One-bond C–H NMR Coupling Constants in 1,2,4-Trioxanes: a Reversed Perlin Effect

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In a reversal of the Perlin effect, the values of $^{1}J_{C-H}$ for the equatorial protons at C(3) and C(6) in 1,2,4-trioxanes are *less* than those for the corresponding axial protons; this is ascribed to homoanomeric interactions between equatorially directed nonbonding electron pairs on oxygen and the equatorial C(3)–H or C(6)–H σ^* orbitals.

In 1969, Perlin and Casu[1] showed that the value of the NMR coupling constant $^{1}J_{C-H}$ is greater for the equatorial anomeric hydrogen atom in α-D-glucopyranose than it is for the axial anomeric hydrogen in β-D-glucopyranose (^{13}C labelled). This effect has since been shown to be general in pyranosides and cyclohexanes and in six-membered heterocyclic rings in which the methylene group in question is flanked by one or two first-row heteroatoms. It has been referred to by Wolfe[2] as the Perlin effect; the results from the literature have recently been summarised,[2] and a few examples are given in Scheme 1.

The Perlin effect in the oxygen heterocycles can be considered to be a manifestation of the anomeric effect[5] which has been discussed in terms of the interaction of the nonbonding electron pair on oxygen with the σ^* orbital of the *anti*-oriented (axial) C–H bond. By populating the antibonding orbital this weakens the axial C–H bond and attenuates the Fermi one-bond coupling. Wolfe[2] has established an inverse correlation between the C–H bond length, as derived from *ab initio* 6-31G* MO calculations, and the observed values of $^{1}J_{C-H}$.

We have prepared a series of 1,2,4-trioxanes **1**,[6] which are structurally related to the naturally occurring antimalarial Qinghaosu (Artemisinin).[7] In order to relate pharmacological properties to structure we needed to know the configuration at C-3, which cannot be determined from *vicinal* coupling constants, and to that end we have measured the values of $^{1}J_{C-H}$ by undecoupled ^{13}C NMR spectroscopy; the relevant signals were free from any second-order effects. We find
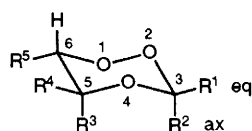
Table 1 $^1J_{C-H}$/Hz at C(3) and NOE effects (%) in 1,2,4-trioxanes 1 (by 100 MHz ^{13}C and 400 MHz ^{1}H NMR spectroscopy, respectively; CDCl$_3$ solvent)

Compound	R^1	R^2	R^3	R^4	R^5	$^1J_{C-H}$(ax)	$^1J_{C-H}$(eq)	NOE
2	H	H	H	CH$_2$HgBr	H	168.6	164.8	
3	Me	H	H	Me	H	169.0	—	
4	Me	H	H	CH$_2$HgBr	H	169.6	—	
5	Me	H	Me	H	Me	168.4	—	
6	Me	H	CH$_2$HgBr	H	H	167.8	—	
7	Me	H	H	Me	Me	168.6	—	
8	Me	H	Me	Me	H	169.8	—	
9	Me	H^{ob}	H^{ira}	Me	Ph	168.9	—	4^{c,d}
10	Me	H^{ir}	H^o	CH$_2$HgBr	Ph	169.4	—	7.5
11	H	Me	H	Me	Ph	—	164.6	
12	H	Me^{ir}	H^o	CH$_2$HgBr	Ph	—	163.5	4
13	Pr^i	H^{ir}	CH^{o}MeHgBr	Me	H	166.8	—	8
14	Pr^i	H^o	Me^{ir}	Et	H	—	—	4
15	Pr^i	H	Me	CHMeHgBr	H	169.3		
16	Pr^i	H^{ir}	H^o	CH$_2$HgBr	Pr^i	167.8	—	5
17	Pr^i	H^{ir}	H^o	CH$_2$HgBr	Ph	169.0	—	4
18	H	H	Me	Me	Me	168.4	161.6^{e,f}	

^{a} ir = Irradiated protons in NOE. ^{b} o = Observed proton in NOE. ^{c} There was zero NOE effect at R^1. ^{d} In compounds **9, 10, 11, 16** and **17**, the values of $^3J_{H5-H6}$ were in the range 7.62–8.98 Hz. ^{e} At −58 °C. ^{f} The axial H at C(6) is replaced by Me.

Table 2 $^1J_{C-H}$/Hz at C(6) in 1,2,4-trioxanes 1 (by 100 MHz ^{13}C NMR spectroscopy; CDCl$_3$ solvent)

Compound	R^1	R^2	R^3	R^4	R^5	$^1J_{C-H}$(ax)	$^1J_{C-H}$(eq)
9	Me	H	H	Me	Ph	155.2	—
10	Me	H	H	CH$_2$HgBr	Ph	150.7	—
13	Pr^i	H	CHMeHgBr	Me	H	151.6	137.9
15	Pr^i	H	Me	CHMeHgBr	H	147.9	140.7
16	Pr^i	H	H	CH$_2$HgBr	Pr^i	149.9	—
17	Pr^i	H	H	CH$_2$HgBr	Ph	153.6	—
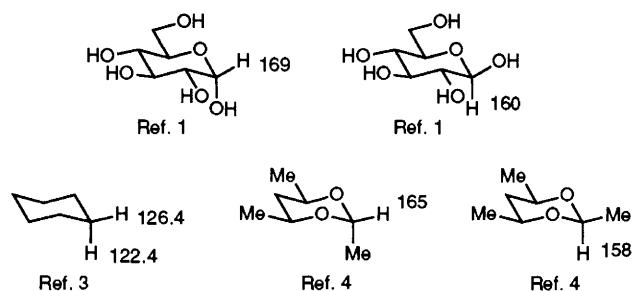
Scheme 1 One-bond NMR ^{13}C–^{1}H coupling constants/Hz. The values for cyclohexane were obtained by measurements on C$_6$D$_{11}$H at low temperature.

(Table 1) that in these trioxanes, the value of $^1J_{C-H}$(equatorial) at C-3 is consistently *less* than that of $^1J_{C-H}$(axial) by 4–6 Hz, *i.e.* a reversal of the usual Perlin effect.

Molecular mechanics (MM3)[8] calculations, which take into account the effect of the nonbonding electrons on oxygen, suggest that these 1,2,4-trioxanes have structures close to a chair. It is, therefore, reasonable to describe the protons as being axial and equatorial.

NOE (nuclear Overhauser effect) experiments were carried out, as shown in Table 1, between the axial substituents R^2 and R^3 on C(3) and C(5). The results with the C(3) epimeric pair **10** and **12** unequivocally locate the proton on C(3) in **10**, with $^1J_{C-H}$ 169.4 Hz, as being axial, and that in **12**, with $^1J_{C-H}$ 163.5 Hz, as being equatorial. Similarly the NOE experiments on compounds **13–17**, where $^1J_{C-H}$ is 166.8–169.3 Hz, locate

Scheme 2 Homoanomeric interactions with the equatorial C–H bonds at (a) C(3), and (b) C(6), in 1,2,4-trioxanes

the C(3)–H bond as axial. We conclude that the range of high values of $^1J_{C-H}$, which we observe (166.8–169.8 Hz) relates to axial hydrogen, and the lower range (161.6–164.8 Hz) to equatorial hydrogen. It is significant that compounds **3–8** and **13–17**, which were the only C(3) epimers isolated from the preparations, all have the alkyl group in the equatorial position, and MM3 calculations indicate these to be the more stable isomers by *ca.* 2.5 kcal mol^{-1} (1 cal = 4.184 J).

We note that an equatorially directed sp^3-type orbital carrying a nonbonding pair of electrons at O(1) would occupy a W-conformation with respect to the equatorial C–H bond at C(3), and we suggest that donation of electrons into the σ* antibonding C–H orbital (a homoanomeric interaction) may weaken this bond and reduce the one-bond coupling as shown in Scheme 2.

On this basis one would expect a similar reversed Perlin effect at C(6), where the axial C–H bond would be subject to one anomeric interaction and the equatorial C–H bond to two homoanomeric interactions (Scheme 2), and indeed this is observed. The relevant data are given in Table 2.

Compound **13** shows values of $^1J_{C-H}$ at C(6) of 151.6 and 137.9 Hz, and in **15**, where the corresponding values are 147.9 and 140.7 Hz, the lower value can unequivocally be assigned to the equatorial proton because it can be measured both by ^{13}C NMR and by observation of the ^{13}C satellites in the proton NMR spectrum. In compounds **9, 10, 16** and **17**, the C–H bond is known to be axial from the values of the *vicinal* coupling

constants, and all these axial protons show large (149.9–155.2 Hz) one-bond coupling constants.

We are at present looking for further examples of this effect in other oxygen-containing heterocycles.

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