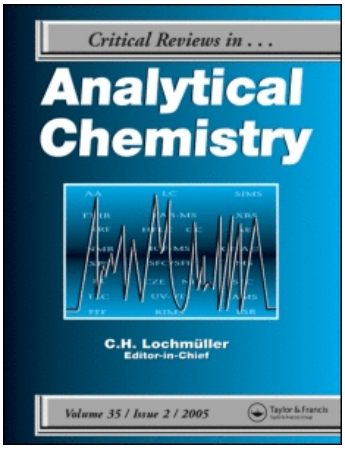

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LANTHANIDE SHIFT REAGENTS IN NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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I. INTRODUCTION

Three decades have elapsed since the first detection of nuclear magnetic resonance (NMR) effects in bulk matter. The intervening period has been rich in rewarding results as the relevant theory has been thought through, the experimental techniques developed, and the applications accumulated. Nevertheless, a review of the current "state of the art" shows that significant progress continues to be made on almost all fronts. Within the last few years new fields of application have been opened by the development of superconducting solenoids,[1-3] by the introduction of various spin-decoupling techniques,[4,5] and by the method of pulse Fourier transform NMR spectroscopy.[6-9] As these innovations originate mainly from progress in instrumentation, acquisition of the techniques by individual laboratories involves the expenditure of considerable sums of money. A much less expensive, but nonetheless important, development in NMR spectroscopy has been the recent introduction of paramagnetic lanthanide complexes as "chemical shift reagents." The theoretical background, practical aspects, and applications of these reagents form the subject of this review.

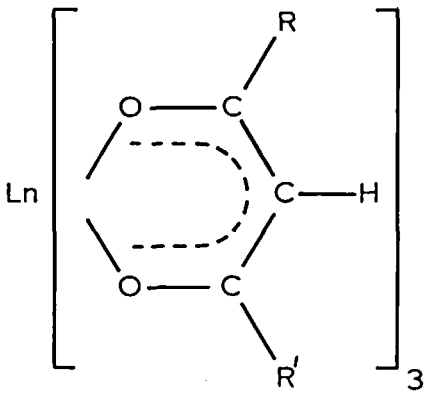
II. HISTORICAL BACKGROUND

The ease with which the NMR spectrum of a sample can be analyzed depends primarily upon the magnitude of the chemical shifts of the atomic nuclei relative to the spin-spin coupling effects. If the shift differences of the multiplet centers are large compared to the components of the multiplets, the spectrum can be interpreted using a first-order analysis. Proton chemical shifts, however, exhibit an intrinsically low sensitivity to changes in both the chemical and stereochemical environment. As a result, many resonances in the ^1H NMR spectra of complex molecules overlap extensively, rendering the evaluation of chemical shifts and coupling constants difficult. Possible

means of achieving spectral simplification include the utilization of solvent-induced shifts, spin decoupling, isotopic substitution, and higher frequency (100, 220, or 300 MHz) spectrometers. An alternative, and often extremely powerful, technique is to run the spectrum of the sample in the presence of a paramagnetic shift reagent. The use of a paramagnetic species as a shift reagent depends on its ability to associate with the molecule under study and thereby bring the molecule under the influence of a strong local magnetic field. The effect of an efficient shift reagent is, therefore, to increase the chemical shift differences between the nuclei of the particular compound without, if possible, significantly affecting the coupling constants or broadening the lines. In favorable instances a complex spectrum that arises from coupled nuclei with nearly coincident chemical shifts can be transformed into one amenable to first-order analysis. Specific protons can display unique chemical shifts in systems where, in the absence of a shift reagent, no resonance line would be observed. Although there are many examples of shift reagents being successfully employed in the NMR spectroscopy of nuclei such as ^{13}C, ^{19}F, and ^{31}P, these nuclei are characterized by an inherently larger range of chemical-shift values than the proton. Consequently, by far the greatest amount of interest and effort has been concerned with the use of shift reagents in ^{1}H NMR spectroscopy, their efficiency for spectral resolution being most marked here.

The effects of paramagnetism on nuclear magnetic resonances have been studied since the beginning of NMR spectroscopy,[10] but the first report on the use of paramagnetic species as shift reagents appeared in 1960. In that paper Jackson et al.[11] showed that addition of the paramagnetic cobalt(II) ion to aqueous solutions of certain diamagnetic salts resulted in a well-resolved two-line ^{17}O NMR spectrum: one line due to the water of hydration of the diamagnetic ion and the other due to the solvent water. Since the cobalt(II) ion has a labile hydration shell, the solvent water resonance is shifted due to the rapid exchange between free solvent molecules and molecules in the hydration mantle, the resonance of the latter being greatly shifted relative to that of pure water. The ^{17}O NMR signal from the water bound to the diamagnetic ion is not shifted appreciably from its normal position in pure water. Comparison of the areas under the two peaks led to the determination of the hydration numbers of the beryllium(II) and aluminum(III) ions.[12] For a subsequent determination of hydration numbers,[13] the rare-earth dysprosium(III) ion was chosen instead of cobalt(II) because it induced a large shift of the ^{17}O resonance of water without appreciable line broadening. In this investigation the shift of the ^{17}O resonance of the solvent water by the dysprosium ion was measured both in the presence and in the absence of the diamagnetic ion. In the absence of the diamagnetic ion, the magnitude of the shift was a measure of the ratio of the paramagnetic ion concentration to the solvent (labile) water in the system. On the addition of the diamagnetic ion, a decrease occurred in the amount of water available to interact with the paramagnetic ions due to some water being retained in the nonlabile environment of the diamagnetic species. This produced an increase in the shift of the solvent $H_2{}^{17}O$ resonance by the paramagnetic ion. Determination of the hydration numbers of beryllium and aluminum ions by this method yielded values in agreement with those obtained by comparing the areas under the two $H_2{}^{17}O$ resonances.[12] The dysprosium ion was also used in a study of the reversible hydration of aliphatic aldehydes and ketones to resolve the ^{17}O resonance of the *gem*-diols from that of water.[14]

Successful attempts to use paramagnetic complexes as chemical shift reagents have been reported since the early 1960's. In most of these studies cobalt(II) and nickel(II) diacetylacetonates, which form labile complexes with various O-, N-, and P-donor ligands,[15-18] were used, although other transition metal complexes were also investigated.[19,20] These shift reagents, however, have not found wide application. Generally, the induced shifts are small, and line broadening is a serious problem. A decisive step for the development of the shift reagent technique was the change to lanthanide derivatives. In 1969 Hinckley[21] reported that addition of the dipyridine adduct of tris(2, 2, 6, 6-tetramethyl-3,5-heptanedionato) europium(III) (abbreviated in this text to $(tmhd)_3$, but also commonly represented by $(dpm)_3$, i.e., (dipivalo-methanato)$_3$) (Figure 1) to a carbon tetrachloride solution of cholesterol produced substantial selective downfield shifts in the ^{1}H spectrum of the steroid without serious line broadening. Shortly afterwards, Sanders and Williams[22] reported that the unsolvated Eu-$(tmhd)_3$ was superior as a shift reagent, the



tmhd (or dpm): R = R' = $C(CH_3)_3$
fod: R = $C(CH_3)_3$, R' = $CF_2 \cdot CF_2 \cdot CF_3$

FIGURE 1. General structure of lanthanide shift reagents of the chelate type.

absence of pyridine eliminating ligand competition. Later Briggs et al.[23] showed that the praseodymium analogue, $Pr(tmhd)_3$, was an efficient shift reagent and generally induced upfield shifts. With the capability of producing shifts in either direction through the use of either the praseodymium or the europium complex, the utility of the method was greatly increased. Thus, a specific peak lying under an envelope otherwise composed of relatively unaffected peaks of "distant" protons could by this means be moved to whichever side of the envelope was clear of other resonances. That effective shift reagents were not limited to $Ln(tmhd)_3$ complexes (the notation "Ln" will be used for any element in the series La-Lu) was first demonstrated by Rondeau and Sievers.[24] They showed that complexes of europium and praseodymium with 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione (abbreviated to fod), of the type $Ln(fod)_3$ (Figure 1), could be used successfully in systems where the tmhd analogues were of little use.

The immediate potential of an efficient shift reagent is apparent from Figure 2, which shows the ^1H spectrum of *cis*-4-*tert*-butylcyclohexanol in the presence of various quantities of $Eu(tmhd)_3$. Only H_1 and the *tert*-butyl protons are readily assignable in the absence of the shift reagent (Figure 2A). Sequential addition of $Eu(tmhd)_3$ improves the resolution, and at a molar ratio of complex to solute of 0.7 the spectrum becomes amenable to first-order analysis (see Figure 2E), all the signals being readily assigned from the spin-spin splitting pattern. As an example of upfield shifts induced by lanthanide complexes, the ^1H spectrum of styrene oxide with and without added $Pr(tmhd)_3$ is shown in Figure 3. In the presence of the shift reagent, the initially coincident *ortho*-, *meta*-, and *para*-proton signals are well separated. With increasing distance from the coordination site (the oxygen atom in this compound), the magnitudes of the reagent-induced shifts decrease. Line broadening, however, is greatest for those protons closest to the site of complexation, the aliphatic protons in the above compound. Illustrative of what can be achieved using $Eu(fod)_3$ is the ^1H spectrum of elatol, a marine natural product, in the presence of various quantities of this reagent, as shown in Figure 4. The extent of induced shift observed for each proton, and the calculated value in parenthesis, are given in the line drawing.

Controlled alteration of NMR spectra by addition of lanthanide shift reagents has been a source of ever-increasing interest since the 1969 report by Hinckley.[21] During the intervening 6 years the stream of publications concerned with this area of NMR spectroscopy has grown from a mere trickle to a veritable deluge. Many of these papers are not listed here. However, these reagents have been the subject of a number of recent reviews,[27-41] and the reference collections of these articles, when combined, provide a comprehensive literature coverage. In this article, which attempts a critical survey of the field, the efficiency, understanding, and application of lanthanide shift reagents are considered in detail. Although much effort has been devoted to the elucidation of the principles and to the establishment of optimum methods for obtaining and analyzing shift data, many important points remain controversial.

III. PRINCIPLES

A. General

Lanthanide shift reagents (LSR's) of the chelate type – complexes of paramagnetic rare-earth ions with β-diketones (Figure 1) – are Lewis acids. The action of these complexes as shift reagents depends entirely on their ability to form labile adducts with suitable molecules (substrates) in solution. Lanthanide-induced shifts (LIS's) have been observed with most organic molecules that contain heteroatoms with a lone pair of electrons (oxygen, nitrogen, sulfur, phosphorus), i.e., substrates possessing some degree of Lewis basicity. The complexed lanthanide ion expands

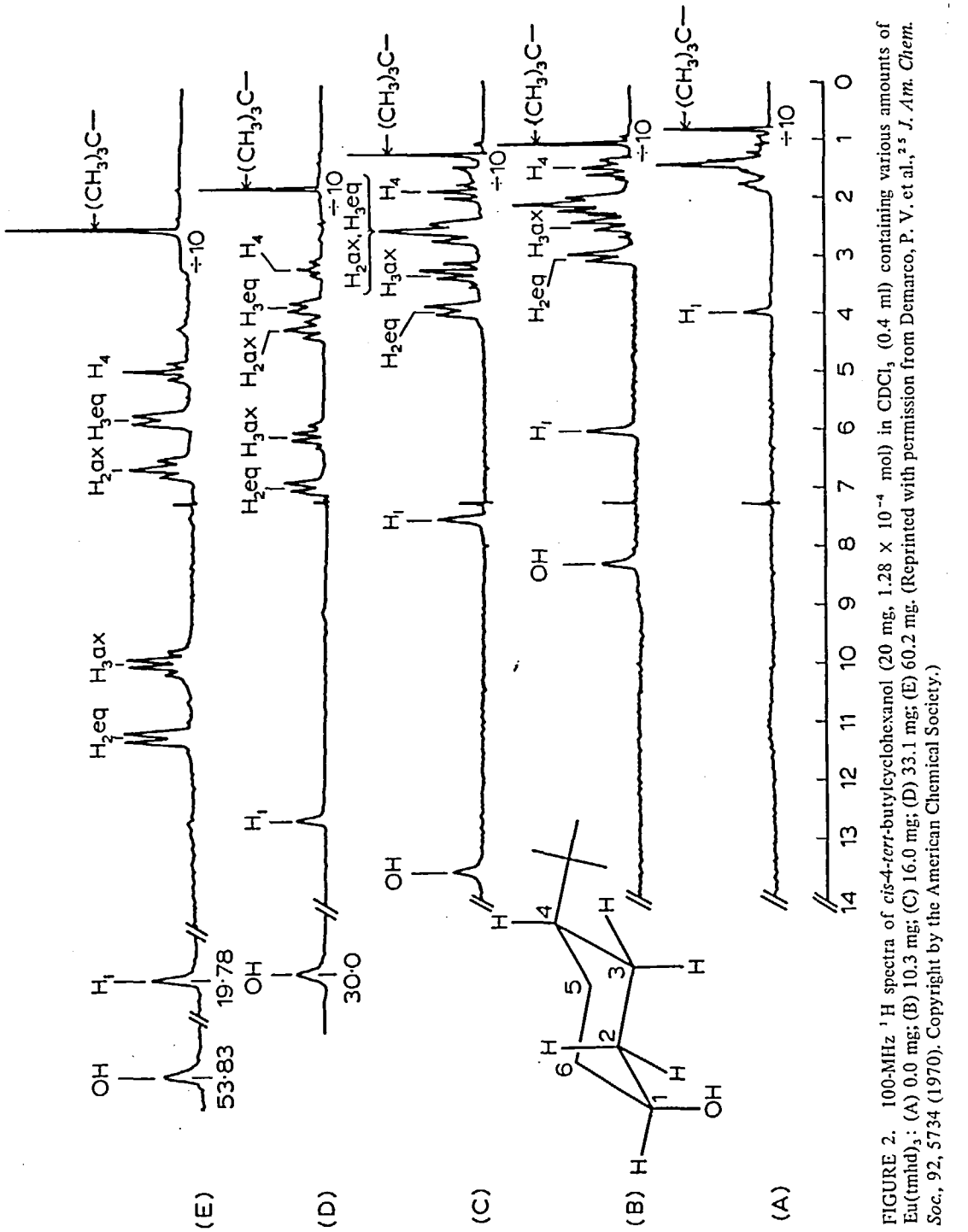


FIGURE 2. 100-MHz ^{1}H spectra of *cis*-4-*tert*-butylcyclohexanol (20 mg, 1.28×10^{-4} mol) in $CDCl_3$ (0.4 ml) containing various amounts of Eu(tmhd)$_3$: (A) 0.0 mg; (B) 10.3 mg; (C) 16.0 mg; (D) 33.1 mg; (E) 60.2 mg. (Reprinted with permission from Demarco, P. V. et al.,[25] *J. Am. Chem. Soc.*, 92, 5734 (1970). Copyright by the American Chemical Society.)

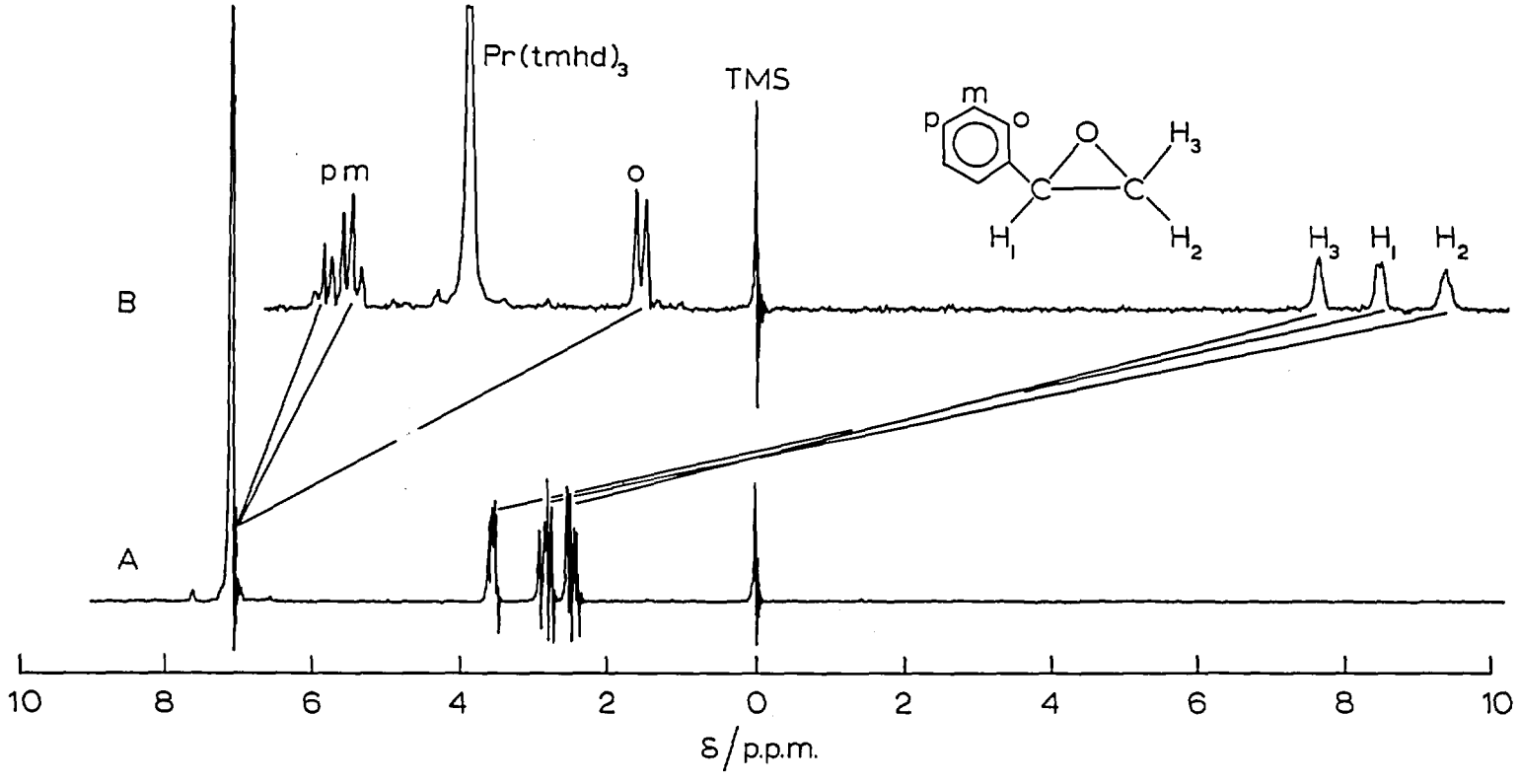


FIGURE 3. 60-MHz ^{1}H spectra of styrene oxide in CCl_4: (A) unshifted spectrum; (B) 0.25 mol equivalents $Pr(tmhd)_3$ added. (Courtesy of Perkin-Elmer Limited.)

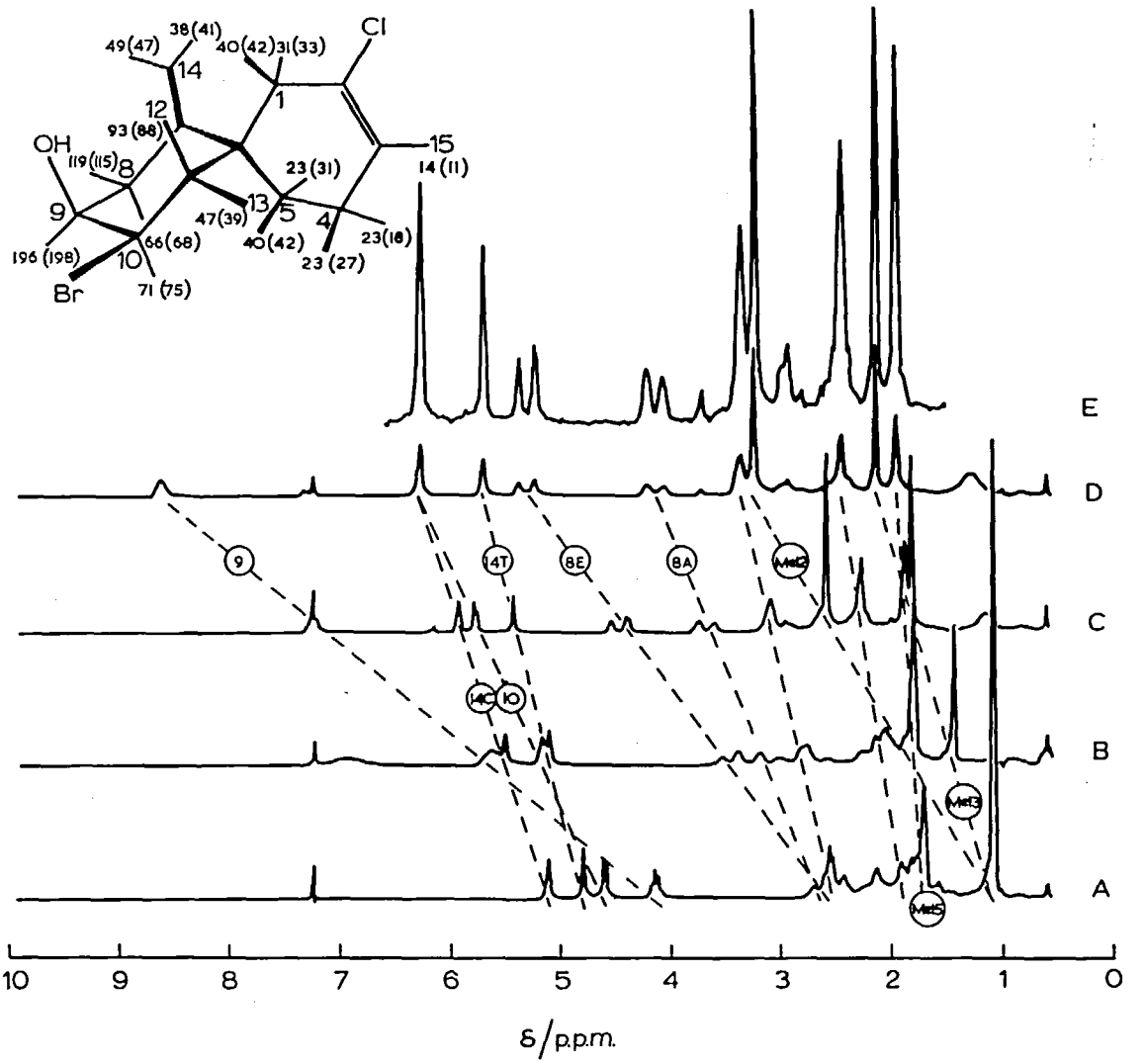


FIGURE 4. 100-MHz ^{1}H spectra of elatol in $CDCl_3$: (A) unshifted spectrum; (B), (C), and (D) increasing increments of $Eu(fod)_3$; (E) same as D with increased amplitude. (From Sims, J. J., Lin, G. H. Y., and Wing, R. M.,[26] *Tetrahedron Lett.*, p. 3487 (1974). With permission.)

its coordination sphere by interaction with the lone-pair electrons on the donor atom, thereby forming a new complex in solution. Under the usual conditions of the experiment (room temperature, moderate excess of substrate), the equilibrium between substrate molecules coordinated to the lanthanide ion and excess uncomplexed substrate free in solution is a rapid process on the NMR time scale. Only a time-averaged substrate spectrum is, therefore, recorded, and the observed resonance positions of the nuclei are the concentration-weighted averages of the appropriate chemical shifts in the free and complexed state. Because of the paramagnetism of the complex, the latter shifts may be very different from the former. The overall effect is that the substrate resonances are shifted from their normal diamagnetic values by an amount which depends on the relative concentration of shift reagent. More than a mere displacement of spectral lines is involved, however. Whereas enhancement of the external primary magnetic field applied to a sample causes a linear expansion of the spectrum leaving the relative chemical shifts (in ppm) unchanged, the internal secondary field in a paramagnetic system causes a differential expansion of the spectrum, since factors such as the distances of the nuclei from the paramagnetic ion are important. The familiar sequence of signals may, therefore, be altered.

Although the utility of aromatic solvent-induced shifts (ASIS) as aids in the analysis of complex spectra has long been recognized, the ASIS phenomenon continues to be a controversial NMR problem.[42a-42c] Clearly, however, there is a similarity between the mode of action of solvents such as benzene and pyridine and paramagnetic ions on NMR spectra. Both types of shift reagent are sources of internal secondary magnetic fields, which are usually anisotropic, their magnitude and direction changing with the direction of the primary field. The ASIS effects are normally small (<1 ppm), however, and often only affect a small part of the organic molecule.[43] On the other hand, paramagnetic ions with at least one unpaired electron exert much stronger secondary fields and therefore afford potentially greater spectral spreading properties. A point to note is that although the internal secondary field is practically always anisotropic, the nuclear shift is referred to as isotropic because it is the averaged result over all orientations of a molecule tumbling freely in solution.

B. Contact and Dipolar Interactions

Unpaired electron spins can perturb the nuclear resonance positions of complexed substrates by a (Fermi) contact interaction, a dipolar interaction or a combination of both mechanisms. Δ_B denotes the chemical shift of a given nucleus in the LSR-substrate complex relative to its diamagnetic (uncomplexed) position; Δ_B can, therefore, be expressed as the sum of two contributions

$$\Delta_B = \Delta_{con} + \Delta_{dip} \quad (1)$$

where

Δ_{con} = the contact shift;
Δ_{dip} = the dipolar, or pseudocontact, shift.

The LIS in resonance of the ith nucleus is given by

$$\Delta\delta_i = \delta_i\,[\text{LSR} \neq 0] - \delta_i\,[\text{LSR} = 0] = \alpha\,\Delta_B{}^i \quad (2)$$

where α = the fraction of substrate present as complex; $\Delta\delta_i = \Delta H_i/H$, where ΔH_i is the change in field strength at nucleus i.

Contact, or direct nuclear spin-electron spin, interaction requires the presence of a finite unpaired electron spin density at the resonating nucleus. This may occur either from direct delocalization or via spin polarization.* Both π and σ bonds may be involved in the process, although the interaction attenuates rapidly through a series of σ bonds. For contact nuclear resonance shifts to be observed, either the electronic spin-lattice relaxation time, T_{1e}, or the electronic exchange time, T_E, must be short compared with the isotropic hyperfine interaction constant, a_i.[44] The nucleus will then experience a single average hyperfine magnetic field, the resonance being shifted according to the populations of the Zeeman levels of the electron spin. Under these conditions and for a spin-only system (i.e., no spin-orbit coupling), the contact shift is given by[44,45]

$$\Delta_{con}{}^i = -a_i \frac{\gamma_e}{\gamma_N} \frac{g\,\beta\,S\,(S+1)}{3\,k\,T} \quad (3)$$

where

γ_e = the magnetogyric ratio of electron;
γ_N = the magnetogyric ratio of nucleus;
g = the spectroscopic splitting factor of the paramagnetic species;
S = the total electron spin;
β = the Bohr magneton;
k = the Boltzmann constant;
T = the thermodynamic temperature.

a_i is proportional to the unpaired spin density at nucleus i. If spin-orbit coupling is included in the treatment, more complex equations are required.[46] Contact shifts are a potential source of information about the nature of the paramagnetic atom-ligand bond and about the bonding within the ligand itself.

Electron-nuclear dipolar interaction is a magnetic field effect acting through space, rather than an effect through bonds, and it gives rise to the so-called pseudocontact shifts. In McConnell and Robertson's theory,[47] the pseudocontact shift results from a failure of the dipolar interaction to average to zero if the paramagnetic ion possesses an anisotropic g tensor. For a complex of axial symmetry with a tumbling time much longer than

*The movement of unpaired electron spin density within a molecule can be described in simple, if rather inexact, terms. Partial unpairing of the electrons about a nucleus may be caused either by a partial transfer of the unpaired electron to the immediate environment of the nucleus (direct delocalization) or by a partial transfer of one of the formerly paired electrons from the region of the nucleus to pair off with the paramagnetic electron (spin polarization).

the electronic spin-lattice relaxation time, the pseudocontact shift is then given by

$$\Delta_{dip}{}^{i} = -c \cdot F(\theta_i, r_i) \cdot G(g_{\parallel}, g_{\perp}) = -\frac{\beta^2 J(J+1)}{45 k T} \cdot \frac{3\cos^2\theta_i - 1}{r_i{}^3} \cdot (3g_{\parallel} + 4g_{\perp})(g_{\parallel} - g_{\perp}) \quad (4)$$

where

r_i = the length of the vector between nucleus i and the paramagnetic ion, which is regarded as a magnetic point-dipole;
θ_i = the angle between this vector and the principal magnetic axis of the molecular complex (commonly assumed to be collinear with the lanthanide-substrate bond;
$g_{\parallel}$ = the parallel component of the g tensor with respect to this axis;
$g_{\perp}$ = the perpendicular component of the g tensor with respect to this axis;
J = the total angular momentum.

A dipolar, axially symmetric field, with the principal magnetic axis of the lanthanide taken to be collinear with the lanthanide-substrate bond, is illustrated in Figure 5. (In McConnell and Robertson's paper,[47] there is an error of signs in the G $(g_{\parallel}, g_{\perp})$ term;[19] the equation given here is the corrected form.) The relative signs of the g tensors determine whether the induced shifts occur predominantly to low or high field. For axially symmetric systems, the $(3\cos^2\theta_i - 1) r_i{}^{-3}$ term is a potential source of information about the geometry of the substrate molecule and, for a given complex, controls the relative induced shifts. Thus, in a complex containing several similar nuclei $i, j, \ldots$ the distribution of these shifts can be described solely in terms of the molecular geometry, i.e.,

$$\Delta_{dip}{}^{i} : \Delta_{dip}{}^{j} : (\ldots) = \frac{3\cos^2\theta_i - 1}{r_i{}^3} : \frac{3\cos^2\theta_j - 1}{r_j{}^3} : (\ldots) \quad (5)$$

The r^{-3} dependence predicts that the dipolar shift decreases rapidly with distance. The angular dependence predicts that within the same substrate there may be shifts of different signs since $(3\cos^2\theta - 1)$ changes sign at $\theta = 54.736°$ ($\approx 54°$ 44′) and 125.264° ($\approx 125°$ 16′), being negative between 54.736° and 125.264° (Figure 6). For complexes of axial symmetry, $g_x = g_y \neq g_z$, $g_x = g_y = g_{\parallel}$, and $g_z = g_{\perp}$. The equation for the

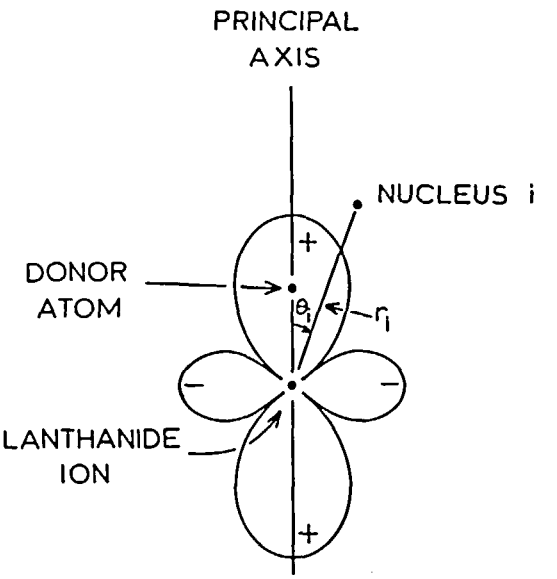


FIGURE 5. The dipolar field for an axially symmetric complex.

dipolar shift for dissolved complexes in which $g_x \neq g_y \neq g_z$ has also been obtained.[48]

Equation 4 was derived primarily to explain dipolar shifts induced by transition-metal ions, and, in an extended form, the equation was first used in the context of lanthanide shift reagents by Hinckley.[21] The more recent treatise by Bleaney[49] is designed to account for LIS's. Rather than ascribing dipolar shifts in a lanthanide complex to anisotropic g factors, this theory attributes these shifts to anisotropy in the magnetic susceptibility arising in less than cubic geometries. The magnetic susceptibility depends on the electronic configuration of the paramagnetic ion, the ligand field, and the temperature. For an axially symmetric complex the dipolar shift predicted by Bleaney's theory is given by

$$\Delta_{dip}{}^{i} = \frac{\beta^2}{60(k T)^2} \cdot \frac{3\cos^2\theta_i - 1}{r_i{}^3} \cdot 2A_2{}^0 \langle r_i{}^2 \rangle \cdot g^2 J(J+1)(2J-1)(2J+3) \langle J \| \alpha \| J \rangle \quad (6)$$

where

$A_2^0 \langle r_i^2 \rangle$ = the crystal field coefficient;
$\langle J \| \alpha \| J \rangle$ = a numerical coefficient.

An important point to note is that the angular and distance sequence dependence of the second factor on the right-hand side of Equation 6 is the same as

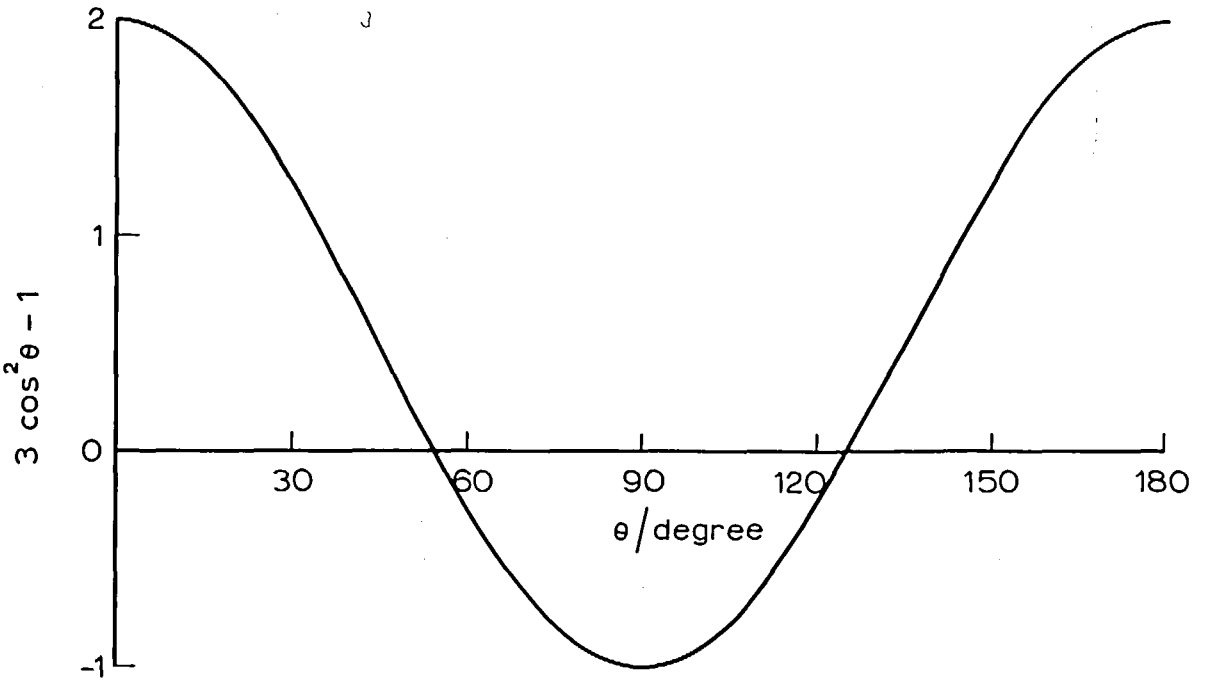


FIGURE 6. The variation of $(3\cos^2\theta - 1)$ with the angle θ.

that found for anisotropic g factors in axially symmetric complexes (Equation 4) so that comparisons within a complex (or among complexes of similar structure) made using this assumption should remain valid.

A major difference between these two theoretical treatments of the dipolar shift is the expected temperature dependence. According to Equation 4, the shift should be proportional to T^{-1} (i.e., should exhibit a Curie law behavior), provided the molecular geometry is independent of temperature, whereas Equation 6 predicts a T^{-2} temperature dependence for the shifts of all lanthanide ions other than Eu^{3+} amd Sm^{3+}. For Eu^{3+} ($4f^6$), with $J = 0$ as the ground state, the shift given by Equation 6 is zero. However, both Eu^{3+} and Sm^{3+} have low-lying excited J states, and interaction terms involving these excited states must be included in the theoretical treatment. As a result, the dipolar shifts for Eu^{3+} and Sm^{3+} have a more complex temperature dependence, but one that should approximate T^{-1} near room temperature.[49] With the other lanthanide ions, the excited states make little contribution to the predicted shifts.[49] Various experimentally determined relationships between the LIS and temperature have been reported, and some of these are considered in Section IV.F.2.

As already mentioned, the angle-dependent term that occurs in both Equation 4 and Equation 6 may account for shifts of different sign within the same substrate. The crystal-field coefficients of the third factor of Equation 6 furnish an additional reason for sign reversals of chemical shifts on going from one series of lanthanide complexes to another. These coefficients may change sign upon change of symmetry of a complex.[50] The constancy of the crystal-field coefficient for a given complex throughout the lanthanide series can be tested by comparing the ratios of shifts of different nuclear resonances for the different lanthanides. When these ratios are independent of the lanthanide cation, it is reasonable to assume that the shifts have their origin in dipolar coupling, that the geometry of the Ln(III) ligand complex is the same along the lanthanide series, and that, to a good approximation, the observed anisotropy of the magnetic susceptibility of the complex has axial symmetry.[50,51]

Although Equation 4 applies to a complex with an anisotropic g factor and Equation 6 depends on the anisotropy in the magnetic susceptibility of the complex, both equations require the anisotropy to be axially symmetric. The problem of axial symmetry in complexes formed between a LSR and a substrate continues to be a vexed one,

however. If the substrate-shift reagent complex has an axially symmetric magnetic anisotropy, the dipolar shifts may be expressed in terms of a site factor $F(\theta, r)$, as in Equations 4 and 6. If such a situation does not obtain, a further angular term must be introduced. Equation 7 gives the most general form of the expression for dipolar shifts[41]

$$\Delta_{dip}{}^{i} = C_1 (3\cos^2\theta_i - 1) r_i^{-3} + C_2 (\sin^2\theta_i \cos 2\phi_i) r_i^{-3} \quad (7)$$

where

- r_i = the length of the vector that joins the rare earth ion and the nucleus being examined;
- θ_i = the angle this vector makes with the z magnetic axis (as shown in Figure 7);
- ϕ_i = the angle which the projection of r_i into the xy plane makes with the x magnetic axis;
- C_1 and C_2 = functions of the magnetic anisotropy of the complex.

Comparing the relative shifts now no longer effectively cancels the constant terms, as occurs when axial symmetry obtains. Most workers, however, have chosen to ignore the second term in Equation 7, and from studies on a variety of rigid substrate molecules there is, indeed, compelling evidence that in many of these systems the first term of Equation 7 satisfactorily accounts for the observed shift ratios. Since the rigorously axially symmetric system is rarely met in practice,[52,53] effective axial symmetry must somehow be achieved in solution. Models that have been proposed to account for the apparent axial symmetry of many lanthanide complexes in solution are considered in Section IV.F.4.b.

C. Origin of the Lanthanide-induced Shifts

If only a "spread-out" spectrum is required, the source of the spectral spreading properties may be disregarded. Any shift reagent with sufficient spectral shifting potential may be used in any desired manner. Distinction between contact and dipolar shifts only becomes important if information about the electronic structures of paramagnetic complexes or about the geometrical structures and conformations of substrate molecules in fluid solution is sought. Since no means are available for correlating the contact shift with geometrical coordinates, and since a reliable separation of the observed shift into contact and dipolar contributions is seldom possible, the utility of shift reagents for structural (i.e., geometrical structure) and stereochemical analyses relies on the assumption that the nuclear resonance displacements are exclusively or nearly exclusively dipolar in origin.

There is, as yet, no direct evidence regarding the origin of the shifts induced by LSR's. The resonating nuclei commonly encountered in organic compounds fall into two classes, and two distinct classes of shift are evident: (1) nuclei such as ^{1}H, ^{13}C, and ^{19}F and (2) nuclei such as ^{14}N, ^{17}O, and ^{31}P, which carry lone-pair electrons and are capable of direct bonding with the coordinating lanthanide ion with consequent direct interaction with the metal electron spin vector. Much of the proton shift data presently available are consistent with a dominant dipolar mechanism,[37,53,54] but instances are becoming increasingly common where contributions from contact interactions on protons as well as on other nuclei may be considerable. Since the radial extension of the 4f orbitals is small, unpaired electrons in these orbitals are well screened from the ligand by the s and p electrons and are unlikely, therefore, to be involved to any great extent in lanthanide-ligand bonding. The situation thus differs significantly from that of the d-series transition metals where the valence 3d electrons are exposed and, therefore, suitably situated to participate in covalent bonding with ligands. Nevertheless, contact contributions to LIS's cannot be discounted, because even as little as 1% covalency should be observable.[55] Such contributions might be expected to be greatest at the substrate atom directly coordinated to the lanthanide ion and, in general, to be confined, with saturated substrates at least, to carbons and hydrogens in the immediate vicinity of the coordination site. At the present time, however, no firm basis exists for the prediction of either the direction or magnitude of contact contributions to LIS's on carbon or proton spectra. A theoretical study of the ^{14}N and ^{17}O NMR shifts in lanthanide complexes has been performed by Golding and Halton.[56] Their second-order perturbation treatment of the calculation of the mean value of the spin polarization at the

thermal motion of the molecules), the coupling of the nuclear spin with the lattice is largely eliminated. As a result, the nuclear spin-lattice relaxation times become longer, and the line width of the NMR signals accordingly decreases. The electron spin relaxation times of cobalt(II) and nickel(II) complexes are generally short enough that reasonably narrow NMR lines occur. Nevertheless, line broadening is usually sufficient to degrade the fine structure of the resonances markedly, particularly for nuclei in close proximity to the transition metal ion.[18] For the lanthanide series, the situation is analogous to that for cobalt(II) and nickel(II) shift reagents; some ions of the series have short T_{1e} times and do not exhibit pronounced NMR line-broadening effects. Complexes of europium(III) and praseodymium(III) are of special interest in that the electron spin relaxation times are generally sufficiently short that very narrow NMR lines are observed, the multiplet structure still remaining resolved up to quite high relative concentrations of shift reagent to substrate.

Measurements of line broadenings and longitudinal nuclear spin relaxation rates for quinoline in the presence of $Eu(tmhd)_3$ have shown that $1/T_2 > 1/T_1$, where T_1 and T_2 are the longitudinal and transverse relaxation times of the substrate protons.[72] From a consideration of the factors contributing to the line width, it was concluded that line broadening caused by the enhancement of the transverse relaxation rate arises mainly from the chemical shift difference between the complexed and uncomplexed states of the substrate. Consequently, a greater degree of broadening is to be expected with reagents that induce larger shifts.

IV. METHODOLOGICAL STUDIES

A. Requirements for an Effective Shift Reagent

Among the many known lanthanide ion complexes, only a few have found application as shift reagents. Two requirements, in particular, limit the selection: (1) the magnitude of the induced shift and (2) the broadening characteristics of the shifted resonances. While both optimal shifting power and minimal signal broadening effects are clearly highly desirable, the relative importance of these factors varies according to the specific application involved. Other important requirements for an effective and versatile shift reagent are (3) the ability to interact with a wide range of substrates, (4) sufficient solubility of both the shift reagent and its complexes with added substrates, and (5) the absence of NMR signals from the shift reagent nuclei in the usual range of substrate spectra.

A reagent that fulfills the above requirements should be generally effective in generating shifts for spectral simplification. For possible use in structural and stereochemical studies, however, the reagent must satisfy additional requirements. (6) Dipolar interactions should dominate over contact interactions. (7) The secondary fields should be axially symmetric. (8) The shift reagent-substrate complex should be conformationally uniform, although the substrate itself may exist in several conformations. (9) The induced shifts should exhibit a straightforward temperature dependence.

The results of studies relating to the use of shift reagents and to the selection of the most suitable LSR for a particular application are considered in this section. As additional information becomes available, the goal of selective shift reagents designed for special problems will become more accessible. Since most of the published work on LSR's concerns ^1H NMR spectra, much of what follows relates to protons. For nuclei other than ^1H the range of chemical shift values is such that signal coincidence is seldom a problem, and good resolution is usually obtained. Accordingly, LSR's cannot offer the same outstanding advantages for spectral simplification, but with these nuclei they may still be of considerable help in the problem of resonance assignment. In this, as in all quantitative geometry determinations, however, their usefulness depends greatly on the size of the contact contribution to the induced shift.

B. Lanthanide Chelates

1. Central Ion

In selecting a shift reagent for a particular problem, the shift magnitude, line-broadening effect, position of the ligand resonance, and direction of the induced shift may be important. The effect of variation in the paramagnetic central ion on the induced shift has been investigated for several series of analogous lanthanide complexes. Table 1 and Figure 8 show some results of these comparative studies of shifting abilities for proton resonances. Positive values denote shifts towards lower field. Lanthanum(III) and lutetium(III) are diamagnetic, possessing no unpaired electrons, and

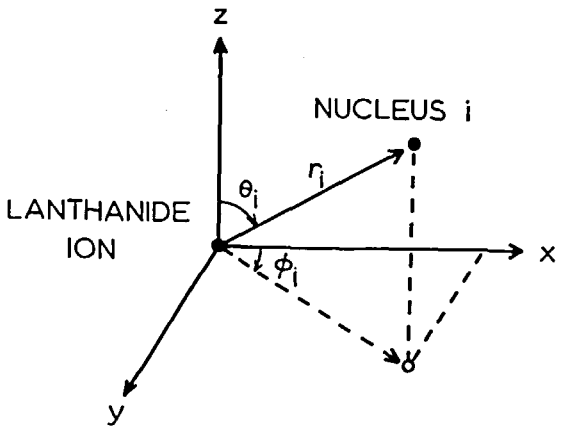


FIGURE 7. Coordinates r_i, θ_i, and ϕ_i of a nucleus i in the coordinate system x, y, z.

paramagnetic ion includes the effects of mixing with higher energy spectroscopic states. According to these investigators, bonding will occur primarily through the 6s metal orbital, and the orbital overlap will result in a transfer or metal electron spin density to the coordinated atom. The calculations also indicate that no significant direct bonding of the 4f orbitals with the orbitals of the ligand nuclei is involved.

An exclusive dipolar interaction cannot account for the observed LIS's of protons near the sites of coordination in steroids,[57] pyridine *N*-oxides,[58] anilines,[59] and phenols.[59] Stereospecific contact interactions in the ^{1}H NMR spectra of polyol-lanthanide complexes have been reported.[60] According to this report, the contact interaction is greatest when the bonds connecting the proton and the cation form a planar zigzag arrangement; in such complexes the contact interaction can apparently be detected even over five intervening bonds. Lanthanide-induced contact shifts have been observed in the ^{13}C NMR spectra of ketones,[61] pyridines,[62] and organonitriles.[63] The ^{13}C resonances appear to be more sensitive to contact contributions than proton resonances involving the same number of intervening bonds to the site of the metal atom coordination.[64,65] From ^{17}O NMR studies of aquo complexes of lanthanides,[66] it was concluded that the contact shift was dominant for the oxygen atoms in the first coordination sphere. Evidence has been presented for a significant, sometimes dominant, contact contribution to the resonances of ^{14}N coordinated to a wide range of lanthanide tmhd chelates;[67] thus, for Eu(tmhd)$_3$ the ^{14}N shifts in various organic molecules are upfield, whereas the expected dipolar shifts would be downfield. Significant contact shift contributions are also required to account for the direction and magnitude of LIS's in the ^{31}P spectra of various organophosphorus substrates.[68] Lanthanide-induced ^{19}F shifts in various aliphatic compounds appear to be due to both the dipolar and contact shift mechanisms.[69] On the other hand, the agreement between experimentally induced shifts and calculated values for ^{19}F nuclei in a trifluoroindanol indicates a dominant dipolar mechanism.[70] A possible reason why dipolar shifts dominate for protons but not necessarily for nuclei such as ^{13}C has been advanced.[71]

The papers just cited, and many references contained therein, indicate clearly that LIS's for atoms located adjacent to the complexing site in the ligand are not suitable for use in quantitative structural studies. Indeed, when undertaking structural evaluations using the dipolar-mechanism equations, it is probably only safe to neglect contact contributions to LIS's if at least three atoms (i.e., four bonds) are situated between the nucleus under study and the lanthanide ion.[41]

D. Nuclear Relaxation in Lanthanide Complexes

Since the interaction of nuclei with unpaired electrons can lead to an enhancement of the nuclear spin relaxation rates, large contact or dipolar shifts are often accompanied by appreciable signal broadening. It is, in fact, the severe line broadening caused by most of the d-series transition metals (Co^{2+} and Ni^{2+} are the exceptions) that prevents the more general use of transition metal complexes as shift reagents in NMR spectroscopy. Because electrons have very large magnetic moments, strong fluctuating magnetic fields are associated with paramagnetic species in thermal motion. These electromagnetic "stray fields" shorten the lifetime of a given spin state by inducing nuclear transitions and, consequently, increase the line width of the resonance signal. If the nuclear spin relaxation is sufficiently rapid, the signal may be broadened to such an extent that detection and, particularly, resolution become extremely difficult. If, however, the *electronic* spin-lattice relaxation time, T_{1e}, is sufficiently short (i.e., if the mean lifetime of the electron spin states is brief in comparison with the correlation time for the

TABLE 1

Comparisons of Lanthanide-induced ^{1}H Shift Values[a]

LSR		$Ln(tmhd)_3$	$Ln(tmhd)_3$	$Ln(fod)_3$	$Ln(C_5H_5)_3$	$Ln(ClO_4)_3[OP(NMe_2)_3]_4$
Substrate		4-Vinylpyridine	Cyclohexanone	Tetrahydrofuran	Cyclohexylisonitrile	Acetonitrile
^{1}H resonance		H-2	α-CH_2	α-CH_2	H-4	CH_3
LSR/substrate mole ratio		0.125	1	0.1		
Solvent		$CDCl_3$	CCl_4	CCl_4	Toluene-d_8	Acetonitrile
Ln(III)	f^n	Δδ/ppm	Δδ/ppm	Δδ/ppm	Δδ/ppm	Δδ/ppm
Ce	f^1				− 4.19	− 1.5
Pr	f^2	− 6.6	−11.25	− 5.00	− 6.23	− 3.0
Nd	f^3	− 3.2	−5.55	− 2.67	~− 2.90	− 1.15
Sm	f^5	− 0.8	~− 1.35	− 0.42	− 1.14	− 0.27
Eu	f^6	3.5	2.95	3.08	11.04	1.33
Tb	f^8	−30.7	−26.25		−28.8	−19.2
Dy	f^9	−33.8	−54.05	− 0.33[b]	−56.6	
Ho	f^{10}	−24.0	−51.45	−18.0	−36.9	−17.0
Er	f^{11}	9.1	25.55	0.97[c]	4.26	4.4
Tm	f^{12}	23.6		18.2	16.4[d]	6.9
Yb	f^{13}	11.0	12.15	7.08	12.9[d]	6.66
Reference		73	74	75	76	23

[a]Positive values indicate downfield shifts.
[b]Because of marked broadening, a LSR/THF mole ratio of 0.001 was used.
[c]Because of marked broadening, a LSR/THF mole ratio of 0.01 was used.
[d]Substrate: $P(n\text{-}C_4H_9)_3$.

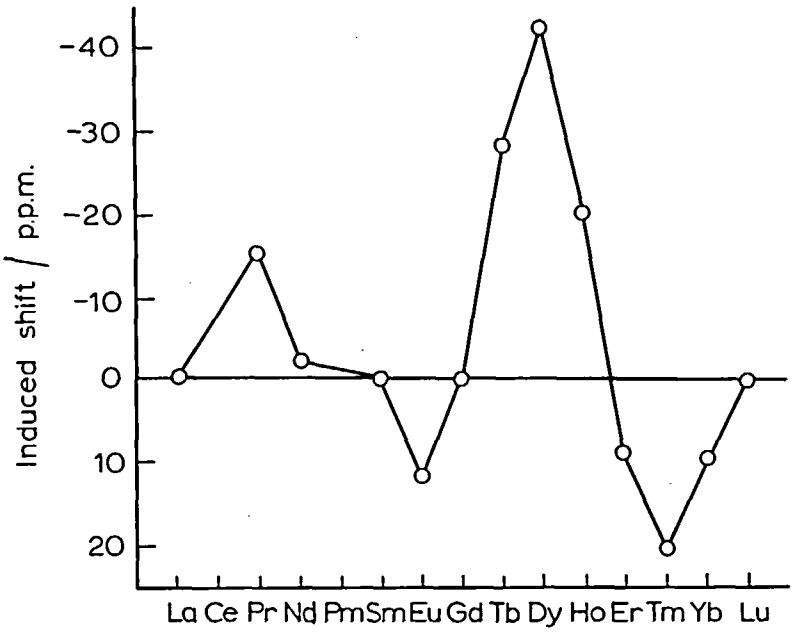


FIGURE 8. Observed shift of H-1 resonance in spectra of 1-hexanol (0.8 *M* solution in $CDCl_3$ at 30°C) produced by Ln(tmhd)$_3$ at a LSR/substrate mole ratio of 0.125. (After Horrocks and Sipe.[73])

may be used to ascertain the "complex-formation shift" (i.e., the change in chemical shift due to complex formation with a diamagnetic lanthanide) in the absence of the paramagnetic shift.[50,59,61,77-79] Of the lighter paramagnetic lanthanides, Pr complexes produce the largest upfield shifts and Eu complexes the largest downfield resonance displacements. The heavier lanthanides (Tb-Yb) generally induce shifts that are greater in magnitude than those observed with the lighter elements of the group. Since comparative data of the type shown in Table 1 and Figure 8 are highly dependent on the particular substrate, extrapolations to other systems may not always be valid. According to available data,[76] the lanthanide complexes of each of the three triads (Ce, Pr, Nd), (Tb, Dy, Ho), and (Er, Tm, Yb) induce dipolar shifts of the same sign for nuclei in corresponding positions. In general, the central member of each triad (Pr, Dy, and Tm) produces the largest shifts.

The line width of the NMR signals of paramagnetic complexes is determined mainly by the electronic spin-lattice relaxation time, T_{1e} (Section III.D). Apparently, strong spin-orbit coupling and the presence of rather closely spaced energy levels cause the T_{1e} times of some $4f^n$ systems to be very short compared with molecular reorientation times. This results in relatively ineffectual relaxation of ligand nuclei. Cations such as Eu(III) and Pr(III) are in this category and should, therefore, cause little broadening of NMR lines. Gadolinium(III), on the other hand, has a relatively long electron spin relaxation time, which will give rise to enhanced nuclear relaxation and extensive relaxational broadening. Cations such as Ho(III) with intermediate relaxation times may be expected to cause a considerable degree of line broadening. Broadening at low lanthanide concentrations is undesirable since it prevents the resolution of small couplings that may otherwise be useful for assignments. At higher concentrations of lanthanide, broadening becomes a more serious problem and leads to eventual loss of the signals. Table 2 presents the widths at half-maximum peak height of corresponding ^{1}H NMR signals as observed in the presence of members of three series of analogous lanthanide complexes. The results show that, although the heavier lanthanides generally possess greater shifting ability, they usually cause more extensive broadening. Of these latter elements, Yb is the most attractive, producing only moderate broadening.

The results of these surveys suggest that for maximum resolution and significant shifting in ^{1}H spectra, the Eu, Pr, and Yb systems may be most useful. For applications requiring particularly large

TABLE 2

Line Widths at Half Height of ^{1}H NMR Signals of Some Lanthanide Systems

LSR	$Ln(tmhd)_3$	$Ln(tmhd)_3$	$Ln(C_5H_5)_3$
Substrate	2-Picoline	Cyclohexanone	Cyclohexylisonitrile
^{1}H resonance	CH_3 of 2-picoline	α-CH_2	H-4
LSR/substrate mole ratio	0.125	1	
Solvent	$CDCl_3$	CCl_4	Toluene-d_8
Ln(III)	$\Delta\nu_{1/2}$/Hz	$\Delta\nu_{1/2}$/Hz	$\Delta\nu_{1/2}$/Hz
Ce			23
Pr	5.6	>20	30
Nd	4.0	>20	32
Sm	4.4	>20	20
Eu	5.0	~15	40
Tb	96	75	35
Dy	200	85	100
Ho	50	92	55
Er	50	61	40
Tm	65	90	60
Yb	12	23	70
Reference	73	74	41

upfield or downfield shifts, however, complexes of Tb, Dy, or Ho may be found useful, despite their substantial line-broadening effects with resultant loss of spin coupling information.

Severe line broadening makes spectra difficult to observe in the presence of Gd(III) complexes, but in several investigations[73,80,81] it has been shown that addition of these complexes produces no detectable shifts in ^{1}H NMR spectra. Since Gd(III) has a magnetically isotropic ($^8S_{7/2}$) ground state and cannot, therefore, in this state exhibit a dipolar shift, the absence of observable shifts suggests the absence of contact interactions in these instances. Because of its relatively long electron spin relaxation time and highly isotropic magnetic moment, Gd(III) has potential value as a line-broadening or "relaxation" reagent (severe broadening with negligible shift).[82] The general procedure proposed is that of inducing large shifts between resonances by addition of one of the usual LSR's and then adding a Gd complex to broaden the lines. Simultaneous use of a shift reagent and a relaxation reagent has been advocated as a method for effecting structural analyses complementary to the technique based on analysis of the assumed dipolar shifts. The potential of this relaxation reagent method for structure determination is discussed in Section IV.F.4.c. Because of the effectiveness of gadolinium in causing relaxation, gadolinium complexes may also have potential value as spin decoupling reagents for use in conjunction with shift reagents for elucidating couplings between protons in complex molecules;[83] they may also prove to be a valuable tool for the assignment of carbon-13 resonances.[84]

An analysis of the available data concerning the origin of LIS's (outlined in Section III.C) would appear to support the following broad picture. For protons remote from the lanthanide ion, a good fit with experiment is obtained by the dipolar mechanism alone. For nuclei such as ^{13}C and ^{19}F, and also for protons close to the lanthanide ion, both contact and dipolar mechanisms may be important. For nuclei such as ^{14}N, ^{17}O, and ^{31}P, which carry lone-pair electrons and are capable of direct bonding with the coordinating lanthanide ion, the shift may be attributed to a predominantly contact mechanism. Clearly, therefore, no one shift reagent is likely to be the best choice for all applications. In the preceding paragraphs of this section the selection of lanthanide ions most suitable for ^{1}H NMR studies has been considered. Complexes of these ions will not necessarily be the shift reagents of choice for other magnetic nuclei participating to different extents in the two types of interaction.

Interestingly, however, comparative studies of the effects of lanthanide $(tmhd)_3$ chelates on the ^{1}H NMR spectrum of aniline, ^{19}F NMR spectrum of 2,4,6-trifluoroaniline, and ^{14}N NMR spectrum of pyridine have shown that, in terms of shift

magnitude, line broadening, and solubility, $Dy(tmhd)_3$ and $Yb(tmhd)_3$ are the best high- and low-field shift reagents, respectively.[67,85] A study of LIS's in the ^{13}C NMR spectra of ketones has shown that $Yb(tmhd)_3$ is an excellent shift reagent for ^{13}C NMR structural studies since contact contributions are minimized and the observed shifts are large.[61] This shift reagent also appears to be the chelate of choice for both ^{13}C and ^{1}H NMR spectra of nitrogen heterocycles.[86]

2. Chelate Ligand

All LSR's of the chelate type are β-diketonate complexes of the general formula Ln (β-diketonate)$_3$ B_n, where B represents other donor ligands. Complexes with $n = 0$ provide several free, acidic coordination sites. Because of the variability of the coordination number of lanthanide ions,[87] complexes with $n = 1$ or 2 may still provide at least one free coordination site. The original LSR introduced by Hinckley,[21] $Eu(tmhd)_3(pyridine)_2$, represents an eight-coordinate species. Lanthanide-β-diketonates with bulky substituents function as the most efficient shift reagents. The probable explanation[88] is that *intra*complex *inter*ligand interactions caused by the presence of voluminous substituents limit the complex to a single or perhaps a few geometrical isomers. If a variety of different stereoisomers were present in solution, each with its own susceptibility tensor and geometric factors, the dipolar shifts when averaged over all species present would tend towards zero. This will not occur if one, or at most a few, isomers are present. Apart from insufficient bulk of the ligand, factors such as a low solubility or a small complex-substrate association constant may also render a lanthanide chelate relatively ineffective as a shift reagent.

The acetylacetonates (Figure 1: $R = R' = CH_3$) are inadequate as shift reagents because of their hydroscopic nature, the coordinated water leading to weak complexation with further ligands and very small shifts.[89] The dibenzoylmethanates (Figure 1: $R = R' = C_6H_5$) are of little value in this context because of low solubility in nonpolar solvents.[89] Limited solubility in the normal NMR solvents is also a problem with the widely used tmhd ligands (Figure 1: $R = R' = C(CH_3)_3$). Although the tmhd complex of europium was first used as the dipyridine adduct,[21] the pyridine-free complex is greatly superior as a shift reagent.[22] Substitution of fluorocarbon moieties in β-diketonate ligands enhances the solubility of the metal complex, and the electron-withdrawing fluorines increase the Lewis acidity of the cation, making it a better coordination site for weak donors. The most widely used partially fluorinated ligand at the present time is undoubtedly fod (Figure 1: $R = C(CH_3)_3$, $R' = n - C_3F_7$).[24] For applications in which even more acidic shift reagents are desired for use with very weak nucleophiles, lanthanide chelates of 1,1,1,2,2,3,3,7,7,7-decafluoro-4,6-heptanedione (Figure 1: $R = CF_3$, $R' = n\text{-}C_3F_7$)[90] (the notation "dfhd" being currently used in the literature for this ligand), of 1,1,1,2,2,6,6,7,7,7-decafluoro-3,5-heptanedione (Figure 1: $R = R' = C_2F_5$)[91] (written "fhd"), and of 1,1,1,2,2,3,3,7,7,8,8,9,9,9-tetradecafluoro-4,6-nonanedione (Figure 1: $R = R' = n - C_3F_7$)[92] (written "tfn"), offer promising potential. With some weakly basic organic substrates, the following order of effectiveness seemed apparent:[92] $Eu(tfn)_3 \approx Eu(fhd)_3 > Eu(fod)_3 > Eu(tmhd)_3$. Other chelates that have been tried as potential shift reagents include 1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedionato (Figure 1: $R = C(CH_3)_3$, $R' = CF_3$)[93] (written "pta" and 1,1,1,2,2-pentafluoro-6,6-dimethyl-3,5-heptanedionato (Figure 1: $R = C(CH_3)_3$, $R' = C_2F_5$).[94] These are less effective as shift reagents than the tmhd and fod chelates. Optically active LSR's, which have been developed for the purpose of determining enantiomeric purity, are described in Section V.H.

3. Comparisons of Several Shift Reagents

For the ^{1}H NMR studies published up to the time of writing, $Eu(tmhd)_3$ and $Eu(fod)_3$ have been the most frequently used shift reagents, with the Pr analogues appearing as the most popular alternatives. This comparative estimate is restricted to these complexes.

The tmhd chelates have a relatively low solubility in nonpolar solvents. Introduction of fluorine atoms into the β-diketonate ligand increases the solubility; thus, $Eu(fod)_3$ is about ten times as soluble as $Eu(tmhd)_3$ in common NMR solvents.[52] In addition, fluorination produces a more acidic lanthanide ion through inductive effects. This higher Lewis acidity effects a stronger association with the substrate and thus extends the range of the shift reagent to less basic species, such as ethers and esters. Only two examples of the ineffectiveness of $Eu(tmhd)_3$

relative to that of $Eu(fod)_3$ will be cited here. Addition of $Eu(fod)_3$ to a solution of di-*n*-butyl ether in carbon tetrachloride greatly simplified and clarified the ^1H spectrum of the ether, whereas the maximum shift obtainable with $Eu(tmhd)_3$, achieved by saturating the carbon tetrachloride solution with this reagent, was negligible by comparison.[24] A comparison of the efficiencies of $Eu(fod)_3$ and $Eu(tmhd)_3$ in separating the resonances of the methoxy protons of an isomeric mixture of unsymmetrically parasubstituted azoxybenzenes was made by adding approximately equimolar amounts of the two shift reagents to identical solutions of the isomeric mixture.[75] After the addition of 10 mg of $Eu(fod)_3$, the resonances for the two isomers were easily identified. In contrast, addition of 10 mg of $Eu(tmhd)_3$ did not induce any observable shifts under the same conditions. Presumably, the ineffectiveness of $Eu(tmhd)_3$ with these substrates is due to its poorer Lewis acidity relative to that of $Eu(fod)_3$. In the first example given, the inferior solubility of $Eu(tmhd)_3$ in nonpolar solvents is also emphasized.

Although the chemical shift for the substrate in the complexed state is smaller for the fod chelates than for the tmhd complexes,[95] the observed LIS can be larger because of the lower dissociation constant of the substrate-reagent adduct due to the higher Lewis acidity induced by the fluorinated substituent. However, $Eu(fod)_3$ is not necessarily a more powerful LSR than $Eu(tmhd)_3$. Indeed, with various kinds of oxygen-containing substrates it has been shown[96] that, at the same number of molar equivalents, $Eu(tmhd)_3$ actually gives rise to larger shifts than does $Eu(fod)_3$. With substrates of high donor ability, the greater Lewis acidity of the fluorinated reagent can be a distinct disadvantage. For strongly basic substrates, $Eu(fod)_3$ and the closely related $Eu(pta)_3$ seem to change the stoichiometry of their adducts with variations in the LSR/substrate mole ratio.[38,93] These stoichiometry changes lead to drastic shift ratio changes. Some proton resonances shift upfield after a large initial downfield displacement; other proton resonances continue to shift downfield. With the proton shift ratios dependent on the concentration of shift reagent, interpretation of the data becomes very difficult. Apparently, in no published spectra have proton shift ratios induced by $Eu(tmhd)_3$ changed to any great extent ($< \pm 10\%$) for monofunctional substrates with changes in the relative concentration of this shift reagent.[93]

Shifts induced by $Pr(tmhd)_3$ are larger than those obtained with the europium analogue, but the concomitant line broadening is also slightly greater. With $Pr(tmhd)_3$, a "bunching" effect on the ^1H resonances occurs at lower LSR/substrate mole ratios, tending to increase the complexity of the spectrum. This arises because protons nearest the coordination site generally resonate furthest downfield in the normal spectrum and are shifted furthest upfield in the presence of a high-field shift reagent.

The chemical shifts of the chelate resonances are only of concern in the interpretation of ^1H NMR spectra; in some systems the *tert*-butyl resonance of the complex may interfere with the spectrum of interest, but the vinyl proton resonance is not normally observable. In dry carbon tetrachloride solution, $Eu(tmhd)_3$ gives two peaks, one at δ ca. 0.5 (the major peak) and the other at ca. 3.3, the exact positions of both resonances being slightly concentration dependent (ca. ± 0.2 ppm in the range 0.003 to 0.03 *M*).[93] Addition of traces of water or other polar substrates to the solution causes the chelate resonances to move upfield. Further substrate addition produces coalescence of the two resonances, and the resulting single peak shifts to between δ -0.5 and -1.3, depending on the substrate. With $Eu(tmhd)_3$ as shift reagent, the induced substrate shifts are downfield and result in increased separation of the proton signals of the substrate ligand and the *tert*-butyl resonance of the chelate, making interference of minimal concern. The behavior of the *tert*-butyl resonances of $Pr(tmhd)_3$ is analogous to that observed for $Eu(tmhd)_3$, the resonances appearing at δ ca. 0.6 (major) and ca. -2 (minor) in dry carbon tetrachloride solution. In the presence of substrates, the *tert*-butyl resonance of $Pr(tmhd)_3$ occurs in the 3 to 5 δ range.[97] Since $Pr(tmhd)_3$ is a high-field shift reagent, the chelate resonance may obscure resonances of interest until the induced shifts of the substrate peaks are sufficiently large. Similarly, the usefulness of $Eu(fod)_3$ as a shift reagent is hampered slightly by the *tert*-butyl resonance, which appears 1 to 2 ppm downfield

from tetramethylsilane (TMS) even in the presence of polar solutes.[24] To avoid potential interference with spectral analysis arising from the fod chelate resonances, the deuterated reagent Eu-fod-d_{27} has been employed.[98]

Because it is sometimes inconvenient to work with rigorously anhydrous reagents, a comparison of the effectiveness of anhydrous and hydrated shift reagent was made using $Eu(fod)_3$, which, as ordinarily prepared, is obtained as the monohydrate. The anhydrous shift reagent was found to be 1.5 to 2.7 times as effective as the monohydrate for the four substrates tested.[52] Nevertheless, because anhydrous $Eu(fod)_3$ is more difficult to prepare, keep, and use than $Eu(fod)_3(H_2O)$, it was concluded that for noncritical spectral clarification purposes it may be quite acceptable to add a little more of the shift reagent rather than take elaborate precautions to dry and keep rigorously dry the shift reagent, solutions, NMR tube, etc. The deleterious effect of water on the shifting ability of $Eu(tmhd)_3$ is very marked, however; it makes careful drying of solvents necessary for best results with this reagent.[99]

The complex $Eu(tmhd)_3$ is chemically unstable towards carboxylic acids and phenols; consequently, it is unsuited for use as a shift reagent with these classes of compounds.[22] In contrast, the more acidic $Eu(fod)_3$ is stable in the presence of both phenols and carboxylic acids and may be used for the characterization of both types of compounds.[52,100,101]

With substituted pyridine *N*-oxides and anilines as substrates, increasing contact contributions to the ^1H induced shifts have been reported[102] for the series $Pr(fod)_3$, $Eu(tmhd)_3$, $Eu(fod)_3$. For the C-2 nucleus in quinoline, the contact contribution to the ^{13}C induced shifts decreases along the series $Eu(fod)_3 > Eu(tmhd)_3 >> Pr(fod)_3 > Pr(tmhd)_3$.[103] Other workers[58-60,86] using other substrates have also concluded that the degree of contact interaction is greater in the europium than in the praseodymium complex and larger with $Ln(fod)_3$ than with $Ln(tmhd)_3$. The latter result may be due partly to the stronger Lewis acidity of $Ln(fod)_3$ than of $Ln(tmhd)_3$, since contact interaction depends on the degree of covalent character of the metal-ligand bonding. However, a loosening of the metal-ligand bonding by steric hindrance may also be responsible, since tmhd has two bulky *tert*-butyl groups, whereas fod has only one.

4. Synthesis and Storage

The synthesis of $Ln(tmhd)_3$ and $Ln(fod)_3$ complexes from the lanthanide chlorides or nitrates and the corresponding diketones in aqueous-alcoholic media has been described.[104-106] Exclusion of oxygen during the preparation of the tmhd complexes may be unnecessary.[22,93] Lanthanide shift reagents, including deuterated analogues, are commercially available as solids or precalibrated solutions from a number of sources. The synthesis of chiral shift reagents is described in papers cited in Section V.H.

Purification of lanthanide chelates is usually accomplished by vacuum sublimation or by recrystallization from an inert solvent such as dry *n*-hexane or methylcyclohexane; however, a combination of both procedures has been recommended. Sublimation generally gives a pure substance, but one that is finely divided and difficult to handle; recrystallization yields a crystalline solid, which is not as subject to static problems.[29] The lanthanide chelates are hygroscopic and should be stored in vacuo over a suitable desiccant (e.g., phosphoric oxide or magnesium perchlorate) until just before use. The anhydrous tmhd chelates have the following colors:[107] red (Ce), green (Pr), violet (Nd), white (Sm, Gd, Tb, Dy, Tm, Yb), yellow (Eu, Ho), and pink (Er).

The presence of small amounts of impurity in the shift reagent can have a marked influence on the magnitude of the induced shift, e.g., a 30% difference has been reported in the LIS's of two batches of $Eu(tmhd)_3$.[108] Clearly, the measurement of the LIS of a suitable standard substrate should provide an acceptable criterion of LSR purity. The shift of the methylene resonances of *p*-nitrobenzyl alcohol with a 0.1:1.0 molar ratio of shift reagent to substrate has been proposed for this purpose.[29] Further proposals are that the calibration should be made in deuterochloroform to enable comparison of results with those of other workers (and also in the particular solvent being used for the studies in hand), that the substrate concentration should be 0.5 *M*, and that the reaction temperature should be between 30 and 33°C.[29] Typical interpolated induced shifts for the methylene hydrogens of *p*-nitrobenzyl alcohol obtained in the presence of $Eu(tmhd)_3$, $Eu(fod)_3$, and $Pr(fod)_3$ are given in Reference 29.

Precious organic compounds may be recovered, after completion of the NMR measurements, by thin-layer chromatography[22] or liquid chromatography[109] of the complex-substrate solution.

5. Selection of Solvent

Solubility and stability of the shift reagent dictate the choice of solvent, but the compatibility of solvent and substrate must also be taken into account. The reagent solubility increases with increasing concentration of a coordinating substrate; with reagents of limited solubility, greater shifts can be achieved by adding them in the solid form to the substrate solution. Thus, $Eu(tmhd)_3$ is soluble to the extent of ~40 mg cm^{-3} in deuterochloroform;[25] in the presence of polar substrates, concentrations of 200 to 300 mg cm^{-3} are obtained in this solvent.[89]

The lanthanide β-diketonates are normally used in nonpolar solvents such as carbon tetrachloride and deuterochloroform. Less commonly used solvents include perdeuterobenzene, carbon disulfide (useful for low-temperature investigations due to its low melting point (-110.8°C) and good solubility of $(tmhd)_3$ complexes; offers certain advantages when the substrates are strong Lewis bases such as alcohols),[110,111] and 1,1,2,2-tetrachloroethane. Lanthanide fod chelates can be used successfully in an arsenic trichloride-deuterochloroform system, which is a superior solvent for compounds without hydroxyl and amino groups sparingly soluble in deuterochloroform or carbon tetrachloride.[112] If the solvent is capable of coordinating with the shift reagent, competition between solvent and substrate greatly reduces the observed shifts. Although perdeuteroacetonitrile has been used as a solvent for amines in an investigation of the shifting ability of $Eu(tmhd)_3$, this solvent complexes with the shift reagent and thus effectively competes with less basic substrates.[89] Solvents that possess strong Lewis base properties, such as alcohols, are precluded. Careful drying of solvents is necessary since water acts as a competing donor. Deuterochloroform and carbon tetrachloride often contain traces of acid which decompose the $(tmhd)_3$ complexes.[74,89] Preheated zeolite samples (molecular sieves) may be used to remove the acidic impurities and any water present. Carbon tetrachloride that has been stored over sodium hydroxide pellets and redistilled is also satisfactory.[74]

Complex formation between solvent and substrate, e.g., through hydrogen bonding, may lead to lower induced shifts. Thus, the effectiveness of $Eu(tmhd)_3$ for alcohols and amines in deuterochloroform solutions is only 75 to 80% that in carbon tetrachloride solutions.[89] Deuterochloroform can hydrogen bond to the oxygen of the alcohol and the nitrogen of the amine, thereby decreasing their coordinating ability. This solvent is also capable of forming hydrogen bonds with the π system of the LSR,[113] thereby sterically inhibiting the approach of the substrate.

The shifting ability of $Eu(tmhd)_3$ for the ^1H resonances of 1-adamantanamine is highly solvent dependent and decreases in the order[114] $CCl_4 > C_6D_6 >> CDCl_3 >>$ acetone-$d_6 >>$ pyridine-$d_5 \approx$ methanol-d_4. The effectiveness of the reagent is clearly greatest in noncoordinating solvents and decreases with increasing solvent-coordinating ability. The latter three solvents compete with adamantanamine for coordination sites on the metal; acetone, being a weaker base than pyridine, does not compete as effectively. Deuterochloroform, on the other hand, inhibits the shift reagent by hydrogen bonding (see preceding paragraph), resulting in reduced LIS's relative to those observed in the other two nonpolar solvents.

C. Other Lanthanide Shift Reagents

1. Lanthanide Salts

The lanthanide β-diketonates are insoluble in water. For applications in water and other polar solvents, the ionic salts of the rare earths may be used. Hydrated lanthanide ions are capable of additionally coordinating a polar substrate, but the shifts induced are much smaller than those of the chelated rare-earth ions in nonpolar solvents; hydration of the lanthanide ion greatly reduces its acidity towards other donor atoms. The shift direction is usually upfield for hydrated europium salts and downfield for hydrated praseodymium salts, in contrast to analogous β-diketonates in nonaqueous solution.

When deuterium oxide solutions of unsubstituted, hydroxy- or amino-carboxylic acid salts were treated with europium or praseodymium perchlorates, shifts of up to 4 ppm were produced, the magnitudes of the shifts decreasing along the alkyl chain in the sequence $\alpha > \beta > \gamma > \delta$.[115] Europium chloride has been used in an NMR study of esters in aqueous solution.[116] This reagent also coordinates to steroids in dimethylsulfoxide solution.[117] Europium and praseodymium nitrates have been used successfully as shift

reagents in deuteroacetone for the investigation of phosphates and phosphonates by ^{31}P NMR.[93,118] The potentialities of unchelated rare-earth ions in biochemical applications are large since lanthanide(III) ions can frequently act as substitute probes for the calcium(II) ion in biological systems. To give one illustration of this potential, complexation phenomena of the calcium ion in aqueous solution play an essential role in the regulation of biological processes; in this respect, the elucidation of the complexation behavior of polyhydroxy derivatives is of the utmost importance. In an ^{1}H NMR study of the complex formation of alditols with multivalent cations in aqueous solutions, praseodymium (as the nitrate) was applied instead of the isosteric calcium ion because of the additional advantage of paramagnetically induced shifts.[119] Several rare-earth ions have been used as paramagnetic probes in an ^{1}H NMR investigation of the structure of transfer ribonucleic acid molecules in water.[120]

2. Organometallics

The purely organometallic lanthanide complexes $Ln(C_5H_5)_3$ are relatively strong Lewis acids that form thermally stable 1:1 adducts with bases such as ammonia, isonitriles, and carbonyl compounds.[121] The shifting potential of these complexes is comparable to that of the corresponding chelate complexes (see Table 1). Although the solubility of the free $Ln(C_5H_5)_3$ complexes in solvents such as benzene is rather limited, the solubilities of the adducts are often quite high.[41] However, the tricyclopentadienyl complexes have a major drawback as shift reagents: their sensitivity towards acids, water, and oxygen greatly exceeds the sensitivity of the chelate complexes. Consequently, they must be manipulated in an inert gas atmosphere and in carefully purified solvents.[41]

3. Metalloporphyrins

Lanthanide complexes of *meso*-tetraphenylporphine and some of its derivatives have been synthesized, the procedure employed being suitable for the entire rare-earth series.[122] These complexes are reasonably soluble in organic solvents, are stable to air and water, and possess considerable dipolar shifting ability. Analogous complexes of naturally occurring porphyrins may serve as specific NMR shift and broadening probes in biological systems.

D. Functional Group in Substrate

Only substrates that have a sufficiently polar and exposed group to form a complex with the reagent can be gainfully investigated with the aid of shift reagents. Typical functional groups involving one donor atom include –OH (alcohols, phenols), $-\underset{|}{C}=O$ (ketones, aldehydes, esters), –O– (ethers, epoxides), $-NH_2$ (amines), =N– (aza heterocyclics), and –CN (nitriles). Functional groups that possess more than one potential donor atom include –CH=N–OH (oximes), =N–O (nitrones, nitroxides), $-C\lesssim^{O}_{NH_2}$ (amides), –P=O (phosphine oxides, phosphonates), –S=O (sulfoxides), and $-C\lesssim^{S}_{NH_2}$ (thioamides). Nitro- and trifluoroacetate groups combine weakly with lanthanide tmhd chelates; halides and olefinic double bonds probably do not interact at all.[89,123] However, the fod complexes may be more useful with these groups, since the electron-withdrawing perfluoropropyl group increases the acidity of the metal ion, making it a better coordination site for weak donors. Hydrocarbons show significant LIS's due to $Eu(tfn)_3$.[92] Unpublished results[92] suggest that aliphatic nitro and aliphatic cyano compounds are also significantly shifted with this reagent.

Basic strength and steric hindrance are the factors primarily responsible for the degree of binding between shift reagent and substrate. Consequently, the magnitude of the induced chemical shifts depends markedly on these two factors. Thus, an almost linear correlation exists between the basicity of a series of *para*-substituted anilines and the LIS of the phenyl protons in the *ortho* and *meta* positions.[108] When deuterium is substituted for hydrogen geminal to a hydroxyl group, the ^{1}H resonances of the deuterium-substituted alcohol are found to be shifted further than those of the unsubstituted compound.[124-126] The probable explanation is an increase in the basicity of the hydroxyl oxygen due to the geminal deuterium substitution. As the site of deuteration is more separated from the hydroxyl group, the isotope effect attenuates rapidly. An NMR study of the effect of $Eu(tmhd)_3$ on an equimolar amount of ethyl mercaptan and ethanol has indicated that a sulfhydryl group coordinates with this shift reagent less effectively than a hydroxyl group by the factor of 1:9, which is in good agreement with the known relative basicity of thiol and

strongly displaced, but at higher concentrations protons beside the weaker donor experience greater LIS's. As a result, the proton signals may overtake one another in the spectrum.[136,137] Separation of the observed shifts of bifunctional molecules into contributions arising from complexing at each site is necessary, if the induced shifts are to be used in calculations of molecular structure. At present, no general method appears to be available to achieve this separation. A graphical method has been used to separate the shift contributions arising from complexation at the hydroxyl and keto groups in testosterone, the assumption being made that each contribution obeys an r^{-3} relationship, where r is the distance between the proton under consideration and the europium ion.[57] Other workers,[138] using 17-carbomethoxy-methylene-5-androsten-3β-ol as substrate, concluded that the proper shift-distance relationship permitting the separation of contributions is the one with $r,^{-2}$ where r is the average distance between the proton and the center of the oxygen atom as measured from models. A mathematical analysis has been described[93] whereby the induced shifts of bifunctional molecules may be dissected into contributions due to coordination at each site, but this form of analysis is only applicable to compounds where the relative association constants are known.

If the groups in a bifunctional molecule are sufficiently close together for interaction to occur, the displacements are no longer additive.[139] A substrate with a favorable conformation can interact as a bidentate ligand, both functions being complexed by the same lanthanide ion.[140]

A reduction or an enhancement of the donor properties of a substrate may sometimes be required before treatment with a LSR can yield useful additional NMR information. Thus, polyfunctional compounds that complex strongly at each functional group may give induced shifts which are not readily interpreted. Difficulties of this type can be overcome by derivatization, suitable derivatives being those that reduce the basicity and introduce as few additional resonances as possible. For example, hydroxyl groups may be converted to trifluoroacetates which provide only a weak site of coordination.[123] Tosylation or silylation of a hydroxyl group has a similar deactivating effect.[141] Conversion of a ketone into its ethylene thioketal renders it effectively inert to tmhd complexes.[123] Examples of the enhancement of the donor power of a group include the reduction of an ester function to an alcohol and the oxidation of a thioether to a sulfoxide. Since alkyl halides, olefins, saturated hydrocarbons, and nitro compounds coordinate weakly, or not at all, with lanthanide $(tmhd)_3$ chelates,[89,123] chemical modification of these compounds is required to make them potentially more suitable as substrates for tmhd-type reagents.

Because water acts as a competing donor, substrates should be distilled, sublimed, or recrystallized and then sealed, or kept in a vacuum desiccator over a suitable desiccant, (e.g., phosphorus pentoxide) until just before use. Another commonly occurring competitive substrate is tetrahydrofuran which often occurs in nontrivial amounts in commercially available TMS. Tetramethylsilane may be freed from tetrahydrofuran by washing with concentrated sulfuric acid; this should be followed by a potassium bicarbonate wash and distillation.

E. Techniques for Obtaining Induced Shifts

The commonly used method for studying induced shifts involves the incremental addition of known amounts of the LSR, as a solid or a solution, to a solution of the compound under study, with the NMR spectrum being recorded after each addition. This procedure facilitates the identification of peaks and also reveals the optimum degree of shift for clarity. Since signal crossover often occurs, a shift reagent can make a spectrum more difficult, rather than less difficult, to interpret if the shifts are not gradual. Many workers have chosen to add the LSR as a solid, solution being effected by agitation or gentle warming of the substrate solution. Volume changes caused by the addition of the solid LSR are negligible. If a constant substrate concentration has to be maintained, addition of the LSR as a solution necessitates the use of several aliquots of substrate with different concentrations of LSR. This is troublesome when only a small amount of substrate is available. Since broadening of the signals increases markedly with the magnitude of the induced shift, spectral assignments should be attempted with the minimum quantity of LSR to achieve signal resolution.

An alternative procedure for obtaining induced chemical shifts involves incremental addition of the substrate to the LSR in solution. The first

alcohol.[127] If a selection of the donor site is possible, it is clearly advantageous to use compounds possessing the most Lewis-basic groups.

The importance of steric factors in determining the degree of complexing is shown by the shift changes induced in aniline, *N*-methylaniline, and *N,N*-dimethylaniline by $Eu(tmhd)_3$.[108] *N*-methyl substitution, although increasing the basicity, leads to smaller shifts. Carbon-13 NMR studies on a group of organonitriles containing an ether, as well as a nitrile donor site, have shown that, due to steric hindrance effects in the oxynitriles, the nitrile was the preferred site of complexing.[63]

The concept of hard and soft acids and bases (HSAB principle)[128] provides an important basis for anticipation of the degree of significant interaction of substrates with shift reagents. Lanthanide ions are hard acids and, therefore, bind hard bases best, e.g., O > S > Se, in order of decreasing hardness. A study of a variety of organosulfur compounds has indeed indicated that the response of thioethers, relative to oxygen ethers, to shift reagents is an order of magnitude less.[129] The hardness of a base decreases as its electrons are delocalized in any fashion. In accord with this prediction are the facts that 5-*p*-bromophenyl-2,3-dihydrothiophene, phenyl disulfide, and 2,4-dinitrophenyl benzyl thioether, all substrates with high delocalization of the nonbonded electron pairs on sulfur, show no detectable interaction with LSR's.[129] Despite the high polarizability of the C=S group (and thus the high, partial negative charge on sulfur) in thioadamantanone, the thioketone shows a much weaker interaction with $Eu(fod)_3$ than the oxyketone.[129] This result again indicates the importance of HSAB theory as a criterion for recognizing the coordinating ability of organic functional groups. Other workers[130] have pointed out the use of this theory for shift reagent interpretations.

Various comparative investigations have been made of the coordinating ability of different functional groups. Shifts of $-CH_2-R$ protons induced by $Eu(tmhd)_3$ decrease in the order $-NH_2 > -OH > \geq C=O > -O- > -CO_2R > -CN$.[89] This order reflects the formation constant of the corresponding substrate-reagent adduct and, to a smaller extent, the geometry (distance and angle) of the protons relative to the lanthanide ion. Comparison of the relative donor powers of the phosphoryl and amide groupings and their thia analogues has established the order P=O > C=O (amides) > C=S (thioamides) > P=S.[131] An NMR study of thiadecalones has shown that ketones are more effective than thioethers in intramolecular competition with $Eu(tmhd)_3$.[132] With functional groups that contain two possible donor atoms, coordination appears to occur mainly with the oxygen atom when present. For a number of thioamides, the induced shifts are consistent with coordination occurring at the sulfur atom.[133,134]

If two or more substrates are present in a solution, a shift reagent will be distributed between the substrates according to the relative formation constants of the adducts and the concentrations of the components, corresponding changes being produced in the shifts of the signals from each substrate. For example,[135] when equimolar amounts of acetone and tetrahydrofuran were allowed to compete for $Eu(tmhd)_3$, the induced ^1H shifts in ppm, at a 1:1 mole ratio of shift reagent to substrate, were 1.2 and 24.9 (α protons), respectively, as compared to values of 11.1 and 28.0 (α protons) obtained when only one substrate was present. From the changes of the shifts it can be deduced that $Eu(tmhd)_3$ coordinates tetrahydrofuran about eight times better than it does acetone.

When two functional groups are present in the same molecule, but are spatially so far apart that no interaction occurs, the displacement of the signals is simply the sum of the shifts caused by coordination at each group separately. If the complex-formation constants of the groups differ greatly, the weaker basic group does not coordinate with the shift reagent until most or all of the stronger function has reacted. For example, only the hydroxyl group in a bifunctional hydroxyester coordinates at low concentrations of $Eu(tmhd)_3$.[136] At higher concentrations, as complexing at the hydroxyl group approaches saturation, the shift reagent begins to complex appreciably with the carbonyl oxygen of the ester group. With various molecules containing both P=O and other lone-pair electron sites, complexing by $Eu(tmhd)_3$ was found to be greater at the P=O, and only when this site was fully complexed did the other moieties undergo considerable complexing.[137] Consequently, proton shift ratios in bifunctional substrates vary greatly with the concentration of the shift reagent. At low concentrations of the reagent, signals from protons situated near the stronger donor site are more

experimental sample is prepared at the highest LSR concentration to be run, and subsequent samples are prepared by dilution with a substrate stock solution of the same substrate molarity as the first sample. This method provides high precision in the concentrations, and the possibilities of the LSR being contaminated by water from the atmosphere are reduced.[142] For experiments in which the correctness of the LSR concentration is crucial, all sample preparations should preferably be carried out in a glove box filled with dry nitrogen. This procedure is essential, however, for experiments that involve low concentrations of LSR, as these are highly sensitive to traces of moisture.

The induced shifts are usually expressed as displacements from the resonance positions observed in the absence of the shift reagent. Internal standards that have been used for ^1H NMR studies include TMS, chloroform (useful in strong solutions of $Eu(tmhd)_3$ where the broad band of the *tert*-butyl resonance hinders the use of TMS[143]), and acetone (for aqueous solutions).[115] The introduction of an LSR, as of any paramagnetic additive, produces a displacement of the whole NMR spectrum of the solution owing to a change in the bulk magnetic susceptibility of the solution. This shift probably needs only to be considered when an external standard is employed. The resonance of an internal standard may be shifted to a considerable extent in the presence of an LSR, e.g., shifts of up to 1.4 ppm have been recorded for TMS.[117] However, the change in bulk susceptibility also causes a displacement of the signals from the substrate nuclei. Consequently, chemical shifts measured from the internal standard probably do not change. At very high concentrations of LSR, however, bulk susceptibility changes become substantial, and it is not clear whether even an internal standard will properly compensate for them.

F. Analysis of Shifted Spectra

1. Concentration Dependence of the Induced Shifts

a. Initial Chemical Shifts

If the addition of a shift reagent reduces a complicated spectrum to one of first order without significant loss of resolution, the problem of signal assignment can usually be solved by a visual analysis (observed signal intensities and splitting patterns). An expanded spectrum is also susceptible to decoupling experiments. If these experiments are required, they should be conducted as soon as a satisfactory degree of spectral dispersion has been achieved, as further addition of LSR will lead to additional loss of multiplet resolution. The extrapolation of resonance positions to zero concentration of LSR enables the chemical shift of the uncomplexed substrate to be obtained, thus providing another guide to signal identification. Plots of induced shift vs. the mole ratio of shift reagent to substrate are illustrated in Figures 9 and 10. The graphical method is particularly useful for obtaining the initial chemical shifts of nuclei whose resonances are not evident in the unshifted spectrum due to spin-system complexity and/or fortuitous overlaps and coincidences. Clearly, diamagnetic chemical shifts estimated in this way provide excellent trial parameters for iterative computer-aided simulations of complex spectra. A computerized approach has also been outlined for the automatic sorting of signals in LIS spectra.[144]

Figure 9 shows the variation in the chemical shift of some of the protons in *cis*-1,3,5,5-tetramethyl-3-(1-naphthyl)cyclohexan-1-ol upon the addition of $Eu(tmhd)_3$;[145] deviations from linearity occur at low concentrations of the reagent. Figure 10 illustrates the changes in chemical shift in the ^1H NMR spectra of mixtures of bis (4-aminocyclohexyl)methane stereoisomers in the presence of the same shift reagent;[146] deviations from linearity are evident in these plots at high $Eu(tmhd)_3$ concentrations. With the majority of LRS-substrate systems, plots of the LIS vs. $[L]_0/[S]_0$, where $[L]_0$ and $[S]_0$ are the respective initial molar concentrations of LSR and substrate, appear to be sensibly linear in the range 0.2 to 0.6 mol ratio; outside this range the plots usually show some curvature, although the deviations at low shift-reagent concentrations are generally slight. Curvature at low LSR concentrations has been attributed to competition between the substrate and an impurity, e.g., water, for the LSR (see, for example, references 93 and 99). Curvature at high ratios of $[L]_0/[S]_0$ has been ascribed to effectively complete complexation of the substrate,[24] to a combination of medium and association effects,[143] and to solubility limitations of the LSR.[147] An analysis of the complexation equilibrium of substrate with shift reagent has yielded the following equation;[148]

$$\Delta\delta_i = \Delta_B^i \, (1 - [L]/[L]_0) \, [L]_0/[S]_0 \qquad (8)$$

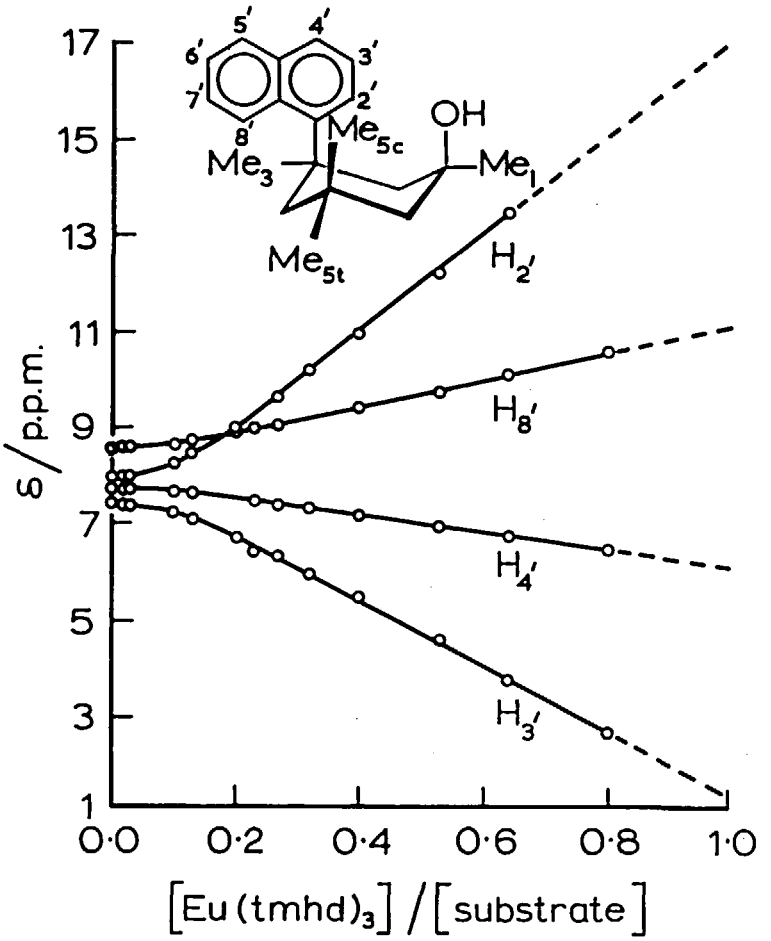


FIGURE 9. Chemical shifts of the aromatic protons of *cis*-1,3,5,5-tetramethyl-3-(1-naphthyl) cyclohexan-1-ol in $CDCl_3$ solution as a function of the $Eu(tmhd)_3$ concentration. (Reprinted with permission from Shapiro, B. L. et al., *J. Am. Chem. Soc.*, 93, 3281 (1971). Copyright by the American Chemical Society.)

where

$\Delta\delta_i$ = the observed lanthanide-induced shift of the *i*th nucleus, measured with respect to the shift in the uncomplexed species;

$\Delta_B{}^i$ = the shift of the nucleus in the lanthanide-substrate complex, measured with respect to the shift in the uncomplexed species;

[L] = the concentration of uncomplexed shift reagent;

0 = total (i.e., free and complexed) concentrations.

This equation predicts that the slope for $\Delta\delta_i$ vs. $[L]_0/[S]_0$ is not constant; the plot should show curvature at low $[L]_0/[S]_0$ where $[L]/[L]_0$ varies and at high $[L]_0/[S]_0$ where $[L]/[L]_0 \rightarrow 1$ and the slope $\rightarrow 0$. This is in broad accord with published data. Values for the "normal" chemical shift of substrate nuclei, obtained by extrapolation of the linear portion of the LIS vs. $[L]_0/[S]_0$ plot to zero concentration of the LSR may, therefore, be inexact because of possible curvature in the initial part of the graph. In most LSR-substrate systems, however, the recovery of chemical shift data by backwards extrapolation appears to be justified, deviations from linearity at low LSR concentrations being generally small. For example, it has been reported[149] that many chemical shifts estimated by this technique agree to better than

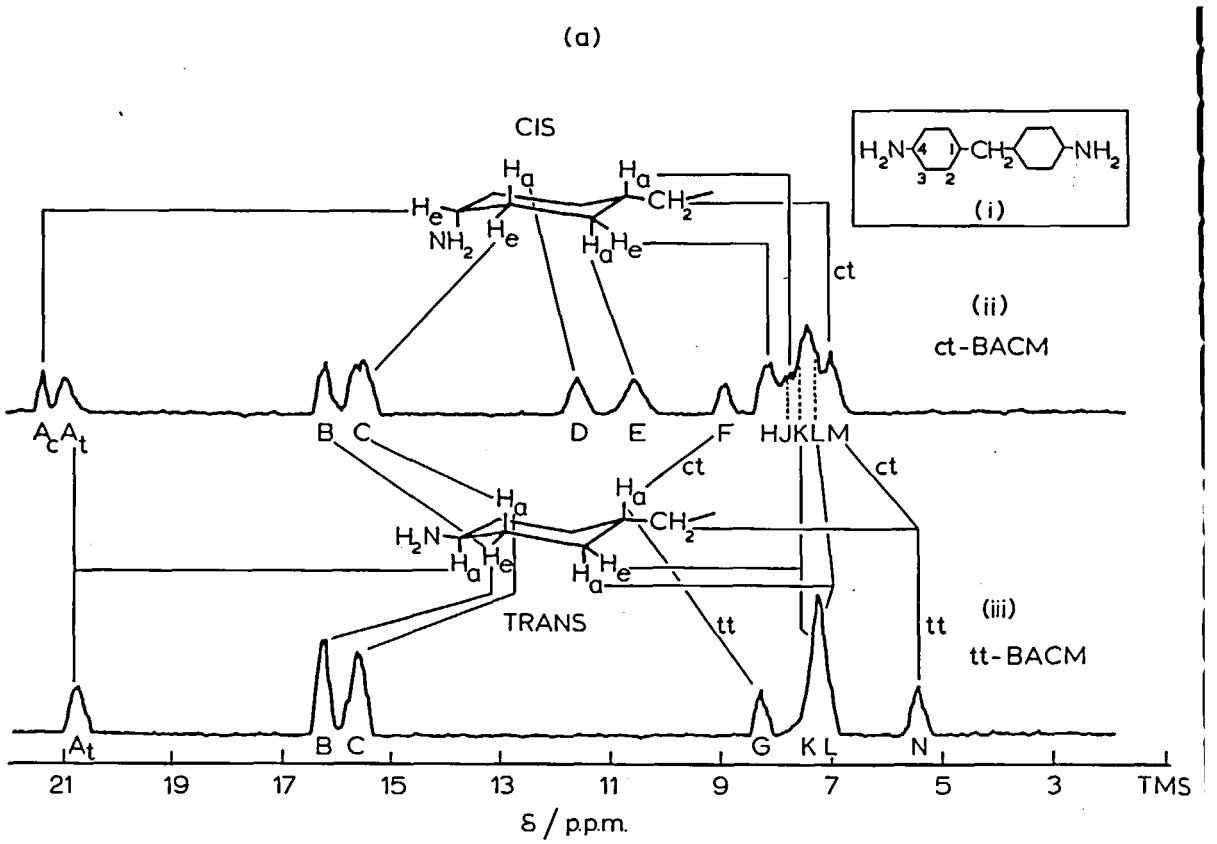


FIGURE 10a. 100-Mhz ^{1}H spectra of bis(4-aminocyclohexyl) methane [BACM, (i)] in CCl_4 with added Eu(tmhd)$_3$ at 25°C, (ii) *cis-trans*-BACM; [Eu(tmhd)$_3$] / [BACM], 0.92. (iii) *trans-trans;* 0.91. (From van Brederode, H. and Huysmans, W. G. B., *Tetrahedron Lett.*, p. 1695 (1971). With permission.)

0.05 ppm and often to within ±0.01 ppm with shift values obtained by direct observation in those systems where this was possible.

b. Limiting Incremental Shifts, Stoichiometry, and Complex-formation Constants

The correct evaluation of the LIS of the complexed or bound substrate [i.e., the limiting incremental shift (Δ_B)] is extremely important, these shifts being the data that form the basis for subsequent determinations of molecular geometry in solution. Determination of the stoichiometry of the L_pS_q complex is important, since any rigorous application of the dipolar equation (4 and 6) requires the sole existence of one complexed species, and the g tensor principal axis will be most easily located in a 1:1 adduct. Equilibrium constants (K), commonly described in the present context as binding or (complex-) formation constants, are of importance since they provide information on the stability of the complexes. The equilibrium constant and the limiting incremental shift are sometimes termed *intrinsic* LIS *parameters,*[150] being independent of reagent concentrations.

The interaction beetwen a LSR and a substrate may involve the following equilibria.

$$\begin{aligned} L\,L &+ S \rightleftharpoons L{\cdot}S \\ L{\cdot}S &+ S \rightleftharpoons L{\cdot}S_2 \\ L &+ L \rightleftharpoons L_2 \end{aligned} \qquad (9)$$

and the possibility of other adduct formations ($L{\cdot}S_3$, $L_2{\cdot}S$, $L_2{\cdot}S_2$) cannot be excluded.[142,147] Since these interactions usually occur in the fast-exchange limit (the NMR spectrum of a substrate in the presence of a LSR at ambient temperatures shows only one set of peaks for the substrate, even for $[L]_0/[S]_0$ ratios of unity), the LIS should conform to the following equation.

$$\Delta\delta = \frac{1}{[S]_0} \sum_{I=1}^{N} n_I c_I \Delta_B \qquad (10)$$

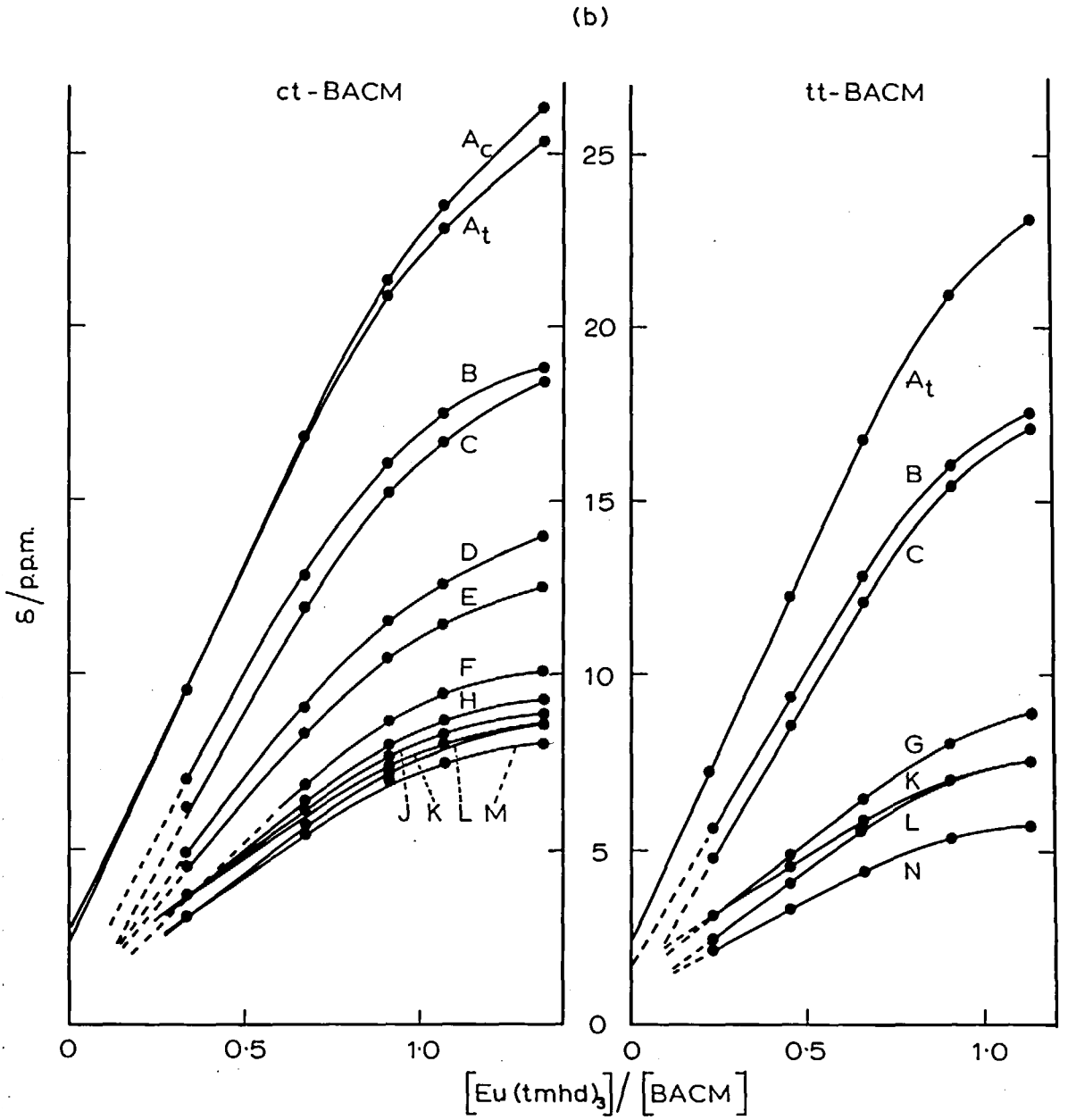


FIGURE 10b. Chemical shifts as a function of added $Eu(tmhd)_3$ to 10^{-4} mol BACM in 0.5 ml CCl_4. (From van Brederode, H. and Huysmans, W. G. B., *Tetrahedron Lett.*, p. 1695 (1971). With permission.)

where

n_l = the number of substrate molecules in a given complex;

c_l = the molar concentration of that complex;

Δ_B = the incremental shift of the nucleus that would be observed for total complex formation;

N = the number of different types of complexes present.

A direct analysis of shift data in terms of this equation therefore requires the derivation of $2N$ parameters: N limiting incremental shifts and N equilibrium constants. Computerized procedures utilizing Equation 10, and graphical methods employing various modifications of it, have been

applied to the analysis of the concentration dependence of LIS's.

Controversy still exists over the method of obtaining induced shifts, as well as over the interpretation of the values so obtained. Some investigators[148,151] have advocated a graphical analysis of shift data obtained in experiments where $[S]_0 >> [L]_0$. When measurements are restricted to this concentration range, a multistep interaction mechanism might be expected to behave as if it were a one-step binding process, with a single effective binding constant (K_B) and single bound shift (Δ_B); thus,

$$L + nS \rightleftharpoons L{\cdot}S_n \tag{11}$$

where $L{\cdot}S_n$ = the predominant species of complex. The binding constant is defined by

$$K_B = [L{\cdot}S_n]/[L][S]^n \tag{12}$$

When the principal complex is a 1:1 adduct,

$$K_B = \frac{[L{\cdot}S]}{[L][S]} = \frac{[L{\cdot}S]}{([L]_0 - [L{\cdot}S])([S]_0 - [L{\cdot}S])} \tag{13}$$

and the induced chemical shift

$$\Delta\delta = \frac{[L{\cdot}S]}{[L{\cdot}S] + [S]}\Delta_B = \frac{[L{\cdot}S]}{[S]_0}\Delta_B \tag{14}$$

Substituting the expression for [L·S] given by Equation 14 into Equation 13 yields

$$1/K_B = [L]_0\,\Delta_B\,(1/\Delta\delta) - [L]_0 - [S]_0 + [S]_0\,(\Delta\delta/\Delta_B) \tag{15}$$

which under the conditions $[S]_0 >> [L]_0$ (so that $\Delta\delta << \Delta_B$) reduces to

$$[S]_0 = [L]_0\,\Delta_B\,(1/\Delta\delta) - \{(1/K_B) + [L]_0\} \tag{16}$$

Thus, a plot of $[S]_0$ vs. $(1/\Delta\delta)$ at constant $[L]_0$ should give a straight line whose slope is $[L]_0\Delta_B$ and whose intercept on the $[S]_0$ axis is $-\{(1/K_B) + [L]_0\}$. If $n = 2$ for the binding process shown in Equation 11 and if experiments are again restricted to the range $[S]_0 >> [L]_0$, the equation corresponding to Equation 16 is

$$[S]_0^2 = [L]_0\,[S]_0\,\Delta_B\,(1/\Delta\delta) - \{(1/K_B) + 4[L]_0[S]_0\} \tag{17}$$

so that a plot of $[S]_0^2$ vs. $[S]_0\,(1/\Delta\delta)$ should be linear of slope $[L]_0\Delta_B$. It should be noted, however, that in deriving this equation, the authors[151] used the expression $\Delta\delta = [L{\cdot}S_2]\,\Delta_B/[S]_0$ rather than the relationship $\Delta\delta \approx 2\,[L{\cdot}S_2]\,\Delta_B/[S]_0$ to compute $[L{\cdot}S_2]$. Considerable experimental evidence supporting the consistency of this method in determinations of Δ_B and K_B has now been obtained.[151-153] The mathematical consistency of the approach is demonstrated by Figure 11 which shows that although the three substrate protons have markedly different bound shifts (and thus different slopes), the three lines intersect in a point; that point lies on the $[S]_0$ axis, in accord with Equation 16. The chemical consistency of the method is illustrated by Figure 12 which shows that although LSR's that contain different lanthanides give different bound shifts towards the same substrate, the binding constant in each case is about the same, in accord with the similarity in chemical properties across the lanthanide series. The method cannot, however, give good values for large equilibrium constants (> 100).[151] When K_B is large, the intercept on the $[S]_0$ axis is so close to zero that only a lower limit for the binding constant may be deduced.

The fact that, with only a few exceptions (see, for example, Reference 152), fits to Equation 16 so far reported have yielded excellent straight lines has been used as evidence for simple 1:1 interaction of LSR and substrate. Electronic spectra and molecular weight studies also seem to imply that $Ln(tmhd)_3$ reagents form 1:1 adducts with typical substrates.[154] It has been pointed out, however, that while 1:1 association between $Ln(tmhd)_3$ and alcohols, or compounds less basic than alcohols, seems to be the rule, 1:2 complexation appears to be significant when substrates more basic than alcohols are involved.[155] Certainly, evidence for 1:2 complexation continues to accumulate in the literature, particularly for systems involving the fod shift reagents. Crystallographic studies[88,156] have identified 1:2 lanthanide-substrate adducts in the solid state. An NMR study of mixtures of the deuterated

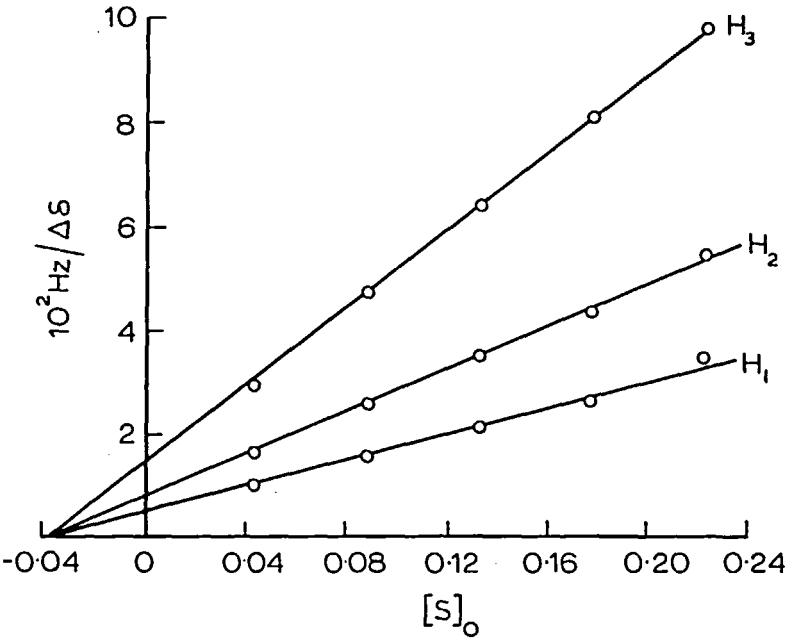


FIGURE 11. Plot of the initial concentration of *n*-propylamine, $[S]_0$ vs. $(1/\Delta\delta)$ for the three sets of protons in *n*-propylamine at constant Eu(tmhd)$_3$ concentration (ca. 0.006 *M* in $CDCl_3$). (From Armitage, I. et al., *Can. J. Chem.*, 50, 2119 (1972). Reproduced by permission of the National Research Council of Canada.)

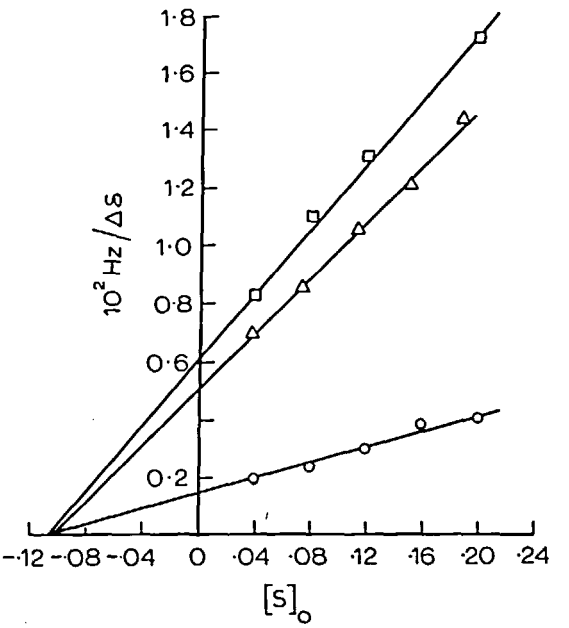


FIGURE 12. Plot of $[S]_0$ vs. $(1/\Delta\delta)$ for the H-1 proton of *neo*-pentanol at constant Ln(tmhd)$_3$ concentration (ca. 0.006 *M*): Eu(tmhd)$_3$ (downfield shift) in $CDCl_3$ (□); Pr(tmhd)$_3$ (upfield shift) in $CHCl_3$ (Δ); Tm(tmhd)$_3$ (upfield shift) in $CDCl_3$ (○). (From Armitage, I. M. et al., in *Nuclear Magnetic Resonance Shift Reagents*, Sievers, R. E., Ed., Academic Press, New York, 1973, 313.)

analogue of $Eu(fod)_3$ and excess of dimethylsulfoxide in dideuterodichloromethane has shown that at −80°C the rate of chemical exchange is sufficiently slow to allow resolution of the free and complexed substrate signals.[157] Comparison of the relative areas of the two peaks indicated that 2.0 ± 0.2 mol of substrate were coordinated per mole of shift reagent. The NMR spectrum of $Eu(tmhd)_3$ $(3\text{-picoline})_2$ in carbon disulfide at −105°C also shows peaks from both free and complexed ligands.[71] Comparison of the integrated areas of the chelate peaks and the coordinated 3-picoline peaks revealed that the species present was the 1:2 adduct. These NMR experiments may not apply at room temperature, however. An investigation of the gradients of lines in $\Delta\delta$ vs. $[L]_0/[S]_0$ plots has indicated that both 1:1 and 1:2 complexation occurs in the $Pr(fod)_3$-borneol system.[158] Studies[159] involving Job's method of continuous variation in which $\Delta\delta\ [S]_0$ is plotted against $[L]_0/([S]_0 + [L]_0)$ at constant $([S]_0 + [L]_0)$ seem to imply a 1:1 complex between $Eu(fod)_3$ and *tert*-butanol, but multiple complex formation between this reagent and *tert*-butylamine. The equilibria between $Ln(fod)_3$ (Ln = Pr, Eu, Ho, or Yb) and the substrate $(\pi\text{-}C_5H_5)Fe(CO)_2(CN)$ has been studied by vapor-phase osmometry on benzene solutions.[160] The osmometry results indicate the formation of both 1:1 and 1:2 complexes; with $Pr(fod)_3$, 1:3 adduct formation is also indicated. In a study of $Eu(fod)_3$ with a chiral substrate, circular dichroism in the electronic transitions of the lanthanide induced by the substrate suggests that both 1:1 and 1:2 lanthanide-substrate complexes occur simultaneously for $[S]_0/[L]_0 < 0.75$, with a preponderance of the 1:2 complex above this value.[161]

Essentially the same result has been obtained from an investigation of the ^1H NMR spectra of 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone with $Eu(fod)_3$ in carbon tetrachloride at 30°C over a wide range of LSR and substrate concentrations.[142] A computer analysis of the concentration dependence of the LIS's using Equation 10 revealed that LSR-substrate systems can obey a two-step equilibrium, $L + S \rightleftharpoons L{\cdot}S$, $L{\cdot}S + S \rightleftharpoons L{\cdot}S_2$, within experimental error, whereas fits to a single-step mechanism, $L + S \rightleftharpoons L{\cdot}S$, exhibited significant deviations (see Figure 13). Another finding of this study is that plots of $1/\Delta\delta$ vs. $[S]_0$ at constant $[L]_0$ where $[S]_0 >> [L]_0$, or of $\Delta\delta$ vs. $[L]_0/[S]_0$ at constant $[S]_0$ under the same relative concentration conditions, yield directly the limiting LIS value for the $L{\cdot}S_2$ species. The $1/\Delta\delta$ vs. $[S]_0$ plot has a slope of $1/2\ [L]_0\Delta_2$, and the $\Delta\delta$ vs. $[L]_0/[S]_0$ plot has a slope of $2\ \Delta_2$, where Δ_2 is the limiting shift of the $L{\cdot}S_2$ complex and the factor of 2 enters in to correct for stoichiometry. Thus, according to this study, linearity in these plots within the range $[S]_0 >> [L]_0$ does not establish 1:1 complexing. Furthermore, the equilibrium constants derived from these plots are considered to be unreliable, being off by an activity coefficient.[142]

Another study directed towards the problem of the stoichiometry of LSR complexes has involved an investigation of complex formation between $Eu(fod)_3$ and acetone, dimethylsulfoxide, 2-propanol, and β-picoline, dissolved in carbon tetrachloride, as a function of the reagent-to-substrate ratio.[162] From an analysis of the shift data it has been concluded that the total stoichiometry of the reagent-substrate adduct is 1:2, with $L{\cdot}S$ and $L{\cdot}S_2$ complexes present in equilibrium. The dissociation constants of the two complexes were found to differ greatly in magnitude: $K_2 > 4K_1$ for acetone and dimethylsulfoxide, $K_2 < 4K_1$ for 2-propanol and β-picoline. A possible interpretation of these results is that substrate binding induces a ligand rearrangement around the central lanthanide ion, and the nature of the new ligand arrangement determines the affinity of the 1:1 adduct towards a second substrate molecule.

When using the slope of LIS plots at low LSR concentration to measure limiting shifts, extreme caution must be exercised to be sure that no competitive substrates such as water are present in solution. A possible method of overcoming this difficulty employs a monitor substrate of known K and Δ.[150] For a solution in which departures from ideality are due solely to equilibria of the type: $L + S \rightleftharpoons L{\cdot}S$, the following equation has been derived.

$$\frac{1}{\Delta\delta_j} = \frac{1}{\Delta\delta_m}\frac{K_m\Delta_m}{K_j\Delta_j} + \frac{K_j - K_m}{K_j\Delta_j} \qquad (18)$$

where the subscripts refer to the parameters of the investigated substrate (j) and the monitor substrate (m). Thus, a plot of $1/\Delta\delta_j$ against $1/\Delta\delta_m$ should be linear; from the slope and intercept, the parameters of interest, K_j and Δ_j, can be calculated, provided the parameters of the monitor substrate are known. If the latter have been determined in the absence of impurities, then the

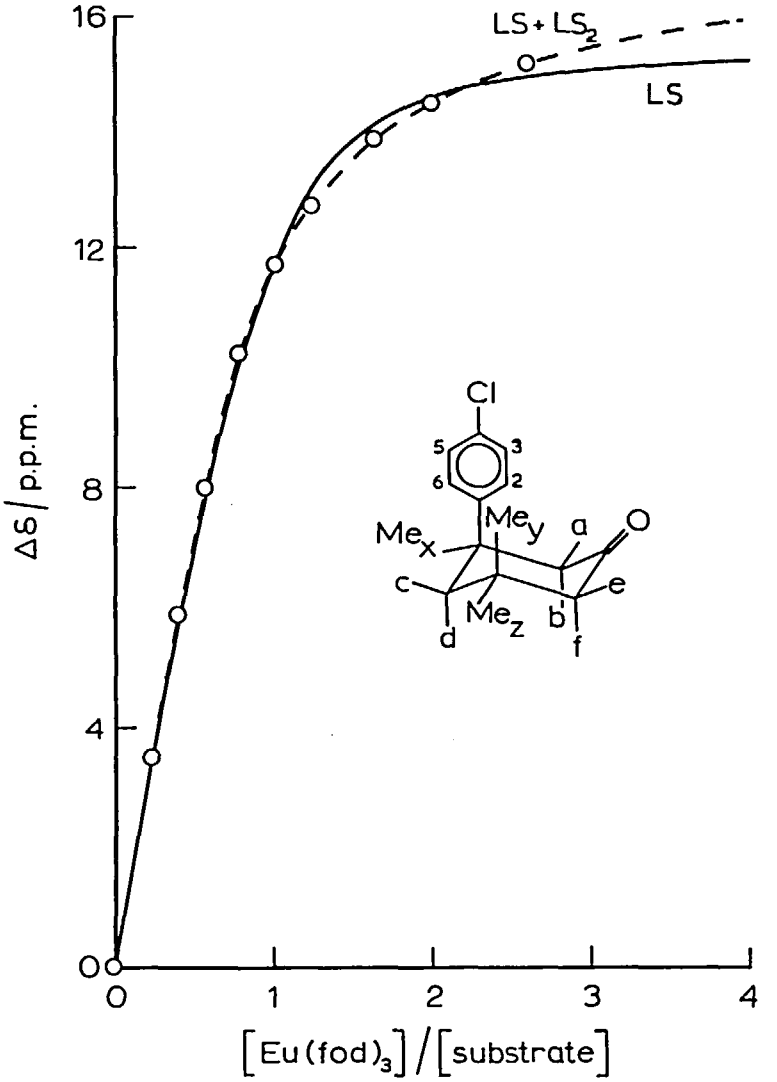


FIGURE 13. A comparison of fits to the observed LIS data for the H_a proton of 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone for the one- and two-step mechanisms (solid and dashed curves, respectively). (Reprinted with permission from Shapiro, B.L. and Johnston, M.D., *J. Am. Chem. Soc.*, 94, 8185 (1972). Copyright by the American Chemical Society.)

presence of impurities in an experiment with the substrate under investigation will be inconsequential.

Considerable uncertainty exists regarding the stoichiometry of the LSR's themselves in solution. The lanthanide tmhd chelates (Ln = Pr, Eu) in carbon tetrachloride solution in the absence of a substrate were found to exhibit more proton resonances than expected from equivalent ligands. These findings were interpreted as showing the presence of the dimeric species $[Ln_2(tmhd)_6]$ in addition to the monomer.[93,163] Other investigators,[109,154] however, have suggested that the extra peaks were due to impurities. Molecular weight measurements have indicated that the $Ln(tmhd)_3$ reagents are essentially monomeric in noncoordinating solvents.[109,154,164] Corresponding osmometric studies of $Ln(fod)_3$ reagents have indicated that substantial dimerization occurs in these solvents.[109,160] On the other hand, from an NMR study no self-association of $Eu(fod)_3$ could be detected.[165] According to the vapor-phase osmometry results,[160] the relative concentration of the dimer decreases with decreasing LSR

concentration. Thus, for studies in which the substrate is in excess over the LSR, the aggregation of the residual free-fod chelate is likely to be very low and is unlikely to be reflected in the observed chemical shifts. Under circumstances in which the substrate and $Ln(fod)_3$ reagent are of similar concentration, it may be necessary to take the dimer equilibrium into consideration in discussing shift reagent data. Provided the dimer does not coordinate substrate, the principal effect of reagent dimerization will be one of competition with the substrate. Data analyses in which dimeric species have been included do not yield significantly different results.[155,162]

2. Temperature Dependence of the Induced Shifts

Lanthanide-induced shifts are in practice temperature dependent, an effect that can be successfully employed for the clarification of NMR spectra by varying the temperature until the required signal separation has been achieved.[166] With a decrease in temperature, the magnitude of the induced shift usually increases. The use of temperature as a variable, instead of reagent concentration, to remove accidental signal coincidences can, in fact, be advantageous; reduction of temperature can increase the induced shift without the increase in line broadening that might be observed if more shift reagent was used at higher temperature. However, an increase in broadening resulting from a reduced rate of interconversion of free and complexed substrate, particularly at temperatures below room temperature, is also possible. Shift variations with temperature arise from at least two sources: the temperature-dependent paramagnetism of the complex and the temperature-dependent equilibria affecting the fraction of complexed species. With LSR's containing samarium(III) and europium(III), there is the additional temperature dependence of the population of the excited state.

Equation 6 predicts that if the molecular geometry is independent of temperature, the isotropic dipolar shift in solutions of lanthanide ions should be proportional to T^{-2} for all lanthanides other than Sm^{3+} and Eu^{3+}. Contact shifts, on the other hand, should be proportional to T^{-1}, according to Equation 3. Therefore, on this basis LIS's could in general be expressed as

$$\Delta\delta = a/T + b/T^2 \qquad (19)$$

where the first term on the right-hand side of the equation represents the contact contribution and the second term the dipolar contribution. To facilitate graphical analysis, this equation may be rearranged to

$$\Delta\delta\, T = a + b/T \qquad (20)$$

which shows that a plot of the product of the LIS and the temperature against the reciprocal temperature should be linear, with the slope giving the dipolar contribution and the intercept on the ordinate giving the contact contribution. In a study of the temperature dependence of lanthanide-induced proton shifts,[167] $Yb(fod)_3$ was selected as the lanthanide complex most likely to give a small relative contact contribution and, to overcome the problem of temperature-dependent equilibria affecting the fraction of complexed species, the shift reagent was dissolved in neat substrate (acetone), thereby attaining a molar excess of the substrate of more than 100. For the proton resonance of acetone in hexadeuteroacetone containing $Yb(fod)_3$ (the quintet of CHD_2COCD_3 was observed in a sample of deuteroacetone enriched to ca. 99 atom % deuterium), the plot of $\Delta\delta T$ against T^{-1} was, in fact, found to be linear with a zero intercept. Accordingly, it was suggested that studies of the temperature dependence of LIS's may serve the purpose of separating the dipolar and contact contributions.[167] Good straight lines were also obtained[168] when the shifts for the methyl and methylene protons of dimethoxyethane present in a 1:1 mixture of $Pr(fod)_3$ and dimethoxyethane in carbon tetrachloride were plotted against T^{-2}. The intercept for the methyl protons was almost zero, but a significantly nonzero intercept was observed for the methylene protons, pointing to contact contributions to the latter shift. In agreement with the predictions of Bleaney's theory regarding the effects of nearby excited states (Section III.B), straight lines were obtained[168] when the shifts for the protons of dimethoxyethane present in a 1:1 mixture of $Eu(fod)_3$ and dimethoxyethane in carbon tetrachloride were plotted against T^{-1}.

Not all authors are in accord with the prediction that for most of the lanthanides the dipolar shift should vary with temperature as T^{-2}. Both experimental and theoretical results have been advanced to indicate that a dependence of induced shifts on T^{-2} is unjustified and that a

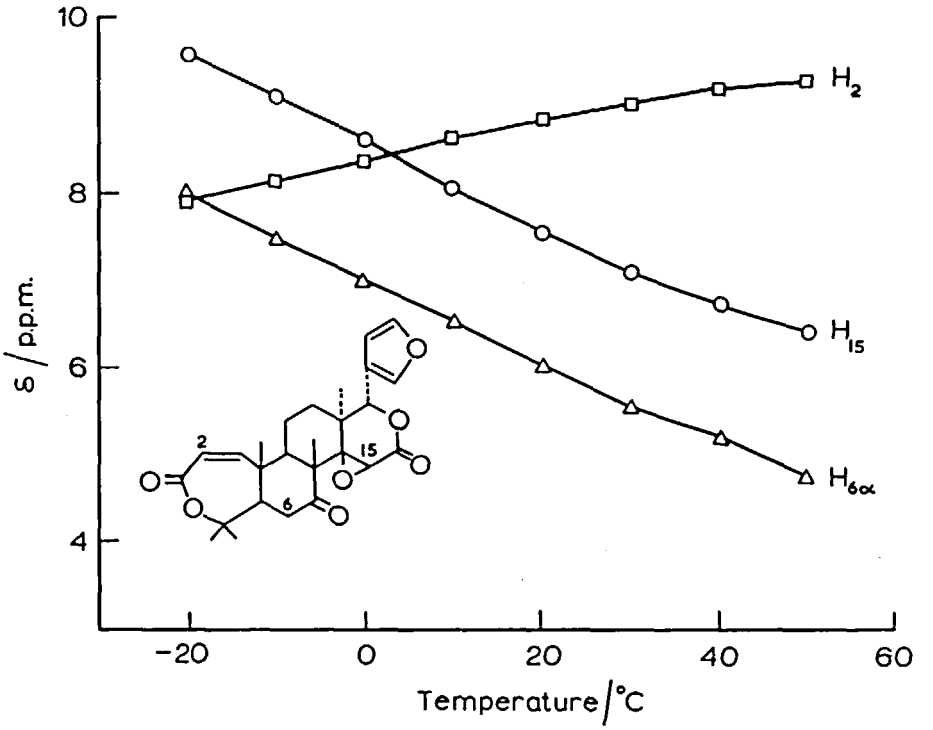


FIGURE 14. Chemical shifts of three protons of obacunone in $CDCl_3$ solution [$Eu(fod)_3$/substrate mole ratio of 0.6] as a function of temperature. (From Bennett, R. D. and Schuster, R. E., *Tetrahedron Lett.*, p. 673 (1972). With permission.)

reasonably good dependence on T^{-1} may be expected over the limited temperature range available to dipolar shift experiments.[169] From the studies of the variation of the induced shifts with temperature so far reported, it seems clear that the temperature dependencies are, in general, not simple; in particular, the effect of temperature on the equilibrium between free and complexed substrate requires more careful investigation. Another relevant point is that in any single molecule all the protons may not always respond uniformly to temperature changes. For example, a linear relationship between the $Pr(tmhd)_3$-induced shifts of several alcohols [(1-methylcyclopropyl) methanol, 1-methylcyclobutanol, and *n*-pentanol] and the inverse of temperature has been reported[111] for the temperature range 50 to 90°C. However, the slopes of the lines were found to be different for different protons, some of the lines even intersecting; protons closer to the site of coordination showed the larger slopes. Crossing of the lines was attributed to a temperature-dependent change in the proton positions relative to the rare-earth metal.[111] In the $Eu(fod)_3$-shifted spectra of limonoids, shift of proton signals in opposite directions was observed over a variety of temperature ranges (see, for example, Figure 14).[166] Since the limonoids are polyfunctional substrates, these results can be attributed to a change in the site of coordination.

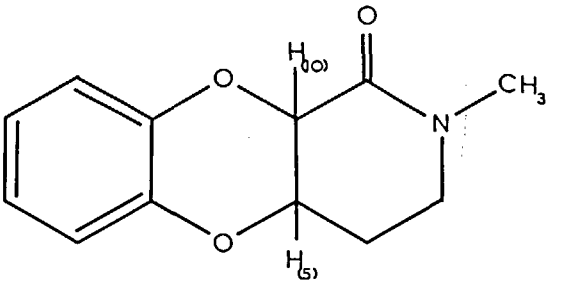
3. Nuclear Spin-spin Coupling Constants

The ability of LSR's to lower the order of a spectrum of a substrate without broadening the signals excessively can provide a simple method for extracting nuclear spin-spin coupling constants that are either difficult or impossible to obtain because the relevant resonances are obscured or the spectrum is too complicated to make the derivation of these parameters practical. The coupling constants are taken directly from the first-order spectra or extracted from appropriate spectral analysis of the simplified spectra. Couplings observed in shifted spectra are the average of those of the free and complexed substrate. Consequently, changes in the electron density distribution in the substrate molecule due to coordination or changes in the substrate confor-

mation due to steric requirements of the complexation can alter the magnitude of the observed splittings. In addition, the relaxation effects of some LSR's can cause spin decoupling and may, therefore, influence the measured values. From a number of studies (see, for example, References 170 to 174) the conclusion has been drawn that coupling constants are not significantly affected by the addition of a LSR. Thus, coupling parameters obtained by this method can often be taken as good approximations to the corresponding values for the free substrate. With some substrates, however, the coupling parameters derived from LIS experiments are not independent of the shift reagent.

A linear increase of up to 10% in several geminal methylene H–H coupling constants of 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone and camphor has been observed upon increasing the concentration of the reagents $Eu(tmhd)_3$ and $Eu(fod)_3$ up to a LSR/substrate mole ratio of ~0.7.[175] The results are considered to be consistent with effects observed for electron-withdrawing substituents on carbonyl compounds, in the above systems that role being played by a Lewis acid (the LSR) binding with the substrate. The coupling constants of the free substrate in such systems can best be obtained by performing a regression analysis between the observed coupling constant and the LSR/substrate ratio. Small but significant increases in a geminal coupling constant of 2-*endo*-hydroxymethyl-5-norbornene on the addition of $Eu(tmhd)_3$ have been reported.[176] This result too is considered to be consistent with the electronic effect of coordination on the substrate.

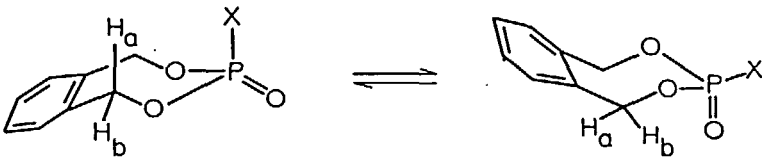
The vicinal coupling constant between protons 5 and 10 in Formula 1 increases from 3 to 8 Hz as the mole ratio of $Eu(fod)_3$ to substrate is increased.[177] This appears to be due to a particular conformation being favored in the formation of the adduct with the shift reagent.[177] The coupling constants of *cis*-2-methyl-5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane have been found to change significantly with increasing $[Eu(fod_3]$/[substrate] mole ratio; this also has been attributed to the influence of the LSR on a possible conformational equilibrium.[178] Likewise, with seven-membered-ring phosphorus heterocycles, large $Eu(fod)_3$-induced variations in coupling constant have been interpreted as due to the perturbation of a conformation equilibrium.[179] Thus, for the 3-substituted 1,5-dihydro-2,4,3-benzodioxaphosphepin 3-oxides (Formula 2; X=OCH_3 or OC_6H_5), the geminal coupling constant, J_{ab}, remains constant on the addition of $Eu(fod)_3$, whereas the two sets of $^3J_{HP}$ vary greatly and in a complementary manner. Coordination in these compounds occurs at the phosphoryl oxygen, and it is suggested that the Eu reagent modifies the nature of the P=O bonding, thereby reducing its normal equatorial preference. Consequently, the equilibrium between the two chair forms (Formulas 2a and 2b) is shifted in the direction of the axial phosphoryl conformer (Formula 2b) on the addition of the shift reagent.



FORMULA 1.

The aromatic proton coupling constants of a number of benzocycloalkenols have been obtained by computer analysis of high-resolution spectra (220 and 300 MHz) and of $Eu(tmhd)_3$-shifted spectra at 60 MHz.[180,181] The values given by the two methods differ by more than the experimental uncertainties, but the mechanism by which the shift reagent alters the magnitude of these couplings remains obscure. An apparent reduction in several spin-spin couplings in quinoline on the addition of $Eu(tmhd)_3$[89] has been explained by a decrease in the relaxation time of the nuclei.[72]

Clearly, the constancy of nuclear spin-spin coupling constants in the presence of LSR's cannot be assumed. Care must, therefore, be exercised in the interpretation of such data. Where necessary, the magnitude of the couplings should be monitored over a range of shift reagent concentrations and extrapolated to zero concentration. Alternatively, chemical shifts and coupling constants derived from shift data should be used to calculate the appearance of the unshifted spectrum, and this should be compared with the original one.



FORMULA 2a. FORMULA 2b.

4. Dependence of Induced Shifts on Geometric Parameters

a. Shift Reagents as Structural Probes

The most important impact of LSR's in chemistry results from the apparent validity of the dipolar equation, because this enables geometric relationships within a substrate molecule to be derived. Few, if any, other physical methods that may be applied to fluid solution have the potential, in principle at least, of yielding such detailed structural information. Equation 21, obtained by ignoring the second term on the right-hand side of Equation 7, is a simplified form of the dipolar Equations 4 and 6.

$$\Delta = C(3\cos^2\theta - 1)r^{-3} \qquad (21)$$

If shift values other than the limiting incremental shift are employed, the constant C will depend not only on the magnetic anisotropy of the complex, but also on the complex-formation constant and the concentration. The use of Equation 21 to extract geometric information from LIS data rests on the following assumptions.[53]

1. The observed shifts used in the analysis are solely dipolar in origin.
2. Only a single complex species exists in solution in equilibrium with the uncomplexed substrate.
3. Only a single geometric isomer of this complex species is present.
4. This isomer is magnetically axially symmetric, so that the shifts are proportional to the geometric factor.
5. The principal magnetic axis has a particular known orientation with respect to the substrate ligand(s).
6. The substrate ligand exists in a single conformation, or an appropriate averaging over internal motions is achieved.

In comparatively few investigations have attempts been made to justify these assumptions, yet if any one of the conditions is not met, the results of an analysis based on Equation 21 will not be strictly valid. An exacting, experimental approach towards assessing the validity of the above assumptions has now been outlined,[50] the main points of which are as follows.

1. Both high- and low-field LSR's should be used.
2. The induced shifts must be corrected for diamagnetic contributions by substracting the observed shifts due to complex formation with lanthanum (III) or lutetium (III).
3. Ratios of shifts at different proton sites should then be compared for the different lanthanides, thereby eliminating effects due to changes in the crystal field coefficient. If these 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.
4. 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.
5. 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.
6. The computer search can best be made if data from line broadening or relaxation times are also incorporated (as the line broadening depends upon r^{-6}) using gadolinium (III) as a relaxation probe.
7. If the computer fails to find a solution, the temperature dependence of the shift ratios should be examined, for the shift data could arise through an averaging of the shifts of a molecule that had several configurations in thermal equilibrium.

For many structural studies, the rigor of the above procedure is possibly not necessary, e.g., where the method is being used to distinguish

between two grossly different molecular geometries. Where such differences are rather more subtle, however, the underlying assumptions should be checked and more sophisticated treatments applied if necessary, particularly where the structure suggested by a shift reagent study is at variance with independent evidence. The analysis of much LIS data using Equation 21 appears to be justifiable on the grounds of its apparent success. Good correlations between a given substrate geometry and observed LIS's using this equation do not, of course, prove the validity of the approach since, *inter alia*, the position of the metal ion is not known and, in calculations of dipolar shifts, may be acting as a smoothing parameter, effectively hiding inadequacies of the method.[42c]

The predominantly dipolar nature of proton resonance shifts in LSR systems has undoubtedly been established. From an analysis of the available data, reference to which has been made in Section III.C, it is clear that isotropic shifts for substrate protons separated from the lanthanide ion by four or more bonds may generally be considered exclusively dipolar in origin. Caution must be used, however, when including protons that are closer to the metal ion in the dipolar shift analysis. For nuclei other than ^1H a contact-shift contribution to the dipolar interaction probably precludes their widespread use in structural and stereochemical analyses.

While the dipolar nature of LSR-induced ^1H shifts suggests that they might serve as useful probes of the geometry and conformation of substrate molecules in solution, it is important to be clear what is meant by the word *useful*. Structures are not determined from LIS data in the sense of deriving positional coordinates from the information. Instead, various structural possibilities are proposed, and the shift data are then used to test these proposals, hopefully, to either validate or reject them. Further, the successful analysis of shift data will only yield the shape of the substrate in its bound form. Except for a conformationally rigid molecule, the bound conformation need not necessarily be the same as that of the free-solution form. Evidence has been obtained[182] that the shift reagent can disturb the conformation of the substrate being examined. Moreover, with a nonrigid substrate, the calculated conformation will represent the weighted-average conformations of the molecule interacting with the LSR.

b. Application of the Dipolar Equation

i. Quantitative Procedures

Any quantitative approach to fitting LSR spectra has three aspects:[183] (1) the physical-mathematical model (on what description of the phenomena being studied, attempts to fit the observations should be based); (2) the operational or computational model (by what method the attempts at fitting should be carried out); (3) the assessing function (how the attempts to fit the observed data should be evaluated).

Up to the time of writing, most attempts at fitting LSR data have used, as the physical-mathematical model, an axially symmetric (or effectively axially symmetric) complex, with the principal magnetic axis of the complex taken to be collinear with the lanthanide-to-substrate bond. For such a model the dipolar contribution to the LIS of a nucleus is given by Equation 21.

One approach to the process of fitting the data has been to assume a reasonable geometrical model for the LSR-substrate complex, calculate intramolecular shift ratios using Equation 21, and then compare these ratios with the observed ones.[73,184,185] The structural model of the molecule is altered to obtain the best correlation of the shift data. Dreiding molecular models have often been used to estimate the angle-distance factors. The use of shift ratios, rather than the shifts themselves, circumvents the difficulty of not knowing the value of C; whereas Δ_i and Δ_j both require a knowledge of C, the ratio Δ_i/Δ_j is independent of C.

Another approach to the problem involves fitting Equation 21 to experimental Δ values by incremental variations of the position of the lanthanide ion with respect to the substrate molecule, until the correlation between calculated and experimental shifts is maximized.[64,186-190] One of these computational methods has been described in some detail.[183,191] The substrate molecule is placed in a cartesian coordinate system with the complexing atom at the origin. With the coordinates of the substrate model held fixed, the position of the lanthanide ion is moved incrementally over the surface of closely spaced spheres of radii corresponding to the assumed distance from the coordinating atom. The location of the ion on each sphere is described by two angles: the colatitude (measured from the positive z-axis) and the azimuth (measured counterclockwise from the x-z plane). At each lanthanide ion position, the

geometric term in Equation 21 is calculated for each atom. This set of calculated values is then scaled by least squares against the observed LIS values to yield a set of calculated shifts.

Several functions have been proposed and used for assessing the agreement between observed and calculated LIS values, including standard deviation and correlation coefficients. A statistical agreement factor (AF) that has been found convenient to use is defined by[191,192]

$$AF = [\sum_i w_i(\Delta_{i,obs} - \Delta_{i,calc})^2 / \sum_i w_i(\Delta_{i,obs})^2]^{1/2} \quad (22)$$

where w_i = the weight applied to the observation for the ith nucleus. The dependence of the AF on the colatitude and azimuth angles and on the assumed lanthanide ion-heteroatom distance has been conveniently displayed using contour lines on a map projection.[183,191] These contour maps have shown that several values of r and θ will often give satisfactory fits of the experimental data. Reasonably good agreement between observed and calculated shift values should not, therefore, be taken as proof of the model used. Clearly, only a model that produces good results for both the chelate and substrate protons is acceptable. By considering *all* the protons of the complex, some of the pitfalls inherent in the study of LIS's may doubtless be avoided.

A more elaborate computer treatment than that described in References 186 to 191 is required if the conformations of nonrigid substrates are to be determined. Investigation of the conformation of nonrigid molecules is greatly assisted if the molecular species contains a rigid unit that gives rise to several observable NMR resonances because the protons of the framework can be used to define the position of the lanthanide ion before a search for the more flexible part of the structure is commenced.[193,194] With molecules of flexible conformation, however, a simple trial-and-error procedure will be uneconomical. In a determination of the possible conformations of two representative nucleotides in aqueous solution, the total number of conformations to be examined was substantially reduced by using the constraints imposed by the interatomic van der Waals contact distances, the LIS's, and the line broadenings as filters.[80] The computer program analyzed the raw data by searching for conformations that were sterically possible and which agreed with the NMR results. Thus, from a total of 64×10^6 conformations of 9-β-D-ribofuranosyladenine-5′-monophosphate, only 195 were found to be consistent with both the van der Waals radii and the induced shifts, and only 12 of these conformations were also consistent with the line broadenings.

A graphical method for the analysis of LIS's has been described[195] that, for conformationally rigid molecules, may be a satisfactory substitute for computer-optimized fits. The method requires positioning a Dreiding model of the compound on a map of the dipolar field for an axially symmetric complex, the field being drawn to the same scale as the molecular model. The relative shifts are then read directly from the plot and scaled to match the observed shifts. Figure 15 illustrates the method using pyridine as an example. Symmetry requirements place the metal on the C_2 axis of pyridine. The molecule is, therefore, positioned on the graph so that the C_2 axis coincides with the principal magnetic axis, and the nitrogen lies about 3.0 ± 0.5 Å away from the metal.

The fact that Equation 21, which implies axial symmetry in the complex, appears to rationalize much LIS data is somewhat puzzling, since X-ray structural and magnetic susceptibility studies[52,53,88,156,169,196] show that LSR adducts do not possess axial symmetry in the solid state. It has been pointed out, however, that if a substrate molecule is freely rotating (or is confronted with an n-fold barrier, where $n \geq 3$, and the populations of the rotamers are equal) about an axis that passes through the lanthanide ion, the rhombic component of the anisotropy (the second term in Equation 7) averages to zero, so that a form of effective axial magnetic anisotropy is generated.[188,197] With this model θ will, therefore, refer to the angle made by the radius vector with the axis of rotation rather than the symmetry axis. An alternative explanation for the apparent axial symmetry assumes that LSR adducts exist in solution as an ensemble of rapidly interconverting geometric isomers, but that the substrate, through its influence on the ligand field in the individual isomers, exhibits a statistical bias to lie in proximity to an axis of maximum or minimum susceptibility.[198] Using this model, it has been shown that resonance shift ratios will, within reasonably broad limits, conform to those derived from an axial model. Substrate ligand rotation and/or ligand exchange would thus appear to provide a satisfactory theoretical rationalization for the earlier indiscriminate use of axial symmetry in the analysis of dipolar shifts.

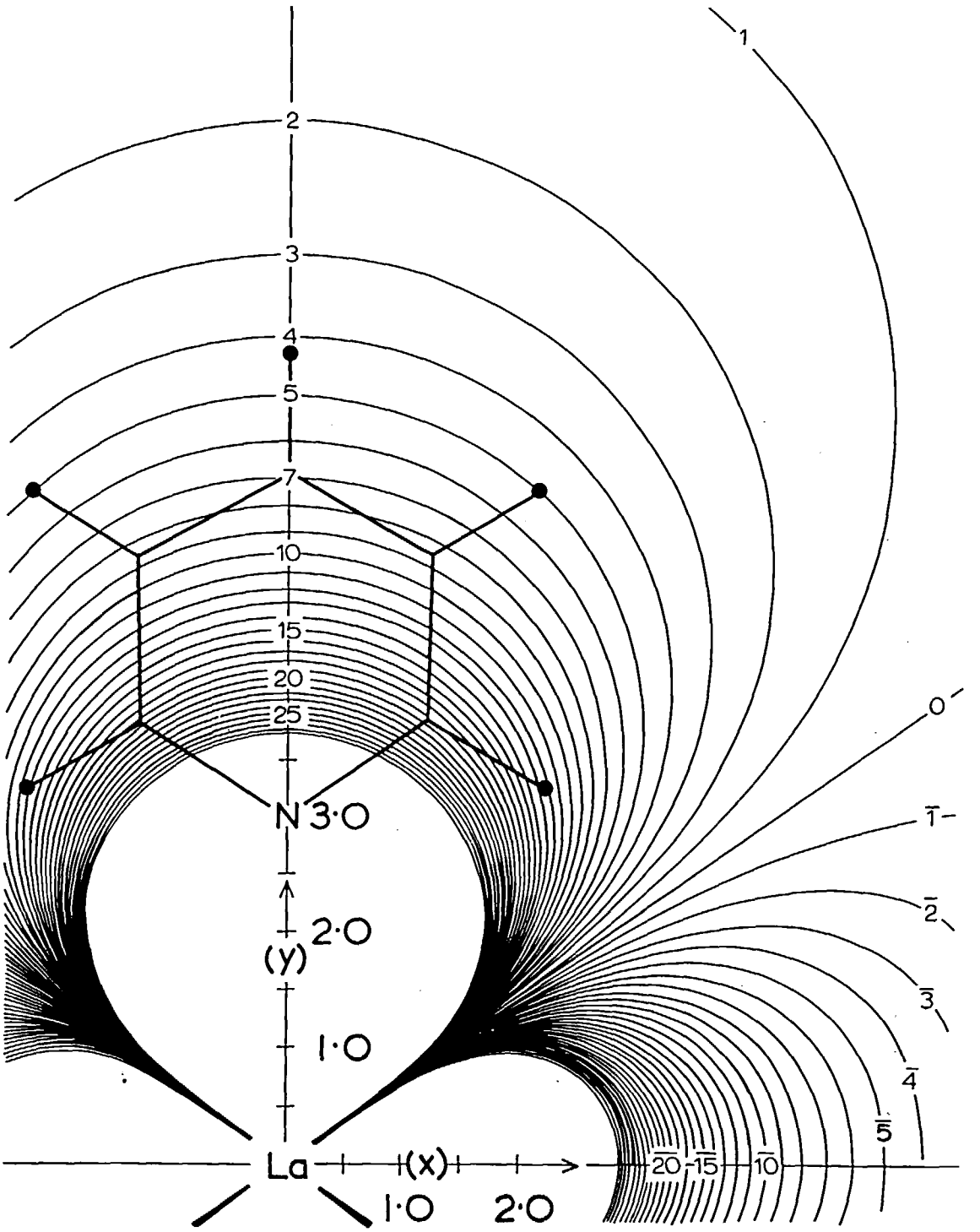


FIGURE 15. Pyridine placed on the map of the dipolar field for an axially symmetric complex; $(3\cos^2\theta - 1)r^{-3}$ where $y = r\cos\theta$ and $r^2 = y^2 + x^2$. (From Wing, R. M., Early, T. A., and Uebel, J. J., *Tetrahedron Lett.*, p. 4153 (1972). With permission.)

A further assumption made in applying Equation 21 is not only that the magnetic anisotropy is axially symmetric, but also that the lanthanide-to-substrate bond corresponds to the principal magnetic axis of the LSR-substrate adduct, so that values of θ may be estimated with respect to this bond. The possibility that the principal axis of the complex and the vector from the lanthanide ion to the coordinating atom in the substrate molecule are not collinear has been considered, and an experimental approach to the problem of locating the magnetic axis has been outlined.[199] The conclusion of two recent studies[194,200] is that optimization of the direction of the principal magnetic axis invariably results in placing it along the lanthanide-donor bond.

Not all complexes, however, exhibit LIS's that can be satisfactorily explained on the basis of a single-term equation which assumes that the principal magnetic axis passes through the donor atom. Thus, an ambient-temperature NMR study of the dipyridine adduct of Eu(tmhd)$_3$ and a low-temperature study of the dipicoline adduct of the same reagent show that collinearity between the principal magnetic axis and the metal-ligand bond does not exist; with these systems the induced shifts can be properly correlated only with the double-term dipolar equation, i.e., Equation 7.[71] Since the second term was found to comprise from 29 to 80% of the total shift, the importance of considering this term, at least for those complexes that form 1:2 adducts, is obvious. It has been suggested that the binding strength of pyridine nitrogen may be responsible for the formation of a tight LSR complex in solution with pyridine in a preferred ϕ orientation.[194] The two-term equation has also been tested for a number of 1:1 complexes.[200] Although improved fits to LIS data again resulted, these improvements were only of marginal significance.

In complexes with rapid internal rotational degrees of freedom, the observed shifts are the result of an averaging of molecular orientations. With these systems it is, therefore, necessary to average the entire quantity, $(3\cos^2\theta_i - 1)r_i^{-3}$, before comparing observed and calculated shift ratios. The use of rotamer-averaged models has been described.[153,200,201] Generally speaking, equivalent or superior fits were obtained by rotamer averaging. In several instances the correct proton assignments were inconsistent with the one arrived at by using a static model (i.e., averaged atom positions).[200]

ii. Approximate Methods

Equation 21 has proven extremely valuable for the application of LSR's in practical NMR spectroscopy. Where only partial assignment of signals has been possible by conventional NMR techniques, the use of this equation has enabled lines in the spectrum of a molecule of known structure to be assigned comparatively easily. Conversely, as outlined in the previous section, information on molecular geometry can often be obtained if the line assignment is known. For spectral analysis, however, it is not always necessary to resort to the use of the full equation. Frequently the problem of signal assignment can be solved by the use of a simple relationship involving only LIS's and distance factors.

The logarithmic equivalent of Equation 21 is

$$\log \Delta_i = -3 \log r_i + [\log (3 \cos^2 \theta_i - 1) + \log C] \qquad (23)$$

If $\log C \gg \log (3\cos^2\theta_i - 1)$, a plot of $\log \Delta_i$ against $\log r_i$ should approximate to a straight line with a slope of -3. Many authors (see, for example, References 21, 57, 89, 133, 202 to 205) have reported a reasonable correlation with a r_i^{-3} relationship, where r_i, the distance between the estimated average position of the lanthanide nucleus and the proton under consideration, is measured from molecular models, e.g., Dreiding. In analysis of this kind, Ln-donor atom distances that vary from the van der Waals radius of the donor atom to roughly 1.5 times the sum of the covalent radii of Ln and the donor atom have been employed. Usually, this distance is adjusted to improve the fit; values in the literature range from 1.5 to 3.5 Å. Other workers have ignored the position of the metal ion and have taken r as the distance from the resonating nucleus to the center of the coordinating atom[25,138,206-208] or to the lone-pair periphery of this atom.[139,143,172] In such cases, plots of $\log \Delta_i$ against $\log r_i$ give slopes that vary from -0.2 to -3.6.[209,210] Equally good fits may, in fact, be obtained by a variety of methods of handling such correlations.[210] Since the lanthanide-proton distance (r) will, in general, be greater than the donor atom-proton distance (r_0), one can write $r \approx r_0 + d$, where d is an approximately constant increment that represents

the lanthanide ion-donor atom distance. Clearly, shifts that are proportional to $(r_0 + d)^{-3}$ will fall off less quickly than r_0^{-3} if plotted against r_0. Although methods of calculation that neglect the angular factor are convenient and may provide a fairly reliable aid in signal assignment, such methods only give at best a rough indication of structure.

With most molecular geometries, the values of θ are smaller than $\cos^{-1}\sqrt{3}$ (i.e., 54.736°), so that the term $(3\cos^2\theta - 1)$ is nearly always positive. Indeed, for most of the nuclei in most organic substrates θ lies between 0 and 30°, which accounts for the usual dominance of the distance parameter over the angular factor. When θ exceeds 54.736°, the angle-dependent term becomes negative and assumes great importance, since the "normal" direction of the LIS is reversed. These nuclei are located in either the shielding or the deshielding portion of the LSR field, depending on the metal ion. With europium, deshielding occurs along the effective magnetic axis; with praseodymium, this is the shielding portion of the field. Thus, the occasional observation of upfield shifts induced by Eu complexes is probably attributable to a change in sign of the angular function.[145, 189,194,211] The presence of significant contact interaction can also explain a reversal of shift direction for atoms close to the donor site. Clearly, however, an "angleless" shift analysis should be employed with caution, and the results obtained should be accepted only after an adequate evaluation of the consequences of angle neglect has been made.

c. Line Broadening

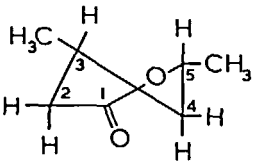
The possible use of lanthanide complexes as relaxation reagents for the determination of relative distances within the complexed substrate has been suggested.[82] Molecular structures deduced from dipolar shift studies could, in principle, be tested by requiring a simultaneous fit to the relative line widths induced by the lanthanide ion. Because the broadening is approximately proportional to r^{-6}, where r is the length of the metal-nucleus vector, the method should allow significant error in the measured line width without sacrificing acceptable accuracy in the determination of relative values for r. The use of $Gd(tmhd)_3$ and $Gd(fod)_3$ for inducing line broadening was advocated,[82] since gadolinium(III) exhibits negligible magnetic anisotropy and the broadening shows a very close correlation with r^{-6}. It has now been demonstrated,[212] however, that LSR-induced relative line widths fail to reflect the true geometry if axial symmetry is assumed. An explanation for the contrast in behavior with respect to effective axial symmetry noted for the line width and shift data has been suggested.[212] The possibility of obtaining information of rhombic anisotropy from experimental line-width data under conditions where such effects vanish for dipolar shifts is at present being investigated.[212]

V. APPLICATIONS

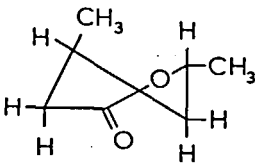
This section surveys some general and two special lines of application of the lanthanide shift technique; most of these have already been described or alluded to in the preceding sections. Only a limited number of additional references are cited here; more exhaustive sets of specific examples are given in several of the review articles referred to in Section II (see References 29 and 37 in particular).

A. Simplification of Spectra

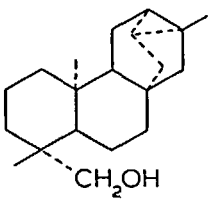
Lanthanide shift reagents are frequently used merely to provide a convenient and economical means by which interfering NMR resonances can be separated. Line overlap and complex spectral patterns with resonances not only coincident but also highly coupled have long been major obstacles in the application of NMR spectroscopy to the study of many important classes of organic compounds. Signal displacement induced by shift reagents produces a marked increase in the chemical shift relative to the spin-spin coupling constant, usually enabling spectra of (quasi-) first-order (or at least more highly dispersed) nature to be obtained, even for complicated spin systems. With such systems the alternatives to the use of LSR's would be either to go to higher external fields, use multiple resonance techniques, or attempt a computer-aided analysis of the spectrum. Applications involving LSR's are more or less revolutionizing ^1H NMR studies of complex organic molecules, at least for those that are soluble in a suitable organic solvent. In one of the first reported applications of LSR's for spectral simplification, $Eu(tmhd)_3$ was added to a carbon tetrachloride solution of *cis*- or *trans*-3,5-dimethylvalerolactone (Formulas 3a and 3b, respectively).[213] Addition of the shift reagent moved the $C_{(2)}$-methylene group into a spectral



FORMULA 3a.



FORMULA 3b.



FORMULA 4.

region where the splitting pattern became amenable to first-order analysis. Thus, the coupling constants, in particular those between the protons at positions 2 and 3, were evaluated.

B. Assignment of Signals

The resolution achieved in the presence of shift reagents can make the assignment of signals considerably easier. With suitably shifted spectra, multiplicities are discernible, nonequivalence is greatly amplified, and useful integrated areas are easily obtained. Spin-decoupling techniques can be applied to the expanded spectrum, if necessary. Thus, with the aid of $Eu(tmhd)_3$ and some decoupling experiments, spectral assignment was achieved for all the protons of trachyloban-19-ol (Formula 4).[214] The same shift reagent was employed in a ^1H NMR study of calciferol (vitamin D_2) to provide the necessary spectral resolution required to assign multiplets.[215] Frequently, a rapid solution to the problem of spectral assignment can be achieved by making use of the fact that the induced shifts decrease with increasing distance of the respective nuclei from the bonding site between shift reagent and substrate (see Section IV.F.4.b.ii).

C. Determination of Chemical Shifts and Spin-spin Coupling Constants

Extrapolation of the linear portion of the LIS vs. $[L]_0/[S]_0$ plot to zero concentration of the LSR enables satisfactory estimation of the chemical shifts of those substrate protons whose signals overlap in the absence of a shift reagent (see Section IV.F.1.a). Nuclear spin-spin coupling constants, previously inaccessible because of the superposition of signals, can also be obtained from NMR spectra simplified through the use of shift reagents. Since the constancy of coupling constants in the presence of LSR's cannot be assumed, however, values so obtained should be treated with caution unless adequate precautions have been taken (see Section IV.F.3).

D. Study of Molecular and Stereochemical Structure

Lanthanide shift reagents have been extensively applied to the determination of the molecular geometry of conformationally rigid compounds. With the aid of LSR's, NMR spectroscopy is now being employed to establish the structure and stereochemistry of molecules of such complexity that previously the use of the technique was hampered or altogether precluded both by extensive line overlap and by the complexity of the splitting pattern.

Two methods for the use of LSR's in molecular structure elucidation have evolved: the qualitative approach using chemical shifts and coupling constants derived from shifted spectra (with structural assignments being made on the basis of available empirical knowledge) and the quantitative approach (relying heavily upon the magnitudes and directions of the shifts to validate or reject proposed three-dimensional geometries). The qualitative aspects of the LSR experiment, emphasized in the examples given below, can be sufficient to remove structural ambiguities. The calculations involved in the quantitative procedures are generally computerized, with various correlation coefficients being employed to assess the correspondence between computed and observed LIS values. Some examples of the quantitative stereochemical analysis of substrate molecules are described in Section IV.F.4.b.i; other examples are given in Section V.E.

Determining the position of substitution in

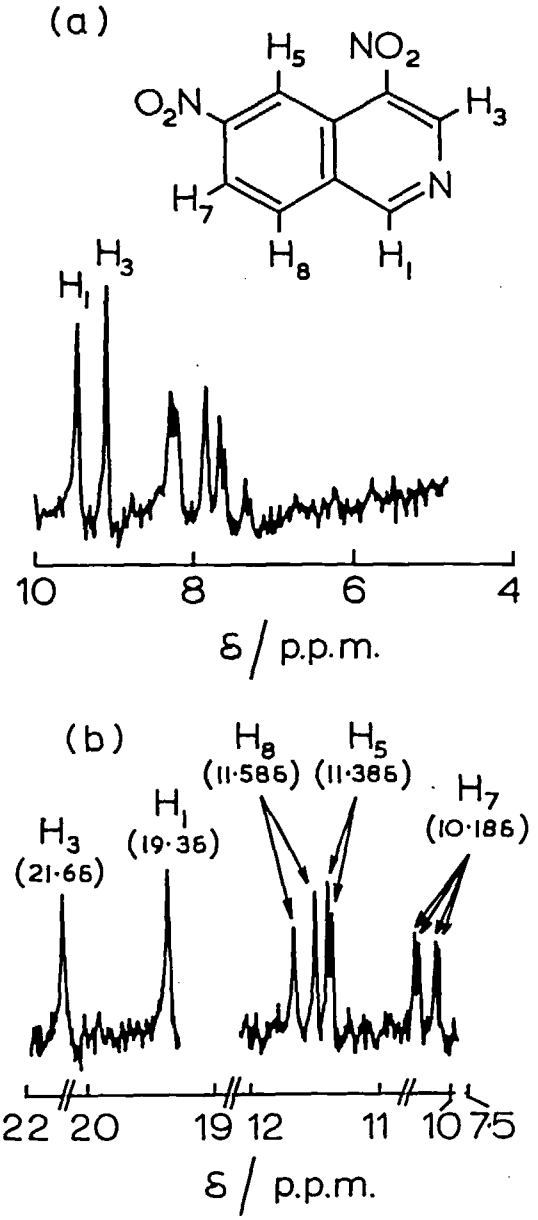


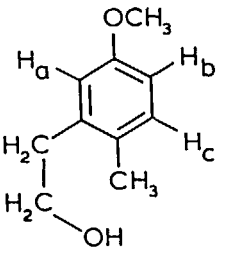
FIGURE 16. 60-MHz ^{1}H spectra of 4,6-dinitroisoquinoline in $CDCl_3$: (a) 0.640 *M*; (b) in the presence of 0.428 molar equivalent of $Eu(fod)_3$. (From Atkins, R. L., Moore, D. W., and Henry, R. A., *J. Org. Chem.*, 38, 400 (1973) With permission.)

heterocyclic systems is by no means a trivial task; in many instances classical and spectroscopic determinations lead to equivocal results. Unequivocal structural assignments have been made for a number of substituted isoquinolines through the application of $Eu(fod)_3$.[216] For example, it is not possible to distinguish 4,6-dinitroisoquinoline from the 4,5-substituted isomer by means of the 60-MHz NMR spectrum shown in Figure 16a. The spectrum illustrated in Figure 16b was obtained in the presence of $Eu(fod)_3$. The shift reagent has removed the fortuitous equivalence and overlap of chemical shifts observed in spectrum 16a and has made it possible to assign the structure of this previously unknown compound as that of 4,6-dinitroisoquinoline with absolute certainty.

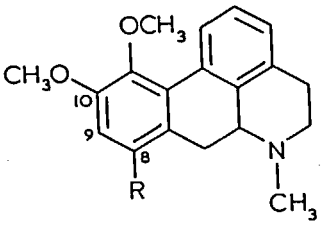
The aromatic region of the 60-MHz ^{1}H NMR spectrum of 3-methoxy-6-methylphenethyl alcohol (Formula 5) yields little information.[217] Addition of $Eu(tmhd)_3$ produced a well-resolved spectrum in which multiplets could be easily identified (H_a and H_c doublets, H_b a quartet), the molecular structure being established from the values of the coupling constants (J_{ab} = 2.5 Hz, J_{bc} = 8.0 Hz).

An important application of LSR's concerns deuterium location in partially deuterated molecules. Thus, the structural elucidation of 10,11-dimethoxyaporphine-$d_{(8)}$ (Formula 6) was unequivocally achieved by the use of $Eu(fod)_3$ and Formula 7.[218] When the spectrum of Formula 7 was obtained in the presence of increasing quantities of $Eu(fod)_3$, a large downfield shift of the CH_3O-10 proton resonance was observed. Studies relating the angular and radial dependencies of LIS's indicated that the downfield doublet of the AX quartet observed at $[Eu(fod)_3]/[7] \geq 0.11$ should be assigned to H-9 with the upfield doublet assigned to H-8. When Formula 6 was studied by NMR in the same way as Formula 7, shifts of CH_3O-10 and its neighboring proton were in accord with the assignment of a proton at C-9 and the deuterium at C-8.

Identification of geometric isomers by LIS's is now well established. For example, $Eu(tmhd)_3$-induced shifts enable a rapid distinction between borneol (Formula 8) and isoborneol (Formula 9),[25] between the *E* and *Z* isomers of 3-chlorocyclobenzaprine (Formulas 10 and 11, respectively),[219] and between the *cis*- and *trans*-isomers of 2,2,3,4,4-pentamethylphosphetan oxides (Formulas 12 and 13, respectively).[220] Sulfines represent a bent heterocumulenic system, and complexation at the oxygen atom of the CSO-system results in a larger induced shift for protons in a *syn* position than for those in an *anti*

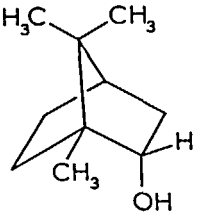


FORMULA 5.



FORMULA 6: R = D.

FORMULA 7: R = H.



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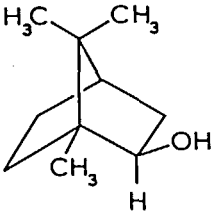

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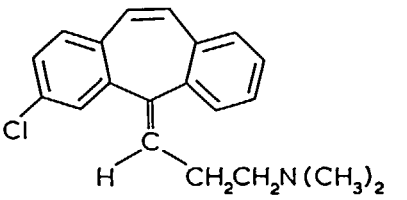
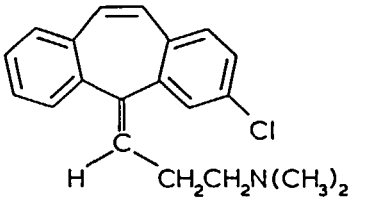
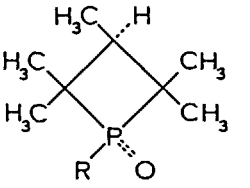


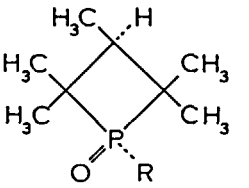
FORMULA 10.



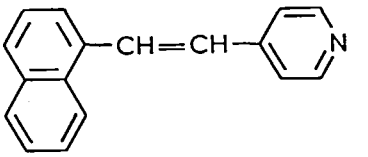
FORMULA 11.



FORMULA 12.



FORMULA 13.



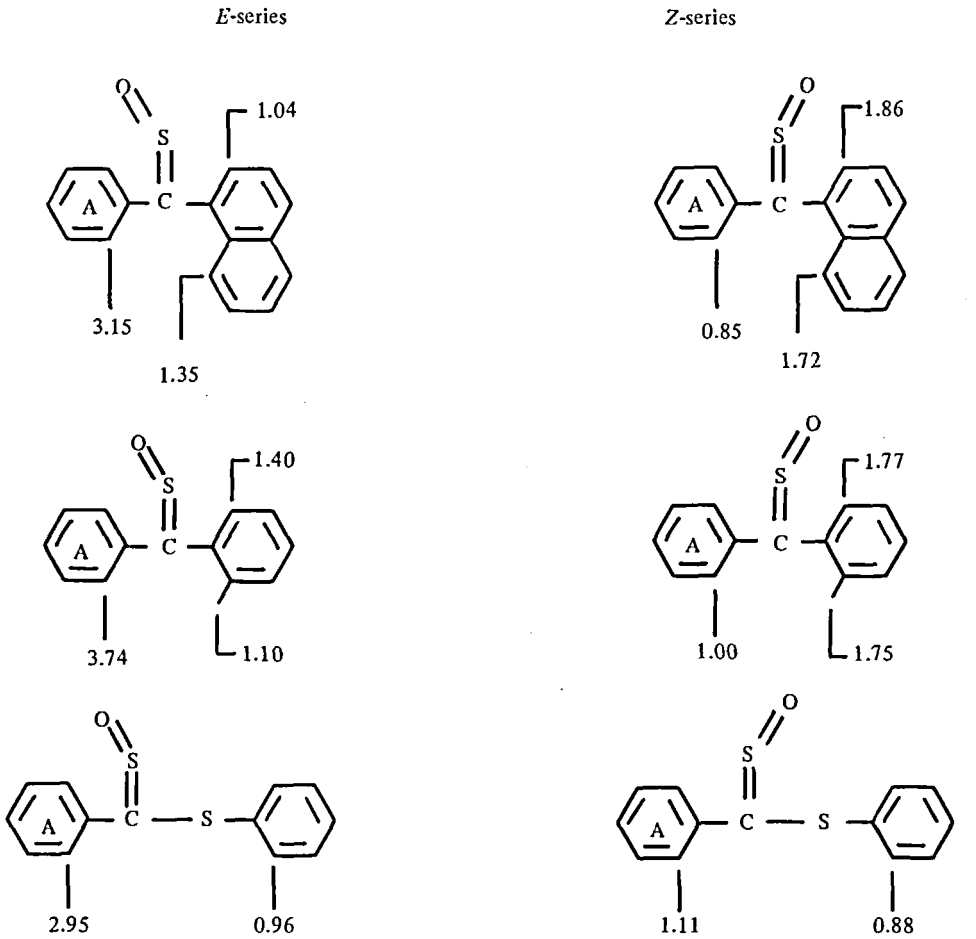
FORMULA 14.

position, provided the protons are situated in the immediate vicinity of the sulfine moiety. This difference in induced shift provides an easy means of assigning the configuration to sulfines.[221] As shown in Table 3, the LIS for *ortho*-protons of the A-ring in the *E* series (*syn* protons) is much larger than that for the *ortho*-protons of the A-ring in the *Z*-isomers (*anti* protons).

The identification of geometric isomers by means of coupling constants obtained from the shifted spectra is also possible, e.g., Eu(tmhd)$_3$ has been so used to distinguish between the *cis*- and *trans*-isomers of 4 [β-(1-naphthyl)-vinyl] pyridine (Formula 14).[222] In the NMR spectrum of Formula 14 in the absence of a shift reagent, the vinyl proton resonances are hidden within the naphthalene envelope, thus preventing the NMR method being used for isomer identification. In the

TABLE 3

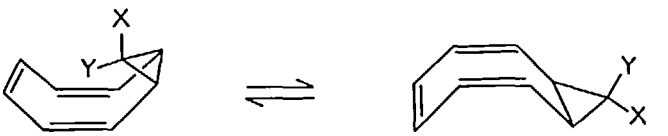
Eu(tmhd)$_3$-induced Shifts for *E*- and *Z*-Sulfines[221]



presence of Eu(tmhd)$_3$, however, these resonances are revealed and give an AB quartet, so that the *cis*- or *trans*-configuration of the compound can be determined from the value of the vinyl coupling constant.

E. Study of Conformation

Increasing use is being made of the lanthanide shift technique to investigate the solution conformational preferences of flexible molecules. Since an analysis based on LIS data provides no direct information on the conformation of the uncomplexed substrate, an important question arises: to what extent does interaction of the substrate with the shift reagent change the conformation of the substrate and/or the position of the conformational equilibrium? The results published so far are divergent. For a series of unsaturated compounds that included aldehydes, ketones, esters, and amides, it was shown[190] that no unusual perturbation of the *cis-trans* conformational equilibrium due to complex formation with Eu(fod)$_3$ occurs. The rotational equilibria in *cis*- and *trans*-1,5,5-trimethyl-3-(α-naphthyl) cyclohexanols (shift reagent, Eu(fod)$_3$)[223] and the equilibrium between the α- and β-chair forms for the A ring of calciferol (Eu(tmhd)$_3$)[215] are also not affected significantly upon coordination. The conformation of the 32-atom side chain of chloroquine when the latter is complexed to Pr(tmhd)$_3$ is probably not significantly different from that of the uncomplexed substrate.[193] On the other hand, the addition of Eu(fod)$_3$ has been shown to shift the equilibrium between equatorial and axial *tert*-butyl to the axial conformer in a *tert*-butyl dioxaphosphorinane.[178] This shift reagent also



FORMULA 15a. FORMULA 15b.

apparently distorts the solution conformations of acyclic alcohols.[182] The results of a conformational study of 1-methylcyclohexanol with $Eu(tmhd)_3$ show a conformational equilibrium shift of the complexed molecule compared to the free one;[224] the equatorial conformation of the functional group is favored by complexation. Clearly, until further studies have been reported, the results of a conformational analysis based on LIS data should be accepted with due caution.

A detailed discussion of LIS data for xanthones, cyclobutanes, and epoxides emphasizes some of the difficulties and pitfalls inherent in the use of the LIS experiment to determine conformational preference in flexible molecules.[225] The conformational preferences of 1,4-cyclohexadiene and its derivatives have been the subject of much controversy. In a recent NMR study of several derivatives of 1,4-cyclohexadiene accomplished by the use of $Eu(fod)_3$, it has been concluded that the ring is planar.[174] NMR studies of some 9-substituted bicyclo-[6·1·0]-nona-2,4,6-triene derivatives using either $Eu(tmhd)_3$ or $Eu(fod)_3$ as the shift reagent have indicated that in deuterochloroform solution these compounds exist primarily in the extended conformation (Formula 15b).[226]

In a determination of the conformation of the antimalarial chloroquine in acetone solution, the "best" location of the lanthanide ion in relation to the rigid quinoline ring system was first established.[193] This rigid part of the LSR-substrate system was then used to define the conformation of the 32-atom side chain, the conclusion being drawn that the side chain was curled over the plane of the quinoline ring. In another study[194] the 12 skeletal protons of a photochemical product were used to provide a rigid frame of reference for fixing the position of the lanthanide ion. The conformation of a mobile ethoxy group attached to the molecule was then determined. Information on the average solution conformations of a number of acyclic molecules in which it is not possible to fix the location of the lanthanide ion in relation to any rigid part of the substrate molecule has been obtained by the use of ^1H and ^{13}C shift reagents.[182] The reagents were complementary, but $Yb(tmhd)_3$ and ^{13}C spectroscopy were found to be more readily utilized than $Eu(tmhd)_3$ and proton spectroscopy.

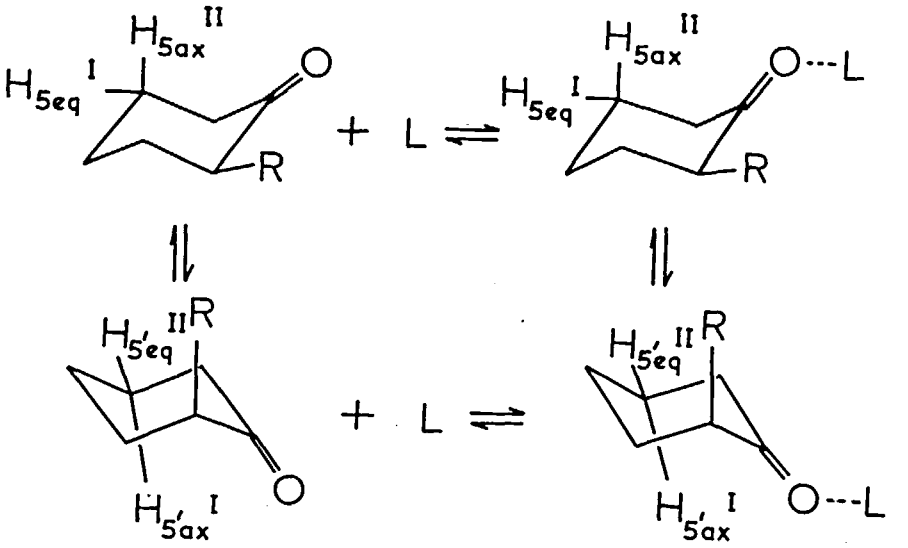
Induced shift ratios have proven useful in the investigation of problems involving dynamic equilibria, as illustrated in the following example.[227] For a conformationally mobile substituted cyclohexanone, the R-axial and R-equatorial isomers of both the free ketone and the LSR-ketone complex will be present simultaneously in solution (Scheme I). Equation 24 gives the relationship derived for the two 5-position protons in the bound complex.

$$\left(\frac{\Delta_B H^I}{\Delta_B H^I + \Delta_B H^{II}}\right)_{av} = n'_{eq}\left(\frac{\Delta_B 5eq}{\Delta_B 5eq + \Delta_B 5ax}\right) + n'_{ax}\left(\frac{\Delta_B 5ax}{\Delta_B 5eq + \Delta_B 5ax}\right) \qquad (24)$$

where

n'_{eq} = the mole fraction of equatorial conformer of the complexed ketone;
n'_{ax} = the mole fraction of axial conformer of the complexed ketone;
$\Delta_B 5eq$ = the limiting incremental shift for the 5-equatorial protons;
$\Delta_B 5ax$ = the limiting incremental shift for the 5-axial protons.

The concentration ratio of the two isomers in equilibrium can, therefore, be determined from the averaged induced shift ratio and characteristic values of the induced shift ratio for each of the isomers. A graphical technique has been described whereby the induced shift ratios may be readily obtained.[228] For any two (or more) protons, H_a and H_b, of the same substrate, the ratio of intrinsic induced shifts, $\Delta_B H_a/(\Delta_B H_a + \Delta_B H_b)$ is given by the slope of the plot of $\Delta\delta_{H_a}$ vs. $(\Delta\delta_{H_a} + \Delta\delta_{H_b})$ for the various solutions with different substrate or reagent concentrations. This procedure for obtaining induced shift ratios has the



SCHEME I.

advantage that the substrate and reagent concentrations need not be known and that no special precautions to exclude competitive scavengers need be taken. The method of relative induced shifts has been applied to the study of the ring inversion process in 2-alkylcyclohexanones.[227] The complexity of the NMR spectra of these ketones prevents a direct analysis of the spectra to obtain chemical shifts for use in conformational analysis. For each of the 2-alkylcyclohexanones, $\Delta\delta_{5eq}$ was found to be a linear function of $(\Delta\delta_{5eq} + \Delta\delta_{5ax})$ over the entire range of ketone and $Eu(fod)_3$ concentrations studied. The slopes of these lines were therefore assumed to be the average induced shift ratios, $[\Delta_B{}^{5eq} / (\Delta_B{}^{5eq} + \Delta_B{}^{5ax})]_{av}$, for the 5-equatorial protons in these $Eu(fod)_3$-alkylcyclohexanone complexes. The induced shift ratios for 4-*tert*-butylcyclohexanone were assumed to be the characteristic relative shifts for the 5-position protons in the absence of conformational averaging. (Since the 4-*tert*-butyl group should remain in the equatorial position, the molecules would be expected to be conformationally homogeneous.) These characteristic induced shift ratios were used together with the average induced shift ratios for the 2-alkylcyclohexanones to determine the mole fractions of equatorial and axial conformers of the complexed ketone by means of Equation 24.

The induced shift ratio method has also been used to provide information on the rotational conformations of alkyl chains attached to the cyclohexanone ring, e.g., to give the rotamer populations for the ethyl and isopropyl groups in the *cis* and *trans* isomers of 2-alkyl-4-*tert*-butylcyclohexanone.[229]

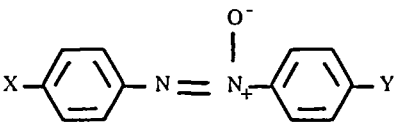
F. Quantitative Analysis of Mixtures

The basic requirement for the application of NMR spectroscopy to the analysis of multicomponent mixtures is that a resolved resonance be available for each component to be analyzed. Mixtures of chemically similar compounds often give rise to spectra characterized by overlapping resonances, and this has severely limited the general applicability of NMR as a technique for quantitative analysis. The shifting ability of LSR's potentially provides a method for resolving such spectra, thus permitting simple integration of individual peaks in the expanded spectrum. Consequently, many mixtures whose spectra previously lacked sufficient clarity are now susceptible to quantitative analysis by the proton magnetic resonance technique.

The analysis of multicomponent mixtures of alcohols by the LSR method has been demonstrated.[230] With normal alcohols containing up to seven carbon atoms, the $Eu(tmhd)_3$-induced shift is determined mainly by the position of a group along the chain, variations among the different compounds being small. Thus, the methyl resonances for the different alcohols

TABLE 4

Isomeric Distributions from Integration of Shifted Spectra[232]



Mixture	Isomer	X	Y	% composition
1	a	CH_3O	n-C_4H_9	55
	b	n-C_4H_9	CH_3O	45
2	a	CH_3O	H	44
	b	H	CH_3O	56
2'	a	CH_3O	H	74.4[a]
	b	H	CH_3O	25.6[a]
3	a	CH_3	H	52
	b	H	CH_3	48
4	a	C_2H_5O	n-C_4H_9	47
	b	n-C_4H_9	C_2H_5O	53
5	a	Cl	n-C_4H_9	47
	b	n-C_4H_9	Cl	53
6	a	CH_3O	$OCOCH_3$	55
	b	$OCOCH_3$	CH_3O	45

[a]Mixture 2' was made up of 75.0% (by weight) of pure isomer a and 25.0% of b and served as an accuracy check.

are shifted to a different extent, and from the integrated intensities of these lines the composition of a mixture can be determined. Mixtures of branched-chain saturated alcohols are also amenable to analysis by NMR using the same approach.[230]

Cyclic oligo-ethers containing up to eight $-CH_2CH_2-O-$ units have identical NMR shifts both in chloroform and carbon tetrachloride.[231] Addition of Eu(tmhd)$_3$ caused a marked downfield displacement that was different for each ring, thus permitting an easy analysis of mixtures of these oligomers.

Determination of the isomeric distributions of unsymmetrical azoxybenzene mixtures has been accomplished by the use of Eu(fod)$_3$.[232] The shifts induced in the 60-MHz spectra of the mixtures listed in Table 4 were sufficiently large and selective to permit the unambiguous assignment of all the protons. For each mixture, integration of either the signals for the aromatic protons *ortho* to the center group or of the methyl singlets yielded the isomer distributions.

For a number of alkyl methyl ketoximes in the presence of Eu(tmhd)$_3$, the separation of resonance lines in the 60-MHz spectra was sufficiently large that an accurate ratio of the syn- and anti-isomers could be obtained directly from the spectra.[233] Quantitative analysis of the geometric isomers of 2,4-hexadienoates and related compounds was facilitated with Eu(fod)$_3$.[234]

G. Elucidation of Polymer Structures

The measurement of sequence distributions in polymers by NMR spectroscopy has met with only limited success. Shifts due to different stereochemical structures of polymers in fluid solution are often not well enough resolved to enable the lines to be assigned with certainty and their intensities to be accurately measured. Since LSR's can produce chemical shift amplifications, their application to the field of macromolecules would appear to be a promising one for study. Polymers such as polyesters and polyethers, which contain heteroatoms, have already proven to be amenable to NMR analysis using this approach. In one of the first studies of polymethacrylate polymers by the LSR method, the LIS was shown to be dependent upon the microtacticity of the polymer.[235] Thus, with atactic poly(methylmethacrylate) in

deuterochloroform, the addition of $Eu(tmhd)_3$ caused the separation of three carbomethoxy and three C-methyl absorptions corresponding to the respective groups in isotactic, heterotactic, and syndiotactic triads in the polymer chain. The application of $Eu(fod)_3$ to investigate polymethacrylate polymers also revealed a clear separation of signals due to the triad tacticity.[236] More recently, splitting of the methoxy protons attributable to pentad tacticity has been observed upon the addition of $Eu(tmhd)_3$ to poly(methylmethacrylate) in benzene.[237]

The spectrum simplification of poly(vinylacetate) in terms of tactic structures has been reported, $Eu(tmhd)_3$ being shown to be more discriminating to the structures than the fod analogue.[147] In a determination of the stereoregularity of poly(methylvinylether), use of $Eu(fod)_3$ enabled the triad tacticity of the polymer to be determined accurately from the areas of the methoxy triad peaks.[238] Not only was the resolution of the three peaks corresponding to the protons of methoxy groups in isotactic, heterotactic, and syndiotactic triads greatly improved by the addition of the shift reagent, but the larger downfield shift for the CH peak than for the OCH_3 peaks allowed the methoxy triads to be observed without interference from the methine proton multiplet. Because of this interference, previous attempts to determine the triad tacticity relied on measurements of relative peak heights rather than peak areas.

Copolyesters such as poly(ethylene terephthalate-isophthalate) could not previously be analyzed by the NMR method because of the absence of detectable chemical shifts between the peaks assigned to the methylene protons in glycol of the ethylene terephthalate unit and of the ethylene isophthalate unit.[239] In the presence of $Eu(tmhd)_3$ the signal from the glycol protons was split into three peaks related to the sequence of phthalate units.[239] Addition of $Eu(tmhd)_3$ caused shifts in the peaks of the ^1H NMR spectra of trioxane-dioxolane copolymers that facilitated the determination of the microstructure and monomer sequence of the copolymer.[240]

In the ^1H NMR spectra of poly(chloroprene-methylmethacrylate), the signal assigned to the methoxy protons of the methylmethacrylate units was split into six peaks by the addition of $Eu(tmhd)_3$.[241] These splittings were assigned to pentad sequences with a methylmethacrylate unit as a center. The peaks were resolved into six Lorentzian components by a curve resolver, and the fractions of the pentad sequences were obtained from the relative peak areas. Each observed concentration was found to be in close agreement with that calculated by copolymerization theory.

End-group analysis is a classical method for the determination of the number average molecular weight, $\bar{M}_n$, of polymers. Because it is rapid and does not require calibration standards, NMR affords an attractive technique for $\bar{M}_n$ determinations, if the chemical shift of the end-group resonances are sufficiently different from those of the polymeric chain to enable accurate integrations to be made. At 60 MHz the end-group protons of poly(ethylene glycol) and of poly(propylene glycol) cannot be resolved from those of the bulk polymer.[242] With the former polymer this difficulty was overcome by the use of pyridine-hydrochloric acid, benzene, or α-chloronaphthalene as the solvent, thus enhancing the chemical shift of the end group. With the latter polymer, solvent-shift methods were not satisfactory, but the greatly enhanced resolution induced by $Eu(tmhd)_3$ allowed a clear separation of the ^1H NMR signals of the end methyl group from the complex methyl multiplet of the polymeric chain, thus permitting molecular weight measurements by direct comparison of signal intensities. Molecular weights obtained by this method are compared with those found by other means in Table 5.

H. Chiral Lanthanide Shift Reagents

Determination of enantiomeric compositions (optical purities) is a central problem in the chemistry of chiral substances. Classical methods for these determinations are experimentally cumbersome.[243] Before the introduction of LSR's, NMR procedures were restricted to the use of either diastereomeric compounds (indirect method)[244] or optically active solvents (direct method).[245,246] The indirect method involves derivatization of the chiral compound with an optically pure reagent and determination of the diastereomeric composition of the derivative by NMR analysis. An original shortcoming of the method, small shift differences for diastereotopic protons, was largely eliminated by making use of a normal achiral LSR.[247] At best, however, the method is laborious and limited to those compounds that can be derivatized with an

TABLE 5

Number Average Molecular Weights of Poly(Propylene Glycol) Samples[242]

Sample	Supplier's data	Osmometric	NMR
1	790	757	771 ± 17
2	1,220	1,144	1,254 ± 43
3	2,020	1,549	1,985 ± 54
4	1,010	1,025	1,103 ± 35

optically pure reagent without racemization or isomeric fractionation. The direct NMR method referred to above is based on chemical-shift nonequivalence of enantiomers in optically active solvents. This method, however, is restricted to polar solvent-solute combinations because nonequivalence results from diastereomeric solute-solvent interactions. Also, the shift differences tend to be small (≤ 0.04 ppm),[245,246] which again limits the usefulness of the technique.

The introduction of tris chelates of optically active β-diketonate ligands with lanthanide ions has greatly facilitated the direct determination of enantiomeric compositions by NMR spectroscopy. In addition to the expected LIS, the presence of asymmetric centers in the β-diketonate ligands produces a differential shift, $\Delta\Delta\delta$, between the resonances of corresponding nuclei in an enantiomeric pair (*R*, *S*). The situation is described by Equation 25

$$\begin{aligned} L_+ + R &\rightleftharpoons L_+ \cdot R \\ L_+ + S &\rightleftharpoons L_+ \cdot S \end{aligned} \qquad (25)$$

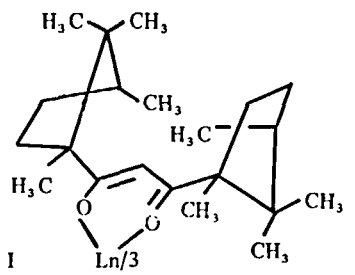
where the association of L_+ (where + denotes one optical isomer of the chelate) with *R* and *S* forms two diastereomeric (and, in principle, NMR distinguishable) adducts in solution. In practice, the enantiomeric shift differences are usually much larger than those observed in procedures employing optically active solvents. Moreover, chiral LSR's are applicable to those classes of compounds that respond to conventional shift reagents such as $Eu(tmhd)_3$ and $Eu(fod)_3$, offering the same inherent first-order-type simplification of spectra that arises from dipolar interactions. Thus, it is possible to carry out a quantitative determination of the enantiomeric composition of structures having such complexity that analysis of their unshifted spectrum would be difficult.

Table 6 lists some chiral shift reagents of the chelate type. Details of the synthesis of these and other optically active LSR's are given in References 248 and 249. Figure 17 shows the effect of *III* (Ln = Eu) on the ^{1}H NMR spectra of α-phenylethylamine. The resonances of the *S*-enantiomer exhibit the expected downfield dipolar shift due to the interaction with the europium ion. As illustrated in Figure 17b, all the signals observed in the spectrum of the pure *S*-isomer appear doubled in the spectrum of a mixture of the enantiomers, the resonances of the *R*-isomer being the more shifted. That enantiotopic protons are anisochronous only in a chiral environment is illustrated in Figure 18 which shows the spectra of *dl*-2-phenyl-2-butanol in the presence of achiral $Eu(tmhd)_3$ and in the presence of the chiral reagent *V* (Ln = Eu). Although both reagents induce comparable dipolar shifts, only *V* is effective for the resolution of enantiotopic resonances. The enantiotopic α-methyl singlets are separated by 0.29 ppm, and the β-methyl triplets are separated by 0.22 ppm, which corresponds to $\sim 2J$ and gives rise to a quintuplet. Table 7 gives a survey of the chiral shifting potential of *I*. Clearly, the application of chiral LSR's in determination of enantiomeric purity is broad; according to one group of workers,[248] almost every enantiomeric organic base that was examined seemed to give useful separations of resonances with some shift reagent, provided that the chiral center was reasonably close to the site that coordinated to the lanthanide ion. It is not presently possible, however, to predict in any detail the influence of a particular chiral shift reagent on a mixture of enantiomers. Consequently, the generation of a shifted spectrum containing well-separated, isolated resonances that are suitable for integration may require trying several chiral shift reagents and varying sample concentrations and temperature. The isolation of separated enantiotopic signals from other resonances can sometimes be achieved by changing from a europium complex to the praseodymium analogue. Experimental conditions most likely to yield large enantiomeric shift differences are described in Reference 248.

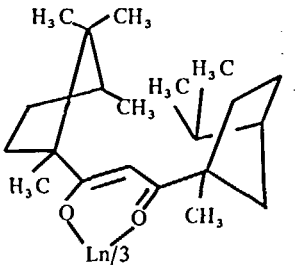
Enantiomeric shift differences possibly arise from at least two, probably mutually dependent, interactions: (1) the equilibrium constants for formation of the various possible complexes between the enantiomeric substrates and the chiral chelate may differ and (2) the geometries of the

TABLE 6

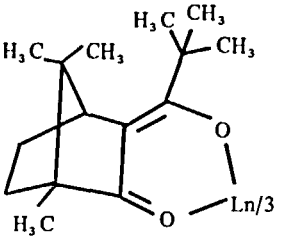
Chiral Shift Reagents of the β-Diketonate Type



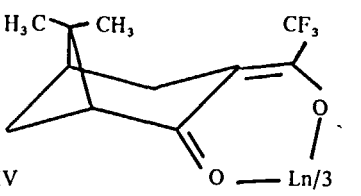
I



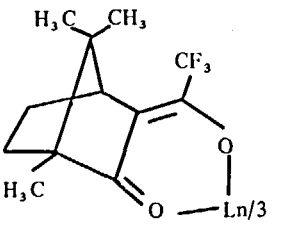
II



III



IV



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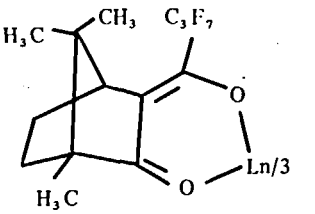

VI

resulting diastereomeric complexes may be distinct. Various results, however, demonstrate the complexity of the associational and conformational equilibria involved.[249] While the utility of chiral LSR's should ensure their widespread use in the determination of enantiomeric purity, the establishment of absolute configurations through their use is not presently possible.

VI. SUMMARY

Induced shifts in NMR spectra resulting from complexation of a substrate with lanthanide chelates extend significantly the usefulness of the NMR technique. Information obtainable from a NMR spectrum determined at a frequency of 60 MHz in the presence of a LSR may be much greater than that provided by the spectrum at 220 MHz in the absence of the shift reagent. The low financial cost involved in the application of the LSR method is an added attraction. Lanthanide SR's have hitherto been employed predominantly in ^{1}H NMR spectroscopy, not only because the proton is still the nucleus most widely used, but also because the spectral resolution efficiency of the reagents is greatest here. For nuclei such as ^{13}C, ^{19}F, and ^{31}P, the range of chemical shift values is such that signal coincidence is seldom a problem. With these nuclei, however, LSR's may still be of considerable help in the matter of spectral assignment. Clearly, many of the problems that have been investigated by measuring changes in chemical shifts between different solvents could be solved with less ambiguity by the use of shift reagents.

The effectiveness of a given shift reagent system is a complex function of magnetic anisotropy,

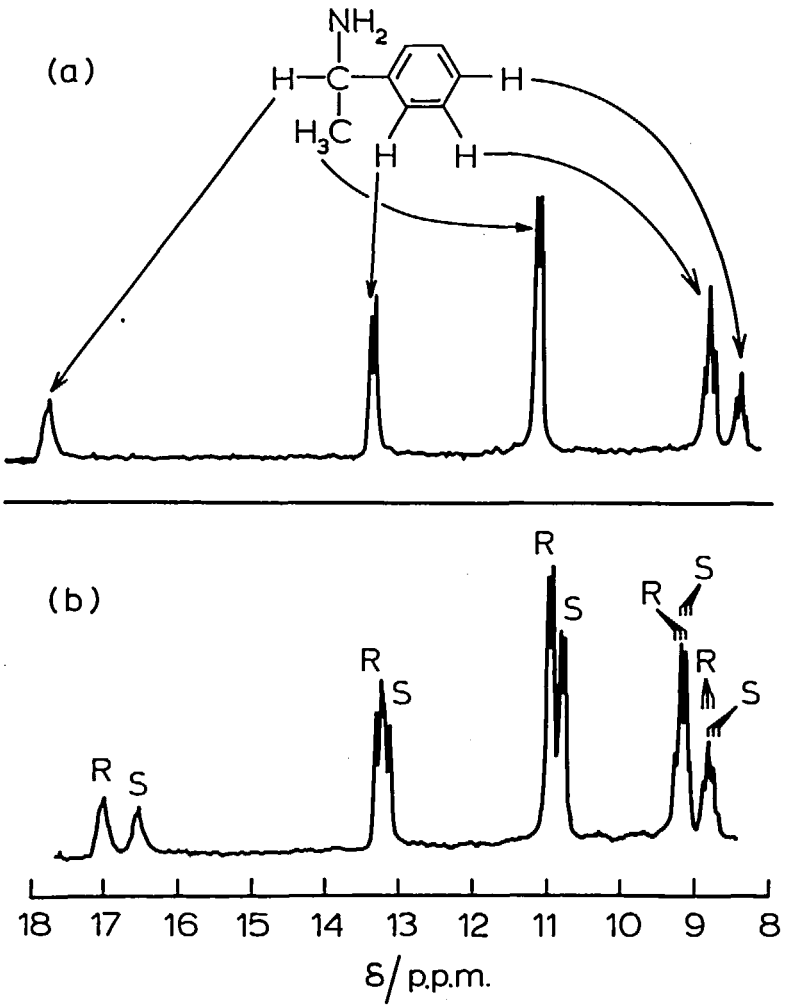

FIGURE 17. 60-MHz ^{1}H spectra of α-phenylethylamine in CCl_4 containing tris[3-(*tert*-butylhydroxymethylene)-*d*-camphorato] europium (III): (a) (S)-α-phenylethylamine; (b) mixture of (*R*)- and (*S*)-α-phenylethylamine. The chemical-shift scale applies only to the spectrum of the mixture. (Reprinted with permission from Whitesides, G. M. and Lewis, D. W., 250 *J. Am. Chem. Soc.*, 92, 6979 (1970). Copyright by the American Chemical Society.)

electron spin relaxation time, solubility, and substrate affinity. No one LSR will be the best choice for all applications. In the ^{1}H NMR studies so far reported, $Eu(tmhd)_3$ and $Eu(fod)_3$ have been the most frequently used shift reagents, with the Pr analogues appearing as the most popular alternatives. At the present time, $Yb(tmhd)_3$ appears to be the chelate of choice for ^{13}C spectra. Lanthanide SR's represent a vast improvement over the d-series transition-metal variety, the most important features being the almost negligible signal broadening caused by some of the lanthanide chelates and the predominantly dipolar nature of proton resonance shifts in LSR-substrate complexes. As additional information becomes available, the goal of selective shift reagents designed for special problems should become more accessible.

Lanthanide-induced shifts have been observed with most organic molecules that contain heteroatoms with a lone pair of electrons, i.e., substrates possessing some degree of Lewis basicity. The presence in the substrate solution of an efficient LSR produces large isotropic shifts which generally spread out the NMR spectrum, frequently reducing it to (quasi-) first order and

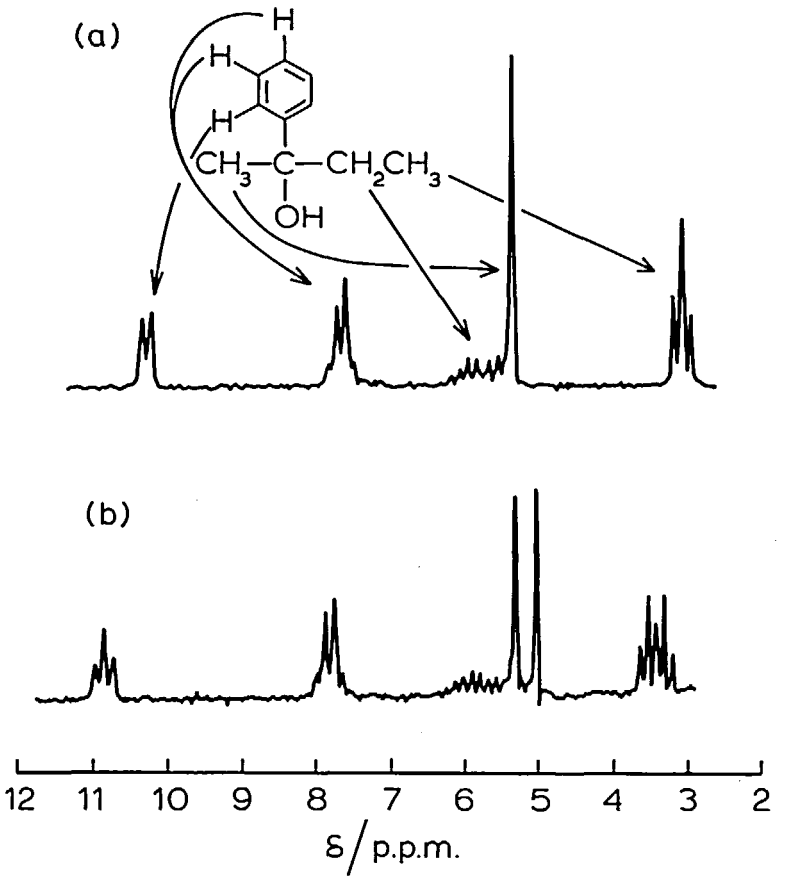

FIGURE 18. 60-MHz ^{1}H spectra of 2-phenyl-2-butanol in CCl_4: (a) in the presence of 0.24 molar equivalent of Eu(tmhd)$_3$; (b) in the presence of 0.78 molar equivalent of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato] europium(III). (Reprinted with permission from Goering, H. L. et al., 251 *J. Am. Chem. Soc.*, 93, 5913 (1971). Copyright by the American Chemical Society.)

thereby facilitating analysis. Although some studies have shown that nuclear spin-spin coupling constants are not significantly affected by the addition of a LSR, other studies with other substrates have indicated that coupling parameters derived from LIS experiments are not independent of the shift reagent. Where the latter is true, steps must be taken to obtain the coupling constants of the uncomplexed substrate. In many laboratories LSR's are taking their place as a routine method for effecting simplification and resolution enhancement of the NMR spectra of compounds of such complexity that previously the use of this spectroscopic technique was hampered or altogether precluded both by extensive line overlap and by the complex multiplet structure of the spectrum. In addition to spectral clarification, LSR's have the potential, in principle at least, of yielding valuable information about the geometric structures and conformations of molecules in fluid solution. Although the development of dipolar shift analyses as a reliable tool in structure determination appears to be materializing, detailed structural inferences drawn from LSR data must at present be accepted with considerable caution. Certainly, the possibility that LSR-substrate binding may distort the conformation of the substrate and/or perturb the position of the conformational equilibrium cannot always be ruled out. With nuclei other than ^{1}H, the problem of nonnegligible contact contributions generally precludes the quantitative use of these nuclei in molecular geometry determinations; a reliable factorization of the induced shift into dipolar and contact contributions is not presently possible.

Other analytical applications of the LSR tech-

TABLE 7

Enantiomeric Shift Differences Induced by Tris[*d,d*-dicampholylmethanato] europium(III) in 2-Butyl Derivatives, $CH_3CHXCH_2CH_3$ [248]

	ΔΔδ/ppm			
X[a]	*H*[b]	$CHCH_3$	*CH*X	CH_2CH_3
NH_2		0.36	2.90	0.36
$NHCH_3$	1.20	1.45		0.70
$N(CH_3)_2$	1.38	0.30		
OH		0.76		0.50
CH_2OH		0.02		0.02
$COCH_3$	0.12	0.27	0.0	0.11
OC*H*O	0.48	0.40	0.0	0.25
$OCOCH_3$	0.29	0.35	0.37	0.06
$OCOC_6H_5$ (ortho *H*)	0.42	0.05	0.37	0.07
NHC*H*O		0.30		0.22
$CO_2CH_2CH_3$		0.21		
OCH_3	0.45	0.19	0.0	
HgCNO		0.06		0.0
CN		0.00		0.03
SH		0.00	0.00	0.00
$SCH(CH_3)CH_2CH_3$		0.00	0.00	0.00
NO_2		0.00	0.00	0.00
Br		0.00	0.00	

[a]The concentration of substrate was 0.3*M*; the solvent was CCl_4, except for X = amine, in which instances the solvent was $CDCl_3$. The concentration of shift reagent ranged between 0.2 and 0.6 *M*.
[b]These values of ΔΔδ are for the indicated resonances of the group X.

nique include the quantitative analysis of multicomponent mixtures, the measurement of sequence distributions and molecular weights of polymers, and the determination of enantiomeric compositions. Compared with their use in organic NMR spectroscopy, relatively few applications of LSR's to inorganic or organometallic systems have thus far been reported. The indications are indeed strong that despite the vast amount of work with LSR's since 1969, the applications of these reagents to analytical problems are far from exhausted.

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