Tris(carboxymethyl)oxatriazamacrocycles and their metal complexes†

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The protonation constants of H_3L^1 [4,8,12-tris(carboxymethyl)-1-oxa-4,8,12-triazacyclotetradecane] and of H_3L^2 [4,7,11-tris(carboxymethyl)-1-oxa-4,7,11-triazacyclotridecane] and the stability constants of the complexes formed by both with alkaline-earth metal ions, divalent first-row transition-metal ions, Cd^{2+}, Pb^{2+} and Fe^{3+} were determined by potentiometric methods, at 25 °C and ionic strength 0.10 mol dm^{-3} in tetramethylammonium nitrate. The co-ordination properties of both ligands for alkaline-earth and divalent first-row transition-metal ions are quite different. The 13-membered macrocycle, $(L^2)^{3-}$, exhibits fairly high stability constants but unsatisfactory selectivity with the first-row transition-metal ions. The 14-membered ligand, $(L^1)^{3-}$, is very selective for the same series of metal ions, the difference in stability between its complexes of Cu^{2+} and Mn^{2+} being 10.96 log units and that of the complexes of Cu^{2+} and Zn^{2+} 7.29 log units, the constant of the complex of Mn^{2+} is sufficiently high for its possible quantitative determination by $(L^1)^{3-}$, at pH values higher than 7. However, the metal complexation behaviour of the $(L^1)^{3-}$ is similar to that of the corresponding bis(carboxymethyl) derivative, therefore the difficult preparation of H_3L^1 does not compensate the benefits. Increase in size of the macrocycle cavity leads to a sharp decrease in stability of complexes of metal ions involved mainly in electrostatic interactions (the alkaline-earth metal ions, Mn^{2+} and Pb^{2+}). Cobalt(II) complexes also undergo a significant decrease in stability with increase in cavity size and the constant for $[ZnL^1]^-$ is much lower than that of $[ZnL^2]^-$. However, the complexes of Cu^{2+} and Ni^{2+} with both macrocycles have about the same values of the stability constants. To explain these results it is proposed that all the donor atoms of the ligands are involved in co-ordination to metal ions which form complexes mainly by electrostatic interactions, although the distances and principally the orientation of the lone pairs of electrons are gradually more disfavoured for co-ordination with increasing cavity size. Complexes of the first-row transition-metal ions undergo the same effects, each being able to choose the donor atoms from the ligands most appropriate for their strict co-ordination preferences. So Co^{2+}, Ni^{2+} and Cu^{2+} adopt five- or six-co-ordination with these potentially seven-co-ordinate ligands, as shown by electronic and EPR spectroscopic measurements in solution and the magnetic moments of the complexes.

The search for more selective ligands towards first-row transition and alkaline-earth metal ions led us to synthesize two new tris(carboxymethyl)oxatriazamacrocycles, H_3L^1 and H_3L^2 (Scheme 1). This work completes our study of poly(carboxymethyl)oxatriazamacrocycles which began with 12-membered ligands, H_3L^3 [4,7,10-tris(carboxymethyl)-1-oxa-4,7,10-triazacyclododecane][1] and H_2L^5 [4,10-bis(carboxymethyl)-1-oxa-4,7,10-triazacyclododecane],[2] and proceeded with H_2L^4 [4,12-bis(carboxymethyl)-1-oxa-4,8,12-triazacyclotetradecane].[3] Only the 14-membered compound containing contiguous propane chains was synthesized; the compound with alternate propane chains is missing due to synthetic difficulties. Even so the study of the two compounds prepared in this work was delayed owing to complications of the synthesis, which led to mixtures of two and three carboxymethyl derivatives difficult to separate.

The series of macrocycles now synthesized allows the study of the effect of the increase of the ring cavity size on the stability constants of their metal complexes. The analogous series for the tetraazamacrocycles, dota to teta (*cf.* Scheme 1), already published,[4,5] allows some general conclusions to be drawn about this question. The dioxadiazamacrocycle series[6] and that of tetraazamacrocycle with a pyridine incorporated in the ring[7,8] are not complete, the 14- and the 13-membered compounds, respectively, being missing.

The series already published suggest that the increase in the size of the cavity in macrocycles having appended *N*-carboxymethyl groups, from 12- to 14-membered rings, causes a sharp decrease in the stability of complexes with metal ions involved mainly in electrostatic interactions, such as the alkaline-earth ions, Mn^{2+} or Pb^{2+},[4,5,7,9,10] but almost does not affect the stability of the complexes of metal ions when covalent interactions are determining, such as Fe^{2+} to Zn^{2+}.[4,5,7,9,10] So, the 14-membered compounds are more selective for the first-row transition-metal ions than are the corresponding 12-membered ones. These conclusions have important repercussions in analytical and medical applications and need to be confirmed for other series of ligands.

This paper contributes also to the study of the effect of replacement of a nitrogen (carrying an acetate group) by an oxygen in the macrocyclic ring by comparison with the tetraazamacrocyclic compounds.

Experimental

Reagents

The commercial chemicals were of reagent grade and used without further purification. Bromoacetic acid (99%) was obtained from Merck, Dowex 1 × 8 (18-52 U.S. mesh) anion-exchange resin in the Cl^- form (treated with 1.0 mol dm^{-3} formic acid before use) from BDH, and K_2H_2edta (dipotassium ethylenedinitrilotetraacetate) from Fluka. 1-Oxa-4,7,11-triazacyclotridecane and 1-oxa-4,8,12-triazacyclotetradecane were prepared as described.[11] The organic solvents were purified by standard methods.[12]

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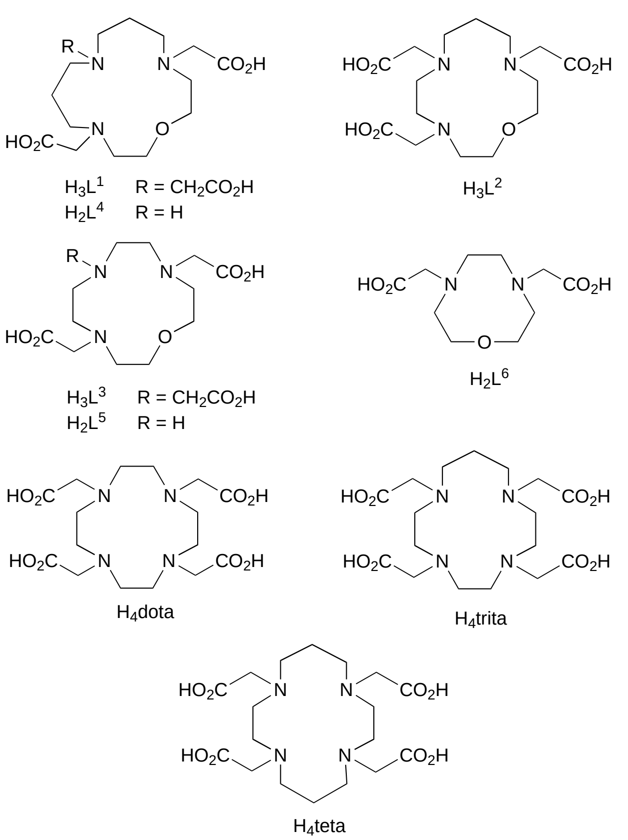
† *Non-SI unit employed*: $\mu_B \approx 9.27 \times 10^{-24}$ J T^{-1}.



Scheme 1

Preparations

H_3L^2. The tris(carboxymethylated) compound $(L^2)^{3-}$ was synthesized by condensation of the parent amine, in the trihydrobromated form (1.18 mmol, 0.50 g) with sodium bromoacetate [obtained by addition of 3 mol dm^{-3} NaOH solution to concentrated aqueous bromoacetic acid (3.67 mmol, 0.51 g) at 5 °C], in aqueous basic solution, during 5 h. The temperature was increased slowly during the reaction to a maximum of 70 °C and the pH was kept between 9 and 11.5, by slow addition of 3 mol dm^{-3} NaOH. After this time the mixture was stirred for 24 h at 80 °C and pH 11. Upon withdrawal of part of the solvent by vacuum a precipitate of NaBr was formed and filtered off. The remaining mixture comprising three products was purified by chromatography using an anionic resin in the formate form (column 22.0 × 2.0 cm). The flow rate was kept at 1.0 cm^3 min^{-1}. After washing with water (≈400 cm^3), the mixture was eluted with a solution of 0.005 mol dm^{-3} formic acid. The desired pure product was isolated from the column fractions 23 to 40 (each 15 cm^3). The fractions were collected, the solvent evaporated and the white solid obtained was dissolved in ethanol and precipitated from acetone. Yield: ≈20%; m.p. 128–130 °C. ^{1}H NMR [D_2O, sodium [$^2H_4$]-3-(trimethylsilyl)propionate]: δ 3.79 (t, 2 H), 3.72 (t, 2 H), 3.65 (s, 4 H), 3.44 (m, 6 H), 3.30 (t, 2 H), 3.24 (t, 2 H), 3.07 (t, 2 H), 2.95 (t, 2 H) and 1.97 (q, 2 H). ^{13}C NMR (D_2O, 1,4-dioxane): δ 173.34, 171.45, 169.99, 65.17 (double intensity), 57.49, 56.93, 54.60, 54.36, 53.95, 53.44, 52.76, 52.56, 49.19 and 20.49 (Found: C, 47.87; H, 7.95; N, 10.11. Calc. for $C_{15}H_{27}N_3O_7$·C_2H_5OH·H_2O: C, 48.00; H, 8.24; N, 9.88%). The microanalysis data were provided by the Laboratório de Análises Químicas, IST, Lisbon.

H_3L^1. The synthesis of H_3L^1 was similar to that described for H_3L^2. The mixture obtained after reaction, consisting of two products, H_3L^1 and H_2L^4 in a 1 : 1 ratio, was purified by a chromatographic system using a peristaltic pump P1 (Pharmacia LKB) and a column packed with an anionic resin in the formate form (17.5 × 2.5 cm). The flow rate was kept at 2.5 cm^3 min^{-1}. The column was loaded with 0.56 g of the mixture dissolved in a small amount of water (1.5 cm^3), washed with water (≈400 cm^3), and then with a solution of 0.005 mol dm^{-3} formic acid. The water fraction contained inorganic matter and a small amount of H_2L^4 and the first fractions eluted with formic acid were mixtures of increasing percentage of H_3L^1. The desired pure product was isolated from column fractions 22 to 26 (each 15 cm^3). The fractions were collected, the solvent evaporated, and the white solid obtained was dissolved in ethanol and precipitated from acetone. Yield: ≈5%. More pure product was obtained when the fractions containing 65 to 95% of H_3L^1 were collected and passed again through a chromatographic system using a column of 12.0 × 0.9 cm. M.p. 132–134 °C. ^{1}H NMR (D_2O, dss): δ 3.81 (t, 4 H, OCH_2), 3.72 (s, 4 H, CH_2CO_2), 3.68 (s, 2 H, CH_2CO_2), 3.52 (t, 4 H, NCH_2), 3.32 (m, 8 H, NCH_2) and 2.12 (q, 4 H, CH_2). ^{13}C NMR (D_2O, 1,4-dioxane): δ 169.63, 169.48, 65.29, 57.20, 56.91, 52.27, 51.83, 47.75 and 17.28 (Found: C, 44.86; H, 7.97; N, 9.60. Calc. for $C_{16}H_{29}N_3O_7$·$3H_2O$: C, 44.76; H, 8.16; N, 9.79%).

Potentiometric measurements

Reagents and solutions. Metal-ion solutions were prepared at about 0.010 and 0.100 mol dm^{-3} from the nitrate salts of the metals, of analytical grade, with demineralized water obtained by a Millipore/Milli-Q system, and were standardized by titration with K_2H_2edta. Carbonate-free solutions of the titrant, $(CH_3)_4NOH$, were prepared as described before.[13] Solutions were discarded when the percentage of carbonate was about 0.5% of the total amount of base.

Equipment and conditions. A Crison Microph 2002 measuring instrument was used together with an Orion 91-01 glass electrode and an Orion 90-05 Ag–AgCl reference electrode. The titrant was added with a Crison MicroBU 2031 burette. All the experiments were monitored by computer. The temperature was kept at 25.0 ± 0.1 °C with a Haake thermostat; atmospheric CO_2 was excluded from the cell by passing purified N_2 across the top of the experimental solution. The ionic strength of the solutions was kept at 0.10 mol dm^{-3} with $(CH_3)_4NNO_3$.

Measurements. The hydrogen-ion concentration, $[H^+]$, was determined by measurement of the electromotive force of the cell, $E = E'° + Q \log [H^+] + E_j$; $E'°$ and Q were obtained by previous calibration, titrating a standard solution of known hydrogen-ion concentration at the same ionic strength, using values in the acid range. The liquid-junction potential, $E_j = j_H[H^+] + j_{OH}[OH^-]$, constants j_H and j_{OH} being determined by acid–base titration of concentrated solutions,[14] was found to be negligible under the experimental conditions used. The value of $K_W = ([H^+][OH^-])$ was determined from data obtained in the alkaline range of the calibration, considering $E'°$ and Q valid for the entire pH range, and found equal to $10^{-13.77}$ mol^2 dm^{-6}. The term pH is defined as $-\log [H^+]$.

The potentiometric equilibrium measurements were performed on 20.00 cm^3 of ≈2.50 × 10^{-3} mol dm^{-3} ligand solutions, diluted to a final volume of 30.00 cm^3, first in the absence of metal ions and then in the presence of each metal ion for which the $c_M : c_L$ ratios were 1 : 1, 2 : 1 and in some cases 1 : 2. The emf values were taken after additions of 0.025 or 0.050 cm^3 increments of standard 0.102 mol dm^{-3} $(CH_3)_4NOH$ solution, and after stabilization in this direction equilibrium was then approached from the other direction by adding standard 0.100 mol dm^{-3} nitric acid solution.

In the cases of Cu^{2+} and Fe^{3+} with both $(L^1)^{3-}$ and $(L^2)^{3-}$ and also Ni^{2+} with $(L^2)^{3-}$ the extent of formation of the metal complexes, at the beginning of the titration, was too high to preclude the use of the direct potentiometric method, therefore ligand–ligand competition titrations or a spectrophotometric

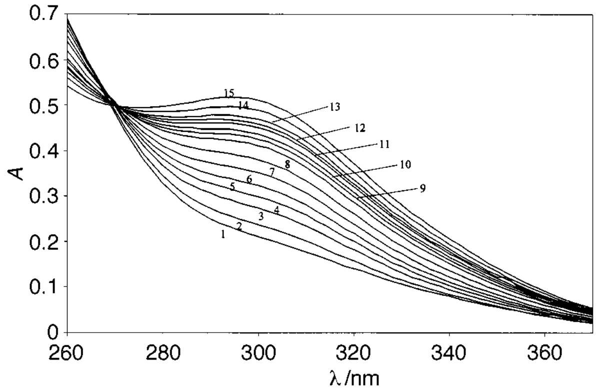


Fig. 1 Spectrophotometric titration of the system Fe^{3+}–$(L^1)^{3-}$ (1 : 1) at the following pH values: 1, 2.04; 2, 2.12; 3, 2.21; 4, 2.27; 5, 2.33; 6, 2.41; 7, 2.48; 8, 2.57; 9, 2.62; 10, 2.66; 11, 2.71; 12, 2.74; 13, 2.78; 14, 2.84 and 15, 2.90

method were employed to determine the constants; K_2H_2edta was selected as the second ligand for the Cu^{2+} complex of $(L^2)^{3-}$ (in the ratio 1 : 1 : 1, $c_{L^2}:c_{L'}:c_M$).[7,8] In the other cases, the spectrophotometric method was employed and also applied to the Cu^{2+}–$(L^2)^{3-}$ system to confirm the results obtained by potentiometry.

The attainment of equilibrium of the competition reaction monitored by potentiometry was so slow that an automated titration was impossible to perform; a 'batch method' was necessary.[11] About 4 weeks were needed for stabilization of the solutions at the pH range (7 to 10) where competition took place.

In the spectrophotometric method the solutions were prepared in the same way as described for the potentiometric measurements and spectra recorded at various pH values upon stabilization of the system. The batch method was only used in the case of Ni^{2+}–$(L^2)^{3-}$. Fig. 1 shows the spectra obtained by variation of the pH of solutions of $(L^1)^{3-}$ with Fe^{3+} (1 : 1).

Stabilization of the systems studied. The formation of the complexes of $(L^1)^{3-}$ and $(L^2)^{3-}$ with all the metal ions studied in this work was fairly rapid, as verified by the rapid stabilization of the emf of the solutions and potentiometric titrations could be performed by an automated technique, except for Ni^{2+}–$(L^2)^{3-}$. For the cobalt(II) complexes [the slowest cases after Ni^{2+}–$(L^2)^{3-}$] the equilibrium was verified by a back titration with an HNO_3 solution as titrant.

Calculation of equilibrium constants. Protonation constants $K_i^H = [H_iL]/[H_{i-1}L][H]$ were calculated by fitting the potentiometric data obtained for the free macrocycle using the SUPERQUAD program.[15] Stability constants of the various species formed in solution were determined from the experimental data corresponding to the titration of solutions of different ratios of the macrocycle and metal ions, also with the aid of the SUPERQUAD program. The results were obtained in the form of overall stability constants or $\beta_{M_mH_hL_l} = [M_mH_hL_l]/[M]^m[L]^l[H]^h$.

Only mononuclear species, ML, M(HL) and $MH_{-1}L$ ($\beta_{MH_{-1}L} = \beta_{MLOH}K_W$), were found. Differences, in log units, between the values $\beta_{M(HL)}$ (or $\beta_{MH_{-1}L}$) and β_{ML} provide the stepwise protonation reaction constants. 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 (three titration curves) and stability constants for each metal ion from 100 to 150 experimental points (two to four titration curves).

When spectrophotometric titrations were performed the stability constants were determined by the SQUAD program.[16]

Hydrolysis species of Fe^{3+}. Iron(III) easily forms hydrolytic species in aqueous solution, for which the constants are in some disagreement in the literature. We have used the values selected before,[17] namely: $\log K_{11} = [FeOH^{2-}]/[Fe^{3+}][OH^-] = 11.27$, $\log K_{12} = [Fe(OH)_2^-]/[Fe^{3+}][OH^-]^2 = 21.7$ and $\log K_{22} = [Fe_2(OH)_2^{2-}]/[Fe^{3+}]^2[OH^-]^2 = 24.8$.

Spectroscopic studies

Proton NMR spectra were recorded with a Varian Unity 300 spectrometer at probe temperature. Solutions of the macrocycles for the measurements (≈0.01 mol dm^{-3}) were made up in D_2O and the pD was adjusted by addition of DCl or CO_2-free KOD with a Crison 2001 instrument fitted with a combined Ingold 405M3 microelectrode. The $-\log [D^+]$ was measured directly in the NMR tube, after calibration of the microelectrode with buffered aqueous solutions. The final pD was calculated from pD = pH* + 0.40.[18] The value of pH* corresponds to the reading of the pH meter previously calibrated with two standard aqueous buffers at pH 4 and 7.[18] The compound dss 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. For the determination of magnetic moments, 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 obtain the final pH, and after water evaporation were taken up in D_2O. The magnetic moments were determined by the Evans method in solution[19] at room temperature.

Electronic spectra were recorded with a Perkin-Elmer, model Lambda 9 spectrophotometer, using aqueous solutions of the complexes prepared as indicated in the above paragraph, in 1 cm cells. The temperature of the solutions was kept at 25.0 ± 0.1 °C using a Grant W6 thermostat. The spectra were recorded in the range 250–1350 nm. 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 (0.72×10^{-3} to 1.66×10^{-3} mol dm^{-3} in 1.0 mol dm^{-3} $NaClO_4$) were recorded at 110 or 130 K. The spectra were simulated with a program for a microcomputer.[20]

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

Results and Discussion

Synthesis

The compounds H_3L^1 and H_3L^2 have been synthesized for the first time in the present work. The usual technique of condensation of the parent amines with chloro- or bromo-acetate under basic conditions led to mixtures of two and three carboxymethyl substituents which were very difficult to separate. In the case of the 13-membered macrocycle, the percentage of the tris derivative in the mixture obtained upon reaction was high (>70%) and purification by ion-exchange chromatography was possible. However, the introduction of the third carboxymethyl group in the 14-membered compound is very difficult, probably because the nitrogen atom between the two propane chains is stereochemically less available for the reaction,[21] and a mixture of about 50% of each derivative was obtained. Other techniques were tried, such as condensation in non-aqueous media using ethyl bromoacetate and trimethylamine,[3] or other bases in the reaction in aqueous or non-aqueous solution, but without success. So the preparation of H_3L^1 and H_3L^2 was very difficult and only small amounts of the final products were obtained.

Table 1 Protonation (log K_i^H) constants of L^1, L^2 and other similar compounds (L^3–L^5) for comparison [$T = 25.0$ °C; $I = 0.10$ mol dm^{-3} in $(CH_3)_4NNO_3$]

Equilibrium quotient	L^1	L^2	L^{3a}	L^{4b}	L^{5c}
[HL]/[H][L]	10.25(1), 10.59(5)^d	11.59(2)	11.61	11.03	11.24
[H_2L]/[HL][H]	8.33(2), 8.27(5)^d	8.39(3)	7.70	6.97	6.02
[H_3L]/[H_2L][H]	5.52(3), 5.56(4)^d	4.17(4)	4.05	3.58	2.94
[H_4L]/[H_3L][H]	—, 2.25(5)^d	2.31(5)	2.77	0.8	1.38
[H_5L]/[H_4L][H]	—, 1.30(6)^d	—	—	—	—
[H_4L]/[L][H]^4	26.35	26.46	26.13	22.38	21.58

[a] Ref. 1. [b] Ref. 3. [c] Ref. 2. [d] Determined in this work by an NMR spectroscopy technique.

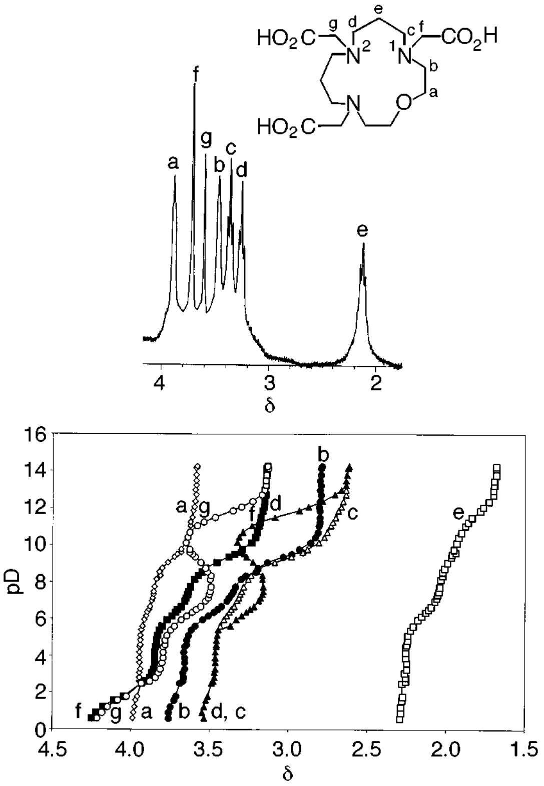


Fig. 2 Proton NMR spectrum of H_3L^1 at pD 6.50 and titration curves

Protonation

Protonation reactions of the two compounds L^1 and L^2 have been studied by potentiometric titrations and also by NMR spectroscopy for L^1. Both have six basic centres, but only four constants of each were possible to determine by potentiometric measurements. The other two were determined for L^1 by NMR titration. The values determined by ^{1}H NMR, in D_2O, were converted into values in water by the relation $pK_D = 0.11 + 1.10\ pK_H$.[18] The numbers shown in parentheses correspond to the standard deviations of the values determined from different curves. The ^{1}H NMR titration curves obtained allowed also the study of the sequence of protonation for L^1. Fig. 2 shows the NMR titration curves and the ^{1}H NMR spectrum at pD 6.50 for L^1.

The ^{1}H NMR spectrum of L^1 shows seven resonances for almost the entire pD range, although only five and six resonances are observed at pD values higher than 13 and lower than 2, respectively. The assignment of the resonances, very similar to that of L^4,[3] is straightforward taking into account the pattern of each absorption, the area ratio and the profile of the titration curves. The two singlets are readily assigned to the methylenic protons of the two carboxymethyl groups and the area ratio (2:1) allows us to distinguish them as f and g and the quintuplet at high field as due to protons e. The methylene 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 values 7.61 and 12.0 allowed the assignment of the adjacent methylenic b protons and the irradiation of the quintuplet e at the same pD values allowed the assignment of methylenic protons c and d. The last two resonances can be differentiated by taking into account the profile of the titration curves as the d methylenic protons are affected by the protonation of N^2 and the c methylenic protons by the protonation of N^1, *cf.* Fig. 2.

The ^{1}H NMR titration curves show that the first equivalent of acid added to the basic form of the ligand, L^1, protonates the N^2 centre since only resonances d, g and e shift downfield, e to a lesser degree due to its larger distance to the centre being protonated. Further acidification (between pD 10 and 7) protonates centre N^1 but simultaneously there is a partial deprotonation (about 50%) of the centre already protonated, N^2, as can be observed in Fig. 2 where resonances d and g shift to high field in this pD region. The third equivalent of acid (pD between 7 and 5) leads to complete protonation of the nitrogen centres of the molecule, as all the resonances move downfield. So, in this pD region the N^2 centre was once again protonated. Subsequent addition of acid (pD values below 5) mainly shifts downfield resonances f and g indicating protonation of the three carboxymethyl groups simultaneously.

Table 1 summarizes the protonation constants (K_i^H, in log units) for the macrocycles studied in the present work and also for other N-carboxymethyl 12- and 14-membered macrocycles for comparison. The sequence of protonation is known for all the ligands shown in Table 1 except for L^2.[3,22] However the similarity of constants between L^1 and L^2 easily allows the interpretation of the behaviour of the last compound. All the compounds exhibit one high value for the first protonation constant and one fairly high value for the second one, which correspond to the protonation of two nitrogen atoms of the ring. The first protonation occurs at the nitrogen opposite to the ring oxygen and the second at the other two nitrogen atoms with simultaneous total (as with L^3) or partial (all the other cases, except L^4) deprotonation of the centre previously protonated. This deprotonation is easily understandable for the 12-membered compounds, L^3 and L^5, showing that the macrocycles prefer a conformation with the positive charges on the two nitrogen atoms more distant from each other, minimizing the electrostatic repulsions in the ring. Even so the K_2 values for these compounds are lower than for the 13- or 14-membered ligands. In this respect L^4 has an abnormal behaviour because the mentioned deprotonation of the first nitrogen already protonated in favour of N^1 did not occur,[3] which can be attributed to the larger size of the macrocycle, although the same does not happen in L^1 which has the same ring size.

The K_3^H value of L^1 corresponds to protonation of the third nitrogen atom of the ring, as should be expected from the size of the macrocycle and the high value obtained (5.52, in log units). Indeed, protonation of a carboxylate group has a lower constant: the value for acetic acid is 4.8, in log units, and it can be lower for polyaminepolycarboxylates. However for all the other compounds indicated in Table 1 the third protonation occurs at a carboxylate group, even for L^4. The third constant of L^2 is closer to the value for L^3 than that for L^1, and probably corresponds to protonation of a carboxylate group bound to a

Table 2 Stability constants (log $K_{M_mH_hL_l}$) of complexes of L^1, L^2 and similar ligands L^3–L^5 with some divalent metal ions and Fe^{3+} [$T = 25.0$ °C, $I = 0.10$ mol dm^{-3} in $(CH_3)_4NNO_3$]

Ion	Equilibrium quotient	L^1	L^2	L^3[a]	L^4[b]	L^5[c]
Ca^{2+}	[ML]/[M][L]	4.85(3)	9.79(1)	12.984	2.1	8.12
	[M(HL)]/[ML][H]	—	—	3.93	—	5.46
	[ML]/[ML(OH)][H]	9.91(6)	—	—	—	—
Ba^{2+}	[ML]/[M][L]	—	6.90(1)	9.915	—	5.25
	[M(HL)]/[ML][H]	—	—	6.04	—	7.82
Mn^{2+}	[ML]/[M][L]	9.18(2)	—	16.09	7.08	12.737
	[M(HL)]/[ML][H]	—	—	—	6.87	3.143
	[ML]/[ML(OH)][H]	10.63(6)	—	—	—	—
Co^{2+}	[ML]/[M][L]	12.94(1)	17.393(6)	19.54	11.81	16.80
	[M(HL)]/[ML][H]	—	3.52(1)	2.64	3.89	—
Ni^{2+}	[ML]/[M][L]	—	19.94(4)	18.04	14.7	17.17
	[M(HL)]/[ML][H]	—	3.74(5)	3.66	—	—
Cu^{2+}	[ML]/[M][L]	20.14(5)	20.94(3)	20.17	17.62	17.85
	[M(HL)]/[ML][H]	4.36(6)	3.87(3)	3.10	2.66	1.73
	[M(H$_2$L)]/[M(HL)][H]	—	3.17(4)	—	—	—
	[ML]/[ML(OH)][H]	—	7.9(1)	—	—	—
Zn^{2+}	[ML]/[M][L]	12.85(2)	17.564(6)	18.66	12.597	16.12
	[M(HL)]/[ML][H]	—	3.628(7)	2.85	—	—
	[ML]/[ML(OH)][H]	—	11.08(8)	—	—	—
Cd^{2+}	[ML]/[M][L]	—	19.854(5)	19.25[d]	11.55	16.362
	[M(HL)]/[ML][H]	—	2.70(1)	—	3.85	1.50
	[ML]/[ML(OH)][H]	—	—	—	9.55	—
Pb^{2+}	[ML]/[M][L]	11.26(5)	17.032(9)	19.27[d]	8.01	15.66
	[M(HL)]/[ML][H]	5.56(7)	3.47(1)	3.48[d]	6.40	2.36
	[M(H$_2$L)]/[M(HL)][H]	—	2.23(8)	—	—	—
Fe^{3+}	[ML]/[M][L]	21.93(5)	21.24(3)	26.8[e]	—	—
	[M(HL)]/[ML][H]	2.63(7)	3.02(3)	2.15[e]	—	—
	[ML]/[ML(OH)][H]	3.8(1)	—	7.75[e]	—	—

[a] Ref. 1. [b] Ref. 3. [c] Ref. 2. [d] Ref. 27. [e] 0.10 mol dm^{-3} in KCl, ref. 17.

non-protonated nitrogen (values around 4) and the lower values correspond to protonation of a carboxylate bound to nitrogen centres already protonated due to the presence of the positive charge and probably also the simultaneous disruption of the hydrogen bonds in which these carboxylate groups are involved.

The abnormal behaviour of L^4 leads to K_2^H and K_3^H values significantly lower than those of L^1, therefore lower also its overall basicity. This behaviour seems to be related to the existence of the secondary nitrogen N^2 in L^4. Indeed, the charge effect of protonated N^2 in L^1 will be partially neutralized by the negative charge of the carboxylate group bound to it and also by hydrogen-bond formation, decreasing the global charge in the ring and allowing protonation of the third nitrogen before the carboxylate groups.

The first protonation constant of L^1 is lower than expected. Usually this kind of aza- or oxaazamacrocycle exhibits a K_1^H value higher than those of linear amines.[23] An error in the determination of the value is out of the question as it was obtained by two different techniques. The higher values for the cyclic compounds are generally explained by the formation of hydrogen bonds with the macrocyclic ring involving the proton of the ammonium ion formed or by the increased electron density in the macrocyclic cavity if the non-bonded electron pairs of the nitrogen are directed towards the centre.[24] The formation of hydrogen bonds inside the ring cavity is generally accepted although not satisfactorily demonstrated for tetraaza- or oxatriaza-macrocycles. The crystal structure of [Me$_3$[9]aneN$_3$H]ClO$_4$ (Me$_3$[9]aneN$_3$ = 1,4,7-trimethyl-1,4,7-triazacyclononane) showed the proton forming N · · · H hydrogen bonds to the other two nitrogen atoms of the ring.[24] Probably it can be inferred that the behaviour of the 14-membered compound in this aspect is closer to that of linear compounds and that hydrogen bonds do not occur in L^1. Also, the same seems to happen with the tetraazamacrocycle series, or at least in part: teta, the 14-membered ligand, presents a value of 10.68 while dota, the 12-membered one, has 12.09 for log K_1^H.[4,5] However two contradictory results appear in the literature for the crystal structure of H$_4$teta: Desreux and co-workers[25] could not observe intramolecular hydrogen bonds while Herlinger and co-workers[26] found that the protonated amine makes an intramolecular hydrogen bond to the contiguous nitrogen of the ring separated from the former one by an ethane chain and to an oxygen of a water molecule which is positioned above the ring. However, there is a lower probability of formation of this kind of hydrogen bond in L^1 as the nitrogen atoms are separated by propane chains.

The values determined by potentiometric and NMR titrations for L^1 were very similar, except for K_1 for which the better value is certainly that obtained by potentiometry, as it is more difficult to maintain the ionic strength and the solutions free of carbonate in the NMR technique.[18]

The overall basicity of H$_3$L^1–H$_3$L^3 is about the same because the first constant is higher for the 12-membered compound but the third constant is higher for the 14-membered macrocycle and about 10^4 times lower than that of compounds having only two carboxymethyl substituents, H$_2$L^4 and H$_2$L^5.

Complexation

The stability constants of L^1 and L^2 with some alkaline-earth and divalent first-row transition-metal ions are collected in Table 2 together with those for the complexes of some other 12- and 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 macrocycles. In most cases only ML and protonated species [M(HL)] are formed, but hydroxo complexes [ML(OH)] species were also found for some and [M(H$_2$L)] species were detected for Cu^{2+} and Pb^{2+} with L^2. We have checked the possibility of formation of other species such as other protonated, M(H$_i$L) ($i \geqslant 2$), or polynuclear, but they are not formed under our conditions.

The examination of Table 2 and Fig. 3 allows the following considerations. (1) The stability constants of complexes formed with the alkaline-earth metal ions, Mn^{2+} and Pb^{2+} steadily decrease with increasing macrocycle cavity size. Complexes of Co^{2+} behave in the same way for this series of ligands. The

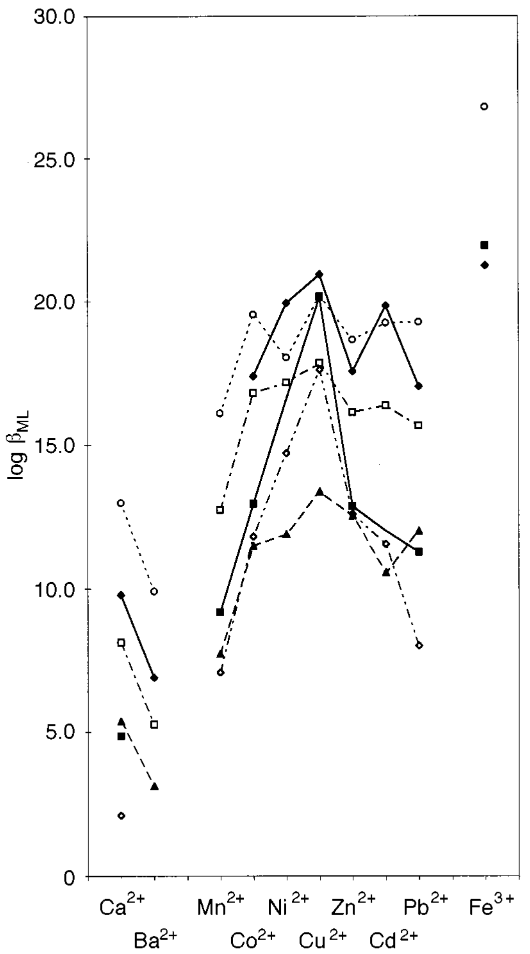


Fig. 3 Variation of the stability constants (log K_{ML}) of the metal complexes of L^1 (■), L^2 (◆), L^3 (○), L^4 (◇), L^5 (□) and L^6 (▲) with the atomic number of the metal ion

decrease is sharper on going from the 13- to 14-membered ligands than from 12- to 13-membered macrocycles. (2) 14-Membered ligands have all metal stability constants (for the ions studied) lower than with the 12- and 13-membered ligands, except for the copper(II) complex of L^1 which has a value of the same order as that of L^3. Therefore, L^1 and particularly L^4 are remarkably selective for the first-row transition-metal ions. This behaviour is very interesting for analytical applications. Using L^1 or L^4 it is possible to determine the amount of copper in the presence of manganese, cobalt, zinc, cadmium or lead or to determine cobalt in the presence of manganese and lead. (3) 12-Membered macrocycles are less selective for the first-row transition-metal ions and 13-membered ligands have an intermediate behaviour, as observed before for other series of polycarboxymethylated polyoxapolyazamacrocycles.[2,4–6] However, in the series studied in the present work, a decrease in stability of the manganese(II) complex with L^3 relative to those of the other first-row transition-metal ions is observed, and has not been noticed in other series.[2,4–6] (4) Compound L^2 forms complexes with Ni^{2+} and Cu^{2+} which are more stable than the corresponding complexes of L^3, a situation also found in the series of dioxadiaza macrocycles[6] and partially occurring in the tetraazamacrocycle series.[4,5] In the last family inversion takes place only for the nickel(II) complexes. *N*-Acetate derivatives of 12-membered ligands tend to have stability constants for Ni^{2+} lower than predicted by the Irving–Williams series, which was interpreted in terms of the possible five-co-ordinate arrangement adopted by Ni^{2+} in these complexes.[1,2,6] We shall return to this below. (5) The stability constants of L^1 and L^2 with Fe^{3+} are lower than expected when compared with that of L^3. Although the values for both complexes are of the same order, the value for the 14-membered ligand is slightly higher. (6) While the differences in stability are negligible on going from complexes of the first-row divalent metal ions with L^4 to L^1, corresponding to the addition of one more carboxymethyl group, the copper(II) complex being an exception, they are very significant for the 12-membered macrocycles, L^5 and L^3. Important are also the differences in stability of complexes of both types of macrocycles with the alkaline-earth metal ions and Pb^{2+}. In fact the majority of the complexes formed with the divalent first-row transition-metal ions adopt five- or six-co-ordinated arrangements, and the ligands of the series with two acetate groups provide enough donor atoms to fulfil the co-ordination number of these metal ions. Nevertheless, caution is necessary in the latter comparison because the differences in overall basicity of the ligands with and without a third carboxymethyl group are enormous (4.55 and 3.97 in log units, for the 12- and 14-membered ligands, respectively). The behaviour of the complexes of the 12-membered ligands with the first-row transition-metal ions and of both ligands with the alkaline-earth metal ions is as predicted, taking into account only the differences in ligand basicity, even in the case of no co-ordination of the third carboxymethyl group. So it is possible to propose that in the L^1 complexes the third carboxymethyl group is not co-ordinated, except probably with Pb^{2+} and alkaline-earth metal ions, and that the structure adopted by the complexes of Co^{2+} and Zn^{2+} with L^1 is more strained than that with L^4.

The reason why the complexes of the 12-membered polyacetate polyaza- or polyoxapolyaza-macrocycles are more stable than those of the 13- and 14-membered ligands was discussed before.[5,9] The determination of thermodynamic functions (ΔH and ΔS) for the complexes of dota to teta has revealed that for those with mainly electrostatic interactions the difference is especially due to the enthalpic variations, although a decrease in the entropic variations was also found. The decrease in the values of ΔH with increasing ring size is probably due to longer distances between the metal ions and the donor atoms and also to a less favourable orientation of the lone-pair electrons of the donor atoms of the ring, probably with a more distorted arrangement of the macrocycle. However, the metal ions which form more covalent bonds and have more strict specific co-ordination preferences (Fe^{2+} to Zn^{2+}) probably select the donor atoms of the ligand which are in better position to provide the preferred geometry, using all or part of them in the co-ordination.[5,9] X-Ray diffraction analysis of complexes of Cu^{2+} and Ni^{2+} with dota and teta has also confirmed this hypothesis.[28]

Nevertheless, the steep fall in stability constants observed for the complexes of L^1 and L^4 with larger metal ions, such as Ca^{2+}, Mn^{2+} and Pb^{2+} but also Co^{2+} and Zn^{2+}, is so important that speculation about the non-co-ordination of one of the nitrogens of the macrocycles is possible. This hypothesis was advanced before[3] to explain the results obtained for L^4 but could not be confirmed till now because we have not succeeded in getting crystals appropriate for X-ray diffraction studies. More support comes from the values of the stability constants of complexes of L^6 with Ca^{2+}, Mn^{2+}, Co^{2+} and Zn^{2+},[29] which are close to those of L^4 (*cf.* Fig. 3). The nine-membered ligand L^6 gives an N_2O_3 co-ordination sphere (possibly N_2O_4 with a water molecule completing the six-co-ordination) but an overall basicity lower than that of L^4 (about 5 log units lower), reflecting the conformational entropy losses of L^1 and also L^4 on complexation.

To have more insight about the co-ordination spheres of the complexes of Co^{2+}, Ni^{2+} and Cu^{2+} some spectroscopic measurements were performed.

Spectroscopic measurements

The UV/VIS/near-IR data for complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with L^1–L^4 and EPR parameters for the copper(II) complexes of the same ligands in aqueous solution are collected in Tables 3 and 4, respectively.

Table 3 Spectroscopic UV/VIS/near-IR data and magnetic moments for the complexes of Co^{2+}, Ni^{2+}, Cu^{2+} and Fe^{3+} with L^1–L^4 (T = 25.0 °C)

Complex (colour)	pH	λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1})	μ/μ_B
$[CoL^1]^-$ (pink)	7.04	1053 (6.3), 610 (sh, 6.6), 526 (sh, 19.5), 498 (24.3), 486 (sh, 23.8), 300 (sh, 60.1)	4.97
$[CuL^1]^-$ (blue)	5.86	730 (sh, 24.5), 612 (sh, 41.5), 602 (42.4), 256 (4.1 × 10^3)	—
$[FeL^1]$ (yellow)	2.90	294 (2.05 × 10^3)	—
$[CoL^2]^-$ (pale pink)	6.77	1292 (sh, 5.0), 1168 (5.6), 1060 (sh, 5.2), 936 (4.8), 568 (sh, 11.2), 528 (sh, 13.2), 508 (sh, 14.1), 496 (14.3), 468 (sh, 12.0), 304 (sh, 57.4)	4.82
$[NiL^2]^-$ (violet)	4.50	1156 (sh, 6.2), 1126 (sh, 7.7), 1000 (11.6), 908 (sh, 9.6), 793 (5.6), 624 (sh, 7.2), 568 (10.4), 420 (sh, 19.5), 349 (33.9), 300 (86.9)	3.38
$[CuL^2]$ (turquoise)	4.67	1104 (27.4), 760 (sh, 81.0), 692 (111.8), 288 (2.3 × 10^3)	—
$[FeL^2]$ (yellow)	4.12	296.1 (7.6 × 10^3)	—
$[CoL^3]^-$ (pale pink)	6.20	1160 (11.4), 1028 (11.1), 992 (11.1), 756 (14.8), 684 (15.8), 640 (sh, 13.2), 604 (sh, 14.2), 536 (sh, 20.7), 518 (23.2), 484 (sh, 23.0), 297 (45.9)	5.03
$[NiL^3]^-$ (blue)	6.13	1228 (sh, 17.7), 1116 (sh, 25.5), 1046 (sh, 29.5), 1001 (28.6), 946 (sh, 28.1), 804 (21.2), 646 (sh, 22.3), 594 (sh, 25.7), 570 (26.6), 372 (25.0), 296 (46.4)	3.38
$[CuL^3]^-$ (blue)	5.75	1012 (43.6), 780 (sh, 87.2), 736 (100.5), 269 (3.2 × 10^3)	—
$[FeL^3]$ (yellow)	4.68	286 (7.5 × 10^3), 264 (7.7 × 10^3)	—
$[NiL^4]$ (pale green)	6.15	1206 (sh, 5.4), 1070 (8.7), 936 (sh, 8.5), 820 (7.6), 650 (sh, 13.1), 587 (17.0), 368 (36.4), 296 (128.0)	2.89
$[CuL^4]$ (blue)	6.08	864 (sh, 33.3), 772 (sh, 65.1), 686 (95.8), 273 (3.8 × 10^3)	—

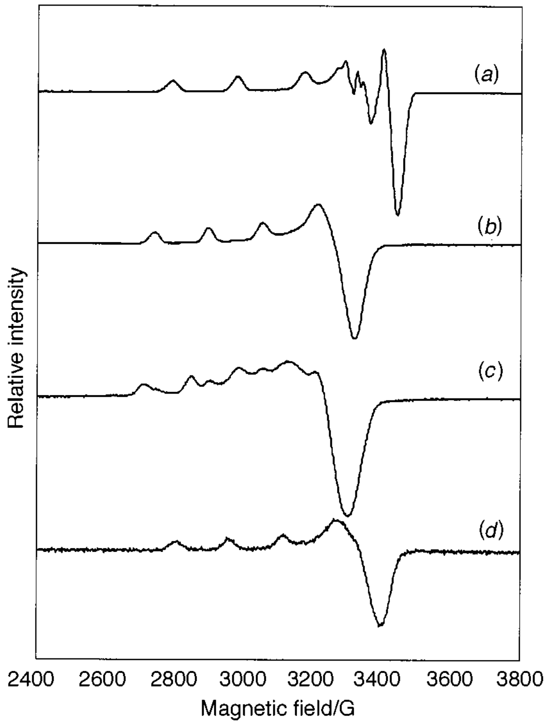


Fig. 4 The EPR X-band spectra of the copper(II) complexes of L^1 (*a*), L^2 (*b*), L^3 (*c*) and L^4 (*d*), in 1.0 mol dm^{-3} $NaClO_4$, recorded at 110 [(*a*) and (*b*)] and 130 K [(*c*) and (*d*)], microwave power 2.4 mW, modulation amplitude 0.9 mT. The frequency (ν) was 9.61, 9.41, 9.41 and 9.61 GHz for (*a*), (*b*), (*c*) and (*d*), respectively

The electronic spectrum exhibited by $[CoL^1]^-$ (*cf.* Table 3), the low-intensity bands presented and the value of the magnetic moment (4.97 μ_B) point to a six-co-ordinate tetragonally distorted symmetry of a high-spin species.[31–33] The calculated values for the octahedral field splitting parameter,[32] $10Dq$, and the electronic repulsion parameter, B, are 10 680 and 784 cm^{-1}, respectively. The complex of the 12-membered ligand, $[CoL^3]^-$, exhibits a completely different electronic spectrum, with several small bands in the infrared region and another at 756 nm although the visible band is also multiply structured. The intensity of the bands is higher than that of the former complex. This electronic spectrum points to a five-co-ordinate structure, in spite of the magnetic moment of 5.03 μ_B being slightly higher than usual.[31,32] Bertini and Luchinat[31] indicated that when the spectrum shows evidence of a weak absorption between 830 and 670 nm, as is the case for $[CoL^3]^-$, five-co-ordination can be proposed. The complex $[CoL^2]^-$ exhibits a spectrum which is intermediate between those described above, with a multiply structured visible band, without bands in the 600 to 900 nm region, but with a split band in the infrared region. The magnetic moment of 4.82 μ_B points to a six-co-ordinate tetragonally distorted symmetry or a distorted five-co-ordinate square-pyramidal symmetry.[31,32] All complexes undergo degradation with time at pH values higher than about 9.

The electronic spectra of both $[NiL^2]^-$ and $[NiL^3]^-$ exhibit five broad but well defined bands and several shoulders (*cf.* Table 3), characteristic of five-co-ordinate high-spin derivatives.[32,34,37] The magnetic moments (3.38 μ_B for both complexes) also fall in the range normally observed for high-spin five-co-ordinate nickel(II) environments.[32,34,38] Without X-ray diffraction analysis the actual stereochemical arrangement of five-co-ordinate Ni^{2+} is not safely assigned. The non-equivalence of the donor atoms of this ligand also contributes to the difficulty in assignment of a strictly trigonal-bipyramidal or a square-pyramidal geometry, and probably an intermediate structure is what actually occurs. The electronic spectrum observed for the pale green solution of $[NiL^4]$ (*cf.* Table 3) and the value of the magnetic moment (2.89 μ_B) are characteristic of a tetragonal (D_{4h}) symmetry.[32–37,39] The ratio of the near-IR band and of that appearing in the visible is 1.82, also characteristic of tetragonal nickel.[32] Following the considerations of Busch and co-workers[39] for some tetraazamacrocycles, we tentatively assigned the bands of our spectrum and values of Dq^{xy} and Dq^z were calculated based on this assignment (1220 and 649 cm^{-1}). Interpretation of the spectral data requires the assignment of two transitions: $^3B_{1g} \longrightarrow {}^3B_{2g}$ which is directly related to $10Dq^{xy}$ and $^3B_{1g} \longrightarrow {}^3E_g{}^a$ which equates to the difference between $10Dq^{xy}$ and $(35/4)D_t$; Dq^z is strongly influenced by the in-plane ligand field, decreasing as Dq^{xy} increases.

The copper(II) complexes of the 14-membered ligands, $[CuL^1]^-$ and $[CuL^4]$, exhibit a broad band in the visible region at 602 and 686 nm, respectively, each one with two shoulders at lower energies, due to the copper d–d transitions, and an intense band in the ultraviolet region. The spectra of the other two complexes, $[CuL^2]^-$ and $[CuL^3]^-$, show another broad band in the near-IR region.

The EPR spectra of the four copper(II) complexes are shown in Fig. 4. All exhibit three well resolved lines of the four expected at low field, due to the interaction of the unpaired electron spin with the copper nucleus, and no superhyperfine splitting due to coupling with the four nitrogen atoms of the macrocycle. The fourth copper line is completely overlapped by the much stronger and unresolved band of the high-field part of the spectra. The spectrum of the complex with the 12-membered ligand shows two isomers in a 1 : 1 ratio, as revealed by computational simulation,[20] and variation of pH (from 3.95 to

Table 4 The EPR data for copper(II) complexes of L^1–L^4 and other similar complexes

Complex	Visible band λ/nm (ε/dm^3 mol^{-1} cm^{-1})	EPR[a] g_x	g_y	g_z	A_x	A_y	A_z	Ref.
$[CuL^1]^-$	602 (42.4)	2.040	2.061	2.235	23.9	22.4	195.6	[b]
$[CuL^2]^-$	1104 (27.4), 692 (111.8)	2.048	2.083	2.259	5.8	11.4	166.8	[b]
$[CuL^3]^-$	1012 (43.6), 736 (100.5)	2.050	2.109	2.259	5.4	29.3	159.8	[b]
		2.044	2.137	2.309	14.3	52.6	146.3	
$[CuL^4]$	686 (95.8)	2.040	2.087	2.262	0.7	18.4	163.0	[b]
$[Cu([14]aneN_3O)(H_2O)]^{2+}$	780 (sh), 622 (147)	2.050	2.059	2.224	10.9	20.5	183.1	[c]
$[Cu([13]aneN_3O)Br]^+$	780 (sh), 626.4 (160)	2.027	2.082	2.216	26.9	15.1	160.2	[c]
$[Cu([12]aneN_3O)Br]^+$	840 (sh), 690.6 (161)	2.037	2.077	2.226	23.8	21.6	162.8	[c]

[a] 10^4 A/cm^{-1}. [b] This work. [c] Ref. 30.

7.18) does not affect the proportion of the isomers. The simulation of the spectra[20] also indicated three different principal values of g, showing that the 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 EPR spectra of the copper(II) complexes of L^1–L^4 show $g_z > (g_x + g_y)/2$ and the lowest $g \geqslant 2.04$, typical of rhombic symmetry of Cu^{2+} with elongation of the axial bonds and a $d_{x^2-y^2}$ ground state. Elongated rhombic octahedral, rhombic square-coplanar or distorted square-based pyramidal stereochemistries would be consistent with these data and trigonal-bipyramidal geometry or a tetragonal structure involving compression of axial bonds should be excluded.[40,41]

The molecular g values and hyperfine constants (A_i) may be related to the electronic transitions by the usual factors derived from ligand-field theory:[42–44] the strength of the axial donor and the displacement of the copper from the donor atom plane. The g values increase and the A_z value decreases as the planar ligand field becomes weaker or as the axial ligand field becomes stronger and this occurs with the simultaneous red-shift of the d–d absorption bands in the electronic spectra.[43–46] This sequence, in principle, parallels the degree of distortion from a square-planar arrangement to a square-pyramidal geometry, C_{4v}, and then to an octahedral (O_h) or tetragonal symmetry (D_{4h}).

The data of Table 4 show that on progressing from $[CuL^1]^-$ to $[CuL^3]^-$ (both isomers) all the g values increase, the A_z parameter decreases and the visible band of the electronic spectra shifts gradually to the red. This is an indication that with the decrease in size of the macrocycle there is an increase of the axial ligand field or a decrease of the equatorial ligand field. The same is found when comparing the EPR parameters of the parent amine complex[30] $[Cu([14]aneN_3O)(H_2O)]^{2+}$ ($[14]aneN_3O$ = 1-oxa-4,8,12-triazacyclotetradecane) listed in Table 4 with those of the corresponding bis(carboxymethyl) derivative, $[CuL^4]$. For these two complexes X-ray diffraction structures exist and have shown that the Cu^{2+} in the complex of the parent amine adopts a five-co-ordinate arrangement in a distorted square-pyramidal geometry, with the basal plane formed by the donor atoms of the macrocycle and a water molecule in axial position, the six-membered rings showing a half-boat conformation while the five-membered rings have twisted conformations.[30] The crystal structure of $[CuL^4]$ is a distorted octahedron, tetragonally elongated, where the equatorial plane is formed by the three nitrogen atoms of the macrocycle and the oxygen atom of one carboxylate group, and the axial positions are occupied by the oxygen atom of the other carboxylate group and the oxygen atom of the ring. The macrocycle is in a very strained conformation, the equatorial plane showing tetrahedral deviations and the angle between the axial donor atoms is 149.5°, smaller than the expected 180°.[3] The EPR spectra of both complexes show an increase in the axial ligand field {by the increase in g values and the decrease in A_z on going from $[Cu([14]aneN_3O)(H_2O)]^{2+}$ to $[CuL^4]$} in agreement with the crystal structures. Altering the oxygen of the ring by the carboxylate group is not perceived by EPR spectroscopy.

The comparison of $[Cu([12]aneN_3O)Br]^+$ ($[12]aneN_3O$ = 1-oxa-4,7,10-triazacyclododecane) with $[CuL^3]^-$ leads to identical conclusions. The crystal structure of the former complex is also known:[30] the Cu^{2+} has a distorted square-pyramidal environment, the basal plane being formed by the nitrogen atoms of the macrocycle and the Br atom and the oxygen of the ring is in axial position; the macrocycle is in a folded arrangement, presenting a pronounced tetrahedral distortion. Both isomers of $[CuL^3]^-$, the structure of which is not known, should present distorted octahedral symmetry based on the EPR parameters, the macrocycle maintaining probably the same arrangement with one carboxylate oxygen replacing the Br of $[Cu([12]aneN_3O)Br]^+$ in equatorial position and a second one occupying the other axial position. The third carboxylate probably would remain free.

The comparison of $[Cu([13]aneN_3O)Br]^+$ ($[13]aneN_3O$ = 1-oxa-4,7,11-triazacyclotridecane) with $[CuL^2]^-$ or $[Cu([14]aneN_3O)(H_2O)]^{2+}$ with $[CuL^1]^-$ cannot be rationalized in the same way, both the g and the A_z parameters increasing on going from the parent amine to the tris(carboxymethyl) derivatives. With both amines the copper ion adopts five-co-ordinate arrangements, using the donor atoms of the ring as equatorial ligands and the bromine atom as axial ligand, with the 13-membered ligand,[47] and the water molecule with 14-membered ligand.[30]

As we have mentioned before, the analysis of the EPR parameters led to the conclusion that the decrease in the size of the macrocycles in the series $[CuL^1]^-$ to $[CuL^3]^-$ leads to an increase of the axial ligand field or a decrease of the equatorial ligand field. This conclusion is in agreement with that mentioned in the previous paragraph if five-co-ordination is postulated for $[CuL^2]^-$ and $[CuL^1]^-$, with this arrangement probably achieved in a different way from that of $[Cu([13]aneN_3O)Br]^+$ or $[Cu([14]aneN_3O)(H_2O)]^{2+}$, for instance by folding of the macrocycle bringing the oxygen of the ring in axial position and a carboxylate oxygen completing the equatorial plane. This hypothesis is also consistent with the decreasing g values and increasing A_z parameters on going from $[CuL^4]$ (six-co-ordinate) to $[CuL^1]^-$ (five-co-ordinate) and also, the increase in g values, decrease in A_z values, and the red shift of the visible band on going from $[CuL^1]^-$ to $[CuL^2]^-$. In this last case, the increase in the axial field is probably due to the shorter distance of the oxygen of the ring to the metal ion with the 13-membered ligand when compared with that of the 14-membered ligand.

Although we know that electronic and EPR specra of copper(II) complexes are not especially good indicators of geometry and the stereochemical assignments based on them can hardly be considered conclusive,[40] the comparison between spectra of complexes of the same series, such as those compiled in Table 4, allows some interesting deductions, especially when there is one or more crystal structure for orientation of the conclusions.

Conclusion

The two macrocycles studied in the present work have completely different co-ordination properties for alkaline-earth and divalent first-row transition-metal ions. The 13-membered L^2 exhibits fairly high stability constants but unsatisfactory selectivity with the first-row transition-metal ions, despite being more selective than the 12-membered L^3. The 14-membered L^1 is very selective for the same series of metal ions, the difference in stability between the complexes of Cu^{2+} and Mn^{2+} being 10.96 log units and that between those of Cu^{2+} and Zn^{2+} 7.29 log units. The constant of its manganese(II) complex is still high enough for quantitative determination of this metal by L^1 at pH values higher than 7. However, the behaviour of L^1 is similar to that of L^4 and so the difficult preparation of the former does not compensate the benefits. The increase in the size of the cavity of the macrocycle leads to a sharp decrease in stability of the complexes of metal ions where mainly electrostatic interactions are present (the alkaline-earth metal ions, Mn^{2+} and Pb^{2+}). Cobalt(II) complexes also undergo a significant decrease in stability with increase in macrocycle size and the constant for the zinc complex of L^1 is much lower than that of L^2. The complexes of Cu^{2+} and Ni^{2+} with L^1–L^3 have about the same values of the stability constants.

To explain these results we propose that all the donor atoms of the ligands (L^1–L^5) are involved in co-ordination when the interactions are mainly electrostatic, however the distances and especially the orientation of the lone pairs of electrons are not the best for co-ordination when the macrocycle cavity size increases. The complexes of the first-row transition-metal ions undergo the same effects, but as they have more strict co-ordination preferences and the ligands have more donor atoms than those required, the more appropriate ones will be chosen for co-ordination. So Co^{2+}, Ni^{2+} and Cu^{2+} adopt five- or six-co-ordination as shown by electronic and EPR spectroscopic measurements in solution and the value of the magnetic moments of the complexes. The ions Co^{2+} and Ni^{2+} seem to adopt similar arrangements with L^2 and L^3, generally with five-co-ordination, the complexes of Cu^{2+} with L^1 and L^2 are also five-co-ordinated but that of L^3 seems to be six-co-ordinated. The nickel(II) complex of L^3 presents a lower constant than that of Co^{2+}, so the complexes of the first-row divalent transition-metal ions with L^3 do not obey the Irving-Williams series. Indeed, Ni^{2+} adopts a five-co-ordinated arrangement in this complex, as postulated before,[1,2] which is not favoured in terms of crystal-field stabilization energy (CFSE),[1,2,48] but L^2 exhibits the same symmetry with Ni^{2+} and in this case the inversion of the usual trend is not observed. Probably, it is the combination of a particularly stable cobalt(II) complex and a not favoured structure for Ni^{2+} that leads to the mentioned inversion. Cobalt(II) is relatively more stable in a high-spin configuration when trigonal bipyramidal than square pyramidal[48] and this is probably adopted by $[CoL^3]^-$. The copper(II) complexes of L^1 and L^2 present similar values of stability constants which are slightly higher than that with L^3 because the copper ion is more stable (by crystal-field stabilization energy) when five-co-ordinated (square pyramidal or trigonal bipyramidal)[48] and the structure adopted by the complexes of L^1 and L^2 points to five-co-ordination, that of L^3 to six-co-ordination.

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