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THE USE OF Eu(DPM)$_3$ WITH BIFUNCTIONAL MOLECULES.
ADDITIVITY OF THE INDUCED CHEMICAL SHIFT CHANGES IN THE NMR SPECTRUM

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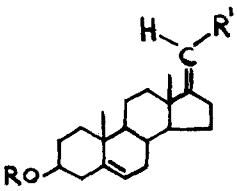
Since the work of Hinckley [1,2] on the use of Eu(DPM)$_3$ [<u>tris</u>-dipivalomethanato Eu(III)] as a chemical shift reagent many papers have appeared in which the technique has been perfected and the possibilities of its application amplified. It has been shown that this reagent, preferable to the corresponding pyridine adduct [3], produces notable paramagnetic shifts in molecules containing co-ordinating groups without, however, any great broadening of the line widths of the p.m.r. signals. In general the molecules so far studied have contained only one co-ordinating group, little having been done with those containing two groups [4,5].

Here we report the results of our studies on the progressive addition of Eu(DPM)$_3$ to the bifunctional compound 17-carbomethoxy-methylene-5-androsten-3β-ol (III) and to 5,17-pregnadien-3β-ol (I) and 17-carbomethoxy-methylene-5-androsten-3β-yl-trifluoroacetate (II) which has enabled us to distinguish between the effect produced by complexation at the hydroxyl and at the α-β unsaturated ester groups in (III). It should be noted that in both (I) and (III) the hydroxyl group is in an equatorial position, and that the methylester group in both (II) and (III) is <u>trans</u> with respect to the 18-CH$_3$ since (II) was obtained from (III) by treatment with trifluoroacetic-anhydride.



(I) R = H, R' = CH$_3$;
(II) R = CF$_3$CO, R' = CH$_3$COO;
(III) R = H, R' = CH$_3$COO;

It should also be noted that trifluoroacetate esters show negligible co-ordination to Eu(DPM)$_3$ [6] and hence compound (II) is essentially monofunctional.

The n.m.r. spectra were obtained using a Perkin Elmer 60 MHz R 12 spectrometer with Mr

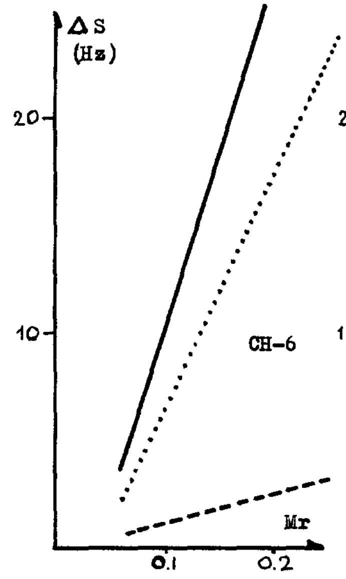


Fig. n. 2a

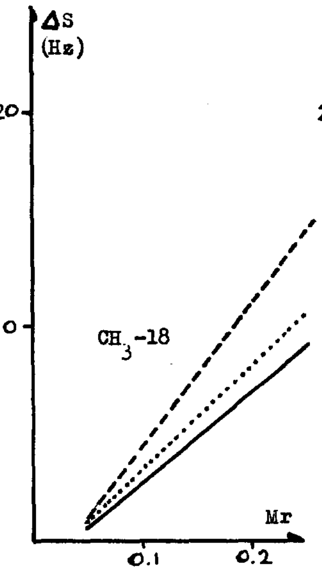


Fig. n. 2b

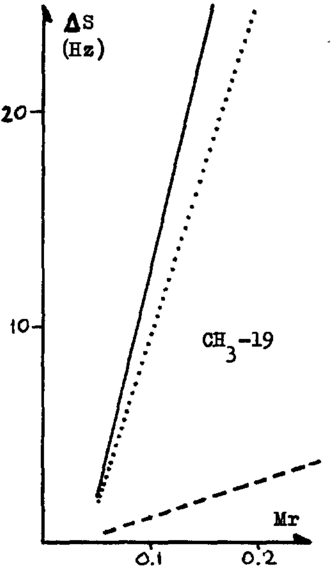


Fig. n. 2c

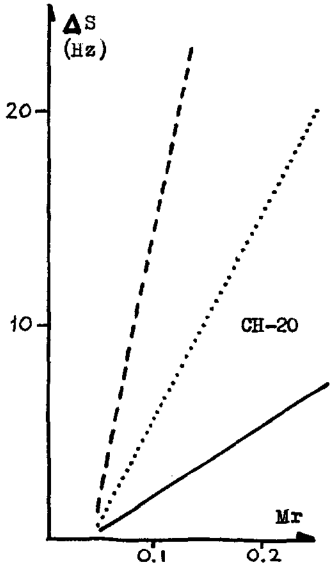


Fig. n. 2d

Compound (I) ————

Compound (II) – – – – –

Compound (III) ··········

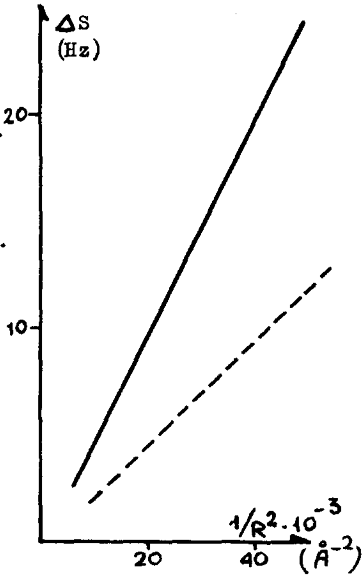


Fig. n. 3

values between 0.05 and 0.25 (Mr = molar ratio of $Eu(DPM)_3$: substrate). The solvent used was $CDCl_3$ dried over 4Å molecular sieves previously heated to 120°C [7].

In order to avoid ambiguity only the shifts of protons equivalent in each molecule were monitered, those bonded to carbons 6,18,19 and 20. The results are shown graphically in Fig. 2 as Δ S, the difference in chemical shifts relative to that of the non complexed substrate (internal TMS as reference) versus the Mr value. As can be seen linear relationships were obtained not only for (I) and (II) but also for (III).

Postulating that for each proton in (III) the induced chemical shift changes due to partial complexation at the two functional groups are additive one can write for every proton

$$\Delta S = A \cdot Mr \cdot x + B \cdot Mr \cdot (1-x) = C \cdot Mr \qquad (1)$$

where A,B and C are the gradients of the graphs shown in Fig. 2 for (I), (II) and (III) respectively for that proton under consideration,

and where x = the fraction of Eu^{3+} complexed to the hydroxyl group

and (1-x) = the fraction of Eu^{3+} complexed to the methylester group.

Because of the relatively low concentrations of $Eu(DPM)_3$ used we have assumed that all the Eu^{3+} was complexed and also that x is invariant.

Substitution in Eq (1) of the values obtained for A,B and C (obtained from the graphs shown in Fig. 2) gave a value for x of 0.7 (the average of those obtained for the four protons studied). This value agreed with that obtained for an equimolar mixture of (I) and (II) with successive addition of $Eu(DPM)_3$, this intermolecular competition method [8] also giving a value of 0.7 for x.

According to Hinckley [2] the shifts obtained are predominantly the result of pseudo-contact interaction and their magnitude therefore proportional to $1/R^3$ according to the equation of McConnell and Robertson [9], where R is the distance between the proton under consideration and the Europium atom. Nevertheless other later authors [10,11,12,13] have reported a proportionality with $1/R^2$ or $1/R^{2.2}$ as being more consistent with the experimental data.

Such discrepancies could be explained by the different methods used to measure the value of R, or as due to experimental error, or as due to the assumption that the angular factor in the equation for the contact shift is constant being invalid [12].

We have also found for compounds (I) and (II) that Δ S is proportional to $1/R^2$, where R is the average distance between the proton and the centre of the oxygen atom [11] [hydroxyl in (I) and carbonyl in (II)] as measured from Drieding models. It has previously been reported that esters co-ordinate through the carbonyl oxygen [8].

In Fig. 3 the graphs of Δ S versus $1/R^2$ is shown for compounds (I) and (II).

If the additivity of the contributions of the two co-ordinating groups in (III) is valid then for every proton for a given value of Mr:

$$\Delta S = a \cdot \frac{1}{R_1^2} \cdot x + b \cdot \frac{1}{R_2^2} \cdot (1-x) \qquad (2)$$

where a and b are the gradients obtained from Fig. 3 for (I) and (II) respectively,

R_1 = the distance in Å between the proton and the centre of the hydroxyl oxygen atom in (I) and (III);

R_2 = the distance in Å between the proton and the centre of the carbonyl oxygen atom in (II) and (III).

As can be seen from the results shown in Table 1 there is good agreement between the experimental values of ΔS and those calculated from eqn. (2) with $x = 0.7$ (values obtained with $Mr = 0{,}15$).

Table 1

	CH_3-19	CH_3-18	CH-6	CH-20
ΔS calc.	17,1	6,2	12,2	10,8
ΔS expt.	17,2	5,8	11,5	10,3

In conclusion, within the limits of the $Eu(DPM)_3$ concentrations used, the contributions to ΔS for each proton in (III) due to co-ordination at the two functional groups are additive. This additivity could be used to resolve other stereochemical problems regarding bi-functional molecules with rigid skeletons.

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