

1-Oxa-4,8,12-triazacyclotetradecane-4,12-diacetic Acid (H_2L^2): Studies on Protonation and Metal Complexation; Crystal Structure of $[CuL^2] \cdot 5H_2O$ †

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A new *N*-diacetate derivative of an asymmetrical 14-membered oxatriaza macrocycle, 1-oxa-4,8,12-triazacyclotetradecane-4,12-diacetic acid (H_2L^2), has been synthesised from the parent amine by the method of complete carboxymethylation followed by anion-exchange chromatography. Its protonation constants have been determined by potentiometric and 1H NMR techniques (at 25.0 °C and $I = 0.10$ mol dm^{-3}). The first two protonations occur at the nitrogen atoms, the third at a carboxylate group and not at the last nitrogen atom. The stability constants of the complexes formed by this ligand with various first-series transition metal ions, Zn^{2+} , Cd^{2+} , Pb^{2+} and Ca^{2+} were determined by potentiometric measurements. The value for the copper complex (and also for the nickel one) is very high while the complexes of Ca^{2+} , Mn^{2+} and Pb^{2+} have relatively low stability. An X-ray structure determination of the complex $[CuL^2] \cdot 5H_2O$ has been performed in order to understand these values. Crystals are monoclinic, space group $P2_1/c$, $a = 11.19(3)$, $b = 12.19(2)$, $c = 16.22(6)$ Å, $\beta = 110.16(9)^\circ$. The structure was refined to a final $R = 0.089$ for 3656 reflections with $|F_o| \geq 2\sigma|F_o|$. The co-ordination geometry around the copper atom can be described as a distorted octahedron in which the equatorial plane is defined by the three nitrogen atoms of the ring and an oxygen atom of one of the carboxylate groups of the ligand. Two oxygen atoms occupy the axial positions, one from the remaining carboxylate group and the other from the macrocyclic ring. Hence, in the crystalline state (and probably also in solution) all the donor atoms co-ordinate to the metal ion, the ligand being in a folded, very strained conformation. The low stability of the complexes of the larger metal ions (Ca^{2+} , Mn^{2+} and Pb^{2+}) could be understood if one of the nitrogen-donor atoms of the ring were not involved in the co-ordination.

Extensive studies have been done in the past two decades on the synthesis and characterization of metal complexes of saturated macrocyclic ligands with nitrogen, oxygen or sulfur as donor atoms. The selectivity shown by some of the ligands on metal complexation, the very high values of the stability constants as well as the remarkable inertness of some of their metal complexes, even in very acidic media, are some of the most interesting properties of these kinds of macrocycles.¹

The introduction of additional ligating groups in the macrocyclic backbone can modify its properties, especially in the case of substituents with ionizable groups and/or with additional donor atoms, leading to more stable or more selective complexes or to complexes with faster kinetics.² In recent years most work has concentrated on the selective functionalization, at both carbon and nitrogen, of the skeleton of some tri- and tetra-aza macrocycles, with a view to the application of these ligands in medicine (tumour targeting with radiolabelled monoclonal antibodies or tumour seeking), ion selection and catalysis.³

Synthetic routes towards incompletely *N*-alkylated aza macrocycles are more complicated than to the complete *N*-substituted relatives. However, in the literature, there are several examples of selective *N*-functionalization especially mono but also di and tri derivatives. Nevertheless, the selective alkylation of polyoxapolyaza derivatives has received less attention.⁴

In the present work we have synthesised a *N*-diacetate derivative of an asymmetrical 14-membered oxatriaza macrocyclic compound by the method of complete carboxymethyl-

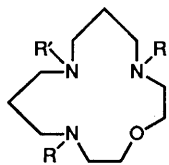
ation of the macrocycle followed by separation of the several alkylated forms by anion-exchange chromatography. As expected this method led to low yields of the final compound H_2L^2 even when only 2 equivalents of alkylated reagent were used. Then we undertook a study of the protonation and metal complexation of this ligand. The striking stability of its copper complex led us to study its solid-state structure.

Experimental

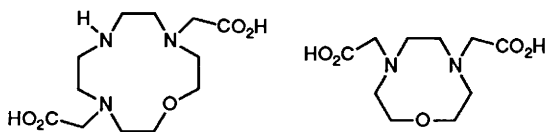
Chemical Studies.—Reagents. The ligand was synthesised and purified in our laboratories. The chemicals used were of reagent grade and organic solvents were purified by standard methods.⁵

Synthesis of the ligand. The cyclic amine L^1 was synthesised following previously described procedures⁶ and its diacetate derivative by a non-aqueous technique using ethyl bromoacetate in basic solution.⁴ In a typical experiment ethyl bromoacetate (8.30 mmol, 0.92 cm^3) was added to a solution of L^1 (2.25 mmol, 1 g) in ethanol (20 cm^3) and triethylamine (15.87 mmol, 2.2 cm^3). The mixture was heated to reflux (24 h), then cooled, filtered and evaporated under reduced pressure. Water (10 cm^3) was added to the residue and the solution extracted with chloroform (4 \times 20 cm^3). The chloroform extracts were evaporated to dryness, water (20 cm^3) added to the residue, and heated to reflux for 1 week. The mixture was then extracted with chloroform (2 \times 35 cm^3). The aqueous layer was concentrated and a solid residue (0.51 g) was precipitated by ethanol. The pure compound was obtained by anion-exchange chromatography, using a Dowex 1-X8 (20–50 U.S. mesh) resin in the formate form. The solid residue was dissolved in water and applied to the column (23.5 \times 2.0 cm). The flow rate of the

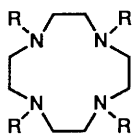
† Supplementary data available: see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1992, Issue 1, pp. xx–xxv.



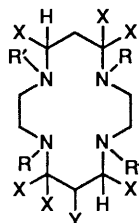
- L^1 $R = R' = H$ 1-oxa-4,8,12-triazacyclotetradecane ([14]aneN₃O)
 H_2L^2 $R = CH_2CO_2H$, $R' = H$ 1-oxa-4,8,12-triazacyclotetradecane-4,12-diacetic acid



- H_2L^3 1-oxa-4,7,10-triazacyclododecane-4,10-diacetic acid
 H_2L^4 1-oxa-4,7-diazacyclononane-4,7-diacetic acid



- L^5 $R = H$ 1,4,7,10-tetraazacyclododecane (cyclen)
 H_4L^6 $R = CH_2CO_2H$ 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid



- L^7 $R, R', X, Y = H$ 1,4,8,11-tetraazacyclotetradecane (cyclam)
 H_4L^8 $R, R' = CH_2CO_2H$; $X, Y = H$ 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid
 H_2L^9 $R = CH_2CO_2H$; $R', X, Y = H$ 1,4,8,11-tetraazacyclotetradecane-1,8-diacetic acid
 H_2L^{10} $R = CH_2CO_2H$; $X = Me$; $R', Y = H$ 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-1,8-diacetic acid
 H_4L^{11} $R, R' = CH_2CO_2H$; $X = H$; $Y = p\text{-NO}_2C_6H_4CH_2$ (6-*p*-nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid

column was kept at $1.0 \text{ cm}^3 \text{ min}^{-1}$. After washing the column with water (300 cm^3), the compound was eluted with a solution of formic acid ($0.005 \text{ mol dm}^{-3}$), fractions 10–15 (15 cm^3 each fraction) being collected. The fractions were concentrated and H_2L^2 obtained from a methanol–acetone mixture.

The pure product, very hygroscopic, was obtained in a small amount: 0.113 g, 14.2% yield. NMR (D_2O): 1H (pD 1.20), δ 2.178 (4 H, qnt), 3.279 (4 H, t), 3.443 (4 H, t), 3.567 (4 H, t), 3.922 (4 H, t) and 4.064 (4 H, s), cf. Fig. 1; ^{13}C (pD 14), δ 24.26, 50.70, 54.67, 56.56, 60.79, 68.93 and 180.75. The molecular weight was determined by potentiometric titration as 347.82 corresponding to $C_{14}H_{28}ClN_3O_5 \cdot 2H_2O$. The constitution of this diacid was confirmed by X-ray crystallographic analysis of the copper(II) salt.

Synthesis of the copper complex. To ligand H_2L^2 (0.020 g, $6.3 \times 10^{-5} \text{ mol}$), dissolved in the minimum amount of water, was added a concentrated solution of copper sulfate (15.7 mg, $6.3 \times 10^{-5} \text{ mol}$) and the pH adjusted to 5 with $Ba(OH)_2$. The precipitate formed was filtered off and the solution concentrated to a small volume. Blue needle crystals were obtained when acetone was allowed to diffuse into the aqueous solution.

Other reagents and standard solutions. Metal nitrates of analytical grade were used and solutions prepared in water obtained by a Millipore/Milli-Q system and standardized by ethylenediaminetetraacetate titrations. Carbonate-free solutions of the titrant, NMe_4OH , were prepared as described before.⁶ Solutions of the ligands for NMR measurements ($\approx 0.01 \text{ mol dm}^{-3}$) were made up in D_2O (99.8 atom % deuterium from Merck) and the pD was adjusted by adding D_2SO_4 or CO_2 -free CsOD. In all cases sodium 3-(trimethylsilyl)propane-1-sulfonate was used as internal reference.

Equipment. For the potentiometric titrations an Orion 720 measuring instrument was used together with a 91-01 glass electrode and a 90-05 Ag–AgCl reference electrode, with a Wilhelm-type salt bridge containing $0.10 \text{ mol dm}^{-3} NMe_4NO_3$ solution. Titrations were carried out in a thermostatted cell kept at $25.0 \pm 0.1^\circ C$ and the ionic strength of the solutions was kept at 0.01 mol dm^{-3} with NMe_4NO_3 , as described previously.⁶

The adjustment in pD for the NMR measurements was made using an Orion 420A instrument fitted with a combined INGOLD 6030-02 microelectrode. The electrode was calibrated with buffer aqueous solutions and the final pD calculated from $pD = pH + 0.40$.⁷

Proton and ^{13}C NMR spectra were recorded with a Varian Unity 300 spectrometer at probe temperature ($25.0^\circ C$).

Formation constant studies. Equilibration of ligand H_2L^2 with all the metal ions studied in the present work was fairly rapid, with the exception of Ni^{2+} which required about 4 d. In the case of slow equilibration an 'out-of-cell' titration was used.⁶

Calculation of protonation and stability constants. The protonation and stability constants of the various species formed were obtained from the experimental titration data with the aid of the SUPERQUAD program.⁸ A minimum of two titrations, performed by the automated system, for which the c_M/c_L ratios were 1:1 and 2:1, was used, but only the 1:1 ratio for the case of Ni^{2+} where the titration was performed by the 'out-of-cell' procedure. The errors quoted are the standard deviations given directly by the program and do not represent the total experimental errors.⁶

Crystal Structure Determination.—Crystal data for $[CuL^2] \cdot 5H_2O$, $C_{14}H_{35}CuN_3O_{10}$, $M = 468.55$, monoclinic, space group $P2_1/c$, $a = 11.19(3)$, $b = 12.19(2)$, $c = 16.22(6)$ Å, $\beta = 110.16(9)^\circ$, $U = 2077 \text{ \AA}^3$, $Z = 4$, $D_c = 1.50 \text{ g cm}^{-3}$, $F(000) = 996$, $\lambda(\text{Mo-K}\alpha) = 0.71069 \text{ \AA}$, $\mu(\text{Mo-K}\alpha) = 12.29 \text{ cm}^{-1}$.

Data collection. A blue needle-like crystal, with dimensions $1.0 \times 0.3 \times 0.2 \text{ mm}$, was mounted in a Lindmann capillary under a saturated atmosphere of the mother-liquor. Data were collected at 273 K with an Enraf-Nonius FAST diffractometer, equipped with a rotating anode, using SADNES, a modified version of MADNESS,⁹ for small molecule data collection. The orientation matrix and unit-cell parameters were determined from 50 reflections collected by the ω -scan mode in two approximately orthogonal zones of reciprocal space. Throughout data collection the detector was kept at 40 mm from the crystal and at a θ angle of 25° . An exposure time of 20 s was used per 0.2° frame of collected data.

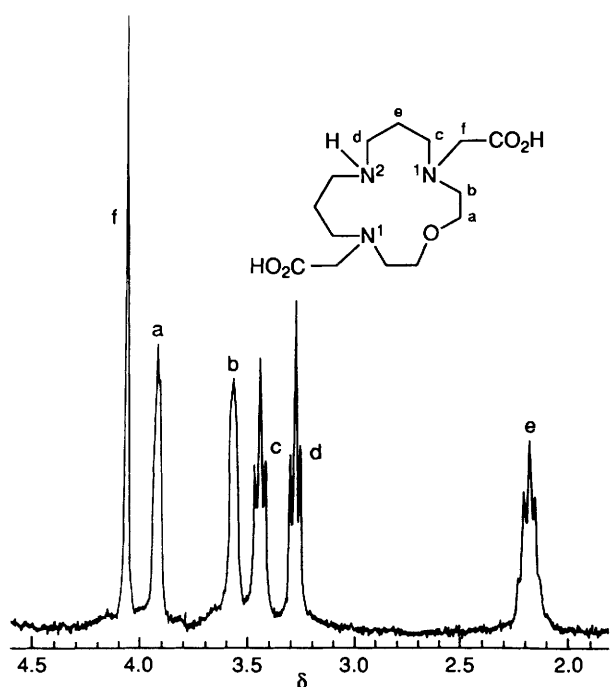
During data collection the unit-cell parameters together with the orientation matrix were refined every 10° of measured data. Data reduction was carried out by the Kabsch method of profile fitting using PROCOR.¹⁰ Intensities were corrected for Lorentz and polarization effects but not for absorption.

Structure solution and refinement. Merging of the data, solution and refinement of the structure were carried out with SHELX 76.¹¹ 22 216 Reflections from six different batches of data were merged in the Laue symmetry group $2/m$ to give 5618 unique reflections with $R_{\text{merge}} = 0.068$. The copper coordinates were obtained from a three-dimensional sharpened Patterson function and the remaining positions of the non-hydrogen atoms were then found by successive Fourier difference synthesis. 3495 Reflections with $|F_o| \geq 3\sigma|F_c|$ were used in the

Table 1 Protonation ($\log K_i$)^a and stability constants ($\log \beta_{M_nL_nH_n}$)^b of metal complexes of $[L^{2-}]^{2-}$ ^c

Metal ion	Species	
H ⁺	HL	11.03(2)
	H ₂ L	6.97(2)
	H ₃ L	3.58(3)
	H ₄ L	0.8(1) ^d
Ca ²⁺	ML	2.1(1)
	ML	7.08(2)
Mn ²⁺	MLH	13.95(5)
	ML	11.81(1)
Co ²⁺	MLH	15.7(1)
	ML	14.7(1)
Ni ²⁺	ML	17.62(4)
	MLH	20.28(8)
Cu ²⁺	ML	12.597(6)
	ML	11.55(1)
Zn ²⁺	MLH	15.4(1)
	MLH ₋₁	2.0(1)
Cd ²⁺	ML	8.01(2)
	MLH	14.41(6)
Pb ²⁺	ML	
	MLH	

^a $K_i = [H_iL]/[H_{i-1}L][H^+]$ where L is the completely deprotonated form of the ligand H_2L^{2-} i.e. $[L^{2-}]^{2-}$. ^b $\beta_{M_nL_nH_n} = [M_nL_nH_n]/[M]^n[L]^{2-}[H]^n$, $\beta_{MLH_{-1}} = K_w\beta_{ML(OH)}$, $\beta_{ML(OH)} = [ML(OH)]/[M][L][OH]$, where K_w is the ion product constant for water. ^c $T = 25^\circ C$; $I = 0.10$ mol dm⁻³ (NMe₄NO₃); by potentiometric measurements. ^d This work by NMR measurements. Titration with CsOD and D₂SO₄.

**Fig. 1** Proton NMR spectrum of the ligand at pD 1.20

solution and initial stages of refinement by full-matrix least squares.

Isotropic refinement of all non-hydrogen atoms gave $R = 0.012$, which was lowered to 0.088 after anisotropic refinement. The hydrogen atoms were introduced in the refinement in calculated positions, except those of the water molecules which were not found and were not included. The methylenic hydrogen atoms were refined in three different groups with global thermal parameters: $U_{iso} = 0.056(5) \text{ \AA}^2$ for the hydrogen atoms of the carbon macrocycle backbone, 0.07(2) and 0.06(2) \AA^2 for those of each acetate group. The hydrogen atom bonded to the nitrogen was refined with a constant $U_{iso} = 0.05 \text{ \AA}^2$. The C-H and N-H distances were constrained to 0.95 \AA .

Final refinement of 334 parameters converged to $R = 0.089$

and $R' = 0.121$ for 3656 reflections with $|F_o| \geq 2\sigma|F_o|$, using a weighting scheme $w = 1.0598/(\sigma^2|F_o| + 0.00815|F_o|^2)$. The maximum and minimum residual electron densities in the F map were 1.23 and -0.98 e \AA^{-3} ; the maximum shift/e.s.d. was 1.28 on the atomic coordinate X/a of the H(121) atom.

Atomic scattering factors and anomalous scattering terms were taken from ref. 12. The molecular diagrams presented were drawn with ORTEP II.¹³ All calculations were done on a Micro Vax-3600 computer.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters and remaining bond lengths and angles.

Results and Discussion

Protonation reactions of the new diacetate derivative of the oxatriaia macrocycle, $[L^{2-}]^{2-}$, have been studied as well as its complexation reactions with several metal ions. Table 1 summarizes the protonation ($\log K_i$) and the stability constants ($\log \beta_{M_nL_nH_n}$) of the complexes formed by this ligand with several first-series transition-metal ions, Zn²⁺, Ca²⁺, Cd²⁺ and Pb²⁺, calculated from potentiometric titrations.

Protonation Constants.—From the five basic centres of the ligand it has been possible to determine only three protonation constants by potentiometric measurements. By NMR titration of the ligand it was possible to determine another one (cf. Table 1) and to know the sequence of protonation. These values are not so different from those of similar *N*-acetate 12-membered compounds.^{4,7}

The ¹H NMR titration curves of $[L^{2-}]^{2-}$ allow the interpretation of these data.⁷ The ¹H NMR spectrum of this compound at pD 1.20 is shown in Fig. 1. The assignment of the resonances is straightforward taking into account the area ratio, the pattern of each absorption and the profile of the titration curves. The spectra exhibit six resonances for low pD values, but resonances b and c are superimposed at pD > 4: one singlet is readily assigned to the methylenic protons of the acetate groups, one quintuplet at high field to protons e and four triplets. The methylenic protons a are deshielded by the nearby ether oxygen atom and were assigned to the triplet at lower field. Irradiation of this signal (at pD 14 and 1.39) allowed the assignment of the adjacent methylenic b protons and the irradiation of the resonance e allowed the assignment of methylenic protons c and d. In this last case the resonances can be distinguished by taking into account the profile of the titration curves (the d methylenic protons are influenced by protonation of nitrogen N² and the c methylenic protons by the protonation of nitrogen atoms N¹).

The ¹H NMR titration curves show that the first equivalent of acid added to the basic form of the ligand protonates the centre N² since only resonances d and e shift downfield; the second equivalent of acid protonates 50% of nitrogen atoms N¹ (resonances a–c, e and f move downfield). The third equivalent of acid protonates a carboxylate group (only resonance f has an appreciable shift), probably the group bonded to the non-protonated nitrogen atom because of the relatively high value of the corresponding protonation constant. The last two centres (the second carboxylate group and the second nitrogen atom N¹) begin to be protonated at pD < 3, and the protonation is far from complete at pD 0.

It is interesting that, contrary to what happens with the parent amine⁶ and to what could be inferred from the cavity size, the third protonation occurs at a carboxylate group and not at the remaining non-protonated nitrogen atom. The protonation sequence is essentially similar to that of *N*-acetate derivatives of 12-membered macrocycles,⁴ the differences arising from the size of the ring, which allows the nitrogen atoms N² in $[L^{2-}]^{2-}$ to stay protonated when protonation of nitrogen N¹ starts, which is not possible for the 12-membered macrocycles.⁴ The triprotonated form of the ligand seems to be very stable.

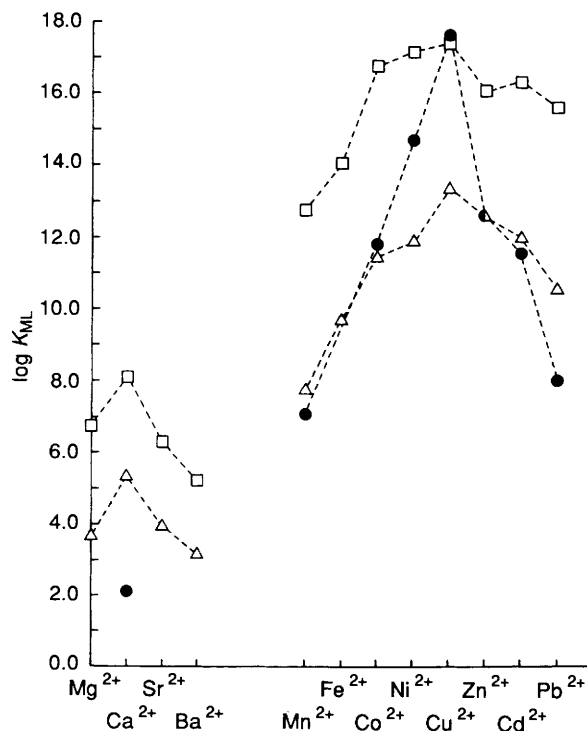


Fig. 2 Variation of the stability constants of the complexes of ligands $[L^2]^{2-}$ (●), $[L^3]^{2-}$ (□)¹⁴ and $[L^4]^{2-}$ (△)¹⁵ with the atomic number of the metal ions

Table 2 Fractional atomic coordinates ($\times 10^4$) for $[\text{CuL}^2] \cdot 5\text{H}_2\text{O}$ with estimated standard deviations (e.s.d.s) in parentheses

Atom	x	y	z
Cu	1407(1)	475(1)	3121.6(4)
N(1)	-117(5)	511(4)	1916(3)
N(2)	2499(4)	1406(4)	2669(3)
N(3)	2333(4)	895(4)	4513(3)
O(1)	169(4)	1976(4)	3374(3)
O(2)	222(4)	-488(3)	3445(3)
O(3)	-1626(4)	-1366(4)	2976(3)
O(4)	2777(4)	-833(4)	3640(3)
O(5)	3101(5)	-1995(4)	4744(3)
C(1)	265(7)	355(6)	1124(4)
C(2)	1313(8)	1093(6)	1085(4)
C(3)	2555(7)	1000(6)	1820(4)
C(4)	3808(5)	1646(6)	3289(5)
C(5)	3822(6)	2163(6)	4125(5)
C(6)	3651(6)	1311(6)	4761(4)
C(7)	1577(7)	1699(6)	4819(4)
C(8)	190(6)	1716(6)	4242(4)
C(9)	-1033(6)	1863(6)	2696(4)
C(10)	-774(6)	1584(5)	1856(4)
C(11)	-810(5)	-770(5)	2848(4)
C(12)	-998(7)	-403(5)	1934(4)
C(13)	2802(5)	-1081(5)	4389(4)
C(14)	2389(6)	-209(6)	4923(4)
O(1W)	4146(5)	8043(5)	2841(4)
O(2W)	5969(6)	9503(5)	2703(5)
O(3W)	5580(6)	948(6)	1243(4)
O(4W)	7349(6)	3230(5)	4007(4)
O(5W)	6604(6)	111(6)	-65(4)

The fourth protonation, although at a carboxylate group, has a very low $\log K$ value, probably due to the formation of hydrogen bonds between the protonated carboxylate groups and non-protonated nitrogen atoms (N^1) and between non-protonated carboxylate groups and protonated nitrogen atoms (N^1).

Table 3 Selected bond distances (\AA) and angles ($^\circ$) in the copper co-ordination sphere

N(1)-Cu	2.106(7)	N(2)-Cu	1.983(7)
N(3)-Cu	2.194(7)	O(1)-Cu	2.414(6)
O(2)-Cu	1.973(6)	O(4)-Cu	2.171(6)
N(2)-Cu-N(1)	92.8(3)	N(3)-Cu-N(1)	153.4(2)
N(3)-Cu-N(2)	96.6(3)	O(1)-Cu-N(1)	79.3(3)
O(1)-Cu-N(2)	95.3(3)	O(1)-Cu-N(3)	75.2(3)
O(2)-Cu-N(1)	81.7(3)	O(2)-Cu-N(2)	174.1(2)
O(2)-Cu-N(3)	89.3(3)	O(2)-Cu-O(1)	85.9(3)
O(4)-Cu-N(1)	127.8(3)	O(4)-Cu-N(2)	96.9(3)
O(4)-Cu-N(3)	75.7(3)	O(4)-Cu-O(1)	149.5(1)
O(4)-Cu-O(2)	84.8(3)		

Stability Constants.—In most cases ML and MLH species are formed; however, for Ca^{2+} , Ni^{2+} and Zn^{2+} only the species ML is formed according to the best set of stability constants calculated by the SUPERQUAD program.⁸ We have also checked the possibility of formation of M_2L and ML(OH) species but they do not appear to be formed under the conditions used, except in the case of Cd^{2+} where a ML(OH) species has been found.

The Irving-Williams order of stability is obeyed for this ligand, but the striking fact is its selectivity for the different types of metal ions. This ligand forms very stable complexes with copper(II) and also with nickel(II), but those formed with Ca^{2+} , Mn^{2+} and Pb^{2+} have relatively low stability constants.

The selectivity can be better appreciated in Fig. 2 by comparison with similar ligands. Ligand $[\text{L}^3]^{3-}$ with the same set of donor atoms (N_3O_3 , two of the oxygen atoms from acetate groups) but smaller ring size, presents higher stability constants for the complexes formed with all the metal ions studied in this work than does $[\text{L}^2]^{2-}$ (with the exception of Cu^{2+}).¹⁴ Ligand $[\text{L}^4]^{2-}$, an even smaller ligand with only 9 atoms in the ring, having N_2O_3 as potential donor atoms and less basic than $[\text{L}^2]^{2-}$, forms complexes with Mn^{2+} , Co^{2+} , Zn^{2+} and Cd^{2+} with similar stability to those of $[\text{L}^2]^{2-}$, having even larger values for the complexes of Pb^{2+} and Ca^{2+} than with $[\text{L}^2]^{2-}$.¹⁵

Hence, similarly to what happens with the parent amines,⁶ the larger ions seem to prefer the smaller rings, contrary to what might be expected if the metal ions were inserted in the ring, showing that the fitting between the size of the metal ion and the size of the cavity of the macrocycle seems to be irrelevant.

The low values of the stability constants of $[\text{L}^2]^{2-}$ with the larger metal ions, which are even lower than those presented by $[\text{L}^4]^{2-}$ complexes, may only be understood if one nitrogen atom of the ring of $[\text{L}^2]^{2-}$ is not involved in the co-ordination to these ions. In accord with this point, it is known that Mn^{2+} and Pb^{2+} have little affinity for nitrogen atoms and tend to behave more like the alkaline-earth-metal ions in their complexes. However, only the molecular structural determination of these complexes by X-ray crystallography could elucidate these questions.

X-Ray Analysis.—Final atomic coordinates of the non-hydrogen atoms and selected bond distances and angles in the copper co-ordination sphere are presented in Tables 2 and 3, respectively. Fig. 3 shows a molecular diagram of the $[\text{CuL}^2]$ complex with the adopted atomic labelling scheme.

The co-ordination geometry around the metal atom can be described as a distorted octahedron, tetragonally elongated approaching a skew trapezoidal geometry. The equatorial plane is determined by the three nitrogen atoms [N(1), N(2), N(3)] of the oxa-triazine ring and the oxygen atom O(2) of one of the carboxylate groups. Six-co-ordination is completed via the oxygen atom O(1) of the macrocyclic ring and atom O(4) of the remaining carboxylate group.

The angle between the axial donor atoms O(4)-Cu-O(1) of $149.5(1)^\circ$ is much smaller than the expected 180° for ideal

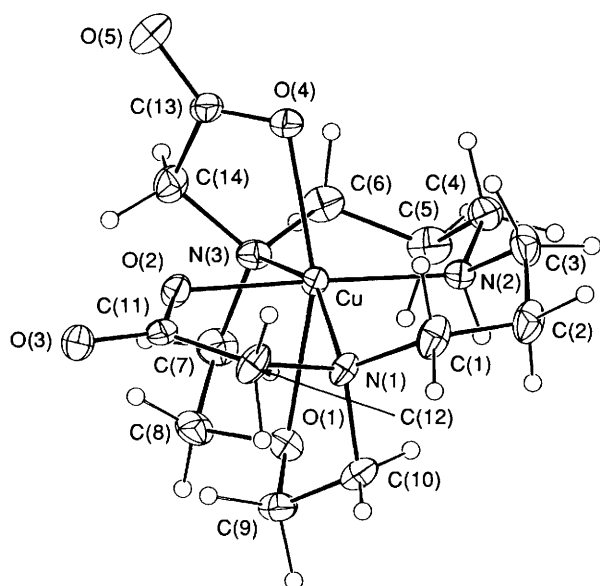


Fig. 3 Molecular diagram of $[\text{CuL}^2]\cdot 5\text{H}_2\text{O}$ showing the atomic labelling scheme. Thermal ellipsoids are drawn at the 30% probability level and the hydrogen atoms are represented with a U_{iso} of 0.09 \AA^2

octahedral geometry. Also the best least-squares plane, through the four equatorial atoms N(1), N(2), N(3), O(2), shows tetrahedral deviations of $\pm 0.24(1) \text{ \AA}$. The copper atom deviates from this plane by $0.21(1) \text{ \AA}$.

No direct comparison of the geometry is possible as no *N*-substituted derivatives of L^1 were found. Nevertheless, in spite of the different stereochemical pattern of the ligands, a comparison is presented with some copper and nickel complexes of 1,4,7,10-tetraazacyclododecane (cyclen)¹⁶ and 1,4,8,11-tetraazacyclotetradecane (cyclam) derivatives^{16–20} also exhibiting octahedral co-ordination in which one or both of the axial sites are occupied by atoms of the macrocyclic ring.

In the present complex the deviation of the axial donor atoms from the linear arrangement is probably a consequence of the strain in the asymmetric macrocyclic ligand. There are two consecutive six-membered rings followed by two consecutive five-membered rings, while in the cyclam derivatives the two types of rings are in alternating positions. However when all chelating rings are five membered, a similar distortion is observed as in complexes of H_4L^6 , namely $[\text{Cu}(\text{H}_2L^6)]$,^{16a} $[\text{Ni}(\text{H}_2L^6)]$ ^{16a} and $[\text{Cu}_2L^6]\cdot 5\text{H}_2\text{O}$ ^{16b} where the axial angle N–M–N is $152.6(3)$, $158.6(3)$ and $151.3(3)^\circ$, respectively. On the other hand, if the six- and five-membered chelating rings are alternated the axial angle is close to 180° . Examples are the complexes of *N*-acetate derivatives of cyclam, like $[\text{NiL}^{10}]$ where O–Ni–N is $176.8(1)^\circ$ ¹⁷ and $[\text{Cu}(\text{H}_2L^{11})]$ where N–Cu–N is $179.3(2)^\circ$.¹⁸ Furthermore in complexes $[\text{Cu}(\text{H}_2L^8)]$ ¹⁹ and $[\text{CuL}^9]$,²⁰ where the axial positions are occupied by two oxygen atoms from two carboxylate groups, the macrocycle adopts also an unstrained configuration. The copper is at a crystallographic inversion centre and therefore the axial O–Cu–O angle is exactly 180° .

The present macrocycle is folded along a diagonal passing through atoms N(1)–N(3), with a $101.7(2)^\circ$ dihedral angle between the planes defined by the atoms Cu,N(3),N(2),N(1) and Cu,N(3),O(1),N(1). According to the nomenclature proposed by Bosnich *et al.*,²¹ this folded configuration is of the *cis-V* type, *cf.* Fig. 3.

The conformation of the chelating rings was determined using the puckering parameters defined by Cremer and Pople.²² Both five-membered chelating rings adopt a twisted configuration; one of the six-membered rings, Cu,N(2), C(3),C(2),C(1),N(1), is in a 'half-chair' while the other, Cu,N(3),C(6),C(5),C(4),N(2), is in a 'half-boat' conformation.

The copper–nitrogen equatorial distances range from 1.983(7) to 2.194(7) Å (*cf.* Table 3) and the Cu–O(2) distance is 1.973(6) Å . These distances are similar to those found in complexes of 14-membered (L^1) oxatriaia parent amines,²³ even though these have square-pyramidal co-ordination. As expected for a tetragonally elongated octahedral copper(II) complex, the axial bond lengths, Cu–O(4) 2.171(6) and Cu–O(1) 2.414(6) Å , are longer than the equatorial ones due to the Jahn–Teller effect.²⁴ Surprisingly, the longer distance is between the copper and the oxygen atom of the macrocyclic ligand, which is again evidence of the strained folding of the ligand.

The bonding distances in the macrocyclic ring are as expected.^{16–20} The complex molecule and five water molecules are connected to each other by hydrogen bonds.

In conclusion, the molecular structure of the copper complex shows that all the donor atoms of the ligand are involved in co-ordination to the metal, thus forming a very stable complex with a strained *cis-V* configuration. This co-ordination is believed to persist in solution both for the copper and the nickel complex. On the other hand, complexes with larger metal ions, namely Ca^{2+} , Mn^{2+} and Pb^{2+} , have relatively low stability, which could be understood if one of the nitrogen-donor atoms of the ring were not involved in the co-ordination.

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References

- 1 *Coordination Chemistry of Macrocyclic Compounds*, ed. G. A. Melson, Plenum, New York, 1979; R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.*, 1991, **91**, 1721; L. F. Lindoy, *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press, Cambridge, 1989.
- 2 T. A. Kaden, *Top. Curr. Chem.*, 1984, **121**, 157; R. W. Hay, in *Current Topics in Macrocyclic Chemistry in Japan*, ed. E. Kimura, Hiroshima, 1987, p. 56; P. V. Bernhardt and G. A. Lawrance, *Coord. Chem. Rev.*, 1990, **104**, 297.
- 3 J. P. L. Cox, K. J. Jankowski, R. Katakay, D. Parker, N. R. A. Beeley, B. A. Boyce, M. A. W. Eaton, K. Millar, A. T. Millican, A. Harrison and C. Walker, *J. Chem. Soc., Chem. Commun.*, 1989, 797; I. M. Helms, D. Parker, J. R. Morphy and J. Chapman, *Tetrahedron*, 1989, **45**, 219; I. M. Helms, D. Parker, K. J. Jankowski, J. Chapman and P. E. Nicholson, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2079; A. Riesen, T. A. Kaden, W. Ritter and H. R. Mäcke, *J. Chem. Soc., Chem. Commun.*, 1989, 460; A. D. Sherry, R. D. Brown III, C. F. G. C. Geraldes, S. H. Koenig, K.-T. Kuan and M. Spiller, *Inorg. Chem.*, 1989, **28**, 620; E. Kimura, S. Joko, T. Koike and M. Kodama, *J. Am. Chem. Soc.*, 1987, **109**, 5528.
- 4 M. T. S. Amorim, J. R. Ascenso, R. Delgado and J. J. R. Fraústo da Silva, *J. Chem. Soc., Dalton Trans.*, 1990, 3449.
- 5 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon, Oxford, 1988.
- 6 M. T. S. Amorim, S. Chaves, R. Delgado and J. J. R. Fraústo da Silva, *J. Chem. Soc., Dalton Trans.*, 1991, 3065.
- 7 R. Delgado, J. J. R. Fraústo da Silva, M. T. S. Amorim, M. F. Cabral, S. Chaves and J. Costa, *Anal. Chim. Acta*, 1991, **245**, 271.
- 8 P. Gans, A. Sabatini and A. Vacca, *J. Chem. Soc., Dalton Trans.*, 1985, 1195.
- 9 J. W. Pflugrath and A. Messerschmidt, *Crystallography in Molecular Biology*, Bischenberg, 1985, Abstracts; A. Messerschmidt and J. W. Pflugrath, *J. Appl. Crystallogr.*, 1987, **20**, 306.
- 10 W. Kabsch, *J. Appl. Crystallogr.*, 1988, **21**, 916.
- 11 G. M. Sheldrick, SHELX 76, Crystallographic Calculation Program, University of Cambridge, 1976.
- 12 *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, 1974, vol. 4.
- 13 C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, TN, 1976.

- 14 M. T. S. Amorim, R. Delgado and J. J. R. Fraústo da Silva, *Polyhedron*, in the press.
- 15 M. F. Cabral, J. Costa, R. Delgado, J. J. R. Fraústo da Silva and M. F. Vilhena, *Polyhedron*, 1990, **9**, 2847.
- 16 A. Riesen, M. Zehnder and T. A. Kaden, (a) *Helv. Chim. Acta*, 1986, **69**, 2067; (b) *Helv. Chim. Acta*, 1986, **67**, 2074; *J. Chem. Soc., Chem. Commun.*, 1985, 1336.
- 17 X. Ji-De, N. Shi-Sheng and L. Yu-Juan, *Inorg. Chem.*, 1986, **111**, 61.
- 18 M. K. Moi, M. Yanuck, S. V. Despande, H. Hope and S. J. DeNardo, *Inorg. Chem.*, 1987, **26**, 3458.
- 19 A. Riesen, M. Zehnder and T. A. Kaden, *Acta Crystallogr., Sect. C*, 1988, **44**, 1740.
- 20 I. M. Helps, D. Parker, J. Chapman and G. Ferguson, *J. Chem. Soc., Chem. Commun.*, 1988, 1094.
- 21 B. Bosnich, C. K. Poon and M. L. Tobe, *Inorg. Chem.*, 1965, **4**, 1102.
- 22 D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, 1975, **97**, 1354.
- 23 M. T. S. Amorim, S. Chaves, R. Delgado, M. T. Duarte, J. A. L. Silva, J. J. R. Fraústo da Silva, M. A. A. F. de C. T. Carrondo and V. Felix, unpublished work.
- 24 B. J. Hathaway, in *Comprehensive Coordination Chemistry*, eds. G. Wilkinson, R. D. Gillard and J. A. McCleverty, Pergamon, Oxford, 1987.

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