temperature of 35 °C. The reactions were monitored by ^1H NMR. In case of CD_3OD, the integral of the methanol peak was corrected for the small amount of CHD_2OD (quintet) which is always observed in this solvent.

The methine (OCH) resonances of the cyclic compounds were found at about 5.1 ppm, whereas methine peaks around 4.4 ppm were attributed to ring-opened products. ^1H NMR data for the methoxy resonances of the various products are as follows. In CD_3OD: **5**, 3.81 (d, J = 12 Hz), 3.82 (d, J = 12 Hz, 2 isomers); **6**, 3.73 (d, J = 11 Hz); CH_3OD, 3.36 (s). In D_2O: **5**, 3.86 (d, J = 12 Hz), 3.87 (d, J = 12 Hz); **9**, 3.67 (d, J = 11 Hz); CH_3OD, 3.42 (s).

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Registry No. **3**, 77727-50-5; **3'**, 77727-57-2; **4**, 77727-51-6; **4'**, 77727-58-3; **5** (isomer 1), 77727-52-7; **5** (isomer 2), 77790-01-3; **6**, 77727-53-8; **9**, 77727-54-9; *cis*-1,2-cyclopentanediol, 5057-98-7; *cis*-1,2-cyclohexanediol, 1792-81-0; *p*-chlorobenzenesulfenyl chloride, 933-01-7; *cis*-1,2-cyclopentylene bis(*p*-chlorobenzenesulfenate), 77727-55-0; *cis*-1,2-cyclohexylene bis(*p*-chlorobenzenesulfenate), 77727-56-1.

Conformational Analysis of 5-Thio-D-glucose

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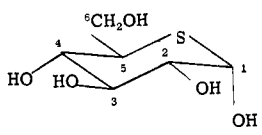
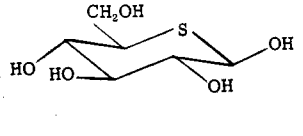
The proton and carbon-13 magnetic resonance spectra of 5-thio-D-glucopyranose have been fully analyzed. This molecule differs from D-glucopyranose in replacement of the ring oxygen by sulfur. The ^1H spectrum showed the presence of two anomers, with an α/β ratio of 85/15. Analysis of the ^1H–^1H vicinal coupling constants showed that the ring of the major anomer, 5-thio-α-D-glucopyranose, is slightly puckered in comparison to that of α-D-glucopyranose. All the axial–axial couplings are smaller in the sulfur heterocycle, and, most critically, $J_{1,2}$ (an axial–equatorial coupling) also is smaller. The electronegativity change for an O to S change would have predicted an increase in $J_{1,2}$. The observed decrease confirms the puckered distortion that is also a property of the unsubstituted heterocycle thiane. The ^{13}C resonances were assigned by a series of selective ^{13}C {^1H} experiments. The resonance positions are readily understood in terms of standard α, β, and γ shielding effects.

Replacement of the ring oxygen atom in D-glucopyranose with sulfur produces 5-thio-D-glucopyranose (**1**). This



1α



1β

material has been found to have a variety of physiological activity. It is effective in killing hypoxic cells, particularly in combination with mild hyperthermia. It inhibits D-glucose transport and sensitizes the hypoxic cells to radiation.[2] It has also been found to be a nontoxic male antifertility agent by inhibiting spermatogenesis[3] and a growth inhibitor for parasites with a high D-glucose requirement.

Differences between D-glucopyranose and 5-thio-D-glucopyranose may be attributed either to the electronic effects of replacement of oxygen by sulfur or to the steric/conformational effects of the altered bond lengths and valence angles. Probably the most effective tool for studying the latter geometric properties in solution is nuclear magnetic resonance spectroscopy. In the present paper we utilize both proton and carbon-13 NMR spectroscopy to explore the conformational changes that occur on replacement of the ring oxygen in D-glucose with sulfur. In earlier studies we have made similar comparisons between the unsubstituted oxane and thiane systems.[4] We will use these latter results as a model for the changes expected in the highly substituted sugar molecules.

Table I. Analysis of the ^1H Spectrum of 5-Thio-D-glucopyranose

proton	anomer	δ-(S)[a,b]	J(S)[b,c]	δ-(O)[a,d]	J(O)[c-e]
H_1	α	5.00	$^3J_{1,2}$ = 3.1	5.25	3.8
	β	4.77	$^3J_{1,2}$ = 9.3	4.65	8.1
H_2	α	3.78	$^3J_{2,3}$ = 9.4	3.54	9.8
H_3	α	3.65	$^3J_{3,4}$ = 8.9	3.73	9.5
H_4	α	3.60	$^3J_{4,5}$ = 9.1	3.42	9.5
	β		$^3J_{4,5}$ = 9.8		9.0
H_5	α	3.23	$^3J_{5,6'}$ = 3.0	3.82	1.5[f]
	β	2.98	$^3J_{5,6'}$ = 3.6	3.49	1.8
$H_{6'}$	α	3.87	$^2J_{6',6''}$ = −11.4	3.98	−12.0
	β				−12.2
$H_{6''}$	α	3.91	$^3J_{5,6''}$ = 5.1	3.90	3.9[f]
	β		$^3J_{5,6''}$ = 6.2		5.2

[a] In parts per million downfield from Me_4Si. [b] For 5-thio-D-glucopyranose. [c] In hertz. [d] For D-glucopyranose, the average from ref 5 and 6. [e] See column J(S) for notation. [f] Because of considerable disagreement between ref 5 and 6, this value was remeasured in our laboratory.

Results

The ^1H spectrum of 5-thio-D-glucopyranose was obtained at 360 MHz in pure D_2O (Figure 1) and in 10/1 Me_2SO-d_6/D_2O. To the latter solvent has been attributed the property of more closely maintaining the anomeric mixture

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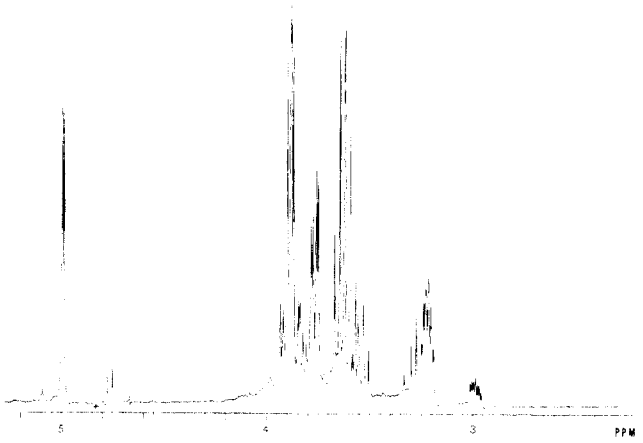


Figure 1. 360-MHz ^1H spectrum of 5-thio-D-glucopyranose in D_2O, with solvent suppression.

Table II. Analysis of the ^{13}C Spectrum of 5-Thio-α-D-glucopyranose

carbon	$\delta(S)^{a,b}$	multiplicity[c]	$^1J^{b,d}$	$\delta(O)^{a,e}$
C_1	75.4	d	158	92.8
C_2	77.6	d	146	72.2
C_3	75.9	d	144	73.6
C_4	75.9	d	144	70.3
C_5	45.4	d	137	72.1
C_6	62.6	t	149	61.5

[a] In parts per million downfield from Me_4Si. [b] For 5-thio-α-D-glucopyranose. [c] Single frequency, off-resonance decoupling. [d] The one bond ^{13}C-^1H coupling, in hertz. [e] For α-D-glucopyranose, the average from ref 5 and 6.

that is present in the solid.[5] The spectra were analyzed first by hand and then by computer simulation. The results of the second-order analyses are given in Table I. The assignments are discussed in the next section.

The ^{13}C spectra were obtained both at 20 and at 90 MHz in pure D_2O. The spectral frequencies for the major anomer (α) are given in Table II. The assignments were made by establishing a one-to-one correlation with the assigned ^1H resonances through a series of selective decoupling experiments. The known ^1H resonance frequencies were irradiated one at a time, and the appropriate ^{13}C resonances were identified by the collapse of the one bond coupling. These experiments were carried out intially at 2.1 T and then were confirmed at 8.4 T.

For the sake of comparison, we also obtained the ^1H and ^{13}C spectra of D-glucopyranose under conditions identical with those used for the thio analogue.

Discussion

Proton Spectrum. The assignments of the individual protons follow from a first-order analysis of the splitting patterns and chemical shifts. The lowest field resonance (δ 5.00) is clearly from H_1, the anomeric proton, because of the strong combined deshielding effect of sulfur and the 1- and 2-hydroxyls. The splitting of the resonance is small (3.1 Hz), so the coupling is axial–equatorial (ae) rather than axial–axial (aa). Thus the dominant anomer in solution is the α, in which the anomeric hydroxyl is axial (1α). A smaller resonance at δ 4.78 is from the less abundant β isomer, in which $^3J_{1,2}$ is measured to be 9.3 Hz. This larger coupling must be aa, corresponding to an equatorial hydroxyl group. The ratio (α/β) of the resonances of the anomeric protons is 85/15, in approximate agreement with an eariler report.[6]

The highest field resonance must derive from H_5, since it experiences only the deshielding effect of sulfur, without a direct effect from the hydroxyls. Both the α (δ 3.23) and the β (δ 2.98) resonances are evident for H_5. Their form is an octet, from coupling to H_4, $H_{6'}$, and $H_{6''}$.

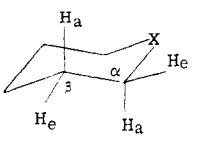
The α resonances from $H_{6'}$ and $H_{6''}$ are easily identified because of their appearance as the AB part of an ABX spectrum (δ 3.9). The α resonance from H_2 is at slightly lower field (δ 3.77) than those for H_3 and H_4 (δ 3.60–3.65), because the axial 1-hydroxyl group exerts a larger inductive effect on the axial H_2 than the corresponding equatorial hydroxyls do on H_3 and H_4. Antiperiplanar polar effects are known to be larger than those for other dihedral geometries. The α resonances for H_3 and H_4 can be distinguished, despite their near overlap, by the values of their respective couplings to H_2 and H_5. The corresponding H_2, H_3, H_4, and H_6 resonances from the β anomer are obscured by peak overlap.

The spectrum in the Me_2SO/D_2O mixture is essentially the same as that in pure D_2O. This result contrasts with that for D-glucopyranose, which shows different anomeric proportions in the two solvents.[5,7] We are probably seeing rapid mutarotation for **1**, even in Me_2SO. Anomerization has been found to be more rapid for 5-thio-D-glucopyranose than for D-glucopyranose.[6] The integrated α/β ratio of 85/15 from the ^1H spectrum for 5-thio-D-glucopyranose compares to 38/62 for D-glucopyranose in D_2O.[7]

The primary objective in obtaining a second-order analysis of the ^1H spectrum was to determine the vicinal couplings (^3J) in order to assess the changes in ring shape that occur upon replacement of the ring oxygen by sulfur. This replacement affects ^3J not only through dihedral angle changes but also through the differences in electronegativities of O and S. Thus before we can consider conformational effects, we must assess these electronic effects.

Normally, a decrease in substituent electronegativity (O to S) results in an increase in coupling constant.[8] Thus, the vicinal coupling in ethyl ether is 7.0 Hz and that in ethyl sulfide is 7.4 Hz. These open-chain systems are subject to an averaging process through C–X bond rotation that is not present in rigid rings. Because the influence of electronegativity on vicinal coupling constants is dependent on the dihedral relationship between the substituent and the coupling pathway,[8] this dynamic process cannot be ignored.

A better model is the heteracyclohexane system **2**. The couplings between the α and β protons are influenced by the identity of the heteroatom. The AA'XX' spin system has two vicinal couplings, J_{trans} (the average of J_{aa} and J_{ee}) and J_{cis} (the average of J_{ae} and J_{ea}). The change from oxane (**2**, X = O) to thiane (X = S) results in a change of



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J_{trans} from 7.41 to 8.51 Hz and a change of J_{cis} from 3.87

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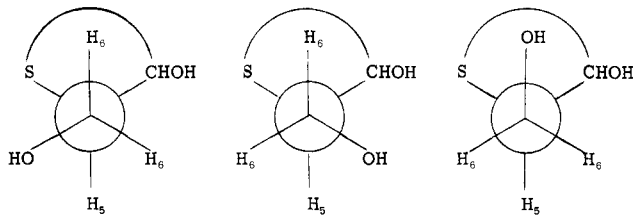
to 3.26 Hz.[9] The puckering that occurs on replacement of O by S decreases the J_{aa} component of J_{trans} and increases the J_{ee} component,[9] so there is little net geometric effect. Thus the observed increase in J_{trans} from 7.41 to 8.51 Hz probably reflects the electronegativity change alone. There is no such compensation in J_{cis}, since both J_{ae} and J_{ea} decrease on ring puckering. Thus the decrease in J_{cis} from 3.87 to 3.26 Hz signifies that the conformational effect of puckering, which would decrease ^3J, must be more important than the electronegativity effect, which would increase ^3J. This analysis of thiane indicates that the C_2/C_3 region of the molecule is puckered. A similar analysis of the C_3/C_4 region also indicates puckering.

In the glucopyranoses, $J_{2,3}$ and $J_{3,4}$ (both are J_{aa}) experience little effect from the electronegativity change of the heteroatom, because of the distance involved. These coupling constants decrease slightly (9.8–9.4 and 9.5–8.9 Hz) on going from α-D-glucose to 5-thio-α-D-glucose (Table I), in opposition to the normal electronegativity effect. This decrease is expected on puckering of the ring when O is replaced by S.

To interpret $J_{1,2}$ and $J_{4,5}$, however, we must take three factors into consideration: change in conformation, change in electronegativity, and dihedral orientation of the heteroatom with respect to the coupling pathway. The third factor becomes important when the C–X bond is antiperiplanar to any bond along the coupling pathway.[8] Neither $J_{1,2}$ nor $J_{4,5}$, fortunately, has such a dihedral relationship. Only when the C–H bond at C_2 is equatorial is part of the coupling pathway antiperiplanar to C–X. Since this position is occupied by an hydroxyl group in all the structures under consideration, the dihedral dependence of electronegativity can be ignored. The straight electronegativity factor will always produce an increase in the coupling constant on going from O to S.[8] The $J_{4,5}$ is a J_{aa}, like $J_{2,3}$ and $J_{3,4}$, and it likewise decreases from 9.5 to 9.1 Hz for the α anomer, contrary to the expected electronegativity effect. We conclude again here that the conformational effect dominates the electronegativity effect, as the result of ring puckering caused by the introduction of the S atom. The $J_{1,2}$ is a J_{ea} for the α anomer. This coupling constant also decreases, from 3.8 to 3.1 Hz, contrary to the electronegativity effect. Such a decrease is only possible for a puckered six-membered chair. Thus all vicinal coupling constants around the ring are consistent with puckering.

Replacement of O by S may alter the rotameric equilibrium (3) around the C_5–C_6 bond. In glucose, the measured couplings are 1.5 and 3.9 Hz, and in thioglucose they are 3.0 and 5.1 Hz (α anomers). The increase may reflect nothing more than the electronegativity change. We can discern no evidence for a change in the rotameric populations, although small changes can be obscured by the electronegativity effect.



3a 3b 3c

Another approach to assessing the effect of electronegativity on the vicinal coupling constants in carbohydrates is an adaptation of a recent report by Altona and Haasnoot.[10] These authors calculated substituent contributions to vicinal coupling constants that appear to be additive. The procedure involves adding a factor for each substituent on the coupling pathway to a coupling constant based on a minimally substituted system. Thus we can calculate the expected coupling constants for the thioglucose system in the absence of distortions, since the method of group constants assumes no change in geometry.[10] According to the Altona–Haasnoot procedure, the following vicinal coupling constants are calculated for 5-thio-α-D-glucopyranose: $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 9.9, $J_{3,4}$ = 9.4, and $J_{4,5}$ = 10.5–11.0, depending on the preferred C_5–C_6 rotamer. The corresponding observed couplings (3.1, 9.4, 8.9, and 9.1 Hz) are smaller in every case, with the deviation increasing with the magnitude of the coupling. These observations are consistent with the puckering we have already described, since the Altona–Haasnoot calculation does not take the distortion into account that is brought about by the replacement of oxygen by sulfur within the ring.

The group constants also can be used to calculate the individual couplings expected for the rotamers **3**, unadjusted for angle deformations, which in this case should not be especially important. The calculated values are 10.5 and 4.6 Hz for **3a**, 5.2 and 10.5 Hz for **3b**, and 2.7 and 1.5 Hz for **3c**. The observed couplings are 5.1 and 3.0 Hz. The small size of these couplings requires a substantial contribution from the double gauche rotamer **3c**, although clearly contributions from one or both of the gauche/anti rotamers are required.

The ^1H spectra thus indicate that 5-thio-α-D-glucopyranose is more puckered than α-D-glucopyranose, i.e., that the internal dihedral angles are larger for the S system. Replacement of O by S has no discernible effect on the rotameric populations about the $HOCH_2$–C bond, although small changes would not be detected because the measured coupling constants ($J_{5,6}$) are small.

Carbon-13 Spectrum. Because some conformational information might be obtained from the ^{13}C resonances, we decided to make a complete assignment of the spectrum. Our initial examination was at 20 MHz. When decoupled from protons, the spectrum contained five major peaks, whose frequencies are given in Table II. Smaller peaks for the minor (β) anomer were observed but not assigned. The highest field peak, a doublet (off-resonance decoupling) at δ 45.5, is easily assigned to C_5, since this carbon is attached to no oxygen atom. The next highest peak, a triplet (off-resonance decoupling) at δ 62.6, is assigned to C_6 because of its multiplicity and because it is the only secondary carbon of those attached to a single oxygen.

The remaining resonances are all doublets (off-resonance decoupling) in the region δ 75–78. To make reliable assignments, we carried out selective decoupling experiments. The decoupling frequency was set at a narrow band corresponding to specific ^1H resonances. The corresponding carbon resonances could be identified by collapse of appropriate multiplets. Because of the closeness of some of the ^1H frequencies, these experiments were repeated and confirmed with the ^1H frequency at 360 MHz.

The assignments of Table II are firm, so that we may interpret ^{13}C resonance positions in terms of known substituent effects. The positions of C_5 and C_6 have already been discussed. Because the remaining four carbons are all tertiary and attached to a single oxygen atom, they resonate over a very small range. The C_2 resonance is at

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lowest field because it experiences not only the α-OH effect but also two β-OH effects. Carbon 3 has the same three influences, which are slightly offset by the upfield γ-gauche effect of the axial 1-hydroxyl group. The C_3 resonance coincides with that of C_4, which is subject only to the effects of one α- and one β-hydroxyl. The resonance of C_1 is at the highest field. Apparently the α effect of sulfur in this context is smaller than or of opposite sign to the β effect of OH (C_1 experiences one α-OH, one β-OH, and one α-S effect).

Summary and Conclusions

5-Thio-D-glucopyranose exists primarily as the α anomer in D_2O and in Me_2SO/D_2O. The ^1H spectrum shows that the α/β ratio in D_2O is stable at about 85/15. Analysis of the ^1H spectrum of the α anomer shows that the ring is puckered in comparison with that of D-glucopyranose. The smaller C–S–C bond angles deform the ring in such a way that the various carbons are lifted further from the average plane. The deformation appears to be general throughout the ring, since all the ring vicinal coupling constants show this effect. Complete assignments were made for both the ^1H and the ^{13}C spectra, but the latter yielded no useful conformational information.

Experimental Section

5-Thio-D-glucopyranose was obtained from Pfanstiehl Laboratories. Proton spectra (0.3 Hz/point) were obtained at 360 MHz on a Nicolet NT-360 at the Purdue University Biochemical Magnetic Resonance Laboratory.[11] Solvent suppression was accomplished by strong irradiation at the appropriate frequency. Carbon-13 spectra were obtained at 20 MHz on a Varian CFT-20 and at 90 MHz on an NT-360.[10] Selective ^1H decoupling experiments were carried out on both instruments. Second-order spectral analyses were carried out with the software package of the CFT-20.

Acknowledgment. We thank Professor Roy L. Whistler of Purdue University for assistance in this research.

Registry No. 1α, 10227-19-7; 1β, 37850-98-9.

(11) This facility is supported by the National Institutes of Health, Division of Research Resources (Grant No. RR01077).

Syntheses and a Conformational Study of Certain Selected 3-Oxa-7-azabicyclo[3.3.1]nonan-9-ones. Single-Crystal X-ray Diffraction Analysis of 6,8-Bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one

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Isomers of 2,4,6,8-tetraphenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ones, 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one, and *N*-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one have been prepared by Mannich-type cyclocondensations with appropriate tetrahydro-4*H*-pyran-4-ones. The carbonyl group in *N*-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one was reduced to a CH_2 group under modified Wolff–Kishner conditions. Nucleophilic additions ($NaBH_4$, C_6H_5MgBr) to this same ketone produced isomeric alcohols. IR and ^1H and ^{13}C NMR spectral data indicate that these bicyclic ketones preferred a chair–chair conformation. A single-crystal X-ray diffraction analysis of 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (a = 9.353 (4), b = 7.733 (4), c = 23.03 (2) Å; space group *Pnam*) was completed to confirm a chair–chair conformation for the ketone in the solid state. The O(3)–N(7) contact distance of 2.776 (3) Å is less than the sum of the van der Waals radii. Consequently the oxygen-containing ring is slightly flattened, and the nitrogen-containing ring is somewhat more puckered than the ideal system.

3,7-Diheterabicyclo[3.3.1]nonanes are of considerable interest both from a theoretical point of view as well as for potential biological activity.[1-4] Nitrogen analogues of bicyclo[3.3.1]nonan-9-ones[5-8] have been studied, but work on other hetero (O, S, P, etc.) analogues has been quite limited. To date, only a few 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones have been recorded.[9] Herein we report the syntheses and conformational analyses of certain 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones (1) and their derivatives.

Results and Discussion

Syntheses of derivatives of 1 were approached via two routes: (1) Mannich condensations of tetrahydro-4*H*-pyran-4-ones with appropriate aldehydes and amines and

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