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Note

N.m.r. spectra and tautomeric equilibria of 5-thio-D-fructofuranose and 6-thio-D-fructopyranose in aqueous solution

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5-Thio-D-fructofuranose[1] (**1**) and 6-thio-D-fructopyranose[2] (**2**) have thiol groups suitably positioned to engage in the formation of thio-oxy hemiacetals, having sulfur as the ring heteroatom, that are comparatively thermodynamically stable. Such expected involvement of sulfur in the sugar ring seems to predominate to the nearly complete exclusion of other ring-forms. However, additional supporting data are needed to clarify this concept further. This information is given here by ^{1}H- and ^{13}C-n.m.r. spectroscopy, which also provide data on the ratio of anomeric forms in aqueous solution.

D-Fructose exists in aqueous solution as anomeric mixtures of furanose and pyranose ring-forms. Examination of D-fructose in D_2O by ^{1}H-n.m.r.[3], ^{13}C-n.m.r.[4–8], and hydroxyl-proton resonance[6] in dimethyl sulfoxide-d_6 has revealed the presence of the β-pyranose, β-furanose, α-furanose, and α-pyranose in the ratios of 6:3:1:trace, respectively[5–8]. Proof that the two major forms have the β-D arrangement is derived, not only from ^{13}C-n.m.r. spectra[5–8], but also from polarimetric data[9,10].

These data establish the ratio of tautomers in aqueous equilibrium. As might be expected, the ratios of the α- and β-D anomers of **1** and **2** are not the same as in solutions of natural D-fructose, but the conformations of the sulfur-ring forms are probably the same as those of the oxygen-ring forms.

DISCUSSION

The proton-decoupled ^{13}C-n.m.r. spectrum of 5-thio-D-fructose (**1**) in water (Table I) reveals 12 individual signals divided into two sets of clearly different intensity. Integration of resonances corresponding to two sets of signals indicates that the equilibrium composition of anomers at 25° is 89:11. Comparison of the spectrum of **1** (Table I) with those characteristic of D-fructofuranoses[8] permits the

TABLE I

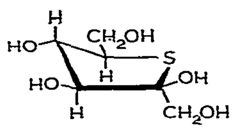
^{13}C CHEMICAL SHIFTS OF 5-THIO-D-FRUCTOFURANOSES AND 6-THIO-D-FRUCTOPYRANOSES[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
5-Thio-β-D-fructofuranose (**1a**)	66.1	87.8	78.7	76.8	47.7	64.4
5-Thio-α-D-fructofuranose (**1b**)	65.6	90.0	84.4	76.1	49.1	63.4
6-Thio-β-D-fructopyranose (**2a**)	66.4	85.3	70.1	71.9[b]	71.7[b]	30.4
6-Thio-α-D-fructopyranose (**2b**)	64.8	84.4	72.7[c]	73.3[c]	68.0[c]	27.1

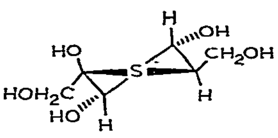
[a] In D_2O in p.p.m. downfield from Me_4Si. Measured with respect to internal 1,4-dioxane, which was taken as 67.4 p.p.m. [b] Assignments may be reversed. [c] Assignment uncertain.

assignment of resonances to the respective carbon atoms of the β-**1a** and α-**1b** anomers. The chemical shifts of C-1, C-3, C-4, and C-6 are in good agreement with the reference spectra, although the resonances of C-2 and C-5 show a relative upfield shift because of the introduction of the sulfur atom, which is less electronegative. Resonances corresponding to the major component are ascribed to the β-furanose (**1a**) form. The assignment is based on the upfield shift of the C-2 and C-3 resonances of the major component in comparison with the respective signals of the minor component (**1b**) to which the α-D configuration is assigned. The observed shift is caused by the *cis* relation of the C-2 and C-3 hydroxyl groups in the β-D anomer[7]. The higher stability of the β-D anomer in water solution is in agreement with previous findings[1], and with the literature data for D-fructose[4-8]. When water is replaced by pyridine as a solvent, the proportion of α-D anomer (**1b**) increases to 20%. This is reflected by the change of specific optical rotation, which is —7.7° in water and +13.5° in pyridine solution[1].

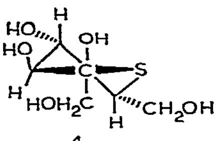
In the ^1H-n.m.r. spectrum at 300 MHz of 5-thio-D-fructose (**1**) (Fig. 1, Table II) signals are detected for the β-D anomer (**1a**) only. The resonances of the α-D anomer (**1b**) are overlapped by the signals of the more-abundant isomer (**1a**) and cannot be readily assigned. The values of $J_{3,4}$ = 9.4 Hz and $J_{4,5}$ = 8.3 Hz in the ^1H-n.m.r. spectrum of **1a** are typical for an axial–axial relationship and suggest that, in **1a**, the geometry of the ring at the energy minimum along the pseudorotation circuit corresponds closely to the ^4E envelope conformation (having C-4 above the plane) or the half-chair forms $^4T_3$ and $^4T_5$. These conformations have dihedral angles H-3–H-4 ≈ H-4–H-5 close to 180°, consistent with the observed, large coupling-constants $J_{3,4}$ and $J_{4,5}$. It is noteworthy that the pentaacetate of the α-D anomer



^4E



$^4T_3$



$^4T_5$

of **1** shows $J_{3,4}$ = 6.2 and $J_{4,5}$ = 6.9 Hz, whereas the pentaacetate of the β-D anomer has[1] $J_{3,4}$ = 7.8 and $J_{4,5}$ = 6.0 Hz. These values indicate that the same dominanting

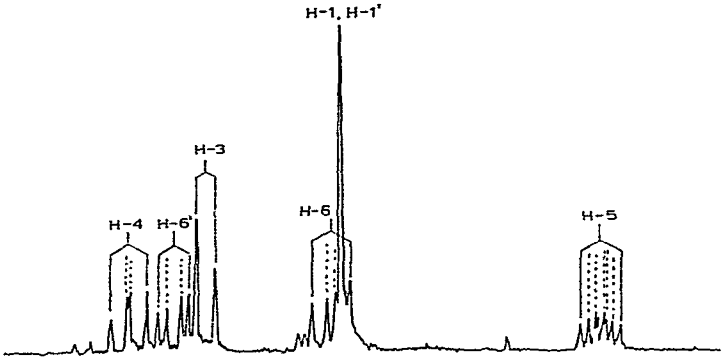


Fig. 1. ^{1}H-N.m.r. spectrum of 5-thio-D-fructofuranose (**1**) at 300 MHz in D_2O with *tert*-butyl alcohol as internal reference.

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF ^{1}H RESONANCES OF 5-THIO-β-D-FRUCTOFURANOSE AND 6-THIO-D-FRUCTOPYRANOSES IN D_2O[a]

Compound	*H-1*	*H-1'*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	$J_{1,1'}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1a	3.66	3.66	3.88	3.93	3.22	3.68	3.90		9.4	8.3	7.0	4.0	−11.3
2a	3.72	3.76	3.93	3.79	4.26	3.19	2.65	−11.9	9.7	3.0	4.2	1.6	−14.2
2b	3.68	3.73	4.07	3.86	4.16	2.93	2.6	−11.9	5.9	2.9	3.3	9.3	−14.0

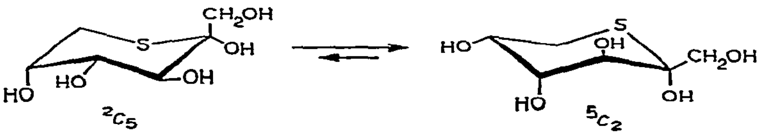
[a] The internal reference compound[13] was *tert*-butyl alcohol, δ 1.23.

conformations also prevail for the pentaacetates. This inference for conformation in solution is corroborated by the results obtained for the β-D-fructofuranosyl groups of sucrose in crystalline sucrose bromide dihydrate[11], in melezitose, and in raffinose[12]. It should be pointed out, however, that DeBruyn, Anteunis and Verhegge[3], using ^{1}H-n.m.r. spectroscopy at 300 MHz, have tentatively deduced a flattened E_4 conformation for β-D-fructofuranose in water.

6-Thio-D-fructopyranose (**2**) is a colorless solid having $[\alpha]_D^{25}$ +193.8° in water. By analogy with β-D-fructopyranose, one might expect that **2** exists as the β-D anomer. The ^{13}C-n.m.r. spectrum of **2** in D_2O shows resonances of two components in the ratio 9:1. The major set of resonances may be assigned to the β-D-pyranose form (**2a**) in the $^2C_5$ conformation. Comparison of the resonances of **2a** (Table I) with those of β-D-fructopyranose[8] allowed assignment of signals to the respective carbon atoms. The empirical rules of Dorman and Roberts[14,15] and of Que and Gray[7] allow assignment of the signals in the ^{13}C-n.m.r. spectrum to the appropriate carbon atoms in **2b**. The chemical shift of a carbon atom is a function of the configuration of substituents at the β, γ, and δ carbon atoms. In pyranoid rings, the chemical shift of the α carbon atom may be correlated with epimerization of hydroxyl groups about adjacent carbon atoms from the equatorial to the axial disposition.

An axial group on a β or δ carbon atom causes a large upfield shift of the α carbon atom if the latter bears an equatorial hydroxyl group, but causes a slight downfield shift of the α carbon atom if it bears an axial hydroxyl group. The chemical shifts of C-2 and C-6 of ketopyranoses may also be correlated with the change of hydroxyl position at β, γ, and δ carbon atoms from the equatorial to the axial disposition[7,15]. It has been shown that axial γ hydroxyl groups cause an upfield shift of the C-6 resonance, whereas, β and δ groups cause a downfield shift. The resonance of C-2 is shifted upfield by β and γ hydroxyl groups.

The ^{13}C-n.m.r. spectrum of 6-thio-α-D-fructopyranose (**2b**, Table I) shows an upfield shift at C-2 and C-6 relative to the β-D anomer; the assignment of C-2 and C-6 resonances is straightforward. It is obvious that the large shifts of C-6 (+3.3 p.p.m.) and C-2 (+0.9 p.p.m.) are connected with the inversion of the pyranose ring of **2b**. The C-6 atom in the $^5C_2$ conformation is opposed by two γ hydroxyl groups (large upfield shift), whereas C-2 has axial hydroxyl groups at the β and γ carbon atoms (upfield shift, see formulas). Because of the preponderating $^5C_2$ conformation of **2b**, an upfield shift of the C-1 and C-5 resonances and a slight downfield shift at C-3 and C-4 may be expected. On this basis, assignment could be made of the chemical shifts of C-1, C-3, C-4, and C-5 in the ^{13}C-n.m.r. spectrum of 6-thio-α-D-fructopyranose (**2b**).



The ^{1}H-n.m.r. spectrum at 300 MHz of **2** (Fig. 2, Table II) fully supports the deductions made from the ^{13}C-n.m.r. spectrum. The spectrum shows resonances characteristic of **2a** (major component) and **2b** (minor component). The integration of respective peaks gives the anomeric equilibrium as 85% of **2a** and 15% of **2b**. The

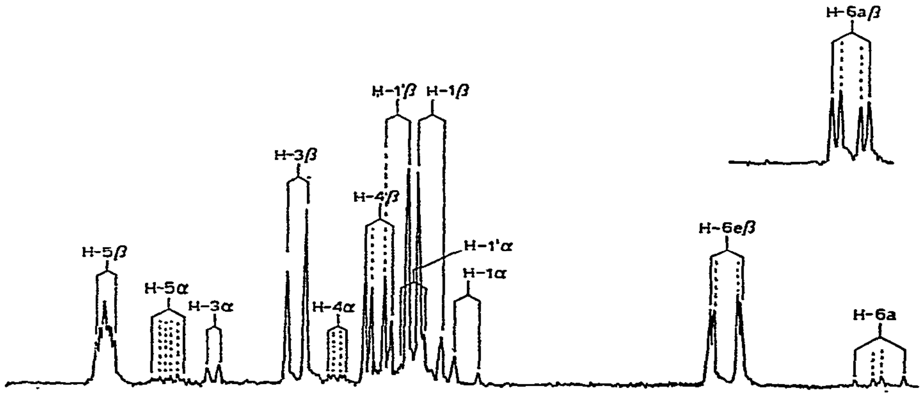


Fig. 2. ^{1}H-N.m.r. spectrum in D_2O of 6-thio-D-fructopyranose (**2**) at 300 MHz with *tert*-butyl alcohol as the internal reference.

spectrum of **2a** (Table II) shows $J_{3,4} = 9.7$, $J_{4,5} = 3.0$, $J_{5,6a} = 4.2$, and $J_{5,6e} = 1.6$ Hz, whereas these values for **2b** are: $J_{3,4} = 5.9$, $J_{4,5} = 2.9$, $J_{5,6a} = 9.3$, and $J_{5,6e} = 3.3$ Hz. These data also testify to the $^2C_5$ conformation of **2a** and the $^5C_2$ predominianting conformation of **2b**.

These investigations have established the tautomeric equilibria and conformations of 5-thio-D-fructofuranoses (**1a** and **1b**) and 6-thio-D-fructopyranoses (**2a** and **2b**). The ratios of α and β anomers of sugars **1** and **2** are different from those measured for natural D-fructose. The conformations of **1a**, **1b**, **2a**, and **2b** are probably the same as those of their oxygen analogs.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian HR-300 spectrometer at 300 MHz for protons, and on Bruker F. T. (22.63 MHz) or Varian XL-100 (25.2 MHz) instruments for ^{13}C.

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