Setting the Anomeric Effect against Steric Effects in Simple Acyclic Acetals. Non-anomeric Non-classical Conformations. An N.M.R. and Molecular Mechanics Investigation

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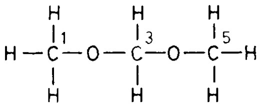
N.m.r. parameters for a series of simple aliphatic acetals indicate that the preferred conformation changes from the anomeric one found in formaldehyde dimethyl acetal (formal), to a new one whose structure is suggested by molecular mechanics calculations.

In simple acetals like formal, formaldehyde dimethyl acetal (**1**), the anomeric effect[1] appears as a preference[2] for the conformation (**2**) over the conformation (**3**) which is the equivalent of the most stable one in pentane. The 'eye' symbol shows one, illustrative dihedral angle.† When substitution is introduced on the central C-3 carbon, (*i.e.* in the methyl acetal of a higher aldehyde RCHO), the substituent R cannot be *anti* to both methyl groups in the anomeric conformation like (**2**), so there is a destabilising methyl–R steric interaction. Likewise when substitution is introduced at C-1 or C-5 in (**1**), further steric interactions are inevitable.

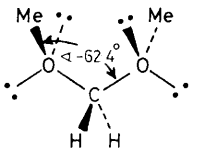
We now report three sets of n.m.r. measurements which give a clear indication of dramatic changes in conformation with substitution in the methyl, ethyl, and isopropyl acetals of formaldehyde, acetaldehyde, propionaldehyde, isobutyraldehyde, and pivalaldehyde. Molecular mechanics calculations, exploiting a recent modification which parameterises the C–O–C–O–C anomeric effect,[3] help define these changes.

Studies of rigid molecules[4–6] show that the one-bond coupling constant in a $R^{13}C^{1}H(OR')_2$ fragment should be about 166—169 Hz when the hydrogen is *gauche* to four oxygen lone pairs,[4,5] it should be about 162 Hz when the hydrogen is *gauche* to three lone pairs and *anti* to one,[6] and it should be about 155—158 Hz when the hydrogen is *gauche* to two lone pairs and *anti* to two.[4,5]

The first column in Table 1 shows experimental measurements of the one bond coupling in a series of acyclic acetals. The 162.1 Hz coupling in formaldehyde dimethyl acetal fits well for the anomeric conformation (**2**). All other compounds show noticeably smaller values for this coupling, whether the substitution be at C-1 (or C-5), or at C-3.


$H-\underset{H}{\overset{H}{C_1}}-O-\underset{H}{\overset{H}{C_3}}-O-\underset{H}{\overset{H}{C_5}}-H$

(1)



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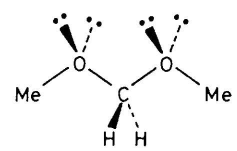

(3)

The second column of data in Table 1 shows the vicinal coupling constant between ^{13}C-1 (or C-5) and a hydrogen on C-3 (the 'anomeric' hydrogen). Although the intrinsic substituent effect of alkyl groups on this coupling should be small, all values are less than that found in the parent formal (**1**), slightly so for formaldehyde derivatives, and markedly so for higher aldehydes.

The right hand columns of data in Table 1 show ^{13}C chemical shifts of the C-3 carbon of the acetals. Much is known (from work on methylated 1,3-dioxanes[7]) about the changes in chemical shift produced at C-3 by substituting H at C-1 or C-5 by CH_3, without changing the conformation. By this means C-3 chemical shifts have been calculated for ethyl and isopropyl acetals as perturbations (from substituent effects) on the *experimental* value for the methyl acetal. These agree poorly with experimentally determined chemical shifts.

Each of these three n.m.r. criteria suggests that conformations and their populations change down the series and molecular mechanics studies help suggest what these changes are. For example calculations on the dimethyl acetal of acetaldehyde show that an anomeric conformation (**4**) with dihedral angles similar to those in (**2**) is still the most stable, so the different n.m.r. parameters are not explained thereby. A second conformation (**5**) however is calculated to be only 0.46 kcal/mol (cal = 4.184 J) less stable, and should be significantly

Table 1. ^{13}C N.m.r. data for the acetals $R^{13}CH(OR')_2$.

R	R′	$^{1}J_{CH}$/Hz	$^{3}J_{CH}$/Hz[a]	δ(C-3), obs.	δ(C-3),[b] calc.	Δδ[c]
H	Me	162.1	6.4	97.3		
H	Et	161.6	6.2	95.0	96.5	−1.5
H	Pr^i	161.4	6.1	90.7	85.9	4.8
Me	Me	161.1	4.8	100.8		
Me	Et	159.6	4.5	99.1	100.0	−0.9
Me	Pr^i	157.4	4.3	96.7	89.4	7.1
Et	Me	159.7	4.9	105.5		
Et	Et	158.2	4.6	103.8	104.7	−0.9
Et	Pr^i	156.0	4.3	101.3	94.1	7.2
Pr^i	Me	158.2	5.1	109.4		
Pr^i	Et	157.1	4.6	107.7	108.6	−0.9
Pr^i	Pr^i	154.7	4.3	104.2	98.0	6.2
Bu^t	Me	155.6	4.9	113.6		
Bu^t	Et	155.7	4.7	110.2	112.8	−2.6
Bu^t	Pr^i	153.0	4.2	105.5	102.2	3.3

[a] Coupling of the anomeric proton to ^{13}C of R′. [b] For each set of three compounds with the same group R, δ_C calc. for R′ = Et or R′ = Pr^i is based on δ_C obs. for R′ = Me, modified by Pihlaja's substitution parameters.[7] [c] $\delta_{obs.} - \delta_{calc.}$.

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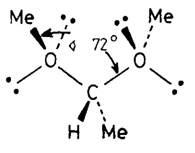
† All diagrams (**2**)—(**7**) are stylised. Tetrahedral bond angles and 60 and 180° dihedral angles are not necessarily obtained.



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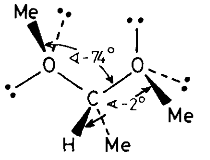

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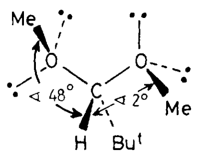

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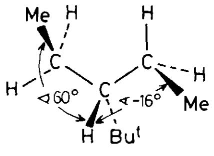

(7)

populated. Thus even on a simple substitution by one methyl group, a change to a mixture of conformations is indicated, and this is reflected in the observed n.m.r. parameters. In pivalaldehyde dimethyl acetal, a conformation (**6**) similar to this new one (**5**) is calculated to be more stable than the anomeric one like (**4**) by 3.26 kcal/mol.[‡]

The striking features of these conformations, (**5**) and (**6**), is that while one alkoxy group adopts a near-to-anomeric arrangement, with a lone pair *anti* to the C–O bond, and the alkoxy methyl *anti* to the central substituent to reduce the steric interaction, the second alkoxy group is displaced by almost 180° compared with (**2**), and *eclipses* the anomeric hydrogen, more or less. This reduces its torsional interaction with the central methyl or t-butyl group and its 1,3-interaction with the first methoxy group, while perhaps retaining some anomeric stabilisation, although the lone pair to C–O dihedral angle is far from 180°.

Acetals of higher aldehydes are better compared with the appropriate substituted pentane, so we have calculated the preferred conformation of 3-methylpentane and 3-t-butylpentane. In the former, well staggered conformations are found and the *anti,anti* pentane arrangement is still favoured. However, the *anti,gauche* is of almost as low energy, for it puts a terminal methyl group *anti* to the central methyl substituent. In 3-t-butylpentane, the *anti,anti* pentane arrangement is very unfavourable, and one with a single terminal methyl *anti* to the chain is only slightly more stable. The dominating feature is the need for the terminal methyls to be remote from the t-butyl substituent, and a conformation like (**7**) is calculated to be the most stable.

Comparison of (**6**) and (**7**) indicates the similarity of the preferred conformations of the acetal and the hydrocarbon when t-butyl substituted. Calculations suggest that in contrast to formal (**1**), the anomeric effect now produces only a small perturbation in dihedral angle. The various changes in the n.m.r. spectra (Table 1) bear out the calculated change away from the anomeric conformation. The decrease in the two coupling constants, found for pivalaldehyde dimethyl acetal compared with formal, fits well with the difference between the conformations (**2**) and (**6**).[§] Furthermore, the gradual change in these coupling constants down the series suggests a steady decrease in the relative importance of the anomeric effect with increasing substitution.

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References

1 The subject has been reviewed recently in two recent monographs: A. J. Kirby, 'The Anomeric Effect and Related Stereoelectronic Effects of Oxygen,' Springer Verlag, Berlin, 1983; P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry,' Pergamon, Oxford, 1983.
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[‡] Various other distinct but less stable conformational minima are indicated, and will be discussed in a fuller account.

[§] The direct effect of substitution on one-bond coupling constants is illustrated by the comparison of ethane (^{1}J 125 Hz) with 2,2-dimethylpropane (124.2 Hz) or, for an sp^2-hybridised carbon, acetaldehyde (172.4 Hz) with pivalaldehyde (168.6 Hz). (Orginal references for these and similar comparisons can be found in 'Carbon-13 NMR-Spectroscopy,' J. B. Stothers, Academic Press, New York, 1972, ch. 10.) The former is probably a better indicator for the present results, which are however far beyond the range of even the latter comparison.