Eclipsed Ground-state Conformations for Methoxycyclohexanes with Adjacent Methyl-group Substitution. An NMR Criterion and Molecular Mechanics Calculations

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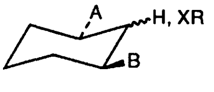
Molecular mechanics calculations suggest that the conformation of the ring-to-oxygen bond in several methoxycyclohexanes with equatorial methyl substituents in both the 2- and 6-positions is eclipsed. The three bond coupling constant of the methine proton with the methoxy carbon, which is large compared with that of methoxycyclohexane, confirms this and is diagnostic of an eclipsed conformation. The corresponding acyclic compound 2,4-dimethyl-3-methoxypentane is also concluded to have an eclipsed C–O bond.

It has recently been demonstrated[1-6] mainly from X-ray crystallographic studies of solid state structures or from molecular mechanics calculations of gas-phase structures, that a common stereotype for a preferred eclipsed conformation of a saturated carbon–X bond (X = CH_2, NH, O) is an equatorial or axial X–R substituent on a six-membered ring with equatorial substitution in the 2- and 6-position **1**, shown in Newman projection as **2** or **3** respectively. While eclipsing has also been reported in totally different situations[5,7] model **1** is a special case of a more general stereotype[1-6,8] for eclipsing *viz.* the X–Y bond in $R^1X{-}{-}{-}YR^2R^3$ (Y = CH, N *etc.*), where groups R are sterically demanding.



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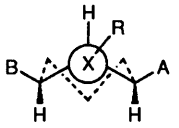

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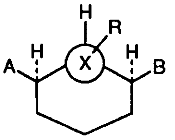

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In this paper we consider methoxycyclohexanes with from none to four adjacent methyl substituents **4–17** (see Table 1) and some simple acyclic methyl secondary alkyl ethers **18–21** and show a correlation between the three-bond coupling constant of the methine proton with the methoxy carbon and the conformation of the HC---O bond defined by φ, the ^{1}H–C–O–^{13}C torsion angle as suggested by molecular mechanics calculations,[9,10] see **22**.

The relationship between such a coupling constant and the carbon–oxygen bond conformation for more normal values of φ between 60° and 180° has been considered previously for *O*-alkylated sugars[11,12] and simple methyl ethers,[13] and a Karplus-like $\cos^2\varphi$ relationship has been suggested. The possibility of eclipsed conformations was considered only briefly at the end of long discussions, in terms which though vague and tentative will now be shown to point to the truth. Thus,[13] '... the substantially larger coupling observed may indicate a distortion of the conformation away from the perfectly staggered form to a situation wherein the alpha proton approaches the eclipsed disposition relative to the C-methyl carbon', and[14] '... it is tempting to explain these large coupling constants in terms of a conformation ... in which the dihedral angle between Me–O and C–H bonds is significantly less than 60°'.

Vicinal carbon–proton coupling has also been investigated for the inter-ring CH–O–CH fragment of disaccharides[15-17] and related to torsion angles about the two exocyclic C–O bonds, but the substituent O-6, atom seems to lower vicinal coupling constants by more than 1.0 Hz as the discussion will show.

Results

The three-bond coupling constant between the carbon of the methoxy-group and the adjacent methine proton for a series of methyl ethers **4–21** is shown in Table 1. Many of the values for the methoxycyclohexanes are taken from the literature.[13,14] The couplings for methoxycyclohexane **4** and *cis*-2-methyl-1-methoxycyclohexane **7** undoubtedly reflect significant amounts of two different chair conformations, but the torsion angle φ is calculated to be very similar in these two conformations.

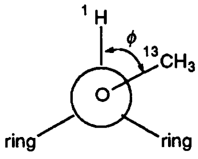

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Table 1 also shows values of the torsion angle φ for each compound as calculated using Allinger's MM3 program[9] whose suitability for ethers and methoxycyclohexane has been explicitly considered.[10] In each case 360° of rotation of the methoxy-group was explored using the dihedral drive option to ensure that all conformational minima for the bond were considered. For all symmetrical compounds two enantiomeric minima at $+\varphi$ and $-\varphi$ were indicated, giving rise to identical values of the coupling constant. Other C–O bond conformations calculated to lie within 1.3 kcal mol^{-1} of the one shown were encountered only in the case of **19**. This implies that at room temperature, be the preferred conformation staggered or eclipsed, the population of less stable conformations is less (usually much less) than 10%. In molecules for which an eclipsed minimum is calculated, *gauche* conformations are not minima although *gauche* and eclipsed minima in the same molecule are not unprecedented.[5]

Discussion

Following Dorman, Bauer and Roberts,[13] and with the support of calculations, the result for methyl neopentyl ether with ^3J = 2.65 Hz represents a 60° torsion angle, since methyl and *tert*-butyl groups much prefer to be *anti* across the C–O bond. The coupling in dimethyl ether represents the average of two *gauche* and an *anti* arrangement of the coupling atoms. We have remeasured this coupling as 5.4 Hz (the historic value[18] is 5.7 Hz), so the pure *anti* coupling is concluded to be 10.9 Hz.

Table 1 Experimental vicinal ^{13}C–O–C–^{1}H coupling constants (J/Hz) and calculated optimum carbon–oxygen bond conformations for methoxycyclohexanes and other methyl ethers

Compound		φ^a(°)	J/Hz	H^b/kcal mol^{-1}
Equatorial methoxycyclohexanes				
4	none	46.0	$3.7^{c,d}$	2.59
5	eq 4-Bu^t	42.8	3.8^{d}	2.55
6	eq 2-Me	40.4	4.7^{a}	2.51
7	ax 2-Me	44.6	$4.1^{a,c}$	2.50
8	2,2-Me_2	37.3	5.5^{d}	4.37
9	eq,ax 2,6-Me_2	41.2	$4.3^{a,e}$	6.48
10	eq,eq 2,6-Me_2	0.0	$7.3^{a,e}$	1.33
11	eq 2,2,6-Me_3	0.7	7.3^{d}	5.21
12	2,2,6,6-Me_4	0.4	7.5^{d}	8.29
13	eq 4-Bu^t-2,2,6,6-Me_4	0.3	7.7^{d}	8.24
Axial methoxycyclohexanes				
14	none	41.9	$3.7^{c,d}$	6.81
15	eq 2-Me	40.7	$4.1^{a,c}$	7.23
16	eq 4-Bu^t	41.5	3.9^{d}	6.82
17	eq,eq 2,6-Me_2	0.2	$7.3^{a,e}$	7.26
Acyclic methyl ethers				
18	Pr^i	46.6	3.9^{f}	2.14
19	3-$\mathrm{C}_5\mathrm{H}_{11}$	35.4	4.6^{a}	0.10
20	$\mathrm{Pr}^i{}_2\mathrm{CH}$	1.8	7.6^{a}	1.95
21	Me		5.4^{a}	
22	Bu^t		4.0^{g}	

[a] This work. [b] Relative enthalpy of next minimum for the HC–O bond. Usually the *anti* conformation except for the acyclic ethers **19** and **20** where pentyl bond conformations change. 1 cal = 4.18 J. [c] The coupling for a mixture of two chair conformations with the methoxy-group equatorial or axial. [d] Ref. 14. [e] Ref. 14 reports 4.3, 7.3 and 9.2 Hz for **9**, **10** and **14**. [f] Ref. 13. [g] Ref. 20.

The preferred conformation of all the cyclohexyl compounds are calculated to have $\varphi < 60°$ and to be much more stable than any conformation with the methoxy group *anti* to the methine proton. Those methoxycyclohexanes which fit the stereotype for eclipsing of the opening paragraph have values of the ^{13}C–O–C–^{1}H coupling constant between 7.3 and 7.7 Hz, while those which do not fit the stereotype have markedly smaller values, between 3.7 and 3.9 Hz when there are no methyl groups, and between 4.3 and 5.5 Hz when there are adjacent methyl groups (but not two equatorial). All the compounds with coupling constants over 7 Hz are calculated to have the exocyclic C–O bond eclipsed, while other methoxy compounds have torsion angles between about 30 ° and 60 ° and are found to have a coupling constant greater than the 2.65 Hz value associated with perfect 60° staggering, though notably less than the eclipsing value of about 7.4 Hz. With a single flanking substituent, the methoxy group takes up an orientation *gauche* to the unsubstituted flanking position.

The axial methoxy compounds behave much as the equatorial. In the one example with two flanking equatorial substituents, there is a large coupling constant and the preferred conformation is calculated to be eclipsed. Otherwise torsion angles and coupling constants have intermediate values. This confirms the equivalence of the conformational situations illustrated by diagrams **2** and **3**.

It is reasonable to wonder how substituents affect the coupling constant of 7.3–7.7 Hz diagnostic of eclipsing in the methoxycyclohexanes. The inter-ring carbon–oxygen bonds in disaccharides are sometimes near-to-be-eclipsed, when a carbon–proton coupling constant of 5.5 Hz is considered to be diagnostic.[17,19] This low value probably reflects the fact that eclipsing is not complete, φ usually being[17,19] about 10°, but also that the ring oxygen substituent attached to the coupling pathway reduces the eclipsed coupling constant compared with the present values.

There is some reason to expect a substituent effect, for *tert*-butoxycyclohexane[20a] is calculated[20b] to be eclipsed yet only shows a 5.4 Hz coupling between the quaternary carbon and the methine proton. However the $^{3}J_{\mathrm{H–C–O–C}}$ coupling in *tert*-butyl methyl ether[20] is only 4.0 Hz whereas it is 5.4 Hz in dimethyl ether, two molecules with the same staggered conformation. The reduction of more than 25% produced by three methyl substituents suggests that the observed coupling of 5.4 Hz in *tert*-butoxycyclohexane is equivalent to a 7.3 Hz coupling if the three methyl substituents were absent, a value that corresponds well to eclipsing.

It is remarkable that this exocyclic bond in *tert*-butoxycyclohexane seems to be eclipsed. Compared with the methoxy-compounds above, three methyl substituents on the alkoxy group mean that two flanking equatorial hydrogen atoms are sufficient to produce eclipsing. This is reminiscent of Forsyth's observations[21] of an eclipsed N–CH_2 bond for *N*-neopentylpiperidine.

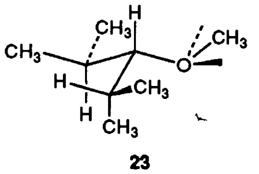
From the 60° coupling of 2.65 Hz, and the 180° coupling of 10.9 Hz derived above, along with an eclipsed coupling of 7.5 Hz, a Karplus-like relationship $^{3}J = 7.6\cos^2\varphi - 1.7\cos\varphi + 1.6$, between torsion angle φ and the coupling constant ^{3}J can be derived. All the observed couplings and calculated torsion angles for methoxycyclohexanes lie within 0.5 Hz of this line. For the inter-glycoside fragment in disaccharides[16] just mentioned, the relationship $^{3}J = 5.7\cos^2\varphi - 0.6\cos\varphi + 0.5$ has recently been suggested. This does suggest a lower diagnostic value of 5.6 Hz for eclipsing, but for the results of Table 1 it is not very satisfactory.

The susceptibility of coupling to steric and electronic effects of substituents is apparent and encourages caution, but for all cases, the association of a large coupling constant with eclipsing is clear. If an *anti* conformation (which also has a large coupling constant) is implausible, a ^{13}C–O–C–^{1}H coupling constant, large relative to a well chosen reference compound, is diagnostic of eclipsing.

Diagrams **2** and **3** show how axial methyl groups in the 2- and/or 6-positions should not affect methoxy-group conformations and eclipsing, and the observed coupling constants in **11**,

12, and **13** with eclipsed carbon–oxygen bonds agrees with this. It is also clear how the absence of either equatorial methyl group disencumbers the methoxy group and makes quite favourable a *gauche* conformation on the unencumbered side.

A consideration of the conformational analysis of 3-methoxy-2,4-dimethylpentane **20** shows that the eclipsing suggested by the 7.6 Hz H–C–O–C coupling constant is quite reasonable. If the two isopropyl groups rotate to minimise parallel-1,3-interactions of their methyl groups, see **23**, parallel-1,3-interactions with the methoxy group result, but the latter group can reduce these by taking up an eclipsed conformation **23** which is shown by calculation to be more stable than any other by 1.96 kcal mol^{-1}. The extra wedge and broken line in **23** indicate perfect staggering of the C–O bond and show how flanking interactions with methyl groups occur even in this acyclic case and result in bond eclipsing. The isopropyl groups have freedom to rotate to minimise the flanking interaction yet eclipsing is a preferred way of reducing steric strain.



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The fact that in the relatively unrestricted molecule **20** the methoxy-group takes up an eclipsed conformation rather than the isopropyl groups rotating to accommodate the methoxy group reflects how the rotation barrier of 1.07 kcal mol^{-1} in methanol[22] is so much smaller than that of 2.89 kcal mol^{-1} in ethane.[23] These barriers measure the inherent eclipsing instability of carbon–oxygen and carbon–carbon bonds. The correctly disposed flanking interactions in all the eclipsed examples above easily overcome this inherent prejudice against eclipsing.

For similar reasons, and by analogy with *tert*-butoxycyclohexane mentioned briefly above, eclipsing is calculated to persist even in isopropyl *tert*-butyl ether.[20b]

Experimental

Carbon-13 NMR spectra have been reported[14,18,19,24] for all compounds except the following which are nonetheless known compounds. 3-Methoxy-2,4-dimethylpentane[25] **19**, [δ(CDCl$_3$; 100.6 MHz) 17.52, 20.21 (4 C, C-1), 30.78 (2 C, C-2), 92.41 (1 C, *C*-3) and 61.74 (1 C, O-CH$_3$)]. *cis*-2-Methyl-1-methoxycyclohexane[14] **6**, major conformation (70%) presumably methyl-equatorial, methoxy-axial [δ(CDCl$_3$, -60 °C, 100.6 MHz) 18.60 (1 C, C*C*H$_3$), 19.12 (1 C, C-5), 25.58 (1 C, C-4), 27.27 (1 C, C-6), 28.24 (1 C, C-3), 35.72 (1 C, C-2), 55.84 (1 C, OCH$_3$) and 79.03 (1 C, C-1)]; minor conformation (30%) presumably methyl-axial, methoxy-equatorial [δ(CDCl$_3$, -60 °C, 100.6 MHz) 10.13 (1 C, C*C*H$_3$), 19.14 (1 C, C-4), 24.65 (1 C, *C*-5), 29.18 (1 C, *C*-6), 29.73 (1 C, *C*-2), 54.66 (1 C, O*C*H$_3$) and 80.46 (1 C, *C*-1)].

Molecular mechanics calculated conformational minima[9] were confirmed as genuine although not very steep-sided, by using the dihedral drive option to approach them from different directions and to drive away from them after minimisation.

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