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Solution structure and dynamics of DTPA–Ln(III) complexes (DTPA = diethylene triamine penta acetate; Ln = La, Pr, Eu)

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Abstract

Variable temperature ^{1}H and ^{13}C NMR spectra and proton and carbon longitudinal relaxation times allow the complete characterization of the solution structure and dynamics of three Ln(III) complexes of DTPA (Ln = La, Pr and Eu). Our results show that a rapid interconversion between octadentate structures occurs on the NMR time scale which can be 'frozen out' at low temperature for Pr and Eu complexes.

The high formation constants commonly shown by the DTPA ligand with a number of metallic ions has suggested many applications for its complexes in biomedicine [1]. Among them Gd–DTPA (and some variously substituted derivatives) is now under intense scrutiny in clinical diagnosis as a contrast agent for MRI [2–4].

Two solid state X-ray structure determinations have been reported so far, for In [5] and Nd [6] complexes. In both cases DTPA is shown to act as an octadentate ligand and the resulting coordination polyhedron has been accounted for in terms of a distorted Archimedian antiprismatic configuration or a tricapped trigonal prism model if the coordinated water molecule is considered.

Several papers have dealt with the solution structures of DTPA complexes. In ref. 5, the proton and carbon spectra of the DTPA–In complex were used to confirm that the octacoordination found at the solid state is maintained in solution. Also the ^{13}C NMR spectrum of the DTPA–Tl(III) complex shows a 2:1:2 pattern for the coordinated carboxylate groups [7].

The same pattern has been observed for three diamagnetic DTPA–M(III) complexes (M = La, Lu and Y) [8] but a heptadentate structure (with the unbound ligand group being the lone acetate group of the middle nitrogen) is proposed in this case. A ^{139}La NMR observation of DTPA–La has been found to be consistent with the suggested heptadenticity of DTPA but this empirical relationship cannot be assumed too confidently [9].

Recently, Jenkins and Lauffer [10a, b] chose DTPA complexes of Pr, Eu and Yb as representative examples to test the applicability of 2D-NMR techniques (1H-COSY and 2D-exchange spectroscopy) to paramagnetic systems with relatively rapid relaxation times. These studies led them to suggest that DTPA acts as an octadentate ligand towards lanthanide(III) ions in contrast to the suggestion forwarded in refs. 8 and 9.

In this paper we deal with the complete characterization of the solution structure and dynamics of three Ln(III) complexes of DTPA (Ln = La, Pr, Eu) by measuring their variable temperature (v.t.) ^{1}H and ^{13}C NMR spectra and proton and carbon relaxation times T_1. Our results confirm the occurrence of the octadenticity of DTPA ligand in these complexes.

Experimental

The DTPA chelates of La, Pr and Eu were prepared by adding equimolar quantities of the corresponding chlorides to a D_2O solution of Na_5-DTPA. The sodium salt was prepared by dissolving H_5-DTPA with NaOH in stoichiometric quantities; to this solution absolute ethanol was added until a persistent cloudiness was observed. Fine white crystals were separated by crystallization at +5 °C from the water–ethanol mixture.

Partial deuteration of the acetate methylenic groups (50–60%) of the ligand was obtained by

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heating 0.5 g of DTPA at pH 11 at 90–95 °C in D_2O (30 ml) for 28 h.

In the NMR experiments the concentration of the lanthanide–DTPA complexes was approximately 0.10 M and the pH 7.3.

NMR spectra were recorded on a Jeol GX 270/89 spectrometer operating at 270 MHz for proton and at 67.9 MHz for carbon observation frequency, respectively.

The spin-lattice proton and carbon relaxation times were measured by using the non-selective inversion–recovery pulse sequence. Errors are estimated to be less than 2%.

Results and discussion

Figure 1 reports the v.t. proton NMR spectra of the DTPA–Pr complex. The low temperature limiting spectrum (−5 °C) shows eighteen resonances (two of them are partially overlapped) as expected from the solid state structure of the neodymium complex [6]. The presence of both dipolar and contact contributions to the observed shifts does not allow a precise assignment of each resonance to a given proton. However an aid to the assignment of the proton resonances arises from the use of ligand molecules containing ^2H-labelled acetate groups (see 'Experimental').

As the temperature is increased, an exchange process takes place leading to the coalescence of couples of resonances. The resulting high temperature limiting spectrum (98 °C) consists then of 9 resonances (five acetate and four ethylenic) of the same intensity.

The v.t. ^{13}C NMR spectra of the DTPA–Pr complex (Fig. 2) are more informative. Selective decoupling experiments and use of a partially deuterated ligand allowed the assignment of methylenic acetate and ethylenic carbons. At −6 °C the spectrum consists of five CO_2^-, five CH_2COO^- and four ethylenic carbon resonances. At high temperature an averaging process simplified the spectrum to a 2:1:2 pattern for the carboxylate resonances (and for the methylenic acetates as well) and to two resonances of equal intensities for the remaining ethylenic carbons. This is actually the pattern previously observed at ambient temperature [5–7], for the diamagnetic complexes which have then to be referred to fast exchange limiting spectra.

The observed v.t. behaviour of ^1H and ^{13}C NMR spectra may be understood in terms of the mechanism depicted in Scheme 1 involving only octadentate structures.

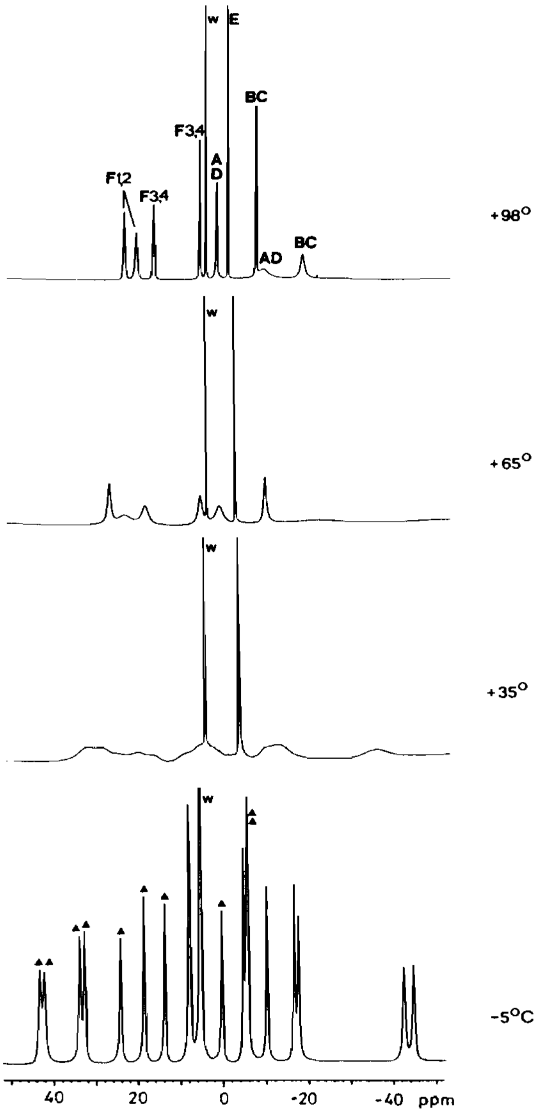
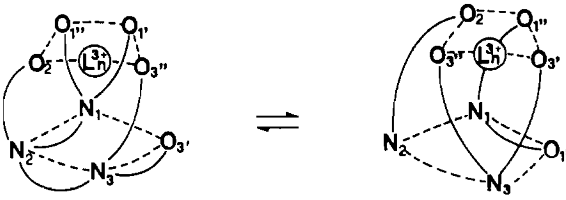


Fig. 1. 270 MHz ^1H NMR spectra of 0.2 M $[Pr(DTPA)]^{2-}$ in D_2O (pH = 7.3) at different temperatures. The HDO residual peak has been labelled 'w'. Distinction between ethylenic and acetate (▲) resonances has been possible by recording proton spectra of the partially deuterated complex. In the highest temperature spectrum A and F are used to show carbon–hydrogen connectivities as obtained by selective proton decoupling experiments of the ^{13}C NMR spectrum at the same temperature.



Scheme 1. Ln = La, Pr, Eu.

This intramolecular rearrangement leads to the equilibration of the acetate arms 3′–1′ and 3″–1″,

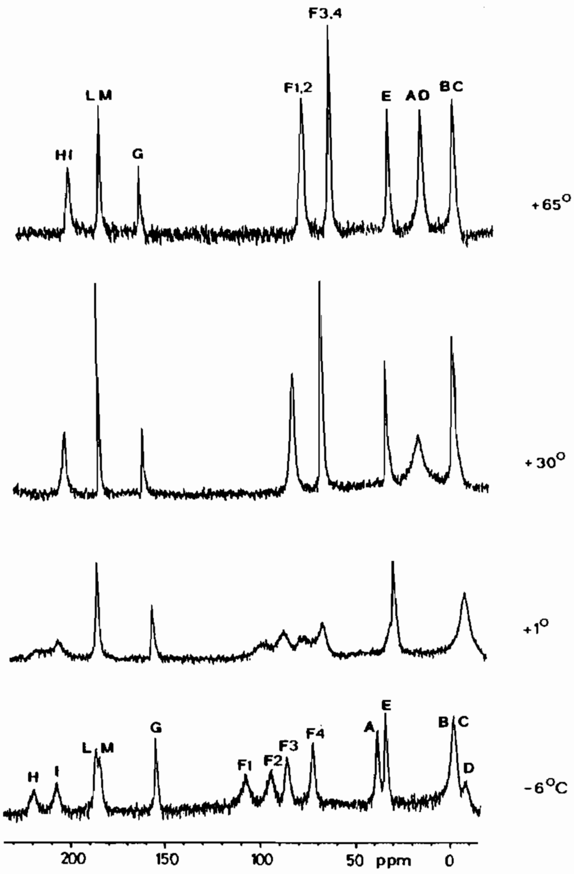


Fig. 2. 67.9 MHz ^{13}C NMR spectra of 0.2 M $[Pr(DTPA)]^{2-}$ in H_2O/D_2O (80:20) (pH=7.3) at different temperatures. Distinction between ethylenic (A–D) and acetate (E and F1,4) carbons has been possible by recording proton-coupled ^{13}C NMR spectra of a sample partially deuterated in the acetate groups. E and G resonances are easily assigned to methylenic and carboxylate carbons of the lone acetate group since their linewidths are unaffected by changes in temperature.

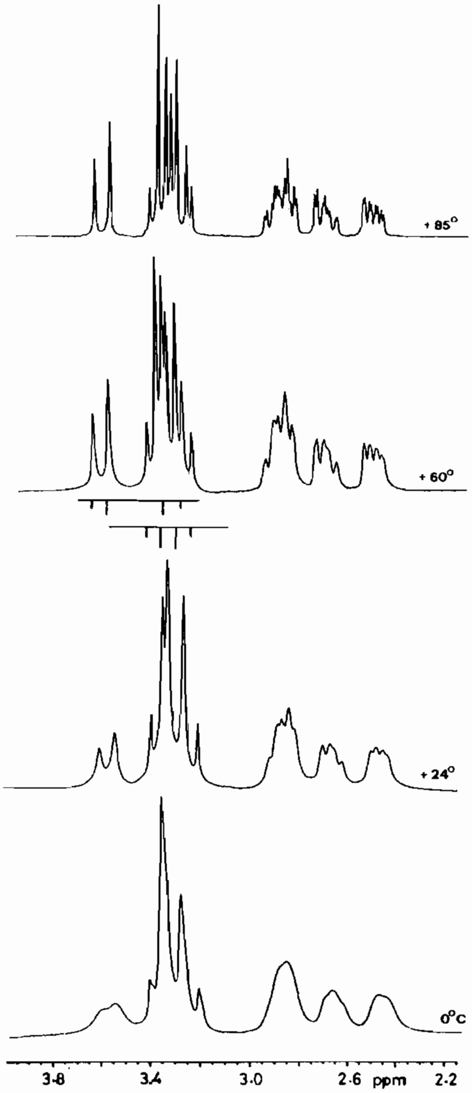


Fig. 3. 270 MHz ^1H NMR spectra of 0.1 M $[La(DTPA)]^{2-}$ in D_2O (pH=7.3) at different temperatures. The acetate protons appear as two AB spin systems overlapped a singlet of intensity 2 unambiguously assigned to the methylenic protons of the middle acetate group.

whereas the oscillation of the lone acetate group between two equivalent positions in the coordination polyhedron renders equivalent its methylenic protons. The process also converts axial ethylenediammine protons to equatorial and vice versa.

These findings lead us to re-consider the case of the DTPA–La complex, whose v.t. proton NMR spectra are reported in Fig. 3. At high temperature two different AB patterns for the four acetate groups and a singlet for the middle acetate are observed to confirm the previous report [8]. However the assignment of the resonances in the AB spin systems at room temperature (see Fig. 3) is slightly different from ref. 8 (as checked by proton decoupling experiments) and this rules out the need for an interpretation of the supposed broader lines of the lowfield half of one of the AB systems (in the room temperature spectrum the latter half is broadened and masked under the set of resonances of the second AB spin system).

As the temperature is decreased, all the proton resonances broaden (to a different extend) to indicate that an exchange process is slowed down. Unfortunatelly the 'frozen' structure in water is not accessible at this magnetic field. The ^{13}C v.t. spectra did not add further information.

Since our results indicate the occurrence of a dynamic process which might also be consistent with an eptadentate structure, we carried out some experiments to discover whether the middle acetate group was bound or not to the metal ion.

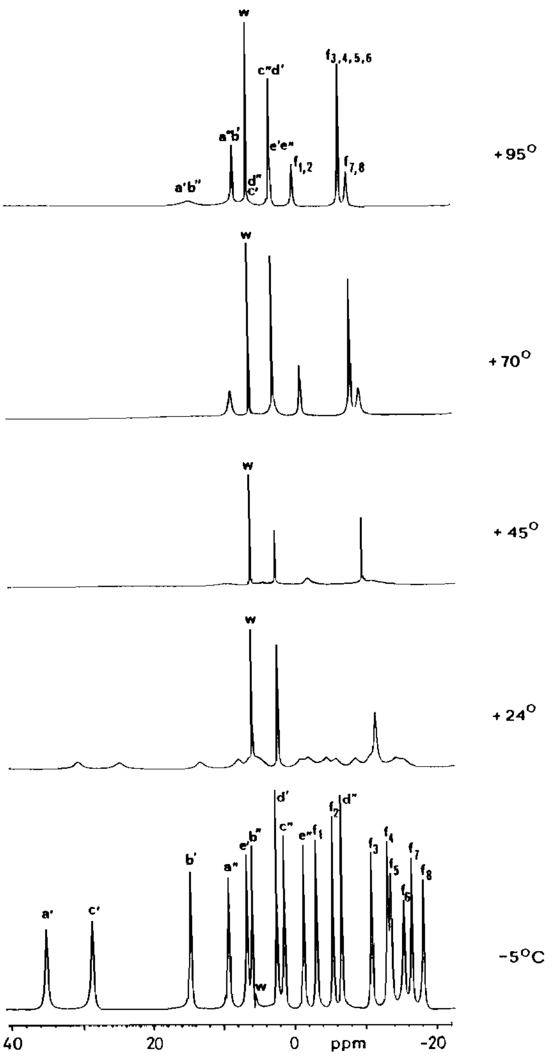


Fig. 4. 270 MHz ^{1}H NMR spectra of 0.2 M $[Eu(DTPA)]^{2-}$ in D_2O (pH = 7.3) at different temperatures. The residual HDO resonance is labelled 'w' and, in the spectrum at -5 °C, it has been suppressed by using the inversion–recovery pulse sequence $(180\text{-}\tau\text{-}90)_n$ with a τ value of 0.35 s. Assignments of the resonances: a′–d″, ethylenic; f_1–f_8, terminal acetate; e′ and e″, middle acetate. These assignments follow from: (a) partial deuteration of the DTPA acetate groups; (b) selective $\{^1H\}^{13}C$ spectra and (c) averaging behaviour as a function of temperature (temperature dependence of the spectra).

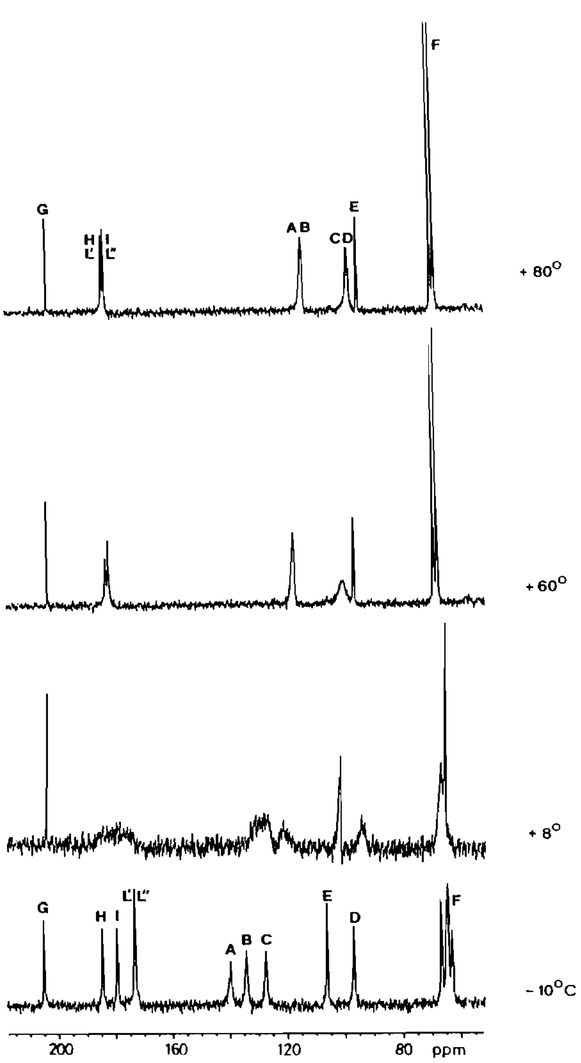


Fig. 5. 67.9 MHz $\{^1H\}^{13}C$ spectra of 0.2 M $[Eu(DTPA)]^{2-}$ in D_2O (pH = 7.3) at different temperatures. Peaks A–F have been labelled in analogy with Fig. 4. Relative assignment of the ethylenic (A–D) and acetate (E–F) resonances has been obtained by the proton coupled ^{13}C spectrum of the partially deuterated complex at -5 °C. Peaks G–L″ correspond to the carbonyls of the middle (G) and terminal (H–L″) acetate groups. The low temperature limiting spectrum (-10 °C) has been recorded in D_2O/CD_3OD mixture (80:20).

To this end we measured the relaxation time T_1 of ^{13}C nuclei of the diamagnetic lanthanum derivative. We found that carboxylate and methylenic carbons show very similar values (7.1 and 0.35 s, respectively) for all five acetate arms ruling out a superimposition of a freely rotating acetate chain on the molecular tumbling motion.

Then we extended our observation to the DTPA–Eu (III) complex with the expectation that the increased charge/ionic radium ratio would favour a higher rigidity of the system. Proton and carbon v.t. NMR spectra of this complex are reported in Figs. 4 and 5. Eighteen resonances are observed in the ^{1}H NMR spectrum at -5 °C which again average to nine signals in the high temperature limiting spectrum. By ^{1}H decoupling experiments in the ^{13}C NMR spectra and by selective deuteration techniques we assigned (among several others) the resonances at 6.0 and -1.5 ppm to the methylenic protons of the middle acetate group. In order to ascertain the relative distance of these protons from the paramagnetic metal centre we measured their proton spin-lattice relaxation times. It is well established that in paramagnetic lanthanide complexes the longitudinal relaxation times of ^{1}H nuclei on the ligand are determined simply by the strength of the dipolar interaction modulated by the electronic correlation time ($\tau = \tau_s$) of the lanthanide ion [11].

$$\frac{1}{T_{1p}} = \frac{K}{r^6}\tau_s$$

where K is a constant characteristic of the given lanthanide, r is the distance between the metallic ion and the proton. It follows that the ratio of the longitudinal relaxation rates of a couple of protons on the ligand depends on the ratio of their distances from the lanthanide

$$\frac{(1/T_{1p})_A}{(1/T_{1p})_B} = \frac{r_B^6}{r_A^6}$$

From our measurements we found an r_B/r_A ratio of 1.073 which is in good agreement with the value of 1.098 calculated from the X-ray structure [6] of Nd–DTPA. Furthermore the close similarity found among the relaxation rates of all the acetate protons (ranging from 37 to 22 s^{-1} corresponding to distances from 3.9 to 4.3 Å in the Nd–chelate) rules out the possibility that the non-equivalence of these methylenic protons may be caused – in an unbound situation – by the bond to a pro-chiral nitrogen centre.

The v.t. ^{13}C NMR spectra of the Eu–DTPA complex (Fig. 5) are similar to those of the Pr derivative with the advantage that the higher energy barrier to the exchange provides better resolved signals in the low temperature limiting spectrum.

The body of these observations lead us to conclude that all three systems considered in this work are octadentate but, if hepta-coordinated species are present, they may only represent intermediate structures in the intramolecular exchange process. Our results are then fully consistent with those obtained by the 2D-NMR approach [10b].

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