Lanthanide Shift Reagents in Nuclear Magnetic Resonance Spectroscopy

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1 Introduction

Nuclear magnetic resonance (n.m.r.) spectroscopy is a most valuable technique for structural investigations of complex organic molecules. However, owing to the relatively low sensitivity of proton chemical shifts to changes in the chemical and stereochemical environment, the application of n.m.r. spectroscopy has been severely restricted. Such terms as the 'methylene, methine envelope' used frequently in connection with the proton n.m.r. spectra of steroids and terpenes illustrate this frequent overlapping of resonance of non-equivalent protons.

Shift reagents are used in n.m.r. spectroscopy to reduce the equivalence of nuclei by altering their magnetic environment, and are of two types: aromatic solvents such as benzene or pyridine, and paramagnetic metal complexes. The latter function by co-ordinating to suitable donor atoms in the compound under study, thereby expanding their co-ordination shell and forming a new complex in solution. Apart from effects due to shielding by bonding electrons, the chemical shifts are altered by the paramagnetic metal ion by a transfer of electron spin density, *via* covalent bond formation, from the metal ion to the associated nuclei (contact shift), or by magnetic effects of the unpaired electron magnetic moment (pseudocontact shift). First-row transition-metal complexes can be used as shift reagents and operate by both contact and pseudocontact mechanisms, although the former predominates owing to the covalent character of these compounds. Unfortunately, these shift reagents exhibit an adverse effect on the resolution of the n.m.r. spectra by causing severe line-broadening. In 1969 Hinckley[1] initiated a major advance in this field by introducing the use of a lanthanide-metal complex as a shift reagent and since then it has become established that lanthanide complexes produce far less linewidth broadening and give shifts which are caused virtually exclusively by the pseudocontact mechanism. The complexes found most useful are lanthanide acetylacetonate derivatives, some of which are fluorinated and exhibit greater shifting power.

The most common practice is to successively add known amounts of the lanthanide shift reagent (LSR) to the compound under study (substrate) and record the n.m.r. spectrum after each addition. The chemical shift of each proton in the substrate alters, to a greater or lesser degree, with each addition of shift

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[1] C. C. Hinckley, *J. Amer. Chem. Soc.*, 1969, **91**, 5160.

reagent and the extent of this lanthanide induced shift (LIS) is measured. A plot of the LIS against the ratio of LSR: substrate is a straight line at low values of this ratio. The slope of this line is characteristic of the compound under study. Apart from spectral clarification, the factors determining pseudocontact shift allow relative distances within the complex to be determined, permitting studies of the stereochemistry of the substrate under examination. The application of LSRs in n.m.r. spectroscopy has permitted the solution of a large number of structural problems and one example of this occurs in the use of chiral lanthanide shift reagents for estimating the composition of mixtures of enantiomers.

2 Substrate–Lanthanide Shift Reagent Interaction

The lanthanide shift reagent consists of a six-co-ordinate metal complex which readily expands its co-ordination in solution to accept further ligands.[2,3] The substrate co-ordinates to the LSR by virtue of the requirement that it contains heteroatoms which exhibit some degree of Lewis basicity. Addition of the LSR to a solution of the substrate in a normal n.m.r. solvent leads to the formation of an equilibrium mixture, as shown in equations (1) and (2)

$$\mathrm{L} + \mathrm{S} \overset{K}{\rightleftharpoons} [\mathrm{LS}] \tag{1}$$

$$[\mathrm{LS}] + \mathrm{S} \overset{K_2}{\rightleftharpoons} [\mathrm{LS_2}] \tag{2}$$

where L and S are the concentrations of the LSR and substrate, respectively, and [LS] the concentration of the complex formed in solution; the ratios of these species depends on K and K_2, the binding constants. The latter binding constant K_2 is usually assumed negligible (see later), *i.e.* a 1 : 1 complex is thought to be formed. Owing to the magnetic interactions with the metal ion (Section 3) in the complexed substrate [LS], the n.m.r. positions of associated nuclei in the substrate differ from those in the uncomplexed state. The equilibrium in solution between these species is rapid on the n.m.r. timescale,[4] so that only a single average signal is recorded for each nucleus in the different environments.* This does not mean that the whole spectrum is merely displaced since factors such as the distances of the nuclei from the metal ion cause a differential expansion of the spectrum. Consequently, the foremost use of LSR is in effectively increasing the resolution, in many cases producing first-order spectra. An expression can be derived for the lanthanide induced shift (LIS), denoted by $\delta\Delta$, of the nuclei of the substrate before and after addition of the LSR:[6]

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* Slow chemical exchange is reported[5] to occur at −80 °C with a solution of dimethyl sulphoxide and the LSR tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)-europium(III) [Eu(fod)$_3$] in deuteriomethylene chloride.

[2] R. G. Charles and R. C. Ohlmann, *J. Inorg. Nuclear Chem.*, 1965, **27**, 119.

[3] J. E. Schwartzberg, D. R. Gere, R. E. Sievers, and K. J. Eisentraut, *Inorg. Chem.*, 1969, **6**, 1933.

[4] F. A. Hart, J. E. Newbery, and D. Shaw, *Nature*, 1967, **216**, 261.

[5] D. F. Evans and M. Wyatt, *J.C.S. Chem. Comm.*, 1972, 312.

[6] D. R. Eaton, *Canad. J. Chem.*, 1969, **47**, 2645.

$$\delta\Delta = \frac{K[\mathrm{LS}]\,\Delta_{\mathrm{B}}}{1 + K[\mathrm{LS}]} \qquad (3)$$

where Δ_{B} is the LIS of the complexed substrate [LS], *i.e.* the bound chemical shift, and K the equilibrium constant of expression (1). At low concentration of LSR, a linear concentration dependence of LIS is observed, which is used to control the magnitude of the shift. For the purpose of obtaining shift parameters which are independent of concentration of LSR, Demarco *et al.* have proposed[7] a technique used by many others[8-14] whereby the concentration–shift plots are extrapolated to concentrations where the molar ratio of LSR to substrate is 1 : 1. These LISs at such high concentrations can often not be checked directly owing to the limited solubility of the LSR. The chemical shift of the uncomplexed substrate can be obtained by a graphical method whereby the chemical shift of each nucleus is plotted against the concentration of LSR and the plot extrapolated to zero concentration of LSR,[8,14-16] a technique useful when individual resonances are part of a complex, multiple adsorption band. However, deviations between extrapolated and observed chemical shifts are cited[7] even at low concentrations of LSR.[17]

By studying expression (2), it is apparent that as the concentration of LSR is increased, the deviation from linearity should also increase, as shown in Figure 1. Such curves cannot be produced using the dipivalomethanato LSR

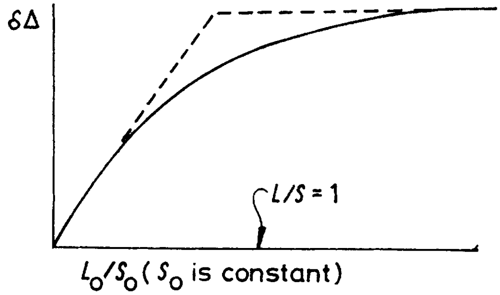

Figure 1 *Relationship of LIS* ($\delta\Delta$) *with the concentration of added LSR* [L_0] *and added substrate* [S_0]

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[7] P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, 1970, **92,** 5743.

[8] K. K. Anderson and J. J. Uebel, *Tetrahedron Letters*, 1970, 5253.

[9] H. Hart, and G. M. Love, *Tetrahedron Letters*, 1971, 625.

[10] C. Beaute, Z. W. Wolkowski, and N. Thoai, *Tetrahedron Letters*, 1971, 817.

[11] Z. W. Wolkowski, *Tetrahedron Letters*, 1971, 821.

[12] Z. W. Wolkowski, *Tetrahedron Letters*, 1971, 825.

[13] M. Witanowski, L. Stefaniak, H. Januszewski, and Z. W. Wolkowski, *Tetrahedron Letters*, 1971, 1653.

[14] A. F. Cockerill and D. M. Rackham, *Tetrahedron Letters*, 1970, 5149.

[15] K. C. Yee and W. G. Bentrude, *Tetrahedron Letters*, 1971, 2775.

[16] D. R. Crump, J. K. M. Sanders, and D. H. Williams, *Tetrahedron Letters*, 1970, 4949.

[17] J. Goodisman and R. S. Matthews, *J.C.S. Chem. Comm.*, 1972, 127.

owing to its limited solubility, but they are produced experimentally by: (*a*) using $Eu(NO_3)_3,6D_2O$ in an aqueous solution in a study of ^{31}P n.m.r. spectra;[18] and (*b*) using $Eu(fod)_3$ or $Pr(fod)_3$, which are fluorinated LSRs having higher solubilities.[19]

It should be noted that the extrapolation of the linear portions of the curve does not coincide with the line drawn at a 1 : 1 molar ratio. The quantity of LSR needed to reach the flat part of the curve in Figure 1 depends on the Lewis basicity of the substrate, and for weakly basic substrates up to two molar equivalents of the fluorinated LSR are necessary.[19] However, when used in a large excess these LSRs give LISs approaching that of the bound substrate. Deviations from the curves expected from expression (3) occur at high concentrations of LSR, which have been explained by a combination of medium and associated effects.[14] The praseodymium complexes are reported to exist as dimers in the solid state,[20] varying from 7 to 8 co-ordinate and the consequences of polyfunctional substrates[21,22] have yet to be studied in detail.

The shift parameters derived by these approaches are somewhat dependent on the initial substrate concentration and an alternative approach has been advocated which provides a method for obtaining quite accurate bound chemical shifts, and also a value for K the binding constant. From the LIS ($\delta\Delta$), the uncomplexed chemical shift, and the bound chemical shift Δ_B, the following is derived:

$$\delta\Delta = \frac{[LS]\Delta_B}{S_0} \tag{4}$$

From this expression a useful relationship is derived relating K and Δ_B

$$S_0\left(1 - \frac{\delta\Delta}{\Delta_B}\right) = \frac{L_0 \cdot \Delta_B}{\delta\Delta} - \left(\frac{1}{K} + L_0\right) \tag{5}$$

Armitage and co-workers[23] use this expression with an assumption that $\delta\Delta/\Delta_B$ is negligible at low concentration of LSR. Hence:

$$S_0 = \frac{L_0 \cdot \Delta_B}{\delta\Delta} - \left(\frac{1}{K} + L_0\right) \tag{6}$$

In a plot of S_0 against $1/\delta\Delta$ the slope equals $L_0 \cdot \Delta_B$ and the intercept equals $1/K + L_0$. Therefore, from the slope, the 'first reliable values' of the bound chemical shift Δ_B are determined. These and other estimates[24] show previous results[7] to be much too low and provide a more accurate basis for comparison of substrates. As seen from expressions (2) and (4), dilution effects alter the LIS,

[18] J. K. M. Sanders and D. H. Williams, *Tetrahedron Letters*, 1971, 2813.

[19] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.

[20] C. S. Erasmus and J. C. A. Boeyens, *Acta Cryst.*, 1970, **B26**, 1843.

[21] H. van Brederode and W. G. B. Huysmans, *Tetrahedron Letters*, 1971, 1695.

[22] I. Fleming, S. W. Hanson, and J. K. M. Sanders, *Tetrahedron Letters*, 1971, 3733.

[23] I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Comm.*, 1971, 1281.

[24] J. Bouquant and J. Chuche, *Tetrahedron Letters*, 1972, 2337.

whereas the bound chemical shift is independent of concentration. The equilibrium constant K can be derived from the intercept, but the values obtained will be upset by the extent of dimerization of the LSR. A twofold advantage exists in measurements at low concentrations of the LSR (a factor favouring the fluorinated LSRs which have greater 'shifting power') since (i) this minimizes the possibility of dimerization of the LSR and (ii) that the bulk susceptibility changes caused by the metal ion are minimal. Various papers report values of the equilibrium constants (see Table 1), obtained in some cases from slightly different approaches to that described. It is interesting to note that greater values of the equilibrium constant occur with fluorinated as opposed to non-fluorinated LSRs. This phenomenon is the cause of the larger LIS observed for the fluorinated reagents and not the value of the bound chemical shift, which is smaller for the dipivalomethanato reagents.[25,31] Optically active LSRs, which are used to separate resonances of enantiomers,[32,33] are thought to distinguish these isomers by forming diastereoisomeric complexes with the LSR which have different binding constants.

Table 1 *Equilibrium constants of LSRs and various substrates*

Substrate	*LSR*	*Equilibrium constant* (K)	*Ref.*
Cholestanol	$Eu(dpm)_3$	61	24
Neopentanol	$Eu(dpm)_3$	6*	25
Pyridine	$Eu(dpm)_3$	100	26
n-Propylamine	$Eu(dpm)_3$	12*	25
Nucleoside phosphates	Eu^{III}	4 to 17	27, 28
Neopentanol	$Eu(fod)_3$	100*	25
t-Butyl alcohol	$Eu(fod)_3$	280	29
Isopropyl alcohol	$Eu(fod)_3$	97*	30
Tetrahydrofuran	$Eu(fod)_3$	57*	30
Butan-2-one	$Eu(fod)_3$	32*	30
Isopropenyl acetate	$Eu(fod)_3$	27*	30
Allyl acetate	$Eu(fod)_3$	26*	30
n-Propylamine	$Eu(fod)_3$	100*	25

* Values estimated from the technique reported by Armitage and co-workers.[23]

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[25] I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. and Ind.*, 1972, 79.

[26] H. Huber and J. Sellig, *Helv. Chim. Acta*, 1972, **55**, 135.

[27] C. D. Barry, A. C. T. North, J. A. Glasel, R. J. P. Williams, and A. V. Xavier, *Nature*, 1971, **232**, 236.

[28] C. D. Barry, A. C. T. North, J. A. Glasel, R. J. P. Williams, and A. V. Xavier, *Biochem. Biophys. Acta*, 1972, **262**, 101.

[29] K. Roth, M. Grosse, and D. Rewicki, *Tetrahedron Letters*, 1972, 435.

[30] D. R. Kelsey, *J. Amer. Chem. Soc.*, 1972, **94**, 1764.

[31] B. L. Shapiro, M. D. Johnston, jun., A. D. Godwin, T. W. Proulx, and M. J. Shapiro, *Tetrahedron Letters*, 1972, 3233.

[32] G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, 1970, **92**, 6979; 1971, **93**, 5914.

[33] H. L. Goering, J. N. Eckenberry, and G. S. Koermer, *J. Amer. Chem. Soc.*, 1971, **93**, 5913.

One difficulty in determining the intrinsic LIS parameters, namely the bound chemical shift and the binding constant, is the interference by other substrates and impurities in the solution being examined. A possible method of overcoming this difficulty[34] employs a reference substrate having a known bound chemical shift and binding constant. From an expression similar to equation (3) the following is derived:

$$\frac{1}{\partial \Delta_j} = \frac{1}{\partial \Delta_m} \cdot \frac{K_m \Delta_{Bm}}{K_j \Delta_{Bj}} + (K_j - K_m) \frac{K_j}{\Delta_{Bj}} \tag{7}$$

where the subscripts refer to the parameters of the investigated substrate (j) and the reference substrate (m). In a plot of $\frac{1}{\partial \Delta_j}$ against $\frac{1}{\partial \Delta_m}$, the slope and intercept should give Δ_B and K of the investigated substrate (*i.e.* Δ_{Bj} and K_j). Without the knowledge of Δ_{Bm} and K_m for the reference substrate, the slope and intercepts are nevertheless used to characterize the compounds examined. Values of these parameters are not reported, but this approach is illustrated by an analysis of a mixture of four compounds. A similar approach is also referred to,[35] which is extended to a mixture of (x) substrates. An internal reference signal of examined substrates can also be used to analyse and compare a solution containing two or more substrates.[30] For two protons (m and j) in the same substrate:

$$\partial \Delta_j = \frac{\Delta_{Bj}}{\Delta_{Bm}} \cdot \partial \Delta_m \tag{8}$$

By plotting $\partial \Delta_j$ against $\partial \Delta_m$, slopes which are independent of substrate or reagent concentrations are obtained, which are applied to the analysis of mixtures of substrates which contain the same internal standard protons, *e.g.* acetoxy or methoxy. Results showed that for a similar geometric arrangement in a series of compounds, the slopes of such plots are characteristic.

Armitage and co-workers have developed a scheme[25] for evaluating the stoicheiometry of the complex formed in solution. Thus, modifying equation (1) to:

$$\mathrm{L} + n\mathrm{S} \overset{K}{\rightleftharpoons} [\mathrm{LS}_n] \tag{9}$$

where n is the number of moles of S that combine with one mole of L, then:

$$\log \mathrm{S} = (1/n) \log [\mathrm{LS/L}] - (1/n) \log K \tag{10}$$

Combination with expression (3) permits evaluation of S, L, and [LS], which by plotting a graph of log S against log [LS/L] gives a slope equal to $1/n$. Values of unity are calculated with $\mathrm{Eu(dpm)_3}$ for both n-propylamine and neopentanol, although this method is invalid when the binding constant is large.[25] Other

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[34] D. E. Williams, *Tetrahedron Letters*, 1972, 1345.

[35] J. K. Sanders and D. H. Williams, *J.C.S. Chem. Comm.*, 1972, 436.

investigations have been made;[29] one in particular concludes that pyridine and $Eu(dpm)_3$ form a 1 : 1 complex,[26] although the possibility of $n = 2$ is seriously considered as the pyridine di-adduct, a solid isolable compound, is known,[1] and dimethyl sulphoxide is thought to form a di-adduct at low temperatures in deuteriochloroform.[5]

The lowering of the LIS with different solvents are reported;[36] one explanation attributes this to competitive inhibition of weakly complexed substrates, particularly with donor solvents such as acetonitrile, pyridine, acetone, and dimethyl sulphoxide. Approximate orders of magnitude of the decrease in LIS are 10, 20, and 30% for deuterio-benzene, -chloroform, and -acetonitrile, respectively, when compared with carbon tetrachloride or carbon disulphide using tris(dipivalomethanato)europium(III), $Eu(dpm)_3$, on alcohols and amines.[36] Therefore, the use of donor competing solvents should be avoided when using the tris-β-diketonate LSR, although alternative reagents are available for use in more highly polar solvents (see Section 7),[18,37] and one has been used in aqueous solution.[38] Finally, as the magnitude of LIS is geometry dependent (see Section 5) and lanthanide complexes are predominantly electrostatic, the solvation spheres can influence this geometry so that different solvents may alter shifts.

The presence of other donor substrates as impurities can reduce the effective concentration of the LSR[39] if they form stronger co-ordination complexes than the substrate under study. The presence of water inhibits the LIS in this way,[10,40] as shown by the 60% reduction in the LIS of cholesterol hydrate protons when compared with the anhydrous form,[16] owing to competitive co-ordination by water. The presence of moisture in some LSRs can easily be observed by a change in colour,[41] *e.g.* $Pr(dpm)_3$ and $Eu(dpm)_3$ are pale green and pale yellow when anhydrous, but yellow and white, respectively, when hydrated. It appears that extremely small amounts of impurity in the LSR, insufficient to cause a change of melting point, nevertheless cause deviations in the LIS, *e.g.* 30% difference in the LIS of two batches of LSR.[42] It has been proposed that a standard substrate for measurement of the LIS with the LSR be adopted, which could provide a better criterion for measuring purity than melting point.

As the LSR is only a weak Lewis acid, steric hindrance reduces the LIS either because of a smaller value of the equilibrium constant or a greater nucleus–cation distance or both. Steroidal acetals, thioacetals, and methoxy-derivatives have been shown[37] to co-ordinate selectively to LSRs according to the degree of steric hindrance, *e.g.* a 3β-methoxy-steroid co-ordinates to a greater extent than the more hindered 3α-methoxy-steroid. A further report illustrates the effect of the steric hindrance[42] in a study of substituted anilines, which shows that a

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[36] J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.

[37] J. E. Hertz, V. M. Rodriquez, and P. Joseph-Nathan, *Tetrahedron Letters*, 1971, 2949.

[38] F. A. Hart, G. P. Moss, and M. L. Staniforth, *Tetrahedron Letters*, 1971, 3389.

[39] L. Tomic, Z. Majerski, M. Tomic, and D. E. Sunko, *Chem. Comm.*, 1971, 719.

[40] I. Armitage and L. D. Hall, *Canad. J. Chem.*, 1971, **49**, 2770.

[41] D. R. Crump, J. K. M. Sanders, and D. H. Williams, *Tetrahedron Letters*, 1970, 4419.

[42] L. Ernst and A. Mannschreck, *Tetrahedron Letters*, 1971, 3023.

linear correlation of basicity in terms of pK_a with proton LIS is upset when steric hindrance is present, such as with *ortho*- and *N*-substitution.

In conclusion, the quoting and comparison of LIS or bound chemical shift with different substrates should be made with caution; as seen later, other parameters such as the geometry of the complexed substrate and the particular LSR affect the magnitude of the LIS. A number of comparisons of co-ordinating ability of different substrates, as indicated by the LIS, are discussed in Section 8.

3 Shift Mechanism

In the lanthanide–substrate complex, interaction between the paramagnetic metal ion and the nuclei of the substrate causes changes in the chemical shift of the nuclei. Two types of interaction between metal cation and ligand have been proposed, contact and pseudocontact interactions, and the resulting shifts referred to as the contact and pseudocontact shifts.

Pseudocontact shift[43] is caused by a dipolar interaction between the nucleus and the electron spin magnetization of the paramagnetic metal ion. Two theories have been developed giving expressions for the magnitude of the pseudocontact shift, both of which can be expressed as follows:

$$\delta\Delta = \frac{x(3\cos^2\theta_i - 1)}{r_i^3} \tag{11}$$

where θ_i is the angle between (*a*) the distance vector, r_i, joining the metal cation to the particular nucleus, i, in the complexed substrate, and (*b*) the crystal field axis of the complexed substrate, often assumed as the line joining the metal atom to the lone-pair-bearing atom.

Now

$$x = \frac{-\beta^2 S(S+1)}{27\,kT}\,\mathrm{f}(\mathbf{g}) \tag{12}$$

from the theory by McConnell and Robertson,[44] and

$$x = \frac{\beta^2\,J(J+1)\,(2J-1)\,(2J+3)\,\langle J\|\propto\|J\rangle}{60\,k^2\,T^2}\,.\,2A_2^0\,\langle r^2\rangle\,\mathbf{g}^2 \tag{13}$$

from the more recent theory of Bleany,[45] where β is the Bohr magneton; S the electron spin; k is Boltzmann's constant; $A_2^0\langle r^2\rangle$ the crystal field coefficient; and **g** the **g** tensors. The value of x is different for each complex studied as it involves the **g** tensor, which is split into $\mathbf{g}_\perp$ and $\mathbf{g}_\parallel$, the tensors perpendicular and parallel to the molecular axis. According to McConnell and Robertson's theory, the pseudocontact shift arises from a failure of the dipolar interaction to average zero owing to the metal possessing an anisotropic **g** tensor. However, Bleany

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[43] P. J. McCarthy, in 'Spectroscopy and Structure of Metal Chelate Compounds,' ed. K. Nakamoto and P. J. McCarthy, Wiley, New York, 1968, p. 346.

[44] H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, 1958, **29**, 1361.

[45] B. Bleaney, *J. Magn. Resonance*, submitted for publication.

proposes[45] a theory in which x encompasses a different set of parameters Rather than attributing pseudocontact shift to the anisotropic $\mathbf{g}$ factors, he suggests that the dipolar shift is caused by anisotropy in the susceptibility which occurs in less than cubic geometries. One difference arising from this approach is the temperature dependance, which is T^{-2} (except in the cases of Eu^{3+} and Sm^{3+}), as opposed to T^{-1} expected from McConnell and Robertson's theory. For europium and samarium, effects of the excited states give a more complex temperature dependence, approximating to T^{-1}. Various temperature relationships have been reported which vary from $T^{-\frac{1}{2}}$ for $Yb(dpm)_3$[46] to T^{-1} using $Pr(dpm)_3$.[39] The shift $\delta\Delta$ is also dependent on the distance r_i of the nuclei from the metal cation through space and not *via* the covalent bonds of the molecules, a distinction important in studying the consequences of the various parameters involving the shifts. Furthermore, the shift is dependent on the geometric term $(3\cos^2\theta_i - 1)$, a factor neglected in many studies. The expressions (11) and (12), derived for axially symmetric complexes, may not necessarily be applicable to the wide range of complexes of lower symmetries, although it is reported as adequate for at least systems of C_2 and C_{2v} symmetry.[43] The crystal structures of $Ho(dpm)_3$,2(4-picoline)[47] and $Eu(dpm)_3$,2(pyridine)[48] are not axially symmetric with respect to the adduct ligands, but possibly in solution an approach to axiality is achieved by rapid ligand exchange.

Contact shifts[43] occur by direct electron–nucleus magnetic interaction as distinct from the classical dipolar interactions. Consequently, shifts occur by movement of unpaired electron spin density from the metal cation to the ligand by covalent bond formation. Hence, this mechanism operates through the metal cation co-ordinating bond and so depends on the degree of covalency in this bond. This interaction is independent of the $3\cos^2\theta_i - 1$ term and falls off rapidly with increasing distance except in conjugated systems, which facilitate delocalization of unpaired electrons.

The distinction between contact and pseudocontact shift is important for a better understanding of the factors affecting the LIS. The assumption that lanthanides interact by a pseudocontact mechanism is based on their high electropositive character and the shielding of unpaired electrons of the *f* orbitals.[49] As the lanthanides form complexes by electrostatic interaction, this precludes the operation of a contact mechanism of the same order of magnitude as those found with first-row transition-block metal complexes,[50] but with even as little as 1% covalency contact shift should be observed.[51] Therefore, even with lanthanides, a small degree of contact interaction is possible[51] and is seen in deviations from the expression (11), particularly for protons attached to the

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[46] C. Beaute, S. Cornuel, D. Lelandais, N. Thoai, and Z. W. Wolkowski, *Tetrahedron Letters*, 1972, 1099.

[47] W. De Horrocks, jun., K. P. Sipe, and J. R. Luber, *J. Amer. Chem. Soc.*, 1971, **93**, 5258.

[48] R. E. Cramer and K. Seff, *J.C.S. Chem. Comm.*, 1972, 400.

[49] F. A. Cotton and G. Wilkinson, 'Advanced Inorganic Chemistry', Wiley, New York, 2nd edn.

[50] D. R. Eaton, *J. Amer. Chem. Soc.*, 1965, **87**, 3097.

[51] E. R. Birnbaum and T. Moeller, *J. Amer. Chem. Soc.*, 1969, **91**, 7274.

carbons nearest the lone-pair-bearing atoms.[52] It has been suggested that contact shift is significant for aromatic amines,[53] where the presence of conjugation may increase the electron delocalization, thus increasing the degree of contact contribution,[1] but this view is contradicted in a study of quinoline and isoquinoline.[54] Pseudocontact and contact interactions are distinguished in a graphical analysis[52] using the log of expression (11) [see later, expression (15)], and contact shift is only reported to occur on the protons vicinal to the lone-pair-bearing atom. A similar deviation from an otherwise linear plot of log r_i against log $\delta\Delta$ is reported by Demarco,[7] who attributes this to the presence of contact shift.

The relative magnitude of the $\mathbf{g}$ tensors correlates with the direction of shift, as indicated in electron paramagnetic resonance experiments, which show good agreement of the relative magnitudes of $\mathbf{g}_\perp$ and $\mathbf{g}_\parallel$ with those observed in the shielding or deshielding of the different lanthanides.[55] However, magnetic susceptibility anisotropy data correlate qualitatively with the observed signs of LISs,[56] and Bleany's theory, which excludes the anisotropic $\mathbf{g}$ tensor, still calculates shift data having excellent agreement with observed LISs by use of an expression for pseudocontact shift.[57] A detailed analysis of *trans*-4-t-butylcyclohexanol and adamantan-2-ol achieves such good correlation using only the pseudocontact term that contact shift is excluded.[58] However, one investigation of such correlations concludes that no experimental results confirm (or disprove), the pseudocontact expression, owing to the wide deviation in the experimental results dealt with.[17] The similarity of x in expression (11) for ^{1}H and ^{13}C n.m.r. spectra of borneol[59] and the similarity of LIS ratios of aniline and 2,4,6-trifluoroaniline in the ^{1}H and ^{19}F n.m.r.[60] both indicate that ^{13}C and ^{19}F nuclei are subject to predominantly a pseudocontact interaction. The ^{31}P n.m.r. results of phosphates and phosphonates indicate a significant contact interaction operating[18] and the ^{14}N n.m.r. studies on amine–M(dpm)$_3$ systems (M is ytterbium or europium) indicate a predominance of contact interaction.[13] Nuclei with lone pair electrons (^{14}N, ^{15}N, and ^{31}P) may be expected to interact predominantly by a contact mechanism.

4 Distance–Shift Relationships

Assuming the interaction of the lanthanide complexes is predominantly pseudocontact, the magnitude of the LIS of the ith nucleus is inversely proportional to the cube of the average distance from the metal ion [expression (11)]. In fact, this distance parameter is often assumed to be the predominant term as the

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[52] C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, 1971, **93**, 2417.

[53] F. A. Hart, J. E. Newbery, and D. Shaw, *Chem. Comm.*, 1967, 45.

[54] H. Huber and C. Pascaul, *Helv. Chim. Acta*, 1971, **54**, 913.

[55] G. A. Hutchinson and E. Wong, *J. Chem. Phys.*, 1958, **29**, 754.

[56] W. De W. Horrocks, jun., and J. P. Sipe, *J. Amer. Chem. Soc.*, 1971, **93**, 6800.

[57] B. Bleaney, C. M. Dobson, B. A. Levine, R. B. Martin, R. J. P. Williams, and A. V. Xavier, *J.C.S. Chem. Comm.*, 1972, 791.

[58] S. Farid, A. Ateya, and M. Maggio, *Chem. Comm.*, 1971, 1285.

[59] J. Briggs, F. A. Hart, G. P. Moss, and E. W. Randall, *Chem. Comm.*, 1971, 364.

[60] Z. W. Wolkowski, C. Beaute, and R. Jantzen, *J.C.S. Chem. Comm.*, 1972, 619.

remaining factors, namely the angle term, are regarded as constant. Thus expression (11) is simplified to:

$$\delta\Delta = b/r^3 \qquad (14)$$

where *b* is assumed as a constant.

The distance–shift relationship is clearly illustrated in the proton n.m.r. spectrum of n-heptanol. As seen in Figure 2,[61] addition of Eu(dpm)$_3$ renders the spectrum amenable to first-order analysis, shifting the resonance nearest the hydroxy-group furthest; on increasing distance the LIS is less. Substantial shifts for protons up to 13 Å from the site of co-ordination have been measured,[1] smaller shifts (0·1 p.p.m.) for distances up to 27 Å are also reported.[7] Hinckley reported[1] the first use of a LSR in distance–shift relationships with the steroid cholesterol. The distances of each nucleus from the co-ordinated metal ion in the complex are estimated from Dreiding models. The inverse cube of this distance term is plotted against the values of the LIS for each nucleus and frequently produces a linear response, substantiating this aspect of the relationship for pseudocontact shifts. Consequently this approach enables relative distances of the nuclei from the metal ion to be estimated, which can contribute to structural information. This can be applied by altering the possible structural models of the molecule to obtain the best correlation of.the distance–shift data.

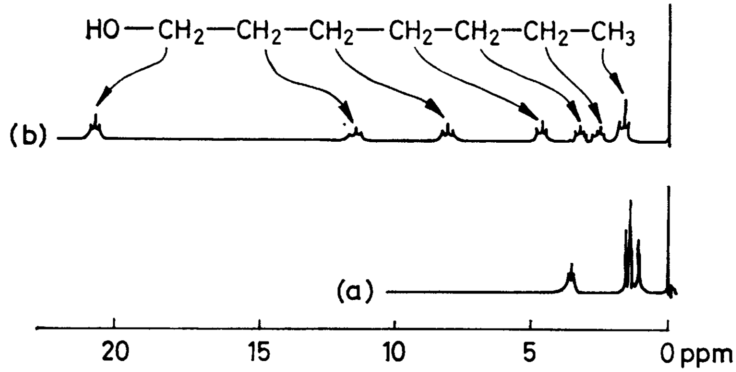

Figure 2 *Proton* (60 MHz) *n.m.r. spectra of n-heptanol;* (a) 0.3 mol l^{-1} *in* CDCl$_3$; (b) *with a molar ratio of* 0.78 *of* Eu (dpm)$_3$/n-heptanol
(Reproduced with permission from *Analyt. Chem.*, 1971, **43**, 1599.)

The presence of more than one co-ordination site in the organic substrate complicates the interpretation of the measured shifts since these represent sums of the interactions with the LSR at each site,[62] although some groups form stronger co-ordination complexes than others. At each co-ordination site, equilibrium constants, and hence pseudocontacts, contribution differ and so result in

[61] D. L. Rabenstein, *Analyt. Chem.*, 1971, **43**, 1599.
[62] A. Ius, G. Vecchio, and G. Carrea, *Tetrahedron Letters*, 1972, 1543.

different proportionality constants in expression (14). These complications make straightforward plots of the LIS against the inverse cube of the distance ineffective aids in analysis, but fortunately the log of this expression renders an important simplification:

$$\log \delta \Delta = -3 \log r_i + \log c \tag{15}$$

A plot of $\log \delta \Delta$ against $\log r_i$ should be linear irrespective of *c*, a constant. By assuming expression (15) correct, a graphical analysis by this approach allows a distinction between the relative contributions of co-ordination at each site of a bifunctional steroid.[52] This approach is only useful when co-ordination sites are far apart so that some protons are only affected by co-ordination at one site. The slope of -3 would be expected but it is not in fact obtained with these graphs, which is attributed to errors in the distance measurement or geometric factors.[7] One generalized interpretation suggests that molecules which produce slopes greater than three are flexible, but those of slopes less than three are rigid.[17]

In many cases good linear relationships between the LIS and the inverse *square* of the distance parameter have been found.[14,63–65] However, an analysis of these different values of the power of the distance term[66] concludes that too little is known about the detailed nature of the geometry to allow definite structural conclusions to be drawn and crude approximations may not reflect the complex nature of the interactions involved. Deviations from the distance–shift correlations may be due to over-simplification with respect to the shift mechanism or the geometric terms. The angle term is frequently considered reasonably constant in many substrates and if free rotation occurred about the metal ion–heteroatom bond of the labile complex,[67] the angle term may be averaged out.

Measurements of the broadening of resonances, caused by the metal ion increasing the transverse relaxation rate (T_2), can also lead to estimates of relative distances within the complexed substrate. A simplified form of an expression[68] is used to relate the half bandwidth ($\Delta\nu_{i,\frac{1}{2}}$) and the inverse sixth power of the distance term (r_i) of the ith nucleus,

$$\Delta\nu_{i,\frac{1}{2}} = C/r_i^6 \tag{16}$$

where *C* is a constant for the particular complex being investigated. This approach was first used with two transition-metal complexes,[69] and has since been applied to LSRs,[27,28,70] in particular those lanthanides which produce appreciable broadening, *e.g.* gadolinium(III).

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[63] M. R. Willcott, J. F. M. Oth, J. Thio, G. Plinke, and G. Schroder, *Tetrahedron Letters*, 1971, 1579.

[64] L. W. Morgan and M. C. Bourlas, *Tetrahedron Letters*, 1972, 2631.

[65] A. F. Cockerill and D. M. Rackham, *Tetrahedron Letters*, 1970, 5153.

[66] A. J. Rafalski, J. Barciszewski, and M. Wiewiorowski, *Tetrahedron Letters*, 1971, 2829.

[67] R. F. Fraser and I. Y. Winfield, *Chem. Comm.*, 1970, 1471.

[68] H. Sternlicht, *J. Chem. Phys.*, 1965, **42**, 2250.

[69] E. E. Zaev, V. K. Voronov, M. S. Shvartsberh, S. F. Vasilevesky, Yu. N. Molin, and I. L. Kotljarevsky, *Tetrahedron Letters*, 1968, 617.

[70] J. Reuben and J. S. Leigh, jun., *J. Amer. Chem. Soc.*, 1972, **94**, 2789.

5 Consequences of Geometric Factors

Deviations from the distance–shift correlations due to neglect of the geometric term as in expression (14) are common and by including the term $(3\cos^2\theta_i - 1)$, improved correlations are obtained. In order to measure the angle θ_i for each nucleus, the position of the metal ion with respect to the substrate needs to be known. This problem has been avoided by some workers by measuring distances of nuclei from either the heteroatom[12,63] or the perimeter of the lone pair on this atom.[14] These results may be sufficient for the cases in hand, but do not contribute to a more complete understanding of the shift mechanism. The orientation of this lone-pair is more predictable in cases of restricted rotation in the carbon–heteroatom bond, *e.g.* carbonyl groups, but is less predictable for systems which rotate freely, *e.g.* hydroxy-groups. Table 2 summarizes the positions postulated for the metal ion with respect to the substrate where some estimates are made by comparison with analogous complexes studied by *X*-ray crystallography, others by modifying values of the metal position and evaluating the most linear response to expression (11). The most successful attempts to locate the metal atom, firstly by Briggs, Hart, and Moss,[71] and later by others,[27,58,72,73] were achieved by varying the metal-atom position and computing the correlation with minimum deviations from expressions (11) and (16) using the LIS and broadening parameters.

The results show that for an accurate positioning of the metal ion a set of calculations needs to be worked out for each molecule studied. This approach may be used to calculate the ratio of conformers by computing the percentage contribution of each conformer required to obtain the best correlation. However, a possible disadvantage of this technique is that the ratio of conformers may be altered on co-ordinating to the LSR. A ^{13}C n.m.r. study of some phosphorinans does show that the ratio of conformers is altered by the quantity of LSR present.[74] Conversely, other reports[21,75] indicate very little change in the ratio of conformers when complexed to the LSR, but presumably this will depend on the energy barrier between the conformers concerned.

In certain cases the angle θ_i may be sufficiently large that the direction of 'normal shift' is reversed. A plot of the $3\cos^2\theta_i - 1$ term against angle, as in Figure 3, shows how the LIS can be varied from positive to negative as the angle is altered. Thus with $Eu(dpm)_3$ shielding as opposed to the 'normal' deshielding, shifts are produced when the angle θ_i is between 54.7 and 125.3 °, but in most cases the angle appears to be below 54.7 °. Many reports of europium upfield shifts are reported,[37,38,63,76-80] most of which enable direct interpretation

[71] J. Briggs, F. A. Hart, and G. P. Moss, *Chem. Comm.*, 1970, 1506.

[72] M. R. Willcott, tert., R. Lankinski, and R. E. Davis, *J. Amer. Chem. Soc.*, 1972, **94**, 1742.

[73] M. Ochiai, E. Mizuta, O. Aki, A. Morimoto, and T. Okada, *Tetrahedron Letters*, 1972, 3245.

[74] W. G. Bentrude, H. W. Tan, and K. C. Yee, *J. Amer. Chem. Soc.*, 1972, **94**, 3264.

[75] S. G. Levine and R. E. Hicks, *Tetrahedron Letters*, 1971, 311.

[76] B. L. Shapiro, J. R. Hlubucek, and G. R. Sullivan, *J. Amer. Chem. Soc.*, 1971, **93**, 3281.

[77] T. H. Siddall, *Chem. Comm.*, 1971, 452.

[78] P. H. Mazzocchi, H. J. Tamburin, and G. R. Miller, *Tetrahedron Letters*, 1971, 1819.

[79] S. B. Tjan and F. R. Visser, *Tetrahedron Letters*, 1971, 2833.

[80] M. Kishi, K. Tori, and T. Komeno, *Tetrahedron Letters*, 1971, 3525.

Table 2 *Postulated positions of the lanthanide ion in the complexed substrate*

Substrate	*Functional group*	*Distance (heteroatom to metal)/Å*	*Angle* $\widehat{MXC}$ */degrees*	*Lanthanide ion*	*Method of assessing*	*Ref.*
Adamant-1- or -2-ol	OH	Radii of O plus Eu	115	Eu	Estimate	81
4-t-Butylcyclohexanol	OH	2.3	139	Eu	Computed optimum	58
Adamant-2-ol	OH	3.0	128	Eu	Computed optimum	58
Borneol	OH	3.0	126	Pr	Computed optimum	71
General	OH	2.7—0.4	—	—	Computed optimum	58
Cyclic ketones	C=O	2.8	109	Eu	Analogy with RCO–$HgCl_2$	82
Halogenovinyl ketones	CHO	3.0	150	Yb	Best linear fit	83
Indanone and fluorenone	C=O	1.5	120	Yb	Best linear fit	11
Sulphoxides	S=O	3.5	—	Eu	Analogy with La(edta)	67
Amines	NH_2	3.0	—	Yb	Best linear fit	10
Analogous complexes of known stereochemistry						
Cyclononanone–$HgCl_2$		2.8		Hg	—	84
$Yb(acac)_3,H_2O$		2.34		Yb	*X*-Ray crystallography	85
La(edta)		2.55		La	*X*-Ray crystallography	86
$Eu(dpm)_3,2py$		2.65		Eu	*X*-Ray crystallography	48

[81] G. H. Wahl, jun., and M. R. Peterson, jun., *Chem. Comm.*, 1970, 1167.
[82] P. Kristiansen and T. Ledaal, *Tetrahedron Letters*, 1971, 2817.
[83] C. Beaute, Z. W. Wolkowski, J. P. Merda, and D. Lelandais, *Tetrahedron Letters*, 1971, 2473.
[84] S. Dahl and P. Groth, unpublished results.
[85] J. A. Cunningham, D. E. Sands, W. F. Wagner, and M. F. Richardson, *Inorg. Chem.*, 1969, **8**, 22.
[86] J. L. Hoard, B. Lee, and M. D. Lind, *J. Amer. Chem. Soc.*, 1965, **87**, 1612.

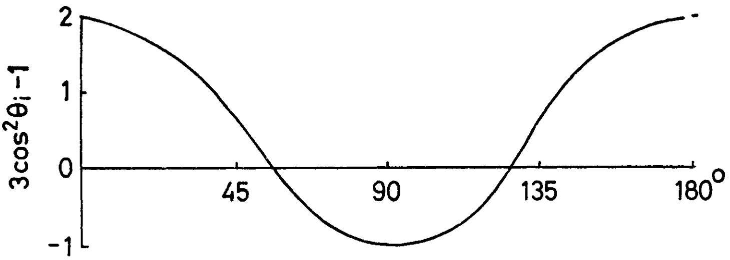

Figure 3 *The variation of* $3\cos^2\theta_i - 1$ *with the angle* θ

of structural problems. By altering the solvent or ligand of the LSR, the direction of the shift is often altered,[37,38,51,87] as these factors can also affect the geometry of the complexed substrate. An alternative explanation for the reversal of the 'normal' direction of the LIS is attributed either to the presence of significant contact interaction,[79] or to changes in magnetic susceptibility g tensors,[38] (although disagreement has been expressed with this latter reason[77]) or to changes in the sign of crystal field coefficients.[57]

A further point involves the definition of the angle θ_i, which is derived using the crystal field axis as one vector. This axis need not coincide, as is often assumed, with the metal atom–heteroatom bond;[88] the difference is not necessarily compensated by free rotation around the bond.

6 Lanthanide Metal Ion

Transition-metal complexes could be used as shift reagents in n.m.r. spectroscopy if it were not for the excessive linewidth broadening these metal ions exhibit in solution.[89] This phenomenon is related to similar effects caused by oxygen and free radicals when present in solution in the n.m.r. tube. These species provide a mechanism for shortening the relaxation times (T_2) of the protons and, therefore, increasing the bandwidth. Europium(III), the most frequently selected lanthanide, is selected by virtue of its anomalously inefficient nuclear spin–lattice relaxation properties.[90] It has a low-lying Russell–Saunders state and a diamagnetic $^7F_0$ ground state, which gives a very small separation of the highest and lowest occupied metal orbitals and which leads to inefficient relaxation; the excited $^7F_1$ state presumably contributes to the pseudocontact shift.[91] Thus the presence of such metal ions as europium(III) in solution causes very little broadening in n.m.r. spectra.

[87] H. Donato, jun., and R. B. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 4129.

[88] C. L. Honeybourne, *Tetrahedron Letters*, 1972, 1095.

[89] A. Carrington and A. D. McLachlan, 'Introduction to Magnetic Resonance', Harper and Row, 1967, p. 225.

[90] J. H. Van Vleck, 'The Theory of Electric and Magnetic Susceptibilities', Oxford University Press, 1932, chap. IX.

[91] S. I. Weissman, *J. Amer. Chem. Soc.*, 1971, **93**, 4928.

Table 3 *Comparison of the lanthanide- and transition-metal complex proton n.m.r. bandwidths*

Lanthanide	*Bandwidths/Hz*[a]	*Half-height bandwidths/Hz*[b]	*Relative broadening/ Hz per Hz of shift*[c]
Pr	40	5.6	0.005
Nd	16	4.0	—
Sm	7	4.4	0.02
Eu	10	5.0	0.003
Gd	1500	—	—
Tb	250	96.00	0.1
Dy	180	200.00	—
Ho	180	50.00	0.02
Er	250	50.00	—
Tm	400	65.00	—
Yb	60	12.00	0.02
Transition metal as M^{III}	*Bandwidth/Hz*[d]		
Ti	2000		
V	25		
Cr	1000		
Mn	100		
Fe	800		
Mo	200		
Ru	100		

[a] Lanthanide bandwidths[92] of t-butyl in $M(dpm)_3$ in carbon tetrachloride.
[b] Lanthanide half bandwidths[56] of methyl in 2-picoline using $M(dpm)_3$.
[c] Lanthanide relative broadening[41] of t-butyl in $M(dpm)_3$.
[d] Transition-metal bandwidths[50] of methyl in $M(acac)_3$.

Several comparisons of the lanthanides for use as LSRs have been reported and Table 3 shows some comparisons of lanthanide broadening properties alongside those of some first-row transition-block metal complexes. Close comparison of these figures is not possible as different ligands and solvents were used in the measurements.

Narrow bandwidths are exhibited by the lanthanides praseodymium (Pr), neodymium (Nd), samarium (Sm), and europium (Eu), and moderate broadening is found with ytterbium (Yb), but a notable exception to these characteristics occurs with gadolinium (Gd), which is used explicitly as a broadening probe.[18,27,93] Europium and praseodymium are used most extensively and ytterbium also appears satisfactory for use, although it causes greater broaden-

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[92] N. Ahmad, N. C. Bhacca, J. Selbin, and J. D. Wander, *J. Amer. Chem. Soc.*, 1971, **93**, 2564.

[93] K. G. Morallee, E. Nieboer, F. J. C. Rossotti, R. J. P. Williams, and A. V. Xavier, *Chem. Comm.*, 1970, 1132.

ing. Further comparison of broadening properties have been investigated[53] using $M(NO_3)_3(dbbp)_2$ where dbbp is 4,4′-di-n-butyl-2,2′-bipridyl and M are various lanthanides. An investigation of these complexes shows that lanthanum, lutetium, and ytterbium cause extensive broadening; cerium, praseodymium, neodymium, and samarium only cause moderate broadening; and europium is cited as the only metal permitting a distinction between three aromatic protons in the complex. A similar ^{14}N n.m.r. study[94] of the half bandwidths shows a significantly different situation, with dysprosium (Dy) and holmium (Ho) giving the least broadening.

A secondary factor in selection of the correct lanthanide as a LSR is the magnitude of the shift produced. Some comparisons of this factor have been made for the lanthanides, as seen in Table 4. The largest shifts are unfortunately exhibited by the metals which cause greatest broadening, *e.g.* terbium to thulium, and, therefore, the metals selected for use as LSRs are necessarily a compromise of these factors, with a greater consideration given to the broadening factor. Consequently, europium produces relatively small but adequate shifts and is the lanthanide used most extensively since the first paper was published by Hinckley.[1] This metal ion produces large enough shifts with sufficiently minimal broadening to allow gross multiplet adsorption bands to be resolved at relatively large shifts.

Table 4 *Comparisons of lanthanide induced shifts*[a]

Metal	*Shift caused by* $M(dpm)_3$. *α-methylene* /Hz[b]	*Shift caused by* $M(dpm)_3$. *γ-methylene* /Hz[b]	*Shift power relative to* $Eu(dpm)_3$ /Hz[c]	*Shift by* $M\{OP(NMe_2)_3\}_4(ClO_4)$ *of* MeCN /Hz[d]
Pr	−11.25	−3.7	−1.1	−3.00
Nd	−5.55	−1.8	—	−1.15
Sm	−1.35	−0.6	−0.2	−0.27
Eu	2.95	1.8	1.0	1.33
Gd	—	—	—	—
Tb	−26.25	−10.9	−5.5	−19.2
Dy	−54.00	−17.9	—	—
Ho	−51.45	−18.1	−7.0	−17.0
Er	25.55	8.8	—	4.4
Tm	−44.65	−14.8	—	6.9
Yb	12.15	4.4	4.0	6.9
Lu	0.00	0.0	—	—

[a] A more recent survey gives analogous results.[56]

[b] The α and γ groups refer to the methylene protons of cyclohexanone (0.1 mol l^{-1}) in a saturated solution of $M(dpm)_3$ in CCl_4.[92]

[c] Shift power relative to $Eu(dpm)_3$ calculated from 'representative' selection of lanthanides refer to slopes of concentration *vs.* shift plots.[41]

[d] Ref. 95.

[94] M. Witanowski, L. Stefaniak, and H. Januszewski, *Chem. Comm.*, 1971, 1573.

Furthermore, the t-butyl resonance of $Eu(dpm)_3$ occurs upfield of TMS in proton n.m.r. and is, therefore, not interfering with the spectra. In ^{14}N n.m.r., europium causes three times as much shift as ytterbium,[13] reversing the relative shift power found in proton n.m.r. spectroscopy (*cf.* Table 4). Praseodymium follows europium in its popularity, owing to two factors: (i) the shifts are larger than those caused by europium, in proton n.m.r.,[95] compensating for the slightly poorer broadening properties; (ii) praseodymium causes upfield shifts and is, therefore, a useful complimentary reagent. A disadvantage of praseodymium and other shielding LSRs, however, is the added complication of crossing over of resonances, which confuses analysis in some cases. A series of papers,[10,11,76,96] largely by Beaute and Wolkowski, advocates the use of ytterbium and holmium[97a] owing to their relatively greater shifting powers (*cf.* europium), but these advantages are balanced by their greater bandwidths. Thulium has been used as a LSR,[40] but although shifts are greater than those caused by europium, drastic broadening again limits its application. In ^{13}C n.m.r. the praseodymium/europium shift-ratio and the terbium/europium LIS ratios are given as 1.8 and 8.6, respectively,[59] but as usual the advantage of terbium has to be balanced against its extensive broadening properties. The reference to a LSR as deshielding or shielding refers to its use under 'normal' conditions (as a β-diketonate complex, in fairly non-polar solvents and with angle θ_i outside the 54.7 to 125.3° limits). Finally, diamagnetic lanthanum is used[97b] in LSR studies although the shifts produced are probably due to changes in shielding by bonded electrons and not indicative of any pseudocontact shift. The main use of lanthanum may, therefore, lie in taking accurate measurements of the LIS due to pseudocontact shift only, by subtracting shifts caused by the lanthanum complex from the LIS caused by a paramagnetic LSR.[57]

7 Lanthanide Shift Reagent (LSR)

Lanthanide tris(β-diketonates), often air stable and soluble in organic solvents, are known to expand their co-ordination by accepting further ligands[49] and have a very simple n.m.r. spectrum, *i.e.* factors desirable in a shift reagent. The simplest β-diketonates, the acetylacetonates, are used with first-row transition-block metals as shift reagents, but these ligands are hygroscopic and the co-ordinated water leads to weak complexation with further ligands, giving poor shifts.[36] The t-butyl derivative dipivaloylmethanate is a more satisfactory LSR, whose proton n.m.r. spectra in $CDCl_3$ consists of only one singlet which is shifted to higher field by approximately -0.7 p.p.m. when co-ordinated to a substrate such as an alcohol.[7] Bulky ligands in the LSR are an advantage as this restricts mobility in the complex, preventing the susceptibility tensors being averaged out by a combination of different configurations (see Section 3).[47] The dipivaloyl-

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[95] J. Briggs, G. H. Frost, F. A. Hart, G. P. Moss, and M. L. Staniforth, *Chem. Comm.*, 1970, 749.

[96] C. Beaute, Z. W. Wolkowski, and N. Thoai, *Chem. Comm.*, 1971, 700.

[97a] L. Tomic, Z. Majerski, M. Tomic, and D. E. Sunko, *Croat. Chem. Acta*, 1971, 267.

[97b] E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis, and F. M. Schell, *J. Amer. Chem. Soc.*, 1971, **93**, 6271.

methanato-complex of europium was first used by Hinckley[1] as the dipyridine adduct $Eu(dpm)_3,2py$. This was later improved by Sanders and Williams[98] by use without the associated pyridine, rendering the complex more amenable to expanding its co-ordination and accepting substrates, which effects a fourfold increase in shifts. These complexes are available commercially, but they can be prepared in the laboratory from the metal nitrate.[99] The complexes have only a limited solubility in the normal n.m.r. solvents, which prevents a 1 : 1 molar ratio being reached. In the absence of the substrate, $Eu(dpm)_3$ has a maximum concentration of approximately 40 mg ml^{-1} in deuteriochloroform,[7] and solubility increases with co-ordination to a basic substrate, *e.g.* concentrations of 200 to 300 mg ml^{-1} are obtained with alcohols in chloroform or deuteriobenzene, but only 100 mg ml^{-1} in carbon tetrachloride.[36] It is probable that the substrates less basic than alcohols will not permit such comparatively high concentration of the LSR. However, the dipivaloylmethanato-complexes are widely used reagents which give quite satisfactory shifts even at the low concentrations governed by their limited solubility. Other similar reagents with no particular advantage over the dipivalomethanates have been reported, *e.g.* tris(dibenzoylmethanate)[36,100] and tris-(1-benzoylacetonate).[100]

The introduction of fluorine atoms on the β-diketonate ligand overcomes the solubility problem and has led to new superior LSRs. One such complex, the 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato (fod) lanthanide,[19] apart from having improved solubility (of the order of 400 mg ml when complexed to a substrate), has a more acidic metal ion owing to the electron-withdrawing power of the fluorines. This greater Lewis acidity causes a stronger association with the substrate and thus extends its range to less basic groups; although the bound chemical shift is smaller for these fluorinated LSRs,[25] the observed LIS is larger because of the stronger binding in the complex. However, an alternative method for comparing the shifting power of LSRs, by measuring their vinylic proton shifts,[101] allows a comparison of the shifting power of various fluorinated LSRs with the non-fluorinated reagents,[102]

$$Eu(fod)_3 > Eu(pfd)_3 > Eu(fhd)_3 > Eu(dpm)_3$$

where (pfd) represents 1,1,1,2,2-pentafluoro-6,6-dimethylheptane-3,5-dione and (fhd) represents 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione. Various LSRs appear to exhibit different degrees of contact interaction with aromatic substrates, and a series of the reagents with an increasing degree of contact interaction operating is reported:[103]

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[98] J. K. M. Sanders and D. H. Williams, *Chem. Comm.*, 1970, 422.

[99] K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, 1965, **87**, 5254.

[100] G. V. Smith, W. A. Boyd, and C. C. Hinckley, *J. Amer. Chem. Soc.*, 1971, **93**, 6319.

[101] H. E. Francis, Ph.D. Thesis, University of Kentucky, Lexington, Kentucky, 1972.

[102] H. E. Francis and W. F. Wagner, *Org. Magn. Resonance*, 1972, **4**, 189.

[103] B. F. G. Johnson, J. Lewis, P. M. Ardle, and J. R. Norton, *J.C.S. Chem. Comm.*, 1972, 535.

$$\mathrm{Pr(fod)_3} < \mathrm{Yb(fod)_3} < \mathrm{Eu(dpm)_3} < \mathrm{Er(dpm)_3} < \mathrm{Eu(fod)_3}$$
$$\xrightarrow[\text{increasing contact interaction}]{\hspace{6cm}}$$

Finally, one disadvantage in using the fluorinated LSR is that the t-butyl resonance occurs in the 1—2 p.p.m. region when complexed, hence interfering with proton resonances in this region.

Optically active LSRs such as tris-[3-(t-butylhydroxymethylene)-(+)-camphorato]europium(III) have been developed for the purpose of determining enantiomeric purity.[32] Once again the idea of using fluorinated ligands to improve the relative shifting power of these LSRs has been applied to these reagents and has led to tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-[33] and tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium- and -praseodymium-(III)[104] which are used* to distinguish resonances of a number of enantiomorphs. These LSRs are assumed to distinguish between enantiomorphs by forming diastereoisomeric complexes which have either different stability constants[32] or just a different magnetic environment.[33]

Further LSRs used mainly for application in highly polar solvents include europium trichloride, reported to co-ordinate to polyfunctional steroids in dimethyl sulphoxide, causing upfield shifts,[37] and praseodymium and europium nitrate hexadeuterium oxide, used successfully[18] in deuterioacetone for investigation of phosphate and phosphonates by ^{31}P n.m.r. The use of praseodymium perchlorate in deuterium oxide is reported[38] in the study of carboxylic acids, and a poorer reagent, $\mathrm{M\{N(CH_2CO_2)_3\}(H_2O)_3}$, where M is a lanthanide, is also used in studying carboxylic acids as their sodium salts.

Table 5 shows the structures of some lanthanide shift reagents.

8 Organic Functional Groups

As already pointed out, greater shifts are caused by functional groups which are most basic, and this aspect has been investigated by Ernst and Mannschreck, who found[42] an almost linear correlation of pK_a with LIS for a series of substituted anilines. The basicity factor appears a most important criterion on which to judge the effectiveness with which a group will give a LIS, although factors such as steric hindrance cannot be ignored.

Alcohols are the most widely used functional group, followed by ketones and esters, which give slightly smaller shifts. These groups, together with quinones,[106] aldehydes,[11,83] acetals,[37] epoxides,[63,107] lactones,[108] tetrahydrofurans,[10] ethers,[19,79] particularly methoxides,[63,78,109] carboxylic acids,[38] and a number of phos-

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* A simple method for the preparation of these reagents is reported.[105]

[104] R. R. Fraser, M. A. Petit, and J. K. Sanders, *Chem. Comm.*, 1971, 1450.

[105] V. Schurig and R. Israel, *Tetrahedron Letters*, 1972, 3297.

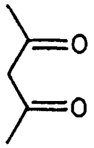
[106] J. Grandjean, *Chem. Comm.*, 1971, 1060.

[107] L. H. Keith, *Tetrahedron Letters*, 1971, 3.

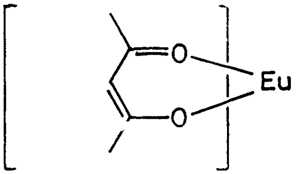
[108] F. I. Carroll and J. T. Blackwell, *Tetrahedron Letters*, 1970, 4173.

[109] A. F. Bramwell, G. Riezebos, and R. D. Wells, *Tetrahedron Letters*, 1971, 2489.

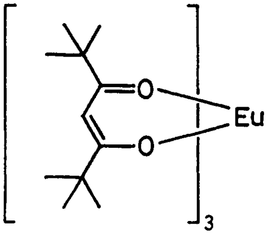
Table 5 *Lanthanide shift reagents*



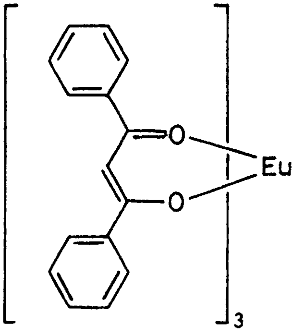
Acetylacetone (acac)



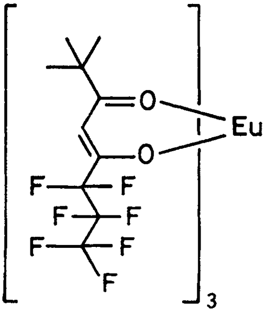
Tris(acetylacetonato) europium(III) [Eu(acac)$_3$]



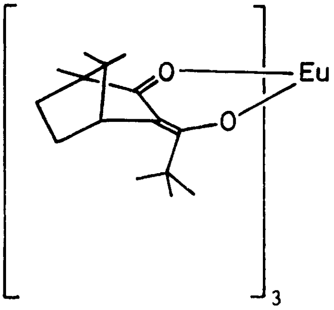
Tris(dipivaloylmethanato europium(III) [Eu(dpm)$_3$]



Tris(dibenzoylmethanato) europium(III) [Eu(dbm)$_3$]



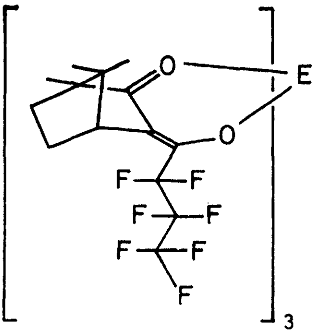
Tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimenthyloctane-4,6-dionato)europium(III) [Eu(fod)$_3$]



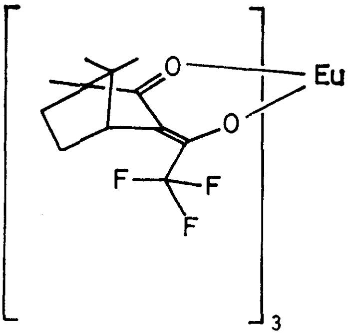
Tris-[3-(t-butylhydroxymethylene)-(+)-camphorato]europium(III)

(continued overleaf)

Table 5 *continued*



Tris-[3-(heptafluoro-n-propylhydroxymethylene)-(+)-camphorato]europium (III)



Tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato] europium (III)

phorous oxides,[15,18,74,110–112] all give LISs useful for spectral clarification. A wide range of comments and comparative investigations have been made on the preferred selective co-ordination of oxygen-containing groups, which necessarily involves either a comparison of LISs in different monofunctional molecules or a study in polyfunctional molecules. These observations are largely empirical and the factors which affect the shift should be considered in each case (steric hindrance, geometry, *etc.*). Only the alcohol in a difunctional hydroxy-ester is reported[22] to co-ordinate at low concentrations of LSR, as expected. By increasing the LSR concentration, co-ordination eventually occurs at the carbonyl of the acid group, presumably only at a stage when co-ordination is complete at the hydroxyl-function. A detailed graphical analysis of a hydroxy-keto-steroid[52] separates the relative contribution of the shift from co-ordination at each group, a method which could be developed for a wider range of polyfunctional molecules. Conversion of carbohydrates into the 5-*O*-acetate and 5-deoxy-analogues of methyl-2,3-*O*-isopropylidene-*p*-D-ribofuranoside shows a decrease in shift by 40 to 50% and 10 to 20%, respectively.[113]

Ketones are reported to co-ordinate better than ethers and esters, although only 35 to 40% as well as alcohols.[98] Quinones also give a satisfactory LIS, the carbonyl group being regarded as the preferred site of co-ordination in comparison with an aromatic methoxy-group.[106] A wide range of oxygen compounds are compared in a variety of intra- and inter-molecular competition experiments,[9] where tetrahydrofuran–acetone co-ordinate comparatively in a ratio of 8 : 1; dimethyl ether–acetone, 7 : 3; dioxan–cyclohexane-1,4-dione, 6 : 4; and dioxan–methyl acetate or –acetone, 5 : 1. The presence of conjugation decreases

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[110] T. M. Ward, I. L. Allcox, and G. H. Wahl, jun., *Tetrahedron Letters*, 1971, 4421.

[111] B. D. Cuddy, K. Treon, and B. J. Walker, *Tetrahedron Letters*, 1971, 4433.

[112] J. R. Corfield and S. Trippett, *Chem. Comm.*, 1971, 721.

[113] R. F. Butterworth, A. G. Pernet, and S. Hanessian, *Canad. J. Chem.*, 1971, **49**, 981.

co-ordination in an $\alpha\beta$-unsaturated ether, and if oxygen is part of a furan ring, co-ordination is very poor.[9] Investigations of esters in polymers indicates preferred co-ordination to the carbonyl and not the ether oxygen.[114,115]

In the case of functional groups consisting of two possible donor atoms, co-ordination is thought to occur mainly with the oxygen atom when present. As amides protonate preferentially at the oxygen,[116,117] the nitrogen lone pair being delocalized, preferential co-ordination of the LSR to the oxygen is expected. This is found with amides[96,118] and also oximes,[12,96] azoxybenzenes,[119] trimethylene sulphites,[120] sulphoxides,[67] hemithioacetals,[37] thiadecalones,[121] phosphates,[27,28] and the phosphoryl oxygen in phosphorinans.[15,74] However, the converse is thought to occur with oximes,[122] where results indicate preferred co-ordination to the nitrogen lone pair. The carboxylate ion gives a greater shift to associated protons than the basic amine group when in an aqueous solvent.[38] Phenols, hydroxy, and, particularly, carboxylic compounds can be studied with normal LSRs, but these may decompose the complexed substrate on standing.

Together with sulphoxides,[8,67] which co-ordinate 25 to 30% less than alcohols,[9] thioamides,[110,123] sulphinyls,[124] and thiocarbamate esters[125] all give appreciable LISs, as well as hemithioacetals,[37] which co-ordinate *via* the oxygen. The sulphonyl oxygen (R_2SO_2) co-ordinates less than the sulphinyl oxygen (R_2SO), which is analogous to the nitro (RNO_2) and amine oxide (R_2NO) systems.[80]

Amines[10,126] give larger shifts than alcohols;[23] and amides,[118,127] oximes,[12,122] quinolines,[36] pyrazines,[109] pyridines,[10] and nitroso-amino-carbanions[128] all give reasonable LISs; *N*-oxides give slightly smaller shifts;[56,103,129] pyrroles and nitriles[96] only give small shifts and imines, azobenzenes, and nitro-compounds remain unperturbed[36,96] by LSRs. In ^{14}N n.m.r., a survey[13] of nitrogen substrates shows that largest shifts are caused by alkylamines and pyridines; acetonitrile has less interaction with LSRs owing to its poorer basicity. Surprisingly, co-ordination is reported[130] to occur preferentially with a phosphine in a phosphine–amine compound. The effect of deuteriating the substrate is shown to increase

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[114] J. E. Guillet, I. R. Peat, and W. F. Reynolds, *Tetrahedron Letters*, 1971, 3493.
[115] A. R. Katritzky and A. Smith, *Tetrahedron Letters*, 1971, 1765.
[116] T. Birchall and R. J. Gillespie, *Canad. J. Chem.*, 1963, **41**, 148.
[117] R. L. Middaugh, R. S. Drago, and R. J. Niedzielski, *J. Amer. Chem. Soc.*, 1964, **86**, 388.
[118] L. R. Isbrandt and M. T. Rogers, *Chem. Comm.*, 1971, 1378.
[119] R. E. Rondeau, M. A. Berwick, R. N. Steppel, and M. P. Serve, *J. Amer. Chem. Soc.*, 1972, **94**, 1096.
[120] G. Wood, G. W. Buchanan, and M. H. Miskow, *Canad. J. Chem.*, 1970, **50**, 521.
[121] A. van Bruijnsvoort, C. Kruk, E. R. de Waurd, and H. W. Huisman, *Tetrahedron Letters*, 1972, 1737.
[122] K. D. Berlin and S. Rengaraju, *J. Org. Chem.*, 1971, **36**, 2912.
[123] W. Walter, R. F. Becker, and J. Thiem., *Tetrahedron Letters*, 1971, 1971.
[124] J. L. Greene, jun., and P. B. Shevlin, *Chem. Comm.*, 1971, 1092.
[125] R. A. Bauman, *Tetrahedron Letters*, 1971, 419.
[126] H. Burzynska, J. Dabrowski, and A. Krowczynski, Bull. Acad. polon. Sci., *Sér. Sci. chim.*, 1971, 587.
[127] A. H. Lewin, *Tetrahedron Letters*, 1971, 3583.
[128] R. R. Fraser and Y. Y. Wigfield, *Tetrahedron Letters*, 1971, 2515.
[129] R. A. Fletton, G. F. H. Green, and J. E. Page, *Chem. and Ind.*, 1972, 167.
[130] R. C. Taylor and D. B. Walters, *Tetrahedron Letters*, 1972, 63.

the shift,[35,100,131–133] possibly owing to an increase in base strength caused by the deuterium. Alkyl halides, olefins, and saturated hydrocarbons, as expected, co-ordinate weakly or not at all.[36]

Some general conclusions have been made concerning comparisons of co-ordinating ability of different functional groups. The co-ordinating power of thiols, thio-ethers, and arylphosphines are generally much less than their oxygen and nitrogen analogues.[16] The following series of functional groups have been put in order of their ability to co-ordinate and cause a LIS:

phosphoryl > carbonyl > thiocarbonyl > thiophosphoryl[110]
ethers > thioethers > ketones > esters[9]
amines > hydroxyls > ketones > aldehydes > ethers > esters > nitriles[36] (for RCH_2X)
(Note: there are contradictions with respect to relative shifts, *e.g.* ketones and ethers)

9 Application of Lanthanide Shift Reagents

By applying the principles outlined in the review, apart from spectral simplification, a great deal of information can be gained by using LSRs. This varies from producing spectra amenable to first-order analysis to configurational and conformational analysis[11,21,28,63,82,83,108,134a,134b] using the distance–shift and distance–broadening relationships. A unique application is apparent when, for example, upfield shifts are produced by $Eu(dpm)_3$ in fairly non-polar solvents, which is peculiar to structures which are often described as 'folded'[63,78] and have the angle θ_i between 54.7 and 125.3 °.

Shift reagents are used in spectral simplification of aliphatic systems[95,98] and are also applied to their configuration and conformational analysis, *e.g.* oximes,[12] thioamides,[123,127] and thiocarbamate esters.[125] Monocyclic systems are studied either in order to clarify spectra[7,36,39,135] or in configurational[21,63,76,136,137] and conformational analysis.[82,134b] The proton n.m.r. of heterocyclic systems are also simplified, *e.g.* pyrazines,[109] pyridines,[138] pyridine *N*-oxides,[129] carbohydrates,[113,134b,139] and alkylidenefuranones,[79] and examples of conformational elucidation are cited with valerolactones,[108] dioxaphosphorinans,[15,74] and thiadecalones.[121] Bicyclic systems, bicyclononanes in particular,[14,134,140] are studied alongside other rigid molecules chosen to simplify analysis of the distance and

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[131] A. M. Grotens, C. W. Hilbers, and E. de Boer, *Tetrahedron Letters*, 1972, 2067.
[132] A. M. Grotens, J. Smid, and E. de Boer, *Tetrahedron Letters*, 1971, 4863.
[133] D. A. Lightner and G. D. Christiansen, *Tetrahedron Letters*, 1972, 879.
[134a] M. R. Vegar and R. J. Wells, *Tetrahedron Letters*, 1971, 2847.
[134b] D. Horton and J. K. Thomson, *Chem. Comm.*, 1971, 1389.
[135] P. Belanger, C. Freppel, D. Tizane, and J. C. Richer, *Chem. Comm.*, 1971, 266.
[136] C. Casey and R. A. Boggs, *Tetrahedron Letters*, 1971, 2455.
[137] C. Freppel, D. Tizane, and J. C. Richer, *Canad. J. Chem.*, 1971, **49**, 1984.
[138] K. E. Stensio and U. Ahlin, *Tetrahedron Letters*, 1971, 4729.
[139] I. Armitage and L. D. Hall, *Chem. and Ind.*, 1970, 1537.
[140] L. F. Johnson, J. Chakravaty, R. Dasgupta, and U. R. Ghatak, *Tetrahedron Letters*, 1971, 1703.

geometric factors and allow correlation of the LIS with the pseudocontact shift expression. Thus the LIS of all protons in the n.m.r. spectra of adamant-1-ol[74] and -2-ol,[14,81] 2-hydroxy-1-(2-hydroxyethyl)adamantane,[65] borneol,[7,71] and isoborneol[7] have been reported, as well as that for the methyl resonances of (+)-camphor.[141] The ^{13}C n.m.r. spectra of borneol,[59] isoborneol[142], cholesterol,[143] cyclopentanols,[144] and ribo-5-phosphate[145] have been similarly assigned using LSRs.

Stereochemical problems have been solved in a wide range of compounds including pesticides[107,146] and natural products.[75,147] In one such structural elucidation of a new diterpene, trachyl-oban-19-ol,[147] 32 proton resonances were assigned with the aid of LSRs. Steroids are another group of compounds studied;[1,7,37,95,148,149] one result indicates the position of the C_{17} side-chain in solution.[86] References on the application of LSRs to conformational analysis are numerous.[63,75,82,83,108] Detailed investigation of polyfunctional substrates are less common, although an example of a satisfactorily assigned spectrum of a difunctional system is reported for 2-hydroxy-1-(2-hydroxyethyl)adamantane.[65] However, complicated molecules can be simplified before using the LSR by reducing the number of functional groups available; one paper suggests the conversion of an alcohol into a trifluoroacetic ester, a group with very poor basicity, as an effective blocking group.[16] Formation of first-order spectra with LSRs permits the measurement of coupling constants,[36,98,109] although complexation of the substrate with the LSR is reported to alter this parameter.[150a]

Lanthanide shift reagents have been used as structural probes in studying co-ordination sites of enzymes by observing the shifts of acetamido and glycosidic methyl groups.[93] The distinction of the resonances of iso-, hetero-, and syno-tactic polymers with LSRs has been applied in an analysis of poly(methyl methacrylate),[114,115] and is even used in molecular weight determinations.[150b] The optically active LSRs are used to distinguish enantiomorphs;[32] the fluorinated reagents appear to have a wider application[33,104]—one case cites the separation of enantiotropic protons at a prochiral centre.[151] Application of LSRs to ^{14}N n.m.r. spectroscopy[13,94] is restricted by the large extent of broadening, but it is

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[141] C. C. Hinckley, *J. Org. Chem.*, 1970, **35**, 2834.

[142] O. A. Gansow, M. R. Willcott, and R. E. Lenkinski, *J. Amer. Chem. Soc.*, 1971, **93**, 4295.

[143] W. B. Smith and D. L. Deavenport, *J. Magn. Resonance*, 1972, **6**, 256.

[144] M. Christl, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 3463.

[145] B. Birdsall, J. Feeney, J. A. Glasel, R. J. P. Williams, and A. V. Xavier, *Chem. Comm.*, 1971, 1473.

[146] J. D. McKinney, L. H. Keith, A. Alford, and C. E. Fletcher, *Canad. J. Chem.*, 1971, **49**, 1992.

[147] O. Achmatowiez, jun., A. Ejchart, J. Jurczak, L. Kozerski, and J. St. Pyrek, *Chem. Comm.*, 1971, 98.

[148] P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J, Amer. Chem. Soc.*, 1970, **92**, 5737.

[149] D. G. Buckley, G. H. Green, E. Ritchie, and W. C. Taylor, *Chem. and Ind.*, 1971, 298.

[150a] F. Floyd and L. Ho, *J. Polymer Sci., Part B, Polymers Letters*, 1971, **9**, 491.

[150b] B. L. Shapiro, M. D. Johnston, jun., and R. L. R. Towns, *J. Amer. Chem. Soc.*, 1972, **94**, 4381.

[151] M. R. Frazer, M. A. Petit, and M. Miskow, *J. Amer. Chem. Soc.*, 1972, **94**, 3253.

useful to use the LIS to characterize the mode of nitrogen bonding. More useful is ^{31}P n.m.r.,[18] and as ^{2}H n.m.r. has been used with transition-metal reagents,[152] there is a further possible application of LSRs with this nucleus.

10 Practical Aspects

A widely used method for studying shifts is by addition of portions of LSR, as a solid or a solution, so that the gradual shifts of each resonance can be followed. This permits identification of peaks, initially part of a complex adsorption band, by reverse extrapolation to zero concentration of LSR, and is also one method of measuring the shift parameter. However, an alternative approach[23] gives more accurate shift parameters or bound chemical shifts, by starting with a solution of the LSR in the n.m.r. tube and adding portions of the substrate. A plot of substrate concentration against the inverse of the LIS gives a slope equal to $(L_0\Delta_B)$, where Δ_B is the bound chemical shift;[23] see Section 2.

The internal standard from which chemical shifts are measured is also displaced by the LSR, albeit a fairly small shift. This is a consequence of changes in the bulk magnetic susceptibility of the solution, which shifts the TMS signal by up to 1.4 p.p.m. in one case.[37] However, these shifts are linear, with respect to the LSR concentration, so that no drastic errors in structural conclusions should arise, noting that the magnitude of these shifts is invariably smaller than the shifts of the substrate. Acetonitrile has been used as an internal standard; the lack of broadening at high concentration of LSR indicates a minimal shift;[18] benzene[115] and cyclohexane[8] have also been used, the latter being shifted 3 Hz in the concentrations studied. Alternative standards such as chloroform are proposed to avoid interference by the LSR resonances in the 1 p.p.m. region.[14] The effect of changes in bulk magnetic susceptibility may also cause displacement of the nucleus being studied, but such variables need only be considered in detailed measurements.

Use of the temperature-shift relationship is reported either in just improving resolution[115] or in substituting the concentration-shift studies.[92] Sensitivity of instruments may be enhanced by increasing the radiofrequency field, as the limit of saturation could be increased by the presence of the paramagnetic ions even though these LSRs have fairly inefficient spin relaxation properties.

The author wishes to thank Dr. A. P. Johnson for many useful discussions.

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[152] A. Johnson and G. W. Everett, jun., *J. Amer. Chem. Soc.*, 1970, **92**, 6704.