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FULL PAPER

Copper(II) complexes of the isomeric tetraazamacrocyclic ligands 1,11- and 1,8-bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane and of the 1,4,8,11-tetraazacyclotetradecane-5,12-dione analogue at neutral and basic pH

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Received 27th January 2000, Accepted 3rd May 2000
Published on the Web 26th May 2000

The regioselective synthesis of the new N,N′-dialkylated tetraazamacrocycle 1,11-bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane, L^1, has been achieved. The copper(II) complexes of L^1 and of the isomeric ligand 1,8-bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane, L^2, have been isolated and their crystal structures determined. The structure of $[CuL^2]^{2+}(CH_3CO_2^-)_2$, reveals planar N_4 co-ordination of the copper by the macrocycle, which adopts the *trans*-III configuration, and with the pendant pyridine nitrogens occupying the elongated axial sites. In contrast, in $[CuL^1]^{2+}(ClO_4^-)_2$, the copper is 5-co-ordinated by the four nitrogen atoms of the macrocycle, which adopts the *trans*-I configuration, and one pendant pyridine nitrogen, forming a distorted square pyramid with the pyridine nitrogen at the apex. The new macrocyclic dioxotetraamine 1,8-bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane-5,12-dione, L^3, has also been prepared. The crystals obtained upon reaction of L^3 with copper(II) perchlorate under neutral conditions have been shown by X-ray diffraction analysis to contain two distinct macrocyclic units containing copper ions. In the first a single copper centre is co-ordinated by the two *trans*-orientated amino nitrogens of the macrocycle, the two pyridine nitrogens and one deprotonated amide nitrogen, forming a distorted trigonal bipyramid. The second has a 2 : 1 metal:ligand stoichiometry and, in the unit cell, bridges two complexes of the first type. In contrast, crystallisation under basic conditions leads to a 1 : 1 complex in which the two amides are deprotonated and the copper ion is bound within the macrocycle, weakly co-ordinated by the two pyridine nitrogens in elongated axial sites. The behaviour of the three complexes in solution has been studied by ESR, UV-visible absorption spectroscopy and by cyclic voltammetry.

Introduction

Tetraazamacrocycles continue to attract a huge amount of research interest, owing to their ability to form complexes with a large range of metal ions, often with very high thermodynamic and kinetic stability with respect to metal ion dissociation.[1] Macrocycles bearing additional pendant co-ordinating groups have been of particular interest, as their properties and selectivity for certain metal ions over others may be quite different from those of the unsubstituted parent macrocycles. Whilst the majority of studies have focused on fully N-substituted derivatives, with four additional co-ordinating arms, the number of selective syntheses of mono-, di- and tri-substituted derivatives reported is increasing. For example, in the case of the macrocycle cyclam, which occupies a central position in this field, new syntheses have appeared very recently both for mono- and tri-substituted derivatives.[2,3]

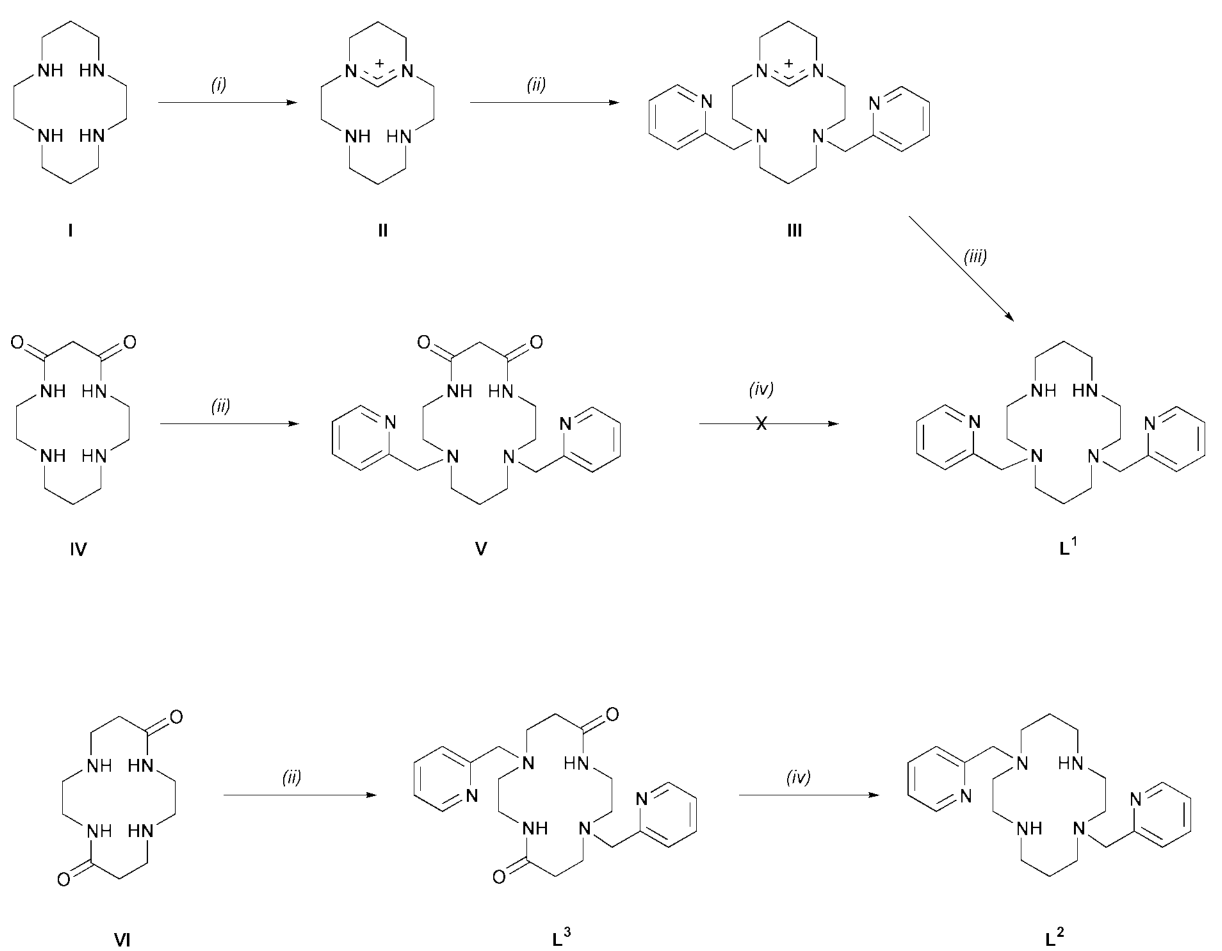
Di-N-alkylation of cyclam has also been investigated. In this case, there are three possible isomers, namely the 1,8-, 1,11- and 1,4-disubstituted derivatives, and routes have emerged for the selective preparation of all three.[4–7] Disubstitution with co-ordinating groups should lead to hexadentate ligands and potentially octahedral complexes with metal ions, as has been found for some 1,8-disubstituted systems.[8] Nevertheless, there has been very little attempt to investigate the co-ordinating properties of analogous 1,11-disubstituted ligands: the effect of 1,11 *versus* 1,8 isomerism on the structures of the resulting complexes has gone largely unexplored.[9] Here, we describe the preparation of the copper(II) complexes of the isomeric ligands L^1 and L^2 and report on their structural characterisation both in the solid state and in solution.

Macrocyclic dioxotetraamines, which contain two amino nitrogens and two amides, have also received attention.[10] They are able to bind to metals like copper(II) and nickel(II) with simultaneous dissociation of the two amide protons, such that metal binding is highly pH-sensitive. The reversibility of metal binding has led to recent interest in such ligands for metal-sensing applications.[11] A number of studies have examined dioxocyclam (1,4,8,11-tetraazacyclotetradecane-5,7-dione) and its 1,11-dialkylated derivatives,[12] but the isomeric *trans* dioxocyclams based on 1,4,8,11-tetraazacyclotetradecane-5,12-dione (herein referred to as *trans*-dioxocyclam) have received little attention. Indeed, there appear to be no reports of the metal-complexing properties of such ligands. The ligand 1,8-bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane-5,12-dione is reported here, together with the structural charcterisation of its copper(II) complex at neutral and at basic pH.

Results and discussion

Ligand synthesis

The synthetic routes used to prepare ligands L^1–L^3 are summarised in Scheme 1. Since the attempted reduction of compound **V** with BH_3–thf or $LiAlH_4$ failed to provide L^1, an alternative route for selective 1,11-disubstitution of cyclam was employed, involving the intermediacy of a formamidinium salt, **II**, as reported by Wainwright and co-workers.[6] In the



Scheme 1 (i) $(CH_3)_2NCH(OCH_3)_2$, chloroform, reflux; (ii) 2-(chloromethyl)pyridine hydrochloride, sodium carbonate (4 equivalents), potassium iodide (catalytic), acetonitrile, reflux; (iii) NaOH (aq, 10 M); (iv) BH_3–thf, reflux.

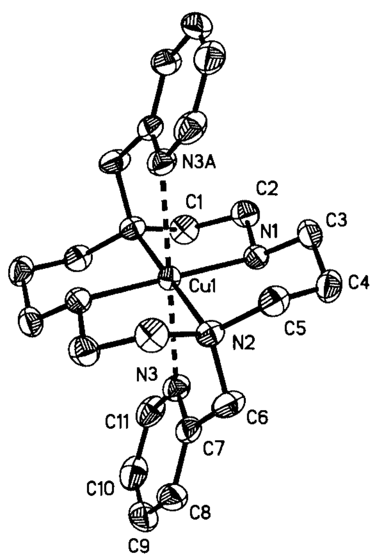


Fig. 1 Molecular structure of $[CuL^2]^{2+}$ in the acetate salt, showing the atom numbering scheme used in Table 1. Hydrogen atoms are omitted for clarity.

case of L^3, reduction of the amide groups using BH_3-thf did lead to the formation of the desired ligand L^2, albeit in very low yield and the overall viability of this route is further limited by the low yield of formation of the precursor **VI**.[13] A more convenient and much higher-yielding route to this ligand has been reported recently, involving dialkylation of 1,4,8,11-tetraazatricyclo[9.3.1.$1^{4,8}$]hexadecane using an excess of 2-chloromethylpyridine, and this method was therefore adopted here.[5] The copper(II) complexes were prepared by addition of a stoichiometric amount of copper(II) acetate or copper(II) perchlorate to a solution of the ligand in methanol or ethanol, followed by slow recrystallisation from methanol or acetonitrile–diethyl ether.

Table 1 Selected bond lengths (Å) and angles (°) for $[CuL^2]^{2+}(CH_3CO_2^-)_2$

Cu(1)–N(1)	2.015(1)	N(1)–Cu(1)–N(1)#1	180.00(6)
Cu(1)–N(2)	2.079(1)	N(1)–Cu(1)–N(1)#1	86.65(4)
Cu(1)–N(3)	2.524(1)	N(1)–Cu(1)–N(2)	93.35(4)

Symmetry operator: #1 $-x + 1$, $-y$, $-z + 1$.

Structural characterisation in the solid state

Crystallographic analysis of $[CuL^2]^{2+}(CH_3CO_2^-)_2$ shows the metal ion to be co-ordinated by the four nitrogen atoms of the macrocycle and by the nitrogen atoms of the pyridine rings, which occupy axial sites at a much greater distance, leading to a severely tetragonally elongated octahedral geometry with an inversion centre at the metal (Fig. 1). Selected bond lengths and angles are shown in Table 1; the Cu–NH bond length of 2.015(1) Å is close to that in the copper complex of cyclam itself (2.02 Å),[14a] whilst the bonds to the alkylated ring nitrogens are rather longer, at 2.079(1) Å. This is to be expected, a large number of studies having demonstrated that M–N bond lengths are increased by N-alkyl substitution.[14b] The Cu–N (pyridyl) bond lengths of 2.524(1) Å are clearly much longer than those to the alkyl nitrogens. This large difference in bond lengths is, of course, consistent with a strong in-plane ligand field provided by the nitrogen atoms of the macrocycle compared to the weaker pyridine donors, notwithstanding the

Table 2 Selected bond lengths (Å) and angles (°) for $[CuL^1]^{2+}(ClO_4^-)_2$

Cu(1)–N(2)	2.030(3)	Cu(1)–N(3)	2.091(2)
Cu(1)–N(1)	2.048(3)	Cu(1)–N(5)	2.209(3)
Cu(1)–N(4)	2.059(3)		
N(2)–Cu(1)–N(1)	92.77(13)	N(4)–Cu(1)–N(3)	95.32(11)
N(2)–Cu(1)–N(4)	178.18(11)	N(2)–Cu(1)–N(5)	101.14(11)
N(1)–Cu(1)–N(4)	85.42(13)	N(1)–Cu(1)–N(5)	104.37(12)
N(2)–Cu(1)–N(3)	86.35(11)	N(4)–Cu(1)–N(5)	79.17(12)
N(1)–Cu(1)–N(3)	150.86(12)	N(4)–Cu(1)–N(5)	104.37(10)

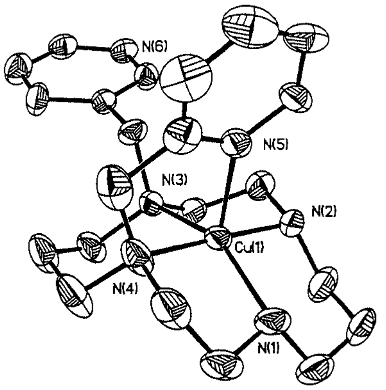
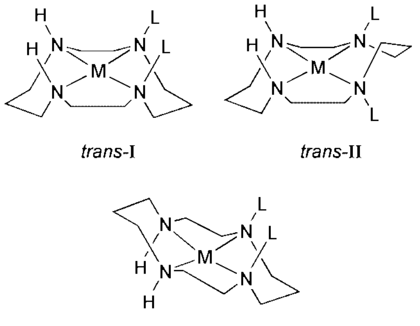


Fig. 2 Molecular structure of $[CuL^1]^{2+}$ in the perchlorate salt (hydrogen atoms omitted), showing the atom numbering scheme for the data in Table 2.

Table 3 Selected bond lengths (Å) and angles (°) for the copper(II) complex of ligand L^3, with the structure shown in Fig. 4

Cu(1)–O(2)	1.947(3)	Cu(2)–N(6)	2.134(3)
Cu(1)–O(3)	1.956(3)	Cu(2)–N(3)	2.316(3)
Cu(1)–N(9)	1.991(3)	O(1)–C(3)	1.239(5)
Cu(1)–N(7)	2.050(3)	O(2)–C(8)	1.292(4)
Cu(1)–O(1W)	2.385(3)	O(3)–C(25)	1.260(4)
Cu(2)–N(4)	1.969(3)	N(2)–C(3)	1.354(6)
Cu(2)–N(5)	1.997(3)	N(4)–C(8)	1.308(5)
Cu(2)–N(1)	2.080(3)	N(8)–C(25)	1.333(5)
O(2)–Cu(1)–O(3)	92.01(11)	N(4)–Cu(2)–N(1)	92.89(13)
O(2)–Cu(1)–N(9)	92.95(12)	N(5)–Cu(2)–N(1)	83.52(13)
O(3)–Cu(1)–N(9)	171.74(12)	N(4)–Cu(2)–N(6)	91.12(12)
O(2)–Cu(1)–N(7)	168.39(12)	N(5)–Cu(2)–N(6)	89.16(13)
O(3)–Cu(1)–N(7)	90.09(11)	N(1)–Cu(2)–N(6)	130.52(13)
N(9)–Cu(1)–N(7)	83.76(12)	N(4)–Cu(2)–N(3)	83.31(12)
O(2)–Cu(1)–O(1W)	98.60(11)	N(5)–Cu(2)–N(3)	101.16(12)
O(3)–Cu(1)–O(1W)	99.87(11)	N(1)–Cu(2)–N(3)	151.09(13)
N(9)–Cu(1)–O(1W)	85.92(12)	N(6)–Cu(2)–N(3)	78.32(12)
N(7)–Cu(1)–O(1W)	92.29(12)	C(8)–O(2)–Cu(1)	135.1(2)
N(4)–Cu(2)–N(5)	175.48(13)	C(25)–O(3)–Cu(1)	133.5(2)



trans-I

trans-II

trans-III

Fig. 3 Three of the possible stereoisomers of cyclam-type metal complexes, in which the four nitrogen donors and the metal are coplanar. L represents a substituent that incorporates a potentially co-ordinating group (such as the 2-pyridylmethyl substituent here). For a 1,11-bis-substituted cyclam, adoption of the *trans*-I or *trans*-III geometry clearly rules out the possibility of octahedral co-ordination, although feasible for *trans*-II.

expected Jahn–Teller distortion. The 14-membered macrocycle adopts a [3434] quadrangular conformation with an *RSSR* configuration at the nitrogen stereogenic centres; in other words, this is the preferred *trans*-III conformation of cyclam, in which the two six-membered chelate rings are in the chair form and the two five-membered rings in the *gauche* form.[15] As expected, the N–Cu–N angles of the five membered chelate rings are less than 90°, whereas those of the six membered chelates are greater than 90°.

The crystal structure of $[CuL^1]^{2+}(ClO_4^-)_2$ reveals a very different co-ordination geometry (Fig. 2). Here, the copper is 5-co-ordinate, in a distorted square pyramidal geometry, with the four nitrogen atoms of the macrocycle forming the base and with a nitrogen of one of the pyridine groups at the apical position. An interesting feature of the structure is that the second pyridine group remains unco-ordinated. The lengths of the Cu–N(macrocycle) bonds are in the range 2.030(3)–2.091(2) Å, with the bond to the nitrogen carrying the co-ordinated pyridine rather shorter than that to the nitrogen substituted by the unco-ordinated pyridine [2.059(3) *vs.* 2.091(2) Å], presumably to allow for efficient five-membered chelate ring formation incorporating the pyridine. The formation of this chelate ring also leads to a smaller (py)N–Cu–N angle, of 79.2(1)°, for the nitrogen carrying the co-ordinating pyridine, compared to angles of 101.1(1) to 104.4(1)° for the other three (py)N–Cu–N. The Cu–N(py) bond length of 2.209(3), whilst significantly longer than the bonds to the aliphatic nitrogens, is substantially shorter than the *trans*-axial Cu–py distances in $[CuL^2]^{2+}$. The macrocycle is seen to adopt the less stable *trans*-I conformation, in which the five-membered chelate rings are in the eclipsed form.

There is little precedent for a structure of this type; indeed, there are very few examples of 1,11-bis-substituted cyclam ligands where the substituents incorporate co-ordinating groups. Clearly, if the macrocycle were to adopt the preferred *trans*-III conformation, then octahedral co-ordination of the bound metal would be ruled out for such 1,11-bis-substituted systems, as the additional co-ordinating groups would be on the same side of the N_4 plane (Fig. 3). On the other hand, octahedral co-ordination would become feasible if the macrocycle were to twist to the *trans*-II conformation, and this is indeed observed for the nickel(II) complex of 1,11-bis(2-hydroxyethyl)-4,8-dimethyl-1,4,8,11-tetraazacyclotetradecane.[9a] Adoption of the 5-co-ordinate, *trans*-I structure observed here is rather surprising, as it offers neither the metal the possibility of 6-co-ordination nor the macrocycle its preferred conformation. A related structure has been reported very recently for the copper complex of 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-1-acetate, which adopts a distorted square pyramidal structure with the copper co-ordinated by the four macrocycle nitrogens and the $CH_2CO_2^-$ group at the apex.[8c] In that case, however, there is only a single co-ordinating arm available, so the option of octahedral co-ordination with a *trans*-II conformation does not arise in any case.

Copper(II) complex of L^3. Although prepared using a stoichiometric amount of copper(II), the compound which crystallised following reaction of ligand L^3 with copper(II) perchlorate under neutral conditions was found to have a Cu : L ratio of 4 : 3. The structure shows two distinct macrocyclic units containing copper ions (Fig. 4, with important bond lengths and angles listed in Table 3). In the first a single copper centre is 5-co-ordinate, with a distorted trigonal bipyramidal geometry. The axial sites are occupied by the deprotonated nitrogen of one of the amide groups and the nitrogen of one of the pyridyl

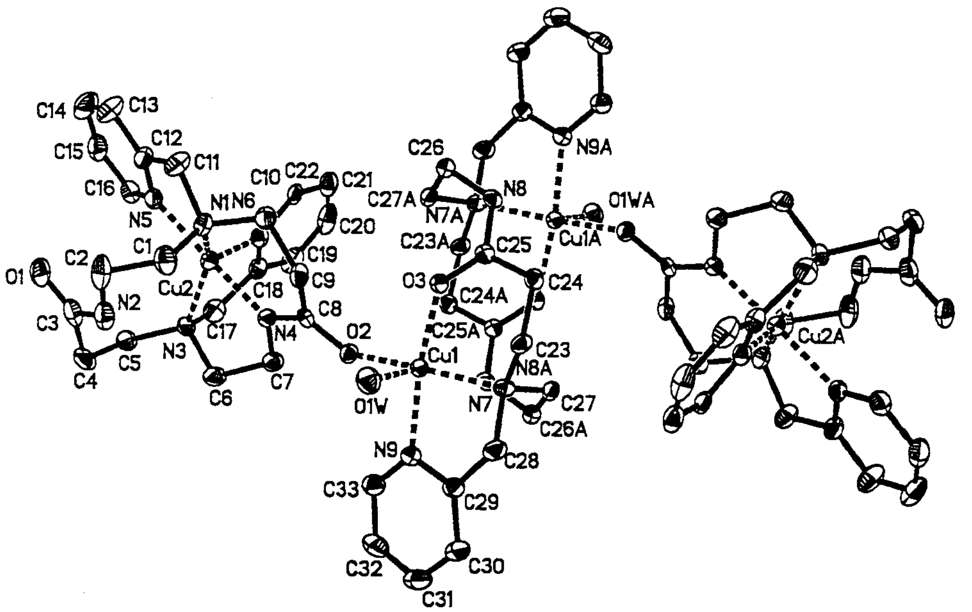


Fig. 4 Molecular structure of the crystals obtained from reaction of ligand L^3 with copper(II) perchlorate, including the atom numbering scheme used in Table 3.

arms, with short bond lengths of 1.969(3) and 1.997(3) Å respectively, and an axial N–Cu–N angle of 175.5(1)°. The amino nitrogens of the macrocycle and the nitrogen of the second pyridine group occupy the equatorial positions, with rather longer bonds to the copper (Table 3). A striking feature of the structure of this unit, and in which it differs from the majority of structurally characterised *cis*-dioxocyclam metal complexes, is the fact that the other amide group is *not* deprotonated and is not involved in co-ordination to the metal, neither through the amide N nor through the carbonyl oxygen. Deprotonation of an amide group RCONHR′ should lead to a shortening of the C–N bond and a lengthening of the C=O, through delocalisation of the negative charge into the carbonyl group. These effects are clear upon comparing the respective bound and unbound amide bond lengths: C(8)–N(4) (bound amide) is shorter than C(3)–N(2) (unbound), namely 1.308(5) and 1.354(6) Å respectively, whilst C(8)–O(2) is longer than C(3)–O(1), 1.292(4) and 1.239(5) Å respectively.

The second macrocyclic unit in the structure has a 2:1 metal:ligand stoichiometry and bridges two complexes of the first type through binding of the oxygens of their deprotonated amides to the two copper centres in this central macrocycle. Each copper is also co-ordinated by an amino nitrogen of the macrocycle, one of the carbonyl oxygens and the nitrogen of one of the pyridyl arms which together form the base of a distorted square pyramid, with a water molecule occupying the fifth apical position. Neither amide group in this unit is deprotonated.

The observation that only one of the two amides in one of the macrocyclic units was deprotonated prompted an attempt to prepare and crystallise the copper complex of L^3 under basic conditions. Deprotonation of *both* of the amide groups within the macrocycle should then be favoured. Suitable crystals were obtained from a solution of the complex basicified to pH 12 with potassium hydroxide. The structure confirmed these predictions, revealing that the copper ion is now bound within the N_4 plane by all four macrocycle nitrogens, with both amides deprotonated to give a stronger in-plane ligand field. The copper ion is also weakly co-ordinated by the pyridyl nitrogens. In fact, there are two independent molecules in the unit cell, which are conformationally different. In one of them the pyridyl ring is situated above the six-membered ring, in the other above the five-membered ring (Fig. 5). The distances between the pyridyl nitrogen and the copper are significantly different in the two cases: 2.632(6) and 2.809(6) Å respectively. The structure is further complicated by the occurrence of a small proportion (*ca.* 15%) of the other conformer in each site. Copper–nitrogen bond lengths and angles for the two conformers are summarised in Table 4; the shorter bond lengths to the deprotonated amide nitogens are consistent with values found in related *cis*-dioxocyclam complexes.[12] Short amide

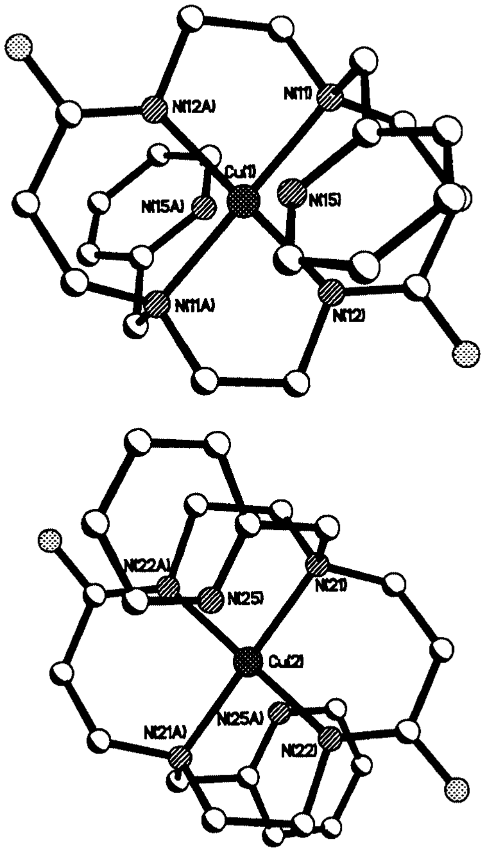


Fig. 5 Molecular structure of the crystals obtained from reaction of ligand L^3 with copper(II) perchlorate under *basic* conditions, including the atom numbering scheme used in Table 4. Top: conformer 1. Bottom: conformer 2.

Table 4 Selected bond lengths (Å) and angles (°) for the copper(II) complex of ligand L^3 crystallised at basic pH, with the structure shown in Fig. 5

Conformer 1		Conformer 2	
Cu(1)–N(11)	2.062(3)	Cu(2)–N(21)	2.046(3)
Cu(1)–N(12)	1.961(4)	Cu(2)–N(22)	1.962(4)
Cu(1)–N(15)	2.632(6)	Cu(2)–N(25)	2.809(6)
N(11)–Cu(1)–N(12)	95.6(2)	N(21)–Cu(2)–N(22)	95.3(2)
N(11)–Cu(1)–N(12A)	84.5(2)	N(21)–Cu(2)–N(22A)	84.7(2)

Table 5 Physical properties of the copper(II) complexes $[CuL^1]^{2+}$ and $[CuL^2]^{2+}$ in solution

	$[CuL^1]^{2+}$	$[CuL^2]^{2+}$
λ_{max}/nm (ε[a])	578 (203)	546 (69)
$E°$ (Cu^{2+}–Cu^+)/V[b]	−0.15[c]	−0.17[d]
g_{iso} (293 K)[e]	2.105	2.106
a_{Cu} (293 K)/G[e]	77	71
$g_{\parallel}$ (110 K)[f]	2.21	2.21
$A_{\parallel}$ (110 K)/G[f]	173	179

[a] In aqueous solution. [b] At 293 K in acetonitrile solution, 0.1 M $[NBu_4][PF_6]$, using ferrocene as an internal standard, values relative to SCE. [c] Quasi-reversible. [d] Irreversible. [e] In acetonitrile. [f] In 50% methanol–acetonitrile.

N–C(O) distances {1.311(6) and 1.317(8) Å} are also consistent with the partial double bond character expected to accompany amide deprotonation.

Solution properties

Electronic absorption spectroscopy. The UV-visible absorption parameters for the complexes of L^1 and L^2 are listed in Table 5. The absorption maximum of 546 nm for the 1,8-bis-substituted complex, $[CuL^2]^{2+}$, in aqueous solution, is typical of square planar copper complexes with a strong ligand field; for example, the same value is observed for the copper(II) complex of 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane in solution in water.[8a] This suggests that the pyridyl groups are not co-ordinated in aqueous solution. No significant changes in the spectrum were observed over the pH range 1.0–12.5. In contrast, the absorption maximum for the complex in solution in acetonitrile appeared at a longer wavelength of 593 nm; upon acidification with trifluoroacetic acid the band shifted to higher energy (λ_{max} 549 nm), similar to the value in aqueous solution. This could be indicative of a rather more significant interaction of the metal with the axial pyridines when dissolved in CH_3CN (perhaps due to poorer solvation of unbound pyridine nitrogens in this solvent), accompanied by slight elongation of the equatorial Cu–N bonds and a reduction in the in-plane ligand field strength. Protonation of the pyridyl nitrogens then restores a co-ordination environment comparable to that in water.

Compared to $[CuL^2]^{2+}$, the absorption maximum of $[CuL^1]^{2+}$ appeared at significantly longer wavelength: $\lambda_{max} = 578$ nm in aqueous solution. This is consistent with the square pyramidal structure observed for this complex in the solid state, as opposed to effectively square planar co-ordination of the copper in $[CuL^2]^{2+}$, where a rather stronger ligand field would be expected; the average of the Cu–N distances (for the macrocyclic nitrogens) in the two complexes is 2.057 and 2.047 Å respectively. Again, no significant change in the spectrum was observed over the pH range 1.0–12.5.

The crystals of the copper(II) complex of L^3 (with the structure shown in Fig. 4) gave a deep blue solution upon dissolution in water at neutral pH. The electronic absorbance spectrum showed two bands in the visible region, with absorbance maxima at 602 and 798 nm. The profile and position of the longer wavelength band resembles that of simple aqueous copper(II) salts, whilst the other, rather more intense band is more similar to that observed for the copper complexes of L^1 and L^2. Since the crystal structure reveals an excess of copper over ligand (ratio 4 : 3 as noted above), it is likely that upon dissolution the additional copper ion is expelled from the bimetallic "central" unit in the structure to allow formation of a further equivalent of the complex of the second type. This would account for the appearance of "free" copper in the absorbance spectrum, as well as the higher energy absorbance band arising from the copper co-ordinated by the stronger-field, mono-deprotonated macrocyclic ligand. Support for the proposal that the ligand remains mono-deprotonated at neutral pH comes from observations of the effect of pH on the spectrum. Upon increasing the pH the higher energy band shifts to shorter wavelengths, with a limiting absorbance maximum of 519 nm at pH > 11.2, and an observed pK_a of approximately 9.8. Clearly, this must be due to deprotonation of the second amide group, resulting in an increase in the ligand field strength, and formation of the structure shown in Fig. 5. The situation is then more comparable to that of the *cis*-dioxocyclam analogues, which are generally doubly deprotonated at rather lower pH values.[10–12]

On the other hand, decreasing the pH to below 7 by addition of acid also resulted in a marked change in the spectrum. In this case the two bands observed at neutral pH collapse to a single band centred at 705 nm. Although substantially longer than the wavelengths of the bands for macrocycle-bound copper in all three systems, this value is nevertheless shorter than that of aqueous copper(II). Decreasing the pH will result in protonation of the amide group, such that the copper will be co-ordinated only weakly, presumably by a mixture of the pyridine nitrogen atoms, the amino nitrogens of the macrocycle and water molecules. Again, this is reminiscent of the reversibility of copper and zinc binding by *cis*-dioxocyclams induced by lowering the pH, a process which has been exploited for fluorescent sensing of these metal ions.[11]

ESR spectroscopy

The ESR spectra of the complexes $[CuL^1]^{2+}$ and $[CuL^2]^{2+}$ in solution in acetonitrile and in a methanol–acetonitrile glass were recorded at room temperature and at 110 K respectively. The room temperature spectra showed four equally spaced absorptions, as expected from the coupling of the unpaired electron density to the copper nucleus ($I = 3/2$); the isotropic ESR parameters are listed in Table 5. The form of the low temperature spectra was typical of near axial symmetry. The $g_{\parallel}$ values were found to be the same for both complexes, namely 2.21. This value is a little higher than that of $[Cu(cyclam)]^{2+}$ and is consistent with a trend to higher $g_{\parallel}$ values upon N-alkylation of tetraazamacrocycles, as true square-planar co-ordination becomes disfavoured upon increasing N-substitution.[16a] The hyperfine coupling constant, $A_{\parallel}$, is a better indicator of distortion from square-planar towards pyramidal or tetrahedral co-ordination in copper(II) complexes, the values ranging from 217 G for $[Cu(cyclam)]^{2+}$ to around 60 G for blue copper proteins such as azurin, where the geometry is close to tetrahedral.[16b] In the present instance the values are closer to the square planar values, although it may be noted that $A_{\parallel}$ for $[CuL^1]^{2+}$ is lower than that for $[CuL^2]^{2+}$, which is certainly consistent with the crystal structure of the former, with its distortion away from planar N_4 co-ordination by the macrocycle.

No super-hyperfine coupling to the nitrogen donors was observed. In a study of the effect of aromatic nitrogen donors (such as pyridine and imidazole) on the ESR spectra of copper(II) complexes of polyamines including cyclam, Siddiqui and Shepherd noted that incorporation of aromatic N-donors activated the system such that all the nitrogen donors exhibited super-hyperfine coupling in the $g_\perp$ region.[17] In the absence of such aromatic donors, such coupling was either very weak or not observed at all. Thus, the lack of super-hyperfine coupling in the present instance is also consistent with either weak or no interaction of the metal with the pyridyl arms in solution.

Cyclic voltammetry. Cyclic voltammetry of the copper(II) complexes of L^1 and L^2 was carried out in acetonitrile at a platinum electrode (Table 5). Redox waves corresponding to the reduction of copper(II) to copper(I) were observed at −0.15 V (quasi-reversible) for $[CuL^1]^{2+}$ and −0.17 V (irreversible) for $[CuL^2]^{2+}$. This amounts to a stabilisation of 0.7–0.8 V of the copper(I) oxidation state relative to the value in non-N-alkylated cyclam-type complexes, which is in line with recently reported data on some other 1,8-dialkylated tetraazamacrocycles.[8c] A second reduction process was observed for both complexes, at −0.54 V for $[CuL^1]^{2+}$ and −0.65 V for $[CuL^2]^{2+}$. This reduction, which was irreversible in both cases, led to a copper stripping peak in the subsequent oxidation cycle, indicative of decomposition of the zerovalent complex to elemental copper at the platinum electrode. Such an effect has been described for $[Cu(cyclam)]^{2+}$, where a stripping peak was observed following reduction at potentials of −0.90 V or lower.[18] In contrast with $[Cu(cyclam)]^{2+}$, however, there is no evidence of an oxidation wave corresponding to oxidation of copper(II) to copper(III) over the range investigated (0–2 V). In the case of $[Cu(cyclam)]^{2+}$ a chemically reversible one-electron oxidation is observed at +1.58 V. The destabilisation of higher oxidation states upon N-alkylation of polyamine metal complexes is well established, having being variously attributed to poorer σ-donor strength of tertiary nitrogen atoms, increased cavity size of the N-methylated ligand (in the case of tetraazamacrocycles) and decreased solvation caused by the hydrophobic nature of the alkyl groups.[19]

Conclusion

Two isomeric compounds based on cyclam have been studied, N-substituted with 2-pyridylmethyl groups disposed 1,8 or 1,11 to one another. These ligands are potentially hexadentate. Their copper(II) complexes have been prepared and structurally characterised. Whilst the 1,8-disubstituted system binds to the metal such that the macrocycle adopts its preferred conformation, and leads to tetragonally elongated octahedral geometry at the metal, the 1,11 analogue acts as a pentadentate ligand, with one of the pyridyl units remaining unco-ordinated. The copper(II) complex of the related dioxotetraamine ligand incoporating 1,8-disposed 2-pyridylmethyl units has been found to contain two distinct units in the solid state, in one of which one of the two amide groups is deprotonated. Electronic absorption spectroscopy indicates that double deprotonation occurs in solution at higher pH, which has been confirmed by the crystal structure of the complex when isolated under basic conditions. These results indicate that *trans*-dioxocyclam derivatives (easily accessible from the intermediate VI) may prove useful in applications where only the *cis*-dioxocyclam compounds have hitherto been studied.

Experimental

Cyclam was prepared according to the method of Barefield *et al.*[20] and *cis*-dioxocyclam was obtained from Aldrich. 2-(Chloromethyl)pyridine was supplied and used as the hydrochloride salt. Acetonitrile was HPLC grade and water was purified by the Purite system. Chromatography was carried out on silica gel (60, 40–63u, Fluorochem) or on alumina (neutral, Brockman I). Proton and ^{13}C NMR spectra were recorded on a Varian Mercury-200 (200 and 50.3 MHz respectively) or Varian Unity-300 (300 and 75.5 MHz) spectrometer and referenced to residual protio solvent resonances (^1H spectra) or to chloroform (^{13}C); coupling constants are in Hz. ESR spectra were measured using a Bruker ESP300 spectrometer at the University of York. Electrospray mass spectra were recorded on a VG Platform II instrument and visible absorption spectra using a Unicam UV-2 spectrophotometer. Cyclic voltammetry was carried out with an EG&G Instruments VersaStat II using acetonitrile solutions of the complexes (2 mM) containing $[NBu_4][PF_6]$ as the supporting electrolyte (0.1 M); solutions were purged with nitrogen gas pre-saturated with acetonitrile prior to each scan. A three-electrode system was employed using platinum working, reference and counter electrodes; the voltammograms were referenced to the ferrocene–ferrocenium couple as an internal standard (E° 0.40 V *vs.* SCE in acetonitrile, with $[NBu_4][PF_6]$ as the supporting electrolyte[21]).

Syntheses

Compound III. The required intermediate **II** was prepared according to the published method.[6] The dimethyl acetal of dimethylformamide (0.71 g, 5.6 mmol) was added to a solution of cyclam (1.1 g, 5.5 mmol) in chloroform. After refluxing for 4 d the solvent was removed under vacuum, to give the formamidinium salt of cyclam, **II**, the ^1H NMR spectrum of which was consistent with the published data. 2-(Chloromethyl)pyridine hydrochloride (1.8 g, 11 mmol) was subsequently added to a solution of **II** (1.0 g, 5.0 mmol) in acetonitrile, together with sodium carbonate (2.4 g, 22.6 mmol) and potassium iodide (0.1 g, 0.6 mmol). The mixture was heated at reflux for 4 d and the solvent then removed under reduced pressure, to give a brown oil. Purification of the compound was effected by chromatography on silica gel (gradient elution from CH_2Cl_2 to 10% MeOH–CH_2Cl_2, $R_f = 0.25$ in 5% MeOH–CH_2Cl_2); yield 1.57 g (80%). δ_H ($CDCl_3$) 9.5 (1 H, s, NCHN), 8.52 (2 H, d, ^3J 4.8, py H^6), 7.69 (2 H, dd, observed ^3J 7.5, py H^4), 7.25 (2 H, d, ^3J 7.8, py H^3), 7.19 (2 H, dd, observed ^3J 5.4, py H^5), 3.66 (4 H, s, $NCH_2C_5H_4N$), 3.51 (4 H, t, ^3J 5.3, $NCH_2CH_2NCH_2C_5H_4N$), 3.23 (4 H, t, ^3J 5.7, $NCH_2CH_2CH_2N$), 2.75 (4 H, t, ^3J 5.4, $NCH_2CH_2NCH_2C_5H_4N$), 2.44 (4 H, br t, $NC_5H_4CH_2NCH_2CH_2CH_2N$), 2.07 (2 H, quintet, ^3J 5.7, $CH^+NCH_2CH_2CH_2$) and 1.65 (2 H, quintet, ^3J 6.0, $NC_5H_4CH_2NCH_2CH_2CH_2$). MS (ES+): *m*/*z* 393 [M^+].

1,11-Bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane L^1. The 1,11-N,N′-protected compound **III** (1.5 g, 3.8 mmol) was converted into the free base by reaction with sodium hydroxide (10 M, 30 cm^3) at reflux for 7 d. After extraction into dichloromethane (3 × 75 cm^3), the solution was dried over potassium carbonate and the solvent removed under reduced pressure to give ligand L^1; yield 0.66 g (45%). δ_H ($CDCl_3$) 8.50 (2 H, d, ^3J 4.8, py H^6), 7.64 (2 H, dd, observed ^3J 7.5, py H^4), 7.44 (2 H, d, ^3J 7.8, py H^3), 7.14 (2 H, dd, ^3J 5.4, py H^5), 3.67 (4 H, s, $NCH_2C_5H_4N$), 2.80–2.50 (16 H, m), 1.79 (2 H, m, $NC_5H_4CH_2NCH_2CH_2CH_2$) and 1.69 (2 H, m, $NHCH_2CH_2CH_2$). δ_C ($CDCl_3$) 160.6, 149.2, 136.7, 123.3, 122.2 (py C), 61.3, 54.6, 51.4, 48.9, 47.9 (NCH), 28.6, 27.1 ($CH_2CH_2CH_2$). MS (ES+): *m*/*z* 383 [M + H^+].

1,4,8,11-Tetraazacyclotetradecane-5,12-dione VI. This compound was prepared according to the literature procedure,[13] by the dropwise addition of methyl acrylate (52 g, 0.6 mol) into an equimolar amount of ethylenediamine (36 g) with stirring. Addition was conducted at a rate such that the reaction temperature did not exceed 45 °C, which required 1 hour. The resulting clear liquid was dissolved in deionised water (100 cm^3) from which a white precipitate formed upon standing at room temperature for up to 2 weeks. During some preparations of this compound further concentration of the solution under reduced pressure or addition of more water was required before crystallisation occurred. The product was carefully washed with cold water and obtained as a fine white powder. The typical yield was around 2%. δ_H ($\mathrm{D_2O}$) 3.37 (4 H, t, ^3J 5.1, $\mathrm{CH_2CO}$), 2.89 (4 H, t, ^3J 5.7 , $\mathrm{CH_2C}H_2\mathrm{NHCO}$), 2.75 (4 H, t, ^3J 5.1, $\mathrm{C}H_2\mathrm{CH_2CO}$) and 2.43 (4 H, t, ^3J 5.7, $\mathrm{C}H_2\mathrm{CH_2NHCO}$). ν_max (KBr) 1635 $\mathrm{cm^{-1}}$ (C=O).

1,8-Bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane-5,12-dione L^3. 2-(Chloromethyl)pyridine hydrochloride (0.96 g, 5.86 mmol) was added to a solution of 1,4,8,11-tetraazacyclotetradecane-5,12-dione (0.66 g, 2.9 mmol) in acetonitrile, together with sodium carbonate (1.24 g, 11.7 mmol) and potassium iodide (0.1 g, 0.6 mmol). The solution was stirred under nitrogen for 5 days at reflux. After removal of the solvent, the residue was taken up into a mixture of dichloromethane (80 $\mathrm{cm^3}$) and aqueous sodium hydroxide solution (1 M, 60 $\mathrm{cm^3}$); the organic layer was separated and the aqueous solution extracted with dichloromethane (3 × 60 $\mathrm{cm^3}$). The extracts were combined, dried over potassium carbonate and the solvent removed under reduced pressure to give a pale brown residue. Purification was achieved by column chromatography on silica gel (gradient elution from $\mathrm{CH_2Cl_2}$ to 10% MeOH–$\mathrm{CH_2Cl_2}$), to give compound L^3 (0.89 g, 75%). δ_H ($\mathrm{CDCl_3}$) 9.13 (2 H, br t, CONH), 8.55 (2 H, d, ^3J 4.8, py H^6), 7.69 (2 H, dd, observed ^3J 7.5, py H^4), 7.40 (2 H, d, ^3J 7.5, py H^3), 7.17 (2 H, dd, observed ^3J 6.2, py H^5), 3.80 (4 H, s, $\mathrm{NCH_2C_5H_4N}$), 3.41 (4 H, br t, $\mathrm{CH_2CO}$), 2.69 (8 H, overlapping t, $\mathrm{COCH_2C}H_2$, and $\mathrm{NHC}H_2\mathrm{CH_2NCH_2C_5H_4N}$) and 2.38 (4 H, t, ^3J 5.6, $\mathrm{NHCH_2C}H_2\mathrm{NCH_2C_5H_4N}$). δ_C ($\mathrm{CDCl_3}$) 172.3, 158.0, 149.5, 136.6, 124.1, 122.7 (py C), 59.59, 52.72, 50.15, 36.39, 32.80 ($\mathrm{CH_2}$). ν_max (thin film) 1658 $\mathrm{cm^{-1}}$ (C=O).

1,8-Bis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane L^2. A solution of borane in tetrahydrofuran (1 M, 100 $\mathrm{cm^3}$) was added to the dione L^3 (0.8 g, 1.95 mmol) and refluxed under nitrogen for 48 h. Excess of borane was destroyed with methanol, after which the solvent was removed under reduced pressure and the residue heated to reflux in 6 M HCl for 4 h. Removal of water gave a dark residue, to which was added aqueous base (20% KOH, 30 $\mathrm{cm^3}$). The mixture was extracted with dichloromethane (5 × 60 $\mathrm{cm^3}$) and the extracts dried over anhydrous potassium carbonate. Compound L^2 was obtained as a pale yellow oil upon removal of the solvent; yield 95 mg (13%). δ_H ($\mathrm{CDCl_3}$) 8.51(2 H, d, ^3J 4.8, py H^6), 7.59 (2 H, dd, observed ^3J 7.4, py H^5), 7.39 (2 H, d, ^3J 7.5, py H^3), 7.11 (2 H, dd, observed ^3J 5.4, py H^4), 3.67 (4 H, s, $\mathrm{NCH_2C_5H_4N}$), 2.5–2.8 (16 H, m, $\mathrm{NCH_2}$ within macrocycle) and 1.85 (4 H, q, ^3J 5.6, $\mathrm{CH_2C}H_2\mathrm{CH_2}$). The recently published method that involves the intermediacy of 1,8-bis(2-pyridylmethyl)-4,11-diazoniatricyclo-[9.3.1.1^{4,8}]hexadecane provides greatly improved yields of this compound, and was therefore used in subsequent preparations.[5]

Complexes. The copper(II) complexes were obtained from the respective ligands by addition of an equivalent amount of copper(II) acetate monohydrate in deoxygenated methanol (for L^2) or copper(II) perchlorate hexahydrate in ethanol (for L^1 and L^3) followed by gentle heating under nitrogen for 30 min. Crystals suitable for X-ray diffraction studies were obtained following slow evaporation of methanolic solutions (L^1 and L^3) or a solution in acetonitrile–diethyl ether (L^2); the crystals with the structure shown in Fig. 5 were isolated from water basicified to pH 12 with potassium hydroxide. Typical yields were 50–80% for the complexes of L^2 and L^3 but the complex of L^1 was isolated in only 20% yield.

Crystal structure data

$[\mathrm{CuL^1}]^{2+}(\mathrm{ClO_4^-})_2$. $\mathrm{C_{23}H_{38}Cl_2CuN_6O_9}$, $M_\mathrm{r} = 677.03$, monoclinic, space group $P2_1/c$ (no. 14), $a = 8.270(1)$, $b = 18.666(2)$, $c = 18.717(2)$ Å, $\beta = 97.879(3)°$, $U = 2862.0(6)$ Å^3, $T = 150$ K, $Z = 4$, μ(Mo-Kα) = 1.011 $\mathrm{mm^{-1}}$, 25878 reflections measured, 8036 unique ($R_\mathrm{int} = 0.0353$) which were used in all calculations and 6033 greater than $2\sigma(I)$. The final $R(F)$ was 0.06 ($I > 2\sigma(I)$ data) and the $wR(F^2)$ was 0.1479 (all data).

$[\mathrm{CuL^2}]^{2+}(\mathrm{CH_3CO_2^-})_2$. $\mathrm{C_{26}H_{52}CuN_6O_{10}}$, $M_\mathrm{r} = 336.14$, monoclinic, space group $P2_1/n$ (no. 14), $a = 8.6790(5)$, $b = 15.6748(9)$, $c = 11.7179(7)$ Å, $\beta = 93.064(3)°$, $U = 1591.84(16)$ Å^3, $T = 150$ K, $Z = 2$, μ(Mo-Kα) = 0.748 $\mathrm{mm^{-1}}$, 19962 reflections measured, 4454 unique ($R_\mathrm{int} = 0.027$) which were used in all calculations and 3863 greater than $2\sigma(I)$. The final $R(F)$ was 0.028 ($I > 2\sigma(I)$ data) and the $wR(F^2)$ was 0.0775 (all data).

Copper(II) complex of L^3. $\mathrm{C_{33}H_{63}Cl_3Cu_2N_9O_{21}}$, $M_\mathrm{r} = 1155.35$, monoclinic, space group $P2_1/n$ (no. 14), $a = 13.7841(4)$, $b = 21.5077(6)$, $c = 15.9374(4)$ Å, $\beta = 97.544(1)°$, $U = 4684.0(2)$ Å^3, $T = 120$ K, $Z = 4$, μ(Mo-Kα) = 1.168 $\mathrm{mm^{-1}}$, 31888 reflections measured, 10727 unique ($R_\mathrm{int} = 0.0498$) which were used in all calculations and 7383 greater than $2\sigma(I)$. The final $R(F)$ was 0.0531 ($I > 2\sigma(I)$ data) and the $wR(F^2)$ was 0.1434 (all data).

Copper(II) complex of L^3 at basic pH. $\mathrm{C_{22}H_{32}CuN_6O_4}$, $M_\mathrm{r} = 508.08$, triclinic, space group $P\bar{1}$ (no. 2), $a = 9.7924(3)$, $b = 10.3659(3)$, $c = 12.6077(3)$ Å, $\alpha = 66.602(1)$, $\beta = 81.966(1)$, $\gamma = 75.804(1)°$, $U = 1137.37(6)$ Å^3, $T = 120$ K, $Z = 2$, μ(Mo-Kα) = 1.002 $\mathrm{mm^{-1}}$, 11566 reflections measured, 5888 unique ($R_\mathrm{int} = 0.0719$) which were used in all calculations. The final $R(F)$ was 0.0752 ($I > 2\sigma(I)$ data) and the $wR(F^2)$ was 0.1525 (all data). The rather large $R(F)$ arises from a small proportion of the other conformer (*ca.* 15%) at the sites of each of the two conformers in the crystal examined.

CCDC reference number 186/1964.

See http://www.rsc.org/suppdata/dt/b0/b000739k/ for crystallographic files in .cif format.

Acknowledgements

We thank Professor Bruce Gilbert and Dr Adrian Whitwood of the University of York for kind assistance with ESR spectroscopy and Mrs Emma Dowson (née Smart) for the preparation of cyclam. Financial support from the University of Durham, including a studentship to D. M., is gratefully acknowledged, and the EPSRC for a Senior Research Fellowship (J. A. K. H.).

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