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Synthetic and structural aspects of the chemistry of saturated polyaza macrocyclic ligands bearing pendant coordinating groups attached to nitrogen

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Abstract

Developments in the synthetic and structural aspects of the chemistry of saturated polyaza macrocyclic ligands bearing pendant coordinating groups attached to nitrogen, that have occurred since 1989, have been reviewed. The review is organised in terms of the types of reaction that have been used on saturated triaza, tetraaza, pentaaza, and hexaaza macrocyclic ligands to attach pendant donor groups to the nitrogen atoms. Where structural studies have been undertaken on metal complexes of these ligands the results of these studies are described.

Keywords: Macrocycles; Complexes; Pendant donor macrocycles; Crystal structures

1. Introduction

The term "pendant donor" macrocycle, as applied to a macrocyclic ligand that has had additional donor groups attached to its periphery, appears to have first been used in the chemical literature in 1980 [1]. The ligand to which it was applied, tetrakis(2-cyanoethyl)-1,4,8,11-tetraazacyclotetradecane, was by no means the first ligand of this type to have been reported; that had occurred some four years earlier [2]. However, the coining of the term paid formal recognition to this structural motif as an important one, and one with the potential to influence the future development of chemistry in a major way.

The past 16 years have proved this to be the case and new pendant donor macrocyclic ligands are now being produced in large numbers and for a variety of different chemical applications. These embrace enzyme simulations [3], attachment to monoclonal antibodies, for the purpose of carrying a radionuclide to a targeted cell [4,5], use in magnetic resonance imaging reagents [6], as well as for progressively more elaborate investigations of their structure/activity relationships. The underlying reasons for their use remain the same: they provide a collectively non-labile set of macrocyclic donors, which serve to immobilise a metal ion, along with a set of possibly more labile donors which can perturb the metal ion at additional coordination sites, in competition with external substrates, or which can be used as attachment points for other molecules.

The literature associated with pendant donor macrocycles has been comprehensively reviewed in 1984 [7] and in 1990 [8] and it is now timely to do so again, but with ever more stringent constraints on the scope of the review which are brought on by the burgeoning literature. This review will be confined to work which has entered the literature between 1989 and mid-1996 and will only address saturated polyaza macrocycles, not containing another hetero-atom within the macrocyclic ring, to which one or more pendant donors are attached through the nitrogen atoms of the ring.

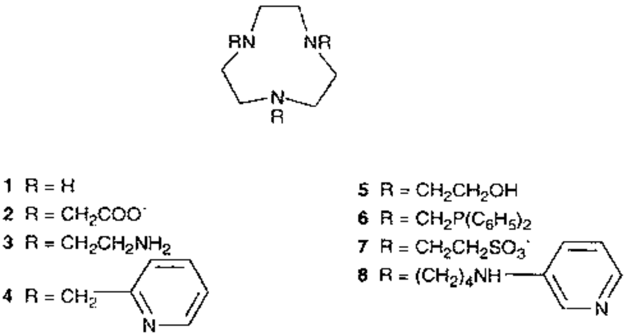
2. Pendant donor triazamacrocycles

Functionalising triaza macrocycles with three nitrogen attached pendant donors affords a means for forming six coordinate complexes in which there are two groups of facial donors: the macrocyclic nitrogen atoms on the one hand and the pendant donors on the other. The bifacial arrangement is a consequence of the fact that, invariably, all three pendant donors project in the same direction. In some cases not all three pendant donors coordinate and instances of five coordinate complexes, particularly with Cu(II), are not unusual. When needed this situation can be engineered by functionalising the macrocycle at only one or two of the nitrogen atoms. There are a number of synthetic strategies for doing this. The simplest, which often works, is to perform the reaction with the amine in excess, and then separate the mono- and/or di-*N*-functionalised product from the unconverted amine. Other widely used methods, which involve a chemical protecting group, include protecting via orthoamide formation [9], selective tosylation [10], selective carbamation [11] or selective protonation [12].

A number of triazamacrocycles, of various ring sizes, have been structurally developed in one of these ways since the last review [8] and these are discussed below in order of increasing ring size.

2.1. 1,4,7-Triazacyclononane (tacn) derivatives

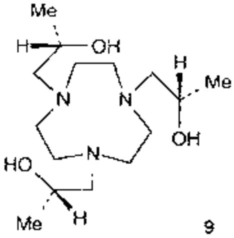
Ligands **1**–**8** were reviewed in 1990, and the reader is referred to Ref. [8], and the references cited therein, for details of their synthesis and the coordination chemistry which had been investigated up to that date. New ligands and advances in the coordination chemistry of **1**–**8** are discussed below under a heading that describes the nature of the pendant donor addition.



2.1.1. Hydroxyalkylation

2-Hydroxyalkylation of the nitrogen atoms of the ring has generally been carried out, usually in near quantitative yield, by reacting oxirane (ethylene oxide) or a substituted oxirane with the macrocycle. The reaction is favoured not only for its high yield, but also for the fact that no by-products are produced. Any single substituent present on the epoxide finishes the reaction at the 2-position of the arm owing to the fact that nucleophilic attack by nitrogen on the epoxide occurs exclusively at the less hindered carbon atom. The hydroxyl group may or may not deprotonate depending upon the prevailing pH and the Lewis acidity of the metal ion to which it is coordinated.

Since the last review the crystal structure of **5**.HBr has been solved showing that the ligand is pre-organised for complexation, having all three arms on the same side of the macrocyclic plane. The proton attached to nitrogen lies within the macrocyclic cavity, hydrogen bonded to two nitrogen atoms and one of the hydroxyl groups [13]. The crystal structure of the quaternary salt *N,N,N′,N″*-tetrakis(2-hydroxyethyl)tacn bromide has also been solved [13], showing the tacn ring forced into an irregular structure owing to the fact that, unlike a proton, the 2-hydroxyethyl group cannot occupy the macrocyclic cavity. The structure of $[(\mathrm{Fe}\mathbf{5})_2\mathrm{H}_{-3}](\mathrm{ClO}_4)_3$ has been solved [13] and is similar to the structure of the complex of **9** with Co(III) discussed in the next section.



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Using three equivalents of (2*S*)-2-methyloxirane Peacock and coworkers have produced *N,N′,N″*-tris[(2*S*)-2-hydroxypropyl]-tacn (**9**) [14]. With divalent metal ions Ni(II) [15] and Mn(II) [16] monomeric complexes of the neutral ligand have been crystallised and their structures solved. Both complexes have *fac*-N_3O_3 donor sets. The twist angle is 41° in the Ni(II) complex[1], whereas the corresponding angle is 22.6° in the Mn(II) complex. Cobalt(III) [14], chromium(III) [17], and manganese(IV) [16,18] induce deprotonation of **9** and dimeric structures result. In the case of cobalt(III) both halves of the dimer have the metal ion in the same oxidation state, one-half of the dimer has a *fac*-N_3O_3(alcohol) donor set (twist angle 48.8°) and the other a *fac*-N_3O_3(alkoxide) (twist angle 49.8°). The two halves of the dimer are connected by an asymmetric hydrogen bond between each alcohol and the adjacent alkoxide. The Cr(III) dimer is similar, and similar also to the structure of $[\mathrm{Cr}_2\mathbf{5}]^{3-}$ which has been briefly reported [19], except that the hydrogen bonding is symmetrical and the twist angle is 45° in each of the near identical half-units. If the Mn(II) complex of **9** is allowed to oxidise in air at pH 8 the mixed oxidation state, MnIV/Mn(II), dimer, shown in Fig. 1, results. This complex has a structure superficially similar to the Co(III)/Co(III) dimer, but with greater asymmetry owing to the two different oxidation states. Thus, the metal–donor bond lengths are shorter in the Mn(IV) (alkoxide) half than in the Mn(II) (alcohol) half. The Mn(IV) half has a twist angle of 49.1° compared to 0° for the Mn(II) half making the Mn(II) half of the dimer the only known case of a metal complex of a pendant arm ligand based on tacn which has perfect trigonal prismatic geometry. A similar dimer containing vanadium(IV) and zinc(II) was isolated by addition of **9** to a solution of $VOCl_2$, which had undergone reduction with zinc amalgam, followed by air oxidation [20]. The zinc(II) half of the dimer contains the ligand in the alcohol form and is nearly trigonal prismatic (twist angle 4.5°). The vanadium(IV) alkoxide

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[1] The convention used in this review is that a twist angle of 0° corresponds to a trigonal prismatic structure, and a twist angle of 60° corresponds to an octahedral structure. This is in accord with Ref. [8].

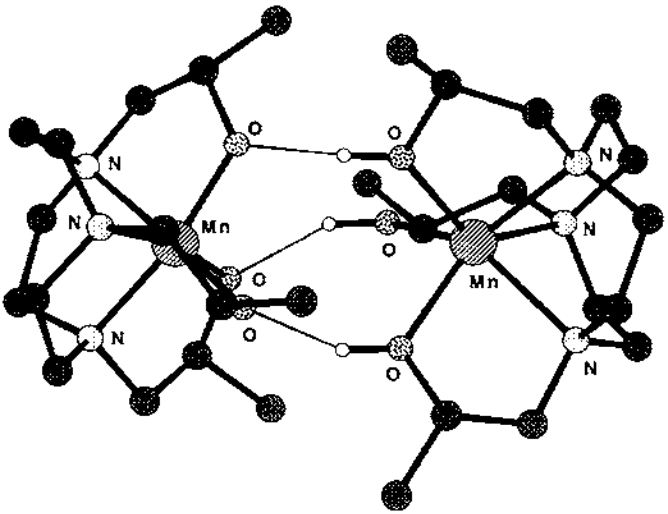
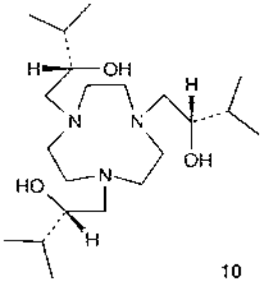


Fig. 1. Drawing of the cationic portion of the Mn(IV)/Mn(II) dimer of **9** showing the near octahedral geometry of the Mn(IV) half-unit (left-hand side) and the near trigonal prismatic geometry of the Mn(II) half-unit (right-hand side).

unit has a twist angle of 39.4°. It is believed that all of these dimeric structures remain intact in non-aqueous solvents. It has been noted that the relative lengths of the M–N and M–O bonds can be quite different. In cases where the metal ion has a filled set of t_{2g} orbitals (Zn(II), Co(III), Ni(II)) and no pπ donation from the filled p orbitals on oxygen is possible, the M–N and M–O distances are essentially equal. However, when the t_{2g} set is half-full the M–O distance is shorter than the M–N one by 11 pm (Mn(II), alcohol donors) or 19 pm (Mn(IV), alkoxide donors) and when the t_{2g} set is singly occupied (V(IV), alkoxide donors) this difference increases to 30 pm.



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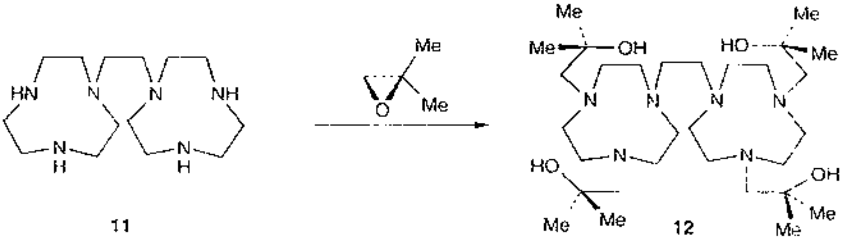
The Mn(IV) structure of **5** has been solved [16] and is almost identical to the Mn(IV) half of the Mn(II)/Mn(IV) dimer of **9** discussed above.

As a way of reducing the probability of dimer formation occurring when higher valent metal ions are used Peacock and co-workers have studied the complexation of *N,N′,N″*-tris[(2*R*)-2-hydroxy-3-methylbutyl]-tacn (**10**) [21], which is prepared in quantitative yield from the reaction of (2*R*)-2-isopropyloxirane with the macrocycle.

Monomeric complexes with V(IV), Cr(III), Mn(IV), Ni(II), Cu(II) and Zn(II) have been prepared and the structures of the Mn(IV) and Ni(II) complexes have been solved. The Mn(IV) complex is of the fully deprotonated **10** and the structure is very similar to the structure of the $[Mn^{IV}\mathbf{9}]^+$ half-unit and $[Mn^{IV}\mathbf{5}]^+$ complex cations discussed above. The Mn–O bonds are slightly shorter in $[Mn\mathbf{10}]^+$ compared to $[Mn\mathbf{9}]^+$, which is attributed to more effective oxygen–metal pπ–dπ overlap in the absence of hydrogen bond participation. The Ni(II) complex contains protonated **10** and the structure is again similar to the corresponding complex of **9** [22].

Schröder and co-workers have reacted the linked tacn ligand (**11**) with



2,2-dimethyl oxirane to produce the potentially ten coordinate ligand (**12**) [23]. Complexes with Co(II), Ni(II), Cu(II) and Zn(II) have been isolated and structurally characterised. With the exception of Cu(II), the ligand binds two metal ions, each of which is approximately octahedral with either a solvent molecule or an anion complementing the five donors available from the macrocycle, the coordinating hydroxyl groups remain protonated and the arrangement of the half-units around the bridging ethano moiety is *anti*. The Co(II) complex is remarkable for its stability towards oxidation to the Co(III) species when in air and at neutral pH; by contrast the Co(II) complex of **9** is easily oxidised by air to the Co(III) species described above. The Cu(II) complex (Fig. 2) has a *syn* arrangement around the ethano bridge and one hydroxyl group in each half-unit is de-protonated allowing for the formation of a pair of hydrogen bonds between the half-units. This appears to be a unique case of a pendant hydroxyalkyl group coordinated to a divalent metal ion undergoing deprotonation at neutral pH. Each Cu(II) ion is five coordinate with a distorted square pyramidal stereochemistry.

2,2-Dimethyloxirane has also been used to alkylate 1-formyl-tacn giving ligands **13** and, after base hydrolysis, **14** [24]. The structure of the Cu(II) complex of **13** has been determined in the salt $Na[Cu\mathbf{13}(CH_3CN)](BF_4)_2NO_3$, and is shown in Fig. 3. The Cu(II) is bound to both pendant arm alcohols, two *N*-donors of **13** and one CH_3CN molecule. In addition, the complex cation shows long-range interaction to the amido-*N* donor at 2.611 Å. The structure of the free ligand **14** has also been solved.

2.1.2. *Mercaptoalkylation*

The mercaptoalkyl ligands **15** [25] and **16** [26] have both been reported since 1989. These are the sulfur analogues of **5** and **9** and are made by reacting tacn with the appropriate thiirane, although it would appear from the limited experimental

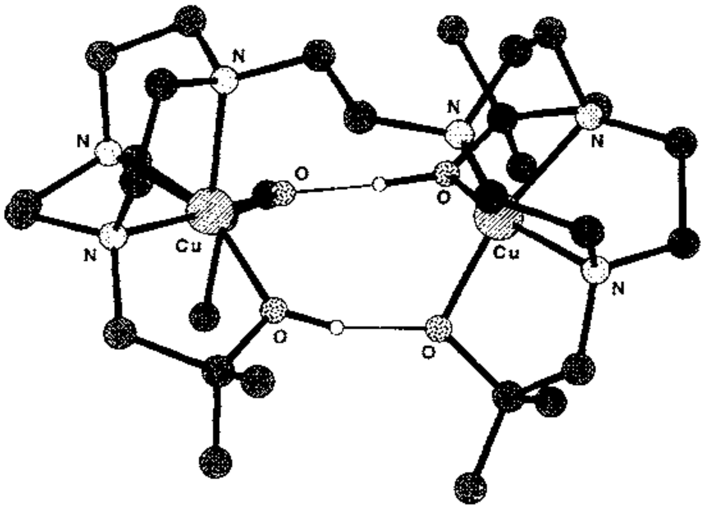
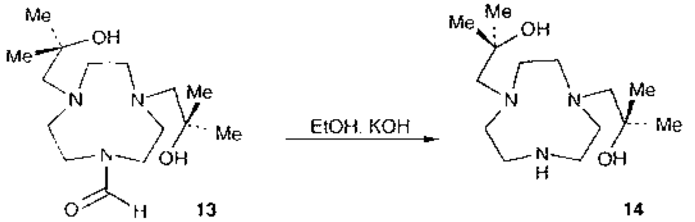


Fig. 2. A view of the cationic portion of the structure of the Cu(II) dimer of **12**, which provides a rare example of pendant hydroxyl group deprotonation that has occurred at neutral pH.



13 **14**

data given for **16** that it was made from racemic 2-methylthiirane, in which case the ligand described has probably been used as a mixture of diastereomers. The structures of the indium(III) [27,28] and gallium(III) [25] complexes of triply deprotonated **15** have been reported. The metal ion adopts near octahedral geometry lying between *fac*-N$_3$ and *fac*-S$_3$ sets of donors, which have a twist angle of 46° for In(III), and 49.6° for Ga(III). Formation constants for **15** with a range of metal ions have been determined [28]. Ligand **16** has been investigated as a means of forming models for the iron sulfur centre in the enzyme nitrile hydratase from *Brevibacterium*, sp.; it is reported as forming a neutral, monomeric high-spin Fe(III) complex.

2.1.3. Sulfomethylation

Sherry and coworkers have demonstrated that both mono- and di-sulfomethylation of tacn can be accomplished by reacting the macrocycle with the sodium salt of formaldehyde bisulfite [12]. The reaction is performed in aqueous solution, where the pH determines the level of substitution by selectively protonating one (pH 9.5) or two (pH 4) of the amines, protecting them from substitution. Compounds **17** and **18** are useful intermediates in the formation of mixed pendant arm macrocycles as the sulfonate groups can be replaced by cyano groups, which

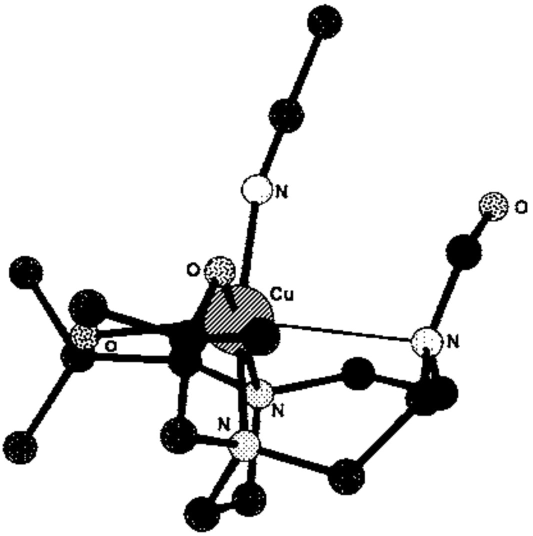
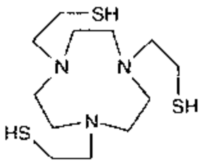


Fig. 3. Drawing of the cation in $Na[CuI3(CH_3CN)](BF_4)_2NO_3$ showing the long interaction (2.611(5) Å) between the amide nitrogen atom and the copper ion.



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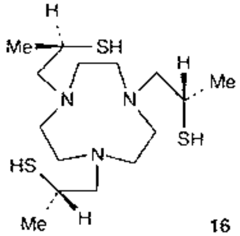

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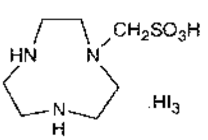

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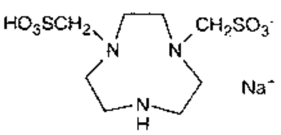


18

can then be hydrolysed yielding pendant carboxymethyl groups. Alternatively the sulfomethyl groups can be converted directly to phosphinates or phosphonates [12]. The crystal structure of **18** has been solved [29].

2.1.4. *Carboxymethylation*

Although ligand **2** was first synthesised in 1977 [30] crystal structures of its complexes are still appearing, thus structures of [Al**2**] [27,31] and [Ga**2**] [25,32,33] have recently been reported. Both complexes have structures which are close to being octahedral with twist angles of 51 and 47.6 , respectively. The structure of the seven coordinate neutral complex [In**2**Cl] has also been solved showing it to be a pentagonal bipyramid with one carboxylic group coordinating without deprotonation [33,34]. Preparation of **2** with ^{13}C enrichment at the carbonyl carbon atoms has been reported [33].

The optically active analogues of **2**, *N*,*N*′,*N*″-tris[(2*R*)-2-methylcarboxymethyl]-tacn and its enantiomer, have been prepared from the reaction of the appropriate enantiomer of 2-chloropropanoic acid and the macrocycle in the presence of LiOH [35,36]. The structure of the neutral In(III) complex (crystallised in the absence of Cl^-) has been solved and found to be a distorted trigonal prism (twist angle 20.8°) involving complexation of the macrocycle alone [35].

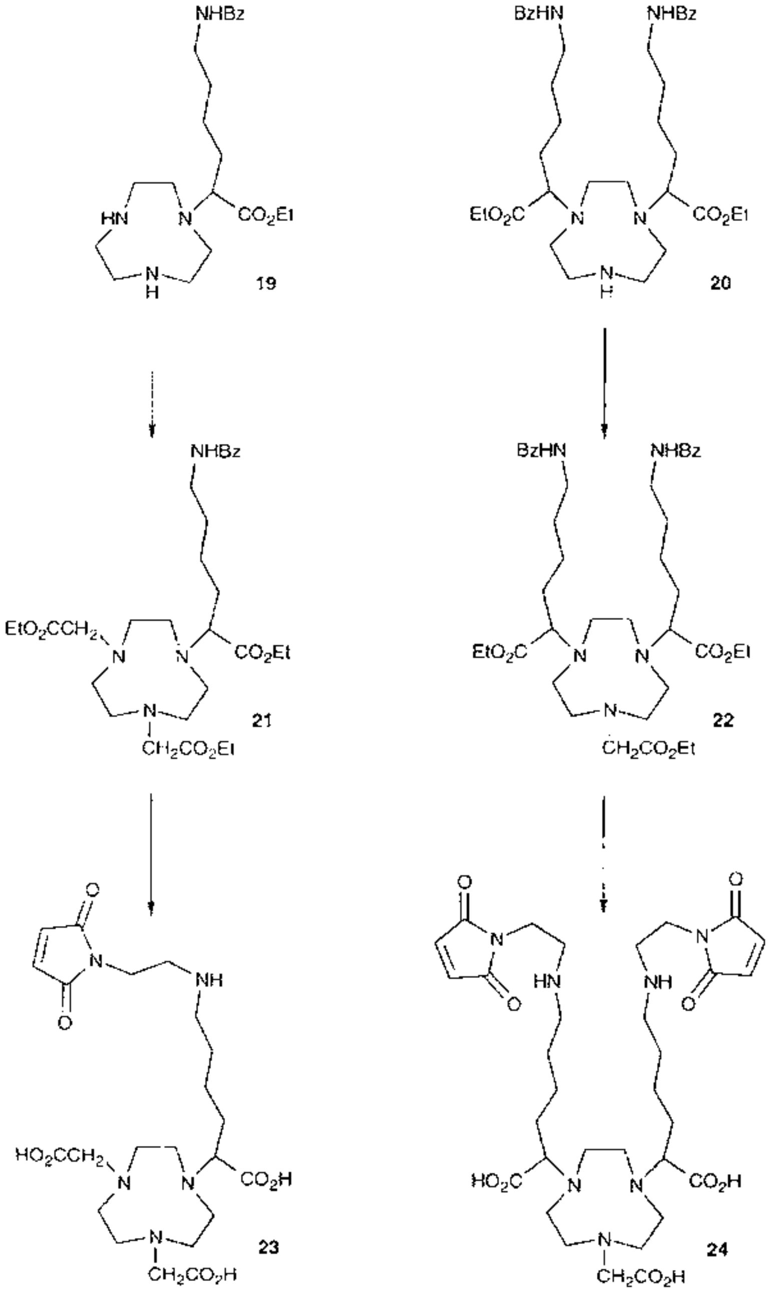
New methods for producing the mono-*N*-functionalised or di-*N*-functionalised analogues of **2**, via their tert-butyl esters, have now been reported [37], which use pH control to direct the course of the reaction. Mono-(carboxymethyl)-tacn has also been produced from **17** by converting it to the nitrile and hydrolysing to give the acid [12] or from tacn orthoamide [9,38]. Copper(II) complexes [39] and vanadium(IV) and (V) complexes [38] of this ligand have been studied showing that coordination of the deprotonated pendant arm readily occurs. Bis-(carboxymethyl)-tacn has been produced in 90% yield by reacting the macrocycle with 2.1 equivalents of bromoacetic acid in water at pH 9.5 [40] and its vanadium(IV) and (V) complexes have also been studied [41].

For the purpose of attaching a radioactive ^{67}Ga or ^{111}In labelled complex to a monoclonal antibody, tacn has been mono- and di-*N*-functionalised by reaction with racemic 6-benzamido-2-bromohexanoate [42]. When done in DMF with K_2CO_3 as base this affords a mixture of **19** and **20** which can be separated by cation exchange HPLC. The unreacted sites on **19** and **20** were reacted with ethyl bromoacetate in DMF with K_2CO_3 giving triesters **21** and **22**, which were then hydrolysed with 6 M HCl over 48 h and reacted with the maleimide active ester MPHS to give compounds **23** and **24**.

Various *C*-functionalised derivatives of **2** have also been prepared for use in attaching a complex containing radioactive Ga(III) or In(III) to a monoclonal antibody [42,43].

2.1.5. *Carbamoylalkylation*

Ligand **25** was prepared in 63% yield by reacting tacn with three moles of bromoacetamide in the presence of triethylamine [44]. The structure of the yttrium(III) complex, [Y**25**$(CF_3SO_3)_2(H_2O)$](CF_3SO_3), has been solved showing that the metal ion is nine coordinate, having a bound water molecule, two bound triflate ions and the hexadentate macrocycle. The coordination geometry may be described as a 3:5:1 arrangement in which the three nitrogens atoms of the macrocycle comprise the three donors and the water molecule the one [44]. The *N*,*N*-dimethyl analogue (**26**) has been prepared in a similar way using *N*,*N*-dimethylbromoacetamide and the corresponding ligand bearing C_3 substituents on each nitrogen atom (**27**) by the conjugate addition of *N*,*N*-dimethylpropenamide [45].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EtO2CCH2
N
N
CO2Et
N
CH2CO2Et
21
BzHN
NHBz
EtO2C
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CO2Et
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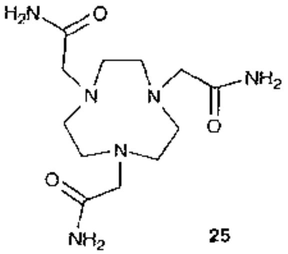
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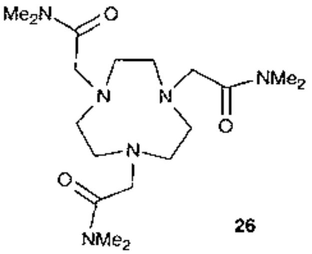
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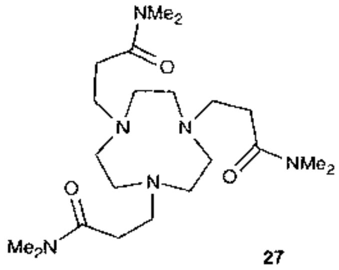
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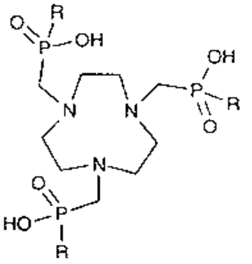
2.1.6. *Phosphinomethylation*

Pendant methylenephosphinic acids have been the focus of some attention due to the fact that the $P(R)O_2H$ moiety provides the opportunity both for coordination to a metal ion and for variation of the R group, which offers the potential to vary the lipophilicity of the molecule or to link it with other species such as proteins. Furthermore, as the coordinating phosphinate generally protonates at lower pH than a coordinated carboxylate or phosphonate it provides a pathway to neutral complexes with a greater resistance to acid catalysed metal dissociation than afforded by pendant carboxylates or phosphonates. Complexes of this type are much sought after for in vivo applications.

The pendant phosphinates are generally prepared via a Mannich reaction. Thus **28** is synthesised in 25% yield through the reaction of tacn with paraformaldehyde and H_3PO_2 in aqueous solution at 40°C [46]. Details for the preparation of **29**–**31** can be found in Ref. [47], Refs. [48,49] and Ref. [50], respectively. A by-product of the formation of **29** is the mono(methylenemethylphosphinic acid) [47] which may find applications in the synthesis of mixed pendant arm macrocycles. The preparation of tacn derivatives with a combination of one t-butyl-carboxylate and two phosphinate esters or various combinations of carboxymethyl and methylene-(phosphinic acid) pendant donors have also been described [37,51]. The mono-*N*-functionalised ethyl ester analogue of **30** has been produced from **17** by reaction with ethyl ethylphosphonite [12]. This has been hydrolysed to the mono-phosphinic acid along with the introduction of two carboxymethyl groups [40]. The di-*N*-functionalised analogue of **30** has also been prepared in which the third nitrogen atom carries a carboxymethyl group [40].

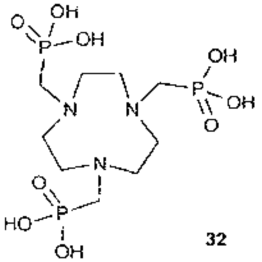

28 R = H
29 R = Me
30 R = Et
31 R = Ph

Neutral complexes of **29** with Ga(III) and In(III) have been isolated and from

^{71}Ga NMR spectroscopy judged to have at least approximate C_3 symmetry. Stability constant measurements indicate that the ligand has a good selectivity for Mg^{2+} over Ca^{2+} [37,52]. The coordination chemistry of **30** has been more exhaustively explored and crystal structures of the Fe(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II), Ga(III) and In(III) complexes have been solved [52,53]. All show distorted octahedral geometry with twist angles in excess of 45°.

2.1.7. Phosphonomethylation

Ligand **32** has been prepared using a Mannich reaction in which the macrocycle, formaldehyde, and H_3PO_3 were combined to give a 55% yield of the product [54].



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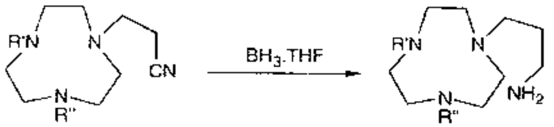
Although a detailed study has been made of the protonation sequence, complexation studies have yet to be reported. The preparations of various phosphonate mono- and di-esters are described in Refs. [37,48,49]. Refs. [37,40] describe the synthesis of tacn with two carboxymethyl arms and one methylenephosphonic acid or methylene(mono- or di-alkyl phosphonate). Tacn with a single methylene phosphonic acid or phosphonate diethyl ester has also been prepared [12].

2.1.8. Aminoalkylation

Partial or complete 3-aminopropylation of tacn has been accomplished using cyanoethylation (Michael addition of acrylonitrile to the macrocycle) to form **33**–**35**, followed by reduction of the cyano groups to primary amines with sodium in ethanol giving **36**–**38** [55,56]. Selective partial reaction has not yet been accomplished, as reaction of less than three moles of acrylonitrile gives mixtures of **33**–**35**. From the reduction of such a mixture, **36**–**38** have been separated as their nickel(II) complexes using ion exchange, and liberated by decomplexation with concentrated HCl. In a later modification of this synthesis, BH_3 in THF was used as the reducing agent [57].

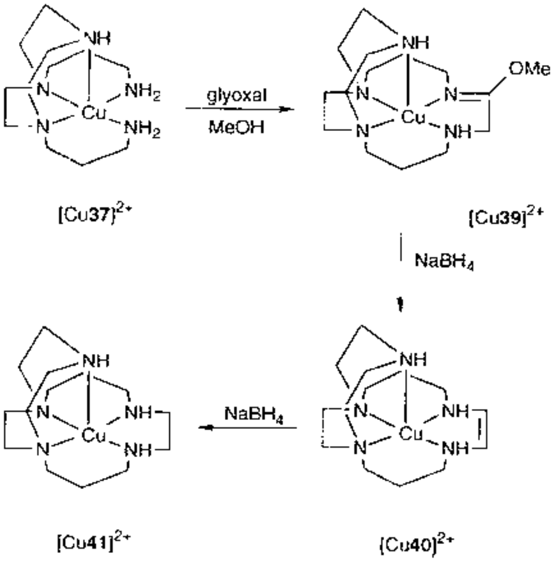


33 R' = R'' = H	**36** R' = R'' = H
34 R' = H, R'' = CH_2CH_2CN	**37** R' = H, R'' = $CH_2CH_2CH_2NH_2$
35 R' = R'' = CH_2CH_2CN	**38** R' = R'' = $CH_2CH_2CH_2NH_2$

Crystal structures of the Co(III) and Ni(II) complexes of **38** have been solved

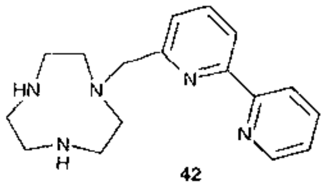
[55] which show that the ligand acts as a hexadentate, forming mononuclear complexes which have slightly distorted octahedral stereochemistry with twist angles close to 60°. All three six-membered chelate rings are in the chair configuration in both complexes. The pentadentate ligand **37** forms a square pyramidal complex with Cu(II) in which the macrocycle is located on a triangular face and the two pendant arms complete the square base. With Co(III) the resulting complex is octahedral with a chloro group *trans* to one of the tertiary nitrogen donors [56]. The quadridentate ligand **36** forms an octahedral complex with Ni(II) in the presence of chloride. The complex is a dimer in which two *cis*-coordinated chloro groups bridge the half-units. The macrocyclic ligand is coordinated to the remaining four coordination sites of each metal ion [56].

Ligand **37** is amenable to ring closure which results in the fusing of a tetraaza macrocyclic ring to the tacn moiety. This has been done by McAuley and coworkers in a copper(II) template reaction in methanol, whereby glyoxal condenses with the primary amines of the pendant arms [58]. After reduction of the intermediate with sodium borohydride, followed by demetallation with sodium sulfide, the Cu(II) complex of the double macrocycle **41** was isolated. In the course of this work the imidate complex [Cu**39**]$^{2+}$ was crystallised and its structure solved, as was that of the enamine complex [Cu**40**]$^{2+}$. The isolation and structural identification of these intermediates has considerably clarified the mechanistic detail of this type of metal template reaction.



2.1.9. Heterocycle attachment

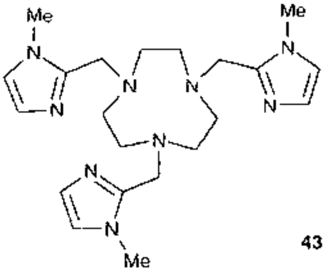
A single 2,2′-bipyridyl moiety has been attached to tacn via a methylene group, giving **42**, through the reaction of 6-(chloromethyl)-2,2′-bipyridine with a large excess of the macrocycle [59]. Compound **42** has been methylated at the two



42

secondary amines using a mixture of formaldehyde and formic acid. The Ni(II) complex of **42** is octahedral with a water molecule, located *trans* to one of the macrocycle amines, complementing the five donor atoms of the ligand. The zinc(II) structure is a highly distorted trigonal bipyramid in which the macrocycle occupies one axial and two equatorial sites. In addition, there are two long contacts (> 3 Å) to perchlorate counterions. ^{13}C NMR data suggest that the Pd(II) complex also has a trigonal bipyramidal structure. The kinetics of complex formation between **42** and Co(II), Ni(II), Cu(II) or Zn(II) in DMSO have been reported [60].

Three methylene(*N*-methylimidazole) moieties have also been attached to tacn



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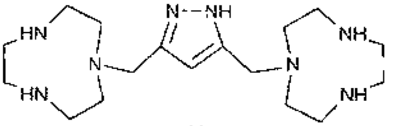
giving ligand **43** [61]. This was achieved in 74% yield by reaction of 1-methyl-2-chloromethylimidazole with the macrocycle in acetonitrile using triethylamine as the base. The crystal structure of $[\mathrm{Ni}\mathbf{43}]^{2+}$, which shows it to have near octahedral stereochemistry, has been solved [61]. In a similar way, using 1-(hydroxymethyl)pyrazole, three pyrazole groups have been linked to tacn, each via a methylene group. The lithium complex is six coordinate with a twist angle of 40 [62].

Two tacn macrocycles have been linked by a bridging pyrazole moiety in ligand

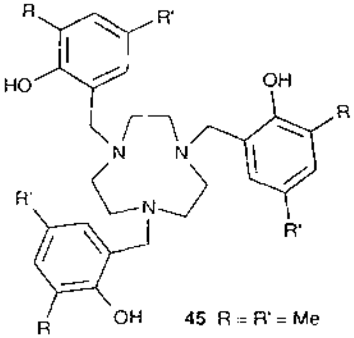


44

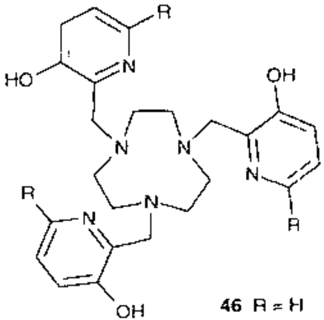
44 [63]. This is done by reacting the macrocycle, with two nitrogen atoms protected by tritylation, with 3,5-bis(chloromethyl)pyrazole. The resulting product (75% yield) is detritylated in 37% HCl giving **44** in 66% yield. Potentiometric titration studies of copper(II) complexation indicate that both monometallic and bimetallic species may form. The bimetallic species $[\mathrm{Cu}_2(\mathbf{44}_{-\mathrm{H}})]^{3+}$ reacts with an azide ion to give the ternary complex $[\mathrm{Cu}_2(\mathbf{44}_{-\mathrm{H}})(\mathrm{N}_3)]^{2+}$. The crystal structure of this complex, which is shown in Fig. 4, indicates that each copper ion is square pyramidal with azide and pyrazolide both bridging between basal coordination sites.

2.1.10. o-Hydroxy-benzylation and -picolylation

A number of ligands in this category (**45**–**50**) have now been produced. Synthesis is accomplished either by the Mannich reaction or by nucleophilic substitution on the appropriate benzyl halide. Thus **45** has been synthesised in 26% yield by a Mannich reaction involving the macrocycle, formaldehyde and 2,4-dimethylphenol [64]. This particular phenol is chosen as the methyl groups restrict reaction to a single site on each aromatic ring, thereby eliminating the possibility of forming unwanted linkage isomers. Ligands **46** and **47** are synthesised in 13 and 46% yield from the Mannich reaction using 3-hydroxypyridine or 3-hydroxy-6-methylpyridine [65,66]. On the other hand, **48**, **49** [67] and **50** [68] are synthesised in 25, 60 and 55% yield from the macrocycle and 2-(bromomethyl)phenyl acetate, 2-(bromomethyl)-6-tert-butylphenyl acetate and 2-(bromomethyl)-4-tert-butylphenyl acetate, respectively. In each case the triacetate was finally hydrolysed to the triphenol using sodium methoxide in THF. A one-step synthesis of **48** has recently been reported [65].



45 R = R' = Me
48 R = R' = H
49 R = Bu^t, R' = H
50 R = H, R' = Bu^t



46 R = H
47 R = Me

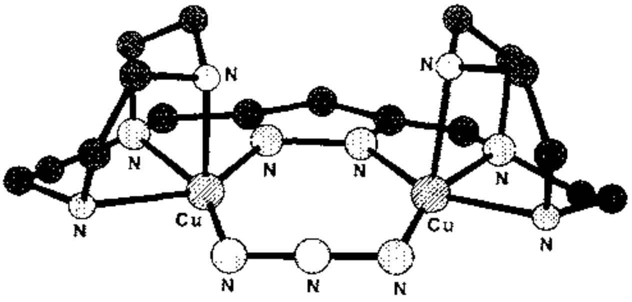


Fig. 4. Structure of the cation $[Cu_2(44_{-H})(N_3)]^{2+}$ showing the combination of pyrazolide and azide bridging.

The structure of both **45** and [Ga**45**H]ClO$_4$ have been solved [64]. The free ligand shows intramolecular hydrogen bonding between each phenolic proton and the nitrogen atom to which it is appended. The Ga(III) structure is a slightly distorted octahedron involving three nitrogen and three phenolate donors. The location of the acidic hydrogen was not determined. A preliminary report of the structure of monoprotonated [Fe**47**] has appeared [66], which shows it to be similar to the Ga(III) structure of **45** with one of the pyridine nitrogen atoms (none of which coordinate) protonated. A potentiometric pH study of the formation constant for [Fe**47**] reveals that it is higher than that of any synthetic iron(III) chelate previously reported and that the ligand binds Fe(III) more strongly at physiological pH than the microbial siderophore enterobactin [69]. Copper(II) forms a neutral five coordinate species with **48** in which one phenol remains protonated and does not coordinate, whilst two phenolate donors together with the three nitrogen atoms take up a square pyramidal arrangement around the metal ion [67]. The mono-*N*-functionalised analogue of **48** has been produced from tacn orthoamide and its vanadium(IV) and (V) complexes investigated [9,38]. Two copper complexes have been formed with **49**. One is green and analyses as [Cu(**49**$_{-\mathrm{H}}$)]ClO$_4$ and has been shown by preliminary X-ray analysis to consist of a square pyramidal cation in which, besides the three nitrogen atoms, one phenolate and one phenol coordinate, the third phenol is not coordinated. The second complex is red and analyses as [Cu(**49**$_{-2\mathrm{H}}$)]NaClO$_4$. Since it is converted into the green form upon protonation, it is presumed to have two phenolate and three nitrogen donors coordinated to the copper ion. The structure of the high-spin iron(III) complex, [Fe**49**], has been solved and is found to be pseudo-octahedral [67]. The neutral complexes [Cr**50**] and [Fe**50**] of Cr(III) and Fe(III), respectively, and the Ti(IV) and V(IV) cations [Ti**50**]$^+$ and [V**50**]$^+$ have had their structures solved [68,70] and are isostructural with the usual near octahedral *fac*-N$_3$O$_3$ coordination sphere. Upon acidification the complexes of the trivalent metal ions protonate at one of the phenolate groups and the resulting complex dimerises by way of two asymmetric O–H···O hydrogen bonds. This is seen in the structure of the monoprotonated iron(III) complex [68]. In contrast to the alkoxide-alcohol hydrogen bonded dimers discussed in Section 2.1.1, further protonation to create a third hydrogen bond between the two halves of the dimer does not appear possible. The basicity of the phenolate groups in complexes of **50** which involve a trivalent metal ion has been exploited as a way of forming trimetallic complexes [71]. Thus, when the cobalt(III) complex [Co**50**] in acetone solution is treated with M(H$_2$O)$_6$ cations, where M = Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+} or Zn^{2+}, complexes of the type shown in Fig. 5 result where the central metal ion is coordinated by six bridging phenolate groups. If the Cr(III) or Fe(III) complex of **50** is used, analogous structures do not result, apparently because of the lower basicity of the phenolate groups in these complexes, brought on by the greater extent of the pπ–dπ donation into the partly filled t$_{2g}$ orbitals of these metal ions. Instead, a central metal ion is incorporated into a trimetallic assembly of similar overall configuration, but remains fully hydrated with each coordinated water molecule hydrogen bonding to a coordinated phenolate. A certain amount of metal ion selectivity has been observed when the central metal ion is sequestered from

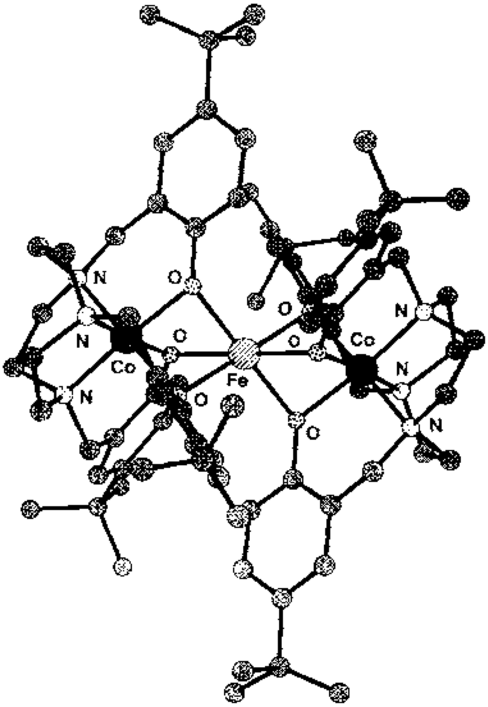
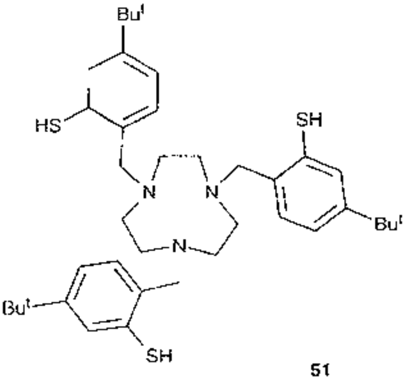


Fig. 5. Structure of the cation arising from the bridging of two [Co^{III}**50**] molecules by an Fe^{2+} ion.

mixtures of metal ions; thus from a Zn(II)/Mn(II) mixture Zn(II) is four times as likely to be incorporated, whereas from a Zn(II)/Ni(II) mixture there is little discrimination at all [71].

2.1.11. *o-Mercapto-benzylation*

Ligand **51** has been prepared in good yield from the reaction of the macrocycle with 3-benzylmercapto-4-bromomethyl-t-butylbenzene in toluene with KOH as base [19,72,73]. Debenzylation was accomplished using sodium in liquid ammonia. A variety of mononuclear complexes of the type [M^{III}**51**] or [M^{IV}**51**]PF$_6$ have been isolated. The crystal structures for the Fe(III) and Co(III) complexes show that the *fac*-N$_3$S$_3$ (thiophenolate) donor set is coordinated in the usual way giving pseudo-octahedral geometry [19,73]. Reaction of **51** with divalent metal chlorides in a 1:2 ratio affords the homo- and hetero-dinuclear compounds [M^1**51**M^{2}Cl] where one metal is six coordinate (N$_3$M^{1}S$_3$) and the other four coordinate (S$_3$M^{2}Cl). The two polyhedra are linked by three μ_2-thiolato bridges. Trinuclear complexes with the formulation [**51**NaM^{IV}Na**51**] (M = Ru, Os) have also been isolated where it has been shown from X-ray crystallography that the sodium ions are bound within a trigonal prismatic N$_3$S$_3$ donor set while the central MS$_6$ core is octahedral [72].



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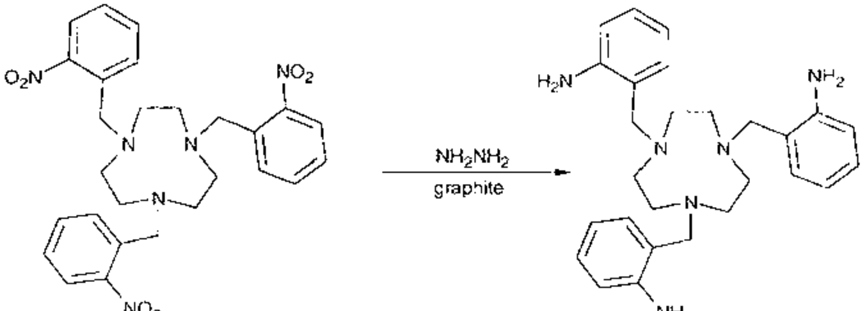
2.1.12. o-Amino-benzylation

Reaction of tacn with *o*-nitrobenzyl bromide in toluene using KOH as base gives compound **52** in 98% yield. This can be reduced to **53** using hydrazine hydrate and a graphite catalyst in 90% yield [74].



52 **53**

With divalent metal ions **53** coordinates without deprotonation of the aniline moieties [74,75]. The structures of the perchlorate salts of the Zn^{2+}, Cd^{2+} and Hg^{2+} complexes have been solved and it is seen that in the solid state the ligand coordinates with the expected *fac*-N_3N_3 arrangement giving near trigonal prismatic geometry in each case (twist angles are 13.6°, 18° and 18° for the Zn(II), Cd(II) and Hg(II) complexes, respectively). The structures are unusual, however, in that of the three six-membered chelate rings two have the boat structure whereas the third adopts the twist-boat conformation giving the complex C_1 symmetry (Fig. 6). In solution, NMR studies of the diamagnetic complexes indicate facile boat to twist-boat (and vice versa) interconversion. Powder diffraction data for the, Mn^{2+}, Fe^{2+} and Co^{2+} complexes (all high spin) show that they are isostructural. The nickel(II) complex is six coordinate with a distorted octahedral NiN_6 polyhedron (twist angle 50°). In this case all three six-membered chelate rings have the boat configuration giving the complex C_3 symmetry (Fig. 6). The Cu(II) complex is square pyramidal, with one aniline nitrogen donor dangling, and is similar in

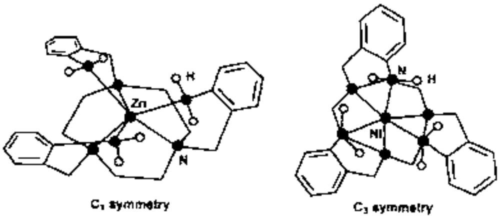


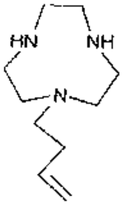
Fig. 6. Schematic diagram showing the relative disposition of the aromatic rings in the C_1 and C_3 structures that can arise from the coordination of **53**.

structure to the Pd(II) complex, although the apical $M–N_{amine}$ bond in the latter complex is considerably longer than in the former [75].

The Mn(II), Fe(II) and Co(II) complexes of **53** are oxygen sensitive in solution. In the case of the latter two ions, exposure of the complex to oxygen in the presence of a small amount of triethylamine has led to the isolation of neutral high-spin Fe(III) or low-spin Co(III) complexes in which each of the aniline moieties has undergone deprotonation [76]. A Mn(IV) complex of deprotonated **53** has been formed from air oxidation of an acetonitrile solution of $[Mn^{II}$**53**$](ClO_4)_2$, or, starting with "Mn(III) acetate", by allowing the reaction mixture either to oxidise in air or to disproportionate. The structure of $[Mn^{IV}($**53**$-_{3H})]BPh_4$ has been solved and shows a *fac*-N_3N_3 arrangement of the amines and the anilide donors with the complex in a distorted octahedral environment. The average $Mn–N_{anilide}$ distance of 1.877 Å is the shortest Mn–N distance in octahedral manganese(IV) complexes observed to date, indicating that anilides are strong π-donors and that the $M–N_{anilide}$ bond has appreciable double bond character [76].

2.1.13. *Pendant alkene addition*

Use has been made of tacn orthoamide [9] to mono-*N*-functionalise the macrocycle, using 4-bromo-but-1-ene or allyl bromide, producing **54** or **55**, respectively [77].



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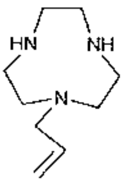

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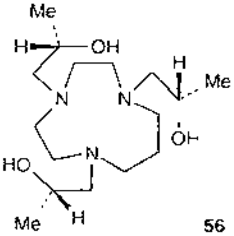
With Cu(I) it is thought from infrared data that **54** coordinates via the three nitrogens and the olefin, probably in a tetrahedral arrangement. In the case of Cu(II), the crystal structure of $[(Cu$**54**$OH)_2](BPh_4)_2$ has been solved in which it is seen to be a dimer involving two hydroxo-bridges linking Cu(II) ions to which the ligand is coordinated through the amines alone [77].

2.2. 1,4,7-Triazacyclodecane derivatives

Prior to 1989 only the tricarboxymethyl derivative of this macrocycle had been synthesised [30].

2.2.1. Hydroxyalkylation

To investigate the effect of increasing the steric strain in triazamacrocycles ligand **56** has been produced, presumably by a similar method to that used for **9**, and the structure of its cobalt(II) complex, $[(Co\mathbf{56})_2(NO_3)_2][PF_6]_2$, determined [78]. Both cobalt(II) ions in the dimer have near trigonal prismatic geometry (twist angles of 7.5 and 12°) which is rare for a d^7 metal ion. The two halves of the dimer are linked by two bridging nitrate ions. These adopt an unusual bridging mode in which one oxygen atom of each is hydrogen bonded to two hydroxyl hydrogen atoms, one from each half of the dimer, and a second oxygen atom of each nitrate ion is hydrogen bonded to a single hydroxyl group.



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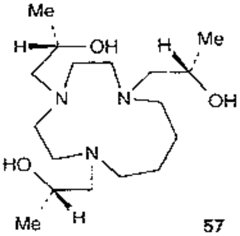

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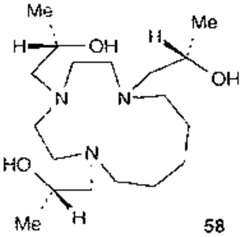

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2.3. 1,4,7-Triazacycloundecane derivatives

2.3.1. Hydroxyalkylation

A preliminary account of the crystal structure of the Co(II) complex of **57** indicates that it has a structure half way between trigonal prismatic and octahedral (twist angle 31°) [78].

2.4. 1,4,7-Triazacyclododecane derivatives

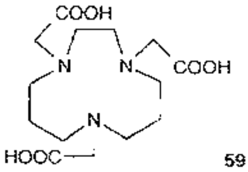
2.4.1. Hydroxyalkylation

The crystal structure of $[Co\mathbf{58}][NO_3]_2$ has been solved which shows that the Co(II) ion is approximately trigonal prismatic [78]. A very large N–Co–N angle within the eight-membered chelate ring (116.5°) creates an unusual situation where the O_3 set of ligators is not twisted away from the N_3 set in either a right-handed or left-handed sense.

2.5. 1,4,8-Triazacycloundecane derivatives

2.5.1. Carboxymethylation

Ligand **59** has been produced in 39% yield from the reaction of chloroacetic acid with the macrocycle in the presence of LiOH [33].



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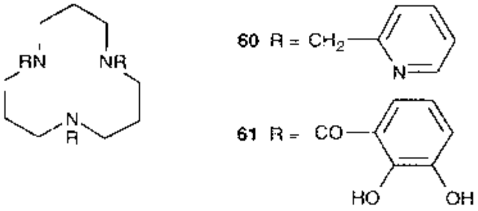
2.6. 1,5,9-Triazacyclododecane derivatives

Whereas tacn is chosen as the platform onto which three pendant donors are mounted in an effort to secure highly stable octahedral complexes, or the more unusual trigonal prismatic complexes, 1,5,9-triazacyclododecane has been used as a platform from which to mount one pendant donor with the expectation of producing tetrahedral complexes. Thus, more effort has been made with this macrocycle to protect, and subsequently deprotect, two of the nitrogen atoms so that a single pendant arm can be attached with high efficiency.

The chemistry associated with ligands **60** and **61** was reviewed in Ref. [8] and no subsequent work on them appears to have been reported.



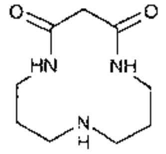
2.6.1. Hydroxyalkylation

Ligands **63**–**65** have been prepared so that their Zn(II) complexes can be examined as models for alkaline phosphatase [79]. To achieve clean monofunctionalisation, the cyclic diamide, 2,4-dioxo-1,5,9-triazacyclododecane (**62**) [80] was reacted with ethyl bromoacetate, methyl acrylate or methyl vinyl ketone, respectively. Treatment of the intermediate with diborane in THF then accomplishes reduction of the amide moieties as well as the ester or ketone.

Only the coordination chemistry of **63** with Zn(II) has been pursued [79], as the association of the pendant hydroxyl with the metal ion was found to be weak in **64** and **65**, which have longer arms. ^{1}H NMR and potentiometric titration data for the Zn(II) complex of **63** indicate that at basic pH the complex is tetrahedral with the pendant donor deprotonated (p$K_a = 7.4$). In non-aqueous solvents there is a tendency for dimerisation of [Zn(**63**$_{-H}$)]$^+$ to occur and the crystal structure of the dimer is shown in Fig. 7.

2.6.2. Carboxymethylation

Complete carboxymethylation of 1,5,9-triazacyclododecane to give **66**, which had earlier proved troublesome, has now been accomplished, in 28% yield, by alkylation of the macrocycle with ethyl bromoacetate in ethanol, using caesium carbonate as



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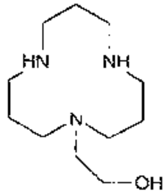

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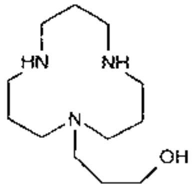

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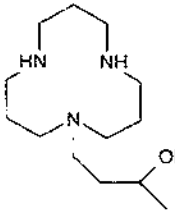

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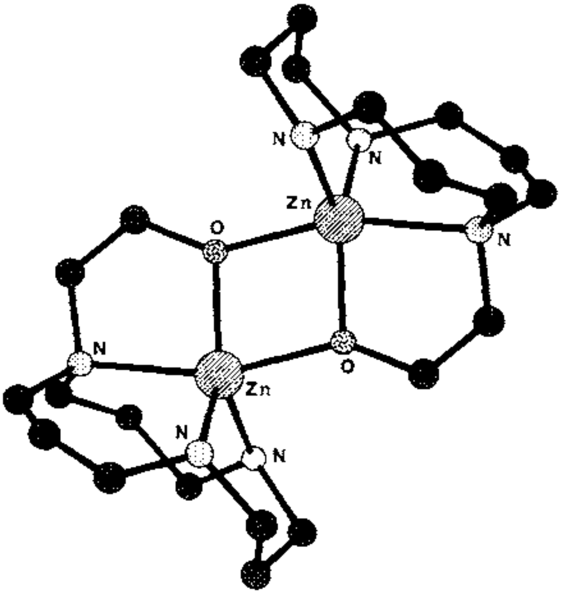
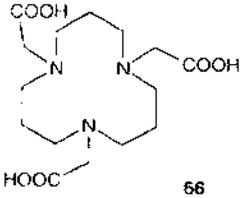


Fig. 7. The structure of the dimer of $[\mathrm{Zn}\mathbf{63}_{-\mathrm{H}}]^+$ that can be crystallised from aqueous solution at pH 9.

base, and subsequent hydrolysis, in 6 M HCl, of the resulting triester [80]. Various C-functionalised derivatives of **66** have been described.

Carboxymethylation at two nitrogen sites has been achieved by monotosylating **62** and then carrying out diborane reduction of the product, which produces the monotosylated triamine. This can be dialkylated with ethyl bromoacetate and then hydrolysed to the diacid (**67**). Compound **67** has also been produced from the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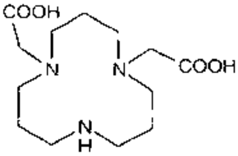
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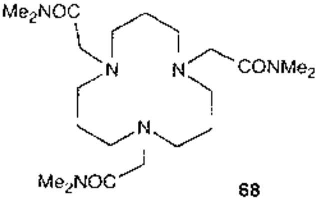
1,5,9-triazacyclododecane analogue of **18** by converting it to the dinitrile and then hydrolysing to give the di-acid in 19% overall yield [12].

2.6.3. *Carbamoylalkylation*

1,5,9-Triazacyclododecane and its monotosylate, prepared as described in Section 2.6.2, both undergo reaction with *N*,*N*-dimethylbromoacetamide in the presence of caesium carbonate to give (after detosylation) the pendant tertiary amide macrocycles **68** and **69** [45,80].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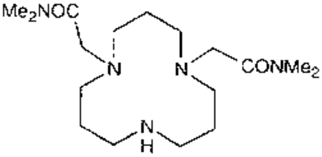
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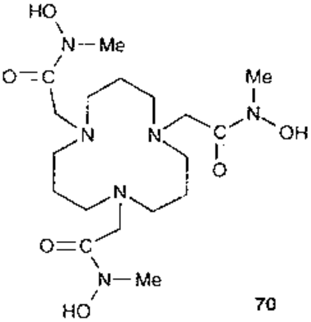
2.6.4. *Hydroxamalkylation*

The first example of the attachment of a pendant hydroxamic acid to a macrocycle is the synthesis of **70**, which has been prepared as a model for naturally occurring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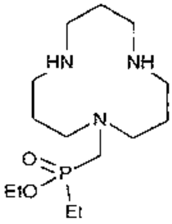
siderophores [81]. The ligand is made by reaction of *o*-benzyl-2-bromo-*N*-methylacetohydroxamic acid with the macrocycle in DMF, using NaH as base, followed by de-benzylation. Potentiometric titration data and spectroscopic investigations suggest that in its Cu(II) and Fe(III) complexes the metal ion is coordinated by the hydroxamate groups and that the macrocycle remains unbound.

2.6.5. Phosphinomethylation

Ligand **71** has been produced from the 1,5,9-triazacyclododecane analogue of **17**, in 73% yield, by reacting it with ethyl ethylphosphonite [12].



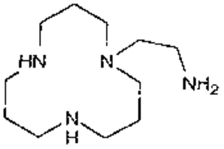
71

2.6.6. Phosphonomethylation

The analogue of ligand **32** has been prepared and its acid–base behaviour studied [54]. The diethyl ester of the mono-*N*-functionalised methylene(phosphonic acid) has been produced from the 1,5,9-triazacyclododecane analogue of **17** and diethylphosphite in 31% yield [12].

2.6.7. Aminoalkylation

Mono-2-aminoethylation and mono-3-aminopropylation have both been accomplished using the doubly protected form of the macrocycle (**62**) [82,83]. This is either cyanomethylated or cyanoethylated whereupon reduction with diborane gives **72** or **73** directly. $[Zn\mathbf{72}(ClO_4)]ClO_4$ has been crystallised and its structure solved showing that it is trigonal bipyramidal with the coordinated perchlorate adopting one of the axial binding sites [82]. The Ni(II) complex of **73** has been crystallized as $[Ni\mathbf{73}(NCS)_2]$ which has an octahedral structure with two *cis*-bound isothiocyanates [82]. The complexation of the dimethylamine analogue of **73** (**74**) has also been studied. This more sterically hindered pendant donor is more reluctant to coordinate than a primary amine and this facilitates hydration of atmospheric CO_2 and the formation of carbanato complexes. This is seen in the structure of $[\{(H\mathbf{74})Ni(NCS)\}_2(CO_3)]^{2+}$ in which the protonated pendant arm is dangling and two coordination sites on each metal ion are occupied by a bridging carbonate [84]. With zinc(II), on the other hand, a tetrahedral complex of **74** has been formed (average N–Zn–N angle 104.8°) in which all four nitrogen atoms of the ligand are bound [85]. Ligand **74** is prepared from an ab initio Richman–Atkins synthesis [86].



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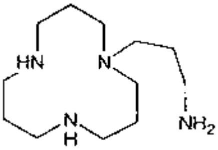

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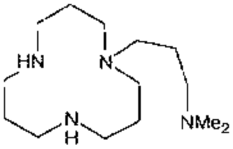

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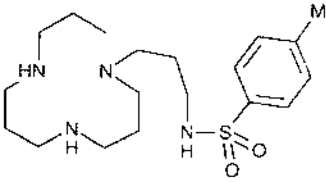
2.6.8. Sulfonamide attachment

For the purpose of modelling carbonic anhydrase inhibition by sulfonamides, **73** has been monotosylated, at the primary amine, by reacting monoprotonated **73** with tosyl chloride giving **75** [83]. Complexation of **75** with Zn(II) has been studied and it is found that the sulfonamide deprotonates upon coordination at pH < 7. This intramolecular N$^-$ binding to Zn(II) completely inhibits Zn–OH bond formation which is believed to be essential for the normal functioning of carbonic anhydrase. The structure of the cation in tetrahedral [Zn**75**$_{-H}$]PF$_6$ is shown in Fig. 8.



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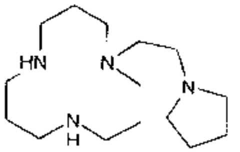
2.6.9. Heterocycle attachment

In a variation of the reaction used to produce **74**, the pyrrolidine heterocycle has been attached to 1,5,9-triazacyclododecane through the 1-position via an ethyl chain giving **76** [85]. The crystal structure of [Zn**76**(ClO$_4$)]ClO$_4$ has been solved, showing



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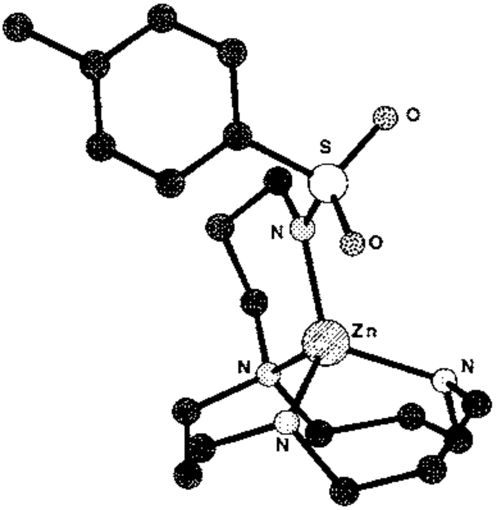
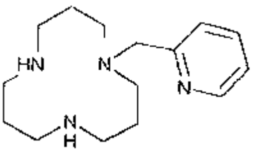


Fig. 8. Structure of the cation in [Zn**75**$_{-H}$]PF$_6$, showing coordination of the deprotonated sulfonamide.

the metal ion to be trigonal bipyramidal with the pyrrolidine in an equatorial position and an axial perchlorate.

A single pendant pyridine has been attached to the macrocycle through the 2-position with either a methylene or ethylene link giving **77** and **78** [87]. Both are produced in an ab initio Richman Atkins synthesis using the appropriate components [86]. The structure of $[Ni\mathbf{77}(O_2NO)]NO_3$ has been solved showing that pseudo-octahedral stereochemistry is adopted with two *cis*-positions filled by a bidentate nitrate ion and the pyridine moiety coordinated *trans* to one of the secondary amines. With Zn(II) **78** forms a tetrahedral complex in the solid state (average N–Zn–N angle 106.0°), but in acetonitrile solution NMR studies indicate that an equilibrium probably exists between the tetrahedral structure and one in which a nitrato group has coordinated to an equatorial site of a trigonal bipyramidal structure [87].



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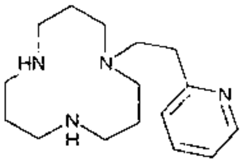


78

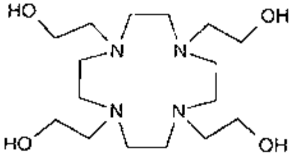
A single pendant 2,2′-bipyridyl moiety has been attached to 1,5,9-triazacyclododecane giving the analogous ligand to **42** [59]. No details of its coordination chemistry appear to have been reported.

3. Pendant donor tetraaza macrocycles

Saturated tetraaza macrocycles are known with ring sizes ranging from 12 atoms to at least 44 atoms [88]. Of these it is only the pendant donor derivatives of the 12- and 14-membered rings 1,4,7,10-tetraazacyclododecane (cyclen) and 1,4,8,11-tetraazacyclotetradecane (cyclam) that have been the subject of intensive investigation. Early investigations focussed on cyclam as this is the easiest of the cyclic tetraamines to prepare, but as it became apparent that the introduction of four pendant arms (which is synthetically the most straightforward elaboration of the macrocycle) generally leads to complexes having the *trans*-III geometry [89], in which two arms project from one side of the macrocyclic plane and two from the other, attention tended to switch to cyclen which usually generates complexes in which all pendant arms project in the same direction (the *trans*-I conformation [89]). The significance of this is that the coordinating capability of four pendant donors is unlikely to be fully utilised if they exist on two sides of the macrocyclic plane whereas it is quite likely that it can be, at least by metal ions able to adopt a coordination number ≥8, when they are grouped on one side. If a single metal ion is unable to utilise all of the pendant donors there is a tendency for bimetallic complexes to form where both metal ions are exocyclic and unable to derive the stabilisation associated with location within the macrocyclic annulus.

3.1. 1,4,7,10-Tetraazacyclododecane (cyclen) derivatives

Ligands **79**, **80** and their complexes have been discussed earlier [8]. Advances on this work are discussed below.



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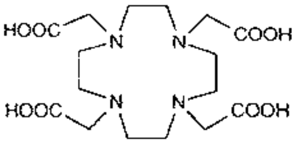


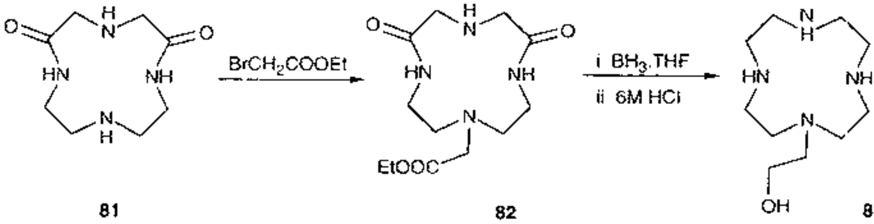
80

3.1.1. Hydroxyalkylation

Introduction of the hydroxyalkyl group has generally been via the epoxide opening reaction, referred to in Section 2.1.1.

NMR studies have shown that complexes of **79** with the Li(I), Na(I), K(I) [90,91], Cd(II), Hg(II) and Pb(II) [92] are eight coordinate and approximately square anti-prismatic in methanol solution, which is interesting since earlier work has shown that, in the solid state, whilst the K(I) complex is eight coordinate the Na(I) and Li(I) complexes are seven and five coordinate, respectively [93]. In a similar way, the La(III) and Eu(III) complexes of **79** have also been shown to be eight coordinate in water and methanol [94].

To study the catalytic properties of zinc(II) complexes of macrocycles with pendant alcohols towards ester hydrolysis, the monofunctionalised cyclen derivative **83** has been formed from 2,6-dioxocyclen (**81**) [95] via the pendant ethyl acetate (**82**) [96]. A crystal structure of the zinc(II) complex of **83**, as the diperchlorate, shows that the complex is square pyramidal with the pendant alcohol occupying the apical site. When crystallised at pH 9.5 in the presence of hexafluorophosphate, however, a trimeric assembly (Fig. 9) in which three square pyramidal [Zn**83**]$^{2+}$ cations are linked through a single phosphate group results. The counterions are three PF_6^- anions, and the phosphate apparently arises from partial hydrolysis of these. Each pendant alcohol is hydrogen bonded to the phosphate.



81 **82** **83**

1,7-Bis(2-hydroxyethyl)cyclen has been produced in 72% yield by protecting two *trans*-amines as methylcarbamates, reacting with oxirane and then deprotecting by base hydrolysis [97]. Alternatively, protection can be effected through the formation of 1,7-ditosyl cyclen or the 1,7-diphosphoramidate [98]. No complexes have been

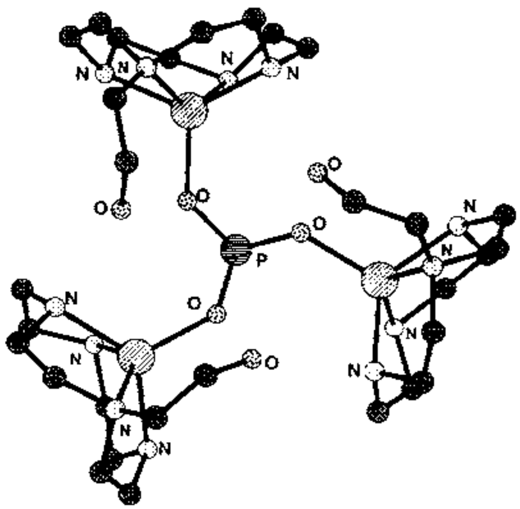
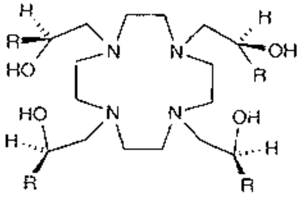


Fig. 9. Drawing of the trimeric assembly of $[Zn83]^{2+}$ cations that results when phosphate oxygen donors occupy the apical sites to the exclusion of the pendant hydroxyl groups (hydrogen atoms are not shown).

reported. The two secondary amines of 1,7-bis(2-hydroxyethyl)cyclen have been carboxymethylated through reaction with bromoacetic acid [98].

Hydroxyalkylation leading to the attachment of four 2-hydroxypropyl arms has been carried out, initially using racemic 2-methyloxirane, which leads to a mixture of diastereomers of **84** [99,100], or more recently using (2*S*)-2-methyloxirane which

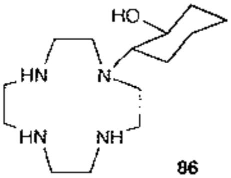


84 R = Me
85 R = Ph

gives a single enantiomer [100–102]. The solid state structures of the Pb(II) [99], Eu(III) [100], and Bi(III) [102] complexes of **84** have been solved and show that the ligand binds as an octadentate to these metal ions with the donor atoms adopting an approximately square antiprismatic arrangement around the centrally positioned metal ion. The spiralling of the pendant arms between the plane of the four nitrogen atoms and the plane of the four oxygen atoms is always seen to be uniformly clockwise or anticlockwise which influences the chirality of the complex (Λ or Δ) in addition to that imposed by the stereogenic centre in each arm (*SSSS* if prepared from (2*S*)-2-methyloxirane). For complexes which have been formed using the optically pure ligand only one of the two possible diastereomers, Λ*SSSS* rather than Δ*SSSS*, is formed as this keeps the methyl groups towards the periphery of the structure.

The related ligand **85** has been formed using *S*- or *R*-styrene oxide and the diperchlorate salt of its Cd(II) complex is known to be square antiprismatic having either the ΛSSSS or ΔRRRR structure depending on which enantiomeric form of the ligand is used [103]. The corresponding ligand with a single 2-phenylhydroxypropyl arm has also been formed from **81**, by reaction with one equivalent of styrene oxide followed by reduction [3]. The crystal structure of the Zn(II) complex of the deprotonated form of this ligand has been solved showing the bonding of the pendant alkoxide in a structure which imparts distorted square pyramidal geometry to the Zn(II) ion.

Reaction of cyclen with cyclohexene oxide, even in large excess, results in the addition of just a single pendant 2-hydroxycyclohexyl arm, shown in structure **86**

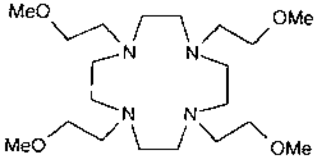


86

[104]. This reaction may provide a useful way of forming multi-functionalised polyaza macrocycles.

3.1.2. *Methoxyethylation*

Ligand **87** has been prepared from cyclen and 2-chloroethyl methyl ether in good yield [105]. The solution chemistry of its metal complexes has been studied and compared with that of **79** and **84** in Refs. [91,101,106].



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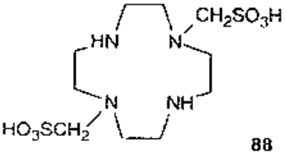
3.1.3. *Sulfomethylation*

For use as a precursor to pendant carboxylic and phosphonic acids the 1,7-disulfomethylated derivative (**88**) has been prepared by reaction of di-protonated



88

cyclen with the sodium salt of formaldehyde bisulfite [12,107]. No coordination chemistry has yet been reported, but the crystal structure of the dihydrate of **88** has been solved [29].

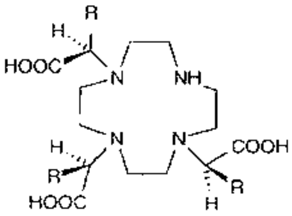
3.1.4. Carboxymethylation

Ligand **80** (DOTA) still continues to attract considerable attention. The structure of the Zn(II) complex has recently been solved which shows that it binds as a *cis*-octahedral ligand with two bound carboxylates and two dangling carboxylic groups [108]. The structure of the sodium complex of the tetra-tert-butyl ester of DOTA has been determined and the sodium is found to be eight coordinate within an approximately square antiprismatic structure [109]. Lanthanide(III) ions form nine coordinate complexes in which there is a coordinated water molecule in addition to the macrocyclic ligand, which binds in a square antiprismatic fashion. The structures of $Na[M(DOTA)(H_2O)]\cdot 4H_2O$, where M = Y [110,111], Gd [110,112], Eu [113] and Lu [114], have been solved. Solution studies of the lanthanide complexes have revealed two dynamic processes; one arising from enatiomerisation associated with a Λ to Λ helicity interchange, similar to that described in Section 3.1.1, simultaneous with the concerted inversion of the five-membered chelate rings of the cyclododecane unit, and the other an isomerisation, corresponding to one or other of these processes occurring in isolation [114–117]. The sodium salt of high-spin Fe(DOTA) has also been structurally characterised in the solid state [110] and is a monocapped trigonal prism with one uncoordinated carboxylate.

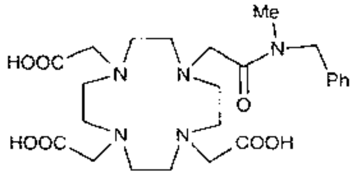
For a number of reasons yttrium-90 is an attractive isotope for use in radioimmunotherapy [118]. To be used in this way it must be irreversibly bound to a carrier which can be attached to a monoclonal antibody. DOTA has been identified as probably the most useful carrier for ^{90}Y as it complexes rapidly and, after extensive screening of other polyaminopolycarboxylic acids [33,118], appears to offer the best combination of thermodynamic and kinetic stability. This work has led to the formation of a wide variety of *C*-substituted derivatives of DOTA [33,42,118–120].

The tri-carboxymethyl analogue of **80** (**89**) (DO3A) has been the focus of some attention owing to the fact that it offers a means for forming non-ionic water soluble complexes of high thermodynamic and kinetic stability that are sought for the various different bio-medical applications, where trivalent cations tend to be employed. The ligand was first synthesised by Kaden and coworkers [121] and the synthesis is fully discussed by Tweedle et al. [6], who have solved the X-ray structure of the diprotonated sulfate salt [109]. The first two protonations of DO3A occur at the secondary nitrogen and at the *trans*-annular nitrogen. The ligand is pre-organised for complexation in the *trans*-I configuration [89]. The indium(III) complex has been characterised structurally and found to have a seven coordinate capped trigonal prismatic structure [121]. The structure of high-spin $[Fe(DO3A)]\cdot 3H_2O$ is similar [110]. [Gd(DO3A)] has been crystallised as $[Gd(DO3A)]_3\cdot Na_2CO_3$ [110]. The three Gd(DO3A) units have essentially the same structure as the Fe(III) structure, just described, but with the eighth and ninth coordination sites for all three Gd(DO3A) units filled by a single carbonate ion: pairwise bidentate combinations of the three carbonate oxygens join the three DO3A units to form a nearly C_3 symmetric arrangement in which the bridging carbonate dianion is completely encapsulated.

Formation of ligand **90** with *RRR*-stereochemistry has been undertaken [122] following reports that complexes of the analogous DOTA analogue have greater stereochemical rigidity than DOTA itself [123]. The synthesis originates from



89 R = H
90 R = Me



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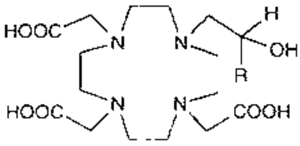
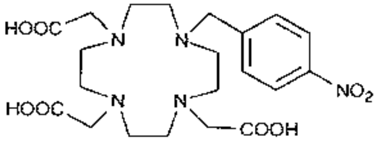


92 R = CH_3
93 R = CH_2OH
94 R = CH_2OCH_3



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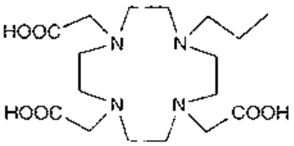

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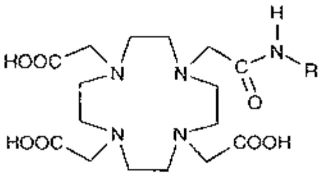
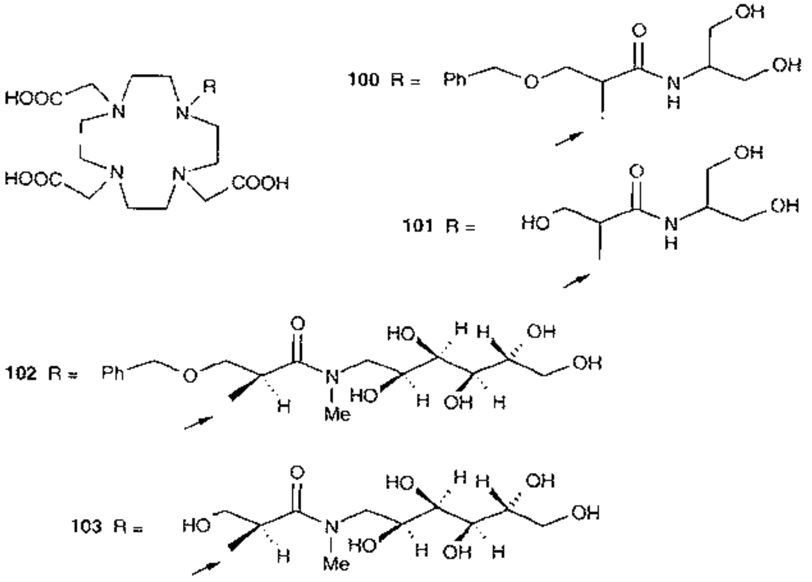


97 R = H
98 R = CH_3
99 R = CH_2CH_2OH

1-formylcyclen [6], but could not be successfully carried out through reaction with optically active 2-chloropropanoic acid, as used in the synthesis of the tacn analogue [35]. Instead, L-benzyl-2-(triflyloxy)propionate was used as the alkylating agent and deprotection was effected by subsequent hydrogenation in acidified methanol. This method is also advocated for the formation of the DOTA analogue. The structure of the Gd(III) complex of **90** has been solved. It is a non-symmetrical dimer in which each nine coordinate Gd(III) half-unit is brought together by the carboxylate of one half-unit which bridges through both the non-coordinating oxygen atom and the coordinating oxygen atom [122].

The unreacted secondary amine in DO3A is available for the introduction of a further pendant arm and this has been utilised in forming **91**–**99** [33,6,124]. The structures of the Y(III) and Gd(III) complexes of **92** have been solved and both are seen to be nine coordinate involving the square antiprismatically arranged macrocycle and a coordinated water molecule [109]. Stability constants for complexes formed from ligands **89** and **92–96** with alkaline earth metal ions have been determined [124]. Some C-substituted derivatives of DO3A and its tri-ethyl ester are discussed in Ref. [42]. DO3A derivatives have also been prepared by mono-*N*-alkylation of the cyclen ring followed by carboxymethylation [125,126].

Another group of DO3A derivatives is **100–103** in which a multifunctional arm



has been appended [127]. The structure of the Gd(III) complex of **100** is shown in Fig. 10. Square antiprismatic coordination around the Gd(III) is completed using the amide oxygen of the unique arm in addition to the three carboxylates and the

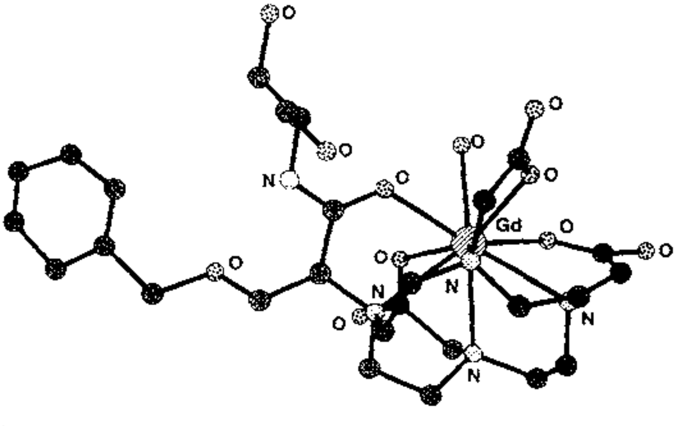
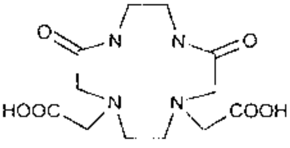


Fig. 10. The coordination mode of ligand **100** in its Gd(III) aquo-complex.

four nitrogen atoms; there is also a capping water molecule located on the pseudo C_4 axis above the oxygen atom plane.

1,7-Bis(carboxymethyl)cyclen (DO2A) has been prepared by conversion of **88** to the dinitrile followed by hydrolysis to the diacid [12], or by protection of two *trans*-secondary amines as benzylcarbamates whilst the remaining two are reacted with t-butylbromoacetate. Simultaneous acid hydrolysis of both the carbamate and the ester then gives the protonated diacid [97]. The structure of the Ni(II) complex of DO2A has been solved [107] and is similar to the structure of the Zn(II) DOTA complex, described above, minus the uncoordinated carboxylic groups.

1,4-Bis(carboxymethyl)cyclen has not yet been reported, but the dioxo form (**104**) and its dimer (**105**) have been formed from the reaction of 1,2-diaminoethane with the dianhydride of EDTA [128,129] in good yield. The crystal structure of **104** has been reported [130]. The structure of the Cu(II) complex of **104** has been solved [128] which shows that the metal ion does not sit within the macrocyclic annulus, but draws upon two amino nitrogens, two carboxylates and one amide oxygen, from one ring together, with a carboxylate oxygen from an adjacent molecule to form a six coordinate complex. The structure of the Zn(II) complex is similar [131]. The structure of the di-Mn(II) complex of **105** has also been determined [125]. Again the metal ions do not sit within the macrocycle, but each attains pseudo-seven-coordination through use of two amino nitrogens, two amide oxygens, two carboxylate oxygens and a water molecule.



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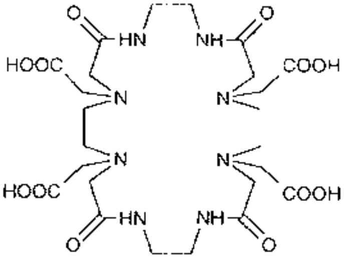
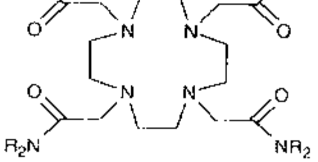


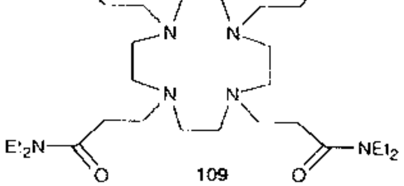
105

3.1.5. *Carbamoylalkylation*

1,4,7,10-Tetrakis(carbamoylmethyl)cyclen (**106**) has been prepared from the reaction of chloroacetamide with cyclen in the presence of triethylamine [132,133].

106 R = H
107 R = Me
108 R = Et





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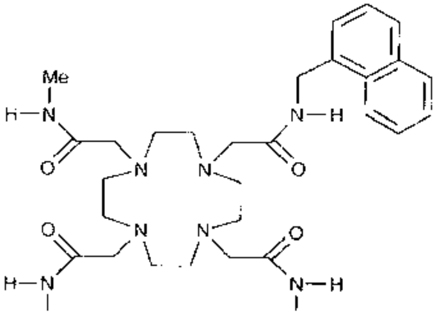
Crystal structures of the Zn(II), Hg(II), Cd(II), Ca(II), Pb(II) and Eu(III) complexes, as their perchlorate salts, or triflate in the case of Eu(III) [134], have been determined and show a transition from six coordination to eight coordination (nine in the case of Eu(III), as it has a bound water molecule) as one crosses this series. In all cases the ligand takes on the *trans*-I conformation [89], placing the nitrogen and amide oxygen donor atoms approximately at the vertices of a square antiprism, but with the smaller metal ions only two *trans*-oxygen atoms are able to encroach within normal bonding distance of the metal ion leaving the other pair with markedly greater M–O separations. The analogous tetrakis(dimethylamide) (**107**) and tetrakis(diethylamide) (**108**) have also been prepared using a similar procedure [45,136]. A combined NMR and molecular mechanics study indicates that **108** arranges itself in the usual square antiprismatic manner around lanthanide(III) ions [135]. The 2-carbamoylethyl analogue (**109**) is easily formed from the Michael addition reaction of acrylamide with cyclen [136], however caution must be exercised when using the ligand, particularly in aqueous solution at basic pH, as the retro-Michael addition, resulting in loss of acrylamide, is quite facile. Ligand **109** forms a square antiprismatic complex with La(III) which is reported as being much more labile than the corresponding DOTA complex, a fact which is attributable to the presence of the six-membered chelate rings [136].

To investigate the luminescence behaviour of macrocycles incorporating naphthyl fluorophores the two ligands **110** and **111** have been prepared [137,138]:



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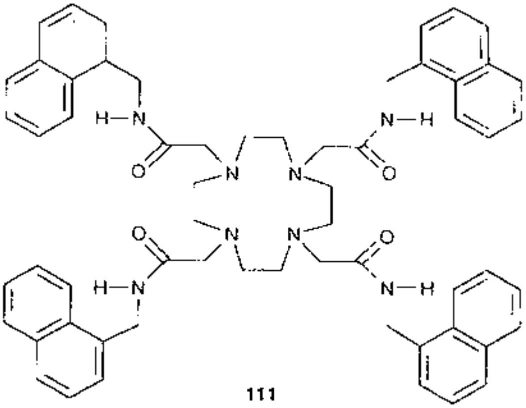
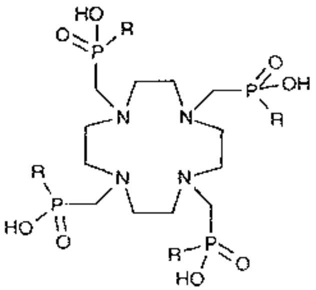


111

The former by protecting three of the amines with the molybdenum tricarbonyl moiety [139] whilst alkylating with *N*-(2-naphthylmethyl)-2-chloroacetamide and then, after deprotection, by further alkylation with three equivalents of 2-chloro-*N*-methylacetamide. The latter by direct reaction of cyclen with *N*-(2-naphthylmethyl)-2-chloroacetamide in DMF in the presence of caesium carbonate.

3.1.6. Phosphinomethylation

A family of ligands **112**–**117**, analogous to those formed from tacn, **28**–**31**, has been produced by using the corresponding reaction with cyclen [46,140–142,52,143]. The crystal structure of **117**.HCl has been solved [144] showing that it has the *trans*-I conformation [89] and is pre-disposed for eight-fold coordination of a metal ion. These ligands have applications both in the development of ^{90}Y(III) labelled



112 R = H
113 R = Me
114 R = Et
115 R = Ph
116 R = n-Bu
117 R = CH_2Ph

conjugates of tumour localising molecules and of Gd(III) complexes suitable as paramagnetic contrast agents in magnetic resonance imaging. The Y(III) complex of **117** has been characterised by X-ray crystallography and is eight coordinate (no bound water molecule) with approximately square antiprismatic geometry, as shown in Fig. 11 [144].

A wide variety of tribasic lipophilic ligands, which lead to neutral fat soluble complexes with these ions, have been produced and investigated. The strategy for doing this has been to protect three of the amino groups on cyclen by coordinating it to molybdenum tricarbonyl [139] and to monoalkylate the unprotected nitrogen using an *N*,*N*-dialkyl- or *N*-alkyl-bromoacetamide. Removal of the $Mo(CO)_3$ residue then allows the other three nitrogens to be used for the attachment of pendant phosphinic acids. In some cases the alkyl substituent on the pendant amide nitrogen

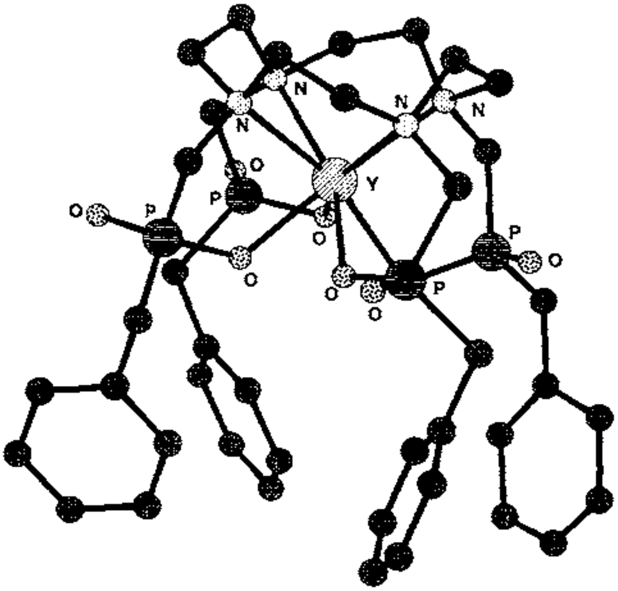
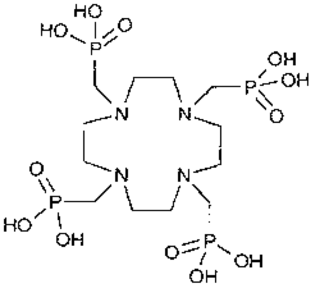


Fig. 11. Structure of the [Y117]$^-$ anion showing how aquation at the ninth coordination site of the Y(III) ion is obstructed by the ligand superstructure.

atom has a terminal quaternary ammonium functional group as a means of producing cationic complexes with trivalent metal ions [143,145–147]. The same strategy has been employed as a means for attaching an *N*-anthryl group for use in luminescence studies [148].

3.1.7. Phosphonomethylation

The tetrakis(methylenephosphonate) (**118**) has been prepared in analogous fashion to **32** [54,149,150]. Complexation with alkali and alkaline earth and lanthanide metal ions has been noted, but at the present time no solid state structure determinations appear to have been made. The thulium(III), [Tm**118**]$^{5-}$, complex anion has been investigated as an in vivo ^{23}Na NMR shift reagent [151] and the ytterbium(III), [Yb**118**]$^{5-}$, complex has been suggested as an NMR pH probe [152].



118

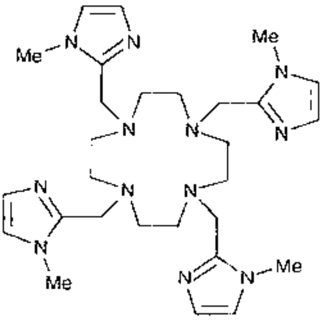
1,7-Bis(phosphonomethyl)cyclen and its di- and mono-ethyl ester precursors have been prepared by protection of two *trans*-secondary amines as benzylcarbamates whilst the remaining two are reacted with triethyl phosphite and formaldehyde [97]. By using an appropriate hydrolysis technique the desired level of de-esterification as well as removal of the carbamates can be achieved. Mono(phosphonomethyl)cyclen has been prepared from **88** in a complex reaction: Compound **88** is first oxidatively hydrolysed by reaction with triodide, which is apparently accompanied by loss of one of the sulfomethyl groups, giving the monohydroxymethylene species, which then is reacted with phosphorous acid to give the product in 24% yield [12].

3.1.8. Aminoethylation

Little has been reported about the *N*-aminoalkyl derivatives of cyclen. Kovacs and Sherry have described a synthesis for 1,7-bis(2-aminoethyl)cyclen which originates from cyclen, protected at the other two amines as the benzylcarbamate, and tosyl aziridine. Removal of the protecting group and the tosyl groups is effected by refluxing in triflic acid for 5 min [97]. 1,4,7,10-Tetrakis(2-aminoethyl)cyclen has been prepared in our laboratories from cyclen and tosyl aziridine and is currently under investigation [153].

3.1.9. Heterocycle attachment

Cyclen carrying four pendant *N*-methylimidazole donors (**119**) has been synthesised in the same way as **43**, but no structures have been reported [61]. Ligands



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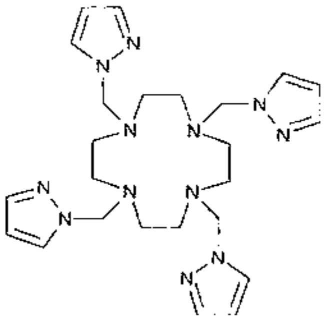


120

having two pendant *N*-methylimidazole donors in a 1,7-relationship, with or without the remaining two nitrogen macrocycle atoms methylated, have also been reported. The structures of their Ni(II) complexes have been solved and show *cis*-octahedral geometry with both heterocycles coordinated in each case [154]. A similar ligand (**120**) but with four pendant 1-pyrazolylmethyl donors has also been prepared from cyclen and 1-(hydroxymethyl)pyrazole in 92% yield [155]. The structure of the sodium(I) complex has been solved (Fig. 12) showing that the Na(I) ion is eight coordinate with square antiprismatic geometry. This is believed to be the only structurally characterised case of an eight coordinate sodium ion bound exclusively by nitrogen donors. The structure of the Mn(II) complex is similar [156]. From solution studies, Li(I) appears to bind to **120** giving two complexes which have

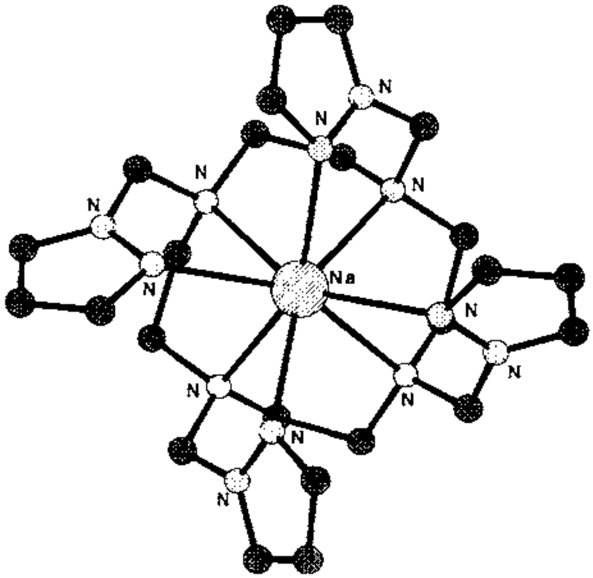


Fig. 12. Structure of [Na**120**]$^+$: the first structurally characterised example of eight coordinate sodium(I) involving exclusively nitrogen donor atoms.

different coordination numbers. The Ni(II) complex of **120** in the presence of iodide crystallises as a *cis*-octahedral species with all pendant groups projecting in the same direction; two of which coordinate [157]. In the presence of tetraphenylborate the Ni(II) and Zn(II) complexes undergo solvolysis which leads to the replacement of the pyrazole group on one of the pendant arms by an ethoxo group. The complexes are six and seven coordinate, respectively, with the ethoxo group uncoordinated. The iron(II) complex also shows this tendency in the presence of hexafluorophosphate to a limited extent [157].

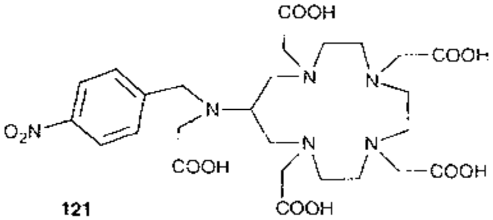
3.1.10. o-Hydroxy-picolylation

The cyclen analogue of ligand **47**, which has been designed for Th(IV) complexation, has been prepared using cyclen and 3-hydroxy-6-methylpyridine under Mannich conditions in 25% yield [158].

3.2. 1,4,7,10-Tetraazacyclotridecane derivatives

3.2.1. Carboxymethylation

Tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclotridecanes **121** and **122**, which have been C-functionalised in such a way that they may be attached to a monoclonal antibody, have been prepared. The rate of incorporation of radioactive yttrium(III) is higher with **121** than **122**, which is believed to be due to pre-coordination of Y(III) by the carboxymethylamino group outside the macrocyclic ring [159]. No structural information has been reported.



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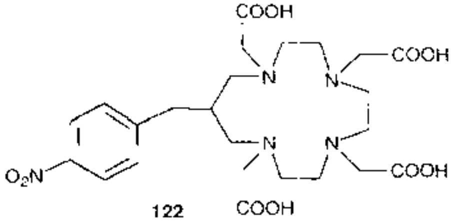
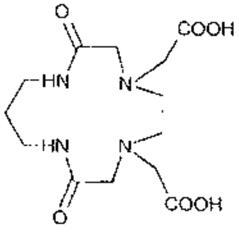


122

Ligand **123** has been prepared by the same method as **104**, but with 1,3-propanediamine as the amine [160]. Crystal structures of the Ca(II), Cd(II) [130] Mn(II) [131] and Pb(II) [160] complexes have been solved and in all cases the metal ion is exocyclic. The Cd(II) and Mn(II) complexes both have a distorted



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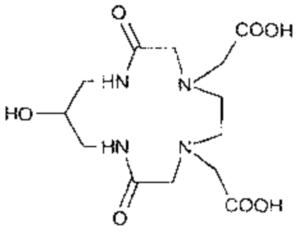
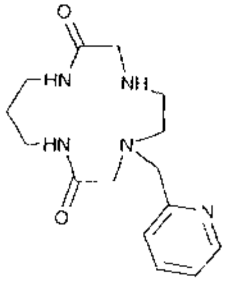


124

trigonal prismatic structure in which five donor atoms from the ligand (one amide oxygen is uncoordinated) and a water molecule are bound. The Ca(II) and Pb(II) structures are both eight coordinate. While the former is a distorted square antiprism, involving five donor atoms from the ligand, two water molecules and a bridging carboxylate, the latter is closer to being dodecahedral, owing to the fact that both amide oxygen atoms coordinate and only a single water molecule. In a variation of this work, ligand **124** has been prepared using 1,3-diamino-2-hydroxypropane as the diamine [161]. In the structure of its hydrated Mn(II) complex two non-equivalent molecules are present: One is very similar to [Mn**123**(H_2O)] described above, whereas within the other both amide oxygen atoms are within the first coordination sphere as well as a water molecule giving the molecule a distorted capped trigonal prismatic structure.

3.2.2. Heterocycle attachment

A single picolyl group has been attached to 11,13-dioxo-1,4,7,10-cyclotetratridecane [162], forming **125**, through the reaction of picolyl chloride with the parent dioxo macrocycle [163]. The ligand stabilises the trivalent oxidation state of nickel, but destabilises the trivalent state of copper.



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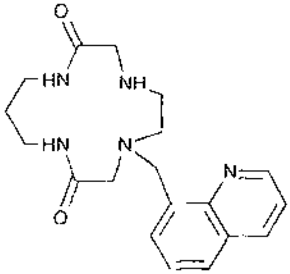

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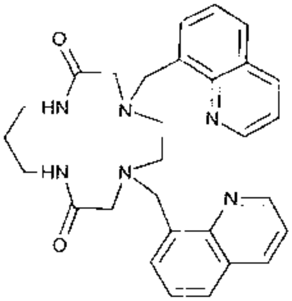
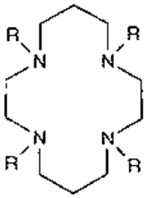


127

One (**126**) or two (**127**) 8-quinolylmethyl pendants have been attached to 11,13-dioxo-1,4,7,10-cyclotetratridecane through the reaction of 8-bromomethylquinoline with the parent macrocycle [163,164]. Depending upon the molar ratio of the reactants the product distribution can be directed to favour one or other of the compounds, which are separated by chromatography. Structures of the neutral Cu(II) complexes of both **126** and **127** have been solved. In each case the Cu(II) ion is square pyramidal and lies above the macrocyclic plane, binding to two deprotonated amide nitrogen atoms and the other two nitrogen atoms of the macrocycle, in the direction of an apical quinoline nitrogen atom [164].

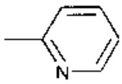
3.3. 1,4,8,11-Tetraazacyclotetradecane (cyclam) derivatives

Owing to its ease of synthesis, cyclam was the ligand first used to investigate the possibility of functionalising polyaza macrocycles at the nitrogen atoms [2], and so a large number of pendant arm macrocyclic derivatives (**128**–**135**) and their coordi-



128 R = H
129 R = CH_2CH_2OH
130 R = CH_2COOH
131 R = $CH_2CH_2CONH_2$
132 R = CH_2CH_2CN
133 R = $(CH_2)_3NH_2$
134 R = $CH_2CH_2NH_2$

135 R =

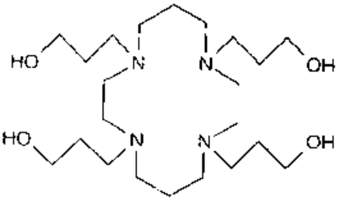


136 R = $CH_2PO_3H_2$

nation chemistry have been described in earlier reviews [7,8]. A considerable number of single pendant arm donors have also been reported in Ref. [8]. The crystal structures of **131** and its diprotonated form have now been reported [165] and, by analogy with **32**, compound **136** has been synthesised, although there is no detail of its structure or the structure of its complexes available [149]. More extensive developments are described in the following sections.

3.3.1. Hydroxyalkylation

In 1984 Hancock and co-workers commented on the enhanced rate of metal ion uptake by **129**, the cyclam derivative bearing four hydroxyethyl arms [166]. This provided considerable stimulus for a large amount of kinetic and mechanistic work [167] directed towards explaining this phenomenon and exploring its extent, during the course of which ligands **137**–**143** were synthesised [168–171]. The conclusion from this was that **137**–**140** show similar rate enhancements to **129**, indicating that extension of the alkyl chain by one methylene unit is unimportant as is the loss of one or two of the pendant arms, providing that at least two remaining arms are on adjacent nitrogen atoms. Ligands **141**–**143** do not show the effect, suggesting that the rate enhancement arises because of precoordination of the metal ion via two adjacent nitrogen atoms and the hydroxy groups which are appended from them. The crystal structures of **129** [172] and **137** [168] have been solved, showing that they are to some extent pre-organised against metal ion complexation owing to the fact that they exist in the *trans*-IV [89] configuration with considerable hydrogen bonding both between the hydroxyl groups and to the nitrogen atoms to which they are appended. The synthesis of **137** was accomplished by a high pressure reaction between oxetane (trimethylene oxide) and cyclam in quantitative yield, the other ligands were synthesised by the reaction of ethylene oxide or 2-bromoethanol with the appropriate macrocycle. Crystal structures of the Ni(II) complexes of **139**, **140** [170] and **141** [171] have been solved showing that in all cases both pendant alcohols coordinate to the Ni(II) ion resulting in octahedral stereochemistry. In the case of [Ni**140**]$(ClO_4)_2$ this results in the ligand adopting the unusual *trans*-II geometry with one of the six-membered chelate rings being forced into a twist-boat conformation. Complexes of the other two ligands adopt the more common *trans*-III geometry with both six-membered chelate rings in the chair conformation. The Ni(II) complex of **141** has been oxidatively dehydrogenated with nitric acid giving a *trans*-diimine [173]. Solution studies of the Cd(II) [174], Hg(II) and Pb(II) [175] complexes of **129** show that the *trans*-III structure is adopted and that the metal ion oscillates through the macrocyclic annulus between equivalent trigonal prismatic structures.



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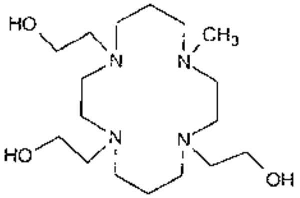

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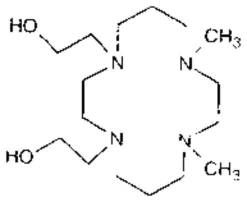

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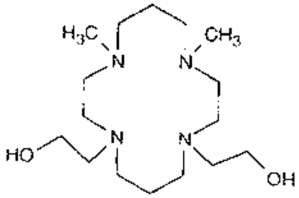

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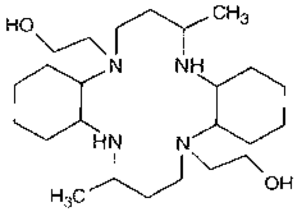

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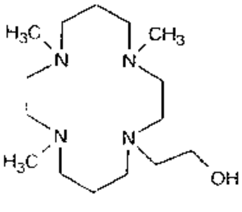

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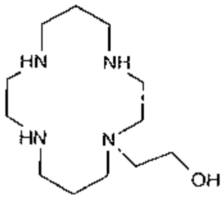
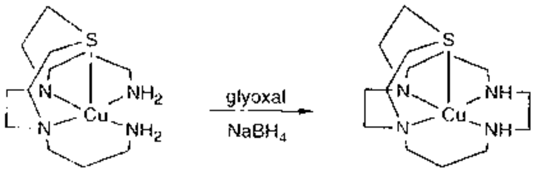


143

3.3.2. Pendant thioether formation

The Cu(II) complex of 4,7-bis(3-aminopropyl)-1-thia-4,7-diazacyclononane (**144**), which is the thioether analogue of ligand **37**, has been cyclised, using glyoxal,



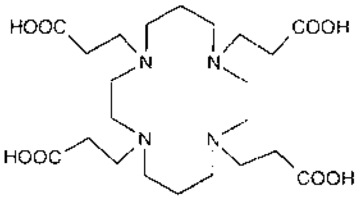
$[Cu\mathbf{144}]^{2+}$ $[Cu\mathbf{145}]^{2+}$

producing **145** [176]. Demetallation was accomplished with sodium sulfide. Structures of both the Cu(II) and Ni(II) complexes have been solved and in both cases the ligand adopts the *trans*-I conformation. The former is square pyramidal with the sulfur atom at the apex of the pyramid, whilst the latter is octahedral with a coordinated perchlorate group *trans* to the sulfur donor [176].

3.3.3. Carboxyalkylation

Ligand **130** (teta) still continues to attract attention. Two independent crystallographic determinations of H_4-teta have confirmed earlier suggestions that the first four protonation sites are two *trans*-related amines and the two carboxylate groups which are appended to the non-protonated amines [177,178]. The structure of the Mg(II) complex has been solved showing that the metal ion is exocyclicly bound via two *trans*-related, monodentate carboxylate groups from two different H_2-teta molecules. Octahedral coordination is completed by four water molecules [177]. Zn(II), on the other hand, binds within the *trans*-III macrocyclic cavity to the four nitrogen atoms and two trans-related carboxylates, the other two carboxylates are protonated and left dangling [108]. A *C*-functionalised derivative of teta suitable for attachment to a monoclonal antibody has also been prepared [120].

The carboxyethyl analogue of **130** (**146**) has recently been prepared in good yield



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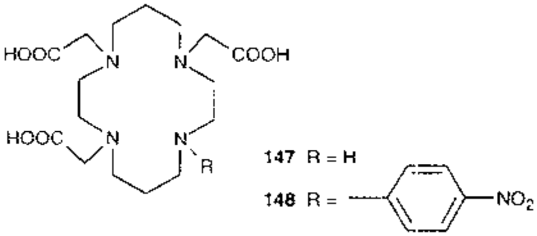
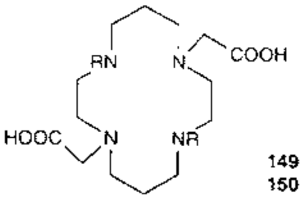


147 R = H
148 R = $-C_6H_4-NO_2$

from the reaction of acrylic acid with cyclam [179]. Structures of the ligand in the tetraprotonated, pentaprotonated and octaprotonated forms have been solved and the protonation sequence studied.

The tris(carboxymethyl) analogue of teta (**147**) has been prepared in the same way as **89** and the crystal structure of its indium(III) complex determined [121]. The structure of [In**147**] is superficially similar to that of [In**89**], but is more symmetrical and compact. This is reflected in the higher lability of [In**147**] which makes it less suitable as a carrier for ^{111}In than [In**89**]. Reaction of **147** with *p*-nitrobenzylbromide gives **148**.

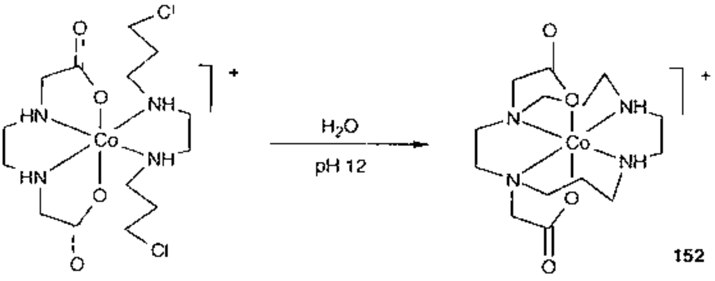
Two of the three possible bis(carboxymethyl)cyclam ligands have now been prepared. The 1,8-derivative (**149**) is prepared from 1,8-ditosylcyclam by reaction



149 R = H
150 R = Me

with ethylbromoacetate [180,181]. Hydrolysis of the tosyl groups results in simultaneous hydrolysis of the esters. This compound readily forms a stable dilactam unless methylation of the secondary amines, which can be accomplished by reacting with formic acid and formaldehyde, giving **150**, is undertaken [182]. Complexation of **149** or **150** with copper(II) produces an octahedral complex with the ligand in the *trans*-III conformation and two *trans*-carboxylate groups positioned on the Jahn–Teller elongated axis [180, 182].

The cobalt(III) complex of the 1,4-derivative (**152**) can be prepared from the acyclic precursor complex **151**, by heating it at pH 12 for four days [183]. The structure of **152** has been solved showing the ligand in the *trans*-III conformation with both carboxylates bound in a *trans*-relationship.



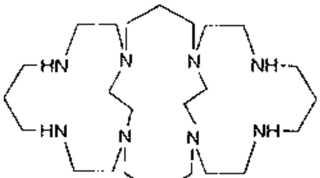
151

152

3.3.4. Aminoalkylation

Following an extensive series of papers concerning the transition metal chemistry of ligand **134** [8] the complexes with Zn(II), Cd(II) and Hg(II) have now been examined [184]. Like the transition metal ions, Zn(II) only forms bimetallic complexes with neutral **134**, Cd(II) and Hg(II) form both bimetallic and monometallic species. Crystal structures of $[Zn_2(OH)\mathbf{134}]^{3+}$ and $[Cd_2(Cl)\mathbf{134}]^{3+}$ show that each metal ion is bound in an exocyclic fashion to two of the macrocycle nitrogen atoms and two pendant arm nitrogen atoms; square pyramidal geometry is completed by way of a bridging anion. Stability constants for bridging anion binding in the Cu(II) complexes of **134** have been redetermined [185].

An extension of the chemistry associated with **134** has been to react the tosylated pendant arms with the ditosylate of 1,3-propanediol under basic conditions and so generate the triple macrocycle **153**, after detosylation [186]. Structural determinations of $[Cu_2(tos)_2\mathbf{153}]^{2+}$ (tos = *p*-toluenesulfonate) and $[Co_2(CO_3)\mathbf{153}]^{2+}$ show that the two types of structure that have been observed with complexes of **134** are also accessible to complexes of **153**. These are shown in Fig. 13 and can loosely be described as the chair and boat forms.



153

In a more limited study, **133** has been converted to a tricyclic macrocycle through tosylation of the primary amines and reaction with tritosylated diethanolamine [187]. No structural information has been reported, but spectroscopic studies suggest

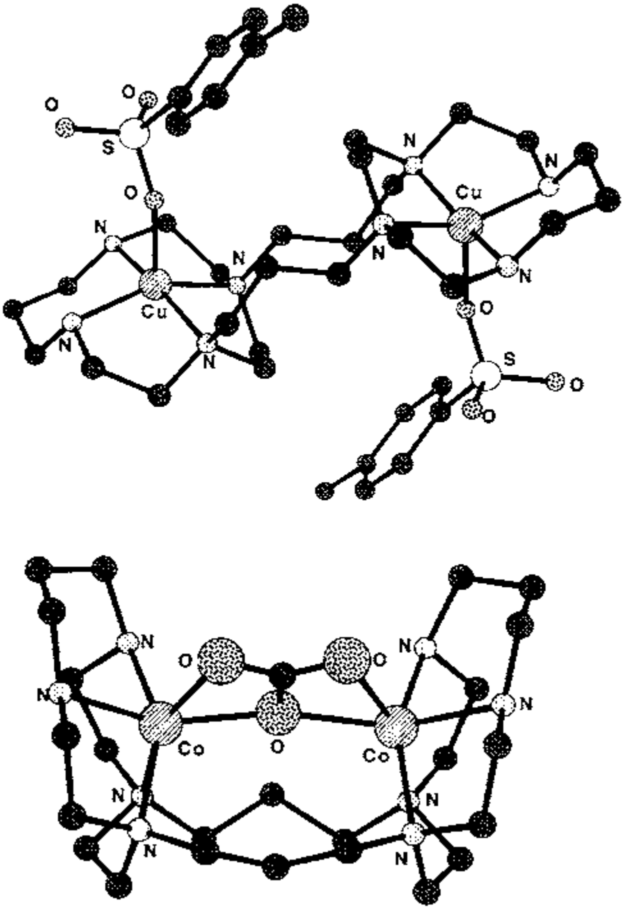
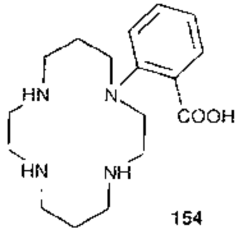


Fig. 13. The chair (upper) and boat (lower) configurations that can be adopted by ligand **153** upon complexation. The upper structure is of $[\mathrm{Cu_2(tos)_2}\mathbf{153})]^{2+}$ (tos = p-toluenesulfonate) and the lower is of $[\mathrm{Co_2(CO_3)}\mathbf{153}]^{2+}$.

that three metal ions can be bound. Cobalt(II) and (III) and rhodium(III) complexes of **133** have also been reported [188].

3.3.5. o-Carboxybenzylation

Ligand **154** is one of a number of monocarboxylic acid derivatives of cyclam synthesised by Studer and Kaden [189] and reviewed earlier [8]. The crystal structures of the Cu(II) complexes of **154** in the carboxylate and the carboxylic form have now been determined [190] and are remarkably similar considering that there are significant differences in the visible absorption spectra. Each form of the complex is square pyramidal with the pendant group occupying the apical position.



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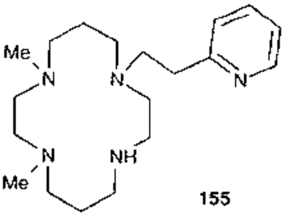

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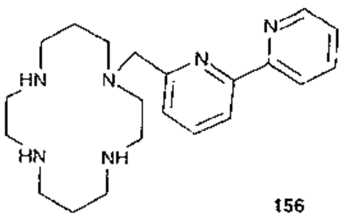

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3.3.6. *Heterocycle attachment*

The dicopper(I) complex of **135** has been synthesised and found to react with dioxygen at low temperature, forming two different peroxo species which ultimately degrade to bis(pyridine-2-carboxylato)copper(II) [191]. The structure of the dicopper(I) species involves two three coordinate copper(I) ions, each bound by two pyridine nitrogen atoms and one nitrogen atom of the macrocycle. A single 2-pyridylethyl pendant arm has been attached to 1,4-dimethylcyclam, in 70% yield, by the reaction of vinyl pyridine with the macrocycle, giving **155** [192]. With Cu(II) the ligand appears to bind in either the *trans*-I or *trans*-III conformation, without coordination of the pendant arm.

Ligand **156** is an analogue of **42** and is synthesised by the same procedure [59]. The ligand is unable to bind a single metal ion simultaneously in the macrocyclic cavity and at the pendant arm. Instead the metal ion chooses between the bipyridyl unit and the macrocycle on the basis of its own kinetic and thermodynamic preference and the nature of the metallic precursor. Thus Cu(II), Ni(II) and Zn(II) bind within the macrocyclic cavity, whereas Fe(II) and Ru(II) bind to three bipyridyl units from three ligand molecules. Fluorescence quenching of the $\{Ru(bipy)_3\}^{2+}$ core in $[Ru(bipy)_2$**156**$]^{2+}$ occurs upon coordination of Cu(II) within the macrocyclic cavity [193].

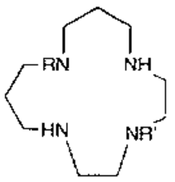
The cyclam analogue of **127** has been synthesised and found to bind to Cu(II) via the four nitrogen atoms of the macrocycle with, in addition, two long $Cu–N_{quinoline}$ interactions of 2.800 and 2.686 Å. The quinoline moieties are in a *trans*-relationship to each other, which forces the six-membered chelate ring to which they are attached into a skew-boat conformation [194].

3.3.7. *o-Hydroxy-picolylation*

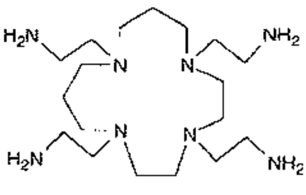
The cyclam analogue of ligand **47**, which has been designed for Th(IV) complexation, has been prepared using cyclam and 3-hydroxy-6-methylpyridine under Mannich conditions in 51% yield [158].

3.4. *1,4,7,11-Tetraazacyclotetradecane (isocyclam) derivatives*

Several mono-*N*-functionalised ligands based on this particular 14-membered ring framework (**157**–**160**) have been reviewed previously [8]. Only one tetra-*N*-functionalised ligand appears to have been produced, this being tetrakis(2-aminoethyl)isocyclam (**161**) [195]. As with **134**, two metal ions may be bound in an exocyclic fashion and these are capable of trapping a coordinated anion between them.



157 R = $CH_2CH_2NMe_2$, R' = H
158 R = CH_2CONH_2, R' = H
159 R = $CH_2CH_2CONH_2$, R' = H
160 R' = CH_2CONH_2, R = H



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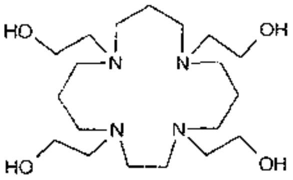
3.5. 1,4,8,12-Tetraazacyclopentadecane derivatives

Only two pendant donor derivatives of this 15-membered tetraaza macrocycle appear to have been made. These are the tetrakis(2-hydroxyethyl) derivative (**162**) [196] and the tetrakis(2-aminoethyl) derivative (**163**) [195]. No structural information is available for the former, but kinetic studies of its rate of decomplexation show that the Co(II) and Ni(II) complexes have half-lives of >24 h in 1 M HNO_3 whilst the Cu(II) complex is considerably more labile. The latter ligand has been used to study anion binding between the two metal ions that bind exocyclicly to a pair of pendant arms and to two of the macrocycle nitrogen atoms. The structure of $[Cu_2\mathbf{163}]^{4+}$ shows two square-planar Cu(II) centres with a separation of 5.048 Å. Stability constants for anion binding have been measured [185].



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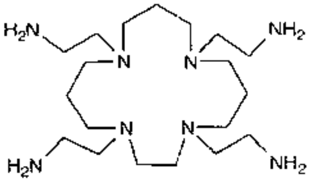

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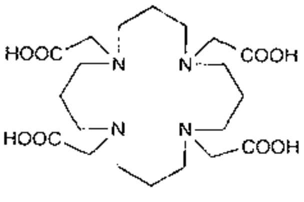
3.6. 1,5,9,13-Tetraazacyclohexadecane derivatives

Two pendant donor macrocycles derived from this 16-membered macrocycle have been synthesised. These are the tetrakis(carboxymethyl) (**164**) [197] and the tetrakis(2-aminoethyl) (**165**) derivatives [195]. Both bind two Cu(II) ions in exocyclic positions using two pendant donors and two macrocycle nitrogen atoms. With **164** each Cu(II) ion becomes five coordinate by binding solvent or an anion in the



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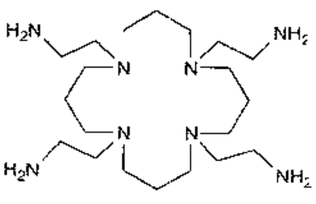

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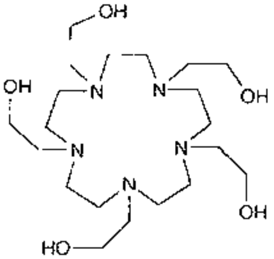
position which is remote from the second copper ion, whereas with **165** an anion is bound between the two copper ions. Stability constants for anion binding have been measured [185].

4. Pendant donor pentaaza macrocycles

Little work has been done on pentaaza macrocycles probably due to the fact that metal ions of sufficiently large size to fill the cavity tend to favour oxygen donors rather than nitrogen donors. Only the smaller 15- and 16-membered pentaaza macrocycles have been investigated and of these more work has been directed towards the smaller sized ring where exclusively five-membered chelate ring formation can be expected.

4.1. 1,4,7,10,13-Pentaazacyclopentadecane derivatives

Only two penta-*N*-substituted derivatives have been reported: the pentakis(2-hydroxyethyl) (**166**) [198] and pentakis(carboxymethyl) (**167**) [199].



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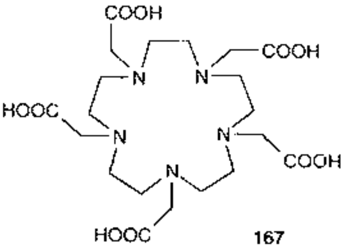

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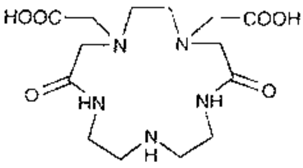
Both are made in the conventional way for these classes of pendant donor macrocycle. No complexes of **166** have been reported, but the stability constants for complexation of **167** with lanthanide(III) ions have been measured showing that 1:1 metal/ligand complexes are formed, which are of comparable stability to those formed from corresponding tetraaza ligands [199].

Three different 15-membered macrocyclic diamides with pendant carboxymethyl groups (**168**–**170**) have been prepared by starting from the anhydride of EDTA [200] or dianhydride of DTPA (diethylentriamine pentaacetic acid) [201] and condensing it with diethylenetriamine or ethylenediamine, respectively. Carboxymethylation of **168** using t-butyl bromoacetate followed by hydrolysis with



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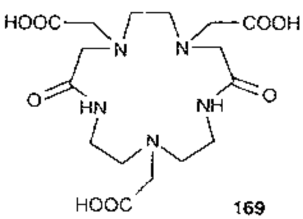

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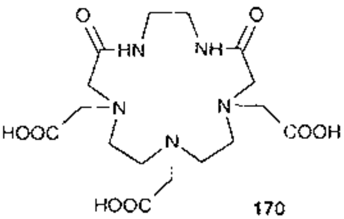

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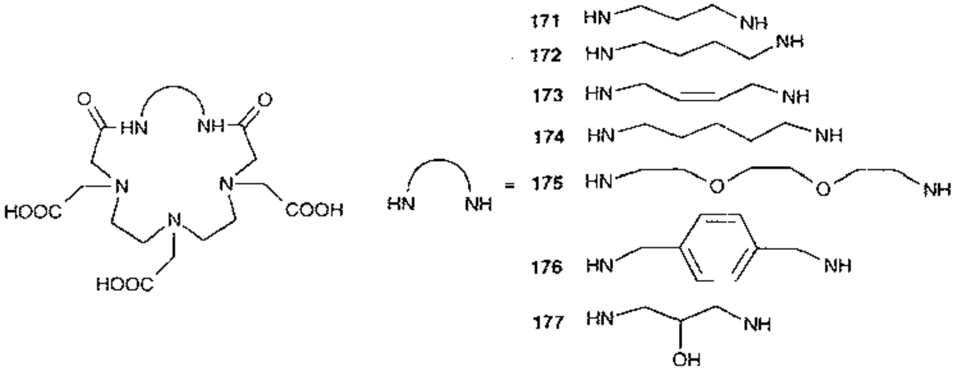
trifluoroacetic acid gives **169** [200]. Ligand **169** shows extremely good discrimination for Gd(III) over Zn(II), there being a difference of over six orders of magnitude in their binding constants. Crystal structures for the Gd(III) [201], Y(III) and La(III) [202] complexes of **170** have been solved. All three compounds are isostructural. In each case two nine coordinate metal ions are sandwiched between two ligands. Each metal ion is coordinated by one amide oxygen, two carboxylate oxygens and two amine nitrogen atoms from one ligand, an amide oxygen, a carboxylate oxygen and an amine nitrogen from a second ligand and a water oxygen atom. The coordination geometry is that of a distorted tricapped trigonal prism.

4.2. 1,4,7,10,13-Pentaazacyclohexadecane derivatives

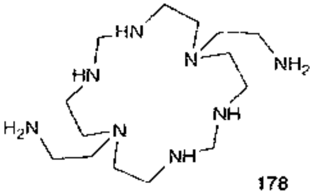
Sixteen-membered and larger variations of **170** have been prepared by condensing DTPA with larger amines than ethylenediamine giving rise to **171**–**177**. X-ray structures of the Gd(III) complexes of **171** and **177** are available [201,161] which show that Gd(III) forms nine coordinate 1:1 complexes with these ligands, in which the metal ion is coordinated by the three amines, the three carboxylates, and the two amide oxygens of the macrocycle together with a coordinated water molecule.



5. Pendant donor hexaaza macrocycles

5.1. Derivatives of 1,3,6,9,11,14-hexaazacyclohexadecane

Lanthanide(III) complexes of the 6,14-bis(2-aminoethyl) derivative of this 16-membered hexaaza macrocycle (**178**) are synthesised by lanthanide(III) ion templated reactions involving tris(2-aminoethyl)amine (tren) and bis(dimethylamino)methane [203]. Using La(CF_3SO_3)$_3$ as the source of the template the isolated La(III) complex is ten coordinate, being coordinated by the eight nitrogens of the macrocycle and two triflate ions. The corresponding ytterbium(III) complex is nine coordinate having only a single bound triflate ion. Recently it has been shown that both pendant amines on **178** can be condensed with salicylaldehyde to form **179** when the metal ion is La(III), but not when it is Gd(III) [204]. This observation forms the basis for a method of separating La from Gd.



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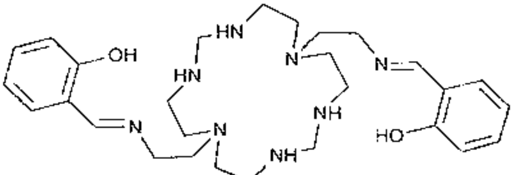

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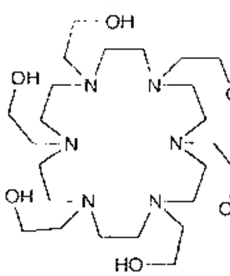
5.2. *Derivatives of 1,4,7,10,13,16-hexaazacyclooctadecane*

As is the case with pentaaza macrocycles, the only two hexa-*N*-substituted derivatives of the 18-membered hexaaza macrocycle 1,4,7,10,13,16-hexaazacyclooctadecane are the hexakis(2-hydroxyethyl) (**180**) [198] and the hexakis(carboxymethyl) (**181**) [199] derivatives. No structural information is available for either of these ligands or their complexes, but it has been noted that **181** forms complexes with the lanthanide(III) ions which are more stable than the corresponding DTPA complexes [199].



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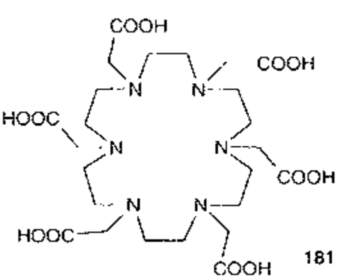

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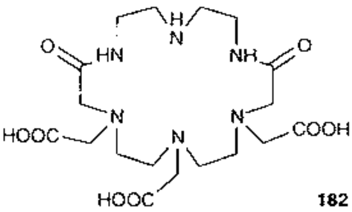
The 1,7,13-tris(methanesulfonate) of 1,4,7,10,13,16-hexaazacyclooctadecane has been prepared [12] and could presumably be used as a precursor to the corresponding phosphinic, phosphonic and carboxylic acids, although this has not yet been reported.



182

An 18-membered macrocyclic diamide (**182**) has been synthesised from the reaction of DTPA with diethylenetriamine [205]. The La(III) complex of protonated (at the secondary amine) **182** crystallises as a dimer, as shown in Fig. 14, in which each La(III) ion is eleven coordinate, being chelated by three amines, two amide oxygen atoms and the three carboxylate oxygens of its own ligand, plus asymmetric bidentate chelation from one carboxylate moiety of a second ligand and a coordinated water molecule. In the solid state the Eu(III) complex of protonated **182**

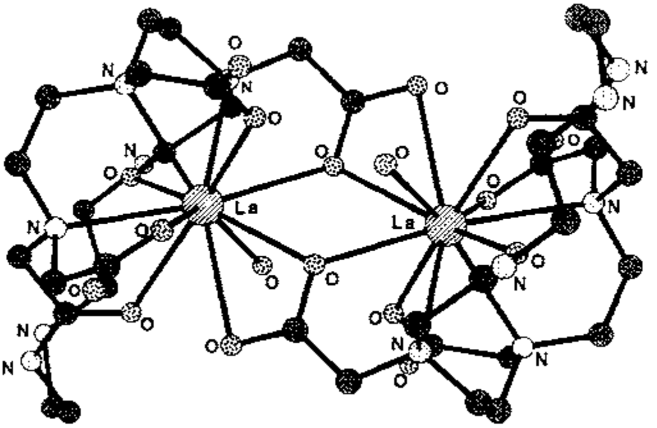


Fig. 14. Structure of the $[\mathrm{La}(18\text{–}2\mathrm{H})(\mathrm{H_2O})]_2^{2+}$ dimer showing eleven coordinate La(III) ions.

crystallises as a tetramer in which each Eu(III) ion is nine coordinate and has the geometry of a tricapped trigonal prism. The coordination is via the eight donor atoms of the principal ligand (the secondary amine is presumed to be protonated) plus a bridging carboxylate from a second ligand. Luminescence lifetime studies and vapour phase osmometry suggest that in solution the complex is monomeric with one coordinated water molecule.

Acknowledgements

It is a pleasure to acknowledge the individual contributions made by my students and academic colleagues to this area of chemistry. Their names are recorded in the collection of references. We are grateful to the Australian Research Council and to The Flinders University of South Australia for supporting our work financially, and to Dr Ian Atkinson, of James Cook University of North Queensland, for preparing the figures used in this review.

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