Separation of Contact and Pseudo-contact Contributions to Shifts Induced by Lanthanide(III) Ions in Nuclear Magnetic Resonance Spectra

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A method for the separation of pseudo-contact and contact contributions to the shifts of n.m.r. lines has been devised. The method is tested on the ^{31}P resonance of Ln^{III} complexes of cytidine 5′-monophosphate.

THE shifts of n.m.r. spectral lines which are induced by paramagnetic ions may arise from both contact (through bond) and pseudo-contact (through space) mechanisms. The determination of molecular conformations in solution requires a knowledge of the pseudo-contact contribution alone[1] and thus a general method is required for the separation of the two terms. In our recent work we have made use of lanthanide ion-induced shifts and have shown that for proton resonances, or for resonances of other nuclei (*e.g.*, ^{13}C) far from the lanthanide ion, the shifts are almost purely pseudo-contact in origin.[1,2] In other cases, the shifts may have a large contact contribution.[3] One series of molecules which we studied were the simple nucleotides such as cytidine 5′-monophosphate. We were unable to use the shift induced on the ^{31}P resonance by a lanthanide ion bound to the phosphate group as this shift was known to be a sum of contact and pseudo-contact terms. In this paper we shall show that the study of ^{31}P shifts in cytidine 5′-monophosphate with different lanthanide cations has allowed separation of the pseudo-contact from the contact term. The value of the pseudo-contact shift for a given lanthanide is then an extra parameter in the determination of structure in solution. The procedure for the separation of these two types of shift can be used generally in lanthanide series of complexes, but not in transition-metal complexes, and therefore has decided advantage over previous work in which the two contributions have been separated in special cases.[4-6]

EXPERIMENTAL

Lanthanide chloride solutions were prepared from the oxides. The oxides (Koch–Light) were heated at 900 °C for several hours. Solutions up to $0{\cdot}5\,\text{M}$ in lanthanide salt were prepared by dissolving weighed quantities of oxide in DCl. Cytidine 5′-monophosphate was obtained from Sigma Chemical Company. After lyophilisation from D_2O, 30 mM solutions were prepared by dissolving the solid in 99·8% D_2O or in lanthanide chloride solutions. The nominal pD of all samples was adjusted to $2{\cdot}0 \pm 0{\cdot}1$ with NaOD and DCl.

N.m.r. spectra were recorded at 27 ± 1 °C on a Brücker HX 90 spectrometer with use of a Nicolet 1085 computer for Fourier transformation, operating at 90 MHz for ^1H and 36·436 MHz for ^{31}P. ^1H Broad-band spin decoupling was used to simplify the ^{31}P spectrum. 3-(Trimethylsilyl)propane sulphonic acid sodium salt was used as an internal standard for ^1H measurements, and trimethyl phosphate for ^{31}P measurements.

THEORY

The pseudo-contact shift (Δ_{pc}/p.p.m.) in the resonance position of a nucleus in a molecule bound to a lanthanide cation is given by equation (1)[7,8] for cases when the

$$\Delta_{pc} = \frac{\nu_{pc}}{\nu_0} = \frac{-g^2\beta^2 J(J+1)(2J-1)(2J+3)\,D_z(3\cos^2\theta - 1)}{60(kT)^2\,r^3} \qquad (1)$$

symmetry of the ligand field of the bound ion is axial. Here D_z is a constant for a given lanthanide,[8] r is the distance of the nucleus from the metal ion, and θ the angle between the vector joining the nucleus and the metal ion and the principal axis of symmetry of the complexed ion.[2] The other symbols have their usual meaning.

The contact shift (Δ_c/p.p.m.) on the same nucleus due to the lanthanide ion can be described,[3,4] by equation (2)

$$\Delta_c = \frac{\nu_c}{\nu_0} = \frac{-2\pi\beta A J(J+1)}{3kT\gamma_N}\cdot g_L(g_L - 1) \qquad (2)$$

where A is the scalar coupling constant in frequency units, g_L the Landé g-factor, and other symbols have their conventional meaning.

The total observed shift Δ_t will then be as in equation (3) for a given nucleus, i.

$$\Delta_t^{\,i} = \Delta_{pc}^{\,i} + \Delta_c^{\,i} \qquad (3)$$

For axial symmetry, which has been found to be the case for the complexes treated below,[2] the ratio (R_{ij}) of the pseudo-contact shift of this given nucleus (i) to another (j) in the same molecule is the same for all lanthanides[1] [equation (4)]. Now let the nucleus j be

$$R_{ij} = \frac{\left\langle \dfrac{3\cos^2\theta_i - 1}{r_i^3} \right\rangle}{\left\langle \dfrac{3\cos^2\theta_j - 1}{r_j^3} \right\rangle} = \frac{\Delta_{pc}^{\,i}}{\Delta_{pc}^{\,j}} \qquad (4)$$

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in such a position in the molecule that it is not subject to contact shifts, then $\Delta_t^j = \Delta_{pc}^j$ and $\Delta_{pc}^i = R_{ij} \,.\, \Delta_t^j$. Then we can write equation (5).

$$\Delta_t^i = R_{ij}\Delta_t^j + \Delta_c^i \qquad (5)$$

A plot of Δ_t^i/Δ_t^j against Δ_c^i/Δ_t^j for the different lanthanides will give a straight line of intercept R_{ij} at the point where $\Delta_c^i/\Delta_t^j = 0$. Although Δ_c^i is not directly measurable, it is given by equation (2), *i.e.*

$$\Delta_c^i = KAJ(J+1)\,.\,g_L(g_L - 1) \qquad (6)$$

where $K = -2\pi\beta/3kT\gamma_N$ for all lanthanides. As Reuben and Fiat [4] have shown that for the Ln–H_2O system A is approximately independent of lanthanides (±10% for Nd—Tm) we shall take it that A is the same for all lanthanides with some given ligand. Thus equation (7) is true for all the different lanthanides, and a plot

$$\Delta_t^i = R_{ij}\,.\,\Delta_t^j + \text{const.}J(J+1)g_L(g_L - 1) \qquad (7)$$

of Δ_t^j/Δ_t^i against $J(J+1)g_L(g_L - 1)\Delta_t^i$ gives at $\Delta_t^j/\Delta_c^i = 0$ (where $\Delta_t^i = \Delta_c^i$) the value of $J(J+1)$-$g_L(g_L - 1)/\Delta_t^i$ for a cation which gives rise to no pseudo-contact shift, that is Gd^{3+}. In effect Reuben and Fiat [4] used the last relationship to find the contact shift in lanthanide–water complexes but usually it is not possible to determine accurate resonance positions in Gd^{3+} complexes as the lines are greatly broadened. We therefore chose to plot equation (7) in the form (8) which gives an intercept R_{ij}.

$$\frac{\Delta_t^i}{\Delta_t^j} \text{ against } \frac{J_j(J_j + 1)g_L(g_L - 1)}{\Delta_{pc}^j} \qquad (8)$$

RESULTS AND DISCUSSION

The shifts of the ^1H and ^{31}P resonances of cytidine 5′-monophosphate have been measured by use of various lanthanides.[9] Under the conditions of fast exchange obtained here the observed shift in a given resonance position (δ_t^i) is the shift in the fully bound complex (Δ_t^i) times the fraction (f) of cytidine 5′-phosphate bound to the lanthanide, $\delta_t^i = f\Delta_t^i$. Analysis of titration curves, obtained by increasing the concentration of any given lanthanide ion in solutions of constant cytidine 5′-monophosphate concentration, show that a 1 : 1 complex is formed in each case. The titration curves for different lanthanides are extremely similar showing that the binding constants are effectively the same for all the lanthanides. In the concentration range 0—0·2M the data are well described by $K = 5$ l mol^{-1}.

In these circumstances of fast exchange and equal binding constants, the fraction of lanthanide bound to cytidine 5′-monophosphate at a given concentration is the same for each lanthanide. Now the ratios of the *proton* shifts in cytidine 5′-monophosphate have been observed to be same for all lanthanides,[9] and are thus purely pseudo-contact in origin. In addition, we have shown that in these circumstances the ligand-field symmetry at the metal ion is effectively axial. Therefore for these complexes we can plot equation (7) in the form (9) where δ_t^j and δ_t^i are the shifts observed

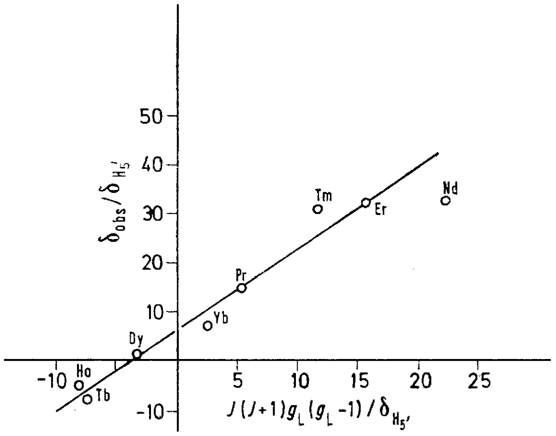
$$\frac{\delta_t^i}{\delta_t^j} \text{ against } \frac{J(J + 1)g_L(g_L - 1)}{\delta_t^j} \qquad (9)$$

at any chosen lanthanide concentration. In the Figure we have used for δ_t^i the shift of the ^{31}P resonance position and for δ_t^j, the shift observed on the H_5' protons (which are equivalent) at 0·015M-lanthanide ion concentration. The numerical data shown in Table 1 were obtained from titration curves carried out at concentrations of up to 0·2M in lanthanide chloride for ^{31}P spectra and up to 0·5M for ^1H spectra. The observed shifts have been corrected for the small shifts obtained with the diamagnetic La^{3+}.

TABLE 1

Observed shifts/p.p.m. at 0·015M-lanthanide(III)

	^{31}P	^1H
Pr	−8·80	−0·60
Sm	0·80	(−0·06)
Nd	−7·21	−0·22
Eu	24·60	0·34
Tb	37·00	−4·24
Dy	−3·54	−8·48
Ho	14·00	−2·81
Er	32·35	0·99
Tm	22·00	0·70
Yb	6·84	1·00



Plot of $\delta_{obs}/\delta_{H_5'}$ against $J(J + 1)g_L(g_L - 1)/\delta_{H_5'}$ at 0·015M-lanthanide chloride and 0·03M-cytidine 5′-monophosphate. Note that there is a larger error on those points where the shift for H_5' is very small (see Table 1)

The near linearity of the plot shows that the assumptions used are reasonable. The only marked exceptions are for Sm^{3+} (not plotted) and Nd^{3+} but the ^1H shift on Sm^{3+} was too small to measure accurately at any concentration, and the shift with Nd^{3+} was less accurate than that for the other lanthanides. The value of R_{ij}, the ratio of the ^{31}P to the H_5' pseudo-contact shifts, found from the plot is 6·0 ± 1·0, which compares well

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[9] C. D. Barry, C. M. Dobson, R. J. P. Williams, and A. V. Xavier, to be published.

with the value predicted from the structure of cytidine 5′-monophosphate determined from the proton shift data (5·8 ± 0·5).[9] Spin–lattice relaxation studies using Gd^{3+} with cytidine 5′-monophosphate have confirmed the ratio of the distances from Gd^{3+} to ^{31}P and H_5'.[9] Calculated values of contact and pseudocontact shifts of ^{31}P are given in Table 2.

TABLE 2

Shift magnitudes/p.p.m. at 0·015M Ln^{3+}

	Total shift	Pseudo-contact shift (P.C.)	Contact shift (C.)	P.C./C.
Pr	−8·80	−3·60	−5·20	0·69
Sm	0·80	(−0·36)	(−1·16)	(0·31)
Nd	−7·21	−1·32	−5·89	0·22
Eu	24·60	1·84	22·76	0·08
Tb	37·00	−25·44	62·44	−0·41
Dy	−3·54	−50·88	47·34	−1·07
Ho	14·00	−16·86	30·86	−0·55
Er	32·35	5·84	26·51	0·22
Tm	22·00	4·20	17·80	0·24
Yb	6·84	6·00	0·84	7·14

In addition we compared the magnitude of the calculated contact shift for each lanthanide (relative to $Dy^{3+} = 100$) with values of $J(J + 1) \cdot g_L(g_L - 1)$ on the same scale to illustrate the agreement between theory and experiment in a different way (Table 3).

TABLE 3

Contact shift magnitude relative to Dy = 100

	Theory	Experimental
Pr	−11·3	−11·0
Sm	−6·3	(−2·5)
Nd	−17·3	−12·4
Eu	—*	48·1
Gd	111·1	—†
Tb	111·1	131·8
Dy	100·0	100·0
Ho	79·4	65·2
Er	54·0	56·0
Tm	28·8	37·6
Yb	9·1	1·8

* $J = 0$. † See text.

The confirmation of a structural parameter by the use of pseudo-contact data determined in the presence of large contact terms suggests that the above procedure can be used generally and should be very valuable for the analysis of shift data taken from ^{13}C resonance studies.

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