-1,5,9-triazacyclodecane (0.121 gms) in ethanol (20 cc) was added caesium carbonate (0.26 gms) and ethylbromoacetate (0.125 gms), and the mixture was heated at reflux for 24 hours. It was then cooled, filtered and evaporated under reduced pressure to yield a yellow oil which was purified by chromatography on "flash" silica gel

(2% MeOH and 98% CH_2Cl_2) to yield a colourless oil (0.149 gms, 83%). R_f (10% MeOH and 90% CH_2Cl_2) 0.75; m/e (DCI) 515 (M^++2), 514 (M^++1); δ_H ($CDCl_3$) 7.69 (2H, d, J=8.5), 6.92 (2H, d), 4.10 (4H, quart, CH_2O), 3.84 (3H, s, CH_3O), 3.43 (4H, t, CH_2N), 3.12 (4H, s, CH_2CO), 2.56 (4H, t, CH_2N), 2.49 (4H, t, CH_2N), 1.56 (2H, mult, $CH_2\underline{CH_2}CH_2$),1.45 (2H, mult, $CH_2\underline{CH_2}CH_2$), 1.24 (6H, t, CH_3); δ_C($CDCl_3$), 171.4 (C=O), 162.3, 133.0, 128.9, 113.9, 60.2 (NCH_2CO), 55.4 (CH_3O); 54.5 (CH_2O), 52.5, 47.2, 42.2 (CH_2N); 24.1 ($CH_2\underline{CH_2}CH_2$), 14.2 (CH_3).

9-Methyl-1,5-bis(carboxymethyl)-1,5,9-triazacyclododecane

1,5-Bis(carboxymethyl)-1,5,9-triazacyclododecane (51 mgs) was heated to reflux with formaldehyde (2 cc, 37% solution) and formic acid (2.2 cc) for 18 hours. Hydrochloric acid (6M, 20 cc) was added to the cooled solution to yield a cloudy solution later giving a crystalline precipitate too and the solution was evaporated to dryness under reduced pressure to give a white crystalline solid of the dihydrochloride salt. Yield 39 mgs (13.6%). NMR (^1H, $CDCl_3$) δ_H 2.10 (2H, mult, CH_2C), 2.35 (4H, mult, CH_2C), 3.02 (3H, s, CH_3), 3.23-3.61 (12H, or mult, CH_2N), 3.84-3.91 (4H, d, CH_2CO AB system); δ_C ($CDCl_3$) 171.2 (C=O), 54.6, 53.0, 52.2 (CH_2N), 48.3 (CH_2CO), 42.2 (CH_3), 19.7, 18.9 (CH_2C) ppm. m/e 303 (M^++2), 302 (M^++1), 258, 246 and 202.

5.3 Synthetic Procedures for Complex Formation

Copper(II) complex of 1,8-dibutyl-1,4,8,11-tetraazacyclotetradecane 20 (Cu-L)$(PF_6)_2$.

A solution of copper perchlorate hexahydrate (75 mgs, 0.2 mmol) in

methanol (1 cc) was added to a solution of the ligand in its free base form (62 mgs, 0.2 mmole) in tetrahydrofuran (2 cc). The mixture was warmed and after removal of solvent a purple gummy solid was obtained which did not crystallise well from different solvents. The counterion was now exchanged by warming a solution of the complex in acetonitrile (1 cc) and adding to this a six-fold excess of ammonium hexafluorophosphate (200 mgs, $1.2x10^{-3}$ mmol) in methanol (1 cc). After filtering and standing at room temperature for 12 hours and allowing slow evaporation of solvent needle-like crystals were obtained. Crystals suitable for X-ray diffraction studies were grown from a solution of the complex in a MeCN-MeOH-$Pr^{i}_{2}O$ mixture. m/e (FAB, m-nitro benzyl alcohol) 377 and 375 (M^{+}) (^{65}Cu-L and ^{63}Cu-L); λ_{max} (H_2O) 528 nm (ε 152 dm^3 $mole^{-1}cm^{-1}$). X-ray crystal data - see appendix.

Nickel(II) complex of 1,8-dibutyl-1,4,8,11-tetraazacyclotetradecane 20 (Ni-L)$(ClO_4)_2$.

To solution of the ligand (62 mgs, 0.2 mmol) in methanol (4 cc) was added a solution of nickel perchlorate hexahydrate (74 mgs, 0.2 mmol) in methanol (1 cc). After removal of solvent, the orange residue crystallised from water during slow evaporation to yield orange prismatic crystals (75 mgs, 66%). Found: C, 37.6, H, 7.20; Cl, 12.2; N, 10.1; Ni, 10.1. $C_{18}H_{40}Cl_2N_4NiO_8$ requires C, 37.9; H, 7.00; Cl, 12.45; N, 9.80; Ni, 10.3%; m/e (FAB, m-nitrobenzyl alcohol (matrix) 571 (M^{+}+1); λ_{max} (H_2O) 461 nm (ε 50 $dm^3mole^{-1}cms^{-1}$).

On further concentration of the mother-liquors and allowing the solution to evaporate slowly, plate-shaped crystals were deposited over a period of 7

days; λ_{max} (H_2O) 473 nm (ε 48 $dm^3mole^{-1}cms^{-1}$), Found: C, 38.0, H, 7.30; N, 9.65%, $C_{18}H_{40}Cl_2N_4NiO_8$ requires C, 37.9; H,7.00; N, 9.80%. For X-ray crystal structure cell data for both complexes - see appendix.

Copper(II) complex of 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane 15 (Cu-L)(ClO_4).2H_2O.

A solution of copper perchlorate hexahydrate (75 mgs, 0.2 mmole) in water (1 cc) was added to a solution of the ligand dihydrobromide (78 mgs, 0.2 mmol) in water (1 cc). After warming and removal of solvent a pale purple solid was obtained which was stirred in methanol (2 cc) to remove the potassium chloride salt made. Slow evaporation of the solvent over 12 hours gave a purple crystalline solid. m/e (FAB, m-nitrobenzyl alcohol) 293, 291 (M^+) (^{65}Cu-L and ^{63}Cu-L); λ_{max} (H_2O) 546nm (ε 79 dm^3 $mole^{-1}$ cm^{-1}).

Nickel(II) complex of 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane 15 (Ni-L)(ClO_4)$_2$.2H_2O.

Synthesis as for the copper complex, using nickel perchlorate hexahydrate. Yellow crystalline solid, m/e (FAB, m-nitrobenzyl alcohol) 288, 286 (M^+) (^{60}Ni-L and ^{58}Ni-L); λ_{max} (H_2O) 456 nm (ε 18 dm^3 $mole^{-1}$ cm^{-1}).

Copper(II) complex of 1-butyl-8-methyl-1,4,8,11-tetraazacyclotetradecane :18, (Cu-L) (ClO_4)$_2$ 18A.

A solution of copper perchlorate hexahydrate (75 mgs, 0.2 mmole) in methanol (1 cc) was added to a solution of the ligand as its free base form (54

mgs, 0.2 mmol). The mixture was warmed and after removal of solvent an indigo coloured crystalline solid was made which did not crystallise from a variety of different solvents. m/e (FAB m-nitrobenzyl alcohol) 335, 333 (M^+) (^{65}Cu-L and ^{63}Cu-L); λ_{max} (H_2O) 537 nm (ε 15 dm^3 $mole^{-1}$ cm^{-1}).

Nickel(II) complex of 1-butyl-8-methyl-1,4,8,11-tetraazacyclotetradecane 18: $(Ni\text{-}L)(ClO_4)_2$

Synthesis as for 18A before using nickel perchlorate hexahydrate. Yellow crystalline solid, m/e (FAB, m-nitro benzyl alcohol) 330 and 328 (M^+) (^{60}Ni-L and ^{58}Ni-L); λ_{max} (H_2O) 458 nm.

Copper(II) complex of 1,8-N,N'-bis(carboxymethyl)-4,11-dimethyl-1,4,8,11-tetraazacyclotetradecane 12: $(Cu\text{-}L)(ClO_4)_2.2H_2O$ (12A).

A solution of copper perchlorate hexahydrate (58 mgs, 0.15 mmol) in water (ice) was added to a solution of the ligand dihydrochloride (64 mgs, 0.15 mmole) in water (2 cc). The mixture of a white precipitate and pale blue solution was warmed and the pH was raised to 6 by careful addition of dilute potassium hydroxide solution, the mixture filtered and the solution allowed to stand. After 48 hours at room temperature, blue crystals had deposited, which were collected by filtration, washed with cold water and dried in air. Yield 62 mgs (78%). Found: C, 29.6; H, 5.80; Cl, 11.2, N, 8.60. $C_{16}H_{36}Cl_2$ CuN_4O_{14} requires C, 29.9; H, 5.60; Cl, 11.0; N, 8.70%. m/e (FAB, m-nitrobenzyl alcohol matrix) 409, 407 (M^+) (^{64}Cu-L and ^{63}Cu-L); λ_{max} (H_2O) 573 nm (ε 75 dm^3mole^{-1} cm^{-1}). For X-ray crystal structure cell data - see appendix.

Nickel(II) complex of 1,8 N,N'-bis(carboxymethyl)-4,11-dimethyl-1,4,8,11-tetraazacyclotetradecane 12: (Ni-L)(ClO_4).$_2H_2O$).

Synthesis as for 12A using nickel perchlorate hexahydrate. m/e (FAB, m-NBA matrix) 404, 402 (M^+) (^{60}Ni-L and ^{58}Ni-L); λ_{max} (H_2O) 580 nm.

Manganese(II) complex of 1,8-N,N'-bis(carboxymethyl)-4,11-dimethyl-1,4,8,11-tetraazacyclotetradecane 12: (Mn-L)(ClO_4)$_2$.2H_2O

Synthesis as for 12A using 50% w/v manganese nitrate stock solution. m/e (FAB, m-NBA matrix) 399 (M^+) (^{55}Mn-L); λ_{max} (H_2O) 610 nm.

Copper(II) complex of 1,8-N,N'-bis(carboxymethyl)-1,4,8,11-tetraazacyclotetredecane 8: (Cu-L)ClO_4)$_2$.2H_2O.

Synthesis as for 12A. Pale blue crystals by slow evaporation from water; m/e (FAB, m-NBA) 381, 379 (M^+) (^{65}Cu-L and ^{63}Cu-L); λ_{max} (H_2O) 565 nm. (ε 70 $dm^3mole^{-1}cms^{-1}$). X-ray crystal data - see appendix.

Nickel(II) complex of 1,8-N,N'-bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane 8: (Ni-L)(ClO_4). 2H_2O

Synthesis as for 12A, using nickel perchlorate hexahydrate. m/e (FAB, m-NBA) 376, 374 (M^+) (^{60}Ni-L and ^{58}Ni-L); λ_{max} (H_2O) 528 nm.

Copper(II) complex of 1,5,8,12-tetraazatricyclo[10,2,2,2^{5,8}]octadecane 15: (Cu-L):

15A

A solution of copper perchlorate hexahydrate (75 mgs, 0.2 mmol) in methanol (1 cc) was added to a solution of the ligand (50 mgs, 0.2 mmol) in methanol (1 cc). After warming a brown gelatinous precipitate was made which was removed by filtering and centrifugation to give a distinctively reddish solution. Slow evaporation of solvent over a few days yielded a pale red purple crystalline solid (72 mgs, 40%). m/e (FAB, m-nitrobenzyl alcohol) 317 and 315 (M^+) (^{65}Cu-L and ^{63}Cu-L); λ_{max} (MeOH) 516 nm, (H_2O) 538 nm.

Nickel(II) complex of 1,5,8,12-tetraazatricyclo[10,2,2,2^{5,8})octadecane 15: (Ni-L),

15B

Synthesis as for 15A using nickel perchlorate hexahydrate. Yellow crystalline solid (58 mgs, 78%); m/e (FAB, m-nitrobenzyl alcohol) 312 and 310 (M^+) (^{60}Ni-L and ^{58}Ni-L); λ_{max} (H_2O) 450 nm.

Copper(II) complex of 1,5-bis(carboxymethyl)-1,5,9-triazacylocdodecane 14:

(Cu-L)(ClO_4)$_2$.2HBr 14A

A solution of copper perchlorate hexahydrate (75 mgs, 0.2 mmol) in water (1 cc) was added to a solution of the ligand dihydrobromide (90 mgs, 0.2 mmol) in water (1 cc). The mixture was warmed and the pH was raised to 6 by careful addition of dilute potassium hydroxide solution, the mixture was filtered and allowed to stand. After 48 hours a blue solid was obtained which was dissolved in dry methanol (1 cc). To this was added ammonium

hexafluorophosphate (200 mgs, 1.2 x 10^{-3} mmol) in methanol (1 cc). Slow evaporation over several days yielded fine royal blue crystals. m/e (FAB, m-nitrobenzyl alcohol) 352 and 350 (M^+) (^{65}Cu-L and ^{63}Cu-L); λ_{max} (H_2O) 675 (ε = 37 dm^3 $mole^{-1}cms^{-1}$).

Nickel(II) complex of 1,5-bis(carboxymethyl)-1,5,9-triazacyclodecane 14: (Ni-L)$(ClO_4)_2$.2HBr

Synthesis as for 14A using nickel perchlorate hexahydrate. Yellow crystalline solid. m/e (FAB, m-nitrobenzyl alcohol) 374 and 345 (M^+) (^{60}Ni-L and ^{58}Ni-L); λ_{max} (H_2O) 535 nm.

Copper(II) complex of 9-methyl-1,5-bis(carboxymethyl)-1,5,9-triazacyclododecane 18 (Cu-L)$(ClO_4)_2$: 18A

Synthesis as for 14A using copper perchlorate hexahydrate. Pale blue crystalline solid. m/e (FAB, m-nitrobenzyl alcohol) 366 and 364 (M^+) (^{65}Cu-L and ^{63}Cu-L); λ_{max} (H_2O) 685 nm.

5.4 pH-Metric Titrations

5.4.1 Apparatus

The titration cell was a double walled glass vessel (capacity 5 cc) which was maintained at 25°C, using a Techne Tempette Junior TE-8J. Titration solutions were stirred using a magnetic stirrer and kept under an atmosphere of nitrogen. Titrations were performed using an automatic titrator (Mettler DL20, 1 cc capacity) and burette functions (volume increments and

equilibrations time) were controlled by a BBC microprocessor. The pH was measured using a Corning 001854 combination microelectrode which was calibrated using buffer solutions at pH 4.008 ($HOOC.C_6H_4COOK$, 0.05M) and 6.865 (KH_2PO_4, 0.025M/Na_2HPO_4, 0.025M). Data was stored on the BBC microprocessor and transferred to the MTS mainframe using KERMIT and subsequently analysed by two non-linear least squares programs SCOGS-2 and SUPERQUAD[3].

5.4.2 Acid dissociation constants

Stock solutions of the ligand (0.002 M) in milli-Q water (25.0 cc) with nitric acid (1 eq. per amine of the ligand) and tetramethyl ammonium nitrate (I=0.01 mol dm^{-3}) were prepared. In each titration 3.5 cc of the stock ligand solution was titrated with tetramethylammonium hydroxide (0.109 M), the exact molarity of which was determined by titration against hydrochloric acid, 0.100M.

5.5 X-ray crystal structure determinations

The X-ray crystal structures of the [Cu-Bu_2cyclam][PF_6]$_2$, cis and trans [Ni-Bu_2cyclam] (ClO_4)$_2$, [Cu[14]N_4-diacid](ClO_4)$_2$.$2H_2O$ and [Cu-Me_2][14]N_4-diacid](ClO_4)$_2$.$2H_2O$ complexes were determined by Professor George Ferguson (Department of Chemistry, University of Guelph, Ontario, Canada). The cell and intensity data were collected with an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo-K_α radiation. All calculations were carried out on a PDP11-73 computer system using the SDP-Plus system of programs and data therin[4]. The structures were solved by the heavy-atom method.

Hydrogen atoms (visible in difference maps) were allowed for, and refinement was by full-matrix least-squares calculations with all non-H atoms allowed anisotropic motion.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom co-ordinates, thermal parameters and remaining bond lengths and angles.

The structure of cis-Bu_2[14]$N_4(ClO_4)_2$ presented some difficulties (as noted in chapter 3). The crystals only diffracted poorly at room temperature and even at -100°C enough data could not be obtained adequately to define the structure (presumably because of disorder in the crystal lattice). The systematic absences allow the space group to be either Pnma or $Pn2_1a$. A satisfactory solution to the Patterson function was found in the centrosymmetric space group with the asymmetric unit containing two independent half-cations having their Ni atoms on mirror planes and four "half" perchlorate anions with the chlorine atoms on mirror planes. This situation then demands that the cations be disordered. Solution in the non-centrosymmetric space group was also considered (in this case there would be two independent cations in the asymmetric unit) but led to the same impasse as with the centrosymmetric solution (with a pseudo-centrosymmetric map and very poor resolution).

Cell data, experimental details, positional and thermal parameters and molecular dimensions for each structure are given in the Appendix.

5.6 References

1. A. Buttafava, L. Fabbrizzi, A. Perotti, G. Poli and B. Seghi, Inorg. Chem. 25, 1456 (1986); M. Ciampolini, L. Fabbrizzi, A. Perotti, A. Poggi, B. Seghi and F. Zanobini, Inorg. Chem., 26, 3527 (1987).

2. I.M. Helps, G. Ferguson, D. Parker and J. Chapman, J. Chem. Soc., Chem. Commun., 1094 (1988). Selected crystallographic data for the Cu^{2+} complexes of 8 and for the tricyclic lactam 14 are given in this reference: full data has been deposited at the Cambridge Crystallographic data centre.

3. P. Gans, A. Sabatini and A. Vacca, J. Chem. Soc. Dalton Trans., 1196 (1985).

4. B.A. Frenz and Associates, Inc., SDP Structure Determination Package, College Station Texas and Enraf-Nonius, Delft, 1983.

PUBLICATIONS, COLLOQUIA AND CONFERENCES

PUBLICATIONS

1. Selective N,N-Functionalisation of Cyclam: Crystal Structure of the Cu^{2+} Complex of 1,4,8,11-Tetraazacyclotetradecane-1,8-diacetic Acid and the Tricyclic Lactam 15,18-Dioxo-1,5,8,12-tetraazatricyclo[10.2.2.$2^{5,8}$]-tetradecane. I. M. Helps, D. Parker, J. Chapman and G. Ferguson, J. Chem. Soc. Chem. Comm., 1988, 1094.

2. General Routes for the Synthesis of Moni, Di and Tri-N-substituted Derivatives of Cyclam. I. M. Helps, D. Parker, J. R. Morphy and J. Chapman, Tetrahedron, Vol. 45, No. 1, pp219 to 226, 1989.

3. Syntheses of C- and N-Functionalised Derivatives of 1,5,9-Triazacyclo-dodecane. I. M. Helps, D. Parker, K. J. Jankowski, J. Chapman and P. E. Nicholson, J. Chem. Soc. Perkin Trans. 1, 1989, pp2079 to 2082.

4. Cooper and Nickel Complexes of 1,8-Disubstituted Derivatives of 1,4,8,11-tetraazacyclotetradecane, J. Chapman, G. Ferguson, J. F. Gallagher, M. C. Jennings and D. Parker, J. Chem. Soc. Dalton Trans., 345 (1992).

RESEARCH CONFERENCES ATTENDED

1. R.S.C. Graduate Symposium, University of Durham, 27th March (1987).

2. Molecular Recognition, University of Sheffield, 14th December (1987).

3. R.S.C. Perkin Division, North East Regional Meeting, University of Newcastle Upon Tyne, 21st September (1987).

4. R.S.C. Graduate Symposium, University of Durham, 19th April (1988).

5. R.S.C. Perkin Division, North East Regional Meeting, University of York, 16th December (1988).

6. U.K. Macrocycle Group, Annual Meeting, University of Durham, 6th January (1989).

7. R.S.C. Graduate Symposium, University of Durham, 12th April (1989).

8. U.K. Macrocycle Group, Annual Meeting, University of Warwick, December (1989).

RESEARCH COLLOQUIA, LECTURES AND SEMINARS

A list of all the research colloquia, lectures and seminars arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student is presented: "*" indicating the author's attendance.

1st August 1986 to 31st July 1987

*16th October 1986	Professor N. N. Greenwood (University of Leeds) Glorious Gaffes in Chemistry
*23rd October 1986	Professor H. W. Kroto (University of Sussex) Chemistry in Stars. Between Stars and in the Laboratory
29th October 1986	Professor E. H. Wong (University of New Hampshire, U.S.A) Co-ordination Chemistry of P-O-P Ligands
* 5th November 1986	Professor D. Döpp (University of Duisburg) Cyclo-additions and Cyclo-reversions Involving Captodative Alkenes

* 6th November 1986	Dr. R. M. Scrowston (University of Hull) From Myth and Magic to Modern Medicine
*13th November 1986	Professor Sir G. Allen (Unilever Research) Biotechnology and the Future of the Chemical Industry
20th November 1986	Dr. A. Milne/Mr. S. Christie (International Paints) Chemical Serendipity - A Real Life Case Study
26th November 1986	Dr. N. D. S. Canning (University of Durham) Surface Adsorption Studies of Relevance to Heterogeneous Ammonia Synthesis
* 3rd December 1986	Dr. J. Miller (Dupont Central Research, U.S.A.) Molecular Ferromagnets: Chemistry and Physical Properties
8th December 1986	Professor T. Dorfmüller (University of Bielefeld) Rotational Dynamics in Liquids and Polymers
*22nd January 1987	Professor R. H. Ottewill (University of Bristol) Colloid Science. A Challenging Subject
28th January 1987	Dr. W. Clegg (University of Newcastle-Upon-Tyne) Carboxylate Complexes of Zinc; Charting a Structural Jungle
4th February 1987	Professor A. Thomson (University of East Anglia) Metalloproteins and Magneto-optics
* 5th February 1987	Dr. P. Hubberstey (University of Nottingham) Demonstration Lecture on Various Aspects of Alkali Metal Chemistry
11th February 1987	Dr. T. Shepherd (University of Durham) Pteridine Natural Products; Synthesis and Use in Chemotherapy
12th February 1987	Dr. P. J. Rodgers (I.C.I. Billingham) Industrial Polymers from Bacteria
*17th February 1987	Professor E. H. Wong (University of New Hampshire, U.S.A.) Symmetrical Shapes from Molecules to Art and Nature

*19th February 1987	Dr. M. Jarman (Institute of Cancer Research) The Design of Anti Cancer Drugs
4th March 1987	Dr. R. Newman (University of Oxford Change and Decay: A Carbon-13 CP/MAS NMR Study of Humification and Coalification Processes
* 5th March 1987	Professor S. V. Ley (Imperial College) Fact and Fantasy in Organic Synthesis
* 9th March 1987	Professor F. G. Bordwell (North Eastern University, U.S.A.) Carbon Anions. Radicals. Radical Anions and Radial Cations
11th March 1987	Dr. R. D. Cannon (University of East Anglia) Electron Transfer in Polynuclear Complexes
*12th March 1987	Dr. W. M. Goodger (Cranfield Institute of Technology) Alternative Fuels for Transport
*18th March 1987	Professor R. F. Hudson (University of Kent) Homolytic Re-arrangements of Free Radical Stability
6th May 1987	Dr. R. Bartsch (University of Sussex) Low Co-ordinated Phosphorus Compounds
7th May 1987	Dr. M. Harmer (I.C.I. Chemicals & Polymer Group) The Role of Organometallics in Advanced Materials
11th May 1987	Professor S. Pasynkiewicz (Technical University, Warsaw) Thermal Decomposition of Methyl Copper and its Reactions with Trialkylaluminium
17th May 1987	Professor R. F. Hudson (University of Kent) Aspects of Oragnophosphorus Chemistry
27th May 1987	Dr. M. Blackburn (University of Sheffield) Phosphonates as Analogues of Biological Phosphate Esters
*24th June 1987	Professor S. M. Roberts (University of Exeter) Synthesis of Novel Antivital Agents

26th June 1987	Dr. C. Krespan (E. I. Dupont de Nemours) Nickel(0) and Iron(0) as Reagents in Organofluorine Chemistry

1st August 1987 to 31st July 1988

15th October 1987	Dr. M. J. Winter (University of Sheffield) Pyrotechnics (Demonstration Lecture)
*22nd October 1987	Professor G. W. Gray (University of Hull) Liquid Crystals and their Applications
*29th October 1987	Mrs. S. van Rose (Geological Museum) Chemistry of Volcanoes
4th November 1987	Mrs. M. Mapletoft (Durham Chemistry Teachers' Centre) Salters' Chemistry
* 5th November 1987	Dr. A. R. Butler (University of St. Andrews) Chinese Alchemy
12th November 1987	Dr. J. Davidson (Heriot-Watt University) Metal Promoted Oligomerisation Reactions of Alkynes
*12th November 1987	Professor D. Seeback (E.T.H. Zurich) From Synthetic Methods to Mechanistic Insight
*26th November 1987	Dr. D. H. Williams (University of Cambridge) Molecular Recognition
*27th November 1987	Professor R. L. Williams (Metropolitan Police Forensic Science) Science and Crime
* 3rd December 1987	Dr. J. Howard (I.C.I. Wilton) Chemistry of Non-Equilibration Processes
*10th December 1987	Dr. C. J. Ludman (Durham University) Explosives
16th December 1987	Mr. R. M. Swart (I.C.I) The Interaction of Chemicals with Lipid Bilayers

19th December 1987	Professor P. G. Sammes (Smith, Kline and French) Chemical Aspects of Drug Development
*21st January 1988	Dr. F. Palmer (University of Nottingham) Luminescence (Demonstration Lecture)
*25th January 1988	Dr. L. Harwood (University of Oxford) Synthetic Approaches to Phorbols Via Intramolecular Furan Diels-Alder Reactions: Chemistry Under Pressure
*28th January 1988	Dr. A. Cairns-Smith (University of Glasgow) Clay Minerals and the Origin of Life
*11th February 1988	Professor J. J. Turner (University of Nottingham) Catching Organometallic Intermediates
*18th February 1988	Dr. K. Borer (University of Durham Industrial Research Labs.) The Brighton Bomb - A Forensic Science View
*25th February 1988	Professor A. Underhill (University of Bangor) Molecular Electronics
* 3rd March 1988	Professor W. A. G. Graham (University of Alberta, Canada) Rhodium and Iridium Complexes in the Activation of Carbon-Hydrogen Bonds
16th March 1988	L. Bossons (Durham Chemistry Teachers' Centre) GCSE Practical Assessment
7th April 1988	Professor M. P. Hartshorn (University of Canterbury, New Zealand) Aspects of Ipso-Nitration
13th April 1988	Mrs. E. Roberts (SATRO Officer for Sunderland) Durham Chemistry Teachers' Centre Talk: Links Between Industry and Schools
18th April 1988	Professor C. A. Nieto de Castro (University of Lisbon and Imperial College) Transport Properties of Non-Polar Fluids
*19th April 1988	Graduate Chemists (North East Polytechnics and Universities) R.S.C. Graduate Symposium

25th April 1988	Professor D. Birchall (I.C.I. Advanced Materials) Environmental Chemistry of Aluminium
27th April 1988	Dr. R. Richardson (University of Bristol) X-ray Diffraction from Spread Monolayers
*27th April 1988	Dr. J. A. Robinson (University of Southampton) Aspects of Antibiotic Biosynmthesis
*28th April 1988	Professor A. Pines (University of California, Berkeley, U.S.A.) Some Magnetic Moments
*11th May 1988	Dr. W. A. McDonald (I.C.I. Wilton) Liquid Crystal Polymers
11th May 1988	Dr. J. Sodeau (University of East Anglia) Durham Chemistry Teachers' Centre Lecture: Spray Cans, Smog and Society
8th June 1988	Professor J.-P. Majoral (Université Paul Sabatier) Stabilisation by Complexation of Short-Lived Phosphorus Species
*29th June 1988	Professor G. A. Olah (University of Southern California) New Aspects of Hydrocarbon Chemistry

1st August 1988 to 31st July 1989

6th October 1988	Professor R. Schmutzler (Technische Universitat Braunschweig) Fluorophosphines Revisited - New Contributions to an Old Theme
18th October 1988	Mr. F. Bollen (Durham Chemistry Teachers' Centre) Lecture about the use of SATIS in the classroom
*18th October 1988	Dr. J. Dingwall (Ciba Geigy) Phosphorus-containing Amino Acids: Biologically Active Natural and Unnatural Products
18th October 1988	Dr. C. J. Ludman (University of Durham) The Energetics of Explosives

*21st October 1988	Professor P. Von Rague Schleyer (Universitat Erlangen Nurnberg) The Fruitful Interplay Between Calculational and Experimental Chemistry
*27th October 1988	Professor C. W. Rees (Imperial College London) Some Very Heterocyclic Compounds
* 9th November 1988	Dr. G. Singh (Teesside Polytechnic) Towards Third Generation Anti-Leukaemics
*10th November 1988	Professor J. I. G. Cadogan (British Petroleum) From Pure Science to Profit
16th November 1988	Dr. K. A. McLauchlan (University of Oxford) The Effect of Magnetic Fields on Chemical Reactions
24th November 1988	Drs. R. R. Baldwin and R. W. Walker (University of Hull) Combustion: Some Burning Problems
1st December 1988	Dr. R. Snaith (University of Cambridge) Egyptian Mummies: What, Where, Why and How?
7th December 1988	Dr. G. Hardgrove (St. Olaf College, U.S.A.) Polymers in the Physical Chemistry Laboratory
9th December 1988	Dr. C. Jäger (Friedrich-Schiller University GDR) NMR Investigations of Fast Ion Conductors of the NASICON Type
14th December 1988	Dr. C. Mortimer (Durham Chemistry Teachers' Centre) The Hindenberg Disaster - An Excuse for Some Experiments
*26th January 1989	Professor R. R. Jennings (University of Warwick) Chemistry of the Masses
1st February 1989	Mr. D. Waters and T. Cressey (Durham Chemistry Teachers' Centre) GCSE Chemistry 1988: A Coroner's Report
* 2nd February 1989	Professor L. D. Hall (Addenbrooke's Hospital, Cambridge) NMR - A Window to the Human Body

* 9th February 1989	Professor J. E. Baldwin (University of Oxford) Recent Advances in the Bio-organic Chemistry of Penicillin Biosynthesis
*13th February 1989	Professor R. R. Schrock (M.I.T.) Recent Advances in Living Metathesis
*15th February 1989	Dr. A. R. Butler (University of St. Andrews) Cancer in Linxiam: The Chemical Dimensions
*16th February 1989	Professor B. J. Aylett (Queen Mary College, London) Silicon-Based Chips: The Chemist's Contribution
22nd February 1989	Dr. G. MacDougall (University of Edinburgh) Vibrational Spectroscopy of Model Catalytic Systems
23rd February 1989	Dr. B. F. G. Johnson (University of Cambridge) The Binary Carbonyls
1st March 1989	Dr. R. J. Errington (University of Newcastle-Upon-Tyne) Polymetalate Assembly in Organic Solvents
* 9th March 1989	Dr. I. Marko (University of Sheffield) Catalytic Asymmetric Osmylation of Olefins
14th March 1989	Mr. P. Revell (Durham Chemistry Teachers' Centre) Implementing Broad and Balanced Science 11-16
15th March 1989	Dr. R. Aveyard (University of Hull) Surfactants at your Surface
*20th April 1989	Dr. M. Casey (University of Salford) Sulphoxides in Stereoselective Synthesis
*27th April 1989	Dr. D. Crich (University College London) Some Novel Uses of Free Radicals in Organic Synthesis)
3rd May 1989	Mr. A. Ashman (Durham Chemistry Teachers' Centre) The Chemical Aspects of the National Curriculum
* 3rd May 1989	Dr. P. C. B. Page (University of Liverpool) Stereocontrol of Organic Reactions Using 1,3-dithiane-1-oxides

10th May 1989	Professor P. B. Wells (University of Hull) Catalyst Characterisation and Activity
11th May 1989	Dr. J. Frey (University of Southampton) Spectroscopy of the Reaction Path: Photodissociation Raman Spectra of NOCl
16th May 1989	Dr. R. Stibr (Czechoslovak Academy of Sciences) Recent Developments in the Chemistry of Intermediate-Sited Carboranes
*17th May 1989	Dr. C. J. Moody (Imperial College) Reactive Intermediates in Heterocyclic Synthesis
23rd May 1989	Professor P. Paetzold (Aachen) Iminoboranes XB≡NR: Inorganic Acetylenes?
14th June 1989	Dr. M. E. Jones (Durham Chemistry Teachers' Centre) Discussion Session on the National Curriculum
15th June 1989	Professor J. Pola (Czechoslovak Academy of Sciences) Carbon Dioxide Laser Induced Chemical Reactions - New Pathways in Gas-Phase Chemistry
28th June 1989	Dr. M. E. Jones (Durham Chemistry Teachers' Centre) GCSE and A Level Chemistry 1989
11th July 1989	Dr. D. Nicholls (Durham Chemistry Teachers' Centre) Demo: Liquid Air

APPENDIX - CRYSTAL DATA

Summary of cell data, data collection and refinement details.

Compound	trans-[Ni-20] $[ClO_4]_2$	cis-[Ni-20]$[ClO_4]_2$	[Cu-20]$[PF_6]_2$	$[CuH_2$-12$][ClO_4]_2 \cdot 2H_2O$	[Cu-8][H_2-14]$[ClO_4]_2$
Formula	$C_{18}H_{40}Cl_2NiN_4O_8$	$C_{18}H_{40}Cl_2NiN_4O_8$	$C_{18}H_{40}CuF_{12}N_4P_2$	$C_{16}H_{36}Cl_2CuN_4O_{14}$	$C_{28}H_{52}Cl_2CuN_8O_{14}$
Colour, habit	Yellow, block	Orange, plate	Pink, diamond	Blue, block	Deep blue, plate
Crystal size/mm	0.29 x 0.33 x 0.57	0.15 x 0.41 x 0.55	0.07 x 0.56 x 0.65	0.14 x 0.32 x 0.38	0.30 x 0.25 x 0.24
Crystal system	Triclinic	Orthorhombic	Triclinic	Monoclinic	Triclinic
a/Å	9.214(2)	15.047(3)	9.357(2)	8.089(4)	9.547(2)
b/Å	9.315(2)	12.689(3)	9.297(2)	9.269(2)	12.014(2)
c/Å	8.507(2)	26.471(5)	8.552(2)	17.552(4)	8.929(1)
α/°	113.90(1)		112.60(2)		98.97(1)
β/°	104.64(2)		103.63(2)	96.34(3)	114.56(1)
γ/°	75.52(1)		77.31(1)		80.44(2)
U/Å^3	636.9(4)	5054(2)	660.6(4)	1308(1)	914.2(6)
Space group	P1	Pnma/Pn2$_1$a	P1	P2$_1$/c	P1
Z	1	8	1	2	1
Molecular symmetry	1		1	1	1
F(000)	302	2416	343	670	451
D_{calc}/g cm^{-3}	1.49	1.50	1.67	1.63	1.56
μ/cm^{-1}	10.2	10.3	10.5	11.1	8.2
Min., max. absorption correction	0.69, 0.79		0.59, 0.93	0.71, 0.86	0.70, 0.82
2θ range/°	4 to 54	4 to 48	4 to 54	4 to 54	4 to 54
T/°C	21	-100	21	21	21

Summary of cell data, data collection and refinement details. (Continued/.....)

Compound	trans-[Ni-20] $[ClO_4]_2$	cis-[Ni-20][ClO_4]$_2$	[Cu-20][PF_6]$_2$	[Cu(H_2-12][ClO_4]$_2$.$2H_2O$	[Cu-8][H_2-14][ClO_4]$_2$
Reflections measured	2857	3800	2944	3320	4097
Unique reflections	2857		2423	2848	3985
Reflections with $1 > 3\sigma(1)$	2331	2109	2420	1934	2643
No. variables in least squares	187		170	169	241
p in weighting scheme	0.057		0.07	0.08	0.05
R, R′	0.049, 0.072		0.044, 0.064	0.053, 0.075	0.053, 0.081
Density in final difference map/e Å^{-3}	0.54		0.65	0.67	0.92
Final shift/error ratio	0.02		0.01	0.01	0.02

Ni-[14]$N_4Bu_2(ClO_4)_2$

Table of Experimental Details

A. Crystal Data

C18 H40 CL2 NI N4 08

F.W. 570.16 F(000) = 302

crystal dimensions: 0.29 x 0.33 x 0.57 mm

peak width at half-height = 0.00

Mo K_α radiation (= 0.71073 A)

temperature = 23 21

triclinic space group P-1

a = 9.214 (2) A b = 9.315 (1) A c = 8.507 (2) A

α = 113.90 (1) β = 104.64 (2) γ = 75.52 (1)

V = 636.9 A^3

Z = 1 D_c = 1.49 g/cm

μ = 10.2 cm-1

Table of Experimental Details

B. Intensity Measurements

Instrument:	Enraf-Nonius CAD4 diffractometer
Monochromator:	Graphite crystal, incident beam
Attenuator:	Zr foil, factor 17.6
Take-off angle:	0.3
Detector aperture:	2.0 to 2.5 mm horizontal
	4.0 mm vertical
Crystal-detector dist.:	1 cm
Scan type:	ω-2θ
Scan rate:	1 - 7 /min (in omega)
Scan width, deg:	0.6 + 0.350 tan
Maximum 2θ:	54.0
No. of refl. measured:	2857 total, 2332 unique
Corrections:	Lorentz-polarization
	Numerical absorption (from69.17 to79.52 on I)

Table of Experimental Details

C. Structure Solution and Refinement

Solution:	Patterson method
Hydrogen atoms:	Included as fixed contribution to the
structure factor	
Minimization function:	w(|Fo|-|Fc|)
Least-squares weights:	4Fo / (Fo)
Anomalous dispersion:	All non-hydrogen atoms
Reflections included:	2331 with Fo >3.0 (Fo)
Parameters refined:	187
Unweighted agreement factor: R	0.049
Weighted agreement factor: R_w	0.072
Esd of obs. of unit weight:	2.12
Convergence, largest shift:	0.02
High peak in final diff. map:	0.54 (7) e/A
Computer hardware:	PDP-11
Computer software:	SDP-PLUS (Enraf-Nonius &
	B. A. Frenz & Associates, Inc.)

Table

Positional and thermal parameters and their e.s.d.'s

Atom	x	y	z	B(A)
Ni	0.0	0.0	0.0	3.42(1)
N1	0.1971(3)	-0.1446(3)	-0.0079(3)	4.19(5)
C2	0.1896(5)	-0.2560(4)	-0.1933(4)	6.13(9)
C3	0.0370(6)	-0.3056(4)	-0.2581(5)	6.6(1)
N4	-0.0774(3)	-0.1579(3)	-0.2181(3)	4.64(6)
C5	-0.2272(5)	-0.1979(4)	-0.2375(5)	6.5(1)
C6	-0.3544(4)	-0.0554(4)	-0.2159(5)	6.6(1)
C7	-0.3339(4)	0.0680(4)	-0.0385(4)	5.91(8)
C11	0.2048(3)	-0.2311(3)	0.1109(3)	4.13(6)
C12	0.3382(4)	-0.3629(4)	0.1118(4)	5.61(8)
C13	0.3379(5)	-0.4394(4)	0.2378(5)	6.7(1)
C14	0.3577(8)	-0.3381(6)	0.4188(6)	11.3(2)
CL	0.1786(1)	0.2044(1)	-0.2915(1)	6.21(2)
O1	0.1149(7)	0.0911(6)	-0.2505(8)	9.5(2)
O2	0.3152(8)	0.199(1)	-0.186(1)	18.9(3)
O3	0.231(1)	0.088(1)	-0.439(1)	10.7(3)
O4	0.057(1)	0.2930(8)	-0.352(1)	15.9(3)
O5	0.105(1)	0.343(1)	-0.154(1)	12.5(3)
O6	0.244(1)	0.330(1)	-0.325(1)	13.2(3)
O7	0.163(2)	0.197(2)	-0.147(1)	13.4(5)
O8	0.095(1)	0.134(1)	-0.437(1)	13.0(4)

The disordered oxygen atoms had occupancy factors of 0.55, 0.74, 0.40, 0.63, 0.50, 0.50, 0.32, 0.36 for O1 to O8 respectively.

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as:

(4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table

Molecular dimensions

(a) Interatomic distances (A)

Ni	N1	1.970(2)	CL	O1	1.514(8)
Ni	N4	1.939(2)	CL	O2	1.351(7)
N1	C2	1.491(3)	CL	O3	1.390(8)
N1	C7(I)	1.492(5)	CL	O4	1.340(8)
N1	C11	1.507(4)	CL	O5	1.495(8)
C2	C3	1.490(6)	CL	O6	1.587(12)
C3	N4	1.482(4)	CL	O7	1.305(15)
N4	C5	1.471(6)	CL	O8	1.289(10)
C5	C6	1.518(5)			
C6	C7	1.481(4)			
C11	C12	1.505(4)			
C12	C13	1.509(7)			
C13	C14	1.436(5)			
O1 ...	Ni	3.072(8)			
N4 ...	O3(II)	3.150(9)			
N4 ...	O8(II)	2.997(13)			
H4 ...	O3(II)	2.37			
H4 ...	O8(II)	2.16			

(b) Bond angles ( )

N1	Ni	N4	87.45(9)
N1	Ni	N4(I)	92.55(9)
Ni	N1	C2	105.1(2)
Ni	N1	C7(I)	115.8(2)
Ni	N1	C11	106.1(2)
C2	N1	C7(I)	107.2(3)
C2	N1	C11	111.2(2)
C7(I)	N1	C11	111.4(2)
N1	C2	C3	109.0(3)
C2	C3	N4	106.9(3)
Ni	N4	C3	109.4(2)
Ni	N4	C5	118.4(2)
C3	N4	C5	109.5(3)
N4	C5	C6	113.1(3)
C5	C6	C7	112.2(3)
N1(I)	C7	C6	114.9(3)
N1	C11	C12	116.3(3)
C11	C12	C13	112.3(3)
C12	C13	C14	115.4(4)
Ni	O1	CL	152.0(3)
N4	H4	O3(II)	139.4
N4	H4	O8(II)	146.5

O1	CL	O2	97.9(5)
O1	CL	O3	94.1(5)
O1	CL	O4	105.0(5)
O1	CL	O5	90.5(5)
O1	CL	O6	177.2(4)
O1	CL	O7	46.2(7)
O1	CL	O8	76.3(7)
O2	CL	O3	94.8(5)
O2	CL	O4	148.0(5)
O2	CL	O5	93.4(5)
O2	CL	O6	81.2(6)
O2	CL	O7	70.0(8)
O2	CL	O8	146.9(6)
O3	CL	O4	105.3(5)
O3	CL	O5	169.9(5)
O3	CL	O6	88.6(6)
O3	CL	O7	131.2(8)
O3	CL	O8	54.0(6)
O4	CL	O5	64.7(5)
O4	CL	O6	74.8(6)
O4	CL	O7	111.2(8)
O4	CL	O8	62.2(6)
O5	CL	O6	86.8(6)
O5	CL	O7	57.6(8)
O5	CL	O8	118.9(6)
O6	CL	O7	131.2(7)
O6	CL	O8	105.9(8)
O7	CL	O8	120.(1)

The roman numerals refer to the following equivalent positions:

(I) $-x, -y, -z$ (II) $x, y, -1+z$.

Deposition data: Torsion Angles

Atom 1	Atom 2	Atom 3	Atom 4	Angle	
C7	N1	C2	C3	-166.6	(0.3)
C11	N1	C2	C3	71.4	(0.4)
C2	N1	C7	C6(I)	176.2	(0.3)
C11	N1	C7	C6(I)	-62.0	(0.4)
C2	N1	C11	C12	59.7	(0.4)
C7	N1	C11	C12	-59.8	(0.3)
N1	C2	C3	N4	51.5	(0.4)
C2	C3	N4	C5	-165.8	(0.3)
C3	N4	C5	C6	-174.5	(0.3)
N4	C5	C6	C7(I)	-63.3	(0.4)
C5	C6	C7(I)	N1(I)	64.6	(0.4)
N1	C11	C12	C13	178.6	(0.3)
C11	C12	C13	C14	-65.2	(0.5)

Deposition data

Calculated hydrogen coordinates (C-H 0.95 A)

Atom	x	y	z	B(A)
H21	0.2048	-0.2040	-0.2620	7
H22	0.2662	-0.3471	-0.2006	7
H31	0.0244	-0.3634	-0.3804	7
H32	0.0263	-0.3702	-0.2007	7
H51	-0.2495	-0.2758	-0.3504	7
H52	-0.2228	-0.2405	-0.1517	7
H61	-0.3564	-0.0099	-0.2984	7
H62	-0.4483	-0.0903	-0.2372	7
H71	-0.4213	0.1488	-0.0299	7
H72	-0.3260	0.0198	0.0433	7
H4	-0.0825	-0.1067	-0.2963	7
H111	0.2082	-0.1548	0.2265	7
H112	0.1146	-0.2759	0.0766	7
H121	0.3344	-0.4419	-0.0023	7
H122	0.4294	-0.3201	0.1442	7
H131	0.2433	-0.4752	0.2088	7
H132	0.4182	-0.5280	0.2229	7
H141	0.3559	-0.3961	0.4877	12
H142	0.2776	-0.2492	0.4371	12
H143	0.4525	-0.3020	0.4512	12

Deposition data

General Temperature Factor Expressions - U's

Name	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
NI	0.0599(3)	0.0348(2)	0.0339(2)	0.0009(2)	0.0132(2)	0.0132(1)
N1	0.061(1)	0.0522(9)	0.0498(9)	0.0044(9)	0.0191(8)	0.0246(7)
C2	0.097(2)	0.068(2)	0.051(1)	0.028(2)	0.031(1)	0.018(1)
C3	0.120(3)	0.046(1)	0.051(2)	0.007(2)	0.006(2)	0.003(1)
N4	0.082(2)	0.0422(9)	0.045(1)	-0.008(1)	0.005(1)	0.0134(7)
C5	0.116(3)	0.060(1)	0.073(2)	-0.036(1)	0.003(2)	0.021(1)
C6	0.077(2)	0.090(2)	0.101(2)	-0.033(1)	0.006(2)	0.046(1)
C7	0.076(2)	0.082(1)	0.092(1)	-0.005(1)	0.036(1)	0.0485(9)
C11	0.053(1)	0.051(1)	0.059(1)	-0.003(1)	0.013(1)	0.0293(8)
C12	0.076(2)	0.060(1)	0.078(2)	0.014(1)	0.024(1)	0.036(1)
C13	0.087(2)	0.075(1)	0.104(2)	0.010(2)	0.018(2)	0.058(1)
C14	0.204(6)	0.120(3)	0.092(2)	0.056(3)	0.043(3)	0.064(2)
CL	0.0690(5)	0.0944(5)	0.0641(4)	0.0024(4)	0.0093(4)	0.0309(3)
01	0.125(4)	0.125(3)	0.153(3)	-0.025(2)	0.030(3)	0.087(2)
02	0.110(4)	0.332(7)	0.317(7)	-0.050(4)	-0.051(5)	0.203(5)
03	0.195(7)	0.106(6)	0.090(4)	0.027(5)	0.088(3)	0.013(4)
04	0.174(6)	0.199(4)	0.276(5)	0.057(4)	0.043(5)	0.182(3)
05	0.183(7)	0.132(5)	0.162(6)	-0.041(5)	0.049(5)	0.036(4)
06	0.225(8)	0.136(6)	0.137(6)	-0.046(6)	0.059(5)	0.019(5)
07	0.20(1)	0.23(1)	0.083(5)	-0.012(9)	0.030(6)	0.085(5)
08	0.184(7)	0.251(8)	0.086(5)	-0.138(5)	-0.027(5)	0.059(5)

he form of the anisotropic thermal parameter is:

xp[-2PI2(h2a2U(1,1) + k2b2U(2,2) + l2c2U(3,3) + 2hkabU(1,2) + 2hlacU(1,3) 2klbcU(2,3))] where a, b, and c are reciprocal lattice constants.

$Cu\text{-}[14]N_4Bu_2(PF_6)_2$

Table of Experimental Details

A. Crystal Data

C18 H40 CU F12 N4 P2

F. W. 666.02 F(000) = 343

crystal dimensions: 0.07 x 0.56 x 0.65 mm

peak width at half-height = 0.50

Mo K radiation (= 0.71073 A)

temperature = 21 1

triclinic space group P-1

a = 9.357 (2) A b = 9.297 (2) A c = 8.552 (2) A

= 112.60 (2) = 103.63 (2) = 77.31 (1)

V = 660.6 A

Z = 1 = 1.67 g/cm

= 10.5 cm-1

Table of Experimental Details

B. Intensity Measurements

Instrument:	Enraf-Nonius CAD4 diffractometer
Monochromator:	Graphite crystal, incident beam
Attenuator:	Zr foil, factor 17.6
Take-off angle:	2.8
Detector aperture:	2.0 to 2.5 mm horizontal
	4.0 mm vertical
Crystal-detector dist.:	21 cm
Scan type:	ω-
Scan rate:	2 - 7 /min (in omega)
Scan width, deg:	1.0 + 0.350 tan
Maximum 2 :	54.0
No. of refl. measured:	2944 total, 2423 unique
Corrections:	Lorentz-polarization
	Numerical absorption (from59.09 to93.06 on I)
	Extinction (coefficient = 0.0000000)

Table of Experimental Details

C. Structure Solution and Refinement

Solution:	Patterson method
Minimization function:	w(|Fo|-|Fc|)
Least-squares weights:	4Fo / (Fo)
Anomalous dispersion:	All non-hydrogen atoms
Reflections included:	2420 with Fo >3.0 (Fo)
Parameters refined:	170
Unweighted agreement factor:	0.044
Weighted agreement factor:	0.064
Esd of obs. of unit weight:	1.57
Convergence, largest shift:	0.00
High peak in final diff. map:	0.65 (8) e/A
Computer hardware:	PDP-11
Computer software:	SDP-PLUS (Enraf-Nonius & B. A. Frenz & Associates, Inc.)

Table

Positional and thermal parameters and their e.s.d.'s

Atom	x	y	z	B(Å^2)
Cu	0.0	0.0	0.0	2.273(8)
N1	0.1975(2)	-0.1518(2)	-0.0111(3)	2.59(4)
C2	0.1809(4)	-0.2593(3)	-0.1936(4)	3.64(6)
C3	0.0281(4)	-0.3066(3)	-0.2513(4)	3.97(7)
N4	-0.0819(3)	-0.1624(2)	-0.2184(3)	2.99(5)
C5	-0.2318(4)	-0.1969(3)	-0.2282(4)	3.81(7)
C6	-0.3495(3)	-0.0540(4)	-0.2041(4)	3.98(7)
C7	-0.3286(3)	0.0697(3)	-0.0278(4)	3.40(6)
C11	0.2102(3)	-0.2378(3)	0.1094(3)	2.72(5)
C12	0.3491(4)	-0.3586(3)	0.1159(4)	3.85(6)
C13	0.3528(4)	-0.4348(4)	0.2448(4)	4.46(7)
C14	0.3837(7)	-0.3278(6)	0.4275(5)	7.7(1)
P	-0.16276(9)	-0.21367(9)	0.28462(9)	3.52(2)
F1	-0.1012(2)	-0.1012(2)	0.2236(2)	4.79(4)
F2	-0.1032(3)	-0.3606(3)	0.1310(3)	7.22(7)
F3	-0.0089(3)	-0.2402(3)	0.3995(3)	8.30(7)
F4	-0.2162(4)	-0.0750(3)	0.4410(3)	9.24(8)
F5	-0.3147(3)	-0.1968(3)	0.1679(3)	8.16(7)
F6	-0.2228(3)	-0.3327(3)	0.3428(3)	6.87(6)

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as:

(4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table

Molecular dimensions

(a) Interatomic distances (Å)

Cu	N1	2.062(2)
Cu	N4	2.005(2)
N1	C2	1.488(3)
N1	C7(I)	1.490(4)
N1	C11	1.500(4)
C2	C3	1.503(5)
C3	N4	1.475(4)
N4	C5	1.483(4)
C5	C6	1.508(4)
C6	C7	1.504(4)
C11	C12	1.525(4)
C12	C13	1.513(6)
C13	C14	1.494(5)
P	F1	1.588(3)
P	F2	1.592(2)
P	F3	1.569(3)
P	F4	1.552(3)
P	F5	1.548(2)
P	F6	1.617(3)
F1 ...	Cu	2.840(2)
N4 ...	F1(I)	3.303(4)
N4 ...	F3(II)	3.269(4)
N4 ...	F4(II)	3.221(4)
H4 ...	F1(I)	2.76
H4 ...	F3(II)	2.57
H4 ...	F4(II)	2.38

(b) Bond angles (°)

N1	Cu	N4	86.61(8)
N1	Cu	N4(I)	93.39(8)
Cu	N1	C2	103.3(2)
Cu	N1	C7(I)	112.6(2)
Cu	N1	C11	108.3(2)
C2	N1	C7(I)	108.9(2)
C2	N1	C11	111.8(2)
C7(I)	N1	C11	111.6(2)
N1	C2	C3	110.0(3)
C2	C3	N4	108.3(2)
Cu	N4	C3	108.2(2)
Cu	N4	C5	116.5(2)
C3	N4	C5	111.4(2)
N4	C5	C6	113.3(3)
C5	C6	C7	114.1(2)
N1(I)	C7	C6	114.3(3)
N1	C11	C12	115.9(3)
C11	C12	C13	111.5(3)
C12	C13	C14	113.6(3)
Cu	F1	P	158.48(9)
N4	H4	F1(I)	117.5
N4	H4	F3(II)	130.2
N4	H4	F4(II)	147.5

F1	P	F2	89.2(1)
F1	P	F3	91.0(2)
F1	P	F4	92.6(2)
F1	P	F5	91.1(2)
F1	P	F6	178.3(1)
F2	P	F3	87.8(1)
F2	P	F4	177.0(2)
F2	P	F5	90.1(1)
F2	P	F6	89.1(2)
F3	P	F4	89.7(2)
F3	P	F5	177.0(2)
F3	P	F6	88.7(2)
F4	P	F5	92.3(2)
F4	P	F6	89.1(2)
F5	P	F6	89.2(2)

The roman numerals refer to the following equivalent positions:

(I) $-x, -y, -z$ (II) $x, y, -1+z$.

Deposition data

Calculated hydrogen coordinates (C–H 0.95 Å)

Atom	x	y	z	B(Å^2)
H21	0.2529	−0.3506	−0.2043	5
H22	0.1952	−0.2068	−0.2634	5
H31	0.0161	−0.3672	−0.1888	5
H32	0.0145	−0.3671	−0.3705	5
H51	−0.2276	−0.2383	−0.1413	5
H52	−0.2590	−0.2732	−0.3378	5
H61	−0.4433	−0.0872	−0.2244	5
H62	−0.3483	−0.0082	−0.2856	5
H71	−0.3169	0.0207	0.0544	5
H72	−0.4152	0.1462	−0.0179	5
H4	−0.0862	−0.1165	−0.3016	5
H111	0.1261	−0.2911	0.0754	5
H112	0.2090	−0.1618	0.2217	5
H121	0.4344	−0.3074	0.1476	5
H122	0.3500	−0.4378	0.0053	5
H131	0.4282	−0.5237	0.2271	5
H132	0.2591	−0.4680	0.2254	5
H141	0.3846	−0.3823	0.5016	8
H142	0.4776	−0.2942	0.4492	8
H143	0.3086	−0.2385	0.4476	8

Deposition data: Torsion Angles

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C7	N1	C2	C3	-163.4 (0.2)
C11	N1	C2	C3	72.8 (0.3)
C2	N1	C7	C6(I)	174.6 (0.3)
C11	N1	C7	C6(I)	-61.5 (0.3)
C2	N1	C11	C12	65.7 (0.3)
C7	N1	C11	C12	-56.6 (0.3)
N1	C2	C3	N4	54.7 (0.3)
C2	C3	N4	C5	-165.0 (0.2)
C3	N4	C5	C6	-177.2 (0.2)
N4	C5	C6	C7(I)	-65.6 (0.3)
C5	C6	C7(I)	N1(I)	68.8 (0.3)
N1	C11	C12	C13	178.4 (0.2)
C11	C12	C13	C14	-71.9 (0.4)

Deposition data

General Temperature Factor Expressions - U's

Name	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
Cu	0.0301(2)	0.0249(2)	0.0268(2)	0.0000(1)	0.0024(1)	0.0078(1
N1	0.0316(9)	0.0353(8)	0.0331(8)	0.0029(7)	0.0089(7)	0.0161(6
C2	0.054(2)	0.042(1)	0.036(1)	0.012(1)	0.015(1)	0.0126(9
C3	0.067(2)	0.032(1)	0.036(1)	0.003(1)	-0.001(1)	0.005(1)
N4	0.044(1)	0.0316(9)	0.0335(9)	-0.0054(8)	0.0005(9)	0.0105(7)
C5	0.055(2)	0.046(1)	0.042(1)	-0.022(1)	-0.001(1)	0.012(1)
C6	0.040(1)	0.062(1)	0.057(1)	-0.019(1)	-0.001(1)	0.029(1)
C7	0.035(1)	0.053(1)	0.054(1)	-0.0028(9)	0.0135(9)	0.0309(8)
C11	0.032(1)	0.038(1)	0.038(1)	-0.0008(9)	0.0077(8)	0.0193(7)
C12	0.049(1)	0.048(1)	0.056(1)	0.012(1)	0.017(1)	0.0315(9)
C13	0.064(2)	0.051(1)	0.063(1)	0.006(1)	0.011(1)	0.0360(9)
C14	0.120(4)	0.095(3)	0.060(2)	0.028(3)	0.002(2)	0.038(2)
P	0.0443(4)	0.0515(3)	0.0406(3)	-0.0042(3)	0.0104(3)	0.0185(2)
F1	0.054(1)	0.0644(8)	0.0781(9)	-0.0106(7)	0.0127(8)	0.0386(6)
F2	0.122(2)	0.063(1)	0.093(1)	-0.018(1)	0.052(1)	0.009(1)
F3	0.084(2)	0.151(2)	0.103(1)	-0.029(1)	-0.022(1)	0.0850(9)
F4	0.181(2)	0.071(2)	0.105(1)	-0.002(2)	0.093(1)	0.006(1)
F5	0.049(1)	0.160(1)	0.143(1)	-0.027(1)	-0.010(1)	0.1074(9)
F6	0.106(1)	0.088(1)	0.096(1)	-0.0202(9)	0.0363(9)	0.0478(7)

The form of the anisotropic thermal parameter is:

exp[-2PI2{h2a2U(1,1) + k2b2U(2,2) + l2c2U(3,3) + 2hkabU(1,2) + 2hlacU(1,3) + 2klbcU(2,3)}] where a, b, and c are reciprocal lattice constants.

Cu-[14]N_4Me_2-diacid$(ClO_4)_2.2H_2O$

Table of Experimental Details

A. Crystal Data

C16 H36 CU CL2 N4 O14

F. W. 642. 93 F(000) = 670

crystal dimensions: 0. 14 x 0. 32 x 0. 38 mm

peak width at half-height = 0. 30

Mo K radiation (λ = 0. 71073 A)

temperature = 21 ± 1°C

monoclinic space group P21/c

a = 8. 089 (4) A b = 9. 269 (2) A c = 17. 552 (4) A

β = 96. 34 (3)

V = 1308. 0 A 1308(1) Å^3

Z = 2 D_c = 1. 63 g/cm

μ = 11. 1 cm-1

Table of Experimental Details

B. Intensity Measurements

Instrument:	Enraf-Nonius CAD4 diffractometer
Monochromator:	Graphite crystal, incident beam
Attenuator:	Zr foil, factor 17.6
Take-off angle:	2.8
Detector aperture:	2.0 to 2.5 mm horizontal
	4.0 mm vertical
Crystal-detector dist.:	21 cm
Scan type:	ω-2θ
Scan rate:	1 - 7 /min (in omega)
Scan width, deg:	0.6 + 0.350 tan θ
Maximum 2θ:	54.0°
No. of refl. measured:	3320 total, 2848 unique
Corrections:	Lorentz-polarization
	Linear decay (from 1.000 to 1.034 on I)
	Reflection averaging (agreement on I = 1.9%)
	Numerical absorption (from71.47 to86.40 on I)

Table of Experimental Details

C. Structure Solution and Refinement

Solution:	Patterson method
Minimization function:	w(|Fo|-|Fc|)
Least-squares weights:	4Fo / (Fo)
Anomalous dispersion:	All non-hydrogen atoms
Reflections included:	1934 with Fo >3.0 (Fo)
Parameters refined:	169
Unweighted agreement factor:	0.053
Weighted agreement factor:	0.075
Esd of obs. of unit weight:	1.60
Convergence, largest shift:	0.00
High peak in final diff. map:	0.67 (12) e/A
Computer hardware:	PDP-11
Computer software:	SDP-PLUS (Enraf-Nonius & B. A. Frenz & Associates, Inc.)

Table

Positional and thermal parameters and their e.s.d.'s

Atom	x	y	z	B(Å^2)
Cu	0.0000	0.0000	0.0000	2.24(1)
N1	-0.0714(4)	-0.1813(4)	-0.0642(2)	2.52(6)
C2	0.0110(6)	-0.3009(5)	-0.0173(3)	3.34(9)
C3	0.1857(6)	-0.2597(5)	0.0115(3)	3.12(9)
N4	0.1815(4)	-0.1297(4)	0.0608(2)	2.55(7)
C5	0.3488(5)	-0.0583(5)	0.0658(3)	3.07(8)
C6	0.3565(5)	0.0845(5)	0.1092(3)	3.41(9)
C7	0.2550(5)	0.2046(5)	0.0705(3)	3.15(9)
C8	0.0114(6)	0.1800(5)	0.1414(2)	3.04(9)
C9	-0.1255(5)	0.0703(5)	0.1487(2)	2.89(8)
O10	-0.1744(4)	-0.0141(3)	0.0996(2)	3.09(6)
O11	-0.1776(5)	0.0758(4)	0.2170(2)	4.38(8)
C12	0.1514(6)	-0.1779(5)	0.1389(3)	3.38(9)
OW	-0.3696(5)	-0.1291(4)	0.2457(2)	5.59(9)
CL	-0.3360(2)	-0.4717(1)	0.13898(7)	3.43(2)
O1	-0.1835(9)	-0.4361(9)	0.1791(5)	10.5(2)
O2	-0.4670(7)	-0.3906(6)	0.1655(4)	8.3(1)
O3	-0.3255(9)	-0.4488(7)	0.0625(3)	8.8(2)
O4	-0.3683(6)	-0.6184(5)	0.1513(3)	7.3(1)

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as:

$$4/3[a^2B_{11}+b^2B_{22}+c^2B_{33}+ab(\cos\gamma)B_{12}+ac(\cos\beta)B_{13}+bc(\cos\alpha)B_{23}]$$

Table

Molecular dimensions

(a) Bond lengths (Å)

Cu	N1	2.070(3)
Cu	N4	2.096(3)
Cu	O10	2.369(3)
N1	C2	1.494(5)
N1*	C7	1.493(6)
N1	C8	1.488(6)
C2	C3	1.497(6)
C3	N4	1.487(5)
N4	C5	1.500(5)
N4	C12	1.488(6)
C5	C6	1.525(7)
C6	C7	1.500(6)
C8	C9	1.519(6)
C9	O10	1.198(5)
C9	O11	1.315(5)
CL	O1	1.391(7)
CL	O2	1.419(6)
CL	O3	1.371(5)
CL	O4	1.406(4)

(b) Bond angles (°)

1	Cu	N4	87.1(1)	C3	N4	C5	108.2(3)
1°	Cu	N4	92.9(1)	C3	N4	C12	108.0(3)
1	Cu	O10	101.8(1)	C5	N4	C12	108.5(3)
1°	Cu	O10	78.2(1)	N4	C5	C6	113.5(4)
4	Cu	O10	91.9(1)	C5	C6	C7	115.3(4)
4°	Cu	O10	88.1(1)	N1°	C7	C6	114.6(4)
u	N1	C2	102.8(2)	N1	C8	C9	113.4(3)
u	N1	C7°	111.9(3)	C8	C9	O10	124.2(4)
u	N1	C8	112.9(3)	C8	C9	O11	111.2(4)
2	N1	C7°	108.2(3)	O10	C9	O11	124.6(4)
2	N1	C8	109.8(3)	Cu	O10	C9	108.6(3)
7°	N1	C8	110.9(3)	O1	CL	O2	111.1(4)
1	C2	C3	110.1(4)	O1	CL	O3	108.1(5)
2	C3	N4	108.7(4)	O1	CL	O4	108.7(4)
u	N4	C3	103.2(2)	O2	CL	O3	111.7(4)
u	N4	C5	110.7(3)	O2	CL	O4	107.7(3)
u	N4	C12	117.7(3)	O3	CL	O4	109.5(4)

The * refers to equivalent position

$-x, -y, -z$

Deposition data

Calculated atom coordinates (C-H 0.95 Å, Biso 5 Å^2)
(O-H 0.95 Å, Biso 6 Å^2)
(CL-O 1.39 Å, Biso 7 Å^2)

Atom	x	y	z
H21	0.0124	-0.3852	-0.0479
H22	-0.0493	-0.3195	0.0251
H31	0.2460	-0.2389	-0.0306
H32	0.2380	-0.3369	0.0404
H51	0.3753	-0.0407	0.0152
H52	0.4287	-0.1220	0.0912
H61	0.4693	0.1149	0.1162
H62	0.3182	0.0680	0.1576
H71	0.2863	0.2156	0.0202
H72	0.2799	0.2906	0.0988
H81	-0.0176	0.2776	0.1303
H82	0.1096	0.1766	0.1763
H121	0.1481	-0.0962	0.1714
H122	0.0482	-0.2275	0.1363
H123	0.2385	-0.2405	0.1589
H11	-0.2498	0.0000	0.2279
HW1	-0.4021	-0.2165	0.2187
HW2	-0.4551	-0.1261	0.2790
O1*	-0.1856	-0.4576	0.1082
O2*	-0.3276	-0.3982	0.2083
O3*	-0.4631	-0.4140	0.0883

for H11, bound to O11, Biso=5.0 Å^2.

Deposition data

General Temperature Factor Expressions - U's

Name	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
Cu	0.0273(3)	0.0298(3)	0.0283(3)	-0.0004(3)	0.0043(3)	0.0019(3)
N1	0.032(2)	0.031(2)	0.033(2)	-0.004(1)	0.006(1)	-0.000(1)
C2	0.050(3)	0.029(2)	0.046(3)	-0.002(2)	-0.002(2)	0.003(2)
C3	0.041(2)	0.035(2)	0.042(2)	0.007(2)	0.001(2)	0.003(2)
C4	0.030(2)	0.034(2)	0.033(2)	0.001(1)	0.004(1)	0.004(1)
C5	0.022(2)	0.054(2)	0.040(2)	0.002(2)	0.004(2)	0.004(2)
C6	0.029(2)	0.054(3)	0.046(2)	-0.007(2)	0.001(2)	-0.002(2)
C7	0.033(2)	0.042(2)	0.044(2)	-0.012(2)	0.003(2)	-0.001(2)
C8	0.043(2)	0.041(2)	0.033(2)	-0.002(2)	0.005(2)	-0.005(2)
C9	0.036(2)	0.046(2)	0.028(2)	0.009(2)	0.007(2)	0.001(2)
C10	0.040(2)	0.046(2)	0.033(1)	-0.007(1)	0.011(1)	-0.001(1)
C11	0.067(2)	0.068(2)	0.035(2)	-0.008(2)	0.025(1)	-0.008(2)
C12	0.046(2)	0.047(2)	0.036(2)	0.004(2)	0.007(2)	0.013(2)
W	0.088(2)	0.063(2)	0.071(2)	0.001(2)	0.051(2)	-0.000(2)
.	0.0461(6)	0.0419(5)	0.0445(6)	-0.0001(5)	0.0142(5)	0.0011(4)
I	0.099(4)	0.149(5)	0.140(5)	-0.041(4)	-0.030(4)	-0.005(5)
?	0.090(3)	0.071(3)	0.165(5)	0.026(2)	0.064(3)	-0.003(3)
I	0.172(6)	0.107(4)	0.060(3)	-0.024(4)	0.038(3)	0.005(3)
	0.104(3)	0.050(2)	0.134(3)	-0.002(2)	0.063(2)	0.007(2)

e form of the anisotropic thermal parameter is:

$$p[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)]$$

Table of Torsional Angles in Degrees

Atom 1	Atom 2	Atom 3	Atom 4	Angle
N4	CU	N1	C2	15.2
N4	CU	N1	C7*	131.1
N1*	CU	N1	C2	114.4
N1*	CU	N1	C7*	-129.7
N4*	CU	N1	C2	-164.9
N4*	CU	N1	C7*	-48.9
N1	CU	N4	C3	14.6
N1	CU	N4	C5	130.2
N1	CU	N4	C12	-104.2
N1*	CU	N4	C3	-165.4
N1*	CU	N4	C5	-49.8
N1*	CU	N4	C12	75.8
N4*	CU	N4	C3	-79.5
N4*	CU	N4	C5	36.2
N4*	CU	N4	C12	161.7
N1	CU	N1*	C7	-50.3
N1	CU	N1*	C8	-176.2
N4	CU	N1*	C7	48.9
N4	CU	N1*	C8	-77.0
N4*	CU	N1*	C7	-131.1

Atom 1	Atom 2	Atom 3	Atom 4	Angle
N4*	CU	N1*	C8	103.0
CU	N1	C2	C3	-43.6
C7*	N1	C2	C3	-162.1
CU	N1	C7*	C6*	61.3
C2	N1	C7*	C6*	173.8
N1	C2	C3	N4	61.2
C2	C3	N4	CU	-42.4
C2	C3	N4	C5	-159.8
C2	C3	N4	C12	83.0
CU	N4	C5	C6	62.4
C3	N4	C5	C6	174.9
C12	N4	C5	C6	-68.1
N4	C5	C6	C7	-67.6
C5	C6	C7	N1*	66.6
C6	C7	N1*	CU	-61.2
C6	C7	N1*	C8	65.8
N1*	C8	C9	O10	4.7
N1*	C8	C9	O11	-178.3
C9	C8	N1*	CU	-15.8
C9	C8	N1*	C7	-142.2

The * refers to equivalent position -x, -y, -z.

where A, B, C & D are constants and x, y & z are orthogonalized coordinates.

Plane No.	A	B	C	D	Atom	x	y	z	Distance	Esd
1	0.7221	0.2385	-0.6494	0.0000						
					----------Atoms in Plane----------					
					CU	0.0000	0.0000	0.0000	0.000	0.000
					N1	-0.4528	-1.6806	-1.1206	0.000	0.003
					N4	1.3505	-1.2018	1.0602	0.000	0.003
					----------Other Atoms----------					
					O10	-1.6038	-0.1309	1.7382	-2.318	0.003
2	-0.6449	0.5877	-0.4886	0.0000						
					----------Atoms in Plane----------					
					CU	0.0000	0.0000	0.0000	0.000	0.000
					N1	-0.4528	-1.6806	-1.1206	-0.148	0.003
					C8	-0.1822	1.6680	2.4663	-0.107	0.004
					C9	-1.3040	0.6519	2.5944	-0.043	0.004
					O10	-1.6038	-0.1309	1.7382	0.108	0.003
					Chi Squared = 3893.					
					----------Other Atoms----------					
					O11	-1.8578	0.7027	3.7859	-0.239	0.004
3	-0.3885	-0.8230	-0.4144	0.0000						
					----------Atoms in Plane----------					
					C12	0.9552	-1.6489	2.4238	-0.019	0.005
					N4	1.3505	-1.2018	1.0602	0.025	0.003
					CU	0.0000	0.0000	0.0000	0.000	0.000
					O10	-1.6038	-0.1309	1.7382	0.010	0.003
					Chi Squared = 86.					
4	-0.5050	0.5273	-0.6834	-1.8095						
					----------Atoms in Plane----------					
					OW	-3.4659	-1.1968	4.2858	0.000	0.004
					HW1	-3.6770	-2.0067	3.8169	0.000	0.000
					HW2	-4.2232	-1.1688	4.8671	0.000	0.000
					----------Other Atoms----------					
					O11	-1.8578	0.7027	3.7859	0.531	0.003
					HW3	-2.4626	0.0005	3.9757	0.337	0.000

Table of Least-Squares Planes (continued)

Plane No.	A	B	C	D	Atom	x	y	z	Distance	Esd
					O2	-4.0983	-3.6205	2.8876	-0.003	0.006

Dihedral Angles Between Planes:

Plane No.	Plane No.	Dihedral Angle
1	2	90.5
1	3	102.0
1	4	78.2
2	3	91.8
2	4	14.2
3	4	87.4

Table of Torsional Angles in Degrees

Atom 1	Atom 2	Atom 3	Atom 4	Angle
N4	CU	N1	C2	15.2
N4	CU	N1	C7*	131.1
N1*	CU	N1	C2	114.4
N1*	CU	N1	C7*	-129.7
N4*	CU	N1	C2	-164.9
N4*	CU	N1	C7*	-48.9
N1	CU	N4	C3	14.6
N1	CU	N4	C5	130.2
N1	CU	N4	C12	-104.2
N1*	CU	N4	C3	-165.4
N1*	CU	N4	C5	-49.8
N1*	CU	N4	C12	75.8
N4*	CU	N4	C3	-79.5
N4*	CU	N4	C5	36.2
N4*	CU	N4	C12	161.7
N1	CU	N1*	C7	-50.3
N1	CU	N1*	C8	-176.2
N4	CU	N1*	C7	48.9
N4	CU	N1*	C8	-77.0
N4*	CU	N1*	C7	-131.1

Atom 1	Atom 2	Atom 3	Atom 4	Angle
N4*	CU	N1*	C8	103.0
CU	N1	C2	C3	-43.6
C7*	N1	C2	C3	-162.1
CU	N1	C7*	C6*	61.3
C2	N1	C7*	C6*	173.8
N1	C2	C3	N4	61.2
C2	C3	N4	CU	-42.4
C2	C3	N4	C5	-159.8
C2	C3	N4	C12	83.0
CU	N4	C5	C6	62.4
C3	N4	C5	C6	174.9
C12	N4	C5	C6	-68.1
N4	C5	C6	C7	-67.6
C5	C6	C7	N1*	66.6
C6	C7	N1*	CU	-61.2
C6	C7	N1*	C8	65.8
N1*	C8	C9	O10	4.7
N1*	C8	C9	O11	-178.3
C9	C8	N1*	CU	-15.8
C9	C8	N1*	C7	-142.2

The * refers to equivalent position -x, -y, -z.

Cu-[14]N_4-diacid(H_2lactam).(ClO_4)$_2$

Table of Experimental Details

A. Crystal Data

C28 H52 CU CL2 N8 014

F.W. 859.22 F(000) = 451

crystal dimensions: 0.30 x 0.44 x 0.47 mm

peak width at half-height = 0.30@

Mo K@ radiation (@ = 0.71073 A)

temperature = 21 @ 1@

triclinic space group P-1

a = 9.547 (2) A b = 12.014 (2) A c = 8.929 (1) A

@ = 98.97 (1) @ @ = 114.56 (1) @ @ = 80.44 (2) @

V = 914.2 A@

Z = 1 @ = 1.56 g/cm@

@ = 8.2 cm-1

Table of Experimental Details

B. Intensity Measurements

Instrument:	Enraf-Nonius CAD4 diffractometer
Monochromator:	Graphite crystal, incident beam
Attenuator:	Zr foil, factor 17.0
Take-off angle:	2.8@
Detector aperture:	2.0 to 2.5 mm horizontal
	4.0 mm vertical
Crystal-detector dist.:	21 cm
Scan type:	w-@
Scan rate:	1 - 4@/min (in omega)
Scan width, deg:	0.7 + 0.350 tan @
Maximum 2@:	54.0@
No. of refl. measured:	4097 total, 3985 unique
Corrections:	Lorentz-polarization
	Numerical absorption (from70.08 to82.42 on

Table of Experimental Details

C. Structure Solution and Refinement

Solution:	Patterson method
Minimization function:	@w(|Fo|-|Fc|)@
Least-squares weights:	4Fo@/@@(Fo@)
Anomalous dispersion:	All non-hydrogen atoms
Reflections included:	2643 with Fo@>9.0@(Fo@)
Parameters refined:	241
Unweighted agreement factor:	0.053
Weighted agreement factor:	0.081
Esd of obs. of unit weight:	2.79
Convergence, largest shift:	0.02@
High peak in final diff. map:	0.92 (9) e/A@
Computer hardware:	PDP-11
Computer software:	SDP-PLUS (Enraf-Nonius & B. A. Frenz & Associates, Inc.)

Table

Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B(Å^2)
Cu	0.0	0.0	0.0	2.22(1)
N1A	-0.1294(4)	-0.0848(3)	-0.2280(4)	2.94(7)
C2A	-0.0518(6)	-0.0636(4)	-0.3313(5)	4.2(1)
C3A	0.1199(6)	-0.0857(4)	-0.2431(6)	4.4(1)
N4A	0.1683(4)	-0.0133(3)	-0.0843(4)	3.22(8)
C5A	0.3260(5)	-0.0505(4)	0.0340(7)	4.6(1)
C6A	0.3794(5)	0.0309(4)	0.1857(7)	5.0(1)
C7A	0.2962(5)	0.0364(4)	0.2994(6)	4.1(1)
C8A	-0.1160(5)	-0.2084(3)	-0.2147(5)	3.3(1)
C9A	0.0159(4)	-0.2508(3)	-0.0597(5)	2.84(8)
O10A	0.0700(3)	-0.1819(2)	0.0624(3)	3.23(7)
O11A	0.0580(4)	-0.3550(2)	-0.0657(4)	4.24(8)
N1B	0.2408(4)	0.5914(3)	0.2410(4)	2.97(8)
C2B	0.1224(5)	0.5774(4)	0.3025(6)	3.7(1)
C3B	0.1959(5)	0.5535(4)	0.4818(6)	4.1(1)
N4B	0.3218(4)	0.6214(3)	0.5832(4)	3.07(8)
C5B	0.3961(5)	0.6070(4)	0.7611(5)	4.1(1)
C6B	0.5191(5)	0.5048(4)	0.7975(5)	4.2(1)
C7B	0.6498(5)	0.5152(3)	0.7513(5)	2.89(9)
C8B	0.3160(5)	0.6932(3)	0.3382(5)	3.3(1)
C9B	0.3788(5)	0.6903(3)	0.5231(5)	3.10(9)
O10B	0.4813(4)	0.7488(3)	0.6090(4)	4.94(9)

CL	0.2726(1)	0.2566(1)	-0.2260(1)	3.96(3)
O1	0.1836(8)	0.1722(5)	-0.2721(8)	19.2(2)
O2	0.1978(7)	0.3377(6)	-0.3264(9)	17.3(2)
O3	0.4084(7)	0.2358(7)	-0.2352(11)	19.4(2)
O4	0.2750(14)	0.2849(10)	-0.0819(9)	22.8(4)

nisotropically refined atoms are given in the form of the
sotropic equivalent thermal parameter defined as:

$$4/3[a^2B_{11} + b^2B_{22} + c^2B_{33} + abcos\gamma B_{12} + accos\beta B_{13} + bccos\alpha B_{23}]$$

Table

Molecular dimensions

(a) Interatomic distances (Å)

Cu	N1A	2.095(3)	C2B	C3B	1.510(7)
Cu	N4A	2.014(4)	C3B	N4B	1.456(5)
Cu	O10A	2.263(3)	N4B	C5B	1.471(5)
N1A	C2A	1.473(7)	N4B	C9B	1.341(7)
N1A	C7A*	1.498(5)	C5B	C6B	1.524(7)
N1A	C8A	1.488(5)	C6B	C7B	1.496(8)
C2A	C3A	1.491(7)	C8B	C9B	1.508(6)
C3A	N4A	1.478(5)	C9B	O10B	1.216(5)
N4A	C5A	1.478(5)	CL	O1	1.336(7)
C5A	C6A	1.493(7)	CL	O2	1.332(7)
C6A	C7A	1.516(9)	CL	O3	1.313(8)
C8A	C9A	1.523(5)	CL	O4	1.270(9)
C9A	O10A	1.238(4)	N4A ...	O1	3.046(9)
C9A	O11A	1.250(5)	HN4A ...	O1	2.21
N1B	C2B	1.489(7)	N1B ...	O11A	2.676(4)
N1B	C7B	1.503(5)	HN1B ...	O11A	1.76
N1B	C8B	1.485(5)			

Table

Molecular dimensions

(a) Interatomic distances (Å)

Cu	N1A	2.095(3)	C2B	C3B	1.510(7)
Cu	N4A	2.014(4)	C3B	N4B	1.456(5)
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N1A	C8A	1.488(5)	C6B	C7B	1.496(8)
C2A	C3A	1.491(7)	C8B	C9B	1.508(6)
C3A	N4A	1.478(5)	C9B	O10B	1.216(5)
N4A	C5A	1.478(5)	CL	O1	1.336(7)
C5A	C6A	1.493(7)	CL	O2	1.332(7)
C6A	C7A	1.516(9)	CL	O3	1.313(8)
C8A	C9A	1.523(5)	CL	O4	1.270(9)
C9A	O10A	1.238(4)	N4A ...	O1	3.046(9)
C9A	O11A	1.250(5)	HN4A ...	O1	2.21
N1B	C2B	1.489(7)	N1B ...	O11A	2.676(4)
N1B	C7B	1.503(5)	HN1B ...	O11A	1.76
N1B	C8B	1.485(5)			

(b) Bond angles (°)

N1A	Cu	N4A	86.3(1)	Cu	O10A	C9A	112.6(2)
N1A	Cu	N4A*	93.7(1)	C2B	N1B	C7B#	111.2(4)
N1A	Cu	O10A	79.7(1)	C2B	N1B	C8B	106.5(4)
N1A	Cu	O10A*	100.3(1)	C7B#	N1B	C8B	114.7(3)
N4A	Cu	O10A	90.0(1)	N1B	C2B	C3B	111.6(3)
Cu	N1A	C2A	101.5(2)	C2B	C3B	N4B	113.3(5)
Cu	N1A	C7A*	113.1(2)	C3B	N4B	C5B	117.0(4)
Cu	N1A	C8A	110.9(2)	C3B	N4B	C9B	124.2(4)
C2A	N1A	C7A*	109.7(3)	C5B	N4B	C9B	118.7(3)
C2A	N1A	C8A	110.7(4)	N4B	C5B	C6B	111.6(4)
C7A*	N1A	C8A	110.6(3)	C5B	C6B	C7B	113.1(5)
N1A	C2A	C3A	110.6(4)	N1B#	C7B	C6B	114.5(4)
C2A	C3A	N4A	108.4(4)	N1B	C8B	C9B	114.2(4)
Cu	N4A	C3A	107.8(3)	N4B	C9B	C8B	118.5(3)
Cu	N4A	C5A	115.4(3)	N4B	C9B	O10B	123.7(4)
C3A	N4A	C5A	113.0(3)	C8B	C9B	O10B	117.7(5)
N4A	C5A	C6A	112.1(4)	O1	CL	O2	107.9(4)
C5A	C6A	C7A	115.5(5)	O1	CL	O3	118.5(5)
N1A*	C7A	C6A	114.4(4)	O1	CL	O4	98.9(7)
N1A	C8A	C9A	114.9(3)	O2	CL	O3	103.9(5)
C8A	C9A	O10A	118.7(3)	O2	CL	O4	111.9(6)
C8A	C9A	O11A	116.1(3)	O3	CL	O4	115.9(7)
O10A	C9A	O11A	125.1(3)				

* refers to equivalent position -x, -y, -z

\# refers to equivalent position 1-x, 1-y, 1-z

Deposition Data

Calculated hydrogen coordinates (C-H, N-H, = 0.95 Å, B = 5.0 Å^2)

H21A	-0.0786	0.0131	-0.3559
H22A	-0.0849	-0.1122	-0.4313
H31A	0.1686	-0.0679	-0.3085
H32A	0.1482	-0.1632	-0.2227
HN4A	0.1787	0.0607	-0.1002
H51A	0.3957	-0.0567	-0.0186
H52A	0.3259	-0.1224	0.0655
H61A	0.3655	0.1044	0.1517
H62A	0.4865	0.0095	0.2471
H71A	0.3485	0.0821	0.3980
H72A	0.3009	-0.0383	0.3249
H81A	-0.1006	-0.2483	-0.3082
H82A	-0.2104	-0.2246	-0.2159
HN1B	0.1961	0.6035	0.1270
H21B	0.0667	0.5159	0.2378
H22B	0.0529	0.6450	0.2916
H31B	0.2356	0.4756	0.4873
H32B	0.1184	0.5690	0.5252
H51B	0.3192	0.5967	0.7976
H52B	0.4435	0.6732	0.8191
H61B	0.4715	0.4391	0.7369
H62B	0.5600	0.4967	0.9126
H71B	0.7073	0.5731	0.8247
H72B	0.6069	0.5360	0.6413
H81B	0.2415	0.7579	0.3092
H82B	0.3993	0.6996	0.3095

Table of General Temperature Factor Expressions - U's

lame	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
:u	0.0328(3)	0.0208(3)	0.0253(2)	-0.0093(2)	0.0040(2)	0.0019(2)
l1A	0.050(2)	0.022(1)	0.026(1)	-0.010(1)	-0.001(1)	0.003(1)
:2A	0.084(3)	0.043(2)	0.030(2)	-0.018(2)	0.019(2)	-0.002(2)
:3A	0.078(2)	0.048(2)	0.053(2)	-0.018(2)	0.036(2)	-0.003(2)
l4A	0.045(1)	0.030(2)	0.049(2)	-0.009(1)	0.018(1)	0.004(1)
5A	0.038(2)	0.045(2)	0.088(3)	-0.008(2)	0.020(2)	0.009(2)
6A	0.035(2)	0.040(2)	0.090(4)	-0.011(2)	0.000(2)	0.003(2)
7A	0.050(2)	0.030(2)	0.048(2)	-0.007(2)	-0.010(2)	0.010(2)
8A	0.051(2)	0.022(2)	0.034(2)	-0.006(2)	-0.002(2)	0.002(1)
9A	0.041(2)	0.026(2)	0.034(2)	-0.008(1)	0.005(1)	0.007(1)
10A	0.052(1)	0.023(1)	0.032(1)	-0.007(1)	-0.001(1)	0.007(1)
11A	0.068(2)	0.021(1)	0.045(2)	-0.000(1)	-0.002(1)	0.002(1)
1B	0.037(2)	0.027(1)	0.034(1)	-0.005(1)	-0.003(1)	0.008(1)
2B	0.030(2)	0.042(2)	0.055(2)	-0.005(2)	0.004(2)	0.001(2)
3B	0.047(2)	0.054(2)	0.059(2)	-0.014(2)	0.025(1)	0.003(2)
4B	0.041(2)	0.036(2)	0.035(1)	-0.003(1)	0.014(1)	-0.001(1)
5B	0.057(2)	0.061(3)	0.035(2)	-0.002(2)	0.019(1)	0.004(2)
6B	0.061(2)	0.059(3)	0.045(2)	0.002(2)	0.024(1)	0.022(2)

Table of General Temperature Factor Expressions - U's (Continued)

Name	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
C7B	0.042(2)	0.028(2)	0.032(2)	-0.003(1)	0.008(1)	0.001(1)
C8B	0.049(2)	0.025(2)	0.038(2)	-0.007(2)	0.003(2)	0.002(2)
C9B	0.043(2)	0.023(2)	0.039(2)	-0.001(2)	0.006(1)	0.002(1)
O10B	0.072(2)	0.047(2)	0.051(2)	-0.030(1)	0.001(1)	-0.004(1)
CL	0.0502(5)	0.0484(6)	0.0532(5)	-0.0116(4)	0.0209(4)	0.0022(4)
O1	0.454(5)	0.233(4)	0.110(3)	-0.279(3)	0.116(3)	-0.064(3)
O2	0.108(3)	0.210(4)	0.407(5)	0.061(3)	0.131(3)	0.229(3)
O3	0.164(3)	0.166(5)	0.522(6)	0.072(3)	0.236(3)	0.170(4)
O4	0.35(1)	0.40(1)	0.088(4)	-0.147(9)	0.074(5)	-0.122(4)

Coefficients in the temperature factor expression:

$$\exp\left[-2\pi^2(\underline{U}_{11}\underline{h}^2\underline{a}^{*2}+\underline{U}_{22}\underline{k}^2\underline{b}^{*2}+\underline{U}_{33}\underline{l}^2\underline{c}^{*2}+2\underline{U}_{12}\underline{hk}\underline{a}^*\underline{b}^*+2\underline{U}_{13}\underline{hl}\underline{a}^*\underline{c}^*+2\underline{U}_{23}\underline{kl}\underline{b}^*\underline{c}^*)\right]$$

Table of Torsional Angles in Degrees

Atom 1	Atom 2	Atom 3	Atom 4	Angle
N4A	CU	N1A	C2A	-21.0
N4A	CU	N1A	C8A	96.7
N4A	CU	N1A	C7A*	-138.4
O10A	CU	N1A	C2A	-111.7
O10A	CU	N1A	C8A	6.0
O10A	CU	N1A	C7A*	130.9
N1A*	CU	N1A	C2A	-95.4
N1A*	CU	N1A	C8A	22.3
N1A*	CU	N1A	C7A*	147.2
O10A*	CU	N1A	C2A	68.3
O10A*	CU	N1A	C8A	-174.0
O10A*	CU	N1A	C7A*	-49.1
N1A	CU	N4A	C3A	-7.3
N1A	CU	N4A	C5A	-134.7
O10A	CU	N4A	C3A	72.3
O10A	CU	N4A	C5A	-55.0
N1A*	CU	N4A	C3A	172.6
N1A*	CU	N4A	C5A	45.3
O10A*	CU	N4A	C3A	-107.7
O10A*	CU	N4A	C5A	125.0
N1A	CU	O10A	C9A	5.2
N4A	CU	O10A	C9A	-81.0
N1A*	CU	O10A	C9A	-174.8
O10A*	CU	O10A	C9A	42.9
N1A	CU	N1A*	C7A	32.8
N1A	CU	N1A*	C2A*	-84.6
N4A	CU	N1A*	C7A	-41.6
N4A	CU	N1A*	C2A*	-159.0
O10A	CU	N1A*	C7A	49.1
O10A	CU	N1A*	C2A*	-68.3
O10A*	CU	N1A*	C7A	-130.9
O10A*	CU	N1A*	C2A*	111.7
CU	N1A	C2A	C3A	46.7
C8A	N1A	C2A	C3A	-71.1
C7A*	N1A	C2A	C3A	166.5
CU	N1A	C8A	C9A	-15.2
C2A	N1A	C8A	C9A	96.7

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C7A*	N1A	C8A	C9A	-141.5
CU	N1A	C7A*	C6A*	-55.3
C2A	N1A	C7A*	C6A*	-167.8
C8A	N1A	C7A*	C6A*	69.8
N1A	C2A	C3A	N4A	-57.2
C2A	C3A	N4A	CU	34.7
C2A	C3A	N4A	C5A	163.4
CU	N4A	C5A	C6A	-61.7
C3A	N4A	C5A	C6A	173.6
N4A	C5A	C6A	C7A	69.1
C5A	C6A	C7A	N1A*	-67.3
C6A	C7A	N1A*	CU	55.3
C6A	C7A	N1A*	C2A*	167.8
N1A	C8A	C9A	O10A	21.5
N1A	C8A	C9A	O11A	-160.5
C8A	C9A	O10A	CU	-15.4
O11A	C9A	O10A	CU	166.7
C8B	N1B	C2B	C3B	-63.6
C7B*	N1B	C2B	C3B	62.1
C2B	N1B	C8B	C9B	53.4
C7B*	N1B	C8B	C9B	-70.2
C2B	N1B	C7B*	C6B*	-175.1
C8B	N1B	C7B*	C6B*	-54.1
N1B	C2B	C3B	N4B	41.0
C2B	C3B	N4B	C5B	177.6
C2B	C3B	N4B	C9B	-6.3
C3B	N4B	C5B	C6B	82.9
C9B	N4B	C5B	C6B	-93.4
C3B	N4B	C9B	C8B	-3.8
C3B	N4B	C9B	O10B	178.1
C5B	N4B	C9B	C8B	172.2
C5B	N4B	C9B	O10B	-5.9
N4B	C5B	C6B	C7B	62.3
C5B	C6B	C7B	N1B*	-170.4
N1B	C8B	C9B	N4B	-21.1
N1B	C8B	C9B	O10B	157.1