Isotope Shifts in ^{13}C-N.M.R. Spectra of ^{18}O-labelled Acetals; Multiple Labelling Effects at β-Carbons

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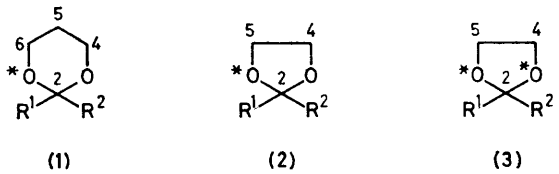
Summary Acetals which are isotopically mono- or di-substituted with ^{18}O show ^{13}C-n.m.r. isotope shifts, both at directly attached carbons and at β-carbons, which are dependent on the number of labelled oxygens in an additive fashion.

OXYGEN-18 isotopic substitution causes a measurable structure-dependent upfield shift in the ^{13}C-n.m.r. signals of directly attached carbon atoms.[1,2] Because this permits easy non-degradative observation of the location and extent of oxygen labelling in highly oxygenated compounds, the method has already seen use in recent metabolic[3,4] and mechanistic[5] studies. We embarked on the present study to establish an empirical basis for investigation of the biosynthetic path to acetal-containing metabolites such as the carcinogenic aflatoxins,[3,6] and to examine the additivity effects of multiple oxygen-18 substitution[2] on this functional group. We now report the syntheses of a series of mono- and di-labelled ^{18}O-acetals, and their 100·6 MHz ^{13}C-n.m.r. spectra which show additivity of isotope shifts not only at directly bonded carbons, but also at carbons separated by an intervening methylene group (β-effect).

The acetals depicted in the Table were prepared in *ca.* 80% yield by adopting the small scale acetalization procedure of Barton *et al.*[7] Typically, 0·5 mmol of unlabelled carbonyl compound (heptanal, cyclohexanone, or nonan-5-one) and 0·5 to 1·5 mmol of the appropriate ^{18}O-diol were refluxed overnight in benzene containing a trace of toluene-*p*-sulphonic acid; water was continuously removed using a Soxhlet apparatus containing granular calcium hydride. The [1-^{18}O]propane-1,3-diol required for syntheses of (**1a**) and (**1b**) could be obtained from 3-bromopropan-1-ol by displacement[8] with sodium [$^{18}O_2$]acetate[9] in methanol followed by basic hydrolysis. Singly labelled [^{18}O]ethylene glycol for the preparation of (**2a**—**c**) was generated by acidic hydrolysis[10] of ethylene oxide in [^{18}O]water (96% isotopic purity). The corresponding doubly labelled starting material for (**3a**—**c**), [$^{18}O_2$]ethylene glycol, was made by exchange[11] of oxalic acid with [^{18}O]water followed by reduction[12] of the dried[13] acid with diborane.



(1) (2) (3)

*O = ^{18}O

a; R^1 = Me[CH_2]$_5$, R^2 = H
b; R^1R^2 = –[CH_2]$_5$–
c; R^1 = R^2 = Bu^n

Comparison of the isotope shifts (Table) at C(2) suggests that replacement of hydrogen at R^2 (**1a**) or (**2a**) by an alkyl group (**1b**), (**2b**), or (**2c**) increases the magnitude of the effect

TABLE. Isotope shifts in 100·6 MHz ^{13}C-n.m.r. spectra[a] of ^{18}O-acetals.

Compound	100 × Shift[b] in p.p.m. C(2)	C(4)	C(5)	C(6)
(**1a**)	2·1			2·0
(**1b**)	2·6			2·2
(**2a**)	2·3	0·8	2·0	
(**2b**)	2·8	0·7	2·3	
(**2c**)	2·7	0·6	2·1	
(**3a**)	4·6	2·8	c	
(**3b**)	5·5	2·9	c	
(**3c**)	5·5	2·8	c	

[a] See ref. 1 for experimental conditions. [b] Shifts are ±0·1 Hz and are upfield from the corresponding signal for the $^{16}O_2$-species which was used as internal standard. [c] C(4) and C(5) identical because of symmetry.

by about 0·005 p.p.m. A similar phenomenon has also been observed with alcohols and carbonyl compounds.[1,2] Risley and Van Etten have shown that within experimental error the effect of multiple oxygen-18 substitution in esters and orthocarbonates is additive on the central carbon.[2] The same is true for acetals; the shifts at C(2) of the doubly labelled compounds (**3a**—**c**) are twice those of the singly labelled analogues (**2a**—**c**).

Currently available high-field n.m.r. spectrometers are not usually able to resolve ^{18}O-induced shifts at carbons β to the site of isotopic substitution, although such effects are visible in favourable cases.[1] Apparently the bridging carbons C(4) and C(5) in the ethylene glycol-derived acetals (**2**) and (**3**) constitute such a case (Figure), whereas the β-methylenes [C(5)] of acetals (**1a**) and (**1b**) appear as somewhat broadened signals. Comparison of mass-spectral isotope ratios with ^{13}C-n.m.r. peak intensities of mixtures of (**2**) or (**3**) with unlabelled material allowed assignment of the various resonances. Within experimental error this β-effect is also additive. For example, adding the β-shift at C(4) in mono-labelled (**2**) to the α-shift at C(5) in the same compounds gives reasonable agreement with the observed isotope shift at C(4) in the corresponding di-labelled compounds (**3**). This additivity is illustrated by the spectrum of a mixture of (**2b**) and (**3b**) (Figure). The alkyl groups (R^1 or R^2) show only slight peak broadening at the carbon β to the labelled oxygen.

The additive isotope shifts of acetals at directly-attached carbons (0·020 to 0·028 p.p.m./^{18}O atom) are slightly smaller than those at the alkyl carbon of esters,[1,2] but larger than those in orthocarbonates (0·015 p.p.m. ^{18}O atom).[2] This supports the emerging empirical trend that the presence of an atom having a lone pair of electrons adjacent to the ^{18}O-substituted carbon reduces the shift, and that conjugation of that lone pair with an electron-withdrawing group

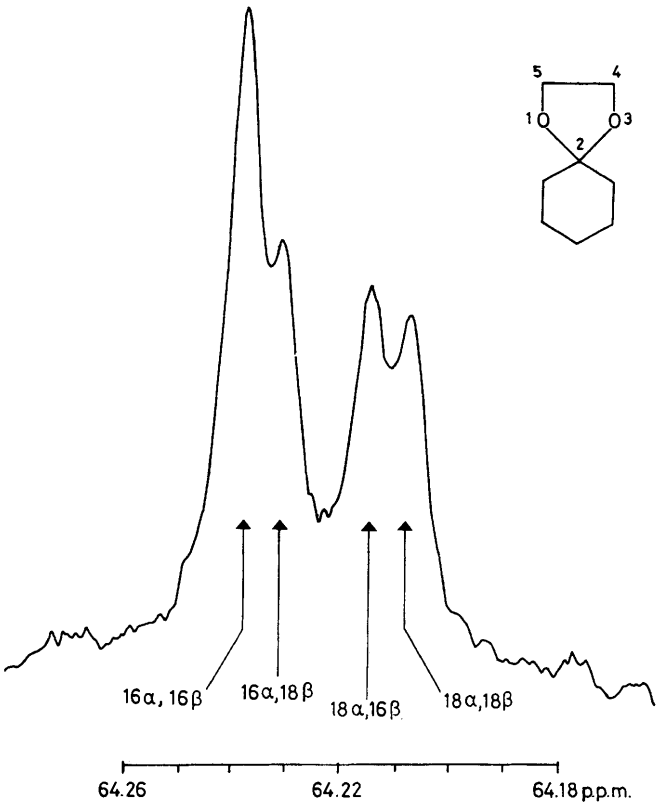


FIGURE. Proton-decoupled 100·6 MHz ^{13}C-n.m.r. spectrum [showing signals for C(4) and C(5)] of a mixture of (**2b**) and (**3b**), and the corresponding unlabelled compound. The numbers 16 and 18 refer to the isotope of oxygen which is directly-attached (α) or separated by a CH_2 group (β).

increases the shift. The β-effects (*ca.* 0·007 p.p.m.) are also additive, but spectrometers operating at much higher field will be necessary to make accurate structure–magnitude relationships accessible.

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