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DISTORTION ANALYSIS OF THIO SUGARS

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ABSTRACT

The ^{1}H and ^{13}C spectra have been analyzed fully for 5-thio-α-D-xylopyranose and in part for the β anomer. Comparison with our analyses for both anomers of 5-thio-D-glucopyranose and 6-thio-D-fructopyranose and with analyses of the analogous oxygen sugars for all three systems provides a general perspective for the characterization of ring distortions brought about by the presence of the sulfur atom within the ring. Puckering of the thio sugar ring is demonstrated in the α anomers of both the xylose and the fructopyranose by a decrease in axial–equatorial couplings and an increase in equatorial–equatorial couplings. The β anomers of 5-thioglucose and 5-thioxylose appear to be more resistant to puckering, possibly because of the buttressing effects of numerous adjacent equatorial groups. These conformational factors may be responsible in part for the decreased stability of the β thio sugar, relative to the α anomer, in comparison with the oxygen analogues.

INTRODUCTION

Introduction of a sulfur atom into a sugar ring, in place of the oxygen atom, brings about significant changes in the properties of the molecule[1]. One possible contributor to these changes is an alteration in the overall shape of the ring. Even when the chair conformation is maintained, and specific substituents remain in their axial or equatorial dispositions, the ring geometry can be appreciably altered through distortion of the torsional angles. The smaller C-S-C angle (in comparison with C-O-C) has been shown to increase torsional angles within the ring, e.g., C-S-C-C and S-C-C-C, and give rise to a puckering distortion[2]. In the resulting conformation, the ring atoms are displaced further from the average plane than in an undistorted chair. Furthermore, vicinal equatorial–equatorial relationships are brought closer together, axial–equatorial relationships are pushed further apart, and axial–axial relationships are brought closer together.

Previous nuclear magnetic resonance studies of thio sugars did not examine the possibility of distortions within the ring[3]. We have recently reported that the ring of 5-thio-α-D-glucopyranose is indeed puckered with respect to that of α-D-glucopyranose itself[4]. We have now analyzed the ^{1}H and ^{13}C spectra of 5-thio-D-xylopyranose and have reanalyzed the spectra of 6-thio-D-fructopyranose. These results,

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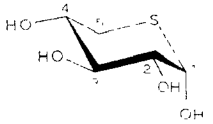
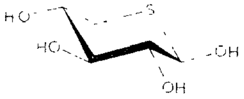
which we report herein, establish that ring puckering is a general phenomenon in α-thio sugars and that ring distortion is less pronounced in some β anomers. The differences may be understood in terms of the buttressing effects of substituents.

RESULTS

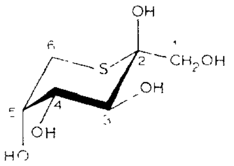
The 360- or 470-MHz ^1H and the 20-MHz ^{13}C spectra were recorded in D_2O at ambient temperatures for the anomeric mixtures of 5-thio-D-xylopyranose (**1**) and of 6-thio-D-fructopyranose (**2**). The xylose derivative (**1**) shows an α/β ratio of ~17:3. Full analysis could be obtained only for the α anomer. The ^1H parameters for the α anomer of **1** appear in Table I and the ^{13}C parameters in Table II, together with the literature values for the analogous natural oxygen sugar[5,6]. The available ^1H parameters for the β anomer are given in Table III, together with the literature data on the oxygen sugar. Although small peaks attributable to the β anomer appear in the ^{13}C spectrum, we did not attempt to make assignments.



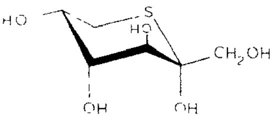
1-α



1-β



2-β



2-α

TABLE I

^1H PARAMETERS FOR 5-THIO-α-D-XYLOPYRANOSE AND α-D-XYLOPYRANOSE IN D_2O

Proton	$\delta(S)^a$	$\delta(O)^b$	$J(obs)(S)^c$		$J(calc)(S)^d$	$J(obs)(O)^{b}$	$J(calc)(O)^d$
H-1	4.92	5.83	$J_{1,2}$	2.2	3.2	3.3	3.6
H-2	3.76	4.18	$J_{2,3}$	9.65	9.8	9.0	9.8
H-3	3.58	4.66	$J_{3,4}$	9.65	9.3	8.4	9.3
H-4	3.73	4.26	$J_{1,5}$	3.0	5.0	5.2	5.4
H-5	2.59	4.16	$J_{5,5'}$	−13.2		−10.4	
H-5′	2.88	4.53	$J_{1,5}$	11.25	11.2	10.0	10.0

[a] In p.p.m. from Me_4Si, for **1**-α [b] Ref. 5; data for the oxygen analogue of **1**-α. [c] In Hz, for **1**-α. [d] By the method of ref. 10.

TABLE II

^{13}C PARAMETERS FOR 5-THIO-α-D-XYLOPYRANOSE AND α-D-XYLOPYRANOSE IN D_2O

Carbon atom	*δ(S)*[a]	$^1J(^{13}C\text{-}^1H)$ *(S)*[b]	*δ(O)*[c]
C-1	75.7	157(d)	93.3
C-2	78.0	148(d)	72.5
C-3	76.2	148(d)	73.9
C-4	75.7	152(d)	70.4
C-5	29.6	142(t)	62.1

[a] In p.p.m. from Me_4Si, for **1**-α. [b] In Hz, for **1**-α. [c] Ref. 6; data for the oxygen analogue of **1**-α.

TABLE III

^1H PARAMETERS FOR 5-THIO-β-D-XYLOPYRANOSE AND β-D-XYLOPYRANOSE IN D_2O

Proton	*δ(S)*[a]	*δ(O)*[b]	*J(obs)(S)*[c]	*J(calc)(S)*[d]	*J(obs)(O)*[b]	*J(calc)(O)*[d]
H-1	4.68	4.57	$J_{1,2}$ 9.1	9.0	7.8	7.9
H-2		3.23	$J_{2,3}$ 9.3	9.3	9.2	9.3
H-3	3.22	3.42	$J_{3,4}$ 9.3	9.3	9.0	9.3
H-4		3.63	$J_{4,5}$	5.0	5.6	5.4
H-5		3.93	$J_{5,5'}$		−11.4	
H-5′		3.32	$J_{4,5'}$	11.2	10.5	10.0

[a] In p.p.m. from Me_4Si, for **1**-β. [b] Ref. 7; data for the oxygen analogue of **1**-β. [c] In Hz, for **1**-β. [d] By the method of ref. 10.

The spectral analysis of the fructose derivative (**2**) has been reported previously[3]. We repeated the ^1H and ^{13}C analyses of the major (17:3) β anomer, for the sake of comparison, and these new data are recorded in Tables IV and V, together with the oxygen data[8,9]. Fairly complete ^1H data could also be obtained for the minor α anomer (Table VI), but no ^{13}C data were obtained, nor were comparative data for the natural oxygen system available.

Altona and Haasnoot[10] have recently described an empirical procedure for calculating the vicinal ^1H–^1H coupling constants in sugar molecules, provided that there is no change in the ring geometry. This highly parameterized method requires knowledge of the axial or equatorial nature of the various substituents and allows for the effects of electronegativity on coupling constants. We have calculated the expected couplings according to this method for both anomers of 5-thio-D-xylopyranose and their oxygen analogues, for the β anomer of 6-thio-D-fructopyranose and its oxygen analogue, and for the α anomer of the fructose derivative. These values may be found in Tables I, III, IV, and VI, under the headings *J*(calc). They provide a useful frame of reference for possible geometry changes that occur in the 5-thio sugars.

TABLE IV

^{1}H PARAMETERS FOR 6-THIO-β-D-FRUCTOPYRANOSE AND β-D-FRUCTOPYRANOSE

Proton	δ(*S*)[a]	δ(*O*)[b]	J(*obs*)(*S*)[c]	J(*calc*)(*S*)[a]	J(*obs*)(*O*)[b]	J(*calc*)(*O*)[d]
H-1	3.72	3.71	$J_{1,1'}$ −11.75		−11.8	
H-1′	3.77	3.77				
H-3	3.94	3.80	$J_{3,4}$ 9.85	10.3	10.0	10.3
H-4	3.81	3.89	$J_{4,5}$ 3.1	3.1	3.2	3.1
H-5	4.29	3.99	$J_{5,6}$ 4.35	2.8	1.8	1.3
H-6	2.65	3.71	$J_{6,6'}$ −14.7		12.4	
H-6′	3.21	4.03	$J_{5,6'}$ 1.9	2.3	1.3	0.8

[a] In p.p.m. from Me_4Si, for **2**-β. [b] Ref. 8; data for the oxygen analogue of **2**-β. [c] In Hz, for **2**-β. [d] By the method of ref. 10.

TABLE V

^{13}C PARAMETERS FOR 6-THIO-β-D-FRUCTOPYRANOSE AND β-D-FRUCTOPYRANOSE

Carbon atom	δ(*S*)[a]	^{1}J(^{13}*C*-^{1}*H*)(*S*)[b]	δ(*O*)[c]
C-1	68.1	145(t)	64.9
C-2	86.8	(s)	98.9
C-3	73.5	147(d)	68.6
C-4	73.6	144(d)	70.7
C-5	71.7	142(d)	70.2
C-6	32.1	141(t)	64.2

[a] In p.p.m. from Me_4Si, for **2**-β. [b] In Hz, for **2**-β. [c] Ref. 9; data for the oxygen analogue of **2**-β.

TABLE VI

^{1}H PARAMETERS FOR 6-THIO-α-D-FRUCTOPYRANOSE

Proton	δ(*S*)[a]	J(*obs*)(*S*)[b]	J(*calc*)(*S*)[c] ($^5C_2$)	J(*calc*)(*S*)[d] ($^2C_5$)	J(*calc*)(*S*)[e] (*mixture*)
H-1	3.67	$J_{1,1'}$ 12.3			
H-1′					
H-3	4.10	$J_{3,4}$ 5.95	3.6	9.8	5.5
H-4	3.88	$J_{4,5}$ 2.45	3.1	3.1	3.1
H-5	4.18	$J_{5,6}$ 9.0	11.7	2.8	9.0
H-6		$J_{6,6'}$ −14.2			
H-6′		$J_{5,6'}$ 3.6	5.0	2.3	4.2

[a] In p.p.m. from Me_4Si, for **2**-α. [b] In Hz, for **2**-α. [c] By the method of ref. 10, for the $^5C_2$ conformation. [d] By the method of ref. 10, for the $^2C_5$ conformation. [e] By the method of ref. 10, for 70% $^5C_2$ and 30% $^2C_5$.

DISCUSSION

Essentially any distortion of an ideal chair will decrease the axial–axial dihedral angle, thereby decreasing any J_{aa} value. Therefore, couplings involving equatorial protons more accurately define the type of distortion. A puckering distortion decreases the equatorial–equatorial dihedral angle and hence increases the J_{ee}, according to a Karplus analysis. Similarly, the axial–equatorial angle increases in a puckering distortion, thereby decreasing J_{ae}. A flattening distortion has the opposite effect on these couplings. Our distortion analysis compares the observed couplings of equatorial protons with those calculated by the Altona–Haasnoot method[10], which takes electronegativity effects into consideration. Any difference between the observed and calculated couplings may be attributed to ring distortions.

In 5-thio-α-D-xylopyranose (**1**-α, the major anomer), $J_{1,2}$ and $J_{4,5}$ are between axial and equatorial protons. The smaller observed value (by 1.0 and 2.0 Hz, respectively) (Table I) than those calculated is strong evidence for puckering in these portions of these rings. By contrast, the analogous couplings in the oxygen sugar are within 0.3 Hz of the observed values, indicating little distortion. Replacement of oxygen by sulfur normally increases a coupling, if the only effect is that of electronegativity[4]. Therefore, the observed decrease in these two couplings is in accord with considerable puckering of the ring. The axial–axial couplings are close to their calculated values. Although it is possible that there is less distortion in parts of the ring further from sulfur, the lower sensitivity of the Karplus curve near 180° may decrease the effect. Agreement between observed and calculated values is poor (0.8–0.9 Hz) for two of the axial–axial couplings in the oxygen system. Altona and Haasnoot noted this discrepancy and excluded these values from their calculations. It is possible that the observed couplings are experimentally in error.

Distortion analysis of the vicinal couplings in 6-thio-α-D-fructopyranose (**2**-α, the minor anomer) produces similar conclusions (Table VI). The observed axial–equatorial couplings again are smaller than the calculated ones ($J_{4,5}$ by 0.65 Hz, $J_{5,6'}$ by 1.4 Hz), and the observed equatorial–equatorial coupling is larger ($J_{3,4}$ by 2.35 Hz). The direction of all three couplings indicates a puckering distortion. Our analysis confirms the conclusion of Chmielewski and Whistler that **2**-α adopts mainly the $^5C_2$ conformation, having three axial hydroxyl groups[3]. Data are not available for the α anomer of the oxygen sugar.

Alternatively, **2**-α may be a mixture of the $^5C_2$ form illustrated and the "ring reversed" $^2C_5$ form. The calculated couplings for the $^2C_5$ form are well removed from the observed values (Table VI), but an admixture of 30% $^2C_5$ with the dominant $^5C_2$ form gives calculated couplings (Table VI, last column) that are very close to the observed values. The $J_{4,5}$ is axial–equatorial in both forms and is overestimated by calculation in either case, in agreement with ring puckering. The analysis of $J_{3,4}$ and $J_{5,6'}$ is not clear, however, because the identities (*aa*, *ee*, or *ae*) are different in the two conformers. Without analysis at low temperature to obtain couplings from the distinct conformers, we cannot clarify this case fully. From $J_{4,5}$, the molecule appears to be puckered.

We observed several signals from the minor 5-thio-β-D-xylopyranose anomer (**1-β**) (Table III). Unfortunately, the observed couplings were all axial axial. The observed and calculated values are very close together, but the relative insensitivity of axial–axial couplings has been mentioned already. Without information on $J_{4,5}$, a final definition of the conformation cannot be made. The observed and calculated values also are very close for all the couplings in the oxygen sugar, indicating a distortion-free ring.

In 6-thio-β-D-fructopyranose (**2-β**, the major anomer), the observed axial–equatorial couplings (Table IV) are not very different from the calculated values (a difference of 0.0 and 0.4 Hz for $J_{4,5}$ and $J_{5,6'}$, respectively). The direction for $J_{5,6'}$ is appropriate for a slight puckering. The equatorial–equatorial coupling ($J_{5,6}$) is 1.5 Hz larger than the calculated value, indicative of some puckering. The analogous coupling ($J_{5,6}$) in the oxygen system, however, is also somewhat different (0.5 Hz) from the calculated value. This difference of 0.5 Hz may decrease the extent of puckering reflected in the 1.5 Hz variance for $J_{5,6}$ in the thio sugar. With the possible exception of the 5,6 portion of the ring, the β anomer of this thio sugar may have less puckering than the α anomer.

Two of the α anomers in the systems observed to date, 5-thio-D-glucopyranose[4] and 5-thio-D-xylopyranose, exhibit significant puckering, in comparison with their oxygen analogues. The third, 6-thio-D-fructopyranose, probably is puckered. We have found less evidence for distortion in the β anomers. A puckering distortion brings two vicinally related equatorial substituents closer together, but moves adjacent axial–equatorial substituents further apart. As the β anomers in 5-thioglucose and 5-thioxylose have only equatorial substituents, buttressing of many equatorial–equatorial interactions will oppose the puckering distortion. The result will be a less puckered β anomer. Furthermore, these interactions (equatorial buttressing and angle strain from less puckering) may decrease the overall stability of the β anomer in comparison with that of the α anomer.

The α anomer of 5-thioglucose or 5-thioxylose has a single axial hydroxyl group. Ring puckering relieves the gauche interaction of an axial substituent with an adjacent equatorial substituent. These effects of distortion by the sulfur atom may contribute to the inversion of the anomeric ratio, from a β preference in the oxygen cases (all equatorial substituents and a strain-free ring) to an α preference in the sulfur cases (one axial substituent, whose interactions are relieved by the puckering distortion of sulfur). Because 5-thioglucose has one more equatorial substituent (the 5-CH_2OH group) than 5-thioxylose, it is possible that the xylose can permit more puckering (less substituent buttressing). Comparison of the coupling constants seems to support such a conclusion. The more complex mix of substituents and conformers in the fructose derivative makes any analysis of buttressing more difficult. The β preference here may be the simple result of the normal preference for the equatorial disposition, coupled with the fact that buttressing in **2**-β occurs between only one pair of equatorial groups (C-3–C-4). The absence of substituents at C-6 permits puckering in the C-5–C-6 portion of the ring.

CONCLUSIONS

Comparison of the observed vicinal axial–equatorial and equatorial–equatorial couplings in thio sugars with those in oxygen sugars and with those calculated by the method of Altona and Haasnoot provides a sensitive measure of the type and extent of distortion within the sugar ring. The puckering distortion for the thiane type of ring found in 5-thio sugars is demonstrated by a decrease in J_{ae} and an increase in J_{ee}. In addition, J_{aa} may decrease. In this fashion, substantial puckering distortions have been found in the α anomers of 5-thio-D-xylopyranose, 5-thio-D-glucopyranose, and possibly 6-thio-D-fructopyranose. Smaller distortions appear to be present in the β anomers. The puckering distortion is accompanied by a movement of vicinal equatorial–equatorial relationships closer together, whereas axial–equatorial relationships become more distant. The presence of a larger number of equatorial groups in the β anomers of 5-thioglucose and 5-thioxylose may increase the resistance to puckering through equatorial–equatorial buttressing. The increase in the internal strain of these anomers may contribute to the increased preference for the α anomer in these thio sugars, as compared with the oxygen sugars.

EXPERIMENTAL

The samples of 5-thio-D-xylopyranose and of 6-thio-D-fructopyranose were kindly provided by Prof. R. L. Whistler of Purdue University. All spectra were taken in D_2O solutions with sodium 4,4-dimethyl-4-silapentane-1-sulfonate as standard. The ^1H spectra were recorded at 360 or 470 MHz with a Nicolet NT-360 or NT-470 spectrometer at the Purdue University Biochemical Magnetic Resonance Laboratory*. Solvent suppression was accomplished by strong irradiation at the appropriate frequency. Carbon-13 spectra were obtained at 20 MHz with a Varian CFT-20 spectrometer. The ^1H chemical shifts and coupling constants were calculated by second-order simulation of the spectra by SIMEQ, a program supplied by Varian for use with the CFT-20.

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