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Paramagnetic Shift Reagents in Nuclear Magnetic Resonance Spectroscopy

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The physical foundations and the applications of a new method in nuclear magnetic resonance spectroscopy—the simplification of spectra by means of paramagnetic shift reagents, complexes of lanthanides with diketones—are examined, and data given on the properties of the most widely used reagents. The discussion covers the mechanism of interaction of the shift reagent with the organic compound (substrate), the dependence of the displacement of the signals on the concentration of the components and the temperature, the equilibrium in the reagent-substrate system, the effect of the nature of functional groups in the substrate, of the lanthanide ion, and of the ligand in the reagent on the magnitude of the shift in the n.m.r. spectra, the dependence of the shift and the line width on geometrical factors, and the effect of the shift reagent on spin-spin coupling constants. The use of shift reagents in the nuclear magnetic resonance of protons and other nuclei is considered briefly. The paper includes a summary of compounds whose spectra have been studied in the presence of shift reagents and also 348 references.

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I. INTRODUCTION

Nuclear magnetic resonance spectroscopy has become probably the most powerful method for determining the structure of organic compounds, including polymers and biopolymers. However, the information content of proton magnetic resonance spectra is substantially diminished by the fact that the protons in methine, methylene, and methyl groups unaccompanied by electronegative atoms give signals having closely similar chemical shifts in the range 0.8–2.5 ppm. A new and extremely effective method, which in several cases completely overcomes difficulties due to the overlapping of signals, is the use of paramagnetic shift reagents.

The effect of paramagnetism on nuclear magnetic resonance was detected soon after discovery of the latter [1]. Detailed theoretical and experimental studies of n.m.r. in paramagnetic systems have been reviewed [2-12]. Successful attempts were made to use nickel(II) and cobalt(II) complexes as shift reagents [13,14], but these compounds have not found wide application. A decisive step for development of the method was the change to lanthanide derivatives—complexes of europium [15,16], praseodymium [17], and other lanthanides [18-24] with 2,2,6,6-tetramethylheptane-3,5-dione, complexes with fluorine-containing [25] and with optically active [26-29] diketones.

Lanthanide shift reagents—complexes of tervalent ions Ln^{3+} with β-diketones—are Lewis acids. In solution they form complexes (adducts) with organic molecules (substrates) containing atoms having a lone pair of electrons (oxygen, nitrogen, sulphur, phosphorus), the substrates being Lewis bases. The paramagnetic ion displaces the lines in the n.m.r. spectrum. Because of rapid exchange between free and complexed molecules the observed spectrum is intermediate between those of the free and the bound substrate.

The Review will survey the physical principles underlying the action of paramagnetic shift reagents, discuss the effects of various factors on the n.m.r. spectrum of the substrate—reagent system, and briefly consider the application of paramagnetic shift reagents in organic and polymer chemistry.

II. PARAMAGNETIC SHIFT REAGENTS USED IN n.m.r. SPECTROSCOPY

Among the many known complexes of lanthanides (several hundreds were tested in a single study [25]!) only a few have found practical use as paramagnetic shift reagents. This is because shift reagents should satisfy several requirements. Such properties as great coordinating power with substrates, magnetic anisotropy, a ligand of great bulk (in order to fix the relative positions of substrate and reagent molecules in the adduct), and short electronic relaxation time (to keep the spectral lines narrow) are of considerable importance. It is also necessary that the substance should be sufficiently stable in the air, soluble in organic solvents, etc. Tables 1–3 list the properties of β-diketonatolanthanide paramagnetic shift reagents. Salts—chlorides and chlorates—can be used in aqueous solutions, and lanthanide nitrates in acetone solutions [30-34].

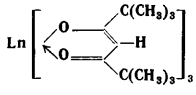
The solubility of the trisdipivalomethanatoeuropium(III) complex in carbon tetrachloride, hexadeuterobenzene, and deuterochloroform at room temperature is respectively [35] 200–300, 100, and 200–300 mg ml^{-1}. The solubility increases in the presence of a polar substrate [36]. The corresponding ytterbium complex is more soluble [37], as is also tris-6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionatoeuropium(III), up to 400 mg ml^{-1} in carbon tetrachloride [25]. This last anhydrous complex, the corresponding praseodymium compound, and the tristetramethylheptanedionatoeuropium complex are strongly hygroscopic [25,38], and should therefore be kept over phosphorus pentoxide in a vacuum desiccator [25]. The solvents used in work with the shift reagents should be especially carefully dried and freed from acidic impurities: chloroform is treated with molecular sieves [35]; carbon tetrachloride is stored over caustic soda and redistilled [42].

III. EFFECT OF PARAMAGNETIC SHIFT REAGENTS ON n.m.r. SPECTRA

1. Shifts of Signals in Spectra

The shift in the n.m.r. signal of the substrate in the presence of lanthanide shift reagents is caused by the local magnetic field produced by the ion at the site of the nucleus. Most authors consider that the main contribution to the shift is made by so called "pseudocontact" (dipole) interaction appearing when the magnetic susceptibility of the complex is anisotropic: the field due to the lanthanide is not then averaged out by the molecular motion.

Table 1. Dipivaloylmethane complexes Ln dpm$_3$—tris-2,2,6,6-tetramethylheptane-3,5-dionatolanthanide complexes



(preparation[37,39,40] and properties[35,38,41,42]).

Ln	Colour	M.p., °C	Magnetic moment, β	Nuclear magnetic resonance spectrum: without substrate, t-butyl δ, ppm	without substrate, line width, Hz	with cyclohexanone, t-butyl δ, ppm	with cyclohexanone, line width, Hz
Pr	light green	222—224	3.7	0.6	40	2.8	2
Nd	violet	215—218	3.7	0.8	16	2.1	10
Sm	white	196—199	2.0	1.08	7	1.2	6
Eu	yellow	187—189	3.4	0.48	10	−0.5	5
Gd	white	182—184	7.6	0.9	1500	1.8	800
Tb	white	177—180	9.6	17.4	250	16.0	170
Dy	white	180—184	10.3	17.7	180	21.9	130
Ho	yellowish white	180—183	10.0	5.30	180	7.3	180
Er	pink	179—181	9.3	−3.6	250	−6.2	70
Tm	white	172—174	7.2	12.8	400	15.2	240
Yb	white	167—169	4.3	−0.3	60	−1.9	20

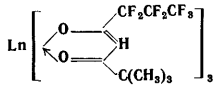
When the rate of molecular reorientation is large in comparison with the n.m.r. line width expressed in the same units, but small compared with the rate of electronic relaxation, and the complex has axial symmetry, the shift is given by the formula[46-49]

$$\delta_i = -10^6 \cdot \frac{1}{3N_A}(\chi_{M\parallel} - \chi_{M\perp})\frac{3\cos^2\theta_i - 1}{r_i^3} \qquad (1)$$

where δ_i (in ppm) is the shift in the signal for the ith nucleus, N_A is Avogadro's number, $\chi M\parallel$ and $\chi M\perp$ are the components of the molar magnetic susceptibility parallel and perpendicular to the symmetry axis, r_i is the length of the vector $\vec{r}_i$ between the paramagnetic ion and the ith nucleus, and θ_i is the angle between this vector and the principal magnetic axis of the complex.

The magnetic susceptibility depends on the electronic configuration of the paramagnetic ion, the ligand field, and the temperature. Equations expressing the pseodocontact shift in terms of the anisotropy of the g-factor were obtained by McConnell and Robertson[50] for ions whose magnetic properties obey the Curie law. More complicated expressions are obtained[49,54-57] for the lanthanide ions, especially for Eu^{3+}, in which the ground state (the $^7F_0$ level) is diamagnetic, and paramagnetism arises only from the excited state $^7F_1$.[51-53] Comparison with experiment shows satisfactory agreement[48,57], although difficulties are caused by the fact that magnetic susceptibilities measured on single crystals[48,58] may differ from those of molecules in solution, and furthermore the magnetic susceptibility may change on coordination of the shift reagent with the substrate[38,59,60]. The mainly pseudocontact (dipole) nature of the shift caused by lanthanide shift reagents is confirmed also by the linear dependence of the shift on the geometric factor $(3\cos^2\theta_i - 1)/r_i^3$ (see below), by the identity of proton and carbon-13 shifts in the presence of tristetramethylheptanedionatoeuropium[61,62], by the fact that the shift and the anisotropy of the g-factor have the same sign[19], and by the constancy of the ratio of shifts in the presence of the above complex to those in the presence of the corresponding praseodymium complex for several compounds[63].

Table 2. Tris-6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionatolanthanide(III) complexes Ln fod$_3$



(preparation[43]).

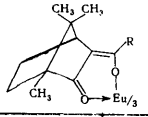
Ln	Colour	Melting point, °C: anhydrous	monohydrate
Eu	white	205—212 (decomp.)	59—67
Pr	green	218—225 (decomp.)	218—225 (decomp.)

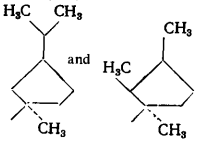
If the electron spin density of a paramagnetic ion is delocalised, and is transmitted through a system of chemical bonds to the nucleus, a contact shift in the n.m.r. signal is observed[64]:

$$\delta_i = -10^6 \cdot A_i \frac{\gamma_e}{\gamma_n} \frac{g\beta\, S(S+1)}{3kT} \qquad (2)$$

where γ_e and γ_n are the gyromagnetic ratios of electron and nucleus, A_i is the isotropic hyperfine electron–nucleus coupling constant, g is the g-factor, β is Bohr's magneton, S is the spin quantum number of the electron, k is Boltzmann's constant, and T is the absolute temperature.

Table 3. Optically active paramagnetic shift reagents—tris-3-alkylhydroxymethylene-(+)-camphorato-europium(III) complexes



Alkyl R	Preparation—Ref.
$(CH_3)_3$—C—	26
CF_3—	28, 44, 45
$CF_2CF_2CF_3$	29
	27

The contact shift usually plays no great part in changing the n.m.r. spectra in the presence of lanthanide shift reagents. The presence of contact interaction is taken into account only in certain cases—for nuclei situated beside a coordination site, e.g. protons in the *geminal* position to a hydroxy-group [66,67] protons [68,69] and carbon nuclei [70] in strong Lewis bases having a π-bond system in the presence of shift reagents that are strong Lewis acids, and also with nitrogen-14 and phosphorus-31 nuclei.

Pseudocontact and contact interactions displace the signals in the n.m.r. spectra only of those substrate molecules that form an adduct with the paramagnetic shift reagent molecules. In addition, the introduction of a paramagnetic additive produces a large general upfield displacement of the whole n.m.r. spectrum of the solution, owing to a change in the magnetic susceptibility of the solution [71]:

$$\delta_l = 10^6\left[\chi - \chi_0 - \frac{\chi_0(d_0 - d)}{m}\right]\frac{2\pi m}{3} \qquad (3)$$

where χ and χ_0 are the magnetic susceptibilities (g^{-1}) of the paramagnetic compound and the solvent, d and d_0 are the densities of solution and solvent, and m is the mass of the paramagnetic compound in 1 ml of solution. This shift need be taken into account only when an external standard is employed. The signal of an internal standard (tetramethylsilane) is displaced together with the whole spectrum: hence chemical shifts reckoned from the standard do not change.

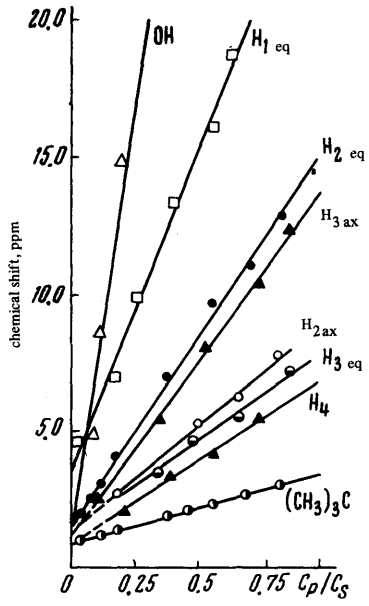
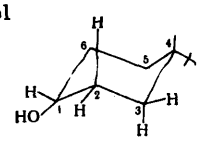


Figure 1. Dependence of chemical shift of protons in *cis*-4-t-butylcyclohexanol



dissolved in $CDCl_3$ in presence of Eudpm$_3$ on the ratio C_P/C_S (frequency 100 MHz and room temperature) [36].

2. Dependence of Shift on Composition of Solution

The shift δ of signals in the presence of a shift reagent is to a first approximation proportional to the ratio of the molar concentration of paramagnetic reagent C_P to substrate concentration C_S (Fig. 1). It has been proposed [36] that the shifts of different protons be compared by using the slopes of the linear plots of δ against C_P/C_S, i.e. by the "specific shifts" or shifts extrapolated to the ratio $C_P/C_S = 1$. For example, this shift ΔEu for the tris-tetramethylheptanedionatoeuropium complex in a solution of *cis*-4-t-butylcyclohexanol in deuterochloroform (Fig. 1) has the values 78.7, 21.7, and 1.8 ppm for OH, $H_{(1)}$, and $(CH_3)_3C$ respectively. Values of the specific shifts ΔEu, ΔPr (for the corresponding praseodymium complex), etc. are given in many papers (see reviews [72-80]). However, they are not true constants: variation in substrate concentration over the range 0.2–0.5 M produces changes in ΔEu of ±15%; values of ΔEu for alcohols and amines are 10% smaller in hexadeuterobenzene, and 20–25% smaller in deuterochloroform, than in carbon-tetrachloride solutions [35].

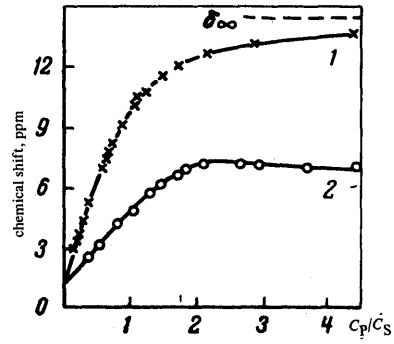


Figure 2. Dependence of chemical shift of signals in n.m.r. spectrum in presence of Eufod$_3$ on C_P/C_S ratio: 1) 0.0183 M t-butyl alcohol, calculated for K = 208 M^{-1}; [84] 2) 0.0130 M t-butylamine.

A departure from the linear dependence of δ is observed at ratios $C_P/C_S \geqslant 0.6$–0.8, the shift reaching a limiting value or even decreasing on further addition of the shift reagents [25,81-84] (Fig. 2). This dependence of the shift on solution composition is due to equilibrium complex formation

$$qP + lS \rightleftarrows P_qS_l \qquad (4)$$

with the constant

$$K = C_{PS}/(C_P - qC_{PS})^q(C_S - lC_{PS})^l \qquad (5)$$

where C_{PS} is the concentration of the complex P_qS_l. When the reagent causes rapid exchange, the shift in the substrate signal is

$$\delta = l(C_{PS}/C_S)\,\delta_\infty \qquad (6)$$

where δ_∞ is the shift of the bound substrate. At low C_P/C_S ratios almost all the reagent in solution is combined with the substrate; when the ratio approaches q/l an appreciable fraction of the reagent remains uncombined, and the dependence of δ on C_P/C_S becomes non-linear.

The parameters characterising the shift reagent–substrate system (composition of complexes (q/l), the constant K, and the shift of the bound substrate δ_∞) can be evaluated from the spectra. Methods for calculating complex-formation equilibria from n.m.r. spectra have been worked out in detail (see for instance reviews [85-88]). But difficulties are encountered in applying these methods to solutions of shift reagents. Variation of the concentration ratio of the components is restricted at high concentrations by the limited solubility of the reagents and at low concentrations by the high sensitivity to impurities, especially to small quantities of water. Calculations are complicated also by possible dimerisation of the complexes in solution [25,38,89-92].

Composition of complexes

In the trisdiketonates the Ln^{3+} ion has the coordination number 6. It can acquire up to three ligand molecules, thereby increasing its coordination number to 9; adducts of Eu dpm$_3$, Pr dpm$_3$, and other lanthanide complexes with pyridine and other substrates containing one, two, and three molecules of the Lewis base have been isolated as crystals [41,93,94]. The composition of a complex in solution can be determined by a method of continuous variation [95]. It follows from Eqn. (6) that

$$C_S\delta = C_{PS}l\delta_\infty \qquad (7)$$

If the concentrations C_P and C_S are varied while their sum is maintained constant, the graph of $C_S\delta$ plotted against $C_P/(C_P + C_S)$ passes through a maximum at

$$C_P/(C_P + C_S) = l/(q + l)$$

This method has established [84] formation of a 1 : 1 complex in the t-butyl alcohol–Eufod$_3$ system, and of 1 : 1 and 1 : 2 complexes in the corresponding t-butylamine system. The displacement of the signal is smaller in the 1 : 2 complex than in the 1 : 1 complex, which leads to the apparent paradox of a decrease in the shift on the addition of excess of the shift reagent (Fig. 2, curve *2*). If exchange in solution is slow, e.g. in the deuterated Eufod$_3$–dimethyl sulphoxide system at −80 °C, two separate signals are obtained—from free and bound substrate—the areas of which give the composition of the complex directly [96] as 1 : 2. A case of stepwise formation on 1 : 2 and 1 : 1 complexes has been examined [97].

The composition of the complex can sometimes be assessed from indirect data. For example, addition of optically active (R)-*N*-methyl-1-phenylethylamine to a solution containing Eu dpm$_3$ and racemic 1-phenylethylamine splits the signal of the CH–NH$_2$ protons of the latter [27]. Obviously this is possible only if an adduct containing both amines, e.g. 1 : 1 : 1, is at once formed with the shift reagent.

Complex-formation constant K and limiting shift δ_∞

These parameters can be found by selecting (by means of an electronic computer) values giving minimum deviation between the measured shifts and the $\delta = f(C_P/C_S)$ curve calculated by simultaneous solution of Eqns. (5) and (6) (Fig. 2, curve *1*). Good agreement confirms the formula for the complex adopted in the calculation.

With small C_P/C_S ratios the equimolecular complex is formed preferentially, and from Eqns. (5) and (6) with $C_P \ll C_S$ we obtain

$$\frac{1}{\delta} = \frac{C_S}{\delta_\infty C_P} + \frac{1}{K\delta_\infty C_P}. \qquad (8)$$

The graph of $1/\delta$ against C_S with C_P constant is a straight line [98,99]; its slope gives the parameter K, and the intercept made on the vertical axis yields δ_∞.

Table 4. Formation constants of complexes of shift reagents with substrates.

No.	Shift reagent	Substrate	Solvent	Temp., °C	K, M^{-1}	Ref.
1	Eu (FOD)$_3$	t-butyl alcohol	CCl_4	room	280±10	84
2	Eu (FOD)$_3$	propan-2-ol	CCl_4	32	97±8	98
3	Eu (FOD)$_3$	oxolan	CCl_4	32	57±3	98
4	Eu (FOD)$_3$	butan-2-one	CCl_4	32	32±3	98
5	Eu (FOD)$_3$	isopropenyl acetate	CCl_4	32	27±3	98
6	Eu (FOD)$_3$	allyl acetate	CCl_4	32	26±3	98
7	Eu (FOD)$_3$	cholesterol	CCl_4	room	237	104
8	Eu (FOD)$_3$	n-propylamine	CCl_4	ditto	>100	105
9	Eu (FOD)$_3$	neopentanol	CCl_4	»	>100	105
10	Eu (FOD)$_3$	acetone	CCl_4	»	12	106
11	Eu (DPM)$_3$	n-propylamine	$CDCl_3$	»	11.5–12.9	99
12	Eu (DPM)$_3$	n-propylamine	$CDCl_3$	»	34.2	105
13	Eu (DPM)$_3$	neopentanol	$CDCl_3$	»	6.2–6.5	99
14	Eu (DPM)$_3$	neopentanol	$CDCl_3$	»	9.7	105
15	Eu (DPM)$_3$	propiophenone	$CDCl_3$	40	15.0	69
16	Eu (DPM)$_3$	ethyl benzoate	$CDCl_3$	40	20.6	69
17	Eu (DPM)$_3$	2-phenylethanol	$CDCl_3$	40	101	69
18	Eu (DPM)$_3$	4-methylpyridine	$CDCl_3$	40	140	69
19	Eu (DPM)$_3$	2,4,6-trimethylpyridine	$CDCl_3$	40	10.8	69
20	Eu (DPM)$_3$	trimethylcholestanol	$CDCl_3$	room	61.5	107
21	Eu (DPM)$_3$	methyladamantanone	$CDCl_3$	ditto	250	89
22	Eu (DPM)$_3$	pyridine	$CDCl_3$	27	97	108
23	Eu (DPM)$_3$	quinoline	$CDCl_3$	20	14	109
24	$EuCl_3$	ribofuranosyladenine monophosphate	D_2O	28	10±2	30
25	$HoCl_3$	ribofuranosyladenine-phosphate	D_2O	28	6±2	30
	$EuCl_3$	ribofuranosylthymine monophosphate	D_2O	28	17±3	30

Published values of K are listed in Table 4. Because of the above difficulties, they evidently cannot be regarded as entirely trustworthy. Relative determinations based on competition between substrates [100] are probably more reliable (subsection 7).

3. Dependence of Shift on Temperature

The displacement of signals caused by a shift reagent diminishes on heating. Such observations have been made for many systems, e.g. pentanol [101], heptan-2-one [42], poly(methyl methacrylate) [102], and terpenoids [81] in the presence of tristetramethylheptanedionatoeuropium, and alcohols and amines in the presence of an optically active shift reagent [29]. Quantitative measurements are few and contradictory. Tomic [103] found a linear temperature dependence of the shift between 40° and 90 °C for the methylcyclopropylmethanol system, with the slope of the δ–T straight lines different for different protons and increasing strongly with the concentration of the shift reagent (Fig. 3). The shifts in the spectra of furfuryl alcohol, octanol, and several vinylalkanones have been shown [110] to be proportional to $T^{-1/2}$ between −30° and +60 °C. If the molecular geometry is independent of temperature, a pseudocontact shift should theoretically [49] be proportional to T^{-2} for all lanthanide ions other than Sm^{3+} and Eu^{3+}.

The samarium(III) ion should exhibit a dependence on T^{-1} near room temperature, and the europium(III) ion should show a variation stronger than T^{-1} but weaker than T^{-2}. Departures from theory, observed not only with lanthanide shift reagents but also with transition-metal

complexes[111], are explained primarily by the strong influence of temperature on the equilibrium between free and complexed substrate.

4. Dependence of Shift on Nature of Functional Group in Substrate

The nature of the functional group has a decisive effect on the displacement, since it influences also the complex-formation constant and the interatomic distances and angles occurring in Eqn. (1). Different groups can be compared on the basis of the specific shift ΔEu (Table 5).

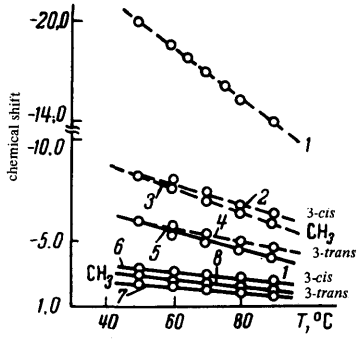
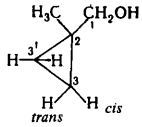


Figure 3. Temperature dependence of chemical shift (on δ-scale) in n.m.r. spectrum of 1-methylcyclopropyl-methanol



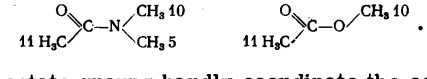
(0.02 M solution in CCl_4) in presence of Pr dpm$_3$: 1–4) 0.09 M; 5–8) 0.05 M.[103]

Table 5. Specific shift ΔEu for various functional groups (0.2–0.5 M solutions in CCl_4 at room temperature)[35].

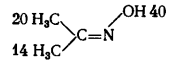
Functional group*	Specific shift, ppm	Functional group*	Specific shift, ppm
$RCH_2\underline{NH_2}$	150	$RC\underline{H_2}CHO$	11
$RCH_2\underline{OH}$	100	$RC\underline{H_2}OCH_2R^1$	10
$RCH_2\underline{NH_2}$	30—40	$RC\underline{H_2}CO_2CH_3$	7
$RC\underline{H_2}OH$	20—25	$RCH_2CO_2C\underline{H_3}$	6.5
$RC\underline{H_2}COR$	10—17	$RC\underline{H_2}CN$	3—7
$RC\underline{H_2}CHO$	19		

*The proton whose signal is observed is underlined.

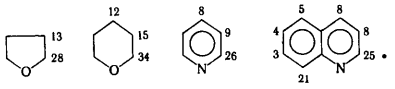
Amide groups bind tristetramethylheptanedionato-europium 4–5 times as strongly as do ester groups[112]; values have been found for substituted amides[113] close to those measured[114] for esters (henceforward numerals accompanying chemical formulae will indicate the values of ΔEu):



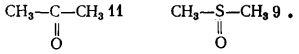
Trifluoroacetate groups hardly coordinate the complex at all[115]. Large shifts are observed with oximes[116,117]:



Similarly with oxygen-containing[114,118] and nitrogen-containing[79] rings:



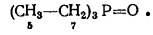
Values of ΔEu for the *N*-oxides of pyridine and quinoline are 30–40% smaller than those for the original heterocycles[119]. Shifts in the spectra of sulphoxides are of the same order as in ketones[114,120]:



Thioacetal groups



do not combine with shift reagents[115]. The latter are successfully used to displace the signals in the spectra of compounds containing phosphoryl groups[83,121,122], e.g. phosphine oxides



Values of ΔEu decrease in the sequence[121]

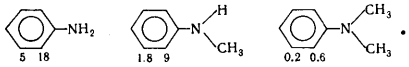
$$P{=}O > C{=}O \text{ (Amides)} > C{=}S \text{ (Thioamides)} > P{=}S.$$

Nitro-groups and phosphines bind shift reagents weakly. Halides and double bonds probably do not interact with lanthanide shift reagents[35].

With compounds having the same functional groups the degree of bonding of the shift reagent depends on basic strength and steric hindrance. This rule is well observed in sulphur-containing compounds[123] and with amines[124] of general formula $p\text{-}XC_6H_4NH_2$, where ΔEu increases slowly with pKa of the amine in the sequence of substituents X

$$NO_2 < CN < Br < Cl < H < F < OCH_3.$$

The effect of steric hindrance is seen on comparing aniline, methylaniline, and dimethylaniline, which have closely similar pKa values:



Similar observations have been made with other amines[125] and with ketones and alcohols[126]. Steric hindrance may make the coordination of tristetramethylheptanedionato-europium at a hydroxy-group even less than at an ether group in the same molecule[127]. The degree of binding of the shift reagent is so sensitive to the basicity of the functional group that replacing hydrogen by deuterium *geminal* to a hydroxyl produces appreciable displacement of the signals in the spectrum ("isotope effect")[128–131].

5. Dependence of Shift on Nature of Shift Reagent

The sign and the magnitude of the pseudocontact shift (for a given substrate) are determined by the magnetic anisotropy (value of $\chi M_{\parallel} - \chi M_{\perp}$) of the shift reagent and the stability of the coordinate bond between reagent and substrate. The sign of the above difference depends mainly on the nature of the central lanthanide ion in the complex, and the degree of coordination on the nature of the ligand (diketone). The dependence of the shift on the

nature of the lanthanide has been studied in detail on the series of Ln dpm$_3$ complexes for the proton [18,20,23,24,42,132,133] and carbon-13 [22,61] n.m.r. spectra. The shift varies regularly in the series of lanthanides (Fig. 4) [19]. Complexes of cerium-group lanthanides (praseodymium, europium) give numerically smaller shifts than do those of the yttrium group (terbium, dysprosium, holmium, erbium, thulium, ytterbium), but line broadening is far less (see below).

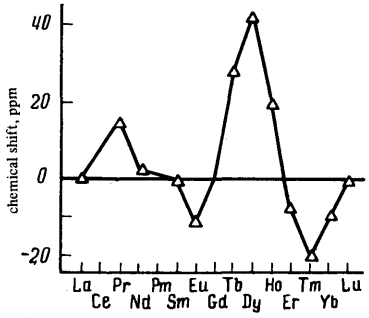


Figure 4. Shift of $H_{(1)}$ proton signal in spectra of n-hexanol (0.8 M solution in $CDCl_3$) produced by lanthanide complexes Ln dpm$_3$ at the ratio Cp/Cs = 0.125. [19]

The effect of the ligand can be observed in the complexes of europium with fluorinated β-diketones [25,134]; increase in the fluorine content is accompanied by an increase in the Lewis acidity (decrease in pK_a) accompanied by increase in the displacements in the n.m.r. spectra. This is especially noticeable in the spectra of substrates that are weak Lewis bases, e.g. ethers [25]. Complexes of lanthanides with pentane-2,4-dione, 1,3-diphenylpropane-1,3-dione, and 1-phenylbutane-1,3-dione are relatively ineffective as paramagnetic shift reagents [35,128,129,135]. This may be due to insufficient bulk of the ligand, low magnetic anisotropy of the complex, or finally a small complex–substrate association constant.

6. Dependence of Shift on Geometric Factors

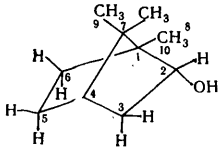
The dependence of the pseudocontact shift on the distance r_i from the given nucleus to the paramagnetic ion and on the angle θ_i between the vector and the axis of the complex, defined by the equation

$$\delta_i = \text{const}\ (3\cos^2\theta_i - 1)/r_i^3$$

is extremely valuable for the employment of shift reagents in practical n.m.r. spectroscopy. Its use enables signals in the spectrum of a molecule of known structure to be assigned comparatively easily; and conversely information on the geometry of the molecule to be obtained if the assignment is known.

In several cases experimental data on the dependence of δ on r and θ for "rigid" cyclic molecules are well described by Eqn. (1). Such results have been obtained, for instance, in the proton magnetic resonance spectra (Table 6) [136] and the carbon-13 n.m.r. spectra [61] for borneol in the presence of tristetramethylheptanedionatopraseodymium, for bicyclic ethers [137] and nitrogen heterocycles [109] in the presence of the europium complex, and for vinylpyridine in the presence of the corresponding complexes of several lanthanides [19].

Table 6. Comparison of specific shifts in spectrum ΔPr with geometric factor for the borneol–Pr dpm$_3$ in CCl_4 solutions at room temperature (100 and 200 MHz) [136].



Proton	*exo*-2H	*exo*-3H	*endo*-3H	4H	*exo*-5H	*endo*-5H	*exo*-6H	*endo*-6H	8CH$_3$	9CH$_3$	10CH$_3$
ΔPr	45.0	16.6	34.2	10.1	10.5	16.0	15.7	35.6	7.78	8.01	17.8
$\frac{3\cos^2\theta_i - 1}{r_i^3 \times \text{const}^{-1}}$	49.0	15.8	30.2	9.84	11.0	16.1	16.0	38.7	7.84	7.88	16.5

The importance of the angle-dependent term in (1) is supported by the fact that signals of nuclei for which $\theta_i \simeq 54°$, e.g. the aromatic protons in t-butylphenylcyclohexanol [138], are not displaced by addition of the europium complex, but when $\theta_i > 54°$ the signals shift in the opposite direction—upfield with the europium complex and downfield with the praseodymium complex [139–144].

Table 7. Position of lanthanide ion in shift reagent–substrate adducts.

Shift reagent	Substrate	Ln to O (N), Å	C-O-Ln (C-N-Ln) angle	Ref.
Eu (DPM)$_3$	4-t-butylcyclohexanol	3—4	180—160	35
Eu (DPM)$_3$	adamantan-2-one	3—4	180—160	35
Eu (DPM)$_3$	quinoline	4.0	180	144
Eu (DPM)$_3$	isoquinoline	3.0	180	144
Eu (DPM)$_3$	pyridine, quinoline	4.0±0.4	180	109
Eu (DPM)$_3$	pyridine	2.9	180	156
Pr (DPM)$_3$	borneol	3.0	126	136
Yb (DPM)$_3$	acrylaldehydes	3.0	180	21
Yb (DPM)$_3$	pyridine	3.0±0.3	180	20

Many attempts have been made to plot the dependence of the shift on separation without considering the angular term, on the assumption that $\delta_i = r_i^{-n} \times$ const. The distance r_i is then measured, not to the lanthanide ion, but to the oxygen or nitrogen atom through which the shift reagent is coordinated [36,40,145–149]. Critical analyses by Rafalski [150] and by Goodisman [151] have shown that values of n = 0.2–3.6 are then obtained, with n = 2 recommended [150] for practical purposes. Such a method of calculation is convenient in not requiring the position of the lanthanide ion in the reagent–substrate adduct to be known, but the procedure should be employed with great caution.

Crystallographic data can be used[152,153] to determine the distance r from nucleus to lanthanide ion, but there is no certainty that distances in solution remain the same as in the crystal. Some complication may arise also from the fact that the principal magnetic axis of the complex does not necessarily coincide with the direction of the bond between lanthanide and donor atom[154]. If we assume that the displacement is given accurately by Eqn. (1), we can determine the position of the lanthanide from the measured shifts. An electronic computer[127] or a graphical method[155] is used to select coordinates of the Ln^{3+} ion at which the deviation from Eqn. (1) is minimal.

Table 8.

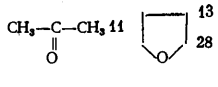
Position of CH_2	1	2	3	4	5	6	7
Shift	1.00	0.58—0.60	0.40—0.42	0.20	0.12—0.14	0.08	0.02—0.05

Table 7 lists data on Ln–O (or Ln–N) distances and C–O–Ln (or C–N–Ln) angles. The appreciable divergence between results obtained by different workers is probably due to errors in measuring the shifts and in determining distances in the models.

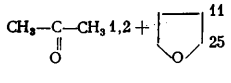
In the case of non-rigid aliphatic molecules interatomic distances are averaged over all possible conformations. Exact calculation of the dependence of δ on r and θ is difficult, and only a gradual diminution in the displacement is observed with distance along the chain from the donor group. Table 8 gives the shifts for successive methylene groups in straight-chain aliphatic alcohols, with the shift due to the hydroxymethyl group taken as unity[35,157]. A methyl group gives a rather smaller displacement than does a methylene group in the same position[101].

7. Displacement due to Shift Reagent in presence of Several Functional Groups

Functional groups of several types may be present in a solution containing a paramagnetic shift reagent. In the simplest case they occur in different molecules: i.e. a mixture of two or more substrates is present. The shift reagent is then distributed between the substrates in proportions depending on the strength of bonding of the reagent and the concentration of the components, with corresponding changes in the shifts of the signals from each substrate. For example[114], the specific shifts



are found for acetone and for oxolan; if, however, the solution contains both compounds, in equimolecular quantities, the values



are obtained: i.e. the displacements have fallen to 11% and 89% of their initial values for acetone and oxolan respectively. From this it may be deduced that oxolan binds tristetramethylheptanedionatoeuropium eight times as strongly as does acetone.

If a solution contains two substrates forming equimolar complexes $PS^{(1)}$ and $PS^{(2)}$ with a shift reagent, we can write for the complex-formation constants K_1 and K_2 and the shifts of the signals $\delta^{(1)}$ and $\delta^{(2)}$ expressions analogous to Eqns. (5) and (6), which contain the concentrations of substrates and complexes together with the displacements of the bound substrates $\delta_\infty^{(1)}$ and $\delta_\infty^{(2)}$. Eliminating concentrations from these equations, we obtain

$$\frac{1}{\delta^{(2)}} = \frac{1}{\delta^{(1)}}\frac{K_1\delta_\infty^{(1)}}{K_2\delta_\infty^{2}} + \frac{K_2 - K_1}{K_2\delta_\infty^{(2)}} \qquad (9)$$

The plot of $1/\delta^{(2)}$ against $1/\delta^{(1)}$ for solutions of varying composition is a straight line of slope $K_1\delta_\infty^{(1)}/K_2\delta_\infty^{(2)}$, making an intercept $(K_2 - K_1)/K_2\delta_\infty^{(2)}$ on the ordinate axis. If values of the parameters K_1 and $\delta_\infty^{(1)}$ for one compound are known, this graph can be used to determine the corresponding parameters for the second compound. This "monitor" method[100] is convenient in not being as sensitive to moisture as direct methods.

When two functional groups are present in the same molecule, but sufficiently far apart not to interact, e.g. at positions 3 and 17 in a steroid molecule[66,149], the same relations hold between coordination at the two groups. The displacement of the signals is then simply the sum of the shifts caused by coordination at each group separately, and can be calculated additively either numerically[149] or graphically[66]. When the complex-formation constants of the two groups differ greatly, the competition between them ensures that the shift reagent combines initially with one group, and only then with the second group on further addition of the reagent. At low concentrations of the reagent, therefore, protons situated near the first functional group are more strongly displaced, but at high concentrations protons beside the second group take over. The signals "overtake" one another on the spectrum; the straight lines corresponding to different protons intersect on the graph of δ as a function of C_P/C_S.[122,158]

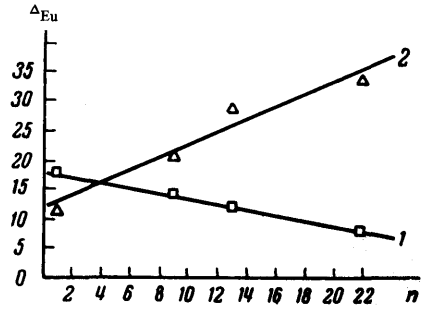
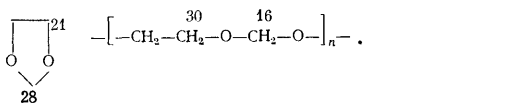


Figure 5. Dependence of specific shift ΔEu on degree of polymerisation n of polyethylene glycols in CCl_4 solution at room temperature (60 MHz) for: 1) terminal CH_2 groups; 2) central CH_2 groups[159].

More complicated relations are observed if the molecule contains different numbers of groups of each type, e.g. for functional groups in the middle and at the ends of a polymer molecule. Thus chain lengthening in the

series of polyethylene glycols $HO[CH_2CH_2O]_nH$ is accompanied [159] by increase in the proportion of tristetramethylheptanedionatoeuropium coordinated at the ether bonds in the central units, and a diminution of coordination at the terminal hydroxy-groups, with a corresponding variation in ΔEu (Fig. 5). Changes in the distribution of the shift reagent between different functional groups are observed also when the solution is heated: a group which is less effective at room temperature may be more effective at a higher temperature [160].

If two functional groups in a substrate molecule are close together, the displacements are no longer additive [146]. The bonding to the shift reagent and the magnitude of the shift depend on the distance between the groups: e.g. the bonding is considerably stronger for *o*-dimethoxybenzene than for the *meta*-derivative [130]. The displacement is influenced also by stereochemical effects. In polydioxolan, for example, the ethoxyl protons are more strongly displaced in the presence of the above shift reagent, but the formyl protons are more strongly displaced in the monomer [161]:



With a favourable conformation the substrate can evidently interact as a bidentate ligand with the lanthanide ion to form chelate complexes [162,163].

8. Effect of Shift Reagents on Width of Lines in Spectrum

A substantial advantage of lanthanide paramagnetic shift reagents is that, in contrast to complexes of transition metals containing the same ligands [164], they cause little line broadening; even when the signal is displaced by several parts per million, the multiplet structure still remains resolved.

Table 9.

Ln	Pr	Nd	Sm	Eu	Tb	Dy	Ho	Er	Tm	Yb
$\Delta\nu_{1/2}$, Hz	5.6	4.0	4.4	5.0	96	200	50	50	65	12

The broadening of an n.m.r. line in the presence of paramagnetic ions is due to acceleration of the relaxation of the nuclear spin, and also to exchange between bound and free substrate molecules. The main factor determining the substrate n.m.r. line width is the electronic relaxation time T_{1e} of the lanthanide ion. Little broadening may be expected with complexes of ions having short T_{1e} times (Eu^{3+}, Pr^{3+}, Nd^{3+}); ions having large T_{1e} values, e.g. Gd^{3+}, should produce great broadening. Table 9 gives the line widths $\Delta\nu_{1/2}$ of the methyl group in 2-methylpyridine in the presence of tristetramethylheptanedionatolanthanide complexes at the same ratio $C_P/C_S = 0.125$. [19] The broadening in the presence of the gadolinium complex is so great that the spectrum could not be obtained.

The broadening of a line is usually greater the larger the displacement. Broadening is therefore sometimes measured by the ratio $\Delta\nu_{1/2}/\delta$. For example, the values found in the spectra of t-butyl alcohol in the presence of the above lanthanide complexes are listed in Table 10. [18,24]

Table 10.

Ln	Pr	Sm	Eu	Tb	Ho	Yb
$\Delta\nu_{1/2}/\delta$	0.013—0.005	0.02	0.003	0.1	0.02	0.02

The relaxation times T_{1M} and T_{2M} of nuclei of a substrate bound in a complex having an anisotropic g-factor and a short T_{1e} time [165] are theoretically [109,166,167] given by the equation

$$\frac{1}{T_{1M}} = \frac{1}{T_{2M}} = \frac{2}{3}\gamma_n^2\beta^2 S(S+1)\frac{1}{r^6} f(g_\parallel, g_\perp, \theta) T_{1e} + \frac{4}{9}\gamma_n\beta S(S+1)\frac{A}{2\pi}(g_\parallel - g_\perp)\frac{3\cos^2\theta - 1}{r^3} T_{1e} + \frac{2}{3}S(S+1)\left(\frac{A}{2\pi}\right)^2 T_{1e} \quad (10)$$

where

$$f(g_\parallel, g_\perp, \theta) = \frac{1}{3}(g_\parallel^2 - 2g_\perp^2) + g_\parallel^2\cos^2\theta + g_\perp^2\sin^2\theta,$$

$g_\parallel$ and $g_\perp$ are components of the g-tensor, and the remaining symbols have the same significance as in Eqns. (1) and (2). The first term in (10) represents dipole–dipole interaction, the second cross relaxation, and the third hyperfine interaction. The dipole contribution predominates, since the hyperfine coupling constant is small (hence according to Eqn. (2) the contribution of contact interaction to the shift is small) in most solutions of the above europium complex and organic compounds. The observed line width is determined by the transverse relaxation time: $\Delta\nu_{1/2} = 1/\pi T_2$. For rapid exchange between bound and free substrate we have theoretically [168-170]

$$\frac{1}{T_1} = \frac{1}{T_1^0} + \frac{\sigma}{T_{1M}} \quad (11)$$

$$\frac{1}{T_2} = \frac{1-\sigma}{T_2^0} + \frac{\sigma}{T_{2M}} + \sigma(\sigma-1)^2\tau_M(2\pi\delta_\infty)^2 \quad (12)$$

where T_1^0 and T_2^0 are the relaxation times in the absence of the chemical shift reagent, σ is the fraction of the substrate combined with the reagent, and τ_M is the mean lifetime of a substrate molecule in the bound state. Equations (11) and (12) can be used to determine τ_M from the measured spin–lattice relaxation time, line width, and shift. The last term in Eqn. (12) is found to make the largest contribution to broadening the signals from protons $H_{(2)}$ and $H_{(8)}$ in quinoline dissolved in carbon tetrachloride in the presence of the europium complex; for this system $\tau_M = 2\times10^{-7}$ s. The strong dependence of line broadening and rate of spin–lattice relaxation on geometric factors (to a first approximation these quantities are proportional to r^{-6}) can be used for the determination of structure [13,30,109].

9. Effect of Shift Reagents on Spin–Spin Coupling Constants

Lanthanide shift reagents have little effect on spin–spin coupling constants J between substrate nuclei. This enables J to be determined by direct measurement of the splittings obtained in first-order spectra after addition of a sufficient quantity of shift reagent to the solution. The invariability of the spin–spin coupling constants has been confirmed by measurements of J_{H-H} in lactones [171],

carbohydrates[172], bicyclic esters[158], nitrogen heterocycles[173], by measurements of J_{Sn-H} in organotin compounds[174], etc.; little change in J has been observed with cyclic alcohols[175].

In several cases the addition of a shift reagent produces a change in J that is not connected with paramagnetism but is due to the effect of complex formation on the distribution of electron density in the molecule[176] or on the conformational equilibrium (see below).

Partial elimination of J_{23} and J_{24} spin–spin coupling in quinoline is observed at high concentrations of the europium reagent[35,109]. This phenomenon is observed also with transition-metal complexes[177–180]. It is analogous to the uncoupling of spins in double resonance, and is explained by a decrease in the relaxation time of the nuclei[181].

10. Effect of Shift Reagents on n.m.r. Spectra of Other Nuclei

The action of paramagnetic shift reagents on carbon-13 and fluorine-19 spectra conforms to the same rules as that on the proton magnetic resonance spectra[65]. Only two special features are evident. Firstly, the displacement of the signals defined by Eqn. (1) is the same as in the latter spectra, but the chemical shifts of other nuclei are far larger than those of protons. Therefore the change in the form of the spectrum is not so striking. Secondly, the n.m.r. spectra of other nuclei are strongly influenced by the change in electronic structure accompanying formation of an adduct with the shift reagent. Therefore the carbon-13 and nitrogen-14 n.m.r. spectra in the presence of the diamagnetic tristetramethylheptanedionatolanthanum exhibit a displacement of the signals comparable with that produced by the paramagnetic europium complex[22,140].

Shift reagents are used in carbon-13 n.m.r. mainly for the assignment of lines by means of the dependence of the displacement on the carbon–lanthanide distance. This method has been applied to the spectra of alcohols[182] and the complicated carbon-13 n.m.r. spectra of natural compounds—cholesterol[183], the alkaloid piperine[140], borneol[61], and isoborneol[62]. Stereoisomers have been identified[184] from the carbon-13 n.m.r. spectra of cyclopentane derivatives in the presence of the europium shift reagent. Shifts in the n.m.r. spectra in the presence of europium, holmium, and neodymium salts in aqueous solution have been used to determine the conformation of mononucleotides[30]. The increased distance between signals in the proton magnetic resonance spectrum substantially facilitates the assignment of signals in the carbon-13 spectrum by selective uncoupling of the $^{13}C-\{^1H\}$ spin–spin interaction[31].

Shift reagents find limited application in fluorine-19 n.m.r., since the introduction of fluorine into an organic molecule diminishes the basicity and weakens coordination of a lanthanide. Perfluorinated alcohols and amines do not coordinate paramagnetic shift reagents. Aromatic amines exhibit[65] the same ratios between shifts in *ortho*- and in *para*-positions as in the proton magnetic resonance spectra.

The nuclei of nitrogen-14 and phosphorus-31 atoms having a lone pair of electrons can interact with paramagnetic shift reagents by a contact mechanism[65]. Use of the tristetramethylheptanedionato-complexes of dysprosium and ytterbium has been recommended for nitrogen-14 n.m.r. (as also for fluorine-19[65]), but the great broadening of the lines makes it very difficult to record the spectra[22,185]. In phosphorus-31 n.m.r. the europium complex has been used to displace the signals in deuterochloroform solution[186], and europium and praseodymium trinitrates in aqueous solution[34].

IV. APPLICATIONS OF PARAMAGNETIC SHIFT REAGENTS IN n.m.r. SPECTROSCOPY

1. Simplification of Spectra

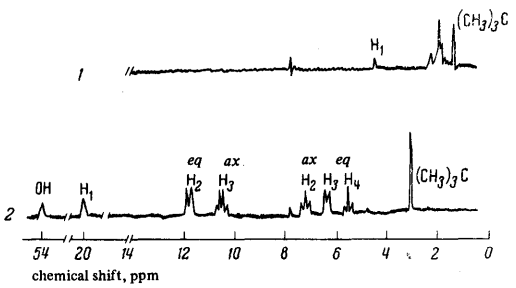


Figure 6. Nuclear magnetic resonance spectrum 100 MHz of *cis*-4-t-butylcyclohexanol in $CDCl_3$ solution: 1) in absence of shift reagent; 2) in presence of Eu dpm$_3$ with $C_P/C_S = 0.7$.[36]

The most important result of the use of shift reagents in n.m.r. spectroscopy is a remarkable simplification of the spectra. The displacement of the signals due to the reagents produces a sharp increase in the chemical shift relative to the spin–spin coupling constant J, which enables first-order spectra to be obtained even for complicated spin systems (Fig. 6)[36].

2. Assignment of Signals

The use of shift reagents makes the assignment of signals in the spectra considerably easier. Their addition separates previously overlapping peaks, so that the signals of protons can be assigned by means of double resonance and analysis of the spin–spin coupling constants.

Above all, however, the method based on the dependence of the displacement on geometric factors is widely used. For example, the structure of *dextro*-camphor shows (Fig. 7) that the distance of the methyl groups from the ketonic oxygen increases in the sequence $10\text{-}CH_3 < 8\text{-}CH_3 < 9\text{-}CH_3$. The distances of the methyl groups from a europium ion coordinated at the keto-group will increase in the same sequence. Therefore the methyl signals that undergo the largest downfield displacement on addition of the shift reagent are assigned to 10-methyl protons, and the least displaced to 9-methyl protons[187]. A similar method has been used to assign signals in the n.m.r. spectra of 1,3-dimethylcyclohexylamine[148], cyclohexyl isocyanide[188], and many other compounds.

3. Determination of Chemical Shifts and Spin–Spin Coupling Constants

Extrapolation to zero shift-reagent concentration of the linear plots of δ against C_P/C_S enables us to determine chemical shifts for those substrate protons whose signals

overlap in the absence of a shift reagent[36,115,172]. Constants J, previously inaccessible because of the superposition of signals—in the n.m.r. spectra of pyrazine derivatives, for example, the couplong constants between protons of the methyl group and *ortho*-, *para*-, and *meta*-protons of the ring[173], and J_{PCH} and J_{PCCH} in those of phosphine oxides[88]—can be obtained from n.m.r. spectra in the presence of shift reagents.

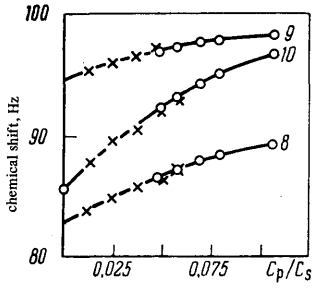
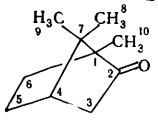
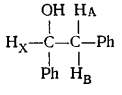


Figure 7. Dependence of chemical shift (at 100 MHz) of 8-, 9-, and 10-methyl groups of (+)-camphor in presence of Eu dpm$_3$.2C$_5$H$_5$N on C_P/C_S ratio (solution



in CCl_4 at room temperature)[187].

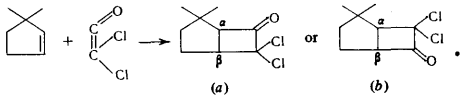
The possibility of evaluating J_{gem} for diastereotopic protons is especially interesting. In the presence of a shift reagent the signals of such protons in the α- and even in the β-position relative to an asymmetric carbon atom are sharply separated[35,115]. Thus the alkyl protons in 1,2-diphenylethanol[35]



give an n.m.r. spectrum of type A_2X, but on addition of the europium shift reagent a spectrum of type ABX is obtained, which enables J_{AB} to be determined.

4. Study of Molecular and Stereochemical Structure

In several cases molecular structure can be determined unambiguously from the dependence of the displacement on geometric factors. For example, dichloroketen can add in two ways to 3,3-dimethylcyclopentene, to yield two structures (*a*) and (*b*)[189]:



The α-hydrogen signal gives a doublet in the n.m.r. spectrum of the reaction products owing to interaction with the β-hydrogen atom, and the β-hydrogen gives a multiplet owing to interaction with the α-hydrogen and with the protons of the five-membered ring. On the addition of tristetramethylheptanedionatoeuropium, which coordinates at the ketonic oxygen, the downfield displacement of the α-hydrogen doublet exceeds that of the β-hydrogen multiplet by 50–100%, which indicates a structure of type (*a*).

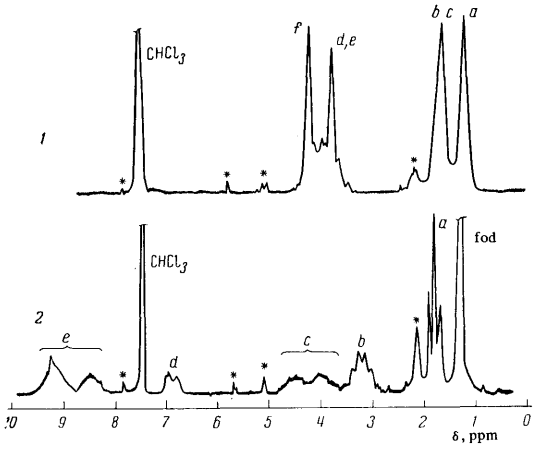
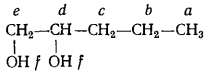


Figure 8. Nuclear magnetic resonance spectrum (at 60 MHz) of pentane-1,2-diol



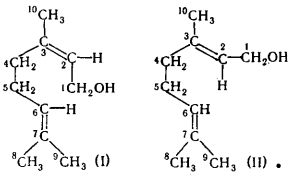
(9 wt.% solution in chloroform at room temperature): 1) in absence of shift reagent; 2) with Eu fod$_3$ (C_P/C_S = 1 : 3). The assignment of the lines is shown on the spectrum; the asterisks denote peaks due to impurities and satellites of carbon-13.[190]

Some difficulty has arisen[190] in establishing the structure of the pentanediol isolated from technical furfuryl alcohol. The n.m.r. spectrum (Fig. 8) may correspond to two structures (1,2- and 1,3-diols). When the spectrum is determined in the presence of trisheptafluorodimethyloctanedionatoeuropium the signal of the CH_2–OH group is strongly displaced downfield and is split into two peaks (corresponding to two diastereotopic protons), whereas the signal from the CH_2CH_3 group is not split. This means that the hydroxymethyl group is in the α-position to the hydroxymethylene group: i.e. the 1,2-diol structure is unequivocally proved.

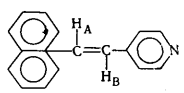
Shift reagents have been used to determine the chemical structure of polycyclic ketones[191], a bicyclic anhydride[192], etc.

Shift reagents are widely used also for identifying geometric isomers. The n.m.r. spectra of nerol (I) and geraniol (II) in the presence of tristetramethylheptanedionatoeuropium show[193] diminishing displacement of the signals of the nerol protons in the sequence $C_{(4)} > C_{(5)} > C_{(10)}$, whereas the corresponding sequence for geraniol is $C_{(10)} > C_{(4)} > C_{(5)}$, which proves that

nerol has the *cis*-configuration (I), and geraniol the *trans*-configuration (II):



In the n.m.r. spectrum of naphthylvinylpyridine



in the presence of the same shift reagent the signals of the vinyl protons no longer overlap those of the naphthalene ring protons, and give a quadruplet of type AB, so that the *cis*- or *trans*-configuration of the compound can be determined from the value of J_{AB} [194].

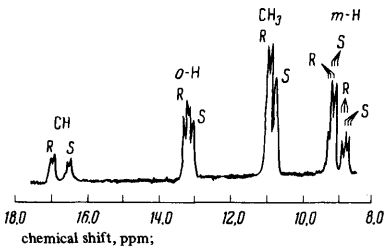
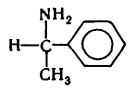


Figure 9. Nuclear magnetic resonance spectrum of solution of mixture of (*R*)- and (*S*)-isomers of 1-phenylethylamine

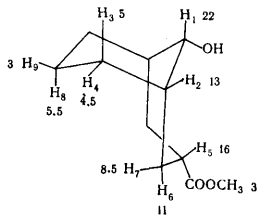


in CCl_4 in presence of 0.15 M tris-3-t-butylhydroxymethylene-(+)-camphoratoeuropium [26].

The enantiomeric purity of compounds—e.g.alcohols [28], sulphoxides [29], amines [26]—can be determined by the use of optically active shift reagents (Table 3). Fig. 9 shows the spectrum of racemic 1-phenylethylamine (mixture of (*R*)- and (*S*)-isomers) in the presence of tris-3-t-butylhydroxymethylene-(+)-camphoratoeuropium [26]. A remarkable feature of this spectrum is the considerable difference between the chemical shifts of corresponding protons in (*R*)- and (*S*)-isomers (from 0.07 ppm for the *para*-protons of the aromatic ring to 0.5 ppm for $CHNH_2$). The signals of the (*R*)-isomer are more strongly displaced than those of the (*S*)-isomer owing to the difference between the stability constants of the complexes they form with the shift reagent. The enantiomeric composition of the mixture is determined from the ratio of the areas of the signals. Tristetramethylheptanedionatoeuropium has been used to identify the *meso*-form and racemic bisphenylsulphinylmethane [195].

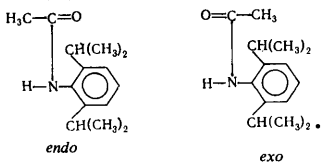
5. Study of Conformation

Paramagnetic shift reagents are used for the conformational analysis of flexible and rigid molecules and for the identification of rotational isomers. Analysis of the shifts of the proton signals in the n.m.r. spectrum of the *cis*-9-hydroxybicyclo[3,3,1]nonane-*endo*-3-carboxylate [158]



in the presence of tristetramethylheptanedionatoeuropium with $C_P/C_S = 0.3$ (when the shift reagent coordinates mainly through the hydroxy-group) shows that the signal of the $H_{(5)}$ proton is considerably displaced downfield, which indicates the boat–chain type of conformation. The conformation of cyclic ketones [196], griseofulvins [197], mononucleotides [30], and bicyclic alcohols [198] has been studied by the use of shift reagents.

It must be borne in mind that formation of a reagent–substrate complex is sometimes able to influence the conformational equilibrium,, e.g. that between *exo*- and *endo*-forms of the substituted amide [142]



In the absence of a shift reagent the ratio of the isomers is *endo*/*exo* = 2/1; addition of 0.1 M of the europium shift reagent changes the ratio of the rotational isomers to *endo*/*exo* = $\frac{1}{2}$. Shift reagents affect also the conformation equilibrium of other amides [133,146], the chair ⇌ chair equilibrium [199], and the equilibrium between carbohydrate anomers [31].

6. Analysis of Mixtures

Impurities can be detected by means of shift reagents, and mixtures of substances having overlapping resonance signals can be analysed by integrating individual peaks in the "stretched" spectrum. This method has been used [101] for the quantitative determination of the components in a binary mixture of 2-methylbutan-1-ol and 2-methylbutan-2-ol, in a ternary mixture of n-pentan-1-, 2-, and -3-ols, and even in a senary mixture of the C_1–C_6 straight-chain alcohols.

7. Study of Polymers

Shift reagents are used to study the stereochemical structure and sequence of units in polymers. The signals from protons in α-methyl and methylene groups are split in the n.m.r. spectrum of poly(methyl methacrylate). The presence of a shift reagent [200] not only facilitates isolation of the signals from α-methyl protons in isotactic (*i*), syndiotactic (*s*), and heterotactic (*h*) triads and the signals from methylene protons in *erythro-mmm* and *threo-rrr* tetrads but also resolves the signal from methoxy-protons into three peaks, corresponding to *i*-, *s*-, and *h*-triads in the polymer chain (Fig. 10). In contrast to this study [200] of the isotactic polymer, an investigation [102] of atactic poly(methyl methacrylate) indicates

that the displacement of the signals of methyl protons diminishes in the sequence i-CH_3 > h-CH_3 > s-CH_3-CH_2, whereas the corresponding sequence for the methoxy-protons is i-CH_3O > h-CH_3O > s-CH_3O. Such a sharp divergence of the results is evidently due to the effect of tacticity on polymer conformation, and hence on the shift, which depends on geometric factors. Resolution of the signal from the protons of a methyl group, under the influence of a shift reagent, into three peaks corresponding to i-, s-, and h-triads has been observed also with poly-(methyl vinyl ether) and polyoxypropylene [201,202].

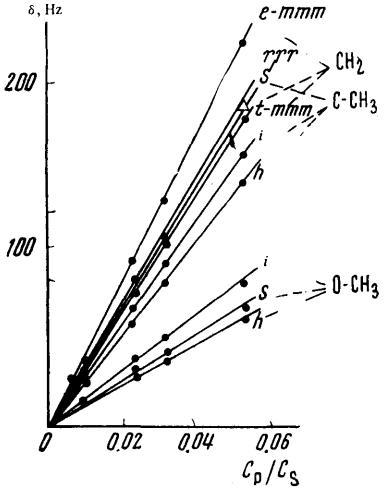


Figure 10. Dependence of shift of signals (at 220 MHz) for protons of poly(methyl methacrylate) in presence of Eufod$_3$ on C_P/C_S (solution in o-dichlorobenzene) [200].

In the n.m.r. spectrum of the trioxan–dioxolan copolymer of general formula $[OCH_2]_x[OCH_2CH_2OCH_2]_y$ the protons of the ethylene oxide group (E) give a singlet, and those of the methylenoxy-group (F) three singlets corresponding to the sequences EFE, EFF, and FFF [161]. On the addition of tristetramethylheptanedionatoeuropium to the solution the three signals due to the methylenoxy-protons coalesce into a single signal, while the peak due to protons of the ethylene oxide group split into three peaks corresponding to the sequences FEFEFEF + FEFEFFF, EFFEFFE + EFFEFFF, and FFFEFFF.

Use of the europium shift reagent enables us to determine the sequence of acid residues in the chain of a copolyester of terephthalic and isophthalic acids with ethylene glycol [203] (the signal from the glycol protons is split into three peaks).

The n.m.r. spectra of glymes—oligomers of formaldehyde and formaldehyde–dioxolan copolymers—in the presence of the europium shift reagent enable a comparative estimate to be made of the basicity of terminal and central oxygen atoms [159], which is important for an explanation of the mechanism of polymerisation. In the spectra of the copolymers $CH_3OCH_2[OCH_2OCH_2CH_2]_nOCH_3$ the signals from methylene protons adjacent to terminal oxygen atoms undergo smaller displacements than with central groups (in Fig. 11 the slope of the straight line a exceeds that of b, and line c is steeper than d): the oxygen atoms obviously become less basic from the middle towards the end of the chain. The signals from protons in methylenoxy-groups in the spectrum of the formaldehyde oligomer $CH_3O[CH_2O]_nCH_3$ are situated further downfield the closer is the group to the end of the chain, which indicates that terminal oxygen atoms have greater coordinating power (basicity). Analogous results have been obtained for glymes $CH_3O[CH_2CH_2O]_nCH_3$.

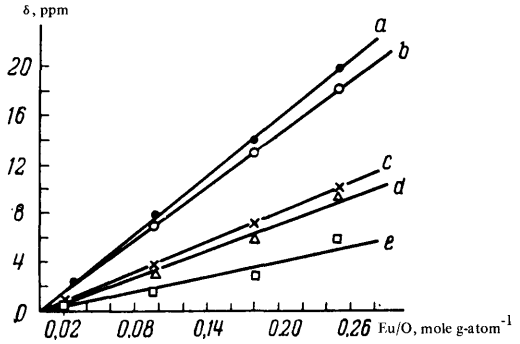


Figure 11. Dependence of shift (at 60 MHz) on ratio of Eu dpm$_3$ to oxygen for different groups in the compound $CH_3\overset{e}{O}CH_2\overset{d}{O}CH_2CH_2\overset{b}{O}CH_2\overset{a}{O}CH_2CH_2\overset{c}{O}CH_2\overset{a}{O}CH_3$ dissolved in CCl_4 at room temperature [159].

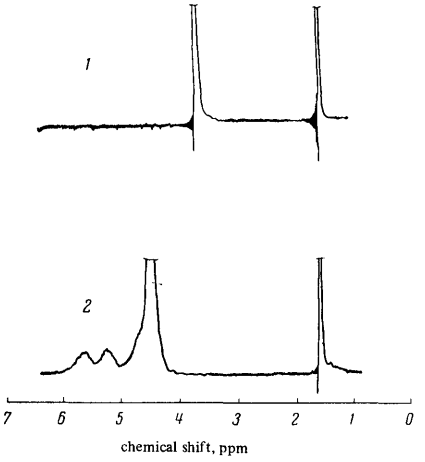


Figure 12. Nuclear magnetic resonance spectrum (60 MHz) of solution of polyethylene glycol PEG-400 in CCl_4 at room temperature: 1) in absence of shift reagent; 2) in presence of Eu dpm$_3$ with C_P/C_S = 0.4.

Use of a shift reagent facilitates determination of the molecular weights of polypropylene glycol [204] and polyethylene glycols [159] by means of the end-groups. Addition of the europium complex to a polyethylene glycol separates the signals due to terminal, penultimate, and central methylene groups (Fig. 12). The degree of polymerisation is calculated from the relative areas of the signals of terminal and central methylene groups. The resulting

molecular weights are close to the specified values (Table 11).

Table 11.

Mol. wt. from specification	400	600	1000
Mol. wt. from spectrum	370	550	986

8. Compounds with Spectra studied in the presence of Shift Reagents

Alcohols

Aliphatic [16,26,28,32,84,99,101,103,105,106,128,157,182,205-220].
Aromatic [35,69,214,221,222,223].
Cyclic [15,23,28,36,40,61,66,87,104,107,128,141,143,145,147,175,183,184,188,193,198,205,216,218,224-260].

Ketones

Aliphatic [33,100,106,110,161,219,220].
Aromatic [69,240,261].
Cyclic [66,89,97,110,126,127,132,160,176,189,191,196,197,215,229,232,235,237,239,240,250,252,262-274].

Ethers and esters [69,100,106,117,131,137,141,149,161,163,171,184,200,201,203,204,206,211,223,234,242,250,252,264,275-294].

Carbohydrates [23,31,203,259,290,295-300].

Other oxygen-containing compounds [20,21,32,33,97,110,112,118,140,160,192,198,218,240,263,267,281,289,292,301-310].

Amines

Aliphatic [20,26,32,99,105,125,220,303,311-313].
Aromatic [20,124,125,259,314].
Cyclic [20,82,148,315-319].

Nitrogen-containing heterocycles [20,48,69,70,84,92,109,119,140,144,150,164,173,194,238,267,268,301,305,317,320-326].

Amides [301,327-335].

Other nitrogen-containing compounds [117,142,220,301,336-339].

Sulphur-containing compounds [96,114,123,195,196,243,272,285,301,306,308,340-346].

Phosphorus-containing compounds [31,34,83,121,122,186,199,219,302,345,347].

Polymers [102,106,159,161,200,201-204,288,348].

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Shift reagents greatly increase the possibilities of nuclear magnetic resonance spectroscopy. In some cases the information obtainable from the n.m.r. spectrum determined at a frequency of 60 MHz in the presence of the europium shift reagent is greater than that provided by the spectrum at 220 MHz in the absence of a shift reagent [173]. It may be expected that the preparation of new shift reagents, in particular with a selective action towards certain functional groups and suitable for application in polar solvents, as well as detailed physicochemical investigation of reagent–substrate–solvent systems, will still further extend the range of application of this method.

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