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Constants in Thiopyranose Derivatives**

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Additivity Constants for the Prediction of H,H-Coupling Constants in Thiopyranose Derivatives

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We report the determination of additivity constants for sulphur substituents on a pyranose ring from a set of 81 experimental H,H-coupling constants ($^3J_{\text{H,H}}$) and their employment for the prediction of $^3J_{\text{H,H}}$ values in the thiopyranose ring, with excellent accuracy.

Relationships of vicinal H,H-coupling constants ($^3J_{\text{H,H}}$ values) as a function of the associated torsion angles ($\phi_{\text{H,H}}$), which include correction factors due to the electronegativity and orientation of the substituents attached to a HC—CH fragment, are usually referred to as generalized Karplus equations.^{1,2} In addition, correction terms have been used to account for the deviations of $^3J_{\text{H,H}}$ values from a J^0 value, regarded as the coupling constant in the unsubstituted fragment. Thus, Abraham *et al.*³ have proposed a set of additivity constants (ΔJ) in order to predict J values in trisubstituted fragments of polypeptides. Similarly, Altona and Haasnoot⁴ have described a simple additivity scheme [eqn. (1)] which allows accurate prediction of all the vicinal coupling constants [$J_{(a,a)}$, $J_{(a,e)}$, $J_{(e,e)}$] in six-membered carbohydrate rings.

$$^3J = ^3J^0 + \sum_1^4 \Delta J(X) \quad (1)$$

In this equation, $^3J^0$ represents the reference value (an adjustable parameter not necessarily identical with the coupling in the corresponding CH₂—CH₂ fragment) and $\Delta J(X)$ are additivity constants. The values of $^3J^0$ and $\Delta J(X)$ were derived from experimental couplings measured for pyranose rings judged to be conformationally homogeneous and geometrically undeformed.⁴ Solution of eqn. (1) gives the calculated $^3J_{\text{H,H}}$ value for a HC—CH fragment of a pyranoside having any combination of substituents (*e.g.* O, N, halogen). However, for sulphur-substituted pyranoses the $\Delta J(X)$ values were assigned only tentatively and were not tested by comparison with experimental results. Direct con-

acetate, thiocyno, *etc.*). The effect of the substituent on the sulphur atom was neglected, it being assumed that this substituent exerts a relatively unimportant effect on $^3J_{\text{H,H}}$. However, as $J_{(a,a)}$ is appreciably influenced by the presence of a substituent on a carbon β to the HC—CH fragment under study and in a *syn*-1,3-axial orientation with respect to one of the coupling protons,⁴ a correction due to this ' β -effect' was introduced as an additional additivity constant (0.5 Hz).

The set of 90 experimental couplings was divided into three subsets according to the relative stereochemistries of the sulphur and other substituents with respect to the coupled protons. Nine couplings were eliminated as they showed large discrepancies with the averaged J values of the corresponding group. The derivation of the $\Delta J(S)$ constants will be briefly outlined for $\Delta J_{(a,e)}(S \text{ anti})$. This parameter appears, for instance, in the calculation of $J_{(1,2)}$ for 2-thio- β -D-manno-pyranosides, and can be expressed, according to eqn. (1) and assuming $\Delta J(C) = 0$, by

$$J_{1,2} = J^0_{(a,e)} + \Delta J(O \text{ gauche}) + \Delta J(O \text{ anti}) + \Delta J_{(a,e)}(S \text{ anti})$$

Replacement of $J^0_{(a,e)}$ and $\Delta J(O)$ by their reported values⁴ gives the following relationship:

$$J_{(1,2)} = 4.4 + 0.5 - 1.8 + \Delta J_{(a,e)}(S \text{ anti})$$

Similar equations for $J_{(a,e)}$ as a function of $\Delta J_{(a,e)}(S \text{ anti})$ can be obtained for $J_{2,3}$ of 2-thiopyranosides, $J_{3,4}$ of 4-thiogalactopyranosides and $J_{4,5}$ of 4-thiogulo-, 4-thiogalacto- and 4-thioido-pyranosides. The resulting equations were fitted to the mean values ($\bar{J}_{1,2}$; $\bar{J}_{2,3}$; ...) of all the available experimental couplings. Five $\Delta J(S \text{ anti})$ values were obtained, and these were averaged taking into account the number (n) of experimental couplings [$\bar{\Delta J}(S \text{ anti}) = \sum_i n_i \Delta J_i(S \text{ anti}) / (\sum_i n_i)^{-1}$]. The other additivity constants were similarly calculated; their values and those previously proposed⁴ are shown in Table 4.

Table 4 Additivity constants, $\Delta J(S)$

	$\Delta J_{(a,e)}$ or $\Delta J_{(e,e)}(S \text{ anti})$	$\Delta J_{(a,e)}$ or $\Delta J_{(e,e)}(S \text{ gauche})$	$\Delta J_{(a,a)}(S \text{ gauche})$
This work	-0.90	+0.40	-0.60
Altona-Haasnoot ⁴	-0.30	+0.10	-0.30

firmation of the self-consistency of these proposed $\Delta J(S)$ values is required as they have already been employed for the calculation of reference coupling constants for 5-thio-sugars.⁵ Therefore, we now report the determination of $\Delta J(S)$ values on the basis of experimental spectral data. In our calculations we employed eqn. (1), which was parametrized for all the substituents, except for sulphur, with the data from ref. 4.

For the derivation of $\Delta J(S)$ a set of 90 experimental couplings for the HC—CH fragment of the pyranose carrying a sulphur substituent was obtained from the spectra of thio-sugar derivatives synthesized in our laboratory,⁶⁻⁸ as well as from data reported in the literature. For the data collection we employed a variety of free or derivatized thiosugars, having different patterns of sulphur substitution (thiol, thio-

The calculated constants were statistically evaluated for the individual couplings ($J_{(1,2)}$, $J_{(2,3)}$, *etc.*) as well as for the total set of 81 coupling constants. The mean ($\bar{\Delta J}$) and root-mean-square (σ) differences between the calculated and experimental J values are given in Table 5.

All the ΔJ values display a normal frequency distribution in the statistical sense, and the overall $\bar{\Delta J}$ and σ differences (-0.01 and 0.36, respectively) obtained by employing the $\Delta J(S)$ values here calculated were considerably lower than those resulting from Altona's values⁴ ($\bar{\Delta J} = -0.38$ Hz and σ 0.62 Hz). However, they were comparable to the $\bar{\Delta J}$ and σ values (0.01 and 0.29, respectively) reported⁴ for pyranosides having different substituents.

Accurate coupling predictions were observed for thiopyranose derivatives with no ring distortions. Thus, the predicted couplings ($J_{1,2}$ 3.6, $J_{2,3}$ 9.9, $J_{3,4}$ 4.0 and $J_{4,5}$ 2.1 Hz) for methyl 6-deoxy-4-thio- α -D-galactopyranoside, determined by means of molecular mechanics calculations⁷ to be in an

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Table 5 Statistics of the agreement between calculated and experimental J values

$J_{(a,a)}$	$J_{(a,e)}$ or $J_{(e,e)}$	$\Delta J/\text{Hz}^a$	N^b	σ/Hz	Ranges of observed values (Hz)
1,2		0.10	7	0.30	8.5–11.5
2,3		0.05	6	0.37	10.0–11.0
3,4		-0.20	5	0.35	10.0–11.0
4,5		-0.10	6	0.15	10.4–11.0
Overall		-0.01	24	0.30	8.5–11.5
	1,2	-0.13	14	0.18	1.0–4.0
	2,3	-0.17	3	0.29	3.5–4.0
	3,4	0.01	20	0.35	2.5–4.5
	4,5; 5,6	0.09	21	0.48	1.0–4.5
	Overall	-0.01	57	0.38	1.0–4.5
All couplings		-0.01	81	0.36	1.0–11.5

^a $\Delta J = [J(\text{exp}) - J(\text{calc})]/N$. ^bNumber of observations.

almost ideal 4C_1 conformation, showed excellent agreement with the experimental values (3.5, 9.8, 4.3 and 2.1). However, discrepancies appeared for 5-thiopyranoses which have the sulphur atom within the ring. For example, the observed coupling constants (3.1, 9.4, 8.9 and 9.1) for 5-thio- α -D-glucopyranose²⁰ are smaller in every case than the calculated ones (3.5, 9.9, 9.4 and 10.2). The decrease in $J_{(a,a)}$ and $J_{(a,e)}$ may be attributed, as has been previously suggested,^{5,20} to a puckering due to the presence of the sulphur in the ring, which brings closer together the diaxial vicinal protons, and pushes further apart the vicinal H-*eq*, H-*ax* protons. In any case, this type of distortion analysis must be carried out with caution when one is dealing with thiopyranose rings in conformational equilibrium.

The use of the corrected additivity constants is particularly recommended for the prediction of ${}^3J_{\text{H,H}}$ values in pyranose systems having various sulphur substituents, as they give a better correlation with the experimental values than do ${}^3J_{\text{H,H}}$ values calculated by means of the Altona-Haasnoot parameters. Thus, $J_{1,2}$ (1.7 Hz) for ethyl 4-*O*-benzoyl-2,3,6-tri-*S*-ethyl-1,2,3,6-tetrathio- α -D-mannopyranoside²¹ and $J_{1,2}$ (9.5 Hz) for 3,4,6-tri-*O*-acetyl-1,2-*S*-ethylene-1,2-dithio- β -D-glucopyranoside²² showed good agreement with our calculated values (1.6 and 9.6 Hz respectively), whereas larger deviations were observed for those estimated (1.0 and 10.2 Hz respectively) using Altona's constants.

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Schemes: 1

Table 1: Experimental coupling constants employed for the calculation of $\Delta J_{(a,e)}$ or $\Delta J_{(e,e)}$ (*S gauche*), and J values calculated by means of eqn. (1)

Table 2: Experimental coupling constants employed for the calculation of $\Delta J_{(a,a)}$, and J values calculated by means of eqn. (1)

Table 3: Experimental coupling constants employed for the calculation of $\Delta J_{(a,e)}$ or $\Delta J_{(e,e)}$ (*S anti*), and J values calculated by means of eqn. (1)

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References cited in this synopsis

- 1 M. Karplus, *J. Am. Chem. Soc.*, 1963, **85**, 2870.
- 2 C. A. G. Haasnoot, F. A. A. M. Leeuw and C. Altona, *Tetrahedron*, 1980, **36**, 2783.
- 3 R. J. Abraham, P. Loftus and W. A. Thomas, *Tetrahedron*, 1977, **33**, 1227.
- 4 C. Altona and C. A. G. Haasnoot, *Org. Magn. Reson.*, 1980, **13**, 417.
- 5 J. B. Lambert and J. M. Wharry, *Carbohydr. Res.*, 1983, **115**, 33.
- 6 O. Varela, D. Cicero and R. M. de Lederkremer, *J. Org. Chem.*, 1989, **54**, 1884.
- 7 D. Cicero, O. Varela and R. M. de Lederkremer, *Tetrahedron*, 1990, **46**, 1131.
- 8 D. Cicero, O. Varela and R. M. de Lederkremer, *Carbohydr. Res.*, in press.
- 20 J. B. Lambert and S. M. Wharry, *J. Org. Chem.*, 1981, **46**, 3193.
- 21 G. S. Bethell and R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1*, 1971, 1400.
- 22 P. Angibeaud and J. Defaye, *Carbohydr. Res.*, 1980, **82**, 385.