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Note

Influence on direct, ^{13}C–^{1}H coupling, and ^{13}C-chemical shift, of replacement of oxygen atoms in aldopyranoses by sulfur. Evidence of differential, γ-anti effects

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The magnitude of the coupling ^{13}C-1 and H-1 ($^{1}J_{C\text{-}1,H\text{-}1}$) of aldopyranoses and their derivatives is related to the bond orientation[1,2]. Values close to 170 Hz are observed when the anomeric proton is equatorial (*e.g.*, as in **1**), whereas couplings are ~10 Hz smaller for their axial counterparts (such as **2**): some representative values are given in Table I. By contrast, methyl 5-thio-α- and -β-D-galactopyranoside (**3** and **4**, respectively)[3], have approximately the *same* $^{1}J_{C\text{-}1,H\text{-}1}$ values (see Table I),

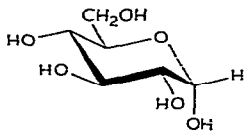
TABLE I

DIRECT, ^{13}C–^{1}H COUPLING ($^{1}J_{C,H}$) IN DERIVATIVES OF THIOALDOPYRANOSES AND THEIR OXA ANALOGS[a]

Compound	$^{1}J_{C\text{-}1,H\text{-}1}$ *(Hz)*	$\alpha - \beta$ *(Hz)*
Methyl 5-thio-α-D-galactopyranoside	160 (160)	1 (3)
β anomer	159 (157)	
Methyl α-D-galactopyranoside	170 (171)	10 (10)
β anomer	160 (161)	
Methyl 5-thio-α-D-glucopyranoside	160 (161)	— (2)
β anomer	— (159)	
Methyl α-D-glucopyranoside	170 (172)	10 (11)
β anomer	160 (161)	
Ethyl 1-thio-α-D-glucopyranoside	163 (169)	9 (14)
β anomer	154 (155)	

	$^{1}J_{C\text{-}1,H\text{-}5}$ *(Hz)*	
	5-thio	5-oxa
Methyl α- and β-D-galactopyranoside	141–144	141–145
Methyl α- and β-D-glucopyranoside	(141–143)	(140–145)

[a]Data for the 5-thioglycosides are from refs. 3 and 4; values in parentheses are for the corresponding tetraacetate derivative.



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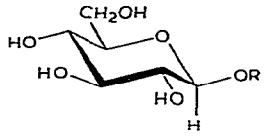
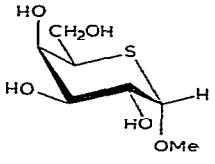


2 R = H
12 R = Me



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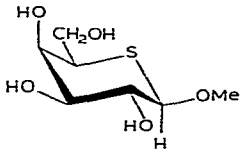

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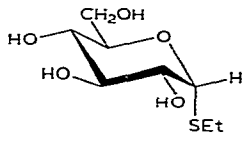

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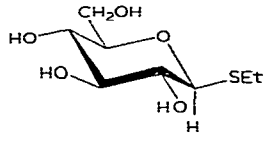

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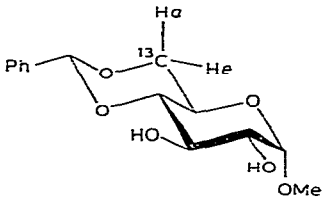
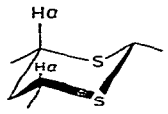
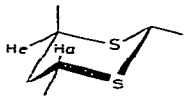


7 $J_{CH\alpha}$ 141
$J_{CH\epsilon}$ 151



8 $J_{CH\alpha}$ 141.3



9 $J_{CH\alpha}$ 143.2
$J_{CH\epsilon}$ 139.9

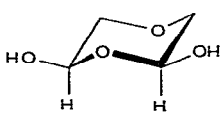
although other data[3] are clearly consistent with an equatorial C–H bond for the α anomer and an axial one for the β anomer. Measurements on additional examples in the 5-thio series (see Table I) indicate that, in general, this difference in coupling, associated with a change in the orientation of the anomeric C–H bond, virtually disappears when the ring-oxygen atom is replaced by a sulfur atom. In effect, the sulfur heteroatom appears to promote a selective diminution in the $^1J_{C\text{-}1,H\text{-}1}$ value of the equatorial C–H bond. This is not due to the change in electronegativity, because, if the anomeric carbon atom is bonded to an exocyclic sulfur atom, as in ethyl 1-thio-α- and -β-D-glucopyranoside (**5** and **6**) and their tetraacetates, a large difference in ^1J is again found (see Table I).

Orientational effects of this kind pertain not only to the anomeric center but also to other C–H bonds adjacent to the ring heteroatom. With pentopyranoses, the coupling between C-5 and H-5*a* is[5] ~8 Hz smaller than that of H-5*e*. We have no comparable data for 5-thioaldoses. However, it is worth noting (see Table I) that coupling between C-5 and the axial H-5 of the 5-thioaldohexoses in the $^4C_1$(D) conformation is about the same as that of their oxygen analogs; *i.e.*, $^1J_{C\text{-}5,H\text{-}5}$ in both series is 140–145 Hz. Hence, as already found in considering the anomeric center, sulfur and oxygen appear to make nearly comparable contributions to the

coupling within an adjacent, *axial* C–H bond. Data[6] for a 1,3-dioxane ring, obtained from the ^{1}H-n.m.r. spectrum of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside-*6*-^{13}C (**7**), provide an additional example of the variation of $^1J_{C,H}$ associated with bond orientation in six-membered rings: the coupling of equatorial H-6 with C-6 is 10 Hz greater than that of axial H-6. In contrast to this, and as would be expected from the foregoing discussion, coupling values for the axial and equatorial C–H bonds in 1,3-dithianes (**8** and **9**) differ[7] by only 1.4–3.3 Hz; indeed, in this instance, ^1J for the equatorial bond is slightly the smaller.

In summary, coupling between ^{13}C and ^{1}H of an equatorial, C–H bond adjacent to a ring-oxygen atom exceeds that of a comparable, axial, C–H bond by an average of ~10 Hz. This difference has been attributed[8] to differences in the orientation of these bonds with respect to the lone pairs on oxygen, one consequence of which should be an increase in the *s* character of the carbon atom of the equatorial bond and, hence, in its value of ^1J. When the oxygen atom is replaced by a sulfur atom, both orientations of the C–H bonds are characterized by almost the same value. It is notable that this equalization in the presence of sulfur is not due to a selective *increase* in ^1J for the axial C–H bond, because numerical values for comparable types of the latter are closely similar, irrespective of whether the adjacent heteroatom is sulfur or oxygen. Therefore, the contribution of a sulfur heteroatom to the interaction between the ^{13}C and ^{1}H nuclear spins, in contrast to that of oxygen, appears to lack an appreciable, orientational component.

An example of an *apparent* increase in ^1J for an axial, anomeric, C–H bond is observed with 1,4-dioxane-2,6-diol[9]; that is, $^1J_{C\text{-}2,H\text{-}2}$ and $^1J_{C\text{-}6,H\text{-}6}$, for the *cis* isomer (**10**) is 164.6 Hz, whereas, for the *trans* isomer (**11** and its conformational enantiomer),



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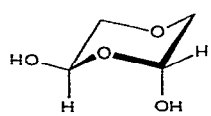

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the mean value is 167.2 Hz. Allowing for a contribution of 164.6 Hz by the axial, C–H bond of **10**, in which there are two axial, anomeric C–H bonds, a value of 169.8 Hz is obtained for the equatorial ^{13}C–^{1}H coupling. Hence, the latter corresponds to that observed for aldopyranoses, whereas the value for the axial bond is smaller by only half the amount (~10 Hz) usually found. Such factors as the relative sizes of bond angles may also be important[10] in determining the relative magnitudes of $^1J_{C,H}$ for axial and equatorial C–H bonds in these, as well as other, pairs of anomers.

Introduction of a sulfur atom instead of the oxygen atom produces, for the anomeric carbon atom, a large upfield shift (15–20 p.p.m.) (see Table II) ascribable to the accompanying decrease in electronegativity, although the displacement, relative to their oxa analogs, is 3–4 p.p.m. greater for β than for α anomers. Also, the magnitude of this effect is almost the same regardless of whether the sulfur atom is exocyclic, as in 1-thioglycosides (**5** and **6**), or is the ring heteroatom of a 5-thioaldose (*e.g.*, **3** and

TABLE II

^{13}C-CHEMICAL SHIFTS OF THIOALDOPYRANOSE DERIVATIVES[a], AND DIFFERENCES IN SHIELDING BETWEEN ANOMERS

Compound	*C-1*	*C-2, 3, 4*	*C-5*	*C-6*	OCH_3	SCH_2	Σ	$\Delta\Sigma^b$ ($\beta - \alpha$)
Methyl 5-thio-α-D-galactopyranoside tetraacetate	85.1	72.3, 71.7, 71.6	44.5	62.3	57.5	—	465.0	
	81.6	71.2, 68.3, 68.3	38.1	60.9	56.5	—	444.9	11.9
Methyl 5-thio-β-D-galactopyranoside tetraacetate	85.9	75.7, 74.8, 71.1	47.2	62.5	59.7	—	476.9	7.9
	82.7	71.1, 71.0, 67.7	40.2	62.2	57.9	—	452.8	
Ethyl 1-thio-α-D-glucopyranoside tetraacetate	85.3	72.6, 71.3, 70.7	74.1	61.0	—	24.4	459.4	
	81.8	70.7, 68.8, 67.6	70.8	62.1	—	24.3	446.1	12.4
Ethyl 1-thio-β-D-glucopyranoside tetraacetate	85.4	77.7, 72.6, 70.0	80.2	61.4	—	24.5	471.8	12.1
	83.5	74.0, 70.0, 68.5	75.9	62.2	—	24.1	458.2	

[a]Data for the 5-thioglycosides are from refs. 3 and 4. [b]Comparable values for the oxygen analogs[12] are ~14–15.

TABLE III

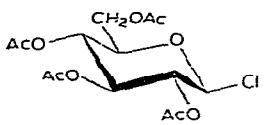
A COMPARISON OF THE ^{13}C CHEMICAL-SHIFTS OF C-3 AND C-5 OF GLYCOSIDES WITH THOSE OF THIOGLYCOSIDES, AND OTHER COMPOUNDS[a]

No.	*Compound*	*C-3*	*Δ-3*	*C-5*	*Δ-5*	*Δ (= Δ5 − Δ3)*
1	Ethyl 1-thio-β-D-glucopyranoside	77.7	1.7	80.2	4.2	2.5
	Methyl β-D-glucopyranoside	76.0		76.0		
2	Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside	74.0	1.5	75.9	4.5	3.0
	Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside	72.5		71.4		
3	Ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside	72.9	0.3	69.9	4.2	3.9
	Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside	72.6		65.7		
4	Phenyl β-D-glucopyranoside	77.4	1.4	77.2	1.2	−0.2
	Methyl β-D-glucopyranoside	76.0		76.0		
5	*p*-Nitrophenyl β-D-glucopyranoside	78.0	2.0	77.3	1.3	−0.7
	Methyl β-D-glucopyranoside	76.0		76.0		
6	Methyl β-D-glucopyranoside	76.0	−0.7	76.0	−0.7	0
	β-D-Glucopyranose	76.7		76.7		
7	2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylchloride	73.0	0.5	74.9	3.5	3.0
	Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside	72.5		71.4		
8	Ethyl 1-thio-α-D-glucopyranoside	72.6	−1.6	74.1	1.8	3.4
	Methyl α-D-glucopyranoside	74.2		72.3		
9	Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside	70.7	1.0	70.8	4.0	3.1
	Methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside	69.7		66.8		
10	*p*-Nitrophenyl α-D-glucopyranoside	74.7	0.5	73.5	1.2	0.7
	Methyl α-D-glucopyranoside	74.2		72.3		
11	1,5-Anhydro-L-galactitol	75.0[b]	1.3	70.0[c]	5.1	3.8
	β-D-Lyxopyranose	73.7		64.9		
12	1,5-Anhydro-D-glucitol	78.3[b]	1.4	69.7[c]	3.8	2.4
	Methyl β-D-xylopyranoside	76.9		65.9		
13	1,5-Anhydro-D-mannitol	74.4[b]	−0.9	70.7[c]	1.8	2.7
	Methyl α-D-arabinopyranoside	75.3		68.9		

[a]Chemical-shift data are from refs. 11, 12, 17, 18, and 19, and the present study. [b]Chemical shift of C-4. [c]Chemical shift of C-6.

4). Consequently, the chemical shift of C-1 (see Table II) is relatively constant for all of the glycosides (and for their 2,3,4,6-tetra-*O*-acetyl derivatives). By contrast, secondary carbon atoms exhibit the differences in shielding normally associated[1,11,12] with an α,β configurational change in the *gluco* and *galacto* series; this is found on (see Table II) comparing overall differences[12,13] ($\Delta\Sigma$) between the numerical sums (Σ) of the chemical shifts for the pairs of anomeric glycosides*. The carbon atoms of α anomers are generally more shielded than those of β anomers. On the average, they resonate 1–2 p.p.m. upfield of carbon atoms of the β-glycosides, a value only slightly less than comparable values for oxa analogs**.

A number of other influences on ^{13}C shielding may be ascribed to the replacement of oxygen by sulfur. For ethyl 1-thio-β-D-glucopyranoside (**6**), C-3 and C-5 resonate 1.7–4.2 p.p.m. downfield of those of methyl β-D-glucopyranoside (**12**) (see Table III), whereas the chemical shifts of C-4 and C-6 are essentially the same. For a variety of compounds, it has been shown[15] that an oxygen, nitrogen, or fluorine atom situated antiperiplanar with respect to a γ-carbon atom promotes increased shielding of that carbon atom (the "γ-anti effect"), whereas no comparable, upfield shift can be attributed to sulfur or chlorine. As the glycosidic sulfur and oxygen atom of **6** and **12**, respectively, are γ-anti relative to C-3 and C-5, the difference noted furnishes an example of this effect in the sugar series. Several other examples are to be found among the data of Table III (see Nos. 2, 3, 8, and 9)‡.



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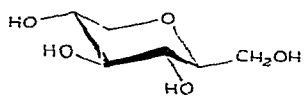

14

15
$\Delta(CH_3-3,5) = -5.9$

16
$\Delta(CH_3-5) = -10.9$

17
R = H, $\Delta(C-3,5) = -2.3$
R = Me, $\Delta(C-3,5) = -2.4$
R = Ac, $\Delta(C-3,5) = -2.1$

*A comparison based on the chemical shifts of individual carbon atoms would be less reliable, because of uncertainty in the assignments of some C-2, C-3, and C-4 signals. For simplicity, the values for these carbon atoms are grouped together in Table II.

**In the cyclitol series, ^{13}C-chemical-shift data for *scyllo*- and *myo*-inositol[14] give a $\Delta\Sigma$ value of 8.7, *i.e.*, an average, upfield shift of $\sim$1.5 p.p.m./carbon atom, associated with an OH*e* → OH*a* orientational change.

‡In an earlier study[16], ^{13}C-shielding contributions that might be attributed to the γ-*anti* effect could not readily be differentiated from those normally associated with the γ-gauche effect of axial substituents in the molecules.

By invoking the γ-anti effect for a comparison of **6** and **12**, it may be concluded that the glycosidic oxygen atom of the latter causes an upfield displacement of 4.2 p.p.m. for C-5, but of only 1.7 p.p.m. for C-3. The other pairs of methyl and ethyl 1-thio-β-D-glycosides show a similar disparity between the chemical shifts of these two nuclei (see Table III). This also holds true when the anomeric alkoxyl group is replaced[17] by chloride (as in **13**) (see No. 7 in Table III), or by CH_2OH, as[19] in 1,5-anhydro-D-glucitol (**14**) and related anhydro derivatives* (Nos. 11–13). Furthermore, it appears that there is a comparable effect when the anomeric substituent is axial. The two examples of α-glycosides included (Nos. 8 and 9) exhibit upfield shifts for C-5 that are ~3 p.p.m. greater than for C-3, although, here, variations in γ-gauche upfield-shifts could be a factor (see footnote ‡, p. 146).

To reinforce this series of comparisons, *O*-glycosyl compounds bearing different substituents on O-1 may be examined. Accordingly, a comparison of *O*-methyl with *O*-phenyl, *O*-*p*-nitrophenyl, or hydroxyl (Nos. 4–6 and 10; Table III), showed that there are no appreciable differences between the chemical shifts of C-3 and C-5.

Overall, these data strongly suggest that O-1 promotes a greater γ-anti upfield-shift for C-5 than for C-3, because of the intervention of an oxygen atom (O-5) as compared with a carbon atom (C-2). Indeed, in view of the exo-anomeric effect[21,22], some form of interaction between exocyclic O-1 and O-5 is to be anticipated**. Hence, it is possible that the preference for an anti-orientation of the *p*-type, lone pair on O-1 with respect to the O-5–C-1 bond, which characterizes the exo-anomeric effect, leads to a greater increase in charge density on C-5 than on C-3. In this context, it is noteworthy that, when the orientation of the lone pairs on the oxygen atom is fixed with respect to the γ-carbon atom (as in **15** and **16**), greater upfield shifts are observed than with such molecules as **17**, the O–R substituents of which probably assume two or more orientations. As an additional factor may be considered the evidence[24] that 1,3-*syn*-diaxial hydrogen atoms are an essential component of the γ-anti effect; consequently, because the C-1–H-1 bond is expected to be closer to the C-5–H-5 than to the C-3–H-3 bond, a greater upfield shift for C-5 might be anticipated.

EXPERIMENTAL

^{13}C-N.m.r. spectroscopy. — ^{13}C-N.m.r. spectra were recorded at 22.6 MHz with a Bruker WH-90 spectrometer, or at 50 MHz with a Varian XL-200 spectrometer. The solvent was $CDCl_3$, or D_2O containing methanol as the internal standard. Chemical shifts (δ) are reported with reference to tetramethylsilane.

Ethyl 1-thio-α-D-glucopyranoside. — Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside was prepared by the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco-

*By analogy, the introduction of a CH_2OH group at C-5 of a pentopyranose (as in xylose → glucose) has no noticeable influence[20] on the chemical shifts of C-1 and C-3.

**In a recent study[23] of some blood-group, antigenic determinants, an evaluation was given of the relationship between the exo-anomeric effect and some n.m.r.-spectral parameters.

pyranosyl bromide with ethanethiol in the presence of potassium, as described[25] for the preparation of the corresponding methyl glycoside. The reaction product, m.p. 80–82°, was equilibrated by treatment with trifluoroacetic acid in chloroform: after 72 h at 65°, the $\alpha:\beta$ ratio was ~2:3 (^{1}H-n.m.r. evidence), and, after three weeks at 55°, it was ~4:1. The acid was neutralized with sodium hydrogencarbonate, the suspension was filtered, and the filtrate evaporated to a solid. On repeated recrystallization from chloroform–petroleum ether, the α anomer was isolated in 95% purity (^{1}H-n.m.r. evidence); m.p. 96°. The title compound was obtained by *O*-deacetylation with sodium methoxide.

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