Carbohydrate Research, 193 (1989) 1–8
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

THE CONFORMATION OF 6-THIO-β-D-FRUCTOPYRANOSE IN THE CRYSTALLINE STATE

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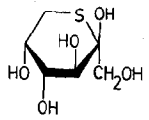
(Received March 29th, 1988; accepted for publication in revised form, November 24th, 1988)

ABSTRACT

The crystal structure of 6-thio-β-D-fructopyranose has been determined by X-ray diffraction techniques. The compound crystallizes in the orthorhombic system, space group $P2_12_12_1$, with cell dimensions $a = 9.727(5)$, $b = 5.228(6)$, $c = 5.363(1)$ Å, and $Z = 4$. The structure was solved by direct methods and refined by full-matrix, least-squares calculations to a residual R value of 0.029. The thiopyranoid ring is in a $^2C_5$(D) chair conformation with the hydroxymethyl group oriented −sc *(gauche)* to the ring sulfur atom.

INTRODUCTION

6-Thio-β-D-fructopyranose[1] (**1**) has been the subject of several investigations[2–4] since the time of the report[5] of its synthesis in 1976. It is significantly sweeter than its ring-oxygen analog, β-D-fructopyranose, when tasted in crystalline form[6], and it is nontoxic[1]. The present work forms part of an investigation of the electronic and conformational properties of thio sugars[7] with regard to the role these properties play in determining sweetness. A crystallographic study was undertaken in order to determine the crystal conformation of **1**; the data have already been employed by us[7] in *ab initio* quantum mechanical calculations on **1**.



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0008-6215/89/$ 03.50

TABLE I

CRYSTAL DATA[a]

Parameter	*Crystal data*
Molecular formula	$C_6H_{12}O_5S$
Molecular weight	196.22
Space group; Z	$P2_12_12_1$; 4
Unit cell parameters (Å)	$a = 9.727(5)$
	$b = 15.228(6)$
	$c = 5.363(1)$
Volume (Å^3)	794.4
Number of reflections used for the determination of unit cell parameters; 2θ range (deg.)	25; 23–32
Density (calc.) (g.cm^{-3})	1.641
Number of measured reflections	2019
Number of observed reflections, $I > 3\sigma(I)$	1268
2θ range scanned (deg.)	1–70
μ (MoKα) (cm^{-1})	3.853
Crystal dimensions (mm)	0.50 × 0.44 × 0.20
Final refinement values R; R_w	0.029; 0.039
Largest shift/error in final least-squares cycle, Δ/σ	0.00
Maximum and minimum residual electron density in the final difference Fourier map (e Å^{-3})	0.377, −0.233
Standard deviation in an observation of unit weight, σ	1.518

[a]Estimated standard deviations are shown in parentheses.

EXPERIMENTAL

A sample of 6-thio-β-D-fructose was kindly supplied by Professor R. L. Whistler of Purdue University. Suitable single crystals were obtained by recrystallization from absolute ethanol. Pertinent data about the crystal used and the measurement of diffraction intensities are summarized in Table I. The intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å) and the θ–2θ scanning technique. Three standard reflections were measured every 7200 s of radiation time and showed no significant variation during the course of data collection. The intensities were corrected for Lorentz and polarization effects.

The structure was solved by direct methods using the program[8] MULTAN-80. Difference Fourier map calculations revealed the positions of all of the hydrogen atoms. However, the hydroxyl hydrogen atoms were relocated such that the O–H bond distances were normalized to a standard value[9] of 0.97 Å. A full-matrix, least-squares refinement was performed for a scale factor, for positional and anisotropic thermal parameters of the non-hydrogen atoms, for positional and isotopic thermal parameters of the non-hydroxyl hydrogen atoms, and for isotropic thermal parameters of the hydroxyl hydrogen atoms. The positional parameters of

TABLE II

POSITIONAL PARAMETERS AND THEIR ESTIMATED STANDARD DEVIATIONS[a]

Atom	x	y	z	$B(Å^2)$
S	0.63145(3)	0.97715(2)	0.25526(7)	1.774(5)
O-1	0.4174(1)	1.09469(6)	−0.0632(2)	2.17(2)
O-2	0.4936(1)	0.93111(7)	−0.1619(2)	1.86(2)
O-3	0.2805(1)	0.84681(7)	0.1038(2)	1.92(2)
O-4	0.4346(1)	0.71509(7)	0.3164(3)	2.57(2)
O-5	0.6432(1)	0.79940(7)	0.5741(2)	1.96(2)
C-1	0.3782(1)	1.03051(8)	0.1150(3)	1.82(2)
C-2	0.4713(1)	0.95000(8)	0.0942(3)	1.35(2)
C-3	0.4078(1)	0.86865(8)	0.2180(2)	1.32(2)
C-4	0.5000(1)	0.78753(8)	0.1972(3)	1.55(2)
C-5	0.6440(1)	0.79674(8)	0.3086(3)	1.62(2)
C-6	0.7198(1)	0.8747(1)	0.1988(3)	1.88(2)
H-1a	0.382(2)	1.053(1)	0.279(3)	1.4(3)[b]
H-1b	0.285(2)	1.015(2)	0.069(5)	2.9(5)[b]
H-3	0.395(2)	0.883(1)	0.410(4)	1.5(3)[b]
H-4	0.518(2)	0.779(1)	0.015(5)	2.4(4)[b]
H-5	0.699(2)	0.738(1)	0.280(4)	2.5(4)[b]
H-6a	0.812(2)	0.881(1)	0.276(4)	2.7(4)[b]
H-6b	0.734(2)	0.871(1)	0.027(4)	2.1(4)[b]
HO-1	0.463	1.138	0.041	3.5(5)[c]
HO-2	0.505	0.989	−0.235	6.4(8)[c]
HO-3	0.206	0.858	0.219	4.4(6)[c]
HO-4	0.337	0.725	0.299	6.0(7)[c]
HO-5	0.598	0.852	0.631	4.7(6)[c]

[a]Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as: $(4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + abB(1,2)\cos\gamma + acB(1,3)\cos\beta + bcB(2,3)\cos\alpha]$. [b]Atoms refined isotropically. [c]Atoms refined isotropically with positional parameters held fixed.

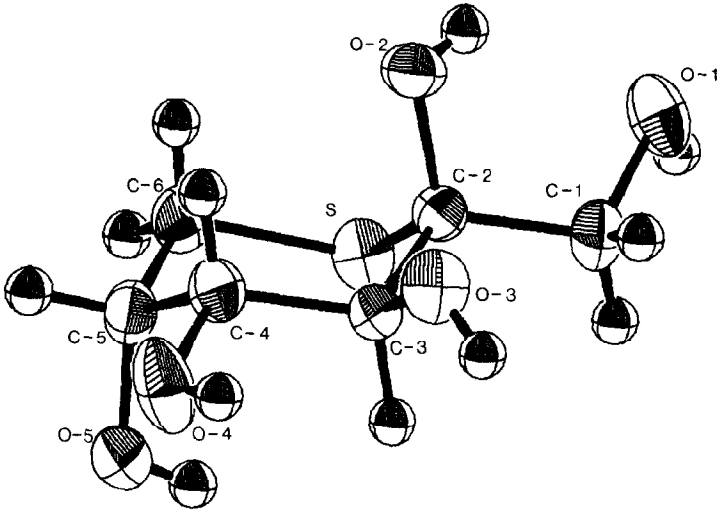

Fig. 1. ORTEP drawing showing atom numbering in 6-thio-β-D-fructopyranose (**1**).

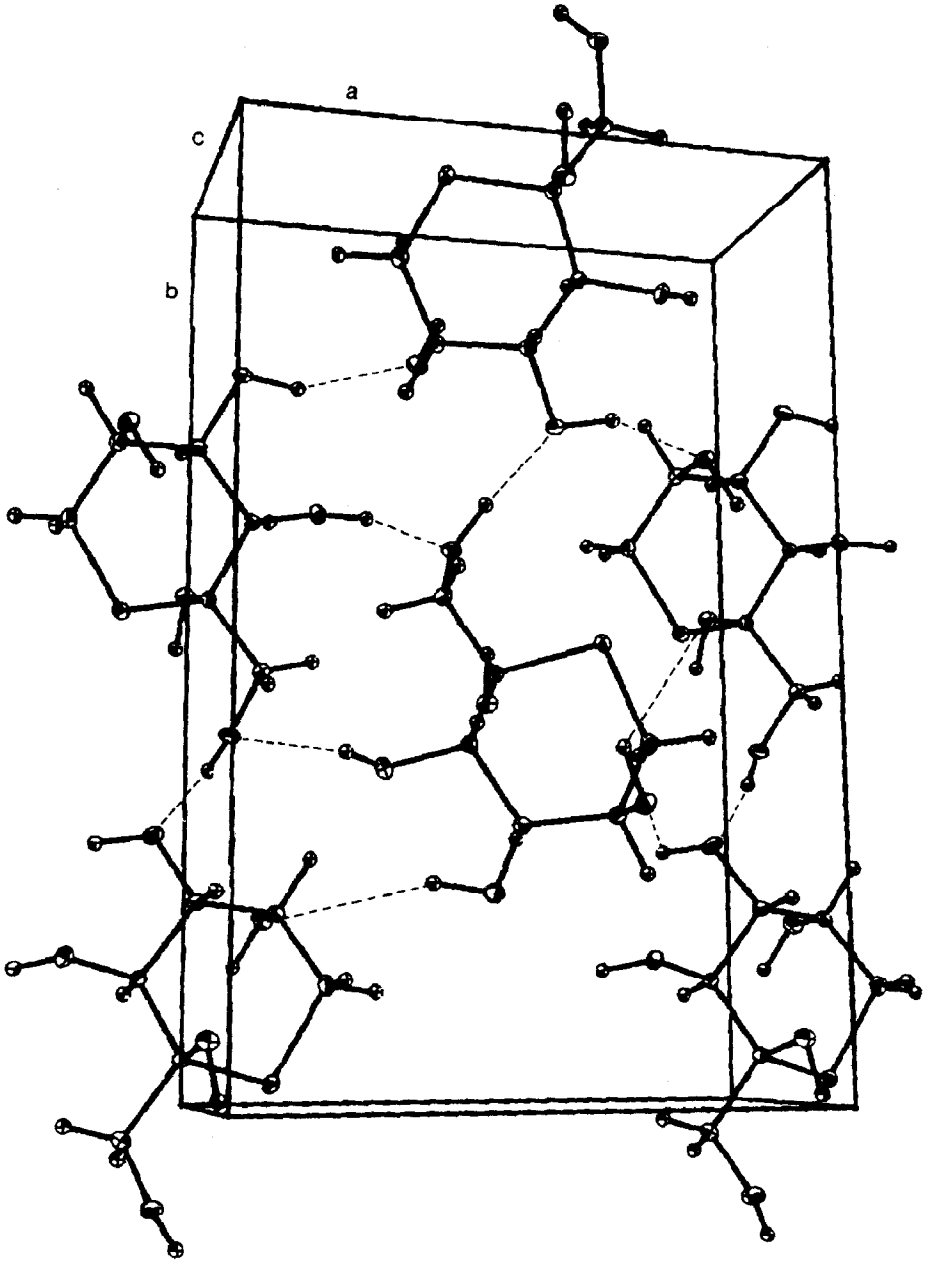

Fig. 2. Molecular packing of **1** within the unit cell. Strong intermolecular hydrogen bonds are drawn as dashed lines.

the hydroxyl hydrogen atoms were held fixed. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, where $w = 4F^2/[\sigma^2(F^2) + (0.04\,F^2)^2]$. The final difference Fourier synthesis was essentially featureless. The scattering factors used were those of Cromer and Waber[10]. The anomalous dispersion coefficients were taken from the data of Cromer[11]. The final atomic coordinates are given in Table II. All calculations were performed on a PDP 11/23 computer using the structure determination package[12] of Enraf-Nonius, SDP. The program ORTEP[13] was used for the preparation of Figs. 1 and 2.

DISCUSSION

The crystal structure of **1** shows that the thiopyranoid ring exists in a $^2C_5$(D) chair conformation, which has also been shown[2,4], by ^{13}C-n.m.r. studies of the solution in D_2O, to be the predominant conformation for **1** in solution. The bond lengths and angles are given in Tables III and IV, respectively. The mean C–S distance is 1.818 Å, and the C-6–S–C-2 angle is 97.52(5)°. The difference of 0.022 Å between the S–C-2 and S–C-6 bond lengths may be due to coulombic interactions between C-2 and S, and C-6 and S, related to the anomeric effect (see ref. 7). The molecule is more puckered than β-D-fructopyranose; the average torsion angle around the ring in **1** is 59.3°, compared to 55.2° for β-D-fructopyranose[14]. The

TABLE III

BOND LENGTHS (Å)[a]

S–C-2	1.829(1)	O-5–C-5	1.424(2)
S–C-6	1.807(1)	C-1–C-2	1.528(2)
O-1–C-1	1.419(2)	C-2–C-3	1.535(1)
O-2–C-2	1.420(1)	C-3–C-4	1.530(2)
O-3–C-3	1.421(1)	C-4–C-5	1.529(2)
O-4–C-4	1.425(1)	C-5–C-6	1.517(2)

[a]Numbers in parentheses are estimated standard deviations.

TABLE IV

BOND ANGLES (DEGREES)[a]

S–C-2–O-2	111.86(8)	O-4–C-4–C-3	109.30(9)
S–C-2–C-1	106.79(8)	O-5–C-5–C-4	112.9(1)
S–C-2–C-3	108.70(7)	C-1–C-2–C-3	112.19(9)
S–C-6–C-5	112.30(8)	C-2–S–C-6	97.52(5)
O-1–C-1–C-2	110.1(1)	C-2–C-3–C-4	112.58(8)
O-2–C-2–C-1	108.89(9)	C-3–C-4–C-5	115.72(9)
O-3–C-3–C-2	110.66(9)	C-4–C-5–C-6	111.43(9)

[a]Numbers in parentheses are estimated standard deviations.

TABLE V

SELECTED TORSIONAL ANGLES (DEGREES)[a]

S–C-2–C-3–C-4	−62.4(1)	O-5–C-5–C-6–S	67.1(1)
S–C-2–C-3–O-3	178.09(8)	C-1–C-2–C-3–O-3	60.2(1)
O-1–C-1–C-2–S	79.4(1)	C-2–S–C-6–C-5	−60.1(1)
O-1–C-1–C-2–O-2	−41.6(1)	C-2–C-3–C-4–O-4	180.0(1)
O-1–C-1–C-2–C-3	−161.6(1)	C-2–C-3–C-4–C-5	58.1(1)
O-2–C-2–C-3–C-4	59.4(1)	C-3–C-4–C-5–O-5	71.2(1)
O-3–C-3–C-4–O-4	−58.4(1)	C-3–C-4–C-5–C-6	−55.3(1)
O-3–C-3–C-4–C-5	180.0(1)	C-4–C-5–C-6–S	60.1(1)
O-4–C-4–C-5–O-5	−51.4(1)	C-6–S–C-2–O-2	−60.1(1)
O-4–C-4–C-5–C-6	−178.0(1)	C-6–S–C-2–C-3	59.6(1)

[a]Numbers in parentheses are estimated standard deviations.

Cremer and Pople[15] puckering parameters for **1** are $q_2 = 0.148$ Å, $q_3 = 0.657$ Å, $Q = 0.673$ Å, $\phi_2 = 129.4°$, and $\theta = 12.70°$; the corresponding values for β-D-fructopyranose[14] are 0.026 Å, 0.555 Å, 0.556 Å, 132.1°, and 2.76°. The torsion angles are listed in Table V. The hydroxymethyl group, C-1(H_2)–O-1–HO-1, is oriented −sc *(gauche)* to the ring sulfur atom, whereas, in β-D-fructopyranose, the corresponding hydroxymethyl group is oriented +sc *(gauche)* to the ring oxygen atom[14].

The hydrogen-bonding pattern was examined by use of an H · · · A cut-off value of 2.85 Å for H · · · O and 3.20 Å for H · · · S interactions[9]. The relevant numerical data are given in Table VI. There are three intramolecular hydrogen bonds; between O-2 and O-1, O-4 and O-3, and O-5 and S. The Cambridge Crystallographic Data Base[16] was searched for carbohydrate structures containing C–S–C

TABLE VI

HYDROGEN BOND DISTANCES (Å) AND ANGLES (DEGREES)[a]

D–H · · · A (code)[b]	*Translation*			*D · · · A*	*H · · · A*	*∠D–H · · · A*
	a	*b*	*c*			
O-1–HO-1 · · · O-4 (4)	1	0	0	2.681(1)	1.715(1)	169.73(8)
O-1–HO-1 · · · O-5 (4)	1	0	0	3.173(1)	2.7330(9)	107.98(6)
O-2–HO-2 · · · S (1)	0	0	−1	3.4729(9)	3.0032(3)	111.03(5)
O-2–HO-2 · · · O-1 (1)	0	0	0	2.652(1)	2.0398(9)	119.07(6)
O-3–HO-3 · · · O-1 (2)	0	2	0	2.773(1)	1.823(1)	166.03(6)
O-3–HO-3 · · · O-5 (3)	−1	1	1	3.119(1)	2.7084(9)	106.09(6)
O-4–HO-4 · · · O-3 (1)	0	0	0	2.751(1)	2.202(1)	114.71(6)
O-4–HO-4 · · · O-5 (3)	−1	1	1	2.903(1)	2.035(1)	148.30(7)
O-5–HO-5 · · · O-2 (1)	0	0	1	2.854(1)	1.9250(9)	160.44(6)
O-5–HO-5 · · · S (1)	0	0	0	3.2035(9)	2.7913(3)	106.55(5)

[a]Numbers in parentheses are estimated standard deviations. D–H bond distances are normalized to 0.97 Å. [b]Symmetry codes (1) x, y, z; (2) $-x, y + 1/2, -z + 1/2$; (3) $x + 1/2, -y + 1/2, -z$; (4) $-x + 1/2, -y, z + 1/2$.

and H–O–C fragments, in which there are intramolecular separations of 2 to 4 Å between the oxygen and sulfur atoms, and in which the S–H–O angle is between 100 and 180°. Only two structures[17], namely methyl 1,5-dithio-α-D-ribopyranoside and methyl 1,5-dithio-β-D-ribopyranoside, were found. In the α-D anomer, there are two symmetry-independent molecules, each adopting a $^1C_4$(D) ring conformation. In one of these, the hydroxyl group at C-4 is oriented in an *endo* position to the sugar ring; the hydroxyl proton, HO-4, is hydrogen bonded to both the axially oriented hydroxyl oxygen atom, O-2, and to the ring sulfur atom. The following data were derived from the reported positional parameters: the O-4–S distance, 3.202(3) Å; the HO-4–S distance, 2.97(3) Å; and the O-4–HO-4–S angle, 105.(3)°. The other symmetry-independent molecule of methyl 1,5-dithio-α-D-ribopyranoside contains an hydrogen bond between the hydroxyl proton, HO-2, and both the ring sulfur atom and the axially oriented hydroxyl oxygen atom, O-4. In the β-D anomer, there are no intramolecular hydrogen bonds involving the ring sulfur atom. In **1**, the hydroxyl group at C-5 adopts a similar *endo* orientation, in which the HO-5 proton is hydrogen bonded to the ring sulfur atom. The O-5–S distance is 3.2035(9) Å, the HO-5–S distance is 2.7913(3) Å, and the O-5–HO-5–S angle is 106.55(5)°.

The molecules of **1** are held together by a three-dimensional network of strong (see ref. 18) intermolecular O–H · · · O hydrogen bonds with interactions O-5–HO-5 · · · O-2 and O-3–HO-3 · · · O-1 linking the molecules in the *c* direction, O-4–HO-4 · · · O-5 in the *a* direction, and O-1–HO-1 · · · O-4 in the *b* direction (see Fig. 2). Weaker hydrogen bonds between O-1 and O-5, O-3 and O-5, and O-2 and S are also found.

ACKNOWLEDGMENTS

The authors are grateful to the Natural Sciences and Engineering Research Council Canada for financial support in the form of grants (to W.A.S. and S.F.) and to the Province of Ontario, Ministry of Colleges and Universities, for an Ontario Graduate Scholarship (to R.J.W.). They also thank Professor R. L. Whistler of Purdue University for his very kind gift of a sample of 6-thio-D-fructose.

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