Chapter Four

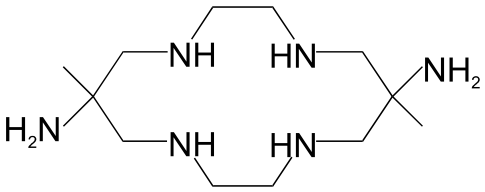
The Sexidentate Pendant Arm Macrocycles

Diammac, Acammac and Diacmac

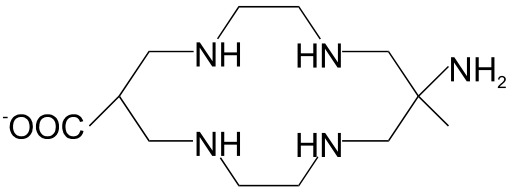
4.1 Introduction

Although the carbon-pendant ligands of the previous chapter have been shown to be efficient in the coordination of metal ions, their single pendant restricts them to coordination of only five sites. For any metal ion which can fit within the cavity of the macrocycle this leaves a site free for coordination of another ligand (assuming the metal has a preference for a coordination number of six). To totally encapsulate such metal ions the macromonocyclic ligand must either incorporate sufficient donors in the ring and assume some form of folded geometry, or else the macromonocycle could have four ring donors and more than one pendant. A large number of macrocycles with multiple pendants attached to their ring donor atoms have been described;[1] however, as has been discussed previously, there are a number of advantages to carbon linked pendants, notably greater steric efficiency.

One approach to synthesis of ligands with two pendants arranged in a suitable manner to totally encapsulate a metal ion is to use the pseudo-square planar bis(ethane-1,2-diamine)copper(II) ion as a precursor. This has two sets of



L1



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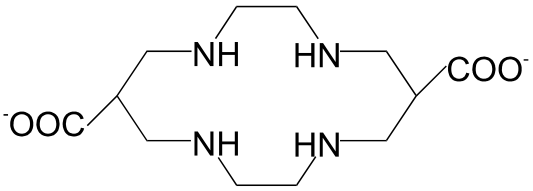

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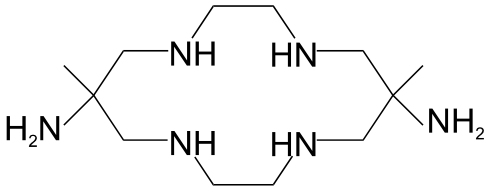

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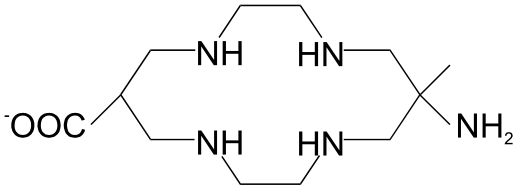

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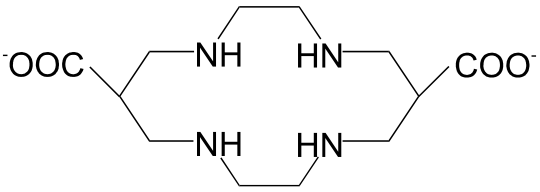

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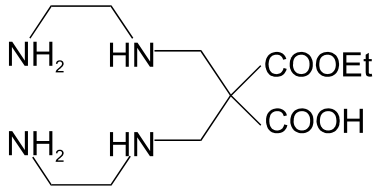

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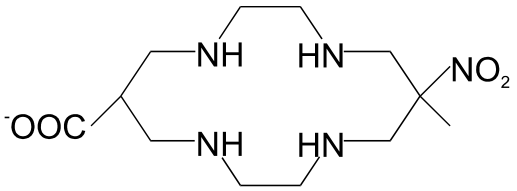

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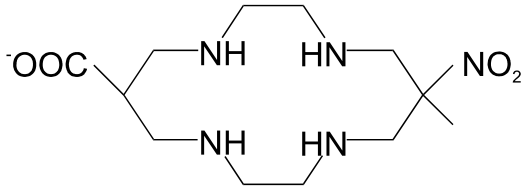
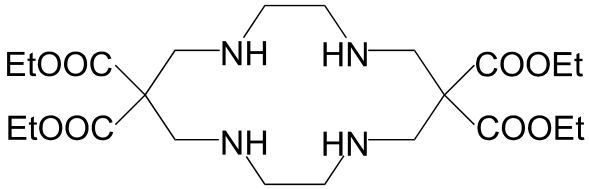
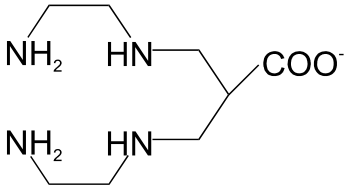


L9



L10



L11

primary amines which may be bridged by a carbon acid / formaldehyde condensation leading to a cyclam analogue with pendants attached to the central carbons of each propane moiety on opposite ends of the macrocyclic ring. If the pendants are arranged in a manner *trans* to each other across the macrocyclic ring, a metal ion can be encapsulated with the metal ion in the centre of the ring and the two pendants taking up the apical sites of the octahedral geometry. The effectiveness of this approach has been shown in the synthesis of the potentially sexidentate ligand L1 using nitroethane as a carbon acid followed by zinc/acid reduction to convert the resultant nitro pendants to primary amines.[2] The reaction provides high yields of the *trans*-pendant form of the ligand with less than 30% of the final yield being the form in which the pendants are arranged *cis* to each other (L4).[3]

Using diethyl (or dimethyl) malonate, routes to both the acyclic 3,7-diazanonane-1,9-diamine-5-carboxylate (L11) and the cyclic dihydrogen *trans*-1,4,8,11-tetraazacyclotetradecane-6,13-dicarboxylate (L3) as well as its *cis* form (L6) have been pursued.[4,5,6] The latter ligand offers two pendant carboxylates in place of the two pendant amines in the analogue *trans*- or *cis*-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine (L1, L4), but has been prepared only in very low yield.[4,6] However, the acyclic ligand bis[(2-aminoethyl)aminomethyl] malonate (L7) can be prepared by a copper(II)-directed reaction in relatively high yield,[5] and the condensation chemistry of a pair of *cis*-disposed primary amines with nitroethane and formaldehyde is known to proceed readily in high yield.[2] We have thus examined proceeding via the copper(II) complex of this acyclic ligand (L7) to prepare the potentially

sexidentate ligand hydrogen 6-methyl-1,4,8,11-tetraazacyclotetradecane-6-amine-13-carboxylate (L2) and its geometric isomer with the pendants arranged in a *cis* manner (L5). This ligand possesses both a pendant amine and a pendant carboxylate group. The chemistry leading to this new polyaminoacid, and comparison with L3, L6 and L1, L4 are described within this chapter. Although the *trans* isomer of L2 predominates, a poorly defined crystal structure of the copper(II) complex of L9, the nitro pendant precursor to L5, confirming selectivity rather than specifity during formation. Indeed, NMR studies of the hydrochloride salts of the dominant trans isomers, L2 and L3, prepared by the methods described herein show the presence of significant amounts of the *cis* isomers (L5 and L6). With this study, the complete set of *trans* and *cis* isomers of cyclam analogues with diamine, amine-carboxylate or dicarboxylate pendants on the sixth and thirteenth atoms of the macrocyclic ring have been observed.

4.2 Experimental

4.2.1 Syntheses

Bis(ethane-1,2-diamine)copper(II) perchlorate was prepared by careful addition of ethane-1,2-diamine to a methanolic solution of copper(II) perchlorate hexahydrate in a 2:1 molar ratio. Precipitation was completed by addition of diethyl ether, and the complex was collected and dried in a vacuum desiccator.

(Ethyl hydrogen bis[(2-aminoethyl)aminomethyl]malonate)copper(II) perchlorate, [Cu(L7)](ClO$_4$)$_2$.

This was prepared essentially as described.[5] To a suspension of bis(ethane-1,2-diamine)copper(II) perchlorate (5 g) in methanol (200 cm^3) was added diethyl malonate (2 cm^3) and triethylamine (2 cm^3). A solution of formaldehyde (2 cm^3, 38% aqueous) in methanol (20 cm^3) was added dropwise over an hour to the refluxing suspension. Reflux was continued for four hours. On cooling, the purple product precipitated and was collected, washed with ethanol and air dried (3.2 g, 46%) (Found C, 24.3; H, 4.8; N, 10.6. Calc. for $C_{11}H_{24}Cl_2CuN_4O_{12}$: C, 24.5; H, 4.5; N, 10.4%). Electronic Spectrum (in water): λ_{max} 531 (ε 75) and 241 nm (ε 7560 dm^3 mol^{-1} cm^{-1}). IR Spectrum (KBr disc): 1730, 1795 (-COOR) cm^{-1}.

(Hydrogen 6-Methyl-6-nitro-1,4,8,11-tetraazacyclotetradecane-13-carboxylate)copper(II) perchlorate monohydrate, [Cu(HL8, HL9)](ClO$_4$)$_2$·H$_2$O.

A solution of [Cu(L7)](ClO$_4$)$_2$ (4 g) in methanol (600 cm^3), triethylamine (4 cm^3) and water (20 cm^3) was stirred at 60°C for four hours. After dilution to 2 dm^3 with water, the solution was sorbed onto a column of SP Sephadex C25 (Na^+ form) resin (20 x 5 cm). A single band was eluted with 0.2 mol dm^{-3} $NaClO_4$ solution, collected and concentrated to 30 cm^3 on a rotary evaporator. This solution of the mono-pendant methoxycarbonyl form of [Cu(L7)](ClO$_4$)$_2$ was then diluted to 200 cm^3 with methanol. To it was added formaldehyde (4 cm^3, 38% aqueous), triethylamine (6 cm^3) and nitroethane (4 cm^3). The solution was stirred at 60°C for 4 hours and then at room temperature for

eight hours. Some 0.5 g of purple precipitate was collected, washed with ethanol and air dried. To the remaining solution, further formaldehyde (2 cm^3, 38% aqueous) and nitroethane (2 cm^3) was added and the solution was stirred at 60˚C for two hours. After this period a further 1.1 g of purple precipitate was collected, washed with ethanol and air dried. Comparison of the infrared spectra of the two separate precipitates showed them to be identical. The combined precipitates were recrystallised from aqueous solution treated with perchloric acid (Found: C, 24.9; H, 4.5; N, 11.6. Calc. for $C_{12}H_{27}Cl_2CuN_5O_{13}$: C, 24.7; H, 4.7; N, 12.0%). Electronic Spectrum (in water): λ_{max} 512 (ε 79), 252 (ε 7770) and 193 nm (ε 6180 $dm^3\ mol^{-1}\ cm^{-1}$). IR Spectrum (KBr disc): 1737, 1716 (-COOR), 1552, 1343 ($-NO_2$) cm^{-1}. Voltammetry: $E_{1/2}(Cu^{II/I})$ -0.46 V (ΔE 330 mV.)

6-Methyl-1,4,8,11-tetraazacyclotetradecane-6-amine-13-carboxylic acid pentahydrochloride tetrahydrate, (HL2, HL5)·5HCl·4H₂O.

$[Cu(HL8,HL9)](ClO_4)_2 \cdot H_2O$ (4 g) was dissolved in 100 cm^3 of water. This solution and hydrochloric acid (3 mol dm^{-3}, 100 cm^3) were added from separate dropping funnels dropwise over one hour to zinc powder (6 g), while stirring. The solution was stirred for a further half hour at 60°C and then filtered to remove copper and any remaining zinc. The solution was diluted to 2 dm^3 with water and sorbed onto a column of Dowex 50Wx2 (H^+ form) resin (4 x 15 cm). The column was washed with 1 mol dm^{-3} HCl until no further evidence of zinc(II) ion elution (i.e. formation of zinc hydroxide on addition of base) was present, and then the product was eluted with 3 mol dm^{-3} HCl (elution of the required macrocycle being indicated by the formation

of an acid stable species on addition of base and Cu^{2+} to an aliquot of the eluent). The product was taken to dryness on a rotary evaporator, washed with ethanol then diethyl ether and dried in a vacuum desiccator (1.5 g). On recrystallization, the major *trans* isomer crystallised preferentially, as indicated by NMR spectroscopy. (Found C, 27.7; H, 7.1; N, 13.3. Calc. for $C_{12}H_{40}Cl_5N_5O_6$: C, 27.3; H, 7.6; N, 13.3%). NMR (D_2O): ^1H, δ 1.60 (s, 3H) 2.8 - 3.8 (m, 17H); ^{13}C, δ 20.8, 50.6, 47.8, 47.3, 41.9, 54.1, 55.6, 174.8 p.p.m.

1,4,8,11-tetraazacyclotetradecane-6,13-dicarboxylic acid Hydrochloride, (H_2L3, H_2L6)·4HCl.

Bis(ethane-1,2-diamine)copper(II) perchlorate (16.3 g) was dissolved in methanol (300 cm^3) and heated to 50°C. To this solution were added diethyl malonate (12.5 cm^3), formaldehyde solution (12 cm^3, 38% aq) and triethylamine (10.5 cm^3), and the solution was refluxed for three hours. Additional diethylmalonate (2 cm^3) and formaldehyde (2 cm^3) were added, and the solution stirred and allowed to cool slowly to room temperature. Following refrigeration, a pink precipitate was collected, dissolved in water (2 dm^3) and sorbed onto a column of SP-Sephadex C-25 resin (20 x 5 cm). Only one major band was recovered upon elution with 1 mol dm^{-3} NaCl. As the volume of the solution was reduced by rotary evaporation, a pink solid precipitated, and was collected, washed with ethanol and air dried (1.4 g, 5%). The synthesis was repeated to obtain more of the intermediate tetraethyl 1,4,8,11-tetraazacyclotetradecane-6,6,13,13-tetracarboxylate complex (L10). This complex (2.8 g) was dissolved in methanol (200 cm^3) containing 4 cm^3 of water by heating to 60°C, the pH was raised to >10 by

addition of triethylamine, and the solution stirred for 20 hr. After dilution to 2 dm^3 with water, the solution was sorbed onto a column of SP-Sephadex C-25 resin (20 x 5 cm) and eluted with 0.2 mol dm^{-3} $NaClO_4$ solution. One major acid-stable band and two minor bands which were not acid stable and hence not macrocyclic compounds were collected. The major band and a solution of 3M HCl (30 cm^3) were placed in separate dropping funnels and added dropwise with stirring to powdered zinc (6 g). The reducing solution was stirred at 60°C after addition for a further 30 min, then filtered to remove reduced copper and unreacted zinc metal. After dilution to 2 dm^3, the solution was sorbed onto a column of Dowex 50Wx2 resin (4 x 15 cm), washed with 0.2 dm^3 water and 0.5 mol dm^{-3} HCl, then eluted with 3 mol dm^{-3} HCl, the product being detected by testing small aliquots regularly with copper ion and base addition. The product was taken to dryness on a rotary evaporator, collected, washed with ethanol and ether, and dried thoroughly (0.9 g). On recrystallization, the major *trans* isomer crystallised preferentially, as indicated by NMR spectroscopy. (Found: C, 32.7; H, 6.9; N, 12.8%. Calculated for $C_{12}H_{24}N_4O_4 \cdot 4HCl \cdot 0.5H_2O$: C, 32.5; H, 6.6; N, 12.65%; acid content confirmed by potentiometric titration). NMR (D_2O): ^1H δ 3.4 - 3.9 (q x 3, overlapping); ^{13}C δ 41.0, 45.4, 48.2, 174.6 ppm.

4.2.2 Physical Methods

Electronic spectra (in aqueous solutions), IR spectra(as KBr discs), electrochemical measurements (at an EG&G PAR Model 303A static mercury drop electrode) and NMR spectra (in D_2O) were recorded as described in earlier chapters. Potentiometric titrations were carried out essentially as

described previously [7] using a Metrohm 665 automated burette and an IBM clone computer fitted with a Fylde Scientific pH card connected to a Metrohm combined glass electrode. All measurements were performed as described in Chapter 2, with equilibrium constants calculated from potentiometric data with a TURBO BASIC version of the program TITFIT[8]. For each system, each titration was repeated at least three times, with good reproducibility (*ca* ± 0.1 log units) in the determined constants.

4.2.3 X-Ray Crystal Structure Determination

Crystal data . [Cu(L8)H_2O]$(ClO_4)_2.H_2O$. $C_{12}H_{33}Cl_2CuN_5O_{16}$, M = 637.87, orthorhombic, space group *Pnma*, *a* = 9.352(4), *b* = 11.194(2), *c* = 24.802(6) Å, *V* = 4305(1) $Å^3$, D_c (*Z* = 4) = 1.632 g cm^{-3}, F(000) = 1324 electrons, μ(MoKα) = 1.127 mm^{-1}. A $_{min.,max.}$ 1.13, 1.21, range of *hkl* 0 to 13, -1 to 11, -29 to 0, *R*1[*I*>2σ(*I*)]= 0.1026, w*R2 = 0.2911*, residual extrema +0.305, -0.927 e $Å^{-3}$, weight = $1/[\sigma^2(F_o^2)+ (0.2532P)^2$ where P = (Max (F_o^2, 0) + 2 x F_c^2)/3.
Data was measured at 294 K on an Enraf-Nonius CAD4F four-circle diffractometer by Dr T. W. Hambley at the University of Sydney employing graphite monochromated MoKa radiation (0.7107 Å). Data were reduced and Lorentz, polarization and absorption corrections were applied using the Enraf-Nonius Structure Determination Package. Of the 2505 independent non-zero reflections collected 2429 with $I > 2.0\sigma(I)$ were considered observed and used in the calculations. The structures were solved by direct methods, using SHELX-86 [9] and the solutions were extended by difference Fourier methods. Hydrogen atoms were included at calculated sites (C-H 0.970, N-H 0.910 Å) with group isotropic thermal parameters. All other atoms were

refined anisotropically. Scattering factors and anomalous dispersion terms used were those supplied in SHELX-93.[10] All calculations were carried out using SHELX-93, and plots were drawn using ZORTEP.[11]

4.3 Results and Discussion

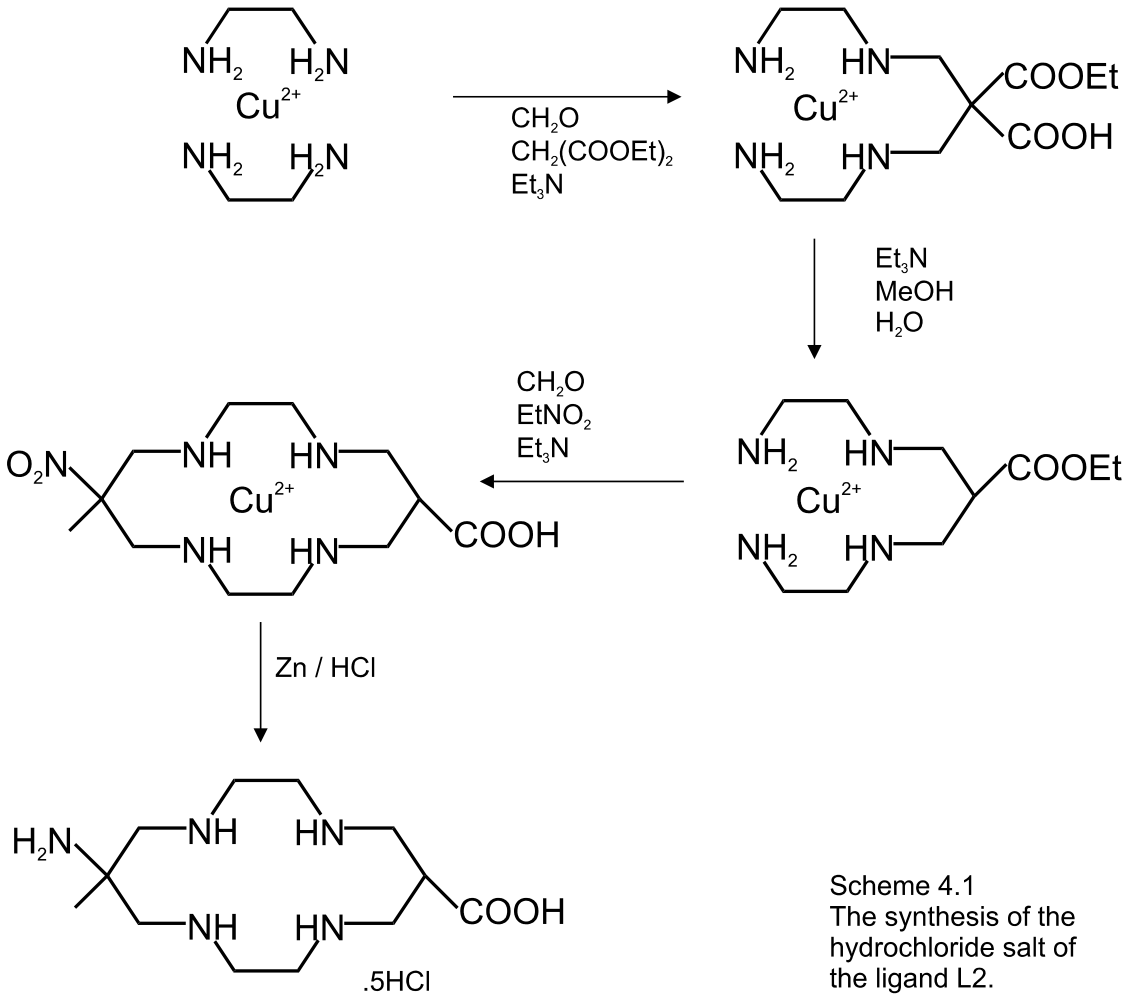
4.3.1 Ligand Synthesis

The synthesis of acammac, which forms selectively as the *trans* isomer L2, proceeded as shown in Scheme 4.1. The second condensation, using nitroethane to produce the complex of the macrocycle L8 was best pursued via the acyclic complex of the monoester L7, as it was found that direct reaction of the acid ester without isolation of the intermediate tended to lead to decomposition and lower yields in reactions where methanol was used as the solvent. If water was used as the solvent and sodium hydroxide as the base, it was found possible to proceed with good yields directly from the acid ester acyclic complex L7. However, the solubility of the product in water meant that it was much more difficult to isolate the product in reasonable yield and further chromatography was necessary to separate the desired product from starting material and decomposition products. Using methanol as a solvent, triethylamine as the base and the monoester as the template, the copper complex of the target macrocycle precipitated as a pure solid, albeit as a mixture of the *cis* and (dominant) *trans* isomers. Zinc acid reduction readily yielded the free acammac ligand, which was characterised by NMR spectroscopy. The less symmetrical nature of the acammac ligand in

comparison with diammac results in a doubling of peaks (from 3 to 6) in the region associated with the ring carbons in the ^{1}H decoupled ^{13}C NMR. The peak due to the primary carbon remain in essentially the same position and a

new peak appears at ~175 ppm corresponding to the carboxylate carbon (see Figure 4.1).

Both acammac (L2, L5) and diacmac (L3,L6) have the potential to bind as sexidentate ligands like their analogue diammac (L1, L4). All ligands are based on the fourteen-membered cyclam macrocycle with pendant groups attached to each central carbon of the two $-(CH_2)_3-$ chains of the molecule. In principle, two geometric isomers may exist in each case, depending on whether the two potentially coordinating pendants are on opposite sides (*trans*) or the same sides (*cis*) of the macrocyclic plane. For diammac, the *trans* isomer (L1) predominates, although the minor and very soluble *cis* isomer (L4) has been isolated.[3] Likewise, the *trans* isomer predominates for acammac and diacmac.



Scheme 4.1
The synthesis of the hydrochloride salt of the ligand L2.

The amount of *cis* isomer of acammac detected was dependant on the method of isolation used. If, after reduction and chromatography, the volume of the eluent containing the free ligand salt was reduced to around 100 cm^3 and then the solution left to crystallise at 4° C overnight (with the addition of some ethanol to aid precipitation), the product isolated tended to be isomerically pure. Chromatographic and NMR studies of the solid and its copper complex showed no evidence for two isomers, the *trans* isomer being the only one found, as defined in a number of x-ray crystal structures of the cobalt complex of this hydrochloride salt (discussed in more detail in the next

chapter). However if the eluent from the chromatography of the reduction step is taken to dryness,

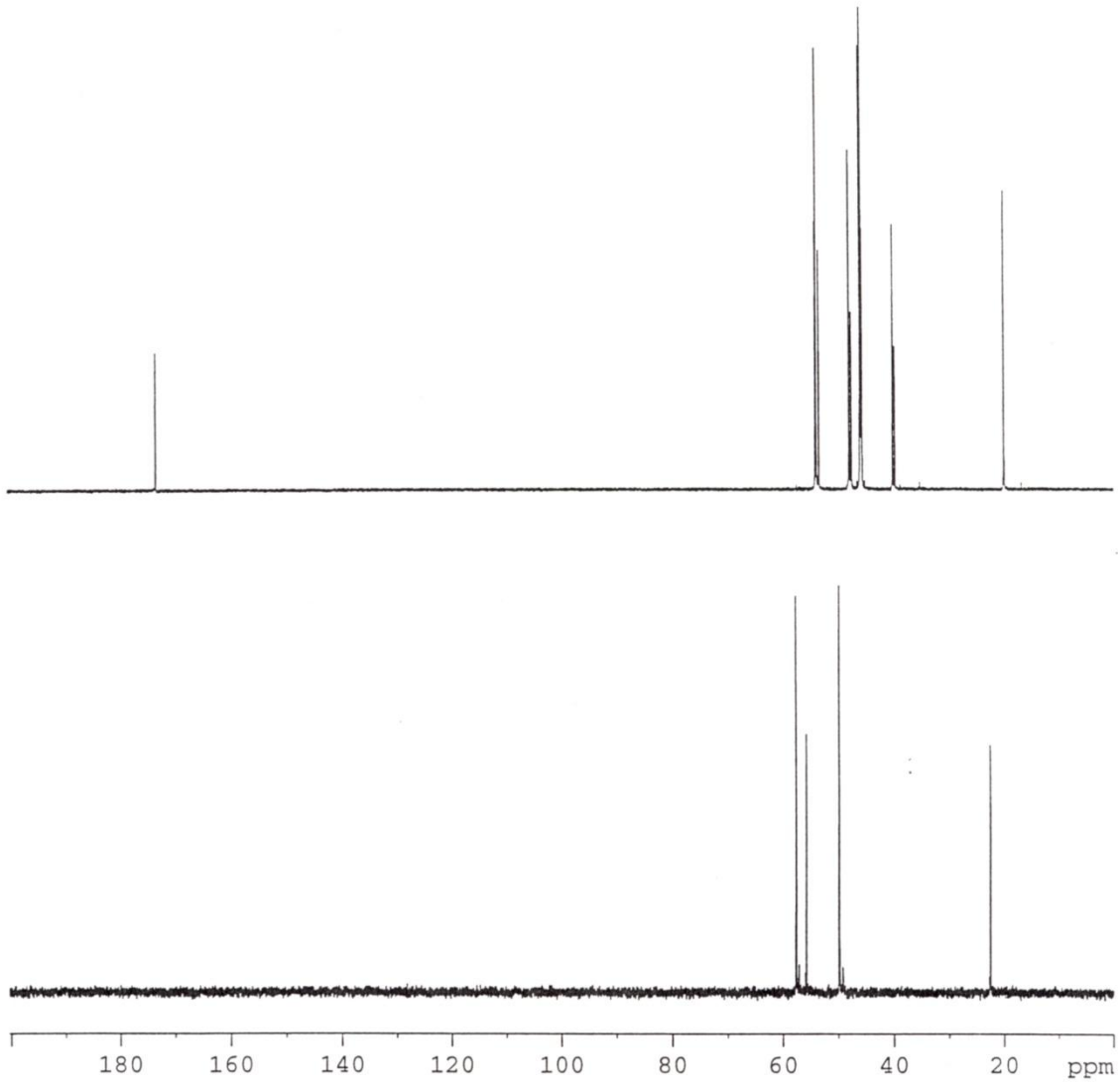


Figure 4.1. The ^{1}H decoupled ^{13}C spectra hydrochloride salts of acammac (L2, upper) and diammac (L1, lower). (*Trans* isomer dominant in both spectra.)

NMR studies of the analytically pure white solid isolated suggest the presence of two isomers. This is apparent in the proton NMR by the appearance of a shoulder on the methyl peak at δ 1.60 and in the ^{13}C by a splitting of the methylene carbon peaks. Shoulders also appear on the methyl and carboxylate peaks. Deconvolution of these spectra at high resolution suggested that up to 20% of the *cis* isomer could be present. Axial interaction of the carboxylate of the half-capped intermediate was considered likely to direct the chemistry towards the *trans* isomer by blocking one site, with additional weak axial interaction of the nitro group in the other *trans* position during ring formation leading to the isomeric selectivity observed, as discussed more fully later. This is supported to some extent by NMR studies of the free ligand mixtures produced from the reduction of the copper complex of acammac produced by the alternative method in which the condensation is carried out directly on L7 in aqueous conditions without the benefit of the intermediate decarboxylation / hydrolysis step described above. NMR studies of the free ligand isolated from this procedure suggested a somewhat greater proportion of the *cis* isomer, around 30 to 40 % (see Figure 4.2). This lower selectivity may be linked to the presence of the gem carboxylate/ester groups, leading to weaker axial interaction, in turn thought to contribute to reduced stereoselectivity.

Although the free polyaminoacid ligand crystallised preferentially as the *trans* isomer, recrystallisation of the copper(II) complex of the nitro pendant precursor resulted in the preferential crystallisation of a small amount of the *cis* isomer (L9). X-ray crystallography of the resulting crystals produced a

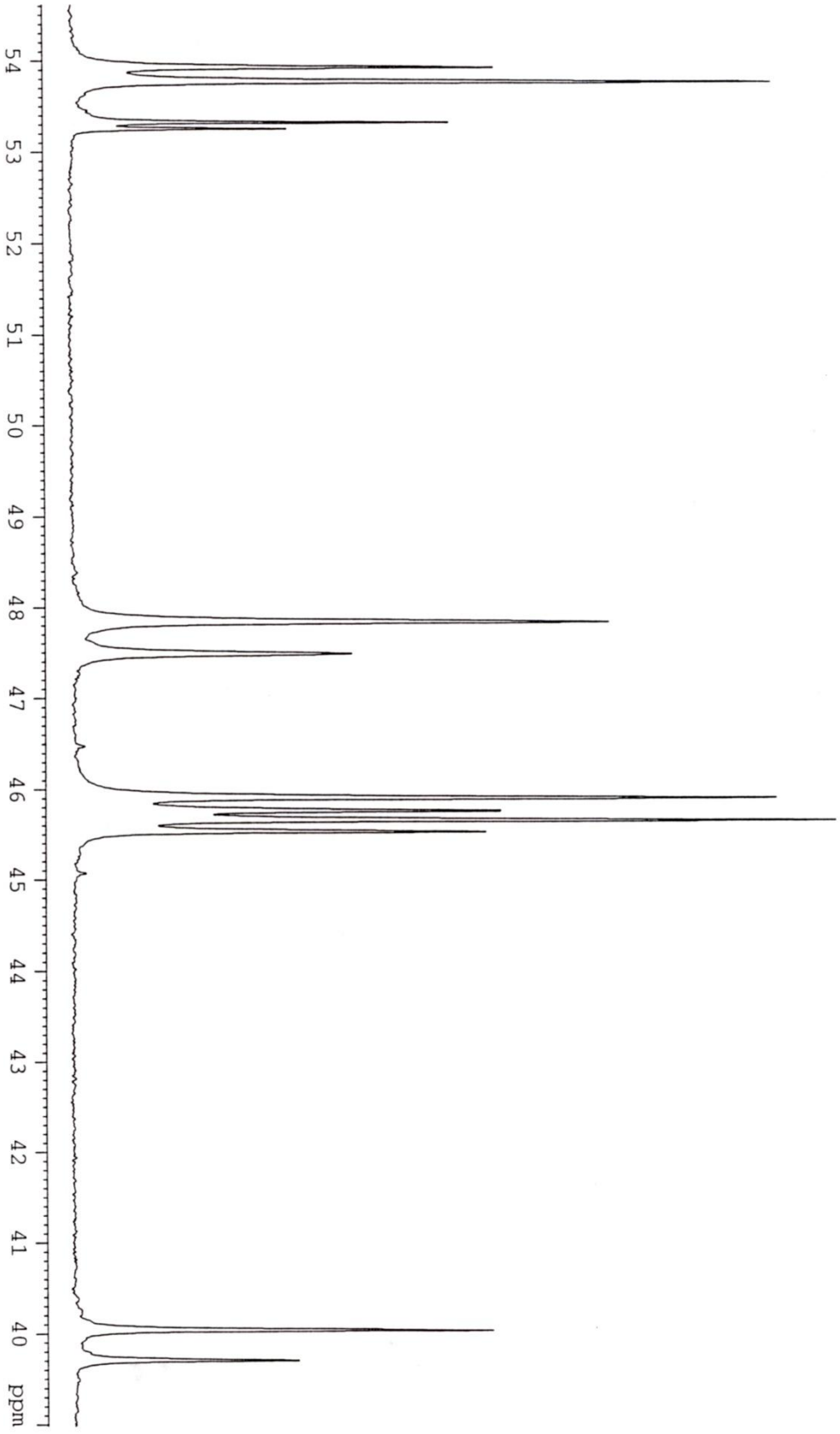
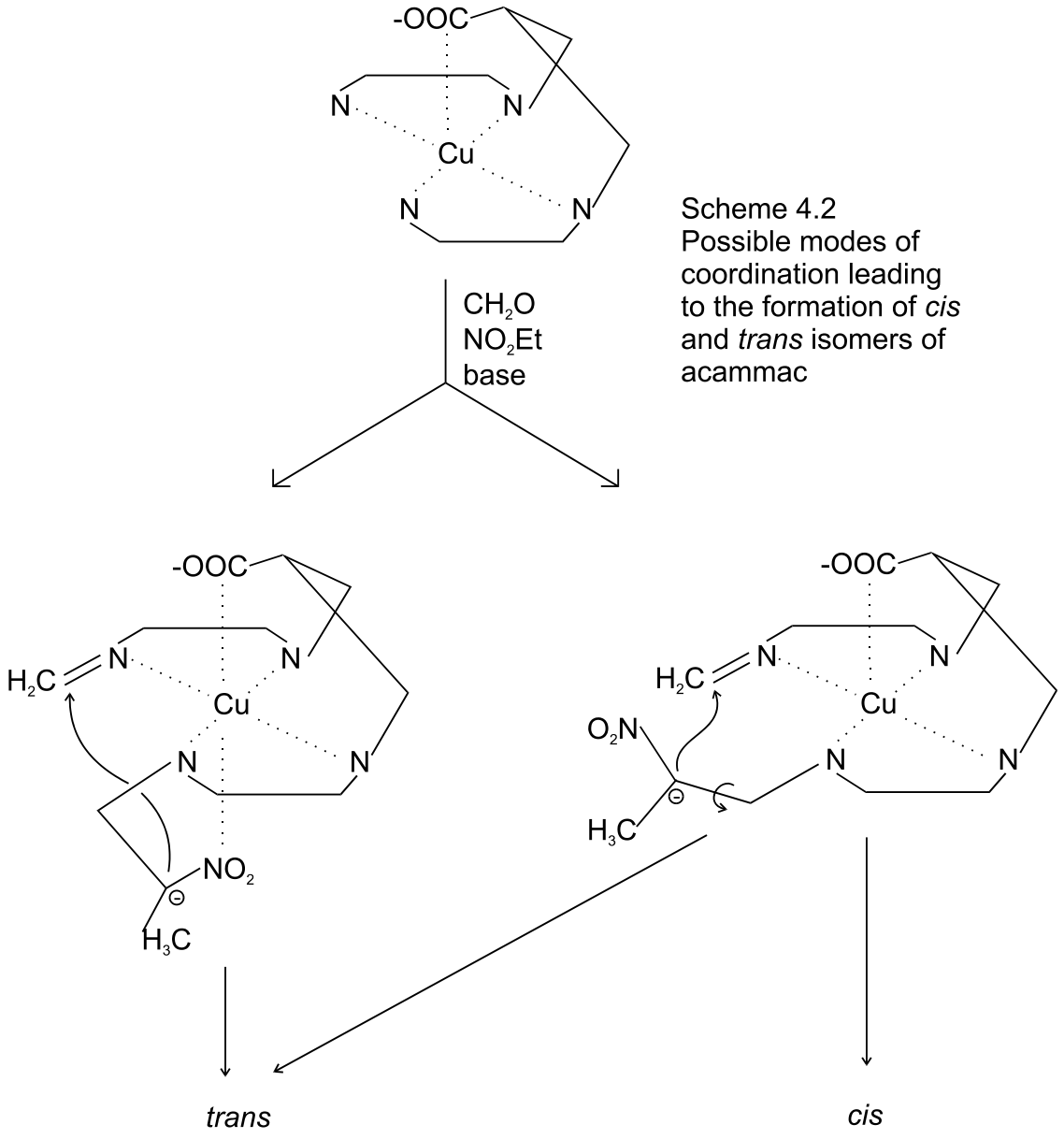


Figure 4.2. A portion of the ^{1}H-decoupled ^{13}C NMR spectrum for a mixture of the hydrochloride salts of L2 and L5.

poorly defined structure of the complex. Limited crystal quality and disorder of the waters and the perchlorate ion in the structure resulted in a relatively large final R value, but connectivity and spatial geometry in the macrocycle itself was sufficiently well defined to confirm the complex as the *cis* isomer, as discussed below. Chromatographic studies of the copper complex of L8, L9 on both Dowex and Sephadex cation exchange columns resulted in a number of bands. The position and number of bands vary with pH conditions, with electronic spectroscopy not supportive of the separation of the different geometric species. The bands probably arise from a combination of protonation / deprotonation of the carboxylate pendant and N based isomers. The presence of the carboxylate groups, which change the overall charge on the complex ion as it is protonated or deprotonated, makes separation of the *cis* and *trans* isomers by chromatography of the copper complex of L8, L9 difficult. It is notable that the dinitro precursor of diammac separated into its isomers by normal-pressure cation exchange chromatography of its copper complex.[12] Although diammac can be separated successfully as its copper complex, the same facility did not transfer readily to acammac. We found separation was achieved only via the inert cobalt(III) complex, described in the following chapter.

The predominance of the *trans* isomer may be a result of the synthetic method, since the carboxylate in the acyclic intermediate may adopt a geometry where it binds weakly in one axial site, effectively 'closing off' one side of the CuN_4 plane. Subsequently, the condensation chemistry with nitroethane and formaldehyde will either occur effectively on the 'opposite'

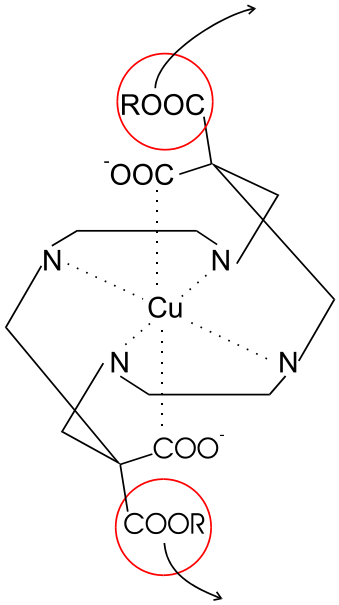
side of the molecule with the -NH-CH_2-$CH(CH_3)NO_2$ arm of the half built strap interacting in the opposite axial site to direct formation of the *trans* isomer, or else reacting when displaced well away from the axial site with modest discrimination anticipated, leading overall to dominantly the *trans* isomer. This is shown in Scheme 4.2. The same type of directing ability by an acyclic nitro-substituted



Scheme 4.2
Possible modes of coordination leading to the formation of *cis* and *trans* isomers of acammac

intermediate has been proposed to account for the dominance of the *trans* isomer L(1) in the synthesis which produces diammac,[3] although in that case the weaker interactions of nitro groups in each axial site permits a greater amount of the *cis* isomer to form. The diacmac ligand (L3, L6), with two pendant carboxylates, has been prepared in only low yield, but NMR studies show a similar splitting of the carboxylate peak in the ^{13}C spectra. Once again, quantifation of the various forms of this complex is difficult, but the *cis* isomer would appear to be present in similar quantities as that found for the isomers of L2. The initial product from the condensation reaction to produce L3 is a tetraester (L10), hence there are no geometric isomers. However, isomeric selectivity probably arises in this case during the hydrolysis/decarboxylation step leading to the formation of diacmac (L3, L6). Coordination of one carboxylate both protects it from decarboxylation and activates hydrolysis and decarboxylation of the 'external' group, leading preferentially to the *trans* isomer (see scheme 4.3). Where axial interaction does not occur, no selectivity is expected, but nor is any activation of the process.

An ORTEP view of the structure of the *cis* isomer of the copper(II) complex of L8 is shown in Figure 4.3. The heavily disordered perchlorate ion and waters have been omitted from this view for clarity, but this does not alter the important features of the structure. The *cis* arrangement of the $-NO_2$ and -COOH pendants is obvious from the figure. The molecule has a plane of symmetry running along the axis made up by the nitrogen of the nitro group, the central copper ion, the carboxylate carbon, O1 of the carboxylate and the



Scheme 4.3
Possible mode of coordination leading to the preferential formation of *trans* diacmac

carbons C4 and C6. The methyl group and O2 also lie partly on this plane contributing to the disorder of the structure. This plane of symmetry can be inferred from the lower view of Figure 4.4. Interestingly, the carboxylate oxygen O1 is also bonded to another copper center in an adjacent molecule. This results in a form of carboxylate bridged polymer in which the adjacent macrocyclic planes are almost at right angles to each other. This can be clearly seen in Figure 4.4. Carboxylates acting as bridging groups between metal centres have been reported for a number of species,[13] including those discussed in Chapter 3. The nitro oxygens show no interaction with the metal centres, although there is evidence of an interaction with one of the three water molecules found with each metal complex. The perchlorate counter ion is weakly bound to the copper atom on the opposite side to the carboxylate oxygen yielding a pseudo-octahedral geometry about the copper ion. Unlike the examples of carboxylate bridged metals centres found for nickel complexes of L2 (discussed in Chapter 5), neither carboxylate oxygen interacts with the

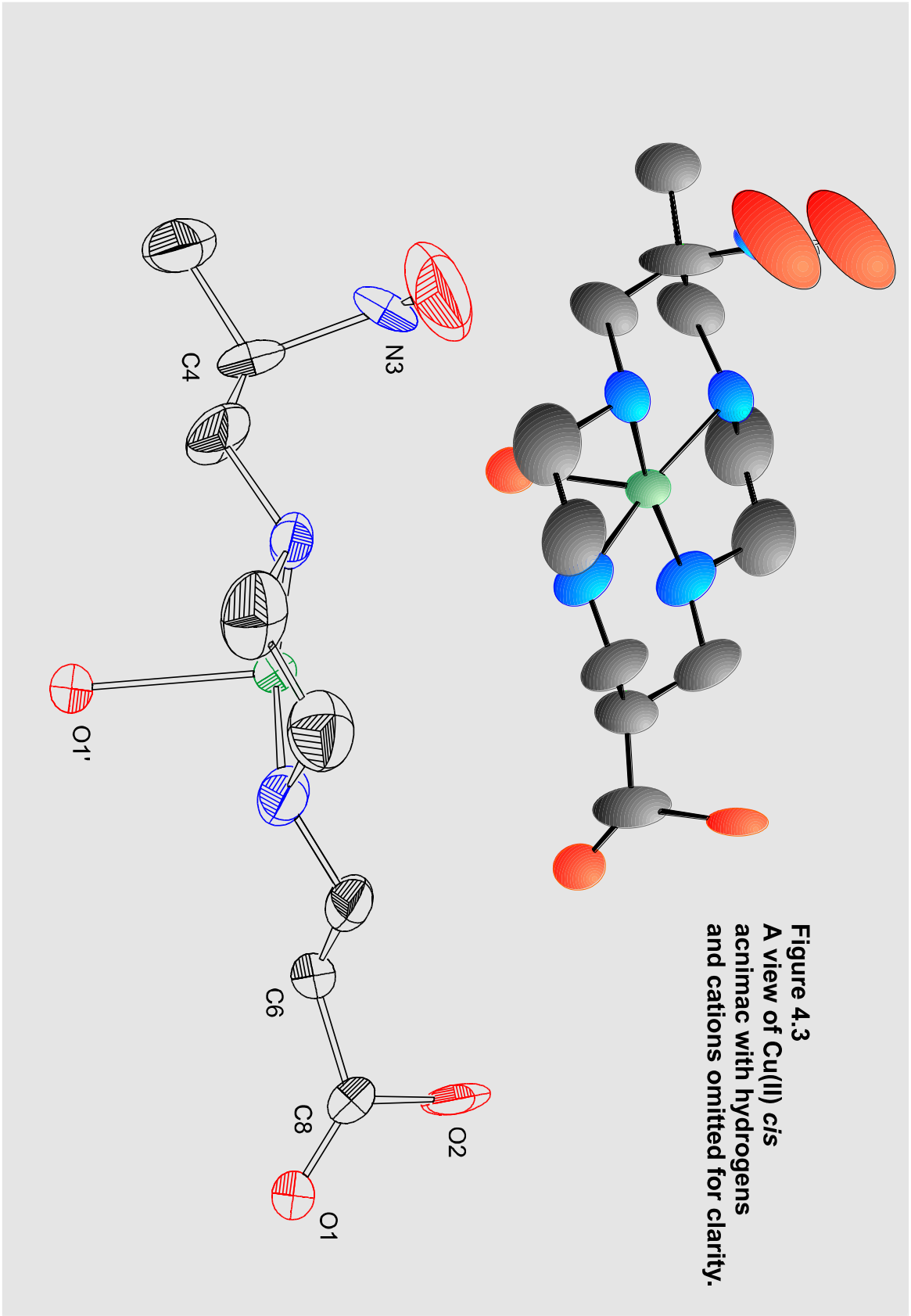


Figure 4.3
A view of Cu(II) *cis* acnimac with hydrogens and cations omitted for clarity.

metal centre of its own macrocycle. This is probably due to the difficulty of accommodating the long axial bond lengths preferred by copper(II) due to Jahn-Teller distortion[14] within the seven membered chelate ring which would need to form for such an interaction.

It was found possible to precipitate the copper(II) complex of L8, L9 as either the protonated or deprotonated species depending on the pH of the solution from which it was crystallised. This was shown in the infrared spectra by a shift in the position of the carboxylate absorbance from 1730 cm^{-1} to approximately 1600 cm^{-1}. The latter value is consistent with that observed for carboxylate ions coordinated to metals.[15] Individual reduction of these compounds both produced the same mixture of isomers of the reduced acammac ligand. The precipitate from the reaction solution generally showed two absorbances near 1730 cm^{-1}, regardless of the batch examined. Since these two peaks are nearly of the same intensity, it is doubtful if this is an indication of the presence of the *cis* isomer as it would imply almost equal quantities of the two isomers which is not supported by the amounts clearly defined by other spectroscopic methods. The doubling of peaks is more likely due to two different environments for carboxylate groups within the solid.

4.3.2 Potentiometric Titrations

Protonation equilibrium studies of the hydrochloride salts of the dominant *trans* isomers L1, L2 and L3 were undertaken as a prelude to complexation studies with d^{10} metal ions (discussed in Chapter 5). Given the common

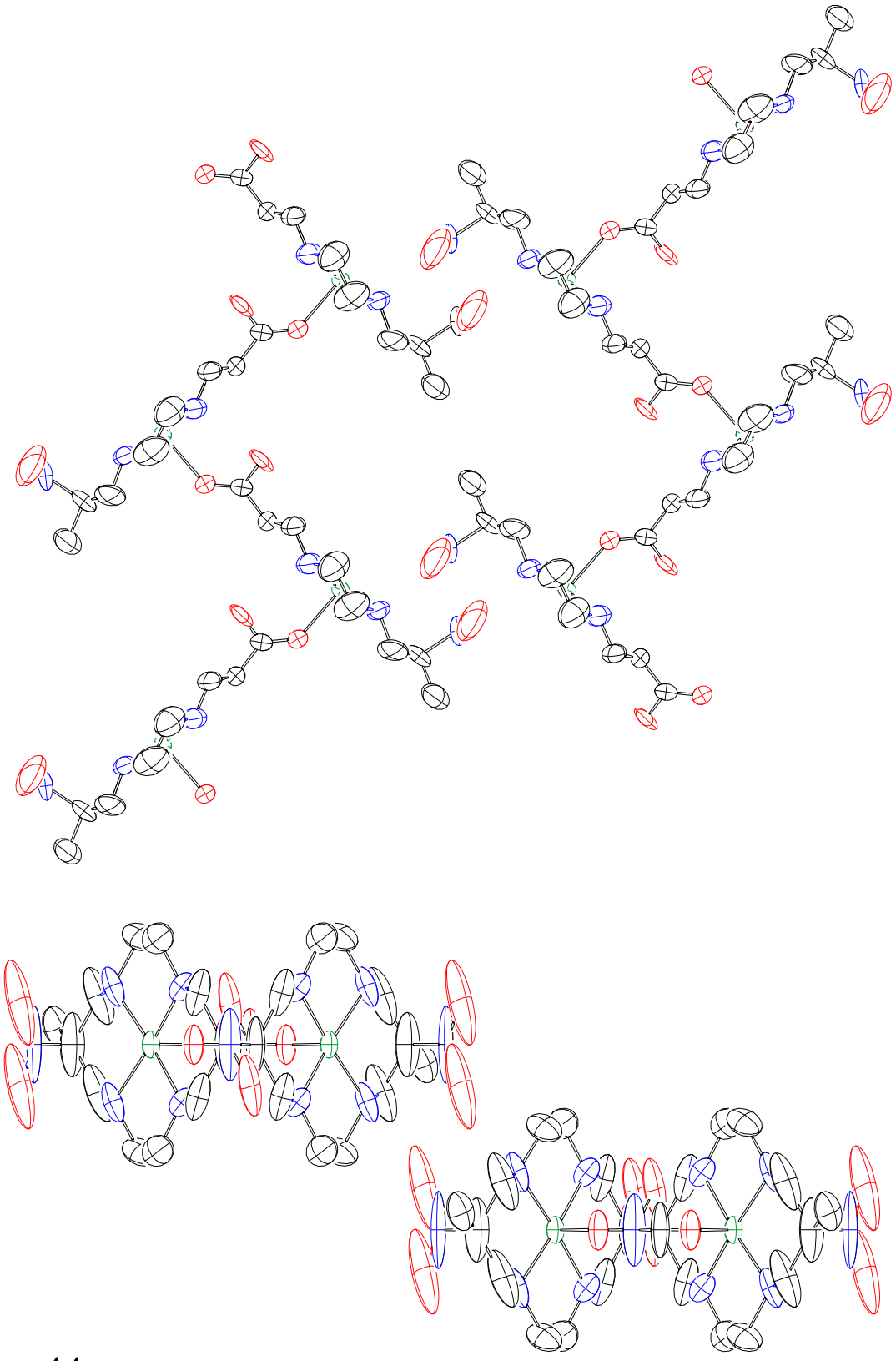


Figure 4.4
Two views showing the arrangement of molecules within the crystal of Cu(II) acnimac (L8). Counter ions, hydrogens and water molecules are omited for clarity.

framework of the ligands, it is not unreasonable to find that the protonation constants of all ligands are somewhat similar (Table 4.1).[16,17,18] In the data presented in the table, L represents the neutral hexamine (L1), or else the deprotonated amino acid (L2 and L3), and hence six protonation steps can be

Table 4.1

The logarithms of the protonation constants for trans dipendant-macrocycles. Some comparative values for cyclam are included; charges are omitted for clarity.[a]

Complex	diacmac (L3)	accammac (L2)	diammac (L1)	cyclam
$H + L \Leftrightarrow HL$	10.5	10.6	11.0	11.6
$HL + H \Leftrightarrow H_2L$	9.9	9.9	10.0	10.6
$H_2L + H \Leftrightarrow H_3L$	6.4	4.0	6.2	-
$H_3L + H \Leftrightarrow H_4L$	5.5	3.2	5.5	-
$H_4L + H \Leftrightarrow H_5L$	3.2	3.1	1.5	1.6
$H_5L + H \Leftrightarrow H_6L$ [b]	<1.5	<1.5	<1.5	<1.5

(a) 25 °C, I = 0.5 mol dm^{-3} KCl, standard errors are ±0.1 units.

(b) sixth protonation not determined (< 1.5).

expected for each ligand. The first and second protonations occur with pK_a values near 11 and 10 in all ligands, and are associated with protonation of the secondary amines in the macrocycle ring, with the protons shared between adjacent pairs of amines within the ring.[17,18] The next two steps in L1 (and the next step in L2), which are absent in the unsubstituted cyclam, are assigned to protonation of the pendant primary amines. Introduction of the last two protons into the ring occurs only with difficulty, and only one of the two can be observed (pK_a *ca* 2), the final protonation being inaccessible in dilute aqueous acid. Protonation of the two carboxylate groups in L3 and the single group in L2 occur with pK_a values between *ca* 3 and 6, as anticipated for such groups. Where two acid groups are present, the pK_a values are higher. In both L3 and L2 the protonation assigned to the final amines occurs more readily, presumably as a result of electronic influences of the carboxylate groups, or else as a result of zwitterionic behaviour. Formation constants for metal ion complexes of this series of cyclam analogues with pendant amine or carboxylate groups are discussed in the following chapter.

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