Communications to the Editor

Paramagnetic Shifts in Solutions of Cholesterol and the Dipyridine Adduct of Trisdipivalomethanatoeuropium(III). A Shift Reagent

Sir:

In an effort to determine whether or not cholesterol would bond in solution with complexes of the rare earth metals, and to examine the manifestations of this bonding with respect to paramagnetic shift, solutions of the dipyridine adduct of trisdipivalomethanatoeuropium(III) and cholesterol monohydrate were prepared in carbon tetrachloride and the pmr spectra taken on a Varian HA100 nmr spectrometer.

The metal chelate $Eu(DPM)_3$ (HDPM represents dipivalomethane whichi s 2,2,6,6-tetramethylheptane-3,5-dione) was prepared by the method of Eisentraut and Sievers,[1] and the adduct, $Eu(DPM)_3 \cdot 2py$, was obtained by recrystallization from pyridine, py. The structure of cholesterol is well known,[2] and full use of this knowledge was made in the analysis of the spectra. Initial pmr assignments were made with the aid of the Varian pmr spectra catalog.

The pmr spectra of cholesterol and the $Eu(DPM)_3 \cdot 2py$–cholesterol solutions are shown in Figure 1. Two features of the second spectrum are immediately obvious: (1) there is very little broadening of the spectrum, and (2) there are substantial shifts of resonance peaks. Narrow pmr lines may be expected for solutions containing complexes of all the rare earths with the exception of gadolinium. The very short electron relaxation times of these metal ions in solution[3] at normal temperatures can result in narrow pmr absorptions.[4-7] This is in contrast to the frequently extensive broadening caused by short transition series paramagnetic ions. The observed paramagnetic shifts are the direct consequence of bonding between the metal complex and cholesterol. There are no pmr absorptions due to the metal complex or free pyridine in the cholesterol region of the spectrum.

Examination of spectrum 2 in detail reveals a number of significant changes in comparison to that of cholesterol alone. In addition to the sizable shifts observed for the vinyl proton f and the proton nearest the hydroxyl group e, which indicate association through the hydroxy group, the methyl resonances a, b, c, and d are shifted, and new resonances g, h, and i have appeared downfield from the unresolved bands characteristic of cholesterol and other steroids. Assignments of methyl resonances were made by following changes in shifts as the metal complex concentration was increased. The splittings of resonances b and c and the relative intensities of all the methyl resonances were considered in the process. Integration of the downfield signals and spin decoupling experiments were used to assign the resonances for the methylene protons labeled g, h, and i (Figure 1).

Paramagnetic shifts may arise from two sources, contact or pseudocontact interactions. When the paramagnetic center is a rare earth ion, the pseudocontact shift is expected to be a substantial contributor,[8] particularly in the absence of extensive conjugation. For ions of C_{2v} or C_2 symmetry[9] the pseudocontact shift experienced by the jth proton in a complex is given by [10]

$$\frac{(\Delta H)}{(H)_j} = -\epsilon\frac{(g_1 + g_2 + g_3)}{R_j^3}\left[\left(g_1 - \frac{1}{2}g_2 - \frac{1}{2}g_3\right)(3\cos^2 X_j - 1) - \frac{3}{2}(g_2 - g_3)\sin^2 X_j \cos 2\Omega_j\right] \quad (1)$$

where the distance from the metal to the jth proton, R_j, and the angles X_j and Ω_j define the position of the proton in the symmetry coordinates of the metal ion. The components of the g tensor are g_1, g_2, and g_3 and $\epsilon = |\beta|^2 S(S + 1)/27kT$. For shifts produced by either the contact interaction in the absence of extensive conjugation or pseudocontact interactions, the general expectation is that the shift produced will decrease with increasing distance between the paramagnetic center and the affected proton.[11] Apparently, the pseudocontact interaction is the major contributor to the observed paramagnetic shifts, with the possible exception of the proton nearest the metal complex, for this system.

Paramagnetic shifts were measured for all protons for which assignments could be made in both cholesterol

Table I. Paramagnetic Shifts, $\Delta\omega$, for the Resonances of Assigned Protons Measured from the Spectrum of a Solution of 0.05 *M* $Eu(DPM)_3 \cdot 2py$ and 0.1 *M* Cholesterol Monohydrate[a]

Proton	$\Delta\omega$, cps	R, Å
a	−14.5	9
b	−1.9	13
c	−6.7	12
d	−67.4	5
e	−347.0	3.5
f	−40.0	6

[a] Listed distances from metal to proton, R, are estimates measured from a molecular model for metal bonding above the ring.

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(5) D. R. Eaton, W. D. Phillips, and D. J. Caldwell, *J. Am. Chem. Soc.*, **85**, 397 (1963).
(6) G. N. La Mar, *ibid.*, **87**, 3567 (1965).
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(8) D. R. Eaton, *J. Am. Chem. Soc.*, **87**, 3097 (1965).
(9) P. J. McCarthy, "Spectroscopy and Structure of Metal Chelate Compounds," K. Nakamoto and P. J. McCarthy, Ed., John Wiley & Sons, Inc., New York, N. Y., 1968, p 346.
(10) This formula is an example taken from G. N. La Mar, W. DeW. Horrocks, Jr., and L. C. Allen, *J. Chem. Phys.*, **41**, 2126 (1964). The symmetry of the complexes under study here is probably C_1; see also G. N. La Mar, *ibid.*, **43**, 1085 (1965).
(11) D. R. Eaton, A. D. Josey, W. D. Phillips, and R. E. Benson, *Discussions Faraday Soc.*, **34**, 77 (1962).

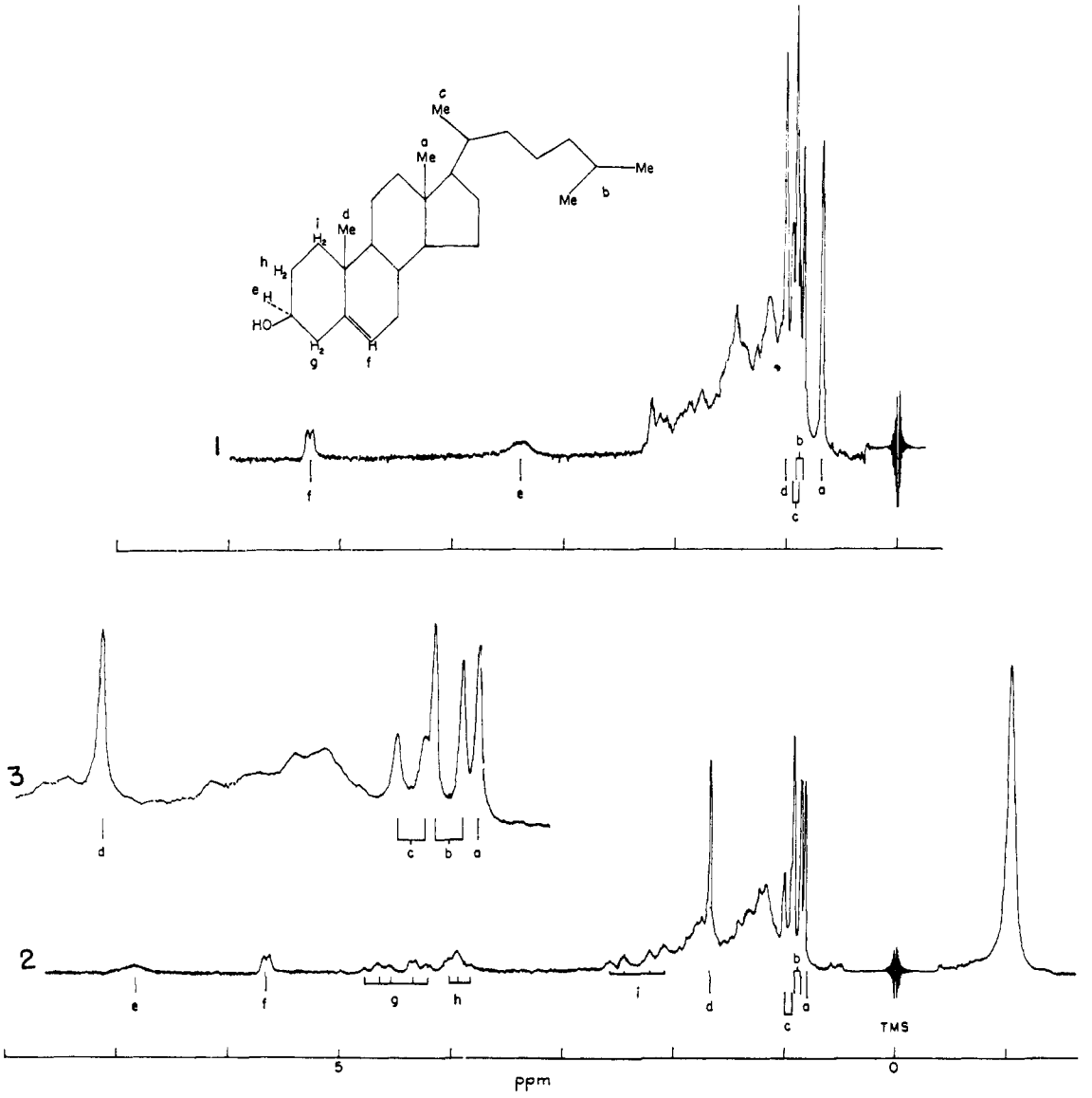

Figure 1. Spectrum 1 is of cholesterol monohydrate in CCl_4. Spectrum 2 is of a CCl_4 solution 0.05 *M* in $Eu(DPM)_3 \cdot 2py$ and 0.1 *M* in cholesterol monohydrate. Spectrum 3 is an expansion of that region of spectrum 2 which includes the methyl resonances. Assignments are indicated by letter on the accompanying molecular diagram. The resonance 1 ppm upfield from tetramethylsilane (TMS) is due to the metal complex.

and metal complex–cholesterol solutions. Shifts for a solution 0.05 *M* in $Eu(DPM)_3 \cdot 2py$ and 0.1 *M* in cholesterol are listed in Table I. General expectations are realized; shifts for protons close to the point of association are larger than those for protons further removed. The shifts are concentration dependent which indicates rapid metal complex–cholesterol exchange.

The mode of metal coordination was considered, and with the aid of a molecular model of cholesterol approximate distances between proton and metal ion were measured (Table I). Two cases were considered: first, the metal coordinated to the hydroxyl group above the ring and, second, coordination below the ring where steric interference with the vicinal proton e is expected. In the first case the methyl group d should be closer to the europium ion than the vinyl proton f, and should experience the greatest shift. In the second case the reverse shift relationship should obtain. Shift magnitudes corresponding to the first case are the experimental finding, which suggests that the metal complex bonds in a *trans* configuration to the hydroxyl vicinal proton and that the steric interference with that proton is sufficient to affect the configuration of the complex.

A plot of the observed shift *vs.* the cube of the reciprocal distance between the metal and proton demonstrates that the distance parameter dominates the shift magnitude. This must be a consequence of the molecular structure of cholesterol. The steroid framework of cholesterol is roughly planar, and the angle variables (eq 1) do not vary greatly from one proton to the next. This would not be the case if the cholesterol molecule folded around the metal complex.

The combined findings of this study, which include (1) the association of the metal complex with the cholesterol hydroxyl group, (2) substantial paramagnetic shifts of resonances for protons up to 13 Å removed from the coordination point, (3) absence of line broadening effects, and (4) the sensitive $1/R_j^3$ dependence of the observed shifts, suggest that nmr studies using the compound $Eu(DPM)_3 \cdot 2py$ can be a useful addition

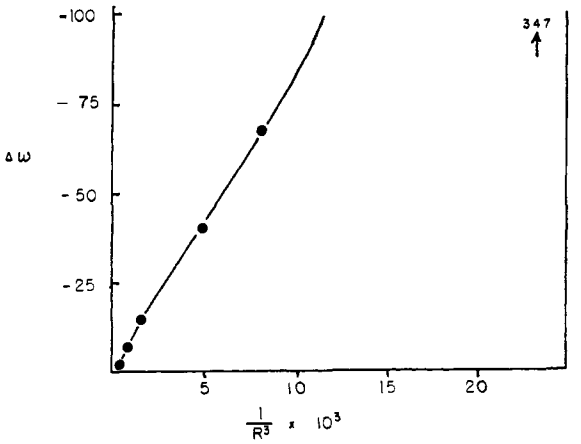

Figure 2. Plot of measured paramagnetic shifts (Table I) *vs.* the cubed reciprocal distance of the proton from the coordination site. Distances were measured from a molecular model of scale 1 Å/in.

to the tools applied in conformation studies of steroids and other similar compounds. Undoubtedly, other rare earth compounds will be of similar use[12] and application will not be confined to steroids. The ability of $Eu(DPM)_3 \cdot 2py$ to produce relatively large, concentration-dependent shifts without serious broadening suggests that the compound may have value as a shift reagent. There are a number of investigations in progress pertinent to the application of the reagent. These include interpretation of spectra obtained when more than one coordination site is available and the examination of cases for which the angular variables (eq 1) are more significant.

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(12) A referee pointed out that Co^{2+}-induced contact shifts have been used in pmr studies of proteins; see C. C. McDonald and W. D. Phillips, *Biochem. Biophys. Res. Commun.*, **35**, 43 (1969).

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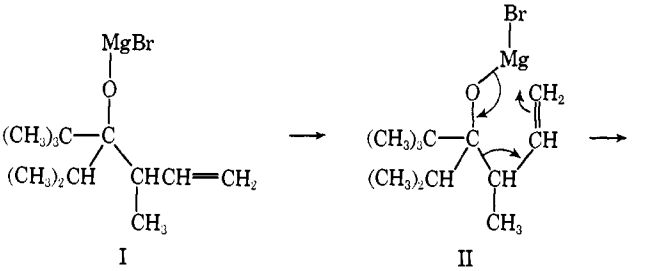
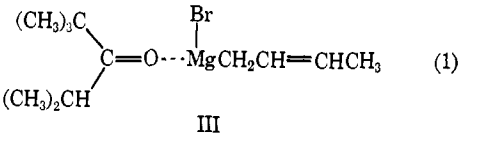
The Reaction of Crotylmagnesium Bromide with Hindered Ketones. The First Examples of a Reversible Grignard Reaction

Sir:

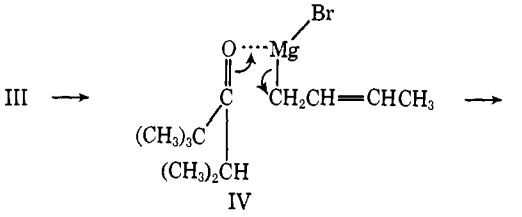
Although reversible condensations, involving the reaction of organoalkali reagents with carbonyl-containing compounds (*e.g.*, aldol,[1] Claisen,[2] and Michael[3] reactions), have been known for quite some time, it is interesting that there has never been a report of a reversible Grignard reaction. This may be due, in large part, to the greater degree of covalent character in the magnesium–oxygen bond of the Grignard product when compared to the alkali metal–oxygen bonds.[1,4]

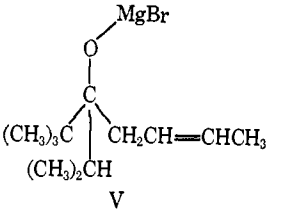
We have found that the reaction of crotylmagnesium bromide with *t*-butyl isopropyl ketone in THF produces a high yield of α-methylallyl addition product (I) initially which then diminishes with time (Table I). Commensurate with this decrease is an increase in the yield of crotyl products (V) and *t*-butyl isopropyl ketone.



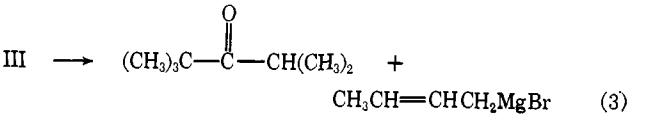


(1)





(2)



(3)

The data shown in Table I strongly suggest that the α-methylallyl-*t*-butylisopropylcarbinoxymagnesium bromide (I) is reversing with time (eq 1) into a *t*-butyl isopropyl ketone–crotylmagnesium bromide complex (III), which then collapses, possibly through a four-membered transition state (IV), to form the more thermodynamically stable crotyl products (V). The latter could also conceivably form by a complete dissociation of complex III into starting ketone and crotyl Grignard (eq 3) followed by a recombination of the two species. Employing the principle of microscopic reversibility, it is not unreasonable to assume that this reversibility (eq 1) proceeds through the same cyclic six-membered transition state (II) that was proposed to account for the formation of α-methylallyl products from the reaction of crotylmagnesium bromide with carbonyl groups.[5]

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