CONFORMATIONAL STUDIES ON PYRANOID SUGAR DERIVATIVES BY N.M.R. SPECTROSCOPY. THE CONFORMATIONAL EQUILIBRIA OF THE PERACETYLATED 1,2-*trans* 1-THIOALDOPENTOPYRANOSES IN SOLUTION*†

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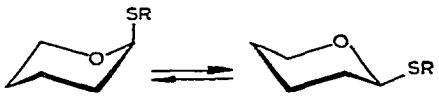
ABSTRACT

The chair–chair conformational equilibria in solution have been measured, by the n.m.r.-spectral method of averaging of spin coupling, for the 1-thio-D-aldopentopyranose tetraacetates having the *β-ribo* (**1**), *α-arabino* (**2**), *β-xylo* (**3**), and *α-lyxo* (**4**) configurations. The axial-directing influence of the 1-acetylthio group is weaker than that of the 1-methoxyl, 1-acetoxy, or 1-benzoyloxy group in those configurations (*β-ribo* and *α-lyxo*) where an axial 1-substituent does not have a *syn*-axial group at C-3; this weaker axial-directing effect can be explained on steric grounds. In contrast, in those configurations (*β-xylo* and *α-arabino*) where the axial 1-substituent is *syn*-axial to the 3-substituent, the axial-directing effect of the 1-acetylthio group is stronger, being comparable to that of the acetoxy group in **3** and stronger than that of the benzoyloxy, acetoxy, and methoxyl groups in **2**. An attractive interaction between *syn*-axial groups may be the cause of the behavior observed with **2** and **3**.

INTRODUCTION

Several investigations dealing with the conformational analysis of 2-(alkylthio)tetrahydropyrans[8–10] have been reported. The aim of these studies was the delineation of the relative roles played by electrostatic and steric interactions in determining conformational and configurational populations for the mobile, heterocyclic ring-systems.

From a study on the conformational equilibria of various 2-(alkylthio)tetrahydropyrans by measurements of dipole moment and by n.m.r. spectroscopy, de



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†For previous papers in this series, see Refs. 1–6, and references cited therein. For a preliminary report, see Ref. 7.

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Hoog and Havinga[10] observed that, in contrast to results in the 2-alkoxytetrahydropyrans[8,9,11,12], the size of the alkyl group does not affect the conformational population. It was, therefore, concluded that the influence of the alkyl group on the equilibrium composition for the 2-alkoxytetrahydropyrans is a steric[9], rather than a polar effect[12].

From a comparison with conformational data previously reported for the 2-alkoxytetrahydropyrans[11], it was deduced[10] that the magnitude of the anomeric effect for the methylthio group is less than that of the methoxyl group; the difference in anomeric effects was related to the lower dipole moment of the C–S bond. Eliel and Giza had previously reported that the anomeric effect of an SR group is somewhat smaller than that of an OR group[9]. The anomeric effect of the methoxyl group in 2-methoxytetrahydropyran dissolved in carbon tetrachloride was estimated[10] as 1.6–1.7 kcal.mole^{-1}, by assuming an "A-value" of 0.7–0.8 kcal.mole^{-1} for the methoxyl group[13]. From the "A-value" of 1.07 kcal.mole^{-1} for the methylthio group[14], determined by the method of peak-area measurement (direct integration of spectra of separate conformers), the anomeric effect of the methylthio group in 2-(methylthio)tetrahydropyran in carbon tetrachloride was estimated as 1.5 kcal.mole^{-1}. However, if the more precise "A-value" of 0.55 kcal.mole^{-1} for the methoxyl group[14], also determined by the direct-integration method, is employed in the calculation, the magnitude of the anomeric effect for the methoxyl group becomes 1.44 kcal.mole^{-1}, that is, it is actually smaller than that of the methylthio group. The difference of 0.52 kcal.mole^{-1} in steric requirements of the two groups can also account for the configurational populations observed for the 2-alkoxy- and 2-(alkylthio)-6-methyltetrahydropyrans[9].

In a general program concerned with the study of conformations of pyranoid sugar derivatives, it has been of interest to evaluate the influence of the aglycon in determining conformational tendencies of multisubstituted tetrahydropyran ring-systems. Previous investigations on the axial-directing influence of the bromo[6], chloro[6], acetoxy[3,5], benzoyloxy[3,5], and methoxyl[1] groups have been reported. The present article describes experimental findings, obtained by n.m.r. spectroscopy, on the effect of the acetylthio group at C-1 on the conformational populations of the four 1,2-*trans* 1-thioaldopentopyranose tetraacetates in solution.

MATERIALS AND METHODS

The 1-thioaldopentopyranose tetraacetates having the α-D-*arabino* (**2**), β-D-*xylo* (**3**), and α-D-*lyxo* (**4**) configurations were prepared from the corresponding thermodynamically "stable" tri-*O*-acetyl-D-aldopentopyranosyl bromides and potassium thiolacetate by the general procedure devised for the preparation of 1-thio-β-D-glucopyranose pentaacetate[15,16]. The compounds prepared under these conditions are the kinetic products resulting from neighboring-group participation of the 2-acetoxy substituent. The α-D-*lyxo* derivative (**4**) was not obtained completely pure, but the impurities present were minor enough (<5%) to permit an interpretation of

the 220-MHz spectrum of **4** in acetone-d_6. 1-Thio-β-D-ribopyranose tetraacetate (**1**) was prepared as previously described[17], by the general procedure of Černý *et al.*[18].

The n.m.r. spectra were measured at 100 or 220 MHz for 20% (w/v) solutions of the compounds in acetone-d_6 or chloroform-*d*, each containing 5% of tetramethylsilane. The time-averaged $J_{4,5}$ and $J_{4,5'}$ spin-couplings employed in the calculation of conformational populations were obtained by ABX analysis[19] of spectra measured at 100-Hz sweep-width. The values reported are considered accurate to within ±0.1 Hz. All other coupling-constants recorded were obtained on a first-order basis, as direct peak-spacings from spectra measured at a sweep width of 100 Hz; they are considered precise to within ±0.1 Hz.

For each of the 1-thioaldopentopyranose tetraacetates (**1–4**) in acetone-d_6 or chloroform-*d* at the temperature indicated, the n.m.r.-spectral method of averaging of spin coupling[20] was used, by procedures already detailed[21], to determine the proportions of the *1C*(D) and *C1*(D) conformers, and thence, the equilibrium constants (K) and free-energy (ΔG^0) values for the *1C*(D)⇄*C1*(D) equilibria. For **1–4**, analysis of the signals of H-4 and the two protons at C-5 as ABX spin-systems gave $J_{4,5}$ and $J_{4,5'}$ values that are weighted time-averages for the two chair conformers in rapid equilibrium. Conformational populations at the temperature indicated were determined from the observed coupling of H-4 with the *trans*-disposed proton at C-5, taken in conjunction with values for $J_{4e,5e}$ and $J_{4a,5a}$ that had been obtained from the following model compounds. The $J_{4,5a}$ value (11.6 Hz)[5] for α-D-xylopyranose tetraacetate was used as the magnitude of $J_{4a,5a}$ for each 1-thioaldopentopyranose tetraacetate. The low-temperature limit of the $J_{4,5'}$ coupling (1.5 Hz) for β-D-arabinopyranose tetraacetate[5] was used as the magnitude of $J_{4e,5e}$ for each 1-thioaldopentopyranose tetraacetate. From the conformational populations determined from the spin-coupling data, the equilibrium constants and values for the free-energy differences given in

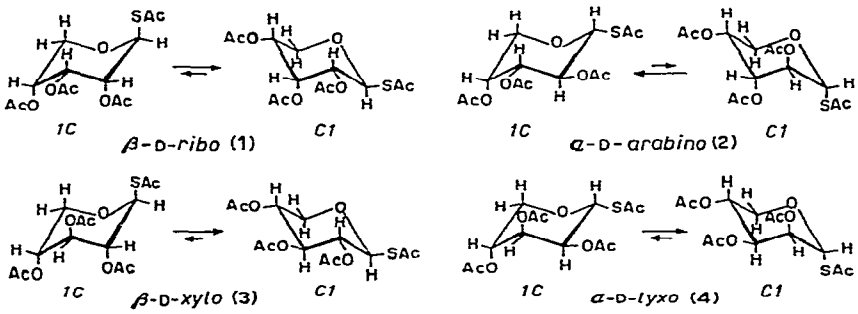
TABLE I

CONFORMATIONAL EQUILIBRIA OF 1,2-*trans* 1-THIOALDOPENTOPYRANOSE TETRAACETATES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Equilibrium data*			ΔG°_{31}, (*kcal.mole*$^{-1}$) *for* 1C(D)⇆C1(D)
		% C1	% 1C	K = C1/1C	
1	β-D-*ribo*	66	34	2.0	−0.41 ±0.28
2	α-D-*arabino*[a]	32	68	0.46	+0.47 ±0.29
3	β-D-*xylo*	72	28	2.6	−0.58 ±0.30
4	α-D-*lyxo*[b]	64	36	1.8	−0.35 ±0.24

[a]In chloroform-*d*. [b]Determined at 220 MHz at 23°.

Table I were calculated. The limits of accuracy for the calculations were determined from the uncertainty of ±0.1 Hz in the experimental values of the time-averaged couplings, in conjunction with a conservative estimate (±0.5 Hz) of the extent to which the "model" coupling-values actually differ from the true couplings in the separate conformers of each compound.



Spin-coupling data for the four compounds (**1–4**) are given in Table II. Chemical shifts for compounds **1–3** have already been reported[17] and chemical-shift data are given for compound **4** in the Experimental Section.

TABLE II

COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS OF 1,2-*trans* 1-THIOALDOPENTOPYRANOSE TETRAACETATES IN ACETONE-d_6 AT 31°

Compound	*Configuration*	*Coupling constants*[a] *(Hz)*					
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	[b,c]$J_{4,5}$	[b,c]$J_{4,5'}$	$J_{5,5'}$
1	β-D-*ribo*[d]	7.6	3.1	3.0	4.2	8.2	−11.8
2	α-D-*arabino*[d,e]	[f]	[f]	[f]	4.7	2.4	−12.7
3	β-D-*xylo*[d]	8.2	7.9	7.9	4.5	8.8	−11.9
4	α-D-*lyxo*[g]	4.5	2.8	[f]	3.4	8.0	−12.0

[a]Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b]The proton on C-5 giving the higher field signal is designated H-5′. [c]Coupling constants calculated by ABX analysis. [d]Compare with data, measured at a sweep width of 500 Hz, given in Ref. 17. [e]In chloroform-*d*. [f]First-order couplings not observed. [g]Determined at 220 MHz at 23°.

RESULTS AND DISCUSSION

Effect of configuration on the relative, axial-directing influence of the acetoxy, benzoyloxy, methoxyl, and acetylthio groups. — The net, axial-directing influence of a substituent at the anomeric center is the resultant of a positive, polar contribution and a negative, steric contribution. The conformational free-energy ("A-value") of the methylthio group has been found to be substantially larger than that of the methoxyl group[14]; thus, A = 0.55 kcal.mole^{-1} for the methoxyl group at −82° in carbon disulfide and 1.07 kcal.mole^{-1} for the methylthio group at −79° in the same solvent. The Van der Waals radii of sulfur (1.85 Å) and oxygen (1.40 Å)[22] appear to be the controlling factor in determining the conformational tendencies of the two groups[14]. The difference in the conformational free-energies between the acetylthio and the acetoxy or benzoyloxy groups can also be expected to be in the vicinity of 0.5 kcal.mole^{-1}. The acetoxy and benzoyloxy groups have[23] very similar "A-values".

Offsetting this difference in conformational free-energies in the peracylated aldopentopyranose derivatives that have the C-1 and C-2 substituents in *trans* orientation is the larger gauche interaction expected between the acetoxy and acetylthio groups than between two acetoxy groups. However, as the repulsive energy of a 1,3-diaxial interaction is greater than that of a 1,2-gauche interaction, the larger "A-value" for the acetylthio group should be the controlling steric contribution. In terms of the polar contribution, the anomeric effect of the acetythio group is anticipated to be smaller than that of the acetoxy group, because the bond moment of C–S is smaller than that of C–O. Therefore, both steric and electronic considerations lead to the prediction of a larger equilibrium proportion near room temperature of that chair conformer having the C-1 substituent equatorial for the 1,2-*trans* 1-thioaldopentopyranose tetraacetates than for the corresponding aldopentopyranose tetraacetates or peracetylated aldopentopyranosyl benzoates.

In the *β-ribo* and *α-lyxo* configurations, where the C-1 substituent does not have a *syn*-axial group at C-3, this prediction holds true. Thus, a solution of 1-thio-*β*-D-ribopyranose tetraacetate (**1**) has a larger proportion of the *CI*(D) conformer (equatorial bond to the C-1 substituent) at equilibrium (66%) than does the corresponding 1-*O*-acetyl derivative (43%). Although the change in the free-energy differences between the 1-*S*-acetyl derivative (**4**) and the 1-*O*-acetyl derivative is smaller in the *α-lyxo* configuration, the 1-*S*-acetyl derivative (**4**), again, has a larger proportion of the chair conformer having the C-1 substituent equatorial [*IC*(D) conformation] than does the 1-*O*-acetyl derivative. Hence, the axial-directing influence of the acetylthio group is smaller than that of the acetoxy or benzoyloxy group for the aldopentopyranoid configurations in which the axial C-1 substituent does not have a *syn*-axial group at C-3. The difference in the axial-directing effects can be rationalized in steric terms alone, and a difference in polar contributions need not be invoked. In a previous report, it was demonstrated[1] that the axial-directing influence of the methoxyl group is larger than that of the acetoxy or benzoyloxy group in just these configurations. Therefore, in the *α-lyxo* and *β-ribo* configurations, the following order of axial-directing influence for the four groups under consideration is apparent:

$$OMe > OAc \approx OBz > SAc.$$

In the *β-xylo* and *α-arabino* configurations, where the axial C-1 substituent is *syn*-axial to an acetoxy group at C-3 and a hydrogen atom at C-5 (axial 1-substituent gauche to C-5), the expected larger proportion of that chair conformer having the C-1 substituent equatorial for the 1-*S*-acetyl derivative was not observed. Thus, 1-thio-*β*-D-xylopyranose tetraacetate (**3**) and *β*-D-xylopyranose tetraacetate have about the same proportion of each chair form present at equilibrium near room temperature, indicating that the axial-directing influences of the acetylthio and acetoxy groups in the *β-xylo* configuration are about equal. The proportion of the *CI*(D) conformer for the 1-*O*-acetyl derivative and 1-*S*-acetyl derivative is larger than that for the 1-*O*-benzoyl analog. The axial-directing influence of the 1-methoxyl group has been reported[1] to be smaller than that of the 1-acetoxy group in the *β-xylo*

configuration. Hence, in the *β-xylo* configuration, the following order of decreasing, axial-directing effects is apparent:

OBz > OAc ≈ SAc > OMe.

In the *α-arabino* series, the proportion of the *C1*(D) conformer (axial C-1 substituent) for the 1-*S*-acetyl derivative (**2**) is larger than that for the 1-*O*-benzoyl analog, and, in turn, the proportion for the 1-*O*-benzoyl derivative is larger than that for the 1-*O*-acetyl derivative. The axial-directing influence of the 1-methoxyl group has also been reported[1] to be smaller than that of the 1-acetoxy group in the *α-arabino* configuration. Therefore, for the *α-arabino* configuration, the following order of axial-directing effects is observed:

SAc > OBz > OAc > OMe.

In conclusion, for the two configurations in which the C-1 substituent has a *syn*-axial acetoxy group at C-3 (the *β-xylo* and *α-arabino* configurations), the proportion of the chair conformer having the 1-(acetylthio) group axial is considerably larger than that predicted from steric and electronic considerations. The relatively strong, axial-directing influence of the 1-(acetylthio) group in these two configurations can be correlated with *syn*-diaxial disposition of the 1-(acetylthio) group and the C-3 acetoxy groups in one of the chair conformers. Either a weakened, repulsive, *syn*-diaxial interaction or an electrostatic attraction between the two groups may be involved. In view of the large steric influence of the sulfur atom, the latter explanation appears the more probable. The higher polarizability of the sulfur atom could lead to a London attraction as a result of an interaction between the electron clouds of oxygen and sulfur[24].

Low-temperature studies. — Studies at 100 MHz of solutions of 1-thio-β-D-ribopyranose tetraacetate (**1**) in acetone-d_6 have shown the effect of "conformational freeze-out" at low temperature (~ −85°). However, because of overlap of signals of the separate conformers in the 100-MHz spectra, assignment of individual peaks is difficult. Studies at higher field-strengths can be expected to yield accurate values for the equilibrium constant at low temperatures and for the rate of conformational interconversion.

EXPERIMENTAL

General. — Evaporations were performed below 50° under diminished pressure. Melting points are uncorrected. Spectra recorded at 100 MHz were measured with a Varian HA-100 n.m.r. spectrometer under the general conditions specified in Ref. 6. The 220-MHz spectrum of **4** in acetone-d_6 was recorded by Dr. A. A. Grey of the Ontario Research Foundation, Sheridan Park, Ontario, Canada.

1-Thio-β-D-ribopyranose tetraacetate (**1**). — This compound was prepared as previously described[17], by the general procedure of Černý, Vrkoč, and Staněk[18]; m.p. 87–88° (lit.[17] m.p. 88–89°).

1-Thio-α-D-arabinopyranose tetraacetate (**2**). — This compound was prepared from tri-*O*-acetyl-β-D-arabinopyranosyl bromide[25] and potassium thiolacetate in acetone as previously described[17], to give crystalline **2**, m.p. 38–39° (lit.[17] m.p. 39°).

1-Thio-β-D-xylopyranose tetraacetate (**3**). — This compound was prepared from tri-*O*-acetyl-α-D-xylopyranosyl bromide[26] and potassium thiolacetate in acetone as previously described[17], to give crystalline **3**, m.p. 103° (lit.[17] m.p. 103°).

1-Thio-α-D-lyxopyranose tetraacetate (**4**). — This compound was prepared from tri-*O*-acetyl-α-D-lyxopyranosyl bromide[6] and potassium thiolacetate in acetone, by the general procedure given previously[17], and was obtained after column-chromatographic purification on silica gel (Merck 7734, with 10:1 dichloromethane–ether as eluant) as a slightly contaminated syrup. However, the impurities were sufficiently minor (<5%) to allow interpretation of its 220-MHz spectrum in acetone-d_6: τ 4.23 (doublet, H-1), 4.75 (perturbed quartet, H-2), 4.85–4.95 (multiplet, H-3,4), 5.99 [quintet (perturbed by virtual coupling with H-3), H-5], 6.33 [octet (showing virtual coupling with H-3), H-5'], 7.55 (SAc), 7.90, 7.94, 7.96 (OAc).

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