The Interpretation of Lanthanide-induced Shifts in ^{1}H Nuclear Magnetic Resonance Spectra

By J. Goodisman and R. S. Matthews*

(*Department of Chemistry, Syracuse University, Syracuse, New York,* 13210)

Summary Owing to the present accuracy of the data and various other factors, it is easy to obtain agreement with experimental results for lanthanide-induced shifts in ^{1}H n.m.r. spectra; some considerations in the formulation of such models which have been ignored previously are discussed.

Lanthanide-induced shifts are of considerable value in resolving n.m.r. spectra of molecules containing various functional groups,[1,2] although there is disagreement over the interpretation of the numerical values of the shifts. We here discuss certain facts which have been ignored previously.

If the induced shift is pseudo-contact in nature, its value (δ) is given by equation (1), where r is the lanthanide-proton distance, and X is the angle between the principal

$$\delta = K(3\cos^2 X - 1)/r^3 \qquad (1)$$

magnetic axis of the complex and a vector from the magnetic moment to the proton. This equation assumes cylindrical symmetry about the bond from the substrate to the complex, which while reasonable, has not been verified. K depends on the concentrations of the lanthanide complex and the alcohol, the g-value of the ion, *etc.* Equation (1) must normally be averaged over internal motions which change r or X or both.

If the angular factor is ignored a plot of log δ *vs.* log r for the various protons in a single molecule should be a straight line with a slope of -3. DeMarco *et al.*[4] considered shift data on several mono- and bi-cyclic alcohols. Excluding protons for which contact shifts may be important, log δ for 28 protons was plotted against log [r(O–H)]. The distance r(Eu–H) was not known, but the attachment site is presumably oxygen. A straight line was obtained, but with a slope of $-2{\cdot}2$. We have applied their procedure to data for other rigid molecules of known structure and obtained similar results. Thus, for adamantan-2-ol, using shifts given in ref. 5, a plot of log δ *vs.* log [r(O–H)] gave a straight line, slope $-1{\cdot}6$ (see Table 1). The errors are similar to those for the corresponding treatment of the data in ref. 4. Similarly, Cockerill and Rackham[6] found an average slope of -2 for data on several rigid molecules.

The fact that the magnitude of the slope is less than 3 has been ascribed to neglect of the angular factor 3 cos^2 X X $-$ 1. We point out that measurement of the distance to oxygen rather than to the lanthanide ion also causes a decrease in this quantity. Since the distance r (H–Eu) will in general be greater than the $\bar{r}$ (O-H), one can write $r = \bar{r} + d$ (d approx. constant). The effect of variation in angle is again neglected. If the shifts actually decrease as $(\bar{r} + d)^{-3}$ they will fall off less quickly than the inverse cube as a function of $\bar{r}$. Indeed, any slope desired can be obtained by plotting log δ *vs.* $\bar{r} + d$ and varying d, and the slope of -3 is obtained for adamantan-2-ol for d 3·19 Å. This is significantly larger than Eu–O distances suggested by Sanders and Williams[10] and by Briggs *et al.*,[8] so this formula also simulates an angular effect. We introduce it only to point out a danger in believing a model on the basis of log–log plots, since the quality of the fit to a straight line as measured by the residuals log δ-log δ_{calc} (see Table 1) is not greatly affected.

Table 1

Distances (from Dreiding models) to oxygen and shifts due to Eu *for adamantan-2-ol*

Hydrogen atom	$\bar{r}$[a]	Measured shift (Hz)[b]	Calc. shifts	
			(1)	(2)
8,10 *cis*	2·6 Å	900	876	873
1,3	2·5	870	933	920
8,10 *trans*	3·9	449	459	475
7	4·3	413	393	403
4,9 *cis*	4·5	391	366	373
4,9 *trans*	4·0	341	441	456
6	5·1	320	300	297
5	5·2	298	291	287

[a] $\bar{r}$ = distance of proton from oxygen. [b] Ref. 5. [c] (1) $\ln \delta = 8{\cdot}298 - 1{\cdot}593 \ln \bar{r}$; (2) $\ln \delta = 12{\cdot}05 - 3{\cdot}00 \ln (\bar{r} + 3{\cdot}19)$.

It is easy to obtain straight lines with low residuals in log-log plots for this kind of data so a fit of this kind may not be significant. While the residuals are generally $\leqslant 0{\cdot}1$, corresponding to errors of $\leqslant 10\%$, log δ values vary only over a range of *ca.* 1·5 units. Further, for any particular molecule for the protons the angular factors and the distances from oxygen (or Eu) are not independent since the molecular structure causes some correlation between them. *E.g.*, if the magnetic axis is the molecular axis, for rigid molecules, χ will be closer to zero for distant protons, and so $3\cos^2\chi - 1$ will be larger, while for flexible molecules the distant protons will be able to move off the axis and so the angular factor will be smaller. Finally, the effect on the shift of the change in r is likely to dominate the effect of the angular factors because of the dependence upon r^3.

The apparent slope of the plots of ln δ *vs.* ln $\bar{r}$ should reflect molecular structure however. For the model in the preceding paragraph, rigid molecules give rise to slopes of greater than -3 and flexible molecules slopes less than -3. The deviation from -3 reflects, among other things, the angular effect, and we have found slopes greater than -3 for all published data on rigid molecules. For flexible molecules such as n-hexanol and heptanol, we calculated the proton–oxygen distance as a root-mean-square average over the configurations generated by free rotation about the intervening bonds, by the methods in ref. 9. In the present case, we assume tetrahedral bond angles and C-O, C–C, and C–H distances of 1·43, 1·59, and 1·10 Å respectively. Table 2 gives calculated mean square distances and the shifts measured by Sanders and Williams.[10]. The linear approximation log–log plot in this case has a slope of $-3{\cdot}6$.

TABLE 2

Root-mean-square distances to oxygen and shifts due to Eu *for n-hexanol*

Carbon	$\bar{r}^{a}$	Observed shift[b]	Calculated shift[c]
2	2·928 Å	$4{\cdot}2_1$ p.p.m.	4·96 p.p.m.
3	3·627	$2{\cdot}8_9$	2·31
4	4·225	$1{\cdot}4_2$	1·34
5	4·751	$0{\cdot}9_0$	0·88
6	5·226	$0{\cdot}5_5$	0·63

[a] $\bar{r}$ = proton–oxygen distance (root-mean-square). [b] Ref. 9. [c] $\ln\delta = 5{\cdot}433 - 3{\cdot}566 \ln \bar{r}$. [d] Shifts are 'normalized' to a 1 : 1 mole ratio of Eu and alcohol.

Hinckley,[1] in his work on cholesterol, reported that the shifts depended upon the inverse cube of assumed hydrogen–metal distances. This has been cited as evidence that the angular variation is unimportant in this and similar molecules. In cholesterol, four of the five protons are attached to the rigid part of the molecule while that furthest from oxygen is on a flexible side chain and the dependence of the shift on distance should be different for this proton from that for the others. A plot of log δ vs. log r (Hinckley's values) for these five points gives a slope of $-3{\cdot}3$, with an average value of the residuals of 0·28, much larger than values obtained above (*e.g.* 0·045 for data in Table 1). Elimination of the point for the flexible chain gives a slope of $-2{\cdot}6$ with an average residual of 0·016, *i.e.* a much better straight line; the choice of any other four points gives only a slight improvement (average residuals *ca.* 0·25). The flexible chain in this case consists of six carbon atoms, so the distance from the metal should be (see Table 2) *ca.* 5 Å more than for the C(18) methyl proton, *i.e.*, *ca.* 14 Å. The shifts (in p.p.m.) for the protons on the rigid part of the molecule obey equation (2).

$$\ln \delta = 8{\cdot}40 - 2{\cdot}61 \ln r(\text{Å}) \tag{2}$$

The shift of 1·9 p.p.m. for the side chain proton corresponds to $r = 20$ Å, so the shift falls off more quickly with r than for the other protons, as expected.

Attempts have been made to fit spectra to more detailed models. Thus, Briggs, Hart, and Moss[8] considered the shift in borneol due to praseodymium THD. Three structural parameters together with K (equation 1) were varied to fit the 10 measured shifts. The C(OH)H shift was excluded although its value was quite well predicted from parameters determined from the others. They obtained a reasonable fit (see Table 3), but in light of some good fits obtained above using $\delta = K\bar{r}^{\alpha}$ this cannot be taken as proof of the model. As an experiment, we calculated a least-squares fit of the dependence of the logarithms of the ten shifts upon an expression with a quadratic dependence upon log $\bar{r}$, the proton–oxygen distance, a physically unreal procedure (see Table 3), and obtained an average error in calculated shifts of 1·2 p.p.m.; the theory of Briggs *et al.*, gives an average error of 1·1 p.p.m. The carbinol methine shift is predicted with only slightly greater error than that from the theory of Briggs, *et al.*

TABLE 3

Distances and calculated shifts due to $Pr(tmhd)_3$ *for borneol*

Hydrogen	r^{a}	Measured shift (p.p.m.)[c,d]	Calc. shift[e]	Calc. shift[c]
exo-3-H	3·125 Å	16·6	19·25	15·8
endo-3-H	2·438	34·2	32·55	30·2
4-H	4·375	10·1	10·17	9·84
exo-5-H	4·5	10·5	9·68	11·0
endo-5-H	3·438	16·0	15·93	16·1
exo-6-H	3·688	15·7	13·92	16·0
endo-6-H	2·312	35·6	36·59	38·7
8-Me	4·5	7·78	9·68	7·84
9-Me	5·2	8·01	7·57	7·88
10-Me	3·4	17·8	16·28	16·5
exo-2-H[b]	2·0	45·0	50·91	49·0

[a] Proton–oxygen distance. [b] Data not used in curve fitting, but shift predicted from expression in footnote e. [c] Ref. 7. [d] Shifts are normalized to a 1 : 1 ratio of Pr to alcohol. [e] $\ln\delta = 5{\cdot}77 - 2{\cdot}87 \ln \bar{r} + 0{\cdot}373 (\ln \bar{r})^2$.

It is thus difficult to derive a model in terms of its ability to fit the observed shifts. If there are three or more parameters in the model, the average error should be much less than 1 p.p.m. for the agreement to be considered good. This in no way implies that the model of Briggs *et al.* is incorrect, of course, since the poorer agreement may be due to errors in the measurement of the shifts (10%, but may be as high as 50%[6] for small shifts). This is especially true if one uses a dilution study to extrapolate the chemical shifts for each proton in the absence of the lanthanide reagent (*e.g.* ref. 4) since Shapiro[11] has recently shown conclusively that such dilution curves are not linear at low concentrations of the reagent. Such problems and/or the presence of effects other than the pseudocontact shift may make it impossible to get highly acccurate values for the pseudocontact shift for comparison of experimental and theoretical results. Nevertheless, no model, however plausible, can be accepted solely on the basis of 'agreement' with experiment to 1 p.p.m.

We therefore conclude the following. For several reasons, it is not difficult to obtain agreement to *ca.* 1 p.p.m. of measured shifts with those calculated from a simple model, even one that ignores important details of the situation. Accurate experimental data (perhaps to within 0·1 p.p.m.) are needed to test the verisimilitude of any model proposed.

(*Received, June 10th,* 1971; *Com.* 948.)

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