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pH-Dependent Mutarotation of 1-Thioaldoses in Water. Unexpected Behavior of (2*S*)-D-Aldopyranoses

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The pH-dependent mutarotation of 1-thioaldopyranoses in aqueous media has been investigated. Anomerization readily occurred at lower and neutral pH for all aldopyranoses studied, whereas mainly for (2*S*)-D-aldopyranoses at higher pH. 1-Thio-D-mannopyranose and 1-thio-D-altropyranose showed very strong pH dependence where the anomeric equilibrium ratios changed dramatically from a preference for the β-anomer at lower pH to the α-anomer at higher pH.

Introduction

Mutarotation of carbohydrate anomers is a fundamental phenomenon in chemistry[1−6] and of particular importance in synthesis when stereochemically pure products are targeted. The different anomers frequently possess distinct biological activities,[7−9] but similar physicochemical properties that can hamper the isolation of each stereoisomer. Although mutarotation has been studied for many decades, it still remains difficult to predict. Multiple factors, such as steric hindrance, electronic properties, solvent effects, and experimental conditions, have to be considered. Thus, the anomerization of aldoses most likely arises from a combination of these different factors.[10]

In aqueous media, the mutarotation process of aldoses has been extensively explored, resulting in mixtures of the different α- and β-pyranoses and furanoses in equilibrium with the corresponding open-chain aldehyde and hydrate.[1,3,6,11,12] The aldose stereochemistry can also dramatically affect the anomeric composition at equilibrium, and therefore, a single configurational change can yield the reverse anomeric preference for a given structure, as, for example, in the case of the epimerization of D-glucose (β-preference) to D-mannose (α-preference).[1,6] In addition, replacement of the endocyclic oxygen and/or the anomeric hydroxyl oxygen by another heteroatom also leads to mutarotation.[1,6,13] However, for sulfur analogues, existing studies on mutarotation are mainly confined to structures with an endocyclic sulfur at the C-5 position.[1,3,11,14] Mutarotation of 1-thioaldoses, on the other hand, has not been thoroughly investigated,[11,15−17] and it is still relatively unclear under what conditions glycosyl

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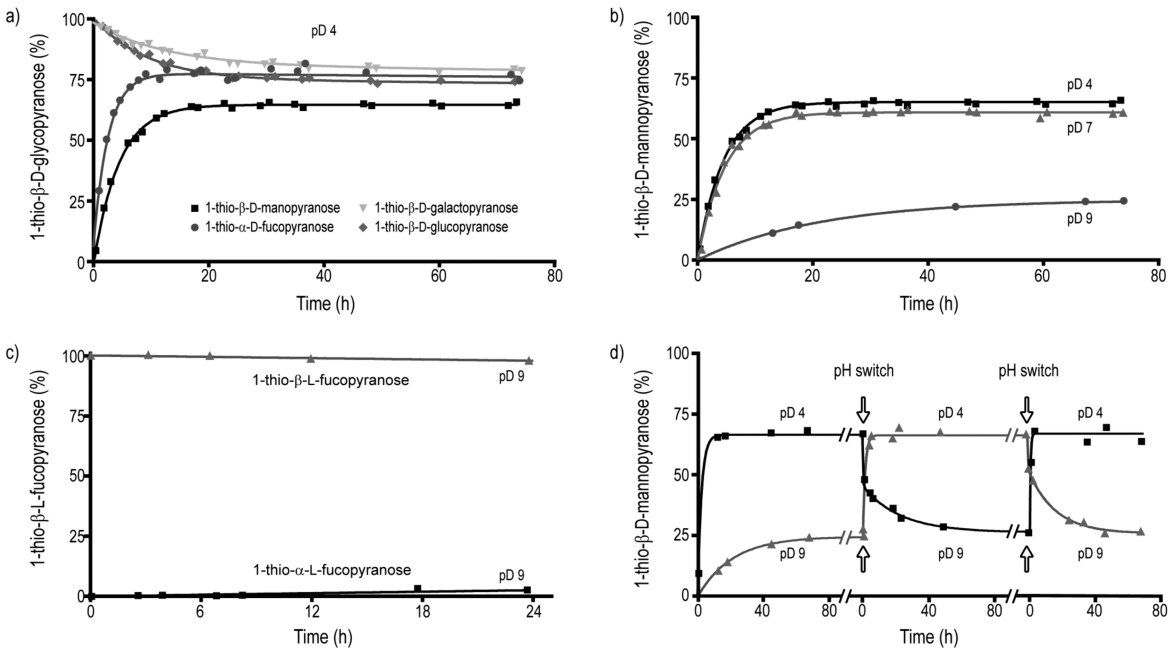

FIGURE 1. ^{1}H NMR kinetic studies: (a) fraction of β-anomer formed from 1-thio-α-D-mannopyranose, 1-thio-β-D-galactopyranose, 1-thio-β-D-glucopyranose and 1-thio-α-L-fucopyranose under acidic conditions (pD 4); (b) fraction of β-anomer formed from 1-thio-α-D-mannopyranose at different pD; (c) fraction of β-anomer formed from 1-thio-α-L-fucopyranose and 1-thio-β-L-fucopyranose under basic conditions (pD 9); (d) pD-dependence for the mutarotation of 1-thio-D-mannopyranose. Only 1-thioglycopyranose species taken into consideration.

thiols effectively undergo mutarotation. This is, however, of high importance, since sulfur-containing aldoses are increasingly used in synthesis owing to their chemical stability, their compatibility with numerous protection/deprotection steps, and the enhanced thiol nucleophilicity compared to the corresponding oxygen analogues.[18−23] Furthermore, this class of compounds is highly compatible with biological systems, yielding stable mimics of natural glycosides due to the improved resistance toward hydrolytic enzymes.[24−27] Therefore, glycosyl thioethers are widely used as glycosyl donors and provide easy and rapid synthetic access to, for example, synthetic vaccines and drugs[28−33] and to neoglycoproteins and neoglycopeptides.[19,34,35] This increasing popularity of glycosyl thiols combined with the need for new synthetic methodologies and the perpetual quest for fundamental understanding of chemical processes led us to investigate and clarify whether 1-thioaldoses undergo mutarotation. In the present study, we thus report on the pH-dependent mutarotation of 1-thioaldoses and their equilibrium anomeric ratios in aqueous media.

Results and Discussion

Four stereochemically pure 1-thioaldoses were initially monitored by ^{1}H NMR spectroscopy under acidic conditions (Figure 1a). Thus, the mutarotation behavior of 1-thio-D-mannopyranose (**1**),[36] 1-thio-D-galactopyranose (**2**), 1-thio-D-glucopyranose (**3**), and 1-thio-L-fucopyranose (**4**)[37] was successively evaluated. The expected favored configurational isomers in aqueous media were used, i.e., the α-anomer for the manno derivative, and the β-anomer for the galacto and gluco derivatives, except for the fuco derivative, likely to possess a β-anomer preference similarly to L-fucopyranose, which was initially tested starting with its α-form. At equilibrium, the resulting mixtures were primarily composed of the cyclic 1-thioaldopyranoses. Disulfide products were generally formed from the concomitant oxidation process but were not taken into consideration in the analyses since they did not influence the α/β anomeric ratio. Control experiments in

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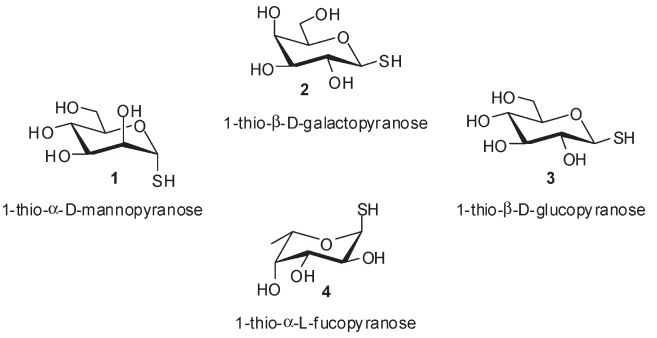
presence of a reducing agent (dithiothreitol or phosphinotriacetic acid) led to the same distributions.

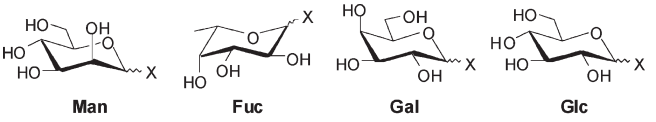


The four glycosyl thiols reached their respective anomeric equilibrium within comparable time lengths but showed slightly different anomeric ratios. Thus, at room temperature, the equilibria were reached within 15 h, resulting in approximately 78% β-anomer for the galactopyranose, 74% β-anomer for the fuco- and the glucopyranose structures, and surprisingly, *66% β-anomer for the manno derivative* (Table 1). This indicates the noninfluence of the carbohydrate structure on the equilibration time but an effect on the anomeric configuration ratio, as expected.

The mutarotation of normal aldoses is usually both acid- and base-catalyzed.[1,38] The pH-dependence for the mutarotation of the thio analogues was thus addressed, and the pD profile of anomerization was investigated at three different pDs (Figure 1b). The results from the ^{1}H NMR analyses were in this case highly conspicuous, and the mutarotation rate of 1-thioaldoses proved pH dependent.[12] Thus, at a lower pD than 7.7, a value corresponding to the thiol pK_a,[39] relatively rapid mutarotation occurred, whereas at higher pD, the mutarotation proceeded at a (considerably) slower rate. For the 1-thio-D-mannopyranose species, half-times of 3.1 and 3.3 h, respectively, were recorded under acidic (pD 4) and neutral (pD 7) conditions, whereas the mutarotation rate diminished under basic conditions (pD 9; $t_{1/2}$ = 14.8 h). For the other aldoses tested, the mutarotation process was almost completely blocked at higher pD. This was most dramatic for the fucose and galactose species, in which case very low anomerization from the initial configurations were observed over the time range. Therefore, the anomerization of the β-anomer of 1-thio-L-fucopyranose was subsequently monitored under acidic (pD 4) and basic (pD 9) conditions to confirm that the mutarotation process of these 1-thioglycopyranoses is restricted under basic conditions. While the anomeric equilibrium composition at pD 4 provided an α/β ratio (~20/80) similar to the one obtained starting with the opposite anomeric form, 1-thio-α-L-fucopyranose (**4**) (~26/74), the results at basic pD proved to be different (Figure 1c). Thus, the α-anomer was only observed in trace amounts, supporting the hypothesis that the mutarotation of these 1-thioglycopyranoses is generally restricted under basic conditions.

Surprisingly, the β-anomer was observed as the major mutarotation product in all cases at acidic and neutral pH, independently of the α- or β-nature of the starting

TABLE 1. Anomeric Composition of 1-Thioglycopyranoses and Their Corresponding Glycopyranoses (Percentage of β-Anomer Shown)



	1-β-thioaldose[a]			1-β-hydroxyaldose	
	pD 4	pD 7	pD 9	ref 2 and 40	pD 4
Man	***66.2***	***60.9***	***24***	34.5	33.3
Fuc	74.3	79.1	< 5	69.3	71.4
Gal	78.1	77.7	> 95	68.1	68.0
Glc	74.1	75.2	93.6	62	62.5

[a]Initial anomers: 1-thio-α-D-mannopyranose (**1**), 1-thio-α-L-fucopyranose (**4**), 1-thio-β-D-galactopyranose (**2**), and 1-thio-β-D-glucopyranose (**3**).

conformer. For the mannose species, this result clearly contrasts with the anomeric equilibrium ratio of the corresponding 1-hydroxyaldose (Table 1).[1,2,40] For the 1-thio-D-mannopyranose, the anomeric distribution totally shifted in favor of the β-configuration, resulting in an α/β ratio of 33.8/66.2 at pD 4. For the normal mannopyranose, the distribution is in favor of the α-anomer (66.7/33.3) under the same conditions. For the other 1-thioaldoses tested, the ratios also shifted in favor of the β-anomer compared to the 1-hydroxyaldose analogues, albeit to a lower extent. For fucose, the increase in β-species amounted to a few percent, whereas for glucose and galactose, the preference for the β-anomers was significantly higher. These results indicate that replacement of a hydroxyl group at the anomeric center by a larger and more polarizable thiol group can dramatically affect the anomeric composition.

This α- and β-character of 1-thio-D-mannopyranose could also be turned on/off by manipulation of the pH (Figure 1d). Thus, the reversibility and adaptability of the mutarotation process toward its environment were demonstrated. This experiment, where acidic or basic conditions were initially chosen, and subsequently switched to basic or acidic media, respectively, clearly confirmed the faster equilibration at low pH (~15 h) compared to the slower rates at higher pH (~60 h). The mutarotation rates and the anomeric equilibrium ratios also proved identical after several rounds of pH switching. In contrast, the observation of restricted mutarotation at basic conditions for the other thioaldoses tested excludes any reversibility of the anomerization process for these species.

The structural analysis of the different 1-thioaldoses results in a clear pattern that may lead to prediction of the main conformer, at equilibrium, for any given 1-thioaldopyranose. First, carbohydrate derivatives from both the D- and the L-series have been monitored with very similar results. Thus, the anomerization of 1-thio-β-L-fucopyranose (6-deoxy-1-thio-β-L-galactopyranose) and 1-thio-β-D-galactopyranose (**2**) reached similar equilibria under both acidic and basic conditions, suggesting the noninfluence from the D- or L-character of the carbohydrate derivative on the mutarotation process. Second, the comparison of the different epimers

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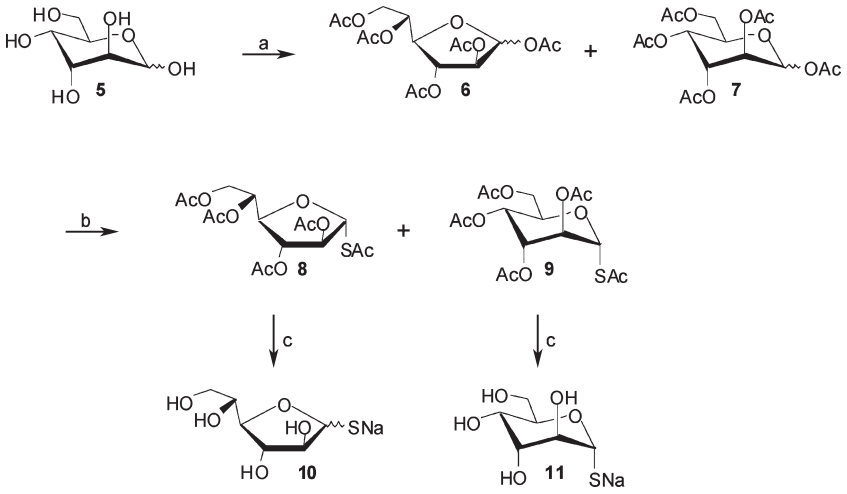
SCHEME 1. Synthesis of 1-Thio-α-D-altropyranose (11)[a]

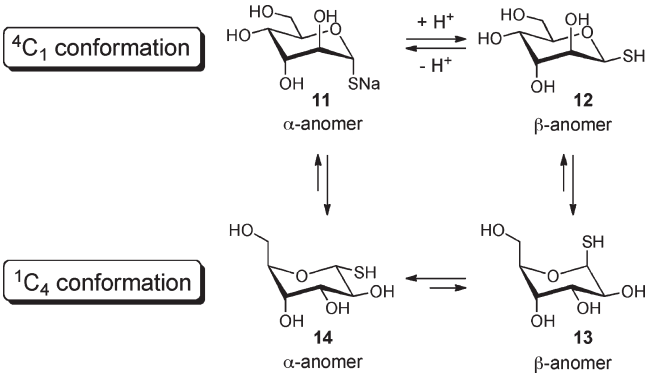


[a]Reagents and conditions: (a) I_2, Ac_2O, 0 °C to rt, 1 h (quant); (b) AcSH, $BF_3 \cdot Et_2O$, DCM, 0 °C to rt, 22 h (95%); (c) NaOMe, MeOH, 5 h (quant).

tested (the glucose/galactose and glucose/mannose derivatives) offered valuable information. The structural changes from an equatorial hydroxyl group at the C-4 carbon of the carbohydrate ring (1-thio-β-D-glucopyranose (**3**)) to the corresponding axial derivative (1-thio-β-D-galactopyranose (**2**)) did not significantly affect the mutarotation behavior, whereas the epimerization of the C-2 hydroxyl group of the glucose derivative leading to an axial C-2 hydroxyl group (D-mannose derivative, 2*S*-configuration) completely affected the anomeric mixture as well as the reversibility properties of the carbohydrate. Finally, the α- or β-preference of the natural carbohydrates could be important to consider for the prediction of the anomeric composition of their corresponding 1-thio analogues. Of the four different 1-thioaldoses, only the mannose derivative possesses, as a natural carbohydrate, an α-preference.

In order to determine which of these structural factors mainly governs both the anomeric composition at equilibrium and the reversibility properties, 1-thio-α-D-altropyranose (**11**) was synthesized and monitored under acidic (pD 4), neutral (pD 7), and basic (pD 9) conditions (Scheme 1). 1-Thio-α-D-altropyranose possesses an axial hydroxyl group at the C-2 carbon of the carbohydrate ring (2*S*-configuration), but contrary to 1-thio-α-D-mannopyranose, its corresponding natural derivative has a β-preference at equilibrium (α/β ratio of 44/56).[41,42] The results were in this case highly intriguing, and at acidic or neutral pDs, 1-thio-α-D-altropyranose was rapidly (<10 min), and entirely, converted to the β-anomer (**12**), whereas under basic conditions, the altrose derivative remained (~100%) in the α-form. Unfortunately, 1-thio-α-D-altropyranose, similarly to D-altropyranose (**5**), isomerized from the $^4C_1$ chair conformation to the $^1C_4$ chair conformation with time (Scheme 2).[41,42] This was most dramatic at low pD where **12** isomerized to the $^1C_4$ chair conformation (**13**), followed by its mutarotation to the more favored $^1C_4$ 1-thio-α-D-altropyranose (**14**). However, the mutarotation kinetics was faster than the isomerization

SCHEME 2. Proposed 1-Thio-D-altropyranose Mutarotation Pathway



of the chair conformations, which enabled the pD switch experiment to be performed and, therefore, allowed the observation of the reversibility properties. Thus, compound **12** instantaneously anomerized back to its original α-conformation after changing the pD of the solution from acidic to basic conditions. These results supported the importance of an axial hydroxyl group at the C-2 carbon of the carbohydrate ring over the anomeric preference of the corresponding natural aldoses.

The mutarotation of 1-thioaldoses is most likely to follow an exo-ring-opening mechanism in analogy to 1-hydroxy- or 1-aminoaldoses (Scheme 3).[43] Protonation of the ring oxygen and formation of a thiocarbenium ion intermediate would rationalize the acid-catalyzed character of the reaction.[44] Under basic conditions, the ring opening is strongly hampered and the mutarotation rate is decreased. However, slow formation of 1-hydroxyaldoses (**19**) as well as the appearance of the characteristic smell of H_2S points to the existence of a competing process other than mutarotation at lower pH. The exo-ring-opening mechanism also enables the formation of

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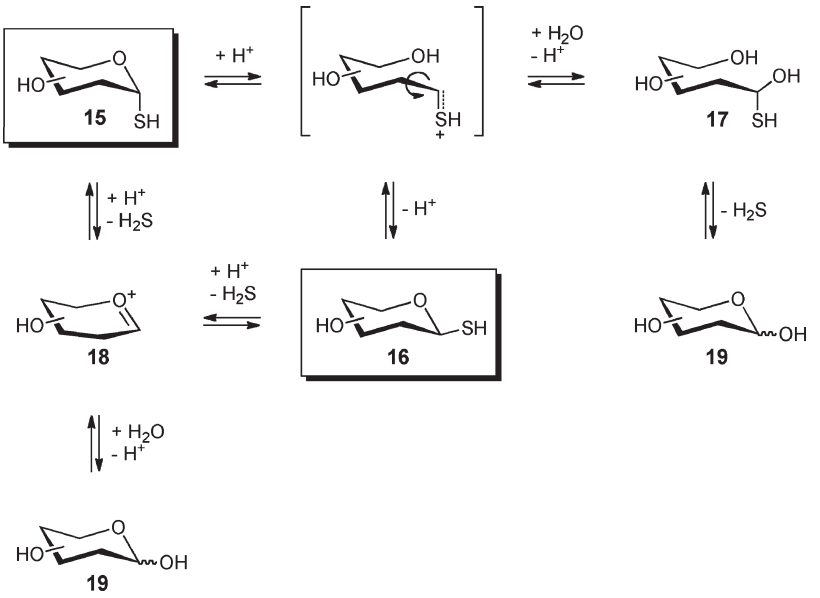
SCHEME 3. Proposed Mutarotation Mechanism



hemithioacetal derivative **17**, a potential intermediate in the formation of aldose species **19**. The very fast ring closure of the thiocarbenium ion intermediate compared to the addition of water would in this case justify the slow formation of the corresponding normal aldoses. A second mechanism involving solvolysis of the 1-thioaldose via oxocarbenium ion intermediate **18** may, however, also be involved. The slower rate of the oxocarbenium ion formation and its conversion to **19** would induce an increasing but still low concentration of **19** compared to **15** and **16**. In addition, during the evaluation of 1-thio-α-D-altropyranose (**11**) anomerization, furanose derivatives (e.g., **10**) could unambiguously be identified by ^{1}H NMR spectroscopy pointing to the existence of an acyclic intermediate. Therefore, the existence of a ring-opening mechanism was supported.

The pH-dependent stereochemistry of the process, especially for the mannose and altrose species, is highly conspicuous. A tentative explanation for the results would concern the effects directing the preferential α-anomer formation: steric hindrance, electronic effects (especially the anomeric effect), and solvation effects. The presence of a thiol group at the anomeric center would thus partially reduce or promote these effects, leading to a configurationally more stable *β*-anomer at low or neutral pH or α-anomer at higher pH exclusively for carbohydrates bearing an axial hydroxyl group at the C-2 carbon of the ring. Considering the first effect, the steric hindrance resulting from a sulfhydryl group is likely to be comparable to a hydroxyl group, as reflected by the conformational energy values for these groups. A *β*-preference would thus generally be expected, in part counteracted by an axial hydroxyl group at the C-2 carbon of the ring.[10] Steric effects are however strongly context dependent, and the effect of sulfur may be larger than predicted. Comparing the influence of the anomeric effect on the axial versus the equatorial preferences of the 1-thioaldoses with the normal oxygen-containing aldoses, the effects are likely subtle and generally difficult to predict. For 5-thiopyranosyl compounds, it has been proposed that the anomeric effect is larger than for the oxygen analogues, resulting in increased α-preference for these compounds.[45,46] The combined *endo*-($n_S \rightarrow \sigma^*_{C-O}$) and *exo*- ($n_O \rightarrow \sigma^*_{C-S}$) anomeric effects in the axial conformer was in this case reported to be more stabilizing than the *exo*- ($n_O \rightarrow \sigma^*_{C-S}$) anomeric interaction in the equatorial conformer. In the present study, the groups are reversed, but with the same reasoning the combined anomeric effects in the axial conformer ($n_O \rightarrow \sigma^*_{C-S}$ and $n_S \rightarrow \sigma^*_{C-O}$) would be more stabilizing than the *exo*- ($n_S \rightarrow \sigma^*_{C-O}$) anomeric interaction in the equatorial conformer. This is, however, contradicted by the experimental results at low pH, where the *β*-anomers are preferred. The combined anomeric effect may on the other hand be more pronounced in the thiolate species. Both the *exo*-anomeric and the *endo*-anomeric effects are likely to result in slightly better matching upon deprotonation, potentially resulting in a higher degree of α-anomer. Besides steric and electronic effects, solvation effects are likely to be involved, and the effect of water as a solvent is important. Further, in order to explain the mutarotation of aldoses in aqueous media, it is well accepted that one or several water molecules are involved in the ring-opening and ring-closing mechanisms.[12,51] Walkinshaw first described the preferential conformation of aldopyranoses in terms of hydrophilicity, a property directly related to the number of solvent molecules surrounding and stabilizing the carbohydrate structure.[47] It was also generally observed for aldoses that there is an increase in the proportion of the α-anomer with decreasing dielectric constant of the solvent.[47] Such a solvent-induced shift is, however, likely to be reduced with the less polar sulfhydryl group compared to the hydroxyl moiety at lower pD. At higher pD, on the other hand, the considerably lower solvation energy of the thiolate anion may invoke additional steric effects, especially for the structures carrying an axial OH-group at C-2.[48−50] Therefore, the

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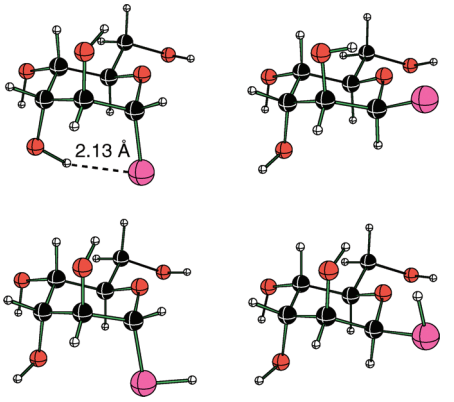

FIGURE 2. Solution structures for the most stable conformers of the α- and β-anomers of the deprotonated (top) and neutral (bottom) forms of 1-thio-D-altrose. Geometries were optimized at the PCM-MP2/6-31+G(d,p) level.

α- and β-preferences observed at high and low pD, respectively, are likely to be affected by solvation effects.

To understand the molecular basis for the shift in α/β preference with protonation state for 1-thio-D-altrose, ab initio calculations with an implicit solvent model (PCM) at the MP2/6-31G(d,p) level were performed. The optimized structures for the most stable conformers in solution are depicted in Figure 2. On the basis of the computed free energies of the anomers in solution, 9:91 and 89:11 distributions between the α- and β-anomers for the neutral and ionic forms of 1-thio-D-altrose, respectively, were predicted. This is in good agreement with NMR measurements, which show the β-anomer to dominate for the neutral form (>95%) and the α-anomer for the ionic form (>95%). Focusing first on the ionic structures, a strong and short internal hydrogen bond between the axial hydroxyl group at the C-3 position and the negatively charged thiolate group of the α-anomer was found. A similar hydrogen bond cannot be formed in the β-anomer. If the gas phase energies of the two conformers are considered, the α-anomer is favored by 8.9 kcal/mol. This is reduced to a free energy difference of 1.3 kcal/mol after inclusion of solvent effects. The stabilizing effect of the internal hydrogen bond of the α-anomer is partly compensated for by a more effective solvation of the β-anomer due to its less shielded thiolate group. However, the remaining effect is sufficient to account for the strong dominance of the α-anomer also in solution. It should be noted that it is not possible to form an internal hydrogen bond of comparable strength in the other 1-thioaldopyranoses, which explains why 1-thio-D-altrose has the most strongly favored α-anomer. Considering the solution structures of the α- and β-anomers of neutral 1-thio-D-altropyranose, no strong internal hydrogen bonds involving the sulfhydryl group could be found; it is more favorable to interact with the solvent. The β-anomer is favored over the α-anomer by a free energy difference of 1.40 kcal/mol in solution. In the gas phase, the energy difference between the corresponding structures is slightly larger, 1.64 kcal/mol.

We have also investigated the shift in α/β preference with protonation state for 1-thio-D-mannose by computational methods. In the case of the neutral form, the calculations predict a preference for the α-isomer by 0.5 kcal/mol. This is in disagreement with the experiments, since the α/β ratio of 34:66 obtained from the NMR experiments shows that the β-isomer is slightly lower in free energy. The computed α/β preference is sensitive to the solvation description, and changing the cavity representation from the Bondi cavity to the UA0 cavity-model reduces the energy difference to 0.1 kcal/mol. For the deprotonated 1-thio-D-mannose, the calculations predict the β-isomer to be 2.0 kcal/mol lower in free energy than the α-isomer, which is in contrast to the dominance of the α-isomer in the NMR experiments. However, the computational results are strongly dependent on the description of solvent effects. The gas-phase energies of the most favored conformers in solution show the β-isomer to be favored by 2.6 kcal/mol. Also here the predictions are improved by changing the cavity representation to the UA0 model; the energy difference is reduced to 0.6 kcal/mol. The computations provide no simple explanation for the observed shift in α/β preference with pH. It seems that the α/β ratio is determined by specific solvents interactions, which cannot be reproduced by an implicit solvent model, such as PCM.

Conclusions

In conclusion, it has been demonstrated that 1-thioaldopyranoses undergo mutarotation in aqueous media, a process that proceeds with comparable rates at lower and neutral pH and is slower or almost blocked at higher pH. For 1-thio-α-D-mannopyranose and 1-thio-α-D-altropyranose, the process is fully reversible upon pH-switching. The carbohydrates tested showed an interesting tendency to preferentially form the β-anomer in acidic or neutral solution, whereas 1-thio-D-mannopyranose and 1-thio-D-altropyranose displayed a strong pH dependence and a preference for the α-configuration in a basic environment. Calculation studies clearly displayed a strong solvation effect involved in the mutarotation process and, in the case of the 1-thio-D-altropyranose, the presence of internal hydrogen bonding at basic conditions providing a conformation totally shifted in favor of the α-anomer at equilibrium.

Experimental Section

General Methods. 1-Thio-α-D-mannopyranose (**1**),[36] 1-thio-α-L-fucopyranose[37] (**4**), and 1-thio-β-L-fucopyranose[52] were synthesized following procedures previously described. 1-Thio-β-D-galactopyranose sodium salt (**2**), 1-thio-β-D-glucopyranose sodium salt (**3**), and all other reactants and reagents were purchased from commercial sources and used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 (100) MHz and/or 500 (125) MHz instruments at 298 K. ^{1}H peak assignments were made by first-order analysis of the spectra, supported by standard ^{1}H−^{1}H correlation spectroscopy (COSY). Buffer solutions were prepared from D_3PO_4 (85% w/w in D_2O) and NaOD (40% w/w in D_2O).

2,3,5,6-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-altrofuranose (8) and 2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-altropyranose (9). Molecular iodine (5.08 mg, 0.02 mmol) was dissolved in acetic anhydride (561 mg, 5.5 mmol), and the mixture was

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stirred at 0 °C. D-Altrose (100 mg, 0.55 mmol) (compound **5**) was added, and the reaction mixture was allowed to stir at 0 °C for 0.5 h and then at room temperature for another 0.5 h. After detection of the reaction completion by TLC, DCM was added, and the mixture was washed with saturated $NaHCO_3$ and extracted with DCM for three times. The organic phase was collected and washed by $Na_2S_2O_5$ and brine and dried over Na_2SO_4. The solvent was then evaporated, and the crude compounds **6** and **7** were used in the next step without further purification. Compounds **6** and **7** (210 mg, 0.54 mmol) and thioacetic acid (165 mg, 2.16 mmol) were stirred in dry DCM (3 mL) at 0 °C, and $BF_3 \cdot Et_2O$ (461 mg, 3.24 mmol) was added dropwise for 5 min. After removal of the ice bath, the reaction mixture was warmed to rt and stirred for 22 h. The mixture was diluted with DCM, washed with saturated $NaHCO_3$, and extracted three times. The organic phase was collected, washed with brine, and dried over Na_2SO_4. The solvent was then evaporated, and the crude was further purified by flash chromatography, providing compound **8** (19%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.39 (s, 3 H, SAc), 4.11 (dd, 1 H, J = 5.7 and 12.3 Hz, H-6b), 4.19 (dd, 1 H, J = 2.8 and 7.6 Hz, H-4), 4.46 (dd, 1 H, J = 3.1 and 12.3 Hz, H-6a), 5.20 (d, 1 H, J = 2.8 Hz, H-3), 5.21 (s, 1 H, H-2), 5.26 (m, 1H, H-5), 6.04 (s, 1 H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.89, 20.93, 21.01, 31.17, 62.52, 69.79, 76.64, 81.26, 82.98, 86.39, 169.30, 169.55, 170.26, 170.66, 192.64. MS (ESI) measured for $C_{16}H_{22}O_{10}S$ ($[M + Na]^+$): m/z 429.13. Anal. Calcd for $C_{16}H_{22}O_{10}S$: C, 47.29; H, 5.46; S, 7.89. Found: C, 47.34; H, 5.28; S, 7.77. Further elution yielded compound **9** (76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.18 (s, 3 H, OAc), 2.20 (s, 3 H, OAc), 2.41 (s, 3 H, SAc), 4.11 (dd, 1 H, J = 2.2 and 12.3 Hz, H-6b), 4.23 (m, 1 H, H-5), 4.32 (dd, 1 H, J = 4.4 and 12.3 Hz, H-6a), 5.01 (dd, 1 H, J = 0.9 and 3.5 Hz, H-2), 5.21 (dd, 1 H, J = 3.2 and 10.1 Hz, H-4), 5.32 (bt, 1H, H-3), 5.99 (bs, 1 H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.78, 20.91, 20.95, 21.05, 30.96, 62.49, 65.02, 66.71, 67.67, 71.32, 78.77, 169.17, 169.37, 169.53, 170.88, 192.04. MS (ESI) measured for $C_{16}H_{22}O_{10}S$ ($[M + Na]^+$): m/z 429.13.

1-Thio-α-D-altropyranose−sodium Salt (11). NaOMe (16 mg, 0.29 mmol) was added to a solution of compound **9** (120 mg, 0.29 mmol) in MeOH (2 mL), and the reaction mixture was stirred at room temperature for 5 h. After evaporation of the solvent, compound **11** was obtained quantitatively as white solid. ^{1}H NMR (500 MHz, D_2O): δ 3.82−3.78 (dd, 1 H, J = 3.5 and 9.5 Hz, H-4), 3.85−3.82 (m, 2 H, H-6a, H-6b), 3.89 (m, 1 H, H-3), 4.04 (dd, 1 H, J = 2.2 and 4.1 Hz, H-2), 4.35 (m, 1H, H-5), 5.29 (bt, 1 H, H-1). ^{13}C NMR (125 MHz, D_2O): δ 61.02, 65.30, 68.40, 72.48, 74.13, 79.82. Flash chromatography led to oxidation of compound **11** and yielded the disulfide product, which was reduced to compound **11** by addition of dithiothreitol. ^{1}H NMR (500 MHz, D_2O): δ 3.89−3.80 (m, 4 H, H-6a, H-6a′, H-6b, H-6b′), 3.98−3.92 (m, 4 H, H-3, H-3′, H-4, H-4′), 4.13 (dd, 2 H, J = 3.4 and 5.1 Hz, H-2, H-2′), 4.19−4.14 (m, 2 H, H-5, H-5′), 5.10 (d, 2 H, J = 3.4 Hz, H-1, H-1′). ^{13}C NMR (125 MHz, D_2O): δ 60.32, 65.03, 69.86, 70.92, 72.76, 90.45. MS (ESI) measured for $C_{12}H_{22}O_{10}S_2$ ($[M + Na]^+$): m/z 413.07.

Quantum Chemical Calculations. Conformational searches were employed to identify the most stable conformation in solution for each investigated isomer. The solution structures were obtained by means of geometry optimization at the MP2/6-31+G(d,p) level using Gaussian03.[53] The effect of the solvent was modeled using the standard PCM method of Gaussian 03 and the default united-atom cavity model (UA0).[54] Subsequent single point calculation were performed at the PCM-MP2/6-31+G(d,p) level with an all-atom cavity model, where the size of each atom was defined by its van der Waals radius according to Bondi[55] and scaled by the factor 1.2. We have found this cavity model to provide accurate relative solvation energies for organic compounds, including neutral and ionic compounds with sulfur.[56] The final free energies in solution included the nonelectrostatic components from the PCM calculations, but were not corrected for nuclear motions. It should be noted that MP2 calculations employing large polarized basis sets have been found to produce accurate relative energies in molecular systems influenced by the anomeric effect.[57]

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Supporting Information Available: NMR spectra of 1-thio-D-mannopyranose and 1-thio-D-altropyranose species, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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