Protonation Scheme for some Triaza Macrocycles Studied by Potentiometry and NMR Spectroscopy

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A series of triaza macrocyclic tricarboxylate ligands with ring sizes of nine to twelve (NOTA, DETA, UNTA and DOTRA) have been synthesized. Their acid–base properties and protonation sequence have been established and compared with those of the corresponding cyclic triamines and trimethyl cyclic triamines, using potentiometric measurements and ^{1}H NMR pH titrations. The first protonation constant of the carboxylate ligands is very high, and larger than the value for the parent cyclic amines. It is also very sensitive to the presence of Na^+ ions in solution. The first two protonation constants correspond to protonation of the ring nitrogens, and their increase with ring size is non-monotonic, reflecting pH-dependent conformational effects. These effects, due to electrostatic interactions as well as to hydrogen bond formation, caused difficulties in the application of methods (previously used for non-cyclic polyaminocarboxylates) to obtain the protonation sequence from the ^{1}H NMR pH titrations, similar to a previous occurrence for tetraaza macrocycles. By studying the pH dependence of the shielding parameters, C_N and $C_{N'}$, the protonation sequences were then obtained. For each of the four compounds studied, two nitrogen atoms are protonated before the carboxylate groups. Formation of hydrogen bonds between protonated nitrogens and non-protonated carboxylates affects the basicity of the latter, reducing the flexibility of these ligands in certain pH intervals.

There has been considerable interest recently in the development of new macrocyclic polyaminopolycarboxylate ligands which, by forming lanthanide(III) chelates of high thermodynamic and kinetic stability, can be used as NMR shift probes for biological systems[1] or as contrast agents for magnetic resonance imaging.[2] Of these, the carboxylate ligands derived from triaza and tetraaza macrocyclic amines have been of much interest to us, although mixed polyazapolyoxa derivatives, such as diazatrioxa-[3–6] and diazatetraoxa-[6–8] derivatives have been extensively studied by other groups. Tetraaza macrocyclic tetracarboxylates such as 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (DOTA) and larger ring analogues have been previously studied in both their acid–base[9–11] and metal complexation[10,12–14] properties, using potentiometry and NMR spectroscopic techniques. Similarly, the triaza macrocyclic ligand 1,4,7-triazacyclononane-*N*,*N*′,*N*″-triacetic acid (NOTA) and some of its transition metal and lanthanide(III) complexes have also been studied using different techniques.[13,15–22] The stability constants of the NOTA and DOTA chelates of the lanthanides, which have slow formation kinetics, have been determined using a colorimetric method.[23] The nuclear relaxivity of solvent water of their Gd^{3+} chelates has also been investigated using the Nuclear Magnetic Relaxation Dispersion (NMRD) technique.[24] It was found that Gd(NOTA) has a higher relaxivity but much lower thermodynamic and kinetic stability than $Gd(DOTA)^-$. In an effort to combine the high stability and relaxivity properties in one single chelate, the metal binding properties of triaza macrocyclic carboxylate analogues of NOTA containing larger rings are currently being investigated.[25]

In this work we report the synthesis, acid-base properties and protonation sequence for the triaza NOTA analogues (see Fig. 1), 1,4,7-triazacyclodecane-*N*,*N*′,*N*″-triacetic acid (DETA), 1,4,8-triazacycloundecane-*N*,*N*′,*N*″-triacetic acid (UNTA) and 1,5,9-triazacyclododecane-*N*,*N*′,*N*″-triacetic acid (DOTRA) as well as of the corresponding cyclic triamines and trimethyl cyclic triamine derivatives. These results are compared with previous studies on the cyclic triamines[26–30] and on the triazacyclononane derivatives.[19,20,22]

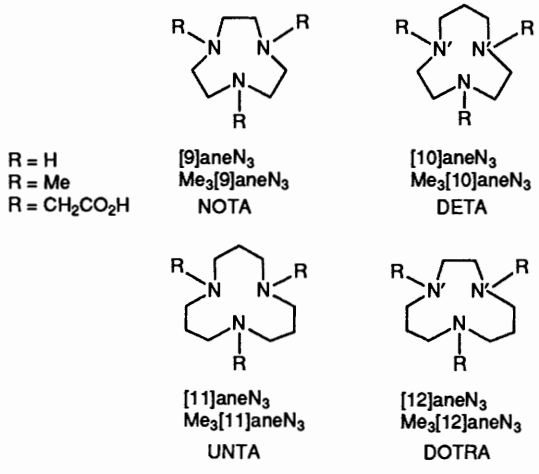

Fig. 1 Structures of the cyclic triamine compounds studied

Experimental

Synthesis and Characterization of the Ligands.—Cyclic amines. 1,4,7-Triazacyclononane ([9]aneN$_3$, see Fig. 1); 1,4,7-triazacyclodecane ([10]aneN$_3$); 1,4,8-triazacycloundecane ([11]aneN$_3$) and 1,5,9-triazacyclododecane ([12]aneN$_3$) were synthesized either by the method of Richman–Atkins[25,26,31–35] or by cyclization of the linear tosylamides over K_2CO_3.[36] The amines were isolated and stored as their trihydrobromide salts.[36]

Methylated amines. Me$_3$[9]aneN$_3$ and Me$_3$[10]aneN$_3$ were obtained by treating the respective cyclic amines with n-butyllithium (6 equiv.) in dry ether,† under N_2 at −78 °C. After being quenched with excess iodomethane, the reaction mixtures were stirred at room temperature for 30 min, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the expected products in 90%

† Ether refers to diethyl ether throughout.

yields. Me_3[12]aneN_3 was obtained by reductive methylation of [12]aneN_3 as follows: to the trihydrobromide of the amine (50 mg, 0.178 mmol) in dry methanol (3 cm^3) was added KOH (9 mg). After dissolution of the pellets, anhydrous formaldehyde (1 mmol) in dry methanol (2 cm^3) was added and the reaction mixture was stirred overnight at room temperature. $NaCNBH_3$ (or $NaBH_4$) (6 equiv.), in dry methanol (5 cm^3) was then added and the reaction mixture was stirred for an additional 2 h. The solvent was removed under reduced pressure, chloroform was added and, after alkaline work up (pH *ca.* 12), the pH was lowered to 1–2 and the organic layer was extracted with water. The aqueous layer was concentrated under reduced pressure and the residue was carefully washed with ethanol to give white crystalline Me_3[12]aneN_3 in 60% yield. Me_3[11]aneN_3 could not be synthesized by either of the methylation methods described above. *N*-Alkylation of the three nitrogens of the larger triaza rings is very slow in aqueous media, because the monoprotonated acid is slow and difficult to deprotonate.[30]

1,4,7-*Triazacyclononane*-N,N′,N″-*triacetic acid.* NOTA was prepared from the trihydrobromide of [9]aneN_3 by addition of bromoacetic acid, using published procedures.[12,20] After the reaction was complete the pH was adjusted to 3.5 with concentrated HBr. White crystals, obtained after addition of ethanol and cooling, were washed with ethanol and dried under vacuum at 70 °C (yield 90%). This form of NOTA, containing 2 mol of NaBr salt, was purified using a Dowex 50W-X2 (200–400 mesh) cation exchange chromatography column, eluted with a 1.5–6 mol dm^{-3} HCl gradient, in 30 cm^3 fractions. All the fractions collected were concentrated under reduced pressure, and the compound was recrystallized from absolute ethanol, dried under vacuum at 150 °C and obtained as the trihydrochloride derivative of NOTA.

1,4,7-*Triazacyclodecane*-N,N′,N″-*tris*(*acetic acid methyl ester*). [10]aneN_3 was first isolated by dissolving the amine salt in 1 mol dm^{-3} NaOH, extracting with chloroform (×3), followed by removal of the solvent and drying under vacuum. Then, in a typical preparation, 1,4,7-triazacyclodecane (0.184 g, 1.29 mmol) was dissolved in dichloromethane (5 cm^3) and diisopropylethylamine (10 cm^3). A solution of methyl bromoacetate (0.60 g, 3.92 mmol) in dichloromethane (5 cm^3) was then added dropwise to the amine solution with stirring at room temperature. The mixture was stirred for an additional 12 h, the solvent was evaporated under reduced pressure, and the residue redissolved in chloroform (10 cm^3). The solution was washed with water (3 × 5 cm^3), dried over NaOH pellets and filtered. Evaporation of the chloroform gave the product in 78% yield (0.36 g) as a yellow oil, which was used without further purification: δ_H(200 MHz, $CDCl_3$) 1.26 (p, 2 H), 2.60 (m, 8 H), 2.88 (m, 4 H), 3.17 (s, 4 H), 3.27 (s, 2 H) and 3.54 (s, 9 H); δ_C(50 MHz, $CDCl_3$) 25.20, 47.74, 50.95, 51.01, 52.47, 54.52, 54.69, 55.10 and 172.31.

1,4,7-*Triazacyclodecane*-N,N′,N″-*triacetic acid.* The trimethylated ester was mixed with water (8 cm^3) and the pH adjusted to ≤1 with 2 mol dm^{-3} HCl. The mixture was allowed to reflux for 12 h, cooled and concentrated under reduced pressure to 1–2 cm^3. The pH was adjusted to 7–8 using 2 mol dm^{-3} NaOH and the solution was loaded on to a Dowex-1X8 anion exchange chromatography column in the chloride form (100–200 mesh). The column was washed with water and then eluted with a 0.2 mol dm^{-3} HCl–H_2O gradient (500 cm^3), monitoring the eluent absorbance at 524 nm. The collected fractions were concentrated and examined by ^1H and/or ^{13}C NMR spectroscopy. Freeze-drying typically afforded the hydrochloride salt of DETA in 80% yield; m.p. 63 °C (decomp.); δ_H(200 MHz, D_2O, pH *ca.* 0.5, HOD at 4.80 ppm) 2.32 (br, 2 H), 3.44 (br), 3.54 (br), 3.86 (s, 2 H) and 4.09 (s, 4 H); δ_H (same sample, 80 °C) 2.90 (p, 2 H), 3.89 (br s, 8 H), 4.00 (t, 4 H), 4.31 (s, 2 H) and 4.44 (s, 4 H); δ_C(50 MHz, D_2O, pH *ca.* 0.5, ref. *p*-dioxane at 67.0 ppm) 20.91, 50.86, 51.95, 53.85, 56.19, 56.77, 169.42 and 172.85 (Found: C, 37.7; H, 6.7; N, 9.8; Cl, 16.0; O, 29.8. Calc. for $C_{13}H_{33}N_3O_6$·2HCl·2H_2O: C, 36.92; H, 6.86; N, 9.86; Cl, 16.63; O, 30.02).

1,4,8-*Triazacycloundecane*-N,N′,N″-*tris*(*acetic acid methyl ester*). UNTA-trimethyl ester was synthesized using procedures identical to that for DETA-trimethyl ester. δ_H(200 MHz, $CDCl_3$) 1.54 (p, 4 H), 2.60–2.90 (m, 12 H), 3.25 (s, 2 H), 3.34 (s, 4 H) and 3.69 (s, 9 H); δ_C(50 MHz, $CDCl_3$) 24.41, 49.56, 50.49, 51.12, 52.53, 54.09, 55.11, 172.21 and 172.40.

1,4,8-*Triazacycloundecane*-N,N′,N″-*triacetic acid.* UNTA, obtained by hydrolysis of the ester as described for DETA, was isolated as a hygroscopic mixture of dihydrochloride hydrates, as suggested by elemental analysis: m.p. 133 °C (decomp.); δ_H(200 MHz, D_2O, pH *ca.* 1.0, HOD at 4.80 ppm) 2.17 (br), 2.34 (br), 3.54 (br), 3.84 (br) and 4.14 (br s); δ_C(50 MHz, D_2O, pH *ca.* 1.0, ref. *p*-dioxane at 67.0 ppm) 19.64, 50.70, 52.53 (br), 55.63, 56.39 (br), 56.90, 169.95 and 171.91 (br) (Found: C, 40.7; H, 6.7; N, 10.1; Cl, 16.1; O, 26.4. Calc. for $C_{14}H_{25}N_3O_6$·2HCl·0.5H_2O: C, 40.68; H, 6.83; N, 10.17; Cl, 17.16; O, 25.16).

1,5,9-*Triazacyclododecane*-N,N′,N″-*triacetic acid.* DOTRA was synthesized as previously described.[25]

Potentiometric Measurements.—pH Titrations were performed using an Orion Research Model 701A pH meter. The glass electrode was calibrated by measuring the EMF of a series of standard buffers with pH values within the range 2.00–12.72. The chelates were dissolved in 0.1 mol dm^{-3} NaCl and titrated with NBS standard 0.100 mol dm^{-3} NaOH (from Aldrich) and in some cases were also dissolved in 0.1 mol dm^{-3} tetramethylammonium chloride, made basic with tetramethylammonium hydroxide and titrated with NBS standard 0.100 mol dm^{-3} HCl (from Aldrich). All samples were kept under N_2 during the pH titrations and the sample temperature was maintained at 25 ± 0.5 °C. The protonation constants of the ligands L are defined as $K_i = [H_iL]/[H_{i-1}L][H^+]$, where $i = 1,2,3\ldots$. Protonation constants were obtained from the potentiometric data using a simplex non-linear regression algorithm[37] written in BASIC. The highest and lowest protonation constants of DETA and UNTA could be determined to within ±0.1 units based upon duplicate measurements while the middle values were reproducible to within ±0.02 units.

NMR Measurements.—Solutions of the ligands (0.01 mol dm^{-3}) for NMR pH titrations were made up in D_2O (99.8% from Sigma), and the pD was adjusted with DCl, CO_2-free NaOD (Sigma) or a 1.106 mol dm^{-3} standardized KOD solution (CO_2 free). The final pH was determined with a Radiometer PHM 64 pH meter equipped with a Philips GA 110-NS electrode and corrected for a deuterium isotope effect using pD = pH + 0.4.[38] The hydrogen electrode used in this work allows a reliable and accurate determination of the proton activity over an extended pH range. ^1H and broad band proton-decoupled ^{13}C spectra were obtained, respectively, at 200 and 50.1 MHz on a JEOL FX-200 or a Varian XL-200 FT spectrometer. Some proton spectra were obtained at 500 MHz on a General Electric GE-500 spectrometer. ^1H and ^{13}C shifts were referenced to either t-butyl alcohol or dioxane as internal standards, or TMS as an external standard. Probe temperatures were accurate to ±0.5 °C.

Results and Discussion

Protonation Constants.—Table 1 summarizes the protonation constants of the triaza macrocyclic tricarboxylate ligands obtained by potentiometry at 25 °C. These are compared with

Table 1 Protonation constants of triaza macrocyclic ligands, obtained by potentiometry (at 25 °C)

	[9]aneN$_3$[a]	[10]aneN$_3$[a]	[11]aneN$_3$[a]	[12]aneN$_3$[a]
log K_1	10.4	12.02	11.96	12.60
log K_2	6.82	6.59	7.61	7.57
log K_3	*g*	*g*	*g*	2.41

	NOTA[b,c,d]			DETA[e]	UNTA[e]	DOTRA[f]
	b	*c*	*d*			
log K_1	11.41	11.3	10.77	13.5	13.9	12.8
log K_2	5.74	5.59	6.03	6.12	7.20	7.55
log K_3	3.16	2.88	3.16	3.69	3.40	3.65
log K_4	1.71	*g*	1.96	2.3	1.7	2.1

[a] From ref. 29 (0.1 mol dm^{-3} KNO_3). [b] From ref. 19 (0.1 mol dm^{-3} $NaNO_3$). [c] From ref. 20 (0.1 mol dm^{-3} $NaClO_4$). [d] From ref. 22 (1.0 mol dm^{-3} $NaClO_4$). [e] This work (0.1 mol dm^{-3} NaCl). [f] From ref. 25 (0.1 mol dm^{-3} NMe_4Cl). [g] Not determined. [h] Obtained by spectrophotometry (ref. 25).

the values reported previously for the corresponding macrocyclic triamines. The observed enhancement of the basicity of the ring nitrogens with increase of ring size from nine to twelve members has been discussed previously.[27,29] This effect can only in part be explained by decreased electrostatic repulsion in the larger rings. In fact, the non-monotonic increase of the protonation constants with ring size may reflect conformational effects, the possibility of different tautomeric forms of the mono- and diprotonated forms of [10]aneN$_3$ and [11]aneN$_3$, or the trapping of hydrogen bonded H_3O^+ ions by the larger rings (see below).[27,29]

Substitution of acetate groups on each nitrogen atom of the parent cyclic amine sharply increases the first protonation constant of NOTA, DETA and UNTA, but not as much in DOTRA.[25] The values of the first protonation constant presented in Table 1 for DETA and UNTA were obtained in the present work, in the presence of 0.1 mol dm^{-3} NaCl, whereas one of the values quoted for NOTA, log K_1 = 11.41,[19] was obtained in the presence of 0.1 mol dm^{-3} $NaNO_3$. Larger concentrations of Na^+ are reponsible for the decrease of this protonation constant, *e.g.* log K_1 = 10.77, in 1.0 mol dm^{-3} $NaClO_4$.[22] In the absence of Na^+ ions, the first protonation constant of these chelates may be significantly higher. The first protonation constant of DOTRA, log K_1 = 12.8, has been obtained by spectrophotometry and NMR pH titrations,[23] as it may be too high to determine accurately by potentiometry. In this work we found that this situation also applies to NOTA, DETA and UNTA (see below). As shown by ^{1}H NMR shifts (see below), protonation first occurs at one of the ring nitrogens, whose basicity is increased by the negative charge of the neighbouring ionized carboxylate group. The appending methylenephosphonate groups of the macrocyclic polyazaphosphonates has a similar effect on the first protonation constant for this type of chelate.[39]

Acetate substitution has only a small effect upon the second protonation constants of these ligands (log K_2 for NOTA shows the largest decrease, Table 1). Since the second protonation also occurs at a ring nitrogen (see below), this must result from a combination of inductive effects of the acetates and the formation of internal hydrogen bonds in the mono- and diprotonated forms of the ligands. The next two protonations occur at the carboxylate groups[20] and are basically independent of ring size.

NMR Studies of Ligand Protonation.—The macroscopic protonation constants do not indicate the sequence of ligand protonation sites. The microscopic protonation scheme can be obtained by following the NMR chemical shifts of the ligand methylene protons as a function of pH, since the protonation of donor atoms generally results in a deshielding of the non-labile hydrogens and changes in chemical shifts can indicate the site of protonation.[20] Such pH titrations, obtained in a broad pH interval, are shown in Figs. 2–4, for the macrocyclic triamines, the trimethylated derivatives and the triacetates, respectively. For these latter compounds, the presence of Na^+ ions markedly affects their proton spectra and titration curves at basic pH values. This indicates that, at pH > 11, Na^+ ions bind within the cavity of these chelates, and, by interacting with both the nitrogen and carboxylate oxygen donor atoms, induce low frequency proton shifts, similar to those previously observed for macrocyclic polyazaphosphonates.[39]

All spectra of the Na^+-free ligands showed single resonances for each magnetically equivalent group of nuclei over the entire pH range, indicating rapid exchange between all protonated species, H_nL. We generally observed pH-dependent linewidth effects on the trimethyl and triacetate derivatives (but not on the simple triamines), which corresponds to slow interconversion processes between the various conformations of those macrocycles, due to nitrogen inversion, as discussed below.

Under conditions of fast proton exchange among the various protonated species, H_nL, the observed averaged chemical shift of nucleus i is given by $\delta^i_{obs} = \Sigma_n \delta^i_n X_{H_nL}$, where δ^i_n are the intrinsic chemical shifts of the H_nL species and X_{H_nL} is the mole fraction of each species. Using the protonation constants obtained by potentiometry (Table 1), the δ^i_n values can be calculated using a multiple linear regression program, which minimizes the sums of the squares of the deviation between the observed and calculated δ^i_{obs} values.[39] In each set of shift data (Figs. 2–4), fits can be performed by fitting the protonation constants to values obtained by potentiometry in NMe_4Cl or by also allowing optimization of the log K_i values. As the ionic strength was not kept constant throughout the NMR pH titrations, the best overall fits were obtained by allowing optimization of the log K_i values. For this reason, the calculated protonation constants, shown in Table 2, are subject to greater uncertainty than potentiometrically determined values.

The proton intrinsic shifts obtained for the various H_nL forms can be used to calculate the percentage protonation of the nitrogen or oxygen sites, using the method of Sudmeier and Reilley.[40] According to this empirical procedure, the observed shifts of the ligand protons a–f (see Figs. 2–4), δ^i_{obs}, are a function of the intrinsic shifts of the fully deprotonated form of the ligand (δ^i_o); the fraction of protonation of the nitrogen (N) and of the carboxylate (O) sites at each pH (f_N and f_O, respectively); the change in proton chemical shift due to α-carboxylate protonation (C_O); and protonation of a N atom in the α position (C_N) or in the β position ($C_{N'}$) relative to the CH_2 group under study. The average number of ligand bound protons at the N ligand basic sites is $n_N = \alpha_N f_N + \alpha_O f_O$, where α_N and α_O are the number of equivalent N and O sites.

For linear polyaminocarboxylates, Sudmeier and Reilley[40] showed that the shift effects of protonation at various basic sites were additive, and obtained a pH-independent set of shielding constants, C_O = 0.20, C_N = 0.75 and $C_{N'}$ = 0.35 ppm. However, in macrocyclic compounds, where there are pH-dependent conformational changes, that additivity is only maintained if the shielding constants are themselves pH-dependent.[9,11,20]

Macrocyclic Triamines and Trimethylated Derivatives.—The plots of the proton chemical shifts *vs.* pH for the triaza macrocycles and the trimethylated derivatives are shown in Figs. 2 and 3, respectively. The assignment of the proton resonances is quite straightforward, taking into account their

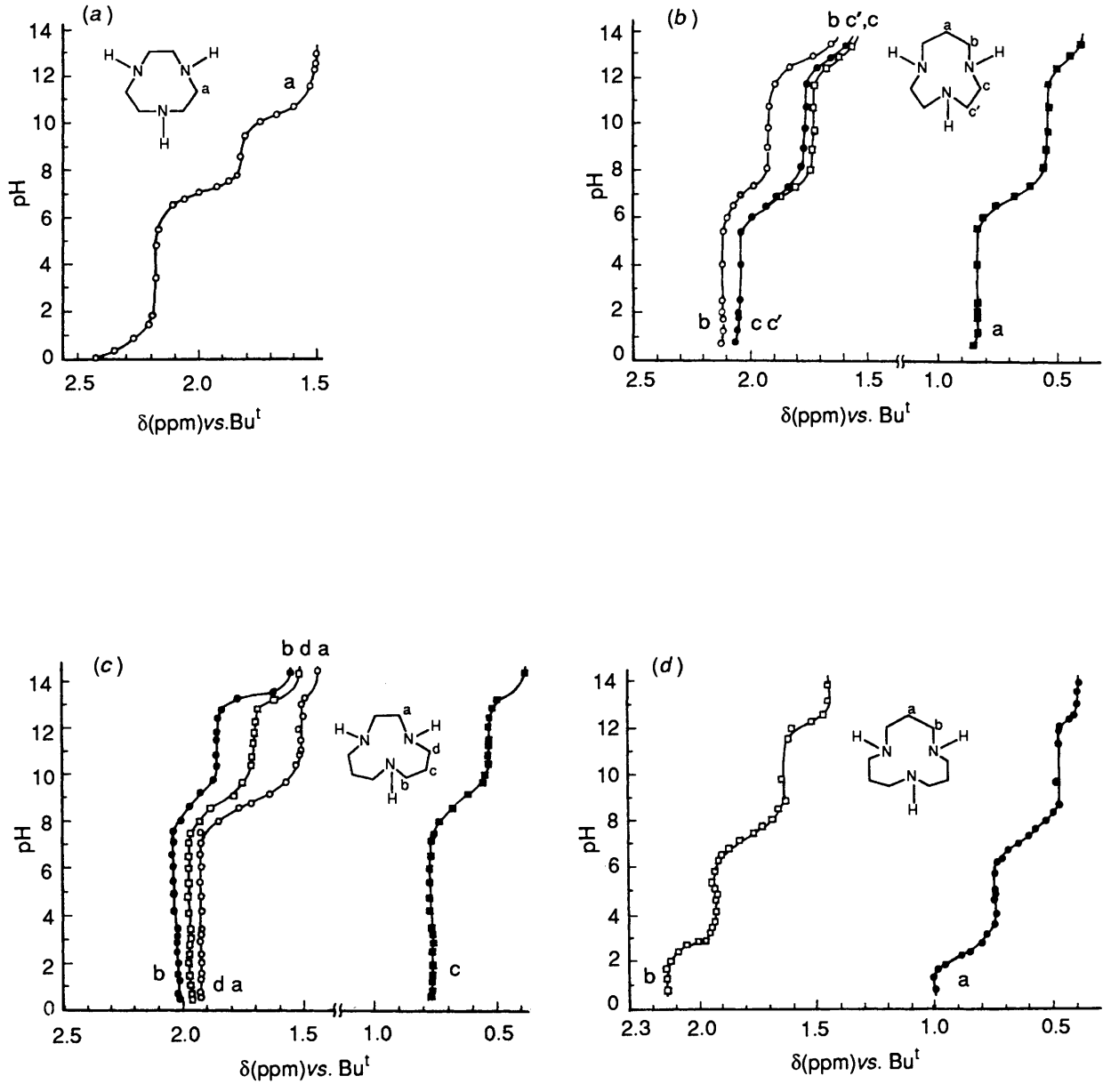

Fig. 2 ^{1}H NMR titration curves (δ as a function of pH), using NaOD, for the triaza macrocyclic amines: (*a*) [9]aneN$_3$; (*b*) [10]aneN$_3$; (*c*) [11]aneN$_3$; (*d*) [12]aneN$_3$

area ratios and multiplet patterns. Hence, the methyl protons give narrow singlets; the same is true for some methylene protons in symmetrically positioned ethylenediamine bridges [a of NOTA, Fig. 4(*a*)]. However, in less symmetrical situations, those methylene protons give, for some pH values, AA′BB′ or AA′XX′ multiplets [*e.g.* c and c′ of [10]aneN$_3$, Fig. 2(*b*), and Me$_3$[10]aneN$_3$, Fig. 3(*b*)]. The methylene protons of propylenediamine bridges in position α relative to nitrogen atoms give triplets [*e.g.* b of [10]aneN$_3$ and [12]aneN$_3$, Fig. 2(*b*, *d*)], while those in the β position give rise to quintuplets at lower frequency [*e.g.* a of [10]aneN$_3$, Fig. 2(*b*)]. The relative assignments of resonances b and d of [11]aneN$_3$ and of c and c′ of [10]aneN$_3$ and Me$_3$[10]aneN$_3$ were made on the basis of the calculated percent protonations f_N and $f_{N'}$ (Table 3) and similar situations described for tetraaza macrocycles.[14]

The NMR titration curves of the seven amines studied show the effect of stepwise protonation of the three nitrogens of the molecules L, with formation of the species HL^+, H_2L^{2+} and H_3L^{3+}. Three inflections are observed in some cases, centred at values shown in Table 2, which should correspond to their three protonation constants (the third inflection, corresponding to formation of $H_3L_3^+$, was not observed for ligands [10]aneN$_3$, [11]aneN$_3$ and Me$_3$[10]aneN$_3$. In some cases, the protonation constants obtained by NMR titrations were significantly larger than those obtained by potentiometry. In the case of the high log K_1 values of [10]aneN$_3$ and [11]aneN$_3$, this fact may reflect large ionic strength effects. However, a similar effect on log K_2 of [11]aneN$_3$ is difficult to explain.

In the symmetric amines [Figs. 2(*a*, *d*); Figs. 3(*a*, *c*)] all the CH_2 and CH_3 protons exhibit the same behaviour, corresponding to equal simultaneous partial protonation of the three ring nitrogens. This is not observed for the asymmetric amines [Figs. 2(*b*, *c*); Fig. 3(*b*)] where the non-equivalent nitrogens are protonated differently at intermediate pH values.

Comparison of the approximate protonation constants obtained by NMR spectroscopy for the compounds studied (Table 2) indicates that methylation of the macrocyclic amines generally leads to larger log K_1 and smaller log K_2 values. These relative values and the absolute values of log K_2 (5.2–8.7) are very different from those observed for the tetraaza macrocycles,[9,11,41] reflecting the very different protonation processes of triaza and tetraaza macrocyclic amines.[42] In the cases which

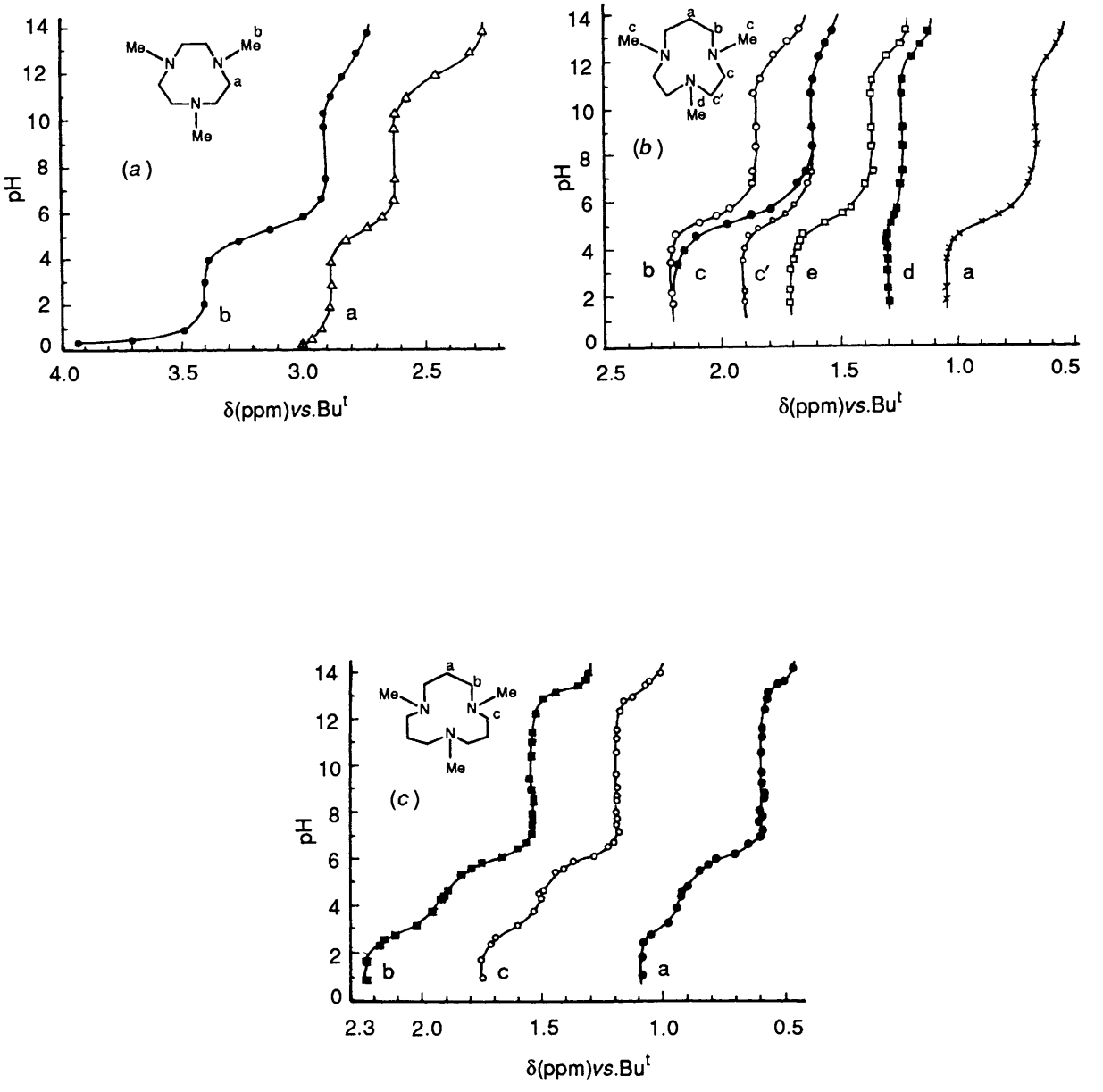

Fig. 3 ^{1}H NMR titration curves, using NaOD, for the trimethylated triaza macrocyclic amines: (*a*) Me_3[9]aneN_3; (*b*) Me_3[10]aneN_3; (*c*) Me_3[12]aneN_3

were measured, nitrogen methylation does not seem to affect the log K_3 values.

When the method of Sudmeier and Reilley[40] is applied to the analysis of the titration curves of Figs. 2 and 3, the shielding constants corresponding to protonation at the nitrogen atoms can be calculated. These shielding constants are C_N ($-CH_2NR_2$ or $-CH_2NHR$), $C_{N'}$ ($-CH_2CH_2NR_2$ or $-CH_2CH_2NHR$) and C_N^m($-CH_3NR_2$). Table 3 shows those calculated shielding constants, obtained for well-defined protonation stages of the macrocyclic triamines, with total number of equivalents of acid added n = 1–3. It also shows the calculated protonation fractions at the two types of nitrogen atoms, N (N_1) and N′ (N_2 or N_3), defined by the symmetry of asymmetric amines. Those protonation fractions, f_N and $f_{N'}$, show clearly, for each value of n, that the non-equivalent nitrogen atoms of the asymmetric amines are protonated differently for values of n = 1 and 2. That is clearly seen for [10]aneN_3, where, for n = 1, and to a lesser extent for n = 2, there is a marked preference for protonation at N′ (86% and 79%, of total available protons, for n = 1 and n = 2, respectively). Methylation of the nitrogens, *e.g.* Me_3[10]aneN_3 slightly decreases this preference for n = 1 (76%), but increases it for n = 2 (83%). In the case of [11]aneN_3, the first protonation shows a marked preference for the N site (52%), but this preference decreases for n = 2 (37%). As a whole, these preferential protonation sites correspond to the possibility of formation of six-membered rings within the protonated macrocycle, through hydrogen bonding between two of the three nitrogen atoms of the ring.

The values of the shielding constants of the macrocyclic triamines (Table 3) are generally very dependent on various factors, such as pH (protonation state, n), macrocyclic ring size and type of proton considered (*e.g.* methylenic group) within each molecule. This situation is quite different from what has been observed for linear polyaminocarboxylates,[40] where constant shielding constants and additive protonation effects of the various basic sites were often observed throughout the whole pH range. The presently observed dependence of the shielding constants on multiple factors, similar to the one previously recorded for triaza[20] and tetraaza[9,11] macrocyclic ligands, results from the existence of pH-dependent preferred conformations of these small macrocyclic molecules, which cause the various substituents not to maintain constant average

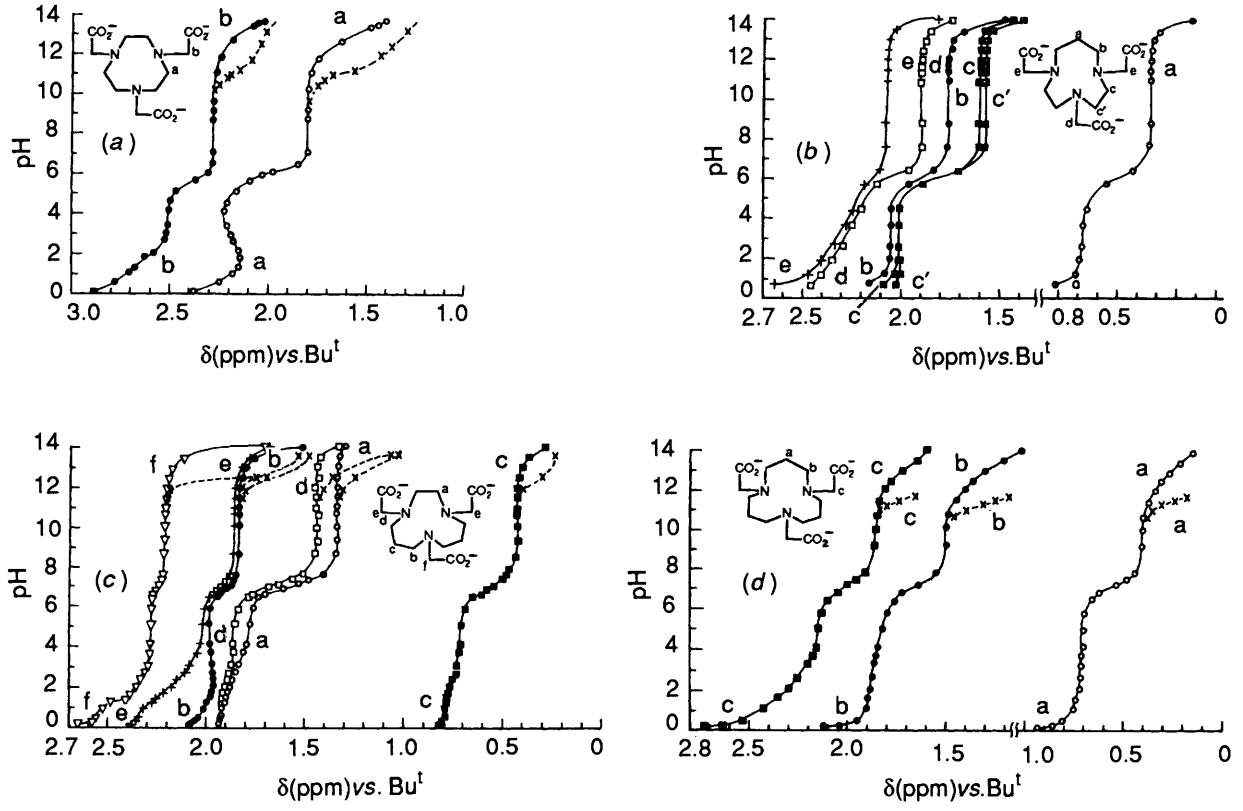

Fig. 4 ^{1}H NMR titration curves for the triaza macrocyclic tricarboxylate ligands: (*a*) NOTA; (*b*) DETA; (*c*) UNTA; (*d*) DOTRA. The full curves correspond to the use of KOD, and the dotted curves to the use of NaOD.

Table 2 Protonation constants of triaza macrocyclic ligands, obtained by NMR pH titrations (25 °C)[a]

	[9]aneN$_3$	[10]aneN$_3$	[11]aneN$_3$	[12]aneN$_3$
log K_1	10.4	12.9	13.4	12.3
log K_2	6.9	6.9	8.7	7.3
log K_3	0.7	*b*	*b*	2.4
	Me$_3$[9]aneN$_3$	Me$_3$[10]aneN$_3$	Me$_3$[11]aneN$_3$	Me$_3$[12]aneN$_3$
log K_1	11.7	12.5	*c*	12.8
log K_2	5.2	5.3	*c*	5.7
log K_3	0.6	*b*	*c*	2.9
	NOTA	DETA	UNTA	DOTRA
log K_1	13.0	>14.5	>14.5	12.8
log K_2	5.6	6.1	6.9	7.1
log K_3	2.5	3.7	3.2	3.5
log K_4	1.9	2.5	2.1	2.4
log K_5	1.3	1.7	1.7	1.6
log K_6	0.2	<0.2	<0.2	0.2

[a] The error of log K_i values is ±0.1 units. [b] Not calculated. [c] Not studied because the compound could not be synthesized.

relative orientations throughout the whole pH range. This leads to deviations from the protonation shift additivity which is the basis of the Sudmeier and Reilley's analysis.[40]

We observe no general trend for the pH dependence of C_N and $C_{N'}$ for methylene groups, which may increase, decrease or remain constant, when the pH decreases, and their values are sometimes much larger or much smaller than those expected for linear and larger macrocyclic amines. Furthermore, these constants show no obvious general decrease when the ring size increases. In the asymmetric amines, the values of C_N and $C_{N'}$ for $n = 1$ are considerably higher for the neighbouring CH_2 groups of the propane than of the ethane chains, but not for $n \geq 2$ (see Table 3). These observations result from the effect that the increase in size of the macrocyclic ring has on its flexibility and conformational preferences. Protonation of one nitrogen next to a propane chain, for instance, can lead, through internal hydrogen bonding, to a stable chair-preferred conformation for the resultant six-membered ring, which causes an increase in the value of log K_1 (such as in [9]aneN$_3$ *versus* the larger amines, or NOTA *versus* DETA, UNTA or DOTA, see Table 2). This conformational effect also increases the shielding constants, as a result of a larger effect of the positive charge at the neighbouring nitrogen atoms. The through-space effect of any positive charge at the third nitrogen atom could also be much greater than anticipated if the middle CH_2 group at the locked propane chain approached it in space from below the ring,

Table 3 Shielding constants (ppm) and fractional protonations calculated from the ^{1}H NMR pH titration curves of various cyclic amines

Molecule	Proton type[c]	n	$(C_N + C_{N'})$[a]	C_N	$C_{N'}$	C_N^m	f_N	$f_{N'}$
[9]aneN$_3$	a	1	1.02	*b*	*b*	—	0.33	0.33
		2	1.05	*b*	*b*	—	0.67	0.67
		3	0.96	*b*	*b*	—	1.00	1.00
Me$_3$[9]aneN$_3$	a, b	1	1.08	*b*	*b*	0.51	0.33	0.33
		2	0.87	*b*	*b*	1.56	0.67	0.67
[10]aneN$_3$	a, b, c′	1	1.15	0.89	0.26	—	0.14	0.43
		2	0.82	0.53	0.29	—	0.42	0.79
	c	1	*b*	0.51	*b*	—	*b*	*b*
		2	*b*	0.53	*b*	—	*b*	*b*
Me$_3$[10]aneN$_3$	a, b, d, e	1	0.76	0.58	0.18	0.54	0.24	0.38
		2	1.26	0.84	0.42	0.75	0.34	0.83
	c, c′	1	*b*	0.18	*b*	*b*	*b*	*b*
		2	*b*	1.10	*b*	*b*	*b*	*b*
[11]aneN$_3$	b, c, d	1	1.18	0.94	0.24	—	0.52	0.24
		2	1.12	0.73	0.39	—	0.74	0.63
	a	1	0.38	*b*	*b*	—	*b*	*b*
		2	1.08	*b*	*b*	—	*b*	*b*
[12]aneN$_3$	a, b	1	0.86	0.72	0.14	—	0.33	0.33
		2	1.29	0.87	0.42	—	0.67	0.67
		3	1.32	0.75	0.57	—	1.00	1.00
Me$_3$[12]aneN$_3$	a, b, c	1	1.31	0.90	0.41	0.63	0.33	0.33
		2	1.64	1.14	0.50	0.99	0.67	0.67
		3	1.31	1.02	0.29	0.81	1.00	1.00

[a] The sum $(C_N + C_{N'})$ is included in this Table for comparison purposes, because separate C_N and $C_{N'}$ values could not be obtained in some cases, *e.g.* for protons a of [9]aneN$_3$. [b] Not calculated. [c] The subdivisions of proton types into groups reflect the mathematical procedure to calculate the shielding constants.

thus increasing its $C_{N'}$ value [*e.g.* $C_{N'}$ for protons CH$_2$(a) in [12]aneN$_3$, see Table 3]. We also observe that the protonation shifts of the methyl groups (C_N^m) increase as the macrocycle becomes protonated, especially for the smaller rings (*e.g.* Me$_3$[9]aneN$_3$, Table 3). This is in agreement with the view[43] that the methylated cyclic amines do not form strong intramolecular hydrogen bonds when an amine group is protonated, which causes the methyl groups to be preferentially directed towards the inside of the ring, therefore experiencing a larger shielding effect due to the nearby positively-charged nitrogens.[20]

The unusual conformational preferences of the various protonated forms of these macrocyclic rings lead to observed pH dependences of the linewidths of some of their ^{1}H NMR resonances.[9,11] This was observed in the methylated cyclic triamines (although not in the non-methylated amines) where the CH$_2$ resonances of the ethane and propane ring chains are sharp for the unprotonated form L, but become increasingly broader for the partially protonated forms HL$^+$ and H$_2$L^{2+}. These resonances generally sharpen at higher temperatures. The linewidths of the methyl resonances, however, remain unaffected by protonation. This process is most probably caused by slow interconversion between the various ring conformations due to slow nitrogen inversion in the partially protonated forms. The presence of the bulky methyl substituents at the nitrogen atoms may not only slow down the nitrogen inversion process, but also increase the chemical shift differences between the CH$_2$ protons in the different conformations, thus causing line broadening.

Triazamacrocyclic Triacetate Ligands.—The ^{1}H NMR spectra of NOTA, DETA, UNTA and DOTRA were assigned on the basis of their signal intensities and multiplicities and also by comparison with the unsubstituted cyclic amines (Fig. 2). Their ^{1}H NMR pH titrations curves (Fig. 4) show various inflections due to the CH$_2$ chemical shifts of the ethane and propane chains of the rings and of the acetate groups, due to stepwise protonation of the nitrogen and carboxylate basic sites. The first two protonations result in deshielding of all of the CH$_2$ protons, to different extents. In the absence of Na$^+$ ions, the first inflection is centred at pH values which are much higher than the first protonation constant of these ligands, obtained by potentiometry in the presence of Na$^+$. For example, the first inflection for NOTA, at pH 13.0, is higher than log K_1 measured for NOTA (11.41) in the presence of 0.1 mol dm^{-3} Na$^+$. This illustrates the effect of Na$^+$ binding to the macrocycle, which has previously been shown[22] to consist of a marked decrease in the first protonation constant, when the Na$^+$ concentration in the medium increases.

The percentage protonation of the nitrogen atoms, f_N and $f_{N'}$, and of the carboxylic oxygen atoms, f_O and $f_{O'}$, of the macrocyclic complexones can be calculated using Sudmeier and Reilley's analysis.[40] However, using the shielding constants derived from the cyclic triamines or their trimethylated derivatives (Table 3), very large or occasionally even negative values of f_N, $f_{N'}$, f_O and $f_{O'}$ are obtained, with very large error limits.[11] This again shows that the methylated cyclic amines are very poor models for the carboxylate derivatives of identical ring size.[9,11] It has previously been shown[20] that the first 2 equiv. of acid added to NOTA protonate exclusively the three nitrogen atoms. That can also be assumed to be the case for the other complexones, because the first two log K_i values of DETA, UNTA and DOTRA are higher than those of NOTA (see Table 1). Therefore, the shielding constants in the first two protonation stages (n = 1 and 2) can be calculated, as well as the protonation percentages, f_N and $f_{N'}$.

The calculated values of f_N and $f_{N'}$ (Table 4) show that, whereas in the symmetric complexones NOTA and DOTRA the three nitrogen atoms are equally protonated, in the asymmetric complexones, DETA and UNTA, there are preferential protonations. The first protonation is predominant where six-membered rings can be formed by internal hydrogen bonding (N′ of DETA and N of UNTA, see Fig. 1 and Table 4), while after the second protonation the three percentages are almost equal.

The calculated values of C_N and $C_{N'}$ for the complexones are, in the case of the cyclic triamines previously discussed, highly dependent on pH, ring size and type of proton considered. This, again, is a result of the complex pH-dependent conformational

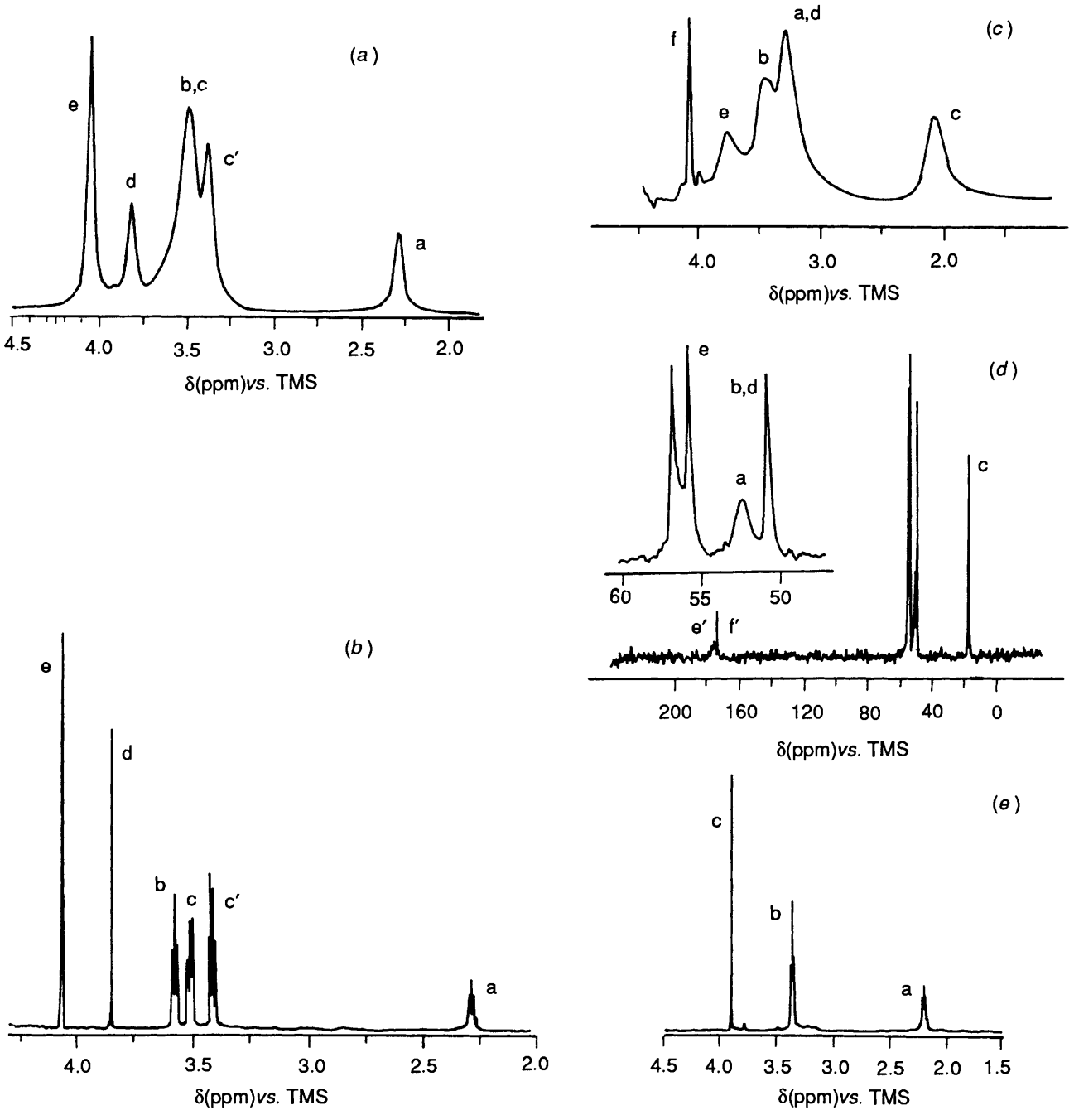

Fig. 5 NMR spectra of the acid form of the complexones in D_2O. Proton spectrum of DETA, pH = 1.0: (*a*) at 25 °C; (*b*) at 80 °C. Spectra of UNTA, pH = 1.0, at 25 °C; (*c*) ^1H spectrum; (*d*) ^{13}C spectrum. (*e*) Proton spectrum of DOTRA, pH = 1.2, at 25 °C [proton spectra (*a*) and (*b*) were obtained at 500 MHz, (*c*) and (*e*) at 200 MHz; ^{13}C spectrum (*d*) was obtained at 50.1 MHz].

equilibria of those complexones. Apart from the effects present in the parent amines, other effects can arise specifically for the complexones. These include the possibilities of hydrogen bonding between protonated nitrogens and non-protonated carboxylates or protonated carboxylates and non-protonated nitrogens.[9,11,19,20] These effects may cause proton shift anomalies, such as the ones detected in CH_2 groups of ethane bridges [Fig. 4(*a*)],[9,20,40] or may slow down the rates of nitrogen inversion, as indeed is observed through broadening effects on the ^1H and ^{13}C NMR spectra of the acid forms of the asymmetric complexones DETA and UNTA, although not for the symmetric ones, NOTA and DOTRA (Fig. 5). These broadening effects disappear at high temperatures [Fig. 5(*a*), (*b*)]. In the case of UNTA, for example, specific broadening is observed for the ^{13}C resonances of the carboxylate and CH_2 carbons of the acetate groups e and the CH_2 groups a of the ethane bridge. These effects reflect the slow rate of inversion of the two nitrogen atoms N′ due to the two types of intramolecular hydrogen bonding interactions referred to above, which involve the acetate arms e and the two nitrogen atoms N′. Although these intramolecular processes cannot be studied in detail due to their complexity, a quantitative analysis of the NMR titration curve of Fig. 4(*c*) shows that, at pH *ca.* 1.0, the three carboxylate atoms and the three nitrogen groups are all partially protonated (*n ca.* 4), but with preferential protonation at N and at the acetate arms e (see later and the fractional protonations of Table 6). These proton distributions are compatible with the types of process discussed above.

The difficulties of using Sudmeier and Reilley's method to obtain the percentage protonations of the triaza macrocyclic

Table 4 Values of C_N and $C_{N'}$ (ppm) and fractional protonations calculated for the various cyclic triaminocarboxylic acids at $n = 1$ ($n = 2$ in parentheses)

Molecule	Proton type	C_N	$C_{N'}$	f_N	$f_{N'}$	$f_O, f_{O'}$
NOTA	a, b	0.85 (0.70)	0.42 (0.66)	0.33 (0.67)	0.33 (0.67)	0 (0)
DETA	a	—	0.42 (0.61)			
	b	0.92 (1.12)	—			
	c, c'	0.30 (0.85)	0.42 (0.40)			
	d, e	0.79 (0.48)	—	0.24 (0.72)	0.38 (0.64)	0 (0)
UNTA	a	$(C_N + C_{N'}) = 0.20$ (1.07)				
	b, d	0.53 (0.98)	—			
	c	—	0.31 (0.43)			
	e, f	0.94 (0.38)	—	0.60 (0.76)	0.20 (0.62)	0 (0)
DOTRA	a	—	0.39 (0.45)			
	b	1.17 (0.96)	—	0.33 (0.67)	0.33 (0.67)	0 (0)
	c	0.87 (0.81)	—			

Table 5 Fractional protonations of nitrogen atoms and carboxylate groups in the symmetric complexones NOTA and DOTRA, as a function of the number of protons added

	NOTA		DOTRA	
n	f_N	f_O	f_N	f_O
1	0.33	0.00	0.33	0.00
2	0.67	0.00	0.67	0.00
3	0.67	0.33	0.67	0.33
4	0.67	0.66	0.67	0.66
5	0.73	0.94	0.69	0.98

Table 6 Fractional protonations of nitrogen atoms and carboxylate groups in the asymmetric complexones DETA and UNTA, as a function of the number of protons added

	DETA				UNTA			
n	f_N	$f_{N'}$	f_O	$f_{O'}$	f_N	$f_{N'}$	f_O	$f_{O'}$
1	0.24	0.38	0.00	0.00	0.60	0.20	0.00	0.00
2	0.72	0.64	0.00	0.00	0.76	0.62	0.00	0.00
3	0.72	0.64	0.32	0.34	0.76	0.62	0.16	0.42
4	0.72	0.64	0.60	0.75	0.76	0.62	0.34	0.83
5	0.78	0.67	0.88	1.00	0.80	0.67	0.86	1.00

complexones from shielding constants, for values of the number of moles of added protons $n > 2$, are similar to those found for the tetraaza ligands.[11] We assumed that the shielding constants C_N and $C_{N'}$, for each type of proton of the four triaza complexones studied in this work, have the same pH dependence of the corresponding protons of the tetraaza ligands,[11] since the processes of hydrogen bond formation for $n > 2$ are similar in both cases, and depend on the probability of protonation of the carboxylate groups, f_O. This may be expressed, *e.g.* for C_N, by the equation $C_N(n > 2) = C_N(n = 2) + \alpha f_O$. The value of α was calculated to be 0.3 for the acetate groups, 0.05 for the methylene protons of ring propane chains and 0.1 for those of the ring ethane chains.[11] Taking these assumptions and the values of C_N and $C_{N'}$ for $n = 2$ (Table 4), we proceeded to estimate the entire sequence of protonation of the four ligands, for $n = 3$–5. The results obtained (with deviations $< 5\%$) are shown in Tables 5 and 6. It was observed that for all the ligands, after the first 2 equiv. of acid have protonated only the nitrogen, the next 2 equiv. protonate exclusively the carboxylate groups. The fifth acid equiv. still adds preferentially, although not exclusively, to the carboxylates. The percentage protonation of the ring nitrogens, achieved at $n = 5$, increases for the larger rings. For the asymmetric complexones DETA and UNTA, preferential protonation of the ring nitrogens for $n = 1,2$ (see discussion above) is followed, for $n = 3,4$, by preferential protonation at the acetate arms bound to the least protonated nitrogens ($f_{O'} > f_O, f_N > f_{N'}$, see Table 6). This observation suggests that the preferential formation of hydrogen bonds in these small chelates occurs between protonated nitrogens and non-protonated carboxylates of the pendant arm bound to them, as this process renders the hydrogen-bonded carboxylate groups less basic.

Finally, we obtained protonation constants for these complexones from their NMR protonation percentages (Table 2), that were taken as the pH values at which n is half-integral. Values of log K_3 and log K_4 agree reasonably well with the results obtained from potentiometry (Table 1). Values of log K_5, and even very low values of log K_6 (largely corresponding to total ring nitrogen protonation), were also obtained (Table 2).

Conclusions

The use of Sudmeier and Reilley's method[40] to determine the protonation sequences of small macrocyclic ligands[11] is complicated by the unusual conformational behaviour of these cyclic compounds, much more complex than their linear polyaminocarboxylate analogues, for which the method was originally developed. The shielding constants C_N and $C_{N'}$ of the methylene protons continuously increase with pH and are different for different types of protons. We analysed, by ^1H and ^{13}C NMR spectroscopy, some of the origins of these conformational properties of the assymmetric complexones. Their restricted flexibility results from changing electrostatic and hydrogen bond interactions, as the various groups are protonated.[11]

Previously proposed[11] empirical relations for the pH dependence of the C_N and $C_{N'}$ shielding parameters proved useful for the small triaza macrocyclic complexones, allowing detailed microscopic interpretation of their macroscopic protonation constants.

The very high values of the first protonation constant of the complexones, which are very sensitive to the presence of Na^+ in the medium, reflect their slow and difficult first deprotonation, particularly of the larger ligands UNTA and DOTRA.[25] This deprotonation step may be rate determining in the process of binding of these chelates to metal ions[25,44] and may also affect the thermodynamic stability of the complexes formed. This problem is under further investigation.

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