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NMR conformational study of diamagnetic complexes of some triazatriacetate macrocycles

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Abstract

The conformational properties of the diamagnetic complexes formed by five triazatriacetic macrocyclic ligands with monovalent (alkaline) and divalent (alkaline-earth, Zn^{2+} and Cd^{2+}) cations have been studied by proton nuclear magnetic resonance spectroscopy (^{1}H NMR) in aqueous solution as a function of pH and temperature. These structurally related triazatriacetic ligands, 1,4,7-triazacyclononane-*N,N′,N″*-triacetic acid (NOTA), 1,4,7-triazacyclodecane-*N,N′,N″*-triacetic acid (DETA), 1,4,8-triazacycloundecane-*N,N′,N″*-triacetic acid (UNTA), 1,5,9-triazacyclododecane-*N,N′,N″*-triacetic acid (DOTRA), and 9,10-benzylidene-1,4,7-triazacyclotridecane-*N,N′,N″*-triacetic acid, (BUNTA) have triazamacrocyclic rings with different sizes and flexibilities, bearing three pendant acetate arms. In the case of the alkaline-earth, Zn^{2+} and Cd^{2+} cations, only one complex form (1:1) has been detected for all the ligands studied. In most cases the metal ion is coordinated to all the ligand ring nitrogens and to all or some of the carboxylate groups of the pendant arms, except when a poor fit of the cations into the macrocyclic hole occurs, such as for the Ba^{2+} complexes of DETA, UNTA and DOTRA and the Ca^{2+} and Sr^{2+} complexes of BUNTA. The resonance patterns of the ring proton resonances, determined by the long lifetime of the metal–nitrogen bonds, indicate that the six-membered rings formed upon chelation are conformationally rigid and the five-membered rings are conformationally flexible. The multiplicity of the acetate proton resonances shows that the metal–oxygen bonds are long-lived or short lived depending whether the acetates are bound to nitrogens involved in two ring bridges of equal or unequal sizes.

Keywords: NMR study; Alkaline complexes; Alkaline-earth complexes; Triazaacetate macrocycle complexes; Diamagnetic complexes

1. Introduction

The polyfunctional macrocyclic ligands display a specific coordination behaviour, highly selective and pH dependent, and form stable complexes with a large variety of metal ions [1–3]. The synthesis of specific complexing agents, containing polyazamacrocyclic rings of varying dimensions and substituent groups as well as distinct pendant arms led to numerous studies of their thermodynamic and kinetic complexation properties and the elucidation of the conformational properties of their metallic chelates, namely of polyaza-polycarboxylates with alkaline-earth, transition and post-transition cations [4–10]. Various polyazamacrocyclic complexes have found a variety of biomedical applications, such as bifunctional complexing agents for radioisotopes in nuclear medicine [11–13], contrast agents for magnetic resonance imaging (MRI) [14] or shift reagents for in vivo magnetic resonance spectroscopy (MRS) [15]. They may also have useful analytical applications or as structural models in bioinorganic chemistry.

The stability of these chelates depends on the relative dimensions of both the macrocyclic cavity and the ionic radius of the metal, as well as on the degree of flexibility of the ligand and the number and nature of their donor atoms and pH sensitive substituent groups. These factors determine the fitting of the cation into the macrocycle, occupying a central position between two parallel planes defined, respectively, by the ring nitrogens and the carboxylate oxygen atoms. The metal ion will coordinate totally or only partially to the cyclic ligand [16], according to its electronic structure and size, in order to attain an optimum fit, yielding a 'cage' type structure [17,18]. The kinetics of the complexation and dissociation processes [19,20] and the solution structures of

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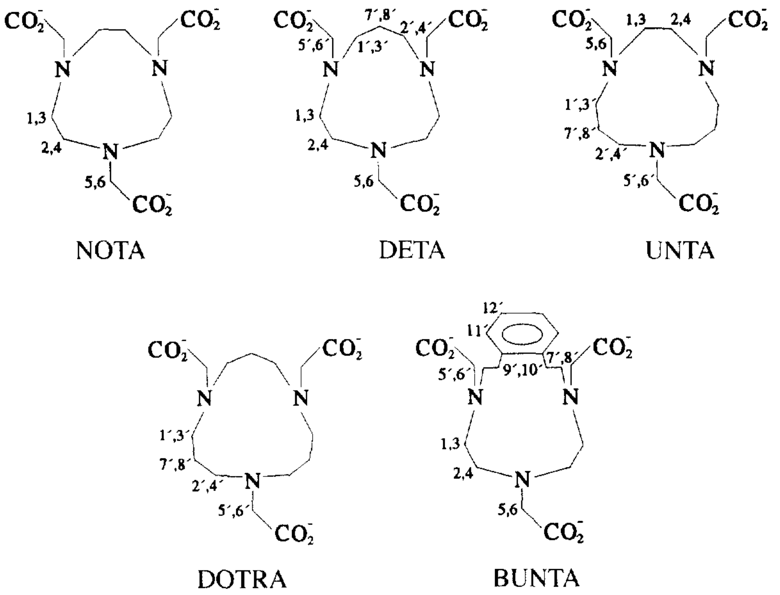

Fig. 1. Chemical structures and atom numbering scheme used for the proton NMR assignments for the triazatriacetate macrocyclic ligands investigated in this work.

these chelates [21,22] are also generally affected by the factor described above.

In this study, the complexes formed by a family of structurally related triazamacrocyclic triacetate ligands, 1,4,7-triazacyclononane-*N*,*N*′,*N*″-triacetic acid (NOTA), 1,4,7-triazacyclodecane-*N*,*N*′,*N*″-triacetic acid (DETA), 1,4,8-triazacycloundecane-*N*,*N*′,*N*″-triacetic acid (UNTA), 1,5,9-triazacyclododecane-*N*,*N*′,*N*″-triacetic acid (DOTRA) and 9,10-benzylidene-1,4,7-triazacyclotridecane-*N*,*N*′,*N*″-triacetic acid (BUNTA) (Fig. 1) with the alkaline, alkaline-earth, Zn^{2+} and Cd^{2+} ions were investigated by ^1H NMR spectroscopy, in aqueous solution at different pH and temperature conditions. The effect of changing the macrocyclic ring size and flexibility and the cation charge and ionic radius on the chelate structural and dynamic properties is investigated. These observations are discussed and correlated with previous studies on some of these ligands and these and other cations, such as solution ligand protonation [23,24], thermodynamics of complexation [4,5,25–28], structural studies in crystals by X-ray diffraction [29–32] and in solution by NMR [28,33,34] and solution water proton relaxivity studies of Gd^{3+} complexes [35].

2. Experimental

2.1. Reagents

The ligand NOTA was synthesized and purified as described elsewhere [23], as well as the macrocycles DETA [24], UNTA [24], DOTRA [24,28] and BUNTA [36]. The purity of the ligands was checked by proton NMR spectroscopy. The chlorides of Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+} and Cd^{2+} were obtained from Aldrich.

2.2. Preparation of the solutions of the complexes

The concentration of the ligand solutions was determined by complexometric titration, using a copper chloride solution and murexide (5,5′-nitrilodibarbituric acid) as an indicator. The complexes were prepared in D_2O (99.8% D, from Sigma) solutions, at 1×10^{-2} mol dm^{-3} concentrations, by adding stoichiometric amounts of D_2O solutions of the macrocyclic ligands to stock D_2O solutions of the corresponding metal chlorides. The pH of the solutions was adjusted with DCl and CO_2-free NaOD (from Sigma) using a Crison MicropH 2002 pH meter with an Ingold 405-M5 combined electrode, and corrected for the deuterium isotope effect using $pD=pH+0.5$.

2.3. NMR spectroscopic studies

^1H NMR spectra were recorded on Varian XL-200, Varian Unity-500 and General Electric GE-500 Fourier transform spectrometers (operating at external magnetic fields of 4.7, 4.7 and 11.8 T, respectively). Either TSP-d_4 (tetradeuterated sodium trimethylsylilpropionate) or 2-methyl-2-propanol ($\delta=1.29$ ppm) were used as internal references for the ^1H NMR spectra. NMR spectra were obtained at temperatures between 20 and 80°C, in the pH range from 1.0 to 13.0. The experiments at variable temperature were run with a precision of ±0.5°C. The ^1H NMR spectra were assigned according to the literature [23,24,28,33,34], or using two-dimensional homonuclear (COSY) correlation spectra [37,38].

3. Results and discussion

Fig. 1 represents the chemical structures of the triazamacrocyclic ligands NOTA, DETA, UNTA, DOTRA and

BUNTA, as well as the numbering scheme adopted for the proton NMR assignments in this study. Methylenic protons on ethylenediamino moieties of the macrocycles were numbered 1,2,3,4, and those on propylenediamino moieties were numbered 1′,2′,3′,4′ for the CH_2 groups in alpha position relative to the nitrogens, and 7′,8′ for the beta CH_2 groups. In the case of BUNTA, the CH_2 groups in alpha and beta positions relative to the nitrogens in the benzylidene containing moiety were numbered 7′,8′ and 9′,10′, respectively, while the alpha and beta benzylidene protons were numbered 11′ and 12′. The CH_2 protons of the acetate pendant arms were numbered 5,6 for those bound to a nitrogen connecting two ethylenediamino bridges (NOTA, DETA and BUNTA) or one ethylenediamino and one propylenediamino bridge (UNTA), and 5′,6′ in the other cases (DETA, UNTA, DOTRA and BUNTA).

Fig. 2 shows some representative proton NMR spectra of the systems studied, illustrated with the Mg^{2+} chelates of the NOTA, DETA, UNTA and DOTRA ligands, and Fig. 7 shows the spectra obtained for various complexes of the ligand BUNTA. Spectral assignments used literature data on similar systems when available [23,24,28,33,34], and in particular the results of two-dimensional homonuclear (COSY) correlation spectra. Such a COSY spectrum is shown in Fig. 6 for the $Zn(DOTRA)^-$ system. In general, strong cross-peaks were observed between methylenic ring protons in geminal and trans-vicinal positions, but only weak or no cross-peaks were observed between gauche-vicinal positions. Tables 1–5 summarize the proton shifts for the complexes studied. The proton assignments in these tables refer to the numbering schemes of Fig. 1 and Fig. 3. The latter figure gives a schematic representation of the conformations of the chelate rings formed in the complexes of the divalent cations with the triazatriacetate macrocyclic ligands: (a) the ethylenediamine ring ($M–N–C_1–C_2–N$) in a δ conformation, where 1,4 and 2,3 refer to the axial and equatorial ring protons, respectively); (b) the propylenediamine ring ($M–N–C_1–C_5–C_2–N$) in a chair conformation, where 1′,4′,8′ and 2′,3′,7′ refer to the axial and equatorial ring protons, respectively).

The proton complexation shifts observed at a given pH value for a coordinated macrocycle result from two factors: the chemical shift due to the protonation of the basic sites of the ligand (Eq. (1)) and the shift resulting from the complexation process (Eq. (2)):

$$L^{x-} + nH^+ \rightarrow H_nL^{(x-n)-} \quad (1)$$

$$M^{n+} + L^{x-} \rightarrow ML^{(x-n)-} \quad (2)$$

$$H_nL^{(x-n)-} + M^{n+} \rightarrow ML^{(x-n)-} + nH^+ \quad (3)$$

The complexation shifts, generally positive (for higher frequencies) and determined by the type of metal ion and its spatial localization relative to the observed proton, are obtained by difference of the shifts observed for the complex at a given pH and the shifts of the same protons for the fully deprotonated ligand (see footnotes to tables). The complexation shift actually observed at a given pH value (Eq. (3)) is strongly pH dependent, as it is obtained by subtracting the protonation shift at the same pH value from the complexation shift. The protonation shift is positive and determined by the number of protons (n) bound to the macrocycle, by the nature of the protonation sites and the position of the proton relative to those sites [39].

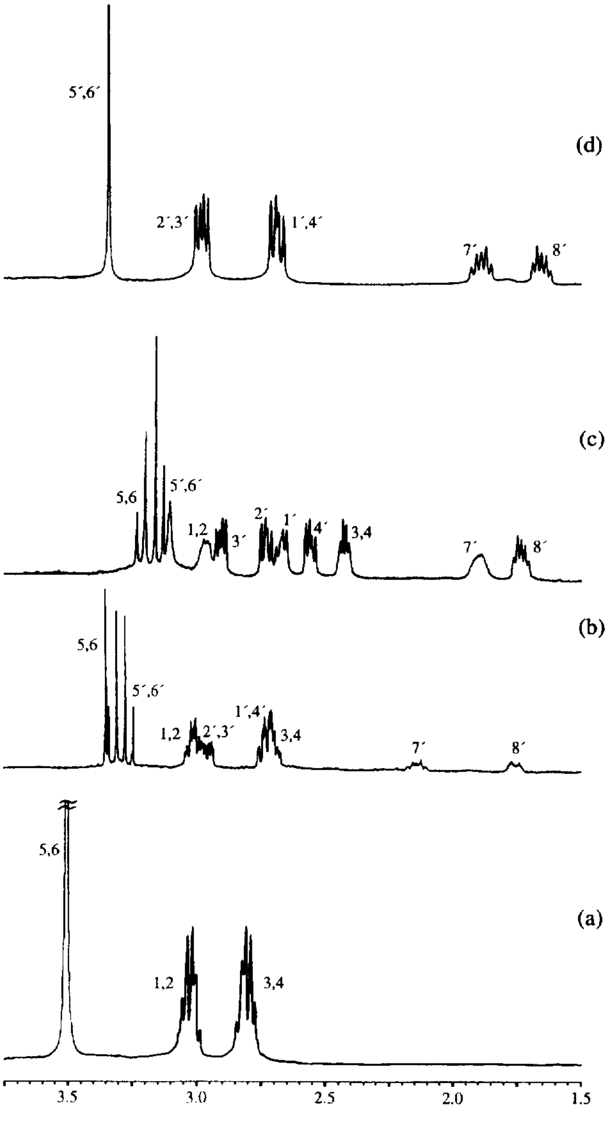

Fig. 2. 500 MHz proton NMR spectra of the 1:1 Mg^{2+} complexes with the triazatriacetate macrocyclic ligands in aqueous solution: (a) $Mg(NOTA)^-$; (b) $Mg(DETA)^-$; (c) $Mg(UNTA)^-$; (d) $Mg(DOTRA)^-$ (20°C, pH 7.0, ligand and metal ion concentrations of 1×10^{-2} mol dm^{-3}).

We now present and discuss in detail the NMR data for complexes of each of the ligands studied.

3.1. NOTA complexes

The proton NMR spectra of aqueous solutions containing stoichiometric mixtures of the triazamacrocycle NOTA and the alkali metal cations ($M = Li^+$, Na^+, K^+, Cs^+) were investigated in the pH range 2.0–11.5. The Li^+/NOTA sys-

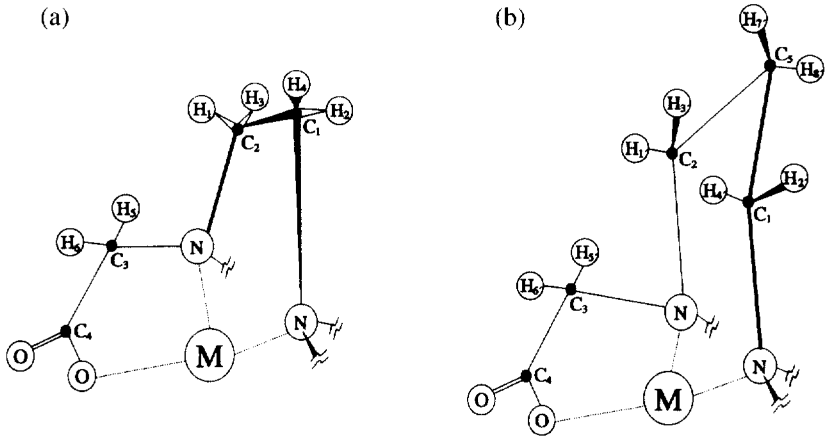

Fig. 3. Schematic representation of the conformations of the chelate rings formed in the complexes of the divalent cations with the triazatriacetate macrocyclic ligands: (a) ethylenediamine ring (M–N–C_1–C_2–N) in a δ conformation; 1,4 and 2,3 refer to the axial and equatorial ring protons, respectively; (b) propylenediamine ring (M–N–C_1–C_5–C_2–N) in a chair conformation; 1′,4′,8′ and 2′,3′,7′ refer to the axial and equatorial ring protons, respectively.

tem gives signals from both the free and the metal-bound forms of the ligand in slow exchange in the pH range of 4.5 to 10.5. Their relative proportions are pH dependent and only the complex species is detected at pH 5.6. The signals of both the ring and acetate methylene protons of the bound form are singlets, indicating that the Li^+ ion coordinates strongly to the oxygens of the acetate pendant arms but not to the ring nitrogens, which explains the absence of splitting of those ring proton resonances. The observed shifts (Table 1) agree with the values reported in the literature for a diprotonated $Li(H_2L)$ complex [27], where the protonations occur probably at two ring nitrogens. In the cases of the M^+/NOTA systems (M = Na, K, Cs) a fast or intermediate exchange situation between the free and the coordinated forms of the ligand is observed at pH 7.0 and 20°C. The acetate protons are sharp singlets with small complexation shifts, and the ethylenediamine protons yield a broader NMR signal, reflecting a weak coordination of these ions to the macrocycle. For the Na^+/NOTA system, the effect of pH on the proton signals was studied in detail. Outside the pH interval of 4.5–10.0 only the free ligand was present, but within this pH region the signals shifted slightly and the ring methylenic proton increasingly broadened as the pH increased.

These results reflect the formation of weak complex species between NOTA and the alkali ions in aqueous solution. The ions probably coordinate preferentially to the carboxylate oxygens of the ligand, and, in some pH regions, also to the ring nitrogens, the metal–oxygen and metal–nitrogen bonds being labile at 20°C.

The proton NMR spectra of aqueous stoichiometric mixtures of NOTA and the alkaline earth cations ($M^{2+} = Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}$), as well as Zn^{2+} or Cd^{2+}, investigated at 20°C in the pH range of 2.0 to 12.5, show only the signals of the 1:1 chelates in the pH intervals of 7.0 to 10.0 for Mg^{2+} and Ca^{2+}, of 6.5 to 8.5 for Sr^{2+} and Ba^{2+}, and 2.0 to 12.5 for Zn^{2+} and Cd^{2+}. The increasing pH interval of complex stability (Sr, Ba < Mg, Ca < Zn, Cd) observed correlates with the thermodynamic stabilities of the complexes (log K values at 25°C for the $M(NOTA)^-$ chelate: 9.69 (Mg), 8.92 (Ca), 6.83 (Sr), 5.10 (Ba), 18.3 (Zn), 16.0 (Cd) [25,27]). Outside these pH ranges, the free and bound ligand forms are observed in slow exchange.

Table 1
Proton NMR chemical shifts (δ_i) [a] of some diamagnetic complexes of the ligand NOTA [b] (20°C, pH 7.0)

Cation	$\delta(1,2)$	$\delta(3,4)$	$\delta(5,6)$	Cation	$\delta(1,2)$	$\delta(3,4)$	$\delta(5,6)$
H^+	3.10	3.10	3.55	Ba^{2+} *	3.06	3.02	3.48
Li^+ *	3.26		3.76	Zn^{2+}	2.81	2.66	3.35
Na^+ *	3.03	2.98	3.48	Cd^{2+}	2.85	2.75	3.40
K^+ *	3.06	3.03	3.52	Ga^{3+} [c]	3.51	3.23	3.88
Cs^+ *	3.05	3.03	3.51	In^{3+} [c]	3.24	3.07	3.70
Mg^{2+} *	2.93	2.75	3.48	La^{3+} [d]	2.97	2.86	3.52
Ca^{2+} *	2.80	2.70	3.40	Lu^{3+} [d]	2.87	2.79	3.46
Sr^{2+} *	2.74	2.68	3.30				

[a] Proton chemical shifts (ppm) relative to TSP-d_4; all spectra were obtained at 11.8 T (500 MHz), except in the cases marked by the symbol * run at 4.7 T (200 MHz).

[b] δ_H (ppm) ($NOTA^{3-}$): $\delta(1$–$4) = 2.70$, $\delta(5,6) = 3.30$ [24].

[c] pD = 5.0 [32–34].

[d] Ref. [23].

The proton spectra of all complexes show a singlet for the acetate methylene protons (H_5, H_6) and a symmetric AA'MM' multiplet pattern for the diastereotopic ring methylene protons (H_{1-4}) (see Fig. 2(a)), consistent with a local C_{3v} symmetry. Similar spectra were also observed previously for the 1:1 chelates of the trivalent ions, M(NOTA) ($M^{3+}=Ga^{3+}$, In^{3+}, La^{3+}, Lu^{3+}) [23,32–34]. The observed shift data is shown in Table 1.

The chiral metal-bound nine-membered macrocyclic ring of NOTA can have two triangular {333} conformations, made up of λ or δ conformations of the three five-membered M–N–C_1–C_2–N chelate rings (Fig. 3(a), Fig. 4 I, II). For a given arrangement of the macrocyclic ring, (λλλ) or (δδδ), the acetate groups can be oriented in a clockwise or anticlockwise fashion (Δ, Λ configuration). Type I [(Δ(λλλ), Λ(δδδ) enantiomers] or type II [Δ(δδδ), Λ(δδδ)] structures can occur, with positive or negative twist angles between the two planes defined by the metal coordinating ring nitrogens and acetate oxygens [29,31]. For each of these structures, the decrease of the macrocycle flexibility results in the magnetic non-equivalence of the axial (H_1 and H_4) and equatorial (H_2 and H_3) ethylenediamine ring protons (Fig. 3(a)). However, if the (λλλ) ⇔ (δδδ) ring conformational interconversion is fast on the NMR time scale, protons H_1 and H_2, as well as H_3 and H_4, are averaged by this process, leading to the splitting of the respective resonances into an AA'MM' pattern. This is observed for all the NOTA chelates studied, which have flexible macrocyclic rings. The multiplicity of the acetate protons depends on the relative metal–oxygen and metal–nitrogen lifetimes [40], which, in turn, is determined by the effective charge of the coordinated ion (Z^2/r) [40–43]. For the systems studied here, the singlet acetate resonances indicate that the metal–nitrogen bonds have long lifetimes and the metal–oxygen bonds have short lifetimes, similar to what has been observed for the corresponding EDTA complexes [40].

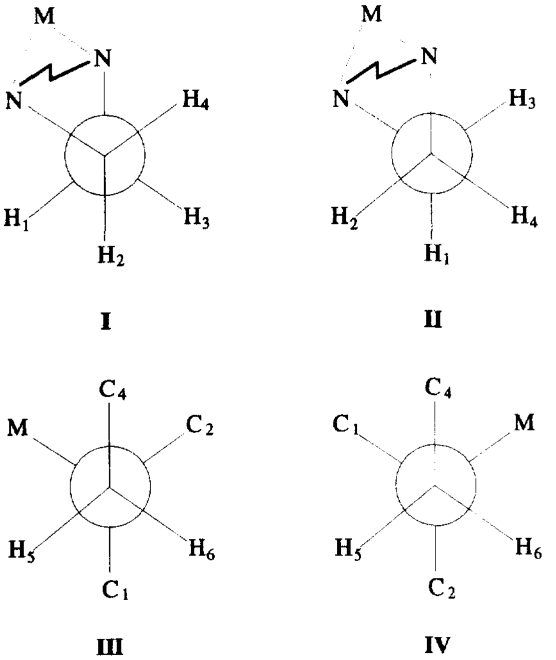

Fig. 4. Newman projections representing the staggered conformations of the ethylenediamine groups of the macrocyclic ring (along the C_1–C_2 bond) – I (δ) and II (λ) – and of the acetate groups (along the C_3–N bond) – III and IV – in the metal chelates.

Fig. 5(a) shows a plot of the proton shifts of the acetate (H_5, H_6) and ethylenediamino (H_1, H_2) protons versus the effective charge density of the metal ion (Z^2/r) for the NOTA chelates with divalent and trivalent ions [23,32–34]. These shifts result from the electrostatic effect of the distinct cations on the ligand nuclei, which is proportional to (Z^2/r) [43]. If a linear correlation is obtained, all the complexes are isostructural, as its slope reflects the way in which a particular type of protons samples its electrostatic environment. This depends on the geometry of the complex, as the electric field effect caused by the metal ion on the polarization of each C–H bond depends on the component of the electric field of the cation at the C–H hydrogen atom along the direction of the C–H bond [44]. Fig. 5(a) shows that such a correlation for the proton shifts of the NOTA complexes is poorer than that found for the corresponding EDTA chelates [43]. This is more clearly shown in Fig. 5(b), where the chemical shift difference ($\Delta\delta_H$) between the two signals of each methylenic group of the macrocyclic ring the difference between the proton chemical shifts of each methylene group of the ring is plotted versus the ratio (Z^2/r). The different slopes of the correlations found for the M^{2+} and M^{3+} cations clearly indicate the different overall structures of the corresponding NOTA chelates. These may reflect different ranges of the twist angle between the metal–nitrogen and metal–oxygen vectors in those structures [32].

3.2. DETA and UNTA complexes

The proton NMR spectra of aqueous stoichiometric mixtures of the DETA or UNTA ligands and the alkaline earth cations ($M^{2+}=Mg^{2+}$, Ca^{2+}, Sr^{2+}, Ba^{2+}), as well as Zn^{2+} or Cd^{2+}, were investigated at 20°C in the pH range 2.0–12.5. In the case of DETA, the 1:1 chelates are fully formed in the pH intervals 4.0–12.5 for Mg^{2+} and Zn^{2+}, 7.0–10.0 for Ca^{2+}, Cd^{2+} and Sr^{2+}, and 9.0–10 for Ba^{2+}. Thus, the amplitude of the pH stability range of the DETA complexes follows the order Mg^{2+}, $Zn^{2+}>Ca^{2+}$, Cd^{2+}, $Sr^{2+}>Ba^{2+}$, which agrees almost exactly with the increasing order of the corresponding Z^2/r ratios. Outside the pH ranges of stability, the free and bound ligand forms are observed in slow exchange. The Ba^{2+} chelate displays a particularly narrow pH stability range, outside which only a broadening of the NMR proton signals of the free ligand is detected, at 20°C, reflecting intermediate exchange between the free and complexed species in solution. This behaviour reflects the weak coordination of the large Ba^{2+} to the ligand ring nitrogens resulting from a poor fit into the small cavity of the macrocycle.

The proton NMR spectra of complexes of DETA with the alkaline-earth and the transition metal Zn^{2+} and Cd^{2+} ions

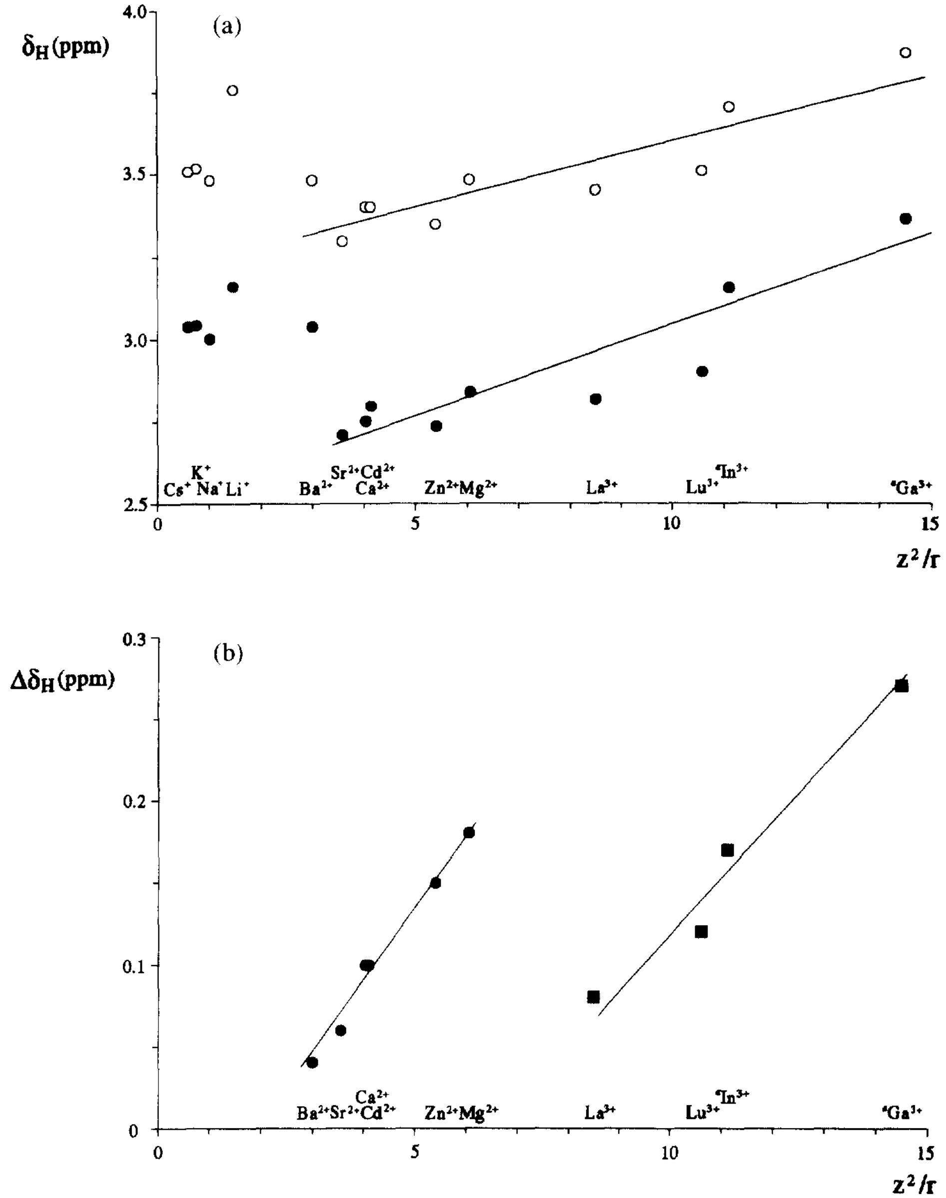

Fig. 5. Correlation of proton NMR chemical shifts with the effective charge density of the metal ion (Z^2/r) for the NOTA chelates with several divalent ions (this work, 20°C, pH 7.0) and trivalent ions [23,32–34]: (a) chemical shifts of acetate (H_5, H_6) (○) and ethylenediamino (H_1, H_2) protons (●); (b) chemical shift difference between the two signals of each methylenic group of the macrocyclic ring ($\Delta\delta_H$).

in aqueous solution, display a large number of signals (Fig. 2(b), Table 2), which result from their asymmetry and (in some cases) conformational rigidity. The metal ion coordinates to the three ring nitrogens, leading to the splitting of the NMR signals of the methylenic protons of the macrocyclic ring, detected for all the systems studied. While all the DETA complexes display a similar conformation of the macrocyclic ring in solution, its flexibility changes as a function of the charge and dimensions of the metal ion, giving rise to distinct proton NMR shifts and resonance patterns (Table 2). Again, the multiplicity of the resonances of the acetate protons depends on the relative metal–oxygen and metal–nitrogen lifetimes [40].

The CH_2 protons of the propylenediamine bridge, $H_{1'-4'}$ and $H_{7',8'}$ (Fig. 1), originate in all cases A_2B_2MN resonance patterns (Fig. 2(b), Table 2), indicating that the six-membered chelate rings formed within the complex species are rigid for all the systems studied, displaying a chair-like conformation shown schematically in Fig. 3(b) (identical to that found in the metal chelates of the 12-membered triazatriacetate macrocycle DOTRA [28]). On the other hand, the diastereotopic methylene protons (H_{1-4}) of the two intramolecular rings comprising the ethylenediamine groups give a symmetric AA′MM′ multiplet pattern for the Mg^{2+}, Sr^{2+} and Zn^{2+} chelates, showing that they are flexible in solution chelates (as for all the NOTA complexes investigated), whereas the Ca^{2+} and Cd^{2+} chelates gave ADMX patterns, typical of conformationally rigid rings. As to the two types of acetate protons, all the complexes studied gave an AB type multiplet for the two acetate groups adjacent to the propylenediamine

Table 2
Proton NMR chemical shifts (δ_i) [a] of the complexes of the ligand DETA [b] with the alkaline-earth, Zn^{2+} and Cd^{2+} ions (20°C, pH 7.0)

Cation	δ(1)	δ(2)	δ(3)	δ(4)	δ(1′,4′)	δ(2′,3′)	δ(7′)	δ(8′)	δ(5,6)		δ(5′,6′)
H^+	3.25	3.31	3.31	3.25	3.25	3.31	2.07	2.07	3.61		3.55
Mg^{2+}	3.05	3.05	2.73	2.73	2.72	3.00	2.11	1.71	3.33	3.36	3.40
Ca^{2+}	2.85	2.95	3.39	3.15	2.57	2.69	2.27	1.68	3.10	3.36	3.26
Sr^{2+}*	3.17	3.17	2.98	2.98	2.49	2.84	2.21	1.83	3.47		3.27
Zn^{2+}	2.88	2.88	2.68	2.68	2.66	2.88	1.97	1.64	3.19	3.23	3.24
Cd^{2+}	2.51	2.72	2.78	2.56	2.00	2.40	1.90	1.54	3.06	2.99	3.14
Ga^{3+}	3.56	3.56	3.16	3.16	3.16	3.56	2.37	1.88	3.81		3.73
In^{3+}	[d]	[d]	[d]	[d]	[d]	[d]	2.24	1.92	[d]		[d]

[a] Proton chemical shifts (ppm) relative to TSP-d_4; all the spectra were obtained at 11.8 T (500 MHz), except in the case marked by the symbol *, run at 4.7 T (200 MHz).
[b] δ_H (ppm) ($DETA^{3-}$): δ(1,3) = 2.72, δ(1′,3′) = 2.78, δ(2,4) = 2.67, δ(5,6) = 3.10, δ(5′,6′) = 3.02, δ(7′,8′) = 1.42 [24].
[c] [34].
[d] Broad multiplet, 18H, 3.90–2.60 ppm.

bridge (H_5 and H_6, Fig. 1) and a singlet for the acetate bound to the nitrogen localized between the two ethylenediamine groups ($H_{5'}$ and $H_{6'}$, Fig. 1), except for the Sr^{2+} chelate, which gave singlets for both kinds of acetate methylenic protons (Table 2). Thus, while in the $Sr(DETA)^-$ system all the metal–oxygen bonds are labile (on the NMR time scale), in the other chelates the M–O bonds of the two equivalent acetates are labile but the M–O bond of the acetate adjacent to the two ethylenediamine groups is inert.

The proton NMR spectra of the Ga(DETA) and In(DETA) chelates have been reported before [34], and their shifts are included in Table 2 for comparison. The spectrum of Ga(DETA) has a symmetry similar to that of $Sr(DETA)^-$, indicating similar flexibility of the macrocyclic ring and labilities of the M–O bonds of the acetate pendant arms in both complexes. The In(DETA) complex gives three broad multiplets difficult to assign, a similar situation to $Ba(DETA)^-$. The Gd(DETA) complex was found to be thermodynamically more stable than Gd(NOTA) (log K_{stab} values of 15.1 and 13.7, respectively [20]).

For the 11-membered triazamacrocycle UNTA, the pH range of stability of the complexes studied follows the order Mg^{2+}, Zn^{2+}, Cd^{2+} (4.0–12.5) > Ca^{2+}, Sr^{2+} (7.0–10.0) ≫ Ba^{2+} (9.0–10.0). Outside the pH ranges of stability, the free and bound ligand forms are observed in slow exchange. In the case of the Ba^{2+} ions the pH range of values where the chelate can be detected is particularly narrow, and outside this range broad NMR proton signals are observed for the $Ba(UNTA)^-$ system at 20°C, reflecting an intermediate-to-slow chemical exchange process between the free and coordinated forms of the ligand in solution. Still, unlike in the $Ba(DETA)^-$ chelate, the ring protons of the $Ba(UNTA)^-$ system give rise to a multiplet, owing to a stronger coordination of this ion to the heteroatoms of the larger UNTA macrocycle.

The flexibility of the intramolecular rings formed within the complexes of this asymmetric macrocycle, as a consequence of the metal coordination of the three ring nitrogens, is quite similar to that found for the chelates of the ligand DETA. The ring containing the ethylenediamine bridge is flexible for all the complexes investigated, yielding AA′MM′ proton resonance patterns. The two six-membered rings formed by the propylenediamine groups are rigid for all the systems studied, displaying a distorted chair-like conformation in solution (see Fig. 3(b)). However, unlike in the DETA or DOTRA complexes, where these chelate rings have a plane of symmetry through the central CH_2 group and yield A_2B_2MN patterns, in the UNTA complexes this symmetry is absent and ABEFMN proton resonance patterns arise owing to the non-equivalence of the adjacent nitrogens (Fig. 2(c), Table 3). The acetate CH_2 protons in the Ca^{2+}, Sr^{2+} and Zn^{2+} chelates originate an AB multiplet for nuclei H_5 and H_6

Table 3
Proton NMR chemical shifts (δ_i) [a] of the complexes of the ligand UNTA [b] with the alkaline-earth, Zn^{2+} and Cd^{2+} ions (20°C, pH 7.0)

Cation	δ(1,2)	δ(3,4)	δ(1′)	δ(2′)	δ(3′)	δ(4′)	δ(7′)	δ(8′)	δ(5,6)		δ(5′,6′)
H^+	2.85	2.85	3.00	3.30	3.00	3.30	1.90	1.90	3.35		3.56
Mg^{2+}	3.09	2.49	2.77	2.82	3.02	2.63	1.90	1.72	3.30		3.25
Ca^{2+}*	2.49	2.43	2.49	2.71	2.71	2.49	1.94	1.60	3.00	3.30	3.00
Sr^{2+}*	2.47	2.37	2.47	2.69	2.69	2.47	1.95	1.63	3.02	3.24	3.02
Zn^{2+}	3.10	2.55	2.88	2.90	3.10	2.74	1.93	1.75	3.27	3.32	3.25
Cd^{2+}	2.93	2.60	2.93	2.93	2.93	2.77	2.12	1.78	3.13		3.23

[a] Proton chemical shifts (ppm) relative to TSP-d_4; all the spectra were obtained at 11.8 T (500 MHz), except in the case marked by the symbol *, run at 4.7 T (200 MHz).
[b] δ_H (ppm) ($UNTA^{3-}$): δ(1–4) = 2.80, δ(1′–4′) = 2.60, δ(5,6) = 3.00, δ(5′,6′) = 3.00, δ(7′,8′) = 1.60 [24].

(of the two equivalent acetate groups), and a singlet for protons $H_{5'}$ and $H_{6'}$ (of the third, non-equivalent, acetate group). For $Mg(UNTA)^-$ and $Cd(UNTA)^-$, however, all the acetate protons yield singlets (Fig. 2(c), Table 3), which reflects a short lifetime for all the metal–oxygen bonds in solution (at 20°C), in contrast to the other chelates, where the M–O bonds of the two equivalent acetate groups are long-lived, the M–O bond involving the third carboxylate being labile.

The UNTA chelate of Ga^{3+} has not been detected by ^{71}Ga NMR, as opposed to the Ga(NOTA), Ga(DETA) and Ga(DOTRA) chelates, which give relatively sharp metal NMR resonances [34]. The UNTA chelates of the Ln^{3+} cations have also not been characterized, as they are too weak to be isolated [45].

3.3. DOTRA complexes

The complexes formed by the ligand DOTRA with the Mg^{2+}, Zn^{2+} or Cd^{2+} ions in stoichiometric amounts, observed between pH 4.0 and 12.5, give quite similar, sharp NMR spectra consisting of A_2B_2MN multiplets for the propylenediamine protons and singlets for the acetate protons, in agreement with previous studies [28] (Fig. 2(d), Fig. 6, Table 4). The assignment of the proton NMR spectra for the macrocyclic moiety was based on the chemical shifts typical of a chair-like conformation (Fig. 3(b)) for the six-membered rings formed by the coordinated propylenediamine groups, where the effect of the electric field due to the metal ion is responsible for the magnetic non-equivalence of the ring protons [28]. In this kind of rigid conformation, the equatorial protons (H_2, H_3 and H_7, Fig. 3(b)) give rise to resonance signals that are shifted to higher frequency values relative to the axial protons (H_1, H_4 and H_8). These multiplets are quite sharp, even after raising the temperature from 20 to 80°C, which reflects the very high rigidity of the chelates in solution. The acetate protons, however, are magnetically equivalent in these systems, giving singlets in the corresponding NMR spectra, which reflect the lability of the M–O bonds.

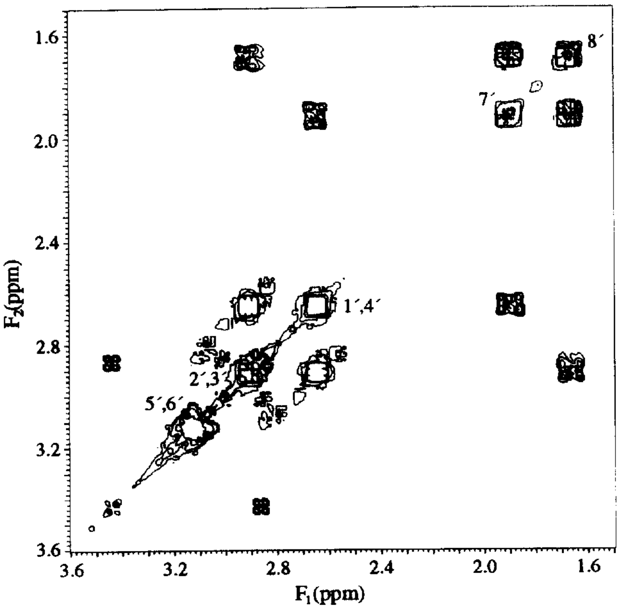

Fig. 6. 500 MHz proton COSY spectrum of the $Zn(DOTRA)^-$ complex in aqueous solution (20°C, pH 7.0, concentration 1×10^{-2} mol dm^{-3}).

Table 4
Proton NMR chemical shifts (δ_i) [a] of the complexes of the ligand DOTRA with the alkaline-earth, Zn^{2+} and Cd^{2+} ions (20°C, pH 7.0)

Cation	$\delta(1',4')$	$\delta(2',3')$	$\delta(7')$	$\delta(8')$	$\delta(5',6')$
H^+	3.02	3.02	1.93	1.93	3.37
Mg^{2+}	2.65	2.93	1.95	1.74	3.26
Ca^{2+}	3.22	3.22	2.12	2.12	3.55
Zn^{2+}	2.64	2.91	1.88	1.65	3.14
Cd^{2+}	2.77	2.97	2.15	1.88	3.24

[a] Proton chemical shifts (ppm) relative to TSP-d_4; all the spectra were obtained at 11.8 T (500 MHz).

[b] δ_H (ppm)($DOTRA^{3-}$): $\delta(1–4) = 2.40$, $\delta(5,6) = 2.90$, $\delta(7,8) = 1.50$ [24].

The $Ca(DOTRA)^-$ complex is detected in the narrow pH range 7.0–11.0, and its proton NMR spectrum at pH 7.0 consists of three broad signals, shifted relative to the free ligand peaks (Table 4). At higher pH values, the observed signals, although broadened, are similar to the ones corresponding to the uncoordinated macrocycle at the same pH. This seems to indicate a much higher lability of the metal–ligand bonds in the $Ca(DOTRA)^-$ complex than in the Mg^{2+}, Zn^{2+} and Cd^{2+} complexes. The weaker coordination of Ca^{2+} is responsible for the increased flexibility displayed by the intramolecular rings within the chelate and its much narrower range of pH stability. The larger Sr^{2+} and Ba^{2+} ions are even more weakly bound to this ligand, yielding proton NMR peaks almost identical to the free ligand, which appear slightly broadened between pH 9.0 and 11.0, owing to the relatively fast chemical exchange process between the coordinated and uncoordinated forms of the macrocycle in solution. This results from an incomplete binding of those larger metal ions, possibly only to the oxygen atoms of the ligand.

The much higher stability of the $Zn(DOTRA)^-$ and $Cd(DOTRA)^-$ complexes (log K values at 25°C of 19.0 and 15.7, respectively [28]) relative to the complexes of the alkaline earth cations (log K values at 25°C for Mg^{2+} and Ca^{2+} of 7.1 and 6.0, respectively [28]) is a consequence of the high affinity of the former cations for the nitrogen donor atoms of the macrocycle. The coordination cavity of DOTRA is not significantly larger than that of the 9-membered triazamacrocycle NOTA, which can help to account for the higher stability of the Mg^{2+} complex relative to the Ca^{2+} complex, observed for both ligands. Yet, while $Mg(NOTA)^-$ and $Ca(NOTA)^-$ are more stable than their DOTRA analogues, the Zn^{2+} and Cd^{2+} chelates formed with NOTA and DOTRA have similar stability constants. This can be explained in terms of the coordination efficiency of the transition metal ions towards the macrocycle nitrogens,

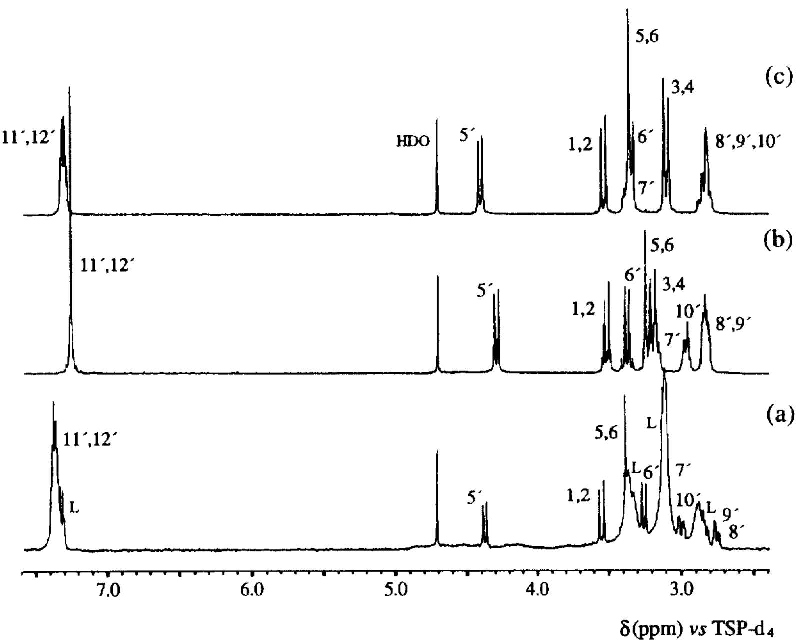

Fig. 7. 500 MHz proton NMR spectrum of the (a) Mg(BUNTA)$^{-}$, (b) Cd(BUNTA)$^{-}$, and (c) Zn(BUNTA)$^{-}$ complexes in aqueous solution (20°C, pH 7.0, concentration 1×10^{-2} mol dm^{-3}). The protons are named according to the scheme of the ligand represented in Fig. 1; 1,4,8',10' and 2,3,7',9' refer to the axial and equatorial ring protons, respectively; L refers to the free ligand.

higher than that displayed by the alkaline-earth cations, driving the metal closer to the plane of the ring in the Zn^{2+} and Cd^{2+} complexes and favouring coordination to the oxygen atoms of the pendant groups. Thus, the fit of the ion to the coordination cavity of the macrocycle is not solely determined by their relative dimensions, but also by the long lifetime of the metal–nitrogen bonds, that appear to have a predominant role in the stability of these systems. Indeed, the Cd^{2+} ion forms a chelate with DOTRA that is much more stable (either thermodynamically or kinetically) than the corresponding Ca^{2+} complex (Ca^{2+} and Cd^{2+} having similar ionic radii), thanks to the higher covalent character, and lower lability, of the Cd^{2+}–N bonds.

The Ga(DOTRA) chelate has been detected in solution by ^{71}Ga NMR, but no proton spectrum has been reported [34]. The DOTRA chelates of the Ln^{3+} cations have also not been characterized, as they are too weak to be isolated [45].

3.4. BUNTA complexes

The proton NMR spectra of aqueous stoichiometric mixtures of the BUNTA ligand and the alkaline earth cations ($M^{2+} = Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}$), as well as Zn^{2+} or Cd^{2+}, were investigated in the pH range 2.0–12.5. While for Mg^{2+} the NMR signals of the free and coordinated forms of the ligand coexist in solution in slow exchange in the whole pH range (7.0–9.0) of complex stability, the Zn^{2+} and Cd^{2+} ions appear to have the best dimensions to fit into the cavity of this macrocycle, as their chelates are the only species present in solution in that pH range (Fig. 7, Table 5). A slight exchange broadening is observed for the free ligand NMR proton signals in the Mg(BUNTA)$^{-}$ system. As for the Ca^{2+} and Sr^{2+} ions, they coordinate weakly to BUNTA, the Ca^{2+}/BUNTA and Sr^{2+}/BUNTA systems giving rise to broad and ill-defined proton resonance signals of the bound forms in the pH range 7.0–8.0 (only the ring protons display a detectable splitting), together with the signals from the uncoordinated ligand. For the larger ion Ba^{2+} no complex species was detected over the whole pH range investigated.

The complexes formed by the Mg^{2-}, Zn^{2+} and Cd^{2+} ions with BUNTA have similar, well-defined proton NMR spectra (Fig. 7). These were assigned through analysis of the proton shift correlations observed in the two-dimensional spectra

Table 5
Proton NMR chemical shifts (δ_i) [a] of the complexes of the ligand BUNTA with the alkaline-earth, Zn^{2+} and Cd^{2+} ions (20°C, pH 7.0)

Cation	δ(1,2)	δ(3,4)	δ(7',8')			δ(9',10')			δ(11',12')			δ(5,6)	δ(5',6')		
H^{+}	3.10	3.10		3.10			2.85			7.33		3.30		3.36	
Mg^{2+}	3.56	3.15	2.75		3.12	2.80		3.02	7.35		7.40	3.40	3.28		4.39
Ca^{2+}	3.96	3.10	3.00		3.05		2.90			7.33		3.28		3.30	
Sr^{2+}	3.90	2.96	2.90		2.94		2.84			7.33		3.20		3.22	
Zn^{2+}	3.55	3.10	2.87		3.35		2.87		7.31		7.35	3.45	3.39		4.40
Cd^{2+}	3.57	3.25	2.86		3.17	2.86		3.00		7.25		3.29	3.41		4.33

[a] Proton chemical shifts (ppm) relative to TSP-d_4; all the spectra were obtained at 11.8 T (500 MHz).

(COSY), and also by comparing the electric field effects of the ion on the proton shifts of the ligand C–H bonds in DETA and BUNTA. The spectra display splittings of the macrocyclic ring protons and, in some cases, of the acetate protons, indicative of metal ion coordination by the ring nitrogens and the oxygens of the carboxylate groups. The protons of the two pendant acetate arms lying closer to the benzene ring ($H_{5'}$ and $H_{6'}$) give a well-defined AM doublet of doublets, while the protons of the third acetate (H_5 and H_6) give a singlet (Fig. 7, Table 5). The marked non-equivalence of the former acetate protons is attributed to the effect of the electronic ring currents of the neighbouring aromatic system. The metal–oxygen bonds are significantly more labile in these BUNTA complexes than in the corresponding DETA complexes.

The AA′MM′ multiplet observed for the ethylenediamine ring protons H_{1-4} (Fig. 7) reflects a high flexibility of this macrocycle moiety. In the case of DETA, the Ca^{2+} and Cd^{2+} chelates had more rigid macrocyclic rings than here, reflecting their looser fit into the larger cavity of BUNTA. The signals corresponding to protons H_{7-10}, located close to the benzene ring, display large splittings, consisting of a ADMN multiplet, as a result of coordination to the metal ion, which is responsible for the non-equivalence of protons H_7 and H_9, on one side, and H_8 and H_{10}, on the other, together with the aromatic ring current shifts that distinguish protons H_7 and H_8, from H_9 and H_{10} (Fig. 7). Two-dimensional COSY NMR spectra show strong correlations between protons H_9 and H_{10}, and H_7 and H_8 (corresponding to large geminal coupling constants), and weak correlations between the vicinal protons H_7 and H_9, and H_8 and H_{10}. This probably reflects some flexibility of this moiety of the molecule, as a preferred, rigid, conformation in solution (where the H_7 and H_{10} protons would be trans relative to H_8 and H_9) would give rise to larger vicinal coupling constants.

4. Conclusions

In the present study, the complexation properties of a series of structurally related triazamacrocyclic triacetate ligands, (NOTA, DETA, UNTA, DOTRA and BUNTA, see Fig. 1), containing macrocyclic rings of sizes increasing from nine to thirteen, with a series of divalent cations of increasing ionic radii ($Mg^{2+} < Zn^{2+} < Cd^{2+} < Ca^{2+} < Sr^{2+} < Ba^{2+}$) were investigated by ^{1}H NMR spectroscopy in aqueous solution.

In most cases, these divalent cations form 1:1 chelates in aqueous solution with those polyfunctional ligands with well-defined proton NMR spectra, where the ion is coordinated to the nitrogen donor atoms of the macrocyclic ring, and to all or some of the carboxylate groups of the pendant arms. When the macrocyclic nitrogens do not completely coordinate the cations, the macrocyclic ring protons no longer give sharp multiplets and the NMR signals are ill defined, reflecting the poor fit of the cations into the macrocyclic hole. This situation occurs for the Ba^{2+} complexes of DETA, UNTA and DOTRA and the Ca^{2+} and Sr^{2+} complexes of BUNTA. No complexation has been found for Ga^{3+}/UNTA, Ln^{3+}/UNTA and Ln^{3+}/DOTRA [34,44]. The very high value of the first protonation constant of the DETA, UNTA and DOTRA ligands ($\log K_1 > 13$ [9,20]) strongly decreases the stability of metal complexes where fit of the dimensions of the coordination cavity of the macrocycle and the radius of the metal ion are far from ideal.

The stability constants of the complexes of NOTA and DOTRA with the cations follow the same order, $Zn^{2+} > Cd^{2+} \gg Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$ [25,27,28]. Thus, independently of the ligand cavity size, the complexes of Zn^{2+} and Cd^{2+} are more stable than those formed with the alkaline-earth cations. This higher stability arises from the higher covalent character of the bonds of those d-block metal ions relative to the alkaline earths. As to the alkaline-earth ions, they have a strong binding affinity for negatively charged oxygen atoms, giving rise to stable chelates with the polyacetate macrocycles investigated when the cation is not too large to fit into the cavity size. As a consequence of such preference, the coordination of the alkaline-earth cations to this kind of macrocyclic ligands is, in general, much weaker than of the d-block ions. The triazamacrocyclic ligands studied display a marked selectivity for Mg^{2+} relative to the other alkaline-earth ions. Thus, for the chelates now studied, (as for similar chelates of some polyoxa-polyazamacrocycles [8]), their stability is mainly determined by entropy variations and/or by stereochemical factors, which in turn define the symmetry of these systems. Indeed, the complexation process of the metal to the macrocyclic ligand (and its stability in solution) is primarily determined by their relative dimensions, yielding totally or partially coordinated species, depending on the radius and charge of the central ion.

The complex stability trends, discussed above for the NOTA and DOTRA chelates of the various cations, are in general maintained for the other ligands DETA, UNTA and BUNTA, as shown by the width of their pH range of stability, which correlates well with the relative complex stability.

The multiplet structure observed for the proton NMR signals of the different moieties of the chelates studied yields direct information on the conformational flexibility of the coordinated ligands. In the macrocyclic rings, the metal-coordinated propylenediamino moieties of DETA, UNTA and DOTRA form six-membered rings which are always locked in a chair-like rigid conformation. The metal-coordinated ethylenediamino moieties form five-membered rings which are conformationally flexible in most cases (NOTA, UNTA, BUNTA and DETA) except for the Ca^{2+} and Cd^{2+} chelates of DETA, where the ideal fit of the cations into the ligand hole gives these complexes added rigidity. Thus, the conformational rigidity of the macrocyclic ring is not related to the thermodynamic stability of the complex.

The multiplicity of the NMR resonances of the acetate protons depends on the lifetimes of the metal–oxygen bonds [40], as the metal–nitrogen bonds in macrocyclic chelates are long lived. We found that the lifetimes of such metal–

oxygen bonds depend on the macrocyclic vicinity of the respective acetate arms. The CH_2 protons of the acetate pendant arms with two equal neighbours, ethylenediamine or propylenediamine, in all ligands, give singlet resonances, indicating that the metal–oxygen bonds to the corresponding carboxylate groups are short lived. When the neighbours are different, one ethylenediamine and one propylenediamine, the acetate CH_2 protons gave sometimes a singlet resonance (in $Sr(DETA)^-$, $Mg(UNTA)^-$, $Cd(UNTA)^-$, $Ca(BUNTA)^-$) but in the other cases an AB doublet was observed, corresponding to long-lived metal–oxygen bonds. Therefore, the lifetimes of the metal–oxygen bonds are not related to the conformational rigidity of the coordinated macrocyclic ring.

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