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SOME APPLICATIONS OF PARAMAGNETIC SHIFT REAGENTS IN ORGANIC CHEMISTRY

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In the preceding communication,* we have described the shift properties of several lanthanide complexes and have shown that $Eu(DPM)_3$ and $Pr(DPM)_3$ are the most satisfactory paramagnetic shift reagents (P.S.R.) for downfield and upfield shifts respectively. Elsewhere,[1] we have presented quantitative shift data for several functional groups and given details of the analysis of these data which enables the location of the M^{3+} ion, and hence the site of the functionality to be determined. We wish in this communication to describe how paramagnetic shift reagents may be used to aid the organic chemist in a variety of situations where p.m.r. spectroscopy or other techniques normally fail.

The complexes slowly absorb water from the atmosphere and should be stored in vacuo over $CaCl_2$ or P_2O_5. Reproducible results are most easily obtained using freshly sublimed material and dry substrates: shifts observed with cholesterol hydrate are only 60% as great as with anhydrous cholesterol. The reagent is preferably added in several small portions to facilitate the assignment of shifted resonances,[2] and in order to find the optimum degree of shift for clarity (frequently one resonance "overtakes" another and this can make the spectrum more difficult, rather than less difficult, to interpret).

The substitution pattern up to six or seven carbon atoms removed from an amino or hydroxyl group is frequently revealed easily in acyclic systems,

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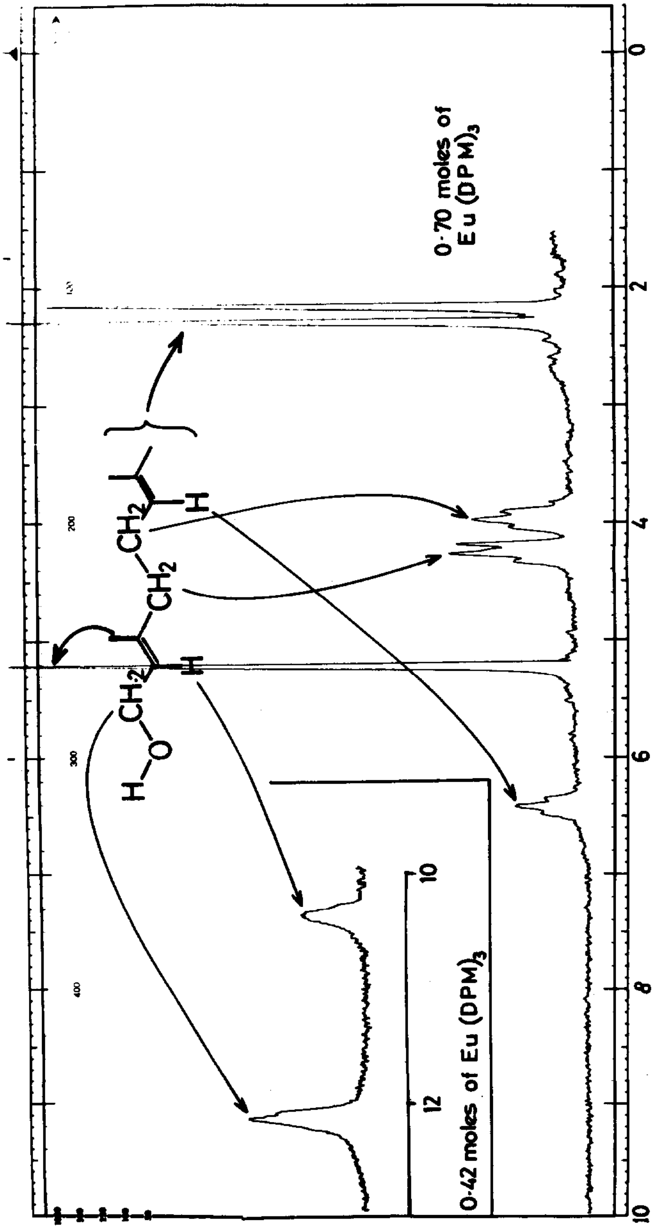
* The present communication was inadvertently separated from the first paper which appears in Tetrahedron Letters No.50, pp. 4419 (1970)


0·70 moles of Eu (DPM)$_3$
0·42 moles of Eu (DPM)$_3$
H–O–CH$_2$
CH$_2$–CH$_2$
H
H
0
2
4
6
8
10
10
12
200
300
400

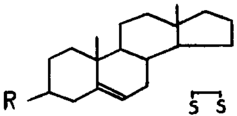
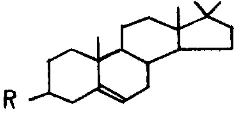
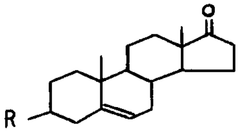
e.g. the figure shows the spectrum of geraniol (ca. 0.3M, in CCl_4) after the addition of $Eu(DPM)_3$ (0.70 mole), ("moles" here and in our previous publication[3] refers to moles of $Eu(DPM)_3$ per mole of substrate). The shift ratio of the low-field methyl protons to the protons on C_1 characterises those protons as being four carbon atoms removed from the hydroxyl group.[1] In acyclic systems, where larger numbers of protons are located at similar distances from polar functional groups, the interpretation is often less obvious. However the expanded spectrum is susceptible to decoupling experiments, and extrapolation of resonance positions to zero concentration of P.S.R. enables the initial chemical shift to be determined, allowing interpretation via traditional chemical shift methods (but with the advantage that the number of protons in each environment may now be known). Aromatic systems such as quinolines and naphthylmethanols also give first order spectra enabling rapid location of substituents which do not complex with $M(DPM)_3$.[1]

P.S.R's accentuate formal non-equivalence so that pairs of geminal protons α (or even β) to asymmetric centres give rise to separate resonances enabling measurement of J_{gem}. Also removal of accidental equivalence, or near equivalence, of A and B in an ABX system ($J_{AB} \neq 0$, $J_{AX} \simeq 0$, $J_{BX} \neq 0$) removes virtual coupling often seen in the X part of the spectrum, leaving readily measured first order multiplets. The detection of impurities and the analysis of mixtures of substrates with overlapping resonances and different affinities for $M(DPM)_3$ is easily achieved by addition of a P.S.R. and integration of isolated peaks.

The location of functional groups in a known carbon skeleton can be determined by measuring relative shift ratios, e.g. of 18- and 19- methyl groups in a steroid, and assuming an r^{-3} dependence of shift on the distance from the metal ion.[1,2] However, such an analysis is possible only for a monofunctional compound which is soluble in CCl_4, $CDCl_3$ (dried over sieves), or C_6D_6. Polar solvents complex strongly with the P.S.R. and are therefore unsuitable. Polyfunctional compounds are sometimes relatively insoluble in non-polar solvents and tend to complex at each functional group, giving shifts which are not readily interpreted. These difficulties can be overcome by suitable derivatisation: conversion of a ketone into its ethylene thioketal renders it effectively inert to $M(DPM)_3$, and hydroxyl groups may be converted to trifluoroacetates which provide only an extremely weak site of coordination. The results in the table show how the shift characteristics of each of the functional groups in an androstenolone can be isolated.

Table

Ratio of the Shifts of 19-methyl and 18-methyl Resonances induced by $Eu(DPM)_3$ in some Mono- and Di-functional Δ^5-Androstenes[†]

Structure	Functionality	G(19-Me)/G(18-Me)*
	R = OH	4.5
	R = $OCOCF_3$	negligible shifts
	R = H	no shifts
	R = OH	4.5
	R = H	0.21
	R = $OCOCF_3$	0.21
	R = OH	2.02

[†] the same ratio would be observed with $Pr(DPM)_3$

[*] ratio of the shift of the 19-methyl to the 18-methyl resonance

The affinity of a substrate for a P.S.R. is effectively a measure of the basicity of its lone pair and hence suitable derivatives should remove or reduce the basicity and introduce as few additional resonances as possible. Ethylene ketals complex strongly and are unsuitable for carbonyl protection. In general, the coordinating power of thiols, thioethers and aryl phosphines is much less than that of the oxygen and nitrogen analogues. Alkyl halides, olefins, and saturated hydrocarbons coordinate extremely weakly, or not at all.

$Eu(DPM)_3$ and $Pr(DPM)_3$ apparently represent the optimum combination of lanthanide ion and β-diketone ligand for P.S.R. In the transition metal series only cobalt(II) acetylacetonate has been used with any success,[4,5] but with this complex the shifts are relatively small and line broadening is serious. In addition, attenuation of shift along an alkyl chain is such that first order spectra cannot usually be obtained.

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References

1. J. K. M. Sanders and D. H. Williams, J. Amer. Chem. Soc., in the press.
2. C. C. Hinckley, J. Amer. Chem. Soc., 91, 5160 (1969).
3. J. K. M. Sanders and D. H. Williams, Chem. Commun., 422 (1970).
4. W. A. Szarek and M. C. Baird, Tetrahedron Letters, 2097 (1970).
5. Y. Yonezawa, I. Morishima and Y. Ohmori, J. Amer. Chem. Soc., 92, 1267 (1970).