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Eclipsed exocyclic carbon–oxygen bonds in the hexamethyl ether of *scyllo*-inositol. X-Ray crystallographic and NMR studies

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Abstract

Hexa-*O*-methyl-*scyllo*-inositol was synthesized and its crystal structure was determined by X-ray diffraction. As predicted by calculations, each oxygen–methyl bond eclipses the adjacent carbon–hydrogen bond. NMR studies show that the same conformation predominates in solution.

Keywords: Eclipsed exocyclic carbon–oxygen bonds; Hexa methyl ether; *scyllo*-Inositol

1. Introduction

It is well known that, except in a few symmetrical cases, simple saturated bonds, particularly between carbon and oxygen atoms, adopt conformations somewhat removed from perfectly staggered since rotation is an inexpensive way of relieving intramolecular strain. It is only recently, however, that interest has developed in bonds which rotate further to adopt a preferred eclipsed conformation [1–13]. This is most likely to occur when substituents flanking the bond in question at one end particularly destabilize the staggered conformation for a substituent at the other end of the bond.

Methyl ethers $R^1R^2CH{-}OCH_3$ (1) with relatively large substituents R^1 and R^2 are particularly likely to provide examples [2,5,13]. This arises because carbon–oxygen bonds are shorter than carbon–carbon bonds, so that substituents at opposite ends interact more strongly, and since the rotational barrier in methanol [14] is only 1.07

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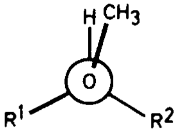

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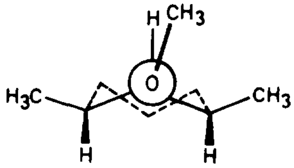

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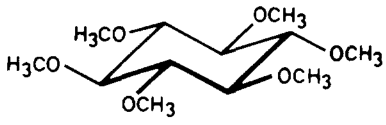

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kcal mol^{-1}, compared to 2.89 kcal mol^{-1} in ethane [15], eclipsing is inherently less unlikely. The exocyclic carbon–oxygen bond in 2-methoxy-1,3-dimethylcyclohexane is a good example of such an eclipsed bond [13]; structure **2** gives an impression of the interactions involved, and shows why it is important that both flanking groups be equatorial.

This led to the suggestion [4], supported by molecular mechanics calculations [14,15], that all six equatorial carbon–oxygen bonds in *scyllo*-inositol hexamethyl ether (**3**) are eclipsed, for each methoxy group in turn is constrained by two adjacent equatorial methoxy groups. In the overall minimum energy conformation, the H–C–O–Me torsion angles in any molecule are calculated to be between 3.9 and 17.8° (see Table 2), so the picture emerged of a set of six eclipsed bonds round the ring continuously changing their torsion angles between limits of about 18° on either side of perfect eclipsing.

The hexamethyl ether (**3**) structure was not yet known but we have prepared it by methylation of *scyllo*-inositol, and we now report on its crystal structure and NMR spectrum, which confirm the eclipsing of all six exocyclic carbon–oxygen bonds.

2. Experimental

*Hexa-O-methyl-*scyllo*-inositol* (**3**).—*scyllo*-Inositol (200 mg) was added to a suspension of NaH (500 mg) in Me_2SO (10 mL) and stirred for 1 h under nitrogen gas [16]. Methyl iodide (1.5 mL) was added and stirring was continued overnight. After the addition of water (30 mL), the solution was extracted with chloroform (4 × 20 mL). The organic layer was concentrated to 40 mL and extracted with water (6 × 20 mL). The purpose of this extraction was to remove all Me_2SO, which prevents crystallization of the compound, but this procedure caused loss of some of the product. Evaporation gave a solid (300 mg); crystallization from a very small amount of petroleum ether (bp 40–60°C) yielded the hexamethyl ether (70 mg, 24%), mp 114–115°C. From the mother liquor, another 20 mg was obtained. The ^{1}H NMR spectrum showed only two signals, of relative intensity 3 : 1, at δ 3.48 and 3.10 in D_2O, and 3.59 and 2.94 in $CHCl_3$. The compound is very soluble in all common solvents and can be crystallized only from concentrated solutions in water or petroleum ether.

NMR spectra.— Spectra for approximately 0.5 M solutions in $CDCl_3$ or D_2O were recorded on a Varian VXR400 spectrometer at a field strength of approx 9.2 T, with the chemical shifts referenced to internal TMS.

Crystal data.— The crystals grown from solution were interlocking conglomerates of thin needles. The same type of crystals resulted from sublimation in conventional apparatus. A small amount of the compound was then sublimed from a 50 mL flask, held at 110°C, into a long air condenser in the vacuum of a water pump; the crystals were dispersed over a large surface and a few single crystals were found amongst them: $C_{12}H_{24}O_6$, M 264.3, monoclinic, space group $P2_1/c$, a 10.035(3), b 8.662(1), c 19.664(5) Å, β 116.96(1)°, V 1523.5(6) Å^3, D_c 1.15 g cm^{-3}, $Z = 4$, μ(Cu) 7.31 cm^{-1}, $2\theta_{max}$ 120°.

Structure determination.— Reflection data were measured with an Enraf–Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using nickel-filtered copper radiation (λ = 1.15418 Å). During unsupervised measurements (over a weekend) the intensity of the standard reflection declined to 40%, apparently due to room-temperature sublimation, and the crystal became rounded and smaller. The data were corrected for this change, apparently successfully as attested by the successful structure outcome, but no absorption correction was applied. Out of 2221 unique data, 869 reflections were considered observed. Reflections with $I > 3\sigma(I)$ were considered observed. The number of unobserved reflections was usually high, due to a combination of the intensity loss and large thermal motions. The structure was determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned isotropic thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the nonhydrogen atoms were refined using full-matrix least-squares. 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 weighed residual is defined as $R_w = (\Sigma w\Delta^2/\Sigma wF_o^{\,2})^{\frac{1}{2}}$. Final residuals R and R_w were 0.050 and 0.067, respectively. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-Ray Crystallography [17]. Structure solution was by MULTAN-80 [18] and refinement used BLOCKLS, a local version of ORFLS [19]. ORTEP-II [20] running on a Macintosh IIcx was used for the structural diagram, and an IBM 3090 computer was used for the calculations.

3. Results and discussion

X-Ray crystallography.— The structure and the atom numbering scheme are shown in Fig. 1. The molecule has, potentially, a high degree of symmetry but the conformation found in the crystal lattice departs somewhat from full symmetry; thus, for example, the bond distances and the torsion angles in the ring are not exactly identical. The variations

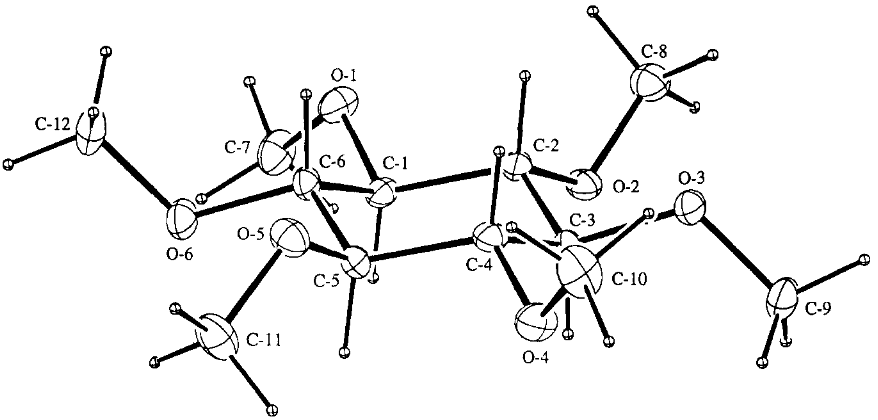

Fig. 1. ORTEP drawing of hexa-*O*-methyl-*scyllo*-inositol (3), showing the numbering scheme.

are slightly greater outside the ring. The atomic parameters are shown in Table 1. [†] The C–C bond lengths range from 1.499(7) to 1.525(7) Å (av 1.513 Å), the C–O bond lengths from 1.388(6) to 1.429(6) Å (av 1.409 Å), the C–C–C bond angles from 110.8(4)° to 112.7(3)° (av 111.9°), the C–C–O bond angles from 108.2(5)° to 109.9(5)° (av 109.1°), and the C–O–C bond angles from 115.3(4)° to 117.2(4)° (av 116.4°). The C–C–C–C torsion angles range from 52.6(6)° to 54.0(5)° (av 53.4°).

The H–C–O–C torsion angles are shown in Table 2, together with the calculated values. The average deviation from full eclipsing is only 6°, even less than the calculated value; thus the eclipsing of all of the six exocyclic carbon–oxygen bonds is confirmed. The calculated minimum [4,14,15] has a succession of torsion angles of sign $- - + - + +$ and a similar succession is found in the crystal. Other combinations have been calculated to give minima with similar overall energies, and with torsion angles always less than 20°. Barriers to most interconversions are small compared with kT.

NMR spectrum.— The ^{13}C spectrum of **3** is of unusual interest. It comprises two signals at δ 84.39 (ring) and 61.01 (*O*-methyl). In the absence of proton decoupling, these peaks appear as a widely spaced doublet ($^1J = 141.4$ Hz), each component of which is a complex multiplet, and a widely spaced quartet ($^1J = 142.0$ Hz). Each peak of the methyl carbon quartet shows further structure (see Fig. 2), but not the simple doublet pattern reflecting three-bond coupling to the adjacent methine proton, expected and usually found [13] for the methoxy carbon in $CH_3O–CHR^1R^2$.

Because of the symmetry of **3**, each methine hydrogen atom has the same chemical shift and is strongly coupled to two identical neighbouring methine hydrogens, with

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[†] Atomic coordinates, bond lengths, and bond angles for this structure have been deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 1
Nonhydrogen atomic coordinates for hexa-*O*-methyl-*scyllo*-inositol with standard deviations in parentheses

Atom	x/a	y/b	z/c	B_{eq} [a] (Å^2)
C-1	0.3257(6)	0.1254(5)	0.2375(3)	7.0(3)
C-2	0.4884(6)	0.1571(5)	0.2582(4)	6.6(2)
C-3	0.5897(6)	0.1264(5)	0.3413(5)	6.6(2)
C-4	0.5402(7)	0.2133(5)	0.3930(4)	7.5(3)
C-5	0.3780(6)	0.1844(6)	0.3727(4)	7.5(3)
C-6	0.2780(6)	0.2143(6)	0.2898(4)	6.9(3)
O-1	0.2371(4)	0.1721(4)	0.1608(2)	8.9(2)
O-2	0.5305(4)	0.0646(3)	0.2126(2)	7.8(2)
O-3	0.7370(4)	0.1718(4)	0.3571(2)	8.8(2)
O-4	0.6315(5)	0.1694(4)	0.4692(3)	10.4(2)
O-5	0.3371(5)	0.2832(4)	0.4171(3)	9.7(2)
O-6	0.1287(5)	0.1696(4)	0.2721(3)	9.8(2)
C-7	0.1345(7)	0.0652(7)	0.1127(3)	10.3(3)
C-8	0.5831(7)	0.1419(7)	0.1668(4)	9.9(3)
C-9	0.8514(7)	0.0642(7)	0.3938(4)	10.8(3)
C-10	0.7151(9)	0.2862(9)	0.5193(4)	13.4(4)
C-11	0.2784(9)	0.2114(9)	0.4626(5)	12.7(4)
C-12	0.0240(8)	0.2928(9)	0.2526(5)	11.9(4)

[a] B_{eq} is the isotropic equivalent of the anisotropic temperature factor.

$^3J \sim 10$ Hz. As a result, the methoxy carbon coupling to its methine neighbour is perturbed by 'virtual coupling' to all the methine protons. This can be confirmed by comparing the experimental spectrum with a calculated one (see Fig. 2). The calculated spectrum (Bruker Aspect 6000) simulates one peak of the methyl group quartet in the proton-coupled ^{13}C NMR spectrum as the A part of an $A^iX^iX^{ii}X^{iii}X^{iv}X^vX^{vi}$ system, where $A = {}^{13}C$, $X = {}^1H$, all $J_{A,X} = 0$ Hz except J_{A,X^i}, and $J_{X^i,X^{ii}} = J_{X^i,X^{vi}} = J_{X^{ii},X^{iii}} = J_{X^{iii},X^{iv}} = J_{X^{iv},X^v} = J_{X^v,X^{vi}} = 10.0$ Hz. The coupling constant J_{A,X^i} needed for this work is easily extracted from the experimental spectrum and is 6.4 Hz, somewhat smaller than the value of 7.3–7.7 Hz reported previously [13] for eclipsed methoxy groups in methoxycyclohexanes like **2**.

These latter compounds have two equatorial methyl groups flanking the methoxy group and are calculated to have an H–C–O–C torsion angle within 1° of perfectly eclipsed. Further calculations suggest that in **2** the potential energy profile on rotating the methoxy group is conveniently paraboloid and fairly steep-sided, for rotation by 30° from eclipsed already increases the energy by 1.35 kcal mol^{-1}, compared with the minimum. Rotational energy levels away from the overall eclipsed minimum will be relatively little populated.

The inositol **3**, with less sterically demanding O–CH$_3$ groups serving as flanking groups, is calculated to have a very different conformational life. There are 12 equivalent minima of the type described in the introduction, with a range of torsion angles removed from eclipsing by between 3.9 and 17.8° (see Table 2). There are,

Table 2
Calculated and X-ray diffraction values for H–C–O–C torsion angles in hexa-*O*-methyl-*scyllo*-inositol (**3**)

Bond	Torsion angles (deg)	
	Calculated [a]	Found (e.s.d.)
H-1–C-1–O-1–C-7	+14.8	+10.3(8)
H-2–C-2–O-2–C-8	+17.8	+3.3(7)
H-3–C-3–O-3–C-9	−16.5	−10.4(8)
H-4–C-4–O-4–C-10	+12.9	+1.1(9)
H-5–C-5–O-5–C-11	−3.9	−4.5(8)
H-6–C-6–O-6–C-12	−8.0	−6.2(8)
Average magnitude	12.3	6.0

[a] Results for the enantiomer of the conformation reported here [4]. Three of the bonds are on the clockwise side of perfect eclipsing, and three on the anticlockwise side, which explains the positive and negative signs in the Table.

moreover, further almost-as-stable conformations (12 each) with a different relative arrangement (+ − − − + −) of nearly eclipsed bonds. Calculations suggest that **3** requires much less additional energy, at most 0.15 kcal mol^{-1}, to reach a conformation having one torsion angle of 30°.

Each molecule is thus calculated to equilibrate easily among a substantial range of conformations, allowing each carbon–oxygen bond to experience a range of torsion

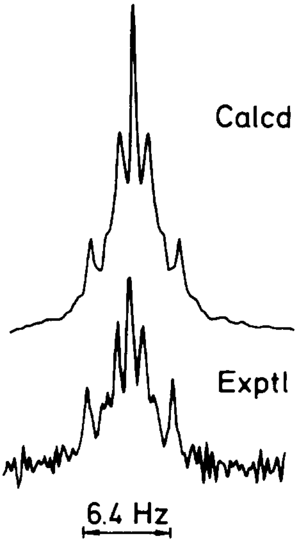

Fig. 2. Experimental and calculated proton-coupled, partial ^{13}C spectra of hexa-*O*-methyl-*scyllo*-inositol (**3**). Shown is the second peak of the methyl–carbon quartet. For the calculated spectrum, $^3J_{H,C} = 6.4$ Hz, $^3J_{H_{ax},H_{ax}} = 10.0$ Hz.

angles between 0° and 30°. Conformational minima are multidimensional and much less steep-sided than in **2**, so that eclipsing, and thus the experimentally observed coupling constant $^3J_{H,C}$ is smaller in **3** than in **2**. The latter has the O–CH_3 bond closely concentrated in conformations near 0°, while in the former these bonds, although centred on the eclipsed conformation, range quite widely in torsion angle.

A Karplus-type relationship linking the coupling constant and the C–H torsion angle in methyl ethers has recently been proposed [13], based on the 7.3 Hz coupling in **2** as diagnostic of a 0° torsion angle, and the 2.6 Hz coupling constant in methyl neopentyl ether [21] as diagnostic of a perfectly staggered 60° torsion angle. Using this equation, the 6.4 Hz coupling constant observed for **3** suggests that the mean torsion angle about the C–O bond is 24°, i.e., the molecule **3** is rather less eclipsed in solution than is suggested by the crystal structure and the calculations. It is perhaps more likely that the coupling constant is reduced by a small intrinsic effect of the flanking methoxy groups.

It is well worth keeping this picture in mind for generalizing to other molecules. For any one methoxy group in **3**, there is, centred around the eclipsed conformation, a flattish multidimensional minimum which is being explored rapidly and continuously. Any movement away from eclipsed in either direction leads to an increase in the torsion angle and thus a reduction in the observed coupling constant.

Generally, eclipsing is expected for a methoxy group attached to a ring of any size if there are flanking substituents which destabilize the normal *gauche*-staggered conformation of the methoxy group. Such destabilizing interference occurs only if the two flanking substituents are *gauche* to both the methoxy group and its geminal proton on the ring, that is, if both flanking substituents are pseudoequatorial [22].

If an *anti* conformation can be excluded, and if flanking substituents have a negligible through-bond effect on coupling, a coupling constant of 7.3–7.7 Hz indicates a well-defined eclipsed minimum energy conformation. A coupling constant of somewhat lower value indicates either two well-defined minima somewhat removed from eclipsed on either side, or a conformational state with some rapidly interconverting population in many different, shallow, near-to-eclipsed minima. The entropy associated with this last situation should favour it.

Acknowledgments

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