Lanthanide Shift Reagents as an Aid in the NMR Analysis of the Normal Alcohols C_6 to C_{11}

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ABSTRACT

A method is described that substantially aids in the interpretation of the nuclear magnetic resonance (NMR) spectrum of a series of six fatty alcohols (C_6 to C_{11}). The lanthanide shift reagent tris (2,2,6,6-tetramethylheptanedionate)praseodymium(III)[Pr(DPM)$_3$] is employed, and produces large shifts in the resonances of the various methylene groups in the chain depending on their position with respect to the hydroxy group. This paramagnetic shift for the first seven methylenes of these six alcohols is found to to be directly proportional to the amount of Pr(DPM)$_3$ added. Measurement of the coupling constants for the methylene groups in the chain are reported. The power of lanthanide shift reagents for both analytical and conformational information derived from their NMR spectra is demonstrated.

INTRODUCTION

The study of lipids has progressed rapidly as a result of recent sophisticated techniques in isolation and analysis (1). Mass spectrometry has proven itself an invaluable aid in identifying lipids (2), while infrared analysis is most valuable in detecting functional groups (3). High resolution nuclear magnetic resonance (NMR), spectroscopy, a powerful tool in many fields of organic chemistry, has been used to advantage in the study of some unsaturated fatty acids (4) but has found only limited application in the analysis of saturated fatty alcohols, acids and esters, due to coincident chemical shifts of the successive methylene groups in the chain. A typical spectrum for a saturated fatty alcohol (Fig. 1) produces four recognizable resonances: (a) the hydroxy proton, (b) the triplet for the methylene protons α to the hydroxy group, (c) the remaining methylenes in the chain, and (d) the methyl group. Attempts have been made to separate overlapping peaks by taking advantage of the change in the chemical shifts produced at 60 vs. 100 MHz (5). However, these differences are not that significant. Recently Hinckley (6) and Sanders and Williams (7) reported that large chemical shifts were induced in the NMR spectra of certain compounds by the addition of tris(dipivalomethanato)-europium(III)[Eu(DPM)$_3$] and the bis-pyridine adduct. Application of this technique to a series of fatty alcohols leads to dramatic chemical shifts, which should prove to be an asset in the analysis of fatty acids and their derivatives.

MATERIALS AND METHODS

NMR spectra were measured on a Varian HA-100 spectrometer at 31.2-31.3 C (probe temperature). Chemical shifts are in τ units (parts per million) from internal tetramethylsilane (TMS). All of the alcohols were obtained. from PolyScience Corporation and were 99.5% pure. The lanthanide shift reagent tris(2,2,6,6-tetramethylheptanedionate)praseodymium(III)[Pr(DPM)$_3$] was obtained from Ventron Alfa Inorganics and was sublimed before use. Assignments of the various chemical shifts to particular carbon atoms were verified by spin decoupling experiments. For direct comparison between the different alcohols the same molar ratio of alcohol to lanthanide shift reagent was maintained. All samples were prepared using Matheson-Coleman-Bell spectroscopic grade carbon tetrachloride.

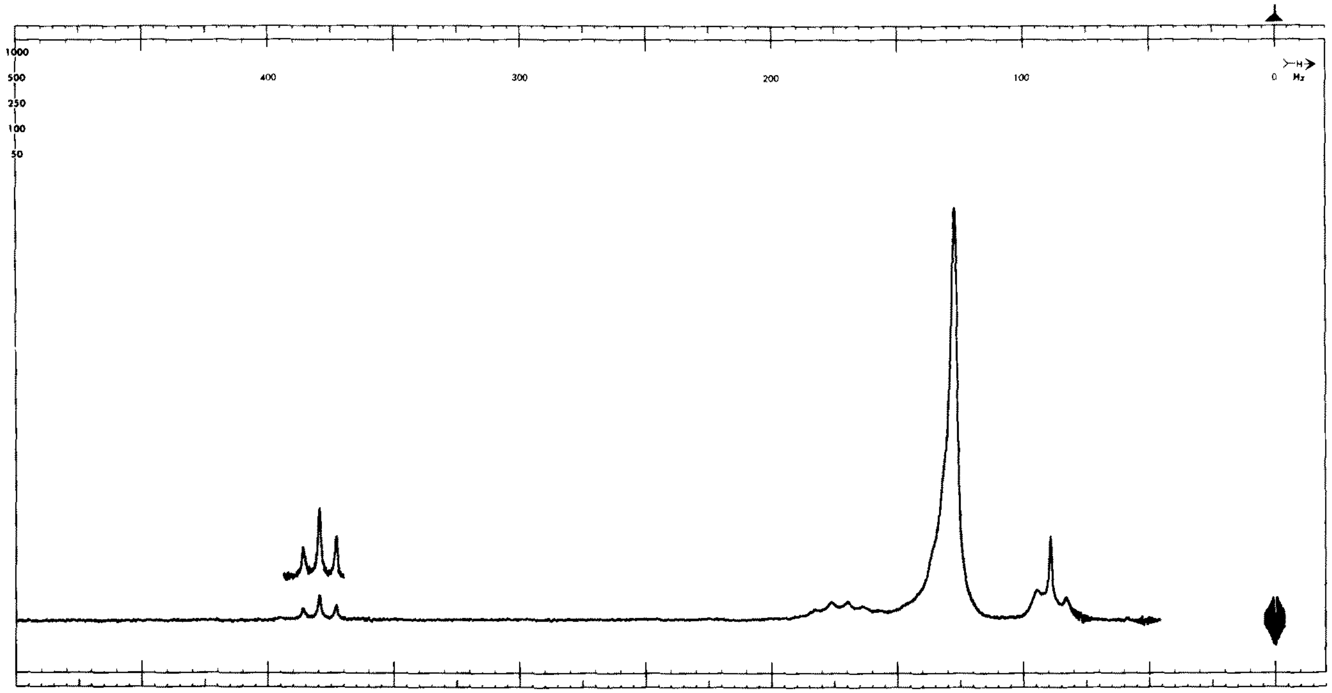

FIG. 1. NMR spectrum (100 MHz) of *n*-undecanol containing two drops of trifluoroacetic acid in CCl_4. Sweep width 500 cps. TMS used as an internal standard.

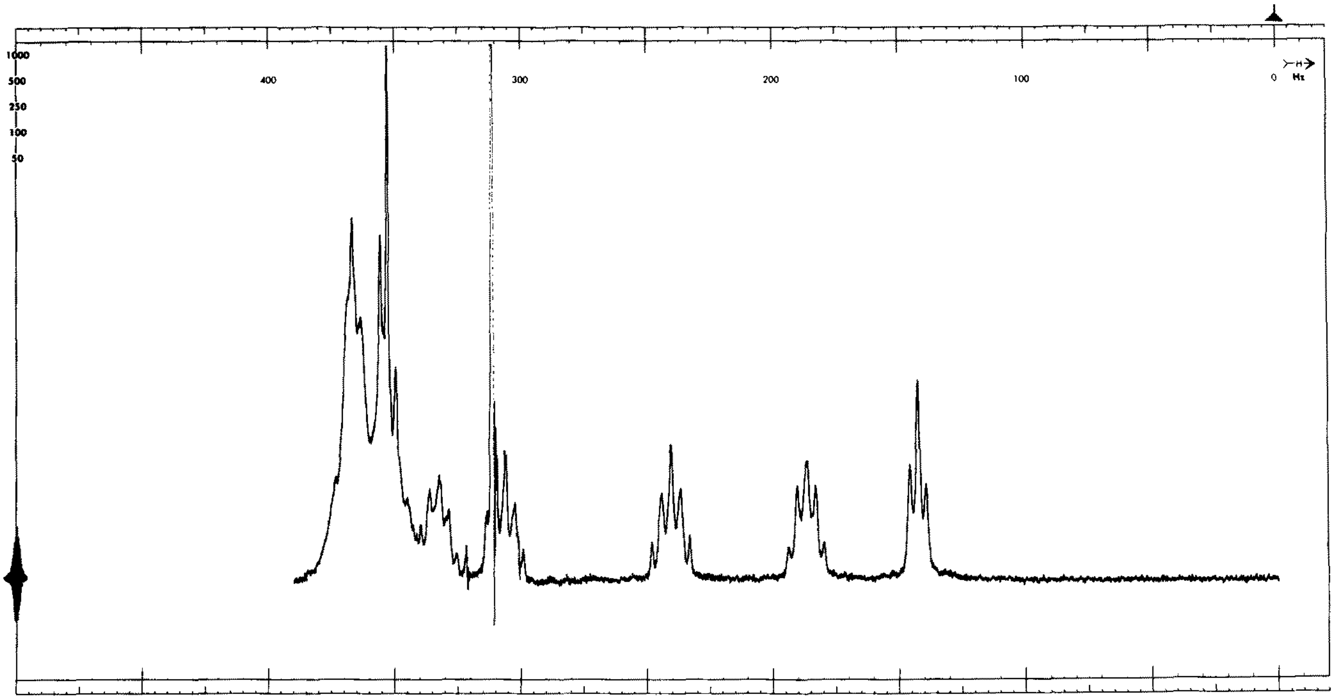

FIG. 2. NMR spectrum (100 MHz) of *n*-undecanol (47.11 mg) in 0.4 ml of CCl_4 containing 25.65 mg of $Pr(DPM)_3$. TMS added as an internal standard. Sweep width 1000 cps (6.23τ to 16.23τ).

TABLE I

NMR Chemical and Paramagnetic Shifts of the Methylene Protons of the Alcohols *n*-Hexanol to *n*-Undecanol Induced by $Pr(DPM)_3$

Alcohol[a]	$Pr(DPM)_3$[b] mg	ν_1[c]	$\Delta\nu_1$[d]	ν_2	$\Delta\nu_2$	ν_3	$\Delta\nu_3$	ν_4	$\Delta\nu_4$	ν_5	$\Delta\nu_5$	ν_6	$\Delta\nu_6$	ν_7	$\Delta\nu_7$
n-Hexanol	26.86	14.01	7.51	12.87	4.35	11.67	3.02	10.23	1.50	9.67	0.94				
n-Heptanol	44.60	18.88	12.38	15.66	7.14	13.62	4.97	11.20	2.47	10.26	1.53	9.70	0.97		
n-Octanol	47.81	19.67	13.17	16.10	7.58	13.91	5.26	11.37	2.64	10.35	1.62	9.77	1.04		
n-Nonanol	39.13	17.25	10.75	14.73	6.21	12.97	4.32	10.88	2.15	10.07	1.34	10.58	0.85		
n-Decanol	52.37	21.05	14.55	16.90	8.39	14.48	5.83	11.64	2.91	10.53	1.80	9.87	1.14	9.43	0.70
n-Undecanol	47.11	19.60	13.10	16.08	7.57	13.90	5.25	11.35	2.62	10.34	1.61	9.74	1.01	9.36	0.63

[a] 0.24 mmol.

[b] Sublimed before use.

[c] Chemical shifts reported in τ units relative to $Si(CH_3)_4 = 10.00$.

[d] Paramagnetic shift (in ppm) which is the difference in chemical shift between a spectrum obtained in CCl_4 and one obtained in the presence of $Pr(DPM)_3$.

TABLE II

NMR Parameters of the Methylene Protons of the Alcohols of Various ROH-$Pr(DPM)_3$-CCl_4 Systems

Alcohol	η_1[a]	J_1[b,c]	η_2	J_2	η_3	J_3	η_4	J_4	η_5	J_5	η_6	J_6	η_7
n-Hexanol	28.0	6.5	16.2	7.0	11.24	7.5	5.58	7.5	3.50	---	---	---	---
n-Heptanol	27.8	6.5	16.0	7.0	11.14	7.5	5.54	7.5	3.43	7.5	2.17	---	---
n-Octanol	27.5	6.5	15.9	7.0	11.00	7.6	5.52	7.5	3.39	7.5	2.18	7.0	---
n-Nonanol	27.5	6.5	15.9	7.0	11.04	7.5	5.49	7.5	3.42	7.5	2.17	7.5	---
n-Decanol	27.8	6.0	16.0	7.0	11.13	7.5	5.56	7.5	3.44	7.5	2.18	7.5	1.34
n-Undecanol	27.8	6.5	16.1	7.0	11.14	7.6	5.56	7.5	3.42	7.5	2.14	7.3	1.34

[a] $\dfrac{\Delta\nu_i}{\text{mg } Pr(DPM)_3}$; using the data from Table I.

[b] Spin-spin coupling constants of the protons on the ith carbon atom of the lipid alcohol for data listed in Table I.

[c] Expressed in Hz(±0.2).

TABLE III

Reduction Factors for the Alcohols
of Various ROH-$Pr(DPM)_3$-CCl_4 Systems

Alcohol	R_{11}[a]	R_{12}	R_{13}	R_{14}	R_{15}	R_{16}	R_{17}
n-Hexanol	1.00	0.603	0.401	0.199	0.125	---	---
n-Heptanol	1.00	0.576	0.401	0.199	0.123	0.078	---
n-Octanol	1.00	0.576	0.399	0.200	0.123	0.079	---
n-Nonanol	1.00	0.578	0.401	0.200	0.124	0.079	---
n-Decanol	1.00	0.576	0.400	0.200	0.124	0.078	0.048
n-Undecanol	1.00	0.579	0.401	0.200	0.123	0.077	0.048

[a] $R_{1j} = \frac{\eta_j}{\eta_1}$; using the data from Table II.

RESULTS

Upon the addition of only 25.65 mg of $Pr(DPM)_3$ the normal spectrum (Fig. 1) of 47.11 mg of *n*-undecanol with three resonances is transformed into a spectrum (Fig. 2) with seven distinguishable resonances. Additional amounts of $Pr(DPM)_3$ produce a spectrum where the chemical shifts of the protons on eight of the eleven carbon atoms can be identified. The triplet (multinomial intensities 1:2:1) at 13.38 τ (Fig. 2) corresponds to two protons on the first carbon atom. Similarly, the successive quintets (multinomial intensities of 1:3:5:3:1) at 12.27, 11.19, 9.88 and 9.35 τ correspond to the methylene protons on carbon atoms 2, 3, 4 and 5, respectively. Spin decoupling verified the assignment of the chemical shifts. Thus, irradiating the highest field quintet collapses the adjacent triplet to a singlet. Similarly, irradiating any other quintet collapses the adjacent quintets to triplets.

Table I reports the values of the chemical (ν_i) and paramagnetic ($\Delta\nu_i$) shifts for the hydrogens on a particular methylene group for the six alcohols, resulting from the amount of $Pr(DPM)_3$ listed. These results are representative of the shifts derived from at least three separate runs on each alcohol.

Table II lists several parameters derived from the $Pr(DPM)_3$ induced NMR spectra of the six alcohols. The constants η indicate that over the concentration range of alcohol and $Pr(DPM)_3$ studied, the paramagnetic shift is directly proportional to the amount of $Pr(DPM)_3$ added. The spin-spin coupling constant, J_i, for all of the hydrogens of a particular methylene group were measured, except for hydrogens on methylene groups more than seven carbon atoms removed from the α-carbon atom. The reduction factors, which are derived from the corresponding constants (η) in Table II, are indicated.

DISCUSSION

Although NMR is a very useful analytical method for the structural identification of many molecules its application to the analysis of fatty acid derivatives has been limited because of overlapping resonances. The use of certain paramagnetic ions to produce contact shifts in a variety of specialized molecules is well known (8). It has been suggested (9) that paramagnetic lanthanide ions should produce a shift that is largely pseudocontact in nature. Likewise the very short electronic relaxation times of these ions (10) indicate the feasibility of using them for shift reagents. Even more recently the usefulness of lanthanide ions as NMR probes of biological systems has been indicated (11).

The lanthanide shift reagent that has received the most attention is $Eu(DPM)_3$. While we also find this reagent to be quite useful we prefer the corresponding praseodymium complex $Pr(DPM)_3$ because smaller amounts of the latter reagent produce comparable shifts. We also find that $Pr(DPM)_3$ has the same advantage as $Eu(DPM)_3$, that is, its short electronic relaxation time gives shifted resonances that are not unduly broadened.

The values of the chemical shifts (Table I) for the hydrogens on a particular methylene group for different alcohols (e.g., $\Delta\nu_2$ of *n*-hexanol = 435 Hz and $\Delta\nu_2$ of *n*-decanol = 839 Hz) seem to bear little relation to one another except to indicate that increased amounts of $Pr(DPM)_3$ lead to an increased shift. However, very similar shifts are noted for the hydrogens on a particular methylene group for different alcohols where approximately the same amounts of $Pr(DPM)_3$ have been used (e.g., $\Delta\nu_2$ of *n*-octanol = 758 Hz, and $\Delta\nu_2$ of *n*-undecanol = 757 Hz). We have found that when the molar ratio of alcohol to $Pr(DPM)_3$ is the same for any of the alcohols *n*-hexanol to *n*-undecanol, the NMR spectra of the protons on the first seven methylene groups are very nearly identical. Over the concentration range of alcohol and $Pr(DPM)_3$ studied, we have found that the shift of the protons on the first seven carbon atoms for these six alcohols is directly proportional to the amount of $Pr(DPM)_3$ added. The values of η_i reported in Table II indicate this result. For the protons of a particular carbon atom of any of the six alcohols, this constant is very similar (e.g., η_3 = 11.14 of *n*-undecanol, and η_3 = 11.04 of *n*-nonanol); except for *n*-hexanol these values vary no more than ±1%.

For a system where the paramagnetic shift is primarily pseudocontact in nature (9), equation 1 is appropriate (12):

$$\Delta H_i/(H)_j = \frac{c_1}{R_j^3}(3\cos^2 X_j - 1) - \frac{c_2}{R_j^3}(\sin^2 X_j \cos 2\Omega_j) \qquad [1]$$

where c_1 and c_2 are constants for a particular alcohol at specified experimental conditions, X_j and Ω_j is the angular dependence of the jth proton with respect to the paramagnetic ion and R_j is a function of the distance from the metal to the jth proton.

What conclusions can be drawn from the results indicated here? Most simply, it can be said that these six alcohols have very similar conformations. The chemical shift observed for the hydrogen atoms of a particular methylene group is the time averaged chemical shift of these protons for all uncomplexed and complexed forms of the alcohol. The very similar chemical shift which is observed for the hydrogen atoms on a particular methylene group of any of these alcohols indicates that: (a) the formation constant(s) of the complexes of each of these alcohols are very similar, (b) the angular dependence of a particular methylene group with respect to the paramagnetic ion is identical for each fatty alcohol, and (c) the distance function for a particular methylene group to the paramagnetic ion is very similar for each of these alcohols.

Before the discovery of lanthanide shift reagents, the spin-spin coupling constants of the protons of only the first few alcohols in a homologous series could be determined. For the higher molecular weight alcohols of a homologous series, only the coupling constants of the protons on or near terminal methyl and hydroxy groups could be determined (Fig. 1). Now, the coupling constants of many of the protons on the methylene groups may be determined (Table II). The reduction factors (Table III) for the six alcohols are very similar. These factors are a measure of the influence of the paramagnetic ion on a particular set of methylene protons of the coordinating ligand.

Application of the lanthanide shift reagents to the study of other fatty acid derivatives is under investigation.

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REFERENCES

1. Chapman, D., "The Structure of Lipids," John Wiley and Sons, Inc., New York, 1965.
2. Beynon, J.H., "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier Publishing Company, Amsterdam, The Netherlands, 1960.
3. Freeman, N.K., JAOCS 45:798 (1968).
4. Hopkins, C.Y., Ibid. 45:778 (1968); C.Y. Hopkins in "Progress in the Chemistry of Fats and Other Lipids," Edited by R.T. Holman, Vol. 8, Pergamon Press, Oxford, England, 1965, p. 213-252.
5. Bekker, Z.M., and Y.N. Molin, Biophysics 14:1053 (1969).
6. Hinckley, C.C., J. Am. Chem. Soc. 91:5160 (1969).
7. Sanders, J.K.M., and D.H. Williams, Chem. Comm. 422 (1970).
8. DeBoer, E., and H. van Willigan, Progr. Nucl. Mag. Res. Spectrosc. 2:111 (1967); D.R. Eaton and W.D. Phillips, Adv. Mag. Resonance 1:103 (1965).
9. Eaton, D.R., J. Am. Chem. Soc. 87:3097 (1965).
10. Low, W., Editor, "Paramagnetic Resonance," Vol. 2, Academic Press, New York, 1963.
11. Morallee, K.G., E. Neiboer, F.J.C. Rossetti, R.J.P. Williams, A.V. Xaiver and R.A. Dwek, Chem. Comm. 1132 (1970).
12. McConnell, H.M., and R.E. Robertson, J. Chem. Phys. 29:1361 (1958); G.N. La Mar, W. DeW. Horrocks, Jr. and L.C. Allen, Ibid. 41:2126 (1964).

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