

Eclipsed Conformations of the Ring-to-Oxygen Bonds in *O*-Methylated α - and β -Cyclodextrin Complexes. A Survey of X-ray Crystallographic Data

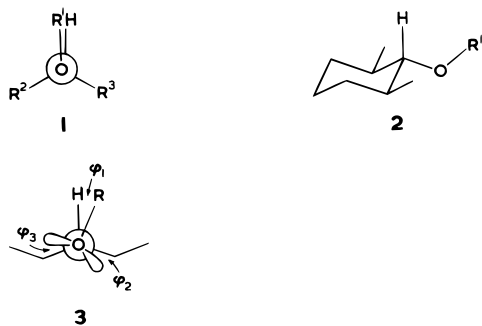
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Consideration of 122 *O*-methylated glucose residues in crystal structures of methylated α - and β -cyclodextrin complexes illustrates the tendency to adopt eclipsed conformations of the exocyclic bond at the various ring positions.

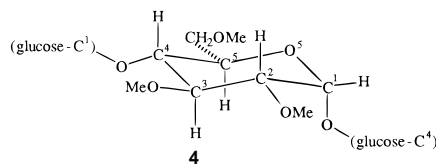
The inherent preference of a saturated carbon–oxygen bond for a staggered conformation is particularly small if the rotational barrier¹ in methanol, 1.07 kcal/mol, is taken as a measure, so a ground-state conformation close to eclipsed may result if substitution that disfavors the staggered conformation is introduced. In a compound $R^1O\text{---}CHR^2R^3$, suitably large substituents R^2 and R^3 on the carbon atom might ensure that a substituent R^1 on the oxygen prefers to be near the remaining hydrogen substituent on the carbon as in **1**. A considerable range of examples which fall into this class has been reported recently.²



One molecular stereotype which favors such eclipsing is an equatorial alkoxy group on a six-membered ring, flanked by further equatorial substituents in the 2- and 6-positions (**2**). Several examples have been shown from published X-ray crystallographic studies^{2a,b} and by calculation^{2b–e} to have the O–alkyl bond more or less eclipsing the axial ring hydrogen bond, as the projection **3** along the oxygen ring bond shows.^{3a} For *tert*-butoxy-

cyclohexane, equatorial *hydrogen* atoms flanking the *tert*-butoxy group are sufficient to lead to eclipsing of the exocyclic C–O bond, but not in the case of methoxycyclohexane,^{2d} where two flanking equatorial methyl groups^{2d} or even methoxy groups^{2b,e} are needed. The conformational potential energy minimum in this last case is not steep sided, and the torsion angle ranges rapidly over 20–30° on either side of eclipsed.^{2b,d,e} Axial alkoxy groups with two appropriate equatorial neighbors are also found to be eclipsed.^{2b,d}

Since carbon–oxygen bonds are prone to eclipsing and this seems to be determined by the balance of the substitution at opposite ends of the bond, it was interesting to consider the many available crystal structures^{4–6} of *O*-methylated α - and β -cyclodextrins and their inclusion compounds, which have a macrocyclic ring of six or seven 1,4-linked glucose moieties **4**. These have the



α -configuration for the glycosidic bond (so are hexa- and heptaamyloses) and have a large number of exocyclic C–O bonds propitious for eclipsing, the C3–O and C4–O bonds in particular fitting the stereotype **2**, being equatorial with two equatorial flanking groups.

The following pertinent questions arise. Are the stereotypical C3–O and C4–O bonds generally eclipsed? Does eclipsing obtain for the C2–O bond which has one flanking equatorial substituent and a flanking equatorial hydrogen? Is eclipsing found for the C1–O bond, which has an equatorial methoxy group neighbor at C2? This would imply (in **4**) that the electron density at oxygen-5

⁵ Abstract published in *Advance ACS Abstracts*, April 15, 1996.

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(3) (a) Representing the oxygen as sp^3 -hybridized with two lone pairs as in **3** may be tendentious.^{3b} The eclipsing discussed in no way depends on their existence as represented. (b) See, for example: Thatcher, G. R. J. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series; American Chemical Society: Washington, DC, 1993; 539, Chapter 2, Section 1.4.

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in the ring (in the form of a lone pair perhaps^{3a}) provides some of the steric compression of the O1-alkyl substituent. This last bond has been much considered elsewhere,⁷ although not in terms of eclipsing.

The relevant torsional angles that can be derived from the crystal structures used⁴⁻⁶ are C–O–C–C and C–O–C–O, and sometimes C–O–C–H. If the methine hydrogen is not located in the crystal, it is assumed to be on the external bisector of the R²–C–R³ angle in the Newman projection. Lone-pair^{3a} projections (see **3**) are assumed to be 120° on either side of the R¹–O bond projection given by the crystal structure.

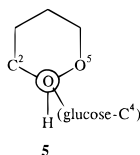
For perfect eclipsing and perfect staggering, $\varphi = 0^\circ$ or 60° , respectively, see **3**, but neither of these is likely (nor are equal values for each of the three angles) because of other molecular distortions. The measure of eclipsing of any C–O bond should reflect the extent to which the three torsion angles of group R in **3** differ from 0, +120, and –120°. The value of $\bar{\varphi}$, the average of the three numerical values of $\bar{\varphi}$ in **3** is therefore taken as an overall measure. The terms “nearly eclipsed” and “eclipsed” can usefully be applied when $\bar{\varphi}$ is less than 20° or 10°, respectively.

A 120° of rotation of R in **3** is represented by two lone-pair orbitals. If such orbitals are thought to be inappropriate,^{3a} they may be taken as nothing more than markers of 120° of rotation. The term $\bar{\varphi}$ as just defined using diagram **3** does not depend on whether these are orbitals or markers.

Nineteen crystal structures⁴⁻⁶ of *O*-methylated cyclodextrin complexes have been recovered with the help of the Cambridge Crystallographic Data Base, and these, each with six or seven glucose residues, provide 122 examples of exocyclic bonds at C1, C2, C4, and C5. Since six of the cyclodextrins⁴ⁱ⁻¹ were not methylated at position C3, there are only 83 examples of the C3–OMe bond.

Table 1 lists the average $\bar{\varphi}$ values for each of the exocyclic C–O bonds. The data are divided into two subsets, the Major one^{5a-h,6,7} (83 examples) comprising compounds with methylation of all OH groups and the Minor set⁵ⁱ⁻¹ (39 examples) with a free OH group at C³. On the basis of such a large number of examples, it is hoped that the average picture which emerges in Table 1 reflects the properties of the C–O bonds rather than any property of crystal lattices. Table 2 shows for each bond the number of examples found that can be described as “eclipsed”, “nearly eclipsed”, and “staggered”.

At the C1 Position. The C¹–OR bond (R = glucosyl) has only one equatorial neighbor but is nearly eclipsed (average $\bar{\varphi} = 17.9^\circ$) with the glucose always on the O5 side of perfect eclipsing, the side predicted by the anomeric effect, see **5**. In only 9 out of 122 examples is this



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Table 1. Average Torsion Angles $\bar{\varphi}$ (deg) Found in *O*-Methylated α - and β -Cyclodextrins

ring position (see 4)	major set: average of 83 values of $\bar{\varphi}$	minor set: average of 39 values of $\bar{\varphi}$	overall: average of 122 values of $\bar{\varphi}$
C1 substituent, axial O-glucose with 1 equat flanker	19.2	12.5	17.9
C2 substituent, equat O-Me with 1 equat and 1 axial flanker	27.6	16.5	24.0
C3 substituent, equat O-Me with 2 equat flankers	11.3	<i>a</i>	<i>a</i>
C4 substituent, equat O-glucose with 2 equat flankers	19.2	10.4	16.4

^a Not observed, see text.

Table 2. Statistical Analysis of Average Torsion Angle Found for the Exocyclic Bonds in *O*-Methylated Cyclodextrins

ring position and no. of examples	0 < $\bar{\varphi}$ < 10 eclipsed	10 < $\bar{\varphi}$ < 20 nearly eclipsed	20 < $\bar{\varphi}$ < 30	30 < $\bar{\varphi}$ < 60 staggered	
C-1	122	22	64	27	9
C-2	122	33	27	18	44
C-3	82	42	26	12	2
C-4	122	40	37	36	9

bond nearer staggered than eclipsed. Eclipsing of this bond in disaccharides is uncommon though not unknown,^{7a} but since this bond and that at the 4-position form part of the dextrin macrocycle, there may thereby be an effect on glycosidic bond conformations that is absent in an acyclic polysaccharide. A closer look at the results, not apparent in Table 1, shows that eclipsing is slightly more pronounced in the presumably more rigid hexamer than in the heptamer. No marked difference was noted between C–O bonds near to or remote from the included molecule. Molecular mechanics calculations (both MM2⁸ and MM3⁹) suggest that eclipsed conformations may be found in simple, albeit acyclic acetals, when steric interactions and the anomeric interaction have opposing conformational effects.^{2f}

At the C2 Position. For the C2–O bond, which again is not stereotypical with a methoxy group and a hydrogen atom as the equatorial flanking substituents, the Minor set is nonetheless nearly eclipsed (average $\bar{\varphi} = 16.5^\circ$) whereas the Major set (average $\bar{\varphi} = 27.6^\circ$) is nearer eclipsed than staggered, with many eclipsed or nearly eclipsed examples, see Table 2.

At the C3 and C4 Positions. In both cases there is an equatorial OR substituent with two equatorial flanking groups. The C3 set is nearly eclipsed with an average of 11.3° (83 examples). At the C4 position the (glucose C1) group nearly eclipses the axial ring hydrogen in both the Major and the Minor sets (average $\bar{\varphi} = 19.2$ and 10.4°, respectively). At both positions many individual examples are eclipsed with $\bar{\varphi}$ less than 10° (Table 2).

The substituent at the C5 position is an equatorial CH₂-OMe group with one equatorial flanker and the unsubstituted O5 on the other side. Such a C–C bond is not propitious for eclipsing, and in most examples the bond is usually well-staggered either *anti* or *gauche* with respect to the ring hydrogen.

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This paper has not attempted to review the long and quite fragmented record of eclipsed conformations in sugar chemistry, but from time to time, when there is a hydroxyl substituent serving as what we now recognize as the necessary flanking group, it has been suggested¹⁰ that hydrogen bonding plays a role in favoring such eclipsing. Clearly, eclipsing and hydrogen bonding may mutually reinforce each other, for an eclipsed methoxy group directs a lone pair which can act as a hydrogen bond acceptor toward the hydroxyl group which provides the flanking steric hindrance. Some experimental support for this is provided by the results in Table 1. When the methoxy group in the 2-position has an equatorial methoxy group neighbor at C3, the average $\bar{\varphi}$ (83 examples) is 27.6°. With an equatorial hydroxy group neighbor, the average $\bar{\varphi}$ (39 examples) is 16.5°. Likewise when the C4 *O*-glycosidic bond has an equatorial methoxy neighbor the average $\bar{\varphi}$ (83 examples) is 19.2°, while with an equatorial hydroxy group the average $\bar{\varphi}$ (39 examples) is 10.4°.

Eclipsing is more marked therefore with an OH rather than an OMe as the flanking substituent, so while hydrogen bonding is not necessary, see the Major series, it is certainly plausible to suggest that it enhances eclipsing, without implying any particular electron distribution around the ether oxygen.^{3a} Care is necessary, however, since the C2–O2 bond is itself eclipsed when methylated and presumably not when unmethylated, so the changing involvement of the O–C–C–O *gauche* effect¹¹ may contribute. As with the anomeric effect at C1, the clear connection between steric crowding and eclipsing ought not to exclude consideration of stereo-electronic effects.

Table 2 shows the distribution of values found for $\bar{\varphi}$ in a way which emphasizes the very large measure of eclipsing about the bonds at C1, C2, C3, and C4 in these

cyclic methylated glucose 1,4-hexamers and heptamers. There is a greater eclipsing tendency for the exocyclic bonds at the C3 and C4 positions which fit the stereotype by having two obvious equatorial flanking substituents. Many examples from the C1 and C2 position are also eclipsed although on one side there is only an equatorial hydrogen atom or lone pair^{3a} to cause steric compression. This reflects how much steric interactions are enhanced along a short C–O bond and the small inherent tendency of the C–O bond to be staggered.

Overall, because of the large sample, the headings in Table 2 which are most populated should indicate the intrinsic preference that bonds have, while the few cases under little-populated headings indicate where other factors, perhaps crystal forces, play a role.

It was pointed out^{2e} in considering the crystal structure of all-equatorial 1,2,3,4,5,6-hexamethoxycyclohexane (*scyllo*-inositol hexa-*O*-methyl ether) and molecular mechanics calculations^{2b} that eclipsed conformations for methoxy groups in that molecule seemed to be shallow minima with methoxy groups librating 30° on either side of eclipsing with little increase in energy. The results from a large number of very similar compounds represented in different ways in Tables 1 and 2 fit quite well with this idea. Exocyclic bonds at C1, C3, and C4 are nearly eclipsed but librate easily over a fair range of torsion angle values. At the C2 position there is a slight tendency toward eclipsing but the full 60° range of conformations between eclipsed and staggered seems to be accessible. This is the final picture to be taken from the present work.

Acknowledgment. I am grateful to Dr. D. G. Watson of the Cambridge Crystallographic Data Base¹² for assistance with recovering data from the data base.

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