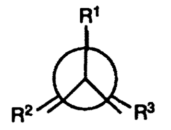
# The Six Eclipsed Sidechains in *scyllo*-Inositol Hexamethyl Ether. A Molecular Mechanics Study

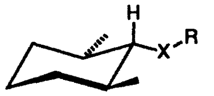
**J. Edgar Anderson**
*Chemistry Department, University College, Gower Street, London, UK, WC1E 6BT*

The most stable conformation of the hexamethyl ether of *scyllo*-inositol (all-*trans*-cyclohexan-1,2,3,4,5,6-hexol) is calculated to be the one with six equatorial methoxy groups with in each case the oxygen-methyl bond eclipsing the adjacent axial carbon-hydrogen bond. Eclipsed bonds are also calculated for other inositol hexamethyl ether stereoisomers. Results contrast with the conformations of the equivalent hexaethylcyclohexane.

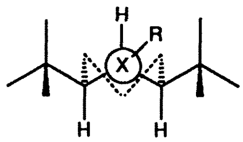
It has recently been shown, mainly by exploitation of the Cambridge Crystallographic Data Base supported by molecular mechanics calculations, that the central bond in the fragment $R^1X-YR^2R^3$ (X = $CH_2$, NH, O; Y = CH, N *etc.*) tends to be eclipsed if $R^1$, $R^2$ and $R^3$ are demanding of space.[1–5] Repulsive steric interactions of $R^1$ with $R^2$ and $R^3$, at their smallest in a near-eclipsed structure like **1**, are the origin of this conformational preference. An equatorial X–R sidechain on a six-membered ring with flanking equatorial substituents in the 2-, and 6-positions as in **2** is a particularly simple stereotype in several examples which the X–R bond is close to eclipsing the adjacent axial carbon–hydrogen bond.[1,3–6]



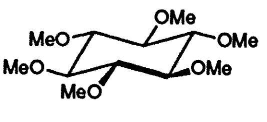
**1**



**2**



**3**

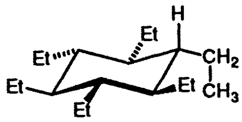


**4**

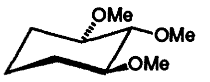
Any feature which enhances interactions of the groups R should make eclipsing more likely so methoxy and other alkoxy cyclohexyl compounds are propitious. The two carbon–oxygen bonds, short compared with carbon–carbon bonds (about 140 pm compared with 154 pm), increase the repulsions particularly in the staggered conformation **3**. Furthermore the inherent preference for a staggered conformation is much less for a carbon–oxygen bond than for a carbon–carbon bond, as shown by the methanol and ethane rotational barriers of 1.07 and 2.9 kcal $mol^{-1}$,* respectively.[7,8] This suggests that **4**, the hexamethyl ether of cyclohexane with six equatorial hydroxy groups, that is of *scyllo*-inositol, should show six examples of eclipsing.

Several previous investigations of eclipsed bonds have shown[3–5] that for molecules whose crystal structure is known, molecular mechanics calculations of the gas-phase structure using Allinger's MM3 program[9,10] reproduce well the experimental solid state structure, particularly in the matter of the eclipsing. In contrast to MM2 which treats lone pairs as substituents on oxygen[11] MM3 incorporates steric interactions of lone pairs in the rotational potential of bonds to oxygen, and seems to reproduce experimental torsional angles satisfactorily.[10] I now report such calculations of the title compound, which does not appear to have been synthesized and of some of its stereoisomers.

Intriguingly relevant to the present investigation are reports of the structure[12] and molecular mechanics investigation[13] of the analogous cyclohexane with six all-*trans* ethyl groups. The most stable conformation is shown from a crystal structure[12] and from calculations[13] to be all-equatorial but with each methyl group staggered antiperiplanar to its adjacent axial hydrogen along the ring–$CH_2$ bond as shown diagrammatically in **5**. This is 180° removed from eclipsed and the methyl group is then *gauche* to two ring carbon–carbon bonds. Attempts to calculate an alternative all-equatorial conformation however, in which any or all of the sidechains are rotated 120° to have methyl *gauche* to axial hydrogen, lead on minimization to a conformation in which the methyl group has rotated to eclipse the axial hydrogen. For each ethyl group the exocyclic bond prefers to be antiperiplanar by between 1.4 and 2.4 kcal $mol^{-1}$, but the next most preferred conformation is eclipsed, the conformation with six eclipsed bonds being 10.4 kcal $mol^{-1}$ less stable than **5**. For the reasons outlined in the second paragraph, the preference may change to eclipsed exocyclic bonds when ethyl groups are replaced by methoxy groups.



**5**



**6**

## Results and Discussion

Using Allinger's MM3 program[9,10] the minimum energy conformation of the hexamethyl ether of *scyllo*-inositol **4** (that is of all-*trans*-1,2,3,4,5,6-hexamethoxycyclohexane) is calculated to have six equatorial methoxy groups in each of which the methyl group/axial hydrogen torsional angle is small, ranging between 3.9 and 17.0°. Table 1 lists some details of the calculation.

It was confirmed that this is the most stable conformation by calculating the all-axial conformation and the all-equatorial conformation with between one and six antiperiplanar exocyclic bonds. These conformations are 7.3 kcal $mol^{-1}$ and 2.1 to 17.0 kcal $mol^{-1}$ less stable than the minimum energy conformation respectively. In the latter cases, no sign of an intermediate *gauche* minimum could be found while driving one ring–oxygen torsional angle from the eclipsed to the anti-conformation.

The minimum energy conformation of **4** in Table 1 is

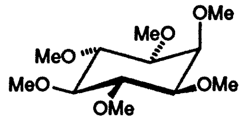
---

* 1 cal = 4.184 J.

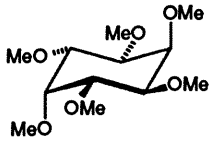
**Table 1** Eclipsing of the exocyclic ring-oxygen bonds in structures **4** and **6**–**9**. Torsional angles along the carbon–oxygen bonds

| | | Carbon atom | | | | | |
|---|---|---|---|---|---|---|---|
| Compound | Torsional angle/° | 1 | 2 | 3 | 4 | 5 | 6 |
| **4** | $H_{ax}$–C–O–Me | 3.9 | 8.0 | −14.8 | −17.8 | 16.5 | −12.9 |
| **6** | $H_{ax}$–C–O–Me | 39.5 | 20.0 | −38.3 | | | |
| **7**[a] | H–C–O–Me | 23.8 | 35.6 | 19.0 | 19.5 | −20.3 | 35.8 |
| **8**[a] | H–C–O–Me | −16.4 | −37.9 | −34.2 | 16.3 | 37.9 | 34.1 |
| **9**[a] | H–C–O–Me | −38.6 | −38.6 | −37.0 | 20.5 | 20.5 | −37.0 |

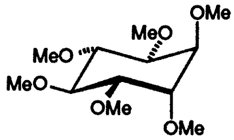
[a] There are axial methoxy groups as follows: in **7** at position 1; in **8** at positions 1 and 4; in **9** at positions 1 and 2. Other positions have an equatorial methoxy group.



**7**



**8**



**9**

unsymmetrical with six different H–C–O–Me torsional angles, and twelve degenerate or enantiomeric versions exist, easily interconverted by small amplitude rotations involving barriers of only a few cal mol$^{-1}$. At room temperature rapid averaging of such conformations makes each bond perfectly eclipsed on all but the shortest timescale.

*trans,trans*-1,2,3-Trimethoxy cyclohexane (**6**) with three adjacent equatorial methoxy groups was then calculated. As shown in Table 1 and comparing with **4**, the methyls of the flanking methoxy groups are somewhat rotated away from the central methoxy group, so buttressing of substituents is reduced compared with the hexa-substituted ring. The central methoxy group in **6** is still nearly eclipsed with an $H_{ax}$–C–O–Me torsional angle of 20.0°. This is a little larger than the six corresponding values in **4**, and suggests that a measure of co-operativity enhances eclipsing in the inositol ether. Eclipsing in the simple molecule **6** shows however the tenuousness of the preference for staggered conformations about quite simple carbon–oxygen bonds.

An axial –X–R group with two equatorial flanking substituents in a six-membered ring is another stereotype for eclipsing along the ring–X bond.[4,5] This is confirmed by calculations of the hexamethylethers of *myo*-inositol **7** and *neo*-inositol **8** with respectively one axial and two axial methoxy groups located in the 1 and 4 positions. The preferred conformations are described in Table 1 and for **7**, $\varphi$, the exocyclic torsional angle $H_{eq}$–C–$OCH_3$ for the axial methoxy-group, is 23.8° showing that the bond is much nearer eclipsed than staggered. For **8** both axial methoxy groups are nearly staggered ($\varphi$ = 16.4°). Each equatorial methoxy group in these last two molecules which does not have two equatorial neighbours has a staggered exocyclic bond, while each stereotypical one is nearly eclipsed. In *chiro*-inositol **9** with 1,2-diaxial methoxy groups only the stereotypical 4- and 5-methoxy groups are nearly eclipsed.

Calculations in these series thus show that the exocyclic bond conformation is reliably linked to the stereotype. An axial or equatorial methoxy- or presumably alkoxy-group on a six-membered ring with equatorial substituents at the 2- and 6-positions has an eclipsed or nearly eclipsed exocyclic bond. If the flanking substituents are not both equatorial, the bond conformation is nearer staggered than eclipsed although hardly perfectly staggered.

The calculations for *scyllo*-inositol hexamethyl ether contrast dramatically with the calculated and experimental structure of all-*trans*-hexaethylethane. The all-eclipsed conformation, 17 kcal mol$^{-1}$ more stable than the all-antiperiplanar conformation in the ether, is 10.6 kcal mol$^{-1}$ less stable in the hydrocarbon[13] a remarkable demonstration that shorter carbon–oxygen bonds lead to greater steric interactions.

The interactions of dipoles should have little effect on the all-eclipsed/all-antiperiplanar conformational equilibrium since every exocyclic bond has rotated by almost exactly 180° in going from one conformation to the other, and the geometry of interaction of adjacent polar groups is thus changed little.

The general question of how calculations handle electrostatic interactions in the various conformations of such molecules is nonetheless clearly important. This has been discussed by Allinger[9,10] with reference to ethanediol, its dimethyl ether, and similar vicinal dimethoxy-compounds but only in terms of the conformation about the central carbon–carbon bond. This is the simple equivalent of the question of an all-equatorial or all axial conformation for *scyllo*-inositol, for which the calculated enthalpy difference favouring the all-equatorial conformation is so large, see above, as to be difficult to doubt. There is no discussion of the topic of this present paper, the conformation about exocyclic or acyclic carbon–oxygen bonds in polyethers, so the reliability of Allinger's program beyond what has been well demonstrated for simple steric interactions, is not known. Some MM3 calculations of bond eclipsing in molecules with several polar groups have been reported however[3,4] and match well the experimental crystal structure at the eclipsed bond. We have repeated our calculations ignoring dipole–dipole interactions, and although we find substantial differences in the total and relative enthalpy of conformations and of stereoisomers, the extent of carbon–oxygen bond eclipsing is little different in the two sets of calculations.

Eclipsing means that the beta O–$CH_3$ bonds in **4** are directed perpendicular to the mean plane of the molecule in a way that recalls MacNicol's hexa-host compounds[14] whose sidechains are directed perpendicular to the mean plane of a benzene ring. Appropriate alkoxy derivatives of *scyllo*-inositol may have comparable ability to include small molecules.

## Experimental

Calculations were carried out using Allinger's MM3 program,[9] whose application to vicinal ethers has been discussed explicitly.[10] Turning points were confirmed as minima by demonstrating a real barrier to changing torsional angles. Optimization was terminated when average movement was reduced to 0.000 003 $N^{\frac{1}{2}}$ where $N$ is the number of atoms in the molecule.

## References

1 J. E. Anderson *J. Chem. Soc., Perkin Trans. 2*, 1991, 299.

2 J. E. Anderson, *Conformational Analysis of Acyclic and Alicyclic Saturated Hydrocarbons* in *The Chemistry of Alkanes and Cycloalkanes*, ed., S. Patai, Wiley, Chichester, 1992, chap. 3.II.D.

3 J. E. Anderson and D. G. Watson, *J. Am. Chem. Soc.*, 1992, **114**, 1517.

4 J. E. Anderson, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1343.

5 J. E. Anderson, D. A. Tocher, J. E. T. Corrie and L. Lunazzi, *J. Am. Chem. Soc.*, in the press.

6 J. E. Anderson, unpublished results.

7 (*a*) J. G. Aston and F. Gittler, *J. Am. Chem. Soc.*, 1955, **77**, 3175; (*b*) D. G. Burkhard and D. M. Dennison, *Phys. Rev.*, 1951, **84**, 408; (*c*) K. T. Hecht and D. M. Dennison, *J. Chem. Phys.*, 1957, **26**, 48; (*d*) T. Nishikawa, *J. Phys. Soc. Jpn.*, 1956, **11**, 781; (*e*) J. D. Swalen, *J. Chem. Phys.*, 1955, **23**, 1739; (*f*) E. V. Ivash and C. M. Dennison, *J. Chem. Phys.*, 1953, **21**, 1804; (*g*) P. Venkateswarlu and W. Gordy, *J. Chem. Phys.*, 1955, **23**, 1200.

8 (*a*) E. Teller and B. Topley, *J. Chem. Soc.*, 1935, 876; (*b*) J. D. Kemp and K. S. Pitzer, *J. Am. Chem. Soc.*, 1937, **59**, 276; (*c*) K. S. Pitzer, *Discuss. Faraday Soc.*, 1951, **10**, 66; (*d*) S. Weiss and G. E. Leroi, *J. Chem. Phys.*, 1968, **48**, 962; (*e*) E. Hirota, S. Saito and Y. Endo, *J. Chem. Phys.*, 1979, **71**, 1183.

9 N. L. Allinger, Y. H. Yuh and J.-H. Lii, *J. Am. Chem. Soc.*, 1989, **111**, 8551.

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

11 N. L. Allinger, S. H.-M. Chang, D. H. Glaser and D. Honig, *Israel J. Chem.*, 1980, **20**, 51.

12 A. Immirzi and E. Torti, *Atti Accad. Naz. Lincei, Cl. Sci. Fis. Mat. Nat. Rend.*, 1968, **44**, 98.

13 O. Golan, Z. Goren and S. E. Biali, *J. Am. Chem. Soc.*, 1990, **112**, 9300.

14 (*a*) D. D. MacNicol in *Inclusion Compounds*, eds., J. L. Atwood, J. E. D. Davies and D. D. MacNicol, Academic Press, London, 1984, vol. 2, ch. 5; (*b*) A. D. Jessiman, D. D. MacNicol, P. R. Mallinson and I. Vallance, *J. Chem. Soc., Chem. Commun.*, 1990, 1619.

*Paper* 2/05569D
*Received* 19*th October* 1992
*Accepted* 4*th December* 1992