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# Lanthanide Shift Reagents for Nuclear Magnetic Resonance Spectroscopy‡

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## *Contents*

## *I. Historical Introduction*[1]

During the last two decades, nuclear magnetic resonance spectroscopy has developed into one of the most powerful analytical techniques for the elucidation of structures of organic compounds. From a knowledge of the chemical shifts of signals and their relative intensities, and coupling constants, a detailed stereochemical framework of an organic molecule can often be deduced. However, measurements can only be made with certainty when the signals are resolved from one another. Most organic molecules contain mainly carbon and hydrogen atoms, and it is from proton magnetic resonance spectroscopy (pmr) that most of the structural information has been gleaned. Unfortunately, the chemical shifts of hydrogen atoms exhibit an intrinsically low sensitivity to changes in chemical and stereochemical environment. Thus, often in the spectra of complex organic molecules, the signals are bunched together in featureless clusters from which little definitive structural information can be obtained. To some extent, this problem has been solved by the advent of higher frequency spectrometers, but the cost of these is often beyond the means of many spectroscopic departments. Some simplification in spectra can be attained using solvent-induced shifts, but approaches of this kind usually only affect a small part of the organic molecule.[1a,2] For example, Demarco has reported solvent shifts induced by pyridine in the pmr spectra of erythromycin aglycones ranging from 0.05 to only 0.8 ppm.[2b] Similar limitations apply to protonation or ion association methods.[3]

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(1) The following "standard" abbreviations are used throughout this text: thd = 2,2,6,6-tetramethyl-3,5-heptanedionato chelate; fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato chelate; acac = acetylacetonato; LSR = lanthanide shift reagent(s); LIS = lanthanide induced chemical shift(s) of nuclei in attached ligands.

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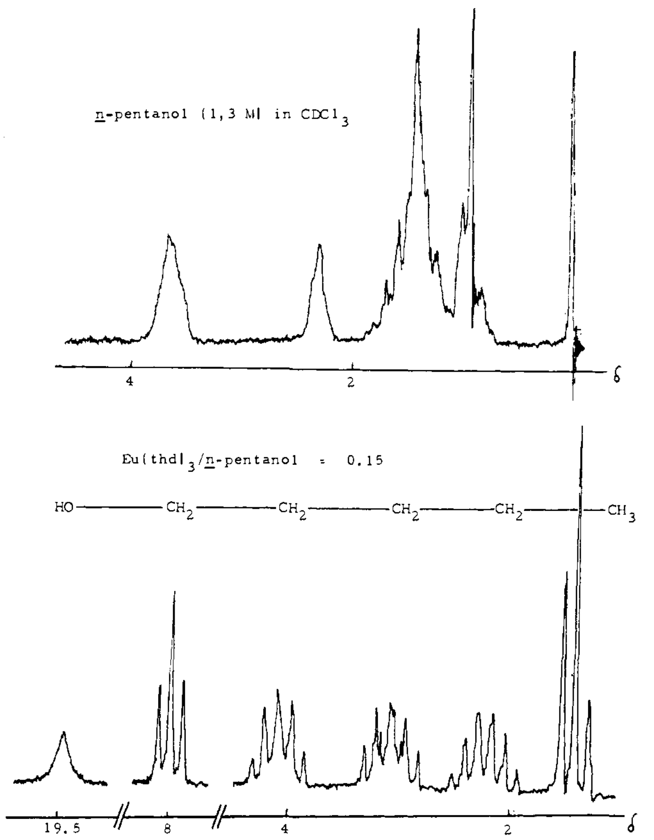

**Figure 1.** Simplification of the pmr spectrum of 1-pentanol by Eu(thd)$_3$.

The possibility of utilizing specific electron-nuclear interactions with paramagnetic ions to resolve accidental coincidences of nmr spectra was realized in 1960 in an $^{17}O$ nmr study of cation hydration.[4] Since that time, there have been numerous reports of the perturbation properties of transition metal complexes on the proton magnetic resonance spectra of the ligands to which they are attached.[5] The $Ni^{2+}$ and $Co^{2+}$ acetylacetonates attracted most interest,[6] although other transition metal complexes were also investigated.[7] The ligands were usually attached by nitrogen- or oxygen-based functional groups. Although the induced chemical shifts were of considerable theoretical interest, they were of little practical value to the organic chemist. The induced shifts were often very small, and, owing to the relatively slow electron spin relaxation times of the transition metal ions, line broadening resulted in the loss of signal multiplicity from which much of the structural information is derived. In 1969, Hinckley[8] reported the influence of the dipyridine adduct of Eu(thd)$_3$ on the pmr spectrum of cholesterol. Significant induced chemical shifts were found with acceptable levels of signal broadening, the downfield shifts ranging from 347 Hz, for the proton $\alpha$ to the hydroxyl group, to 2 Hz for the terminal methyl groups of the C-17 alkyl moiety. Shortly afterwards, Sanders and Williams[9] employed the chelate without the two molecules of pyridine and observed a fourfold increase in the magnitude of the induced shifts owing to the lack of competition with pyridine for the coordination sites. The immediate potential of the shift reagent Eu(thd)$_3$ is apparent from Figure 1, in which the clustered signals of the methylene chain of 1-pentanol are totally separated into clearly defined multiplets. The shift difference of the multiplet centers are large compared to the components of the multiplets, and the spectrum can be interpreted using a first-order analysis.

The initial reports of Hinckley[8] and Sanders and Williams[9] inspired considerable interest in the potential of lanthanide shift reagents. In 1970, only a few additional papers appeared, but in 1971 and 1972 the subject has been one of the most active aspects of chemistry and several hundred citations have now been published (since we began compilation of this review in August 1972, over 250 papers have appeared in the literature). Many of these are of a trivial nature, and we shall not attempt a comprehensive coverage but concentrate on the more significant developments. A wide range of shift reagents has now been developed, and although we shall focus our discussion mainly on the lanthanide complexes, we shall devote a small section to other types of reagents. Some aspects of shift reagents have been discussed in a number of recent reviews.[10-13,69,384,385]

## II. Mechanism of Induced Chemical Shifts

### A. Some Experimental Observations with Eu(thd)$_3$ and Pr(thd)$_3$

The majority of the initial reports on LSR concern the use of Eu(thd)$_3$. In general, the protons of attached ligands experience downfield shifts,[8,9] which usually increase with the concentration of Eu(thd)$_3$ relative to the organic compound. In a few cases, small upfield shifts have been reported,[14-20] and these have been attributed on most occasions to a particular geometrical disposition of specific protons with respect to the principal magnetic axis of the complex.[14-19] The change in chemical shift with the ratio LSR/substrate is most conveniently illustrated graphically, and Figure 2 shows some of the variations observed for *cis*-1,3,5,5-tetramethyl-5-(1-naphthyl)-cyclohexan-1-ol.[14] The upfield shift of the H-3 is much larger than the shallow shifts which have been reported elsewhere, H-4 representing a more typical variation. At room temperature, the equilibrium between complexed and free shift reagent is a rapid process on the nmr time scale, and only a time-averaged spectrum is observed.[7,8] Another shift reagent which attracted early favor, Pr(thd)$_3$, usually induces upfield shifts,[21] but a few shifts to lower field have also been reported.[15]

The variations in the magnitude and direction of the induced chemical shifts mentioned above for Eu(thd)$_3$ and Pr(thd)$_3$ are typical for the majority of the lanthanide complexes. In fact, the signs and sizes of these induced

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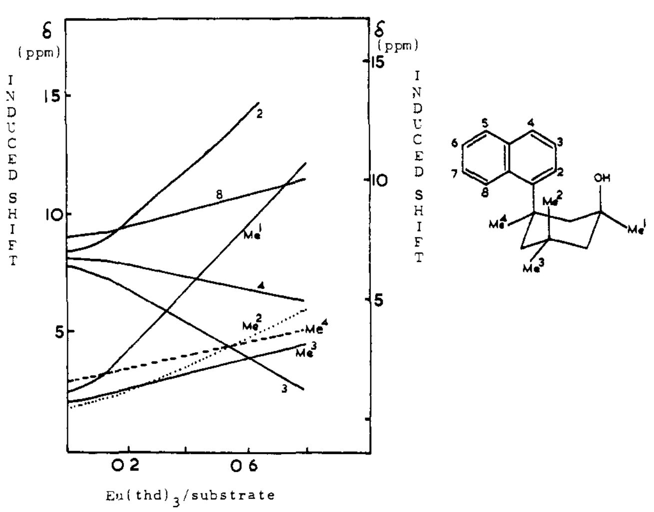

**Figure 2.** Variation in the chemical shift of some of the protons in *cis*-1,3,5,5-tetramethyl-5-(1-naphthyl)cyclohexan-1-ol upon addition of Eu(thd)$_3$ in CDCl$_3$[14] (left-hand ordinate for the aromatic protons, right-hand ordinate for the methyl group protons).

shifts provide the information on which structural analyses can be based. However, application of this analysis requires an understanding of the mechanism of action of the paramagnetic ions, and, to this end, the theoretical knowledge developed in earlier studies with the transition metal ions has proved invaluable.

## B. Contact and Dipolar Interactions

Several detailed theoretical treatments of the causes of paramagnetic induced chemical shifts have appeared previously,[5,23-26] and we shall therefore only summarize the results in this article. There is a similarity between the mode of action of added solvents such as pyridine and benzene and paramagnetic ions on nmr spectra. Both kinds of reagents are sources of secondary magnetic fields, which are usually anisotropic, their magnitude and direction varying with the direction of the primary field. However, paramagnetic ions exert much stronger fields and therefore afford potentially greater spectral spreading properties. The influence of the secondary magnetic fields falls away sharply with distance, and induced shifts will only be significant if the nucleus being observed is in close average proximity to the paramagnetic ion. This requirement is satisfied by the rapid equilibria involving organic compounds possessing Lewis base sites and transition metal or lanthanide ions, which function as Lewis acids.

Studies with transition metal complexes have revealed that the induced paramagnetic shifts may arise by one of two mechanisms. For paramagnetic ions, which possess unpaired electrons, both a contact interaction and a dipolar (pseudo-contact)[26a] interaction are possible. The Fermi-contact interaction involves direct delocalization and/or spin polarization of the unpaired electron *via* the molecular orbitals of the substrate ligand. As a result, the unpaired electron spin density is spread over a number of atomic sites in the ligand, thereby inducing a contact shift.[27] Contact interaction may involve both $\pi$ and $\sigma$ bonds,[28] although it declines rapidly through a series of $\sigma$ bonds.[29] For the case of a spin-only system, eq 1 has been derived to account for the contact shift.[30] The isotropic shifts produced for the spectra of ligands attached to Ni(acac)$_2$ are almost entirely due to the Fermi-contact interaction.[6,31,32]

$$\frac{\Delta\nu_{\mathrm{H}}^{\mathrm{con}}}{\nu_{\mathrm{H}}} = -A_{\mathrm{H}}\frac{\gamma_{\mathrm{E}}}{\gamma_{\mathrm{N}}}\,\frac{g\beta S(S+1)}{3kT} \tag{1}$$

$\gamma_{\mathrm{E}}$ and $\gamma_{\mathrm{N}}$ are the magnetogyric ratios of the electron and nucleus, respectively, $S$ is the spin quantum number, $\beta$ is the Bohr magneton, and $k$ is Boltzmann's constant. $A_{\mathrm{H}}$ is the isotropic hyperfine contact interaction constant for the nucleus (H above) and is a measure of the unpaired spin at that nucleus. $A_{\mathrm{H}}$ can be estimated indirectly using MO calculations of spin density distributions.[31,373]

For transition metal ions with anisotropic $g$ tensors, the electron-nuclear dipolar interaction has also to be considered. When the complex is axially symmetric[32a] and has a tumbling time much greater than the electron-spin relaxation time, the induced dipolar shift is described by eq 2.[7,30,33]

$$\frac{\Delta\nu_{\mathrm{H}}^{\mathrm{dip}}}{\nu_{\mathrm{H}}} = -\frac{\beta^2 S(S+1)}{45kT},\ (3g_{\parallel} + 4g_{\perp})(g_{\parallel} - g_{\perp}),\ \left\{\frac{3\cos^2\theta - 1}{r^3}\right\} \equiv -K_{\mathrm{p}},\ G(g_{\parallel},g_{\perp}),\ \mathrm{f}(r,\theta) \tag{2}$$

The factors for the first term, $K_{\mathrm{p}}$, have the same meaning as in eq 1. The second term includes the $g$ tensor, and the relative signs of these determine whether the induced shifts occur predominantly to low or high field. The third term affords specific structural information of the ligand nuclei relative to the paramagnetic ion, and, for a given complex, controls the relative induced chemical shifts. $r$ is the separation of the nucleus from the paramagnetic ion, which is regarded as a magnetic point -dipole, and $\theta$ is the angle between the vector joining the metal atom to the nucleus H and the principal magnetic axis of the molecular complex. When $\theta$ = 54.7 or 125.3°, $3\cos^2\theta - 1 = 0$, and eq 2 predicts no dipolar shift. For values of $\theta$ between these limits, the sign of the induced shift is opposite to that for angles outside these limits. Values of $\theta > 54.7°$ have been assumed to explain a number of the upfield shifts observed for Eu(thd)$_3$ complexes (see section II.A). Values of $r$ and $\theta$ required to

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(27) J. Reuben and D. Fiat, *Inorg. Chem.*, **8**, 1821 (1969).

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(32a) Equation 2 has been derived for complexes of axial symmetry, *i.e.*, complexes in which $g_x = g_y \neq g_z$, $g_x = g_y = g_{\parallel}$, and $g_z = g_{\perp}$. For the general case in which $g_x \neq g_y \neq g_z$, the derivation is considerably more complex.[48,49] Crystal structures of Ho(thd)$_3$·(4-picoline)$_2$,[50] Eu(thd)$_3$·(3,3-dimethylthietane 1-oxide),[382] and Eu(thd)$_3$·(pyridine)$_2$,[51,368] are not axially symmetric with respect to the adduct ligands, but in solution an approximation to axial symmetry is possibly achieved by rapid ligand reorientation. Certainly, in solution, the *tert*-butyl groups of a series of Ln(thd)$_3$-ligand complexes were found to exhibit only a single resonance, consistent with equivalence arising from a fast fluxional isomerization.[52]

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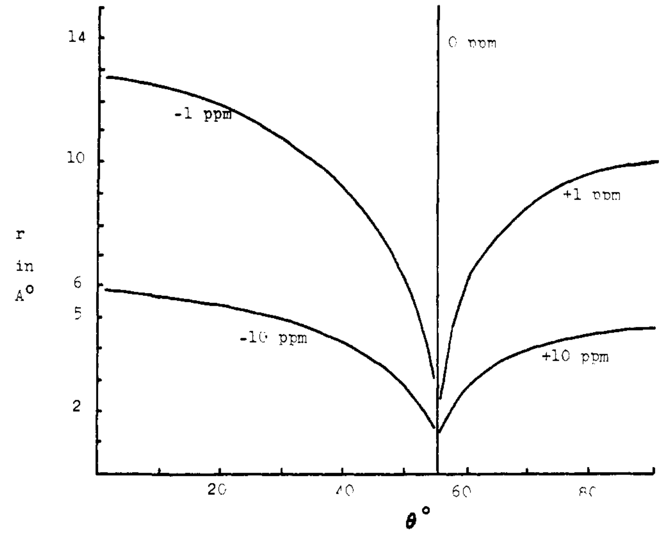
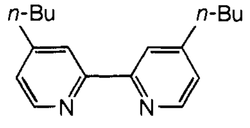


**Figure 3.** Calculated values of $(3\cos^2\theta - 1)/r^3$ to give induced shifts of 0, ±1, and ±10 ppm.

produce shifts of 1 and 10 ppm are shown in Figure 3.[34] It is clear from this graph, that small changes in the critical angle variation $50° < \theta < 60°$ produce pronounced effects on the induced chemical shifts, whereas, for smaller values of $\theta$, the dipolar contribution is dominated mainly by the distance factor.

The dipolar interaction makes a significant contribution to the observed induced chemical shifts for ligands complexed to $Co(acac)_2$.[32,35] To enable factorization of the contact and dipolar contributions, it was assumed that the contact shift was the same for $Co(acac)_2$ and $Ni(acac)_2$ complexes. However, it is not always easy to separate out the contact shift and for reagents which exhibit a strong tendency to this type of interaction quantitative structural evaluations derivable from the dipolar shift may be precluded.

In the transition metal ions, the valence 3d electrons are exposed and therefore ideally situated to participate in covalent bonding with ligands, resulting in extensive contact interactions. However, in the lanthanide series, the radial extension of the 4f orbitals is exceedingly small, and electrons in these orbitals are shielded from the ligand by the s and p electrons. Consequently, contact interactions are greatly diminished and the induced chemical shifts arise predominantly from the dipolar mechanism.[7,10,26] Even so, contact contributions cannot be totally ignored, for as little as 1% covalency would be observable.[36] For example, from $^{17}O$ and pmr spectra of lanthanoid aquo complexes, it was concluded that the contact shift was dominant for the oxygen atoms in the first coordination sphere and contributed, at the most, 60% of the induced shift for the neighboring hydrogen atoms.[29] Hart and his coworkers[37] attributed the shifts observed for $Ln(NO_3)_3 \cdot 2dbbp$ (**1** = dbbp) mainly to contact interactions, but this seems unnecessary as two independent groups have recently shown with $Ln(thd)_3$, where Ln = Eu, Pr, and Yb, that the induced shifts for pyridine and quinoline can be explained almost entirely in terms of dipolar interactions.[33,38] Significant contact contributions are only apparent for hydrogens ortho to the nitrogen atoms. In general, it is advisable to ignore atoms which are located adjacent to the site of complexing in the ligand when undertaking structural estimations using the dipolar-mechanism equation.



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The equations discussed so far were developed to explain induced chemical shifts caused by transition metal ions. Many authors have applied these equations in various abbreviated forms to account for LIS, although, as Hinckley originally indicated, the approximations used in deriving these equations may not be appropriate to the rare earth series.[8,39] Recently, Bleaney has developed a theoretical treatise to account for LIS.[40,41] In McConnell and Robertson's theory, the pseudocontact shift arises from a failure of the dipolar interaction to average to zero, because the metal ion possesses an anisotropic *g* tensor. Bleaney prefers an alternative explanation and attributes the dipolar induced shift to anisotropy in the susceptibility arising in less than cubic geometries. The mathematical result of his approach is shown in eq 3.

$$\frac{\Delta\nu_H^{dip}}{\nu_H} = \frac{\beta^2}{60(kT)^2} \cdot \left\{ \frac{3\cos^2\theta - 1}{r^3} \right\}, 2A_2^0\langle r^2\rangle,$$
$$g^2J(J+1)(2J-1)(2J+3)\langle J||\alpha||J\rangle \quad (3)$$

The major difference from the theory based on anisotropic *g* factors[30] concerns a change in temperature dependence from $T^{-1}$ to $T^{-2}$. For $Eu^{3+}$ ($4f^6$), the lowest electronic ground state is nondegenerate and has no Zeeman splitting.[42,407] As $J = 0$, no induced shift is predicted from eq 3. However, $Eu^{3+}$ and $Sm^{3+}$ both possess low-lying excited states, and Bleaney has developed a more refined theory to include interaction terms for the first excited states. As a result, for these ions, the induced dipolar shifts should exhibit a temperature dependency approximating to $T^{-1}$. The excited states make little contribution to the dipolar shifts predicted for the other lanthanide ions.[40,41] Some experimental variations with temperature are discussed in section V.F, and the application of Bleaney's theory to explain relative dipolar shifts for a series of lanthanide ions is shown in section IV.A.

A second important feature of Bleaney's equation concerns the crystal-field coefficients of the third term. These coefficients may change sign upon change of symmetry of a complex and thereby afford an explanation, in addition to the angular dependence, for sign reversals of chemical shifts on going from one series of lanthanide complexes to another. The constancy of this crystal-field coefficient throughout the lanthanide series can be verified by comparing the ratios of shifts at different proton sites for various lanthanons. If the ratios are independent of the lanthanide cation, the shifts have their origin in dipolar coupling, and, to a good approximation, the anisotropy of the susceptibility has axial symmetry.[41]

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## *III. Changes in Relaxation Times*

Added paramagnetic ions can cause both induced chemical shifts and enhanced relaxation rates.[5,43] Chemical exchange spin decoupling has also been observed as a result of enhanced longitudinal relaxation of spin–spin coupled nuclei.[44] LaMar and his coworkers have recently used added paramagnetic species to undermine the nuclear Overhauser effect and enable quantitation of $^{13}$C nmr spectra.[45-47] To examine the $^{13}$C spectra of some metal carbonyls, they added small amounts of $Cr(acac)_3$, which functioned as a "shiftless" reagent, causing little resonance broadening as it reduced $T_1$ (longitudinal) without seriously affecting $T_2$ (transverse) relaxation times.[47] The impact of paramagnetic ions on the relaxation times is an important consideration, as this interaction determines, to a large extent, the line width of a particular resonance. Changes in relaxation time can also be related to the geometry of a complex, thereby enabling a check on conclusions deduced from the induced chemical shifts.

Reuben and Leigh have recently measured the induced chemical shifts and changes in $T_1$ and $T_2$, when both quinoline and pyridine were complexed with $Eu(thd)_3$ and $Pr(thd)_3$.[33] The changes in pmr spectra can be explained mainly in terms of dipolar interactions. They reached this conclusion using both the magnitude of the induced chemical shifts and changes in the relaxation times and derived a relationship between the two. The longitudinal relaxation rate of the substrate protons is enhanced in the presence of LSR because of the electron-nuclear dipolar interaction. However, line broadening caused by the enhancement of the transverse relaxation rate arises mainly from the chemical shift difference between the complexed and uncomplexed states. Consequently, a greater degree of broadening is associated with increased induced shift.

Both $^{1}$H and $^{13}$C induced shifts have been measured for pyridine in the presence of $Eu(thd)_3$, $Pr(thd)_3$, and $Eu(fod)_3$.[370] Dipolar interactions alone account for the pmr spectra, but substantial contact contributions are required to explain the $^{13}$C spectra.

## *IV. Selection of the Lanthanide Ion*

Complexes of lanthanide ions with bulky chelating groups function as the most efficient shift reagents. These bulky groups probably restrict mobility in the chelate–ligand complex and thus prevent the susceptibility tensors from being averaged out by a combination of different configurations.[50] The exact choice of the chelate is determined primarily by the organic application, an aspect considered in greater detail in sections VII and VIII. It suffices here to say that the thd and fod[53] groups have proved the most useful.

### A. Proton Magnetic Resonance

Following the initial work of Hinckley[8] with $Eu(thd)_3 \cdot 2py$ and Sanders and Williams[9] with $Eu(thd)_3$, the whole series of lanthanide ion complexes have been examined as potential shift reagents. Two requirements limit the selection of the lanthanide ion: (i) the magnitude of the induced chemical shift and (ii) the broadening characteristics of the shifted resonances. The relative importance of these two factors varies widely from one problem to another, and it is therefore unwise to regard any one shift reagent as the best for all circumstances. For example, $Ho(thd)_3$ causes greater signal broadening than $Pr(thd)_3$ but allows separation of all the proton resonances of 1-octanol on a 60-MHz instrument.[59] In general for pmr studies, $Eu(thd)_3$ and $Eu(fod)_3$ have proved to be of most general use, with the corresponding Pr complexes acting as the most attractive alternatives.

Lanthanum(III) and lutetium(III) are diamagnetic, possessing no unpaired electrons, and can be used to assess the changes in chemical shift by bonded electrons, etc., independent of dipolar interactions.[54] Gadolinium(III) has each f orbital singly occupied, and, as there can therefore be no orbital symmetry restriction on electron spin delocalization, a contact interaction, if present in the lanthanide series, is expected to show up for this ion. Horrocks and Sipe[64] reported that $Gd(thd)_3$ caused extensive broadening, making spectra almost unobservable. However, with 4-picoline, the methyl resonance was observable and was found to be unshifted, suggesting the absence of contact interactions. Other workers have used gadolinium(III) as a broadening probe.[55-57]

There are several reports in which the relative shifting ability of a few $Ln(thd)_3$ complexes have been compared.[21,33,58-62] A wider range of lanthanide complexes has been studied by three groups of workers and their results are listed in Table I. The results of Von Ammon and Fischer[10] are for the $Ln(cyclopentadienides)_3$. Figure 4 illustrates the relative shift magnitudes.

For a given complex, it is clear that the line width increases with the magnitude of the induced shift (*cf.* Table I, columns 2, 4, 6), as mentioned previously in section III. Across the series of $Ln(thd)_3$, the induced shifts and line widths do not vary simultaneously in a regular fashion, although reagents causing the largest shifts usually cause most extensive broadening. In fact, for cyclohexanone, the methylenes are only sufficiently resolved to permit identification of multiplicity with $Eu(thd)_3$ and $Pr(thd)_3$.[52]

In general, the lanthanide complexes of each of the three triads [Ce, Pr, Nd], [Tb, Dy, Ho], and [Er, Tm, Yb]

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**TABLE I. Pmr Spectral Changes Induced by Added Lanthanide Complexes[i]**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LSR | *a* | *a* | *a* | *a* | *a* | *a* | *a* | *a* | *a* | *a* | *b* |
| Substrate | *c* | *c* | *c* | *c* | *c* | *c* | *d* | *e* | *f* | *g* | *h* |
| Proton resonance | α-$CH_2$ | | β-$CH_2$ | | γ-$CH_2$ | | H-2 | H-2 | H-1 | Me | H-4 |
| LSR/substrate 1 | 1 | | 1 | | 1 | | 0.125 | 0.125 | 0.125 | 0.125 | |
| Lanthanide ion | A[j] | B[k] | A | B | A | B | A | A | A | B | B |
| Ce | | | | | | | | | | | 23 |
| Pr | 11.25 | >20 | 4.8 | ≃20 | 3.7 | ≃20 | 6.6 | 2.23 | 4.73 | 5.6 | 30 |
| Nd | 5.55 | >20 | 2.4 | >20 | 1.8 | >20 | 3.2 | 0.58 | 1.33 | 4.0 | 32 |
| Sm | | >20 | | >20 | | >20 | 0.8 | | | 4.4 | 20 |
| Eu | −2.95 | ≃15 | −1.8 | ≃15 | −1.8 | ≃15 | −3.5 | −1.62 | −3.11 | 5.0 | 40 |
| Tb | 26.25 | 75 | 14.4 | 32 | 10.9 | 24 | 30.7 | 14.0 | 16.58 | 96 | 35 |
| Dy | 54.0 | 85 | 23.2 | 25 | 17.9 | 21 | 33.8 | 20.0 | 24.3 | 200 | 100 |
| Ho | 51.45 | 92 | 23.6 | 29 | 18.1 | 22 | 24.0 | 12.7 | 10.5 | 50 | 55 |
| Er | −25.55 | 61 | −11.0 | >20 | −8.8 | >20 | −9.1 | −7.4 | −4.6 | 50 | 40 |
| Tm | 44.65 | 90 | 19.3 | 38 | 14.8 | 34 | −23.6 | −15.1 | −11.37 | 65 | 60 |
| Yb | −12.15 | 23 | −5.4 | >20 | −4.4 | >20 | −11.0 | −6.47 | −5.68 | 12 | 70 |
| Ref | 52 | 52 | 52 | 52 | 52 | 52 | 64 | 64 | 64 | 64 | 10 |

[a] Ln (thd)$_3$. [b] Ln(cyclopentadienyl)$_3$. [c] Cyclohexanone. [d] 4-Vinylpyridine. [e] Picoline *N*-oxide. [f] 1-Hexanol. [g] 2-Picoline. [h] Cyclohexylisonitrile. [i] Solvents: columns 1-6 ($CCl_4$); columns 7-10 ($CDCl_3$); column 11 (toluene-$d_8$). Broadening: figures refer to peak widths at half-maximum peak height. [j] Induced chemical shift, ppm. [k] Broadening, Hz.

induce dipolar shifts of the same sign.[10,41,63,64,85] The reported upfield shift[52] for the methylenes of cyclohexanone with Tm(thd)$_3$ is contrary to this statement and should be regarded as uncertain.[64a] For the thd complexes, Dy causes the greatest upfield shifts, whereas Tm induces the greatest downfield shifts. However, for problems requiring multiplet resolution, Pr and Eu complexes are clearly preferable, with Yb as the most attractive alternative.[61,65]

A change in the chelate can bring about a variation in the direction and relative magnitudes of the induced dipolar shifts and also alter the relative extent of line broadening. The latter characteristic is exemplified by the results for the tricyclopentadienyl complexes, where Eu is the best downfield shift reagent, but Tb causes greater induced upfield shifts with less line broadening and is clearly the reagent of choice for this series (see Figure 4).[10]

Bleaney, *et al.*,[41] have recently predicted the relative dipolar shifts for a series of ligands, complexed to various lanthanide ion chelates. Figure 5 shows the excellent agreement between the experimental results and the theoretical predictions of eq 3.[40,41]

## B. Nuclei Other Than Hydrogen

The resonating nuclei, commonly encountered in organic compounds, fall into two classes: (i) those such as $^1H$, $^{13}C$, and $^{19}F$, which are subject mainly to dipolar interactions, and (ii) others such as $^{14}N$, $^{15}N$, $^{17}O$, and $^{31}P$ which carry lone pairs capable of interacting with the coordinating lanthanide ion, thereby allowing a dominant contact interaction. Thus, the shift reagents, which are most appropriate for pmr studies, are not necessarily the most suitable for other nuclei.

Hart, *et al.*, found that Eu(thd)$_3$ and Pr(thd)$_3$ induced $^{13}C$ shifts in a ratio of **1**:1.8 for borneol.[66] The induced shifts are excellently described assuming only dipolar contributions, and only the C-2 resonance, for which a contact contribution is most likely, shows any significant deviation from the theoretical predictions. Tb(thd)$_3$ caused shifts 8.6 times greater than those induced by Eu(thd)$_3$ but with considerable broadening.

Figure 6 shows the induced $^{14}N$ shifts of pyridine for the series of Ln(thd)$_3$ chelates.[67] Dy(thd)$_3$ is clearly the best high-field shift reagent, whereas all the deshielding reagents induce similar shifts, but Yb(thd)$_3$ causes the least broadening. The signs of the induced shifts for several of the lanthanides are different for $^1H$ and $^{14}N$, indicative of significant contact contributions for the latter nuclei.

$^{19}F$ spectra are usually simple to interpret and seldom need expansion. However, of theoretical interest, Wolkowski, *et al.*,[61] have shown that the induced shifts of $^1H$ and $^{19}F$ in substituted anilines can be analyzed on a comparable shift scale in terms of dipolar interactions. Dy(thd)$_3$ and Yb(thd)$_3$ are the preferred high- and low-field shift reagents, respectively, of the series examined to date.

## V. *Experimental*

## A. Lanthanide Chelates

### 1. *Requirements for Effective Shift Reagents*

For cases in which spreading of the spectral resonances is required to enable interpretation, LSR reagents should possess optimal shifting power with minimal broadening effects. They should be capable of associating with a wide range of organic substrates without causing chemical decomposition. Resonances of the LSR should be well separated from the normal nmr range of the substrate nuclei, and both the LSR and their complexes with added substrates should be soluble in solvents which do not complex preferentially with the LSR.

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(64a) It seems unlikely that a contact contribution is involved with Tm(thd)$_3$ alone in this series, as the relative induced shifts, $(CH_2)_\alpha/(CH_2)_\beta$ and $(CH_2)_\alpha/(CH_2)_\gamma$, are similar for the whole series of Ln(thd)$_3$ complexes.

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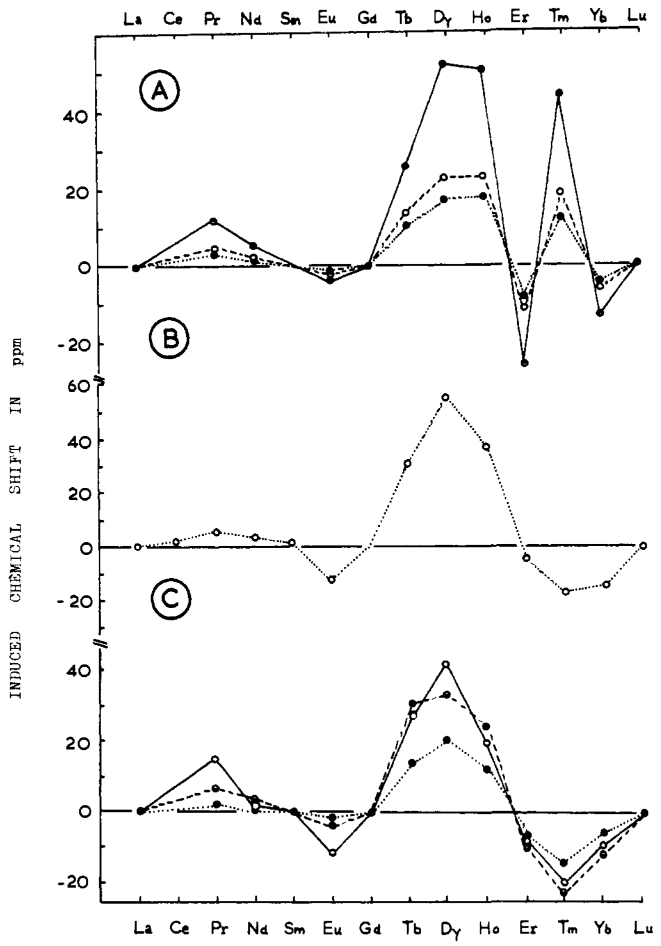

**Figure 4.** Isotropic shifts for various lanthanide complexes: (A) observed isotropic shifts for 0.1 *M* solutions of cyclohexanone (◒, α-$CH_2$; O, β-$CH_2$; ●, γ-$CH_2$) with 0.1 *M* (approximately) $Ln(thd)_3$ in $CCl_4$;[52] (B) observed isotropic shifts for the δ-methylene hydrogens in the adduct between cyclohexylisonitrile and $Ln(C_5H_5)_3$ in toluene-$d_8$ at 30°;[10] (C) observed isotropic shifts for 0.8 *M* solutions of 1-hexanol (O, H-1), 4-picoline *N*-oxide (●, H-2), and 4-vinylpyridine (◒, H-2) for $Ln(thd)_3$/substrate = 0.125 at 30° in $CDCl_3$.[64]

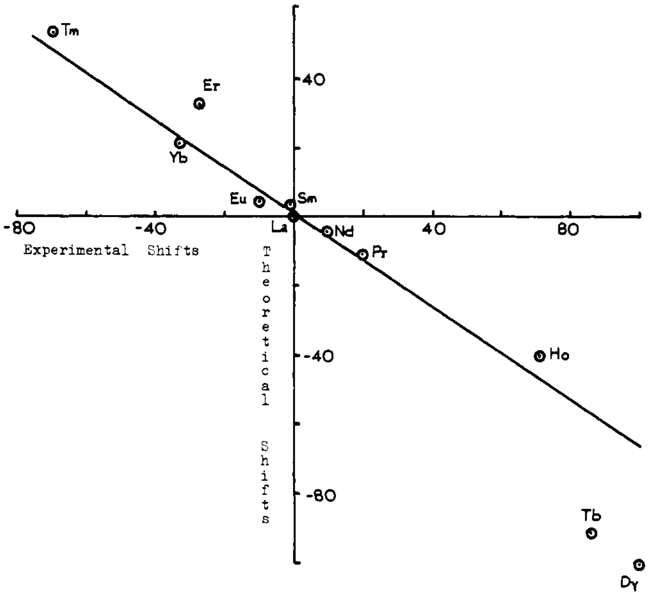

**Figure 5.** Correlation between theoretically calculated induced shifts using eq 3 and the experimental shifts observed for the 2 hydrogen of 4-vinylpyridine complexed with various $Ln(thd)_3$ (all values from ref 41 are normalized to a shift of 100 ppm for $Dy(thd)_3$).

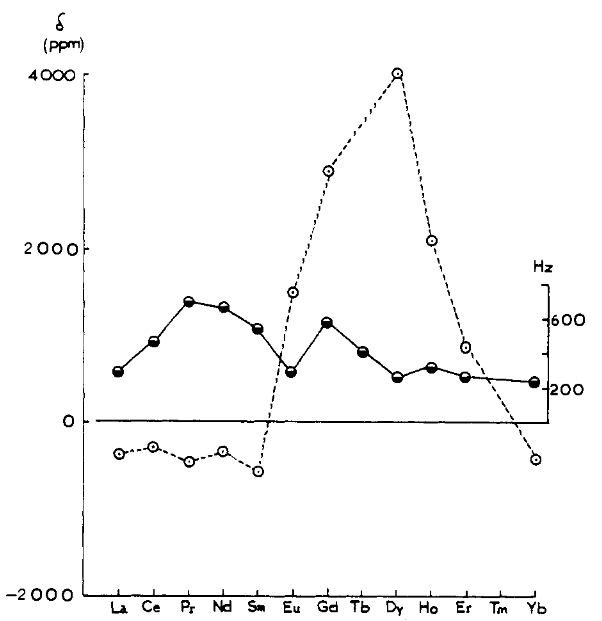

**Figure 6.** Induced shifts and broadening features of $^{14}N$ nmr of pyridine with added $Ln(thd)_3$ in nitromethane:[65] induced shifts in ppm for 1:1 molar complex (⊙). Broadening in Hz refers to peak width at half-height for 0.01 molar ratio of LSR/pyridine (◒).

A number of additional restrictions must be satisfied before attempts to use the induced shifts to obtain quantitative data concerning the molecular structure of the substrate are made. Dipolar interactions should dominate over contact interactions, the secondary fields should be axially symmetric, and the point-dipole approximation should be valid. The complex LSR–substrate should be conformationally uniform, although the substrate may exist in many conformations. The induced shifts should exhibit a straightforward dependence on temperature. If all of these requirements are met, the induced shifts can be analyzed using the equation describing the dipolar interaction, and structural predictions have a high probability of success.

### 2. *Preparation and Storage*

The most widely used lanthanide shift reagents are those of $Eu^{3+}$, and the methods for their preparation are typical for the whole series of lanthanides. Sievers and his coworkers have described the preparation of $Ln(thd)_3$ and $Ln(fod)_3$ from the lanthanum chlorides and nitrates and the corresponding diketones in the presence of alcoholic sodium hydroxide.[70,71] The preparation of the chiral shift reagents,[72] has recently been simplified by Schurig.[73] The new method involves a homogeneous exchange reaction of lanthanide nitrates with the barium salt of *d*-3-trifluoroacetylcamphor in ethanol.

Purification is usually accomplished by sublimation[70] or recrystallization,[22,68] but a combination of both procedures is recommended. Sublimation generally gives very

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**TABLE II. Chemical Shifts (ppm)[a] of the *tert*-Butyl Proton Resonances of $Ln(thd)_3$ Complexes in $CCl_4$[52]**

| Ln | Pr | Nd | Sm | Eu | Gd | Tb | Dy | Ho | Er | Tm | Yb | Lu |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| δ(ppm) $Ln(thd)_3$ | 0.6 | 0.8 | 1.08 | 0.48 | 0.90 | 17.4 | 17.7 | 5.3 | −3.6 | 12.8 | −0.3 | 1.14 |
| δ(ppm) $Ln(thd)_3$ with added cyclohexanone | 2.8 | 2.1 | 1.2 | −0.5 | 1.8 | 16.0 | 21.9 | 7.3 | −6.2 | 15.2 | −1.9 | |

[a] All shifts are relative to TMS. The exact position of the *tert*-butyl resonances of $Ln(thd)_3$ does vary with the added substrate. For $Pr(thd)_3$ and $Eu(thd)_3$, values varying from −5 to +5 and −2 to +2.3 ppm have been reported, respectively.[11,76,88,366]

pure, but finely divided material, which is difficult to handle. Recrystallization yields crystalline material, which is not so subject to static problems. Hinckley prepared $Eu(thd)_3 \cdot 2py$ by recrystallization of $Eu(thd)_3$ from pyridine.[8]

A number of other chelates, which have been tried as potential shift reagents, include 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dionato,[75,76] 1,1,1,2,2-pentafluoro-6,6-dimethylheptane-3,5-dionato,[75] dibenzoylmethanato,[77-79] 1-benzoylacetonato,[78-80] and acetylacetonato.[76] These are less effective as shift reagents than the thd and fod chelates, owing to a combination of low induced shift and poor solubility. Recent reports indicate that a new Eu-fluorinated chelate (1,1,1,2,2,6,6,7,7,7-decafluoroheptane-3,5-dione) offers promising potential as a LSR.[127]

The lanthanide chelates are very hygroscopic[62] and should be stored over a suitable desiccant (*e.g.*, $P_2O_5$) *in vacuo*.[53,75,83] On adsorption of water, the chelates usually become white solids and their shifting power is drastically reduced.[84] The anhydrous $(thd)_3$ chelates should have the following colors:[68] pale green (Pr), white (Sm, Tb, Yb, Gd, Dy, Tm, Lu), pale yellow (Eu, Ho), red (Ce), violet (Nd), and pink (Er).

Following nmr experiments, the lanthanide chelate and the substrate may be separated by tlc[9] or glc,[53,177] enabling recovery of precious materials. Lanthanide chelates have been used as the stationary phase in gas chromatographic columns, an area which is likely to attract increasing interest.[383,488]

## B. Selection of Solvents

The solvent should be capable of solubilizing the chelate, the substrate, and the complex formed between the two,[52,75,77,88,89] without interacting preferentially with the chelate. Thus, for $Ln(thd)_3$ and $Ln(fod)_3$, solvents with strong Lewis base properties (*e.g.*, ROH, $R_2SO$) are precluded. Most often in pmr studies, $CCl_4$ and $CDCl_3$ have been used. Less commonly used solvents include $CD_2Cl_2$,[90] $CD_3CN$,[77] *sym*-tetrachloroethane,[91,126] deuteriobenzene,[77,125] and carbon disulfide.[92-94,123] Nitromethane has been employed as solvent and reference in $^{14}N$ nmr studies.[65]

The induced shift of the H-2 proton of 1-aminoadamantane with $Eu(thd)_3$ attenuates dramatically along the following series:[366] $CCl_4 > C_6D_6 > CDCl_3 \gg$ acetone $\gg$ pyridine $\simeq$ methanol. For the latter three solvents, competition of the solvent and substrate molecules for the LSR reduces the induced shift. $CDCl_3$ is capable of forming hydrogen bonds with the $\pi$ system of the LSR,[367] and thereby sterically inhibits the approach of the substrate,[366] resulting in reduced induced shifts relative to those observed in the other two nonpolar solvents. In a similar study on keto and hydroxy steroids, the induced shifts decrease in the order $C_6H_{12} > CCl_4 \simeq CS_2 > C_6D_6 > CDCl_3$.[374]

For substrates, which are insufficiently soluble in nonpolar solvents, lanthanide salts can be used to effect small induced shifts in DMSO-*d*,[97] $D_2O$,[55,56,99,100] deuterioacetone,[55] and other hydroxylic solvents.[76]

## C. Interfering Chelate Resonances

The chemical shifts of the resonances of the chelates are only of concern in the interpretation of pmr spectra. These resonances undergo small shifts on association with an organic ligand, and typical chemical shifts for the $Ln(thd)_3$ complexes are listed in Table II.[11,52,76,88] For pmr studies, we are mainly concerned with the Pr and Eu chelates. In the case of $Eu(thd)_3$, the induced downfield shifts result in increased separation of the pmr signals of the organic ligand and the *tert*-butyl resonance of the chelate, making interference of minimal concern. For $Eu(fod)_3$, interference is again minimal, the chemical shift of the chelate ranging from δ 1 to 2.[62] However, for

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(97) J. E. Herz, V. M. Rodriguez, and P. Joseph-Nathan, *Tetrahedron Lett.*, 2949 (1971).

(98) K. E. Stensiö and U. Åhlin, *Tetrahedron Lett.*, 4729 (1971).

(99) F. A. Hart, G. P. Moss, and M. L. Staniforth, *Tetrahedron Lett.*, 3389 (1971).

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$Pr(thd)_3$, the chelate resonances may interfere until the induced upfield shifts are sufficiently large.

To circumvent the problem of interfering resonances from the LSR, deuterated chelates have occasionally been employed.[125,128]

## D. Procedures for Obtaining Induced Shifts

The induced shifts are usually expressed as displacements from the initial positions, *i.e.*, in the absence of the chelate. Internal standards which have been used for pmr studies include TMS, cyclohexane, methyl cyanide,[65] benzene,[74] chloroform,[81] and acetone (for aqueous solutions).[99] The resonances of these internal standards are shifted to a small extent (*e.g.*, 1.4 ppm for TMS) in the presence of the LSR because of changes in the bulk susceptibility of the solution.[63,97]

Most workers have obtained induced chemical shifts by the incremental addition of known weights of the solid LSR to a solution of the substrate. Solution is usually effected by the agitation or gentle warming of the reactants,[82] and often the complex is more soluble than both the LSR and the substrate alone. The volume changes caused by the addition of the LSR are negligible. Spectral assignments should be attempted with the minimum quantity of LSR to achieve signal resolution, as broadening of the signals increases markedly with the magnitude of the induced shift.

Other workers have preferred to add the LSR as a solution.[58,86,95,96] To maintain a constant substrate concentration, this procedure necessitates the use of several aliquots of substrate with different concentrations of the LSR and is clearly wasteful with regard to the substrate.[98]

A third procedure[87] involves incremental addition of the substrate to the LSR in solution. This technique suffers from the drawback that in the initial spectra the resonances are weak and broad and cannot be related to the original chemical shifts to aid assignments.

For studies in organic solvents, traces of water or acidic impurities can lead to the formation of insoluble hydrated lanthanide adducts, resulting in loss of spectral resolution.[88] This problem may be reduced by careful purification of the solvents[52,77,105] or alleviated by centrifugation or filtration of the cloudy solutions.[60,107]

## E. Graphical Interpretation of Induced Shifts

Although a large amount of information can be gleaned by a visual analysis of a series of spectra obtained from incremental additions of LSR, the information is more conveniently expressed in graphical form, usually as a plot of induced shift *vs.* the ratio of [LSR]/[substrate] (see Figure 7). Tracing a particular signal back to the ordinate enables verification of the assignment from a knowledge of the initial chemical shift of the particular resonance in the absence of added LSR. (In a recent publication, a computerized approach is outlined for the automatic sorting and assignment of signals in LIS spectra prior to the derivation of the $\Delta\nu$ values for use in eq 4.[179]) In the majority of cases, these plots are not linear over the entire range from 0 to 1 for [LSR]/[substrate], although for one or two instances a linear relationship has been claimed.[108] Usually some curvature is apparent at both extremes of the plot, with a good linear correlation being noted for the range 0.2–0.6 mole ratio. Curvature at low LSR concentrations has been attributed to competition between the substrate and traces of water or acidic impurities for the LSR.[14,58,76,102,103] Curvature at high ratios of [LSR]/[substrate] has been ascribed to incomplete solution of the LSR[104] and medium and association effects.[53,81] In a recent paper, Kelsey has shown mathematically that plots of the type in Figure 7 are expected to exhibit curvature for both high and low molar ratios of the reagents.[119] Values of the chemical shifts of the substrate, obtained by extrapolation of the linear portion of the graph, may not be exact as a result of the initial curvature phenomenon.

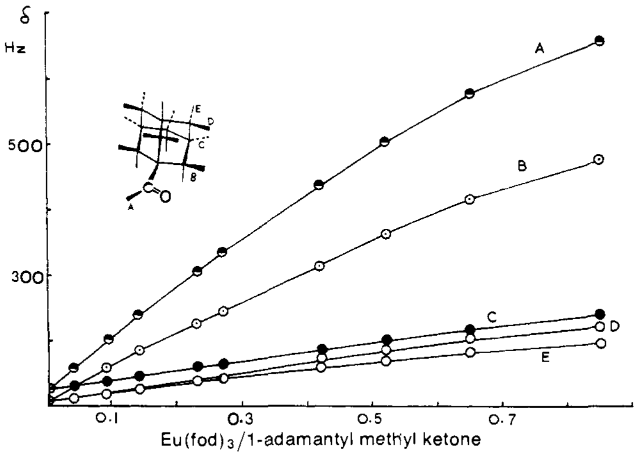

**Figure 7.** Changes in chemical shift in the pmr spectrum of 1-adamantyl methyl ketone in the presence of $Eu(fod)_3$ in $CDCl_3$.[161] The signal multiplicities are as follows: (A) sharp singlet; (B) doublet, $J = 3$ Hz; (C) broad multiplet; (D) broad doublet, $J = 12$ Hz; (E) broad doublet, $J = 12$ Hz.

As is obvious from Figure 7, once the signals have been resolved, assignments can be made from a knowledge of the relative intensities, signal multiplicity, and decoupling experiments. These assignments can then be verified from a knowledge of the initial chemical shifts of the substrate.

## F. Quantitative Evaluation of Induced Chemical Shifts

Most spectral interpretations are more difficult than that outlined in Figure 7, and only partial assignments can often be made using conventional nmr techniques. It is necessary to verify the dipolar mechanism as the sole cause of the induced shift (see section VI.B.1) and to resort to the use of eq 4 (simplified form of eq 2 and 3) to complete the assignment. This section is concerned with the derivation of the $\Delta\nu$ values of the left-hand side of the equation, while section VI is devoted to the use of computer calculations and approximation methods to solve the right-hand side.

To utilize eq 4, it is necessary to obtain the relative induced chemical shifts, $\Delta\nu_i$, for all the nuclei being observed. In deriving the relative changes in chemical shifts, particular consideration should be directed toward

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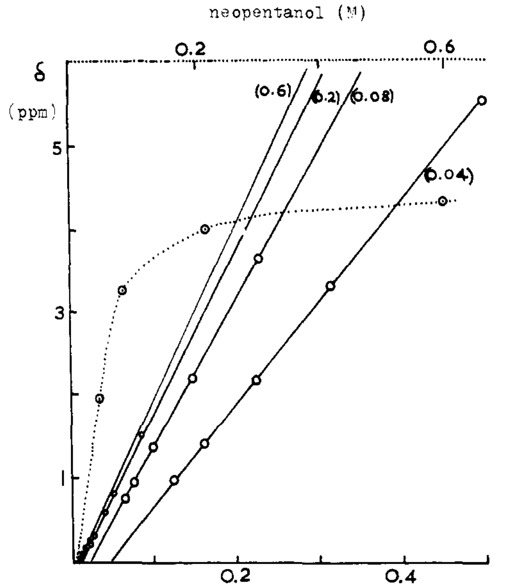

**Figure 8.** The effect of concentration of the reactants on the shift gradients.[118] The broken curve illustrates the limiting LIS ($CDCl_3$) obtainable at the substrate concentrations shown on the upper abscissa for $Eu(thd)_3$/neopentanol = 0.2. The full lines are shift gradients obtained for the substrate concentrations shown in parentheses by each line.

the concentration of LSR and substrate used, the reaction temperature, and the stoichiometry of the complex formed between the substrate and the LSR.

$$\frac{\Delta\nu}{\nu} = K\frac{(3\cos^2\theta - 1)}{r^3} \tag{4}$$

### 1. *Concentration of Substrate*

Several authors have noted the dependence of the magnitude of the induced shift on the substrate concentration,[62,92,104,124] the values for all protons in a molecule increasing linearly[63,76,110,111,119] until a limiting value ($\Delta$) is reached at 0.6–1.0 *M* concentrations (*cf.* Figure 8).

The effect of experimental error in both the LSR and substrate concentrations can be minimized by the use of slope ratios, as outlined by ApSimon and Beierbeck.[106,375] The slopes are normalized to some suitable standard proton in the molecule.[22,62,101a] Most authors use a less exacting procedure by quoting induced shifts for a 1:1 (sometimes 2:1) complex, determined by extrapolation of the shift diagram to the appropriate mole ratio.

### 2. *Stoichiometry of the Complex*

In the lanthanide chelates, the lanthanide can increase its coordination number to 7, 8, or 9 by bonding to substrate ligands (eq 5, $n$ = 1, 2, or 3).[102] In order to apply the pseudocontact equation (4), it is necessary to demonstrate the existence of uncomplexed substrate and only one complexed species, because the relative values of $r$ and $\theta$ for the various nuclei may differ from one complex to another. In most cases steric considerations limit the coordination number to 7, under the experimental conditions employed, although for some molecules complexes up to eight coordination are known (*e.g.*, $Eu(thd)_3 \cdot 2py$).[68]

$$L + nS \xrightleftharpoons{K} LS^n \tag{5}$$

L = LSR, S = substrate

The stoichiometry of the complex can be estimated graphically from the position of maximum curvature on the [LSR]/[substrate] axis of a shift diagram.[76,178] Two more precise methods have been described for the determination of $n$. Armitage, *et al.*,[110] used eq 6, and from a plot of log $S$ against log ([LS]/[L]) determined $n$ from the slope and log $K$ from the intercept. However, for large values of $K$, use of eq 6 gives uncertain values of $n$.[110]

$$\log [S] = \frac{1}{n}\{\log ([LS]/[L]) - \log K\} \tag{6}$$

[LS] is calculated from the relationship $\delta = [LS]/[S]\Delta$, Armitage's method of determining $\Delta$, the limiting slope, being described in section V.G.

"Jobs method of continuous variation" was used by Roth, *et al.*,[120] who plotted the induced shift against [S] (where [S] goes from 0 to 100 mol % and [S] + [L] = constant). A peak maximum at [L] = [S] = 50 mol % is consistent with the formation of a 1:1 complex.

The analysis presented above depends upon the assumption that only one complex species contributes significantly to equilibrium 5. For $Eu(thd)_3$ and $Pr(thd)_3$, the induced shifts do, in fact, appear to arise because of formation of a 1:1 adduct as the principal complex,[412] although exceptions have been noted.[393] However, the situation is more complicated for the fod shift reagents. For example, norcamphor forms a 1:1 (or 2:2) adduct with $Eu(fod)_3$ in $CCl_4$, but a 2:1 adduct in $CDCl_3$.[369] The 2:2 complexes were preferred in $CCl_4$, with the norcamphor molecules acting as bridging ligands between two molecules of LSR, as the induced shifts are almost twice as large as in $CDCl_3$ (greater solvent association between $CDCl_3$ and the LSR could also account for the smaller shifts in this solvent (*cf.* section V.B)). The authors[369] proposed that the more polar $CDCl_3$ cleaves the bridged dimers and an additional norcamphor molecule is thus able to occupy the vacant coordination site.

A more detailed analysis of the pmr spectra of 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone with $Eu(fod)_3$ in $CCl_4$, over a wide range of substrate and LSR concentrations, clearly reveals the need to consider equilibria involving both LS and $LS_2$ adducts (eq 7a,b). The precision of the fit was admirable for the two-step equilibria, whereas significant deviations were noted when the analysis was based on equilibrium 7a only.[393] As a referee has pointed out, even this sophisticated approach is not complete as equilibrium 7c, involving the LSR self-association, is ignored. However, for cases in which LSR < substrate, this contribution should be relatively small (*cf.* section V.F.4).

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$$L + S \overset{K_1}{\rightleftharpoons} LS \qquad (7a)$$

$$LS + S \overset{K_2}{\rightleftharpoons} LS_2 \qquad (7b)$$

$$2L \rightleftharpoons L_2 \qquad (7c)$$

### *3. Temperature*

The use of variable-temperature studies in nmr spectroscopy is now well established in solving problems involving rotamerism and conformational analysis. From eq 1–3, it is clear that the magnitude of the induced shift should increase as a function of decreasing temperature, notwithstanding the effect of temperature on the association constant of the LSR–substrate complex.

Armitage and Hall[58,86] were the first to report increased LIS at lower temperatures. Line broadening is also a consequence of reducing the temperature and has been attributed to reduced rates of interconversion of the free and complexed substrate.[112] This suggestion is supported by the work of Evans and Wyatt,[90] who observed the appearance of free and complexed substrate at temperatures below −80° in solutions of DMSO in $CD_2Cl_2$ containing $Eu(fod)_3$.

Linear relationships between the LIS and the inverse of the absolute temperature have been observed over the temperature range −30 to 90°,[22,91,92,113–115] but it has been stated that in any single molecule all the protons may not always respond uniformly to temperature changes.[92] Curved Arrhenius plots can be attributed to changes in the molecular configuration of the complexes with temperature,[113,115,381] or, in the case of polyfunctional ligands, to a change in the site of coordination.[114] Bennett and Schuster's results exemplify the latter phenomenon (Figure 9).[114]

Recent claims[116] of a dependence of induced shift on $1/T^{-1/2}$ for a series of $Yb(thd)_3$ complexes seem unjustified as our least-squares analysis of the results accords excellently with $1/T$ (correlation coefficient = 0.9993 for 7 points).

### *4. Stoichiometry of the LSR*

The lanthanide chelates are known to exist as dimers in the solid state[53,129] and in concentrated solution.[76,88,130] The relative concentration of the dimer decreases with the LSR concentration, and below $10^{-2}$ *M* the LSR is mainly present in solution in the monomeric form.[76,383,412] Thus, for studies in which the substrate is in excess over the LSR, the concentration of free LSR is small and the LSR will be mainly monomeric. Under circumstances in which the substrate and LSR are of similar concentration, the equilibrium concentration of dimeric, free LSR will be greater and association phenomenon of this kind may partly explain the levelling in the slopes of the shift diagrams (*cf.* Figure 7).

Schwendiman and Zink have examined the induced shifts of the *tert*-butyl resonances of $Eu(thd)_3$, relative to uncoordinated chelate, in a range of solvents.[366] Upfield shifts of 50 Hz are found in noncomplexing solvents ($CCl_4$, $C_6D_6$, $CDCl_3$), along with the appearance of less intense resonances (<10%) at δ 2.5–4.0, attributed to the presence of dimeric $Eu(thd)_3$. Other workers prefer to assign these resonances to traces of water in the solvents.[412] In $CDCl_3$, the induced shifts show a concentration dependence, ascribed to the tendency of $CDCl_3$ to form hydrogen bonds with the π system of the chelate. In more polar solvents, only monomeric species are observed.

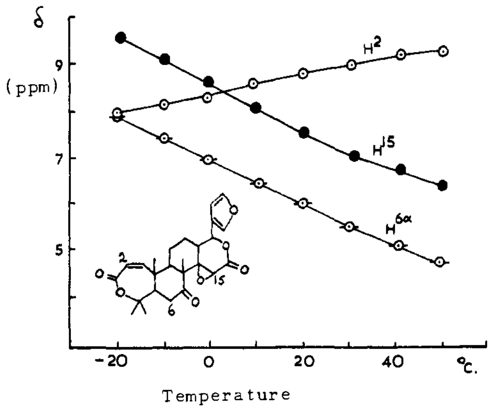

**Figure 9.** Induced chemical shifts of three protons of obacunone ($Eu(fod)_3$/substrate = 0.6) as a function of temperature.[114]

## G. Formation Constants

To understand why the nuclei in some ligands undergo more pronounced induced shifts than corresponding nuclei in other ligands, it is necessary to derive the association constants involving the LSR and the particular ligands. From eq 5, for a 1:1 complex ($n = 1$), the formation constant can be defined by

$$K = [LS]/[L][S] \qquad (8)$$

There has been a considerable amount of controversy concerning the experimental procedures used to derive the induced chemical shifts to enable the calculation of precise values of *K*. Armitage and Hall and their coworkers[117,118] have derived the induced shifts under conditions where $[S]_0 \gg [L]_0$, as they claim that only under this condition are the relative magnitudes of the induced shifts for the various nuclei independent of the substrate concentration. For cases in which $[L]_0 \leq [S]_0$, they have shown that the relative induced chemical shifts for a series of protons in a given molecule vary with substrate concentration.[117] Substituting for [LS] in eq 8 gives eq 9,

$$K = \frac{\delta/\Delta}{[S]_0\left(\frac{[L]_0}{[S]_0} - \frac{\delta}{\Delta}\right)\left(1 - \frac{\delta}{\Delta}\right)} \qquad (9)$$

in which δ is the observed induced chemical shift for a given concentration of $[S]_0$ and Δ is the limiting shift for a 1:1 complex. This rearranges to eq 10, from which a plot of $[S]_0$ against $1/\delta$ gives a slope of $[L]_0\Delta$ and an intercept of $-((1/K) + [L]_0)$. The validity of this approach is confirmed by the common intercept obtained for a series of protons within a given substrate (see Figure 10).[117] However, when *K* is very large (>100), it is not possible to make accurate determinations.[132,180]

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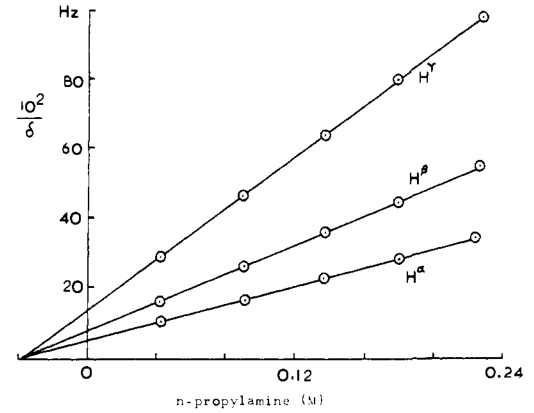

**Figure 10.** Graphical evaluation of eq 10 for the three sets of protons in *n*-propylamine. Induced shifts caused by Eu(thd)$_3$ in CDCl$_3$.[132]

$$[S]_0 = \frac{[L]_0\Delta}{\delta} - \left(\frac{1}{K} + [L]_0\right) \qquad (10)$$

In deriving this latter equation, the approximation $[S]_0 \gg (\delta/\Delta)[S]_0$ has been made as for cases in which $[S]_0 \gg [L]_0$ and $\delta \ll \Delta$.[132a] Roth, *et al.*, have made the same approximation, but at an earlier stage in their derivation, resulting in eq 11.[119,120] Clearly, their intercept values do not allow for the contribution of $[L]_0$.

$$[S]_0 = \frac{[L]_0\Delta}{\delta} - \frac{1}{K} \qquad (11)$$

The methods described above are restrictive when the substrate is scarce. Induced chemical shifts are relatively small and may be insufficient to enable definite assignment of signals. In addition, experiments involving low concentrations of LSR are highly sensitive to traces of moisture, and it is therefore advisable to carry out the work under anhydrous conditions (*e.g.*, sample handling in a glove box filled with dry nitrogen).[117]

A number of workers have operated under conditions where $[S]_0 \simeq [L]_0$ and concentrations were varied by dilution.[105,121,131] Alternatively, simultaneous equations have been used to solve eq 9.

Sanders, *et al.*,[76] calculated $\Delta$ independently from shift diagrams at various substrate concentrations (Figure 8), and from these curves they constructed plots of $[L]_0$ against $[S]_0$ at constant $\delta$ values. The intercepts, when plotted against $\delta/(\Delta - \delta)$, yield a straight line of slope $1/K$ and intercept $[L_w]$, the amount of chelate taken up by water traces.

## H. Standardization of LSR

It has been reported that the purity of the LSR can influence the magnitude of the induced shifts by up to 30%.[84] Variations of this kind emphasize the need for a standard substrate by which the activity of the LSR can be gauged. We suggest that the shift of the methylene resonances of *p*-nitrobenzyl alcohol with a 0.1:1.0 [LSR]/[substrate] ratio might be used as an acceptable standardization reference. The calibration should be made in CDCl$_3$, the most commonly used solvent, to enable comparison of results with those of other workers, and also in the particular solvent being employed for the studies in hand. A substrate concentration of 0.5 *M* and reaction temperature of between 30 and 33° are suggested to complete the operating parameters. Typical interpolated induced shifts for the methylene hydrogens of *p*-nitrobenzyl alcohol are shown in Table III.[161]

**TABLE III**

| LSR | Induced shift (Hz) for LSR/ substrate = 0.1 | $r^c$ | $n^c$ |
|---|---|---|---|
| Eu(thd)$_3$ | 117.3$^a$ | 0.9989 | 6 |
| | 116.3$^b$ | 0.9993 | 4 |
| Eu(fod)$_3$ | 167.0$^a$ | 0.9998 | 5 |
| | 152.0$^b$ | 0.9996 | 4 |
| Pr(fod)$_3$ | −297.4$^a$ | 0.9992 | 5 |

$^a$ Sample stored over P$_2$O$_5$ under reduced pressure. $^b$ Sample stored in a sealed ampoule as received from commercial sources. $^c$ Correlation coefficient for the shift gradient based on *n* points ranging between LSR = 0 and LSR/substrate = 0.15.

## I. Nomenclature for Induced Shifts

A number of symbols have been used to describe spectral changes caused by added LSR; *e.g.*, slope parameters for shift diagrams have been described by the terms *S* (slope), *G* (gradient), $\Delta$(Eu), and $\Delta$(Pr), and the terms $\delta$, $\Delta S$, and $\Delta\delta$ have been used to indicate induced chemical shift. These terms are rather nonspecific and give no information concerning the chelate part of the LSR. We prefer a more detailed nomenclature, which is listed below.

(i) $\Delta$(LSR) in ppm for a given solvent and temperature to describe the limiting slopes (bound chemical shifts[132]).

(ii) $\delta$(LSR) in ppm for a given solvent, temperature, and [LSR]/[substrate] molar ratio to describe the chemical shift with respect to an internal standard.

(iii) *G*(LSR) in ppm for a given solvent, temperature, and substrate concentration to describe the gradient of shift diagrams.

## *VI. Quantitative Evaluation of Results*

## A. Introductory Comments

The uses of LSR in the elucidation of structures of organic molecules fall into three categories. In the simplest case, they merely provide a convenient and economical means by which interfering nmr resonances can be separated. It is sometimes not possible to assign separated resonances, without ambiguity, by means of conventional nmr techniques. A simple empirical interpretation, based on distance factors only, or the use of model compounds, can often enable a rapid solution. The most exciting aspect of lanthanide induced shifts concerns the stereochemical features of the organic compounds, which are potentially derivable if a dipolar interaction alone can be demonstrated as the cause of the LIS. It is to this latter feature that we devote the majority of this section.

## B. Computational Procedures

### *1. Separation of Contact and Dipolar Contributions*

The measurement of accurate and meaningful induced shift values for the left-hand side of eq 4 has already been discussed (section V.D–F). Before application of eq 4, it is necessary to demonstrate that dipolar mechanisms are the sole cause of the induced shifts and that the LSR–substrate complex possesses axial (or pseudo-

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(132a) To avoid making these approximations, Armitage, Hall, and their coworkers have recently preferred to solve a rearranged form of eq 9 using an iterative computer procedure.[132] A similar iterative approach has also been employed by Mackie and Shepherd.[133]

(133) R. K. Mackie and T. M. Shepherd, *Org. Magn. Resonance*, 4, 557 (1972).

axial) symmetry (section II.B). Bleaney and his coworkers have proposed a systematic approach to exclude all but dipolar contributions,[41] the main points of which are as follows.

(i) LSR which cause both high- and low-field shifts should be used. If dipolar interactions alone are the cause of the LIS, then the ratios of the induced shifts should be independent of $G(g\ ,\ g_{\perp})$, which varies in both sign and magnitude across the lanthanide series.[33]

(ii) The induced shifts must be corrected by subtracting the observed shifts due to complex formation with the diamagnetic lanthanides, $La^{3+}$ or $Lu^{3+}$, thereby eliminating contributions due to electron pair shielding (*cf.* section IV.A).

Birnbaum and Moeller measured shifts in aqueous solution for some aromatic amines complexed to the $La^{3+}$ ion, and subtracted these small values from the induced chemical shifts observed with other lanthanides in order to obtain the isotropic nuclear shifts.[36]

(iii) Ratios of shifts at different proton sites should then be compared for the different lanthanides, thereby eliminating effects due to changes in $A_2^0$, the crystal field coefficient. If these ratios are independent of the lanthanide cation, then the shifts have their origin in dipolar coupling, and, to a good approximation, the anisotropy of the susceptibility has axial symmetry.

The two lanthanides most frequently used in this approach are $Eu^{3+}$ and $Pr^{3+}$.[36,55,76,134-136] If a dipolar mechanism is predominant, then a constant ratio of $G(\mathrm{Eu})/G(\mathrm{Pr})$ should be obtained for all the protons in the molecule.

(iv) In general, the dependence of the shift ratios on the concentration of lanthanide and its ligand must be followed so that the stoichiometry of the complex is proved.

Methods of determining stoichiometry have been discussed in detail in section V.F.2, and it suffices here to state that, in general, a 1:1 complex is formed for most monofunctional substrates with $Eu(thd)_3$ and $Pr(thd)_3$, but both LS and $LS_2$ complexes must be considered for the fod reagents.

(v) A computer search for the best fit of the nmr shift data to a structure presents obvious advantages. The search should include positioning of the metal ion and the orientation of the magnetic axis.

A number of workers (including the present authors) have employed computer treatments based on the minimization of deviations between observed shifts and those calculated from the dipolar equation (4). However, a more sophisticated approach has been used by Barry, *et al.*, in the determination of conformations of nucleotides.[56] This involves a search for sterically possible conformations, using lanthanide ion shift and broadening nmr probes, which agree with the nmr data (*cf.* section IX.B.2).

(vi) The computer search can best be made if data from line broadening or relaxation times can also be incorporated (as the line broadening depends upon $1/r^6$) using $Gd^{3+}$ as a relaxation probe.[57]

The procedures outlined above to isolate the induced shifts arising from dipolar interactions are more exacting than normally required. In many cases, satisfactory factorization has been achieved by making use of one or two of the above recommendations only. For example, in some cases, ratios of $G(\mathrm{Eu})/G(\mathrm{Pr})$ for various nuclei are compared and constant values are taken as indicative of dipolar interactions,[135] whereas contact contributions are assumed for the occasional differing ratio.[134,136,376]

Sanders, *et al.*,[76] have shown that 80% of the induced shift of the $^{31}P$ in diethyl ethylphosphonate with $Pr(NO_3)_3 \cdot 6D_2O$ arises *via* the contact interaction. In deriving this quantity, they assumed the dipolar interaction was the same for the P and methylene hydrogens of the ethoxy group. The relative contact contributions to the $^{31}P$ shifts induced by Pr, Eu, and Nd salts were in close agreement with those observed earlier by Taube[137] and Birnbaum and Moeller[36] for similar systems. The contact contribution appears to be considerably depressed by steric encumbrance around the donor site. Whereas in $\gamma$-picoline, with $Eu(thd)_3$, significant contact contributions are apparent for the methyl and ring hydrogens, they are negligible for the ortho-substituted pyridines, *e.g.*, collidine.[133]

### 1. *Application of the Dipolar Equation*

The wealth of LIS data now available in the literature does serve to illustrate that successful interpretations can be made without having to resort to Bleaney's more thorough approach. The following assumptions have generally been made.[85]

(i) The observed shifts used in the analysis are purely of dipolar origin.

(ii) Only a single complex species exists in solution in equilibrium with the uncomplexed substrate.

(iii) Only a single geometric isomer of this complex species is present, *i.e.*, all complexing to one donor site.

(iv) This isomer is magnetically axially symmetric so that the shifts are proportional to the geometric factor.

(v) The principal magnetic axis has a particular, known orientation with respect to the substrate ligand or ligands.

(vi) The substrate ligand exists in a single conformation, or an appropriate averaging over internal motions is achieved.

Assumption i is probably justified where only saturated systems are being considered, as in the presence of unsaturation, especially close to the site of complexing delocalization of electrons through the $\pi$ system can result in contact interactions.

In the simplest cases, assignments have been confirmed from correlations of experimental induced shifts with $(3\cos^2\theta - 1)/r^3$.[99,138-142,377,378] Problems falling into this category concern mainly rigid functional groups (*e.g.*, pyridine, quinoline) with no internal rotational complications.

Other workers[143] have employed a simple graphical method, which requires positioning a model of the compound on a map of the dipolar field for an axially symmetric lanthanide complex. The relative shifts are then read directly from the plot and scaled to match the observed shifts (see Figure 11).

The more exact procedures, however, are those which involve computerized optimizations in which both the angle ($\theta$) and distance ($r$) are varied simultaneously until the correlation between the induced shift and the

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(135) P. Kristiansen and T. Ledaal, *Tetrahedron Lett.*, 4457 (1971).

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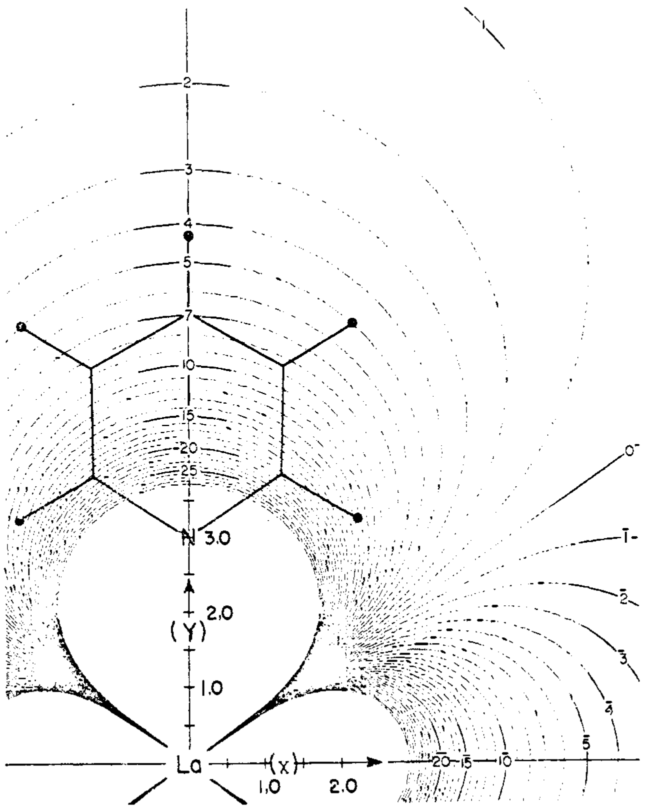


Figure 11. Map of the dipolar field, $(3\cos^2\theta - 1)/r^3$ (*cf.* eq 4) where $Y = r\cos\theta$ and $r^2 = Y^2 + X^2$. Pyridine is placed on the map (reproduced with permission from the authors of ref 143).

geometrical factor for all the protons is maximized,[57,66,142,144,145,379,380] *e.g.*, 2-adamantanol (Table IV). In this latter case, an extra complicating factor arises due to rotation of the hydroxyl group, and the calculated position for the lanthanide ion is an average position on the extended C–O axis.

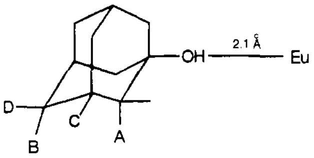
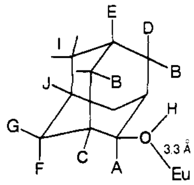
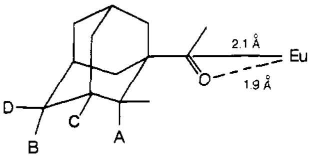
Willcott, *et al.*,[146] have used a statistical agreement factor to test the significance of computer calculations. They have shown by contour maps that several values of $r$ and $\theta$ will often give equally satisfactory fits of the experimental data.

Anomalous results for atoms close to the donor site have been attributed to contact interactions.[95,138] For example, for borneol, only the $^{13}$C-2 induced shift deviates markedly from the predicted value.[66,144] Slight deviations are also apparent for the H-2, H-6(endo), and H-3(endo) atoms (see Figure 12).

In general, these methods have produced satisfactory results with lanthanide-heteroatom distances in good agreement with X-ray data.[50,51,147,148] For freely rotating systems, the lanthanide-heteroatom bond length is usually of the order of 2–4 Å, as illustrated by our results for 2-adamantanol (Table IV). Predictions of bond lengths outside this range indicate weak complexing or an unrealistic optimization.

The applicability of this type of program still has its limitations when a $\sigma$ bond is interposed between the bonding site and the main structural skeleton, thus introducing the possibility of additional rotation. This is well illustrated by computer treatments of the data for 1-adamantyl methyl ketone (Table IV), which positions the lanthanide along the C-1–carbonyl bond, if the methyl induced shift is excluded from the calculations. Failure to obtain any optimization when the methyl result is included suggests that the locus of the lanthanide describes a circle with its center along the extended C-1–carbonyl carbon bond. With respect to the methyl group, the lanthanide ion describes a different locus. Clearly, the relative positions of the lanthanide atom and the carbonyl group in calculations of this type bear little resemblance to reality.

TABLE IV. Comparison of Observed and Calculated Induced Shifts Based on Dipolar Interactions[a]

| Substrate | H | Obsd shift ppm | Calcd shift ppm |
|---|---|---|---|
| <br>∠Eu-O-C2 142°<br>∠Eu-O-C2-$H_A$ 125° | A | 16.22 | 15.71–16.10 |
| | B | 6.13 | 6.24–6.52 |
| | C | 4.94 | 5.82–5.88 |
| | D | 4.36 | 4.70–4.79 |
| <br>∠Eu-O-C1 133°<br>∠Eu-O-C1-$H_A$ 65° | A | 25.09 | 25.35 |
| | B | 15.30 | 14.87, 15.29 |
| | C | 15.00 | 13.77, 14.39 |
| | D | 6.88 | 7.49, 7.56 |
| | E | 6.03 | 6.78 |
| | F | 5.63 | 5.77, 6.14 |
| | G | 4.73 | 5.03, 5.24 |
| | I | 4.25 | 4.48 |
| | J | 3.77 | 3.97 |
| <br>∠Eu-(C=O)-C1 0.3° | A | 8.04 | 7.71–7.89 |
| | B | 2.62 | 3.06–3.20 |
| | C | 2.53 | 2.85–2.89 |
| | D | 1.98 | 2.30–2.35 |

[a] Computerizational procedures were used to optimize the position of the lanthanide ion in the complex.[161] The coordinates of the substrate protons were measured using a telescopic sighting of molecular models against a calibrated background. This method gives rise to small errors, which in turn result in slightly different induced shift predictions for apparently equivalent protons. More accurate Cartesian coordinates can be obtained from X-ray data if available or by calculation using the Westheimer method.[142,145]

So far we have considered coordination complexes with increasing degrees of rotational freedom resulting in calculations, which bring out average rather than specific positions for the lanthanide ion. Obviously, calculations become less certain with increasing degrees of rotational freedom, *e.g.*, coordination to a functional group at the terminus of an extended alkyl chain. The large variations, in $\theta$, which might be observed for specific atoms in the various conformations (*cf.* assumption vi of this section) would result in meaningless correlations.

## C. Approximate Methods

For a large number of applications, there is not always the need to resort to a complicated computerized approach. In many of these cases a simple relationship involving only LIS and distance factors will often suffice

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(144) J. Briggs, F. A. Hart, and G. P. Moss, *Chem. Commun.*, 1506 (1970).

(145) S. Farid, A. Ateya, and M. Maggio, *Chem. Commun.*, 1285 (1971).

(146) (a) M. R. Willcott, III, R. E. Lenkinski, and R. E. Davies, *J. Amer. Chem. Soc.*, **94**, 1742 (1972); (b) R. E. Davies and M. R. Willcott, III, *J. Amer. Chem. Soc.*, **94**, 1744 (1972).

(147) J. L. Hoard, B. Lee, and M. D. Lind, *J. Amer. Chem. Soc.*, **87**, 1612 (1965).

(148) L. A. Aslanov, E. F. Korytnyi, and M. A. Porai-Koshits, *J. Struct. Chem. USSR*, **12**, 600 (1971).

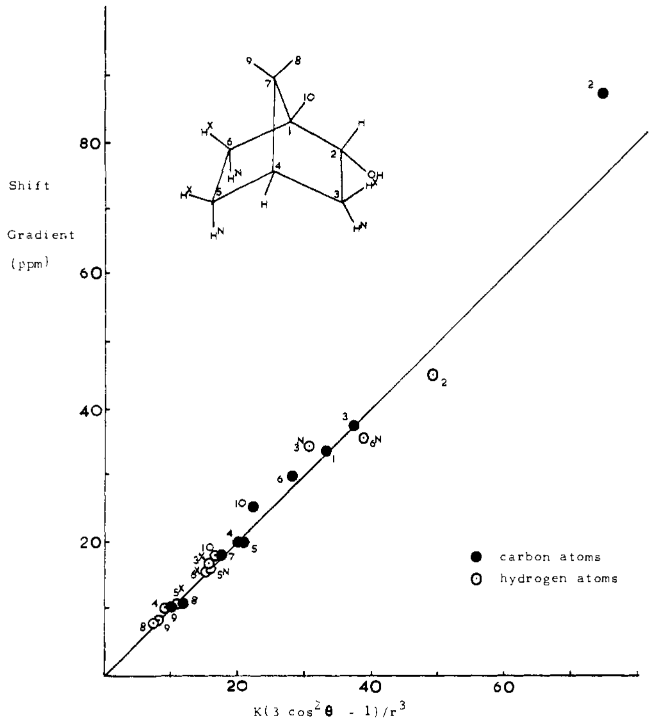


**Figure 12.** Correlation of the observed induced shifts in the $^{13}C$ and $^{1}H$ spectra of borneol with $Pr(thd)_3$ with $(3 \cos^2 \theta - 1)/r^3$. Data are taken from ref 66 and 144. The value of $K$ was chosen to give agreement between the magnitude of the observed and calculated induced shifts (solvent, $CCl_4$).

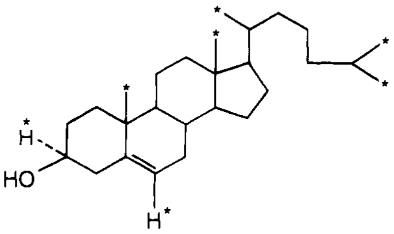
and at other times comparison with model compounds will enable spectral interpretation.

### *1. Neglect of the Angle Factor*

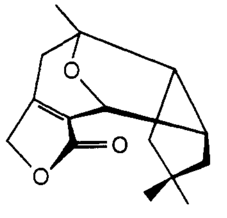
Taking logarithms of both sides of eq 3 gives eq 12, in which $K$ is a multiterm constant. For most organic molecules, values of $\theta$ for most of the nuclei lie between 0 and 30°, and changes in $(3 \cos^2 \theta - 1)$ are therefore small compared with changes in log $r$. Under these conditions, a graph of log $(\Delta\nu)_i$ against log $r_i$ should approximate to a linear correlation with a slope of $-3$. In analyses of this kind, a ligand atom–lanthanide bond distance of 3-4 Å is usually assumed, and measurements from the estimated average position of the lanthanide nucleus to each nuclei are made using Dreiding molecular models.

$$\log (\Delta\nu)_i = -3 \log r_i + \log (3 \cos^2 \theta_i - 1) + \log K \quad (12)$$

Hinckley was the first to observe a linear relationship of slope approximating to $-3$ for a graph of log $(G(Eu(thd)_3 \cdot 2py))$ against log $r$ for the protons in cholesterol indicated (*) in **2**.[8,95] Only the proton $\alpha$ to the hydroxyl deviates significantly from this plot, and, in view of its proximity to the coordination site, a contact interaction was invoked to explain this discrepancy. A number of similarly successful correlations have since been reported for the following functional groups: alcohols,[150,372] epoxides,[138,149,372] amines,[164] aldehydes,[151] ketones,[60,77] and thioamides.[152] For a series of rigid bicyclic ethers, Caple and Kuo[138] found a satisfactory correlation of induced shift with $r^{-3}$, but this was significantly improved by consideration of the angle factor. Using the $r^{-3}$ approach, the stereochemical configuration of lactarorufin A internal ether has been elucidated as **3** rather than **4**. This assignment is also consistent with the unexpected predominant complexing on the ethereal rather than the lactone oxygen, steric factors clearly inhibiting coordination at the latter site.



**2**



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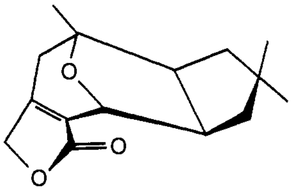

**4**

Following the initial approach used independently by Demarco, *et al.*,[102] and two of the present authors,[81,153] several workers have ignored the position of the lanthanide nucleus and calculated distance measurements from the lone pair periphery of the donor atom to the nucleus undergoing LIS. In such cases, graphs of log $G$ against log $r$ give slopes approximating to $-2$, and this has given rise to the so-called $1/r^2$ method. This method has been used successfully to enable interpretation of the nmr spectra of alcohols,[81,101,102,153,156,159,162,371] amines,[155,157,163] lactams,[154] and esters.[156,158] Although the slopes approximate to $-2$ in each of the above studies, the intercepts vary quite considerably. The latter variation can be attributed to changes in the purity of the LSR or differing binding constants of the organic substrates. The surprisingly good linear correlations obtained by this approach should not be taken as evidence that the induced shifts arise by a quasi-electrostatic interaction rather than a dipolar interaction.[159] It is purely the result of fortuitous cancellations of the impact of neglect of the angle factor and the use of the lone-pair periphery to approximate the position of the lanthanide ion. The main failing of this simple approach (and the $r^{-3}$ method) is the inability to explain anomalous shifts arising from the dominance of the angle term in the dipolar mechanism equation.[377]

(149) W. M. Daniewski, A. Ejchart, J. Jurczak, L. Kozevski, and J. S. Pyrek, *Bull. Acad. Pol. Sci.*, **20**, 131 (1972).

(150) P. Bélanger, C. Freppel, D. Tizané, and J-C. Richer, *Can. J. Chem.*, **49**, 1985 (1971).

(151) C. Beauté, Z. W. Wolkowski, J. P. Merde, and D. Lelandais, *Tetrahedron Lett.*, 2473 (1971).

(152) W. Walter, R. F. Becker, and J. Thiem, *Tetrahedron Lett.*, 1971 (1971).

(153) A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5153 (1970).

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(155) L. Ernst, *Chem. Ztg.*, **95**, 325 (1971).

(156) A. Ius, U. Vecchio, and G. Carrea, *Tetrahedron Lett.*, 1543 (1972).

(157) L. W. Morgan and M. C. Bourlas, *Tetrahedron Lett.*, 2631 (1972).

(158) A. J. Rafalski, J. Barciszewski, and M. Wiewiorowski, *Tetrahedron Lett.*, 2829 (1971).

(159) J. Paasivirta and P. J. Mälkönen, *Suom. Kemistilehti B*, 44, 230 (1971).

(160) A. F. Cockerill, N. J. A. Gutteridge, D. M. Rackham, and C. W. Smith, *Tetrahedron Lett.*, 3059 (1972).

(161) Unpublished work from these laboratories.

(162) P. Granger, M. M. Claudon, and J. F. Guinet, *Tetrahedron Lett.*, 4167 (1971).

(163) D. Barraclough, J. S. Oakland, and F. Scheinmann, *J. Chem. Soc., Perkin Trans. 1*, 1500 (1972).

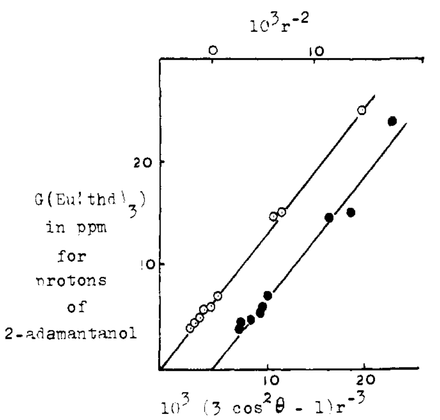
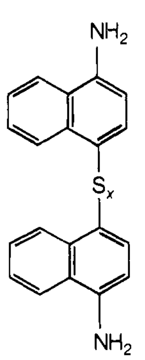


**Figure 13.** Correlation of shift gradients with $(3 \cos^2 \theta - 1)r^{-3}$ and $r^{-2}$. Full circles (upper abscissa): $r$ values refer to separation of hydrogen nucleus from lone-pair periphery of the 2-hydroxyl group.[81] Open circles (lower abscissa): $r$ values refer to the separation of hydrogen nucleus from the optimized position of the europium atom.[145]

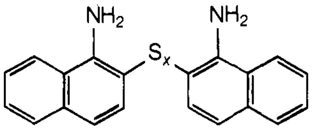
Despite the gross approximations made in this latter method, the agreement between calculated and experimental data compares favorably with the precision achieved using the computerized approach including the angle factor (see Figure 13).

## 2. *Use of Model Compounds*

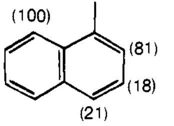
1-Naphthylamine and sulfur react to give a bis(1-aminonaphthalene) trisulfide, which is converted into a disulfide on treatment with triethyl phosphite.[160] The nmr spectra of these two sulfides are consistent with either of two isomeric structures, **5** and **6**. To distinguish between these possibilities, the LIS spectra (with Eu(thd)$_3$) of the sulfides, 1-naphthylamine, and 4-chloro-1-naphthylamine were compared. The absolute values of the shift gradients for specific protons vary from one molecule to another, as electronic and steric interactions lead to changes in the binding constants. However, the relative induced shifts are in close agreement for the two model compounds **7** and **8** (figures in parentheses are shift gradients (Eu(thd)$_3$ in CDCl$_3$) relative to a value of 100 ppm for the 8 proton). The AB system of the disulfide gave LIS relative to the 8 hydrogen of 19 and 18%, clearly consistent with these being the 3 and 4 hydrogens of the substituted benzenoid ring. Subsequent chemical conversion confirmed that the sulfur bridge linked the naphthalene rings at each 2 position.



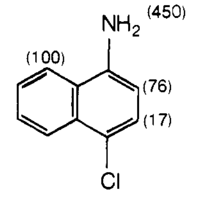
**5**



**6**, $x = 2, 3$



**7**



**8**

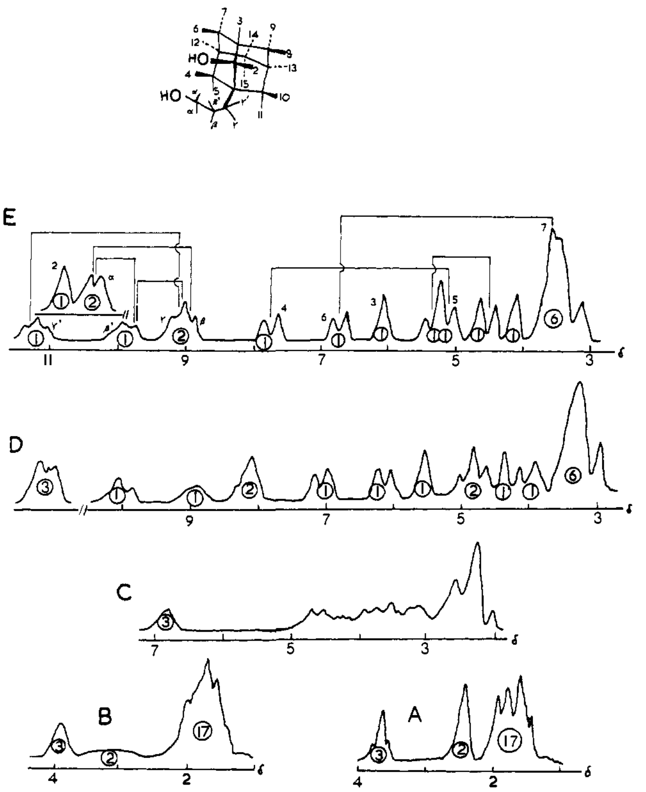


**Figure 14.** Pmr spectra of 1-(3-hydroxypropyl)-2-hydroxyadamantane with varying amounts of Eu(thd)$_3$ in CDCl$_3$ at 33°.[161] The Eu(thd)$_3$/substrate ratios are as follows: A, only substrate; B, 0.03; C, 0.27; D, 0.73; E, 0.82. The numbers in circles indicate the relative signal intensities. Assignments, where certain, are indicated on spectrum E, along with decoupled signals.

In using model compounds as outlined above to aid interpretation of LIS spectra, the following assumptions are made: (i) the effect of variation in binding constant is factorized out by using shifts referenced to a common "internal" hydrogen rather than using shift gradients, and (ii) the $g$ tensor and other coefficients of eq 3 differ insignificantly between the model compound and the unknown.

A slightly modified use of model compounds concerns the use of shift gradients for a series of known adamantanols to aid spectral assignment of 1-(3-hydroxypropyl)-2-hydroxyadamantane.[161] All the spectra were recorded using similar concentrations of the substrates to which increments of Eu(thd)$_3$ were added. The shift gradients for the model compounds were calculated and plotted against the distance of each proton from the lone-pair periphery of the hydroxyl group. The LIS spectra of 1-(3-hydroxypropyl)-2-hydroxyadamantane are shown in Figure 14, and, from the relative intensities of the signals and decoupling experiments, it was possible to assign resonances for the side-chain protons and the 2, 3, 4, and 6 protons of the adamantane nucleus. For all of these assigned protons, the shift gradients were calculated and converted into distances of the nucleus from the lone-pair periphery by reference to the log $G$ against log $r$ graph based on the model compounds. Bond spacers equivalent to these distances were then positioned on a framework molecular model as shown in Figure 15 to enable location of the position of the europium atom as referenced to the lone-pair periphery of the coordinating oxygen.

Finally, measurements of the distance from this point to each of the unassigned nuclei were made, and refer-

**TABLE V. Comparison of Predicted and Observed Pmr Spectra of 1-(3-Hydroxypropyl)-2-hydroxyadamantane with Eu(thd)$_3$**

| H[a] | $\delta$[b] | G(Eu(thd)$_3$)[c] | $r$, Å[d] | $\delta_{\text{calcd}}$[e] | $\delta_{\text{obsd}}$[f] |
|---|---|---|---|---|---|
| $\alpha$ | | 11.93 | 3.24 | 13.5 | 13.5 |
| $\beta'$ | | 10.57 | 3.44 | 10.1 | 10.1 |
| $\beta$ | | 8.70 | 3.75 | 9.2 | 9.2 |
| $\gamma'$ | | 11.95 | 3.24 | 11.4 | 11.4 |
| $\gamma$ | | 8.70 | 3.75 | 9.2 | 9.2 |
| 2 | | 12.30 | 3.19 | 13.9 | 13.9 |
| 3 | 1.90 | 5.47 | 4.81 | 6.15 | 6.15 |
| 4 | 1.66 | 7.40 | 4.14 | 7.78 | 7.78 |
| 6 | 1.73 | 6.13 | 4.55 | 6.78 | 6.78 |
| 5 | 1.60 | 4.44 | 5.35 | 5.25 | 5.15 |
| 7 | 1.67 | 3.11 | 6.40 | 4.2 | 3.9 |
| 8 | 1.67 | 3.32 | 6.20 | 4.3 | 3.4–4.0 |
| 9 | 1.74 | 2.65 | 6.95 | 3.9 | 3.4–4.0 |
| 10 | 1.67 | 4.54 | 5.30 | 5.4 | 5.45 |
| 11 | 1.60 | 3.54 | 6.00 | 4.5 | 4.60 |
| 12 | 1.86 | 2.99 | 6.55 | 4.3 | 4.20 |
| 13 | 1.86 | 2.42 | 7.30 | 3.85 | 3.4–4.0 |
| 14 | 1.68 | 2.27 | 7.55 | 3.55 | 3.4–4.0 |
| 15 | 1.68 | 2.15 | 7.75 | 3.44 | 3.4–4.0 |

[a] Numbers refer to the diagram in Figure 13. [b] Estimated from interpolated shift gradients or approximated to average values observed for corresponding protons in 2-adamantanol and 1-(3-hydroxypropyl)-adamantane (*cf.* ref 153). [c] Induced shift gradients, experimental values above the line, estimated values from reference to the log *G vs.* log *r* graph for model compounds for results below the line. [d] Distance from "periphery" of the lone pair of the complexing hydroxyls to each hydrogen nucleus. Values above the line obtained from the *G* values by reference to the log *G vs.* log *r* graph for model compounds. Values below the line, measured as indicated in *Figure* 14. [e] $\delta_{\text{calcd}} = \delta + G(\text{Eu(thd)}_3) \times 0.82$. [f] See Figure 13, spectrum E. Solvent, CDCl$_3$; Eu(thd)$_3$/substrate = 0.82.

ence again to the log *G* against log *r* graph enabled completion of the assignment. The good agreement between experimental and calculated spectra is shown in Table V. In an earlier report, a similar procedure was described to enable interpretation of the spectra of 1-(2-hydroxyethyl)-2-hydroxyadamantane.[153]

In the above procedure, the possible effect of binding constant variation among the model compounds and the unknown has been ignored. It is possibly fortuitous in the present case as the hydroxyl group binds strongly with the LSR. However, for weaker donors, this assumption may no longer hold, and an internal referencing approach may be required. For both diols mentioned above, the nonequivalence of the protons of the $\beta$-methylene (and in one case also the $\gamma$-methylene) provides good evidence for restricted rotation of the side chain, presumably arising because of chelation of the two hydroxyls to the europium atom in the complex (*cf.* section VIII.B.1). Thus, the conformations of the side chains differ from diol to the monofunctional (model) alcohol as indicated by Sanders, Hanson, and Williams' calculations.[76]

Although a number of gross assumptions and approximations are required in using model compounds to aid interpretation of LIS spectra, the results in many cases are very gratifying and enable the solution of spectra, which often are not amenable to a full analysis using the pseudocontact equation.

## *VII. Application of LSR to Simplify the Pmr Spectra of Monofunctional Compounds*

### A. Introductory Comments

LSR have been used on many occasions to enable the simplification of the pmr spectra of organic compounds possessing only one Lewis base group. Most often, the donor atoms are oxygen or nitrogen, typical functional groups including OH (alcohols, phenols, oximes), C═O (ketones, aldehydes, esters, amides, lactams, and ureas), C-O-C (ethers, epoxides), X$^{\delta+}$-O$^{\delta-}$ (nitrones, N-oxides, sulfoxides, phosphine oxides), NH (amines, imines), ═N- (aza heterocyclics), and -CN. Examples of sulfur as the donor atom include thioamides and thiocarbonyls.

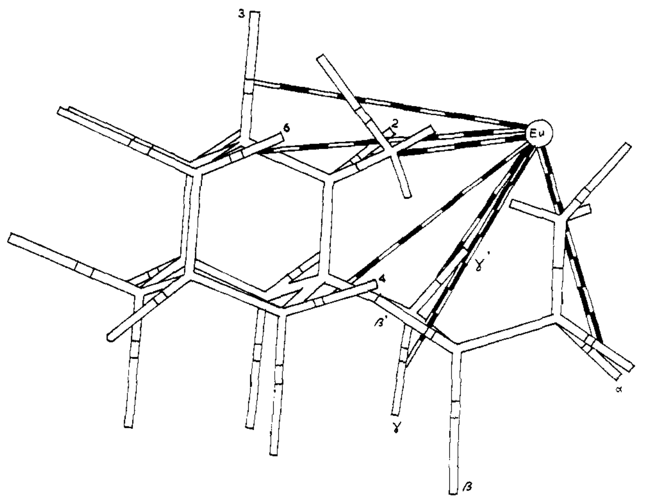


Figure 15. Framework molecular model showing the position of the Eu atom relative to the protons of 1-(3-hydroxypropyl)-2-hydroxyadamantane.[161] Bond spacers, representing the calculated distance of each assigned proton from the "europium atom" are indicated by the striped lines.

### B. Erroneous Deductions from Coupling Constants

Before discussing the particular advantages of LSR in simplifying the nmr spectra of compounds containing specific functional groups, we feel it is imperative to consider the limitations in using coupling constants derived from LIS experiments in conformational analysis. One of the attractive features of LIS is that increased separation of resonances leads to a simple first-order analysis of coupling constants in many cases. However, it should be remembered that the values obtained reflect the conformation of the substrate averaged between its free and complexed forms. In some instances, variations in coupling constant with the ratio LSR/substrate have been reported, which are not always attributable to the electronic effect of the LSR.

Shapiro and his coworkers have noted a slight increase in the magnitude of the geminal coupling constants for the protons, indicated in formulas **9** and **10**, with increasing molar ratio of LSR/substrate.[176] This increase is more pronounced with Eu(fod)$_3$ than Eu(thd)$_3$, reflecting the greater electron-withdrawing effect of the stronger Lewis acid. Liu has observed similarly small increases in the geminal and vicinal coupling constants with Eu(fod)$_3$ for **11**.[165]

The coupling constants of the aromatic hydrogens of **12** and **13** have been calculated from high resolution spectra (220 MHz, AA'BB'; 300 MHz, ABCD, respectively) and from Eu(thd)$_3$ induced shifted spectra at 60 MHz (AA'XX' and AMXY, respectively).[166] Computative analysis gave values for the two methods, which differed by more than the experimental uncertainties. Clearly, complexing of Eu(thd)$_3$ to the hydroxyl groups affects the ab-

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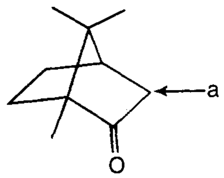
(164) C. S. Ee and R. A. Jones, *Tetrahedron*, **28**, 2871 (1972).

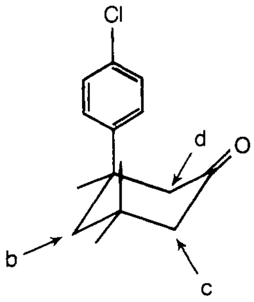
(165) K.-T. Liu, *Tetrahedron Lett.*, 5039 (1972).

(166) T. B. Patrick and P. H. Patrick, *J. Amer. Chem. Soc.*, **94**, 6230 (1972).

solute values of the aromatic coupling constants, but the mechanism of action is somewhat obscure.

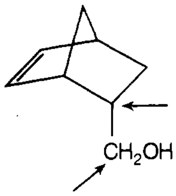


**9**

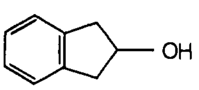


**10**

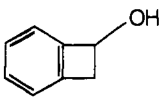
| | Eu(thd)$_3$/substrate | | | Eu(fod)$_3$/substrate | |
|---|---|---|---|---|---|
| | 0 | 0.25 | 0.75 | 0.25 | 0.75 |
| $J^a_{HH}$ | −17.7 | −18.11 | −18.84 | −18.54 | −19.64 |
| $J^b_{HH}$ | −14.02 | −14.14 | −14.08 | −14.22 | . . . |
| $J^c_{HH}$ | . . . . | −13.38 | −14.05 | −13.74 | −14.26 |
| $J^d_{HH}$ | −13.72 | −13.84 | −14.13 | −14.12 | −14.70 |



**11**

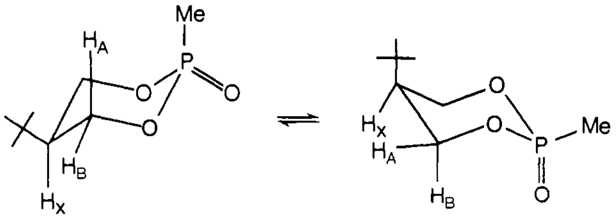


**12**



**13**

The conformational equilibrium involving **14** and **15** is influenced by added Eu(fod)$_3$.[167] Coordination occurs at the phosphoryl oxygen,[168] too distant from the H$_A$ and H$_X$ protons to alter the magnitude of the coupling constant $J_{AX}$ by an electron-withdrawing effect. As the mole ratio of Eu(fod)$_3$/substrate is increased from 0 to 0.7, the magnitude of $J_{AX}$ decreases from 9.94 to 6.4, consistent with an increase in the equilibrium concentration of isomer **15** from 22 to 59%. This trend is not in accord with a steric factor and was attributed to the ability of Eu(fod)$_3$ to modify the electronic interactions involving the phosphoryl oxygen, thereby reducing its normal equatorial preference.[167] The change in $J_{AX}$ with the LSR concentration was monotonic, and consequently extrapolation of the equilibrium ratios to zero LSR enables a meaningful measure of the conformational preference of the uncomplexed substrate to be attained.



($J_{AX}$ = 11.15 Hz)
**14**

($J_{AX}$ = 3.2 Hz)
**15**

## C. LIS of Alcohols and Phenols

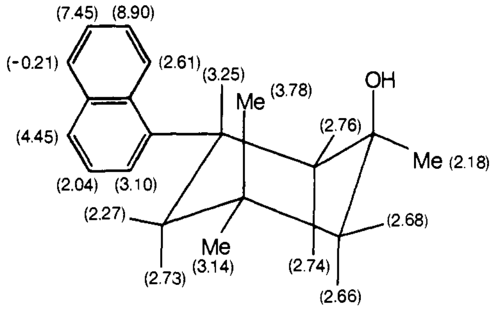
### 1. Selection of Solvent

Conventionally, CDCl$_3$ or CCl$_4$ has been used as the solvent for LIS studies, but recently a number of authors have shown that carbon disulfide offers certain advantages when the ligands are strong Lewis bases such as alcohols.[92,123,169] For example, the induced shifts (for Eu(thd)$_3$) for 1-hexanol are about 10% greater in CS$_2$ than in CDCl$_3$,[169] and low-temperature studies down to −60° are possible with minimal loss of resolution.[123] The fourfold greater solubility of Eu(thd)$_3$ in CS$_2$ compared with CDCl$_3$ has been assumed to explain these advantages,[169] but it seems more probable that the increased shifts arise from variations in the binding constants or changes in the monomer-dimer association constant for the LSR.

Carbon disulfide does not give enhanced shifts for LSR complexes with weaker Lewis bases (*e.g.*, esters) and cannot be used with certain amines and phosphines with which it reacts.[169]

### 2. Selection of Chelate

Both Eu(thd)$_3$ and Eu(fod)$_3$ have been used successfully on many occasions to simplify the pmr spectra of alcohols. Eu(fod)$_3$ is a stronger Lewis acid and is therefore expected to form stronger complexes with strong Lewis bases. In addition, bearing in mind the greater solubility of Eu(fod)$_3$ in CCl$_4$, larger induced shifts are expected for this reagent. However, the results of Shapiro and his coworkers (see **16**) are at variance with this prediction, at low [LSR]/[substrate] concentration, most protons exhibiting a two- to fourfold greater shift with Eu(thd)$_3$.[170] The other interesting feature of the results concerns the wide variability in the ratio of the induced shifts for the two LSR (note well: for the H-5 atom, the sign of the induced shift differs for the two reagents). Clearly, this observation indicates substantially different average geometries for the two complexes. The ratios of these induced shifts may not be typical for all alcohols owing to the encumbered environment of the hydroxyl group in **16**.



**16**

Figures in parentheses are ratios of *G*(Eu(thd)$_3$)/*G*(Eu(fod)$_3$) determined from the induced chemical shift (in CCl$_4$ relative to TMS) caused by a LSR/substrate ratio of 0.4.[170]

### 3. Quantitative Estimation of Alcohol Mixtures

For the series of normal alcohols from C$_1$ to C$_7$, the *G*(Eu(thd)$_3$) values for the methyl resonances decrease regularly along the series (*e.g.*, 21.2 (methanol) to 0.93 (1-heptanol) in CDCl$_3$).[171] Using this information, Rabenstein was able to separate the methyl resonances and quantitate the alcohol components in the following approximately equimolar mixtures: C$_1$–C$_6$ normal alcohols, three isomeric pentanols, and 1-hexanol and 1-heptanol.

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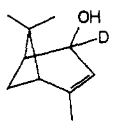
**TABLE VI. Deuterium Isotope Effects on the Induced Chemical Shifts of a Series of Alcohols**

| Deuterated substrate | LSR | $K_D/K_H$[a] | Ref |
|---|---|---|---|
| | $\alpha$ Substitution | | |
| $CH_3CHDOH$ | Eu(thd)$_3$·2py | 1.013 | 79 |
| $CH_3CD_2OH$ | Eu(thd)$_3$·2py | 1.025 | 79 |
| $CH_3CD(OH)CH_2CH_3$ | Eu(thd)$_3$·2py | 1.024 | 79 |
|  | Eu(thd)$_3$ | 1.022 | 79 |
| | Eu(thd)$_3$ | 1.023 | 122 |
| | Eu(thd)$_3$ | 1.026 | 79 |
| | $\beta$ Substitution | | |
| $CH_3CH_2C(CD_3)CH_3OH$ | Eu(thd)$_3$ | 1.035 | 122 |
| $(CH_3)_2CHC(CD_3)CH_3OH$ | Eu(thd)$_3$ | 1.035 | 122 |
| | $\gamma$ Substitution | | |
| $(CD_3)_2CHC(CH_3)_2OH$ | Eu(thd)$_3$ | 1.008 | 122 |

[a] Ratio of equilibrium constants for association of substrate and LSR, calculated from the observed ratios of the shift gradients, $G_D/G_H$.

### 4. *Classification of Steroids*

Buckley and his coworkers have used the relative induced shifts of the methyl protons as a fingerprint system for the 3-hydroxy steroids.[22] They normalized the shift gradients (Eu(thd)$_3$) for the fastest moving methyl to a value of 10. This procedure gives rise to a clear demarcation; *i.e.*, 3$\beta$-alcohols are characterized by normalized gradients of 10 (4$\beta$-Me), 9.4–9.8 (4$\alpha$-Me), 4.4–4.8 (10$\beta$-Me), 2.5–2.8 (8$\beta$-Me), whereas 3$\alpha$-alcohols give values of 10 (4$\alpha$-Me), 5.2–6.1 (4$\beta$-Me), 4.0–4.4 (10$\beta$-Me), 2.5–2.7 (8$\beta$-Me).

### 5. *Influence of Steric and Electronic Effects on the Complexing of Phenols*

The induced shifts for a series of 2-alkyl-substituted phenols are clearly dominated by steric rather than electronic considerations.[172] Phenols with p$K_a$ values less than 10 caused decomposition of the lanthanide chelate.

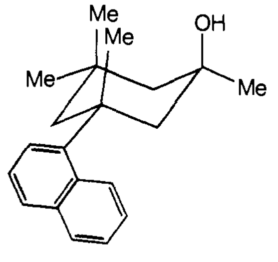
### 6. *Secondary Isotope Effects*

Secondary deuterium isotope effects on the induced chemical shifts have been measured for a series of alcohols (*cf.* Table VI).[78,79,122] The protic and deuterated samples were run simultaneously and the isotope effects were calculated from the ratios of the shift gradients for specific protons in the substrates. In all cases, the deuterated analog complexes more strongly with the LSR, and the isotope effect falls rapidly as the site of deuteration is more separated from the hydroxyl group. These observations are consistent with the smaller size[173] and greater electron-releasing inductive effect[174] of the C–D than C–H bond. The magnitude of the separation of the signals for the deuterated and protic substrates is at a maximum for a LSR/substrate ratio of 0.5. This method of measuring secondary isotope effects is very precise as the difference between the values of the isotopic equilibrium constants can be measured in a single experiment.

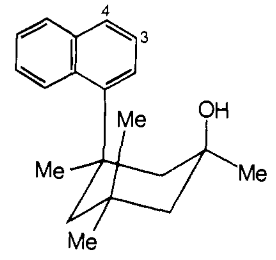
### 7. *Elucidation of Stereochemical Problems*

LSR are particularly useful in enabling a rapid distinction in many cases between corresponding cis and trans isomers. For example, the 8-methyl group in isoborneol gives a much steeper gradient ($G$(Eu(thd)$_3$ = 11 in $CDCl_3$) than that in borneol (4.4).[102] Assignments of the signals for all the other shifted proton resonances in these molecules were initially confirmed using distance calculations only ($r^{-2}$ method; see section VI.C.1),[102] and have since been verified using the equation describing the dipolar interaction (eq 4, section V.F).[142] Tori and his coworkers[175] have used the known relative shift gradients in substituted borneols to derive the position of deuterium substitution.

Classic differences are apparent between the LIS spectra of the trans and cis isomers **17** and **18** with Eu(thd)$_3$.[14] The shift gradient is much steeper for the $\alpha$-methyl group in **18** than in **17**, presumably because the presence of the axially situated $\alpha$-naphthyl group in **18** causes the LSR to coordinate with the hydroxyl much closer to this methyl group. More contrasting is the observation of upfield induced shifts for the 3 and 4 hydrogens of **18** (cf. Figure 2, section II.A), because the angle factor of eq 4 exceeds 54.7°.



**17**



**18**

There are many other examples of the application of LSR to structural elucidation of alcohols, which may be summarized under the classes of compounds studied as follows: simple aliphatic alcohols (ref 9, 21, 59, 62, 77, 109, 141, 181–186, 394) cyclohexanol derivatives (ref 150, 162, 185, 187), borneol analogs (ref 101, 144, 159, 188, 189), adamantanols (ref 81, 108, 112, 153, 371, 392), steroids (ref 9, 106, 121, 190), terpenes and precursors (ref 190–194), and miscellaneous alicyclic substrates (ref 81, 195–203, 372, 387, 390, 396).

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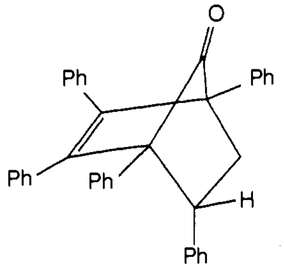
## D. LIS Spectra of Oximes

LSR enable facile separation of the pmr spectra of syn and anti isomers.[204,205] Wolkowski has explained the induced shifts in terms of complexing on the oxygen atom, because correlations of log $G$ against log $r$ (distance from the oxygen to each hydrogen nucleus) for a series of aliphatic and alicyclic oximes give slopes approximating to $-3$.[204] On the other hand, Berlin and Rengaraju[205] deduced coordination involved the nitrogen atom, as protons in the anti isomers experienced greater induced shifts than those in the syn isomers. For the syn and anti oximes of methyl ethyl ketone, the two groups reported completely different relative induced shifts. Wolkowski measured his induced shifts in $CCl_4$ with the LSR $\leq$ substrate, whereas the other workers used 2 $M$ solutions of the oxime mixtures in $CDCl_3$ with the LSR $\ll$ substrate. Clearly, these latter conditions could give rise to substrate association and LSR complexes involving more than one substrate molecule.

## E. LIS Spectra of Carbonyl Compounds

### 1. *Ketones and Aldehydes*

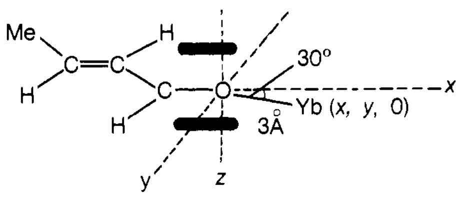
Carbonyl compounds complex much less strongly than hydroxyl compounds with LSR.[206] Typical equilibrium binding constants with Eu(thd)$_3$ for unhindered secondary alcohols range from 500 to 1000, whereas for cyclohexanone and methyl pivalate, values varying from 180 to 250 and 100 to 150, respectively, have been reported.[76] The sterically hindered ketone **19** does not complex with Eu(thd)$_3$.[76] Other than having greater solubility (which enables a greater concentration of LSR to be achieved and hence a greater total induced shift), Eu(fod)$_3$ does not appear to offer any advantage over Eu(thd)$_3$ as a shift reagent for ketones, similar induced shifts being observed with both reagents for 3,5,5-trimethyl-3-(*p*-chlorophenyl)cyclohexanone and 3,5,5-trimethyl-3-(1-naphthyl)cyclohexanone.[170]



**19**

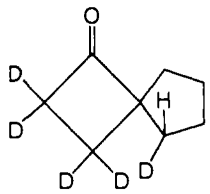
The induced shifts for the methylene hydrogens for a series of alicyclic ketones ($C_5$ to $C_{15}$) generally decrease in a monotonic fashion with increasing separation of the methylene and carbonyl groups.[135,207] The only significant exception is cyclooctanone, in which the transannular separation of the $\delta$ $CH_2$ and carbonyl group is minimal owing to ring buckling, and, consequently, the induced shifts are greater for the $\delta$ $CH_2$ than the $\gamma$ $CH_2$ and even the $\beta$ $CH_2$. For the alicyclic ketones and 2-adamantanone the variation ($< \pm 30\%$) in the ratios $G(\mathrm{Pr})/G(\mathrm{Eu})$, for all hydrogens in a given molecule, was considered to indicate minimal contact interactions for the hydrogens adjacent to the carbonyl group.[135]

In the ground state of the carbonyl group, the oxygen atom carries two lone pairs: in the $2p_y$ orbitals, located perpendicularly to the $\pi$ bond, and in the extended C–O axis as an sp hybrid.[208] Either of these orbitals may be involved in coordination to the lanthanide ion. Approximate calculations of induced chemical shifts in which the angle factor is neglected result in the location of the lanthanide ion at an angle to the extended C–O axis (*e.g.*, **20**[151]).[39,77,208] However, consideration of the angle contribution to the dipolar interaction usually results in location of the lanthanide ion along the extended C–O axis.[151]

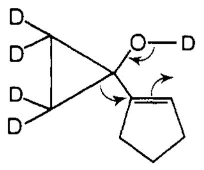


**20**

Of a number of examples involving shift reagents in structural elucidations of carbonyl compounds (ref 52, 60, 75, 116, 178, 209–214, 369, 388, 410), an interesting application concerns the verification of structure **21**, the product of an intramolecular stereospecific cis addition to the olefinic double bond of **22**.[215]



**21**



**22**

### 2. *Esters and Lactones*

Esters are weaker Lewis bases than ketones toward LSR,[77] the preferred coordination site being the carbonyl oxygen. For this reason, the stronger Lewis acid Eu(fod)$_3$ was initially employed for the simplification of the spectra of simple esters.[53] Later work has revealed that an ester analog of **16** experiences induced shifts whose magnitude is two to three times greater with Eu(thd)$_3$ than with Eu(fod)$_3$.[170]

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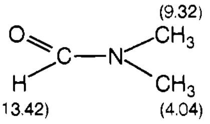
Applications of LSR for studies involving esters and lactones parallel those already mentioned in the preceding sections, *e.g.*, spectrum simplification,[124,192,201,216,386,397] geometrical[192] and conformational isomerism,[217,218,224] and deuterium location in methyl 3-ethylhexanoate.[219]

Inbushi and his coworkers have used two monoesters of triterpenes related to serratenediol as model compounds for their quantitative estimations of complexing at each site in polyacetoxytriterpenes.[220] It has also been possible to estimate the extent of the iodine-catalyzed isomerization of vitamin A acetate from the Eu(thd)$_3$ shifted spectra of the reaction product.[221-223]

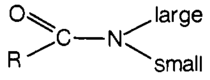
### 3. *Amides and Lactams*

Coordination of LSR to amides and lactams involves the carbonyl oxygen rather than the nitrogen atom. The shift gradients are larger for the *N*-methyl groups cis-related to the carbonyl (*cf.* **23** with Eu(fod)$_3$), whereas similar shift gradients would be expected if coordination involved the nitrogen atom.[226] Other amide complexes are known to involve coordination on the oxygen atom, *e.g.*, with iodine,[256] protonation.[257]

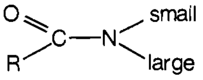


**23** (*G* values in parentheses)

Delocalization of the nitrogen lone pair under the electron-withdrawing influence of the carbonyl group gives rise to partial double-bond character of the C-N bond, and thus the existence of the *Z* and *E* rotamers (*cf.* **24** and **25**).[258] LSR offer an attractive alternative to earlier methods (coupling constants, ASIS, NOE) for determining the rotamer ratios.



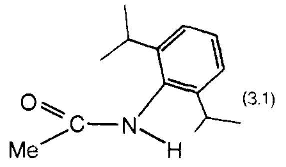
*Z* rotamer
**24**



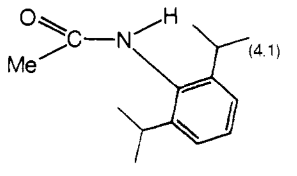
*E* rotamer
**25**

In the absence of steric hindrance, groups cis to the carbonyl experience a larger induced shift than their trans counterparts.[225,226] This situation may be reversed when bulky groups are present, *e.g.*, addition of Eu(thd)$_3$ to 2,6-diisopropylacetanilide (**26**, **27**).[18] The magnitude of the induced shifts is decreased, because of steric factors, if groups larger than acetyl are present.[227]

Work on simple amides and lactams has shown that coordination of LSR can cause a large change in the rotamer ratio;[18,228] *e.g.*, the ratio of **26**/**27** changes from 2:1 to 1:2 upon addition of an equimolar amount of Eu(thd)$_3$.[18] This can be attributed to steric hindrance between the complexing LSR and the bulky aryl group which destabilizes **26** in favor of **27**.[228] For amides with more equally bulky N substituents, no change in rotamer population is found.[391]



**26**



**27**

(gradients in parentheses refer to the methine protons)

Increase in the coalescence temperature of cis and trans amides on complexation with LSR has been attributed to the increased electron-withdrawing power of the complexed carbonyl and/or increased peak separations for the rotamers.[91,228,229]

Other papers concern the applications of LSR to *N*-isopropylamides[230] and to lactam-bridged homotropylidines.[231]

## F. LIS of Ethers and Epoxides

Although ethers are generally regarded as very poor donors toward LSR, the work of Hart and Love[232] has shown that they may compete effectively with esters and ketones; *e.g.*, for an equimolar mixture of tetrahydrofuran and acetone with Eu(thd)$_3$ 90% complexing to the ether function is indicated. When the ether oxygen lone pair is delocalized into an extended $\pi$ system, complexing becomes very weak. For Yb(thd)$_3$, the shift gradients for the $\alpha$ protons of THF are 100 times greater than those for the 2 protons of furan.[233]

The relative merits of Eu(thd)$_3$ and Eu(fod)$_3$ have been discussed.[53,170] Di(*n*-butyl) ether shows enhanced shifts with the stronger Lewis acid with much superior resolution of the multiplets,[53] but for THF the thd reagent induces slightly larger downfield shifts.[170] The need for considering the angle contribution to the dipolar interaction emerges from a study of the shifts induced by Eu(thd)$_3$ with some naphthalene and norbornadiene oxides.[138] The standard deviation between the experimental and the calculated results is decreased by five to ten times when the angle factor is included.

The efficacy of a number of europium chelates as LSR have been compared with di (*n*-butyl) ether. The ligand decafluoroheptanedione (**28**) is a stronger Lewis acid than fod and has fewer interfering ligand proton absorptions. The corresponding europium complex has greater chloroform solubility and induces larger shifts in protons remote from the coordination site.[234] Europium complexes with chelates **29** and **30** fall between Eu(fod)$_3$ and Eu(thd)$_3$ in acidity and relative shifting power.[75]

$F_5C_2COCH_2COC_2F_5$
**28**

$F_3CCOCH_2COBu\text{-}t$
**29**

$F_5C_2COCH_2COBu\text{-}t$
**30**

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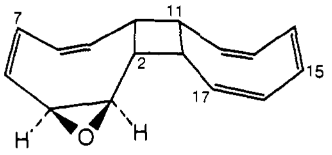
Using measurements to the oxygen atom, the structures of two bridged homotropylidenes and the epoxide **31** have been established.[19] The H-15 and H-16 atoms, which exhibit upfield shifts ($Eu(thd)_3$), were excluded from the calculation, and the remaining induced shifts correlate in a linear manner ($\Delta\nu_i \propto r_i^{-2.22}$) only for the syn isomer shown. The epoxide group is an ideal function for shift calculations because of its rigid nature.



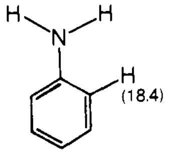
**31**

Other examples include structural elucidations of pesticides and their metabolites[206,235] and aliphatic and alicyclic ethers.[124,236-238,389,406]

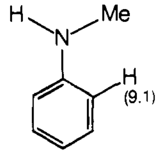
## G. LIS of Compounds with Nitrogen-Atom Donors

### 1. Amines

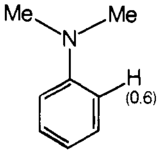
In the absence of steric hindrance, the magnitude of the induced shifts may be directly related to the basicity of the amine donor. The size of the induced shifts for a series of para-substituted anilines is excellently correlated by the Hammett equation.[84] Weakly basic amines such as pyrrole give drastically attenuated induced shifts.[233] The importance of steric effects is clearly demonstrated by the drastic fall in the magnitude of the induced shifts for the ortho protons along the series **32** → **33** → **34**, despite the actual increase in basicity of 0.5 p*K* unit along the same series.[233,239] In quinuclidines, the nitrogen lone pair is readily accessible to the lanthanide atom, and large induced shifts are observed.[233]



**32**



**33**



**34**

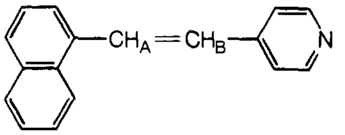
Considerable care must be exercised when interpreting the shifts induced in anilines and analogs, because of the possibility of contact interactions. Large contact contributions occur in aniline and *p*-toluidine, the effect being most apparent for the $Eu(fod)_3$ reagent.[240] By contrast, $Pr(fod)_3$ and $Eu(thd)_3$ show little evidence for contact shifts, the results being interpretable in terms of dipolar interactions alone.

Other applications of LSR include structural and stereochemical assignments of aminopinanes,[164] steroids,[241] cyclohexanes,[155] norbornenes,[163] decahydroquinoline,[365] and 1-aminoadamantane.[366,392]

### 2. Aza Heterocyclic Compounds

Much of the discussion regarding interactions of LSR with aza heterocyclics has been concerned with the controversy surrounding the relative contributions of the contact and dipolar contributions to the observed induced shifts. Reuben and Leigh have shown that the induced shifts for the protons of pyridine and quinoline in complexes with $Eu(thd)_3$ can be accounted for mainly in terms of dipolar interactions.[33] On the other hand, other workers have demonstrated significant contact contributions to the induced $^{13}C$ shifts of quinoline, particularly when $Eu(fod)_3$ was used.[136]

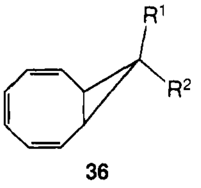
Qualitative observations on the shifts induced in pyridines and quinolines[77,111,139] have been made, and $Eu(thd)_3$ has been used to identify separately the cis and trans isomers of the pyridine derivative **35.**[98] The authors suggested that the $H_A$ resonance of the trans isomer occurs to *ca.* $\delta$ 1 to high field of the $H_B$ resonance in the uncomplexed substrate. Crossing of the resonances ($G$ for $H_A > G$ for $H_B$), in the presence of the LSR, was attributed to the greater proximity of $H_A$ to the lanthanide atom. However, our measurements on Dreiding models show $H_A$ and $H_B$ to be equidistant from the nitrogen donor. In addition, use of the additive shielding increments derived by us for the $\alpha$-naphthyl and $\gamma$-pyridyl substituents[259] clearly leads to the prediction that the $H_A$ resonance should occur about $\delta$ 0.9 to low field of $H_B$, reversing the previous assignment. Consequently, it is the $H_B$ signal which is more dramatically influenced by addition of the shift reagent. This result may be rationalized in terms of a smaller angle factor for $H_B$ than $H_A$ and/or consideration of the contact contribution to the observed induced shift, two factors which were ignored by the previous authors.



**35**

### 3. Nitriles

Nitriles are very weak donors and only small LIS are observed; *e.g.*, for protons $\alpha$ to the CN group, $G(Yb(thd)_3)$ values vary from 5 to 12.[229] Even so, $Eu(thd)_3$ has been used successfully to enable distinction between the *cis*- and *trans*-bicyclo[6.1.0]nonatriene derivatives (**36**) and their thermolysis products.[242] The ketenimine group (=C=NR) is an even weaker donor than the nitrile.[395]



**36**

$R^1$ = Me, $R^2$ = CN
$R^1$ = CN, $R^2$ = Me

## H. Miscellaneous Functional Groups

### 1. Phosphorus-Containing Groups

LSR complex strongly with substrates containing the P=O group, and they have been used in the solution of stereochemical problems concerning cis/trans phosphetane oxides (**37, 38**),[243] phosphine oxides,[181,244] phos-

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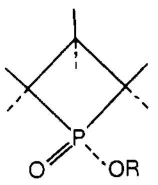
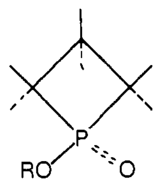

**37**

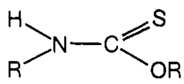

**38**

phonates, phosphole oxides, and phospholene oxides.[245]

Replacement of P═O by P═S results in a dramatic attenuation of the induced shifts, as demonstrated in the phosphetane sulfide analogs of **37** and **38**, which give insoluble europium complexes. Similarly, the phosphonates $(RO)_2(P{=}O)OMe$ give significant induced shifts with $Eu(thd)_3$ ($G$ = 8.5 for the OMe group), but no measureable changes are observed for the phosphorothionates, $(RO)_2(P{=}S)OR$.[227]

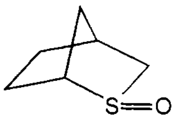
### 2. *Sulfur-Containing Groups*

Replacement of C═O by C═S invariably leads to a decrease in LIS, but the spectrum simplification remains adequate for a number of problems. However, under conditions where all the protons of ethyl acetate experience considerable induced shifts, no changes in the spectrum are noted for *O*-ethyl thioacetate.[246] For thionocarbamate esters, the preferred coordination site is the sulfur atom. Large induced shifts ($Eu(thd)_3$ in $CCl_4$) are noted for the *E* isomer **39**, but little spectral change occurs for the *Z* isomer, a result attributed to steric hindrance by the cis-related alkyl group to complex formation.[246] The rotamer ratio is unaffected by addition of the LSR, in contrast with Siddall's observation for 2,6-diisopropylacetanilide.[18] The induced shifts for a number of thioamides are consistent with complexing involving the sulfur atom.[152,225]


*E* isomer

**39**, R = Me or *t*-Bu, R$^1$ = Me or *t*-Bu

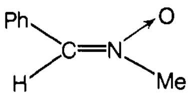
Sulfoxides and sulfones complex readily *via* the oxygen atom, and induced shifts as large as those observed for simple alcohols have been reported.[63] The free and complexed forms of DMSO have been observed in a low-temperature study with $Eu(fod)_3$-$d_{27}$.[90] Spectrum simplification of dialkyl and arylalkyl sulfoxides with $Eu(thd)_3$ clearly shows the diastereotopic nature of the $\alpha$- and $\beta$-methylene functions.[63] The endo/exo sulfoxide ratio for the bicyclic compound **40** has been measured using LSR in combination with selective deuteration techniques.[17,247] LSR provide an easy means of assessing *E*/*Z* geometrical isomer ratios in certain sulfines, in good agreement with ASIS (which are 4–30 times smaller[405]).

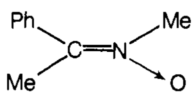

**40**

### 3. *Nitrone and Nitro Groups*

The N→O group in nitrones and *N*-oxides behaves as a powerful donor toward LSR and has been compared with an aliphatic hydroxy group in terms of induced shift magnitudes.[111] The spectra of the syn and anti nitrones **41** and **42** are easily analyzed with the aid of $Eu(thd)_3$ and subsequent application of the expression describing the dipolar interactions.[140] The spectra of the *N*-oxides of pyridine and quinoline have also been simplified by LSR.[111,240]

Nitro groups show virtually no tendency to complex with LSR, and nitromethane has been used as the solvent and reference for the study of $^{14}N$-induced shifts (*cf.* section IV.B).[67,229]

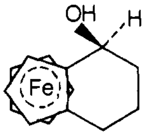

**41**


**42**

### 4. *Organometallic Compounds*

The organotin carbinol $Ph(Me)_2Sn(CH_2)_2CH(Me)OH$ shows diastereotopic methyl groups ($\Delta\delta$ = 0.005 ppm), whose separation is increased on the addition of $Eu(thd)_3$ ($\Delta\delta_{max}$ = 0.046 ppm). Measurement of various $J(^{117/119}Sn\text{-}H)$ proton coupling constants is possible in the shifted spectra.[248]

In the presence of $Eu(thd)_3$, several hydroxy and keto ferrocenes (*e.g.*, the hydroxytetramethylene ferrocene, **43**) give spectra which simplify sufficiently for the determination of ring substitution and endo/exo isomerization.[249]


**43**

## I. LIS of Nuclei Other Than Hydrogen

LSR do not offer such outstanding advantages regarding "spectrum spreading" in the case of nuclei like $^{13}C$, $^{19}F$, or $^{31}P$, because these are characterized by an inherently larger range of chemical shift values. Nevertheless, useful structural information is afforded by nuclei experiencing mainly dipolar induced shifts. Nuclei experiencing largely or wholly contact interactions ($^{14}N$, $^{31}P$) give unpredictable LIS.

### 1. *$^{13}C$ Magnetic Resonance*

The satisfactory analysis of the LIS ($Pr(thd)_3$) for the $^{13}C$ and $^{1}H$ nuclei of borneol in terms of dipolar interactions has been outlined previously (see sections IV.B, VI.B.2, Figure 12). An unexpected change in the relative sign of the LIS of the $\beta$ carbon of a number of simple aliphatic amines has been reported (Table VII).[20] A similar sign reversal, attributable to contact interactions, has been noted for $Ni(acac)_2$ complexes.[250] In contrast, the induced shifts for the protons accord with the expected dipolar interaction,[20] as also do the $^{13}C$ induced shifts of 1-butanol.[20] This may indicate that significant contact interactions involving $^{13}C$ atoms are restricted to the strongest Lewis bases. Clearly, if quantitative structural predictions are required, alcohols appear to be preferential donors to amines.

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**TABLE VII. $^{13}C$ and $^{1}H$ Induced Shifts of Aliphatic Amines**

| Amine | Atom | α | β | γ | δ | Ref |
|---|---|---|---|---|---|---|
| *n*-BuNH$_2$ | $^{13}C$ | −16.72 | 2.16 | −1.61 | −1.30 | 20[a] |
| | $^{1}H$ | −4.95 | −3.14 | −1.79 | −0.95 | 20[a] |
| *n*-PrNH$_2$ | $^{13}C$ | −25.68 | 3.45 | −2.70 | | 20[a] |
| *n*-C$_5$H$_{11}$NH$_2$ | $^{13}C$ | −26.54 | 3.24 | −2.69 | −1.94 | 20[a] |
| Piperidine | $^{13}C$ | 10.00 | −16.00 | 2.00 | | 250[b] |
| *N*-Methylpiperidine | $^{13}C$ | 10.00 | −2.9 | 1.4 | | 250[b] |

[a] Solvent $CDCl_3$ with Eu(thd)$_3$; induced shifts for LSR/substrate = 0.4. [b] Solvent $CDCl_3$ with Ni(acac)$_2$; induced shifts relative to a value of 10.00 for the α carbon.

Contact effects would be expected to influence $^{13}C$ induced shifts in heteroaromatics (*e.g.*, pyridine[370]) and have clearly been demonstrated for the adjoining (C-2 and C-9) carbon nuclei in quinoline for which the contact contribution decreases along the series Eu(fod)$_3$ > Eu(thd)$_3$ ≫ Pr(fod)$_3$ > Pr(thd)$_3$.[136]

Gansow, *et al.*, have made an important contribution to $^{13}C$ spectroscopy. The alternately pulsed nmr method (apnmr)[251] combines much of the Overhauser enhancement of sensitivity on noise-decoupling with retention of information on $^{13}C$-$^{1}H$ coupling (and thus the identification of methyl, methylene, and methine carbon atoms). Elucidation of the $^{13}C$ spectrum of isoborneol with Eu(thd)$_3$ was greatly facilitated by apnmr.

Other compounds studied include alkylpropanols,[109] cyclopentanols,[252] cyclopentyl acetates,[252] cholesterol,[253] and a dioxolane derived from a cyclobutanone dimerization.[254] The reader is referred elsewhere for the discussion of the $^{13}C$ spectra of the alkaloid piperine (section VIII.B.5) and of nucleotides (section IX.B).

### 2. *$^{14}N$ and $^{31}P$ Magnetic Resonance*

Extremely large LIS are observed for $^{14}N$ in various organic compounds; *e.g.*, dimethylformamide (*G*(Yb(thd)$_3$ in $CCl_4$ = −30 ppm, *G*(Eu(thd)$_3$ = 50 ppm), acetonitrile (−135, 490), *n*-propylamine (−340, 1600), pyrrolidine (−410, 1500), pyridine (1425, 1500), and *N*-methylimidazole (N-1, −10, 80; N-3, −205, 1400).[65] The larger induced shifts for the N-3 than the N-1 atom of the imidazole is consistent with complexing involving the less hindered and more basic N-3 atom. Line broadening above 4% LSR/substrate precludes signal identification (*cf.* Figure 6, section IV.B). In all the above examples, the $^{14}N$ induced shift is dominated by contact interactions.[76]

The factorization of the contact shift to the LIS of $^{31}P$ in diethyl phosphonate complexes with Pr(NO$_3$)$_3$·6D$_2$O has been described previously (section VI.B.1). Triphenylphosphine has been used as the internal standard for lanthanide nitrate complexes in hexadeuterioacetone.[76] However, in $CDCl_3$, the $^{31}P$ resonance of triphenylphosphine exhibits a small induced shift (relative to external phosphoric acid) upon addition of Eu(thd)$_3$.[255]

## *VIII. Interaction of LSR with Polyfunctional Molecules*

### A. General Comments

In like manner to monofunctional compounds, those possessing more than one potential coordinating group can yield useful additional nmr information when treated with LSR. Single groups possessing more than one potential donor atom have been discussed in section VII.

Applications of LSR for polyfunctional donors are very similar to (*cf.* (a) and (b) below) or an extension of those encountered in section VII: (a) simplification of second and higher order splitting patterns for facilitating the interpretation of complex spectra, (b) determination of isomer compositions and the stereochemistry of complex protic or partly deuterated molecules, (c) elucidation of polymer structures and their average molecular weights, and (d) enlarging our understanding of the mode of action and preferred sites of complexing of LSR.

The concept of soft and hard acids and bases[260] can be usefully applied to the interactions of soft or hard donor molecules with the hard europium (or lanthanide) ion.[261] This concept predicts stronger interactions, and, hence larger LIS, for hard over soft bases (*e.g.*, N and O rather than P and S). By analogy with section VII, we shall find that not only the extent of delocalization of the donor electron pair but also the inductive and steric effects of proximate groups decide the degree of complexing at competing sites in the donor molecule. A complication not encountered with monofunctional donors arises because the tris(β-diketonyl)lanthanide complexes can achieve a coordination number of 8 or 9 as in the highly stable lanthanide complexes, Ln(thd)$_3$·lig, where lig = 2,2′-dipyridyl or 1,10-phenanthroline.[68] Thus, it is possible for polyfunctional donors to complex at two sites simultaneously, behaving as another chelating ligand with concomitant shifts at both sites.

LIS of monofunctional donors have revealed the following order of donor power:[13,69] NH$_2$ > OH > ketones ≥ esters > ethers > thioethers > nitriles. This series can be extended by work on polyfunctional compounds, and our discussion of any particular polyfunctional compound will be found in the section concerning the stronger donor site in the molecule with cross-referencing to the weaker sites.

## B. Competitive Complexing of Functional Groups

### 1. *Hydroxyl Groups*

As aliphatic alcohols are among the strongest donors, whatever the competing donor, the maximum induced shift is almost invariably found for the protons nearest to the hydroxyl group.

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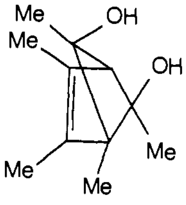
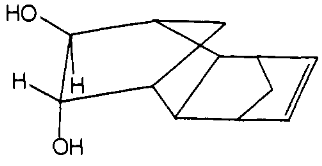
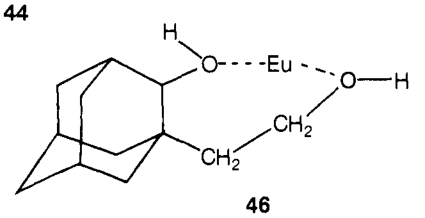
When the competing group is a symmetrically placed hydroxyl (*e.g.*, as in **44**[262] or in a bicyclo[3.3.1]nonanediol[206]), complexation to the two groups is identical and the only extra consideration may be chelation of both functions by a single lanthanide atom. For nonsymmetrical diols (*e.g.*, **45**[206]) we can anticipate a difference in complexing equilibria between the endo and exo hydroxyl groups of the trans isomer shown. This is borne out by the nonequivalence of nearly all of the protons induced by addition of Eu(thd)$_3$ and allows ready differentiation between diol **45** and its symmetrical cis isomer. If the hydroxyl groups of a diol are suitably placed, it may be possible for chelation to occur, and the nonequivalence of the alkyl side-chain protons in the adamantanediol **46** and the location of the europium atom on the line joining the two donor groups is consistent with this interpretation (*cf.* Figures 14, 15, section VI.C.2).



**44**



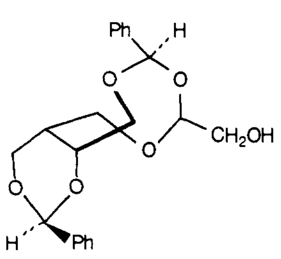
**45**



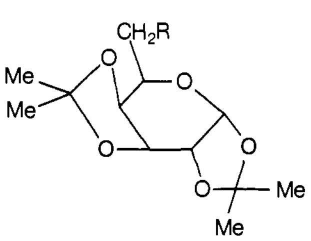
**46**

A major application of LSR concerns the simplification of the pmr spectra of carbohydrates and related pyrans, in which the chemical environment of many protons is similar. Work on pyranoside[263] and furanoside[264] carbohydrates has indicated that coordination to the LSR occurs wholly at the hydroxyl functions. The same conclusion was drawn to explain the expanded spectrum of **47**, which possesses five ether and only one hydroxyl oxygen.[96] Some authors have suggested slight competitive complexing occurs at the ether oxygens,[58,107,265] but the differences in the LIS spectra of the derivatives of **48** (R = OH, H) again accord with the hydroxyl group as the dominant donor. In the absence of model compounds, it is difficult to quantitate the relative donor contributions in aryloxyethanols[266] and a furanosesquiterpene.[267] The contribution of the furan oxygen in **49** is undoubtedly very small.[267]

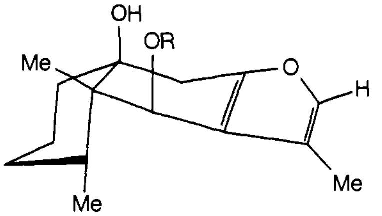
There is good evidence to show that some coordination occurs at the ester or lactone sites in limonoids[103] and, by $^{13}$C resonance, in a cyclobutanone dimer.[254] In three papers, the complexing, which is biased in favor of the hydroxyl group, has been dissected into contributions from each site, and these are discussed in more detail subsequently (section VIII.D).[76,156,268] Steroidal[269] and other ketones[270] (*e.g.*, **50**, **51**) show preferential complexing at a primary or secondary hydroxyl, but steric hindrance around tertiary hydroxyls enables complexing at the carbonyl group to become more competitive. In the interesting case of androstene (**51**) it is possible to protect the hydroxyl group by trifluoroacetylation or the keto group by dithiolane formation such that the derivative becomes virtually monofunctional toward LSR at the alternate site (*cf.* section VIII.D).[402]



**47**



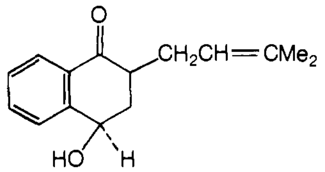
**48**



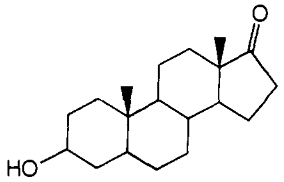
R = H, Me

**49**

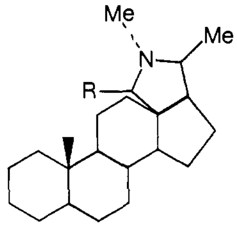
Examples of amino-hydroxyl bifunctionals are limited to tertiary amines (hydroxyconanine[271] (**52**a) and azetidinols[272]) where steric hindrance limits complexing exclusively to the hydroxyl group. In the aza heterocycle **53a,b**, it was found that the very nonbasic imidazole 3-nitrogen atom became a rather effective donor once the primary alcohol was almost totally complexed.[259]



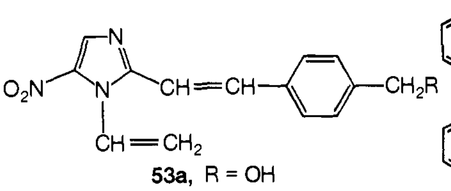
**50**



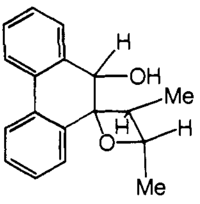
**51**



**52a**, R = OH
**b**, R = COCH$_3$



**53a**, R = OH
**b**, R = H



**54**

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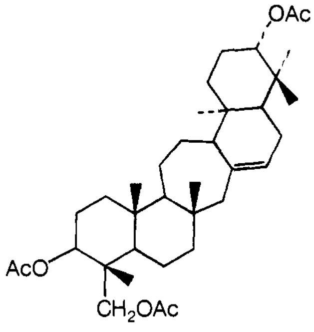
(271) G. Lukacs, X. Lusinchi, P. Girard, and H. Kagan, *Bull. Soc. Chim. Fr.*, 3200 (1971).

(272) T. Okutani, A. Morimoto, K. Kaneko, and K. Masuda, *Tetrahedron Lett.*, 1115 (1971).

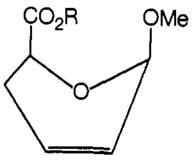
Only in a few cases to date has the donor property of a hydroxyl function been exceeded by competing groups. Farid[145] found that the hydroxyoxetane **54** coordinated preferentially through the ether site (LIS magnitudes decreased along the series $H^a > H^b > H^c$) and Girard's evidence on the series of pyranose sugars (**48**) suggests that the ester (R = COOMe) and the ether (R = $CH_2OMe$) complex more strongly than the alcohol (R = $CH_2OH$).

### 2. Esters and Lactones

There are reports on the behavior of substrates containing two or more ester groups in almost identical chemical environments (*e.g.*, in the bicyclononane,[273] nortricyclene,[274] or triglyceride[275] series) with useful simplification of the initially complex pmr spectra, and the LIS of the serratriol triacetate (**55**) have been carefully dissected into contributions from complexing at each of the three sites by reference to model monoacetates.[220]



**55**



**56**

There are many interesting reports of lanthanide induced chemical shifts of organic compounds possessing both ester and ether groups (see ref 58, 114, 264, 276, 277, and 409). In most cases (*e.g.*, **56**) the ester or lactone is the dominant coordinator, but the behavior of **56** at a mole ratio of LSR in excess of 1:1, and the significant shifts induced in the deacetoxy derivative of **56**, shows complexing to be of some importance at the ether oxygen. A very marked difference is seen between the cis and trans isomers of **56**, the relatively diminished shifts of the cis isomer being attributed to the severe steric hindrance to complex formation. The order of complexing has only been reversed in the case of lactarorufin (**3**, section VI.C.1) in which the ether and not the sterically hindered lactone appears to be the sole donor.[149] It is disappointing that the limited data for certain isogenines[278] and carotenoid pigments[279] (which contain a variety of ester, alcohol, lactone, and epoxide groups) do not permit a quantitative tabulation of the donor properties of the functional groups.

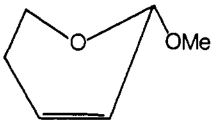
Esters and lactones compete rather unfavorably with a hydroxyl[76,103,254,268] until saturation of this stronger donor by the LSR is achieved. Trifluoroacetate esters[156,269] and, better, heptafluorobutyrate esters[161] are particularly good protecting groups for alcohols and are virtually inert toward LSR. Other examples in which an ester or lactone is the weaker of two donors are discussed under the sections concerning epoxides,[124] ketones,[280] amides and lactams,[281,282] nitrones,[16] aza heterocyclics,[283] and sulfur-containing groups.[284]

### 3. Ethers and Epoxides

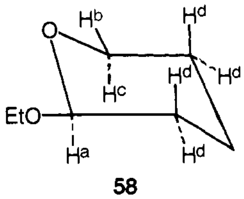
Examples in which ethers compete for LSR with stronger donors include alcohols (ref 58, 96, 107, 145, 254, 263, 265–267), esters (ref 58, 107, 254, 264, 265, 276), lactones,[114,149] ketones,[232,285-287] quinones,[288] amides,[54] lactams,[15,289,290] oximes,[291] nitrones,[16] cyclic amines,[232] and phosphoryl groups.[167,168] Coordination to the LSR only involves the ethereal function to a significant extent when the stronger Lewis bases are sterically hindered.[145,149] A number of examples involving the weakly donating furan group have been reported (ref 103, 114, 232, 267, 292).

For steric reasons, coordination to LSR involves the intracyclic and not the more basic exocyclic oxygen atom in **57** and **58**.[276,293,294,399] For example, in **58** the induced shifts decrease in the order $H^a = H^b > H^c > H^d > OCH_2Me$, thus establishing the stereochemistry of the saturated ring and showing the lower donor properties of the exocyclic ether. By contrast, Scharf has found that **59** forms a chelate with $Eu(thd)_3$ *via* the vicinal cis pair of methoxy groups.[295] In a bisphenol diglycidyl ether, complexing involves the epoxy rather than the exo ethereal oxygen.[408]

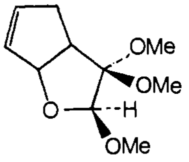
Ethers are invariably stronger donors than thioethers,[72,97,232] *e.g.*, **60**, in which approximately 70% of the LSR is coordinated to the oxygen, and **61**.[97] Surprisingly the



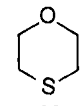
**57**



**58**



**59**



**60**

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(273) J. A. Peters, J. D. Remijnse, A. van Wiele, and H. Bekkum, *Tetrahedron Lett.*, 3065 (1971).

(274) B. Franzus, S. Wu, W. C. Baird, and M. L. Scheinbaum, *J. Org. Chem.*, **37**, 2759 (1972).

(275) P. E. Pfeffer and H. L. Rothbart, *Tetrahedron Lett.*, 2533 (1972).

(276) O. Achmatowicz, A. Ejchart, J. Jurczak, L. Kozerski, J. St. Pyrek, and A. Zamojski, *Rocz. Chem.*, **46**, 903 (1972).

(277) M. Matsui and M. Okada, *Chem. Pharm. Bull.* (*Tokyo*), **20**, 1033 (1972).

(278) A. F. Krasso, M. Binder and Ch. Tamm, *Helv. Chim. Acta*, **55**, 1352 (1972).

(279) H. Rapoport, *et al.*, *J. Amer. Chem. Soc.*, **93**, 1823 (1971).

(280) F. Bohlmann and C. Zdero, *Tetrahedron Lett.*, 621 (1972).

(281) A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron Lett.*, 3599 (1972).

(282) M. Ochiai, E. Mizuta, O. Aki, A. Morimoto, and T. Okada, *Tetrahedron Lett.*, 3245 (1972).

(283) K. J. Liska, A. F. Fentiman, and R. L. Foltz, *Tetrahedron Lett.*, 4657 (1970).

(284) A. Kato and M. Numata, *Tetrahedron Lett.*, 203 (1972).

(285) S. G. Levine and R. E. Hicks, *Tetrahedron Lett.*, 311 (1971).

(286) S. B. Tjan and F. P. Visser, *Tetrahedron Lett.*, 2833 (1971).

(287) M. Okigawa, N. Kawano, W. Rahman, and M. M. Dhar, *Tetrahedron Lett.*, 4125 (1972).

(288) J. Grandjean, *Chem. Commun.*, 1060 (1971).

(289) G. A. Neville, *Can. J. Chem.*, **50**, 1253 (1972).

(290) H. Wamhoff, C. Materne, and F. Knoll, *Chem. Ber.*, **105**, 753 (1972).

(291) J. M. J. Tronchet, F. Barbalat-Rey, and N. Le-Hong, *Helv. Chim. Acta*, **54**, 2615 (1971).

(292) F. Bohlmann and C. Zdero, *Tetrahedron Lett.*, 851 (1972).

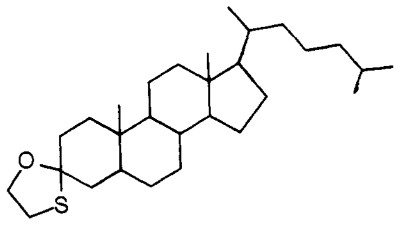
(293) D. Coutourier, M.-C. Fargeau and M. P. Maitte, *C. R. Acad. Sci.*, **274**, 1853 (1972).

(294) F. Lafuma and M. C. Quivoron, *C. R. Acad. Sci.*, **272**, 2020 (1971).

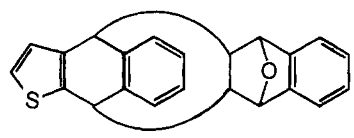
(295) H. D. Scharf and M. H. Feilen, *Tetrahedron Lett.*, 2745 (1971).

sulfone group is a weaker donor than an ether,[296] and in the thiophene derivative **62** complexing is confined to the oxygen, enabling assignment of two isolated isomers to two out of the four possible stereoisomers.[83]

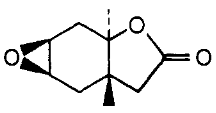
Of several reports concerning epoxides, three are complicated as they concern compounds which contained five to seven other heteroatoms.[103,114,279] Manni's study of the LIS of diepoxybutanes and diepoxyoctanes and the epoxide-lactone **63** is more helpful.[124] The largest LIS is observed for the protons cis to the epoxide ring, but comparison with LIS of the model compound cyclohexene oxide shows that competing coordination is occurring with the lactone. However, clearly epoxidation provides an efficient means of gaining spectral simplification of alkenes.



**61**



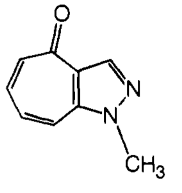
**62**



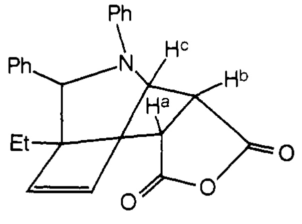
**63**

### 4. Ketones, Quinones, and Anhydrides

As expected alcohols[95,269,270] and amines[161] complex more strongly than ketones. However, steric restrictions as in **52b** and **64** cause complexing to revert to the weaker Lewis donor.[271,298] Similarly, ketone complexing would predominate over esters, lactones, ethers, and thioethers,[114,285-287,292,400] unless the carbonyl group is in an encumbered environment (*e.g.*, complexing occurs at the 3-lactone group rather than the 7-keto group in the limonoid of Figure 9, section V.F.3).[114]



**64**

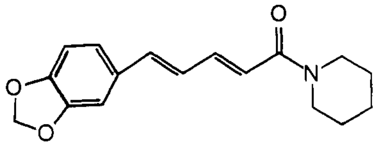


**65**

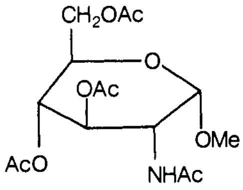
The quinone trimethoxyaverufin complexes with $Eu(thd)_3$ at the quinone carbonyls rather than with the multitude of ether functions, and the stereochemistry of the pentacycle so determined has been confirmed by nuclear Overhauser experiments. The anhydride **65** gives LIS in the order $H^a \simeq H^b > H^c >$ other protons.[299] The authors assumed this trend indicates coordination involving the ether oxygen, but the same order is expected if a time-averaging of shifts due to complexing at each of the carbonyl oxygens is involved, and this assumption is more in accord with the preferred coordination site in esters and lactones.

### 5. Amides and Lactams

In the bifunctional compounds studied to date, an amide or lactam complexes competitively with a secondary alcohol[300] but predominates over a methoxy group,[15] dioxolane ring (**66**),[54] or methoxybarbiturate.[289] Compound **66** showed significant upfield shifts for several protons with $Eu(thd)_3$, as well as a much increased shift gradient for the dioxolane protons after a 1:1 LSR/substrate ratio was achieved. This establishes the weaker coordination ability of the dioxolane oxygen. Amides are stronger donors than esters toward LSR in penicillins,[281] cephalosporins,[282,411] and acylated carbohydrates such as **67**.[264]

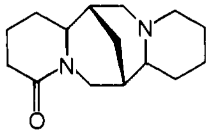


**66**

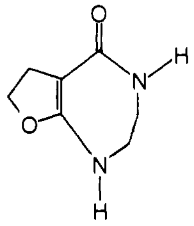


**67**

The approximate $r^{-2}$ method (section VI.C.1) has been used in deriving the stereochemistry of lupanine (**68**), a satisfactory analysis of the observed LIS being achieved if coordination is confined to the lactam carbonyl, a result tentatively supported by infrared studies.[301] The LIS with $Eu(thd)_3$ for **69** are consistent with considerable coordination involving the lactam carbonyl.[290]



**68**



**69**

### 6. Nitrones

The N→O group in furazans,[302] azoxybenzenes,[16,303] and *N*-nitrosoamines[304] is a moderately powerful donor toward LSR.

### 7. Amines

The competition between two amino functions for a LSR is determined often by steric rather than electronic factors. Thus, from studies on nicotine (**70**), it was clear that $Eu(thd)_3$, Eu(benzoylacetonate)$_3$, and the transition metal acetylacetonates all coordinated at the less basic pyridine atom.[80,305] Coordination to benzodiazabicyclo[3.2.1]octanes is biased in favor of the tertiary nitrogen.[157] Differences in the bonding to equatorial and axial primary amino groups yield information concerning the stereoisomerism of bis(4-aminocyclohexyl)methane,

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(296) C. T. Goralski and T. E. Evans, *J. Org. Chem.*, 37, 2080 (1972).

(297) A. van Bruijnsvoort, C. Kruk, E. R. de Waard, and H. O. Huisman, *Tetrahedron Lett.*, 1737 (1972).

(298) L. J. Luskus and K. N. Houk, *Tetrahedron Lett.*, 1925 (1972).

(299) G. Krow, E. Michener, and K. C. Ramey, *Tetrahedron Lett.*, 3653 (1972).

(300) A. W. Johnson, R. M. Smith, and R. D. Guthrie, *J. Chem. Soc., Perkin Trans. 1*, 2153 (1972).

(301) J. Skolik, J. Barciszewski, A. J. Rafalski, and M. Wiewiorowski, *Bull. Acad. Pol. Sci.*, 19, 599 (1971).

(302) J. Ackrell, M. Altaf-ur-Rahman, A. J. Boulton, and P. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1587 (1972).

(303) M. A. Berwick and R. E. Rondeau, *J. Org. Chem.*, 37, 2409 (1972).

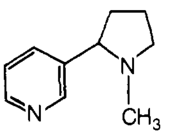
(304) R. R. Fraser and Y. Y. Wigfield, *Tetrahedron Lett.*, 2515 (1971).

(305) M. Cushman and N. Castagnoli, *J. Org. Chem.*, 37, 1268 (1972).

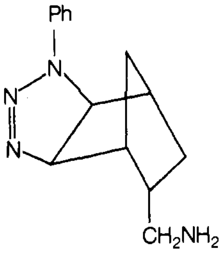
while showing evidence for chelation at low LSR concentrations.[306]

Despite the basicity of tertiary amino groups, steric factors relegate the amino function to the role of minor donor in compounds containing secondary hydroxyls,[271,272] ketones,[271] anhydrides,[299] or lactams[154,290,301] but it remains the dominant donor in the presence of the weakly basic sulfur-containing groups.[307] LSR complex mainly with the amino group in **71**,[163] but with both heteroatoms in morpholine, although the nitrogen is favored by a factor of 2.[160]

Pmr and $^{31}P$ studies indicate that $Eu(thd)_3$ coordinates with $R_2NC_2H_4PPh_2$ *via* the phosphorus atom when R = H, but *via* the nitrogen when R = Me.[255] This was attributed to subtle changes in basicity and steric requirements, but an alternative explanation invoking the absence of intermolecular N···H bonds in the dimethylamine was not considered. An example of chelation involving an aziridine and a phosphate ester has been cited.[398]



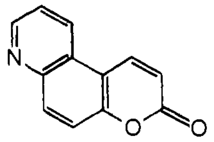
**70**



**71**

### 8. Aza Heterocyclic Groups

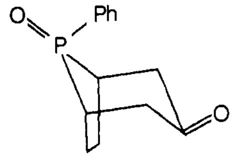
As mentioned in section VII.G.2, pyridine-like, but not pyrrolic nitrogens coordinate effectively with LSR.[310] Studies of many poly(aza heterocyclics) reveal that quinoline-like nitrogens are stronger donors than isoquinoline-like nitrogens.[139] The LIS of a series of aza heterocyclics do not correlate with the nitrogen basicity, but this may be because the contact contributions to the observed shifts have not been factorized out. A similar situation exists for a number of substituted pyrimidines and pyrazines.[289,308,309] Coordination of LSR with certain imidazo[4,5-*b*]pyridines involves the less hindered pyridine-like nitrogen,[311] and the nitrogen atom is also the dominant donor in **72**.[283]



**72**

### 9. Groups Containing Phosphorus and Sulfur

At low LSR concentrations, coordination involves mainly the phosphoryl group in **14**, **15** (section VII.H.1),[167,168] and **73**.[245] A useful comparison of the relative donor powers of the phosphoryl and amide groupings and their thia analogs has established the order P═O > amide C═O > C═S > P═S.[227] Interestingly, these results re-



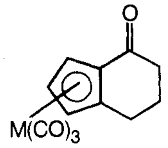
**73**

flect the electric dipole moments of model compounds, *viz.* $POF_3 \gg PSF_3$ and $COCl_2 > CSCl_2$.

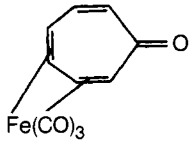
Except for sulfoxides, groups containing sulfur are extremely weak donors toward LSR, and in polyfunctional molecules coordination almost invariably involves the other heteroatom centers (ref 76, 83, 97, 107, 125, 160, 227, 232, 269, 281, 282, 284, 297, 307, 312, 402).

### 10. Organometallic Compounds

Some interesting interactions involving LSR and metal carbonyl derivatives have been reported. In general the carbonyl functions are very weak Lewis bases, and coordination to the LSR involves heteroatoms in the organic ligand, *e.g.*, the ketone group in both **74** and **75**.[249,313] Infrared studies show that $Eu(fod)_3$ bonds to the nitrile in $Fe(CO)_2CN$, and unexpected donor properties of F in $cpMo(CO)_3GeF(Ph)_2$ and the metal ions in $(cp)_2W(H)_2$ and $(cp)_2Sn$ are indicated.[314]



**74**, M = Mn or Cr



**75**

## C. Elucidation of Polymer Structures

It is presently difficult to obtain more than limited information from nmr spectra of polymers without recourse to spectrometers working at 200–300 MHz, or the study of other nuclei (*e.g.*, $^{13}C$), because of the presence of many protons of similar chemical environment. For those polymers which contain heteroatoms (*e.g.*, polyethers, polyesters), it is possible to use LSR to good effect for spectrum simplification.

### 1. Polyesters

$Eu(thd)_3$ bonds with the carbonyl groups of the ester residues, and Katritzky and Smith[74,401] have shown that the induced shift for atactic poly(methyl methacrylate) varies with the distance from the complexing site. Gradual separation of the *C*-methyl peaks of the isotactic, heterotactic, and syndiotactic triads was effected, the magnitude of the induced shifts increasing along this series. Subsequent studies reveal the order of shifts to be solvent and temperature dependent.[315] Recent communications have concerned the spectrum simplification of poly(vinyl acetate) in terms of tactic structures,[104] and of the copolyester ethylene terephthalate-isophthalate with relation to the sequence of the phthalate units.[126]

### 2. Polyethers

Grotens and his coworkers have studied the glyme series $MeO(CH_2CH_2O)_nMe$, $n$ = 1 to 6, as $CCl_4$ solutions

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(306) H. van Brederode and W. G. B. Huysmans, *Tetrahedron Lett.*, 1695 (1971).

(307) D. C. Remy and W. A. van Saun, *Tetrahedron Lett.*, 2643 (1971).

(308) A. F. Bramwell, G. Riezebos, and R. D. Wells, *Tetrahedron Lett.*, 4033 (1972).

(309) A. F. Bramwell and R. D. Wells, *Tetrahedron*, 15, 4155 (1972).

(310) R.-M. Claramunt, J. Elguero, and R. Jacquier, *Org. Magn. Resonance*, 3, 595 (1971).

(311) J. Elguero, A. Fruchier, and S. Mignonac-Mondon, *Bull. Soc. Chim. Fr.*, 2916 (1972).

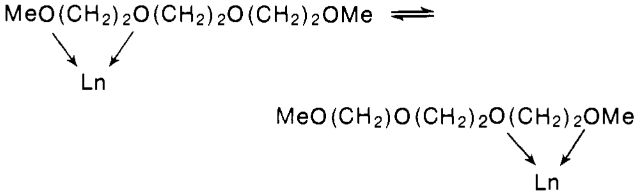
(312) I. K. Nielsen and A. Kjaer, *Acta Chem. Scand.*, **26**, 852 (1972).

(313) M. I. Foreman, and D. G. Leppard, *J. Organometal. Chem.*, **31**, C31 (1971).

(314) T. J. Marks, J. S. Kristoff, A. Alich, and D. F. Shriver, *J. Organometal. Chem.*, **33**, C35 (1971).

(315) J. E. Guillet, I. R. Peat, and W. F. Reynold, *Tetrahedron Lett.*, 3493 (1971).

treated with the thd shift reagents.[87,134,316] To account for the retention of twofold symmetry and the results of selective di- and tetradeuteration, it was suggested that less than 1 equiv of the lanthanide binds, in rapid equilibrium, to the outer two oxygens at one end of the glyme chain (*cf.* **76**). This type of chelation is supported by the observation that the induced shift of the methyl resonances of o-dimethoxybenzene is five times greater than that of the meta isomer.



$$\underset{\searrow\ \swarrow\ \mathrm{Ln}}{\mathrm{MeO(CH_2)_2O(CH_2)_2O(CH_2)_2OMe}} \rightleftharpoons \underset{\searrow\ \swarrow\ \mathrm{Ln}}{\mathrm{MeO(CH_2)O(CH_2)_2O(CH_2)_2OMe}}$$

**76**

Other investigations using LSR have concerned the order of methylene and ethylene in the triads of trioxane–dioxolane copolymers,[317] identification of branching positions in polypropylene[318] and other polyalkylene glycols,[319] and triad tacticity in poly(methyl vinyl ether).[320] For the glycols, a careful integration gave the ratio of "end of chain" to "polymer" methyl peaks, and the average molecular weight. The latter result was in satisfactory agreement with the values derived from osmometric measurements and was a great improvement on a previous method using pyridine solvent shifts.[321]

A note of caution has been made regarding the presence of a very large number of different donor sites in polyfunctional molecules.[13] In certain lipids, phospholipids, nucleic acids, antioxidants, and surfactants, the effect of addition of LSR is only an excessive broadening of the spectral bands due to a combination of a diversity of upfield and downfield shifts.

## D. Protection of Functional Groups and Quantitative Aspects of Polyfunctional Molecules

In the absence of steric encumbrance, polyfunctional molecules complex with LSR at the strongest donor site, and, once this site is saturated, further coordination involves the weaker donors. Thus, protons near the weaker donors often experience their greatest LIS above a 1:1 mole ratio of LSR/substrate. Three principal methods have been used to rationalize induced shifts for polyfunctional molecules.

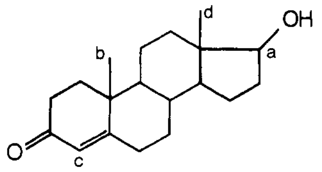
### *1. Protection of More Active Donors*

Chemical derivatization can be used to modify the relative donor properties of a series of functional groups in a given molecule. The hydroxyl group can be deactivated toward LSR by conversion to trifluoroacetyl[107,269] or heptafluorobutanoyl esters,[161] or by tosylation[107,271] or silylation.[107] Primary and secondary amines can be deactivated by conversion to fluorinated amides or tertiary amines. Ketones have been protected by conversion into their ethylene thioketal.[269] Examples of enhancement of the donor power of a group include the reduction of an ester function to an alcohol using lithium aluminum hydride or the oxidation of thioethers to sulfoxides.

### *2. Dissection of Induced Shifts into Contributions from Coordination to Specific Sites*

In order to use induced shifts of bifunctional molecules in calculations of molecular structure, it is necessary to partition the induced shifts into contributions arising from complexing at the individual sites. At present, no general method has been developed to achieve this end.

Hinckley[95] has used a graph of log (induced shift) against log $r$ to dissect the contributions at each of the donor sites in testosterone (**77**), assuming a simple $r^{-3}$ relationship to explain the observed induced proton shifts (*cf.* section VI.C.1). A line of slope $-3$ was drawn through the point corresponding to the induced shift for the $H^d$ proton, which was assumed to be affected only by complexing involving the secondary hydroxyl. The induced shift for the $H^a$ proton is displaced slightly from this line due to a small contact contribution. The deviations of the induced shifts for protons $H^b$ and $H^c$ from this line were attributed to the effect of complexing at the keto group, and a graph of these deviations, again with a slope of $-3$, was constructed as the reference for keto-group complexing. The induced shift for the $H^c$ proton deviates slightly from this second line, again owing to a small contact contribution.



**77**

The relative association constants were calculated by interpolation of the induced shifts for protons 4.0 Å from each donor site from the above graphs. This procedure indicates that the hydroxyl group associates with the LSR 2.13 times more effectively than the keto group in **77**, but only 1.21 times in 17-$\alpha$-methyltestosterone, in which steric hindrance reduces the complexing of the hydroxyl.[95] Hinckley's relative association affinities are relative to pyridine also, as he used $\mathrm{Eu(thd)_3 \cdot 2py}$ as the shift reagent.

Hinckley's method suffers from obvious drawbacks: (i) complexing must be sufficiently remote for the shift of at least one proton to be due exclusively to the effect on complexing at a single site; (ii) factor i usually requires the selection of a proton near one of the donor sites, and protons thus placed are more prone to suffer contact interactions; (iii) angle factors of the dipolar interaction are totally neglected; and (iv) the $g$ tensors for the two complexes (*e.g.*, coordination involving the keto and hydroxy groups of **77**) may not be identical, leading to errors in the relative association constants.

Using a more rigorous mathematical treatment, expressions 13 and 14 have been derived to describe the fraction of LSR complexed at each site in a bifunctional molecule.[76] [LSR] is the total amount of shift reagent added, $A$ and $B$ are the molar concentrations of shift reagent complexed at donors A and B, $K_A$ and $K_B$ are the equilibrium binding constants of the LSR at sites A and B, respectively, and $S_A = S_B$ for the bifunctional molecule is the molar concentration of the substrate.

$$[\mathrm{LSR}] = A[1 + 1/(K_A(S_A - A)) + S_B/(A + K_A(S_A - A)/K_B)] \quad (13)$$

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(316) A. M. Grotens, C. W. Hilbers, E. de Boer, and J. Šmid, *Tetrahedron Lett.*, 2067 (1972).

(317) D. Fleischer and R. C. Schulz, *Makromol. Chem.*, **152**, 311 (1972).

(318) F. F.-L. Ho, *Polym. Lett.*, 491 (1971).

(319) B. S. Perrett and I. A. Stenhouse, United Kingdom Atomic Energy Authority, Analytical Sciences Report, Feb 1972.

(320) H. Yuki, K. Hatada, T. Hasegawa, Y. Terawaki, and H. Okuda, *Polym. J.*, **3**, 645 (1972).

(321) T. F. Page and W. E. Bresler, *Anal. Chem.*, **36**, 1981 (1964).

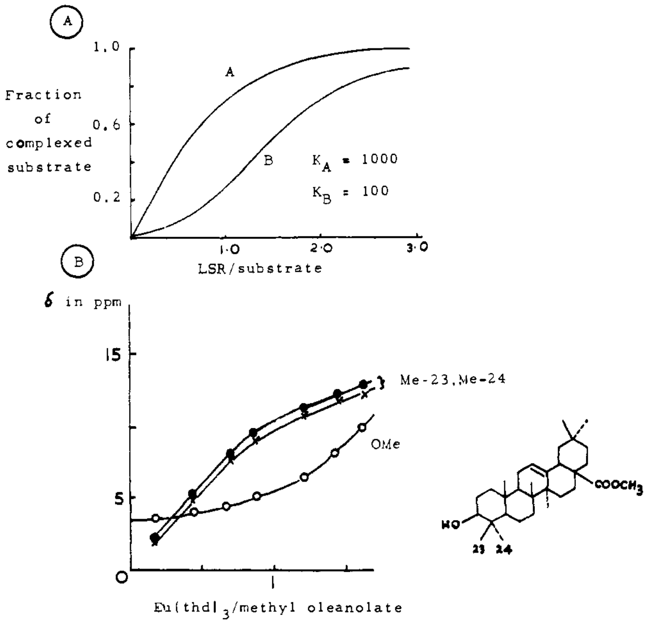


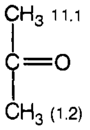
**Figure 16.** (A) The behavior of a bifunctional substrate as predicted by eq 13 and 14 for adduct formation at each site. (B) Shifts induced by the addition of $Eu(thd)_3$ to methyl oleanolate (0.09 *M* in $CCl_4$).[76] Shifts are shown for the OMe, Me-23, and Me-24 groups.

$$[LSR] = B[1 + 1/(K_B(S_B - B)) + S_B/(A + K_B(S_B - B)/K_A)] \qquad (14)$$

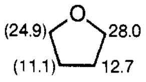
The predicted variations in the fraction of substrate complexed at each site with changing LSR/substrate is shown in Figure 16 for $K_A/K_B = 10$. The shapes of these profiles are similar to the induced proton shifts observed for the 23 and 24 methyls and the OMe group of methyl oleanolate on addition of $Eu(thd)_3$ in $CCl_4$ (see Figure 16).[76] Similarly good agreement is found for shifted spectra of bicyclononane esters.[268] It would seem that an iterative curve-fitting procedure could be used in solving this mathematical analysis to enable calculation of the equilibrium constants for the two donor sites.

### 3. *Dissection of Induced Shifts for Bifunctional Molecules Using Competitive Experiments and Model Compounds*

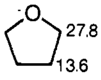
Hart and Love have used a series of intermolecular experiments to define an order of "relative shifting powers" for competing monofunctional donors in the presence of $Eu(thd)_3$.[232] Thus, from the *G* values for acetone (**78a**) and THF (**78b**), and the reduced values in parentheses obtained for an equimolar mixture of the two donors, it can be shown that in this latter mixture, 88% of the THF is complexed.



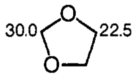
**78a**



**78b**



**79a**



**79b**

A number of other workers have used monofunctional compounds as models for dissecting induced shifts of bifunctional molecules. Thus, *G* values for dioxolane (**79b**) of 27.8 and 20.7, in good agreement with the experimental results, were estimated from the *G* values of corresponding protons in THF (**79a**, slightly different results from those of Hart and Love) by assuming that each oxygen in **79b** is equally complexed with LSR.[76] Monofunctional model compounds have also enabled the analysis of the LIS of dihydroxyadamantanes (see section VI.C.2),[81] the nitroimidazole **53**a,[259] and an androstenol derivative[156] and dissection of coordination at the three ester sites in serratriol triacetate (**55**).[220]

## *IX. Other Shift Reagents*

### A. Chiral Shift Reagents

Prior to the discovery of LSR, two principal methods have been used to distinguish enantiomers by nmr. In the first method, a derivatizing agent ((*R*)-*O*-methylmandeloyl chloride[322] or better, Moscher's (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid[323]) is used to convert optically active amines or alcohols into diastereoisomers, which show useful, but not particularly large, chemical shift differences generally of about a maximum of 0.15 ppm. The second method employs a solute–solvent interaction between a chiral solvent and each of the enantiomers to form diastereoisomers of slightly different chemical shifts ($\Delta\delta < 0.1$ ppm). Optically active 1,1,1-trifluoro-1-phenylethanol has been the most successful reagent for a variety of amines, esters, and sulfur and phosphorus compounds.[324]

Optically active LSR offer the attractive combination of the second method together with the inherent first-order type simplification of spectra arising from the dipolar interactions. Whitesides and Lewis were the first to use the chiral LSR **80**, which shows chelate resonances at δ −1 to 2, away from the spectral region of interest.[72,218] They were able to separate the proton resonances of α-phenylethylamine, maximal for the methine proton at the chiral site and decreasing in magnitude with increasing distance from that site. When the downfield shift of the methine proton was δ 14, the signals for the *R* and *S* components were separated by a maximum of $\Delta\delta = 0.55$ ppm. The variation of Δδ with substrate concentration was explained on grounds of differing formation constants for the diastereoisomers. The Pr analog of **80** gives enhanced Δδ values to high field, but with a greater degree of line broadening. The use of **80** appears to be limited to strong donors, little success being noted for alcohols or other weaker donors.[218,325,326,403]

The trifluoromethyl derivative **81** shows an immediate improvement on **80**, enabling estimation of enantiomeric purity of alcohols, ketones, esters, sulfoxides, and epoxides, Δδ values ranging from 0.1 to 1.5 ppm.[73,325,327-329] Figure 17 shows the shifted spectrum of methyl (*R*,*S*)-2-methyl-2-phenylbutanoate with particularly clear separation for the ester and tertiary methyl groups. Chiral reagent **81** has been used to distinguish between meso and *dl* stereoisomers of 2,3-butylene oxide.[329] In the meso form, the enantiomeric methine protons are rendered anisochronous and exhibit a small mutual coupling constant. However, in the *d* (and *l*) forms, the methine hydrogens are rendered identical rather than diastereotopic and exhibit no mutual coupling.

(322) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968).

(323) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

(324) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **91**, 5150 (1969).

(325) J. L. Greene and P. B. Shevlin, *Chem. Commun.*, 1092 (1971).

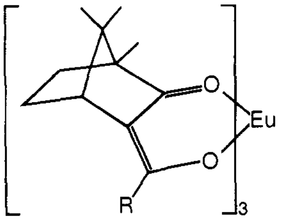
(326) R. R. Fraser, M. A. Petit, and J. K. M. Sanders, *Chem. Commun.*, 1450 (1971).

(327) H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Amer. Chem. Soc.*, **93**, 5913 (1971).

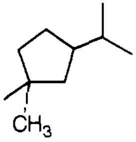
(328) E. B. Dongala, A. Solladie-Cavallo, and G. Solladie, *Tetrahedron Lett.*, 4233 (1972).

(329) M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Amer. Chem. Soc.*, **94**, 5924 (1972).

Chiral reagent **82** gave satisfactory resolution of five racemic compounds with different functional donors, whereas the spectra of only two of these were resolved by **80**.[326] There seems to be no particular advantage in using **82** rather than **81** for typical enantiomers.[327] However, for problems relating to the splitting of enantiotopic protons at a prochiral center (*e.g.*, the methylene signals of substituted benzyl alcohols and neopentanol, or the methyl groups of benzyl methyl sulfoxide and 2-propanol), **82** seems to offer a greater potential ($\Delta\delta$ up to 0.75 ppm) than **81**, although opinion is divided on whether the latter can[329] or cannot[327] be used to resolve the enantiotopic methyl groups of dimethyl sulfoxide.



**80**, R = *t*-Bu
**81**, R = $CF_3$
**82**, R = $C_3F_7$
**83**, R =



In addition to fluorination, the potential of chiral shift reagents can be improved by increasing the size of the chelate group. Thus, **83** gives enhanced $\Delta\delta$ values for esters, amino esters, alcohols, and ketones,[72] the value of 1.65 ppm for 1-phenylethylamine being the largest separation recorded to date. Whitesides and Lewis[72] also made the interesting observation that a solution containing the enantiomer (*R*)-*N*-methylphenylethylamine together with the *nonchiral* reagent Eu(thd)$_3$ is capable of resolving an enantiomeric mixture of 1-phenylethylamine ($\Delta\delta$ = 0.36 ppm), but this discovery has not been exploited further.

Chiral solvents induce relative shifts for the *R*/*S* enantiomers from which the absolute configuration of the enantiomers can be predicted.[332] A disappointing feature of the chiral LSR concerns the relative shifting of the *R*/*S* enantiomers, which is a function of both the differences in equilibrium constants and the actual geometries of the complexes. Thus, chiral LSR give rather unpredictable relative shifts; *e.g.*, the methyl resonance of an *R* enantiomer may be to low field of the *S* enantiomer, whereas the order may be reversed for a methine proton in the same molecule under identical conditions (*cf.* Figure 17). However, Ajisaka, *et al.*, have demonstrated a clear correlation between enantiomeric form and the sense of $\Delta\delta$ in eight of nine $\alpha$-amino acids.[404] Obviously, a careful assessment of very closely related model compounds is necessary for a successful prediction of absolute configuration.

Optical purity as determined by chiral LSR is generally in good agreement with other methods, *e.g.*, (*R*)-$PhCH_2SOMe$, 89% (90%),[326] (*R*)-methyl 2-methyl-2-phenylbutanoate, 28% (26%),[327] and MeSO-*p*-tolyl, 33% (33%).[403]

Optical properties in the ultraviolet region of the electromagnetic spectrum can be changed by interactions with shift reagents, and recently this property has been used effectively in the determination of the chirality of some steroidal $\alpha$-glycols.[333,334] The method is particularly useful for tertiary hydroxyls, which may be difficult to derivatize for alternative methods. The sign of the longer wavelength Cotton peak is invariably in agreement with the chirality of the steroidal $\alpha$-glycol when either Eu(thd)$_3$ or Pr(thd)$_3$ is used. It has been suggested that the method is also applicable to $\alpha$-glycol monoacetates, $\alpha$-amino alcohols, and similar compounds. Recent CD results show that the major species formed between optically active alcohols and Eu(fod)$_3$ is the bis adduct, provided that more than a twofold excess of donor molecules is present.[335]

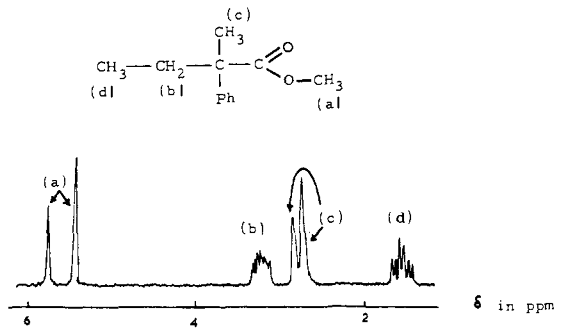


**Figure 17.** Spectrum of methyl (*R*,*S*) 2-methyl-2-phenylbutanoate (0.9 *M*) in the presence of shift reagent **81** (0.5 *M*) in $CCl_4$.[327]

Without question, chiral LSR afford a powerful means of analyzing optical purity and offer a much more convenient alternative to the previous method of deuterium substitution for the determination of geminal methylene coupling constants. The general interest in these reagents is reflected in their recent commercial introduction as the Eu, Pr, and Yb chelates of both **81** and **82**.[331]

## B. Lanthanide Salts

### 1. *Applications to Organic Compounds*

Because of their favorably long $T_1$ relaxation times, and thus minimal line broadening, the ionic salts of the rare earths attracted the nmr spectroscopist's attention as shift reagents long before the introduction of the $\beta$-diketonates of current interest.[137,336-338] The success of the latter has recently stimulated more work on the effects of trivalent lanthanide ions for the simplification of spectra of materials in aqueous solution.

The shifts induced by most commonly used lanthanide salts (the hydrated chlorides, nitrates, and perchlorates) are much smaller than those of the $\beta$-diketonates. This reduction is attributable to hydration of the lanthanide ion, reducing its acidity toward other donor atoms.[99] Nonetheless, the interactions can readily be measured calorimetrically[36] and induced shifts as large as $\delta$ 4 have been recorded for, *inter alia*, substituted pyridines,[6] amino and hydroxycarboxylic acids in which coordination involves only the carboxylate group,[99] amino acids,[339] steroids,[97] nitrones,[76] phosphine and arsine oxides, phosphates, phosphonates,[76] and esters.[340]

The most suitable solvents are deuterated acetone and $D_2O$, attenuated shifts being recorded for both methanol and pyridine, and varying success being reported for acetonitrile.[36,76] A change in stoichiometry of the complex from 1:1 in water to 2:1 and possibly even 3:1 in ac-

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(330) R. W. Kreilick, *J. Amer. Chem. Soc.*, **90**, 5991 (1968).

(331) Willow Brook Laboratories, Inc., Waukesha, Wis. 53186; UK agents, Phase Separations Ltd.

(332) W. H. Pirkle, T. G. Burlingame, and S. D. Beare, *Tetrahedron Lett.*, 5849 (1968).

(333) K. Nakanishi and J. Dillon, *J. Amer. Chem. Soc.*, **93**, 4058 (1971).

(334) K. Nakanishi, D. A. Schooley, H. Koreda, and J. Dillon, *Chem. Commun.*, 1235 (1971).

(335) N. H. Anderson, B. J. Bottino, and S. E. Smith, *J. Chem. Soc., Chem. Commun.*, 1193 (1972).

(336) R. L. Conger and P. W. Selwood, *J. Chem. Phys.*, **20**, 383 (1952).

(337) R. G. Shulman and B. J. Wyluda, *J. Chem. Phys.*, **30**, 335 (1959).

(338) J. Reuben and D. Fiat, *Chem. Commun.*, 729 (1967).

(339) E. W. Robb, P. P. Choma, and E. K. Onsager, Abstracts, 164th National Meeting of the American Chemical Society, New York, N. Y., 1972, No. ORGN-145.

(340) C. Reyes-Zamora and C. S. Tsai, *Chem. Commun.*, 1047 (1971).

etone has been reported for nitrones, phosphates, and phosphonates.[76]

Siddall has observed the spectra of free and bound forms of tri-*n*-butyl phosphate in $CDCl_3$ solutions of $Pr(NO_3)_3$ at −50°,[341] work since complemented by variable-temperature studies on solutions containing DMSO and $Eu(thd)_3$ (*cf.* section V.F.3).[90]

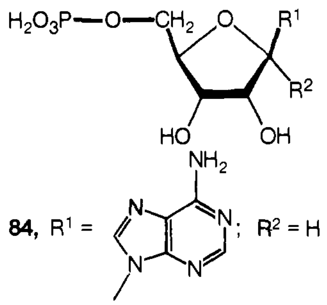
The hydrated lanthanide salts usually give high-field shifts for Eu and low-field shifts for Pr, in contrast to analogous $\beta$-diketonates. Where the observed anisotropic shifts have been dissected, there is clear evidence for the existence of sizable contact shift contributions (*e.g.*, in pyridines[36] and phosphonates[76]). For the pyridines, Birnbaum and Moeller noted a very large contact shift (up to $\delta$ 16) for protons near the coordination site, which is almost exactly balanced by a dipolar contribution of opposite sign.[36] In general the values of the $g$ tensors for the rare earth complexes (presently difficult to measure by esr) and their geometries in aqueous solution are not always known, and it is therefore difficult to assess the relative contributions of the contact and dipolar terms to the observed induced shifts. Thus, structural information deduced is mainly of a qualitative nature.

### 2. *Applications Concerning Macromolecules of Biological Interest*

The divalent calcium and trivalent europium ions have similar spatial properties, and consequently $Eu^{3+}$ has been used as a "shifting" probe in nmr studies of some molecules of biological interest. In addition, $Gd^{3+}$ and $Eu^{2+}$ have been used as broadening probes to provide information concerning relaxation processes.

The nucleotides, 9-$\beta$-D-ribofuranosyladenine 5′-monophosphate (AMP) and 1-$\beta$-D-deoxyribofuranosylthymine 5′-monophosphate (TMP) have been the subject of a unique study, by Williams and his coworkers,[56] in which solutions of the lanthanide chlorides (0–0.5 *M*) were added at pH 2. To analyze the nmr results, free rotation has to be considered about each of the heavily marked bonds in **84**, leading to an estimated 64 × $10^6$ possible conformations for angle increments of 4° in the case of AMP. By means of van der Waals restrictions and distance factors deduced from the Gd-probe experiments, these were reduced by a lengthy computer analysis to only 12, all of which were in a geometrically distinct family. A reduction to only four structures was possible for TMP. The most satisfactory conformations were presented as computer-drawn orthogonal and stereoscopic projections, and these were in good agreement with X-ray structural work on crystalline materials. Nucleotides[100,342] and related compounds have also been studied by $^{13}C$ magnetic resonance with heteronuclear decoupling and ionization studies at less acidic pH values to assist the assignment of lanthanide-salt shifted spectra. The anomers of ribose 5-phosphate **85** appeared to complex with the lanthanide on or near the 2- and 3-hydroxyls, whereas coordination in AMP (**84**) involves the phosphate. Studies of this kind provide invaluable information but, needless to say, require considerable instrument and computer time.

The novel use of gadolinium nitrate as a broadening probe in the study of the molecular interaction between lysosyme and $\beta$-methyl-*N*-acetylglucosamine has been reported.[57,343] The transverse relaxation times of the glycosidic and acetamido methyl groups led to estimates of the vector distances of these from the metal atom, which were in good agreement with X-ray data.



**84,** $R^1$ = ; $R^2$ = H

**85,** $R^1$, $R^2$ = H, OH or OH, H

Charged molecules also show interesting interactions with lanthanide salts. Two groups[344,345] have studied choline in an examination of membrane systems by means of $Eu^{3+}$, $Gd^{3+}$, and $Mn^{2+}$ probes. Whereas the latter two probes caused total disappearance of the choline $^{+}NMe_3$ group proton signals, europium nitrate split the resonance into two. The authors explained this observation in terms of molecules on the "inner" and "outer" vesicles. Only the "outer" molecules interact *via* their phosphate residues with the europium probe, leading to a small high-field shift. In a 250-MHz study, a similar effect was observed with added ferricyanide ion.[345]

## C. Other Lanthanide Shift Reagents

Several authors[21,77] have commented on the unique combination of properties in the thd and fod $\beta$-diketonates, *viz.* (i) expansion of their coordination number beyond six, (ii) highly anisotropic $g$ tensors, (iii) minimal spectral interference from ligand protons, and (iv) useful solubility in nonpolar solvents. The lanthanide acetylacetonates[77,346] and dibenzoylmethanates[77] are closely related, but much inferior as shift reagents (*e.g.*, $Eu(acac)_3$ shows less than 10% of the induced shifts of $Eu(thd)_3$), as also are the series $PrX_3(OPR_3)_4$ in which X = $ClO_4$ or $NO_3$, and $LnN(CH_2COO)_3$.[21,62,99]

The tricyclopentadienyl lanthanide complexes are relatively strong Lewis acids and form a stable and soluble series of 1:1 adducts with neutral donors (*e.g.*, nicotine, isonitriles), which can be isolated from solution and show induced shifts up to 40–50 ppm. Von Ammon and his coworkers found that a useful LIS simplification occurred on complexing cyclohexylisonitrile to $Pr(cp)_3$.[10,113,117] This allowed observation of 14 discrete signals for the equatorial and axial forms of the chair conformers, when the spectrum was recorded at −70°, and assessment of the enthalpy of inversion of the cyclohexyl ring. Induced shifts of the cyclohexyl ring protons were interpreted in terms of dipolar interactions only, but large contact shifts were apparent for the protons of the cyclopentadienyl ligands.

## D. Paramagnetic Salts and Chelates of Transition Metals

This field has been surveyed comprehensively in excellent reviews by Webb[43a] and Eaton and his coworkers[5,23] to which the reader is referred. Only topics related to properties of the lanthanide shift reagents will be briefly considered in this section.

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(341) T. H. Siddall and W. E. Stewart, *Inorg. Nucl. Chem. Lett.*, **3**, 279 (1967).

(342) B. Birdsall and J. Feeney, *J. Chem. Soc., Perkin Trans. 2*, 1643 (1972).

(343) R. J. P. Williams, *et al.*, *Eur. J. Biochem.*, **21**, 204 (1971).

(344) V. F. Bystrov, N. I. Dubrovina, L. I. Barsulkov, and L. D. Bergelson, *Chem. Phys. Lipids*, **6**, 343 (1971).

(345) R. J. Kostelnik and S. M. Castellano, *J. Magn. Resonance*, 7, 219 (1972).

(346) R. D. Green and S. P. Sinha, *Spectrosc. Lett.*, **4**, 411 (1971).

The shifts induced by Co and Ni chelates may vastly exceed those caused by the analogous lanthanide chelates (*e.g.*, induced shifts of 250 ppm have been reported for histidine and $Co^{2+}$),[347] but they are often accompanied by unacceptably large degrees of line broadening. Where a direct comparison of lanthanide and transition metal induced shifts exists, the latter yield considerably less qualitative information.[80,310]

The reason for this broadening (which is inversely proportional to the $T_1$ relaxation time) emerges clearly from the work of Conger and Selwood, who have measured $T_1$ values for lanthanide and transition metal salts.[336] Most of the lanthanides have relatively long $T_1$ values (84 and 24 msec for $Eu^{3+}$ and $Pr^{3+}$, respectively), whereas the transition metals have much shorter values (5.3, 1.7, and 0.9 msec for $Co^{2+}$, $Ni^{2+}$, and $Cu^{2+}$, respectively) as do the lanthanide broadening probes, $Eu^{2+}$ and $Gd^{3+}$ (0.6 and 0.03 msec). The effect of the shorter relaxation times is well demonstrated by the larger line widths of the acetylacetonates[7] (800-2000 Hz for Fe, Cr, and Ti) compared with the thd chelates of Eu and Pr (10 and 40 Hz).[52]

There are several other limitations, which make the transition metal chelates less attractive than the lanthanide chelates.

(i) Only strong Lewis bases exhibit useful induced shifts with metal chelates, small or negligible shifts being observed for ketones, ethers, and sulfoxides.[6c]

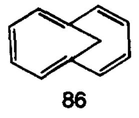
(ii) Contact shift interactions may make a very sizable contribution to the observed anisotropic shifts (*cf.* section II.B).[5]

(iii) The distortion of coupling constants caused by reagents producing contact shifts is apparently more serious[10,77] (due to the electronic disturbances in a bond) than those which exert only dipolar interactions.[176]

The use of transition metal compounds in the elucidation of lone-pair conformation and ion pair and solvation interactions has already been reviewed.[5,23,43a] Chemical shift and relaxation time studies using Cu, Mn, Co, Cr, or Fe compounds have provided valuable structural information concerning proteins,[348,349] nucleotides,[350] nucleic acids,[351] amino acids,[347,352] and enzymes.[353] For reasons outlined above, the lanthanide ions are clearly advantageous, and it seems likely that the use of transition metal ions as nmr probes will diminish in future years.

## E. Diamagnetic and Anionic Reagents

Three of the four classes of diamagnetic reagents discussed below depend on the well-known shielding effects of aromatic systems sustaining substantial ring currents. For example, in the bridged annulene **86**, the chemical shift of the bridging methylene does not occur at the expected value of δ 2.2-2.8 but is heavily shielded to δ −0.5.[354] In general, the diamagnetic induced shifts are relatively small (<δ 10) but are accompanied by no line broadening.



**86**

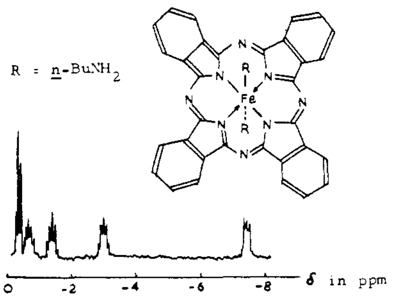


**Figure 18.** Pmr spectrum(100 MHz) of the bis(*n*-butylamine) complex of iron(II) phthalocyanine in $CDCl_3$.[355]

### 1. *Metal Phthalocyanines and Porphines*

Most of the work on the diamagnetic shift reagents has concerned these macrocycles. The $Fe^{2+}$ derivative may be compared with the lanthanide chelates, because of the ready formation of species of higher coordination number through the donation of amine electron pairs, *e.g.*, with *n*-butylamine (Figure 18). Maskasky and his colleagues[355,356] have shown how these complexes may be prepared by treating the iron(II) phthalocyanine, which is paramagnetic, with an excess of the amine to yield a 1:2 complex. This complex is diamagnetic and shows high-field shifts proportional to the proximity of the phthalocyanine ring with first-order patterns and readily resolvable coupling constants. By comparing the high-field shifts induced in the proton signals of the amine by the shielding of the phthalocyanine ring, these workers were able to calculate the Fe–N distance in the 1:2 complexes (*ca.* 1.9-2.0 Å) in very good agreement with literature values from X-ray and other data.

A similar series of diamagnetic metal macrocycles has been prepared from germanium tetrachloride and phthalocyanine or porphyrin.[357] In this case, the organic ligands are joined to the germanium atom by covalent and not donor bonds, but an exactly analogous pattern of first-order simplification occurs with, for example, an *n*-octyl side chain.[358,359] An advantage of the germanium complexes concerns their ability to simplify the spectra of phenols, carboxylic acids, and alkyl halides (attached *via* Grignard reagents); none of these groups is amenable to treatment with the LSR. The phthalocyanine may be preferred to the porphines[56,358-360] on the grounds of vastly lower cost, but poor solubility in nonpolar solvents may sometimes be a limiting factor.[161,355,359,361]

### 2. *Phosphonium Tetraarylborates*

Schiemenz and his coworkers have shown that significant high-field shifts (up to 3 ppm) can be induced in the spectra of phosphonium salts on treatment with the read-

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ily prepared tetraarylborates.[3,362,363] The ring currents of the aryl residues provide the mechanism of shielding, and the phosphonium center acts as a quasi-donor site. Since the interaction is one of short-lived ion pairs, only one signal is observed for each nucleus. In like manner to the series of germanium macrocycles, this reagent can prove particularly useful for certain alkyl halides and carboxylic acid derivatives (*e.g.*, $Ph_3PCH_2CH_2Y$, where Y = COOH or Br).

### 3. *Borate Anions*

Chelates are readily formed between *cis*-hydroxyl pairs in carbohydrates and borate anions under nonacidic conditions with concomitant downfield shifts of up to 6 ppm in their $^{13}C$ spectra.[364] This allows the simplification of the spectra of carbohydrates through the identification of those carbons which bear the chelating hydroxyls (*e.g.*, C-2′ and C-3′ of adenosine). If one of the pertinent hydroxyls is removed (*e.g.*, as in 2-desoxyadenosine) the same interaction cannot occur and the pronounced downfield shifts are no longer found.

### 4. *Radical Anions*

The nmr spectra of organic free radicals are usually characterized by extreme line broadening due to unfavorable relaxation times. In certain cases a rapid exchange can occur between a radical solvent and the organic substrate, leading to a spectrum with reasonably sharp lines, *e.g.*, for phenoxy radicals in di-*tert*-butyl nitroxide solvent.[330]

The sodium salts of the coronene and triphenylene anions cause sizable low-field shifts with an acceptable low degree of broadening in THF solutions of the glyme polyethers.[87] $MeO(CH_2CH_2O)_4Me$, for example, exhibits four resonances, the first at highest field being attributed to the methyl protons, with increasingly deshielded groups of 4,4 and 8 protons assigned nonspecifically to the remaining methylene protons. The authors[87] proposed a ring-type structure for the glyme, which is bound in a sandwich structure about the aromatic plane. A serious drawback to the use of these and similar aromatic radical anions is the extensive contribution of contact interactions to the observed shift.

## *X. Concluding Remarks and Recommendations*

The enormous number of publications which have appeared in the last 2 years concerning the use of lanthanide shift reagents is a tribute to their tremendous potential in the elucidation of nmr spectra of organic compounds. Even so, there are a number of limitations concerning their use, and these are briefly listed below. To the practicing spectroscopist, there are many potential combinations of substrate ligands and various shift reagents. We therefore conclude our discussion with a list of recommended procedures, which we hope will be of use to the uninitiated worker in the field.

## A. Limitations of LSR

a. Line broadening at ratios of LSR/substrate approaching unity can give rise to loss of fine structure.

b. Nuclear Overhauser experiments are often precluded by added LSR as the paramagnetic interactions dominate the spin–spin interactions.

c. Fourier transform analyses should be attempted with caution as "folding-over" effects of expanded spectra may give rise to interpretational difficulties.

d. Compounds possessing acidic groups such as carboxylic acids and some phenols cause decomposition of the lanthanide chelates, and these groups require modification prior to the analysis.

e. Of the commonly occurring organic compounds, alkyl halides, hydrocarbons, thioethers, and nitro compounds are almost totally unaffected by LSR and require chemical modification to enable spectral simplification.

## B. Procedures for the Use of LSR

### 1. *Solvent Selection*

Most studies can be accomplished successfully in $CDCl_3$ or $CCl_4$, and only occasionally are other solvents more beneficial (*e.g.*, $CS_2$ for alcohols and low temperature studies). In some cases, substrate insolubility may necessitate a change in solvent, and suitable alternatives include $CH_3CN$, $CH_3NO_2$, and benzene.

### 2. *LSR Selection*

For the majority of studies, the $Eu^{3+}$ and $Pr^{3+}$ chelates with thd and fod are most suitable. The lanthanide ion should be selected to cause spreading of the signals, and use of both metal ion complexes may enable a more complete analysis. If computer-programmed analyses are contemplated, both lanthanide reagents should be used to enable verification of dipolar interactions for the observed induced shifts.

In some cases, $Yb^{3+}$ complexes may be required to achieve greater spreading of the resonances, but these will cause a simultaneous increase in the degree of signal broadening.

### 3. *Selection of the Donor Site*

The magnitude of the induced shifts is critically dependent on the association affinity of the donor atoms toward the LSR. Clearly, it is advantageous to use compounds possessing the most Lewis-basic groups, such as amines, alcohols, sulfoxides, and, to a lesser extent, ketones and esters. Primary and secondary amines are generally the most powerful donors, but they may cause problems due to ease of carbonate formation,[161] leading to substrate precipitation.[365] Thus LSR studies concerning aliphatic amines should be carried out on degassed solutions.

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### 4. *Interpretation of LIS Spectra*

Incremental additions of LSR should be used to enable reference of each resonance back to the original chemical shift to confirm the chemical environment of the nucleus concerned. Whenever possible, decoupling experiments should be attempted once suitable separation of resonances has been achieved, as further addition of LSR leads to additional loss of multiplet resolution.

### 5. *Calculation of Results*

From the series of LIS spectra, plots of chemical shift *vs.* LSR/substrate should be constructed to enable calculation of the induced shift gradients (*G*) for each resonance and verification of the stoichiometry of the complex.

The same experimental conditions should be used to derive the LIS for the substrate and model compounds, if the latter are used to aid spectral assignment. In some cases, spectral analysis may be completed by ignoring the angle contribution to the dipolar interaction and using only the distance factors, measured on molecular models. Values of *G* used in this approach should be shown to depend only on dipolar interactions (*cf.* section 2 above).

Most certain assignments are made using a computer analysis of the dipolar interaction, making necessary allowances for conformational rotations within the molecular complex in searching for the structure, which gives rise to the least discrepancies between the calculated and experimental results.

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## *XI. Addendum*

More recent publications have described the effect of LSR on nuclear Overhauser effects in $^{13}C$ spectra,[413] CIDNP,[414] and, in particular, the decoupling effects of Gd(fod)$_3$.[415] The advantages of using Gd(fod)$_3$ as a relaxation agent in conjunction with Eu(fod)$_3$ have also been described.[416]

The greater contact shift contributions observed in $^{13}C$ spectra is attracting increased attention, often by direct comparison of $^{13}C$ and $^{1}H$ spectra.[417-421] Yb has been particularly recommended as the lanthanide most suitable for $^{13}C$ shifts in view of its small contact/dipolar shift ratios.[422]

The stoichiometry of LSR complexes is still a subject of commanding interest[423-426] with another simple method now available for ascertaining the presence of 1:2 and 1:1 LSR:substrate complexes, which are the most general cases.[427,428] However, the existence of a 1:3 complex of Pr(fod)$_3$ with ($\pi$-$C_5H_5$)Fe(CO)$_2$CN has been reported.[429]

Further calculations of binding constants and bound chemical shifts for LSR complexes have been made[424] and generally compare favorably with potentiometric results.[430]

Other papers include temperature effects,[431] with a $1/T$ dependence for Eu complexes and $1/T^2$ dependence for Pr complexes,[432] and further applications of the dipo-

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lar equation generally using a least-squares approach.[433-436]

The reliability of some of the predicted configurations and the assumption of collinear magnetic and LSR heteroatom axes is still a subject of discussion.[437,438] Cramer and Dubois have recently shown from low-temperature studies that in a dipicoline adduct of $Eu(thd)_3$ this collinearity does not exist and that in such cases of twofold symmetry a modified dipolar equation must be applied taking into account this angular deviation.[439]

Many further applications have been noted for monofunctional donor substrates. Unequivocal structural assignments have been made for isoquinolines[440] and for a rearrangement product of 16-keto-friedel-3-ene.[441] Stereochemical studies include bicycloheptanes,[442] nortricyclanes and norbornenes,[443] cyclohexanones,[444] cycloheptanols,[445] homoadamantanes,[446,447] amphetamines,[448] pyrazolines,[449] and vinyl phosphates[450] and the nature of the double bond linkages in allylic alcohols[451] and oleate/elaidates.[452] The donor properties of nitriles[453] and thiols[454] have been examined together with the effect of europium reagents on coupling constants in norbornanols[455] and in cyclic phosphates.[456] Organometallic compounds have been further studied.[457,458] Polyfunctional substrates include substituted tetrahydropyran acetals,[459] pinitol,[460] quinones,[461] prostanoids,[462] biflavones,[463] esters of camphenic acid (for alcohol enantiomer purity),[464] ricinoleate and hydroxystearate,[465] anils,[466] diazo ketones,[467] aporphine,[468] tropanes,[469] hexenamides,[470] asparagusic acid esters and *S*-oxides,[454,471] oxynitriles,[453] peptides,[472] and poly(methyl methacrylate).[473]

Other topics of interest with regard to shift reagent work include (a) the use of $^{13}C$ magnetic resonance for signal assignments in a tricycloundecadienol,[474] an oligopeptide,[475] and the amaryllidaceae alkaloids;[476] (b) applications of chiral shift reagents (which may be monomeric or dimeric in nonpolar solvents[477]) to the optical purity of 1-deuterio alcohols[478] and of the dihydroxydihydroaldrins[479] ($^{13}C$ magnetic resonance can now be used to amplify the proton information from chiral molecules[480]); (c) the use of alternative shift reagents (metal porphines and phthalocyanines) now fully reported,[481,482] together with several further contributions from Schiemenz regarding the properties of tetraphenylborate anions with pyridine, quaternary amine, aniline, arsonium, stilbonium, and sulfonium cations.[483-487]

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