Eclipsed conformations for carbon–oxygen bonds in methoxy derivatives of inositols, sugars and similar compounds

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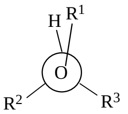
Eclipsing of exocyclic carbon–oxygen bonds in methyl ether derivatives of inositols and carbohydrates is reported and discussed. Structural fragments stereotypical for eclipsing are recognised, namely an axial or equatorial alkoxy group on a six-membered ring with equatorial substituents on either side. The X-ray crystal structure of hexa-*O*-methyl-*epi*-inositol is reported. Some analogous compounds which also have eclipsed bonds are reported.

From time to time for more than 20 years, there have been allusions to the idea that molecular situations exist where a carbon–oxygen bond might prefer an eclipsed conformation.[1–4] Specific examples of eclipsed bonds have been reported in crystal structures, some quite early,[5,6] although authors have not always signalled these explicitly in their text. There has been no understanding as to when eclipsing might be expected, until a stereotype was suggested,[7] which for ethers takes the form of a fragment $R^1O–CHR^2R^3$, where groups R sterically compress each other. It is clearly plausible that if groups R are sufficiently large, the eclipsed conformation **1** which maximises their separation, is preferable to the conventional staggered conformations.



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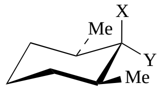
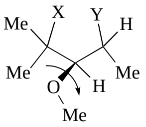


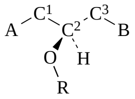
2a X = –OMe, Y = H
2b X = H, Y = –OMe



3a X = H, Y = Me
3b X = Me, Y = H

When R^2 and R^3 are different, exact eclipsing is unlikely and in the overall minimum, R^1 will be nearer the smaller of these other substituents, somewhat removed from perfect eclipsing. The H–C–O–R^1 torsion angle φ may thus be significantly different from 0°, but so much more different from 60° that the conformation is best described as eclipsed or nearly eclipsed. This description will often be supported by calculations, showing that the two conventional staggered *gauche* conformational minima have been replaced by a single minimum as near to eclipsing as the difference in the size of R^2 and R^3 allows. This calculated overall minimum will often be flat-bottomed so that the R–O–C–H torsion angle can range on either side of perfect eclipsing with little addition of energy.[7e]

The substituents R^1–R^3 may be quite small and commonplace; the appropriate carbon–oxygen bonds in *tert*-butoxycyclohexane, in the all-*cis*-**2a** and all-*trans*-**2b** isomers of 2,6-dimethylmethoxycyclohexane, in 3-methoxy-2,4-dimethylpentane **3a**, and in 3-methoxy-2,2-dimethylpentane **3b**, have all been shown[7d,8] to be eclipsed. These cyclic and acyclic examples have suggested a subtype of bond prone to be eclipsed, namely an O–R^1 group attached to C^2 of a fragment A–C^1–C^2–C^3–B which, importantly, adopts the extended *anti,anti*-conformation, see **4**. In this paper we report studies in the inositol and sugar field, involving specific examples of stereotype **4**, *viz*. **5a** and **5b**, that is –O–R groups either axial or equatorial on a six-membered ring, with substituents in the two adjacent *equatorial* positions (and of course further substitution not shown). Such an –O–R group or the C–OR bond will be described as stereotypical, but it should be noted that if a substituent is lacking (*i.e.* A or B is hydrogen or a lone pair) the non-stereotypical C–O bond may occasionally be eclipsed, as in *tert*-butoxycyclohexane for example. This last example shows that when R^1 is sufficiently large, a hydrogen or lone-pair may be constraining enough to play the role of a substituent. Here we report results for only primary alkyl ethers, but will refer briefly to inositol phosphates and sugar acetates in the discussion.



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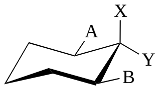

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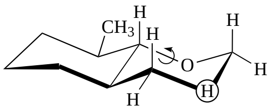
Diagram **6** shows a regularly *staggered* conformation for **2b** which emphasises the origin of the phenomenon. Such staggering leads to two hydrogen atoms competing for the same space (shown as H in a circle) and while various bond rotations might obviate this problem, the strain associated with this perfect staggering is often avoided in fact by rotation about the exocyclic bond shown, towards an eclipsed conformation, but not beyond, since the same problem exists with the other methyl substituent.



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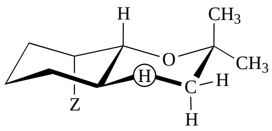

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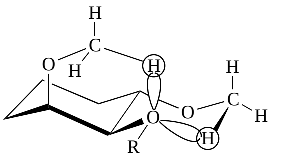
When, occasionally the flanking equatorial substituents of stereotypes **4** and **5** are hydrogen atoms, as in *tert*-butoxycyclohexane, competition for space in a regularly staggered conformation can be demonstrated once again, see **7**, so it is reasonable that eclipsing of the exocyclic bond is preferred. Flanking *axial* substituents have no obvious role in eclipsing as the group Z in **7** indicates, but, by hindering the *anti*-conformation of the exocyclic C–O bond, which is the only staggered alternative to eclipsing, such an axial substituent may favour the eclipsed conformation.

We here consider stereotypical *O*-alkylated (usually *O*-methylated) inositols, sugars and their derivatives, in which flanking O–R equatorial substituents are usually OH, *O*-alkyl or acetate groups. The competition for space discussed above is now between a hydrogen atom and the electron distribution around an oxygen atom (see **8**, which illustrates the crowding of both an equatorial or axial methoxy group with a flanking equatorial OR group). It is reasonable to wonder if such competition disfavours staggered conformations so much as to induce eclipsing. As an example of this type of molecule we have previously shown[7b,7e] that the six exocyclic C–O bonds in *scyllo*-inositol hexamethyl ether **9** are eclipsed in solution and in the crystal.



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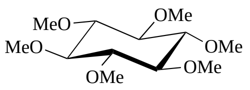

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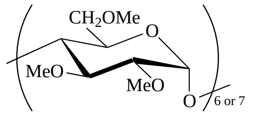

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We have also reported[7i] that in a range of complexes of methylated α- and β-cyclodextrins **10**, crystal structure determinations show that exocyclic H–C–O–C torsion angles are much more likely to be less than 20° than greater, and this is particularly true for the C–OMe bond at the 3-position on the ring and for the glycosidic bond at the 4-position, in both of which cases there are two equatorial neighbours. Eclipsing is not uncommon however for the methoxy group at the 2-position and for the axial glycosidic bond at the 1-position, where the adjacent equatorial steric compression comprises an O–Me group and a hydrogen atom and an O–Me group and an oxygen lone pair respectively. Eclipsing of stereotypical exocyclic C–O bonds is thus an almost invariable occurrence in the crystal, but not unknown in the absence of obvious flanking substituents. In 39 examples the 3-position was not methylated, and the torsion angles at the 2-position and the 4-position were on average 11.1° and 8.8° nearer eclipsed, respectively, than in the 83 examples where the 3-position is methylated. We will include in this paper some examples of eclipsing of C–OMe bonds in cyclitols and sugars with OH-groups adjacent. Hydrogen bonding may be involved and may favour eclipsing, but eclipsing is seen in analogues where the OH-group has been methylated, showing that hydrogen-bonding is not necessary.

This paper thus reports eclipsed conformations for a range of exocyclic C–O bonds in *O*-alkylated inositols and sugars. We will comment briefly on eclipsing in acetate and phosphate derivatives but will not deal with eclipsing of the two interglycosidic C–O bonds in di- and oligo-saccharides.

Methods

We present direct evidence of eclipsing in the form of one crystal structure determination and we extract further results from others' already published crystallographic work.† Otherwise we discuss NMR coupling constants reported here for the first time and some molecular mechanics calculations using Allinger's MM3 program[9,10] which includes parametrisation of the anomeric effect and the *gauche* effect, although only the latter appears to be relevant to the present results. The relative permittivity used was 1.5, appropriate for the gas-phase but not ideal for solid state or solution, but there was no intention to model crystal or solution structures.

The readily accessible NMR criterion of the conformation of a C–O bond is the magnitude of the vicinal proton–carbon coupling constant $^{1}H{-}C_{ring}{-}O{-}^{13}C$. We have suggested[7d] an equation linking the coupling constant ^{3}J and the H–C–O–CH$_3$ torsion angle φ for simple methoxy compounds, namely $^{3}J = (7.6\cos^{2}\varphi - 1.7\cos\varphi + 1.6)$, whence $^{3}J_{eclipsing} = 7.5$ Hz. This corresponds to a well-defined conformational minimum centred on $\varphi = 0°$. The coupling of 6.4 Hz found[7e] in hexa-*O*-methyl-*scyllo*-inositol **9**, which has an average torsion angle of only 6° in the crystal[7e] may be the best reference value for eclipsing in the present study, for oscillation over a range of torsion angle values is expected to take place in a flat-bottomed minimum centred on 0°. A coupling constant towards or greater than 6 Hz might then reflect a near-to-eclipsed bond with the overall minimum torsion angle to one side of 0°. The equation suggests a coupling constant of 2.7 Hz for an idealised 60° staggered torsion angle, and 4.7 Hz for the 40° torsion angle so often found for simple $^{13}C{-}O{-}CR_2{-}^{1}H$ systems.

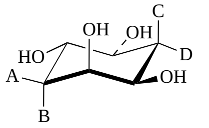
There is a well-known[11–13] torsion-angle–coupling constant relationship for the glycosidic bond in disaccharides, namely $^{3}J = (5.7\cos^{2}\varphi - 0.6\cos\varphi + 0.5)$. This suggests that a coupling constant of 5.6 Hz corresponds to a torsion angle of 0°. This however represents a $^{1}H{-}C_{ring1}{-}O{-}^{13}C_{ring2}$ system with a further oxygen substituent on the C_{ring1} atom which may affect the coupling constant value. Also the two alkyl substituents on $^{13}C_{ring2}$ in this case certainly do reduce the coupling constant, independent of conformation, as is shown by the comparison[7d] of two perfectly staggered compounds dimethyl ether [^{3}J $^{13}C{-}O{-}C(^{1}H)_3 = 5.4$ Hz] and methyl-*tert*-butyl ether [^{3}J $^{13}C{-}O{-}C(^{1}H)_3 = 4.0$ Hz].

Large coupling constant values of *ca*. 6 Hz could also result from a torsion angle near to 180°, or represent an equilibrium between an eclipsed and an *anti*-conformation such as has been demonstrated[8] for compound **2b**. How much weight to give to such alternatives can usually be decided in the light of molecular mechanics calculations.

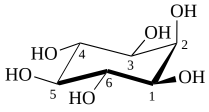
Results

Hexa-*O*-methyl-*epi*-inositol[14]

The X-ray diffraction crystal structure of the hexamethyl ether of *epi*-inositol **11a** is described in the Experimental section and is shown in Fig. 1. Table 1 reports H–C–O–CH$_3$ torsion angles along the exocyclic C–O bonds as found in the crystal and as calculated by molecular mechanics. The symmetrically substituted molecule takes up a very unsymmetrical conformation in the crystal, indicating significant intermolecular interactions and this is born out by the poor agreement of the crystal conformation with that calculated and with that expected from the stereotype. The ^{13}C NMR spectrum was recorded to provide the significant $^{13}C{-}^{1}H$ coupling across the exocyclic C–O bonds that tell about the solution conformation so NMR data are also in Table 1.



A–D = Hydrogen except
11a A = C = OH
11b B = OH, D = OMe



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Of the stereotypical bonds, that at C–6 is fully eclipsed both in solution and in the crystal, while those at C-2 and C-4 are much closer to eclipsed than to staggered in solution, as shown by coupling constants, but half-way between eclipsed and staggered in the crystal. The non-stereotypical bonds at C-1, C-3 and C-5 are not eclipsed in solution, that at C-3 being close to staggered as shown by the coupling constant, but in the crystal, C-3 and C-5 are eclipsed.

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† Papers cited often do not report the torsion angle quoted in the text, so the angle is derived from data in the paper or in accompanying reference material.

Table 1 Hexa-*O*-methyl-*epi*-inositol MM3-calculations and crystal structure determinations of exocyclic C–O torsion angles ($\varphi°$) along with ^{13}C chemical shifts (δ) and $^{1}H–C–O–^{13}C$ coupling constants (^{3}J) of the methyl carbons

Position on ring	φ (°) Calculated[a]	φ (°) Observed[b]	^{3}J/Hz	δ Estimated[c]	δ Observed[d]
C–1 eq	−40.4 (−40.3)	−37.4	5.1	57.5	58.43
C–2 ax	−23.5 (−28.6)	−30.6	5.6	63.0	61.26
C–3 eq	−40.9 (−41.5)	18.5	4.4	56.5	57.33
C–4 ax	30.7 (35.4)	27.2	5.6	63.0	61.26
C–5 eq	41.8 (41.0)	0.5	5.1	57.5	58.43
C–6 eq	18.6 (19.5)	−3.2	6.3	60.5	61.00

[a] The first torsion angle is *without* inclusion of a dipole term,[10] the second (in brackets) is *with*. [b] In the X-ray diffraction study reported here. [c] Estimated by comparison with the chemical shifts of monomethyl inositols.[3] [d] For a 0.2 M solution in $CDCl_3$.

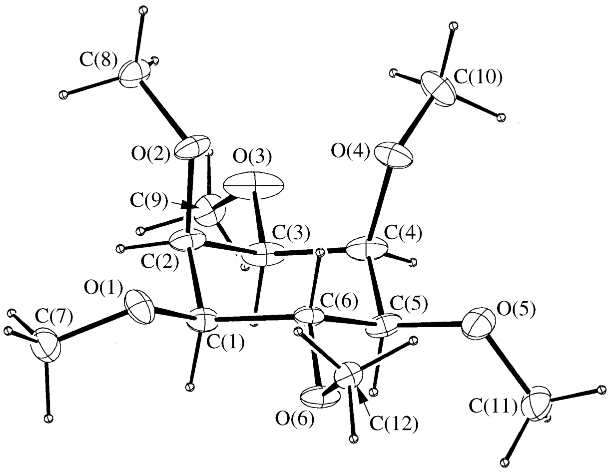
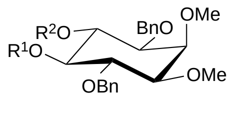


Fig. 1 X-Ray molecular structure of hexa-*O*-methyl-*epi*-inositol with the crystallographic numbering scheme

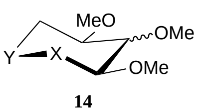
O-Alkylated derivatives of *myo*-inositol 12

The conformation of the methoxy-group in the 2-*O*-methyl-derivative of *myo*-inositol **12**, is particularly interesting, since it has already been suggested[3] on the basis of discrepancies in the changes in chemical shifts induced by *O*-methylation, that the exocyclic C–OMe bond is eclipsed. It is clear now in retrospect that the data also suggest eclipsing in the 5-*O*-methyl-derivative but this was not then recognised. This early suggestion fits with the proposed stereotype, an axial or equatorial methoxy group flanked on both sides by equatorial substituents. On this basis, methylation at all except the 1- and 3-positions should lead to eclipsed exocyclic C–O bonds.

Molecular mechanics calculations for hexa-*O*-methyl-*myo*-inositol present a much less striking picture[7b] of eclipsing than was found[7e] for the corresponding *scyllo*-derivative **9**. At the non-stereotypical 1- and 3-positions (see **12**) the calculated torsion angles are 35.7°, while for the C–O bonds which fit the stereotype, the calculated dihedral angles are clearly but not dramatically nearer eclipsed than staggered,[7b] with values of 19.6°, 23.8° and 19.0°. Perhaps the complete set of equatorial methoxy-groups in the *scyllo* derivative enhances eclipsing. Hexa-*O*-methyl-*myo*-inositol is liquid at room temperature so an X-ray crystal study is impractical.



13a R^1 = Me, R^2 = Bn
13b R^1 = Bn, R^2 = Me



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The hexa-*O*-alkyl *myo*-inositol derivatives **13a** and **13b** have three methoxy-groups and three benzyloxy groups.[15] Three methyl carbon signals can be distinguished and show coupling constants of 5.1, 5.5 and 6.4 Hz (at δ 58.5, 61.1 and 61.3, respectively) in both cases, but other ^{1}H NMR evidence shows convincingly that the compounds are different. By comparison with the spectra[3] of monomethylated inositols, the coupling of 5.1 Hz in **13a** is assigned to the methoxy group in the 1-position which is not expected to be eclipsed, although far from staggered. Which of the two remaining coupling constants is assigned to the 2-, 4- or 5-positions cannot be decided from the chemical shift values but if the 6.4 Hz coupling is assigned to the 5-methoxy group, the remaining 5.5 Hz coupling constant is assigned to the stereotypical axial methoxy group at the 2-position. Moving to **13b**, if the 5.1 and 5.5 Hz couplings are assigned to the 1- and 2-positions as in **13a**, the large 6.4 Hz coupling is satisfyingly assigned to the stereotypical methoxy group at the 4-position, which is thus eclipsed. The benzylic carbons of the *O*-benzyl groups do not lead to useful coupling constant information, because couplings into the phenyl ring in each case obscure the diagnostic vicinal coupling.

Eclipsing is expected at the 5-position in the pentaacetate of sequoyitol,[16] the 5-*O*-methyl derivative of *myo*-inositol **12**, and we find that the proton to carbon-13 vicinal coupling for the methyl carbon is 6.5 Hz, in good agreement with such a conformation. There has been a crystal structure determination[17] of (+)-ononitol (4-*O*-methyl-*myo*-inositol). The methoxy group is stereotypical for eclipsing and is found† to have a torsion angle of 14°. Pinitol (3-*O*-methyl-D-*chiro*-inositol) **11b** has a stereotypical equatorial methoxy group which appears at δ 60.5, and we find the vicinal proton–carbon coupling across the H–C–O–Me fragment is 6.0 Hz, confirming eclipsing.

NMR data from some of the above compounds suggest that the chemical shift of the methyl carbon is a good indicator of eclipsing, since it suffers a downfield shift when this occurs. Equatorial methyl groups resonate at δ 60.1–61.1 when eclipsed whereas staggered ones resonate at δ 57.3–58.4. Axial methoxy groups resonate at δ 61.3–63.0 for eclipsed and at δ 59.4 for non-eclipsed conformations.

A crystal structure determination of an *O*-benzylated *myo*-inositol has been reported[18] which provides information on the conformation of exocyclic C–OBn bonds. Five polymorphs of (±)-3,4-di-*O*-acetyl-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol were studied. Of the benzylated ring-positions, C-1 is not stereotypical and has a conformation which is always more than 19° away from eclipsing, averaging 28° over the five examples. The C-2 position is stereotypical axial but the conformation is at least 24° removed from eclipsing, averaging 31° over five examples. The C-5 position is stereotypical equatorial and in the five polymorphs the bond is 0, 7, 14, 30 and 36° from eclipsing. The C-6 position is stereotypical equatorial and is 15, 16, 18, 23 and 31° from eclipsing.

Inositol phosphates

Since a phosphate group is large and tetrahedral at phosphorus, it is reasonable to wonder whether an equatorial or axial C–OP bond in an inositol phosphate is eclipsed when the phosphate substituent has equatorial substituents on both sides. A crystal structure determination[19] of the 2-phosphate derivative of *myo*-inositol **12** shows that the stereotypical axial exocyclic C–O bond at the 2-position is eclipsed with an H–C–O–P torsion angle of 3.7°, and more recent calculations[20a] agree with this. In *myo*-inositol 1,2,3-triphosphate, the same exocyclic C–O bond at the 2-position has an H–C–O–P torsion angle of 13.3° in the crystal.[20b] To the extent that the stereotypical structure at the 2-position is eclipsed, *myo*-inositol with a phosphate group at the stereotypical 4, 5 or 6-position may also be expected to have an eclipsed C–OP bond.

1,2,3-Trimethoxycyclohexanes

It is interesting to speculate how small changes in substitution may affect the position of the eclipsed minimum when this has

Table 2 MM3 Calculated torsion angles H–C–O–Me φ (°) at C-2 in epimeric 1,2,3-trimethoxycyclohexanes **14** and related compounds

Compound	φ OMe axial	φ OMe equatorial
X = Y = CH_2	21.5	20.0
X = O, Y = CH_2	20.9	30.9
X = CH_2, Y = O	22.4	23.2

the shallow nature discussed in the Introduction. The trimethoxycyclohexanes **14** with the central methoxy group either axial or equatorial between equatorial neighbours were chosen for a molecular mechanics study. The central methoxy group has already been calculated[7b] to have a torsion angle increased to 20° compared with the 12° average in the similar compound **9** with equatorial methoxy groups throughout, suggesting that substitution all round the ring buttresses the eclipsed conformation. The ring was then distorted by replacing a CH_2 group by an oxygen atom at either position 4 or 5 producing tetrahydropyran derivatives. Table 2 reports the calculated torsion angles, and shows that such modifications may produce changes in torsion angle ranging from insignificantly small up to 11°, the effects being greater for the all-equatorial molecule. If such changes in conformation occur, this might appear at its largest as a change in coupling constant across the bond of interest, of 0.5–1.0 Hz, even though the immediate environment of the bond has not changed.

Methylated aldohexapyranoses

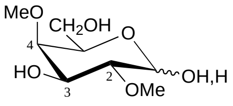
Molecular mechanics calculations. Such calculations have given reliable indications of eclipsing as demonstrated above. We used Allinger's MM3 program[9,10] to investigate the conformation of the exocyclic C–O in the pentamethyl ethers of the two sets of eight D-aldohexapyranoses, with the α- or β-configuration at the 1-position, calculating only the chair conformation with the equatorial CH_2OMe substituent at C-5. The torsion angles H_{ring}–C–O–CH_3 suggest the degree of eclipsing of these bonds.

The two C–OMe bonds which are never stereotypical for eclipsing are at C-1 and C-6, the two sets providing 16 examples of each. At C-1 there is never an equatorial substituent on the O-5 side, and the mean torsion angle is 44.9 ± 1.0°. At C-6, the side chain CH_2–OMe bond has a mean torsion angle of 57.0 ± 3.8°.

At the 2-, 3- and 4-positions the number of stereotypical examples depends on the configuration at the adjacent ring carbons. At the C-2 position the 12 non-stereotypical examples have a mean torsion angle of 37.7 ± 5.2°, while for the four stereotypical examples the value is 17.4 ± 1.8°. At the C-3 position the 12 non-stereotypical examples have a torsion angle of 37.1 ± 4.7°, while the mean for the four stereotypical examples is 17.2 ± 2.4°. At the 4-position there are eight non-stereotypical examples with torsion angle averaging 39.9 ± 1.5°, whereas the eight stereotypical examples average 18.7 ± 2.5°, with the methoxy group always directed away from the CH_2OMe substituent at C-5, towards the OMe substituent at C-3.

Overall, at the 2-, 3- and 4-positions, stereotypical methoxy groups have torsion angles calculated to be on average less than 20°, *i.e.* near to eclipsed. The torsion angles for the non-stereotypical epimers are more than 20° larger on average, *i.e.* nearly staggered.

NMR Spectra. Some methylated derivatives of pyranose sugars have vicinal proton–carbon coupling constants across exocyclic C–OMe bonds which provide experimental evidence of eclipsing. In 2,4-di-*O*-methyl-D-galactose[21] **15**, the 4-methoxy group is stereotypical in both the α and β isomers and we find that the vicinal proton coupling constant is 6.4 and 6.2 Hz respectively confirming that the exocyclic C–O bond is eclipsed in both cases. The methoxy group at the 2-position is stereotypical in only the β isomer and here the vicinal coupling constant changes from 4.5 Hz in the α anomer to 5.8 Hz in the β one suggesting a near-eclipsing conformation in the stereotypical case. The crystal structure of the α anomer of this compound as its monohydrate has been reported,[22] and shows that both methyl groups eclipse their methine hydrogen neighbour, although that at the 2-position (φ = 13°) is not stereotypical, while that at the 4-position (φ = 6°) is. This eclipsing was recognised in the report[22] and discussed in terms of neighbouring groups restricting the methoxy methyl group, in a way that fits well with our introduction above. The difference between the experimental evidence for the conformation at C-2 in the crystal and in solution is striking, and indicates that there is a delicate balance of forces involved in non-stereotypical cases that can lead to eclipsing.



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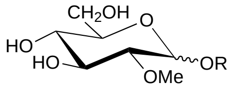


16 R = H
17 R = Me

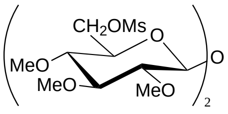
In both 2-*O*-methyl-D-glucose **16** and methyl 2-*O*-methyl-D-glucoside **17** the 2-methoxy group has two equatorial neighbours in the β anomer but not in the α anomer. For both compounds the vicinal ^{1}H–C–O–^{13}C coupling at C-2 is reported[23] to be *ca.* 5.7 Hz in the β anomer and *ca.* 4.2 in the α in agreement with the C–O bond being much closer to eclipsed when it has two equatorial neighbours. The non-stereotypical C–O bond at the 1-position in **17** shows a small vicinal coupling of 3.5(α) or 4.5(β) Hz indicating that it is far from being eclipsed.

In 2,3,4,6-tetra-*O*-methyl-α-D-glucose[24] we find that the stereotypical methoxy groups in the 3- and 4-positions show vicinal couplings of 6.3 and 6.4 Hz, which agree well with eclipsing of these exocyclic C–O bonds. The coupling constant at the 2-position is 5.0 Hz which agrees with a bond not staggered, but not very near to being eclipsed, as expected.

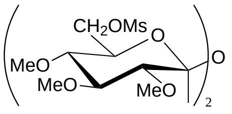
In both anomers of 3-*O*-methyl-D-glucose[25] the vicinal coupling constant is 5.2 Hz. The bond is stereotypical but this coupling suggests the torsion angle is 30° or so. This provides a rare example where the stereotype for eclipsing does not work very well although the bond is somewhat displaced towards eclipsing.

Crystal structures of *O*-methylated sugars. There have been many crystal structure determinations of *O*-methylated sugars, but it is not common for reports to quote exocyclic methoxy torsion angles. Structural data reported and held in the Cambridge Crystallographic Data Base[26] have allowed us to retrieve torsion angles and when methine hydrogens are not located we have placed them on the external bisector of the ring C–C–C bond angle in the Newman projection. Torsion angles of *ca.* 120° for H_3C–O–C–C confirm eclipsing. There are too many papers to describe in detail (2,4-di-*O*-methyl-α-D-galactose is described above[22]) but some are worth particular attention.

The trehaloses are disaccharides with two glucose rings joined at the 1-position. Crystalline derivatives with a methanesulfonyl group at the 6 and 6′ position, and *O*-methylated at the six remaining OH groups, have been studied,[27] and have Data Base Refcodes[26] DUHXEJ and DUHXIN. In the isomer **18** with the β configuration at both the 1 and 1′ positions, there are six stereotypical methoxy groups and the CH_3–O–C–H torsion angles are 10, 4, 19, 36, 14 and 17°. For the isomer **19** with the α configuration at both 1 and 1′ positions, two of the methoxy



18



19

groups are no longer stereotypical due to the axial interglycosidic bonds. These non-stereotypical methoxy groups have torsion angles of 25 and 42° while the four stereotypical methoxy groups have torsion angles of 11, 26, 6 and 33°.

We have located many other studies where stereotypical methyl groups have torsion angles much less than 30° and these can be found[26] under the Refcodes BOLNUL, DETDIP, BELTAD, DUKZOY, DUMHEY, FORTBH, GURXPX, LANKUL, MCRZNB, OLGOSE, VATFAX and VAKJOG. Non-stereotypical methoxy groups in these structures most often have torsion angles between 20 and 40°, and very seldom as much as the 40–50° encountered for primary alkyl-methyl ethers. A statistical analysis of these structures is not justified in view of the relatively small number of examples and the wide range of flanking substituents.

Discussion

There is much evidence from calculations that stereotypical methoxy groups are close to eclipsed. The MM3 program which we have usually used rather underestimates the size of rotational barriers[10] for simple C–O bonds, and so finds eclipsed conformations rather more stable than they in fact are. Nonetheless, the steric interactions which disfavour a staggered conformation in stereotypical cases are well-characterised, and there are sufficient examples where calculations are confirmed by either NMR measurements or crystal structure determinations, as to give credibility to molecular mechanics indications of eclipsing of stereotypical methoxy groups.

The torsion angle calculated for stereotypical groups, while usually below 20°, seldom has the 0° value found in many of the 2,6-dimethylmethoxycyclohexanes.[7d] In many cases this reflects different substitution at the adjacent equatorial positions so that the methoxy group has a mild but distinct preference for one side of perfect eclipsing, but this is often due as well to the flat-bottomed profile of the potential well, extending quite far from perfectly eclipsed. The perfectly staggered conformation is always much higher in energy than the perfectly eclipsed in these stereotypical cases, so 'nearly eclipsed' is a correct description of such conformations. The flat-bottomed potential well for compound **9** was explored by calculation,[7e] and it was shown that rotation of a single group 30° from eclipsing led to only 0.2 kcal mol^{-1} (1 cal = 4.184 J) extra energy yet continuing this rotation the energy increases much more rapidly but monotonically to 6.42 kcal mol^{-1} when the H–C–O–Me torsion angle passes 120°. Thereafter a new and rather less stable potential well is reached with that one methoxy group *anti* to the methine hydrogen. This is the direct evidence for a flat-bottomed well which it would be tedious to demonstrate for eclipsed bonds in less symmetrical compounds, but which should often be a feature of eclipsed bonds with flexible flanking substituents.

Crystal structure data support the idea that stereotypical methoxy groups are nearly eclipsed while non-stereotypical ones are near to being staggered but there are a few exceptions to both these generalisations. The overall structure and in particular the torsion angles we report for the hexa-*O*-methyl derivative of *epi*-inositol are a useful basis for discussing this, for some stereotypes turn out to be unreliable. Interactions between molecules in the crystal affect the conformation for, although substitution is symmetrical, nominally equivalent groups have quite different experimental torsion angles, sometimes strikingly different from what are suggested for solution-phase by NMR coupling constants, see Table 1. One non-stereotypical methoxy group is perfectly eclipsed, and another is nearly eclipsed, while the two axial methoxy groups which are stereotypical, having two equatorial neighbours, nonetheless have torsion angles of *ca*. 30°.

The most striking discrepancy in the crystal is the methoxy group attached to C-5 which is eclipsed although not stereotypical, while the equivalent group on C-1 has a torsion angle of 37°, close to the calculated value. Inspection of the crystal lattice shows that there is only one methyl group of another molecule as close as 4.0 Å in the latter case, but there are four in the former. The methoxy group at C-5 is restricted in its rotation by a crowded environment, so although non-stereotypical, it takes up an unexpected eclipsed conformation. The methoxy group at C-1 is unrestricted and takes up the staggered conformation which agrees with its being non-stereotypical. The torsion angle of *ca*. 30° for the stereotypical methoxy groups at C-2 and C-4, which agrees with the calculated torsion angles and those suggested by measured coupling constants, indicates the flatness of the floor of the potential well especially in the case of an axial methoxy group.

It is not iconoclasmic that non-stereotypical groups be eclipsed, since this means only that an equatorial hydrogen atom provides sufficient steric crowding to induce eclipsing. Similarly, an occasional example of a stereotypical group with a torsion angle of *ca*. 30° can be taken to fit with the idea that the floor of the eclipsed potential well is flat. Generally the expectations we outlined in the introduction for stereotypical and non-stereotypical methoxy groups are met.

The variability of eclipsing when flanking equatorial hydroxy groups are involved deserves comment. For 3-*O*-methylglucose which has a stereotypical C–OMe bond, there is a low coupling constant in both α and β isomers of 5.2 Hz, apparently quite far from eclipsed even if quite far from staggered as well. The pinitol result shows a coupling of 6.0 Hz, rather smaller than in other cyclitol derivatives where the methoxy is flanked by methoxy groups instead of hydroxy groups. The coupling of 5.8 Hz at the 2-position in 2,4-di-*O*-methyl-β-D-galactose is again slightly low compared with some other values indicating less extreme eclipsing, but the coupling is 1.3 Hz larger than in the α anomer, so from that point of comparison, the bond is significantly more eclipsed. In contrast, see the Introduction, in crystals of methylated cyclodextrins,[7i] a range of methoxy groups with one methoxy and one hydroxy equatorial neighbour are *ca*. 10° nearer eclipsed than when both neighbours are methoxy groups. Hydroxy groups can hydrogen bond to the methoxy group being studied, but they may be particularly involved with the lattice (in the solid state) or with the solvent (in solution) so an explanation of their role may not be simple.

None of the examples of eclipsing here reported is quite as impressive as the eclipsing of all exocyclic C–O bonds in **9**, where since each of these bonds is stereotypical, all interact strongly with neighbours round the ring in a mutually reinforcing system. When there are two or more non-stereotypical methoxy groups (there cannot be just one, if all positions are substituted) the reinforcing interaction of neighbouring groups is broken up, for a non-stereotypical group lacks the two counterbalancing strong interactions that act on a stereotypical group and which thus favour the symmetrical eclipsed conformation.

Acetate derivatives are common in inositol and sugar chemistry, and one may wonder whether a C–OAc bond is eclipsed when it has two equatorial flanking neighbours. The acetyl group is much flatter than a saturated alkyl group for the bond β to the ring (the O–Ac bond) is eclipsed, so interaction with the flanking substituents is less important. The crystal structure of hexa-*O*-acetyl-*myo*-inositol has been determined.[28] At the four stereotypical centres φ ranges between 7° and 13°, so the C–OAc bond is eclipsed as well. At the non-stereotypical centres the φ-value is 31°. A few other examples show similar values so it appears that the acetoxy group is even more prone to eclipsing than the methoxy group. We shall investigate this further.

The occurrence of eclipsing of stereotypical ring to oxygen bonds in inositol phosphates even though the oxygen–phosphorus bond is significantly longer than the oxygen–methyl bond, implies that substantial steric interactions still remain in these phosphates. It will be interesting if this is shown to have consequences for the chemical reactivity of such phosphate groups in inositol phosphates.

Experimental

All compounds on which new NMR results are reported have been prepared previously as indicated in the text.

X-Ray crystallography

Suitable crystals of hexa-*O*-methyl-*epi*-inositol[14] were obtained by crystallization from light petroleum.

Crystal data. $C_{12}H_{24}O_6$, $M = 264.3$. Monoclinic, $a = 7.611(3)$, $b = 16.959(7)$, $c = 11.339(4)$ Å, $\beta = 91.93(2)°$, $V = 1463(1)$ Å^3, space group $P2_1/c$, $Z = 4$, $D_c = 1.20$ g cm^{-3}. Colourless tablets. Crystal dimensions: 0.03 × 0.16 × 0.32 mm, μ(Cu) = 7.61 cm^{-1}.

Data collection and processing. Reflection data were measured with an Enraf-Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using nickel filtered copper radiation ($\lambda = 1.5418$ Å). The number of reflections was 907 considered observed out of 2174 unique data (merging $R = 0.013$ for 61 pairs of equivalent $hk0$ reflections; max. and min. transmission factors = 0.97 and 0.87). Reflections with $I > 3\sigma(I)$ were considered observed. Decay of *ca*. 28% was corrected during processing. Data were corrected for absorption using the analytical method of de Meulenaer and Tompa.[29]

Structure analysis and processing. The structure was determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full-matrix least-squares. The rather high R factor is undoubtedly due to the rather poor data quality, small number of observed reflections, decomposition and large thermal motions. Reflection weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o) = [\sigma^2(I_o) + (0.04I_o)^2]^{\frac{1}{2}}$. The weighted residual is defined as $R_w = (\Sigma w\Delta^2/\Sigma wF_o^{\,2})^{\frac{1}{2}}$. The final residuals were $R = 0.082$ and $R_w = 0.113$ for the observed data. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography.[30] Structure solution was by MULTAN80 (ref. 31) and refinement used BLOCKLS, a local version of ORFLS.[32] ORTEP-II[33] running on a Macintosh IIex was used for the structural diagram, and a DEC Alpha-AXP workstation was used for calculations.

The inositol ring is found in a regular chair conformation; an ORTEP drawing, indicating the numbering scheme, is shown in Fig. 1. The C–C and the ring C–O distances are normal but the O–Me distances are shorter than usual; the large thermal motions indicate that there is some disorder in the crystal and these values are averages rather than actual values. The torsional angles in the ring which include C-2 and C-4 (bearing the axial methoxy groups) are 58.1° and 58.8°, the others are 55–56°; Table 1 shows the values of the exocyclic torsion angles. Full details of the crystal structure have been deposited with the Cambridge Crystallographic Data Base. See 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/62.

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