SHORT COMMUNICATION

NMR Chemical Shift Reagents. Application to Structural Determination of Lipid Derivatives

ABSTRACT

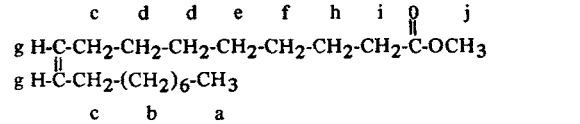
Chemical shift reagents (csr) markedly expand the nuclear magnetic resonance spectra of lipid derivatives thus providing considerably more structural information than it has hitherto been possible to obtain. Preferred csr are rare earth complexes of europium (III) and praseodymium (III) with certain anionic ligands. The use of csr with methyl oleate is described here.

NMR is an extremely useful technique for the structural determination of many types of organic compounds. Although the technique is used by lipid chemists (1), it is severely limited in scope and utility because in most long chain compounds ($> C_4$) the majority of the chain methylene protons are, for all practical purposes, magnetically equivalent. These protons yield a broad signal of overlapping resonances which precludes their identification and counting as well as the determination of their coupling constants (J values). Recently, some interpretation problems similar to those in the lipid field have been overcome for *n*-hexanol and dimethyl tetradecanedioate (3) by determining their NMR spectra in the presence of NMR chemical shift reagents (csr).

The best csr developed thus far are rare earth complexes of europium (2,3) or praseodymium (4). Typical csr complexes combine Eu(III) or Pr(III) with the anionic ligands: 2,2,6,6-tetramethyl-3,5-heptanedione or 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione; abbreviated designations for these complexes are $Eu(thd)_3$, $Pr(thd)_3$, $Eu(fod)_3$ and $Pr(fod)_3$. Csr can markedly expand NMR spectra of compounds containing functional groups with lone pairs of electrons, if the lone pair can coordinate with the rare earth metal. The spectra are expanded because the chemical environment of protons near the coordination site is different from the environment of distant protons in the molecule. The signals of protons near the coordination site are therefore displaced. This displacement is directly related to the distance between the protons in question and the complexed metal atom; the smaller the distance, the greater the shift. Even for distances greater than 25 Å from the coordination site, a measurable displacement (0.1 ppm) of proton absorption can be expected (5). The magnitude of the change in chemical shift is also related to the molar ratio of csr to substrate, and is generally optimized as this ratio approaches 1; in many cases a linear relationship is observed between the effected chemical shift and the molar ratio of csr to substrate (3). Complexes containing Eu and Pr complement each other since, relative to tetramethylsilane (TMS), the Eu complexes shift proton signals downfield from their original position whereas Pr complexes shift them upfield.

We are currently investigating the scope and limitations of using csr to expand the amount of structural information that can be derived from the NMR spectra of: saturated, unsaturated, and chain-substituted fatty alcohols, amines, acids, methyl esters and related derivatives; mono-, di- and tri-glycerides; phospholipids; and other long chain compounds. We prefer to use the csr $Eu(fod)_3$ and $Pr(fod)_3$ since they are more readily soluble than $Eu(thd)_3$ and $Pr(thd)_3$ in CCl_4, which is the solvent of choice. As opposed to $CDCl_3$, CCl_4 can be easily maintained free of strong acid which destroys the complex. $Eu(thd)_3$ is a useful complement to $Eu(fod)_3$, however, since the latter absorbs between 1 and 2δ whereas $Eu(thd)_3$ absorbs upfield of TMS. In some instances solubility problems have been encountered in work with $Eu(thd)_3$ that have led to line broadening and loss of resolution.

To illustrate one application of csr, the nmr spectrum of methyl oleate both with and without $Eu(fod)_3$ is tabulated low. The protons of methyl oleate are coded to correspond to the peaks observed in the NMR spectra. The spectra were determined in CCl_4 using a Varian XL-100 spectrometer.



Comparison of the data in Tables I and II shows that in the presence of $Eu(fod)_3$ many of the complex, uninterpretable, overlapping resonances in the methyl oleate chain become simple first order signals with the anticipated multiplicity (protons e,f,h,i). Furthermore, the splitting patterns and proton shifts demonstrate the absence of both a double bond and branching until at least C_8 in the chain.

The results with methyl oleate (Tables I and II) demonstrate that use of csr can lead to a considerable

TABLE I

Spectrum I[a]

Proton	δ(TMS[b] = 0)	Multiplicity
a	0.89	deformed triplet
b,d,e,f,h	1.29	broad singlet
c	2.05	overlapped peaks
i	2.21	
j	3.59	singlet
g	5.28	multiplet

[a]Twenty milligrams of methyl oleate in 0.5 ml CCl_4.
[b]TMS, tetramethylsilane.

TABLE II

Spectrum II[a,b]

Proton	δ(TMS[c] = 0)	Multiplicity
a	0.89	Deformed triplet
b	1.29	Broad singlet
c,d[d]	1.83-2.29	Overlapped peaks
e[d]	2.60	Pentet
f[d]	4.49	Pentet
g	5.33	Multiplet
h[d]	7.99	Pentet
i[d]	12.51	Triplet
i[d]	12.89	Singlet

[a]Twenty milligrams of methyl oleate in 0.5 ml CCl_4.
[b][Eu(fod)3] / [methyl oleate] = 1.83.
[c]TMS, tetramethylsilane.
[d]Protons which undergo observable changes in chemical shift.

expansion of the structural information normally obtainable through NMR spectroscopy of lipid derivatives. Further details, including the scope and limitations of the use of csr, will be presented at the American Oil Chemists' Society Meeting in Atlantic City, October 1971, and in papers to be submitted later to the Journal.

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