Nuclear Magnetic Shift and Relaxation Effects resulting from Complexation of Lanthanide Ions with *endo-cis*-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid

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The effects on the n.m.r. spectrum of binding various lanthanide complexes to the title dicarboxylic acid in aqueous solution have been studied. It is shown using relaxation-time measurements that all lanthanides and complexes form similar adducts with the acid. The magnetic susceptibility tensor, which determines the shifts induced by a lanthanide, is not related simply to the geometry of the adduct. Rather, an averaged tensor is observed, whose symmetry is close to axial for lanthanides in the first half of the series, but often far from axial for those later in the series. It is proposed that this type of behaviour is general for lanthanide complexes in water.

IN the study of a complex molecule by n.m.r. spectroscopy the incorporation of a paramagnetic species into the molecule is an important method for simplifying the spectrum, assigning resonances, and obtaining structural information.[1-5] The lanthanide ions have received considerable attention because there is good reason to believe [3-5] that for these ions the mechanisms of perturbation may be capable of complete definition more readily than for other paramagnetic species such as the transition-metal ions.

The primary mechanism of both shift and relaxation with the lanthanide ions is a dipolar one. The dipolar relaxation induced in nuclear resonances by Gd^{III} is isotropic, and to a good approximation this is true for the other trivalent lanthanide ions.[6-8] Thus, the relaxation induced in different nuclei in a molecule complexed to a lanthanide ion is related to r_i^{-6} where r_i is the distance between a nucleus i and the paramagnetic ion. Dipolar shifts of resonances are induced by lanthanides other than Gd^{III} and depend not only on a distance factor (r_i^{-3}) but also on an angular factor defined with respect to the magnetic susceptibility tensor. In many cases which have been studied in detail this tensor has been found to be, to a good approximation, axial which considerably simplifies the analysis of the shift data in terms of molecular structure.[4,5]

In this paper we examine the perturbations to the n.m.r. spectrum of *endo-cis*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid produced by binding of lanthanide ions and complexed lanthanide ions. The molecule has a rigidly defined geometry, and contains two carboxylic acid groups in an orientation which is suitable for binding lanthanide ions. The results give insight into the nature of susceptibility tensors of complexed lanthanide ions in solution.

EXPERIMENTAL

Lanthanide chloride solutions were prepared by dissolution of known weights of the oxides, supplied by Koch-Light (99.9% purity), in DCl and D_2O (99.8% from Ciba). The concentration of each lanthanide chloride solution was checked by using an ethylenediaminetetra-acetate (edta) titration employing xylenol orange as an indicator.[9] Ethylenediaminetetra-acetic acid (H_4edta), *N*-hydroxyethylethylenediaminetriacetic acid (H_3hedta), and *trans*-1,2-diaminocyclohexanetetra-acetic acid (H_4cdta) were obtained from B.D.H., Hopkins and Williams, and Koch-Light respectively. *endo-cis*-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid was prepared from the anhydride (B.D.H.) by adding Na[OD] or Li[OD] to a suspension of the anhydride in D_2O. pH Values were measured using a Radiometer pH 24 meter with a combination glass electrode and are quoted as the meter readings.

Proton n.m.r. spectra were recorded at 90 MHz using a Bruker HX 90 spectrometer, or at 270 MHz using a Bruker spectrometer and a Oxford Instrument Company magnet. All spectra were obtained in the Fourier-transform mode, at 27 °C unless otherwise stated. T_1 Measurements were made using a 180°–τ–90° sequence. Chemical-shift values were measured in p.p.m. downfield from the internal standard of dss (sodium 4,4-dimethyl-4-silapentanesulphonate). Computing was carried out on the Oxford University ICL 1906A computer.

RESULTS

endo-cis-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid gives rise to five peaks in the ^1H n.m.r. spectrum. Addition of lanthanide ions or complexes causes differential shifts in the resonances (Figure 1) and the relative shifts of the different resonances (shift ratios) were recorded with each lanthanide ion following previously defined procedures.[4,5]

TABLE 1

Shift ratios with [Ln(hedta)] [a]

	H^1,H^4	H^2,H^3	H^5,H^6	H^7		H^8
Ce	0.27	1.00	0.07	0.31		0.19
Pr	0.32	1.00	0.13	0.33		0.24
Nd	0.29	1.00	0.03	0.29		0.20
Sm	0.26	1.00	0.06		0.29	
Eu	0.34	1.00	0.07	0.33		0.24
Tb	0.21	1.00	−1.79		−0.01	
Dy	1.61	1.00	−1.10		0.25	
Ho	0.28	1.00 [b]	1.10		0.48	
Er	−0.89	1.00 [b]	1.00		0.13	
Tm	0.14	1.00 [b]	1.60		0.52	
Yb	1.00	1.00	0.36		0.51	

[a] At pH 8.0, 27 °C, extrapolated to zero concentration of [Ln(hedta)]. In this and subsequent tables of shift ratios the experimental error is estimated to be approximately ±0.03. [b] The H^2,H^3 proton shifts are in the opposite direction to that predicted and generally observed for these ions relative to the other lanthanides.[12]

Shift ratios for the protons of the carboxylic acid ligand with [Ln(hedta)] complexes were obtained at pH 8.0 (Table 1). The titration curves (Figure 2) were consistent with the formation of 1 : 1 adducts with the ligand, and binding constants with the different lanthanide complexes were measured as 20—50 dm^3 mol^{-1}. Shifts with the free ions were measured at pH 4.6, where binding constants were about 5 dm^3 mol^{-1}, because of precipitation at higher pH values. The shift ratios (Table 2) were independent of the concentration of lanthanide and a single type of complex, with 1 : 1 stoicheiometry, was assumed to be present. Shift ratios with the aquo-ions and hedta complexes of Pr^{III} and Tm^{III} were also measured at 70 °C and are given in Table 3. Experiments with [Pr(cdta)]$^-$ and [Pr(edta)]$^-$ were carried out at pH 8.0 using solutions containing 3 mol dm^{-3} LiCl to increase the solubility of the lanthanide complexes.[10] Data are given in Table 4.

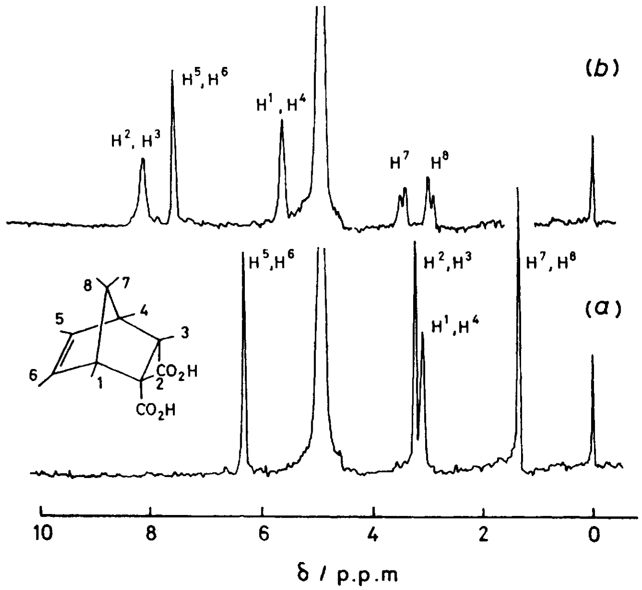

FIGURE 1 90 MHz Proton n.m.r. spectra of *endo-cis*-bicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic acid; (*a*) 5 × 10^{-2} mol dm^{-3}, pH 4.6; (*b*) as (*a*) but containing 1.5 × 10^{-2} mol dm^{-3} Pr^{3+}

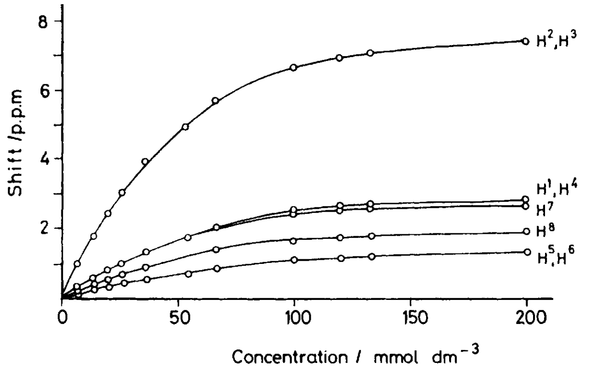

FIGURE 2 Titration curves for shifts induced by [Pr(hedta)] in the ^{1}H n.m.r. spectrum of 5 × 10^{-2} mol dm^{-3} *endo-cis*-bicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic acid at pH 8.0 The shifts are all downfield

Spin–lattice relaxation rates were measured in the presence of [Ln(hedta)]. With [Gd(hedta)] the resonances were first shifted apart using [Pr(hedta)]; for the other lanthanides the induced shifts were sufficient to produce complete resolution of the resonances. Ratios of induced relaxation rates are given in Table 5.

TABLE 2

Shift ratios with lanthanide aquo-ions *

	H^1,H^4	H^2,H^3	H^5,H^6	H^7	H^8
Pr	0.49	1.00	0.25	0.37	0.30
Nd	0.52	1.00	0.17	0.39	0.30
Eu	0.48	1.00	0.22	0.34	0.31
Tb	0.47	1.00	−0.01	0.37	0.26
Dy	0.51	1.00	0.25	0.39	0.32
Ho	0.52	1.00	0.17	0.39	0.30
Er	0.60	1.00	−0.08	0.42	0.31
Tm	0.57	1.00	−0.33	0.39	0.23
Yb	0.58	1.00	0.17	0.45	0.32

* At pH 4.6, 27 °C, extrapolated to zero concentration of Ln^{3+}.

TABLE 3

Shift ratios at 70 °C *

	H^1,H^4	H^2,H^3	H^5,H^6	H^7		H^8
[Pr(hedta)]	0.33	1.00	0.06		0.27	
[Tm(hedta)]	−0.43	1.00	2.34		0.35	
Pr^{3+}	0.49	1.00	0.24	0.37		0.31
Tm^{3+}	0.55	1.00	−0.14	0.41		0.27

* Conditions as in Tables 1 and 2.

TABLE 4

Shift ratios for Pr^{III} in different complexes *

	H^1,H^4	H^2,H^3	H^5,H^6	H^7	H^8
[Pr(cdta)]$^-$	0.47	1.00	0.31	0.41	0.31
[Pr(edta)]$^-$	0.42	1.00	0.22	0.39	0.28
[Pr(hedta)]	0.41	1.00	0.16	0.37	0.24
Pr^{3+}(aq)	0.49	1.00	0.25	0.41	0.30

* Calculated from the fully bound shifts. For the complexed ions, data are for solutions containing 3 mol dm^{-3} LiCl.

TABLE 5

Ratios of relaxation effects with [Ln(hedta)] *

	H^1,H^4	H^2,H^3	H^5,H^6	H^7		H^8
Gd	0.37	1.00	0.63	0.18		0.14
Ho	0.35	1.00	0.68		0.19	
Dy	0.35	1.00	0.63		0.15	
Tb	0.37	1.00	0.60		0.17	
Er	0.37	1.00	0.62		0.17	
Tm	0.36	1.00	0.65		0.15	

* At pH 8.0, 27 °C, from T_1 measurements. These ratios are of the differences between T_1^{-1} for the unbound ligand and for the ligand bound to [Ln(hedta)].

DISCUSSION

The data in Table 5 show that the ratios of induced relaxation rates for the different [Ln(hedta)] complexes are identical. This shows that these complexes form similar adducts with the carboxylic acid ligand. The large variation in shift ratios (Table 1) must therefore be interpreted without recourse to variations in molecular geometry.

The fully bound dipolar shift (Δ) of a nuclear resonance induced by a paramagnetic lanthanide ion can be expressed as in equation (1) where A and B are constants for a given lanthanide ion bound to a given ligand;

$$\Delta = \frac{A(3\cos^2\theta - 1)}{r^3} + \frac{B\sin^2\theta\cos 2\phi}{r^3} \qquad (1)$$

they are related [3-5] to the principal values of the magnetic susceptibility tensor χ_{xx}, χ_{yy}, and χ_{zz}, and are proportional to $[\chi_{zz} - \frac{1}{2}(\chi_{xx} + \chi_{yy})]$ and $(\chi_{xx} - \chi_{yy})$ respectively. The angles θ and ϕ are defined in the co-ordinate system of the magnetic susceptibility: θ is the angle between the z axis and the vector of length r joining the metal and nucleus; ϕ is the angle between the projection of this vector in the xy plane and the x axis. If the molecular geometry is fixed, variations in shift ratios with different lanthanides must arise from variations in the magnitudes or directions of the principal elements of the susceptibility tensor.

The shift ratios with the aquo-ions and the various complexes of Pr^{III} are remarkably constant, particularly at high ionic strength (Table 4), compared with the variation for a given complex of different lanthanides (Tables 1 and 2). This is not the case for lanthanides later in the series, notably Tm^{III}. These observations agree with more limited data obtained previously with phosphate ligands.[6, 11] Reference to equation (1) shows that the relative values of A and B must be similar for Pr^{III} in the different complexes, and therefore that the effective symmetries of the susceptibility tensors are similar. The susceptibility tensor, in a complex rigidly held as in a crystal, is determined by the nature of the ligand field.[12] The ligand field must be very different for Pr^{III} in the various complexes which differ in their charges, co-ordinating ligands, and geometries. The observation that the effective symmetries in the different complexes are similar indicates that these differ from the symmetries that would be found for a rigid complex. This conclusion is consistent with previous proposals that the effective symmetry of a complexed lanthanide ion would be averaged over rapidly interconverting states.[13-15] Complete averaging results in effective cubic symmetry, $\chi_{xx} = \chi_{yy} = \chi_{zz}$, and no shift would result. Averaging to effective axial symmetry ($\chi_{xx} = \chi_{yy} \neq \chi_{zz}$) is sufficient to explain fully the observed data with the praseodymium(III) complexes, provided that the orientation of the z axis is the same in the different complexes. This could arise, for example, by an effective ' rotation ' of each metal complex about the ligand, where the z direction then becomes this axis of rotation.[13]

The supposition that the praseodymium(III) complexes have effective axial symmetry is supported by the values of the relative shifts on the resonances of the different protons. Using approaches described fully earlier [15] and co-ordinates from crystallographic studies,[16] a search was made to determine geometries of the lanthanide adduct which are consistent with the praseodymium(III) shift data and an axially symmetric susceptibility tensor. All such geometries are close to that shown in Figure 3. Here, the z axis is aligned so as to be directed towards and symmetrically between the two carboxylate groups. The position of the metal ion is such that the distances from it to the oxygen atoms are close to 3 Å, which is chemically reasonable. The z axis is along the direction about which ' rotational ' averaging might be expected to occur. Considerable confidence in this analysis comes from the extremely close correlation of the relaxation data with this geometry (Table 6).

Because the position of the lanthanide ion relative to the ligand is invariant throughout the lanthanide series, the praseodymium(III) conformation was used as a basis for understanding the shift data obtained with other lanthanides. The possibility was considered that the symmetry remains essentially unchanged for the different ions, but that the direction of the principal (z) axis differs from one to another. The geometry of the complex requires that the z axis lies in the mirror plane of the ligand molecule. Hence, rotation of the z axis through 180° generates the shift ratios which would arise for the different orientations, Figure 4. The small variations in the shift ratios measured for the different praseodymium(III) complexes (Table 4) and under different conditions (Tables 1 and 4) would correspond to movements of about ±8° in the direction of the axis. The variations seen for each proton with the different ions from the first half of the lanthanide series under all the conditions described could be explained by variations of about ±20° in this direction. Comparisons of Tables 1 and 2 with Figure 4 make it clear, however, that no directions of an axial symmetry axis can explain in any way the shift ratios with later lanthanides. Indeed,

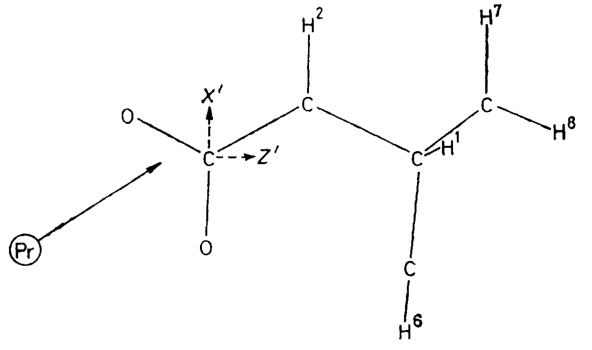

FIGURE 3 Representation of the position of the bound lanthanide ion and the direction of the principal axis of symmetry corresponding to the data of Table 6. The metal is positioned at $r = 4.6$ Å from the centre of the C^2–C^3 bond. The angle β between the vector joining the metal ion and the centre of the C^2–C^3 bond and the z' axis is 26°. Values of r between 3.4 and 6.0 Å all resulted in calculated shift ratios within ±0.05 of the experimental ones, provided that β was 27 ± 7°, and that α, the direction of the symmetry axis (see Figure 4), was 30 ± 10°

TABLE 6

Observed and calculated [a] shift and relaxation ratios

	Shift ratio		Relaxation ratio	
	Obs.[b]	Calc.	Obs.[c]	Calc.
H^2,H^3	1.00	1.00	1.00	1.00
H^1,H^4	0.45	0.42	0.36	0.30
H^5,H^6	0.24	0.25	0.63	0.65
H^7	0.40	0.43	0.17	0.16
H^8	0.29	0.32	0.15	0.12

[a] For the metal ion 4.6 Å from the centre of the bond joining C^2 and C^3, and the angle defined in Figure 3. The direction of the symmetry axis is as shown in Figure 3. [b] Mean of values for different complexes of Pr^{III}. [c] Mean of values for different [Ln(hedta)] complexes.

wide searches failed to reveal any position for the metal ion which would be consistent with a description of the shift ratios in terms of axial symmetry for an ion such as $\mathrm{Tm^{III}}$.

We conclude from this analysis that the apparent magnetic susceptibility tensor is an averaged one, representing, for example, contributions from different rapidly interconverting conformational states of the adduct. For the praseodymium(III) complexes this averaging is extensive, and results in effective axial symmetry with the principal axis oriented along the metal–ligand direction. Small differences in shift ratios with the different complexes and under slightly different conditions may well represent small differences in the direction of the resulting principal symmetry axis. For the later lanthanides with shift ratios significantly different from those with $\mathrm{Pr^{III}}$ the extent of averaging is smaller, and the resulting partially averaged tensor is axially asymmetric.

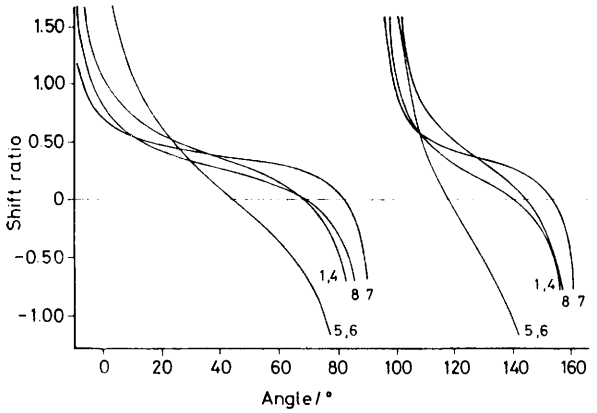

FIGURE 4 Shift ratios relative to H^2, H^3 (= 1.00) for rotation of the direction of the symmetry axis about the y axis (see Figure 3). This restricts the symmetry axis to lie in the mirror plane of the molecule. The angle α defining the direction of the axis is the angle from the z' axis. The data for $\mathrm{Pr^{III}}$ correspond to $\alpha = 32°$. The angle α of 0° is equivalent to 180°. The discontinuity in the graph arises when $(3\cos^2\theta - 1) = 0$ for the H^2, H^3 protons

The extent of averaging depends on the temperature. For example, the shift ratios of $\mathrm{Pr^{III}}$ are virtually independent of temperature whilst those of $\mathrm{Tm^{III}}$ are not (Table 3). The ratios with $\mathrm{Tm^{III}}$ become slightly closer to those with $\mathrm{Pr^{III}}$ at higher temperatures, an observation made more clearly for lanthanides complexed to the phosphate group of a nucleotide.[6] The extent of averaging also depends on the nature of the ligand (Tables 1 and 2). The general pattern of behaviour, however, seems to be independent of the ligand, and it can be seen in previously published data [6,17,18] for a variety of ligands that large variations in shift ratios occur only for later lanthanides, and that $\mathrm{Pr^{III}}$ and $\mathrm{Tm^{III}}$ are the two extremes. An analysis similar to that described above has been carried out for the monocarboxylic acid *endo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid.[19] Again, homologous adducts were found for different lanthanides. The different complexes of $\mathrm{Pr^{III}}$, but not of later lanthanides, gave very similar shift ratios. Co-ordination of the lanthanide symmetrically to the carboxylate group with metal–oxygen distances of 2.5 ± 0.2 Å was consistent with the relaxation data, and with the shift data for $\mathrm{Pr^{III}}$. The effective symmetry axis of $\mathrm{Pr^{III}}$ was directed along the C^2–CO_2^- bond, as expected if rotationally averaged. We propose that the explanation given here for the variations in shift ratios with different lanthanides is a general one for lanthanide complexes in water. Earlier suggestions [17,20,21] that changes in co-ordination geometry occur across the lanthanide series and are responsible for changes in shift ratios are inconsistent with the relaxation data.[8] Rather, the variations are connected with the electronic structures of the lanthanides. Insight into this comes from a study of single-crystal magnetic anisotropies of the different lanthanides [22] which was carried out for bis(4-methylpyridine)tris(2,2,6,6-tetramethylheptane-3,5-dionato)lanthanide complexes. The axial asymmetry of the susceptibility, as measured by the magnitude of $(\chi_{xx} - \chi_{yy})$ relative to $[\chi_{zz} - \frac{1}{2}(\chi_{xx} + \chi_{yy})]$, is smallest for $\mathrm{Pr^{III}}$ followed by $\mathrm{Eu^{III}}$. The largest asymmetries are found for lanthanides in the second half of the series, notably $\mathrm{Tm^{III}}$ followed by $\mathrm{Er^{III}}$. The variations in shift ratios described here correlate strongly with these asymmetries, which suggests that the difference of the effective symmetry of the susceptibility from axiality depends on its asymmetry in the static system.

It seems likely that the errors introduced in structural studies by the assumption of axial symmetry will be least for $\mathrm{Pr^{III}}$, and will be small if shift ratios are temperature independent and independent of the complex used to bind to the ligand. Other errors, for example inaccuracies in molecular co-ordinates and incomplete consideration of internal dynamics, could well be larger, particularly for macromolecular systems.[18,23] For lanthanides other than $\mathrm{Pr^{III}}$, especially those late in the series, the assumption of axial symmetry is likely to be a poor one, and a more elaborate analysis of the shift data will be necessary.

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