Determination of Metal–Proton Distances and Electronic Relaxation Times in Lanthanide Complexes by Nuclear Magnetic Resonance Spectroscopy

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The longitudinal and transverse relaxation times of the proton resonances of three lanthanide(III) complexes of 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetate have been measured. This allows determination of the metal–proton distances and the electronic relaxation times of the paramagnetic metal ions by exploiting the Curie-spin mechanism contribution to the transverse relaxation rates, once the molecular reorientational time τ_r is known by an independent experiment. Values of the parameters calculated from data obtained at a single magnetic field (9.4 T) were in good agreement with those found from the evaluation of the magnetic field-induced line broadening of the proton resonances as measured at 2.1, 4.7 and 9.4 T. A chemical exchange contribution to the linewidths is excluded on the basis of experiments performed at different temperatures.

NMR spectroscopy has played a role in the study of lanthanide complexes since it was shown that a number of structural and dynamic parameters may be obtained through a variety of experimental routes. The most widely used procedure for solution structure elucidation relies upon the measurement of lanthanide-induced shifts (l.i.s.s) and the fit of calculated to observed dipolar shifts which depend on geometrical coordinates.[1] Ytterbium(III) complexes have been used preferentially in these studies since, among the lanthanides, this ion exhibits the smallest contact contribution to the observed shifts.[2]

The measurement of high-resolution NMR spectra is not possible for gadolinium(III) complexes because of the dramatic line broadening of the resonances induced by the very long electronic relaxation time associated with this metal ion.[3] However the analysis of $1/T_1$ NMRD (nuclear magnetic relaxation dispersion) profiles[4] of water protons in solutions of gadolinium(III) complexes may afford several important parameters such as the number of co-ordinated water molecules, their distances from the paramagnetic centre, their mean residence lifetime, the reorientational correlation time of the complex and the electronic relaxation time of the metal ion.

Useful information may also be obtained from the armoury of δ, J, and $T_{1,2}$ parameters of ^{1}H and ^{13}C NMR spectra of the diamagnetic lanthanum(III) and lutetium(III) derivatives.[5]

More recently, analysis of the line broadening of the shifted ^{1}H NMR resonances as a function of the magnetic field has been shown to comprise a method for the determination of proton–metal ion distances.[6,7] Herein we report a closely related approach based on the measurement of longitudinal and transverse relaxation times at a single magnetic field which provides very reliable values for proton–lanthanide distances and the electronic relaxation times of the trivalent ions once the molecular reorientational correlation time τ_r is known from an independent experiment. We have applied this method on three Ln^{III}–tadta complexes (Ln = Tb, Dy, or Ho; tadta = 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetate) and compared the results with those obtained from linewidth measurements at three different magnetic field strengths.

Results and Discussion

The proton NMR spectra of tadta complexes of Tb^{III}, Dy^{III} and Ho^{III} (Table 1 and Fig. 1) show six resonances as previously reported for the analogous paramagnetic derivatives of Eu^{III} and Yb^{III}.[8] These resonances correspond to two methylenic acetate protons and four (two axial and two equatorial) ethylenic protons of the tetraazacyclododecane ring.

Table 1 Proton chemical shifts[a] of the Tb^{III}-, Dy^{III} and Ho^{III}-tadta complexes[b] at 295 K

M	ac 2	ax 2	ac 1	eq 1	eq 2	ax 1
Tb	253.5	135.9	82.1	−97.2	−101.0	−401.7
Dy	310.1	163.2	110.1	−101.2	−108.8	−475.9
Ho	160.7	85.3	52.4	−57.6	−58.0	−243.4

[a] Chemical shifts measured relative to the resonance of Bu^{t}OH. [b] Peak nomenclature corresponds to data in Fig. 1.

From previous work[8] on complexes of La^{III}, Eu^{III} and Lu^{III} it is known that a dynamic process may occur in these systems which exchanges the acetate resonances and one axial and one equatorial proton resonance on adjacent ethylenic carbons. An energy barrier of 60.7 kJ mol^{-1} was calculated for this ring-inversion process, the highest so far reported for a lanthanide complex. However the very large chemical shift separation inside each couple of resonances to be exchanged makes unlikely the detection of this process for the complexes considered in this study.

The six observed ^{1}H NMR peaks can be grouped into two different sets according to their relative line broadening (see Fig. 1): the three most shifted resonances have linewidths at half height of about 400 Hz (at 90 MHz and 295 K), while for the other three resonances the linewidths are in the range 100–200 Hz. These two sets of peaks correspond to two sets of metal–proton distances, the broader resonances being associated with the protons closer to the metal ion. The transverse relaxation rate of protons near a paramagnetic lanthanide ion (excluding Gd^{III}) is given by[7] equation (1) where $\Delta\nu_{\frac{1}{2}}$ is the

$$\pi\Delta\nu_{\frac{1}{2}} = \frac{1}{T_2} = \frac{4}{3}\frac{\gamma^2\mu_{eff}^2}{r^6}T_{1e} + \frac{1}{5}\frac{\gamma^2\mu_{eff}^4H_o^2}{(3kT)^2r^6}\left(4\tau_r + \frac{3\tau_r}{1+\omega^2\tau_r^2}\right) \quad (1)$$

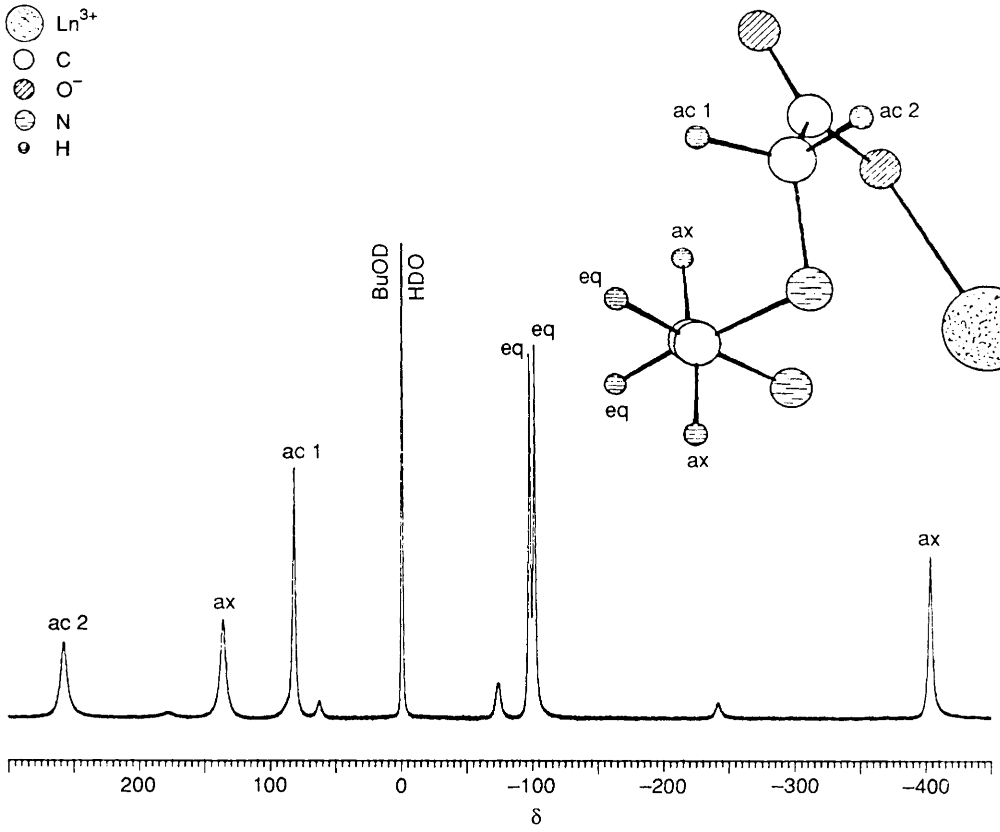

Fig. 1 90 MHz ^{1}H NMR spectrum of Tb^{III}-tadta at 295 K. The symbols ax, ac and eq indicate axial, acetate and equatorial protons, as schematically illustrated in the structure. The small peaks correspond to a second isomer of the Tb^{III}-tadta complexes. Assignment of the resonances has been possible on the basis of the calculated proton–lanthanide distances (Table 2)

linewidth at half height, γ is the nuclear gyromagnetic ratio, μ_{eff} is the effective magnetic moment, H_o is the applied magnetic field strength (in Gauss), T_{1e} is the longitudinal electron spin relaxation time, r is the distance between the proton and the paramagnetic ion, τ_r is the molecular rotational correlation time and the other symbols have their usual meanings. The first term in equation (1) represents the contribution of the electron–nucleus dipolar interaction, while the second term describes the Curie spin-relaxation mechanism.[9,10] These two mechanisms also contribute to the longitudinal relaxation rate according to equation (2).[7] The difference between the transverse and

$$\frac{1}{T_1} = \frac{4}{3}\frac{\gamma^2\mu_{eff}^2}{r^6}T_{1e} + \frac{1}{5}\frac{\gamma^2\mu_{eff}^4H_o^2}{(3kT)^2r^6}\left(\frac{6\tau_r}{1+\omega^2\tau_r^2}\right) \quad (2)$$

longitudinal relaxation rates, measured at the same value of the magnetic field, is given by equation (3). It is straightforward to

$$\frac{1}{T_2} - \frac{1}{T_1} = \frac{1}{5}\frac{\gamma^2\mu_{eff}^4H_o^2}{(3kT)^2r^6}\left(4\tau_r - \frac{3\tau_r}{1+\omega^2\tau_r^2}\right) \quad (3)$$

evaluate r from equation (3) once τ_r is known from an independent experiment.

A molecular reorientational correlation time τ_r of 72 ps, at 298 K, was calculated from the analysis of the $1/T_1$ NMRD profile of the Gd^{III}–tadta complex.[11] A similar value (73 ps) was estimated from ^{13}C T_1 and nuclear Overhauser enhancement (NOE) measurements of the ethylenic carbons of the tetraazacyclododecane ring of the diamagnetic lanthanum(III) derivative,[12] according to equation (4) where R_1^{DD} is the

$$\tau_r = \frac{R_1^{DD}r^6_{CH}}{2\gamma_H^2\gamma_C^2h^2} \quad (4)$$

contribution of the carbon–proton dipolar interaction to the measured longitudinal relaxation rate and r_{CH} has the standard value of 1.08 Å. By applying the same procedure we have calculated a τ_r value of 80 ps for the analogous lutetium(III) complex at 295 K (^{13}C T_1 for the ethylenic carbons of 0.235 s and NOE factor of 1.6 measured at 9.4 T on an undegassed sample).

The longitudinal and transverse relaxation rates of the six proton resonances of the Ln^{III}–tadta complexes were then measured at 295 K and 9.4 T, since the high magnetic field enhances the contribution of the Curie relaxation mechanism. Thus, by adopting the τ_r value of 80 ps we obtained from equation (3) the r distances reported in Table 2. These proton–lanthanide ion distances are in fairly good agreement with those obtained, after positioning the hydrogen atoms, from the X-ray structure of the Eu-tadta complex[13] (Table 3). Now the availability of the r values allows the calculation of T_{1e} parameters (Table 2) from the evaluation of the electron–nucleus dipolar term [equations (1) or (2)]. We found a quite good correspondence among the T_{1e} values obtained from the six proton resonances of each complex.

The above reported results (r and T_{1e}) obtained at a single high magnetic field were then checked by evaluating the transverse relaxation rates from linewidth measurements at different magnetic field strengths as suggested previously.[6,7]

From the Curie contribution [equation (1)] a dependence of the linewidth upon the square of the applied magnetic field strength is expected and thus, from the slope and the intercept of the straight line plot of the transverse relaxation rate as a function of the square of the magnetic field, it is possible to calculate the value of r and T_{1e} if τ_r is already known. As a representative example of this method we report in Fig. 2 the plot of linewidths *vs.* H_o^2 as measured at 90, 200 and 400 MHz for the terbium(III) complex.

The values obtained for r distances and T_{1e} from this procedure (Table 3) are very similar to those found from the method based on proton T_1 and T_2 measurements described above. Again, since T_{1e} is a property of the paramagnetic metal ion in a given co-ordination polyhedron, the same value should be obtained from the analysis of the data for each resonance,

Table 2 Observed longitudinal and transverse proton relaxation rates[a] and derived metal–proton distances and electronic relaxation times of Tb^{III}-Dy^{III}- and Ho^{III}–tadta complexes

	Tb				Dy				Ho			
	R_1/s^{-1}	R_2/s^{-1}	r/Å	$10^{13}\ T_{1e}/s$	R_1/s^{-1}	R_2/s^{-1}	r/Å	$10^{13}\ T_{1e}/s$	R_1/s^{-1}	R_2/s^{-1}	r/Å	$10^{13}\ T_{1e}/s$
ac 2	2839	3125	3.47	3.21	3704	4115	3.47	2.96	2550	2910	3.54	1.48
ax 2	2688	2950	3.52	3.24	3209	3550	3.58	3.27	2300	2615	3.62	1.64
ac 1	1067	1175	4.08	3.03	1279	1426	4.12	2.80	916	1045	4.20	1.52
eq 1	804	886	4.27	2.94	955	1062	4.34	2.92	714	*b*	4.38[c]	—
eq 2	793	874	4.28	3.01	947	1053	4.35	2.89	714	*b*	4.38[c]	—
ax 1	1676	1850	3.77	2.94	1983	2211	3.83	2.80	1784	2043	3.74	1.39

[a] Data measured at 400 MHz and 295 K. [b] Data not reported because of large overlapping of the two resonances. [c] The distance was calculated from equation (3) by using an average value for T_{1e} of 1.5×10^{-13} s.

Table 3 Lanthanide ion–proton distances and electronic relaxation times determined from the magnetic field dependence of the observed linewidths[a]

	Tb		Dy		Ho		Eu
	r/Å	$10^{13}\ T_{1e}/s$	r/Å	$10^{13}\ T_{1e}/s$	r/Å	$10^{13}\ T_{1e}/s$	r^b/Å
ac 2	3.43	3.14	3.47	2.73	3.52	1.33	3.50
ax 2	3.47	2.70	3.50	2.30	3.59	1.40	3.68
ac 1	4.08	3.17	4.08	2.39	4.20	1.58	4.35
eq 1	4.27	3.03	4.29	2.39	—	—	4.51
eq 2	4.27	3.03	4.29	2.39	—	—	4.49
ax 1	3.76	2.82	3.80	2.46	3.73	1.26	3.83

[a] Data for Tb^{III}–, Dy^{III}– and the Ho^{III}–tadta complexes measured at 90, 200 and 400 MHz, at 295 K. [b] Mean metal–proton distances evaluated from the X-ray structure.[13]

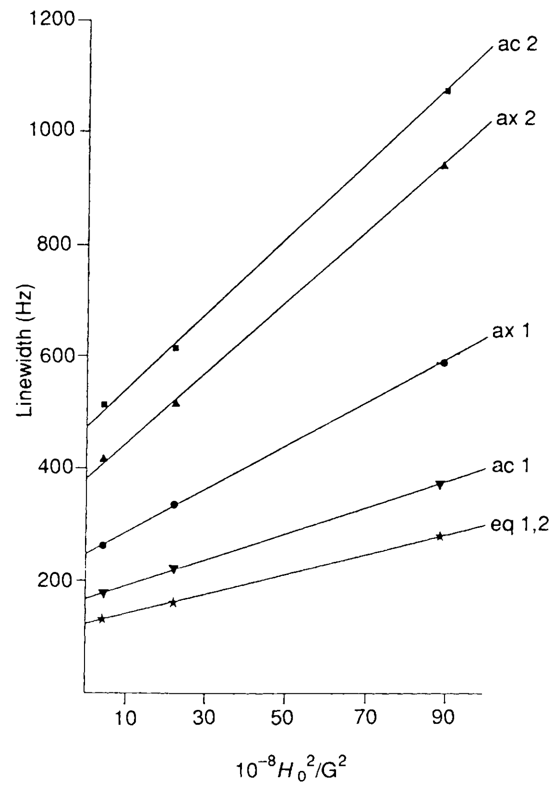

Fig. 2 Plot of the linewidth of the Tb^{III}–tadta resonances *versus* the square of the magnetic field strength. Data measured at 90, 200 and 400 MHz at 295 K; G = 10^{-4} T.

representing then an internal check on the consistency of the entire procedure. Very similar T_{1e} values were obtained from the six different proton peaks indicating a rather good accuracy in the evaluation of this parameter.

Table 4 Metal–proton distances and electronic relaxation times determined from the magnetic field dependence of the observed linewidths for Tb^{III}–tadta complex *

	285 K		275 K	
	r/Å	$10^{13}\ T_{1e}/s$	r/Å	$10^{13}\ T_{1e}/s$
ac 2	3.41	3.30	3.41	3.51
ax 2	3.47	3.07	3.49	3.58
ac 1	4.05	3.11	4.01	3.14
eq 1	4.30	3.35	4.27	3.35
eq 2	4.30	3.35	4.27	3.35
ax 1	3.76	3.00	3.76	3.26

* Data measured at 90, 200 and 400 MHz.

Since a field-dependent contribution to the linewidth may also arise from a chemical exchange process, new sets of measurements were carried out at 285 and 275 K and r and T_{1e} were calculated using τ_r values of 100 and 120 ps respectively, derived from equation (4) with R_1^{DD} data measured for Lu^{III}–tadta. The results of the calculations (reported in Table 4 for Tb^{III}) show a very good agreement among the r values evaluated at three different temperatures, which excludes any sizeable contributions to the bandwidths from chemical exchange processes. Noteworthy, on going from 295 to 275 K the mean T_{1e} value increases as previously observed by Rossotti and co-workers[14] in a series of Ln^{III}–ethylenediaminetetraacetate (edta) complexes.

In conclusion the analysis of T_1 and T_2 at a single magnetic field or of T_2 at different magnetic field strength for the proton resonances of non-labile chelates may represent a powerful tool for investigating solution structure and for assigning the resonances if τ_r may be determined by an independent experiment. Interestingly, the increased availability of molecular reorientational τ_r values, mainly obtained in the context of the potential application of gadolinium(III) complexes as contrast agents for magnetic resonance imaging (MRI),[11,15] indicates that for a given class of complex this parameter is linearly dependent upon the molecular weight. This may largely widen the application of the method reported herein by avoiding the tedious procedure of τ_r determination by T_1 and

NOE measurements of ^{13}C resonances of diamagnetic complexes or by the analysis of $1/T_1$ NMRD profiles.

Finally the values of T_{1e} found in this work are of the same order of magnitude to those reported[14] for the complexes of these three lanthanides with a variety of ligands, supporting the view of a very limited dependence of this parameter upon the co-ordination polyhedron and the lanthanide ion (except Gd^{III}).

Experimental

Lanthanide complexes were prepared at different concentrations, ranging from 0.2 to 0.6 mol dm^{-3}, as described in ref. 6, from stock solutions of the corresponding chlorides. All the solutions, containing 1% Bu^{t}OH as an internal chemical shift standard, were adjusted to pH 7.3 with NaOD.

Proton NMR spectra were obtained on JEOL EX 90, Bruker 200 AC and JEOL EX 400 spectrometers operating at 90, 200 and 400 MHz respectively. The variable-temperature accessories were calibrated with methanol and before the measurements the NMR tubes were allowed to equilibrate in the probe for about 20 min.

Longitudinal relaxation times T_1 were measured by the inversion-recovery technique and NOE factors were determined using standard procedures.[16] Proton T_1 values were measured at 400 MHz, ^{13}C T_1 and NOE factors at 100 MHz. The uncertainty in T_1 values was estimated to be less than 5%. Spin–spin relaxation rates were measured from the half-height widths ($\Delta\nu_{\frac{1}{2}}$) of the resonances. Corrections for field inhomogeneities were made by subtracting the linewidth of Bu^{t}OH from those of the other resonances. All the experimental data represent the average of at least five measurements with a reproducibility within 5%.

For samples of concentration >80 mmol dm^{-3} the experimental $\Delta\nu_{\frac{1}{2}}$ values showed a concentration dependence due to intermolecular contributions to the relaxation pathways. The data reported in Tables 2–4 were obtained on samples of concentration ranging from 80 to 60 mmol dm^{-3} and did not show any appreciable variation in this range. On the other hand no differences in the proton spectra were detected by varying the concentration and the solution pH from 4.0 to 10.0.

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