Lanthanide-induced Shifts in ^{1}H Nuclear Magnetic Resonance: the Significance of the Angle Term in the Geometric Factor of Pseudocontact Shift

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Summary A computer program is used to determine the position of the lanthanide ion which maximizes the correlation between the induced shift and the geometric factor $(3\cos^2\theta - 1)\,r^{-3}$; its use to demonstrate the significance of the angle term and in conformational analysis is described.

The shifts in n.m.r. signals induced by association of organic molecules with paramagnetic lanthanide chelates seem to be entirely or predominantly due to pseudocontact interaction.[1–5] According to McConnell and Robertson[6] the pseudocontact shift is proportional to the geometric factor given in equation 1:

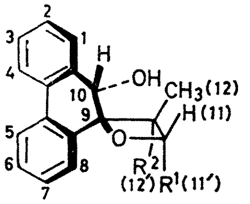
$$\Delta H_i = \text{const.}\ (3\cos^2\theta_i - 1)\,r_i^{-3} \qquad (1)$$

where r_i is the distance between the metal ion and the ith proton and θ_i the angle between this vector and the principal molecular axis. There have been trials to correlate the induced shift only with r^{-3} or even with other orders of the distance between the proton and the heteroatom in the molecule,[1–3,6–8] assuming a constant angle term (*cf.*, however, refs. 4, 5). This seems, according to the examples reported here, to be a limited approximation.

We used a program written for the IBM S/360 computer to determine the location of the lanthanide ion in the complex with the organic molecule which gives the smallest sum of squared errors between the measured shifts and those predicted from equation 1. For comparison purposes we shall refer to a dimensionless measure of the error (ϵ) as

$$\epsilon = \sqrt{\frac{\text{sum of the square errors}}{\text{number of the points}}} \Bigg/ \text{average shift} \qquad (2)$$

defined by equation 2. A nonlinear regression technique is used where the three co-ordinates of the metal ion are the nonlinear parameter to be determined. The linear parameter (the constant in equation 1) was eliminated from the regression by the method discussed by Lawton and Sylvestre.[9] The input to the program is the cartesian co-ordinates with reference to an arbitrary origin of the heteroatom and the protons as well as the corresponding shifts. An estimate of co-ordinates of the metal are given as a starting point for the regression. The unilateral symmetry axis of the lanthanide chelate–organic substrate complex would be along the vector connecting the lanthanide ion with the heteroatom of the organic compound.[4,5] Thus θ_i in equation 1 is taken as the angle between this vector and the vector joining the ith proton with the lanthanide ion. Excellent correlations for the examples studied were obtained without the need of assuming contact shift contributions.



(Ia) $R^1 = H; R^2 = Me$
(Ib) $R^1 = Me; R^2 = H$

The Figure illustrates the correlation between the reported shifts[8] for adamantan-2-ol and the geometric factors calculated† for the computer-determined position of Eu^{III}: 3·0 Å from the oxygen atom with Eu–O–C(2) angle of 128° (ϵ = 0·034). Measured shifts for *trans*-4-t-butylcyclohexanol[3] including the value for the signals of the hydrogen

Measured[a] *and predicted*[b] Eu(pm)$_3$-*induced shifts in* (Ia)[c] *and* (Ib)[c]

	Proton position	1	2	3	4	5	6	7
(Ia)	Measured shift	3·5	1·9	1·9	3·4	2·9	1·4	0·2
	Predicted shift	3·4	1·6	1·6	2·5	2·2	0·7	0·5
(Ib)	Measured shift	3·6	1·9	1·9	3·1	2·2	0·5	−1·3
	Predicted shift	4·5	2·3	2·0	2·9	2·4	0·3	−2·2

	Proton position	8	10	11	11′	12	12′	OH
(Ia)	Measured shift	22·3	15·2	27·3	25·4	10·3	11·9	13·3
	Predicted shift	21·6	16·5	27·1	26·6	9·6	11·3	d
(Ib)	Measured shift	16·8	18·0	27·9	9·5	9·8	19·2	12·1
	Predicted shift	18·0	16·2	28·2	9·0	9·7	19·1	d

[a] Determined from the slopes of the plots of shifts (in p.p.m.) against molar ratios of Eu(dpm)$_3$: (I), concentration of (I) *ca.* 0·2 molar in CCl$_4$.

[b] From the calculated geometric factor multiplied by the slope of the plot of induced shift against $(3\cos^2\theta - 1)r^{-3}$.

[c] Eu–O *distances*: 3·1 Å (Ia) and 2·8 Å (Ib).

[d] Not calculated because of the uncertainty in predicting the predominant position of this rotating hydrogen atom.

atom at C(1) could be similarly correlated with this geometric factor (Figure) without the need of assuming any contact shift contribution. These data were obtained for the Eu ion at 2·3 Å from the oxygen at an Eu–O–C(1) angle of 139° ($\epsilon = 0{\cdot}045$).

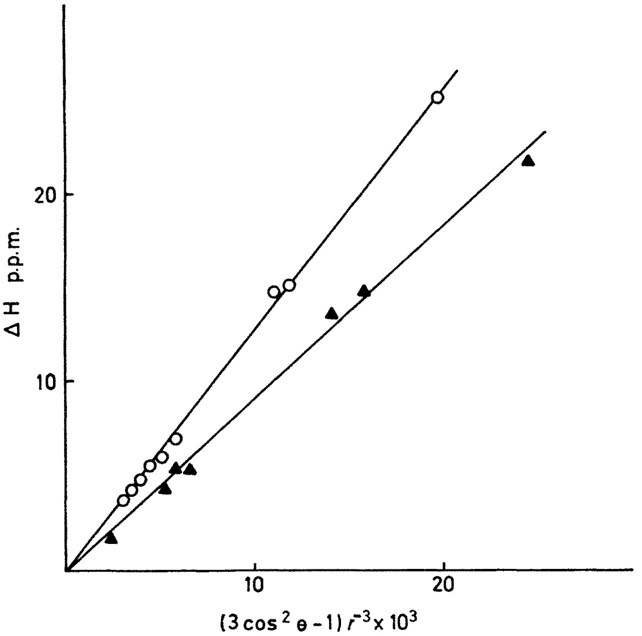


FIGURE. *Plot of measured shift* (ΔH) *against the pseudocontact geometric factor for adamantan-2-ol,*[8] *(circles), and trans-4-t-butylcyclohexanol,*[3] *(triangles).*

The significance of the angle term and the use of the above-mentioned computer program in conformational analysis are demonstrated in the following examples.

The Eu(dpm)$_3$-induced shifts of the proton signals of the hydroxyoxetans (Ia) and (Ib), which are obtained by NaBH$_4$ reduction of the corresponding ketones,[10] are given in the Table. These indicate[‡] that the ethereal oxygen, and not the sterically hindered hydroxy-group, is involved in complex formation, which is in agreement with our finding that steric hindrance suppresses the complex formation.[11] Since the signals of the proton at position 7 in (Ia) undergo a downfield shift which is two orders of magnitude less than that of the proton next to it at position 8 and still an order of magnitude less than those of the far protons located at positions 2 and 3, the shift cannot be dependent on r only. Moreover, the signals of the proton at position 7 in (Ib) undergo an upfield shift, whereas all others are shifted, as usual, downfield.[§] The co-ordinates of the ethereal oxygen and the different protons in (Ia) and (Ib) were calculated on the basis of known bond lengths and angles for trimethylene oxide.[12] An angle of 17° between the planes of the two benzene rings was assumed. This leads to a C(9)–C(10) bond length of 1·54 Å. The co-ordinates of the hydrogen atoms and methyl groups on the oxetan ring were calculated for planar and differently puckered conformers of the four-membered ring. The best agreement between the measured and predicted shifts was obtained for the oxetan ring which is puckered by about 20° in the case of (Ia) ($\epsilon = 0{\cdot}071$) and about 40° in the case of (Ib) ($\epsilon = 0{\cdot}085$). It is interesting that this puckered conformer of (Ib) has both methyl groups in equatorial positions, which is optimum for the most stable conformer. For both compounds such distortion of the oxetan ring leads to less sterically hindered conformers.

In all examples mentioned above the position determined for the lanthanide ion which gave the best correlation between the measured shift and $(3\cos^2\theta - 1)\,r^{-3}$ according to equation 1 is at an expected distance of 2·7 ± 0·4 Å from the heteroatom and in a sterically favourable location with respect to the organic molecule. This supports the applicability of this method in evaluating shift data in which the assumption is made that the Eu$^{\text{III}}$-induced shift is entirely of the pseudocontact type.

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[†] To determine the geometric factor for the protons of a methyl group the average of the factors for several equidistant positions along the orbit described by rotation of the hydrogen atoms was calculated. In case of a t-butyl group an average of the geometric factors of several methyl groups (determined as given above) at equidistant positions along the orbit described by the rotation of the methyl groups was calculated.

[‡] The signals of the ethereal α-hydrogen atoms undergo larger shifts than that of the alcoholic α-hydrogen and the latter is shifted more than the OH signal, whereas on complex formation with an alcoholic oxygen, the shift of the OH signal is 3 to 5 times that of the α-hydrogen.[2,3]

[§] The term $(3\cos^2\theta - 1)$ becomes negative at $\theta > 54° 44'$.

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