Tris(dipivalomethanato)europium. A Paramagnetic Shift Reagent for Use in Nuclear Magnetic Resonance Spectroscopy

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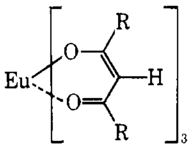
Abstract: The addition of the title compound [$Eu(DPM)_3$] to organic solutions of lone pair bearing organic compounds gives striking spectral simplifications by virtue of reversible complexation leading to pseudocontact shifts. Functional groups give characteristic shift magnitudes in the order $-NH_2 > -OH > \rangle C{=}O > -O- > -CO_2R > -CN$. It is shown how the use of this reagent greatly enhances the power and versatility of nmr spectroscopy and provides a new method for the location of functionality in a molecule.

Although it is one of the most powerful structural tools available to the organic chemist, pmr spectroscopy is severely limited in its utility by the fact that while protons in close proximity to electronegative centers or attached to sp^2-hybridized carbon atoms give rise to resonances in characteristic low-field positions, most other resonances occur in the δ 0.5–2.5 region. This gives rise to coincident peaks from formally nonequivalent protons and nonanalyzable spectra, as exemplified by the methylene envelope of steroids. Induced paramagnetic shifts are an attractive way of removing this accidental equivalence, but until recently very little work of general utility has been published; shifts induced by complexation in solution to the diacetylacetonates of Ni^{2+} and Co^{2+} have been used to determine otherwise inaccessible coupling constants in aryl phosphines and isonitriles[1] and to investigate lone-pair conformational preferences in anilines and piperidines,[2] but line broadening is serious, shifts are small, and we consider that there is doubt over the validity of coupling constants obtained *via* induced contact shifts (see Discussion).

This work was prompted by Hinckley's report[3] that large shifts are induced in the nmr spectrum of cholesterol by the addition of the dipyridine adduct of $Eu(DPM)_3$, but, as we have already reported in a preliminary communication,[4] the pyridine-free complex is greatly superior as a shift reagent. Eu^{3+} is the paramagnetic ion of choice by virtue of its anomalously inefficient nuclear spin-lattice relaxation properties.[5] Eu^{3+} has low-lying Russell–Saunders states, giving a very small separation of the highest and lowest occupied metal orbitals, and this has been found empirically to lead to inefficient relaxation.[6] In addition lanthanide ions are expected[7,8] to induce largely, if not exclusively, pseudocontact shifts dependent only on distance and geometry, rather than contact shifts dependent on covalent bonding.[9] Tris-β-diketone complexes are the best candidates for shift reagents as they are air stable, soluble in organic solvents, and are known to expand their coordination by acquiring ligands with lone pairs.[3,10,11]

Accordingly, we have synthesized three tris-β-diketonates of europium, the hydrated acetylacetonate (**1**, $Eu(acac)_3 \cdot H_2O$), the dibenzoylmethanate (**2**, $Eu(DBM)_3$), and the dipivalomethanate (**3**, $Eu(DPM)_3$), for study as potential shift reagents.



1, R = CH_3; + H_2O
2, R = C_6H_5
3, R = *tert*-Bu

Results

$Eu(DPM)_3$ is by far the most useful shift reagent we have investigated. The acetylacetonate (**1**) contains coordinated water, leading to weak complexation with ligands and very small shifts [$\sim$7% of those seen with $Eu(DPM)_3$]. This weak complexation has also been inferred from ir and other studies.[12] The anhydrous compound has been described,[13] but it is hygroscopic and therefore unsuitable for general use. We find that the dibenzoylmethanate (**2**) is virtually insoluble in nonpolar solvents and therefore also of little value. All further results presented here are for $Eu(DPM)_3$.

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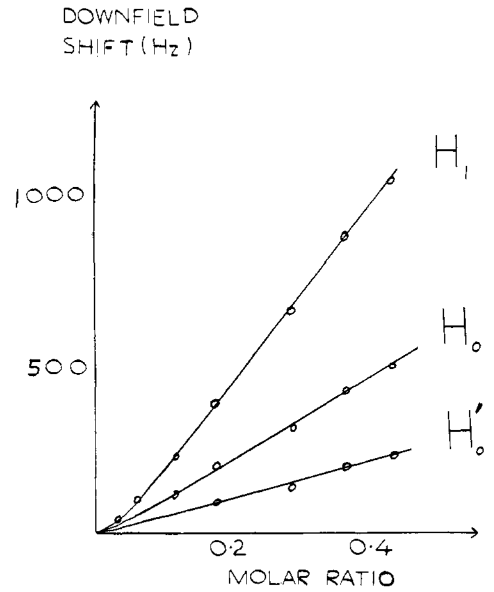

Figure 1. Variation of induced shift with molar ratio [Eu(DPM)$_3$]/[substrate] for 1,2-diphenylethanol in CCl$_4$ solution; for the identification of protons see Figure 5.

Table I. Variation of Gradients with Functionality

Functional group	Ppm/mol of Eu(DPM)$_3$ per mol of substrate
$\mathrm{RCH_2N}\mathit{H}_2$	~150
$\mathrm{RCH_2O}\mathit{H}$	~100
$\mathrm{R}\mathit{CH}_2\mathrm{NH_2}$	30–40
$\mathrm{R}\mathit{CH}_2\mathrm{OH}$	20–25
$\mathrm{R}\mathit{CH}_2\mathrm{COR'}$	10–17
$\mathrm{RCH_2C}\mathit{H}\mathrm{O}$	19
$\mathrm{R}\mathit{CH}_2\mathrm{CHO}$	11
$\mathrm{R}\mathit{CH}_2\mathrm{O}\mathit{CH}_2\mathrm{R}$	10
$\mathrm{R}\mathit{CH}_2\mathrm{CO_2Me}$	7
$\mathrm{RCH_2CO_2}\mathit{Me}$	6.5
$\mathrm{R}\mathit{CH}_2\mathrm{CN}$	3–7

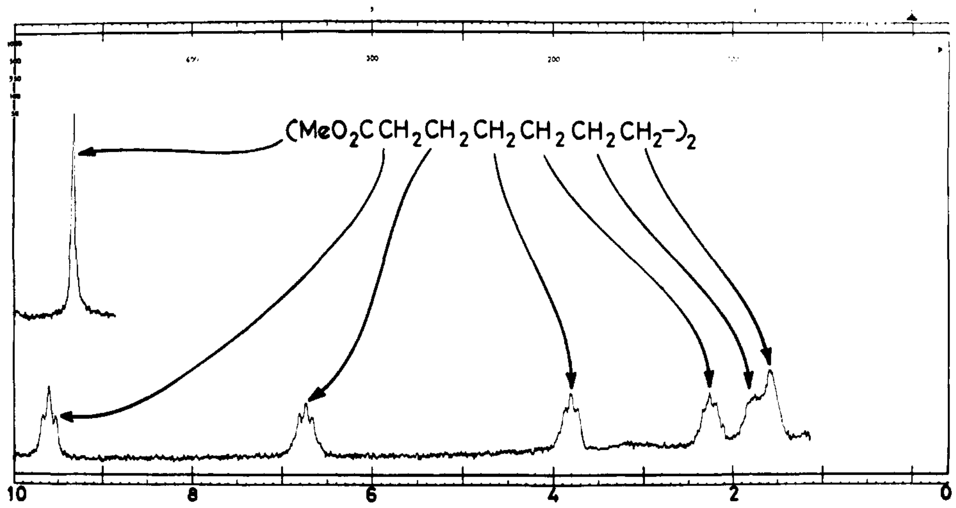

Figure 2. 100-MHz spectrum of dimethyl tetradecandioate in CCl$_4$ solution after the addition of 1.2 mol of Eu(DPM)$_3$ (superimposed methyl resonance offset 1 ppm).

Up to molar ratios of approximately 0.1 ([Eu(DPM)$_3$]/[substrate]), the proton shifts are relatively small; at larger molar ratios, the shifts are larger and good straight lines are obtained on plotting induced shift *vs.* Eu(DPM)$_3$ (see, for example, Figure 1). The gradients of these lines, in parts per million/mole of Eu(DPM)$_3$ per mole of substrate, are characteristic of the functional group and its environment. Table I shows some typical gradients for various unhindered functionalities, determined for 0.2–0.5 *M* solutions of substrate in carbon tetrachloride (CCl$_4$) solution at 100 MHz. The gradients are fairly insensitive (±15%) in this concentration range, being slightly smaller in more dilute solution, and significantly larger in concentrated solution, when the equilibrium is forced over to the complex side. Induced shifts in deuteriobenzene (C$_6$D$_6$) are at least 90% as great, but whereas the complex is soluble to the extent of 200–300 mg/ml in CCl$_4$ (in the absence of polar solutes at room temperature), C$_6$D$_6$ will dissolve only about 100 mg/ml. Deuteriochloroform (CDCl$_3$) must be thoroughly dried over preheated (120°) 4A Molecular Sieves before use to remove traces of acid which are sometimes present and which decompose the complex. CDCl$_3$ will dissolve 200–300 mg/ml of Eu(DPM)$_3$ but the shift power for alcohols and amines is only 75–80% that in CCl$_4$ solution. In deuterioacetonitrile (CD$_3$CN) the complex has a shift power some 60–70% of that in CCl$_4$ for amines, but is less useful for weakly complexed compounds due to competitive inhibition from the solvent of the kind exhibited by Hinckley's complex.[3]

Nitro groups are very weakly complexed, as are phosphines, but halides, indoles, and double bonds are completely inert in compounds so far examined, showing no detectable shifts.

There is a gradual attenuation of induced shift along a freely rotating alkyl chain, as shown in Table II for several long-chain monofunctional alcohols, where relative shifts in CCl$_4$ solution are shown for an increasing

Table II. Shift Attenuation in Long-Chain Alcohols

No. of intervening carbons	1	2	3	4	5	6	7
Rel shift	1	0.60	0.42	0.20	0.14	0.08	0.02

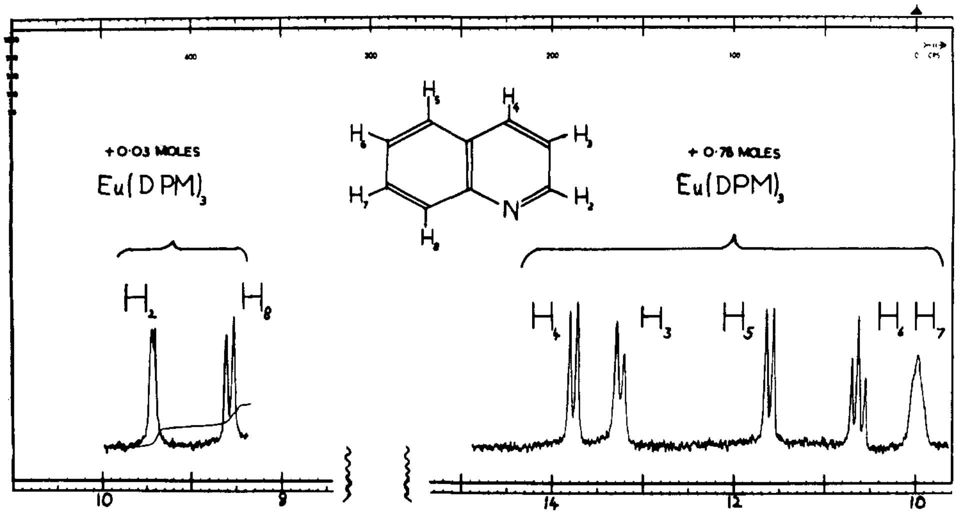

Figure 3. 100-MHz spectra of quinoline in CCl_4 after the addition of 0.03 mol of $Eu(DPM)_3$ (protons 2 and 8, left-hand trace) and of 0.78 mol of $Eu(DPM)_3$ (protons 3, 4, 5, 6, and 7, right-hand trace).

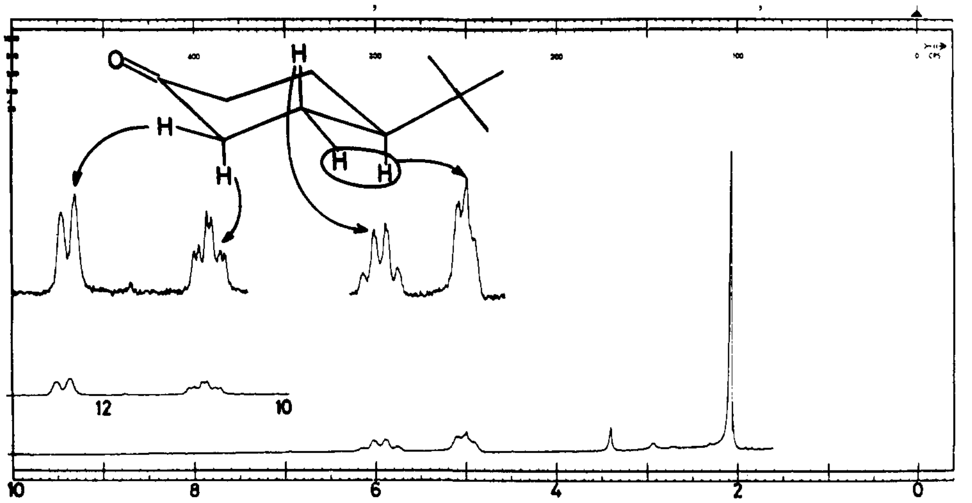

Figure 4. 100-MHz spectrum of 4-*tert*-butylcyclohexanone in CCl_4 solution after the addition of 0.6 mol of $Eu(DPM)_3$. Traces of impurity at δ 2.95, 3.4. Left-hand superimposed traces offset 3 ppm. Upper superimposed traces run at higher gain.

number of carbon atoms intervening between the proton and the hydroxyl group. Uncertainties are approximately 10% for two–six carbons and 50% for seven.

The result of this gradual shift attenuation is that first-order spectra can be obtained as we have reported earlier[4] (see also Figure 2 and Figure 3), and more readily analyzable spectra are available as exemplified by the spectrum of 4-*tert*-butylcyclohexanone (Figure 4). Normally this compound exhibits only featureless bands in the δ 1.0–2.4 region, but the addition of 0.6 mol[14] of $Eu(DPM)_3$ yields the readily analyzable spectrum shown (all assignments have been confirmed by spin decoupling experiments).

The great sensitivity of shift to the H–Eu^{3+} distance means that formally nonequivalent, but usually coincident, resonances of diastereoisomeric protons α to asymmetric centers are readily separated to reveal hitherto unobservable geminal coupling constants. Thus the alkyl protons of 1,2-diphenylethanol normally give resonances characteristic of an A_2X system (*i.e.*, doublet and triplet) but progressive additions of $Eu(DPM)_3$ gradually accentuate the methylene nonequivalence to yield eventually an ABX picture (see the AB portion at δ 10.7 ppm in Figure 5).[15] In long-chain secondary alcohols not only are such geminal proton resonances (α to the asymmetric center) separated, but sometimes even the β proton resonances give complex ABX_4 line patterns rather than the simple first-order quintets seen for protons further down the chain. Compounds with sterically hindered lone pairs often show slightly smaller gradients than less-hindered analogs but we have yet to establish definitely whether this is due to a small equilibrium constant (*K*) for the complexation (eq 1), or to greater substrate–reagent distances in the complex, or to a combination of both.

$$x[\text{substrate}] + [\text{shift reagent}] \overset{K}{\rightleftharpoons} [\text{substrate–reagent complex}] \quad (1)$$

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[14] For brevity, "mol" is used to indicate "moles of $Eu(DPM)_3$ per mole of substrate."

[15] The broad resonance at δ 12.2–13.1 is highly sensitive to both molar ratios and dilution, and integrates correctly for the vinyl protons of $Eu(DPM)_3$. The position of resonance is so sensitive to the six ⇌ eight coordinate equilibrium that it only very rarely happens to be found in the readily observable δ 0–20 region, and is not usually observed.

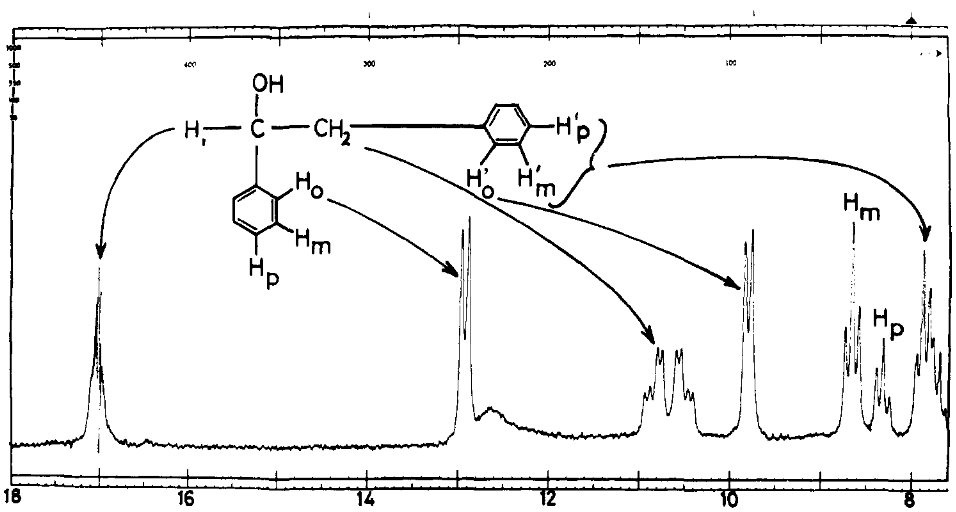

Figure 5. 100-MHz spectrum of 1,2-diphenylethanol in CCl_4 solution after the addition of 0.49 mol of $Eu(DPM)_3$. Peak at δ 12.2–13.1 probably due to reagent.[15]

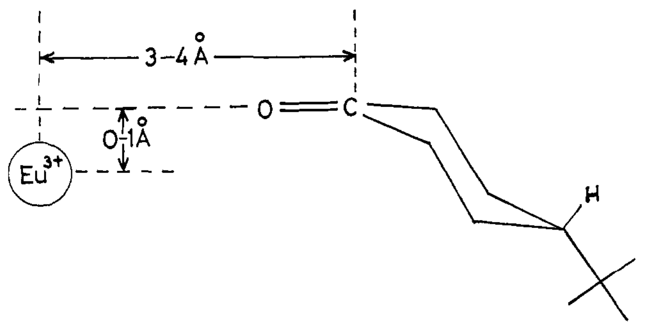

Figure 6. The location of the Eu^{3+} ion.

Consideration of the pseudocontact shift equation of McConnell and Robertson[16] (eq 2), where K is a constant for any given molecule at a known temperature, enables us to locate the position of the Eu^{3+} ion if we follow Hinckley's approximation[3] and assume that ϕ_i

$$\Delta H_i/H_p = \frac{K(3\cos^2\phi_i - 1)}{r_i^3} \qquad (2)$$

(the angle between the ith proton and principal axis) is invariant and consider only the variation in r_i, the distance from the ith proton to the Eu^{3+} ion. For example, comparison of shift ratios for various protons in 4-*tert*-butylcyclohexanone, with distances measured on a 1-in. = 1 Å molecular model, places the Eu^{3+} ion as shown in Figure 6, some 3–4 Å from the carbonyl carbon atom along the line of the carbonyl bond and up to 1 Å below it. Adamantan-2-one gives similar results. Taking the C–Eu^{3+} distance to be 3.5 Å, then by measurements on molecular models we may predict G(19-Me)/G(18-Me) ratios (= r^3(18-Me)/r^3(19-Me)) for a variety of keto steroids (where G represents the gradient as previously defined). As can be seen from Table III, the agreement with experimentally measured ratios is very good considering the large uncertainties (±0.2 Å) in measured distances.

Table III. Predicted and Measured G(19-Me)/G(18-Me) Ratios for Keto Steroids

	r(18-Me), Å	r(19-Me), Å	Predicted[a] ratios	Measured ratios[b]
5α-Androstan-3-one	11.2	7.2	4.4 ± 0.6	4.5
5α-Androstan-11-one	5.3	4.0	2.4 ± 0.8	1.9
5α-Androstan-17-one	5.3	9.2	0.19 ± 0.04	0.21

[a] Predicted ratio = [r(18-Me)/r(19-Me)]^3. [b] Measured ratio = G(19-Me)/G(18-Me).

Discussion

Clearly $Eu(DPM)_3$ has much to offer as a shift reagent, and is certainly far superior to any other compounds investigated in this work or hitherto reported in the literature, both on the grounds of shift magnitude and line broadening. However, some other rare earth dipivalomethanates which are more strongly paramagnetic than Eu^{3+} may give larger shifts at the expense of resolution.[17] The results given in Tables II and III confirm that the shift is, predominantly at least, caused by a pseudocontact mechanism, rather than a contact mechanism, although the possibility of a small contact contribution (especially where π systems are available[8]) cannot be ruled out until our knowledge of ϕ variations and internuclear distances is greatly improved.

On the simplest level, $Eu(DPM)_3$ may be used to remove accidental coincidence of nmr signals enabling multiplicities and coupling experiments to be carried out. This makes structural and stereochemical determinations much easier than was previously possible, assuming that a suitable lone pair is available. Thus, the orientation of substituents in aromatic and naphthalenic alcohols and quinolines is now readily derived from the observable coupling patterns, although the

[16] H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958).

[17] Since submission of this manuscript, this prediction has been verified in our own laboratory (D. R. Crump, J. K. M Sanders, and D. H. Williams, *Tetrahedron Lett.*, 4419 (1970)). See also J. Briggs, G. H. Frost, F. A. Hart, G. P. Moss, and M. L. Staniforth, *Chem. Commun.*, 749 (1970).

normal pmr spectrum often yields virtually no information in this respect. Similarly, sites of chain branching in long alkyl alcohols are easily located if less than seven atoms from the hydroxyl group, and even further removed for the corresponding amines. Rates of shift attenuation provide additional support for assignment and are especially useful, *e.g.*, in locating methyl groups in triterpenes where multiplicities are often too diffuse to give convincing evidence.

The ready separation of the resonances of diastereoisomeric protons, allowing J_{gem} to be measured, should make available to those workers studying the effects of electronegativity (or any other influences) on J_{gem} hitherto unavailable values, and add substantially to the available data. Similarly, β, γ, and δ effects on vicinal couplings are now open to routine study, provided that line broadening does not hamper the acquisition of sufficiently accurate J values. The pseudocontact shift arises[9] only through the magnetic dipolar field effects of unpaired electrons, and does not affect bonding electron density. Therefore, in the aliphatic compounds which we have examined (where only evidence for pseudocontact shifts has been uncovered), coupling constants should not be affected, being field invariant. However, contact shifts arise by transfer of bonding electron density and this throws some doubt on the validity of the coupling constants obtained *via* contact shifts.[1] The $J_{2,3}$ coupling in quinoline appears to decrease at relatively high molar concentrations of Eu$(DPM)_3$ (see the H_3 resonance in the right-hand portion of Figure 3) and it may be that in this and related aromatics there is a significant contact shift contribution; this concept is supported by slightly anomalous shift ratios of the protons in aniline and pyridine. The origin of the broadening of the signal attributed to H-7 is unknown.

The separation of coincident peaks is of great utility in estimating molar ratios of components in a mixture where all nmr peaks are normally overlapping and methods such as vpc are not available due to ready thermal isomerization or decomposition.

Obviously one of the most important potential uses of Eu$(DPM)_3$ is in the location of functionality within a known carbon framework such as the steroid nucleus. The results shown in Table III are very promising, and show that the "distance-only" criterion of Hinckley is at least as good as measurements from a small molecular model in the compounds examined. In addition the G(19-Me)/G(18-Me) criterion will usually allow more facile and less ambiguous assignment of functionality than Zürcher's tables.[18,18a]

Experimental Section

Nmr spectra were measured on a Varian Associates HA 100 spectrometer operated at 100 MHz at normal probe temperatures. Chemical shifts are in δ units (parts per million) from internal TMS. Eu$(acac)_3 \cdot H_2O$ was prepared by the method of Purushotham, *et al.*,[19] Eu$(DBM)_3$ by the method of Charles and Perrotto,[20] and Eu$(DPM)_3$ by the method of Eisentraut and Sievers,[21] the dipivalomethane being derived from methyl pivalate and pinacolone by Claisen condensation with sodium hydride.[22]

Substrates for study were obtained commercially, synthesized by standard routes, or kindly donated by colleagues in this laboratory. They were purified by recrystallization, distillation, sublimation, or vpc as appropririate.

Acknowledgment. J. K. M. S. thanks the S.R.C. for a maintenance grant.

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(18) R. F. Zürcher, *Helv. Chim. Acta*, 46, 2054 (1963).

(18a) Note Added in Proof. Since submission of this manuscript, several reports on the use of Eu$(DPM)_3$ and related compounds have appeared. Eu$(DPM)_3$ has been used as both a conformational (F. I. Carroll and J. J. Blackwell, *Tetrahedron Lett.*, 4173 (1970)) and structural (K. J. Liska, A. F. Fentiman, and R. L. Foltz, *ibid.*, 4657 (1970)) tool, while further evidence of its power in the steroid (P. V. DeMarco, T. K. Elzey, R. Blewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734, 5737 (1970); D. R. Crump, J. K. M. Sanders, and D. H. Williams, *Tetrahedron Lett.*, 4949 (1970)) and carbohydrate (I. Armitage and L. D. Hall, *Chem. Ind.* (*London*), 1537 (1970)) fields has been published. Applications of the less powerful Eu$(DPM)_3 \cdot 2$py have also been reported (C. C. Hinckley, *J. Org. Chem.*, **35**, 2834 (1970); G. M. Whitesides and J. San Filippo, *J. Amer. Chem. Soc.*, **92**, 6611 (1970)). Several attempts have been made to determine the mechanism of the induced shifts (see DeMarco, *et al.*; G. H. Whal and M. R. Peterson, *Chem. Commun.*, 1167 (1970); R. R. Frazer and Y. Y. Wigfield, *ibid.*, 1471 (1970)), but the claims of evidence indicating an important contact contribution to the shifts of protons near to the functional group are of little value as the position of the Eu^{3+} ion was arbitrarily chosen. However, Hart's elegant analysis (J. Briggs, F. A. Hart, and G. P. Moss, *ibid.*, 1506 (1970)) of the Pr$(DPM)_3$–borneol system shows that if the M^{3+} ion is correctly located there is no need to postulate any contact contribution. Our results for alicyclic ketones presented here confirm this view, although the approach is less rigorous than Hart's.

(19) D. Purushotham, V. R. Rao, and B. S. V. Rao, *Anal. Chim. Acta*, **33**, 182 (1965).

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

(21) K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254 (1965).

(22) K. R. Kopecky, D. Nonhebel, G. Morris, and G. S. Hammond, *J. Org. Chem.*, **27**, 1036 (1962).