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COMPLEXES OF POLYAZA MACROCYCLES BEARING PENDENT COORDINATING GROUPS

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CONTENTS

A. Introduction 297
B. Substituted triaza macrocycles 298
C. Substituted tetraaza macrocycles 305
D. Substituted pentaaza macrocycles 321
E. Strapped (cage) macrocycles 323
F. Dimeric macrocycles 333
G. Conclusions 339
Acknowledgements 339
References 340

A. INTRODUCTION

The vast family of macrocyclic ligands and their complexes has been established as an integral part of the general field of coordination chemistry [1–4]. Although very little work had been reported with macrocyclic ligands until approximately 30 years ago, the growth in this field has been such that it is now treated as a field separate from traditional acyclic ligand coordination chemistry. The preference for macrocycles over simple unidentate or bidentate ligands, in certain cases, has arisen from the greater stability and inertness of their complexes as well as the often extreme physical properties that are a result of their strong ligand field, especially in the case of the aza macrocycles. This review will be confined to macrocycles where the ring donor atoms are exclusively nitrogen.

Historically, the tetraaza macrocycles were the first of the aza macrocycles to appear, followed by the triaza and, more recently, the pentaaza macrocycles. Although these ligands have been shown to be capable of producing generally strong ligand fields, their inherent disadvantage is that they cannot completely "wrap up" the majority of transition metal ions, most having preferentially coordination numbers of at least six. The solution to this can

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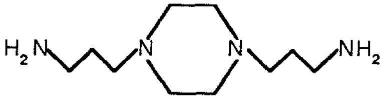
be either to increase the ring size and the number of donor atoms, which has been done, or to append coordinating groups to the periphery of the macrocycle, which themselves may coordinate and thus increase the ligating ability of the macrocycle. The advantage of the latter method is that the numbers of geometric isomers formed when these ligands are coordinated are generally diminished when compared with their unbranched, monocyclic relatives.

Small ring azacycles with pendent arms have been commercially available for some time. For example, the ligands **1** and **2** are both efficient N-donors in contrast with their 1,4-diazacyclohexane parent. The enhancement of binding capacity by introducing pendent ligating groups may be extended to large ring systems. These pendent-arm polyaza macrocycles have become quite common in the field of macrocyclic chemistry and are the subject of this review.



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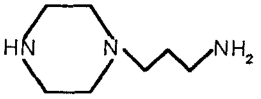

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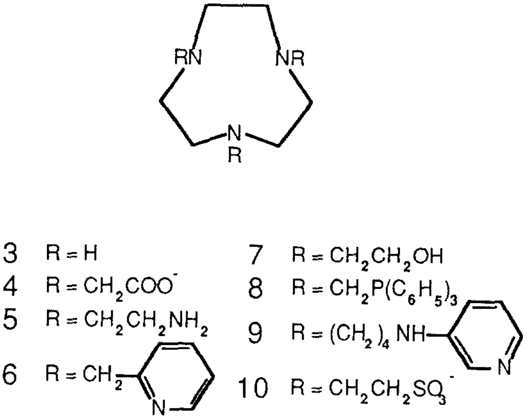
B. SUBSTITUTED TRIAZA MACROCYCLES

The coordination chemistry of the tridentate macrocycle 1,4,7-triazacyclononane, **3**, has been exhaustively studied and reviewed [7], with complexes of most *d*-block elements being reported. The macrocycle generally exhibits a particularly strong ligand field when coordinated as a tridentate ligand, necessarily in a facial manner. An extension of this work has been to introduce one, two or three additional potentially coordinating groups at the nitrogen atoms. The result of this is that the ligand may then act as a quadridentate, quinquedentate or sexidentate ligand, depending on the number of attached pendent arms and, of course, the preferred coordination of the metal ion.



3 R = H

4 R = CH_2COO^-

5 R = $CH_2CH_2NH_2$

6 R = CH_2–

7 R = CH_2CH_2OH

8 R = $CH_2P(C_6H_5)_3$

9 R = $(CH_2)_4$ NH–

10 R = $CH_2CH_2SO_3^-$

Direct alkylation of the amine nitrogen atoms is generally the method employed for synthesis of trisubstituted sexidentate ligands based on **3**. An example of this is the triacetato* derivative, **4**, synthesized by reaction of **3** with bromoacetic acid in aqueous base. The versatility of this mixed-donor ligand was demonstrated by the synthesis of mononuclear complexes of **4** with each of the first-row transition metals except titanium [8]. The ligand generally acts as a sexidentate ligand, the exception being VO (**4**) where the oxo group precludes coordination of one acetate pendent group. The remainder of the complexes, while six coordinate, are by no means isostructural. An X-ray crystal structure has shown that the chromium(III) complex of **4** is essentially octahedrally coordinated (Fig. 1) with only a small trigonal distortion (49°; cf. 60° for perfect octahedral and 0° for trigonal prismatic geometries). The high spin iron(III) complex displays a considerable trigonal twist (25°). The copper(II) complex anion of **4** is structurally similar to its iron(III) analogue, although counter-ions alter the structure somewhat. Stability constants of complexes containing **4** have been determined by several groups [9–12]. Apart from transition metal ions, the ligand has been shown to form also stable complexes with alkaline earths as well as with

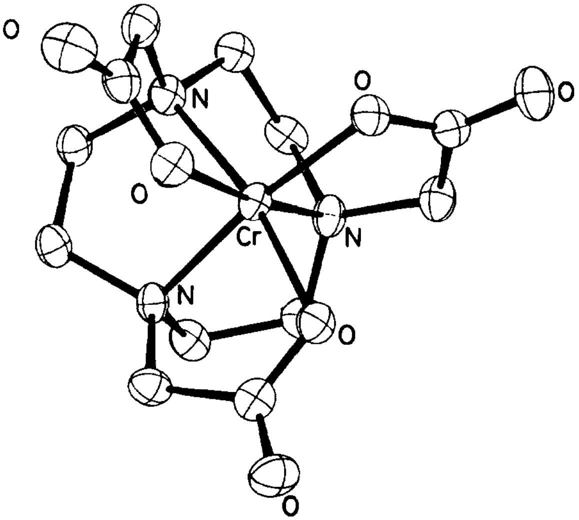


Fig. 1. Drawing of the chromium(III) complex of **4**. The Cr–N distances vary betwen 2.045 and 2.072 Å, whereas Cr–O distances lie between 1.950 and 1.964 Å, each set occupying octahedral faces. The molecule displays a small trigonal distortion (49°), with N–Cr–N angles all below 90° (85.1–85.8°) and all O–Cr–O angles above (96.0–96.2°). (Reprinted with permission from ref. 8. Copyright 1982, American Chemical Society.)

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*The pendent $-CH_2COOH$ (carboxymethyl) group is often referred to as an acetato substituent. This convention is also adopted here.

TABLE 1

Comparative stability constants (log K) of parent and tris(acetato) triazacyclononane macrocycles[a]

Ligand	Mg(II)	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Pb(II)	Ref.
3 (K_1)		5.8	13.4	16.2	15.4	11.3	9.5	10.3	9
(K_2)		3.6	10.5		12.0	9.2	8.4	5.1	
4	8.9	14.3	17.5	28.3	19.8	18.3	16.0	16.6	10–12

[a] Successive stability constants for addition of two triazacyclononane molecules are given; a comparison of log K of **4** and (log K_1 + log K_2) of **3** is the most valid comparison in most cases.

some lanthanide elements. A comparison of stability constants of complexes formed with **3** and **4** is given in Table 1.

Whereas the parent ligand **3** is a strong-field ligand, the N_3O_3 donor set of **4** does not impose a particularly strong ligand field. Although bis(**3**) complexes of iron(II) and iron(III) are low spin [13], the corresponding complexes with **4** are high spin [8]. The synthesis of sexidentate ligands with the **3** core containing 2-aminoethyl, **5** [14], and 2-pyridylmethyl, **6** [15], pendent groups produces ligands with ligand fields approaching those of bis(**3**) complexes. Several complexes containing **6** as a sexidentate ligand have been characterized (Table 2). Most complexes of **6** are octahedral or

TABLE 2

Comparison of physical properties of complexes containing sexidentate ligands based on triazacyclononane

Ligand	Metal ion	Electronic maxima (nm)	Magnetic moment (B.M.)	M–N distance (Å)	E^0 (V vs. SHE)	Ref.
4	Cr(III)	512, 388	3.6	2.053	−1.17	8
	Fe(II)		5.6		+0.20	8
	Fe(III)	257	5.7	2.181		8
	Co(III)	511, 372	Diamagnetic		0.00	8
	Ni(II)	924, 805, 557, 355	2.8	2.04	+1.16	8,12
	Cu(II)	750	1.6	2.117		8
6	Cr(III)	475, 373, 310	3.9		−1.32	15
	Fe(II)	432	0.26	1.979, 2.009	+0.91	20
	Fe(III)	439, 357	2.7			15
	Co(III)	474, 343	Diamagnetic		+0.24	15
	Ni(II)	886, 810, 515	3.17	2.054, 2.109	+1.57	15
	Cu(II)	695	2.2			15

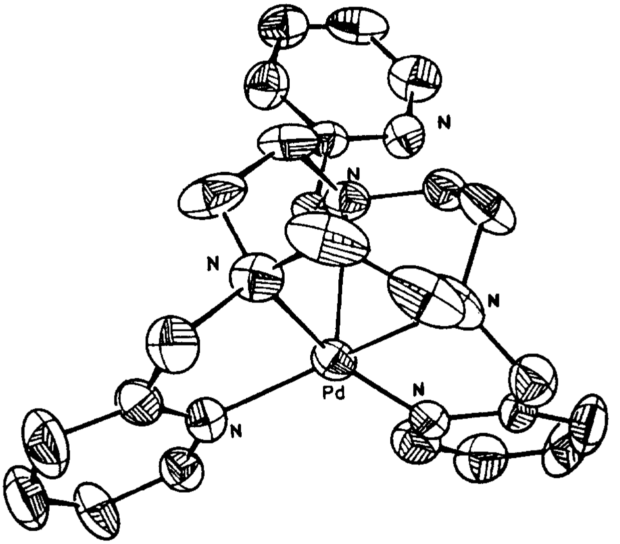
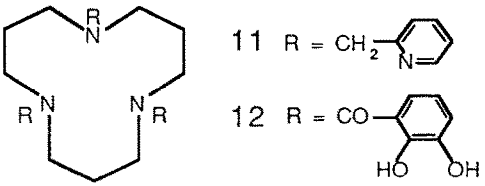
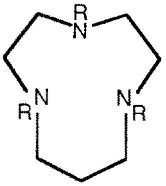


Fig. 2. Drawing of the Pd(II) complex of **6**, which adopts a distorted square-based pyramidal geometry; two pyridine nitrogen atoms (Pd–N 2.040, 2.048 Å) and two tertiary nitrogen atoms (Pd–N 2.010, 2.041 Å) are in the distorted square plane, with the third tertiary nitrogen in an elongated axial site (Pd–N 2.580 Å). Apical N–Pd–N angles vary between 77.9° and 112.4°, indicative of the distortions involved. The third pyridyl group is not coordinated. (Reprinted with permission from ref. 15. Copyright 1986, American Chemical Society.)

distorted octahedral. An interesting exception is provided by the palladium(II) complex of **6** which has been shown to possess a square-pyramidal geometry with one pyridyl group remaining uncoordinated (Fig. 2). There exist several other trisubstituted ligands based on **3** containing 2-hydroxyethyl, **7** [16], diphenylphosphinylmethyl, **8** [17], *N*-(3′-pyridyl)butylamine, **9** [18], and ethanesulphonate, **10** [19], to name but a few, but their properties as ligands have not been as comprehensively studied as those discussed above.

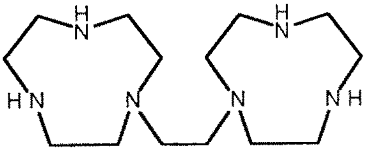
A variation on trisubstituted ligands with the nine-membered ring framework of **3** has been an extension of the ring size to produce ligands such as **11**, **12** and **13** [20–22]. The effect of this ring expansion on the electronic properties of metal complexes can be quite dramatic, as seen in the comparative properties of the iron(II) complexes of **6** and **11**, for example. The nine-membered ring in **6** results in a ligand field sufficiently strong to enforce spin pairing, and a diamagnetic complex results [15]. The larger ring of **11** results in an extension of the Fe–N bond lengths, i.e. a weaker ligand field, and a high spin complex is formed [20]. The ligand **12** was prepared to bind specifically iron(III). Significantly, the ring of tertiary nitrogen atoms plays no direct part in binding but instead acts as a template in holding the catechol pendent groups in the appropriate conformation for binding with its O-donors [21]. The carbonyl oxygen is also thought to play a role in binding.





13 R = CH_2COO^-

Synthetic routes towards monosubstituted and disubstituted ligands based on **3** are somewhat more complicated, with several steps involving protection and deprotection often being required to avoid trisubstituted ligands. An example is the synthesis of the sexidentate polyamine 1,2-bis(1,4,7-triaza-1-cyclononyl)ethane, **14**. The starting material comprises **3** which must be ditosylated prior to reaction with 1,2-bis(*p*-tolylsulphonato)ethane to avoid polymerization as well as cross-linking of the two macrocycles. Deprotection of the nitrogen atoms completes the synthesis.



14

Several mononuclear and binuclear complexes of **14** have been prepared [23]. The properties of the mononuclear complexes of **14** parallel in some ways those of the bis(**3**) analogues, with the former exhibiting a slightly weaker ligand field, presumably as a result of the two tertiary bridgehead nitrogen atoms. There exist some significant differences, however, between properties of bis(**3**) and **14** complexes. An example is the comparison of the structure of $Fe(\mathbf{3})_2^{3+}$, which is essentially trigonal prismatic (5°) [24], with that of $Fe(\mathbf{14})^{3+}$ which is trigonally distorted octahedral (36° trigonal twist) [25]. The ligand **14** may also coordinate to octahedral faces of separate metal ions and the magnetic and electronic properties of these binuclear complexes have been well studied [7]. The propane-linked analogue of **14** has also been made [23].

The bis(2-aminoethyl) relative of **5**, molecule **15**, is formed as a byproduct in the synthesis of **5**. The synthesis of the cobalt(III) complex of this quinquedentate ligand has been reported as well as the base hydrolysis kinetics of the chloro ligand which occupies the sixth site in the coordination sphere [26]. A facile synthesis of the monosubstituted ligand **16** has been reported by reaction of **3** (in excess) with chloroacetic acid [27]. The structures of two distinctly different copper(II) complexes of **16** have been reported [28], both isolated from the same reaction but at different pH. One structure consists of a polymeric arrangement of five-coordinate, square-pyramidal copper(II) centres, the coordination sphere comprising the three nitrogen donors on the macrocycle, the pendent carboxylate and a bridging carboxylate from an adjacent complex. The other complex, isolated from basic solution, shows the four ligand donor groups coordinating in four sites of a distorted square-pyramid with the fifth site being a bridging hydroxo group between the two metal centres (Fig. 3). The Cu–Cu internuclear separation is only 3.17 Å; however, no data are reported for the complex with respect to magnetic coupling, which one would expect to be strong.

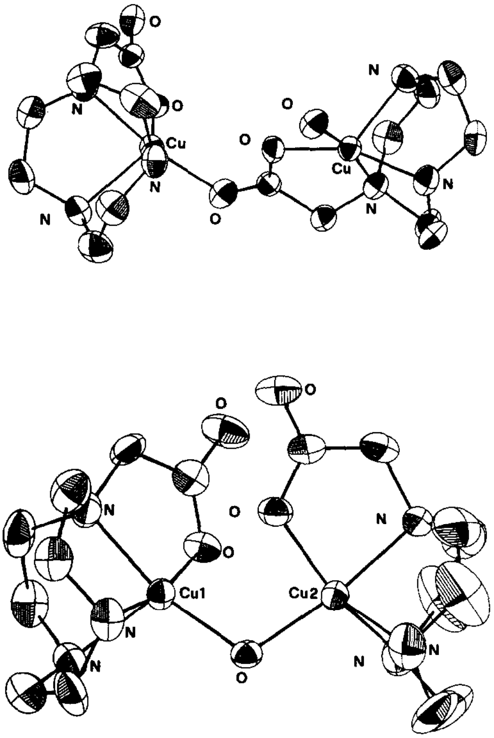
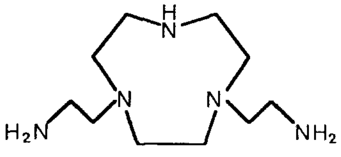


Fig. 3. Two non-equivalent Cu(II) complexes of **16**. The top complex has each copper in a distorted pyramidal geometry of three nitrogen and two oxygen donors, with a carboxylate pendent group bridging two copper ions. The Cu–N distances (2.063, 2.027, 2.195 Å) and Cu–O distances (1.952, 1.982 Å) identify the distortion. The lower structure, with two non-equivalent copper centres bridged by an hydroxide ion are also CuN_3O_2 environments, with variable Cu–N distances (range 2.015–2.200 Å) and Cu–O distances (range 1.930–2.016 Å). (Reprinted with permission from ref. 28. Copyright 1989, Schweizerische Chemische Gesellschaft.)



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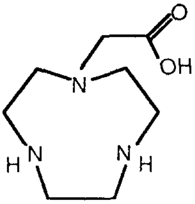
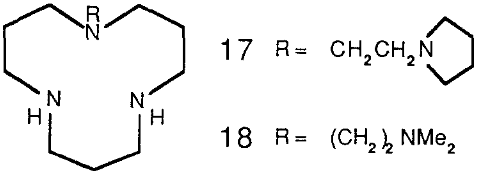
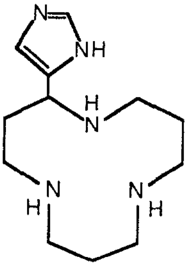


16

The ethylpyrrolidinyl- and dimethylpropylamine-substituted macrocycles, **17** and **18**, have been made. Variable coordination to zinc(II) is apparent, with the structure of Zn(**17**)($OClO_3$)$^+$ revealing a trigonal bipyramidal coordination sphere. The corresponding zinc(II) complex of **18**, in contrast, is tetrahedrally coordinated [29].



Whereas all the above complexes have contained N-functionalized triaza macrocycles, reports of C-substituted triaza macrocycles have been exceptionally sparse. One example is the 12-membered macrocycle **19**, synthesized by condensation of the N-protected, imidazole-substituted acrylate **20** with 4-azaheptane-1,7-diamine. Reduction of the amide and removal of the trityl protecting group produce the desired product [30]. No reports have appeared at this stage, however, of complexes of this ligand. Clearly, the area of C-substituted triaza macrocycles invites study, although the synthetic challenges are greater than those posed by N-substituted macrocycles.



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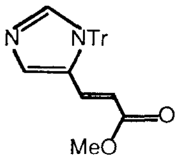

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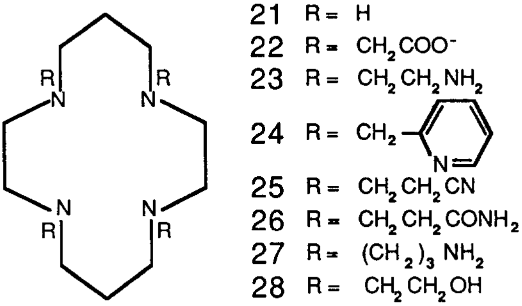
C. SUBSTITUTED TETRAAZA MACROCYCLES

This class of macrocycle has received most attention with respect to attaching pendent coordinating groups. The syntheses and complexes of N-functionalized tetraaza macrocycles have been studied in much greater depth than those of their C-functionalized analogues. The reason for this bias has probably stemmed from the relative simplicity of the syntheses of N-substituted macrocycles. The organic chemistry and synthetic strategies of N-alkylations are well understood, and moreover, the reactions are quite general in applicability. However, there are inherent disadvantages involved in the functionalizing of N-donors. One is the conversion of a secondary amine to a tertiary amine, a poorer donor for steric reasons. Another disadvantage is the possibly unwanted inductive effect of the pendent group on the relatively close metal centre. Both these drawbacks are avoided by the synthesis of C-functionalized macrocycles, and in recent years syntheses and complexation of ligands of this type have received growing attention. Each type will be discussed in turn.

(i) N-functionalized macrocycles

There have been few, if any, macrocycles that have been studied more than 1,4,8,11-tetraazacyclotetradecane, **21**, commonly referred to as cyclam. Since the first reports of complexes of **21** some 25 years ago [31], complexes of most transition metals with this ligand have appeared [32–37]. The evolution of this work has been to functionalize **21** to produce ligands which, in some cases, may occupy as many as eight coordination sites, not necessarily on the same metal ion.



21 R = H
22 R = CH_2COO^-
23 R = $CH_2CH_2NH_2$
24 R = CH_2–
25 R = CH_2CH_2CN
26 R = $CH_2CH_2CONH_2$
27 R = $(CH_2)_3NH_2$
28 R = CH_2CH_2OH

A particularly well-studied N-functionalized cyclam is the tetraacetato macrocycle **22**, synthesized by reaction of **21** with excess chloroacetic acid and base [38]. The ligand is interesting in so much as insertion of a metal ion into the tetraaza cavity is generally not straightforward. Most complexes formed with **22** have been shown to contain the metal outside the macrocyclic cavity and bound to the pendent acetato groups [39–41]. This was found in the crystal structure of the binuclear copper(II) complex of **22** [42]. The metal ions are chelated by two carboxylate groups and their neighbouring tertiary amines, with an alternating water molecule or carboxylate, from an adjacent molecule, completing the coordination sphere, which is square pyramidal. Despite this, the copper(II) centre may enter the macrocyclic ring if special conditions are employed in the synthesis. The crystal structure of the mononuclear copper(II) complex of **22**, where the copper is indeed contained in the macrocyclic cavity, has been reported [43]. Two pendent acetato groups coordinate in the axial sites of the coordination sphere to complete the structure of the tetragonally distorted octahedral complex anion (Fig. 4). Another report of a complex of **22** where the metal ion is contained in the macrocyclic cavity relies on characterization in solution [44]. Application of a constant potential of + 1.2 V to a solution of the nickel(II) complex of **22**, where the metal ion is outside the macrocyclic cavity, results in oxidation to the nickel(III) complex, upon which the metal enters the cavity. The resultant nickel(III) tetraamine gives an electron paramagnetic resonance (EPR) spectrum similar to that of Ni(**21**)$^{3+}$. Reduction to the nickel(II) complex generates a complex with an electronic spectrum typical of a high spin $Ni^{II}N_4O_2$ chromophore. Significantly, the macrocyclic complex is exceptionally stable, more than its "metal-out"

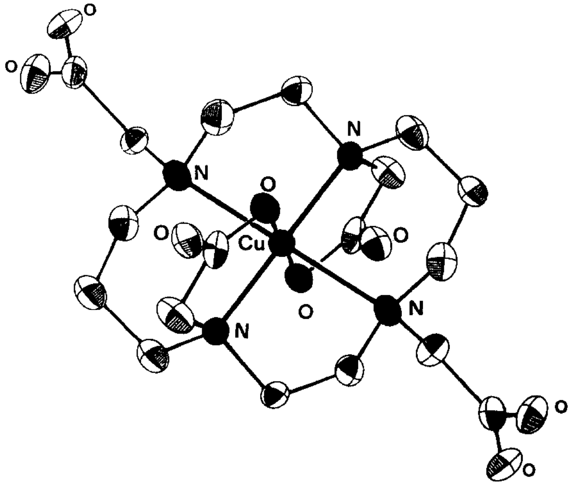


Fig. 4. View of the Cu(II) complex of **22**, with the copper lying in the plane of the four nitrogen donors (Cu–N 2.023, 2.041 Å for tertiary nitrogen atoms which form part of the amino acid chelates; other Cu–N 2.184, 2.153 Å), with two axial carboxylate oxygen atoms (2.278, 2.302 Å) completing the tetragonally distorted octahedron. (Reprinted with permission from ref. 43. Copyright 1988, International Union of Crystallographers.)

analogue. The large kinetic barrier that is overcome by oxidation of the nickel(II) is apparently a result of the contracted coordination sphere, nickel(III) being more able to enter the macrocyclic cavity. The same method does not appear to have been successful for the insertion of copper(II) or cobalt(II) into the macrocycle; nor is it appropriate for zinc(II).

Reaction of **21** with *N*-tosylaziridine followed by deprotection yields the tetrakis(2-aminoethyl) derivative, **23**. This interesting ligand forms several binuclear complexes, the di-nickel(II), -copper(II), -cobalt(II) and -chromium(II) complexes having been reported [45,46]. The remarkable feature of this ligand is its preference for forming binuclear four- and five-coordinate complexes over mononuclear octahedral complexes. This can be understood when one compares the behaviour of **22** with that of **23** where the former has already been shown to form metal-out complexes preferentially. The same behaviour has been shown in the crystal structures of the binuclear complexes of **23**, where the metals do not enter the macrocyclic ring but remain outside, chelated by the pendent aminoethyl groups to the secondary amino groups of the macrocycle. The end result is that stable chromium(II) and cobalt(II) complexes are formed as tetraamines because steric constraints prevent formation of their octahedral chromium(III) and cobalt(III) oxidation products. The dinickel(II) complex of **23** results in a mixed high spin/low spin binuclear complex where one metal is coordinated in a square-planar

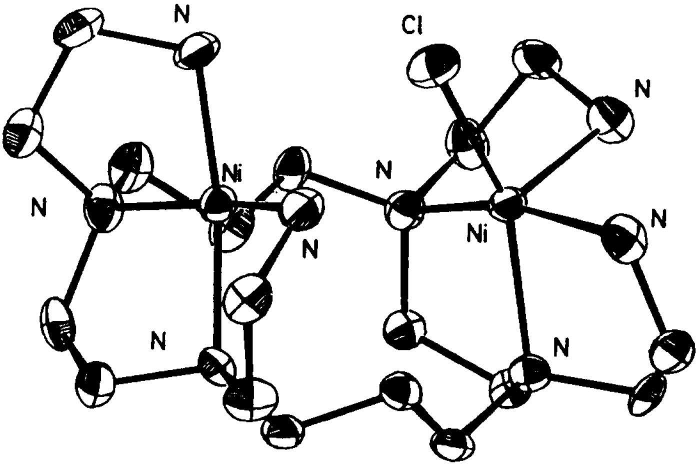


Fig. 5. Drawing of the dinickel(II) complex of **23**, where the ligand binds two metal ions in different geometries. The left-hand metal ion is in a reasonable square planar environment (Ni–N 1.903–1.931 Å, N–Ni–N angles from 85.1° to 90.3°) which includes two macrocyclic nitrogen donors and two pendent primary amines. The right-hand metal ion adopts a square-based pyramidal geometry with four N and a Cl donor, the latter in the apical site (Ni–Cl 2.289 Å) with the nickel above the approximate plane of the four N (Cl–Ni–N angles range from 91.7° to 151.1°) with Ni–N from 2.014° to 2.183 Å. (Reprinted with permission from ref. 47. Copyright 1987, The Royal Society of Chemistry.)

manner and the other has a square-pyramidal geometry, with a chloro ligand occupying the fifth site (Fig. 5) [47]. The coordinating anion plays an important role; when acting as a bridging ligand, the geometry may replicate that found for chromium(II) and cobalt(II).

A less-studied but quite similar ligand to **23** is tetrakis(2-pyridylmethyl) cyclam, **24**, which also forms a binuclear copper(II) complex [48]. In contrast with **23**, a mononuclear ruthenium(II) complex of **24** has been reported, although the crystal structure reveals that the metal ion is coordinated by only three of the four macrocycle tertiary amine groups, with three of the four pyridyl moieties completing the coordination sphere (Fig. 6) [49]. A strong preference for imine nitrogen donors in ruthenium chemistry may mediate the outcome here.

The reactivity of pendent groups on cyclam-based complexes has also received attention. The synthesis, in high yield, of the tetracyanoethyl analogue, **25**, by refluxing **21** and acrylonitrile [50] has provided a versatile starting material which may be hydrolysed to the tetraamide, **26**, but not to the tetracarboxylic acid. Reduction of **25** with sodium in ethanol yields the aminopropyl analogue of **23**, compound **27**, which (in contrast with **23**) appears to form 1:1 metal:ligand complexes quite readily [51]. Several high and low spin nickel(II) complexes have been reported along with the synthesis of **27**, although it is not certain whether the metal ion is in or out

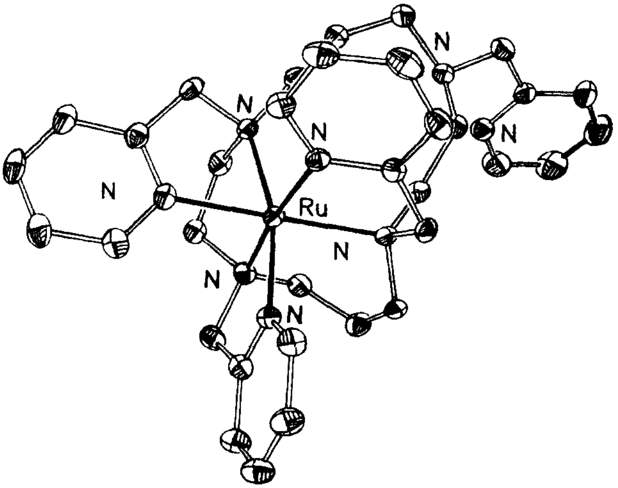
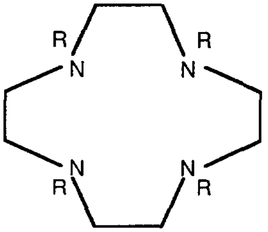


Fig. 6. A view of the Ru(II) complex of **24**, which binds the metal ion with three pyridine molecules and three tertiary nitrogen atoms, leaving the fourth unit dangling. Each type of donors occupy octahedral faces, with Ru–N(pyridyl) distances (2.058–2.093 Å) significantly shorter (on average 0.11 Å shorter) than Ru–N(tertiary) distances (2.105–2.264 Å). The octahedron is consequently distorted with N–Ru–N ranging from 78.2° to 104.4°. (Reprinted with permission from ref. 49. Copyright 1988, The Royal Society of Chemistry.)

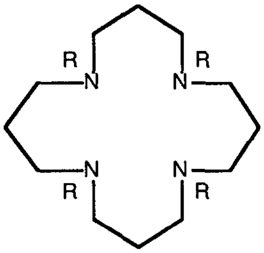
of the macrocycle. The role of these pendent groups in the inversion of coordinated macrocycle nitrogen donors has been discussed [52]. It is proposed that the pendent amide groups catalyse N-based isomerization of the nickel(II) complex of **26** by displacing the nitrogen from the metal which then inverts and recoordinates. Similar intermolecular processes have been reported for N-based isomerizations where coordinating solvents were thought to be involved in displacement of coordinated nitrogen atoms [53]. The 2-hydroxyethyl derivative **28** has been shown to be a rapid complexing agent of several heavy metals [40]. A variable-temperature multinuclear NMR analysis of several complexes of **28** led to the conclusion that the pendent hydroxy groups chelate the metal prior to it entering the macrocylcic ring [54].



29 R = H

30 R = CH_2CH_2OH

31 R = CH_2COO^-



32 R = CH_2COO^-

Other tetraaza macrocycles have been functionalized similarly to the above compounds. Some tetra-N-substituted derivatives of the smaller macrocycle 1,4,7,10-tetraazacyclododecane, **29**, have been reported. Reaction of **29** with ethylene oxide in water produces the tetrakis(2-hydroxyethyl)-substituted macrocycle, **30** [55]. The crystal structure of each of the Li^+, Na^+ and K^+ complexes of **30** as well as the monohydrate of the ligand are reported. The tetraacetato-substituted macrocycle **31** has been studied and its complexes may be compared with those of the 14-membered ring analogue. Like **22**, the smaller macrocycle **31** forms both binuclear [42] and mononuclear [56] complexes with copper(II). The structure of the monomeric copper(II) complex of **31** is significantly different from that of the **22** complex. The copper ion, although coordinated to all four nitrogen atoms, does not lie in the plane of the macrocycle **31** but instead the macrocycle folds and two pendent acetato groups coordinate in cis positions to complete the metal ion environment (Fig. 7). By contrast, the copper(II) complex of **22** has a structure with the metal ion encircled by the nitrogen atoms and the pendent acetato groups coordinated in trans positions [43]. The nickel (II) complex of **31** is isostructural with the copper(II) compound [56]. The

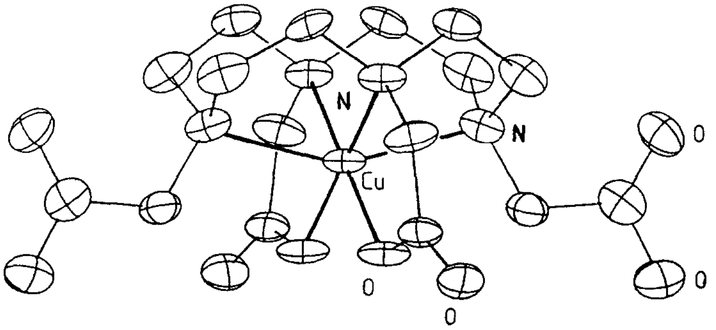
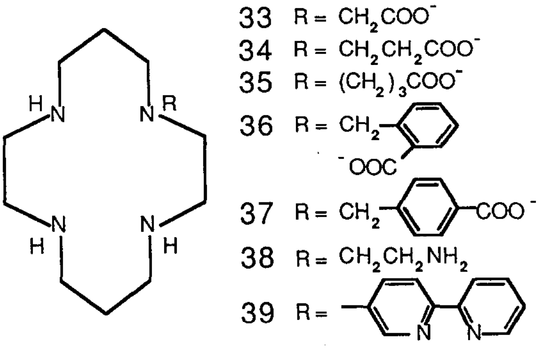


Fig. 7. Drawing of the Cu(II) complex of **31**, with the copper ion in a distorted cis octahedron of four nitrogen (Cu–N 2.107, 2.318 Å) and two oxygen (Cu–O 1.965 Å) donors. The cis macrocycle is significantly folded back (trans N–Cu–N angle of 152.6°), as seen in the figure, whereas the two N and two O donors in the centre of the figure are coplanar with the Cu. (Reprinted with permission from ref. 56. Copyright 1986, Schweizerische Chemische Gesellschaft.)

complexation of lanthanide elements by **31** has been pursued and the crystal structure of the europium(III) complex of **31** has been determined [57]. As in the structure of the copper(II) complex, the ligand folds, with the metal lying above the plane of the four nitrogen atoms. The four acetato groups coordinate and a single water molecule occupies the apical position to complete a capped square antiprismatic geometry. The tetraacetato derivative of the 16-membered macrocycle 1,5,9,13-tetraazacyclohexadecane, **32**, has been synthesized, although only tentative assignments of the structures of its copper(II) complexes have been made [42].

Synthetic routes towards incompletely alkylated tetraaza macrocycles are more complicated than those towards their tetra-substituted relatives, where an excess of alkylating agent may generally be used. The reverse strategy of using excess macrocycle in the presence of alkylating agent has proved to be a relatively efficient method of monoalkylation of tetraaza macrocycles. The single-step synthesis has obvious advantages over multistep protections and deprotections otherwise required. The only disadvantage of this synthesis is the amount of parent macrocycle remaining unreacted; however, selective extraction has been reported to be a satisfactory method for recovering most of the unreacted precursor. This method has been employed in the synthesis of monosubstituted cyclam species containing acetato (**33**), propionato (**34**), butyrato (**35**), *o*- and *p*-methylbenzoato (**36** and **37**) pendent groups, whose copper(II) and nickel(II) complexes are also described [27]. The monosubstituted analogue of **23**, compound **38**, has been synthesized by reaction of tritosylcyclam with *N*-tosylaziridine, followed by deprotection of the nitrogen atoms [58]. The nickel(II) complex of **38** displays a pH-dependent colour change from blue (high spin, pendent coordinated) to yellow (low spin, pendent protonated). From the active role of the pendent "tail" of the ligand, the general name "scorpiand" has been suggested for monosubstituted tetraaza macrocycles of the type described. The attachment of a 2,2′-bipyridyl fragment to the macrocyclic ring produces an interesting ligand, **39**, capable of chelating another metal ion in addition to the one bound in the macrocycle cavity [59]. This has been achieved with a binuclear complex comprising linked Ru(bipy)$_2$(bipy-cyclam)$^{2+}$ and Ni(cyclam-bipy)$^{2+}$ units which has potential in photocatalysis.



It has been shown that the trimethylated species **40** may be prepared in good yield as the nickel(II) complex from reaction of the dimethyl analogue with iodomethane and base [60]. There remains only one reactive nitrogen in **40**, and this may be used to produce a number of derivatives of cyclam with all tertiary nitrogen donors but with a single coordinating pendent group. The crystal structures of the ethyl propionate (**41**) and diethyl ethylphosphonate (**42**) derivatives of **40**, as their copper(II) complexes, have been reported [61]. Significantly, both pendent groups coordinate in the axial sites of their coordination spheres, the four nitrogen atoms encircling the metal ion (Fig. 8). The rates of base hydrolysis of the pendent esters have been determined and the mechanisms discussed. There exists strong evidence for coordination of the phosphonate group of **42** to copper(II) in neutral solution; likewise, the ethyl propionate group in the complex of **41** appears to bind to copper(II) in solution. Polarization, and hence activation toward hydrolysis, of the pendent group is proposed to occur when groups of this type coordinate to metal ions. However, the kinetics of base hydrolysis must remain bimolecular for a mechanism of this type. At high pH, a hydroxy group preferentially coordinates in the axial site of Cu(**42**)$^{2+}$ and the kinetics become unimolecular, i.e. hydrolysis is affected by the coordinated hydroxo ligand. This change in mechanism is not observed in the kinetics of Cu(**41**)$^{2+}$ base hydrolysis, nor is there any spectroscopic evidence for the displacement of the anticipated stronger donor pendent group by hydroxide, and the kinetics remain bimolecular. The crystal structure of the C-hexa-

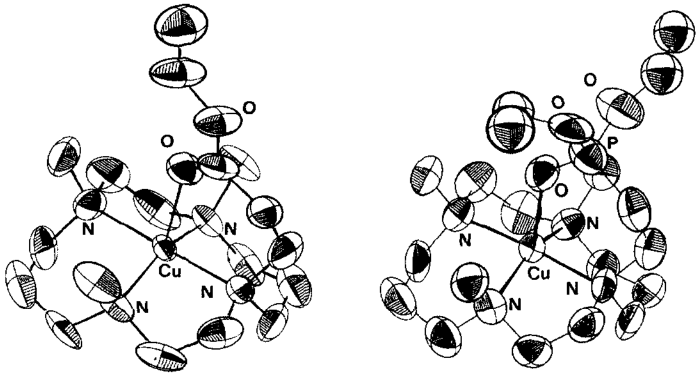
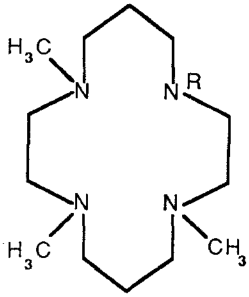


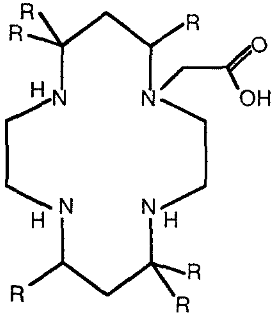
Fig. 8. Views of the Cu(II) complexes of **41** (left) and **42** (right), where the pendent O-donor occupies an axial site of square-based pyramidal geometries in each case. For **41**, Cu–N range from 2.069 to 2.084 Å, with Cu–O 2.224 Å, whereas for **42** Cu–N lie between 2.070 and 2.095 Å with Cu–O 2.161 Å. In each case the Cu lies above the best plane of the N donors, towards the O-donor (0.21 Å for **41** and 0.30 Å for **42**). (Reprinted with permission from ref. 61. Copyright 1989, Schweizerische Chemische Gesellschaft.)



40 R = H

41 R = CH_2CH_2COOEt

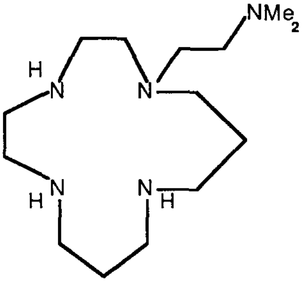
42 R = $CH_2CH_2PO(OEt)_2$



43 (R = CH_3)

methyl analogue of **33**, compound **43**, as its nickel(II) complex has been reported, where the pendent acetato group coordinates in addition to the four nitrogen atoms and thiocyanate occupies the sixth site [62].

A different approach to the synthesis of monofunctionalized tetraaza macrocycles has been to attach the pendent group to a fragment of the final macrocycle before cyclization has been performed. This has the advantage of avoiding polyalkylation, a problem inherent in direct substitutions on macrocycles. An example of this is the synthesis of the *N*,*N*-dimethylaminoethyl-substituted isocyclam, **44** [63]. Reaction of *N*,*N*-dimethylethylenediamine with acrylonitrile, followed by sodium reduction of the nitrile in ethanol, yields the polyamine **45** which is converted to its sulphonamide and coupled with the tris(methanesulphonyl) derivative of diethanolamine. Deprotection by standard methods yields the macrocycle **44**. The copper(II) and nickel(II) complexes of **44** have been reported, and a pH-dependent reversible equilibrium exists between the coordinated and uncoordinated pendent forms. The crystal structure of the high spin nickel(II) complex of **44** reveals a five-coordinate trigonal bipyramidal geometry, with all amines coordinated. The synthesis of ligands of the type **44** is quite general, and other groups such as 2-hydroxyethyl, 3-hydroxypropyl, 2-cyanoethyl and carbamoylethyl, to name a few, have been attached [64,65]. Unsaturated tetraaza macrocycles may also be prepared with pendent ligating groups. A template reaction, directed by nickel(II), of pyridine-2,6-dicarbaldehyde with the *N*-ethylpyrrolidine analogue of **45**, followed by borohydride reduction, yielded the macrocycle **46** [66]. The nickel(II) complex of **46** has been made and the pendent group may coordinate in neutral or basic solution to form a high spin complex whose crystal structure has been determined. The pendent pyrrolidinyl moiety coordinates in the axial site of the coordination sphere, the macrocycle nitrogen atoms encircle the metal and a perchlorate occupies a site trans to the pendent group (Fig. 9). The generality of these cyclizations has been demonstrated by enlarging the ring size and varying the pendent groups [67].



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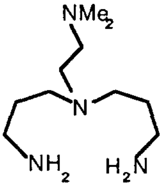

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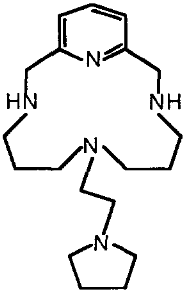


46

(ii) C-functionalized macrocycles

As with the N-functionalized macrocycles, there are several synthetic strategies that lead to C-substituted macrocycles. The two main methods are as follows: (a) incorporation of the pendent group as part of the synthesis of the macrocycle, i.e. the fragment comprises part of the macrocycle ring; (b) reaction of a pendent group with the already formed electrophilic macrocyclic ring. Method (a) may be metal directed or simply an organic condensation without a metal template. Method (b) proceeds generally with coordinated ligands.

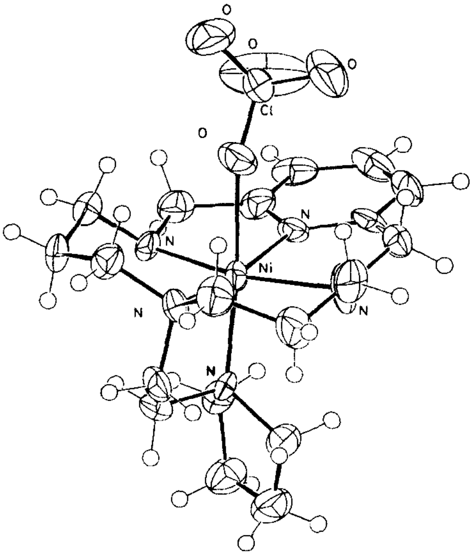
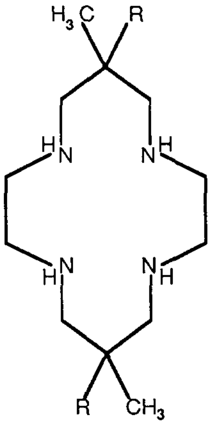


Fig. 9. The Ni(II) complex of **46**, with the pendent tertiary nitrogen donor occupying an axial site trans to ClO_4^-. The Ni–N distances vary with N-donor type, being 1.961 Å (pyridyl), 2.114, 2.134 Å (secondary), 2.034 Å (ring tertiary) and 2.159 Å (pendent tertiary). This leads to a distorted octahedral structure; for example, the N–Ni–N angle involving the two trans secondary amines is reduced to 162.4°. (Reprinted from ref. 66. Copyright 1987, The Royal Society of Chemistry.)

The development of copper(II)- and nickel(II)-directed reactions of polyamines with formaldehyde and carbon acids such as nitroethane has led to an extremely efficient and inexpensive method for the synthesis of macrocycles with pendent groups. An example of this is the reaction of bis(ethylenediamine)copper(II) with formaldehyde and nitroethane in basic methanol [68]. The dinitro macrocycle **47** is formed in good yield, and facile reduction of the nitro groups with zinc and HCl, which also achieves demetallation, allows isolation of the pendent diamino cyclam, **48** [69]. This ambidentate ligand may coordinate in four, five or six sites of metal ions, depending on the degree of protonation of the pendent groups, and so can adapt to the preferred geometries of most transition metal ions. Complexes of **48** with most of the first-row transition metals, and several second- and third-row metals, have been described [68–73]. The ligand may also fold to give a cis cyclam type structure, although both pendent groups cannot simultaneously coordinate with that geometry. A particularly attractive aspect of complexes containing **48** as a sexidentate ligand is that the ligand may coordinate in just one configuration (the secondary nitrogen atoms having the *RRSS* or *trans*-III configuration). The high symmetry (C_{2h}) of the complex ion forbids the existence of enantiomers, a rare example in sexidentate ligands.

Most significantly, all hexaamine complexes of **48** display short metal–N



47 $R = NO_2$

48 $R = NH_2$

bonds with coordination of the pendent amines forcing a bond compression not observed in complexes of its unsubstituted cyclam analogues. This bond compression is seen in crystal structures of chromium(III) [70], iron(III) [72], cobalt(III) [69], nickel(II) [73] and rhodium(III) [71] complexes where the ligand acts as a sexidentate ligand (Fig. 10). In all the above structures,

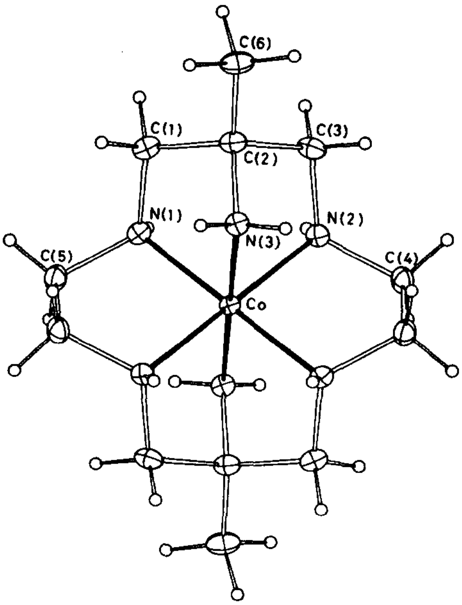


Fig. 10. View of the Co(III) complex of **48**, with the two pendent primary amines in trans dispositions. All Co–N distances are short (Co–N(1) 1.937, Co–N(2) 1.936, Co–N(3) 1.946 Å), although N–Co–N angles (85.0°–94.5°) are not markedly distorted, strain showing up in angles in the ring. The contracted coordination sphere is reflected in physical properties. (Reprinted from ref. 69. Copyright 1989, The Royal Society of Chemistry.)

the metal–N bonds are shorter than those reported for all other respective hexaamine complexes. This bond compression is also seen in the electronic spectra of these complexes, which display maxima at particularly high energy. The strong ligand field imposed by **48** has resulted in the stabilization of complexes in unusual oxidation states. In particular, the low spin iron(III) complex of **48** is stable indefinitely in aerated aqueous solution, a result of a particularly negative iron(III)/(II) redox couple. The volume of data available for sexidentate complexes of **48** has allowed its position in the spectrochemical series to be determined; equal with N-bound nitrito, it lies second to cyanide and is clearly the strongest purely σ-bonding ligand in the series. A comparison of the physical properties of sexidentate complexes of **48** with those of other hexaamines is given in Table 3.

Similar condensations around copper(II) have been performed with a range of acyclic tetraamines to produce macrocycles of various sizes with a

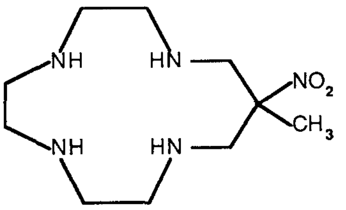
TABLE 3

Comparison of physical properties of hexaaminemetal(III) complexes

Ligand[a]	Electronic maxima (nm)	E^0 (V vs. SHE)	M–N distance (Å)	Ref.
Cobalt(III)				
48	447, 328	−0.57	1.937, 1.946	69
79	471, 343	−0.44	1.974	74, 75
14	495, 346	−0.01		23
$(en)_3$	468, 340	−0.20	1.964	74, 76
$(NH_3)_6$	475, 339	−0.06	1.961	74, 77
Rhodium(III)				
48	289, 243	−1.02	2.044, 2.056	71
82	302, 255	−1.18		78
$(en)_3$	301, 255	−0.48	2.056, 2.067	79, 80
$(NH_3)_6$	305, 255	−0.76	2.069	81, 82
Chromium(III)				
48	427, 322	−1.04	2.040, 2.067	70
82	456, 447, 346	−1.11	2.070	83
14	481, 360	−0.77		23
$(en)_3$	457, 351	−0.62	2.075	79
$(NH_3)_6$	462, 346	−0.59	2.064	84, 85
Iron(III)				
48	476, 417, 332	−0.13	1.965, 1.986	72
79	529, 438, 366	+0.07	2.01	86, 87
14	457, 355	+0.41	2.008, 2.012	23, 25
$(en)_3$	465, 364			88

[a] Macrobicyclic ligands **79** and **82** differ only in apical substituents.

single nitro pendent group. These high-yielding reactions have produced 13-membered (**49**) [89], 14-membered (**50**) [90], 15-membered (**51**) [91] and 16-membered (**52**) [92] macrocyclic tetraamines, with each of the structures of their copper(II) complexes reported. The pendent nitro group coordinates in the axial site of the complexes of the two larger macrocycles in the solid state, whereas the less-flexible 13-and 14-membered rings prevent this interaction. No evidence of axial coordination of the pendent nitro group in solution has been observed for these complexes. Zinc reduction of the nitro group and copper centre yields the corresponding amines which may act as quinquedentate ligands. Fragmentation of the macrocycle has been observed in some of these reductions [93], but in all cases the pendent amine macrocycle is produced, generally in high yield. The substitution of diethyl malonate for nitroethane has been explored in an effort to attach carboxylate groups to the macrocycle. This has been achieved with the synthesis of the gem diester macrocycle **53** [91], in a manner similar to the synthesis of **51**, although the yield of the ester is quite small.



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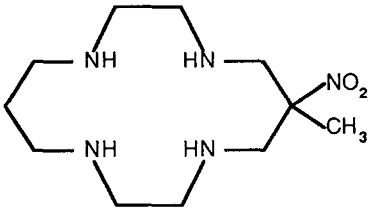

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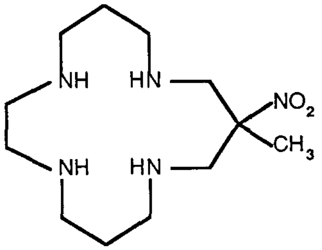

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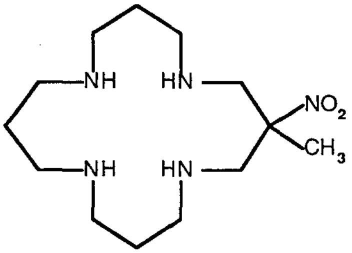

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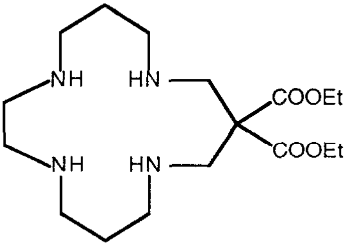
A nitroethane and formaldehyde condensation around the bicyclic hexaamine **54** as its nickel(II) complex generates the macrocycle **55** [94]. Reduction of the nitro group in the nickel(II) complex of **55** produces the amine **56**. A pulse radiolysis study of the nickel(III) complexes of **54**, **55** and **56** showed significant differences between the complexes with and without coordinating pendent groups [95]. The pendent primary amine in **56** and a



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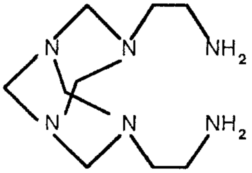

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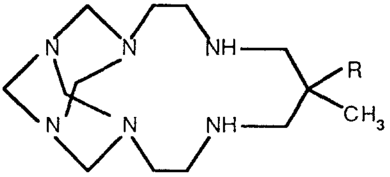
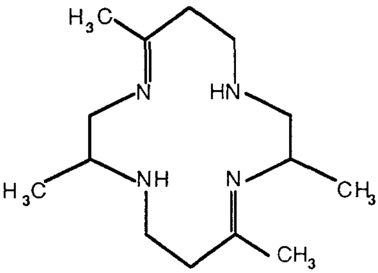


55 R = NO_2

56 R = NH_2

water molecule coordinate in the axial sites upon oxidation to the trivalent state to generate an octahedral coordination sphere. The nickel(III) complexes of **54** and **55** produce visible spectra characteristic of square-pyramidal complexes, a single water molecule occupying the fifth site.



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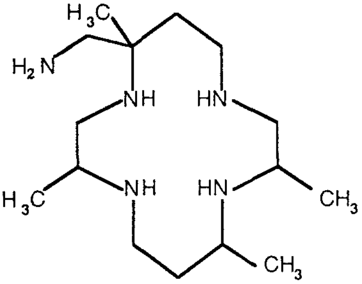

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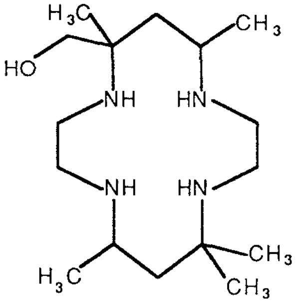


59

A similar method of appending a functional group to a macrocycle has involved the nucleophilic addition of nitromethane, deprotonated, to the nickel(II) complex of the tetraaza-diimine macrocycle **57** [96]. Reduction of the nitro and imine groups, with zinc/hydrochloric acid and sodium borohydride respectively, generates the quinquedentate macrocycle **58** still as its nickel(II) complex [97]. The familiar high spin (pendent group coordinated) and low spin (pendent group protonated) equilibrium is observed in nickel(II) complexes of **58**. Demetallation of the nickel(II) complex of **58** may be achieved with cyanide and the synthesis of the cobalt(III) complex of **58**, as well as its crystal structure, has been reported [98]. The macrocycle encircles the metal with the pendent amino group coordinating in an axial site trans to a chloro ligand. The asymmetric nitrogen atoms adopt the *trans*-III (*RRSS*) configuration and Co–N bond lengths are not unusual in comparison with those in similar polyamine complexes. Unlike complexes of **48**, however, the less-rigid macrocycle of lower symmetry, **58**, may form several N-based isomers and an extra complication is introduced when reduction of the imine is carried out with the production of another asymmetric carbon atom, the one to which the pendent group is attached. Despite these complications, several of these N- and C-based isomers of **58**, as their nickel(II) complexes, have been characterized by NMR spectroscopy [97]. A structurally similar macrocycle, **59**, as its cobalt(III) complex, has been prepared by aerial oxidation of a pendent methyl to a hydroxymethyl group [99]. The crystal structure of the complex shows the ligand retaining its trans geometry and the pendent-deprotonated hydroxymethyl group displacing one of the chloro ligands formerly in an axial site.

An interesing example of a metal-directed introduction of pendent ligating groups into macrocycles was reported from the reaction of the macrocycle **60** with ferrous ion in acetonitrile [100]. Instead of the expected trans bis(acetonitrile) macrocycle complex of iron(II), a crystal structure revealed that the macrocycle had undergone nucleophilic addition by acetonitrile at the apical positions of the macrocycle, and the result was the macrocycle **61** as its iron(II) complex. The structure shows that the ligand has folded and the two pendent groups coordinate in cis positions (Fig. 11). The 15-membered analogue of **60** undergoes a similar condensation; however, the 14-membered analogue does not, and the expected trans bis(acetonitrile) iron(II) complex of the original macrocycle is the product. Flexibility introduced by the six-membered rings clearly plays a role in this chemistry.

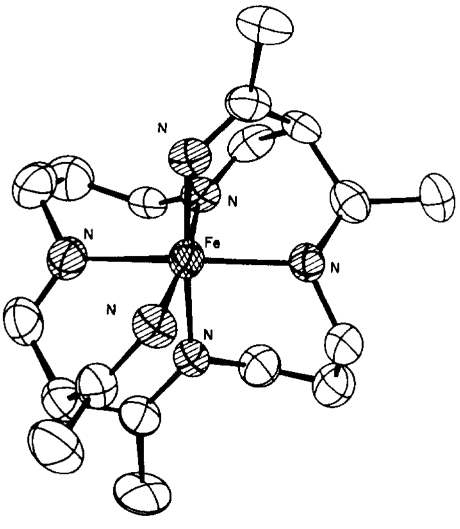
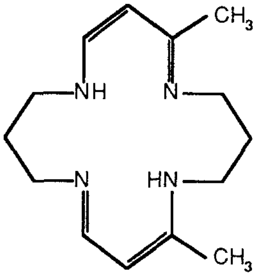


Fig. 11. Drawing of the Fe(II) complex of **61**. Average C–N of 1.256 Å corresponds to double-bond localization in these rings; hence the structure contains six coordinated imines (with an Fe–N range of 1.936–1.971 Å). There is a small trigonal distortion (52°). (Reprinted from ref. 100. Copyright 1977, American Chemical Society.)



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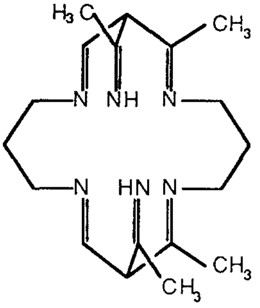
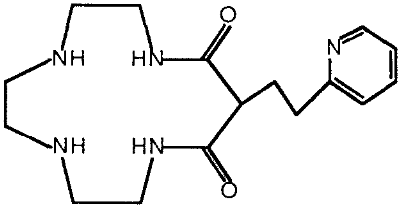


61

Conventional organic routes towards C-substituted pendent-arm macrocycles have also been pursued. Condensations of substituted malonic esters with linear tetraamines have been developed to produce symmetric tetraaza macrocycles (13-membered (**62**), 14-membered (**63**) and 15-membered (**64**)) with a pendent 2′-pyridylethyl group [101]. Direct attachment of a pyridyl group to a macrocyclic ring was achieved by condensation of the pyridyl acrylate **65** with the tetraamine **66**, and reduction of the amide [102]. The crystal structure of the high spin nickel(II) complex of product, **67**, has been reported. This shows that the macrocycle adopts a planar arrangement and the pyridyl group occupies an axial site, trans to a coordinated water molecule.



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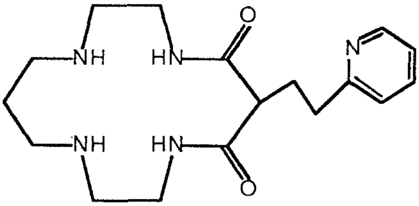

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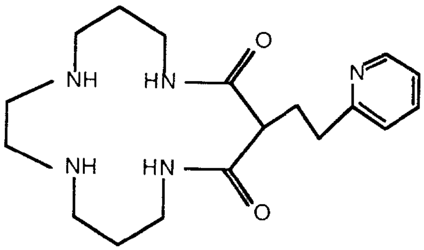

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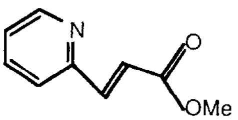

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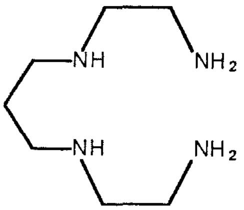
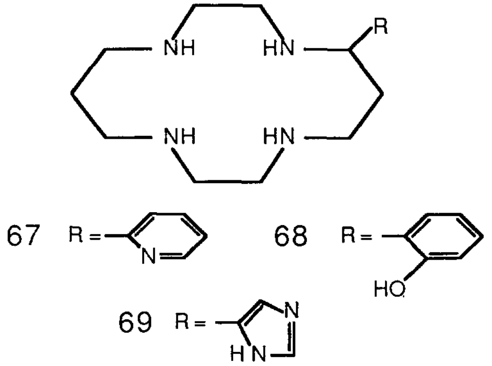
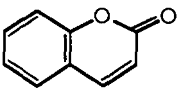


66

A Michael addition of **66** to the coumarin **70** and subsequent diborane reduction of the amide group generate the phenol-appended macrocycle **68** [103]. The phenol group has been shown to coordinate in the axial site of low spin iron(III), stabilizing the complex with respect to the unsubstituted cyclam complex. The nickel(II) complex of **68** has been reported [104], and its structure is similar to that of the analogous complex of **67**. The larger six-membered ring, including the metal formed by the phenolate pendent group, results in less strain than seen for the corresponding five-membered ring in the complex of **67**. Another useful synthon is the imidazole-substituted acrylate **20**. Condensation of **66** with the N-protected **20**, diborane reduction, and finally deprotection yield the imidazole-substituted cyclam **69** in high yield [105]. The ligand may adopt two different geometries about high spin nickel(II), where the cyclam moiety may fold or else encircle the metal ion centre. It has been shown that the folded form is the kinetic product which may be converted, by heating, to the trans form. Crystal structures of both complexes have been reported [30,105], where a perchlorate anion occupies the sixth site in the cis isomer and acetonitrile coordinates in the trans complex. The ligand **69** bears a resemblance to pendent-arm porphyrins that have been employed in the study of model compounds that reversibly bind dioxygen.





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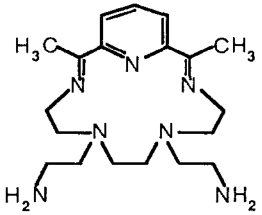
D. SUBSTITUTED PENTAAZA MACROCYCLES

Reports of pentaaza macrocycles with pendent arms have been quite rare. The analogous crown ether macrocycles have been extensively studied, but nitrogen atoms have only been introduced into these polyethers to allow attachment of a pendent group. The paucity of pentaaza macrocycles probably is a result, historically at least, of the lack of suitable metal ions to fit simultaneously in the large cavity and readily form complexes with N-donor ligands. For example, alkali metal ions form stable complexes with predominantly O-donor macrocycles but generally show little affinity for polyaza macrocycles. On the other hand, the lighter transition metals, the ions of which almost all form complexes with N-donor ligands, generally possess quite small coordination spheres which are unsuitable for complexation with large macrocycles, or at least are unable to accommodate all donor atoms conveniently in many cases.

Nevertheless, there have been reports of pentaaza macrocycles with pendent arms and, in some cases, their complexes reveal some interesting modes of coordination. Most of these macrocycles are either 15- or 16-membered, and the distribution between N- and C-functionalized ligands is roughly equal. A particularly interesting macrocycle is **71**, formed by the metal-directed condensation of 2,6-diacetylpyridine and **72**. The high spin manganese(II) complex of **71** has been reported and its geometry is believed to be pentagonal bipyramidal [106]. The macrocycle encircles the metal and the pendent aminoethyl groups coordinate in the axial sites, trans to each other.

Condensations of substituted acrylates with polyamines have been shown to provide routes to triaza and tetraaza macrocycles with pendent arms. Similarly, a pentaaza macrocycle, **73**, has been prepared by reaction of **74** with the substituted acrylate **20** and reduction of the amide [30]. No complexes of this ligand have appeared, as yet.



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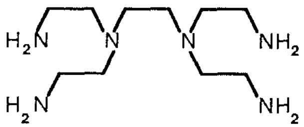

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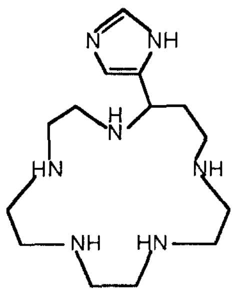

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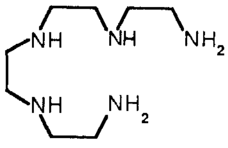
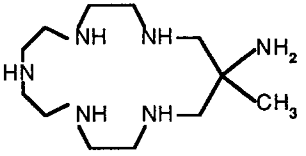


74

A metal-directed condensation of the copper(II) complex of **74** with nitroethane and formaldehyde, followed by reduction of the nitro group, yields the polyamine **75** [107]. This macrocycle may act as a sexidentate ligand, although several geometric isomers of octahedral complexes of **75** are possible. A quite similar macrocycle **76** has been reported, but studies of the complexation of this ligand have been restricted to stability determinations with a few metal ions [108].

The large number of saturated N-functionalized triaza and tetraaza macrocycles is in stark contrast with their pentaaza analogues. To date, the only penta-N-substituted macrocycle reported is the pendent hydroxyethyl ligand **77**, and no complexes of it have been reported [109]. The large number of potential donor atoms in ligands such as **77** suggest that they may coordinate more than one metal ion simultaneously, or will bind lanthanide ions efficiently. Opportunities for research in this area are clearly many.



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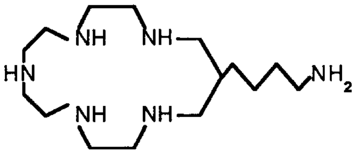

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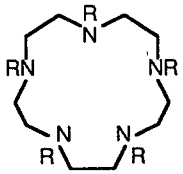


77 $R = CH_2CH_2OH$

E. STRAPPED (CAGE) MACROCYCLES

The field of strapped polyaza macrocycles has only emerged in the last 20 years or so. In that time, syntheses of these ligands and their complexes have received considerable attention as a consequence of their many interesting properties, ranging from models for reversible oxygen binding to studies of electron-transfer reactions. A satisfactory definition of a strapped aza macrocycle, for the purposes of this review, is as a polyaza macromonocycle with a bridging chain between well-separated atoms in the ring. The bridge may contain additional ligating groups, or it may act purely as a blocking group to coordination of ligands in axial sites of its metal complexes.

(i) Cages based on "sepulchrate" and "sarcophagine"

One of the most elegant and facile methods towards polyaza "cages" has evolved from initial work involving metal-directed condensations of tris-(ethylenediamine)cobalt(III) ion with ammonia and formaldehyde to generate the octaaza macrobicycle **78**, commonly referred to by the trivial name sepulchrate, as its cobalt(III) complex [110]. This ligand renders the metal

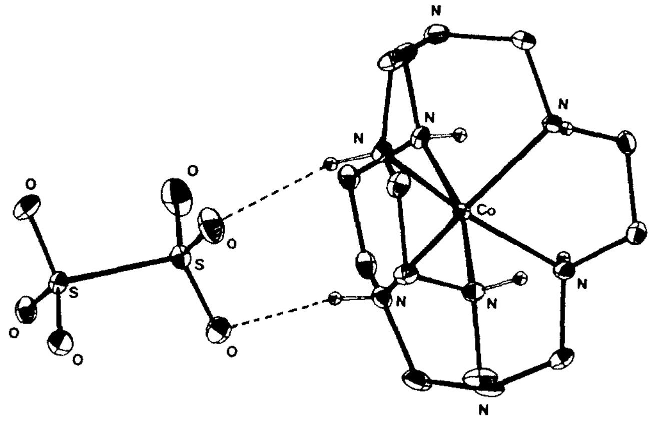
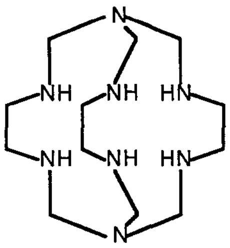


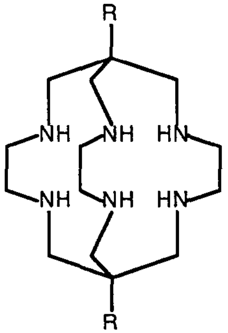
Fig. 12. View of the Co(II) complex of **78**, as the dithionate salt with the cations and anions linked through a two-dimensional hydrogen-bonding network. The high spin cobalt(II) ion lies in a distorted octahedral environment (Co–N range 2.150–2.183 Å, average 2.164 Å; trigonal twist 42.4°). (Reprinted from ref. 111. Copyright 1982, American Chemical Society.)

centre essentially substitution inert, even when reduced to the normally labile cobalt(II) state. Such was the inert nature of the cobalt(II) complex that its crystal structure was determined [111], providing one of the few examples of cobalt(II) hexaamine structures (Fig. 12). The extension of this work was to introduce groups into the "cap" on two octahedral faces other than the essentially inert tertiary nitrogen in **78**. Nitromethane exhibits reactivity similar to that of ammonia in reactions of this type, the apical atom in the cage then becoming carbon, to give cage ligands derived from the parent called "sarcophagine", **79**. The dinitro-substituted derivative, **80**, is produced in high yield from reaction of tris(ethylenediamine)cobalt(III) ion with nitromethane and formaldehyde [112]. If an optically pure starting complex is used, the cage retains the chirality of its precursor. A crystal structure of its cobalt(III) complex reveals an octahedral coordination sphere with the cyclam moiety of the ligand folding in a cis-type geometry. The presence of nitro groups result in considerable acidity of the amine protons, and the structure indicates that one nitrogen is indeed deprotonated.

The nitro groups of **80** may be reduced to hydroxylamines (**81**) using mild reductants, or to more synthetically useful amines (**82**) when more forcing conditions are employed. The possible derivatives of primary amines are many and varied, and under active study. Diazotization of the cobalt(III) complex of **82**, followed by addition of hydrochloric acid, generates chloro and hydroxo derivatives (**83** and **84**), the mixtures of products necessitating column chromatography to afford separation [112]. Zinc reduction in



78



79 R = H   80 R = NO_2

81 R = NHOH   82 R = NH_2

83 R = Cl   84 R = OH

85 R = NH_3^+

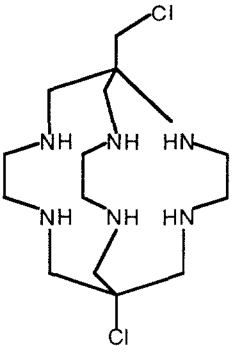
hydrochloric acid of the dichloro derivative generates the parent unsubstituted cage, **79**. A byproduct of these diazotizations was found to involve a rearrangement of the cage; loss of N_2 forms an unstable tertiary carbocation which can convert to a contracted bridgehead with a primary carbocation which captures Cl^- (or OH^-). This contracted cage, **86**, has similarities with the diamino cyclam **48**, where a similar structural unit is observed on a face of the cobalt(III) octahedron [69]. Significantly, the cobalt(III) complex of **86** exhibits higher energy maxima than its sarcophagine parent, indicating a compression of the coordination sphere towards that observed in complexes of **48**.

An extensive electrochemical study of the hexaaza-cobalt(III) cages has been reported [74]. Generally, the Co(III/II) couples are quasi-reversible as a result of the relatively slow heterogeneous electron-transfer rate constant, whereas the couples are chemically reversible. Inductive effects of the apical substituents on the potential of the Co(III/II) couple were examined. It was observed that the most electron-withdrawing substituents ($-NO_2$, $-NH_3^+$) resulted in the most positive couples whereas weakly electron-donating substituents (e.g., $-CH_3$) gave the most negative potentials. The range of potentials reported for the large range of cages based on sarcophagine was -0.18 to -0.65 V (vs. saturated calomel electrode (SCE)), which spans the range of most known cobalt(III) hexaamines. Hence the Co(III/II) couple is readily tunable without changing the structure of the complex significantly. The contracted cages gave potentials at slightly more negative potentials, a result similar to that observed in its macromonocyclic hexaamine relative **48**, whose Co(III/II) couple is the most negative reported (-0.81 V (vs. SCE)) for complexes of this type.

The inert nature of these cage complexes, even in their normally labile cobalt(II) state, generally disallows inner-sphere electron-transfer reactions. However, a study of the superoxide oxidation of the cobalt(II) complex of **78** reveals an isotope effect on the rate of oxidation when the amine protons were deuterated [113]. The explanation for this is that hydrogen abstraction by the superoxide anion from a secondary amine on the cage (formally an oxidation of the metal) was the critical step, followed by a rapid protonation to afford a cobalt(III) product. Deuteration slowed the first step by a factor of 2.1, indicating that an inner-sphere oxidation was the rate-determining step.

The cobalt(III/II) self-exchange rates for several cages have been determined by mixing cobalt(III) and cobalt(II) cages of opposite chirality and monitoring the change in optical rotation [114]. Cross-reactions of the cobalt(III) cages with reductants such as chromium(II) and vanadium(II) may also be used to calculate the same self-exchange rates using the Marcus–Hush theories [115,116]. The results obtained are in agreement with the directly measured self-exchange rates, and these rates serve as standards by which the self-exchange rates of achiral cobalt(III) hexaamines may be determined via appropriate cross-reactions.

The generality of ammonia or nitromethane and formaldehyde condensations around tris(ethylenediamine)metal ion complexes has been demonstrated for the cobalt triad, with rhodium(III) and iridium(III) cages having been synthesized [78]. The synthesis of platinum(IV) cages by this method has also been successful, with complexes of **78** and **80** being reported [117], and the crystal structure of the former having been determined [118]. Reduction of the nitro groups on the platinum(IV) complex of **80** with zinc led to destruction of the cage, so $SnCl_2$ in acid was used as the reductant. A later crystal structure of the product of this reduction revealed that the nitro groups had been reduced to hydroxylamines and not primary amines as was



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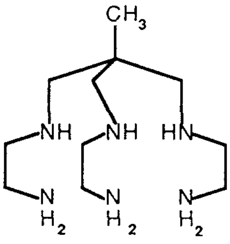
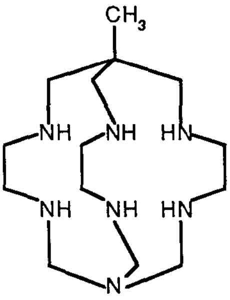


87

previously thought [119]. Reactions involving capping of a single face of an octahedron have also been developed. For example, the hexaamine **87** as its



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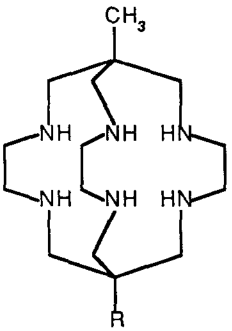
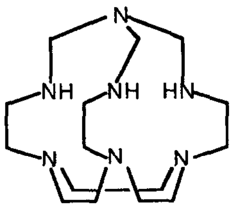


89 R = NO_2

90 R = NH_2

91 R = H

cobalt(III) complex may be capped with ammonia and formaldehyde to form **88** [112]. Similarly, if nitromethane is used as the nucleophile the cage **89** is formed which may then be reduced to form a cage with a single pendent amino group, **90**. More recently, the same nitromethane condensation was successfully performed around chromium(III) to produce the analogous chromium(III) cage [120]. Interestingly, this type of reaction had previously failed when tris(ethylendiamine)chromium(III) ion was used as precursor [83], perhaps owing to the stability of monoimines formed from amine–formaldehyde condensation with that central metal ion. Metal-directed condensations of the cobalt(III) complex of **5** with formaldehyde and nitromethane or ammonia provides routes to the tricyclic cages **92**, **93** and **94**, whose cobalt(III) complexes have been resolved into their optical isomers [121].



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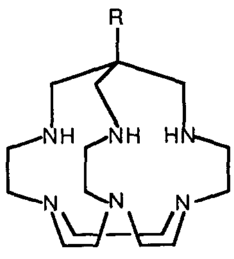


93 R = NO_2

94 R = NH_2

Demetallation of **78** has not been achieved without decomposition of the ligand. Although not facile, demetallation of ligands based on **79**, with an all-carbon cap framework, is possible. Heating in strong acid for extended periods, or precipitation of the metal ion as the sulphide, can remove cobalt(II) from **79**. Isolation of ligands of this type has led to the complexation and characterization of a range of transition and other metal ion complexes, some stabilized in unusual oxidation states. However, a consequence of complexation of ligands such as **79** with metals in unusual oxidation states is often a change in the ligand. An example is the vanadium(IV) complex of **85**, where a crystal structure showed that two of the six amine protons had been lost [122], resulting in two notably short V–N distances, a result similar to that observed in the singly deprotonated cobalt(III) complex of **80** [112]. The ruthenium(II) and ruthenium(III) cages have received much attention as a result of their unusual reactivity and interesting electron-transfer properties. The ruthenium(II) complex of **91** may be prepared by reaction of $\mathrm{Ru(DMF)_6^{2+}}$ with the free ligand under anaerobic conditions [123]. Oxidation in anhydrous solvent generates the corresponding ruthenium(III) cage, which rapidly decomposes, in aqueous solution, to a ruthenium(II) monoimine cage via ligand dehydrogenation. The X-ray crystal structures of the ruthenium(II) complex of **91** and the similar ruthenium(III) complex of **79** reveal almost identical coordination spheres, i.e. the Ru–N bond lengths are the same for both oxidation states [124]. This is in agreement with earlier experiments [125] which determined the Ru(III/II) self-exchange rate to be exceptionally fast in these complexes ($1.2 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$). The implication of this is that very little reorganization of the coordination sphere is required upon electron transfer and thus the observed rate reflects this.

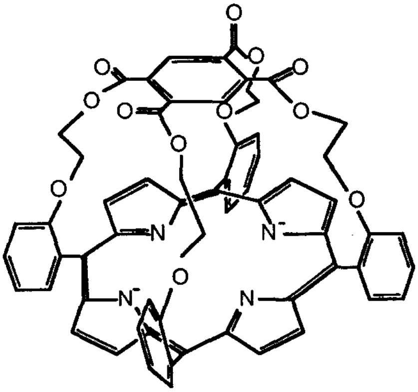
A particularly interesting system is the cage complexes of iron(II) and their high spin/low spin equilibria [126]. Some remarkable differences in the magnetic properties of the iron(II) cages are observed when only subtle changes are made to the apical cage substituents. For example, in the solid state at room temperature, the diprotonated diammonio derivative **85**, as its iron(II) complex, exists in its high spin (d^6) state whereas the non-protonated diamino cage **82** is diamagnetic in the solid state. In solution at 293 K, an intermediate magnetic moment for all cages indicates a spin equilibrium, a result confirmed by the electronic spectra, which show maxima characteristic of both high and low spin electronic configurations.

Although details of many of the structures are yet to appear in the literature, there have been reports of structural aspects of cage complexes of the first-row transition metals [87,127]. The most significant point to be made about these structures is that, despite the fact that the cages invariably act as sexidentate ligands, there are considerable differences in their structures from one metal to another. The most common distortion from octahedral symmetry is a trigonal twist, with 18° for the vanadium(IV) cage being the largest distortion in the series. The structures are essentially a compromise between the steric requirements of the cage and the preferred geometry of the metal ion centre.

(ii) Lacunar macrocycles

Reversible dioxygen binding by heme proteins in biological systems has received much attention, especially with a view to modelling the process with synthetic complexes. Many of the problems associated with producing reversible oxygen binders, specifically attack by the solvent or other metal centres on the coordinated oxygen molecule or irreversible oxidation of the iron(II) centre to iron(III), have resulted in few genuinely successful models being reported. These two inherent problems have been tackled in different ways. For the metal centre not to be reversibly oxidized by the substrate, the Fe(III/II) redox couple must lie in appropriate ranges, i.e. not so negative that metal-centred oxidation is a result of ligation. Judicious choice of substituents on the macrocyclic ligands has proven an adequate method of tuning the Fe(III/II) redox couple. Secondly, the coordinated dioxygen molecule must be shielded from attack by other metal centres or solvent molecules. This has been achieved, with varying degrees of success, by synthesizing cavities into which only small molecules may enter.

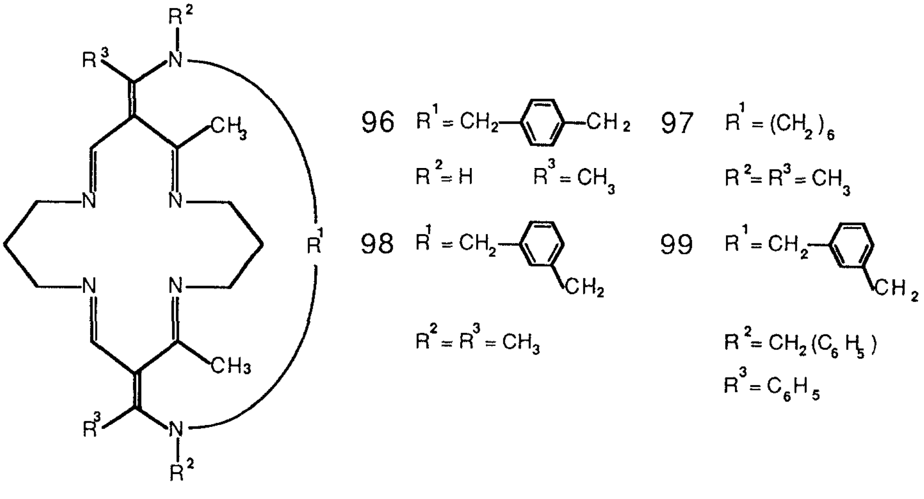
There have been reports of "capped" porphyrins where, for example, condensation of four pyrrole molecules with an aromatic tetraaldehyde has generated a macrocycle, **95**, with a cavity between the aromatic ring and the porphyrin structure [128]. The iron(II) complex of **95** in pyridine solution was shown to be pentacoordinate, with a pyridine coordinating in the site



95

trans to the cavity. When the solution was aerated, dioxygen was observed to bind reversibly in the cavity. Similar porphyrin-based macrocycles have been reported with other groups comprising the cap of the ligand [129].

A special class of strapped macrocycles commonly referred to as lacunar (possessing a cavity or void) macrocycles (**96–99**) have been prepared, and as their iron(II) complexes have proved to be excellent totally synthetic, non-porphyrin reversible oxygen binders. Although the strap portion of these macrocycles does not contain a ligating group, it nevertheless plays a vital role in creating a "dry cavity" into which only small molecules, such as dioxygen or carbon monoxide, may enter. One can view them as "second-order" ligating groups, not directly involved in metal ion binding, but intimately directing what can bind in certain sites. The substrate, when enclosed by the cavity, is protected from attack by other reactive species. Moreover, the composition of the strap and the substituents at each end of the macrocycle may be varied, and this can result in dramatic changes in the reactivity of the complex as a whole.



The template syntheses of these macrocycles are quite straightforward. Starting with the nickel(II) complex of the polyimine macrocycle **100**, reaction with the diamine strap generates the desired lacunar macrocycle as its nickel(II) complex [130]. The cavity above the plane of the metal ion and four nitrogen atoms is defined by the strapping unit; with **96**, the xylyl moiety lies parallel to this plane. Demetallation of the nickel(II) complexes is facile and has led to the study of lacunar complexes of iron(II) and cobalt(II), in particular their dioxygen binding properties. The hexamethylene-strapped macrocycle **97** has been coordinated to cobalt(II), and its

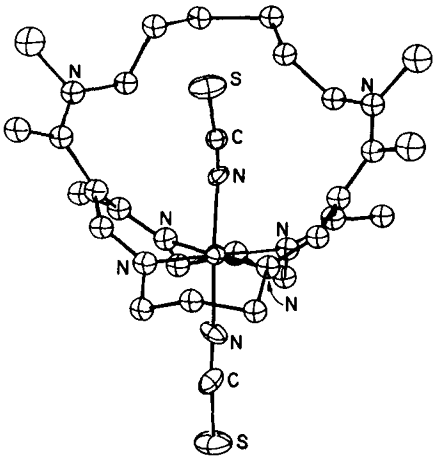


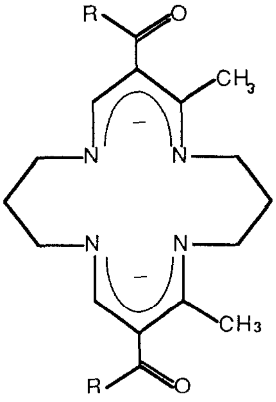
Fig. 13. Drawing of the Co(III) complex of the strapped macrocycle **97**, with thiocyanate ions in trans sites. The "dry cave" cavity (about 7.1 Å wide and 6.2 Å high) can be clearly seen. The NCS^- ligand in the cavity is bent from the normal to the CoN_4 plane by 32° owing to steric interactions. Cavities of this type can accommodate a range of small molecules. (Reprinted from ref. 131. Copyright 1980, American Chemical Society.)

structure is similar to that shown for the nickel(II) complex above, with the obvious difference in the more flexible strap [131]. Coordination of small molecules in the cavity was demonstrated by oxidation of the cobalt(II) complex of **97** in the presence of thiocyanate to give the corresponding six-coordinate cobalt(III) complex, whose crystal structure is shown in Fig. 13. The affinity of the cobalt(II) complex of **97** towards dioxygen has also been examined [132], and was found to approach that of the iron-containing myoglobin.

The report of an iron(II) lacunar complex of **98**, capable of reversible binding of dioxygen, was only the second genuine example of a non-porphyrin iron complex of this type [133]. The major drawback of this complex, however, was that reversible behaviour was only observed at temperatures not greater than −35°C, although this was an improvement on the only other system which operated at −85°C. Increasing the steric bulk of groups situated at each end of the strap resulted in a remarkable iron(II) complex of **99**, which showed reversible binding of dioxygen at 20°C in 20% aqueous solution [134].

(iii) Other strapped macrocycles

In recent years, the syntheses of small macrobicyclic cages **(101–103)** [135–137] have been developed and the coordinating properties of these ligands have been examined with some first-row transition metal ions as well



100

as with some alkaline earth and alkali metal ions. The ligands have the ability to coordinate in a quinquedentate manner, especially with a square-pyramidal geometry as shown by the structure of the copper(II) complex of **101**, where a secondary amine is coordinated from the strap (Fig. 14). A more comprehensive report of recent work with these ligands has appeared elsewhere [138].

A rather novel cage, **104**, has been reported as its low spin iron(II) complex, coming from the metal-directed condensation of cyclohexane-1,2-dione-dihydrazone and formaldehyde [139]. The crystal structure reveals a

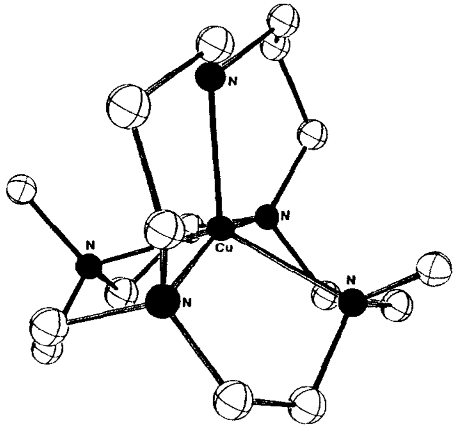
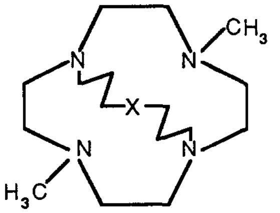
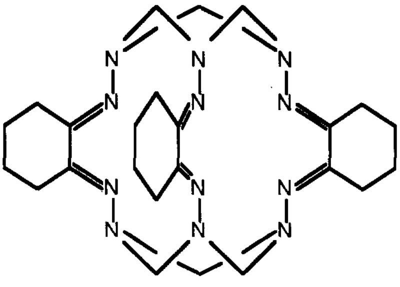


Fig. 14. View of the Cu(II) complex of **101**, a strapped macrocycle with a donor in the strap. The copper lies in a distorted square-based pyramidal geometry, with the secondary amine donor of the strap in the apical site. The Cu lies above the approximate plane of the four tertiary ring nitrogen atoms (all strap N–Cu–N angles are over 106°). (Reprinted with permission from ref. 138. Copyright 1988, Gordon and Breach Scientific Publishers Inc.)



101 X = NH 102 X = S 103 X = O



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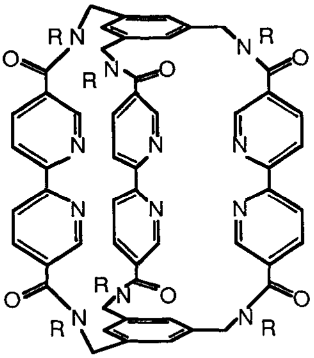


105 [$R = CH_2(C_6H_5)$]

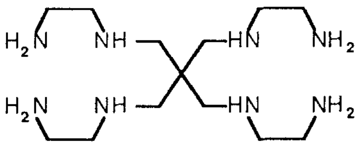
large trigonal twist (22°) imposed by the unsaturated ligand. The pursuit of coordination complexes, especially ruthenium(II) complexes, that have the potential to act as excited-state electron-transfer agents has received much attention in recent years. The Ru(bipy)$_3^{2+}$ ion has many desirable features, e.g. a relatively long-lived excited state and an appropriate excited-state redox potential. However, its major drawback is its lability, upon excitation, which results in poor turnover numbers. The general inertness of macrobicyclic cages has been exploited by the synthesis of ruthenium(II) cages of ligands such as **105**, based on 2,2-bipyridyl, which are not photolabile [140]. Further, the cage structure prevents quenching of the excited state by dioxygen.

F. DIMERIC MACROCYCLES

Binucleating bi-macrocycles may be defined as a special type of substituted macrocycle where the pendent group may encircle another metal ion. When the monomeric units of these binucleating ligands are considered, they do not differ significantly from the macrocycles described in earlier sections. However, when two metal centres are constrained to be within about 9 Å of each other, the magnetic, electrochemical and electronic properties of these binuclear complexes are often different from those of their mononuclear analogues. The use of binucleating dimeric macrocycles has only in the last decade emerged as an efficient way of studying the physical properties of metal ions in close proximity of other metal centres. The obvious advantage offered by macrocycles over other systems is the relatively well-defined constant coordination sphere imposed by the ligand. One is relatively certain about the orientations in solution of each metal centre with respect to the other, e.g. parallel or orthogonal axes of symmetry, from the known preferred geometry of the ligand. Often, the metal–metal interaction can be deliberately altered by lengthening the link between the two macrocycles until the binuclear complex becomes virtually indistinguishable from the monomer.

Not surprisingly, by analogy with monomeric systems, binuclear complexes containing cyclam (**21**) units have received more attention than any other bimacrocycle. The shortest possible link between two macrocycles is achieved when the two rings share a carbon atom (the spiro carbon atom). A condensation of the octaamine **106** with diethyl malonate, followed by diborane reduction of the tetraamide, generates spiro bi-cyclam, **107**, whose dinickel(II) complex has been reported with its crystal structure [141]. The structure shows that both metal ion centres are encircled by the macrocyclic units in a square planar arrangement of nitrogen atoms. Moreover, the two metal/nitrogen planes are nearly perpendicular (84°) (Fig. 15). Oxidation of this complex with Co_{aq}^{3+} generates the dinickel(III) analogue, with an EPR spectrum different from that of the parent nickel(III) complex of **21** as a result of interaction of the metal ion centres.

A similar ligand **108** may be synthesized by a metal-directed condensation, around two copper(II) centres, of **106** with nitroethane and formaldehyde [142]. The macromonocycle **109** is also a byproduct of this synthesis, where the dimetal complex is half macrocyclic and half acyclic. The dicopper(II) complex of **109** possesses three distinctly different electroactive groups when the pendent nitro group is considered in addition to the two non-equivalent metal centres. The EPR spectra at 77 K of dicopper(II)



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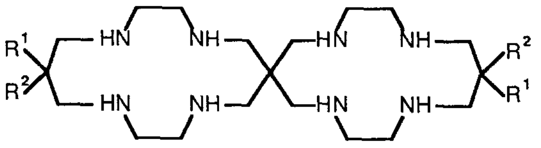
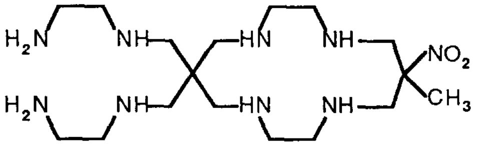


107 $R^1 = R^2 = H$ **108** $R^1 = NO_2$ $R^2 = CH_3$



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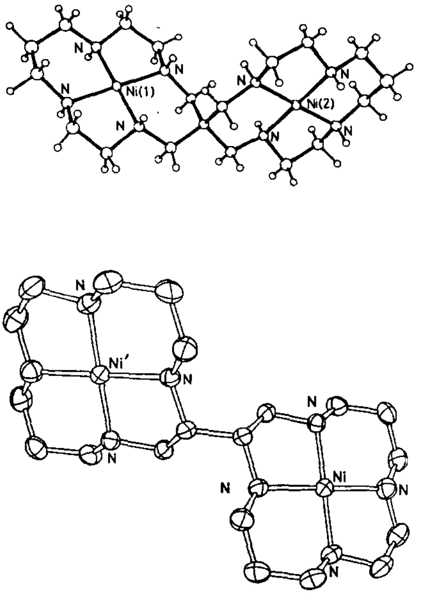
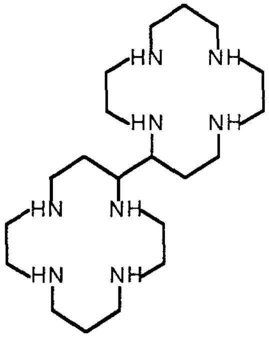


Fig. 15. Views of the dimeric macrocycles **107** (top) and **110** as their dinickel(II) complexes. The spiro macrobicycle **107**, joined at a bridgehead carbon, necessarily has the two NiN_4 planes approximately at right angles (84°), with Ni···Ni 6.495 Å. Average Ni–N distances (1.941 Å) exhibit a slight compression compared with the Ni(II) complex of the monomer analogue **21** (1.955 Å). The dimeric macrocycle **110** consists of two **21** units joined by a single bond, which permits rotation of the rings; in the crystal, the two NiN_4 planes are approximately parallel, with an average Ni–N of 1.95 Å. (Reprinted with permission from refs. 141 and 143. Copyright 1987, 1981, The Royal Society of Chemistry.)

complexes of **106**, **108**, and **109** have been measured and all differ markedly from their mononuclear analogues. Coupling of the nuclear as well as electronic spins between the two metal ions results in a complicated 14-line pattern, with a second 14-line envelope obscured by broader lines in the spectrum [142]. The simple mononuclear system results in, at most, two sets of four lines in the EPR for axially symmetric complexes.

If the distance between the two macrocycles is increased to a single C–C bond length, then one has a completely different system when compared with the spiro bimacrocycles. Apart from there being an increased metal centre separation, the connecting C–C single bond permits essentially free rotation, and the axes of the metal centres are no longer constrained to be orthogonal. An example of this type is the cyclam dimer **110** (the macrocycles connected at their 2-positions), which is formed as a byproduct in the synthesis of cyclam itself. The low spin dinickel(II) complex of **110** has been reported [143], and its crystal structure shows the two planes to be almost parallel, in contrast with the spiro-bicyclam systems (Fig. 15). As isomer of **110** is the most symmetric 6,6′-bicyclam, **111**, which has been prepared, via the amide **113**, by condensation of the tetraester **112** with two molecules of the tetraamine **66** [144]. Reduction of the amide with diborane generates the saturated macrocycle. Both binuclear macrocycles **111** and **113** have been studied, with the stabilities of their copper(II) and some nickel(II) complexes



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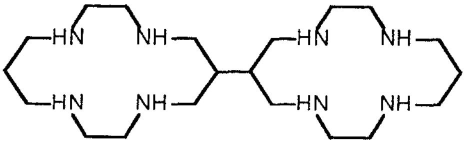

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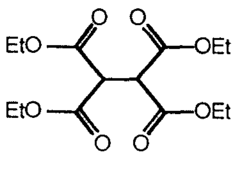

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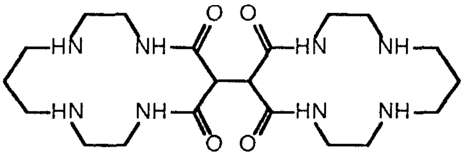

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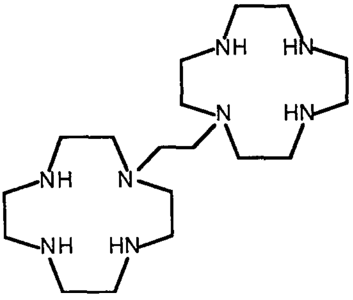
being determined [145]. A heterobinuclear copper(II)/nickel(II) complex of **111** has been made by adding stoichiometric amounts of each metal ion to the solution of the ligand. Coupling of metal centres in dicopper(II) complexes of **111** and **113** is observed from EPR measurements, where the planes of the two macrocycles are thought to be parallel but not coplanar.

Dimeric macrocycles with longer bridges between the rings have generally involved links between nitrogen atoms. The ethylene-bridged bimacrocycle **114** may be prepared via two routes [146]. The macrocyclic moieties are prepared by reaction of the tosylated triamine **115** with bis(chloroethyl)-amine. Connection of the two rings is achieved either by reaction with ditosylated ethylene glycol or by treating with oxalyl chloride followed by LiAlH$_4$ reduction of the diamide intermediate. The dicopper(II) complex of **114** has been made and its EPR spectrum at 77 K stills shows dipole–dipole coupling despite the considerable distance between the metal centres. Similarly, the 14-membered analogue of **114**, the species **116**, has been made by reaction of the tritosylated macrocycle with dibromoethane, followed by deprotection of the amines [147]. The dinickel(II) and dicopper(II) com-



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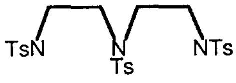

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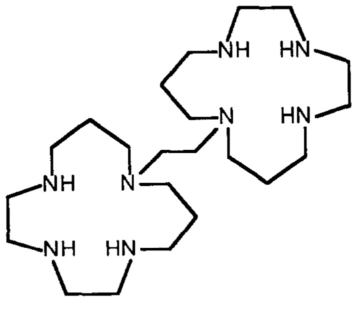

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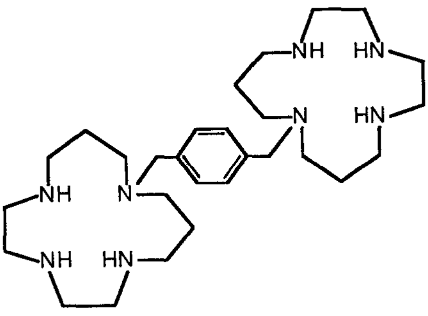

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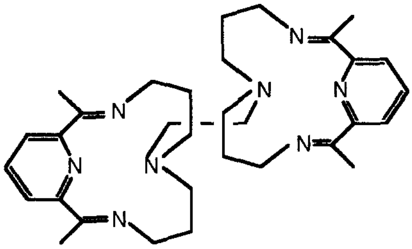
plexes have been reported, with the crystal structure of the former showing the two metal centres to be as far away from each other as possible (7.05 Å). From the EPR spectrum of the dicopper(II) complex of **116**, the internuclear separation was estimated to be 8.7 Å. The same paper reports the *p*-xylyl-bridged analogue **117**, also as its dicopper(II) and dinickel(II) complexes. The crystal structure of the dinickel(II) complex shows that the two centres are separated by 11.56 Å. Electrochemistry of this complex reveals that there is very little electrostatic interaction between the two nickel(II) centres, and the EPR spectrum of the dicopper(II) complex shows only a weak dipole–dipole interaction.



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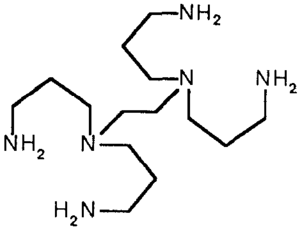

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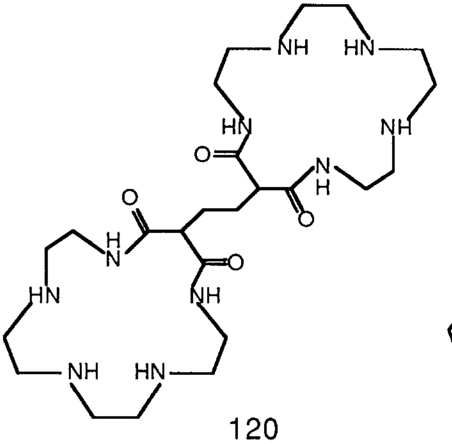
A similar system has been studied with binuclear complexes such as **118** formed by condensation of 2,6-diacetylpyridine with the hexaamine **119**. The dicopper(II) complex of **118** has been reported and its structure determined [148]. The structure showed that the two metal/nitrogen planes were, like in the aliphatic analogues, disposed the maximum distance possible away from each other. The ethylene bridge has been extended to a trimethylene and a tetramethylene link, and the dicopper(II) complexes of all have been examined by EPR spectroscopy. The EPR spectrum of the tetramethylene-bridged dicopper(II) complex was consistent with a superexchange interaction through the aliphatic chain. No evidence of a zero-field splitting, as observed with other dicopper(II) complexes, was seen. The large internuclear separation (greater than 9.0 Å) is thought to be the reason for this absence.

Reports of di-pentaaza-macrocycles, as of their monomeric relatives, are quite rare. Two examples which have appeared are **120** and **121**. These have been employed as inorganic or organic anion complexing agents [149], although no metal complexes have been reported to date.



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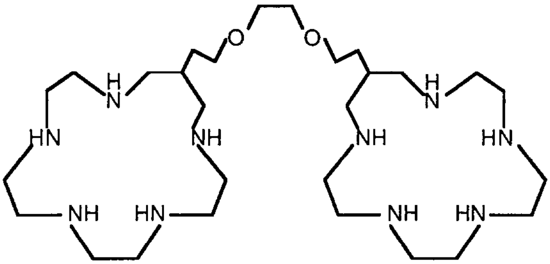

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G. CONCLUSIONS

The vast majority of work discussed in this review has only appeared in the last decade. Clearly, in that time, many advances have been made in the synthetic strategies and physical studies of macrocyclic complexes with pendent coordinating groups. It is now possible to tune the redox, electronic, kinetic and structural properties of metal ion complexes somewhat by judicious choice of ring size, donor atoms (both on the pendent group and in the macrocycle), degree of saturation, the number and type of substituents, and a range of other synthetically based variables. The application of these types of complexes to fields such as biological modelling, medicine and light-induced chemistry is already well advanced or under active study; such applications deserve independent treatment, and have not been dealt with in any detail here.

With the level of sophistication already reached in the syntheses of macrocycles with active substituents, the application of these ligands and their complexes is sure to expand in the coming years. Nevertheless, synthetic challenges still exist, notably in the areas of C-based pendent macrocycles and macrocycles with large numbers of intra- and extra-ring donors, including linked macrocycles. We presume developments in these areas will provide further interesting new chemistry for the future.

ACKNOWLEDGEMENTS

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