A Shift Reagent for Use in Nuclear Magnetic Resonance Spectroscopy. A First-order Spectrum of n-Hexanol

By JEREMY K. M. SANDERS and DUDLEY H. WILLIAMS*
(*University Chemical Laboratory, Lensfield Road, Cambridge,* CB2 1EW)

Summary The use of tris(dipivalomethanato)europium $[Eu(DPM)_3]$ in obtaining first-order, or more readily analysable, ^1H n.m.r. spectra for lone-pair bearing organic compounds with otherwise complex spectra is described: implications for structural studies are discussed.

HINCKLEY has shown[1] that the paramagnetic complex tris(dipivalomethanato)europium containing two molecules of pyridine $[Eu(DPM)_3.2(py)]$ can be used to produce selective shifts of proton resonances in the ^1H n.m.r. spectrum of cholesterol. We reasoned that the pyridine-free adduct, $Eu(DPM)_3$, might be a superior shift reagent in co-ordinating more effectively with lone-pair bearing functionalities in organic substrates. We now report that in our studies using $Eu(DPM)_3$, the selective shifts observed in cholesterol[1] are increased by a factor of 4 at comparable concentrations.[†] Most important, we give examples to illustrate that $Eu(DPM)_3$ can produce dramatic shifts in ^1H n.m.r. spectra, such that many spectra, which have hitherto afforded only limited information as to molecular structure, may now be modified to yield a wealth of information.

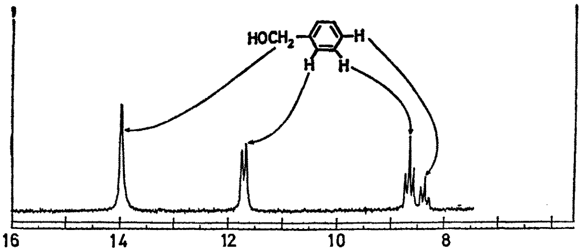


FIGURE 1. 100 *MHz* ^1H *n.m.r. spectrum of benzyl alcohol in* CCl_4 *after the addition of* $Eu(DPM)_3$ (0·39 *moles*). *Chemical shifts in* δ *units* (p.p.m.) *relative to internal* Me_4Si.

In the normal ^1H n.m.r. spectrum of benzyl alcohol (CCl_4 solution) the aromatic protons resonate as a sharp singlet. On addition of $Eu(DPM)_3$ (0·39 moles) to the solution, the spectrum becomes amenable to a first-order analysis (Figure 1). The substrate associates with the complex at the hydroxyl group, and the induced shifts decrease rapidly with increasing distance of the protons from the hydroxyl group.[1] In the normal spectrum of n-hexanol (CCl_4), the proton resonances of all the methylene groups, except that adjacent to the OH group, give rise to a singlet featureless band in the $\delta = 1·2—1·7$ p.p.m. region. On addition of $Eu(DPM)_3$ (0·29 moles), the spectrum is amenable to first-order analysis (Figure 2). In the above examples, the shifts of the hydroxyl protons are of course extremely large and have not been recorded. Line broadening is slight, increasing with increasing shift, but is not serious presumably since (at least in part) Eu^{3+} has a relatively short electron spin–lattice relaxation time.[2] Coupling constants are not significantly changed ($\pm$0·3 Hz)

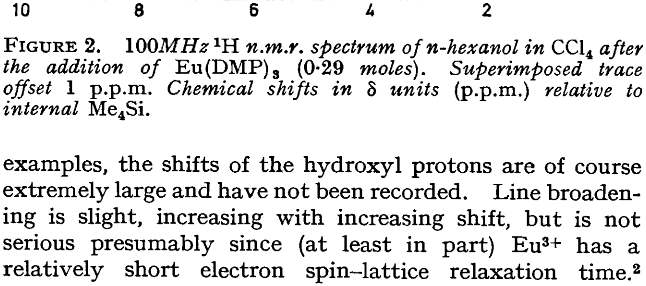


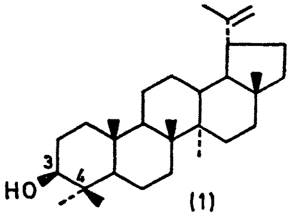
FIGURE 2. 100*MHz* ^1H *n.m.r. spectrum of n-hexanol in* CCl_4 *after the addition of* $Eu(DMP)_3$ (0·29 *moles*). *Superimposed trace offset* 1 p.p.m. *Chemical shifts in* δ *units* (p.p.m.) *relative to internal* Me_4Si.

[†] In the cholesterol spectrum, we reverse Hinckley's assignment of the 2- and 4-proton resonances on the basis of expected line widths and studies of 4,4-disubstituted-3-hydroxy-triterpenoids.

as the concentration of Eu(DPM)$_3$ is increased up to the amounts indicated.

Other functional groups giving similar results are ketones, ethers, esters, and amines. Ketones complex some 35—40% less strongly than alcohols, and ethers and esters less strongly still, but proton resonances in the spectra of amines are strongly shifted. The potential of Eu(DPM)$_3$ in aiding the structure elucidation of natural products by n.m.r. is obviously great. To illustrate this point, we cite the case of the methyl resonances in the n.m.r. spectrum of lupeol (1) (in CCl$_4$), in which the methyl groups attached to C-4 (in the immediate vicinity of the 3β-OH group) are shifted from the $\delta = 1$ p.p.m. region to $\delta = 7{\cdot}3$ and 7·6 p.p.m. upon addition of Eu(DPM)$_3$ (0·67 moles, 18 mg). Under these conditions, no other methyl resonance is shifted below $\delta = 3{\cdot}7$ p.p.m. In steroids and triterpenes it is common for the protons of methylene or methine groups which are three carbon atoms removed from the hydroxyl function to be shifted clear of the usual methylene envelope, and their numbers may then be assessed by integration.

The complex Eu(DPM)$_3$ is very soluble in CCl$_4$ and when used in the pure state as a shift reagent does not give interfering proton resonances between $\delta = 0$—16 p.p.m. The complex does however decompose slowly in the presence of acids (*e.g.* substrates containing phenolic hydroxyl and carboxylic acid groups). We have prepared the complex using the method of Eisenkraut and Sievers,[3] but find it unnecessary to isolate the product with exclusion of oxygen. The complex is thus easy to prepare and to use. Compounds under study may be recovered by t.l.c. of the complex–substrate solution on silica gel. The complex should therefore prove to be a great asset in the study of many problems by n.m.r.



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[1] C. C. Hinckley, *J. Amer. Chem. Soc.*, 1969, **91**, 5160.

[2] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, 1959, p. 210.

[3] K. J. Eisenkraut and R. E. Sievers, *J. Amer. Chem. Soc.*, 1965, **87**, 5254.