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LANTHANIDE INDUCED SHIFT DIFFERENCE OF DIASTEREOTOPIC PROTONS[1]

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In a recent communication by Pirkle and co-workers[2], the use of chiral solvents and lanthanide shift reagents to distinguish meso from d or l diastereomeric epoxides was described; a dramatic difference between the lanthanide induced shift of the methine protons in the meso cis-2,3-butylene oxide (1) and its dl trans-isomer (2) was noted. The greater overall shifts displayed by the protons in the meso isomer were rationalized as a reflection of the fact that one of the two diastereotopically related faces of this isomer is more readily accessible to the europium complex than the sterically hindered faces of the corresponding dl isomers. This phenomenon, in which steric factors control induced shifts in cyclic ether systems seems readily explainable on the basis of either unequal populations of the two diastereomeric lanthanide-ether complexes or closer approach of the europium shift reagent to the unhindered face of the cyclic ether, both being due to steric factors.

Similar observations of lanthanide induced diastereotopic proton shift differences in acyclic systems appear to be less easily predictable and not as well documented[3]. In this regard and in connection with other studies on the stereochemistry of alcohols, we have observed strikingly different lanthanide induced spectral shifts between diastereotopic protons in acyclic systems. The alcohols we have investigated include 1-phenyl-5-methyl-6-exo-hydroxymethyl[3.1.0]hexane (1), its endo-isomer (2), 2-methyl-1-butanol (3), 2-phenyl-1-propanol (4), 2,3-dimethyl-2-pentanol (5) and 2-methyl-2,4-pentandiol (6)[4]. The results of our europium-$(fod)_3$ nmr studies are given in Table 1 which lists the shifts of protons in question vs. the range of europium to alcohol concentration ratios used and in Figure 2 in which shift differences between diastereotopic protons are plotted against molar ratios of Eu-alcohol. Among the most striking features observed are the dramatic differences in the induced shifts of the diastereotopic α-methylene protons in the exo-bicyclic alcohol 1, phenylpropanol 4 and butanol 3. Similar differences are displayed by the α-methyl and γ-methylene protons in the pentanol 5 and by the α-methyl and β-methylene protons in the pentandiol 6.

The factors that cause these dramatic enhanced differences in the lanthanide shifts between diastereotopic protons are not totally clear, especially in view of the fact that there appears to be little relationship between the proximity of the europium to the diastereotopic protons and the induced shift differences (for example, the induced Δν of the γ-methylenes in 5 at Eu/Alcohol ratio of 1.4 is 165 Hz compared to the α-methyl protons Δν of 11 Hz). However, it appears that steric factors would also direct the unsymmetrical positioning of the lanthanide reagent with respect to the diastereotopic protons in acyclic chiral alcohols since approach of the lanthanide reagent to the diastereotopic non-bonded pairs on oxygen should be of unequal energy as in the epoxide systems of Pirkle and co-workers and the systems asymmetry should dictate preferred conformations of the lanthanide about the C-O bond.[6]

Several other interesting phenomena regarding induced shifts were observed during these studies. The diastereotopic γ-methylene protons in alcohols 3 and 5 as mentioned above show much greater induced shift differences than their α-methylene and α-methyl counterparts. In addition, in 2-methylpentan-2,4-diol (6), a much greater lanthanide shift is displayed by the methyl protons at the tertiary alcohol site than those at the secondary alcohol site. Quite interestingly, Cockerill and Rackham[7] have observed just the opposite effect in the 2-hydroxy-1(2-hydroxyethyl) adamantane system, in which the α-methyl protons of the primary hydroxyethyl group showed a much greater induced shift than the methine proton at the secondary alcohol site. It appears that simple explanations based on proximity of the lanthanide to the non-bonded pairs on oxygen (expected to be nearer to secondary hydroxyl than tertiary due to steric factors) do not suffice in diol systems.

In summary, the intriguing observations of dramatic induced shift differences between diastereotopically related protons in chiral alcohol and diol substrates seem general although prediction of their magnitude on the basis of proximity to the complexing atoms seems difficult We hope to continue our initial studies in this area in order to clarify some of the questions raised by these observations.

REFERENCES AND NOTES

1. Support of this research by a Robert A. Welch Foundation grant is greatfully acknowledged.
2. W. H. Pirkle, S. D. Beare, M. Kainosho and K. Ajisaka, J. Amer. Chem. Soc., 94, 5925 (1972).
3. P. E. Pfeffer and H. L. Rothbart (Tetrahedron Lett., 2533 (1972)) have noted that $Eu(fod)_3$ magnifies the difference between the environments of geminal, diastereotopic protons in triglyceride systems, G. Schiemenz and H. Rast (ibid., 4685 (1971)) in alcohols, and J. Greene and P. Shelvin (Chem. Commun., 1092 (1971)) in sulfinyl compounds.
4. The syntheses of alcohols 1 and 2 have been described elsewhere[5]. The alcohols 3-6 were commercially available and purified before use.
5. P. S. Mariano and J. K. Ko, J. Amer. Chem. Soc., 94, 1766 (1972).
6. We have observed no indication of induced conformational preferences about carbon-carbon bonds due to the lanthanide reagent in the alcohol-lanthanide complexes as would have been indicated by variations in vicinal proton-proton coupling constants[8].
7. A. F. Cockerill and D. M. Rackham, Tetrahedron Lett., 5153 (1970).
8. For similar observations and discussion of the lack of induced conformational preferences by the lanthanide reagents see B. L. Shapiro, et al., J. Amer. Chem. Soc., 94, 4383 (1972).
9. Spectra were recorded on a 60 mHz instrument in carbon tetrachloride as solvent.

Figure 1. Lanthanide Induced Shift Differences vs. $Eu(fod)_3$ - Alcohol Concentration Ratios.

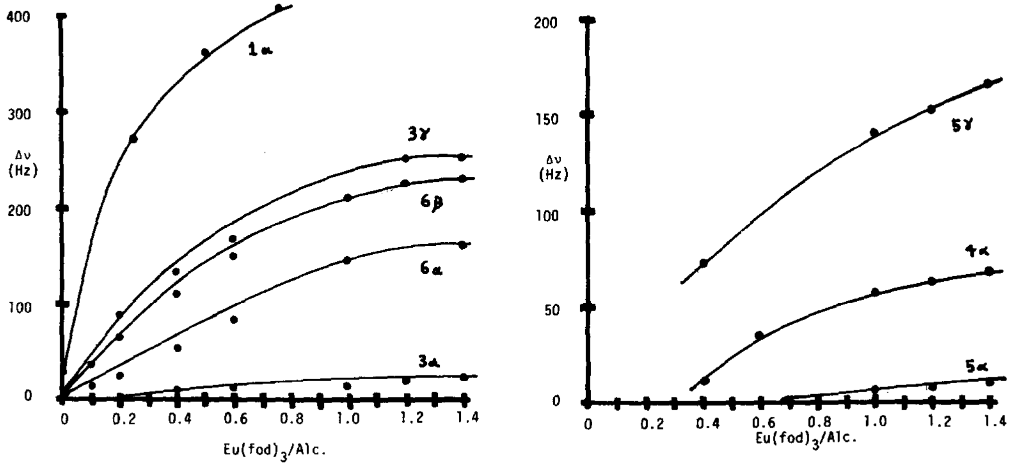
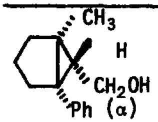
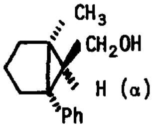
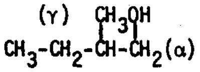
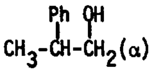
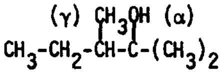
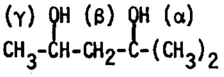


Table 1. Lanthanide Induced Shifts of Diastereotopic Protons and Diastereotopic Proton Shift Differences.

	Alcohols	Eu/Alcohol Range	Protons	$\Delta\nu_{H_1}{}^9$ (Hz)	$\Delta\nu_{H_2}{}^9$ (Hz)	$\Delta\Delta\nu^9$ (Hz)
1		0-0.75	(α)	716	310	406
2		0-0.60	(α)	1003	1003	0
3	 $(\gamma)\ CH_3\text{-}CH_2\text{-}\overset{CH_3}{C}H\text{-}\overset{OH}{C}H_2(\alpha)$	0-1.40	(α) (γ)	973 373	994 626	21 253
4	 $CH_3\text{-}\overset{Ph}{C}H\text{-}\overset{OH}{C}H_2(\alpha)$	0-1.40	(α)	894	961	67
5	 $(\gamma)\ CH_3\text{-}CH_2\text{-}\overset{CH_3}{C}H\text{-}\overset{OH\ (\alpha)}{C}\text{-}(CH_3)_2$	0-1.40	(α) (γ)	704 604	715 869	11 165
6	 $(\gamma)\ CH_3\text{-}\overset{OH}{C}H\text{-}\overset{(\beta)}{CH_2}\text{-}\overset{OH\ (\alpha)}{C}\text{-}(CH_3)_2$	0-1.40	(α) (β) (γ)	281 644 216	440 875	159 231