Paramagnetic Shift Reagents. The Nature of the Interactions

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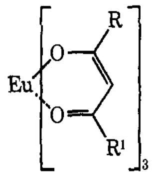
Abstract: Evidence is presented which indicates that in dry carbon tetrachloride solution $Ln(DPM)_3$ samples may exist mostly in dimeric form. Theoretical analyses for adducts of various stoichiometries are given, and it is shown that data for $Ln(DPM)_3$-induced shifts are best explained by the formation of 1:1 substrate–shift reagent adducts. The analysis is extended to bifunctional compounds and substrate mixtures where the relative degree of coordination changes with shift reagent concentration; these theoretical predictions have been confirmed by experimental observations. A fluorinated shift reagent, $Eu(PTA)_3$, is described, with particular reference to its apparent ability to yield either 2:1 or 1:1 adducts, depending on the nature of the substrate and the relative concentrations of the reactants. The change in geometry associated with stoichiometry changes can lead to dramatic variations in the proton shift ratios of the substrate, and it is demonstrated that the shift reagent changes the magnitude of its magnetic anisotropy in this compound. Methods for the determination of equilibrium constants are given, and their physical significance is discussed. Most polar substrates have apparent equilibrium constants of 100–1000. The use of hydrated lanthanide nitrates in aqueous or polar solution as a new class of shift reagents for the functionality $X\text{–}O^-$ (where X is RCO, R_3N^+, R_3P^+ or R_3As^+) is described, the major species in solution apparently being 2:1 or 3:1 adducts. Significant covalent character in this latter interaction is inferred from large contact contributions to ^{31}P shifts. Examples are described where angular variable changes lead to reversals in the direction of the induced shift for both classes of shift reagent. All these results are combined to give a consistent picture of the nature of $Ln(DPM)_3$ adducts, and, somewhat less satisfactorily, of the nitrate adducts.

In the short time since the earliest announcements[1,2] of the nmr shift properties of $Eu(DPM)_3$ (**1**), some 80 reports of the properties and applications of **1** and other lanthanide analogs have appeared. Some of these reports have concentrated on improving our knowledge of the shift powers,[3–7] while many have actually applied them to the solution of chemical problems.[8–13] The most important applications to date seem to be (i) the location of deuterium within a molecule,[8] (ii) determination of stereochemistry in small ring systems,[9,10] (iii) configurations of oximes,[11] (iv) structural determinations,[12] and (v) studies of the conformations of complexed substrates.[13] In addition, there are potential uses of shift reagents in the assignment of ^{13}C nmr spectra,[14] and tris(3-pivaloyl-*d*-camphorato)europium has been used in studies of the optical purity of organic bases.[15]

However, there appears to have been little thought given to the nature of the adducts formed in these substrate–shift reagent interactions, and in particular there have been few soundly based analyses of the behavior of polyfunctional systems. The main object of this investigation, therefore, was to find a simple theoretical model which would adequately describe the various shift phenomena encountered during the routine use of shift reagents with mono- and bifunctional substrates. It is sufficient for our purpose that we can now describe the behavior of such substrates in terms of adduct stoichiometries and *approximate* equilibrium constants. It must be stressed that this has been neither a detailed study of lanthanide coordination chemistry nor an attempted compilation of authoritative equilibrium constant data.

During the course of this work we have also investigated the solution dimerization of **1** and have synthesized and studied the fluorinated complex $Eu(PTA)_3$ (**2**),[16] solvent extraction studies having indicated that fluorinated complexes should have greater Lewis acidity.[17] Rondeau and Sievers have independently



1, $R = R^1 = tert\text{-}Bu$
2, $R = tert\text{-}Bu;\ R^1 = CF_3$
3, $R = tert\text{-}Bu;\ R^1 = CF_2CF_2CF_3$

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[14] J. Briggs, F. A. Hart, G. P. Moss, and E. W. Randall, *Chem. Commun.*, 364 (1971); H. J. Reich, M. Christl, and J. D. Roberts *J. Amer. Chem. Soc.*, **93**, 3463 (1971).
[15] G. M. Whitesides and D. W. Lewis, *ibid.*, **92**, 6979 (1970).
[16] T. Shigematsu, M. Matsui, and K. Utsunomiya, *Bull. Chem. Soc. Jap.*, **42**, 1278 (1969).
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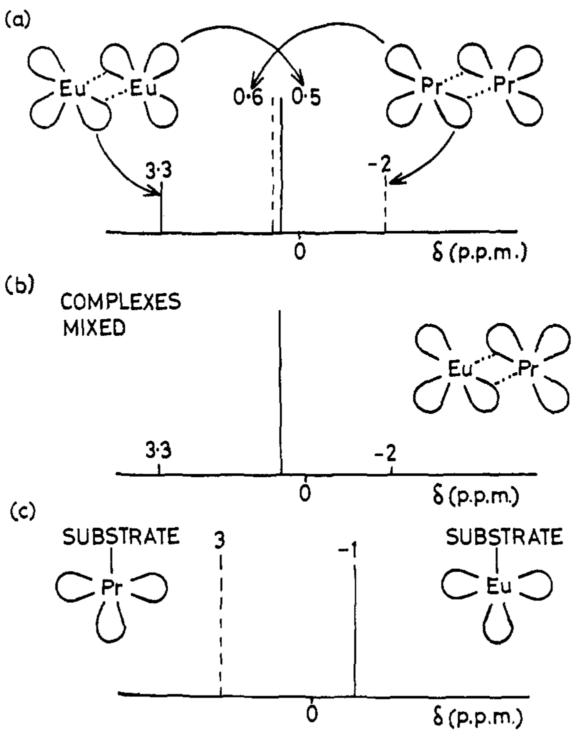

Figure 1. Schematic representation of the spectra of (a) separate solutions of **1** and its Pr analog in dry CCl_4 solution, (b) the mixed solution, and (c) the solution in the presence of excess substrate.

reported the use of the closely related Eu(FOD)$_3$ (**3**).[18] Although **2** is less effective as a shift reagent than either **1** or **3**, the causes of its disadvantages are instructive and some of its properties are discussed here.

Finally, we describe the use of lanthanide nitrates as shift reagents and discuss some properties of the adducts formed with both classes of shift reagent.

Results and Discussion

I. Dimerization of Ln(DPM)$_3$. In connection with our work on equilibrium constants (see section IV), it seemed that the shift of the *tert*-butyl resonance of the shift reagent which occurs on addition of a substrate, as reported by us previously,[19] could be usefully studied in more detail. We find, however, that rigorous drying of the carbon tetrachloride solvent (preheated 4A molecular sieves), the shift reagent (*in vacuo* over P_2O_5 for several days) and the nmr tube (110° for 24 hr) leads to a more complex spectrum than previously reported. **1** gives two important peaks, of somewhat variable relative intensity at δ *ca.* 0.5 (the major peak) and *ca.* 3.3, the exact positions of both resonances being sensitive (*ca.* ± 0.2 ppm in the range 0.003–0.03 M) to concentration.[20] Addition of traces of water or other polar substrates to the solution causes the resonances to move upfield. Further substrate addition causes coalescence of the two resonances, and the resulting single peak shifts to between δ -0.5 and -1.3, depending on the substrate.[21] Plots of the shifts of the individual peaks *vs.* added substrate yield kinked lines, but plots of the weighted average positions *vs.* added substrate yield smooth curves as expected (see section II). In addition, the integrated intensity of the single peak in the presence of substrate is that calculated and is equal to the sum of the intensities of the two peaks in the absence of substrate. We conclude, therefore, that no decomposition has occurred, in contrast to the report of Bhacca, *et al.*[21]

Entirely analogous results, depicted schematically in Figure 1, are obtained for Pr(DPM)$_3$, the resonances being at δ *ca.* 0.6 (major) and *ca.* -2 (minor). A mixed equimolar solution of **1** and Pr(DPM)$_3$ shows coalescence of the major peaks to a midway position, but the outer peaks at δ 3.3 and -2 are still visible in greatly reduced intensity, while addition of a substrate to this mixture yields the two peaks characteristic of complexed Eu(DPM)$_3$ and Pr(DPM)$_3$.

Pr(DPM)$_3$ is known[22] to be dimeric in the solid state with four terminal DPM ligands and two bridging ligands, the metal ions being seven coordinate. It seems reasonable, therefore, to interpret the results presented here in terms of such a dimer persisting in dry solution, exchange between the terminal and bridging positions being slow. The *tert*-butyl groups of the bridging ligands form two nonequivalent groups but only a slight oscillation is required to bring about their equivalence. Such a model predicts a ratio of 2:1 for terminal:bridging *tert*-butyl resonances and we therefore assign the δ *ca.* 0.5 resonance to the terminal ligands. The mixed Pr–Eu experiment indicates rapid exchange of environments of the terminal ligands, *i.e.*, $k > 2\pi\nu_{sep}$ sec^{-1}, where here $\nu_{sep} \leqslant 10$ Hz, but slow exchange of the bridging ligands, *i.e.*, $k < 2\pi500$ sec^{-1}. Alternatively, all exchange rates may be essentially the same, in the range $2\pi10 < k < 2\pi500$, and this is perhaps the best explanation for the relative intensity variation: if the resonance of the, presumably symmetrical, monomer is close to δ 0, then coalescence could occur with respect to the terminal ligands but not with respect to the bridging ligands,[23] making the relative intensities critically dependent on concentration or traces of substrate and water. For the mixed metal experiment, the major species present is presumably Pr(DPM)$_3$·Eu(DPM)$_3$ and the resonance position of the bridging ligands is coincident with those of the terminal ligands (see X-ray data[22] for appropriate geometry of the dimers). This coincidence leads to a spectrum of three resonances, of predicted intensities 1:10:1. The signal to noise ratio on our spectra is too small to allow accurate measurements but the results are not inconsistent with these predicted ratios.

Several compounds of formula Ln(β diketone)$_3$ are known to be partly or wholly dimeric in nonpolar solvents,[24] although one report has claimed that Ln(DPM)$_3$ complexes are monomeric in *n*-hexane.[25] We

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

[19] D. R. Crump, J. K. M. Sanders, and D. H. Williams, *Tetrahedron Lett.*, 4419 (1970).

[20] A peak from δ -2 to -2.5 is also seen, perhaps due to the vinyl proton, but the signal to noise ratio is too poor to estimate its relative intensity accurately.

[21] N. Ahmad, N. S. Bhacca, J. Selbin, and J. D. Wander, *J. Amer. Chem. Soc.*, **93**, 2564 (1971).

[22] (a) C. S. Erasmus and J. C. A. Boeyens, *Acta Crystallogr., Sect. B*, **26**, 1843 (1970). (b) Since submission of this manuscript, further support for the persistence of dimers in solution has been provided by electronic spectral data and magnetic susceptibility measurements: M. K. Archer, D. S. Fell, and R. W. Jotham, *Inorg. Nucl. Chem. Lett.*, **7**, 1135 (1971).

[23] Differential coalescences of this type are not unknown: F.-H. Marquardt, *J. Chem. Soc. B*, 366 (1971).

[24] N. Philipescu, C. R. Hart, and N. McAvoy, *J. Inorg. Nucl. Chem.*, **28**, 1753 (1966).

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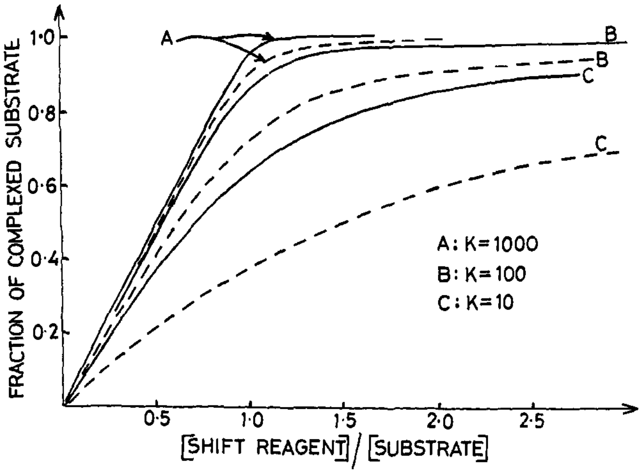


Figure 2. Behavior of substrates forming 1:1 adducts, as predicted by eq 3. Fraction of substrate complexed is $[A]/[S]$ and molar ratio is $[E]/[S]$. Solid lines represent 0.5 M substrate and broken lines represent 0.1 M substrate.

believe that the evidence presented here strongly indicates at least a partly dimeric nature for these compounds in CCl_4, but clearly further investigation is necessary. Indeed, it would seem that nmr studies could be very usefully employed in investigations of the dimeric nature of other β diketonates, but the relevant point for this investigation is that the behavior of the *tert*-butyl resonances is too complex to allow application of the equilibrium constants methods of section IV and is therefore not discussed further.

II. Behavior of Monofunctional Substrates. It is obvious that a rapidly exchanging adduct is being formed, but the stoichiometry of this adduct has not been determined to date. We give here a simple description of the behavior of various n:1 adducts and show that for **1** the best fit to the data is obtained for the 1:1 case.

1:1 Adduct. In this case, $n = 1$ in eq 1. Let the

$$n[\text{substrate}] + [\text{shift reagent}] \overset{K}{\rightleftharpoons} [\text{adduct}] \qquad (1)$$

initial concentration of substrate be S, the concentration of added shift reagent be E,[26] and the concentration of adduct formed be A. We may therefore write eq 2,

$$K = A/[S - A][E - A] \qquad (2)$$

which is readily rearranged to the well-known eq 3.[27]

$$E = A + A/K[S - A] \qquad (3)$$

Figure 2 shows the predicted behavior of 1:1 adducts obeying eq 3 for various values of K and S, and Figure 3 shows the $Eu(DPM)_3$-induced shifts of the methyl group of 2-methyladamantan-2-ol (**4**) in CCl_4 solution. The agreement is clearly very good, apart from the initial "lag" which is clearest in the most dilute case and which we believe is due to residual water in the solvent. Similar shapes for induced shifts have been observed for other alcohols and ketones with **1**,[28,29] and also for ethyl propionate with **3**.[18]

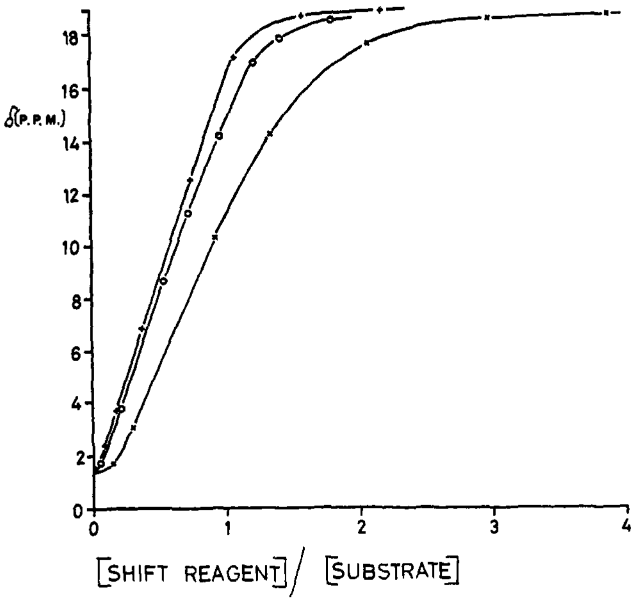
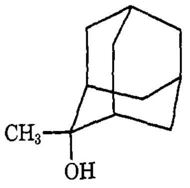


Figure 3. Shifts induced in the methyl group of **4** on addition of **1**. Concentrations of **4** are 0.024, 0.061, and 0.084 M in CCl_4 solution. The more concentrated solutions give the larger shifts.



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To date, most publications on shift reagents have used the gradients (either labeled G or Δ ppm/mol of shift reagent/mole of substrate; throughout this paper, as in our other work, we use G) of the initial straight line sections of Figure 2 to characterize the interaction and it is worthwhile, therefore, to attempt to relate these numbers to genuine physical parameters. Differentiation of eq 3 yields eq 4 and hence, by rearrangement,

$$\frac{\mathrm{d}E}{\mathrm{d}A} = 1 + \frac{1}{K[S - A]} + \frac{A}{K[S - A]^2} \qquad (4)$$

eq 5. For small values of A (due to low values of E),

$$\frac{\mathrm{d}E}{\mathrm{d}A} = \frac{K[S - A]^2 + S}{K[S - A]^2} \qquad (5)$$

$S - A \simeq S$. Substituting this into eq 5 and inverting give us eq 6, which together with eq 7 (where Δ_{lim} is

$$\mathrm{d}A/\mathrm{d}E = KS/(KS + 1) \qquad (6)$$

$$\mathrm{d}A/\mathrm{d}E = G/\Delta_{\text{lim}} \qquad (7)$$

the limiting shift of the adduct, $\delta_{\text{adduct}} - \delta_{\text{substrate}}$) enables the gradient to be related to simple physical quantities (since $\Delta_{\text{obsd}} = A\Delta_{\text{lim}}/S$).

For large values of K, $\mathrm{d}A/\mathrm{d}E$ is approximately equal to unity and the gradient G is very nearly equal to the

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[26] We are here ignoring the proposed dimerization $2Eu(DPM)_3 \rightleftharpoons [Eu(DPM)_3]_2$ (K_D), but calculations show that even for $K_D = 10^3$ there is no significant change in the shape of predicted curves except at high shift reagent concentrations.

[27] D. R. Eaton, *Can. J. Chem.*, **47**, 2645 (1969); D. R. Eaton, H. O. Ohorodnyk, and L. Seville, *ibid.*, **49**, 1218 (1971).

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

[29] M. Yoshimoto, T. Hiroaka, H. Kuwano, and Y. Kishida, *Chem. Pharm. Bull.*, **19**, 849 (1971).

limiting shift in parts per million. Comparison of eq 5 and 6 shows that for normal values of K and S (see section IV) the error in the simplified equation is theoretically only 1% after addition of 0.1 molar equiv of shift reagent and 10% with 0.5 equiv. In practice, initial gradients are slightly smaller (up to 10%) than those anticipated from the limiting shifts (see section IV). Both Figure 2 and eq 6 clearly predict the decreased shifts known to occur in more dilute solution.[3,4,29]

2:1 Adduct. Here $n = 2$ in eq 1 and hence eq 8

$$E = A + A/K[S - 2A]^2 \tag{8}$$

is operative. As we shall see, this case has some relevance also. Plots of eq 8 are similar to Figure 2 except that the scale of the horizontal axis is expanded by a factor of 2, *i.e.*, maximum curvature occurs at a molar ratio of 0.5. The concentration dependence is also more marked than in the 1:1 case, as is clear from the gradient expression: differentiation of eq 8, followed by the same manipulations as previously yields eq 9.

$$\mathrm{d}A/\mathrm{d}E = KS^2/(KS^2 + 1) \tag{9}$$

***n*:1 Adduct.** Clearly eq 8 and 9 can be generalized to eq 10 and 11.

$$E = A + A/K[S - nA]^n \tag{10}$$

$$\mathrm{d}A/\mathrm{d}E = KS^n/(KS^n + 1) \tag{11}$$

However, **1** undoubtedly forms 1:1 adducts. That the initial lag is not due to another adduct species such as a 2:1 adduct is clearly seen from its decrease with increasing concentration of substrate (Figure 3 and Yoshimoto, *et al.*[29]) and its greater magnitude in CCl_4 which has not been rigorously dried. As we shall see, the lag can be explained by a larger equilibrium constant for water binding than for substrate binding. The lack of evidence for 2:1 adducts is perhaps surprising as the adducts isolated or inferred from solvent extraction studies are normally 2:1 for most Ln(β-diketone)$_3$,[7,17,30–32] although a 1:1 adduct with pyridine has been isolated.[33] These adducts are usually isolated from a vast excess of substrate (usually acting as solvent) and the solvent extraction is carried out with radioactive isotopes at the parts per million level, so it is hardly surprising that the highest possible adduct content is frequently observed. Monohydrates are known for Ln(DPM)$_3$ and other β-diketonates so our findings are not, therefore, altogether without precedent.[18,22,34] We shall see in section V that there is evidence for both 1:1 and 2:1 adducts with **2**.

It is important to reiterate a point made by Raftery, *et al.*,[35] that all we can tell from rapidly exchanging spectra is that *on average* a 1:1 adduct, or set of 1:1 adducts, is being formed and that it may be difficult to detect the presence of more than one adduct species. Nevertheless, a recent conformational analysis of bicyclo[3.3.1]nonan-3-one *via* **1**-induced shifts does seem to indicate the presence of two conformers.[36]

III. Substrate Mixtures and Bifunctional Substrates. The preceding analysis lays the ground for an approach to bifunctional substrates. Dahlquist and Raftery[37] have given methods for the determination of equilibrium constants in such a competing system where the substrate is always in excess, but the following gives a description over all shift reagent concentration ranges. We define the equilibria in eq 12 and 13 and assume

$$[\text{substrate A}] + [\text{shift reagent}] \overset{K_A}{\rightleftharpoons} [\text{adduct A}] \tag{12}$$

$$[\text{substrate B}] + [\text{shift reagent}] \overset{K_B}{\rightleftharpoons} [\text{adduct B}] \tag{13}$$

that there is no interaction between the potential coordination sites, each forming a 1:1 adduct with the shift reagent. Initial substrate concentrations are S_A and S_B, respectively, the concentrations of adducts formed are A and B, the total concentration of added shift reagent is E, and the concentration of free shift reagent is E_F, giving us eq 14 and 15.[26] Eliminating E_F from eq

$$K_A = A/E_F[S_A - A] \tag{14}$$

$$K_B = B/E_F[S_B - B] \tag{15}$$

14 and 15 gives us eq 16 which can be simplified for a bi-

$$K_B/K_A = B[S_A - A]/A[S_B - B] \tag{16}$$

functional compound ($S_A = S_B$) in the presence of only a little shift reagent to eq 17. This predicts that the

$$K_B/K_A = B/A \tag{17}$$

ratio of the *initial* gradients (in dimensionless $\mathrm{d}A/\mathrm{d}E$ or $\mathrm{d}B/\mathrm{d}E$, not parts per million!) is equal to the ratio of the equilibrium constants. Clearly, if $K_B \neq K_A$ then $[S - A]$ will change at a different rate from $[S - B]$ as a shift reagent is added, and changes in proton shift ratios are expected. We return to this point presently.

The total shift reagent concentration E is given by eq 18 which can be expanded into a more tractable

$$E = A + B + E_F \tag{18}$$

form: eq 16 is rearranged to eq 19 and E_F is found from

$$B = \frac{S_B A}{A + K_A[S_A - A]/K_B} \tag{19}$$

eq 14. These are then substituted into eq 18 to give eq 20 and, by symmetry, eq 21. These equations (which

$$E = A\left[1 + \frac{1}{K_A[S_A - A]} + \frac{S_B}{A + K_A[S_A - A]/K_B}\right] \tag{20}$$

$$E = B\left[1 + \frac{1}{K_B[S_B - B]} + \frac{S_A}{B + K_B[S_B - B]/K_A}\right] \tag{21}$$

simplify correctly to eq 3 for either K_B or S_B or both being put equal to zero) provide complete descriptions

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(30) F. Halverson, J. S. Brinen, and J. R. Leto, *J. Chem. Phys.*, **41**, 157 (1964).

(31) R. G. Charles and R. C. Ohlmann, *J. Inorg. Nucl. Chem.*, 27, 119 (1965).

(32) L. R. Melby, N. J. Rose, E. Abramson, and J. C. Caris, *J. Amer. Chem. Soc.*, **86**, 5117 (1964).

(33) J. Selbin, N. Ahmad, and N. S. Bhacca, *Inorg. Chem.*, **10**, 1383 (1971).

(34) R. G. Charles and A. Perrotto, *J. Inorg. Nucl. Chem.*, **26**, 373 (1964).

(35) M. A. Raftery, F. W. Dahlquist, S. I. Chan, and S. M. Parsons, *J. Biol. Chem.*, 243, 10 (1968).

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(37) F. W. Dahlquist and M. A. Raftery, *Biochemistry*, 7, 3269 (1968).

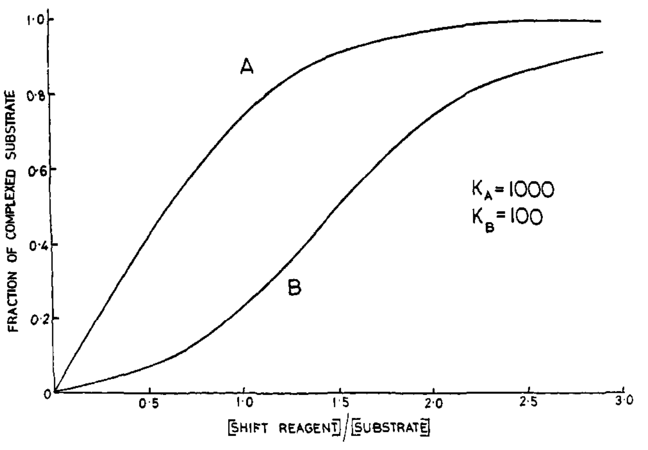
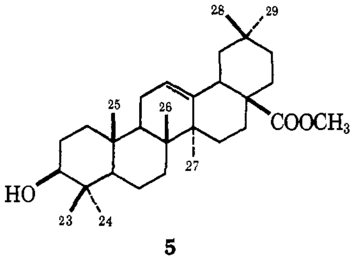


Figure 4. Behavior of a 0.1 *M* bifunctional substrate as predicted by eq 20 and 21 for 1:1 adduct formation at each site.

of coordination behavior, and Figure 4 shows the behavior predicted by them for a 0.1 *M* bifunctional substrate with $K_A = 1000$ and $K_B = 100$. At low shift reagent concentrations coordination occurs 90% at the more active site (A), but as the effective concentration of uncoordinated A decreases, coordination occurs increasingly at the less active site. This is intuitively obvious and is also clearly seen in eq 16.

Figure 5 shows the effect of adding **1** to a CCl_4 solution of methyl oleanolate (**5**), only the shifts of the methyl resonances being plotted. The theoretical predictions of Figure 4, where K_A and K_B were carefully chosen to be realistic on the basis of the results of section IV, are strikingly borne out by the behavior of the 23 and 24 methyls and the ester methoxyl resonance.



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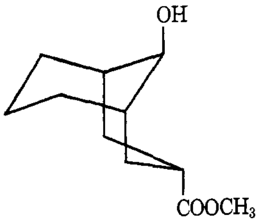

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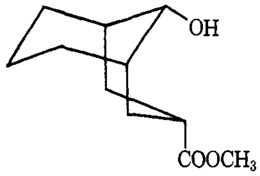

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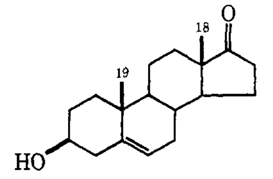

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At relatively low concentrations of $Eu(DPM)_3$, complexing occurs largely at the more strongly associating 3β-hydroxyl group, and at higher concentrations this site becomes effectively saturated, and association at the ester group becomes more important. The 23 and 24 methyl groups are such a distance from the ester group as to be almost unaffected by coordination at that site, and similarly the ester methyl is almost unaffected by coordination at the hydroxyl group. The behavior of methyls 25, 26, and 27 is intermediate between these extremes and to an extent which enables assignments to be confidently made.

The bicyclo[3.3.1]nonane derivatives **6** and **7** behave very similarly, but for **7** especially the compact shape of the molecule and the proximity of functional groups are such that each proton is affected by coordination at either site, and the correspondence with Figure 3 is superficially less convincing. Details of these compounds are described elsewhere.[38] The 18 and 19 methyl resonances of the androstenolone (**8**) also show a change in relative coordination: G_{18} increases as G_{19} decreases at high concentrations of **1**, but to a far less marked degree as the equilibrium constant differences are smaller than in the cases of **5**–**7**. The phenomenon of proton shift ratios being dependent on shift reagent concentrations should be a general one seen whenever $K_A \neq K_B$ but only two cases have been reported in the literature: the interactions of enantiomeric bases with the asymmetric chelate have different equilibrium constants,[15] and the axial and equatorial amino groups of the bis(4-aminocyclohexyl)methane (**9**) interact selectively with **1**,[39] but in neither case is the effect very marked.

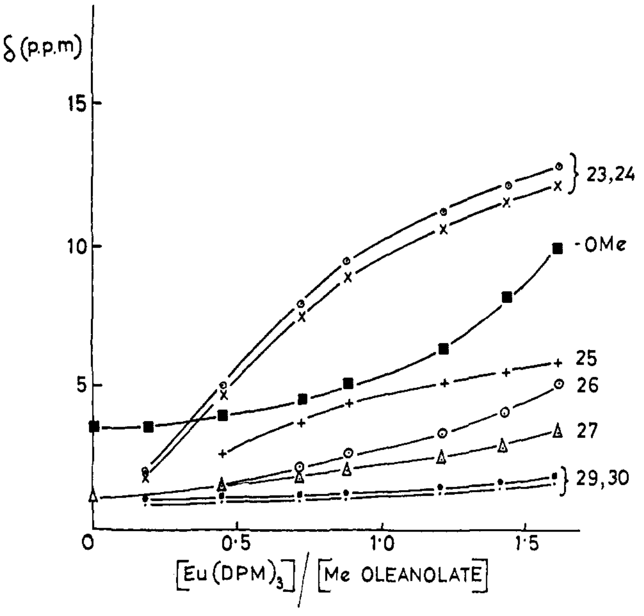
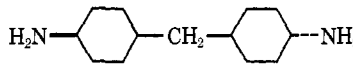


Figure 5. Shifts induced by the addition of **1** to methyl oleanolate (*ca.* 0.09 *M* in CCl_4 solution). Only the shifts of methyl groups are plotted.



9

Further valuable information can be obtained by differentiation of eq 20 to give eq 22, which after the usual simplifying assumptions and inversion gives eq 23 and 24.

$$\frac{dE}{dA} = 1 + \frac{1}{K_A[S_A - A]} + \frac{A}{K_A[S_A - A]^2} + \frac{S_B}{A + K_B[S_A - A]/K_A} + \frac{AS_B[1 + K_A/K_B]}{\{A + K_B[S_A - A]/K_A\}^2} \tag{22}$$

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(38) Synthesis and structure proof: I. Fleming and S. W. Hanson, to be submitted for publication; conformation and effects of $Eu(DPM)_3$: I. Fleming, S. W. Hanson, and J. K. M. Sanders, *Tetrahedron Lett.*, 3733 (1971).

(39) H. van Brederode and W. G. B. Huysmans, *ibid.*, 1695 (1971).

therefore simplifying assuming $A \simeq 0$

$$\frac{dE}{dA} = \frac{K_A S_A/K_B + 1/K_B + S_B}{K_A S_A/K_B}$$

$$\frac{dA}{dE} = \frac{K_A S_A}{K_A S_A + 1 + K_B S_B} \qquad (23)$$

and, by symmetry

$$\frac{dB}{dE} = \frac{K_B S_B}{K_A S_A + 1 + K_B S_B} \qquad (24)$$

Equation 23 simplifies correctly to eq 6 in the case of K_B or S_B or both equal to zero.

In a system of x substrates, each of concentration S_j and equilibrium constant (for a 1:1 adduct) K_j, the behavior of the ith site is given by eq 25, which is the generalized form of eq 20.

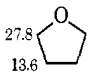
$$E = \frac{A_i}{K_i[S_i - A_i]} + \sum_{j=1}^{x} \frac{S_j A_i}{A_i + K_i[S_i - A_i]/K_j} \qquad (25)$$

Differentiation and simplification as before give eq 26.

$$\frac{dA_i}{dE} = \frac{K_i S_i}{1 + \sum_{j=1}^{x} K_j S_j} \qquad (26)$$

Equations 23 and 26 clearly give us a powerful method for the determination of equilibrium constants *via* competition experiments (see section IV).

The remaining problem associated with the analysis of bifunctional substrates is that of separating observed shifts into separate contributions due to coordination at each site, and no general solution appears to be available as yet. Hinckley, *et al.*,[7] have suggested a graphical method which yields relative equilibrium constants but which is only applicable when the coordination sites are distant from each other. The method which we describe now requires a knowledge of relative equilibrium constants (*via* suitable selective derivatization of the substrate if necessary), but its efficiency is independent of the relative positions of the coordination sites. The data required for the description of this method are shown with compounds **10–17**, values for G being determined by us for 0.5 *M* substrates in CCl_4 (unbracketed) or in $CDCl_3$ (bracketed). Many of the $CDCl_3$ values are from Hart and Love[40] and were determined at an unspecified concentration.



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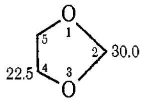

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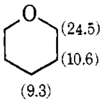

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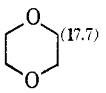
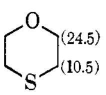
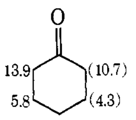


13[40]



14[40]



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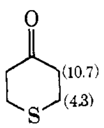
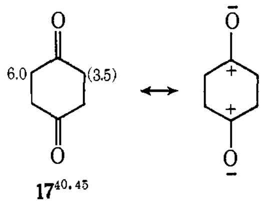


16[40, 41]



17[40, 45]

The decrease in dA/dE for one substrate in the presence of another is given by comparison of eq 6 and 23, but in the present examples $K_A = K_B$ and $S_A = S_B$, so that to an approximation which is at least as good as the experimental data we can say that dA/dE for each site in **11** and **13** is 50% of the dA/dE in the absence of the competing site (**10** and **12**). We can therefore predict that the G value contribution of oxygen 1 in **11** to the protons of C_2 is 50% of 27.8 ppm and similarly for the oxygen 2 contribution, giving a total of 27.8 ppm (found 30.0 ppm). Similarly, the predicted $G(H_4)$ is $^1/_2(27.8 + 13.6) = 20.7$ ppm (found 22.5 ppm). Although the absolute magnitudes here are in error, the ratio $[G(H_2)/G(H_4)]$ is 1.33 in both the calculated and experimental cases indicating experimental error, not a breakdown in the analysis. From the results of **12**, we predict G for **13** to be $^1/_2(24.5 + 10.6) = 17.6$ ppm, in excellent agreement with the experimental result of 17.7 ppm. Comparison of **12** and **14** or of **15** and **16** clearly shows the lack of interaction at sulfur.[40] Prediction of shifts in **17** from those of **15** yields 9.9 and 7.5 ppm for CCl_4 and $CDCl_3$ solutions, respectively, in both cases very much larger than observed (6.0 and 3.5 ppm). It is interesting to speculate whether the dipolar form of **17** is destabilized by juxtaposition of the positive centers to such an extent that the electron density of the carbonyl oxygens is less available for coordination: it seems unlikely that the change from the chair form of **15** to the twist boat of **17** would move the protons so much further from the Eu^{3+} ion. This form of analysis is unfortunately only applicable to heterobifunctional compounds when the relative equilibrium constants are known.

Comparison of Figures 4 and 5 and also the results presented in the previous paragraph indicate that the model of the independent behavior of potential coordination sites is likely to be of general occurrence except where interaction may occur (*e.g.*, **17**). We have been unable to resolve the data of Cockerill and Rackham for 1-(2-hydroxyethyl)adamantan-2-ol into separate contributions from each site for any relative values of K and can only conclude that the conformation of the side chain in the mono- and bifunctional compounds is different.[46] Their suggestion of magnetic field attenuation through a nucleus does, however, seem somewhat unlikely.

Hart and Love[40] have defined "relative shift powers" by means of an intermolecular competition experiment which we may write in the form of eq 27, S_A and S_B

$$\frac{\text{relative shift power of A}}{\text{relative shift power of B}} = \frac{G_A(\text{mixture})G_B(\text{pure})}{G_A(\text{pure})G_B(\text{mixture})} \qquad (27)$$

being equal. Substitution of values from eq 6, 23, and 24 gives eq 28, and therefore, to a good approxi-

$$\frac{\text{relative shift power of A}}{\text{relative shift power of B}} = \frac{K_A S + 1}{K_B S + 1} \qquad (28)$$

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[40] H. Hart and G. M. Love, *Tetrahedron Lett.*, 625 (1971).

[41] We have reversed the assignments of Hart and Love in **16** as it is know that thio ethers have only a very small affinity for **1**, G for $RCH_2SR \leq 1$ ppm.[42,43] This is a general phenomenon and arises from the class "a" character of the trivalent lanthanides.[44]

[42] D. R. Crump, J. K. M. Sanders, and D. H. Williams, *Tetrahedron Lett.*, 4949 (1970); unpublished results.

[43] J. E. Herz, V. M. Rodriguez, and P. Joseph-Nathan, *ibid.*, 2949 (1971).

[44] S. Ahrland, J. Chatt, and N. R. Davis, *Quart. Rev., Chem. Soc.*, 12, 265 (1958).

[45] The "CCl_4" value was in fact obtained in 0.4 ml of CCl_4 plus two drops of $CHCl_3$ to improve solubility.

[46] A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149, 5153 (1970).

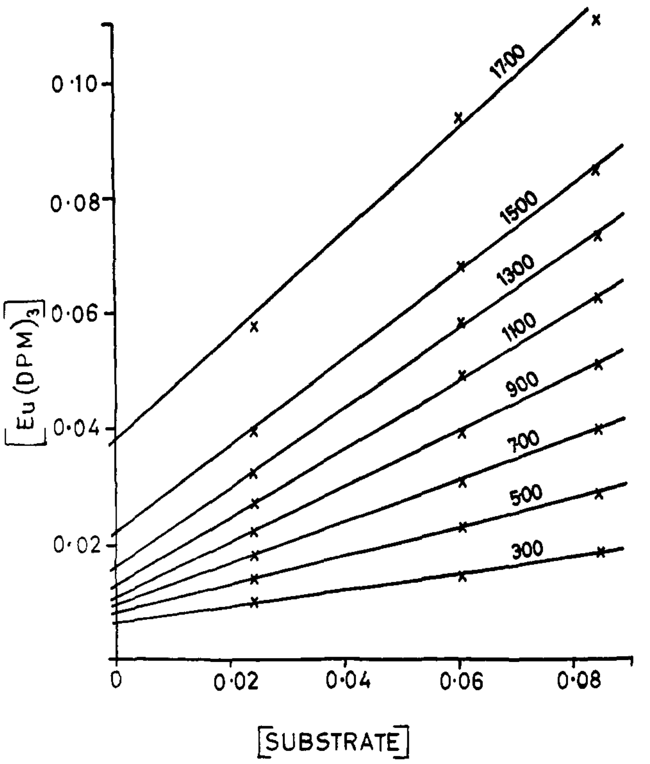

Figure 6. Plots of E *vs.* S for given values of Δ, taken from the data of Figure 3, as suggested by eq 29. For clarity only odd multiples of $\Delta = 1$ ppm are shown, but all the points are used in Figure 7.

mation, the relative shift powers do correlate with relative equilibrium constants. In the following section we develop the intermolecular experiment a little further for the purposes of equilibrium constant determination.

IV. Determination of Equilibrium Constants. In a situation where only a 1:1 adduct is formed then the reverse addition method of Raftery, *et al.*,[35] is excellent, yielding accurate values for K and Δ_{lim} simultaneously. Alternatively, eq 3 shows that plots of E/A *vs.* $1/[S - A]$ yield a straight line of slope $1/K$, where $A = S\Delta_{obsd}/\Delta_{lim}$. This latter method is especially suited to a computer treatment which varies Δ_{lim} systematically until a "best" straight line is obtained. Sykes has also described a computer based method.[47] One may also readily derive graphical methods based on dilution experiments, once again a knowledge of Δ_{lim} being required.

None of these methods, however, are capable of dealing with the complication present in this investigation, *i.e.*, the presence of traces of water. The equilibrium constant for water is apparently so much larger than that for the usual organic substrates that effectively all the initial addition of **1** is taken up by the water, giving shift plots which are an exaggerated form of Figure 4. We make the approximation that the observed G for the substrate is not significantly altered by the presence of the traces of $Eu(DPM)_3 \cdot H_2O$ so that in fact we see substantially the predictive plots of Figure 1 but displaced a little. We have chosen the methyladamantanol (**4**) as a standard because it is readily available, highly crystalline, stereochemically rigid, and CCl_4 soluble, and possesses a methyl group giving a good sharp signal with a large G of 16–19 ppm.

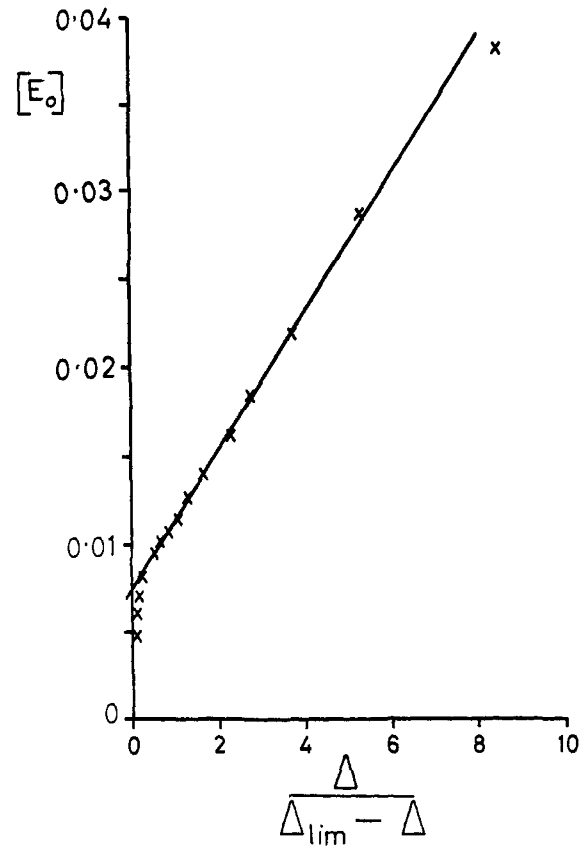

Figure 7. Plots of E_0 *vs.* $\Delta/(\Delta_{lim} - \Delta)$ from the data of Figure 6 (see eq 29).

Now, $A/S = \Delta/\Delta_{lim}$ where Δ is the induced shift, $\delta_{obsd} - \delta_{substrate}$. Substituting this equation into eq 3 gives eq 29. E_w is the shift reagent taken up by water,

$$E = E_w + E_E = \frac{S\Delta}{\Delta_{lim}} + \frac{\Delta}{K(\Delta_{lim} - \Delta)} + E_w \qquad (29)$$

and E_E is the effective shift reagent concentration. We then carry out a series of shift reagent additions to various concentrations of substrate, as shown in Figure 3, and for a series of fixed Δ's we plot E *vs.* S; this is shown in Figure 6. The slopes of the lines are Δ/Δ_{lim} and hence we determine Δ_{lim} to be 19.0 ± 0.5 ppm. The intercepts on the y axis, labeled E_0, are then plotted against their values of $\Delta/(\Delta_{lim} - \Delta)$ (see Figure 7). The slope of the straight line obtained is $1/K$, and in the absence of any water, the line should pass through the origin. The value of the intercept, 0.007 mol/l., is E_w. This is in good agreement with the estimated value obtained from a plot of the Raftery[35] type: the slope should be $E\Delta_{lim}$ and only gives reasonable values of Δ_{lim} when E is reduced by 0.007–0.01 mol/l.

The value of K obtained from Figure 7 for **4** is 250 l. mol^{-1} but in view of the uncertainties in this method we feel that the best estimate at this stage would be 250 ± 50.

We have used the value of $K = 250 \pm 50$ in competition experiments to determine equilibrium constants for other substrates *via* eq 23. It is necessary to monitor only the shift of the methyl group of **4** in the presence of known concentrations of the substrate under study, which can be an advantage with substrates of unknown structure. By this method we obtain the

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(47) B. D. Sykes, *Biochemistry*, **8**, 1110 (1969).

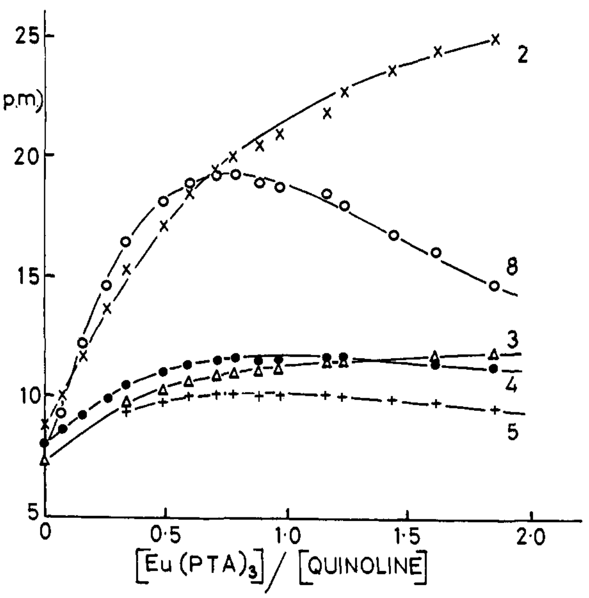
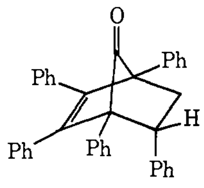


Figure 8. The effect of adding **2** to quinoline, *ca.* 0.19 *M* in CCl_4 solution.

following *estimates of K*: unhindered primary and secondary alcohols, 500–1000; cyclohexanone, 180–250; methyl pivalate 100–150; ketone **18**, 0. The effect of steric hindrance is very clearly demonstrated by the ketone **18** which is quite inert to **1**.



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We do not feel justified in claiming or seeking greater accuracy of *K* values, partly for reasons outlined at the beginning of this paper and partly due to the lack of certainty in true physical meaning of such quantities: there is likely to be a good deal of solvation of the substrate and also of the shift reagent in halogenated solvents.[48] Indeed, from the known[3] solvent dependence of shifts one can calculate a *K* of 2–4 for a 1:1 adduct of $CDCl_3$ and **1**. Such a number, however, is probably too small to represent a genuine adduct with discrete correlation times and the observed *K* is fictitious.[49]

In the case of genuine substrates, the range of observed *K*'s correspond to ΔG values from -2.5 to -4 kcal/mol, which are large enough to give some confidence in the formulation of the interaction as real adduct formation rather than a vague solvation of the shift reagent. It seems reasonable, therefore, to derive distance and angular information from shift data subject to the calculations of Eaton who showed that fairly large deviations on either side of the calculated values must be taken into account.[27] We can readily calculate an upper limit to the lifetime of the adduct, which is given by $1/2\pi\Delta_{\text{lim}}$, where Δ_{lim} is in hertz. The largest reported *G* values, which are approximately equal to Δ_{lim}, are 260–500 ppm/mol, for the RNH_2–$Yb(DPM)_3$ system.[5] This corresponds to an upper limit of 3–6 $\times$ 10^{-6} sec for the adduct lifetime.

V. **Eu(PTA)$_3$ (2).** This compound has many of the properties of the recently described Eu(FOD)$_3$ (**3**),[18] *i.e.*, it is a yellow crystalline solid rapidly taking up water to become a white hydrate, and is very much more soluble than **1**, and gives a 1:1 adduct with ethyl propionate. With alcohols, **2** definitely gives a 2:1 adduct following eq 8, and the results obtained with 1-tetradecanol in CCl_4 solution are compared with those obtained for **1** and alcohols in Table I. The striking thing about these results is that although the relative positions of the Eu^{3+} ion and the alcohol backbone are clearly identical within experimental error, the limiting shifts induced by **2** are only one-third of those induced by **1**. This result is undoubtedly due to a reduced magnetic anisotropy of the Eu^{3+} ion in the $Eu(PTA)_3$–2ROH adduct as compared to the $Eu(DPM)_3$–ROH adduct. This result is perhaps not surprising as the anisotropy is known to be critically dependent on ligand geometry.[50]

Table I. Effects of Adding **1** and **2** to a CCl_4 Solution of 1-Tetradecanol

Proton	H_1	H_2	H_3	H_4	H_5	H_6
Relative shift induced by $Eu(DPM)_3$	1	0.60	0.42	0.20	0.14	0.08
Relative shift induced by $Eu(PTA)_3$	1	0.62	0.41	0.20	0.12	
Δ_{lim} induced by $Eu(PTA)_3$ (ppm)	9.30	5.85	3.80	1.85	1.1	
Approximate Δ_{lim} induced[a] by $Eu(DPM)_3$	26	15.6	11	5.2	3.6	2

[a] $\Delta_{\text{lim}} \simeq G$ for 1:1 adduct and large *K*.

Close examination of the spectra just discussed (**2** + 1-tetradecanol) reveals that having reached their limiting shifts, the H_1, H_3, H_4, and H_6 resonances drift slowly to higher field on addition of further **2**, *i.e.*, Δ decreases, while the H_2 resonance is stationary and the H_5 resonance continues downfield. The correct explanation is not clear in this case. The action of **2** upon quinoline, shown in Figure 8, is much clearer. Measurements of the *initial* gradients and comparison with values of $(3\cos^2\phi - 1)r^{-3}$ taken from a scale drawing indicate that initially the Eu^{3+} ion is *ca.* 3.7 Å along the line of the nitrogen lone pair and *ca.* 0.3 Å displaced toward H_8.[51] The H_8 resonance rapidly reaches a maximum displacement at δ19.3 and then moves back toward the "normal" position. The H_4 and H_5 resonances behave similarly, as does the multiplet due to H_6 and H_7 which never resolves into separate signals. In contrast, the signals due to H_2 and H_3 continue to shift downfield. The geometry of the adduct is clearly changing with increasing shift reagent concentration in such a way that, on average, the Eu^{3+} ion is moving over toward H_2 and away from H_8. We tentatively interpret these results in terms of a stoichiometry change, the

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(48) For example, see J. P. Lorand, *Tetrahedron Lett.*, 2511 (1971), and references therein.

(49) E. M. Engler and P. Laszlo, *J. Amer. Chem. Soc.*, **93**, 1317 (1971).

(50) M. Gerloch and D. S. Mackay, *J. Chem. Soc. A*, 3372 (1971); W. de W. Horrocks and D. DeW. Hall, *Coord. Chem. Rev.*, **6**, 147 (1971).

(51) The shift ratios observed with **1** and quinoline, leading to a first-order spectrum,[3] are consistent with an N-Eu distance of *ca.* 4.1 Å and no significant displacement from the line of the lone pair.

2:1 adduct perhaps being replaced by a 1:1 adduct at high shift reagent concentrations.

Presumably, the greater Lewis acidity of these fluorinated reagents is the cause of the 2:1 adduct formation with substrates of high donor ability, but the stoichiometry changes associated with variations in molar ratio and leading to drastic shift ratio changes can be a distinct disadvantage, offsetting the advantage of high and rapid solubility. In no published examples, nor in any of our own analyzed spectra, have proton shift ratios induced by **1** changed to any great extent for monofunctional substrates ($< \pm 10\%$) with the concentration of **1**, although such a case has been found when using lanthanide nitrates as shift reagents (section VI).

VI. Lanthanide Nitrates as Shift Reagents. Triphenylphosphine oxide and related compounds give the expected downfield shifts with **1**, but as they are known to yield complexes with hydrated lanthanide salts in polar solvents,[52,53] we reasoned that $Eu(NO_3)_3 \cdot 6D_2O$ (**19**) and its Pr analog (**20**) might act as shift reagents for these compounds. We find that the stepwise addition of **19** to a *ca.* 0.2 *M* solution of tri(*m*-tolyl)arsine oxide in acetone-d_6 gives *upfield* shifts so that the complex multiplet at δ 7.4–7.7 becomes first order as shown in Figure 9. As expected,[52] triphenylphosphine oxide gives smaller shifts, but a spectrum which is amenable to a simple first-order analysis ($J_{\text{PH}_o} = 11.4 \pm 0.4$ Hz, $J_{\text{PH}_m} = 3.0 \pm 0.4$ Hz) is readily obtained.

Shifts due to $Eu(NO_3)_3 \cdot 6D_2O$ in CD_3OD as solvent are smaller than those in acetone, while in CD_3CN shifts are large but accompanied by an unidentified precipitate. Pyridine-d_5 as solvent gives very small shifts, but addition of some acetone-d_6 to the solution greatly increases the shifts. The dependence of the shift magnitude on the solvent is clearly a complex matter, perhaps related more to the solvent coordination power than its ionizing ability, acetone-d_6 being the preferred solvent. A systematic investigation of the effect of the anions present has not yet been carried out, although as we are using hydrated salts less dependence than that obtained by Birnbaum and Moeller with anhydrous salts might be expected.[54] We shall discuss in section VIII the reasons for the observation of upfield shifts rather than the downfield shifts of **1**.

Triaryl phosphines and phosphine sulfides are apparently inert, as expected,[52] showing no detectable shifts in the proton nmr spectra. In addition, the noise decoupled ^{31}P resonance of triphenylphosphine neither broadens nor shifts relative to the deuterium solvent signal (which itself shifts by only a few cycles) of our XL-100 instrument, a criterion not available in our earlier ^{31}P work.[55] A more widely available criterion for demonstrating the lack of substrate coordination is to use the Gd^{3+} analog as we have pointed out earlier.[55,56]

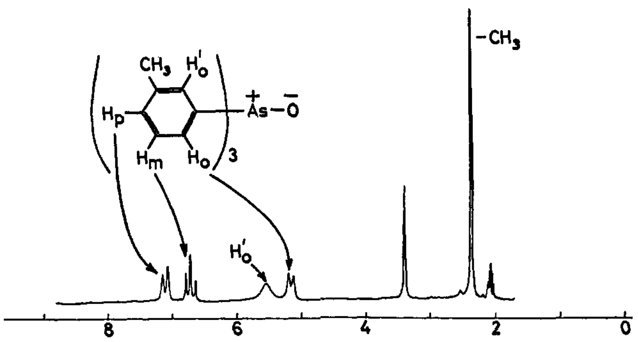
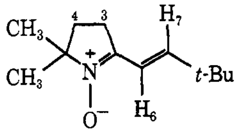


Figure 9. 100-MHz ^1H nmr spectrum of tri(*m*-tolyl)arsine oxide, *ca.* 0.2 *M* in acetone-d_6, after the addition of 0.31 mol of $Eu(NO_3)_3 \cdot 6D_2O$.

Phosphates and phosphonates also complex, yielding upfield shifts, as previously reported,[55,56] and appear to yield 2:1 complexes as the major adduct in acetone, but 1:1 adducts in water. The main interest in these adducts is the large contact shift seen in the ^{31}P spectra and we return to this aspect in section VII. Nitrones such as **21** coordinate at the oxygen atom to give interesting results.[57] On addition of **19** all proton resonances move upfield as normal apart from the *tert*-butyl resonance which moves downfield. This is due to an angular variable effect and is discussed in section VIII. More puzzling is the difference in behavior between the adduct with **19** and that with **20**: for **19**, the initial $G(H_6)/G(CH_3)$ is *ca.* 10 while for **20** the ratio is *ca.* 5, and on further additions of shift reagent the metal ions apparently move over, on average, toward the *gem*-dimethyl group, the $G(H_6)/G(Me)$ ratio smoothly falling to a value of 1.3 for both metal ions. The behavior of other resonances is less dramatic but is in general agreement with the proposed geometrical change. As with the phosphates, the general shape of the plots indicates a 2:1 adduct but the geometry change may well be indicative of some 3:1 adduct formation initially.



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Many carboxylate anions are known to complex with lanthanide ions in aqueous solution and some nmr effects have been studied,[58,59] but the potentialities in chemistry have not been pointed out. The normal relative chemical shifts of the triplet and quartet of sodium propionate (0.3 *M* in D_2O) are reversed by addition of an equimolar amount of **19**, now occurring at δ -1.35 (CH_2) and -0.77 (CH_3). Good initial straight lines are obtained *e.g.*, for **19**: $G(CH_2)$ =

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[52] D. R. Cousins and F. A. Hart, *J. Inorg. Nucl. Chem.*, **29**, 1745, 2965 (1967).

[53] These solutions are readily supersaturated to give good yields of crystals of one of the adducts of Cousins and Hart.[52] This would seem to be a convenient way of removing triphenylphosphine oxide from Wittig reaction mixtures, frequently a troublesome problem.

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

[55] J. K. M. Sanders and D. H. Williams, *Tetrahedron Lett.*, 2813 (1971).

[56] See also C. D. Barry, A. C. T. North, J. A. Glasel, R. J. P. Williams, and A. C. Xavier, *Nature (London)*, 232, 236 (1971), and references therein.

[57] The nitrones are colorless, as are acetone solutions of $Eu(NO_3)_3 \cdot 6D_2O$ (**19**), but mixtures are yellow, presumably due to lengthening of the chromophore onto the metal.

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

[59] J. Reuben and D. Fiat, *J. Chem. Phys.*, **51**, 4909 (1969), and references therein.

-6.0 and $G(CH_3) = -3.6$ ppm, and the general shape of the curve is that of a 2:1 adduct as expected.[60]

It is clear that lanthanide nitrates are of less general utility in organic chemistry than **1** and its related compounds, the potential probably being greatest in the case of polyfunctional compounds with only one $X-O^-$ group (or a readily oxidized X) so that there is effectively only one coordination site. In addition, the equilibria in solution are somewhat more complex than those of **1**. The potentialities in biochemical applications are however very large since Ln^{3+} ions can frequently act as substitute probes for Ca^{2+} in biological systems.[61]

VII. Shift Mechanism. There has been much discussion in the recent literature on the mechanism of $Eu(DPM)_3$ induced shifts, and in particular on the possibility of contact contributions to the shifts of resonances of protons near the coordinate site[7] (see also ref 18a in ref 3). It has been quite clearly shown that if the Eu^{3+} ion is correctly positioned then no significant contact contribution to either ^1H or ^{13}C nmr shifts need be invoked for alcohols at least (apart perhaps for hydroxyl protons).[14] Frequently the center of the metal ion is placed at the end of the oxygen lone pair or even at the oxygen nucleus for the purpose of calculation, but it is in reality normally at least 1.5 Å from the oxygen. A criterion which is satisfied by pseudocontact (PC) shifts is that a position can be found for the metal ion such that all shifts (^1H, ^{13}C, ^{31}P, etc.) can be fitted to eq 30, where ϕ is the X–Eu–O

$$\Delta H/H = K(3\cos^2\phi - 1)/r^3 \qquad (30)$$

angle and r is the Eu–X distance. The implication of this is that the shift ratio Eu/Pr is the same (for a given type of shift reagent and given substrate) for all nuclei unless the geometry of the adducts is different. The ratios of contact shifts (CS) for the various metals are very different from the pseudocontact ratio.[54,62] In the following example we show how contact and pseudocontact contributions may be readily separated.

Shown in Table II are some ^1H and ^{31}P results for the interaction between diethyl ethyl phosphonate and some lanthanide nitrates. Results for Pr and Eu have been given in more detail elsewhere.[55] The proton shift ratios are the same, within experimental error, for all three metal ions and we are confident therefore that only PC shifts are occurring for the proton shifts. The first row in Table II gives the G values for the CH_2 protons of the ethoxyl group, and the second row the ^1H PC shifts relative to Pr defined as 1.0. The relative PC shifts for ^{31}P will be in the same ratio as for the protons, the magnitudes being crudely estimated by distance measurements (Table II, line 4). Subtraction of the PC shift contribution from the observed shifts leaves only the contact shift contribution (Table II, line 5). The observed relative CS (Table II, line 6) are in close correspondence with those observed by Taube, *et al.*,[62] in ^{17}O spectra of the aquo ions, and with those calculated by Birnbaum and Moeller.[54]

Table II. Pseudocontact and Contact Contributions to ^{31}P Shifts in Diethyl Ethyl Phosphonate Induced by $Ln(NO_3)_3 \cdot 6D_2O$[a]

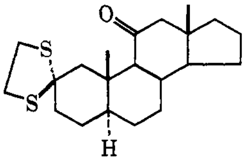
Ln^{3+}	Pr	Eu	Nd
$G(OCH_2) - {}^1H$, ppm	6.0	−2.2	3.2
Relative ^1H PC shift	1.0	−0.36	0.53
$G(^{31}P)$, ppm	285 ± 10	−470 ± 25	320 ± 5
Estimated ^{31}P PC shift, ppm	60 ± 15	−20 ± 5	33 ± 7
Estimated ^{31}P contact shift, ppm	225 ± 25	−450 ± 30	287 ± 12
Relative ^{31}P contact shift	1.0	−2.0 ± 0.3	1.3 ± 0.2
Taube contact shift	1.0	−2.37	1.13
Birnbaum and Moeller contact shift	1.0		1.18

[a] In order to maintain consistency with most recently published work, downfield shifts are positive, upfield shifts are negative.

Contact shifts are dependent on $g_{av}J(J+1)$ where J represents the Russell–Saunders state and g_{av} the average magnetic moment. Although the size of the anisotropy, $g_\parallel - g_\perp$, is very dependent on geometry, g_{av} is virtually geometry independent at room temperature,[50] and therefore the relative contact shifts at room temperature are expected to be the same for all lanthanide systems unless the nature of the bonding changes along the series. This point is borne out by the ^{14}N results of Wolkowski, *et al.*,[63] for $Ln(DPM)_3$ and amines, where the observed Yb/Eu ratio is almost exactly that expected for a contact shift.[62]

The rate of attenuation of CS for the lanthanides is very large indeed, probably several orders of magnitude per bond where only a σ-bond framework is available, but ^{13}C studies of carboxylates and the phosphonate are in hand to test this point.

VIII. Reversals of Shift Direction.[64] The pseudocontact shift equation, eq 30, predicts a reversal of the induced shift when ϕ becomes greater than 54.7°, and we were interested in synthesizing a molecule with assignable protons in that position. The methylene protons of the dithiolane group in the steroidal ketone **22** are in such an environment when coordination occurs at the 11-keto function, and addition of **1** to a $CDCl_3$ solution of **22** causes a small upfield shift of the complex multiplet due to these protons, $G = -0.25$ ppm. All other assignable resonances move downfield.



22

The nitrone **21** coordinates strongly to **1** in CCl_4 solution: $G(Me) = 8.2$ ppm and $G(H_6) = 7.5$ ppm, while the *tert*-butyl resonance moves upfield with a gradient of -1.4 ppm. This result is not unexpected in view of the extended shape of the side chain. Similarly, when the nitrone is complexed in acetone to **19**, the *tert*-butyl resonance moves downfield while all other resonances move upfield.

The $Eu(DPM)_3$ induced upfield shifts described here, and by others, are all readily explained in terms of the sign of the $3\cos^2\phi - 1$ term, without recourse to the

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(60) A. Aziz, S. J. Lyle, and J. E. Newbery, *J. Inorg. Nucl. Chem.*, **33**, 1757 (1971).

(61) R. J. P. Williams, *Quart. Rev., Chem. Soc.*, 24, 331 (1970).

(62) W. B. Lewis, J. A. Jackson, J. F. Lemons, and H. Taube, *J. Chem. Phys.*, 36, 692 (1962).

(63) M. Witanowski, L. Stefaniak, H. Januszewski, and Z. W. Wolkowski, *Tetrahedron Lett.*, 1653 (1971).

differential bulk susceptibility effect invoked by Herz, *et al.*,[43] or the contact contribution suggested by Tjan and Visser.[64] There are two possible explanations for the opposite sign of the "normal" shifts induced by **1** and **19**: the 1:1 adducts of **1** presumably have a threefold axis of symmetry with the Eu–substrate bond along the magnetic axis so that either (a) in adducts of **19**, the substrate is perpendicular to the principal axis, ϕ is greater than 54.7° and the anisotropy of the Eu^{3+} ion has the same sign as **1** or (b) the anisotropy has a different sign and the substrate lies along the principal magnetic axis. The evidence on this point is ambiguous as the adducts of **19** are of unknown stoichiometry and symmetry. An asymmetric adduct without a principal axis actually has a more complex PC shift expression than eq 30, requiring extra angular terms, but the great similarity of behavior of the nitrone with **1** and **19** implies that the simple equation is, to a reasonable approximation at least, adequate.

The sign reversals of lanthanide-induced shifts indicate that the r^{-3} "distance only" criterion, which frequently gives a good fit to the data, must be used with caution. Shift reagents will associate with substrates so as to minimize steric interactions (consistent with association occurring) and inspection of models reveals that frequently such configurations are ones in which ϕ variations are minimized. Large ϕ variations are expected only where the substrate is forced to envelop the metal ion, as is the case with all reported examples.

Experimental Section

Nmr spectra were measured at normal probe temperatures on Varian Associates HA 100 or XL 100-15 instruments operated at 100 MHz for proton work and 40.5 MHz for ^{31}P work. CCl_4 and $CDCl_3$ were dried over preheated 4A molecular sieves. Proton chemical shifts in organic solution are in δ units (parts per million) from internal TMS, while in D_2O solutions tetramethylammonium iodide (NMe_4^+, δ 3.19) was used as an internal standard as DSS appeared to interact with the lanthanide nitrates.

$Ln(NO_3)_3 \cdot 6H_2O$ were prepared by dissolving the oxides (99.9%, Koch-Light) in the stoichiometric amount of standardized AR nitric acid and evaporating the solutions. Deuterated samples were obtained by repeatedly dissolving the hydrated salts in D_2O and evaporating to constant weight over P_2O_5 *in vacuo*. $Ln(DPM)_3$ samples were prepared by standard procedures,[65] but without precautions to exclude air. A more rapidly soluble form of the complex is obtained if the pure sublimed material is dissolved in dry AR benzene and stripped down on a rotary evaporator. $Eu(PTA)_3$ was prepared by the method of Shigematsu, *et al.*[16] All shift reagents were stored *in vacuo* over P_2O_5 until just before use.

Substrates were prepared by standard procedures or donated by colleagues in this laboratory. We are particularly grateful to Dr. D. R. Crump for the synthesis of the ethylene thioketal **22** and several other steroids.

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[64] Since completion of this aspect of our work, several communications have reported upfield shifts induced by **1**:[10] T. H. Siddall, *Chem. Commun.*, 452 (1971); P. H. Mazzocchi, H. J. Tamburia, and G. R. Miller, *Tetrahedron Lett.*, 1819 (1971); S. B. Tjan and F. R. Visser, *ibid.*, 2833 (1971); B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971).

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Carbon-13 Chemical Shifts in Monoalkyl Benzenes and Some Deuterio Analogs[1]

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Abstract: Carbon-13 chemical shifts are reported for all carbons in toluene, ethylbenzene, cumene, and *tert*-butylbenzene, and for six deuterium-substituted analogs. Monotonic trends are observed for the ^{13}C shieldings of all carbon positions, except for two small shifts in the *tert*-butylbenzene case. The ranges of the shifts are in the order $C(\beta) > C(1) > C(\alpha) > C(2) > C(4) > C(3)$. All of the regular trends are toward decreased shielding with increased methyl substitution at the α carbon, except for the C(2) trend, which has the opposite sense.

Alkyl benzenes have been the subject of earlier ^{13}C nmr (cmr) studies.[3–8] However, the early cmr equipment and techniques were incapable of providing chemical shifts with the precision of today's standards, or unequivocal assignments of certain ring carbons. As precise cmr data are now routinely attainable, and because alkyl benzenes often serve as models for concepts such as "inductive effects" and "hyperconjugation," precise ^{13}C shieldings of these species are needed. Furthermore, such data will serve as useful and reasonable challenges to emerging theories of ^{13}C shielding. On this point, these data are especially pertinent, in that they provide good cases for gauging the ability of a theory to account for substituent effects (*e.g.*, methyl substitution), without introducing the uncertainties of

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