Synthesis and Complexation Properties of a New Tetraazatricarboxylate Ligand

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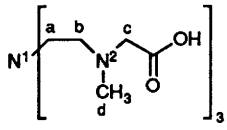
A non-cyclic tetraazatricarboxylate ligand, tris(4-carboxy-3-methyl-3-azabutyl)amine (H_3L), derived from tris(2-aminoethyl)amine, was synthesised and purified. Its macroscopic and microscopic protonation behaviour was studied using potentiometry and proton NMR titrations, respectively. Stability constants for its complexes with Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Gd^{3+} were obtained potentiometrically and compared with those of related ligands. The structure, protonation and dynamics of the complexes of H_3L with Zn^{2+} and La^{3+} were investigated by proton NMR spectroscopy as a function of pH and the results were in accord with the potentiometric data for the complexes of Zn^{2+} and Gd^{3+}. A nuclear magnetic relaxation dispersion study compared the water-proton relaxation parameters of [GdL] and $[Gd(dtpa)]^{2-}$ (H_5dtpa = *N,N,N′,N″,N″*-diethylenetriaminepentaacetic acid), concluding that their water co-ordination numbers are the same but the former complex has a shorter electron-spin relaxation time.

Comparison of the complexation properties of similar non-cyclic and macrocyclic polyaza polycarboxylate ligands is of interest because the structural, equilibrium and kinetic characteristics of their metal-ion complexes differ considerably in the two families of compounds. Some of these ligands are also of practical importance, since their gadolinium(III) and manganese(II) complexes may be used as contrast agents for magnetic resonance imaging, *e.g.* $[Gd(dtpa)]^{2-}$ (H_5dtpa = *N,N,N′,N″,N″*-diethylenetriaminepentaacetic acid) and $[Gd(dota)]^{-}$ (H_4dota = 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid).[1–3] Several triazatricarboxylate and tetraazatetracarboxylate macrocyclic ligands have been prepared and their metal-ion complexes investigated, including 1,4,7-triazacyclononane-*N,N′,N″*-triacetic acid (H_3nota) and H_4dota.[4–20] We have recently prepared a non-cyclic tetraaza tricarboxylate ligand, tris(4-carboxy-3-methyl-3-azabutyl)-amine (H_3L), which should form neutral complexes with the trivalent lanthanide cations (similar to the macrocyclic ligand nota) yet be flexible enough to form metal–ligand complexes rapidly in aqueous solution (similar to the linear polyamine, dtpa). In this work we describe the synthesis of H_3L, examine its acid–base and metal-ion chelating behaviour using potentiometry and NMR spectroscopy, and compare its overall chelating properties with those of nota and dtpa. The magnetic field dependence of the water solvent proton relaxivity (nuclear magnetic relaxation dispersion, NMRD) of the H_3L complexes of Gd^{3+} was also measured and compared with that of $[Gd(dtpa)]^{2-}$.

Experimental

Materials.—The following chemicals were purchased and used without further purification: tris(2-aminoethyl)amine (tren), tosyl chloride, dimethyl sulfate, ethyldiisopropylamine, methyl bromoacetate, anhydrous potassium carbonate, anhydrous sodium sulfate, ethylenediaminetetraacetic acid (H_4edta), potassium chloride, the chloride salts of nickel(II), copper(II), zinc(II), cadimum(II) and gadolinium(III), deuterium oxide, deuterium chloride and potassium deuteroxide (Aldrich),



Dowex 1 × 8–200 anion-exchange resin (hydroxide form, 100–200 mesh) (Sigma), sodium hydroxide and absolute ethanol (J. T. Baker) and hydrochloric acid, diethyl ether, acetonitrile and chloroform (Fischer Scientific). Elemental analysis were carried out by Oneida Research Services (Whitesboro, NY).

Syntheses.—*Tris(2-tosylaminoethyl)amine.* Tris(2-aminoethyl)amine (tren) (9.60 g, 0.066 mol) was combined with NaOH (8.0 g, 0.2 mol) in water (100 cm^3) and the solution warmed to 35 °C. A solution of tosyl chloride (38.0 g, 0.2 mol) in diethyl ether (200 cm^3) was added dropwise with stirring, allowing the ether to evaporate at a rate approximately equal to the rate of addition (12 h). Solid NaOH was added as needed to maintain a pH >10. When the addition was complete, the solvent was evaporated and the resulting syrup redissolved in acetonitrile (100 cm^3) and absolute ethanol (100 cm^3). Water was then added dropwise until a slight cloudiness resulted. After standing at 5 °C overnight, crystals were obtained which were filtered off and recrystallized from acetonitrile–ethanol–water. The tri-tosylated product was obtained in 63% yield. NMR ($CDCl_3$): ^1H, δ 2.20–2.40 (m, 6 H), 2.33 (s, 9 H), 2.82 (m, 6 H), 5.95 (br t, 3 H), 7.22 (d, 6 H) and 7.72 (d, 6 H); ^{13}C, δ 21.49, 40.70, 53.99, 127.11, 129.74, 136.75 and 143.33.

Tris(N-methyl-2-tosylaminoethyl)amine. Tris(2-tosylaminoethyl)amine (5.0 g, 8.2 × 10^{-3} mol) was mixed with anhydrous potassium carbonate (2.3 g, 0.017 mol) and anhydrous sodium sulfate (2.4 g, 0.017 mol) in dry acetonitrile (200 cm^3) under a nitrogen atmosphere. A solution of dimethyl sulfate (3.3 g, 0.026 mol) in dry acetonitrile (50 cm^3) was added dropwise, slowly, and with stirring. The reaction was monitored by TLC (10% methanol in chloroform). The presence of several spots theoretically corresponding to the mono-, di- and tri-methylated

products were detected close together around R_f 0.5. After 12 h, further addition of dimethyl sulfate helped drive the reaction towards the trimethylated product. However, care must be exercised to avoid formation of an adduct methylated at the central (tertiary) nitrogen, which occurs if dimethyl sulfate is added too rapidly or in large excess. The permethylated product may be separated from the desired trimethylated product on a silica-gel column. The product was eluted with chloroform in 38% yield (2.0 g, 3.1×10^{-3} mol). NMR ($CDCl_3$, reference $CHCl_3$ at δ 7.2): ^{1}H, δ 2.33 (s, 9 H), 2.69 (br s, 15 H), 2.98 (t, 6 H), 7.22 (d, 6 H) and 7.58 (d, 6 H); ^{13}C, δ 21.34 (q, J = 128.3), 35.65 (q, J = 139.3), 48.37 (t, J = 139.3), 52.53 (t, J = 135.6 Hz), 127.18 (s), 129.60 (s), 134.12 (s) and 143.18 (s).

Tris(N-*methyl*-2-*aminoethyl*)*amine*. The tritosylated adduct was detosylated under nitrogen with concentrated (97%) sulfuric acid at 105–110 °C for 3 d. The trimethylated product was obtained as a light yellow oil in 49% yield (0.28 g, 1.5×10^{-3} mol). NMR ($CDCl_3$): ^{1}H, δ 1.40 (br s, 3 H), 2.31 (s, 9 H) and 2.43–2.49 (m, 12 H); ^{13}C, δ 36.24 (q, J = 132), 49.53 (t, J = 134) and 54.00 (t, J = 132 Hz).

Trimethyl ester of H_3L. The product of detosylation was dissolved in a mixture of $CHCl_3$ (10 cm^3) and ethyldiisopropylamine (10 cm^3). Methyl bromoacetate (0.688 g, 4.50 mmol) in $CHCl_3$ (10 cm^3) was then added dropwise with stirring at room temperature. After the addition was complete the reaction was allowed to proceed for 12 h. The solvents were evaporated and the residue redissolved in chloroform (20 cm^3). The solution was washed with water (3 × 5 cm^3), dried over NaOH, filtered and evaporated. The trimethyl ester was obtained as a yellow oil in 77% yield (0.462 g, 1.14 mmol). NMR ($CDCl_3$, reference $CHCl_3$ at δ 7.3): ^{1}H, δ 2.27 (s, 9 H), 2.51 (s, 12 H), 3.21 (s, 6 H) and 3.60 (s, 9 H); ^{13}C, δ 42.52 (q, J = 136), 51.14 (q, J = 148), 52.60 (t, J = 132), 54.43 (t, J = 134), 58.30 (t, J = 132 Hz) and 171.01 (s).

H_3L. The trimethyl ester was refluxed in aqueous HCl (pH < 1) for 12 h. The solution was then cooled and concentrated and the pH adjusted to 11.5. The sample was then loaded onto a 2.5 × 30 cm column of Dowex 1 × 8–200 anion-exchange resin (hydroxide form, 100–200 mesh). The column was washed with water (250 cm^3) and the product eluted with a linear gradient of 0–0.05 mol dm^{-3} HCl while monitoring the absorbance at 254 nm. The fraction containing the product was identified by ^{13}C NMR spectroscopy and concentrated. The solution was then boiled with decolorizing carbon for 20 min. After filtration, the solution was concentrated and freeze-dried to afford the product as a white powder (0.507 g). Elemental analysis indicated the presence of the tetrahydrochloride salt with 1.5 waters of hydration. NMR: ^{1}H (D_2O, pH 1, reference HOD at δ 4.8), δ 2.74 (s, 9 H), 2.83 (t, 6 H), 3.22 (br, 6 H) and 3.93 (s, 6 H); ^{13}C (water, pH 1, reference 1,4-dioxane at δ 67.0), δ 42.38 (q, J = 143), 47.72 (t, J = 136), 53.92 (t, J = 143), 57.14 (t, J = 147 Hz) and 168.47 (s) [Found: C, 33.60; H, 6.55; Cl, 27.15; N, 10.00; O, 22.70 (by difference). Calc. for $C_{15}H_{30}N_4O_6 \cdot 4HCl \cdot 1.5H_2O$: C, 33.65; H, 6.95; Cl, 26.50; N, 10.45; O, 22.40%].

Potentiometric Measurements.—pH-Potentiometric titrations were carried out using a Corning Ion Analyzer (250 pH meter), an Orion 8103 ROSS combination electrode and a Metrohm Dosimat automatic burette (Brinkman Instruments). Solutions for titration (10 cm^3) were covered by a layer of cyclohexane to exclude CO_2 and the cell was thermostatted at 25 °C. The ionic strength was kept constant with 0.1 mol dm^{-3} KCl. The hydrogen-ion concentration was obtained from the measured pH values by the method of Irving *et al.*[21] (pK_w = 13.95). The concentration of the ligand stock solution was determined from potentiometric titrations of the ligand in the presence and absence of excess of $CuCl_2$ and by colorimetric complexometric titrations. Excess of copper was titrated with standardized edta in the presence of murexide as indicator. The metal solutions used were standardized by edta titrations. The titrant KOH was standardized by potentiometric titration against potassium hydrogenphthalate and stored under a nitrogen atmosphere.

Protonation constants (K_{H_iL}) and stability constants (K_{ML} and K_{MHL}) are defined by the equations (1)–(3). Protonation

$$K_{H_iL} = [H_iL]/[H_{i-1}L][H^+] \quad (1)$$

$$K_{ML} = [ML]/[M][L] \quad (2)$$

$$K_{M(HL)} = [M(HL)]/[ML][H^+] \quad (3)$$

and stability constants were obtained from the potentiometric data using a Simplex non-linear algorithm[22] run on an IBM PC computer. This program compared calculated *versus* experimental pH values over the entire titration curve and minimizes the sum of the weighted squares of these differences. A titration curve was considered acceptable if the sum of the squares of the residuals was less than 0.1 for 100 data points. All titrations were repeated a minimum of three times and the equilibrium constants are reported as the average value ± the standard deviation.

NMR Measurements.—Solutions of the ligand (0.05 mol dm^{-3}) for proton NMR pH titrations were made up in D_2O (99.8% from Sigma) and pD values between 1.5 and 11.8 were adjusted with DCl or CO_2-free KOD (Sigma). The solution at pD 14.0 was made by dissolution of H_3L in a 1 mol dm^{-3} KOD solution. The final pH was determined from the measured pD values using pD = pH + 0.4 as the correction for the deuterium isotope effect.[23]

Proton NMR data for H_3L and its complexes were obtained on a JEOL FX-200 or a General Electric GN-500 spectrometer. Proton shifts were referenced to $SiMe_4$. Probe temperatures were accurate to ±0.5 °C.

NMRD Measurements.—The field-cycling relaxometer used for these measurements has been described elsewhere.[24] It measures $1/T_1$ NMRD profiles of solvent protons over a continuum of magnetic fields from 2.5×10^{-4} to 1.4 T (corresponding to about 0.01–50 MHz proton Larmor frequency), rapidly, under computer control, and with an absolute uncertainty in $1/T_1$ of ±1% under the present conditions.

ESR Measurements.—X-Band ESR spectra of aqueous solutions of the [GdL] and $[Gd(dtpa)]^{2-}$ chelates were obtained in quartz cells at room temperature using a Bruker ESP-300 spectrometer.

Results

Protonation Studies.—The potentiometric titration curves for H_3L in 0.1 mol dm^{-3} KCl, obtained over the interval pH 2–12 were computer fitted using standard techniques.[22] The four protonation constants obtained from these curves are summarized in Table 1, and compared with protonation constants published previously for tren,[25] nota[7] and dtpa.[26] The first three protonation constants of H_3L agree quite well with those of the parent amine tren, but differ from those of the nota and dtpa ligands.

To obtain information about the relative basicity of the two types of nitrogens in H_3L, the microscopic protonation sequence was determined by measuring the NMR chemical shifts of the ligand methylenic and methyl protons as a function of pH.[27] The data, shown in Fig. 1, provide evidence for a wide inflection between pH 12 and 8, corresponding to protonation of three groups, and another inflection below pH 3.5, corresponding to at least one other protonation (see Table 1). The protonation shifts of the methylene protons (a, b and c) and of the methyl protons (d) of H_3L (see structure) were used to obtain the percentage protonation at the nitrogens (f_N) and

Table 1 Comparison of protonation constants and metal-ion stability constants for H_3L and the ligands tren, nota and dpta

	H_3L[a]	tren[b]	nota[c]	dtpa[d]
$\log K_1$	9.97 ± 0.02	10.29	11.41	10.45
$\log K_2$	9.24 ± 0.01	9.59	5.74	8.53
$\log K_3$	8.08 ± 0.01	8.56	3.16	4.28
$\log K_4$	2.61 ± 0.10	—	1.71	2.65
$\log K_5$	—	—	—	—
$\log K_6$	—	—	—	—
$\Sigma_{i=1}^{4} \log K_i$	29.90	—	22.02	25.97
	$\log K_{ML}(\log K_{M(HL)})$			
	HzL	tren[b]	nota	dtpa[d]
Ni^{2+}	17.87(5.81)	14.8	—	20.17(5.67)
Cu^{2+}	21.53(5.20)	19.09	19.8[e]	21.38(4.81)
Zn^{2+}	14.03(8.55)	14.65	18.3[e]	18.29(5.60)
Cd^{2+}	17.12	12.3	16.0[e]	19.0(4.17)
Gd^{3+}	9.98	—	14.2[f]	22.46(2.39)

[a] Present work, determined by potentiometry (0.1 mol dm^{-3} KCl, 25 °C); the errors in log K_{ML} were ±0.03. [b] From ref. 25 (0.1 mol dm^{-3} KCl, 20 °C). [c] From ref. 7 (0.1 mol dm^{-3} ionic strength, 25 °C). [d] From ref. 26 (0.1 mol dm^{-3} NMe_4Cl, 25 °C). [e] From ref. 4 (0.1 mol dm^{-3} KNO_3, 25 °C). [f] From ref. 11 (0.1 mol dm^{-3} NaCl, 25 °C).

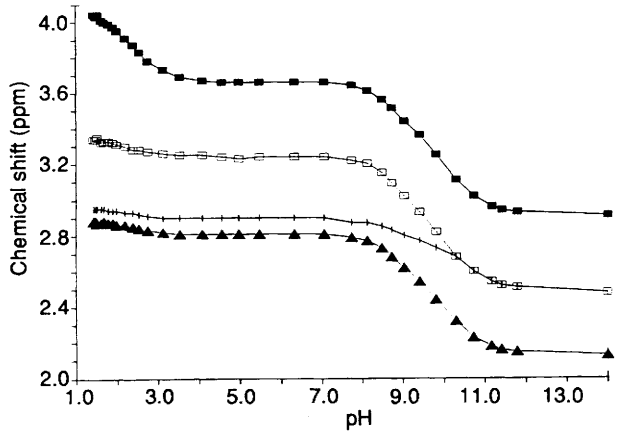


Fig. 1 Proton NMR pH titration curves for a 50 mmol dm^{-3} solution of H_3L in D_2O. Protons: c (■), a (□), b (+) and d(▲)

carboxylate oxygens (f_O) as a function of the number (n) of added protons (Table 2). The shielding constants obtained were $C_N = 0.75$ ppm and $C_{N'} = 0.42$ ppm, respectively, for methylene protons α and β relative to the terminal nitrogens, $C_{N^3} = 0.70$ ppm for the methyl protons and $C_O = 0.44$ ppm for the carboxylate oxygens. These nitrogen shielding constants agree quite well with the literature values.[27] However, the C_O value found in this work, which was calculated from the total shift of protons c below pH 4, measured by extrapolation of the observed curve to low pH, is larger than the previously obtained value of 0.20 ppm.[27] The data in Table 2 show that the central nitrogen of H_3L is much less basic than the other three, which are totally protonated when $n = 3$. Even after the addition of nearly six protons, the carboxylate groups are about 87% protonated while the central nitrogen is only protonated to an extent of about 29%. The acidity of the central nitrogen likely reflects the combined electrostatic repulsions of the three neighbouring protonated nitrogens.[27]

The proton NMR pH titration data between pH 6 and 14 (see Fig. 1) were fit by a model which assumed three protonations over this pH range. A Simplex non-linear algorithm was used to give a best fit of three pK_a values and the chemical shifts of the mono- (HL) and di-protonated (H_2L) species while fixing

Table 2 Percentage protonation of the amino groups (f_N) and the carboxylate groups (f_O) in the ligand H_3L*

n	f_{N^1}	f_{N^2}	f_O
1	0.10	0.30	0.00
2	0.02	0.66	0.00
3	0.00	1.00	0.00
4	0.10	1.00	0.30
5	0.17	1.00	0.61
5.9	0.29	1.00	0.87

* Using $C_N = 0.75$, $C_{N'} = 0.42$, $C_{N^3} = 0.70$ and $C_O = 0.44$ ppm.

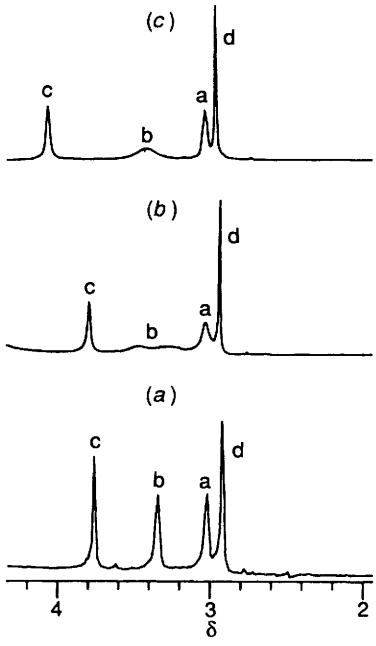


Fig. 2 Proton NMR spectra of a 50 mmol dm^3 H_3L solution in D_2O at pD 8.6 (*a*), 3.6 (*b*) and 1.5 (*c*)

the chemical shifts of the triprotonated (H_3L) species (to the experimental values between pH 6 and 7) and the completely deprotonated (L) species (experimental values at pH 14). The average pK_a values obtained from the four separate titration curves were 9.9 ± 0.1, 9.0 ± 0.1, and 8.2 ± 0.2. These values agree reasonably well the pK_a values obtained by potentiometry, especially when considering that the NMR experiments were carried out in D_2O without control of the ionic strength whereas the potentiometric measurements were made in water at constant ionic strength.

Fig. 2 shows the proton NMR spectrum of H_3L at three pD values. At pD 8.6 and above the proton signals are relatively sharp. Below about pD 8 the triprotonated species is fully formed and the protonated N^2 nitrogens are likely hydrogen bonded to a nearby negatively charged carboxylate group. This makes N^2 an asymmetric centre and the ethylenediamine protons become non-equivalent, yielding a splitting of the closest CH_2 (b) protons and broadening of the more distant CH_2 (a) protons. At pD 1.5 where $n = 5.5$ a partial protonation of the carboxylate oxygens weakens those hydrogen bonds, and the ethylenediamine resonances once again begin to sharpen.

Complexation Studies.—Potentiometric titrations of H_3L in the presence of equivalent amounts of Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Gd^{3+} were carried out without difficulty, as these ions form 1:1 complexes with this ligand quite rapidly in solution. Table 1 shows the stability constants derived from the potentiometric titration data and compares them with

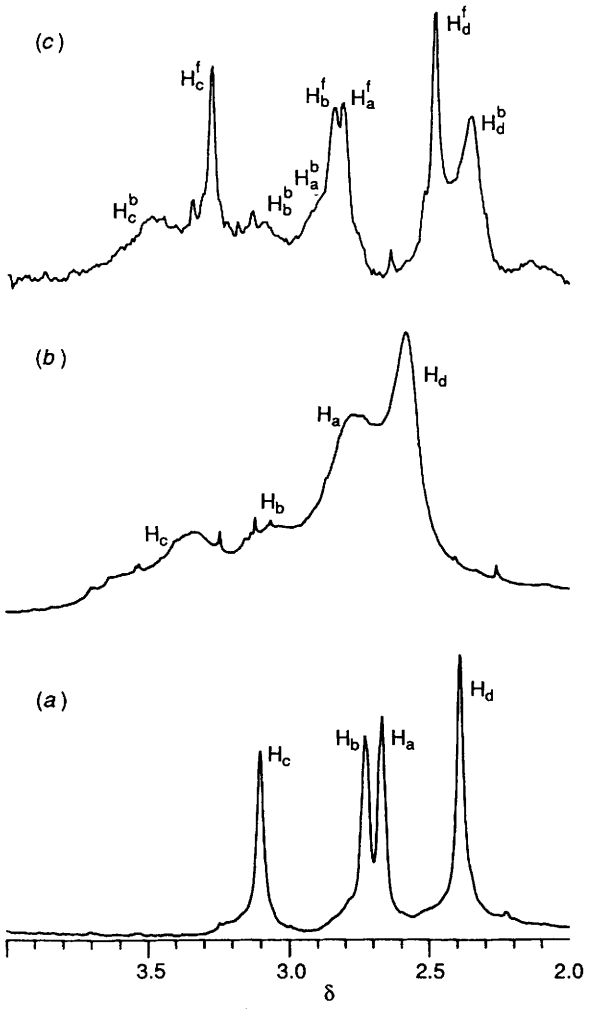


Fig. 3 Proton NMR spectra of (*a*) a 50 mmol dm^{-3} $[ZnL]^-$ solution at pD 12.6, (*b*) the same at pD 7.0 and (*c*) a 50 mmol dm^{-3} [LaL] solution at pD 9.8. The superscripts f and b denote resonances of the free and bound forms respectively

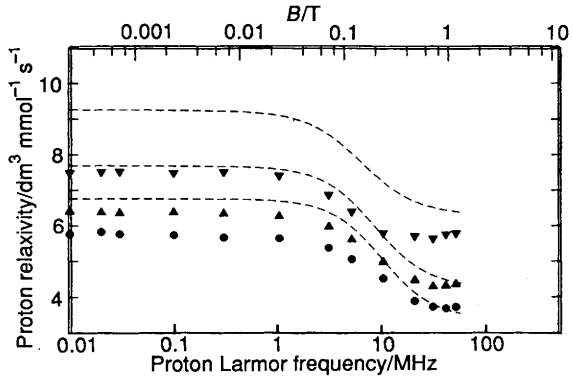


Fig. 4 The $1/T_1$ NMRD profiles for an aqueous solution of (GdL], as a function of temperature (▼, 5; ▲, 25; ●, 35 °C), expressed in relaxivity units (the rate increase per mmol dm^{-3} of added paramagnetic ion). The dashed curves are the data for $[Gd(dtpa)]^{2-}$ at the same temperatures

literature values for the corresponding complexes with tren, nota and dtpa.[4,11,25,26] The relative stabilities of the first-row divalent transition-metal complexes with H_3L show the same order as for the other ligands, $Ni^{2+} < Cu^{2+} > Zn^{2+}$.[28] Like dtpa, H_3L forms a more stable complex with Cd^{2+} than with Zn^{2+}. The complexes of Ni^{2+}, Cu^{2+} and Cd^{2+} with H_3L are several orders of magnitude more stable than those of tren, suggesting a stabilizing effect of the metal–oxygen bonds in these highly co-ordinated complexes. However, the stabilities of the zinc complexes of H_3L and tren are nearly the same, reflecting the important stabilizing role played by the zinc(II)–nitrogen bonds in these complexes. The ligand H_3L also forms substantially less-stable complexes with Gd^{3+} than does either nota or dtpa.

Proton NMR spectroscopy was also used to study the interaction of H_3L with the diamagnetic ions Zn^{2+} and La^{3+}. The 500 MHz spectra of the 1:1 Zn^{2+}–H_3L and La^{3+}–H_3L complexes were obtained as a function of solution pD (Fig. 3). The assignments shown were made by following the chemical shifts to low pH, where exchange became rapid and the free ligand was eventually fully formed. At pD 12.6, the 1:1 Zn^{2+}–H_3L solution showed four sharp signals, all resonances having positive complexation shifts (downfield, ppm): +0.18 (a), +0.24 (b), +0.21 (c) and +0.25 (d) (see structure for proton identification). The observation that all proton complexation shifts for H_3L are positive and in the relative order d ≈ b > c > a suggests that the cation co-ordinates the three N^2 nitrogens and the three carboxylate oxygens. When the pD was lowered to 7.0 the proton resonances of the complex broadened and the resulting complexation shifts (ppm) relative to the free unprotonated ligand at this pH were +0.16 (a), +0.47 (b), +0.32 (c) and +0.33 (d). These positive values are generally larger than the complexation shifts observed at high pD, suggesting that the complex was now partially protonated. This was in agreement with the potentiometric results. Resonances b and c (protons nearest N^2) are particularly broad at this pD, indicating that some exchange process was taking place in the protonated $[Zn(HL)]^+$ complex. One possibility is that one of the terminal nitrogens (N^2) is protonated in $[Zn(HL)]^+$ thus making the neighbouring CH_2 and CH_3 protons less magnetically equivalent. At 80 °C the proton spectrum at pH 7 sharpens considerably.

At pD 9.2 a 1:1 La^{3+}–H_3L solution [Fig. 3(*c*)] gives a proton spectrum consisting of four sharp resonances from the free ligand and four broad resonances from the [LaL] complex, with positive complexation shifts (ppm) relative to the free ligand of +0.40 (a), +0.64 (b), +0.59 (c) and +0.23 (d). At pD 7.2 the spectrum did not change significantly. This indicated that a protonated complex does not form, in agreement with the potentiometric calculations. A 1:2 La^{3+}–H_3L solution yields proton spectra which show that exchange between free and La^{3+}-bound H_3L is slow (on the NMR time-scale) at pD 9.2 but intermediate at pD 7.2.

NMRD.—Fig. 4 shows the $1/T_1$ NMRD profiles of [GdL] as a function of temperature, compared with published data for $[Gd(dtpa)]^{2-}$.[29] The nearly identical 50 MHz relaxivities (where the rates are dominated by the rotational correlation time, τ_R) of the [GdL] and $[Gd(dtpa)]^{2-}$ chelates at 25 and 35 °C, as well as the linear relationship between the 25 °C relaxivity values at 50 MHz and the water co-ordination number (q) recently proposed by us,[30] for a series of gadolinium(III) chelates ($R_{50\ MHz}$), lead us to conclude that $q = 1$ for [GdL]. This value is lower than the proposed value of $q = 2$ for [Gd(nota)],[31] indicating that the ligand surrounds the lanthanide cation more completely in the former complex than in the latter, allowing fewer free co-ordinating positions for solvent molecules. In fact, although the co-ordination schemes of H_3L and nota with the Gd^{3+} ion are probably similar, the macrocyclic ring of nota may not allow the ion to be located as deeply into the ligand pocket as for the non-cyclic H_3L.

The low-field relaxivities of [GdL] are lower than those of $[Gd(dtpa)]^{2-}$ at the same temperatures, indicating that the electron-spin relaxation time τ_s is shorter in the former complex. This is in accord with the observed X-band (0.3 T), 25 °C, ESR linewidths of their solutions, which are found to be, respectively, 140 and 51 mT, yielding calculated values of 47 and 130 ps, respectively.[30] At 5 °C the high-field relaxivities of [GdL] are

lower than those of $[Gd(dtpa)]^{2-}$ due to a residual contribution of τ_s to the correlation time in the former case, even at 50 MHz. This contribution results from the longer rotational correlation times (τ_R) at 5 °C, and the shorter τ_s value for [GdL], compared to $[Gd(dtpa)]^{2-}$; these concepts have been discussed extensively in recent papers.[10,29,30] Finally, we find that the temperature dependence of the [GdL] data is very similar to that of $[Gd(dtpa)]^{2-}$ indicating that no significant self-aggregation occurs under these experimental conditions.

Conclusion

The combined use of potentiometry and proton NMR pH titrations has shown that the non-cyclic polyamino carboxylate ligand H_3L has three high protonation constants, corresponding to protonation of the three peripheral N^2 nitrogens. The central nitrogen is considerably more acidic, and is protonated only at very low pH after the three carboxylate oxygens are largely protonated. The proton NMR signals of the ethylenediamine protons of the triprotonated form H_3L are broad, likely due to hydrogen-bond formation between the protonated N^2 atoms and the corresponding carboxylate oxygens.

Complexation of H_3L with Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Gd^{3+} was studied by potentiometry and compared with proton NMR results for the complexes of Zn^{2+} and La^{3+}. Although we cannot determine from the data presented here whether the acidic central nitrogen N^1 is co-ordinated in these complexes, the rather low stability constant measured for [GdL] (several orders of magnitude lower than expected based upon the known relationship between thermodynamic stability constants and the sum of the ligand pK_a values[31]) at least suggests that N^1 may not be co-ordinated in this complex. This would result in a complex with ostensibly three eight- and three five-membered chelate rings {as compared to six five-membered chelate rings in [Gd(nota)]}. Proton NMR spectra of $[ZnL]^-$ and [LaL] recorded at different pH values show that a monoprotonated [Zn(HL)] complex is formed but that [LaL] is not protonated. These observations agree with the potentiometric results. The complex [Zn(HL)] shows a broad proton NMR spectrum, indicative of a slow intramolecular conformational equilibrium.

A water proton NMRD study of [GdL] indicates that the complex has one inner-sphere co-ordinated water molecule like $[Gd(dtpa)]^{2-}$ but it also has a much shorter electron-spin relaxation time than does $[Gd(dtpa)]^{2-}$. The lower relaxivity and thermodynamic stability of [GdL] relative to $[Gd(dtpa)]^{2-}$ indicates that this new complex will likely not be useful as a non-ionic contrast agent for magnetic resonance imaging.[30]

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