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Why Do so Few Simple Acyclic Acetals Adopt the Classic Anomeric Conformation? The Eclipsed Anomeric Conformation for Acetals. An Analysis of Crystal Structures, Molecular Mechanics Calculations, and NMR Measurements

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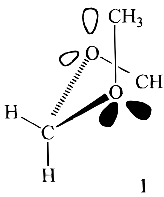
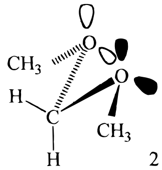
A novel conformation for simple acyclic acetals, the eclipsed anomeric conformation is recognized and shown to be somewhat more common than the classic anomeric conformation, by an analysis of structures in the Cambridge Crystallographic Database and of molecular mechanics calculations, and by NMR measurements of simple model acetals. The classic and eclipsed anomeric conformations differ principally by rotation through 180° about one central carbon−oxygen bond. Both conformations involve anomeric interactions, but the eclipsed conformation better accommodates steric interactions of groups linked by relatively short carbon−oxygen bonds.

Simple acyclic acetals $R^1CH(OR^2)OR^3$ where groups R are not otherwise connected should have conformations that reflect unconstrained interplay of steric and anomeric interactions. It is well-known[1−5] that formal $H_2C(OMe)_2$, the dimethylacetal of formaldehyde, prefers to adopt the conformation **1** (or its enantiomer), with a gauche arrangement along each of the two central C−O bonds, rather than the conformation **2** with two anti bonds, or any others, although **2** is the analogue of the preferred conformation of pentane. In **1a** strikingly, gauche steric interactions are more than counterbalanced by two anomeric interactions—the increased stability when nonbonded electron density (however the orbitals are represented[1−4]) is antiperiplanar to a polarized C−O bond. The physical evidence for the conformation **1** in which there are two such anomeric interactions is described in detail in many texts on stereoelectronic effects,[1−3] and modern calculations[5] bear out the observed preference over other conformations. Moving to acetals $R^1CH(OR^2)OR^3$, the central atom substituent $R^1 \neq H$ introduces classical gauche steric interactions along the central C−O bonds.

I now report evidence, based on crystal structure determinations of such acetals, on their NMR spectra, and on molecular mechanics calculations, that even in simple examples steric effects reassert their importance and lead to population of a conformation that is significantly different from the anomeric conformation **3a**, namely the eclipsed-anomeric conformation **4a** or its enantiomer. In **4a** compared with **3a**, one group, R^3, remains anti to R^1 but, following about 180° of rotation of the other C−O bond, R^2 more or less eclipses the anomeric hydrogen atom. A Newman projection of **3a** is shown as **3b**. Two possible nearly eclipsed forms for **4a** are shown as Newman projections **4b** and **4c**.



1



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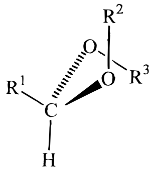
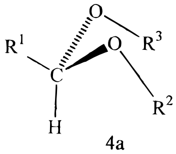
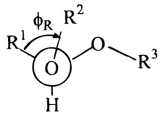


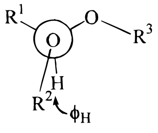
3a



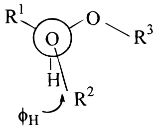
4a



3b



4b



4c

We were led to this result following our recent work[6] on eclipsing of some saturated carbon−oxygen bonds that showed[6f] that if a group OR is attached at the central carbon **C** to a set of atoms AB**C**HDE, *and if this set adopts an extended anti,anti-arrangement*, group R will prefer to eclipse the methine proton, see **5a**,**5b**, if A and E are of any size. Staggered conformations for the R group ($R \neq H$), shown together in **6a**,**6b** are disfavored due to steric interactions with A or E, which can be relieved by rotation of R to eclipse the C−H bond. At the

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(1) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983.

(2) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

(3) a) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019. (b) Thatcher, G. R. J. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series; American Chemical Society: Washington, DC, 1993. (c) Graczyk, P. P.; Mikolajczyk, M. *Top. Stereochem.* **1994**, *21*, 159.

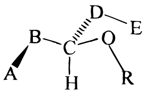
(4) Eisenstein, O.; Anh, N. T.; Jean, Y.; Devacquet, A.; Cantacuzène, J.; Salem, S. *Tetrahedron* **1974**, 1717.

(5) Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821.

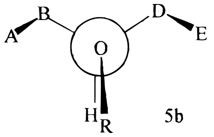
(6) a) Anderson, J. E.; Watson, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 1517. (b) Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 441. (c) Anderson, J. E.; Ijeh, A. I. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1965. (d) Anderson, J. E.; Angyal, S. J.; Craig, D. C. *Carbohydr. Res.* **1995**, *272*, 141. (e) Anderson, J. E. *J. Org. Chem.* **1996**, *61*, 3511. (f) Anderson, J. E.; Angyal, S. J.; Craig, D. C. *J. Chem. Soc., Perkin Trans. 2* **1997**, 729.

10.1021/jo991553z CCC: $19.00

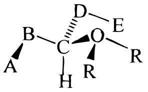
same time as **5b** implies, B and D are eclipsing only oxygen lone pairs. The alternative staggered anti conformation **7** has R gauche to both B and D. Acetal conformations **3a** and **4a** clearly resemble these general conformations **7** and **5a** (with D = oxygen), but acetals have four “short” C−O bonds that bring groups R, A, and E closer together.



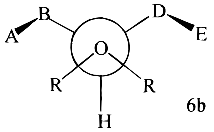
5a



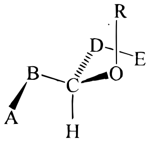
5b



6a



6b



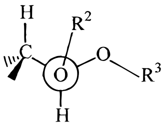
7

Results

Crystal Structures. A search of the Cambridge Crystallographic Database[7] for acyclic acetals $R^1CH(OR^2)OR^3$ (where groups R have their innermost atom sp^3-hybridized and are not otherwise linked to each other), yielded 50 examples. In 98 of the 100 occurrences, groups R^2 and R^3 are primary alkyl groups, preponderantly methyl. R^2 and R^3 are almost invariably identical so there are two enantiomeric versions of conformations. Henceforth the discussion should be taken to imply this possibility. For our analysis, crystal structure determinations will be treated as such as **3a** or **4a**, i.e., with R^3 behind, and always anti to R^1 whether these, or enantiomeric conformations, i.e., with R^2 in front and anti to R^1, were actually reported. It is thus the orientation of R^2 with respect to the anomeric hydrogen that is the main interest of this paper.[8]

The 50 examples fall into two distinct groups. The minor group (22 examples) adopts the classic anomeric conformation **3**. The major group (28 examples) has the eclipsed-anomeric conformation **4**, with R^3 anti to R^1 as before, but with group R^2 rotated by about 180° to be nearly eclipsing the anomeric hydrogen; see **4b**, **4c**.

For the 22 classic anomeric acetals, the mean $R^2{-}O{-}C{-}R^1$ torsion angle $\phi = -65 \pm 5°$, see **3b**, the group R^2 being slightly nearer OR^3 than R^1 on average. In 21 of these, the group R^2 has a parallel-1,3-interaction with no more than a hydrogen atom in R^1, see **8**, but the classic conformation is encountered only once when R^1 has a substituent $X \neq H$; see **9**. When as in **9**, the group R^2 confronts a part X of R^1 that is larger than a hydrogen atom—by no means an exotic structural feature—then overall, *the classic anomeric conformation is most unlikely* for the acetal.



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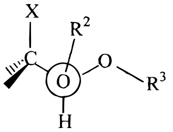

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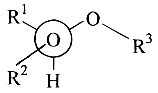

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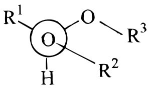
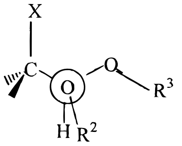
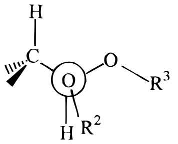


11

Other conventional staggered conformations **10** and **11** are not the alternative to the classic anomeric conformation; instead, there is substantial rotation to minimize the gauche interaction of R^2 with R^1 and OR^3, seen in these staggered conformations, and eclipsed anomeric conformations **4b** and **4c** are adopted. There are 28 such examples in the Cambridge Crystallographic Database. In 15 of these, there is a group X ($\neq$ H) encumbering what would be the classic anomeric position for R^2, see **12**, but this is not the defining explanation for rejection of the classic conformation **3b**, for X is a hydrogen atom see **13** in the remaining 13 eclipsed examples. A substituent $X \neq H$ in R^1, antiperiplanar to the anomeric hydrogen almost guarantees eclipsing (15 examples out of 16, above), but is not *necessary* for eclipsing to occur (being present in only these 15 of the 28 eclipsed examples overall). When in R^1, there is only a hydrogen antiperiplanar to the anomeric hydrogen atom, a classical anomeric conformation is often found (21 of 34 examples), but an eclipsed anomeric conformation is also quite likely (13 of 34 examples).



12



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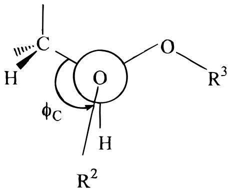

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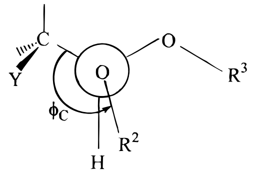

15

The substituent R^1 does influence the exact nature of the eclipsed anomeric conformation. When it contains a group Y = H, as in **14**, that hydrogen weakly completes the extended zig-zag conformation $Y{-}C{-}C{-}O{-}R^3$, which recalls **6**. Of the 28 eclipsed examples, 11 do have Y = H, see **16**, and the mean $C{-}C{-}O{-}R^2$ torsion angle ϕ_C is $103 \pm 14°$ with R^2 much less likely to be on the $O{-}R^3$ side. Seventeen of the eclipsed examples have a group Y that is larger than hydrogen, and 13 of these are eclipsed on the OR^3 side remote from Y with a mean $C{-}C{-}O{-}R^2$ torsion angle ϕ_C of $136 \pm 11°$ while the remaining four are eclipsed on the $C{-}Y$ ($\equiv R^1$) side with a mean torsion angle of $104 \pm 10°$. The differences between the two eclipsed conformations represented by **14** and **15** are not

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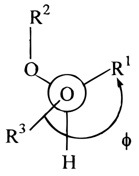
(7) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Maccrae, C. F.; Mitchell, E. M.; Mitchell, G. K.; Smith, J. M.; Watson, D. G. The Development of Versions 3 and 4 of the Cambridge Structural Database System. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187−204. July 1991 CSD Release.

(8) Nonetheless it is usually the $R^2{-}O{-}C{-}R^1$ torsion angle that is available from the crystal structure report and it is these we now discuss. When these are around 120° (rather than 60° or 180°), the C−O bond is eclipsed rather than staggered.

great but are worth attention in that they emphasize the interplay of the lateral compression of O−R^2 by Y and R^3.

The other substituent R^3 is much the same in both the classic and eclipsed anomeric sets. Viewing the classic anomeric conformation along the R^3O−CR^1 bond, see **16**, the mean R^3−O−C−R^1 torsion angle in the 22 examples is −168 ± 6° (reasonably, R^3 is slightly nearer to H than to OR^2). In the eclipsed anomeric set of 28 structures, the R^3 group is hardly different, still anti to R^1 with the R^1−C−O−R^3 torsion angle averaging −165 ± 5°; see **17**.



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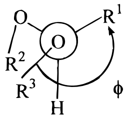
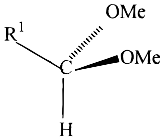


17



18a R^1 = H
18b R^1 = Me
18c R^1 = Et
18d R^1 = i-Pr
18e R^1 = t-Bu

Overall, the crystal structure results point to steric effects playing their traditional conformation-determining role in acetals. This implies that the basic conformation for acetals is the classic anomeric one, adopted by unsubstituted formal $H_2C(OMe)_2$ where it is preferred[5,9,10] by more than 2.0 kcal/mol over any other one, but that steric interactions on introducing a substituent R^1, enhanced due to short carbon−oxygen bonds, readily counterbalance this. Group R^2 in **3b** is gauche to two large substituents, whereas in **4a** or **4b**, when it eclipses hydrogen, R^2 has rotated away from any significant steric compression.

Molecular Mechanics Calculations. The MM2 and MM3 molecular mechanics programs have been specifically adapted to reproduce the anomeric conformations of dimethoxymethane.[9,10] They can be expected to give a good representation of the changes induced by additional alkyl substituents, since the steric interaction of alkyl groups is well-parametrized from a wide selection of good experimental results. The relative stability of the conformations about both the R−C and C−O bonds in the dimethylacetals $RCH(OMe)_2$ **18a**−**18e** (R = hydrogen, methyl, ethyl, isopropyl, or *tert*-butyl) have been calculated, and the usual model series in which steric interactions vary widely as the conformation along the R−C bond and the branching in the group R change; see Table 1. A dielectric constant of 1.5 has been used in all calculations, and only conformations where at least one methoxy group is anti to the substituent R, i.e., **3b**, **4b**, and **4c**, are discussed. Conformational minima not in this class are all much higher in energy by calculation.

Formaldehyde Dimethylacetal $HCH(OMe)_2$, 18a. The MM3 program is parametrized to reproduce the anomeric conformation of **18a** correctly. By calculation it is by far the most stable conformation. The interest here is in other conformations, those clearly populated in succeeding members of the series **18b**−**18e**. Using MM3, a minimum is found that corresponds to the conformation like **10** and is 2.13 kcal/mol less stable than the classic anomeric one and far from being eclipsed like **4b**, is almost perfectly staggered. The other relevant minimum is eclipsed like **4c** (ϕ = 21°) and is 2.63 kcal/mol less stable than **3b**. There is thus a strong bias in favor of the classic anomeric conformation **3b**, which makes it more striking that it is largely wiped out in **18b** by the simple substitution with a methyl group.

Acetaldehyde Dimethylacetal $MeCH(OMe)_2$, 18b. Allinger[10] has reported calculations of two particularly stable conformations, the ±gauche,∓gauche, which is the classic anomeric one like **3b**, and the gauche,anti like **4b**, which is 0.6 kcal/mol less stable and has one methoxy methyl group quite near to eclipsing the anomeric hydrogen, $\phi = -20.4°$. In our hands using MM3(94), this conformation is 0.45 kcal/mol less stable than **3b**, $\phi = -27.8°$. More importantly, there is a better eclipsed anomeric minimum like **4c**, $\phi = +12.8°$, only 0.13 kcal/mol less stable than the classic anomeric one. Steric interactions on introducing R^1 = methyl have destabilized both staggered conformations **3b** and **10** and **11**. For the latter, the strain is relieved by rotating toward an eclipsed conformation **4b**, but there is no comparable relief for this strain within the potential well for **3b**, so the enthalpy favoring the classic anomeric conformation for **18b** is much less than that for formal **18a**.

Higher level calculations of this compound have been carried out by Wiberg and Murcko,[5] but only for the conformations such as **3b** and **10**. The former is still the more stable by 1.22 (MP2/6-31G*) or 1.56 (MPE/6-31G*) kcal/mol, and the geometry of the latter is intermediate between the staggered **10** and the eclipsed **4b**, with Me−O−C−H = 36°. This is satisfactorily close to the molecular mechanics calculations and to some of the crystal structure determinations. These authors did not discuss the potentially more stable conformation like **4c**, and their text implies that they did not seek such a conformational minimum.

These two MM3-calculated eclipsed conformations separated by about 30° of rotation on either side of perfect eclipsing are also found for the subsequent members of the series, i.e., **18c**,**18d**. Thus, for the very simple acetal **18b** at ambient temperature, on the basis of the calculated enthalpies of the minima, there is only 44% of the classic anomeric conformation (**3b**, all R = methyl), and 56% of these two more or less eclipsed anomeric conformations **4b** + **4c**!

Propionaldehyde Dimethylacetal $EtCH(OMe)_2$, 18c. Now three different staggered conformations about the Et−$CH(OMe)_2$ bond have to be considered, and the results above for **8b** suggest that for each of these, three conformations such as **3b**, **4b**, and **4c** will be encountered. Calculations show that the two conformations that put the *C*-methyl and *O*-methyl groups in a parallel-1,3-relationship are of high energy, so two classic and five eclipsed anomeric conformations are significantly populated; see Table 1. The single most stable conformation is classic anomeric, but two eclipsed anomeric conformations are within 0.1 kcal/mol of this. From the enthalpies of these seven conformational minima, it is calculated that compound **18c** exists in classic anomeric conformations for 38% of its lifetime and in eclipsed anomeric conformations for 62% of its lifetime.

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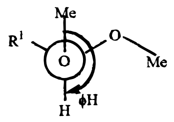
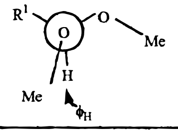
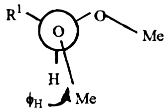
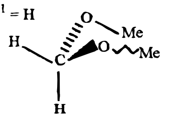
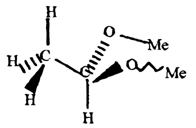
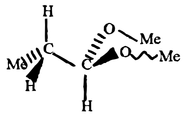
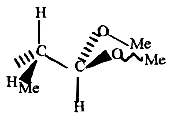
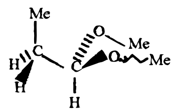
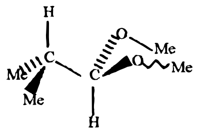
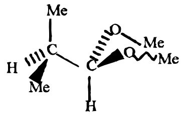
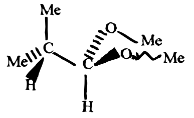
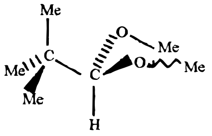
[9] Norskov-Lauritsen, L.; Allinger, N. L. *J. Comput. Chem.* **1984**, *5*, 326.

[10] Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293.

Table 1. Molecular Mechanics Calculations (MM3) of Torsion Angles (°) and Conformational Energies (kcal/mol) Relative to the Most Stable Conformation for Each Compound[a]

Methoxy Conformation → R¹ Conformation ↓	Classic Anomeric	Eclipsed Anomeric	
			
18a R¹ = H 	0.00 (176°)	2.13 (-59°)	2.63 (21°)
18b R¹ = Me 	0.00 (173°)	0.45 (-28°)	0.13 (13°)
18c R¹ = Et 	0.00 (174°)	0.37 (-20°)	0.09 (12°)
	0.17 (177°)	b	0.05 (12°)
	3.18 (175°)	0.91 (-30°)	0.65 (12°)
18d R¹ = i-Pr 	0.16 (178°)	b	0.00 (11°)
	4.03 (177°)	b	0.45 (12°)
	5.78 (177°)	0.72 (-22°)	0.49 (10°)
18e R¹ = t-Bu 	3.92 (177°)	b	0.00 (11°)

[a] "B" indicates where an eclipsed minimum was not located by calculation.

Isobutyraldehyde Dimethylacetal, *i*-PrCH(OMe)$_2$, 18d. With one additional methyl group, more of the nine conformations to be considered are of energy high enough to be neglected safely; see Table 1. There is only one classic anomeric conformation **19** of low energy. There are, however, *four* low energy eclipsed anomeric conformations, one of which is even more stable than the classic anomeric conformation. From the calculated enthalpies, molecules of **18d** spend 74% of their lifetime in eclipsed anomeric conformations and 26% in a classic anomeric conformation.

Pivalaldehyde Dimethylacetal, *t*-BuCH(OMe)$_2$, 18e. In this molecule, parallel-1,3-interactions of methyl groups are difficult to avoid. All classic anomeric conformations have these and are much higher in energy than the one eclipsed anomeric conformation **20** with the

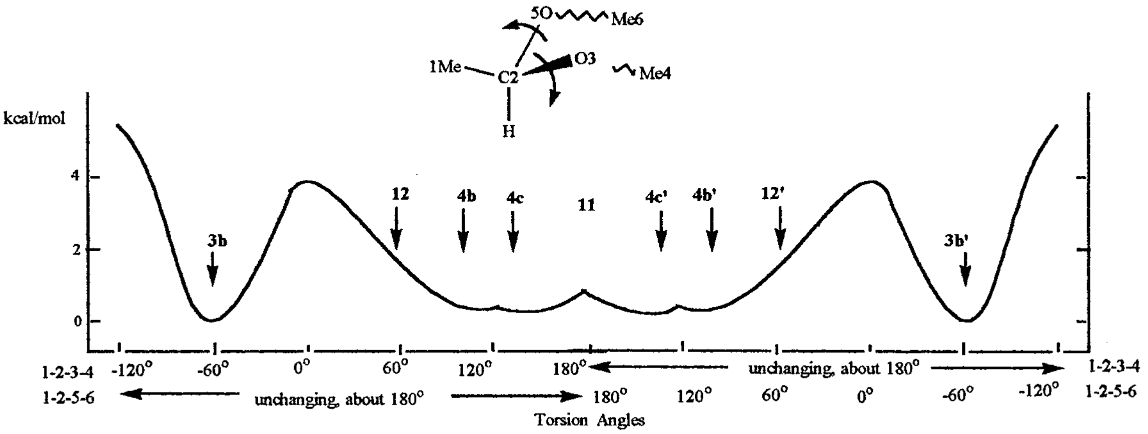
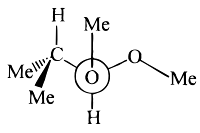
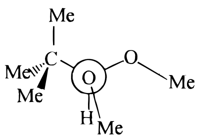


Figure 1. Potential energy diagram for rotation about the central bonds in **18b**. In the left-hand side of the diagram the C2−O3 bond rotates with C2−O5 changing little, while the reverse is true on the right-hand side, which represents enantiomeric conformations of those discussed in the text hence the primed numbers.


19


20

eclipsing methoxy methyl group turned toward the other methoxy group (ϕ = 10.9°). It is calculated that at ambient temperature there is only about 0.14% of the classic anomeric conformation, the remainder being eclipsed like **20**.

These calculations for **18a**−**18e** bear out the crystallographic observations. One methoxy group is always anti to the substituent R^1. The other methoxy group may populate either a classic and an eclipsed anomeric location *provided parallel 1,3-interactions with some part of R^1 other than hydrogen do not result.* The minimum energy eclipsed conformations **4b** and **4c** show what the staggered conformations **10** and **11** become, after distortion by methoxy-group rotation to reduce steric interactions.

It is worth looking briefly at the molecular mechanics calculations of the interconversion of conformations including necessarily enantiomeric ones, using compound **18b** with a symmetrical group R^1 = methyl as an example. The classic anomeric conformation is calculated to sit in a relatively steep-sided potential well, see Figure 1, whose limits correspond to 120° of rotation. There is a second enantiomeric classic anomeric domain, reached most easily by passage through eclipsed anomeric conformation **4b**, **4b′**, etc. There is a relatively high barrier to this process calculated to be 3.9 kcal/mol, the maximum occurring at a more conventional eclipsed conformation when R^2 eclipses R^1 along the C−O bond.

The two minima already described for the eclipsed anomeric conformation, on either side of perfect eclipsing, are supplemented by a second enantiomeric eclipsed domaine with a further two minima, achieved by R^2 rather than R^3 taking up the conformation anti to R^1 and R^3 becoming the methyl to eclipse the anomeric hydrogen. The barrier to this interconversion is very small, about 0.40 kcal/mol, so the eclipsed potential energy well of diagram 1 is very broad.

There should thus be an entropic factor favoring the eclipsed conformation represented by a broad surface with shallow minima extending over two 180° domains that interconvert easily. These contrast with the two steep-sided 120° domains of the classic anomeric conformation. If similar results hold for the generality of acetals, the experimental observation of predominant population of the eclipsed anomeric conformation owes something to entropy as well as to steric repulsion.

Table 2. Carbon-13 to Proton Coupling (Hz) in Compounds 18a−18e at Ambient Temperature unless Otherwise Stated

compd	^1J	^3J
8a	162.1	6.4
8b	160.5 (353 K)	4.8
	161.0	
	161.3 (263 K)	
	161.6 (223 K)	
	161.9 (189 K)	
8c	159.7	4.9
8d	158.2	5.1
8e	155.6	4.9

NMR Spectroscopy. Now that eclipsing particularly of C−O bonds in appropriate steric environments is a well-understood phenomenon,[6] characterized by NMR coupling measurements,[6c] the NMR evidence for acetals in solution deserves elucidation. It has already been suggested on the basis of NMR evidence[11] that acetals with increased branching in groups R^1−R^3 increasingly populate conformations different from the classic anomeric one like **3b**. Associated MM2 calculations suggested[11] that for Bu^{t}CH(OMe)$_2$ **18e** steric interactions overwhelm any anomeric effect, since the preferred conformation, in fact eclipsed like **4d**, is little different in terms of torsion angles, from that preferred for the corresponding hydrocarbon Bu^{t}CH(CH$_2$Me)$_2$. Thus, eclipsing was noted, but at the time, 1987, there was little precedent for bonds adopting such conformations.

The obvious conformation-sensitive coupling constants for compounds **18a**−**18e** are ${}^1J_{^{13}\mathrm{C}-^{1}\mathrm{H}}$ at the anomeric carbon, and ${}^3J_{^{13}\mathrm{C}-\mathrm{O}-\mathrm{C}-^{1}\mathrm{H}}$, and these are listed in Table 2. These observed NMR coupling constants derive from a set of equilibria that involve not only conformations **3b** and (**4b** and/or **4c**), but also includes their enantiomers.

The particularly significant points are that ${}^1J_{^{13}\mathrm{C}-^{1}\mathrm{H}}$ in $\mathrm{R}^1-{}^{13}\mathbf{C}({}^{1}\mathbf{H})(\mathrm{OCH}_3)_2$ decreases in size along the series, and for **18b**, that coupling constant decreases as the

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(11) Anderson, J. E.; Heki, K.; Hirota, M.; Jorgensen, F. S. *J. Chem. Soc., Chem. Commun.* **1987**, 554.

temperature is raised. The vicinal coupling constant $^3J_{^{13}\mathrm{C}-^1\mathrm{H}}$ in $\mathrm{R^1C(^1\mathbf{H})(O^{13}\mathbf{C}H_3)}$ is between 4.8 and 5.1 Hz for each of **18b**−**18e**, but is 6.4 Hz for the unsubstituted formal **18a**. This last compound provides a good model for ^1J and ^3J in the classic anomeric conformation since it adopts only the two enantiomeric versions of that conformation exclusively. Model values for the coupling constants to be expected for eclipsed anomeric conformations **4b** and **4c** can only be arrived at indirectly.

Considering first of all one-bond coupling, such conformations **4b** and **4d** are intermediate between the (+g,−g) and (+g,a) conformations **10** and **11**, in both of which the $^{13}\mathrm{C}-^1\mathrm{H}$ bond is anti to two lone pairs and gauche to two others. In this arrangement the one-bond coupling at the anomeric carbon is expected to be between 155 and 158 Hz,[12] 4−7 Hz less than the classic anomeric value of formal **18a**, where the C−H bond is anti to one lone pair and gauche to three. Some confirmation would come from the equivalent one-bond coupling constant values in the eclipsed methyl *sec*-alkyl ethers.[6c] These were not reported, but a survey of available information[13] suggests that the coupling constant (131−137 Hz) is once again smaller than when the $^{13}\mathrm{C}-^1\mathrm{H}$ bond is staggered anti to the methoxy methyl group (137−144 Hz).

Given that staggered conformations **10** and **11** are excluded by other evidence, the observed one-bond couplings of Table 2 thus agree with an increasing proportion of eclipsed conformations both as the branching of the $\mathrm{R^1}$ alkyl substituent increases and, in the case of **18b**, as the temperature rises.

The observed *vicinal* coupling constant $^3J_{^{13}\mathrm{C}-^1\mathrm{H}}$ of 6.4 Hz for **18a** is the average of value for $^{13}\mathrm{C{-}O{-}C{-}^1H}$ torsion angles of 180° and 60° in the 100%-populated classsic anomeric conformation **3b** and its enantiomer. To interpret the results reported in Table 2 for **18b**−**18e** in terms of three kinds of conformation **3b**, **4b**, and **4c** it is enough to know the vicinal coupling constant to be expected for a 0° torsion angle.

The eclipsed methyl ether study[6c] has shown that the vicinal $^1\mathrm{H{-}C{-}O{-}^{13}CH_3}$ coupling constant value for an eclipsed conformation is 1.2−3.4 Hz less than that for an anti conformation. This is the same conformational difference that obtains between **3b** and **4b** + **4c**, so assuming that the gauche coupling constant (of $\mathrm{R^3} = {}^{13}\mathrm{CH_3}$) is the same in all three conformations, the averaged vicinal coupling constant observed is expected to be 0.6−1.7 Hz less in an eclipsed anomeric conformation than in a classical anomeric one. The vicinal coupling constants reported for **18b**−**18e** in Table 2 are 1.3−1.6 Hz less than that for **18a** and thus fit well with a substantial proportion of eclipsed conformations.

Discussion

Carbon−oxygen bonds have two striking features as far as conformational analysis is concerned. The first is the particular closeness of substituents at either end due to the shortness of two C−O bonds compared with C−C bonds (−1.42 vs −1.54 Å). Gauche and other repulsive steric interactions are thus relatively enhanced. The second feature is the relatively low inherent barrier to rotation about the carbon−oxygen bond exemplified by methanol[14] (1.07kcal/mol) in comparison with ethane[15] (2.89 kcal/mol). Without substitution, the eclipsed C−O bond conformation is not much less stable than the staggered, and rotation away from perfect staggering need not be energy expensive. These features may reinforce each other or cancel out as substitution changes.

In dimethyl ether, short bonds clearly enhance steric interactions, for the methyl rotation barrier is 1.61 kcal/mol higher than in methanol at 2.68 kcal/mol.[16] This is still significantly less than that of 3.17 kcal/mol in propane,[17] which is only 0.28 kcal/mol higher than that in ethane. The methyl−methyl gauche interactions in butane and in methyl ethyl ether are 0.89 and 1.50 kcal/mol respectively, from the experimental gauche/anti equilibrium in the gas phase.[18,19] At the same time, the methyl−X−C−H torsion angle in the gauche conformation is about 50° in butane[20] but is as small as 36 ± 6° in the ether.[21]

Further substitution leads to steric congestion in the ground state and lower rotation barriers. The methyl−oxygen rotational barrier in methyl isopropyl ether[22] is only 1.73 kcal/mol, while in the preferred gauche conformation the Me−O−C−H torsion angle[22] is ±48° and the barrier to passing through the eclipsed conformation[23] is only 1.2 kcal/mol. Generally the rotational potential for a saturated C−O bond seems to be shallower than that for a saturated C−C bond so distortion away from perfectly staggered C−O bond conformations is that much easier.

Our previous work[6] on eclipsed C−O bonds has shown how readily further simple substitution when appropriately placed to produce lateral compression can reduce the Me−O−C−H torsion angle to close to 0°. The results presented here show that this has particularly interesting consequences for the anomeric conformation of acetals.

The present results show that for $\mathrm{R^1CH(OMe)_2}$ the classic anomeric conformation like **3b** with Me of methoxy gauche to $\mathrm{R^1}$ and to the second OMe group is quickly disfavored as $\mathrm{R^1}$ increases in size. The other staggered conformations such as **10** or **11** where Me is gauche to H and to either $\mathrm{R^1}$ or OMe are more propitious only if the methyl group rotates away from $\mathrm{R^1}$ or from OMe respectively, so as nearly to eclipse the methine hydrogen, in fact like **4b** and **4c**.

Formal itself, $\mathrm{R^1} = \mathrm{H}$ undoubtedly adopts the classic anomeric conformation with no significant population of

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(23) Tasaki, K.; Sasanuma, Y.; Ando, I.; Abe, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2391.

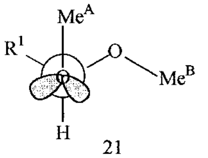
any other, but the NMR results presented indicate the involvement if not necessarily the predominance, of other conformations as soon as R^1 = Me, and this is enhanced for larger substituents R^1. The spectral changes found are as expected if these conformations are either or both of the eclipsed anomeric conformations **4b** and **4c**.

MM3 calculations not only agree with this picture of increasing involvement of eclipsed conformations as R^1 increases in size, but they also show the effect of different conformations about the R^1−CH bond and make a distinction between two slightly different eclipsed conformations depending on the degree of compression that substituent R^1 introduces. The methyl of the methoxy group does not perfectly eclipse H but is either slightly on the R^1 or on the methoxy side of perfectly eclipsing.

Analysis of reported crystal structures shows the occurrence of both classic and eclipsed anomeric conformations with the latter slightly more common. The eclipsed conformation is almost certain to be preferred if the substituent R^1 is such as to introduce a parallel-1,3-interaction with an *O*-methyl group, see **9**, but may quite often be encountered even if such compression is absent from the classic conformation. This fits well with the details of the calculations. When molecules in a crystal structure are not in the classic anomeric conformation, the alternative adopted is NOT the staggered conformations **10** and **11**, but the eclipsed anomeric conformations **4b** and **4c**.

Is there any *stereoelectronic* justification for the eclipsed conformation? In the classic anomeric conformation it is the antiperiplanar arrangement of a lone-pair orbital on oxygen with a polarized C−O bond that favors hyperconjugation, see **21** and **22**, and this lowers the energy. This stabilization is always at an optimum see **22** for the methoxy group with methyl anti to R^1, which is present in all structures discussed, so this will not be alluded to further. For the eclipsed conformations, the interaction of the lone pair does not seem as favorable as in **21**, see **23** and **24**. However, the correct electronic representation of the anomeric interaction is a matter for discussion,[1−5] and if the oxygen is represented as sp^2 hybridized, structures **21**, **23**, and **24** have to be modified[4] to appear as **25**, **26**, and **27** (in which no implication as to electron phase is intended).

It is striking that these latter structures suggest that there is much less difference between the stereoelectronic interactions in classsic and eclipsed conformations than is suggested by sp^3-hybridized oxygen structures **21**−**24**.



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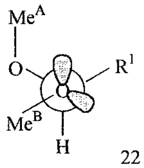

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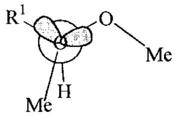

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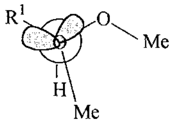

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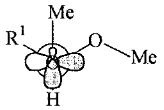

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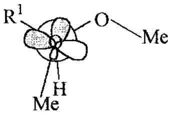

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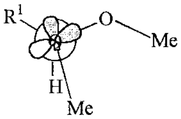

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This is the justification for describing the eclipsed conformation as well as the classic conformation as anomeric.

The eclipsed anomeric conformation is not adopted by formal itself so the classic anomeric one is inherently more stable. This seems to be due to a significant extent to the absence of steric interactions (i.e., R^1 = H), in the classical anomeric conformation of formal, for as soon as R^1 is greater than hydrogen, eclipsed anomeric conformations are populated.

The structures **4b** and **4c**, being on opposite sides of perfect eclipsing, seem clearly to be different, and this distinction has been useful in introducing the eclipsed anomeric conformation. The calculations and crystal structures show, however, that the location of the eclipsed minimum in a given acetal is less important than the idea of a broad potential well around perfect eclipsing, and it is this that is implied by the term 'the eclipsed anomeric conformation'.

Acknowledgment. I am grateful to Jorge Gonzalez-Outeiriño for help with recovering crystal structure data.

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