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Karplus-type equation for vicinal carbon–proton coupling constants for the C–S–C–H pathway in 1-thioglycosides *

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ABSTRACT

The Karplus-type relationship for $^3J_{CSCH}$ values and glycosidic dihedral angles in 1-thioglycosides, based on $^3J_{C,H}$ values for a series of conformationally rigid derivatives, is in the form $^3J_{C,H} = 4.44 \cos^2\Phi - 1.06 \cos\Phi + 0.45$, with $J(0°) = 3.83$, $J(60°) = 1.03$, and $J(180°) = 5.95$ Hz. The $^3J_{C,H}$ values of 5.15 and 2.95 Hz measured for H-4′–C-4′–S-4′–C-1–H-1 of methyl 4-thio-α-maltoside differ from those predicted from the conformation in the crystal. The calculated average $^3J_{C,H}$ values, using PCILO-calculated abundances of conformers in aqueous solution, are 5.12 and 2.6 Hz, respectively.

INTRODUCTION

1-Thioglycosides occur in the seeds of many plants[1] and in some glycopeptides where the oligosaccharide part is linked to cysteine[2]. 1-Thioglycosides can act as inhibitors of enzymes for which the corresponding non-sulphur saccharide is a substrate[3]. The stereochemistry of the glycosidic bond is of fundamental importance in determining the conformation of oligosaccharide derivatives in solution. Various theoretical treatments[4] and several experimental techniques have been applied, including inter-residue ^{13}C–^1H couplings[5].

Since $^3J_{C,H}$ values can now be obtained from natural-abundance ^{13}C-NMR spectra, the question arises as whether or not they can be described by a Karplus-type equation. Experimental work on carbohydrate derivatives predicted that this is possible[6–19] and a Karplus-type equation in the form

$$^3J_{C,H} = A \cos^2\Phi + B \cos\Phi + C \qquad (1)$$

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has been derived on the basis of the couplings measured for conformationally rigid carbohydrate derivatives. Since almost identical sets of constants for eq (*1*) have been found (A, 5.7 and 5.5 Hz; B, −0.6 Hz and −0.7 Hz; C, 0.5 and 0.6 Hz) by two independent groups[18,19], it appears that the proposed Karplus-type equation forms a reliable basis for the estimation of dihedral angles in glycosides.

The use of $^3J_{C,H}$ values for the analysis of the conformation of glycosidic bonds in 1-thioglycosides is hampered because of the lack of information on C–S–C–H segments. The $^3J_{C,H}$ values for such segments of several thiocarbohydrate derivatives are now reported and a Karplus-type relationship is proposed.

EXPERIMENTAL

2,3,4-Tri-*O*-acetyl-1,6-anhydro-6-thio-β-D-glucopyranose[20] (**1**), 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranose[21] (**3**), 1,4-anhydro-2,3,6-tri-*O*-benzoyl-4-thio-α-D-glucopyranose[22] (**4**), 2,3,6-tri-*O*-acetyl-1,4-anhydro-4-thio-α-D-glucopyranose[22] (**6**), and 1,4-anhydro-4-thio-α-D-glucopyranose[22] (**8**) were prepared as described in the literature. *O*-Deacetylation of **1** gave known 1,6-anhydro-6-thio-β-D-glucopyranose[20] (**7**). 2-(3,4,6-Tri-*O*-acetyl-β-D-glucopyranosylthio)aceto-1,2′-lactone[23] (**2**) had mp 188–189°, $[\alpha]_D$ + 184° (*c* 0.7, $CHCl_3$).

*2-(3,4,6-Tri-*O*-acetyl-α-D-glucopyranosylthio)aceto-1,2′-lactone* (**5**). — Following the procedure in ref. 23, a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranose[24] (100 mg, 0.275 mmol) in acetone (2 mL) was treated at 60° for 2 h with ethyl bromoacetate (46 mL, 1.5 equiv) in the presence of $CsCO_3$ (90 mg, 1 equiv), then filtered, diluted with CH_2Cl_2, washed with water, and dried to give ethyl 2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylthio)acetate (96%) after column chromatography (ethyl acetate–light petroleum, 1:3). ^{13}C-NMR data ($CDCl_3$): δ 171.1–169.5 (CO), 86.2 (C-1), 73.7, 70.2, 68.5, 67.9 (C-2,3,4,5), 61.8, 61.6 (C-6 and OCH_2CH_3), 31.3 (CH_2S), 26.6–20.5 (CH_3CO), 14.0 (CH_3CH_2). A suspension of this product in M sodium hydroxide (5 mL) was kept for 30 min at 100°, then neutralised with IRN 77 (H^+) resin, and freeze-dried. Treatment of the product with 1:1 acetic anhydride–pyridine (5 mL), followed by column chromatography (ethyl acetate–light petroleum, 1:2), gave **5** (50%), mp 125–126° (from ether), $[\alpha]_D$ + 14° (*c* 1.6, $CHCl_3$). NMR data ($CDCl_3$): ^{13}C, δ 170.5, 170.0, 169.5 ($COCH_3$), 165.0 ($COCH_2$), 77.4 (C-1), 72.4, 70.4, 70.3, 66.9 (C-2,3,4,5), 61.2 (C-6), 27.1 (CH_2S), 20.6–20.5 (CH_3); ^{1}H, δ 5.71 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.41 (dd, 1 H, $J_{3,4}$ 8.0 Hz, H-3), 4.97 (dd, 1 H, $J_{4,5}$ 7.5 Hz, H-4), 4.58 (dd, 1 H, $J_{2,3}$ 7.0 Hz), 4.33 (m, 2 H, H-5,6a), 4.07 (m, 1 H, H-6b), 3.80 (d, 1 H, $J_{7a,7b}$ 14 Hz, H-7a), 3.38 (d, 1 H, H-7b).

Anal. Calcd for $C_{14}H_{18}O_9S$: C, 46.40; H, 5.00; S, 8.85. Found: C, 46.23; H, 5.16; S, 9.11.

Methyl 4-thio-α-maltoside (**9**) was prepared as described[25].

NMR spectroscopy. — Each purified compound was dissolved (4%) in the appropriate solvent (D_2O, Me_2SO-d_6, dioxane-d_8, pyridine-d_5, or $CDCl_3$). Cou-

pling constants were measured at 30° with a Bruker AM 300 spectrometer equipped with an Aspect 3000 computer. A modified version of the Bax and Freeman sequence[26] for 2D heteronuclear *J*-resolved spectroscopy was used[27]. The 180° selective-proton pulse was provided by a Dante sequence. Experiments were carried out with 32 t_1 increments with a spectral width of 30 Hz in F_1. In F_2, 4096 data points were acquired over a spectral width of 50–60 ppm. After Fourier transformation in F_2, only the slices corresponding to ^{13}C lines coupled to the selected proton were transformed in F_1. In order to avoid errors, no apodisation function was used prior to Fourier transformation in F_1.

The dihedral angles for **1** are those found for the crystal structure[28]. No experimental data on the structures of **2–8** could be found in the literature; consequently, values of dihedral angles of the C–S–C–H segments were derived using the PCILO quantum chemical method[29].

RESULTS AND DISCUSSION

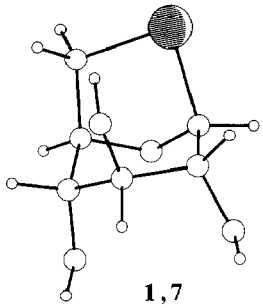
Derivation of the Karplus-type curve for $^3J_{C,H}$ values. — Measurements of the $^3J_{C,H}$ values for the thiocarbohydrate derivatives **1–8** provided 17 couplings for C–S–C–H segments with well-defined conformations and these are summarised in Table I together with the corresponding experimental and calculated dihedral angles. The $^3J_{C,H}$ values cover the whole range of dihedral angles, except from −60° to 35° for which we were unable to synthesise rigid carbohydrate derivatives.

TABLE I

Calculated torsional angles [a] and measured vicinal coupling constants (*J*) for C–S–C–H pathways in thiocarbohydrates

Compound	Array	Torsion angle (°)	$^3J_{C,H}$ (Hz)
1	C-6–S–C-1–H-1	143.3	3.0
	C-1–S–C-6–H-6A	124.3	2.4
	C-1–S–C-6–H-6B	−117.9	0.3
2	C-7–S–C-1–H-1	−61.6	0.5
	C-1–S–C-7–H-7A	79.5	0.9
	C-1–S–C-7–H-7B	−155.8	8.1
3	C-5–S–C-1–H-1	−172.1	5.4
	C-1–S–C-5–H-5	−70.8	0.3
4	C-1–S–C-4–H-4	179.0	6.5
5	C-7–S–C-1–H-1	35.6	1.7
	C-1–S–C-7–H-7A	−59.4	2.4
	C-1–S–C-7–H-7B	178.2	5.0
6	C-1–S–C-4–H-4	179.0	6.4
7	C-6–S–C-1–H-1	143.3	3.1
	C-1–S–C-6–H-6A	124.3	2.3
	C-1–S–C-6–H-6B	−117.9	0.3
8	C-1–S–C-4–H-4	179.0	6.3

[a] Torsional angles were calculated using the PCILO quantum chemical method or Quanta.



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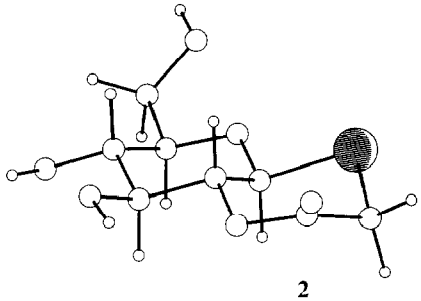

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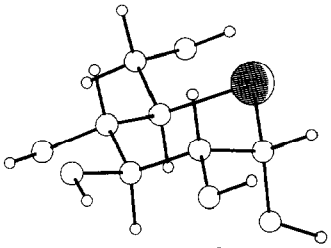

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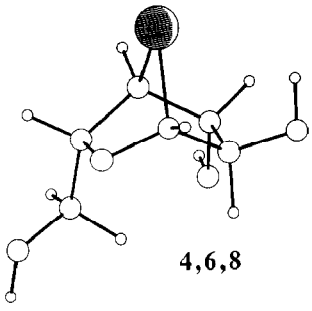

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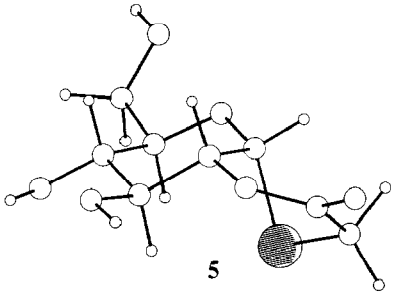

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Whereas the dominating factor that determines vicinal spin–spin interactions is the dihedral angle, there are additional features that may influence the magnitude of $^{3}J_{C,H}$ values, namely, the influence of electronegative substituents, multiple pathways and their cumulative effect in cyclic systems, and variations in bond lengths and bond angles. An ideal system for the determination of the dependence of $^{3}J_{C,H}$ on the dihedral angle is not available, so that it is not possible to account precisely for the above effects. In order to minimise the effects of the factors listed above, the relevant atoms in the compounds considered were sp^3 hybridised and the structures met the condition of a constant sum of the substituent electronegativities. As far as multiple pathways are concerned, the $^{4}J_{C,H}$ contributions in **1–8**

were < 0.3 Hz. Thus, the above effects should be small in comparison with those for changes in dihedral angles. This conclusion is supported by the success of the analogous approach used to determine the Karplus-type relationship for $^3J_{C,H}$ values of C–O–C–H segments[18,19].

The $^3J_{C,H}$ values were fitted by the minimisation program COMPLEX[30] to a curve of the form given by eq (*1*). The resulting relationship,

$$^3J_{C,H} = 4.44 \cos^2\phi - 1.06 \cos \phi + 0.45, \quad (2)$$

is shown in Fig. 1 together with the measured $^3J_{C,H}$ values. The magnitudes $^3J_{C,H}$ for synperiplanar ($\phi = 0°$), synclinal ($\phi = 60°$), and antiperiplanar ($\phi = 180°$) orientations about the C–S bond are 3.83, 1.03, and 5.95 Hz, respectively, and there is satisfactory agreement between experimental and calculated values. There is a large difference between the value (8.1 Hz) for $^3J_{C\text{-}1,H\text{-}7B}$ in **2** and other values for a dihedral angle in the synclinal conformation. A possible origin of this difference may be that the π-electrons of the carbonyl group at the β position increase the magnitude of $^3J_{C,H}$, especially when they are in antiperiplanar orientation with respect to a coupled proton. Therefore, this $^3J_{C,H}$ value was discarded when the constants A–C were derived.

The variation (5.5 Hz) of the $^3J_{C,H}$ values for C–S–C–H segments with torsional angle is smaller than that (6.3 Hz) for C–O–C–H segments. On the contrary, the difference between the $^3J_{C,H}$ values for the torsional angles 180° and 0° is larger in C–S–C–H than in C–O–C–H segments (2.12 versus 1.2 Hz, respectively).

A comparison of the conformation of methyl 4-thio-α-maltoside (**9**) *in solution and in the crystal.* — The crystal structure[31] of **9** is the sole reported structure for a

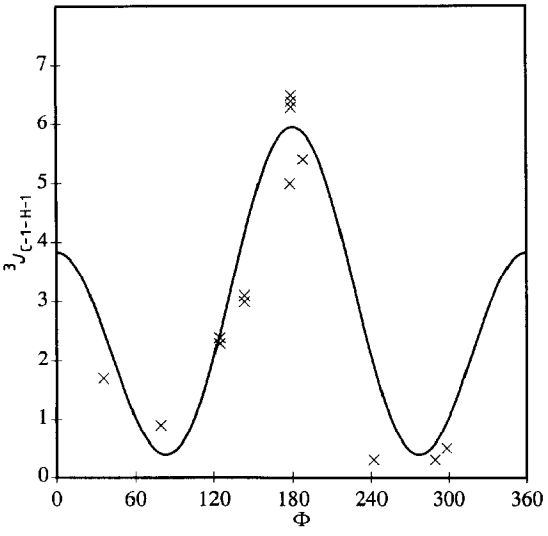

Fig. 1. Relationship between $^3J_{C,H}$ and the C–S–C–H dihedral angle Φ based on the experimental data (×).

thio-oligosaccharide. The torsional angles ϕ (O-5–C-1–S–C-4′) and ψ (C-1–S–C-4′–C-5′) of the glycosidic linkage in the crystal are 89° and −116.8°, respectively, and the corresponding torsional angles ϕ^H (H-1–C-1–S–C-4′) and ψ^H (C-1–S–C-4′–H-4′) are −25.6° and 3.6°, respectively. The $^3J_{C,H}$ values predicted for the conformation in the crystal of **9**, using eq (*2*), are $J_{C\text{-}4',H\text{-}1}$ 3.1, $J_{C\text{-}1,H\text{-}4'}$ 3.8 Hz.

In order to compare the conformations in the crystal and in solution, the $^3J_{C,H}$ values were measured for an aqueous solution. Using a modified version of the Bax and Freeman sequence[27], the values $J_{C\text{-}4',H\text{-}1}$ 2.95, $J_{C\text{-}1,H\text{-}4'}$ 5.15 Hz were obtained. A "virtual" conformation deduced from these couplings can be described by the average torsional angles $\langle\phi^H\rangle$ ±29° or ±130° and $\langle\psi^H\rangle$ ±155°. The experimental values for the solution and those predicted from the crystal structure indicate that the conformations of **9** in aqueous solution and in the solid state are different.

The PCILO method has been used to calculate the relaxed (ϕ, ψ) conformational energy surface in solution[32]. The existence of 15 stable conformers with a different internal geometry was revealed with five main minima for rotation about the glycosidic C–S bonds in aqueous solution. These minima correspond to conformations T1 (ϕ^H −53.1°, ψ^H −155°), T2 (69.2°, 29.2°), T3 (−22.9°, 176.3°), T5 (6.8°, −34.2°), and T8 (−9.8°, −61.6°). The ratios of the conformers in aqueous solution at 25° are T1 : T2 : T3 : T5 : T8 = 0.2 : 22.2 : 76.6 : 0.7 : 0.2. Conformational averaging based on the abundances of the five conformers and the $^3J_{C,H}$ values calculated from eq (*2*) gave the values $\langle^3J_{C\text{-}4',H\text{-}1}\rangle$ 2.6 Hz and $\langle^3J_{C\text{-}1,H\text{-}4'}\rangle$ 5.2 Hz which accorded with the experimental values.

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