Chapter One

Metal-Directed Macrocyclization Reactions Involving Formaldehyde, Amines and Mono- or Bi-Functional Methylene Compounds

1. Introduction

The synthesis of large saturated organic rings incorporating a number of heteroatoms presents a challenge for synthetic chemists which has been approached in a number of ways. A number of routes to macrocyclic molecules have been developed employing standard organic chemistry approaches[1]. In all reactions, an important step must be the cyclization process, but this is not entropically favoured when forming large rings, and consequently reactions may occur in low yield or, in order to promote higher yields, must be accomplished under high dilution conditions where the cyclization is more favoured. Nevertheless, some macrocycles can be prepared conveniently in reasonable yields by direct organic routes.

However, it has been recognised for several decades now that it is possible to make use of the 'organising' capacity of metal ions to promote reactions which lead to macrocyclization[2]. One consequence of binding some reaction components to a metal ion is that co-ordination reduces the large-ring reactions occurring in 'pure' organic routes to small-ring reactions where the building of small (typically six-membered) rings incorporating the metal ion is then important. Formation of the small chelate rings is favoured entropically, in the same way that small-ring formation reactions in organic chemistry are also facile. There are a number of ways in which metal-directed reactions can occur, but dominantly they involve the reaction of two heteroatoms bound in adjacent sites in the co-ordination sphere of a metal ion with other reagents which lead to formation of a new chain linking the originally separate heteroatoms. Where a sufficient number of these reactions occur around a metal ion, a macrocyclic molecule ligated to the metal ion can result; alternatively, a larger polydentate but not cyclic molecule can result if reaction is limited in some way.

Metal-directed reactions leading to macrocyclic molecules are reasonably diverse, and it is the intention of this review to devote itself largely to reactions which produce saturated macrocyclic ligands and related polydentate molecules and involve formaldehyde as a reagent. Moreover, incorporation of additional reagents in the reaction generates alternate products. Where monofunctional or bifunctional methylene compounds of sufficient acidity are involved in addition to formaldehyde, these carbon acids may be incorporated into new rings along with formaldehyde, generating macromonocycles which contain additional pendant groups which may carry potential donor groups. These pendant donor groups increase the capacity of ligands to saturate the coordination sphere of metal ions, and add an additional 'dimensionality' to the macrocycle as a result of their spatial orientation relative to the donors in the macrocycle.

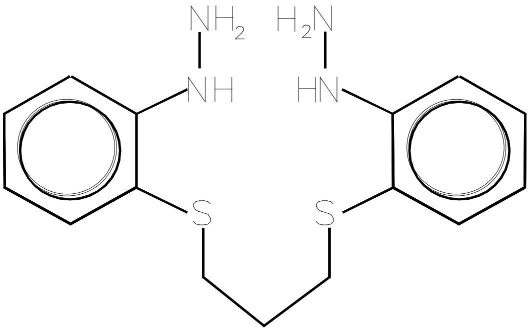
1.2 Reactions Involving Formaldehyde Alone

Coordinated primary amines present the most appropriate sites for reaction with formaldehyde via reaction as in eq. (1).

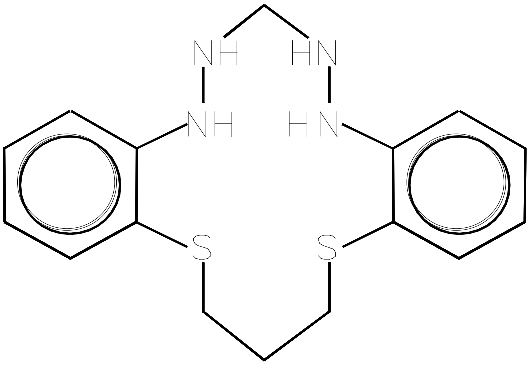
$$R\text{-}NH_2 + CH_2O \rightarrow R\text{-}N{=}CH_2 + H_2O \Leftrightarrow R\text{-}NH\text{-}CH_2\text{-}OH \qquad (1)$$

where the imine an the aminol may exist in equilibrium. Although coordinated imines are more stable than free imines, and have been isolated and characterised in some circumstances[3], they remain susceptible to further nucleophillic attack. Where no other added nucleophile is available, further reaction with accessible components of the precursor complex, such as an additional primary amine, may occur. Reactions between coordinated molecules and formaldehyde alone have received only modest attention compared to some other metal directed reactions. However, they represent a useful starting point for this review, and are addressed below.

One of the earliest reactions involving a polyamine coordinated to a metal ion and formaldehyde was reported by Alcock et al.[4]. The cyclization involved the reaction of a tetrahyrdrofuran solution of L1 with formaldehyde and nickel(II) salts in air to give the macrocyclic nickel(II) complex of L2. Condensation of one formaldehyde molecule with one primary amine has been followed by nuclelophilic attack on the resultant imine (or aminol) by the adjacent primary amine, the intramolecular reaction generating a new chelate ring and completing cyclization. A similar condensation was reported for co-ordinated dihydrazines by Peng et al.[5]



L1

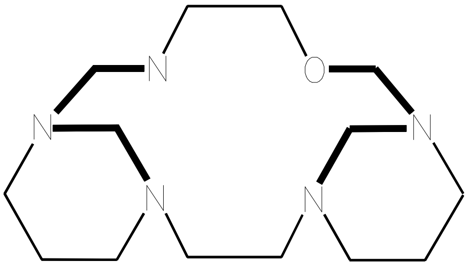


L2

Steric strain in complexes of ligands such as L2 is not marked, as six-membered chelate rings form. However, it has been observed that adjacent coordinated amines can be linked directly in the same manner. Geue et al.[6] have shown that cis-disposed amines may react with formaldehyde to form diaminmethylene (>N-CH_2-N<) links in several cobalt(III) polyamine compounds resulting in 4-membered chelate rings. Despite the strain present in the small chelate rings, formation reactions are surprisingly facile.

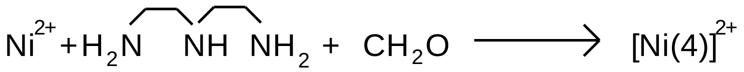
A reaction which produced a macrocyclic ether complex with a coordinated oxygen around a copper(II) template has been reported[7] . This was achieved by the addition of formaldehyde to a reaction mixture of 4,7-diazadecane-1,10-diamine, 2-aminoethanol and copper(II). Four intramolecular condensations occur leading to four new links identified in bold in L3. Apart from >N-CH_2-N<

formation, attack of the ethanolamine oxygen on an aminol has produced an ether via a new -O-CH_2-N< bridge.

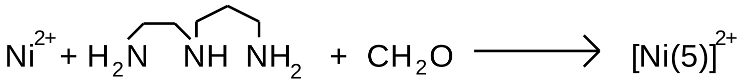


L3

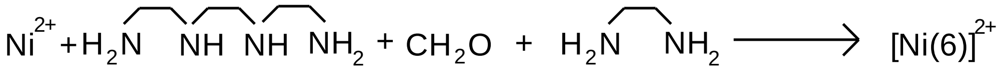
A range of interesting reinforced hexaaza macrocycles with two additional ethylene bridges joining adjacent nitrogens (L4, L5, L6, L7) were synthesised by Suh and co-workers[8,9,10]. These were produced by reacting polyaminoalkanes (see eua. (2)-(5) below) with formaldehyde, using nickel(II) as a template, with the variation that both ethane-1,2-diamine and a tetramine were present in the later two synthesis. It is notable that all reactions produce a 14-membered basic macrocycle framework, a ring size which is generally the most thermodynamically stable in complexes with first row transition metal ions. Again, in L4-L7, new links completing the macrocycles are shown in bold. The similarity to the synthesis forming L3, where again a 14-membered basic ring is formed, are obvious.



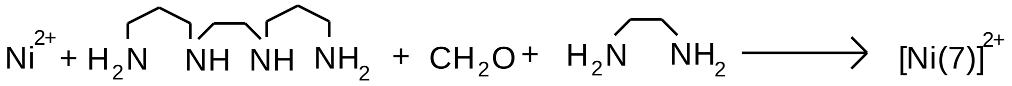
$$\mathrm{Ni^{2+} + H_2N\ \ NH\ \ NH_2 + CH_2O \longrightarrow [Ni(4)]^{2+}} \tag{2}$$



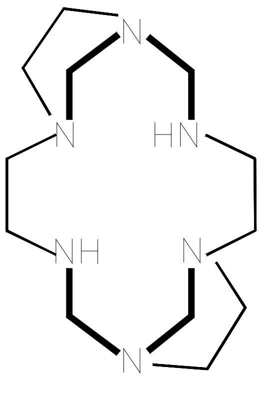
$$\mathrm{Ni^{2+} + H_2N\ \ NH\ \ NH_2 + CH_2O \longrightarrow [Ni(5)]^{2+}} \tag{3}$$



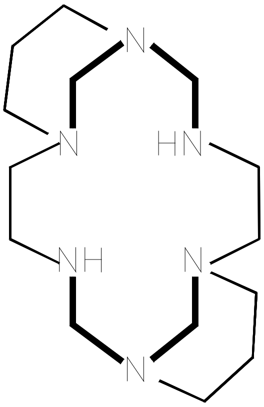
$$\mathrm{Ni^{2+} + H_2N\ \ NH\ \ NH\ \ NH_2 + CH_2O + H_2N\ \ NH_2 \longrightarrow [Ni(6)]^{2+}} \tag{4}$$



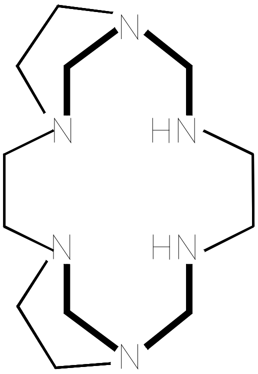
$$\mathrm{Ni^{2+} + H_2N\ \ NH\ \ NH\ \ NH_2 + CH_2O + H_2N\ \ NH_2 \longrightarrow [Ni(7)]^{2+}} \tag{5}$$



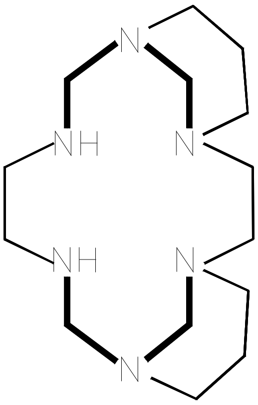
L4



L5

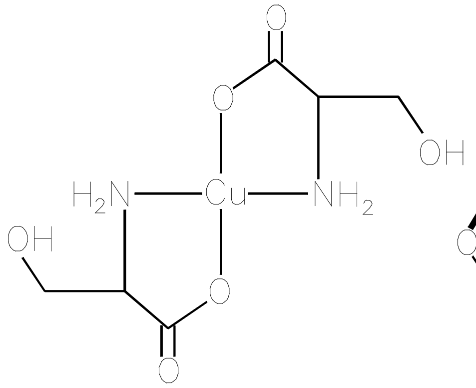


L6

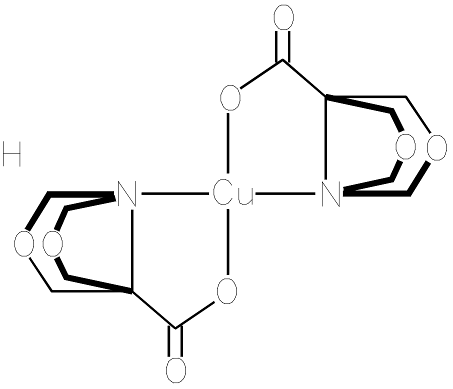


L7

Alternative condensation reactions involving two formaldehyde molecules in concert are known. Also in the early seventies Brush et al.[11] found that bis((S)-serinato)copper(II) L8 reacted with excess formaldehyde at pH 7-9 to form the complex L9. In the absence of the metal ion no reaction was found to take place. Presumably, acidity of the amino acid methylene in the coordinated complex is sufficiently high to act as a nucleophile along with the alcohol arm. Three formaldehyde molecules are incorporated in each amino acid unit, as indicated in bold in the drawing of L9.

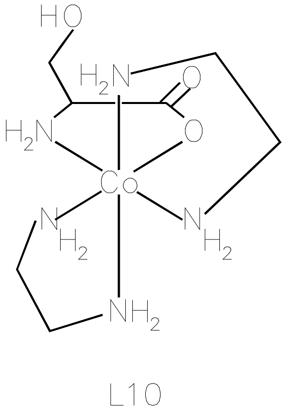


L8

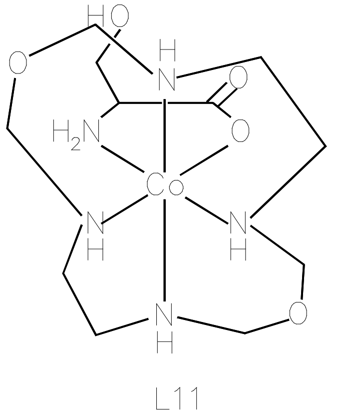


L9

The condensation of formaldehyde with glycinatobis(ethylenediamine)-cobalt(III) to yield [(α-hydroxymethylserine)bis(ethylenediamine) cobalt(III)]$^{2+}$ L10 and the macrocyclic species [(α-hydroxymethylserine) (1,4,8,11-tetraaza-6,13-dioxacyclotetradecane) cobalt(III)]$^{2+}$ L11 was the first reported condensation of this type around a octahedral metal ion[12]. In the latter compound, apart from attack of a formaldehyde on the glycine, new chelate rings containing an ether oxygen are formed by attack of the oxygen of one aminol on an adjacent imine carbon, both arising initially from primary amine and formaldehyde condensation.

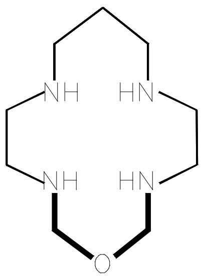


L10

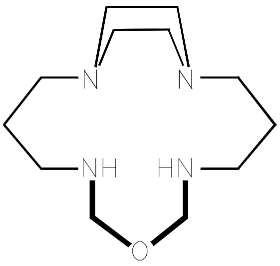


L11

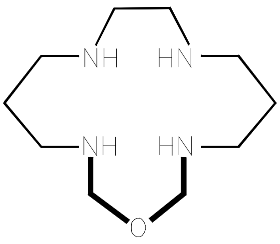
A range of macrocyclic oxatetraazacycloalkanes copper(II) complexes (L12, L13, L14, L15) have been produced in which the oxygen, while still a member of the macrocyclic ring, was not coordinated to the metal ion[13]. They were produced by the condensation of two formaldehyde molecules with two *cis*-disposed amines in the copper(II) complexes of the precursor polyaminoalkanes, as in L11 above. New links formed are shown in bold in L12 →L15. The procedure was only found to be effacious when the final product was essentially a 14- or 15-membered macrocycle; attempts to perform the equivalent chemistry to produce 13- or 16-membered macrocycle were unsuccessful.



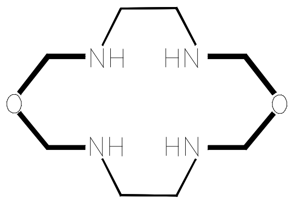
L12



L13



L14



L15

1.3 Reactions Involving Formaldehyde and Ammonia

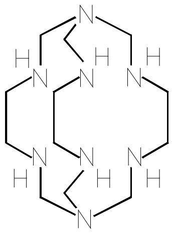
A coordinated imine is highly activated towards nucleophilic attack, and we have seen in the previous section how an adjacent coordinated amine can act as an efficient nucleophile. It is hardly surprising, therefore, to find ammonia itself, as well as uncoordinated primary amines, can participate in reactions in concert with formaldehyde and coordinated amines. In effect, ammonia functions as an acid in these reactions, releasing a proton and permitting the amide ion to attack the imine, as in eq. (6), where coordination of the imine nitrogen is implied.

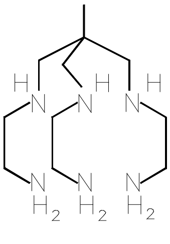
$$\text{R-N=CH[Co(L17)]}^{3+}\ \text{[Co(L17)]}^{3+} + {}^{-}\text{NH}_2 + \text{H}^+ \rightarrow \text{R-NH-CH}_2\text{-NH}_2 \qquad (6)$$

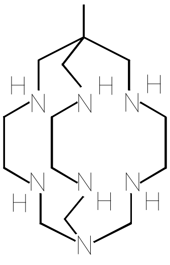
The primary amine terminating the new chain still carries two protons, and in principle can undergo two additional similar reactions until converted to a tertiary nitrogen. This capacity to act as a nucleophile in three successive reactions was first utilised in reactions to form macrobicyclic polyamines, members of the cryptate family of encapsulating molecules.

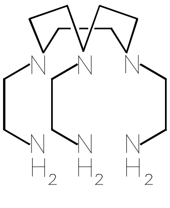
Ligands that effectively encapsulate metal ions have received a great deal of attention since the early seventies and an important class of these ligand are the cryptates. Sargeson and co-workers have used formaldehyde in concert with other reagents as and important synthetic reagent to produce a range of cryptates of varying structures, physical and chemical properties, employing inert complexes as precursors.

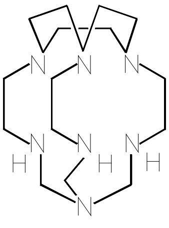
One of the earlier of these ligands produced was the macrobicyclic octaaza cobalt(III) complex of sepulcrhate[14] L16. This was produced by mixing $[\text{Co(en)}_3]^{3+}$, ammonia and formaldehyde in aqueous solution kept strongly basic using Li_2CO_3. The equivalent chemistry was also carried out on the $[\text{Co(sen)}]^{3+}$ complex (sen=L17) to produce the heptaaza $[\text{Co(L18)}]^{3+}$ [15] and on the $[Co(L19)]^{3+}$ complex [16] to produce heptaaza $[Co(L20)]^{3+}$. In the latter two cases, one side of the molecule is already 'capped' with a saturated carbon framework, making them unavailable for facile aminol or imine formation. Condensation of the formaldehyde molecules with three primary amines on an octahedral face produces three imines (or aminols) disposed in such a manner that they can readily undergo reaction with an ammonia molecule which effectively 'caps' the face by formation of three $-NH-CH_2-N<$ links. Although this is presumably a stepwise and not concerted process, in the presence of excess formaldehyde and ammonia the reaction proceeds to completion in high yield under mild conditions. In all of the above complexes, the new aza caps formed by the condensations do not involve coordination of the 'cap' nitrogen to the metal ion as the lone pair of the nitrogen is exo to the cavity.


L16

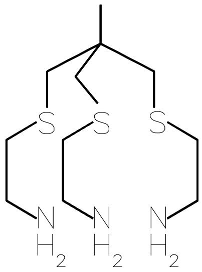

L17


L18

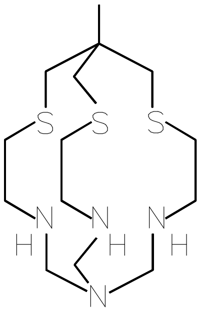

L19


L20

The analogous chemistry to that reported with sen was also achieved with the N_3S_3 donor set ligand 'ten' L21 in which the thioether donors play no part. This produces the macrobicyclic complex of azacapten L22[17].

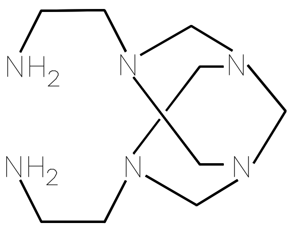


L21

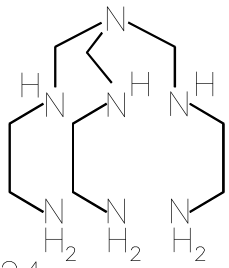


L22

Similar chemistry can be promoted around labile metal ions, although little work involving condensations using formaldehyde and ammonia alone has been reported. Suh et al.[18] have produced an interesting hexaazaalkane L23 by reacting formaldehyde, ammonia and ethane-1,2-diamine in the presence of nickel(II). Also produced in this reaction is the hexadentate tripodal heptaaza ligand L24[19,20] which can be seen to be the half-capped analogue of L16 mentioned earlier. However, when heated with excess formaldehyde and ammonia in dimethyl sulfoxide it readily converts to its square planar co-product $[Ni(L23)]^{2+}$, rather than producing the macrobicycle in any significant yield.

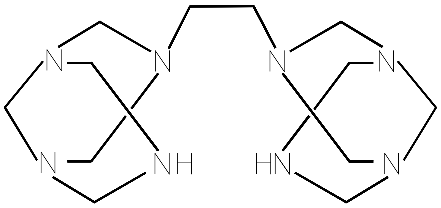


L23

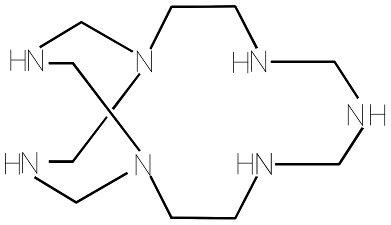


L24

Bernhardt et al.[21] have also described the orange complex $[Ni(L23)]^{2+}$ formed by reacting $[Ni(en)_3]^{2+}$ (en = ethane-1,2-diamine) with ammonia and formaldehyde solution at room temperature, together with another yellow square planar product [Ni(L25)]$^{2+}$. They also found that the equivalent chemistry can be performed using copper(II) as a template, producing the additional species [Cu(L26)]$^{2+}$. The high-field ligands generated in these reactions promote square-planar geometry for Ni(II) rather than octahedral, driving the conversion of L24 to L23 reported above, whereas Cu(II) has a strong inherent preference for square planar geometry. The facility of the formation of these methylene links to an ammonia ion are shown by the ready formation of molecules such as L25 and L26.

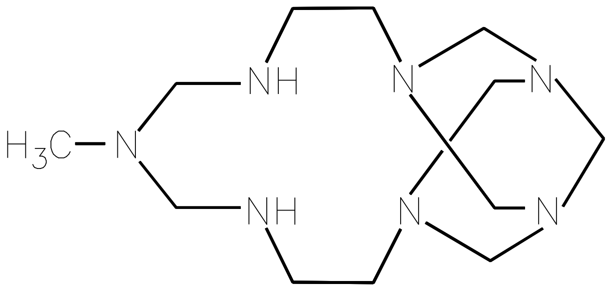


L25



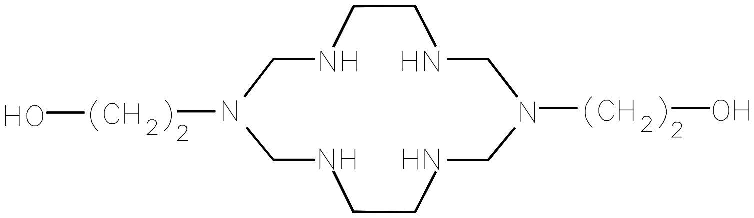
L26

In place of ammonia, unbound amines can participate in condensation reactions, although few examples of this type have appeared. One pendant macrocycle of this type was reported by Suh et al.[22]. They synthesised the nickel(II) complex of the ligand L27 by reacting formaldehyde and methylamine in the presence of the nickel(II) complex of L23. Here a pendant methyl group is attached to the apical nitrogen in the new 6-membered chelate ring of the product, with the two protons of the methyl amine replaced in reaction with two adjacent imines.



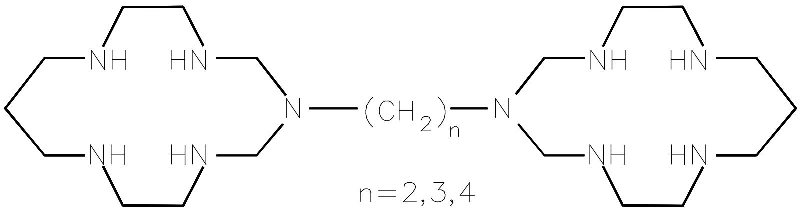
L27

More recently Suh et al.[23] have extended this chamistry by replacing ammonia with ethanolamine and using Au(III) as a template produce the potentially sexidentate ligand L28.



L28

In similar reactions, Rosokha et al.[24] have reported the condensation of the nickel(II) complex of 3,7-diazanonan-1,9-diamine with formaldehyde and aliphatic diamines to produce bis(pentaazamacrocyclic) complexes which consist of two 14-membered macrocycles joined by an aliphatic bridge between the non coordinating nitrogen of the new chelate rings L29.



L29

1.4 Reaction Involving Formaldehyde and Monofunctional Methylene Compounds

To date, essentially all reactions in this category have involved the nitroalkanes [$R\text{-}CH_2\text{-}NO_2$], since these molecules exhibit sufficient acidity in the methylene adjacent to the nitro group to act, in basic solution, as efficient nucleophiles for reaction with imines generated from formaldehyde condensation with coordinated amines. The reaction proceeds as defined in eq. (7), where coordination of the imine nitrogen to a metal ion during the reaction is implied.

$$R\text{-}N{=}CH_2 + {}^{-}CH(R)\text{-}NO_2 \rightarrow R\text{-}NH\text{-}CH_2\text{-}CH(R)^{-}NO_2 \qquad (7)$$

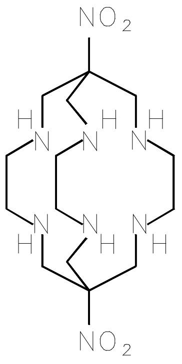
The arm generated in this reaction is still an efficient carbon acid, and can participate in further condensation reactions, at one site if R = alkyl or aryl group, and at two sites if R= H. Consequences of these addition reactions where they are internalised in the same molecule are discussed below.

1.4.1 Nitromethane

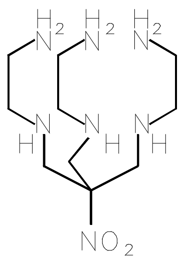
Sargeson and co-workers have expanded their work with cryptates by using nitromethane as an alternative to ammonia as a nucleophile in the condensation with formaldehyde. This still allows condensation with three facially-disposed amines and three formaldehyde molecules, but results in the apical atom being a carbon with an attached pendant nitro group rather than a tertiary nitrogen. The pendant nitro group can then be easily reduced to a primary amine providing a site for additional chemistry, and an additional potential coordination site.

The reaction between $[Co(en)_3]^{3+}$, formaldehyde and nitromethane in aqueous, basic solution produced the cobalt(III) complex of the macrobicyclic hexamine diNOsar L30[25] in good yield, analogous to the synthesis of the sepulchrate ($[Co(L16)]^{3+}$). The ligand is formed in a stepwise process via the condensation of three formaldehyde units and one nitromethane at each end of the molecule via formation of imine intermediates. Also produced in low yield (~2%) by the reaction was the cobalt(III) complex of the half capped analogue NOsen L31 in which only one end of the molecule is capped, giving some indication of the probable stepwise nature of the reaction.

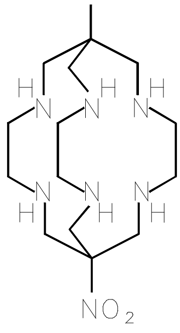
Once again, the reaction has been repeated with a large number of analogous complexes in which one end of the molecule was unavailable for capping, usually with cobalt(III) acting as a template. These included the capping of the cobalt complexes of sen L17,[26] ten L25[27] and taetacn L19[28] to produce the cobalt(III) complexes of L32, L33 and L34. The chemistry has also been described with analogous octahedral complexes of inert metal ions such as Rh(III), Ir(III) and Pt(IV).[29, 30]



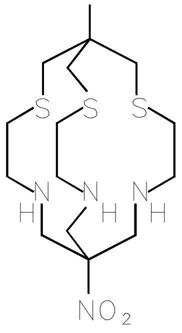
L30



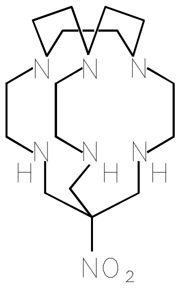
L31



L32

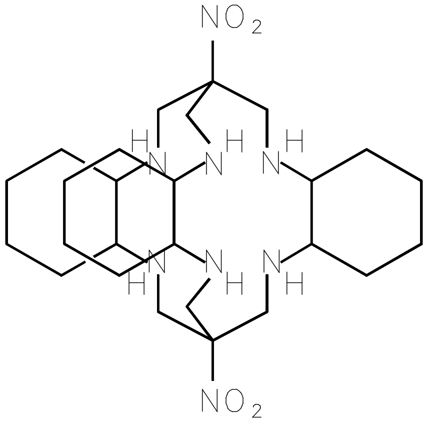


L33

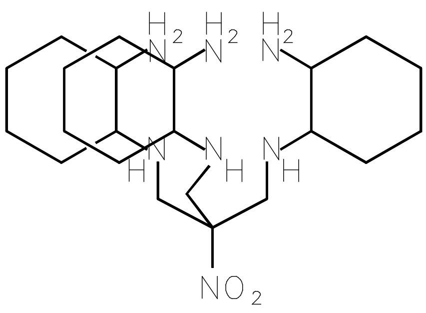


L34

In an attempt to produce a more rigid cryptand Geue et al.[31] substituted *trans*-cyclohexane-1,2-diamine for ethane-1,2-diamine in the precursor cobalt(III) complex. This produced the complex of L34 and the monocapped analogue $[Co(L36)]^{3+}$. The reaction was found not to proceed as easily as that using $[Co(en)_3]^{3+}$ as starting material, and at equivalent temperatures only the monocapped species was produced in reasonable yield. To produce reasonable yields of the dicapped species it was necessary to use higher temperatures.

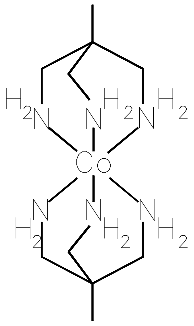


L35

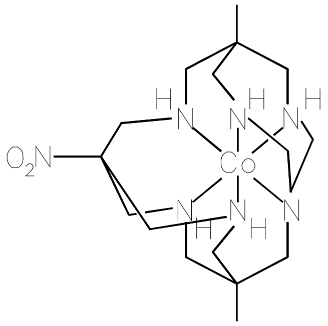


L36

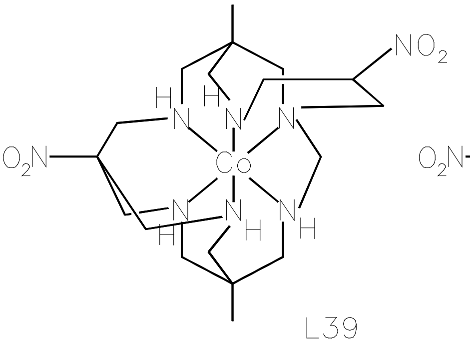
In a reversal of the norm, Gainsford et al.[32] carried out a synthesis on what could be conceptualised as a cryptand with the sides removed. They reacted $[Co(tame)_2]^{3+}$ L37 with formaldehyde and nitromethane to produce the highly constrained macrotricyclic complex L38 in reasonable yield (ca. 50%). The ligand has been formed by three formaldehyde and one nitromethane molecule condensing to form a trigonal cap on one side of the complex, and two formaldehyde units condensing on the other side of the molecule to form two four-membered chelate rings fused at a tertiary nitrogen. Two other products L39 and L40 were found in minor yield (≤10%). In both, a trigonal cap still occupies one side of the molecule; however on the other side only one methylene bridge remains. The other has been replaced by a six member chelate ring with a pendant nitro group on the ring carbon opposite to the metal. This has been formed by the condensation of two formaldehyde units and one nitromethane, and varies in the two molecules in its mode of attachment. In the former, both methylenes are attached to amines of the same 'tame' molecule while in the later there is one methylene attached to each 'tame' molecule.



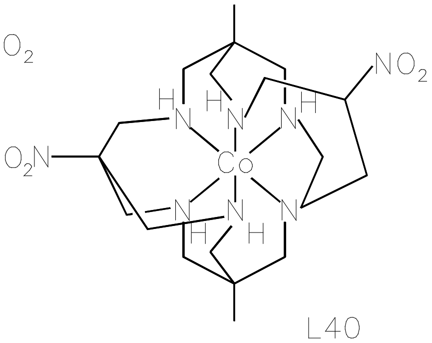
L37



L38

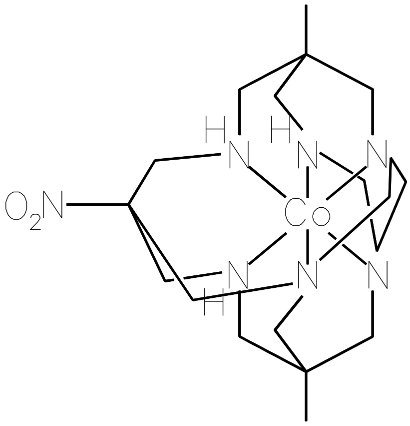


L39



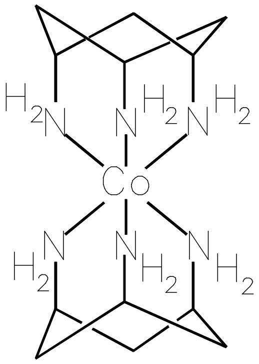
L40

Further work on the same reaction by Geue et al.[33] found the additional product L41, which is essentially similar to the complex L38, but with an additional fused 4-membered chelate ring.

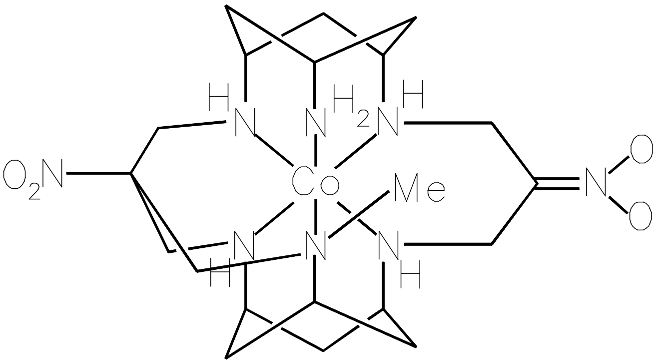


L41

A variation on this theme was the use of [Co(tach)$_2$]$^{3+}$ L42 in a condensation reaction by Geue et al[34]. The product, L43, shows the formation of a trigonal cap composed of three formaldehyde units and one nitromethane on one octahedral face, as occurred in the reactions using 'tame'. However, on another face the capping process has been intercepted to form a stable carbanion chelate and to methylate the remaining tridentate amine. The maintenance of this deprotonated form (retained in acid solution) may be due to delocalisation and the strain engendered in chelating the relatively rigid cage to the metal ion.

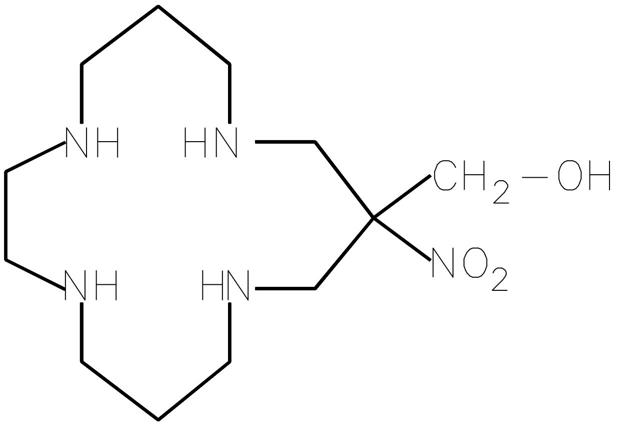


L42



L43

One of the only condensations around a labile metal ion using nitromethane reacted the copper(II) complex of 4,7-diazadecane-1,10-diamine with nitromethane and formaldehyde in methanol to produce the 15-membered macrocycle L44.[35] The alcohol pendant is probably the result of an immediate reaction between a formaldehyde molecule and the acidic proton at the site formed following condensation of two formaldehyde units and one nitromethane. Whereas all the acidic protons of nitromethane are replaced by reaction on a trigonal face, reaction in a plane with only two amines requires only two acidic protons to be employed. In the presence of excess formaldehyde, the $-NH-CH_2-CH(NO_2)-CH_2-NH-$ bridge readily undergoes additional reactions at the central carbon. For reactions directed in one plane, i.e. around metal ions preferring square planar geometry, only molecules of the type R-CH_2-NO_2 are required, as addressed below.

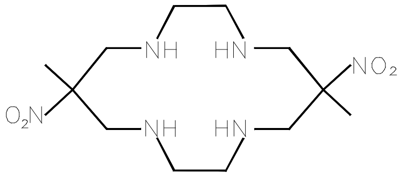


L44

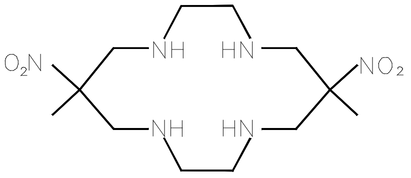
1.4.2 Nitroethane

Reactions similar to those above around labile metal ions such as Cu(II) and Ni(II) do not yield macrobicycles in any measurable yields. However, it has been found that facile high yielding syntheses of monomacrocycles are possible. One of the most carefully examined series of reactions has involved use of formaldehyde and nitroethane. This latter reagent may condense with two formaldehyde residues and two *cis*-disposed amines (via the imine intermediate) in the presence of base to form a six membered chelate ring with pendant nitro and methyl groups attached to the central carbon atom opposite the metal in the chelate ring. This cyclization has been used extensively to synthesise a range of cyclic and acyclic polyamine ligands, especially using copper(II) as a template. As with nitromethane, the nitro pendant group may be easily reduced to an amine which, after the replacement of the original square planar template with a metal ion preferring octahedral geometry, may be used as a ligating arm to encapsulate the metal ion.

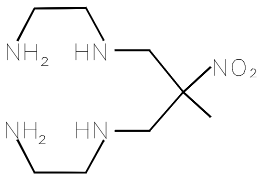
A good example of a ligand capable of this, and also one of the first examples of this type of ligand produced using nitroethane and formaldehyde was synthesised around a $[Cu(en)_2]^{2+}$ template.[36] The macrocyclic ligands L45 and L46 and the half capped analogue L47 were produced around the copper(II) template in the presence of base (triethylamine) in methanol. It was also found that, by carefully controlling the ratio of reagents and the rate of addition of formaldehyde, it is possible to produce almost exclusively either the macrocyclic or half-capped species. The species L45 and L47 can be viewed as 'planar' analogues of L30 and L31 which form on the trigonal face of an inert octahedral complex, the former being directed by the preferred square planar geometry of the metal ion and the choice of carbon acid.



L45



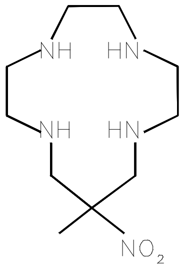
L46

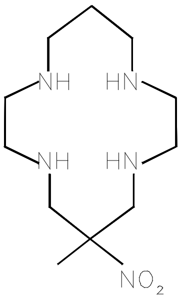


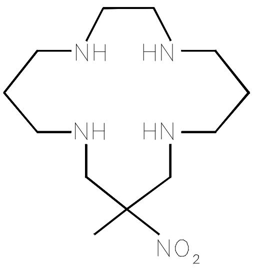
L47

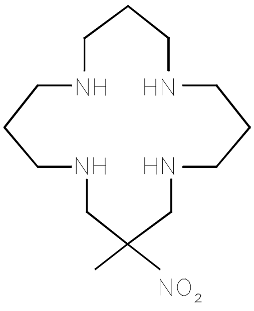
In the synthesis of the macrocycle two generic isomers are possible, with the methyl (and nitro) groups in syn L46 or anti L45 dispositions. The majority (~80%) has anti geometry. As the hydrochloride salt of the free hexamine ligand obtained following zinc reduction, this anti form is markedly less soluble, allowing the two to be separated. The stereoselectivity towards the anti form is thought to be due in part to a weak axial interaction between the copper ion and one of the nitro groups during formation directing the chemistry preferentially toward the anti isomer.

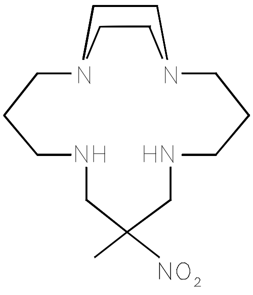
The equivalent chemistry has been extended to the copper(II) complexes of a range of tetraazaalkanes to produce 13-,14-,15- and 16- membered macrocycles and a strapped 15-membered macrocycle (L48[37], L49[38],L50[39], L51[40], L52[41]). Interestingly, unlike the ether analogues produced using formaldehyde alone (L12-L15) the 13- and 16- membered macrocycles form easily in good yield, showing the efficacy of the synthetic procedure. There is little variation in the yield for the reaction with varying ring size; however, the synthesis of the 14- and 15-membered species proceeds noticeably more easily than the other reactions, suggesting that the thermodynamic stability of the product is of importance to the success of these reactions. Following a route similar to that used to produce L52, Hancock and co-workers have produced analogous reinforced macrocycles with different sized cyclic systems[42,43](L53, L54).

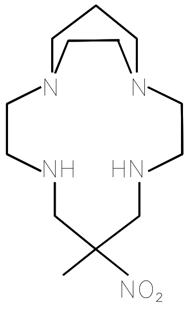

L48

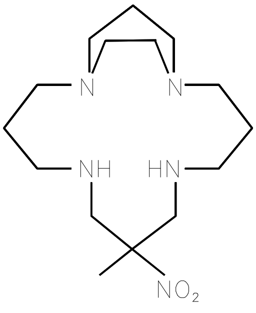

L49


L50

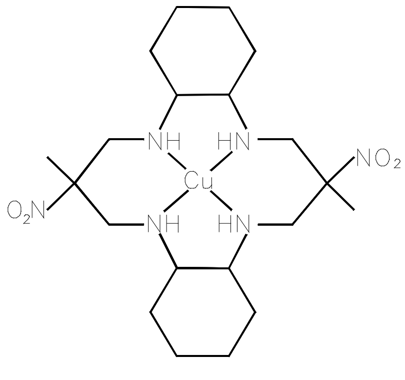

L51


L52

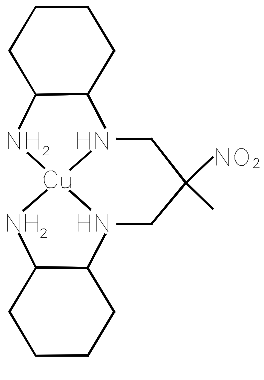

L53


L54

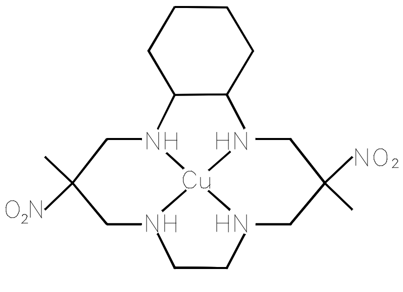
The procedure was also applied to the *(RR,RR)-* [or *(SS,SS)-*] and *(RR,SS)-* $[Cu(chxn)_2]^{2+}$ complex (chxn = *trans*-cyclohexane-1,2-diamine) to produce the cyclam analogue L55 and the half capped species L56. Interestingly, the various chiral forms of the precursor complex tend to produce different ratios of the cyclic and acyclic forms. This has been attributed to spatial constraints enforced on the amines by the various isomers[44], since the central carbon atom of the new six-membered chelate ring is a pseudoasymmetric centre in the *(RR,SS)*-isomer, and disposition of the coordinated chxn residues varies with the chirality in the residues and of this centre. In a manner analogous to L45, the *cis* isomer of L55 with nitro groups disposed on the same side of the macrocyclic plane has also been isolated in proportions similar to that found for the L45, L46 system.[45] The closely related asymmetric complex L57 has also been produced by beginning with a coper complex containing one ethane diamine unit and one 2,3 diaminocyclohexane unit.[45]



L55

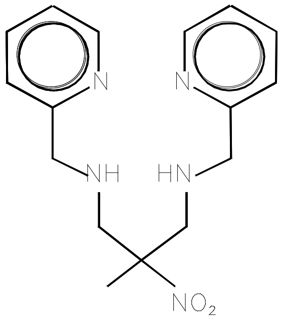


L56

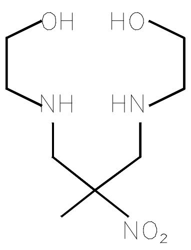


L57

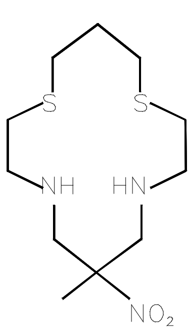
The same procedure has been applied to a number of copper(II) complexes with other donors in addition to a pair of cis-disposed amines to produce a range of corresponding cyclic and acyclic species (L58[46], L59[47], L60[48], L61[49],L62[45]). It is interesting to note that L61 is the result of a two step synthesis in which the immediate precursor is the acyclic complex of L23, formed first by the reaction of formaldehyde and ammonia on $[Cu(en)_2]^{2+}$, as described above.



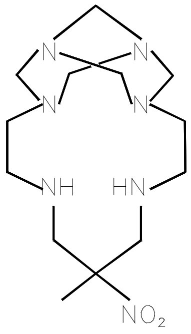
L58



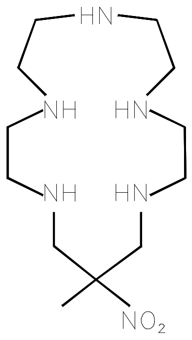
L59



L60

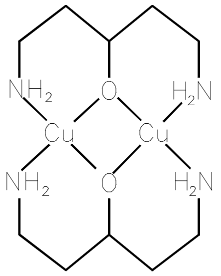


L61

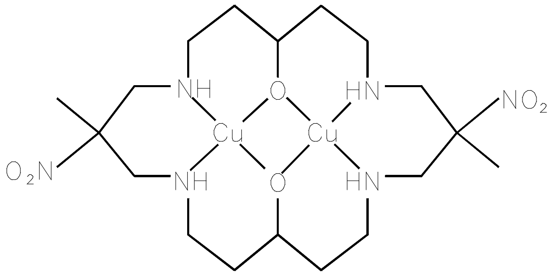


L62

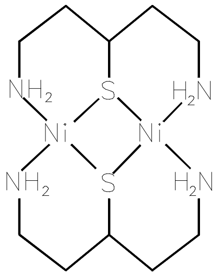
While the majority of the complexes produced using formaldehyde and labile metal templates have been mononuclear, some binuclear species templated by copper(II), nickel(II) and palladium(II) metal ions have been produced. The first synthesis was performed by condensation of bis(1,5-diaminopentan-3-ol)dicopper(II) ion L63[50] with formaldehyde and nitromethane in basic methanol to produce the binucleating macromonocyclic complex L64. A similar reaction was carried out on the bis(1,5-diaminopentan-3-thilato)dinickel(II) ion L65 which is analogous to L63, but with the O^- donors replaced by sulfur atoms. The result was a similar binuclear complex L66[51], except that the former reaction yielded L64 as the *anti* isomer, whereas the latter reaction yielded L66 as the syn isomer. Although it was not clear that the isomers were formed stereospecifically, they were formed dominantly. Why the specificity is directed differently in each case is not clear, although the product L66 adopts a 'butterfly' geometry with both Ni(II) centres 'hinged' through the S atoms, and the -NO_2 groups are weakly coordinated in axial sites. Distortion towards this symmetry in the precusor may drive the outcome. In contrast, L64 has both Cu(II) centres and all donors in a common plane. The nickel(II) chemistry above is reproduced with palladium(II) as the templating metal.[52]



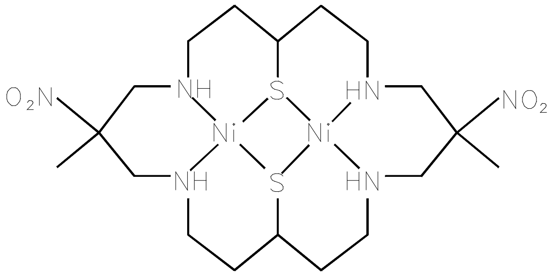
L63



L64

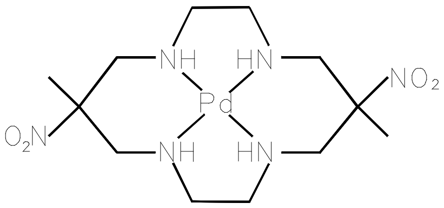


L65

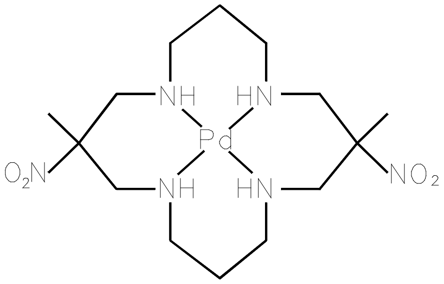


L66

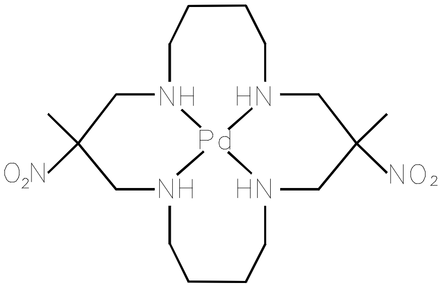
Recently, palladium(II) has also been shown to be an efficient template for some of the related mononuclear reactions described above.[53] Pd(II) forms much stronger complexes than the labile Cu(II) ion that do not tend to decompose under the basic conditions employed in these reactions. This has allowed the synthesis of a number of ‘swollen’ macrocycles (16 and 18 membered macrocycles) which have proven to be difficult to produce using the more conventional copper or nickel templates (L67, L68, L69).



L67

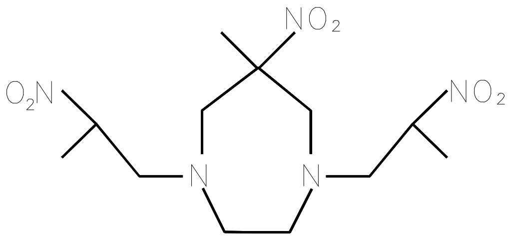


L68



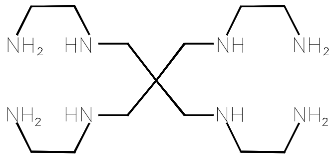
L69

Interestingly the stereo selectivity of the reactions seems greater with the Pd(II) template with L67 forming almost solely as the *trans* isomer depicted. This is in contrast with the same ligand (L45) produced around a Cu(II) template where appreciable amounts of the *cis* form (L46) were formed. For the 16 and 18 membered macrocycles (L68 and L69) there is an apparent reversal with only the *cis* forms and isolated. The chemistry has also been extended to Au(III) and Re(III) ions. The gold template forms an analogue of L46 and the half capped L47, however with both carrying a stable negative charge on one of the secondary amines.[54] When the equivalent chemistry is attempted around rhenium the metal is ejected from the complex and the heterocycle 1,4-bis(2'-nitropropanyl)-6-methyl-6-nitro-1,4-diazacycloheptane (L70) is formed.[54]

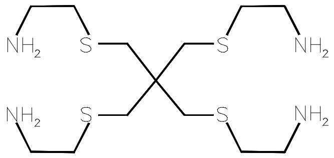


L70

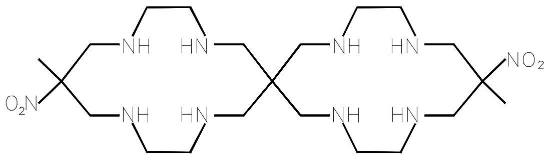
The copper(II) complexes of the potentially binucleating ligands L71 and L72[55] were treated with formaldehyde and nitroethane in basic aqueous media to produce the macrobicyclic species L73 and L74. In the case of L71, the monocapped macrocycle L75 was also isolated. The substituted spiro-bicyclam ligands L73 and L74 require the two macrocyclic planes to lie approximately 90° to each other, as the central spiro carbon of the molecules is a tetrahedral centre, the ligands being fully saturated.



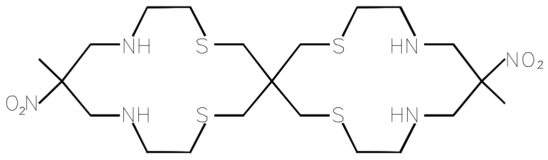
L71



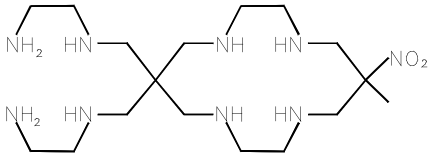
L72



L73



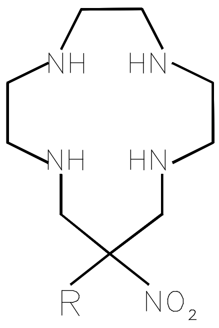
L74



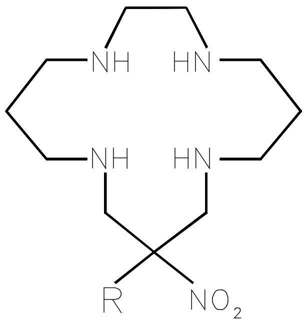
L75

1.4.3 Other Nitroalkanes

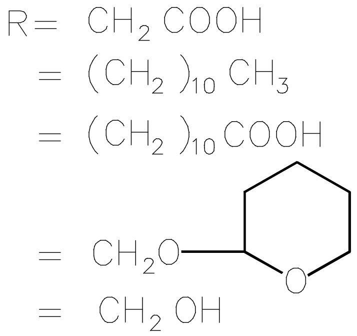
Reaction of a range of nitro substituted molecules of form R-CH_2-NO_2 (where R is an alkyl or substituted alkyl group), formaldehyde and base with the copper(II) and nickel(II) complexes of 4,7-diazadecane-1,10-diamine and 3,6-diazaoctane-1,8-diamine respectively produced a range of 13- and 14-membered macrocyclic products (L76 and L77) with one nitro pendant and the R group remaining as the other pendant. This chemistry is largely unaffected by choice of R group.



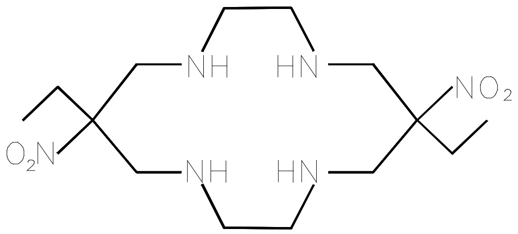
L76



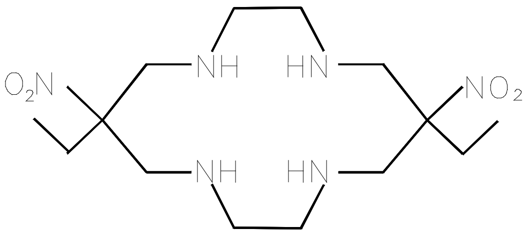
L77



Evidence of this is also given by replacing nitroethane with nitroproane in the reaction with bisethanediamine copper(II) to produce the analogues of L45 and L46, L78[56] and L79.[57] The inclusion of a carbon acid which produces a longer alkyl pendant has little effect on the ratios of the two isomers produced in the reaction.



L78

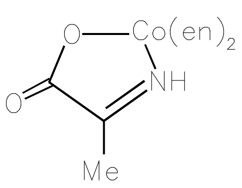


L79

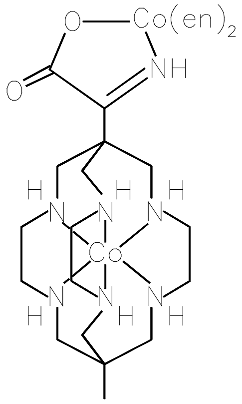
1.4.4 Other Monofunctional Reagents

Considering the efficacy of formaldehyde as a reagent in concert with ammonia, amines and strong carbon acids such as nitroalkanes, it is hardly surprising that a deal of attention has been paid to possible alternate reagents that may be used in concert with formaldehyde to produce new species. Reactions involving formaldehyde and other reagents in organic chemistry are extensive; however, metal template reactions which involved species similar to those discussed above are more limited.

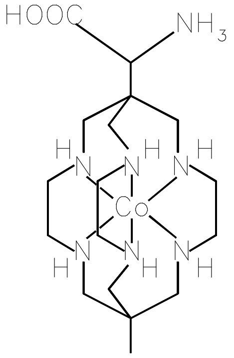
Attention has been focussed recently on modifying the caps of the cryptand species. This is done either to change the actual physical properties of the cage or to allow further organic chemistry to be carried out at the cap (e.g. to attach it to larger molecules). Many of the reaction do not involve chemistry of the type under discussion, but there are some relevant exceptions. One such reaction has been reported by Daszkiewicz et al.[58]. They have shown that a cobalt(III) complex of the pyruvate imine L80 is an effective nucleophile in condensing with formaldehyde and [Co(sen)]$^{3+}$, resulting in a functionalised sarcophagine cage L81. Here, the methyl group of the pyrvate imine is sufficiently acidic to act as a tribasic carbon acid, analogous to the chemistry described for nitromethane earlier. The product L81 may readily be reduced and then reoxidised to form a pendant amino acid L82 from which a range of organic chemistry may proceed.



L80

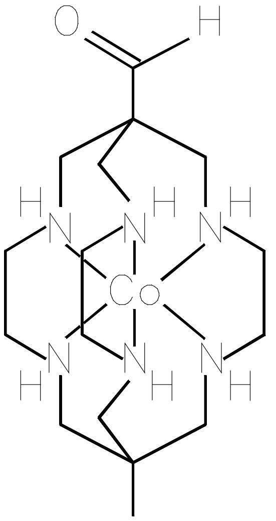


L81

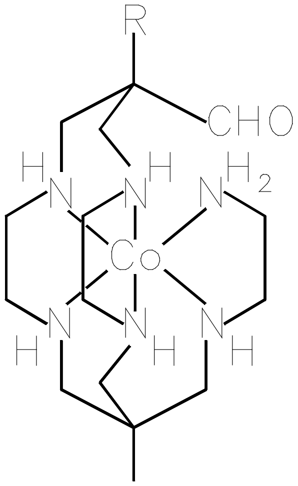


L82

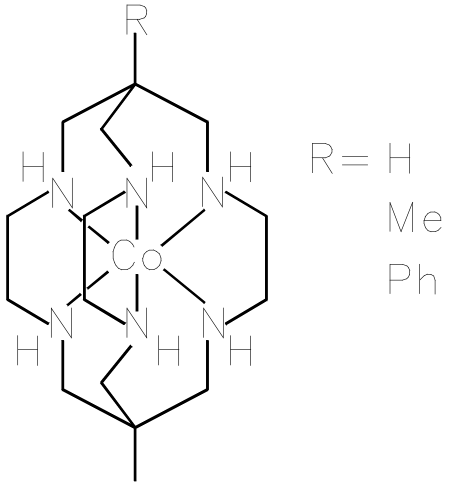
Another method of adding functionality to the cap of cryptands has been described by Hohn et al.[59]. They report the synthesis of cryptand-like molecules from the imine derivatives of $[Co(sen)]^{3+}$ (formed through the action of formaldehyde on the complex) with mixed aldehydes. Reacting the triimine derivative of sen L17 with ethanal result in a cryptand with a methanal pendant on the apical carbon of the new cap L83. If one of the imine groups is removed to leave the diimine derivative of sen as the precursor complex this may be reacted with a functionalised ethanal (RCH_2CHO, R= H, Me, Ph). An intermediate such as L84 results from the reaction of the two acidic protons of the methylene and subsequent intramolecular condensation produces a monoimine with a standard size 'cap'. When reduction with $NaBH_4$ follows, this results in the R-group being the apical pendant to the new cap, as in the cryptand L85. Throughout this chemistry the cobalt ion remains trapped in the macrobicycle.



L83

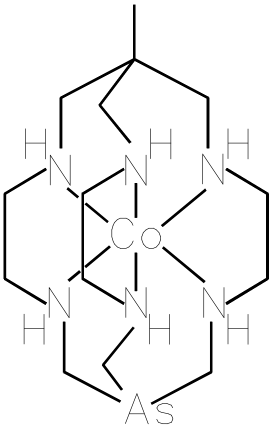


L84

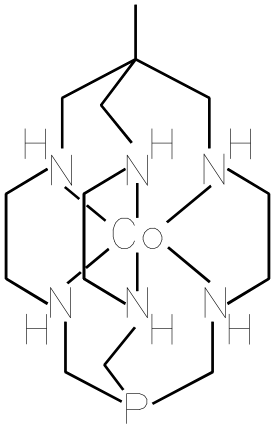


L85

Another variation based on [Co(L17)]$^{3+}$ is to react it with formaldehyde and either AsH_3[60] or PH_3[61] in the presence of base. This results in a capped macrobicycle with either an arsenic L86 or a phosphorous L87 atom occupying the apex of the new cap in a form similar to the reaction between [Co(L17)]$^{3+}$, formaldehyde and ammonia. The products L86 and L87 analogues of L18, but the reactions are performed under more stringently controlled conditions.



L86



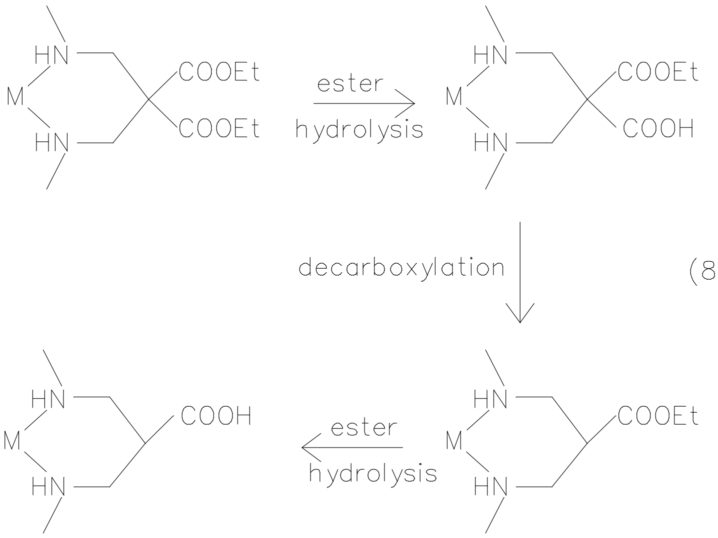
L87

1.5 Reactions Involving Formaldehyde and Bifunctional Methylene Compounds

The acidity of methylene compounds can be enhanced by having two electron-withdrawing groups bound directly to the active methylene, i.e. X-CH_2-Y molecules. Examples of molecules in this category include diethyl malonate (EtOOC-CH_2-COOEt) and related molecules such as NC-CH_2-COOEt and EtOOC-CH_2-NO_2. Clearly, the two acidic protons of the methylene can be employed in condensation reactions, leading to molecules with two pendants carrying additional functionality, although there is the prospect of these being involved in additional or alternate reactions in some cases, as addressed below.

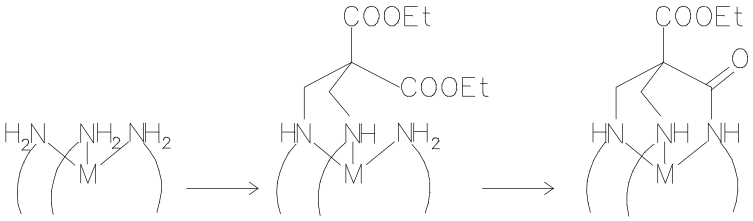
1.5.1 Diethyl Malonate

Diethyl malonate exhibits sufficent acidity , as a result of the two ester groups, to function as a relatively strong carbon acid. The two methylene protons can participate in condenstion reactions with two formaldehyde molecules and two adjacent coordinated amines in the presence of base, generating a new six membered chelate ring with a -NH-CH_2-$C(COOEt)_2$-CH_2-NH- bridge. This is essentially the same behaviour exhibited by nitroethane. The resultant gem diester is susceptible to both ester hydrolysis and decarboxylation, leading eventually to a free acid pendant, possibly by the route in eq. (8).



(8)

Where three coordinated amines are available on an octahedral face, the ester groups in diethyl malonate can be involved in a condensation reaction in addition to the two acidic methylene protons. Following condensation with two primary coordinated amines and two formaldehyde molecules, an intermediate with an ester group and a coordinated primary amine adjacent is formed (eq. 9, centre) which in basic conditions can condense further to produce a coordinate amide and complete the 'cap'. This latter reaction has not been observed as an alternative path in eq. (8), implying that reaction as a carbon acid is more facile.

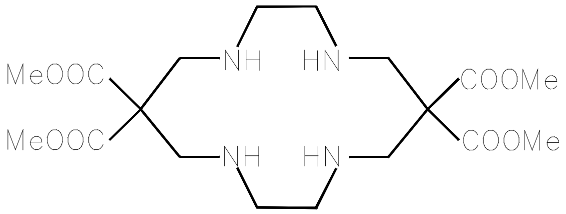


(9)

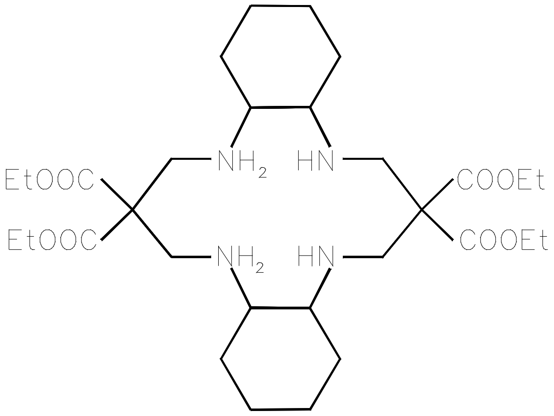
Reactions with labile metal ions such as copper(II) or nickel(II), where square planarity is preferred, have been examined in some detail. The higher pK_a of the acidic protons in diethyl malonate in comparison to those of nitroethane means that reactions involving these reagents do not tend to proceed as easily as those using nitroethane under identical conditions. Depending upon the conditions of the reaction, the diester may hydrolyse and/or decarboxylate to form a mixture of acid ester and monoester products (eq. 8).

The tetramethyl ester cyclam analogue L88 has been prepared using dimethylmalonate and formaldehyde (diethylmalonate is equally effective) in a procedure analogous to that used to produce L45[62]. Both copper(II) and nickel(II) templates have been used, as well as the alternative carbon acid diethylmalonate (which produces the tetraethyl ester). In all instances, however, the yield tends to be low (ca. 10%), with base induced decomposition of the precursor complex taking place in competition under the conditions employed. The analogous procedure has also been carried out on optically active $[Cu(chxn)_2]^{2+}$ using diethylmalonate to produce the tetraester L89.[45]

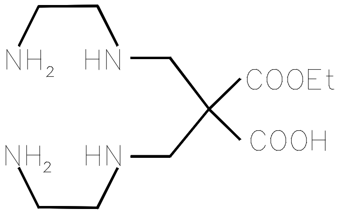
However, the half capped analogue produced by the controlled addition of diethylmalonate and formaldehyde to a basic methanolic suspension of bis(ethane-1,2-diamine)copper(II) perchlorate proceeds readily in good yield (at least 40%)[63]. The final product L90 has one acid pendant and one ethyl ester pendant group as opposed to the retention of all the ester groups in the synthesis of the macrocyclic analogue. It is readily decarboxylated to the monoacid L92. Apart from reactions involving ethane-1,2-diamine, the basic synthetic method has been applied to a large variety of polyamines to produce a number of cyclic and acyclic species, all with either acid or ester pendant groups (L92, L93, L94[64], L95[65], L96[66], L97[45]).



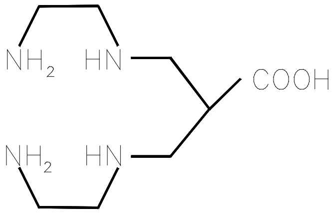
L88



L89

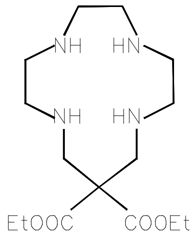


L90

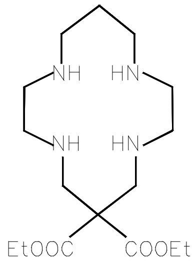


L91

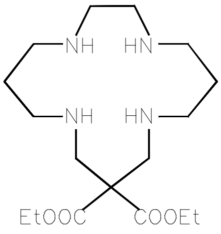
Another variation is the use of diethylmalonate and nitroethane condensation in the same molecule. In a multiple step process commencing with $[Cu(en)_2]^{2+}$, capping using diethylmalonate was employed to produce L90. This species is then stabilised by conversion to the methyl ester derivative of L91 by hydrolysis in basic methanol. The other pair of primary amines of the intermediate complex molecule is then capped using nitroethane, the methyl ester being hydrolyzed in the process. The resulting complex L109AA is a cyclam derivative with both nitro and carboxylate pendant group which, after reduction to convert the nitro to an amine and to remove the metal, is capable of encapsulating a wide range of octahedral metal ions as a sexidentate ligand L99.[67] Also produced from this reaction is the analogous *cis* isomer in proportions similar to that found for the L45, L46.



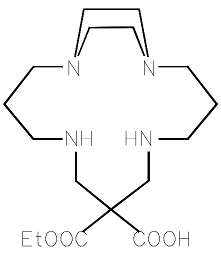
L92



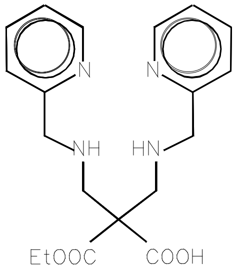
L93



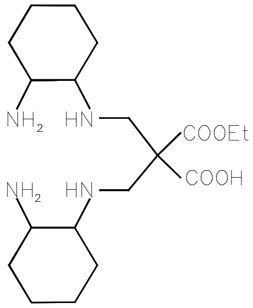
L94



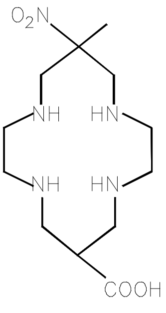
L95



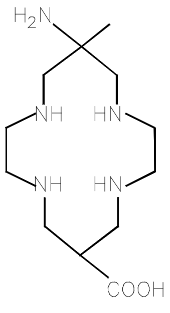
L96



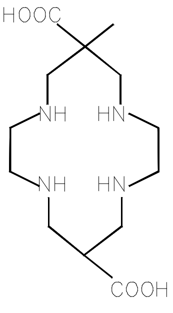
L97



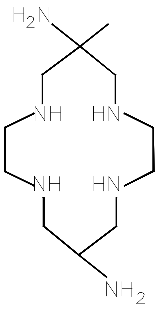
L98



L99



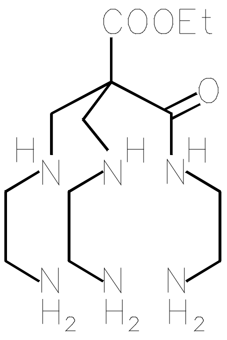
L100



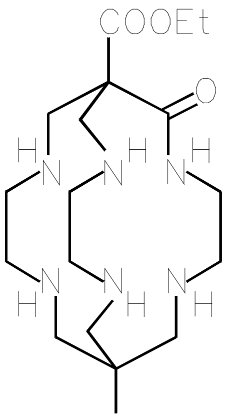
L101

Likewise, L88 can be converted by hydrolysis and decarboxylation reactions to the potentially sexidentate ligand L100 (L89 can also undergo the analogous process to produce diacid species). Although no *cis/trans* isomerisation is possible for the tetraester, the hydrolysis and decarboxylation reactions produces both isomers, with a strong preference for the trans form (4:1, as is discussed in later chapters). Since L45 can be readily reduced to the hexamine L101, the three ligands L99→L101 (and there *cis* analogues) represent a series of potentially sexidentate macrocyclic tetraamines with two pendant donors, where the pendant donors step from two amines, to an amine and a carboxylate, to two carboxylates. The coordination chemistry and synthesis L99 and L100 are discussed in detail in Chapters 4 and 5 and compared with the well characterised complexes of L101.

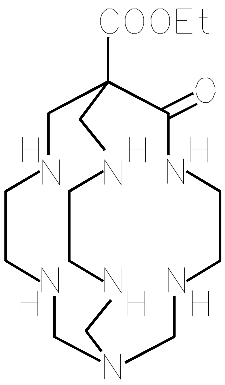
Reaction of inert hexaamine cobalt(III) complexes with formaldehyde and diethylmalonate have been described only recently. Reaction of $Co(en)_3{}^{3+}$ generates essentially only the mono-capped molecule L102, capping at the other face of primary amines not being observed. However, commencing with $Co(L17)^{3+}$ or $Co(L24)^{3+}$ yields macrobicyclic amides L103 and L104 respectively. The pendant ester group can be converted via standard organic chemistry reactions to the acid (via base hydrolysis) and the acid chloride (via reaction with thionyl chloride), the later then capable of facile condensation reaction with amines. The half-capped cobalt(III) complex of L102 can be converted by reaction with formaldehyde and nitroethane to L105. The coordinated amide is extraordinarily robust, being unaffected by these reactions, but is also not conveniently reduced.



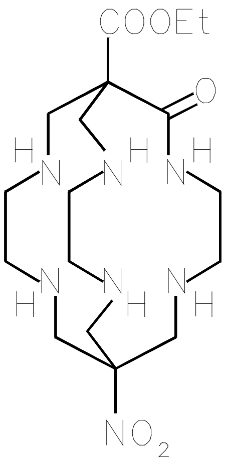
L102



L103



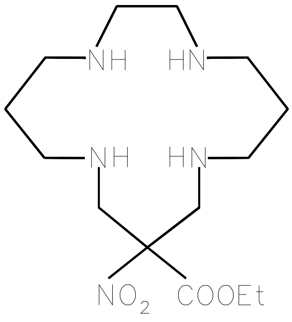
L104



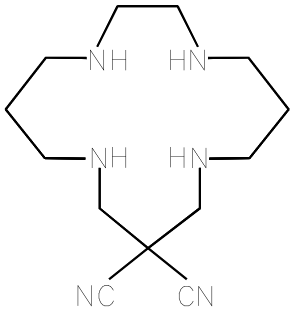
L105

1.5.2 Other Reagents

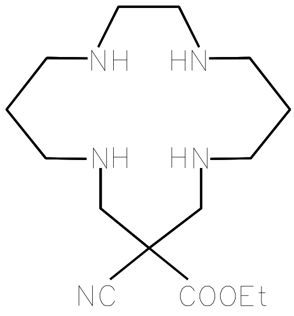
There are a number of other conveniently available bifunctional methylene compounds which are sufficiently strong carbon acids to permit participation in reactions analogous to those described above. The 'composite' molecule $EtOOC-CH_2-NO_2$ is a clear candidate, but few reactions with the molecule have been reported to date, beyond some evidence for the formation of L106[68] in a condensation reaction with formaldehyde and a tetraamine copper(II) ion.



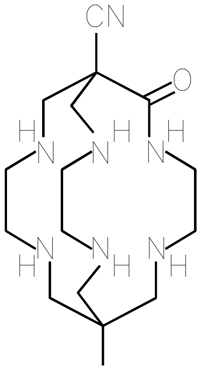
L106



L107



L108



L109

Bifunctional methylene compounds incorporating nitriles are candidates for condensations, and some examination of NC-CH_2-COOEt and NC-CH_2-CN has been performed. The latter appears to yield L107 in condensation reactions analogous to L45, but the stability of the pendant molecule is not apparently great and the product has not been definitely confirmed. The former reagent undergoes an analogous reaction to form L108.[45] The former reagent also undergoes an analogous reaction to diethyl malonate with Co(L17)$^{3+}$ to produce L109. In principle, provided acidity is great enough, reactions should proceed essentially as defined for diethyl malonate, although the possible diversion of the reaction along alternative paths is not well understood, and offers avenues for further examination.

1.6 Conclusions

The synthesis of macrocycles, particularly saturated macromonocycles and macrobicycles incorporating mainly nitrogen donors, is often facile when inert or highly stable labile complexes with appropriately disposed coordinated primary amines are reacted with formaldehyde and ammonia or functionalised methylene compounds which are efficient carbon acids. Around inert octahedral metal ions, saturated and usually macrobicylcic molecules are readily accessible. Around more labile metal ions, such as copper(II), nickel(II) and palladium(II), there is a tendency to form usually saturated macromonocyclic molecules, directed by a preference for four-coordination and square planarity with strong-field ligands in those cases.

In many cases, the resultant ligand can be removed from the metal ion in an intact or slightly amended form. For example, copper(II) complexes of macrocycles produced from reactions described above may often be obtained simply by a zinc/acid reduction reaction with following chromatography on Dowex resin to isolate the metal-free pendant-arm macrocycle in high yield.[69] Where inert complexes such as cobalt(III) complexes of macrobicycles are produced, the metal-free macrobicyclic ligand may be obtained by reaction under an oxygen-free atmosphere of the reduced cobalt(II) complex either with concentrated hydrobromic acid or with excess cyanide ion, which remove the cobalt(II) as $CoBr_4^{2-}$ or $Co(CN)_4^{2-}$ respectively.[70]

The capacity of the pendant-arm macromonocycles and macrobicycles to bind metal ions strongly and in some cases selectively, and the unusual physical properties often shown by complexes of these isolated ligands, provides a wealth of additional chemistry which is still under active investigation. In the following chapters, the synthesis and coordination chemistry of a number of the macromonocycles bearing pendant carboxylates discussed is described and compared with the already extensive information concerning their amine pendant analogues.

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