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Metal complexes of a tetraaza macrocycle with *N*-carboxymethyl groups as pendant arms*

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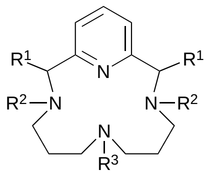
The protonation constants of H_2L^1 (7-methyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-3,11-diacetic acid) and stability constants of its complexes with Mg^{2+}, Ca^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Ga^{3+}, Fe^{3+} and In^{3+} were determined by potentiometric methods. This macrocycle is selective exhibiting a very high stability constant for Cu^{2+} ($\log K_{ML} = 21.61$), while for the remaining complexes of the first-row transition-metal ions the stability decreases sharply. The calcium complex has very low stability ($\log K_{ML} = 3.74$), but that of Mg^{2+} is higher ($\log K_{ML} = 5.30$) and those of trivalent metal ions (Ga^{3+}, Fe^{3+} and In^{3+}) have very low stability, the value for Fe^{3+} ($\log K_{ML} = 20.64$) being lower than that of Cu^{2+}. Spectroscopic studies (electronic and EPR) in aqueous solution have shown that H_2L^1 upon complexation (with Co^{2+}, Fe^{3+} and possibly Cu^{2+}) exhibits a tendency to adopt a folded conformation with the nitrogen atom of the macrocycle opposed to the pyridine in the axial position, the basal plane being formed by the three other nitrogen atoms of the ring and the other carboxylate in a square-pyramidal arrangement for the metal ion. The complex $[Fe(L^1)Br]\cdot 4H_2O$ shows a temperature-dependent magnetic behaviour with μ_{eff} ranging from 3.58 μ_B at 292 K to 1.70 μ_B at 3.1 K.

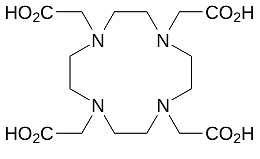
The search for new compounds which may form selective complexes with the first-row transition-metal ions led us to study a *N*-acetate derivative of a pyridine-containing tetraazamacrocycle (H_2L^1), synthesized before[1] and for which the crystal structure of a copper(II) complex, $[Cu(H_2L^1)Cl]Cl$, was described.[1] It is known that *N*-carboxymethyl derivatives of 14-membered macrocycles are more selective for the first-row transition divalent metal ions than are 12- or 13-membered rings,[2–4] although the latter form complexes with higher stability constants.[2,4] In general, the complexes of those ligands obey the Irving–Williams order of stability,[5] without surprising inversions.[2,4] For alkaline-earth-metal ion complexes the stability constants decrease with increasing size of the cavity, any metal ion being particularly favoured. The complexes of these ions with 14-membered macrocyclic ligands having contiguous propane chains exhibit very low stability constants.[3] Although no surprising inversions in the usual trends of stability constants were observed, some remarkably stable complexes (thermodynamic and kinetically) were found, namely the 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate (dota) complexes of Ca^{2+} (ref. 2) and of some trivalent lanthanides.[6,7]

The compound studied in the present work, although having two acetate arms, has a complexing behaviour which is closer to that of linear polyamines than to cyclic polyaminocarboxylate ligands, taking the advantage of some properties of the latter, namely water solubility, easy purification, neutral complexes with divalent metal ions and faster kinetics of formation of metal complexes.

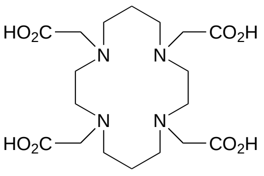
The completely deprotonated form of the macrocycle is $(L^1)^{2-}$ but for simplicity the charge is generally disregarded in the text.



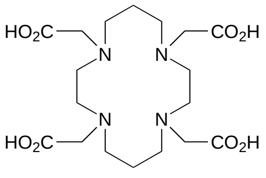
H_2L^1 $R^1 = H$; $R^2 = CH_2CO_2H$; $R^3 = CH_3$
L^2 $R^1, R^2 = H$; $R^3 = CH_3$
L^3 $R^1, R^2, R^3 = H$
L^4 $R^1 = H$; $R^2, R^3 = CH_3$
L^5 $R^1, R^3 = H$; $R^2 = CH_2Ph$
L^6 $R^1, R^2, R^3 = CH_3$
L^7 $R^1, R^3 = CH_3$; $R^2 = H$
L^8 $R^1 = CH_3$; $R^2, R^3 = H$



H_4dota



H_4trita



H_4teta

Experimental

Reagents

The parent L^2 was synthesized in our laboratory by previously reported procedures.[8] Bromoacetic acid and Dowex 1 × 8 ion-exchange resin (20–50 mesh, Cl^- form) were obtained from Aldrich Chemical Co., H_4egta (ethylenedioxydiethylenedinitrilotetraacetic acid) from Sigma, and K_2H_2edta (edta = ethylenedinitrilotetraacetate) from Fluka. All the chemicals

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* *Non-SI units employed*: $\mu_B \approx 9.27 \times 10^{-24}$ J T^{-1}, G = 10^{-4} T.

were of reagent grade and used as supplied without further purification (the resin was treated with 5% KOH before use). The organic solvents were purified by standard methods.[9]

Synthesis and characterization of the macrocycle

The *N*-carboxymethyl groups were introduced by condensation of the parent amine (4.03 mmol, 1.00 g) with potassium bromoacetate (obtained by addition of 3 mol dm^{-3} KOH solution to concentrated aqueous bromoacetic acid, 8.1 mmol, 1.13 g, at 5 °C), in aqueous basic solution (4 cm^3). The temperature was kept at 25–30 °C and the pH < 9, by slow addition of 3 mol dm^{-3} KOH. At the end of the reaction the mixture was cooled and adjusted to pH 1.9 with 3 mol dm^{-3} hydrobromic acid. The solution was then concentrated and a small amount of methanol added. The inorganic matter formed was filtered off and the filtrate purified by chromatography using an anionic resin in the OH$^-$ form, washed with water and then eluted with a solution of 0.1 mol dm^{-3} HBr. Yield: 63%. M.p. 233–235 °C; ^{1}H NMR (D_2O): [sodium 4,4-dimethyl-4-silapentane-1-sulfonate (dss) as reference], δ 7.76 (1 H, t), 7.40 (2 H, d), 4.52 (4 H, s), 4.01 (4 H, s), 3.22 (8 H, m), 2.66 (3 H, s) and 2.17 (4 H, m); ^{13}C (1,4-dioxane), δ 168.36, 149.47, 140.41, 126.53, 56.44, 55.90, 51.28, 49.99, 41.89 and 17.67 (Found: C, 31.6; H, 5.9; N, 8.0. Calc. for $C_{18}H_{31}Br_3N_4O_4\cdot4H_2O$: C, 31.8; H, 5.8; N, 8.3%).

Synthesis of $[Fe(L^1)Br]\cdot4H_2O$

Iron(III) hydroxide was freshly prepared by addition of 0.1 mol dm^{-3} KOH to $Fe(NO_3)_3$ (0.098 mmol). The precipitate formed was separated by centrifugation and added to an aqueous solution of $[H_5L^1]Br_3$ (0.089 mmol). The mixture was heated for 1 h at 40 °C and stirred overnight at room temperature. The solution was then concentrated and diethyl ether was added to the residue. An orange precipitate was obtained which was dried under vacuum. Yield: 70% (Found: C, 38.1; H, 5.75; N, 9.45. Calc. for $C_{18}H_{26}BrFeN_4O_4\cdot4H_2O$: C, 37.9; H, 6.0; N, 9.85%).

Potentiometric measurements

Reagents and solutions. Metal-ion solutions were prepared at about 0.025 mol dm^{-3} from the nitrate salts (analytical grade) with demineralized water (obtained by a Millipore/Milli-Q system) and standardized by titration with K_2H_2edta.[10] 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. Carbonate-free solutions of the titrant, NMe_4OH, were prepared as described.[11] Solutions were discarded when the percentage of carbonate was about 0.5% of the total amount of base.

Equipment and working conditions. The equipment used was as described.[11] All the experiments were monitored by computer. The temperature was kept at 25.0 ± 0.1 °C; atmospheric CO_2 was excluded from the cell during the titration by passing purified N_2 across the top of the experimental solution in the reaction cell. The ionic strength of the solutions was kept at 0.10 mol dm^{-3} with NMe_4NO_3.

Measurements. The [H$^+$] of the solutions was determined by measurement of the electromotive force of the cell, $E = E'^\circ + Q \log [H^+] + E_j$ where E'° and Q were obtained by previous calibration, titrating a standard solution of known hydrogen-ion concentration at the same ionic strength, using the values of the acid range. The term pH is defined as $-\log [H^+]$. The liquid-junction potential, E_j, was found to be negligible under the conditions used. The value of $K_W = [H^+][OH^-]$ was determined from the alkaline region of the calibration, considering E'° and Q valid for the entire pH range, and found equal to $10^{-13.80}$ mol^2 dm^{-6}.

The potentiometric equilibrium measurements were made on macrocycle solutions (≈2.50 × 10^{-3} mol dm^{-3}, 20.00 cm^3) 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, the $c_L : c_M$ ratios being 1:1, 1:2 and in several cases 2:1. A minimum of two replicates were made. The E data were taken after additions of 0.025 or 0.050 cm^3 increments of standard NMe_4OH solution, and after stabilization in this direction, equilibrium was then approached from the other direction by adding standard nitric acid.

In the cases of Cu^{2+}, Ga^{3+}, Fe^{3+} and In^{3+} the extent of formation of the metal complexes, at the beginning of the titration, was too high for the use of the direct potentiometric method, and so ligand–ligand competition titrations were performed to determine the constants; K_2H_2edta was used as the second ligand in the cases of Cu^{2+} and In^{3+} and H_4egta for Fe^{3+}. Ratios $c_{L^1} : c_{L'} : c_M$ 1:1:1, 1:0.7:1 and 1.5:1:1 were used, respectively; L′ is the reference ligand, K_2H_2edta or H_4egta, for which it is necessary to know accurately the stability constants of complexes with the same metal ion.[12] A competition reaction, which can be written in terms of equilibrium (1), was considered appropriate when all complexed species exist in solution at least 30% concentration with respect to the total metal ion; $n = 1$ (for trivalent metal ion) or 2 (for divalent metal ion) and $m = 0$ (for divalent metal ion) or 1 (for trivalent metal ion).

$$[ML']^{n-} + [H_5L^1]^{3+} \rightleftharpoons [ML^1]^{m+} + 3\,H^+ + [H_2L']^{2-} \qquad (1)$$

Stability constants for the gallium complexes were calculated by relying on the competition or displacement reaction (2).[13]

$$[GaL^1(OH)] + 3OH^- \rightleftharpoons [Ga(OH)_4]^- + (L^1)^{2-} \qquad (2)$$

Constants corresponding to the formation of $[GaL^1]^+$ and $[GaL^1(OH)]$ can be determined at pH ⩾ 6, when $[Ga(OH)_4]^-$ starts to be formed, and used in other parts of the titration curves (at low pH) to obtain the constants for the other equilibrium reactions.

As the value of the stability constant for the iron(III) complex was lower than expected, other techniques were used to confirm the value. A competition with another metal ion, Cu^{2+}, in the ratio $c_{L^1} : c_M : c_{M'}$ 1:0.5:0.5 and also a direct redox method using a couple of platinum and reference electrodes to follow the Fe^{3+}–Fe^{2+} equilibrium, at pH 2.[14]

In the competition reactions the equilibria were slow to attain but, even so, automated titrations were possible; 10–15 min were necessary at each point of the titration in the pH range where the competition reaction took place. The same values of stability constants were obtained either using the direct or the back titration curves.

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 obtained 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 initial computations gave overall stability constants or $\beta_{M_mH_hL_l} = [M_mH_hL_l]/[M]^m[L]^l[H]^h$.

Only mononuclear species, ML, MHL, MLH_{-1} ($\beta_{MLH_{-1}} = \beta_{ML(OH)}K_W$), were found. Differences, in log units, between $\beta_{M(HL)}$ (or $\beta_{MLH_{-1}}$) and β_{ML} provide the stepwise protonation reaction 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 normal propagation rules and do not represent the total experimental errors.

Hydrolysis of the trivalent metal ions. The trivalent metal ions studied easily form hydrolytic species in aqueous solution, the constants of which show some discrepancies in the literature. We have used the values reported before, considered more reliable.[11]

Spectroscopic studies

Proton NMR spectra were recorded with a Bruker CXP-300 spectrometer. Solutions of the macrocycle for the measurements ($\approx$ 0.01 mol dm^{-3}) were made up in the D_2O and the pD was adjusted by adding DCl or CO_2-free KOD, using an Orion 420A instrument fitted with a combined Ingold microelectrode. The $-\log[H^+]$ was measured directly in the NMR tube, after the calibration of the microelectrode with buffered aqueous solutions; dss was used as an internal reference. The ^{13}C NMR spectra were recorded with the same spectrometer and 1,4-dioxane as internal reference. The metal complexes were prepared in water by addition of the metal ion, in the form of $Co(NO_3)_2$ or $Fe(NO_3)_3$, to an equivalent amount of the macrocycle and enough KOH to give a final pH of 5.8 and 2.8, respectively, and after evaporation of water were taken up in D_2O. The magnetic moment of the complexes were determined by the Evans method[16] in solution at room temperature.

Electronic spectra were measured with a Shimadzu model UV-3100 spectrometer for UV/VIS/near IR, using aqueous solutions of the complexes prepared by 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 X-band EPR spectra were recorded with a Bruker ESP 380 spectrometer equipped with a continuous-flow cryostat for liquid helium or for liquid nitrogen. The spectra of the complexes of Cu^{2+} and Fe^{3+} (9.0×10^{-4} and 7.55×10^{-3} mol dm^{-3}, respectively, in 1.0 mol dm^{-3} $NaClO_4$) were recorded at 86 K for the first complex, and in the range 4.6–200 K, for the second. The quantification of signals of the iron complex was obtained by comparison of the second integral of its EPR spectra with that of an external standard, corrected by the g_p factor for the sample and the standard.[17] As a standard we used a solution of hydrated copper(II) ion (5 mmol $CuSO_4 \cdot 5H_2O$ + 5 mmol HCl in 2.0 mol dm^{-3} $NaClO_4$). The simulation of the EPR spectrum of the copper complex was carried out with a program for a microcomputer.[18]

Magnetic susceptibility studies

The magnetic susceptibility measurements for the iron(III) complex in the solid state were performed in the range 3–292 K using a longitudinal Faraday system (Oxford Instruments) and a 7 T superconducting magnet. A polycrystalline sample of $[Fe(L^1)Br] \cdot 4H_2O$ (24 mg) was placed into a thin-walled Teflon bucket, previously measured. The magnetic field used was 1 T, and force was measured with a microbalance (Sartorius S3D-V) applying forward and reverse gradients of 5 T m^{-1}. The paramagnetic susceptibility was calculated from the raw susceptibility data, correcting for diamagnetism estimated from Pascal's constants[19] as 3.2×10^{-4} cm^3 mol^{-1}.

Results

Protonation and stability constants

Titration of the macrocycle in the form $[H_5L^1]Br_3$ showed two inflection points, at $a = 3$ and 4, respectively (a being a number of equivalents of base added per mol of macrocycle). The protonation constants obtained are summarized in Table 1 together with the values for other tetraazamacrocycles for comparison.

The titration curves obtained for mixtures of the macrocycle and metal ions (1 : 1) showed one inflection at $a = 5$, with the exception of those of Ga^{3+} and Fe^{3+} due to the formation of stable $ML^1(OH)$ species at low pH which had an inflection at $a = 6$. The curves for Mg^{2+}, Ca^{2+} and Pb^{2+} exhibit another inflection at $a = 3$ at which formation of complexes starts. Titration curves corresponding to other mixtures, like 2 : 1 or 1 : 2, were not significantly different from those of ratio 1 : 1.

The values of the stability constants for the metal complexes of L^1 studied in this work, determined in water, are also compiled in Table 1. In most cases only ML and M(HL) species are formed; but hydroxo complexes are found for some metal ions, especially Ga^{3+}, Fe^{3+}, In^{3+} and also Zn^{2+}. For Fe^{3+} and In^{3+} a precipitate is formed at pH $\approx$ 3.6 and 8, respectively; it is impossible to obtain reliable constants for the $ML^1(OH)$ species. In the case of iron(III) probably a μ-oxo dimer$[(FeL^1)_2O]$ will be formed. We have checked the possibility of formation of other species like protonated, MH_iL ($i \geqslant 2$), or polynuclear M_2L but they do not appear to be formed under our conditions.

As the overall basicity of L^1 is not very high, when compared with that of dota or teta, the complexes of Cu^{2+} and trivalent metal ions (Ga^{3+}, Fe^{3+} and In^{3+}) were completely or almost completely formed even at low pH, and it was impossible to determine the values of stability constants by direct potentiometry. However, competition reactions, (1) and (2), with another ligand (edta, egta or OH^-) enabled the determination of the constants. The values of the protonation and stability constants of edta and egta were taken from the literature[12a] and are compiled in Table 2.

Spectroscopic studies

The UV/VIS/near-IR data for complexes of Co^{2+}, Ni^{2+}, Cu^{2+} and Fe^{3+} and EPR data for those of Cu^{2+} and Fe^{3+} with L^1, in water solution, are collected in Tables 3–5. The electronic spectrum of the cobalt complex exhibits a broad band at 484 nm ($\varepsilon = 267.9$ dm^3 mol^{-1} cm^{-1}) with shoulders at 493 and 591 nm, another at 342.5 nm ($\varepsilon = 362.8$ dm^3 mol^{-1} cm^{-1}) and three smaller bands at 1400, 1520 and 1670 nm ($\varepsilon = 10.0$, 9.0 and 18.0 dm^3 mol^{-1} cm^{-1}, respectively). The magnetic moment of the complex is 4.3 μ_B. This orange-pink complex is slow to form (4.5 h were needed to attain the maximum absorbance, at pH 5.8) but did not suffer any degradation with time. The violet solution of the nickel complex exhibits three main bands at 940, 570 and 355 nm ($\varepsilon = 19.4$, 18.1 and 86.1 dm^3 mol^{-1} cm^{-1}, respectively) and a shoulder at 810 nm ($\varepsilon = 18.1$ dm^3 mol^{-1} cm^{-1}). The copper complex is blue, exhibiting a broad band in the visible region at 630 nm with a shoulder at lower energy (at 780 nm), due to the d–d transitions, and an intense band in the ultraviolet region. The spectrum of the yellow iron complex shows two intense peaks at 276 and 328 nm, a small band at 534 nm with a shoulder at higher energy. The magnetic moment of this complex in aqueous solution is 3.4 μ_B, at 301 K.

The EPR spectra of the complexes of Cu^{2+} and Fe^{3+} are shown in Figs. 1 and 2. The spectrum of $[CuL^1]$ exhibits 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 spectrum. The computational simulation of the spectrum[18] leads to three different principal values of g, which indicates that the Cu^{2+} ion of this complex is in a rhombically distorted ligand field. The hyperfine coupling constants and g values are presented in Table 4. The EPR spectra of $[FeL^1]^+$ were recorded at several temperatures into the range 4.6–200 K. All the spectra exhibit two types of signals the intensity of which decreases with increasing temperature, in the same proportion for both signals. One of the signals is typical of a rhombic iron(III) complex in the low-spin state with signals at 2.683, 2.337 and 1.721, similar to those of iron(III) porphyrin complexes. The other signals can be ascribed to two high-spin iron(III) species. The concentration

Table 1 Protonation (log $K_i^{\mathbf{H}}$) constants of L^1–L^3, dota and teta and stability constants (log $K_{\mathbf{M}_m\mathrm{H}_h\mathrm{L}_l}$) of some of their metal complexes (25.0 °C, $I = 0.10$ mol dm^{-3})

Ion	Equilibrium quotient	L^1	L^2[a]	L^3[a]	dota	teta
H^+	[HL]/[H][L]	10.72(2)	9.74	9.92	12.09[b]	10.52[c]
	$[H_2L]/[HL][H]$	7.74(4)	8.67	8.56	9.76[b]	10.18[c]
	$[H_3L]/[H_2L][H]$	4.05(7)	4.67	4.66	4.56[b]	4.09[c]
	$[H_4L]/[H_3L][H]$	1.8(1)	<1	<1	4.09[b]	3.35[c]
	$[H_4L]/[L][H]^4$	24.31	<24	<24	30.50	28.14
Mg^{2+}	[ML]/[M][L]	5.30(7)	—	—	11.92[d]	1.97[e]
	[M(HL)]/[ML][H]	—	—	—	4.09[d]	—
	[ML]/[ML(OH)][H]	8.74(6)	—	—	—	—
Ca^{2+}	[ML]/[M][L]	3.74(2)	—	—	17.23[d]	8.32[e]
	[M(HL)]/[ML][H]	—	—	—	3.54[d]	—
Co^{2+}	[ML]/[M][L]	14.4(1)	—	—	20.27[b]	16.38[c]
	[M(HL)]/[ML][H]	4.1(1)	—	—	4.08[b]	4.04[c]
Ni^{2+}	[ML]/[M][L]	16.59(1)	—	16.27	20.03[d]	19.83[c]
	[M(HL)]/[ML][H]	2.94(2)	—	—	3.51[d]	4.14[c]
Cu^{2+}	[ML]/[M][L]	21.61(4)	20.23	19.76	22.25[b]	20.49[c]
	[M(HL)]/[ML][H]	2.28(4)	—	—	3.78[b]	3.77[c]
Zn^{2+}	[ML]/[M][L]	14.01(2)	11.91	12.82	21.099[b]	16.40[c]
	[M(HL)]/[ML][H]	4.05(2)	—	—	4.178[b]	4.10[c]
	[ML]/[ML(OH)][H]	7.66(6)	8.06	8.48	—	—
Cd^{2+}	[ML]/[M][L]	14.56(3)	8.77	9.76	21.31[b]	18.02[c]
	[M(HL)]/[ML][H]	3.84(6)	—	—	4.39[b]	4.04[c]
Pb^{2+}	[ML]/[M][L]	10.89(2)	9.03	9.72	22.69[b]	14.32[c]
	[M(HL)]/[ML][H]	4.96(6)	—	—	3.86[b]	4.75[c]
	[ML]/[ML(OH)][H]	9.9(2)	—	10.95	—	—
Ga^{3+}	[ML]/[M][L]	18.02(5)	—	—	21.33[f]	19.91[f]
	[M(HL)]/[ML][H]	3.09(9)	—	—	4.00[f]	3.66[f]
	[ML]/[ML(OH)][H]	3.75(5)	—	—	—	—
Fe^{3+}	[ML]/[M][L]	20.64(6)	—	—	29.4[f]	27.46[f]
	[M(HL)]/[ML][H]	2.84(7)	—	—	3.23[f]	2.64[f]
	[ML]/[ML(OH)][H]	(5.9)[g]	—	—	—	—
In^{3+}	[ML]/[M][L]	18.94(2)	—	—	23.9[f]	23.00[f]
	[M(HL)]/[ML][H]	2.38(5)	—	—	3.44[f]	3.33[f]

[a] $I = 0.10$ mol dm^{-3} KNO_3.[8] [b] $I = 0.10$ mol dm^{-3} NMe_4NO_3.[2b] [c] $I = 0.10$ mol dm^{-3} KNO_3.[2b] [d] $I = 0.10$ mol dm^{-3} NMe_4NO_3.[2a] [e] $I = 0.10$ mol dm^{-3} KNO_3.[2a] [f] $I = 0.10$ mol dm^{-3} KCl.[20] [g] Approximate value only as precipitation occurs.

Table 2 Protonation (log $K_i^{\mathbf{H}}$) constants of edta and egta and their stability constants (log $K_{\mathbf{M}_m\mathbf{H}_h\mathbf{L}_l}$) with metal ions used in competition reactions[12a] (25 °C, $I = 0.10$ mol dm^{-3})

Ion	Equilibrium quotient	edta	egta
H^+	[HL]/[H][L]	10.19	9.40
	$[H_2L]/[HL][H]$	6.13	8.78
	$[H_3L]/[H_2L][H]$	2.69	2.66
	$[H_4L]/[H_3L][H]$	2.00	2.0
Cu^{2+}	[ML]/[M][L]	18.78	—
	[M(HL)]/[ML][H]	3.1	—
	[ML]/[ML(OH)][H]	11.4	—
Fe^{3+}	[ML]/[M][L]	—	20.5
In^{3+}	[ML]/[M][L]	24.9	—
	[M(HL)]/[ML][H]	1.5	—
	[ML]/[ML(OH)][H]	8.49	—

Table 3 Spectroscopic UV/VIS/near IR data for the complexes of Co^{2+}, Ni^{2+}, Cu^{2+} and Fe^{3+} with L^1

Complex	pH, colour	λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1})
$[CoL^1]$	5.8, orange-pink	1670 (18), 1520 (9), 1400 (10), 591 (sh), (9), 493 (sh) (37), 484 (267.9), 342.5 (362.8)
$[NiL^1]$	6.4, violet	940 (19.4), 810 (sh) (18.1), 570 (18.1), 355 (86.1)
$[CuL^1]$	3.95, blue	780 (sh), (25.1), 630 (97.1), 265 (2238)
$[FeL^1]^+$	2.77, yellow	534 (55.4), 458 (sh), (92.4), 328 (1305.4), 276 (1822.7)

of the low-spin species was evaluated at 9.0, 149.0 and 200.0 K and 35 ± 5% was obtained for the three temperatures.

The low-spin signal is typical of d^5 systems in distorted-octahedral environments.[27–29] In general, in this configuration the g values vary widely and are sensitive to small changes in structure. They can be related to the parameters which describe the electronic ground state of the complex by coefficients A, B and C which are related to the axial distortion, μ, the rhombic distortion parameter, R, the energy of the Kramers doublet, E_1, and the spin–orbit coupling constant, λ (see equations in Table 5). The experimental spectra give only the magnitude of the g values, the problem being to assign the values obtained to g_x, g_y and g_z and to determine the sign of each. Substitution of the three g values (having positive or negative sign) into the equations for A, B and C gives 48 combinations, but only six satisfy the normalization condition $A^2 + B^2 + C^2 = 1$. From these six combinations only one satisfies the conditions that $|\mu/\lambda|$ is a maximum and R/λ is positive. The values calculated for our complex together with those of other similar iron(III) complexes from the literature are compiled in Table 5.

The signal of lower field is typical of a high-spin d^5 state of Fe^{3+}. Using the spin-Hamiltonian formalism for high-spin iron(III),[30] the low-field resonances can be assigned to two species, with different rhombic (E/D) distortions: species **I**, with $E/D \approx 0.275$, and **II** with $E/D \approx 0.15$. The effective g values expected for each Kramers doublet are indicated in Table 6 (those observed in the spectra, Fig. 2, are underlined). Since the overall lineshape does not change over the entire temperature range studied, it is not possible to determine the zero-field splitting accurately; the fact that for both species, even at 4.6 K, resonances from the $|\pm 3/2\rangle$ and $|\pm 1/2\rangle$ doublets are observed suggests a very small value for D.

The presence of the two types of signals in the EPR spectra can be interpreted by an equilibrium of two spin states for the iron(III) complex or by the presence of different isomers. To understand this we have studied the temperature-dependent static magnetic susceptibility behaviour over the range 3.1–291.7 K, in the solid state. Plots of the magnetic susceptibility and magnetic moment as a function of temperatures are given in Fig. 3. The magnetic moment is 3.58 μ_B at 292 K and below *ca.* 100 K decreases gradually to 1.70 μ_B at 3.1 K.

Table 4 Spectroscopic EPR data for the copper(II) complex of L^1 and similar complexes

Complex	λ/nm (ε/dm^3 mol^{-1} cm^{-1})	EPR g_1	g_2	g_3	10^4A_1/cm^{-1}	10^4A_2/cm^{-1}	10^4A_3/cm^{-1}	Geometry	$\frac{g_\parallel - 2}{g_\perp - 2}$	Ref.
[CuL^1]	630 (97.1)	2.027	2.084	2.221	14.9	21.3	165.4		3.98	This work
[CuL^3]$^{2+a}$	560 (187)	2.034	2.060	2.188	0.5	3.4	192.9	*SP*	4	8
[CuL^9]$^{2+}$	695 (161)	2.033	2.084	2.210	26.6	38.9	161.0	*SPY*	3.59	8
[CuL^{10}]	599 (250)	2.057		2.198	24.1		184.2	*SPY*	3.47	21
[CuL^{11}]	513 (100)	2.049		2.186	38.7		205.0	*SP*	3.79	24
[CuL^{12}]$^{2+}$	622 (147)	2.050	2.059	2.224	10.9	20.5	183.1	*SPY*^{c}	4.11	22
[CuL^{13}]$^{2+}$	626.4 (160)	2.027	2.082	2.216	26.9	15.1	160.2	*SPY*	3.96	22
[CuL^{14}]$^{2+}$	690.6 (161)	2.037	2.077	2.226	23.8	21.6	162.8	*SPY*^{d}	3.96	22
[Cu(dota)]$^{2-}$	734 (100)	2.062		2.300	—	—	150.3	*OC*	4.84	23
[Cu(trita)]$^{2-}$	719 (370)	2.047		2.202	—	—	190.6	—	4.29	23
[Cu(teta)]$^{2-}$	646 (70)	2.050		2.249	—	—	168.0	*OC*	4.98	23

[a] This work. The values published[8] were redetermined, because the EPR spectrum then obtained exhibited evidence of aggregation. A spectrum considerably better resolved was obtained when the solution was diluted 1 : 1 with 1 mol dm^{-3} NaClO$_4$. [b] *SP* = square planar, *SPY* = square pyramid, *OC* = octahedron. [c] The equatorial plane is formed by the four nitrogen atoms of the ring. [d] The equatorial plane with a degree of tetrahedral distortion. L^9 = 3,6,9,15-Tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene; L^{10} = 1,4,7,10-tetraazacyclododecane(cyclen); L^{11} = 1,4,8,11-tetraazacyclotetradecane(cyclam); L^{12} = 1-oxa-4,8,12-triazacyclotetradecane; L^{13} = 1-oxa-4,8,11-triazacyclotridecane; L^{14} = 1-oxa-4,7,10-triazacyclododecane.

Table 5 Spectroscopic EPR data for the iron(III) complex of L^1 and similar complexes

Complex	g_z	g_y	g_x	μ/λ	*R*/λ	E_1/λ	*R*/μ	Ref.
[FeL^1]$^{+a}$	1.721	2.337	2.683	−3.735	1.925	−2.647	−0.515	This work
[FeL^{15}]$^{2+b}$	1.910	2.237	2.511	−6.103	3.957	−4.166	−0.648	26
[FeL^{11}]$^{3+}$	−1.15	2.23	−3.26	2.595	1.266	−1.789	(0.019)^c 0.488^d	26
[FeL^{16}]$^{3+e}$	1.631	2.463	2.841	−3.033	1.379	−2.214	−0.455	25

$A = (g_x + g_y - 2g_z)/4(g_x + g_y - g_z)^{\frac{1}{2}}$; $B = (g_x + g_y)/2[2(g_x + g_y - g_z)]^{\frac{1}{2}}$; $C = (g_y - g_x)/4(g_x + g_y - g_z)^{\frac{1}{2}}$; $\mu/\lambda = \{-A^2 + B^2 + C^2 + 2^{-\frac{1}{2}}[AB + (BC^2/A)]\}/2^{\frac{1}{2}}[-AB + (BC^2/A)]$; $R/\lambda = (2AC + 2^{\frac{1}{2}}BC)/(C^2 - A^2)$; $E_1/\lambda = (2\mu/3\lambda) - (A/2^{\frac{1}{2}}B)$. [a] Spectrum obtained at 12.4 K, main signal. [b] HL^{15} = 1,4,8,11-Tetraazacyclotetradecane-1-acetic acid. [c] Value presented by Szulbinski and Busch.[26] [d] Our calculation for the experimental values given in ref. 26. [e] L^{16} = 6,13-Dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine.

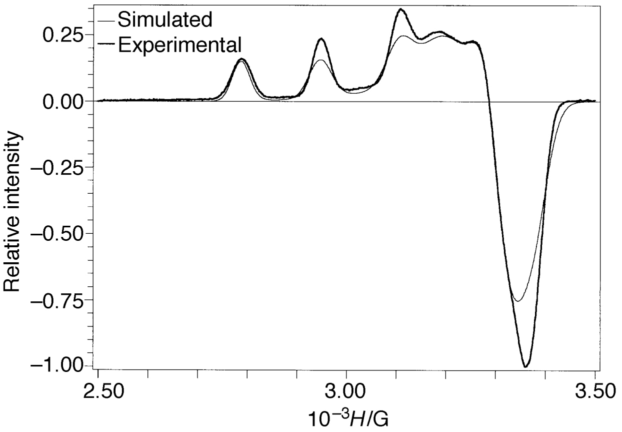

Fig. 1 The X-band EPR spectrum of the copper complex of L^1 in 1.0 mol dm^{-3} NaClO$_4$ recorded at 86 K, ν = 9.41 GHz, microwave power 2.4 mW and modulation amplitude 1 mT, and its simulation

Discussion

The macrocycle L^1 has six basic centres, nevertheless only four protonation constants were obtained; the last two are very low to be determined by potentiometric measurements. All the compounds listed in Table 1 have two high (or fairly high) and two low values of the protonation constants. Taking into account the sequence of protonation of L^2 and L^3 (ref. 8) and other similar *N*-carboxymethyl derivatives of tetraaza macrocycles[31,32] studied by ^{1}H NMR spectroscopy, the interpretation of the values of the protonation constants of L^1 based on the following sequence is straightforward: the first two protons added to the basic form of the macrocycle are spread over all the nitrogen atoms, 50% of them remaining non-protonated; the third protonation will occur at carboxylate groups linked to non-protonated nitrogen atoms (the value is similar to that found for teta, lower than that corresponding to protonation of a third nitrogen of the ring of the parent amine); the very low value of the fourth constant is typical of protonation of a carboxylate group linked to a protonated nitrogen atom[31] and is certainly what occurs in this case. The last two nitrogen atoms of the ring will be only partially protonated at very low pH values. The second and the fourth protonation constants of L^1 are lower than those of dota and teta due to the presence of the pyridine ring and the existence of only two carboxylate groups, which contribute strongly to a lower overall basicity of L^1 compared to that of teta or dota (a decrease of about 4 and 6 log units, respectively), a situation which will have important repercussions in metal complex formation.

Consideration of the stability constants in Table 1 and their variations in Fig. 4 allows some interesting conclusions. (1) Compound L^1 is very selective, exhibiting a very high stability constant for Cu^{2+}, while for the remaining complexes of the first-row transition divalent metal ions the stability decreases sharply, Zn^{2+} and Ni^{2+} having ML constants which are 7.6 and 5.02 log units lower than that of Cu^{2+}. The alkaline-earth-metal ion complexes present very surprising aspects, namely the very low value of the stability constant of the calcium complex, and the value for Mg^{2+} being higher than that of Ca^{2+}. Fig. 4 shows that the trend of stability constants for the various complexes of L^1 with the first-row transition divalent metal ions and also of Cd^{2+} and Pb^{2+} is similar to that of other *N*-acetate derivatives of 14-membered macrocycles, such as teta[2a,b] or H_2L^{18} (1-oxa-4,8,12-triazacyclotetradecane-4,12-diacetic acid),[3] all of them presenting pronounced differences in stability on progressing along the series of metal ions. This behaviour is in complete contrast with that of the 12-membered complexes, such as those of 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid),[11] dota,[2a,b] or H_2L^{18} (1-oxa-4,7,10-triazacyclododecane-4,10-diacetic acid),[4] which are unable to differ-

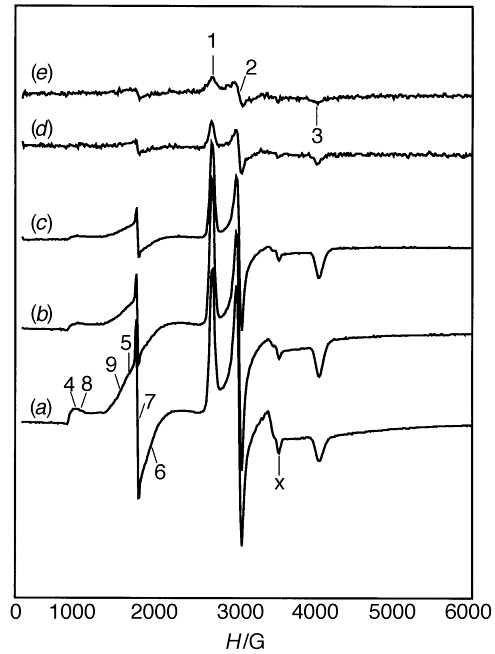

Fig. 2 The X-band EPR spectra of the iron complex of L^1 in 1.0 mol dm^{-3} NaClO$_4$ at different temperatures: (*a*) (4.6), (*b*) (12.0) and (*c*) (25.0 K) were recorded at ν = 9.64 GHz, (*d*) (121.9) and (*e*) (200.0 K) at ν = 9.61 GHz and are expanded four times. Microwave power 2.4 mW, modulation amplitude 1 mT. Resonances: 1–3 $S = \frac{1}{2}$ species; 4–7, one high-spin species ($E/D \approx 0.275$); and 8 and 9, another high-spin species ($E/D \approx 0.15$); x is an impurity of the instrument cavity. *g* values: for low-spin species, 2.683(1), 2.337(2) and 1.721(3); for both high-spin species; 9.50(4), 4.61(5), 3.93(6), 4.20(7), 8.68(8) and 5.39(9)

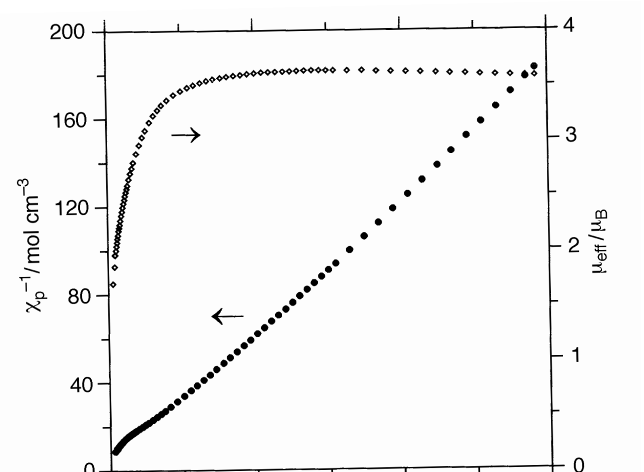

Fig. 3 Reciprocal of the paramagnetic susceptibility, $1/\chi_p$ (●) and magnetic moment, μ_{eff} (◇), of $[Fe(L^1)Br]\cdot 4H_2O$ in the temperature range 3–292 K

entiate between metal ions, exhibiting almost the same value of the stability constant for the entire series, although higher than those of the corresponding 14-membered complexes. In spite of the intermediate values of stability constants exhibited by L^1, between those of teta and L^{17} (*cf.* Fig. 4), apart from the copper complex which shows exceptional high stability, L^1 is the most selective of those macrocycles shown in Table 1 and in Fig. 4, even of all *N*-carboxymethyl macrocyclic compounds studied up to now.[33] (2) In general, complexes formed by L^1 have lower stability constants than those of the corresponding teta complexes, this being expected as teta has two more acetate groups for co-ordination. Nevertheless, it was shown that all donor atoms of teta are involved in co-ordination, but to alkaline-earth or lanthanide ions, *i.e.* in complexes which have mainly electrostatic interactions, and in these cases the macrocycle is in a very strained conformation.[2a,b,34] However, teta complexes of the first-row transition-metal ions have stabilities lower than expected, a fact only explained if some of the donor atoms do not co-ordinate, for structural reasons.[2a,b] Spectroscopic data in solution and X-ray diffraction analysis of crystals have shown that the ML complexes (M = Cu^{2+} or Ni^{2+}) have two free acetate groups linked to opposite nitrogen atoms,[35] and these groups may be involved in the formation of bi- or poly-nuclear species,[36] making teta less interesting for applications involving the first-row transition metals. Compound L^1, however, has only the exact number of donor atoms to form octahedral complexes, the polynuclear species being less probable, as confirmed by the present thermodynamic studies. The lower stability of L^1 complexes compared with those of teta is mainly due to the lower overall basicity of L^1 (a difference of 3.83 log units[2a,b]) and, in general, the stabilities of corresponding complexes of both macrocycles differ by the same amount. Exceptions to this statement would only be explained by a special structural arrangement of the ligand on complexation: the complexes of Mg^{2+} and Cu^{2+}, with L^1 are more stable than those of teta (3.33

Table 6 Rhombic distortions (*E*/*D*) and effective *g* values expected from the high-spin species of the iron(II) complexes of L^1. (The values observed in the experimental spectra are underlined)

E/*D*	Doublet	g_1	g_2	g_3
0.15	|±5/2⟩	9.95	0.14	0.16
	|±3/2⟩	5.39	2.82	3.13
	|±1/2⟩	1.44	8.68	2.71
0.275	|±5/2⟩	9.79	0.43	0.57
	|±3/2⟩	4.61	3.93	4.2
	|±1/2⟩	0.82	9.50	1.24

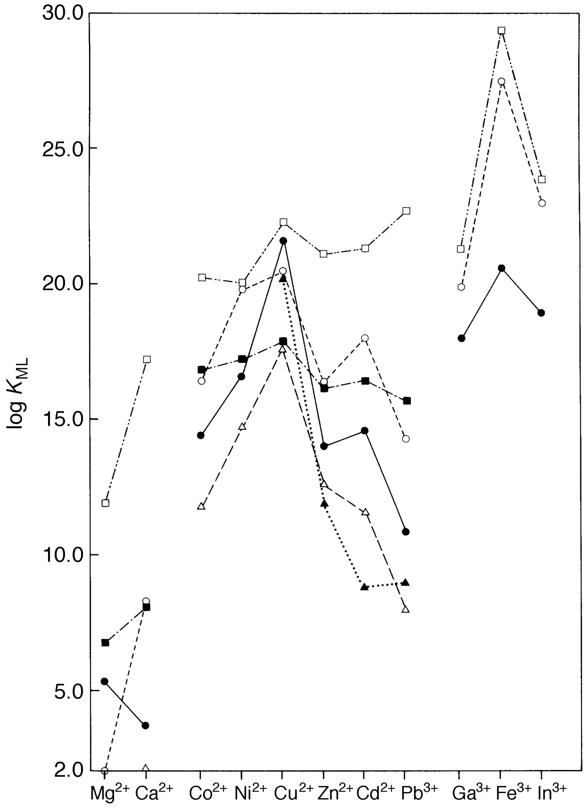

Fig. 4 Variation of the stability constants (log K_{ML}) of the metal complexes of L^1 (●), L^2 (▲),[8] dota (□),[2b,20] teta (○),[2b,20] L^{17} (△)[4] and L^{18} (■)[3] with the atomic number of the metal ion

Table 7 The pCu[a] values for copper(II) complexes of L^1, trien and L^{19}, at pH 7.4

Ligand	pCu
L^1	17.79
trien[b]	15.97
L^{19}[c]	18.54

[a] Values calculated for 100% excess of free ligand under physiological conditions, pH 7.4; $c_{Cu} = 1.0 \times 10^{-5}$ mol dm^{-3}, $c_L = 2.0 \times 10^{-5}$ mol dm^{-3}. [b] log $K_1 = 9.74$, log $K_2 = 9.07$, log $K_3 = 6.59$, log $K_4 = 3.27$, log $K_{CuL} = 20.05$, log $K_{M(HL)} = 3.7$, log $K_{ML(OH)} = 10.7$.[12a] [c] log $K_1 = 10.08$, log $K_2 = 9.26$, log $K_3 = 6.88$, log $K_4 = 5.45$, log $K_{CuL} = 23.2$.[12a]

and 1.12 log units, in inverse position of the overall basicity)[2a,b] and the opposite happens with Ca^{2+}, In^{3+} and especially Fe^{3+}, the complexes of which are destabilized by L^1 when compared with teta (by 4.58, 4.06 and 6.82 log units, respectively).[2a,20] (3) When the stabilities of the metal complexes of L^1 are compared with those of the parent (L^2 or L^3)[8] the values for L^1 are always higher, which is an indication of the co-ordination of at least one acetate group. Also, the cobalt(II) complexes of the parent amines are not stable.[8] (4) The low stabilities of the complexes of trivalent metal ions with L^1 (Ga^{3+}, Fe^{3+} and In^{3+}) are very intriguing. The value for the iron complex is even lower than that of the copper complex, which is very unusual for a polyaminopolycarboxylic ligand.

The extraordinary selectivity for the copper complex renders L^1 an interesting ligand for medical applications, in nuclear medicine using ^{64}Cu (a β^+ emitter of potential use in positron emission tomography),[37] in radioimmunotherapy using ^{67}Cu[38] or for the treatment of copper intoxication in cases of metal poisoning in patients suffering from Wilson's disease.[39] The problem here involves removing the Cu^{2+} without perturbation of the other essential ions present in biological systems, namely Ca^{2+}, Zn^{2+} or Fe^{3+}. The compounds trien (triethylenetetramine) 3,7-diazanonane-1,9-diamine (L^{19}) are the most used ligands in chelation therapy, the last forming a very stable complex with Cu^{2+} (23.2 in log units[12a]). The complex [CuL^1] has a lower stability constant than that of the nonanediamine, however L^1 has a lower overall basicity than that of linear tetraamines, and at physiological pH the competition between protons and Cu^{2+} is less important for L^1 as can be observed from the values of pM determined at pH 7.4 (*cf.* Table 7);[40] also, the linear tetraamines form charged complexes, while [CuL^1] is neutral and therefore most suited for diffusion into tissues.[39] So, L^1 seems to be a useful ligand for this medical application, better than L^{19}, if no important toxic aspects occur.

Structural data

Some of the specificities of L^1 upon complexation may be found in the configuration that the macrocycle seems to show a tendency to adopt when one or more substituents are linked to the nitrogen atoms. Some derivatives of L^2 frequently exhibit a five-co-ordinated arrangement around the metal ion, the macrocycle being folded in such a way that the nitrogen atom opposed to the pyridine binds at an axial position, the basal plane being formed by the three other nitrogen atoms of the ring and another ligand or by a donor atom of one of the substituents at N (in a *trans* position to the pyridine N atom), in a square-pyramidal arrangement for the metal ion. Folding the macrocycle leads to a larger cavity and subsequently to longer M−N bond lengths and probably also to less stable complexes. Examples are: $[Ni(L^4)X][ClO_4]_n$ ($n = 1$, X = Cl; $n = 2$, X = Me_2SO);[41] $[Ni(L^4)X]^{2+}$ (X = H_2O or N_3);[42] $[IrL^2(Cl)H]PF_6$, in which the Ir^{3+} is octahedrally co-ordinated to all four nitrogen donors of L^2, three of them equatorially and the fourth bent away to an axial position, with the chloride and hydride ligands bound *cis* to each other;[43] $[Ni(L^5)Cl]ClO_4{\cdot}H_2O$;[44] $[Co(L^6)Cl][ClO_4]$;[45] $[Ni(L^8)(en)][ClO_4]_2$ (en = ethane-1,2-diamine);[46] $[RuL^7(Cl)(CO)][BPh_4]$, shows octahedral Ru^{2+} co-ordinated to three nitrogen donors of the macrocycle bound equatorially, the fourth N being bent away to bind at an axial position, with the carbonyl and Cl completing the co-ordination.[47] Molecular mechanics theoretical studies also show this tendency of the macrocycle L^4 to fold, the nitrogen donor of the macrocycle opposed to the pyridine being in apical position.[48]

We could not obtain crystals of the complexes with appropriate size for X-ray diffraction analysis, but some spectroscopic studies in solution were undertaken which also show that L^1 seems to adopt the conformation described above, at least in the complexes of Co^{2+} and Fe^{3+}. The electronic spectrum of the cobalt complex, exhibiting near-infrared and visible absorption, together with a low value of the magnetic moment, indicates a five-co-ordinate symmetry of a high-spin species.[49,50] It is difficult to distinguish between spectra of high-spin square-pyramidal or trigonal-bipyramidal complexes, but in general the former have lower intensities (often <100 dm^3 mol^{-1} cm^{-1}).[51–53] The intense band at 342.5 nm is probably a charge-transfer band.

The electronic spectrum of the nickel complex is characteristic of a tetragonal (D_{4h}) symmetry. Following the conclusions of Busch and co-workers[54] on some tetraazamacrocycles we tentatively assigned the bands of our spectrum ($^3B_{1g} \longrightarrow {}^3E_g{}^a$, 940; $^3B_{1g} \longrightarrow {}^3B_{2g}$, 810; $^3B_{1g} \longrightarrow {}^3E_g{}^b$, 570; and $^3B_{1g} \longrightarrow {}^3E_g{}^c$, 355 nm) and values of Dq^{xy} and Dq^z were calculated: 1235 and 893 cm^{-1}; Dq^z is strongly influenced by the in-plane ligand field, decreasing as Dq^{xy} increases. The complex [NiL^1] has spectral parameters similar to those of the teta complex, $Dq^{xy} = 1220$ and $Dq^z = 740$ cm^{-1}, or to those of $[Ni([15]aneN_4)(NCS)_2]$, $Dq^{xy} = 1202$ and $Dq^z = 908$ cm^{-1} ($[15]aneN_4$ = 1,4,8,12-tetraazacyclopentadecane).[54] There is no published structure for the nickel complex of teta but only one for copper, $Ba[Cu(teta)]{\cdot}6H_2O$.[35] The geometry of the latter is a distorted octahedron with four amino nitrogens in a plane and two apical acetate oxygen donors. This geometry seems also be adopted by the nickel complex according to spectroscopic measurements.[36] The low value obtained for Dq^z is also an indication of this. Complexes of 14-membered tetraazamacrocycles (examples can be seen in ref. 54) have stronger equatorial fields. Two hypotheses can be advanced to explain our values: if the equatorial plane is formed by the four nitrogen atoms of the ring, the size of the cavity so formed should not be appropriate for Ni^{2+} and the macrocycle should fold for the co-ordination as happens with the $[15]aneN_4$ complex, or the structure adopted by the complex is such that it has a N_3O set of donor atoms in the equatorial plane (three nitrogen atoms of the macrocycle and one oxygen from a carboxylate), the last nitrogen atom of the ring and the last carboxylate oxygen being in axial positions. The first hypothesis is less probable as L^8 with the same set of donor atoms, exactly in the same position, behaves similarly to other 14-membered ligands.[54] The second hypothesis is supported by the mentioned theoretical molecular mechanics study[48] and the crystal structures.[41–47] This hypothesis also explains the high value of Dq^z, impossible to understand if the two carboxylate oxygens were in axial positions.

It is well known that electronic spectra of copper(II) complexes are not especially good indicators of geometry.[55] However, some comparisons are possible with similar complexes, such as those compiled in Table 4. The EPR spectrum of [CuL^1] shows $g_3 > (g_1 + g_2)/2$, which is typical of rhombic symmetry for the copper(II) ion where the distortion takes the form of elongation of the axial bonds, and where a $d_{x^2-y^2}$ ground state is present, and would be consistent with elongated rhombic-octahedral, rhombic square-coplanar or distorted square-based-pyramidal stereochemistries. It appears that it is possible to exclude a trigonal-bipyramidal geometry or a tetragonal structure involving compression of axial bonds.[21,55]

The electronic properties of the copper(II) complexes can be explained by the usual factors taken from the equations of the EPR parameters derived from ligand-field theory.[56–58] The addition of a fifth ligand to a square-planar arrangement has the effect of decreasing A_z while increasing g_z with a simultaneous red shift in the electronic spectra.[59,60] Comparing the data of Table 4 for the copper complex of the parent L^3 with those of L^1 we can see that there is an increase of g_z, a decrease of A_z and a red shift of the electronic spectra. As the structure of the copper parent complex was considered square planar, it is possible to infer that the structure of $[CuL^1]$ will be square pyramidal or even tetragonal. The ratio $(g_\parallel - 2):(g_\perp - 2)$ is nearly equal to 4:1, which is characteristic for the Cu^{2+} ion in a square-based pyramidal co-ordination.[61,62] Also, the electronic data for $[CuL^1]$ are very similar to those obtained for other complexes considered square pyramidal such as those of L^{14} or L^{13}.[22] Both have a geometry around the copper which can be described as a distorted square pyramid, the first one with an equatorial plane formed by three nitrogen atoms of the ring and a halogen atom, the oxygen of the macrocycle being in the apical position, while in the second the four nitrogen atoms of the macrocycle form the basal plane and the halogen atom completes the co-ordination in the apical position. The spectral data for our complex are also very similar to those of the $[Cu(teta)]^{2-}$ complex,[23] which is a distorted octahedron, as already mentioned.

The crystal structure of the copper complex of the diprotonated form of L^1 was obtained in very acidic media.[1] In this complex, $[Cu(H_2L^1)Cl]Cl$, the copper(II) has a distorted trigonal-bipyramidal geometry, with apical co-ordination to Cl^- and the pyridine nitrogen of the ring, and equatorial co-ordination to the other three nitrogen atoms of the macrocycle and only one of the two acetate groups, the MeN group and one of the two acetate arms of the ligand being protonated and unco-ordinated. However, the complex of the completely deprotonated species, for which there is no crystal structure, is thermodynamically very stable as verified in the present work, the stability constant being of the same order of magnitude as that of the dota complex. It could be predicted for the former complex that all the donor atoms will be involved in co-ordination forming a tetragonal complex or, as the spectroscopic data seem to indicate, a five-co-ordinated complex probably with an acetate arm not involved in the co-ordination (non-co-ordination of a nitrogen of the ring would lead to a less stable complex). Note that the copper ion in a five-co-ordinated geometry (square pyramidal or trigonal bipyramidal) is also stabilized by crystal-field stabilization energy.[53]

The complex of L^1 with Fe^{3+} has a surprisingly low stability constant, as do the other trivalent metal-ion complexes in this work. The electronic spectrum, as expected for a d^5 configuration, gives no information because the tail of the intense charge-transfer absorptions overlaps the weak forbidden bands of the visible region producing the yellow colour. The band at 328 nm is assigned to a metal-to-ligand charge-transfer transition because of the relatively high absorption coefficient. The EPR spectra of this complex in the range of temperature studied show two types of signals, one for a typical low-spin system in a rhombic field, and a high-spin species ($S = \frac{5}{2}$). The low-spin species has a large rhombic distortion $|R/\mu| = 0.515$ (the maximum rhombicity value is equal to 0.667),[28a] although a value which is intermediate between that of the 1,4,8,11-tetraazacyclotetradecane (cyclam, L^{11}) complex and that of the cyclam derivative with only one acetate arm, L^{15} (ref. 26), *cf.* Table 5.

The magnetic moment at room-temperature measured in solution by the Evans method is 3.40 μ_B. This agrees quite well with the value obtained at room temperature from static magnetic susceptibility measurements, μ_{eff} (292 K) = 3.58 μ_B. Two hypotheses can be advanced for the interpretation of this value: it may be due to three unpaired electrons with no orbital contribution ($S = \frac{3}{2}$ spin state) or it results from a weighted average of isomers with different spin states ($S = \frac{5}{2}$ and $\frac{1}{2}$). In the latter hypothesis the magnetic susceptibility could be described as the sum of the contributions of the low-spin (ls) and high-spin (hs) species, $\chi = x\chi_{ls} + (1 - x)\chi_{hs}$ where x is the mole fraction of the low-spin isomer. The calculation using the above equation yields values in very large excess of those found by the EPR experiment in solution (for instance, ≈98% by calculation against 35% from the EPR experiment at 9 K). The first hypothesis implies that in the solid state the ligand geometry around the Fe^{III} is slightly different from that in solution, giving rise to an energy splitting that allows the $S = \frac{3}{2}$ spin configuration. The decrease in the magnetic susceptibility with temperature may then be due to a spin transition or to antiferromagnetic interactions. Several examples are known of Fe^{III} in the $S = \frac{3}{2}$ spin state, mainly five-co-ordinated in a distorted square-pyramidal geometry, which exhibit a $S = \frac{3}{2} \longleftrightarrow S = \frac{1}{2}$ spin crossover, such as [FeL(NO)], with L = *N*,*N*′-bis(salicylidene)ethane-1,2-diaminate,[63,64] 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane,[65] or *N*,*N*′-bis(salicylidene)-*o*-phenylenediaminate.[66] The comparison with $[Fe(L^1)Br]\cdot 4H_2O$ reveals some common features but also some differences. As with $[Fe(L^1)Br]\cdot 4H_2O$, at least at room temperature, all the complexes mentioned above have five-co-ordinated iron and the ligand is somewhat bent. These complexes show an intermediate spin ⟷ low spin equilibrium over a narrow range of temperature. It is known, however, that spin transitions may extend over a wide range of temperature or even be incomplete.[67] It is also worth mentioning that theoretical studies, although performed for the high spin ⟷ intermediate spin transitions of trigonal five-co-ordinated iron(III) species, show that the temperature dependence of the magnetic moment from the state of higher spin (at high temperature) to the lower (at low temperature) extends over a wide range.[68] The temperature profile of μ_{eff} for $[Fe(L^1)Br]\cdot 4H_2O$ resembles those found in these theoretical studies.

To clarify whether the magnetic behaviour at low temperature results from a spin crossover or is due to the onset of antiferromagnetic interactions, requires further studies, particularly Mössbauer experiments.

Conclusions

In spite of forming less stable complexes than those of similar tetraazamacrocyclic ligands without pyridine in the ring, such as dota or teta, L^1 is more selective for divalent metal ions, its complexes of trivalent metal ions, such as Ga^{3+}, Fe^{3+} or In^{3+}, being comparatively less stable. The copper(II) complex is very stable rendering L^1 an interesting ligand for medical applications, in nuclear medicine or for the treatment of patients suffering from Wilson's disease. Besides the high selectivity for Cu^{2+} which some linear tetraamines also have, L^1 exhibits a relatively low overall basicity and forms a neutral complex, which makes it the best candidate for these medical applications, if no toxic effects are found. The special selectivity of L^1 in complex formation is probably due to its tendency to exhibit a folded conformation, the metal ion being in a five-co-ordinated environment.

The observation of a low-spin iron(III) complex with g values such as those found in this work is of particular relevance to the interpretation of EPR spectra of iron(III) porphyrins, in biological systems.[69–71] So far, only a limited number of haem iron axial co-ordinations has been unambiguously found [histidine (N), methionine (S), cysteine (S^-) and amine (N)]; species with g_{max} values of ≈2.6 have been generally assigned to hydroxyl-bound species.[69] The assignment of haem iron co-ordination solely on the basis of EPR g values has recently become less and less reliable, in part due to the lack of suitable model compounds.[70,71] The present study shows that carboxylate ligands can yield the same kind of EPR spectra, opening a large range of new possible assignments of haem iron axial co-ordination.

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