

## Design of selective macrocyclic ligands for the divalent first-row transition-metal ions\*

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The protonation constants of H<sub>2</sub>L<sup>1</sup>, 3,11-bis(carboxymethyl)-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene and H<sub>3</sub>L<sup>2</sup>, 3,7,11-tris(carboxymethyl)-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene, and stability constants of complexes formed by these macrocycles with Mg<sup>2+</sup>, Ca<sup>2+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, Pb<sup>2+</sup>, Ga<sup>3+</sup>, Fe<sup>3+</sup> and In<sup>3+</sup> were determined at 25 °C and ionic strength 0.10 mol dm<sup>-3</sup> in NMe<sub>4</sub>NO<sub>3</sub>. Both compounds are very selective for the divalent first-row transition-metal ions, exhibiting very high stability constants for Cu<sup>2+</sup>, fairly high values for Ni<sup>2+</sup>, but sharply decreasing ones for the remaining metal ions of this row. Their complexes with the alkaline-earth or larger metal ions, such as Pb<sup>2+</sup>, have low stability constants. The crystal structure of [CuL<sup>1</sup>]-4H<sub>2</sub>O was determined. The copper atom is encapsulated by the macrocycle in a distorted octahedral environment. The equatorial plane contains the four nitrogen atoms of the tetraaza ring and six-co-ordination is completed *via* two oxygen atoms of the appended carboxylate groups. The angles at the metal centre are close to the expected values of 90 and 180° for octahedral geometry. Molecular mechanics studies carried out for the *cis* and the *trans* octahedral [ML<sup>1</sup>] complexes were consistent with the structure found in the solid state. For a mean Cu<sup>II</sup>-N distance of 2.01 Å the experimentally observed *trans* isomer is 6.5 kcal mol<sup>-1</sup> more stable than the *cis* one. On the other hand these calculations suggest that larger ions such as Pb<sup>2+</sup>, Ca<sup>2+</sup> or Mn<sup>2+</sup> can be accommodated by the macrocycle in a *cis*-octahedral environment. However, these ions allow co-ordination numbers higher than six and so other structures ought to be also considered. The low stability constants for metal complexes of Co<sup>2+</sup> and Zn<sup>2+</sup> indicate that these complexes do not have a *trans*-octahedral structure, while the molecular mechanics calculations reveal that the *cis* isomer is not the most stable form. Therefore, other structures with co-ordination numbers lower than six should be considered, implying that one or more donor atoms are not co-ordinated. Stability constants of metal complexes of (L<sup>2</sup>)<sup>3-</sup> and EPR studies suggest that not all the donor atoms in this macrocycle are co-ordinated when complexes are formed with first-row-transition divalent metal ions.

The effect of the increase in cavity size of *N*-carboxymethyl tetraaza,<sup>1</sup> oxatriaiza<sup>2</sup> and dioxadiaza<sup>3</sup> macrocycles from 12- to 14-membered on the stability constants of their metal complexes has been studied previously. In the present work two new 14-membered compounds containing pyridine have been synthesized (H<sub>2</sub>L<sup>1</sup> and H<sub>3</sub>L<sup>2</sup>, see Scheme 1) the complexation behaviour of which should be compared with that of 12-membered macrocycles.<sup>4</sup>

In general *N*-carboxymethyl derivatives of 14-membered macrocycles are more selective for the first-row-transition divalent metal ions than are the smaller 12- or 13-membered macrocycles.<sup>1-5</sup> However, the complexes of the former have lower stability constants, with exception of those of Cu<sup>2+</sup> and in some cases also of Ni<sup>2+</sup>.<sup>2-5</sup> The thermodynamic stability of the complexes with the alkaline-earth-metal ions always decreases with increase in cavity size and the constants for the complexes of the 14-membered macrocycles having contiguous propane chains are very low.<sup>2,5,6</sup>

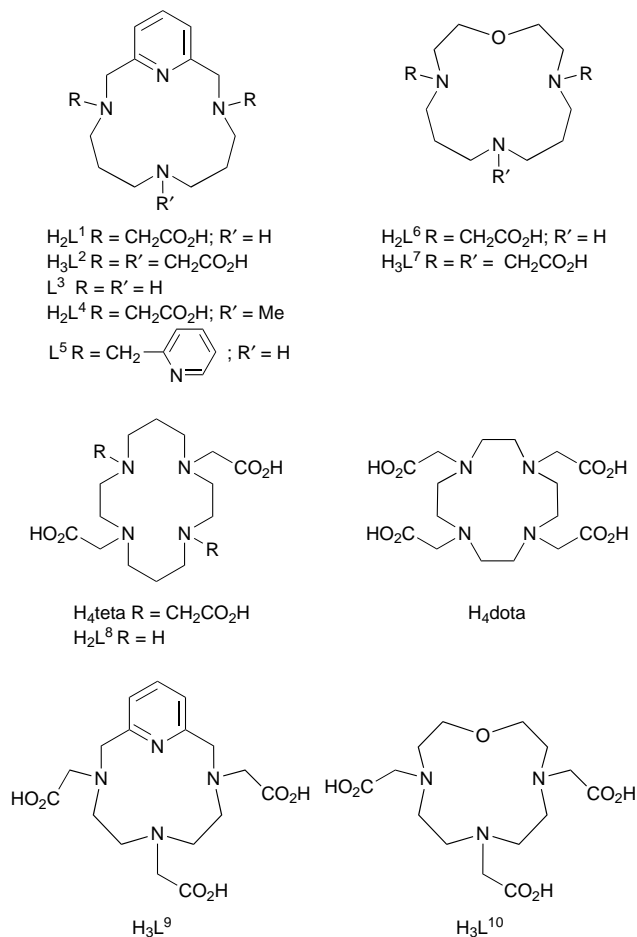
The main purpose of the present work is to study the effect of increasing the number of *N*-carboxymethyl arms on the macrocycle backbone on the stability constants of its metal

complexes. It is known that when H<sub>4</sub>teta, the tetrakis(carboxymethyl) derivative of the 14-membered tetraaza macrocycle (*cf.* Scheme 1), forms complexes with the first-transition-series metal ions not all the eight potential donor atoms are co-ordinated.<sup>1,7,8</sup> However, a different situation occurs with alkaline-earth and lanthanide complexes as these metal ions allow co-ordination numbers of eight or more, as happens with Na[Tb(teta)]·6H<sub>2</sub>O·0.5NaCl.<sup>9</sup> The compound H<sub>2</sub>L<sup>1</sup> has six donor atoms, the exact number required for six-co-ordination, and so we think it will be more appropriate for medical applications than H<sub>4</sub>teta, owing to the reduced possibility to form polynuclear species. In fact, the copper-67 complex of tetra<sup>4-</sup> was used in radioimmunotherapy as a bifunctional chelate conjugated with a monoclonal antibody, with promising results.<sup>10</sup> The major drawback to the use of H<sub>4</sub>teta and other tetraaza macrocycles is the slow kinetics of complex formation,<sup>11</sup> an important limitation especially when these compounds are used as radiopharmaceuticals.

Searching for ligands which could have faster formation kinetics led us to the synthesis of a series of cyclic tetraamines incorporating a pyridine. Previous work has shown that these compounds form complexes faster, though having lower stability constants than those of the corresponding tetraaza macrocycles.<sup>4,5,12</sup> The first observation was important enough to induce us to carry out the determination of the stability constants of H<sub>2</sub>L<sup>1</sup> and H<sub>3</sub>L<sup>2</sup> with a variety of di- and tri-valent metal ions; H<sub>3</sub>L<sup>2</sup> will be useful for the study of the effect of one necessarily unco-ordinated arm on the system.

\* Supplementary data available: SUPERQUAD results for the iron(III) complexes. For direct electronic access see <http://www.rsc.org/suppdata/dt/1998/1063/>, otherwise available from BLDSC (No. SUP 57340, 51 pp.) or the RSC Library. See Instructions for Authors, 1998, Issue 1 (<http://www.rsc.org/dalton>).

Non-SI units employed: μ<sub>B</sub> ≈ 9.27 × 10<sup>-24</sup> J T<sup>-1</sup>, cal = 4.184 J.



Scheme 1

The completely deprotonated forms of the compounds are charged species but for simplicity the charges will generally be omitted in the following text.

## Experimental

### Reagents

The parent compound  $L^3$ , was synthesized in our laboratory by previously reported procedures.<sup>12</sup> Bromoacetic acid, Dowex 1  $\times$  8 ion-exchange resin (20–50 mesh,  $Cl^-$  form) and triethylenetetramine tetrahydrochloride 97% (trien $\cdot$ 4HCl) were obtained from Aldrich Chemical Co., ethyl bromoacetate and  $K_2H_2edta$  (dipotassium ethylenedinitrilotetraacetate) from Fluka and  $H_4egta$  (ethylenedioxydiethylenedinitrilotetraacetic acid) from Sigma. All the chemicals were of reagent grade used as supplied (the resin was treated with 1 mol  $dm^{-3}$  formic acid before use). The organic solvents were purified by standard methods.<sup>13</sup>

### Synthesis and characterisation of macrocycles

The compound  $H_2L^1$  was prepared by condensation of the parent amine  $L^3$  (4.27 mmol, 1.0 g) with potassium bromoacetate (obtained by addition of 3 mol  $dm^{-3}$  KOH solution to concentrated aqueous bromoacetic acid, 8.6 mmol, 1.25 g, at 5 °C), in aqueous basic solution. The temperature was kept at 25–30 °C and the pH below 9 by slow addition of 3 mol  $dm^{-3}$  KOH. The reaction was considered complete in 9 d and then the pH was adjusted to 2 with 3 mol  $dm^{-3}$  hydrobromic acid. The solution was concentrated, methanol added and the inorganic matter formed was filtered off. The filtrate consisted of the desired product and about 10% of the trisubstituted derivative ( $H_3L^2$ ). The purified product was obtained by chromatography

using an anionic resin in the formate form (column 30.0  $\times$  2.0 cm). The flow rate was kept at 1.0  $cm^3 min^{-1}$ . After washing with water ( $\approx$ 250  $cm^3$ ), the mixture was eluted with 0.005 mol  $dm^{-3}$  formic acid. The pure product was isolated from column fractions 15 to 24 (each of 20  $cm^3$ ). The fractions were collected, the solvent was evaporated and the white solid washed several times with water and then ethanol. Yield: 55%. M.p. 261–262 °C.  $^1H$  NMR [ $D_2O$ ,  $Me_3SiCD_2CD_2CO_2Na$ , pD 5.16]:  $\delta$  7.81 (1 H, t, CH of pyridine), 7.41 (2 H, d, CH of pyridine), 4.20 (4 H, s,  $CCH_2N$ ), 3.45 (4 H, s,  $NCH_2CO_2^-$ ), 3.21 (4 H, t,  $NCH_2CH_2$ ), 3.10 (4 H, t,  $NCH_2CH_2$ ) and 2.13 (4 H, q,  $NCH_2CH_2CH_2N$ ).  $^{13}C$  NMR ( $D_2O$ , pD 5.16, 1,4-dioxane):  $\delta$  174.29 ( $CO_2^-$ ), 153.70 (*o*-C of pyridine), 138.84 (*p*-C of pyridine), 125.19 (*m*-C of pyridine), 57.35 ( $CCH_2N$ ), 55.62 ( $NCH_2CO_2^-$ ), 52.08 ( $NCH_2CH_2$ ), 47.07 ( $NCH_2CH_2$ ) and 21.16 ( $NCH_2CH_2CH_2N$ ) (Found: C, 55.3; H, 7.4; N, 15.2. Calc. for  $C_{17}H_{26}N_4O_4 \cdot H_2O$ : C, 55.4; H, 7.7; N, 15.2%).

The compound  $H_3L^2$  was synthesized by condensation of the parent amine ( $L^3$ ) with ethyl bromoacetate under basic conditions. A solution of NaOH (27 mmol, 1.08 g) in water (30  $cm^3$ ) was added to  $L^3$  (3 mmol, 0.7 g) in  $CH_2Cl_2$  (25  $cm^3$ ) and then ethyl bromoacetate (9 mmol, 1.05  $cm^3$ ) in  $CH_2Cl_2$  (6  $cm^3$ ) was added dropwise during 3 h, at room temperature, and the reaction was pursued for more than 48 h. The two phases were then separated and the aqueous phase was extracted with  $CH_2Cl_2$  (4  $\times$  60  $cm^3$ ). The organic phase was collected, dried and concentrated. The oil obtained was purified through a silica gel 60 column (20.0  $\times$  2.5 cm) by elution with  $CHCl_3$ –MeOH (10:1). After evaporation of the solvent the ester, in the form of a yellow oil, was obtained. Yield: 35%.  $^1H$  NMR ( $CDCl_3$ ,  $SiMe_4$ ):  $\delta$  7.54 (1 H, t, CH of pyridine), 7.19 (2 H, d, CH of pyridine), 4.15 (4 H, q,  $OCH_2CH_3$ ), 4.01 (2 H, q,  $OCH_2CH_3$ ), 3.86 (4 H, s,  $CCH_2N$ ), 3.41 (4 H, s,  $NCH_2CO_2^-$ ), 3.01 (2 H, s,  $NCH_2CO_2^-$ ), 2.57 (4 H, t,  $NCH_2CH_2$ ), 2.44 (4 H, t,  $NCH_2CH_2$ ), 1.40 (4 H, q,  $NCH_2CH_2CH_2N$ ), 1.23 (6 H, t,  $OCH_2CH_3$ ) and 1.14 (3 H, t,  $OCH_2CH_3$ ). The ester was hydrolysed under acid conditions (pH 2, by addition of HCl) in 96 h. Then the solvent was evaporated and methanol added. The formed inorganic salts were filtered off and the filtrate passed through an anionic resin in the formate form as described for  $H_2L^1$ . The desired product was obtained as a white solid by collecting column fractions from 10 to 23 (each of 20  $cm^3$ ) and evaporation of the solvent. Yield: 85%. M.p. 249–251 °C.  $^1H$  NMR ( $D_2O$ ,  $Me_3SiCH_2CH_2CO_2Na$ , pD 5.0):  $\delta$  7.80 (1 H, t, CH of pyridine), 7.59 (2 H, d, CH of pyridine), 4.64 (4 H, s,  $CCH_2N$ ), 3.80 (4 H, s,  $NCH_2CO_2^-$ ), 3.77 (2 H, s,  $NCH_2CO_2^-$ ), 3.45 (4 H, t,  $NCH_2CH_2$ ), 3.30 (4 H, t,  $NCH_2CH_2$ ) and 2.38 (4 H, q,  $NCH_2CH_2CH_2N$ ).  $^{13}C$  NMR ( $D_2O$ , pD 5.0, 1,4-dioxane):  $\delta$  169.54 ( $CO_2^-$ ), 169.40 ( $CO_2^-$ ), 149.41 (*p*-C of pyridine), 140.25 (*o*-C of pyridine), 126.17 (*m*-C of pyridine), 57.63 ( $CCH_2N$ ), 56.86 (2 C,  $NCH_2CO_2^-$ ), 56.20 (4 C,  $NCH_2CO_2^-$ ), 51.28 ( $NCH_2CH_2$ ), 48.71 ( $NCH_2CH_2$ ) and 18.00 ( $NCH_2CH_2CH_2N$ ) (Found: C, 47.6; H, 7.3; N, 11.6. Calc. for  $C_{19}H_{28}N_4O_6 \cdot H_2O$ : C, 47.5; H, 7.6; N, 11.7%).

### Synthesis of $[CuL^1]$

The salt  $Cu(ClO_4)_2 \cdot 6H_2O$  (0.100 g, 0.270 mmol) was added to a stirred solution of  $H_2L^1$  (0.100 g, 0.285 mmol) dissolved in the minimum volume of water ( $\approx$ 2  $cm^3$ ) and the pH increased to 4 by addition of KOH. The mixture was kept overnight and then concentrated to dryness. The residue was taken up in methanol, the precipitate formed was filtered off and the filtrate was again concentrated to dryness and dissolved in nitromethane. Blue crystals were formed in 3 weeks by slow diffusion of diethyl ether into the solution. Yield: 70%.

### Potentiometric measurements

**Reagents and solutions.** Metal-ion solutions were prepared at about 0.025 mol  $dm^{-3}$  from the nitrate salts of the metals, of

analytical grade, with demineralised water (from a Millipore/Milli-Q system) and were standardised by titration with  $K_2H_2edta$ .<sup>14</sup> A back titration with a standard solution of  $ZnSO_4$  was necessary for  $Ga^{3+}$ . The solutions of the trivalent metal ions were kept in an excess of nitric acid to prevent hydrolysis. Those of  $Mn^{2+}$  and  $Co^{2+}$  were prepared with freshly boiled demineralised water and maintained under nitrogen. Carbonate-free solutions of the titrant,  $NMe_4OH$ , were prepared by treating freshly prepared silver oxide with a solution of  $NMe_4I$  under nitrogen, as described,<sup>15</sup> and maintained in a closed bottle under nitrogen. Solutions were discarded when carbonate was about 0.5% of the total amount of base.

**Equipment and work conditions.** The equipment used was described before.<sup>5</sup> The temperature was kept at  $25.0 \pm 0.1$  °C; atmospheric  $CO_2$  was excluded from the cell bubbling purified argon into the solution before the beginning of the titration and then by passing the same gas across the top of the experimental solution during the titration. The ionic strength of the solutions was kept at  $0.10 \text{ mol dm}^{-3}$  with  $NMe_4NO_3$ .

**Measurements.** The  $[H^+]$  of the solutions was determined by measurement of the electromotive force of the cell,  $E = E'^{\circ} + Q \log [H^+] + E_j$ ;  $E'^{\circ}$ ,  $Q$ ,  $E_j$  and  $K_w = [H^+][OH^-]$  were obtained as described previously.<sup>5</sup> The value of  $K_w$  was found equal to  $10^{-13.80} \text{ mol}^2 \text{ dm}^{-6}$ . The term pH is defined as  $-\log [H^+]$ .

The potentiometric equilibrium measurements were made on  $20.00 \text{ cm}^3$  of macrocycle solutions  $\approx 2.50 \times 10^{-3} \text{ mol dm}^{-3}$  diluted to a final volume of  $30.00 \text{ cm}^3$ , in the absence of metal ions and in the presence of each metal ion, the  $c_L:c_M$  ratios being 1:1, 1:2 and in several cases 2:1. At least two replicates were made. The  $E$  data were taken after additions of  $0.025$  or  $0.050 \text{ cm}^3$  of standard  $NMe_4OH$  solution, and after stabilisation of this direction equilibrium was then approached from the other direction by adding standard nitric acid.

In the cases of complexes of  $Ni^{2+}$ ,  $Cu^{2+}$  and  $Fe^{3+}$  of  $L^1$  and of  $Ni^{2+}$ ,  $Cu^{2+}$ ,  $Ga^{3+}$ ,  $Fe^{3+}$  and  $In^{3+}$  of  $L^2$  the extent of formation, in the beginning of the titration, seemed to be too high for the use of the direct potentiometric method, and the values needed to be confirmed by ligand–ligand or metal–metal competition titrations; edta and trien were used as second ligands in the complexes of  $Cu^{2+}$  and egta for those of  $Fe^{3+}$ , and  $Cu^{2+}$  and  $Zn^{2+}$  were used as second metal ions in the other cases.<sup>4,5</sup> The protonation of the second ligands and the stability constants of the complexes used in the competition reactions were determined by us under the same experimental conditions. The values for edta and trien have been published.<sup>4,16</sup> The egta values determined in the present work were: protonation constants,  $\log K_1^H = 9.303(9)$ ,  $\log K_2^H = 8.98(1)$ ,  $\log K_3^H = 2.75(3)$  and  $\log K_4^H = 2.26(4)$ ; stability constants with  $Fe^{3+}$ ,  $\log K_{ML} = 19.47(4)$  and  $\log K_{MHL} = 3.01(5)$ .

As the stability constants of the complexes of  $Fe^{3+}$  with both ligands were lower than expected, other techniques were used to confirm the values. A direct redox method with a couple of platinum and reference electrodes was used to follow the  $Fe^{3+}/Fe^{2+}$  equilibrium at pH 2 and 3<sup>16</sup> and a spectrophotometric titration was carried out for the complex of  $L^2$ .

In the cases of competition reactions the equilibria were slow to be attained but, even so, automated titrations were possible; 10 to 30 min were necessary for each point of the titration in the pH range where the competition reaction was carried out. The same values of the stability constants were obtained either using the direct or the back titration curves.

The spectroscopic titration was performed by a batch method (solutions were prepared in separated vials and measurements carried out after stabilisation of the pH, which occurred within 3 d) in the range pH 2.15–4.75, at a 1:1  $Fe^{3+}:L^2$  ratio, the initial concentration of the metal ion being  $1.521 \times 10^{-3} \text{ mol dm}^{-3}$ , in the region of 420 to 240 nm.

**Calculation of equilibrium constants.** Protonation constants  $K_i^H = [H_iL]/[H_{i-1}L][H]$  were calculated by fitting the potentiometric data obtained from the free macrocycle using the SUPERQUAD program.<sup>17</sup> Stability constants of the various species formed in solution were obtained from experimental data corresponding to titration of solutions of different ratios of the macrocycle and metal ions, also with the aid of the SUPERQUAD program. The initial computations were obtained in the form of overall stability constants or  $\beta_{M_nH_nL_n}$  values =  $[M_nH_nL_n]/[M]^n[L]^n[H]^n$ .

Only mononuclear species, ML, M(HL),  $MH_{-1}L$ , where  $\beta_{MH_{-1}L} = \beta_{MLOH}K_w$ , were found. Differences, in log units, between the values of  $\beta_{MHL}$  (or  $\beta_{MH_{-1}L}$ ) and  $\beta_{ML}$  provide the stepwise protonation constants. The species considered were limited to those which can be justified by established principles of co-ordination chemistry. The errors quoted are the standard deviations of the overall stability constants given directly by the program. In the case of the stepwise constants the standard deviations were determined by the normal propagation rules and do not represent the total experimental errors.

The protonation constants were obtained from 150 experimental points (two titration curves) and stability constants for each metal ion from 75 (for the alkaline-earth-metal ions) to 260 (for  $Cu^{2+}$ ) experimental points (two to six titration curves).

The SQUAD program<sup>18</sup> was used for the determination of stability constants from the spectrophotometric titration data.

**Hydrolysis species of the trivalent metal ions.** The trivalent metal ions studied in this work are easily hydrolysed in aqueous solution. There are significant discrepancies in the literature for the constants of the resulting species and so we have used values considered more reliable.<sup>5</sup>

### Spectroscopic studies

Proton NMR spectra were recorded with a Bruker CXP-300 spectrometer. Solutions of the macrocycle ( $\approx 0.01 \text{ mol dm}^{-3}$ ) were made up in  $D_2O$  and the pH was adjusted by adding DCl or  $CO_2$ -free KOD with an Orion 420A instrument fitted with a combined Ingold microelectrode. The  $-\log [H^+]$  was measured directly in the NMR tube, after calibration of the microelectrode with buffered aqueous solutions. The sodium salt  $Me_3SiCH_2CH_2CO_2Na$  was used as an internal reference. The  $^{13}C$  NMR spectra were recorded with the same spectrometer and 1,4-dioxane was used as internal reference. The metal complexes were prepared in water by addition of the metal ion, in the form of its nitrate salt, to an equivalent amount of the macrocycle and enough KOH to attain the desired pH and after evaporation of water  $D_2O$  was added. Magnetic moments of the complexes were determined by the Evans method in solution, at room temperature.<sup>19</sup>

Electronic spectra were measured with Shimadzu model UV-3100 spectrophotometer, using aqueous solutions of the complexes prepared by the addition of the metal ion (in the form of its nitrate salt) to the macrocycle at the appropriate pH value (corresponding to total formation of the metal complex). The EPR spectra were recorded with a Bruker ESP 380 spectrometer equipped with a liquid-nitrogen continuous-flow cryostat, operating at X band. The spectra of the copper(II) complexes,  $2.34 \times 10^{-3} \text{ mol dm}^{-3}$  at pH 3.20 for  $L^1$  and  $6.99 \times 10^{-3} \text{ mol dm}^{-3}$  at pH 4.89 for  $L^2$ , prepared in  $1.0 \text{ mol dm}^{-3} NaClO_4$  were recorded at 100 and 129 K, respectively. Computer simulations of the EPR spectra were carried out with a program for a microcomputer.<sup>20</sup>

### Crystallography

**Crystal data.**  $C_{17}H_{32}CuN_4O_8$ ,  $M = 483.0$ , orthorhombic, space group  $Pbca$ ,  $a = 9.255(10)$ ,  $b = 15.065(17)$ ,  $c = 30.883(33)$  Å,  $U = 4306(8)$  Å<sup>3</sup>,  $Z = 8$ ,  $D_c = 1.493 \text{ g cm}^{-3}$ ,  $F(000) = 2040$ ,  $\mu = 1.065 \text{ mm}^{-1}$ ,  $T = 25$  °C.

**Table 1** Protonation ( $\log K_1^H$ ) constants of L<sup>1</sup>, L<sup>2</sup> and other similar macrocycles (L<sup>3</sup>, L<sup>4</sup>, L<sup>6</sup>, L<sup>7</sup> and tetra) for comparison. 25.0 °C,  $I = 0.10 \text{ mol dm}^{-3}$  in NMe<sub>4</sub>NO<sub>3</sub>

Equilibrium quotient	L <sup>1</sup>	L <sup>2</sup>	L <sup>3a</sup>	L <sup>4b</sup>	L <sup>6c</sup>	L <sup>7d</sup>	tetra <sup>e</sup>
[HL]/[H][L]	11.06(3)	10.27(2)	9.92	10.72	11.03	10.25	10.52
[H <sub>2</sub> L]/[HL][H]	7.15(4)	7.90(4)	8.56	7.74	6.97	8.33	10.18
[H <sub>3</sub> L]/[H <sub>2</sub> L][H]	3.63(5)	5.18(7)	4.66	4.05	3.58	5.52	4.09
[H <sub>4</sub> L]/[H <sub>3</sub> L][H]	<2	2.4(1)	<1	1.8	0.8	2.25	3.35
[H <sub>5</sub> L]/[H <sub>4</sub> L][H]	—	—	—	—	—	1.30	—
[H <sub>4</sub> L]/[HL][H] <sup>4</sup>	<23.8	25.75	<24.14	24.31	22.38	26.35	28.14

<sup>a</sup> Ref. 12. <sup>b</sup> Ref. 5. <sup>c</sup> Ref. 6. <sup>d</sup> Ref. 2. <sup>e</sup> Ref. 1(a).

**Data collection and processing.** A blue needle-like crystal of [CuL<sup>1</sup>] was mounted in a Lindmann capillary under a saturated atmosphere of the mother-liquor. Data were collected with a Mar Research image-plate system using graphite-monochromated Mo-K $\alpha$  radiation ( $\lambda$  0.710 73 Å). The crystal was positioned 75 mm from the plate. An exposure time of 2 min was used per 2° frame collected. Data analysis was performed with the XDS program.<sup>21</sup> Intensities were not corrected for absorption effects.

**Structure analysis and refinement.** 7941 Measured reflections were merged in the Laue symmetry group *mmm* to give 2752 independent reflections with  $R_{\text{int}} = 0.0482$ . The copper coordinates were determined by direct methods and the remaining positions of non-hydrogen atoms were then found by successive Fourier-difference synthesis. The positions of the hydrogen atoms of water molecules and the hydrogen bound to nitrogen were obtained from Fourier-difference maps while the remaining hydrogen atoms were introduced in the refinement at calculated positions. All hydrogen atoms were refined with thermal parameters equivalent to 1.2 times those of the atoms to which they were bonded. Anisotropic thermal parameters were used for all non-hydrogen atoms. The structure was refined by least-square methods until convergence. Final refinements of 300 parameters on  $F^2$  gave  $R$  and  $R'$  values of 0.0806 and 0.2125 for the data with  $I > 2\sigma(I)$  and 0.1267 and 0.2460 for all  $hkl$  data using a weighting scheme of the form  $w = 1/[\sigma^2(F_o)^2 + (0.1683P)^2]$  where  $P = [\max(F_o^2, 0) + 2F_c^2]/3$ . The maximum and minimum residual electron densities in the  $\Delta F$  map were 1.515 and  $-0.629 \text{ e \AA}^{-3}$ , respectively. The positive peak was within 0.06 Å of the copper atom.

All calculations required to solve and refine the structure were carried out with SHELXS 86<sup>22</sup> and SHELXL 93.<sup>23</sup> The molecular diagram was drawn with ORTEP II.<sup>24</sup>

CCDC reference number 186/858.

### Molecular mechanics calculations

Molecular mechanics calculations were carried out using the universal force field<sup>25</sup> within the CERIUS 2 software.<sup>26</sup> Default parameters were used apart from the terms involving the metal centre. An unstrained metal environment was considered to be an ideal octahedral geometry. The angle bending terms at the metal centre L–M–L were restrained to 90 or 180° using a cosine periodic expansion term. This algorithm incorporates the possibility of more than one ideal angle, e.g. 90, 180 or 270° for an octahedral geometry.

The starting coordinates for the *trans*-octahedral isomer were obtained from the crystal structure of [CuL<sup>1</sup>], while those for the *cis*-octahedral isomer were obtained by manipulation of the coordinates of the octahedral complex [NiL<sup>5</sup>]<sup>+</sup>,<sup>27</sup> in which the macrocycle L<sup>5</sup> adopts a folded conformation.

The strain energies of the two different octahedral isomers were calculated using a procedure similar to that described in ref. 28. All six M–L bond lengths were fixed at the same value

using the large force constants for the corresponding bond-stretching terms. The ideal M–L bond lengths were then changed successively at 0.05 Å intervals over the range 1.6–2.5 Å, so that an energy profile of the complex relative to M–L distance was obtained.

## Results

### Synthesis

The macrocycles H<sub>2</sub>L<sup>1</sup> and H<sub>3</sub>L<sup>2</sup> have been synthesized for the first time in the present work. A similar compound which differs from H<sub>2</sub>L<sup>1</sup> by one methyl group appended to the nitrogen opposite to the pyridine one, H<sub>2</sub>L<sup>4</sup>, has been previously studied.<sup>5,29</sup> The compound H<sub>2</sub>L<sup>1</sup>, as well as H<sub>2</sub>L<sup>4</sup>, has been easily prepared by the usual technique of condensation of the parent amine with chloro- or bromo-acetate under basic conditions. However, the introduction of the third carbonylmethyl group is difficult, probably because the nitrogen atom between the two propane chains is stereochemically less available for the reaction.<sup>2,27</sup> Several techniques have been tried, such as condensation in non-aqueous media using ethyl bromoacetate and trimethylamine, or other bases in the aqueous or non-aqueous media, but mixtures of H<sub>2</sub>L<sup>1</sup> and H<sub>3</sub>L<sup>2</sup> were obtained which were very difficult to purify. Only the conditions described here led to a good yield of the desired compound.

### Protonation

Protonation reactions of compounds L<sup>1</sup> and L<sup>2</sup> have been studied and the corresponding constants are summarised in Table 1. They have six and seven basic centres, respectively, but only three and four constants could be determined by the potentiometric technique used. Also compiled in Table 1 are the values for other 14-membered macrocycles from the literature. Compounds L<sup>1</sup> and L<sup>2</sup> exhibit one high value for the first protonation constant and one fairly high value for the second, which correspond to the protonation of two nitrogen atoms of the ring. The first protonation of L<sup>1</sup> occurs at the secondary nitrogen atom (N<sup>2</sup>, opposite to that of the pyridine) and the second one at the two nitrogen atoms (N<sup>1</sup>) adjacent to N<sup>2</sup>, which will be 50% protonated. The same happens with L<sup>2</sup>, however the  $K_1^H$  value of this compound is lower than that of L<sup>1</sup>, because N<sup>2</sup> has been converted into a tertiary nitrogen and differences in solvation of the protonated forms of both compounds probably justify the discrepancy. More difficult to understand are the differences between the  $K_2^H$  and  $K_3^H$  values of the two compounds, as both macrocycles have the same size and position of the basic centres. However, the study of the protonation sequence by <sup>1</sup>H NMR titrations for L<sup>6</sup> (ref. 6) and L<sup>7</sup> (ref. 2) provides the necessary information for the interpretation. These compounds, having a CH<sub>2</sub>OCH<sub>2</sub> moiety replacing the pyridine (Scheme 1), exhibit protonation constants similar to those of L<sup>1</sup> and L<sup>2</sup>, respectively (*cf.* Table 1). The mentioned study of the protonation sequence led to the conclusion that the

**Table 2** Stability constants (log  $K_{M,H,L}$ ) of the complexes of L<sup>1</sup>, L<sup>2</sup> and similar ligands (L<sup>3</sup>, L<sup>4</sup>, L<sup>6</sup>, L<sup>7</sup> and tetra) with some di- and tri-valent metal ions. 25.0 °C,  $I = 0.10 \text{ mol dm}^{-3}$

Ion	Equilibrium quotient	L <sup>1</sup>	L <sup>2</sup>	L <sup>3</sup> <sup>a</sup>	L <sup>4</sup> <sup>b</sup>	L <sup>6</sup> <sup>c</sup>	L <sup>7</sup> <sup>d</sup>	tetra
Mg <sup>2+</sup>	[ML]/[M][L]	—	2.89(4)	—	5.30	—	—	1.967 <sup>e</sup>
	[ML]/[ML(OH)][H]	—	—	—	8.74	—	—	—
Ca <sup>2+</sup>	[ML]/[M][L]	3.32(3)	5.85(1)	—	3.74	2.1	4.85	8.322 <sup>e</sup>
	[ML]/[ML(OH)][H]	—	—	—	—	—	9.91	—
Mn <sup>2+</sup>	[ML]/[M][L]	9.99(2)	11.810(6)	5.477	—	7.08	9.18	11.272 <sup>e</sup>
	[M(HL)]/[ML][H]	—	4.55(3)	—	—	6.87	—	—
	[ML]/[ML(OH)][H]	—	—	—	—	—	10.63	—
Co <sup>2+</sup>	[ML]/[M][L]	15.58(3)	15.07(4)	—	14.4	11.81	12.94	16.38 <sup>e</sup>
	[M(HL)]/[ML][H]	—	4.24(5)	—	4.1	3.89	—	4.04 <sup>e</sup>
Ni <sup>2+</sup>	[ML]/[M][L]	18.53(3)	19.38(3)	16.267	16.59	14.7	—	19.83 <sup>e</sup>
	[M(HL)]/[ML][H]	—	3.84(4)	—	2.94	—	—	4.14 <sup>e</sup>
Cu <sup>2+</sup>	[ML]/[M][L]	21.75(5)	21.84(4)	19.76	21.61	17.62	20.14	20.49 <sup>e</sup>
	[M(HL)]/[ML][H]	—	3.67(3)	—	2.28	2.66	4.36	3.77 <sup>e</sup>
Zn <sup>2+</sup>	[ML]/[M][L]	15.26(1)	15.01(3)	12.816	14.01	12.597	12.85	16.395 <sup>e</sup>
	[M(HL)]/[ML][H]	3.14(2)	4.11(4)	—	4.05	—	—	4.099 <sup>e</sup>
	[ML]/[ML(OH)][H]	8.55(5)	—	8.48	7.66	—	—	—
Pb <sup>2+</sup>	[ML]/[M][L]	11.985(7)	12.83(2)	9.715	10.89	8.01	11.26	14.319 <sup>e</sup>
	[M(HL)]/[ML][H]	3.67(9)	4.64(3)	—	4.96	6.40	5.56	4.75 <sup>e</sup>
	[ML]/[ML(OH)][H]	—	—	10.948	9.9	—	—	—
Ga <sup>3+</sup>	[ML]/[M][L]	—	20.10(2)	—	18.02	—	—	19.91 <sup>f</sup>
	[M(HL)]/[ML][H]	—	—	—	3.09	—	—	3.66 <sup>f</sup>
	[ML]/[ML(OH)][H]	—	—	—	3.75	—	—	—
Fe <sup>3+</sup>	[ML]/[M][L]	20.49(5)	19.21(1)	—	20.64	—	21.93	27.46 <sup>f</sup>
	[M(HL)]/[ML][H]	—	—	—	2.84	—	2.63	2.64 <sup>f</sup>
	[ML]/[ML(OH)][H]	5.03(7)	5.46(9)	—	(5.9) <sup>g</sup>	—	3.8	—
In <sup>3+</sup>	[ML]/[M][L]	—	21.16(4)	—	18.94	—	—	23.00 <sup>f</sup>
	[M(HL)]/[ML][H]	—	1.85(5)	—	2.38	—	—	3.33 <sup>f</sup>

<sup>a</sup> Ref. 12. <sup>b</sup> Ref. 5. <sup>c</sup> Ref. 6. <sup>d</sup> Ref. 2. <sup>e</sup> Ref. 1. <sup>f</sup> Ref. 30. <sup>g</sup> Approximate value, cf. Ref. 5.

lower value of  $K_3^H$  of L<sup>6</sup> when compared to that of L<sup>7</sup> corresponds to the protonation of a carboxylate group while the higher value of L<sup>7</sup> is due to the protonation of the third nitrogen atom of the ring.<sup>2</sup> This intriguing behaviour of compounds differing only in the number of substituents at N seems to be related to the existence of the secondary nitrogen (N<sup>2</sup>) in L<sup>1</sup> and L<sup>6</sup>. However L<sup>4</sup>, which has a methyl group bound to N<sup>2</sup>, exhibits a  $K_3^H$  value closer to that of L<sup>1</sup> than to that of L<sup>2</sup>, and this is consistent with the protonation of a carboxylate group and not that of another ring nitrogen. As the different behaviour occurs when the carboxymethyl group is bound to N<sup>2</sup>, in L<sup>2</sup> and L<sup>7</sup>, electronic effects seem to be more important than stereochemical ones. This means that the charge effect of the protonated N<sup>2</sup> in L<sup>2</sup> and L<sup>7</sup> should be partially neutralised by the negative charge of the carboxylate group bound to it and also by possible hydrogen-bond formation, decreasing the global charge in the ring and so allowing protonation of the third nitrogen before the carboxylate groups.

Owing to the special protonation scheme of L<sup>1</sup> and L<sup>6</sup>, these macrocycles have identical overall basicity, about 10<sup>2</sup> to 10<sup>3</sup> times lower than that of L<sup>2</sup> or L<sup>7</sup>.

### Stability constants

The stability constants of macrocycles L<sup>1</sup> and L<sup>2</sup> with some alkaline-earth, divalent first-row transition-metal ions, Pb<sup>2+</sup> and some trivalent metal ions, such as Ga<sup>3+</sup>, Fe<sup>3+</sup> and In<sup>3+</sup>, are collected in Table 2 together with the constants of the complexes of some other similar 14-membered macrocycles with the same metal ions taken from the literature. Only mononuclear species (1 : 1 metal to ligand ratio) were found for the complexes of both ligands. In most cases only ML species are formed, but protonated (MHL) and/or hydroxo complexes [ML(OH)] were also found in some systems. We have checked the possibility of formation of other species such as other protonated, MH<sub>*i*</sub>L (*i* ≥ 2) or binuclear, but they are not formed under our conditions. In the case of the cobalt(II) complexes the stability constants were difficult to determine as after  $a \geq 3$  (*a* being the number of equivalents of base added per mol of macrocycle)

it was impossible to obtain stabilisation of the pH values although no kind of precipitate or modification of the colour of the solution was observed. Stability constants were obtained using the stabilised data points and it was impossible to determine the species formed at high pH. A reaction with molecular oxygen is probably taking place as the values of the stability constants are low. In fact the magnetic moments of the cobalt complexes are very low and the EPR spectrum of [CoL<sup>2</sup>]<sup>-</sup> showed the typical signal of the superoxide 1 : 1 adduct in the  $g = 2$  region. Studies are being pursued to clarify this point. The titration of the iron(III) complexes also showed problems as precipitation occurs at pH *ca.* 5 and it was uncertain whether a hydroxo complex (FeH<sub>-1</sub>L) or a binuclear species of the type Fe<sub>2</sub>H<sub>-1</sub>L<sub>2</sub> is formed. The SUPERQUAD program also gave convergence for a model containing the species FeL and Fe<sub>2</sub>H<sub>-1</sub>L<sub>2</sub>, with similar standard deviation [values of log β<sub>2-12</sub> = 39.1(1) for L<sup>1</sup> and 36.3(1) for L<sup>2</sup> and the same values of the stability constants for the FeL species]. However we could not confirm the presence of the binuclear species and so have selected the model with simpler chemical species, *i.e.* FeH<sub>-1</sub>L.

Macrocycles L<sup>1</sup> and L<sup>2</sup> are selective ligands for the first-row-transition divalent metal ions, exhibiting very high stability constants for Cu<sup>2+</sup>, fairly high values for Ni<sup>2+</sup>, but sharply decreasing values for the remaining metal ions of this row. The alkaline-earth-metal complexes present very low stability constants in comparison with corresponding complexes involving other polyaminopolycarboxylate ligands, linear or cyclic. This behaviour is shared by other 14-membered macrocyclic ligands, such as L<sup>3</sup>,<sup>12</sup> L<sup>4</sup>,<sup>5</sup> L<sup>6</sup>,<sup>6</sup> L<sup>7</sup>,<sup>2</sup> and tetra.<sup>1a,b</sup> All these macrocycles give rise to a plot of log  $K_{ML}$  versus the atomic number of the first-row transition-metal ions which has a sharp inverted V profile and the thermodynamic stability of their complexes with Mg<sup>2+</sup> and Ca<sup>2+</sup> is so low that it is impossible to determine the amount of these metals by direct titration using these macrocycles as complexing agents, with the exception of tetra. These properties are completely distinct from those exhibited by the corresponding 12-membered macrocycles L<sup>9</sup> {3,6,9-tris(carboxymethyl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene};<sup>4</sup> L<sup>10</sup> [4,7,10-tris(carboxymethyl)-1-oxa-

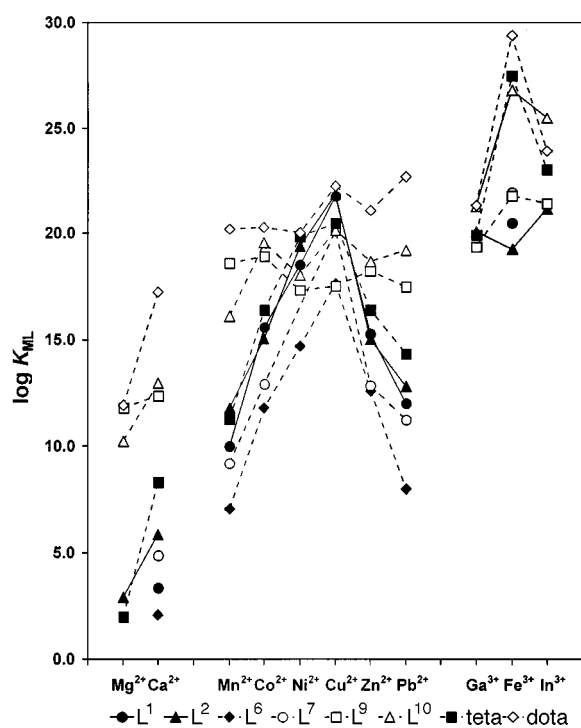
**Table 3** Spectroscopic UV/VIS/near-IR data and magnetic moments for the complexes of Ni<sup>2+</sup> and Cu<sup>2+</sup> with L<sup>1</sup> and L<sup>2</sup> at 25.0 °C

Complex (colour)	pH	$\lambda_{\text{max}}/\text{nm}$ ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ )	$\mu/\mu_{\text{B}}$
[NiL <sup>1</sup> ] (pale yellow)	3.44	1169 (sh) (1.5), 1000 (sh) (3.7), 908 (sh) (5.9), 813 (sh) (14.5), 770 (17.7), 625 (sh) (6.3), 571 (sh) (10.2), 520 (9.6), 373 (70.4)	2.99
[CuL <sup>1</sup> ] (blue)	4.84	1154 (7.1), 800 (sh) (12.9), 632 (101.2), 614 (103.9), 256 ( $4.1 \times 10^3$ )	—
[NiL <sup>2</sup> ] (violet)	3.04	1185 (3.6), 1000 (sh) (7.6), 816 (25.5), 783 (sh) (25.1), 630 (sh) (7.8), 587 (sh) (12.3), 531 (15.5), 346 (97.0)	2.89
[CuL <sup>2</sup> ] (blue)	3.01	645 ( $1.56 \times 10^3$ ), 315 ( $2.25 \times 10^4$ ), 261 ( $2.71 \times 10^4$ )	—

**Table 4** EPR data for the copper(II) complexes of L<sup>1</sup> and L<sup>2</sup> and similar complexes

Complex	$\lambda/\text{nm}$ ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ )	EPR						Ref.
		$g_x$	$g_y$	$g_z$	$10^4 A_x/\text{cm}^{-1}$	$10^4 A_y/\text{cm}^{-1}$	$10^4 A_z/\text{cm}^{-1}$	
[CuL <sup>1</sup> ]	614 (103.9)	2.034	2.080	2.209	14.3	8.5	167.1	<i>a</i>
[CuL <sup>2</sup> ]	645 ( $1.56 \times 10^3$ )	2.050	2.066	2.243	2.2	17.6	192.1	<i>b</i>
		2.229	2.110	2.010	142.5	12.1	5.8	<i>c</i>
[CuL <sup>3</sup> ] <sup>2+</sup>	560 (187)	2.034	2.060	2.188	0.5	3.4	192.9	5
[CuL <sup>4</sup> ]	630 (97.1)	2.027	2.084	2.221	14.9	21.3	165.4	5
[CuL <sup>6</sup> ]	683 (106.9)	2.040	2.087	2.262	0.7	18.4	163.0	2
[CuL <sup>7</sup> ]	602 (42.4)	2.040	2.061	2.235	23.9	22.4	195.6	2
[CuL <sup>9</sup> ]	720 (104.6)	2.039	2.093	2.269	4.1	3.9	103.9	4
		2.272	2.161	2.007	138.3	6.9	10.2	

<sup>a</sup> This work. <sup>b</sup> Isomer A, this work. <sup>c</sup> Isomer B, this work.

**Fig. 1** Variation of the stability constants ( $\log K_{\text{ML}}$ ) of the metal complexes of L<sup>1</sup>, L<sup>2</sup>, L<sup>6</sup>, L<sup>7</sup>, L<sup>9</sup>, L<sup>10</sup>, tetra and dota with the atomic number of the metal ion

4,7,10-triazacyclododecane]<sup>31</sup> and dota [1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane].<sup>1a,b</sup> The latter compounds are unable to differentiate between metal ions of the first-row-transition series, giving almost the same values of the stability constants for the entire series, although in general the values are much higher than those of the complexes with corresponding 14-membered macrocycles (*cf.* Fig. 1).<sup>1a,b,4,31</sup> The different behaviour of both classes of ligands can be used advantageously for analytical and medical applications.<sup>1a,b,4,5</sup>

The stability constants of the corresponding complexes of L<sup>1</sup> and L<sup>2</sup> present small differences, except for those of Ca<sup>2+</sup> and Mn<sup>2+</sup>. This could be expected taking into account that the two ligands differ just by one carboxymethyl group, and L<sup>1</sup> has the right number of donor atoms to satisfy the co-ordination

demands of most of the metal ions studied. Indeed, Ca<sup>2+</sup> and Mn<sup>2+</sup> are metal ions which allow co-ordination numbers higher than six and so may form complexes thermodynamically more stable with L<sup>2</sup>, even if the differences in basicity of the two ligands are considered. The same would be expected for the lead complexes,<sup>2,31,32</sup> but does not occur in this case. So the stability constant of the lead complex of L<sup>1</sup> is higher or that of L<sup>2</sup> is lower than expected, however the last hypothesis is more probable,<sup>2,31,32</sup> and the reason could be subtle variations in structure.

It is interesting that the compounds L<sup>2</sup> and tetra<sup>1a,b</sup> give very similar stability constants (*cf.* Table 2 and Fig. 1), which is predictable as it is known that tetra does not use all the potential donor sites on co-ordination to the first-row transition-metal ions.<sup>1a,b,7</sup> If the difference in basicity of the two ligands is considered ( $\Delta \log \beta_3^{\text{H}} = 1.44$ ), Co<sup>2+</sup>, Zn<sup>2+</sup>, Cu<sup>2+</sup> and Pb<sup>2+</sup> have essentially the same affinity for both, but Mg<sup>2+</sup>, Mn<sup>2+</sup>, Ni<sup>2+</sup> and also Ga<sup>3+</sup> prefer L<sup>2</sup> while Ca<sup>2+</sup> shows much more affinity for tetra.<sup>1a</sup> While the higher stability constant of the calcium complex with tetra is understandable as it is known that all eight donor atoms are involved in co-ordination,<sup>†,1a,b,9</sup> the same cannot be said of the particular stability of the manganese(II) complex of L<sup>2</sup> and it is likely that some unusual structure occurs.

The stability constants of compounds L<sup>1</sup> and L<sup>2</sup> with Fe<sup>3+</sup> are lower than expected when compared with that of tetra (although this value for tetra is much higher than expected, it is the only value in the literature).<sup>30</sup> More interesting is the trend found for the complexes of L<sup>2</sup> with the three trivalent metal ions studied in this work, which is inverted in comparison with the usual one for complexes of polycarboxymethylpolyamines,<sup>33</sup> the iron(III) complex having a very low stability constant. While we have no explanation for the value obtained we have tested several methods to determine this constant, all of them giving the same value.

The abrupt fall in stability constants observed for the complexes of L<sup>1</sup>–L<sup>4</sup> with larger metal ions, such as Ca<sup>2+</sup>, Mn<sup>2+</sup> and Pb<sup>2+</sup> but also to a lesser extent for Co<sup>2+</sup> and Zn<sup>2+</sup>, is so significant that it seems likely that one of the nitrogen atoms of the macrocycle remains unco-ordinated. This hypothesis has been advanced before to explain the results obtained for L<sup>6</sup> (ref. 6) and L<sup>7</sup> (ref. 2) but could not be confirmed till now

† In ref. 9 the structure of Na[Tb(tetra)]·6H<sub>2</sub>O·0.5NaCl is described and that of [Ca(tetra)]<sup>2+</sup> is postulated as being similar due to the equivalent co-ordinating behaviours of the two complexes.

because we have not succeeded in obtaining single crystals for X-ray diffraction studies. To gain more insight about the co-ordination sphere of the complexes some spectroscopic measurements were performed (Tables 3 and 4).

The electronic spectra observed for the aqueous solutions of  $[\text{NiL}^1]$  and  $[\text{NiL}^2]^-$  (*cf.* Table 3), the lower values of absorption coefficients and the magnetic moments (2.99 and 2.89  $\mu_B$ , respectively) are characteristic of tetragonal ( $D_{4h}$ ) symmetry, with strong distortion.<sup>2,5,34–36</sup> The higher values of  $\epsilon$  exhibited by  $[\text{NiL}^2]^-$  point to a more strained structure. Following the considerations of Busch and co-workers<sup>36</sup> for some tetraaza macrocycles, we tentatively assigned the bands and values of  $Dq^{xy}$  and  $Dq^z$  were calculated based on this assignment:  $Dq^{xy} = 1297 \text{ cm}^{-1}$  and  $Dq^z = 701 \text{ cm}^{-1}$  for  $[\text{NiL}^1]$  and  $Dq^{xy} = 1277 \text{ cm}^{-1}$  and  $Dq^z = 723 \text{ cm}^{-1}$  for  $[\text{NiL}^2]^-$ . The values of the ligand-field parameters reveal that the two complexes have the same co-ordination environment, with four nitrogen atoms in the equatorial plane and two oxygen atoms of the carboxylate groups in axial positions. This structural prediction is supported by the similarity of the parameters found for  $[\text{Ni}(\text{tetra})]^{2-}$ ,  $Dq^{xy} = 1220 \text{ cm}^{-1}$  and  $Dq^z = 740 \text{ cm}^{-1}$ .<sup>1a,b,7</sup>

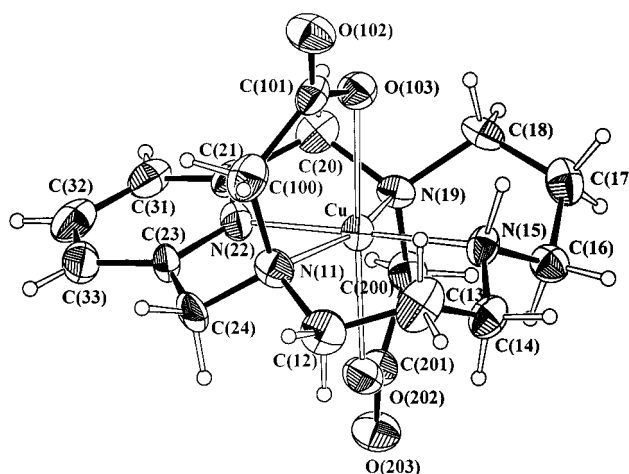
In aqueous solution the copper(II) complexes  $[\text{CuL}^1]$  and  $[\text{CuL}^2]^-$  exhibit a broad band in the visible region due to the copper d–d transitions, and an intense band in the ultraviolet region (*cf.* Table 3). The EPR spectra of the two complexes exhibit three well resolved lines at low field and no super-hyperfine splitting. The fourth copper line is completely overlapped by the strong and not resolved band of the high-field part of the spectra (*cf.* Table 4). The spectrum of the  $[\text{CuL}^2]^-$  anion shows two isomers in a 1:1 ratio, as revealed by computational simulation of the spectrum<sup>20</sup> and distinguished in the spectrum by the duplication of bands clearly observed in the  $g_z$  part. Simulation of the spectra<sup>20</sup> also indicated three different principal values of  $g$ , showing that the  $\text{Cu}^{2+}$  ion in these complexes is in a rhombically distorted ligand field. The hyperfine coupling constants and  $g$  values are compiled in Table 4, together with those of other complexes from the literature.

The complex  $[\text{CuL}^1]$  and the A isomer of  $[\text{CuL}^2]^-$  have  $g_z > (g_x + g_y)/2$ , which is typical of the copper(II) ion in axially elongated rhombic symmetry and a  $d_{x^2-y^2}$  ground state, consistent with elongated rhombic octahedral or distorted square-based pyramidal stereochemistries.<sup>4,5,37,38</sup> The B isomer of  $[\text{CuL}^2]^-$  shows a very unusual set of EPR parameters with one  $g$  value only slightly greater than 2.0, consistent with a  $d_z$  ground state, typical of either trigonal-bipyramidal, tetragonal or square pyramidal axially compressed stereochemistries.<sup>4,38,39</sup> The complex of the tris(carboxymethyl) derivative of the 12-membered macrocycle,  $[\text{CuL}^9]^-$ ,<sup>4</sup> also exhibits under the same conditions two isomers one of them corresponding to the B isomer of  $[\text{CuL}^2]^-$  with very similar values of  $g$  and  $A$  (copper hyperfine coupling tensor), for which an axially compressed square-pyramidal geometry for the  $\text{Cu}^{2+}$  was reported (see Table 4).<sup>4,39</sup>

The electronic properties of  $[\text{CuL}^1]$  and the A isomer of  $[\text{CuL}^2]^-$  can be compared with those of other similar copper(II) complexes compiled in Table 4 and explained by the usual factors taken from the equations of the EPR parameters derived from ligand-field theory.<sup>2–5,40,41</sup> When the electronic parameters of the complex of the parent ligand,  $[\text{CuL}^3]^{2+}$ , are compared with those of  $[\text{CuL}^1]$  an increase of  $g_z$ , a decrease of  $A_z$  and a red shift of the visible band of the electronic spectrum are observed. As the former complex adopts a square-planar geometry, as shown by X-ray analysis,<sup>28</sup> and that of the second one an octahedral arrangement, see below, the values of the electronic parameters are completely consistent and it can be inferred that both complexes exhibit in aqueous solution and in the solid state the same structure. The electronic parameters of  $[\text{CuL}^4]$  are similar to those of  $[\text{CuL}^1]$  and both complexes should present the same structure and the same can be inferred

**Table 5** Bond lengths (Å) and angles (°) for  $[\text{CuL}^1]$

Cu–O(103)	2.300(5)	Cu–O(202)	2.320(6)
Cu–N(11)	2.134(7)	Cu–N(15)	1.992(6)
Cu–N(19)	2.116(7)	Cu–N(22)	1.939(7)
O(103)–Cu–O(202)	178.3(2)	N(15)–Cu–O(103)	85.2(2)
N(11)–Cu–O(103)	81.1(2)	N(19)–Cu–O(103)	100.6(2)
N(22)–Cu–O(103)	96.2(2)	N(11)–Cu–O(202)	100.2(2)
N(19)–Cu–O(202)	78.4(2)	N(22)–Cu–O(202)	85.1(2)
N(15)–Cu–O(202)	93.5(2)	N(15)–Cu–N(19)	97.5(3)
N(15)–Cu–N(11)	101.9(3)	N(15)–Cu–N(11)	79.3(3)
N(22)–Cu–N(19)	81.3(3)	N(22)–Cu–N(11)	160.6(3)
N(22)–Cu–N(15)	178.4(2)	N(19)–Cu–N(11)	160.6(3)



**Fig. 2** Molecular structure of  $[\text{CuL}^1]$  with the labelling scheme adopted (30% ellipsoids)

for  $[\text{CuL}^6]$ , for which an octahedral structure was found by X-ray analysis.<sup>6</sup> However, the parameters for the A isomer of  $[\text{CuL}^2]^-$  do not follow the same behaviour when compared with those of  $[\text{CuL}^1]$ , both  $g_z$  and  $A_z$  increase, indicating a completely different environment around the metal ion. However the EPR parameters are similar to those of  $[\text{CuL}^7]^-$  for which a five-co-ordinated arrangement was predicted with the macrocycle folded and an oxygen atom in the equatorial plane.

The B isomer would have either an axially compressed square-pyramidal or a trigonal-bipyramidal structure. However, it was suggested that square-pyramidal copper(II) complexes have an absorption band in the region 550–670 nm, while trigonal-bipyramidal complexes absorb near 800–850 nm ( $d_{xy}, d_{x^2-y^2} \rightarrow d_z$ ), with a higher-energy shoulder (spin forbidden  $d_{xz}, d_{yz} \rightarrow d_z$ ).<sup>42,43</sup> The fact that for our complex the transition is observed at higher energy points to an axially compressed square-pyramidal geometry.

### Molecular and crystal structure

The molecular structure of  $[\text{CuL}^1]$  including the labelling scheme used is shown in Fig. 2. Selected bond lengths and angles in the copper co-ordination sphere are listed in Table 5. The copper atom is encapsulated by the macrocycle  $L^1$  in an octahedral environment. The equatorial plane is determined by the four nitrogen atoms of the tetraaza ring. Six-co-ordination is completed *via* two oxygen atoms of the appended carboxylate groups.

The structural parameters associated with the copper co-ordination sphere show a distorted octahedral geometry. However the angles at the metal centre are close to the expected values of 90 and 180° for octahedral geometry. The maximum deviation from the ideal octahedral angles is found for the angle N(19)–Cu–N(11) 160.6(3)°. Also, the best least-squares plane,

through the nitrogen atoms, shows only a very small tetrahedral deviation of  $\pm 0.012(3)$  Å, indicating that these atoms are coplanar. The metal centre lies on the  $N_4$  equatorial co-ordination plane. These facts suggest that in this complex there is a good match between the size of the macrocyclic cavity and the size of the  $Cu^{2+}$  ion.

The strongest octahedral distortion observed for the complex is due to the Jahn–Teller effect.<sup>42</sup> As expected for an octahedral copper(II) complex, the axial Cu–O bond lengths are longer than the equatorial Cu–N bond lengths. The axial bond lengths [Cu–O(103) 2.300(5) and Cu–O(202) 2.320(6) Å] are comparable to those observed for other tetraaza macrocyclic complexes such as  $[CuL^8]$  [2.226(3) Å]<sup>44</sup> and  $[Cu(teta)]^{2-}$  [2.302(5) and 2.278(6) Å],<sup>7a</sup> which have also a  $CuN_4O_2$  octahedral co-ordination sphere elongated tetragonally.

The Cu–N distance to the pyridine ring [1.939(7) Å] is shorter than to the other nitrogen atoms [average 2.081(7) Å]. This bond-length pattern is typical of metal complexes with tetraaza macrocycles containing a pyridine moiety.<sup>27–29</sup>

Crystal structure determinations are available for metal complexes of  $L^3$  derivatives with two pendant arms containing co-ordinating sites, a copper(II) complex of  $L^4$ ,  $[Cu(H_2L^4)Cl]^+$ ,<sup>29</sup> and a nickel(II) complex of  $L^5$ ,  $[NiL^5]^{2+}$ .<sup>27</sup> The complex  $[Cu(H_2L^4)Cl]^+$  exhibits approximately trigonal-bipyramidal geometry, with the  $Cl^-$  and the N of the pyridine ring occupying the axial positions and the equatorial plane being defined by the nitrogen atoms adjacent to the pyridine ring and the oxygen of one of the carboxylate groups. The remaining carboxylate pendant arm and the nitrogen *trans* to the pyridine ring are protonated and consequently are not co-ordinated.<sup>29</sup> Therefore, in spite of the structural similarities between these two macrocyclic ligands, the different protonated states of the two complexes led to different co-ordination spheres and precludes comparison of their structures.

The  $[NiL^5]^{2+}$  complex shows a *cis* octahedral geometry with the two 2-pyridylmethyl groups occupying an axial and an equatorial position of the co-ordination sphere. To achieve this geometric arrangement the macrocycle  $L^5$  is folded about the axis defined by the two nitrogen atoms adjacent to the pyridine ring, in contrast with the complex studied in this work where the tetraaza ring of  $L^1$  is planar and the four nitrogen atoms are in the equatorial plane. Both *cis* and *trans* stereochemistries have also been observed for transition-metal complexes of  $L^3$  and its (NMe)<sub>3</sub> derivative.<sup>45</sup>

The analysis of the intermolecular distances of  $[CuL^1]$  reveals the presence of hydrogen bonds between the nitrogen *trans* to the pyridine ring and a water oxygen atom [N(15)–H(N15)⋯O(4) 2.23(8) Å, 135(6)° ( $x - \frac{1}{2}, -y + \frac{1}{2}, -z$ )]. Both hydrogen atoms of another water molecule are involved concomitantly in intermolecular O–H⋯O hydrogen bonds with the oxygens of one appended carboxylate [O(1)–H(O11)⋯O(203) 1.95(3) Å, 169(8)° ( $x + \frac{1}{2}, y, -z + \frac{1}{2}$ ) and O(1)–H(O12)⋯O(202) 1.86(3) Å, 168(9)°].

## Conclusions and Molecular Mechanics Calculations

The values of the stability constants for the ML species in solution (*cf.* Table 2) indicate that  $L^1$  and  $L^2$  are selective ligands for  $Cu^{2+}$  and  $Ni^{2+}$  and exhibit low affinity for the remaining transition-metal ions of the first-row. Low values for the stability constants were also obtained for the complexes of larger ions, such as  $Ca^{2+}$  and  $Pb^{2+}$ . These results suggest that the co-ordination behaviour of  $L^1$  and  $L^2$  is obviously related to stereo-electronic requirements of the metal and its size, but also with the possible conformations adopted by the macrocycle. On the other hand, the X-ray single-crystal data available for metal complexes of  $L^3$  and its derivatives, including structures with four-, five- and six-co-ordination,<sup>45</sup> suggest that the tetraaza ring has enough flexibility to change the conformation in order to accommodate the metal centre. For instance, in  $[CuL^1]$  the

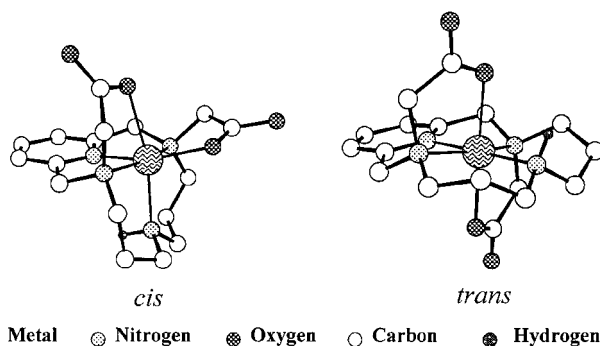


Fig. 3 Sketches of *trans* and *cis* octahedral metal complexes of  $L^1$

macrocyclic ligand  $L^1$  adopts a planar conformation while in  $[NiL^5]^{2+}$  it exhibits a folded conformation. Both conformations are illustrated in Fig. 3 for  $L^1$  in octahedral geometry.

It seems reasonable to suppose that the nickel(II) complex of  $L^1$  adopts a planar conformation consistent with a *trans*-octahedral geometry as indicated by the electronic spectra, similar to that observed for the copper(II) complex. The complexes involving the other quoted metal ions have necessarily other stereochemistries, such as for example a *cis*-octahedral arrangement where the macrocycle adopts a folded conformation.

Molecular mechanics calculations were performed in order to find the structural preferences of six-co-ordinate complexes of  $L^1$ . The calculations were carried out using the universal force field,<sup>25</sup> which was parameterised for the full Periodic Table. We have used the method previously developed of minimising the molecule by fixing the metal-to-ligand distances at specific values (see Experimental section for further details).<sup>28,46</sup> In addition, following the procedure developed by Bernhardt and Comba,<sup>47</sup> the  $M-L_{axial}$  distances were changed concomitantly with the  $M-L_{equatorial}$  distances. The resulting strain steric energy indicates how well the ligand  $L^1$  can adapt to a specific  $M-L$  distance. This methodology has been extensively applied to the calculation of all cavity sizes of macrocyclic ligands and for the prediction of structures of metal complexes.<sup>46</sup>

Our molecular mechanic calculations done for *cis* and *trans* octahedral  $[ML^1]$  complexes indicate that the *trans* isomer is the most stable form for  $M-L$  distances up to 2.25 Å, while the *cis* isomer becomes the most stable form for longer distances. The energy profiles vs.  $M-L$  distances for these two octahedral stereochemistries have a shallow energy minimum close to 2.05 Å. The molecular mechanics calculations indicate a *trans*-octahedral geometry for complexes of  $Ni^{2+}$  and  $Cu^{2+}$  in the gas phase. This prediction is consistent with the structure found for  $[CuL^1]$  in the solid state; for a mean  $Cu^{II}-N$  distance of 2.01 Å the *trans* isomer is 6.5 kcal mol<sup>-1</sup> more stable than the *cis* one, according to our calculations. On the other hand these calculations suggest that larger ions such as  $Pb^{2+}$ ,  $Ca^{2+}$  or  $Mn^{2+}$  can be accommodated by the macrocycle in a *cis*-octahedral environment. However it is necessary to stress that these larger metal ions allow co-ordination numbers higher than six and so other structures ought also to be considered for these cases. The low values of stability constants for metal complexes of  $Co^{2+}$  and  $Zn^{2+}$  indicate that these complexes do not have a *trans*-octahedral structure, while the molecular mechanics calculations reveal that the *cis* isomer is not the most stable form. Therefore, other structures with co-ordination number lower than six should be considered for those metal complexes, implying that one or more donor atoms stay unco-ordinated.

So, the macrocycle  $L^1$  has flexibility and enough donor atoms to accommodate a metal centre in many different co-ordination environments and it is quite impossible to predict all structures of the metal complexes, even using a powerful tool such as molecular mechanics calculations.



Stability constants and the electronic studies of metal complexes of L<sup>2</sup> suggest that this macrocycle does not use all its donor atoms in co-ordination to first-row-transition divalent metal ions. Possible structures have been proposed above and more work is in progress (single-crystal analysis and EPR studies) in order to clarify the structures of these molecules, namely for the cobalt and iron complexes.

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## References

- (a) R. Delgado and J. J. R. Fraústo da Silva, *Talanta*, 1982, **29**, 815; (b) S. Chaves, R. Delgado and J. J. R. Fraústo da Silva, *Talanta*, 1992, **39**, 249.
- S. Chaves, A. Cerva and R. Delgado, *J. Chem. Soc., Dalton Trans.*, 1997, 4181.
- S. Chaves, A. Cerva and R. Delgado, *Polyhedron*, 1998, **17**, 93.
- R. Delgado, S. Quintino, M. Teixeira and A. Zhang, *J. Chem. Soc., Dalton Trans.*, 1997, 55.
- J. Costa, R. Delgado, M. C. Figueira, R. T. Henriques and M. Teixeira, *J. Chem. Soc., Dalton Trans.*, 1997, 65.
- S. Chaves, R. Delgado, M. T. Duarte, J. A. L. Silva, V. Felix and M. A. F. de C. T. Carrondo, *J. Chem. Soc., Dalton Trans.*, 1992, 2579.
- A. Riesen, M. Zehnder and T. A. Kaden, (a) *Acta Crystallogr., Sect. C*, 1988, **44**, 1740; (b) *Helv. Chim. Acta*, 1986, **69**, 2074.
- M. K. Moi, M. Yanuck, S. V. Deshpande, H. Hope, S. J. DeNardo and C. F. Meares, *Inorg. Chem.*, 1987, **26**, 3458.
- M.-R. Spirelet, J. Rebizant, M.-F. Loncin and J. F. Desreux, *Inorg. Chem.*, 1984, **23**, 4278.
- S. V. Deshpande, S. J. DeNardo, C. F. Meares, M. J. McCall, G. P. Adams, M. K. Moi and G. L. DeNardo, *J. Nucl. Med.*, 1988, **29**, 217; M. K. Moi, C. F. Meares, M. J. McCall, W. C. Cole and S. J. DeNardo, *Anal. Biochem.*, 1985, **148**, 249.
- S. P. Kasprzyk and R. G. Wilkins, *Inorg. Chem.*, 1988, **27**, 1834.
- J. Costa and R. Delgado, *Inorg. Chem.*, 1993, **32**, 5257.
- D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon, Oxford, 1988.
- G. Schwarzenbach and H. Flaschka, *Complexometric Titrations*, Methuen & Co, London, 1969.
- G. Schwarzenbach and W. Biedermann, *Helv. Chim. Acta*, 1948, **31**, 331.
- R. Delgado, M. C. Figueira and S. Quintino, *Talanta*, 1997, **45**, 451.
- P. Gans, A. Sabatini and A. Vacca, *J. Chem. Soc., Dalton Trans.*, 1985, 1195.
- D. J. Leggett and W. A. E. McBryde, *Anal. Chem.*, 1975, **47**, 1065; D. J. Leggett, *ibid.*, 1978, **50**, 718.
- D. F. Evans, *J. Chem. Soc.*, 1959, 2003.
- F. Neese, Diploma Thesis, University of Konstanz, June 1993.
- W. Kabasch, *J. Appl. Crystallogr.*, 1988, **21**, 916.
- G. M. Sheldrick, SHELXS 86, in *Crystallographic Computing 3*, eds. G. M. Sheldrick, C. Krüger and R. Goddard, Oxford University Press, 1985.
- G. M. Sheldrick, SHELXL 93 program for crystal structure refinement, University of Göttingen, 1993.
- C. K. Johnson, ORTEP II. A Fortran Thermal-ellipsoid Plot Program for Crystal Structure Illustrations, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
- A. K. Rappé, C. J. Casewit, K. S. Colwell, W. A. Goddard III and W. M. Skiff, *J. Am. Chem. Soc.*, 1992, **114**, 10 024.
- CERIUS 2, version 1.6, Molecular Simulations Inc., Cambridge, 1994.
- K. P. Balakrishnan, H. A. A. Omar, P. Moore, N. W. Alcock and G. A. Pike, *J. Chem. Soc., Dalton Trans.*, 1990, 2965.
- V. Félix, M. J. Calhorda, J. Costa, R. Delgado, C. Brito, M. T. Duarte, T. Arcos and M. G. B. Drew, *J. Chem. Soc., Dalton Trans.*, 1996, 4543.
- N. W. Alcock, P. Moore and H. A. A. Omar, *J. Chem. Soc., Chem. Commun.*, 1985, 1058.
- E. T. Clarke and A. E. Martell, *Inorg. Chim. Acta*, 1991, **190**, 37.
- M. T. S. Amorim, R. Delgado, J. J. R. Fraústo da Silva, M. C. T. A. Vaz and M. F. Vilhena, *Talanta*, 1988, **35**, 741.
- M. T. S. Amorim, R. Delgado and J. J. R. Fraústo da Silva, *Polyhedron*, 1992, **11**, 1891.
- R. Delgado, Y. Sun, R. J. Motekaitis and A. E. Martell, *Inorg. Chem.*, 1993, **32**, 3320.
- A. B. P. Lever, *Inorganic Electronic Spectroscopy*, 2nd edn., Elsevier, Amsterdam, 1984.
- L. Sacconi, F. Mani and A. Bencini, *Comprehensive Coordination Chemistry*, eds. G. Wilkinson, R. D. Gillard and J. A. McCleverty, Pergamon, Oxford, 1987, vol. 5, pp. 1–137.
- L. Y. Martin, C. R. Sperati and D. H. Busch, *J. Am. Chem. Soc.*, 1977, **99**, 2968.
- B. J. Hathaway, *Coord. Chem. Rev.*, 1983, **52**, 87.
- B. J. Hathaway and A. A. G. Tomlinson, *Coord. Chem. Rev.*, 1970, **5**, 1.
- N. Azuma, Y. Kohno, F. Nemoto, Y. Kajikawa, K. Ishizu, T. Takakuwa, S. Tsuboyama, K. Tsuboyama, K. Kobayashi and T. Sakurai, *Inorg. Chim. Acta*, 1994, **215**, 109.
- P. W. Lau and W. C. Lin, *J. Inorg. Nucl. Chem.*, 1975, **37**, 2389.
- M. J. Maroney and N. J. Rose, *Inorg. Chem.*, 1984, **23**, 2252.
- B. J. Hathaway, in *Comprehensive Coordination Chemistry*, eds. G. Wilkinson, R. D. Gillard and J. A. McCleverty, Pergamon, Oxford, 1987, vol. 5, p. 533.
- G. A. McLachlan, G. D. Fallon, R. L. Martin and L. Spiccia, *Inorg. Chem.*, 1995, **34**, 254.
- I. M. Helps, D. Parker, J. Chapman and G. Ferguson, *J. Chem. Soc., Chem. Commun.*, 1988, 1094.
- F. H. Allen and O. Kennard, *Chem. Des. Automat. News*, 1993, **8**, 31.
- (a) P. Comba and T. W. Hambley, *Molecular modeling of inorganic compounds*, VCH, Weinheim, 1995, pp. 85–88; (b) R. D. Hancock, in *Prog. Inorg. Chem.*, 1989, **37**, 187.
- P. V. Bernhardt and P. Comba, *Helv. Chim. Acta*, 1991, **74**, 1834.

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