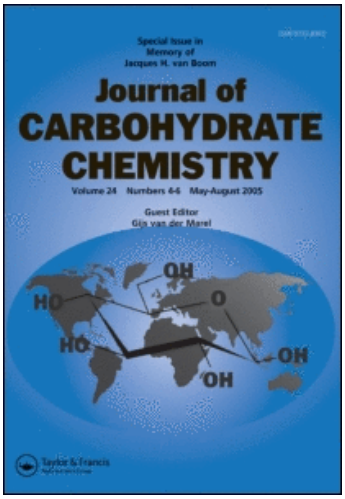

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THE ISOMERIC COMPOSITION OF 6-DEOXY-D-XYLO-HEXOS-5-ULOSE IN AQUEOUS SOLUTION AS DETERMINED BY ^{1}H and ^{13}C NMR

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ABSTRACT

Acid hydrolysis of 6-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose (4) yielded gummy 6-deoxy-D-xylo-hexos-5-ulose (1) as an isomeric mixture of two furanose forms, 6-deoxy-α-D-xylo-hexofuranos-5-ulose and 6-deoxy-β-D-xylo-hexofuranos-5-ulose, and a pyranose structure 1R,5R-6-deoxy-D-xylo-hexopyranos-5-ulose. The combined percentage (64%) of the furanoses represents an unusually large amount of free carbonyl form for a sugar when compared to simple hexoses and 2-hexuloses. Isomeric structures were determined in deuterium oxide solution by ^{1}H and ^{13}C NMR.

INTRODUCTION

In our continuing study of the chemistry of delta dicarbonyl sugars, we have begun determining the isomeric compositions of some 5-ketoaldoses in aqueous solution. We now report the isomeric

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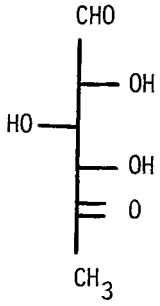
composition of 6-deoxy-D-xylo-hexos-5-ulose (1) in aqueous solution as shown by ^{1}H and ^{13}C NMR studies.

The aqueous solution isomeric composition of a great many aldoses[3-5] and hexuloses[6-11] have been determined by NMR techniques and the results have been summarized by Angyal.[12] Regarding their isomeric composition in aqueous solution, 5-ketoaldohexoses are unusual molecules in that the two carbonyl groups can interact by way of a pyranose hemiacetal linkage, and/or compete in furanose ring formation. However, one would expect that the isomeric composition of such molecules in aqueous solution should be subject to some extent to those factors that influence the composition of the parent aldoses and ketoses.



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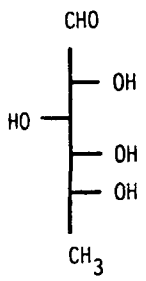
The following factors are considered relevant to a consideration of the aqueous composition of 1. 1. Among the aldopentoses, aldohexoses,[4] and 2-hexuloses,[8] pyranose forms predominate. 2. Aldoses form cyclic acetals more readily than do ketoses.[12] Consequently, ketoses show a higher percentage of carbonyl forms than do aldoses. 3. Cyclic acetal formation from 2-hexuloses is diminished by replacing the electron withdrawing C-1 hydroxyl group with a hydrogen.[11] 4. Aldopentoses and aldohexoses are much less than 1% carbonyl form in solution and aldehydrol proton signals from hydrates of these molecules have not been detected by ^{1}H

NMR.[5] In contrast, the aldehydrol forms of glyceraldehyde and the tetroses have been identified. 5. The carbonyl form of a 2-hexulose is not significantly hydrated in aqueous solution.[11,12]

RESULTS AND DISCUSSION

The molecule of interest in this study was 6-deoxy-D-xylo-hexos-5-ulose (1). It potentially has a much more complex isomeric composition than its parent aldose, 6-deoxy-D-glucose (2) or parent ketose, 1-deoxy-L-sorbose (3). Excluding hydrates, one can envision twelve cyclic structures from 1 (Fig. 1), four pyranose (1a), four furanose (1b and 1c) and four 2,7-dioxabicyclo[2.2.1] heptane isomers (1d and 1e). That the bicyclic structures 1d and 1e seem reasonable isomeric forms of 1 is based on the observation that a homologous 3,8-dioxabicyclo [3.2.1] octane derivative was the predominant isomeric form of D-lyxo-hexos-5-ulose.[13]



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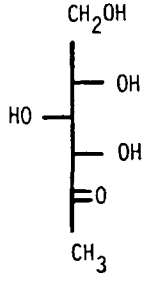

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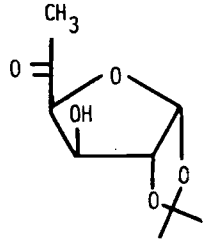

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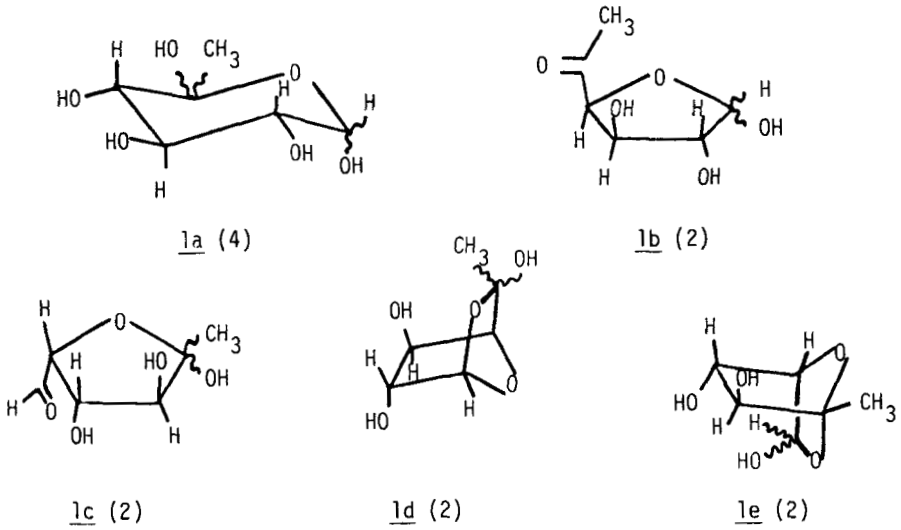
Generation of the mixture of isomers from 1 was achieved by acid catalyzed hydrolysis of the blocked furanose derivative 6-deoxy-1,2-O-isopropylidene- α -D-xylo-hexofuranos-5-ulose (3).[14] Acid catalysis with an H^+ cation exchange resin was achieved at 55 °C or more conveniently at room temperature using the Nafion® membrane.[15] The colorless gummy product obtained after the water was removed by freeze-drying was then analyzed in D_2O solution by



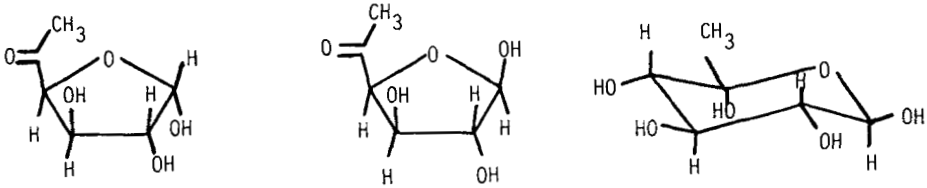
1a (4) 1b (2)

1c (2) 1d (2) 1e (2)

Fig. 1. Possible cyclic isomeric structures (not including hydrates) for 6-deoxy-D-xylo-hexos-5-ulose (1). Numbers in parentheses indicate number of isomers per ring form.

^1H NMR (300 and 400 MHz) and in H_2O solution by ^{13}C NMR (100.6 MHz). The ^1H NMR spectrum of the mixture is shown in Fig. 2.

The spectrum of the mixture turned out to be much simpler than was anticipated, showing only the presence of three isomeric forms of 1 in the mixture, the α- and β-furanose structures I and II, and the β-1,α-5 (1R,5R) pyranose form III. The high-field



I II III

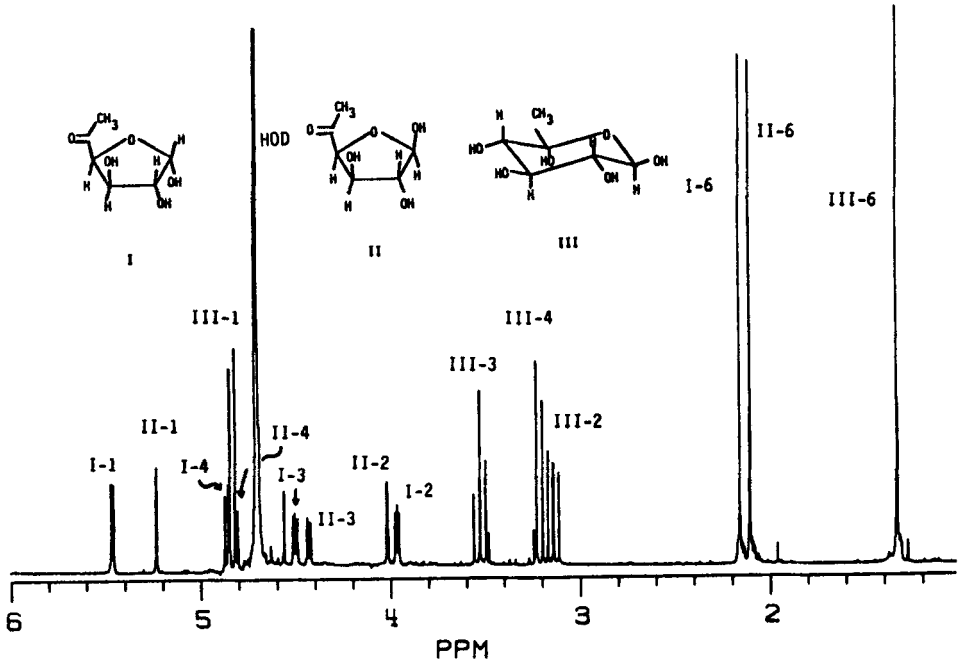


Fig. 2. The ^1H NMR spectrum (300 MHz) of 1 in D_2O. Arabic numbers indicate position of protons.

region of the spectrum (1-3 ppm) is marked by the presence of only three methyl proton singlets at 2.22 (I), 2.27 (II), and 1.45 ppm (III). The H-1 anomeric protons from the furanoses I (5.55 ppm) and II (5.32 ppm) gave the farthest downfield signals, with $J_{1,2}$ = 3.66 Hz, indicating the 1,2-cis α-furanose structure for I, and $J_{1,2}$ = 0.55 Hz corresponding to a 1,2-trans-β-furanose form for II.

The stereochemistry at C-1 of III is that of a β-pyranose ring, the H-1, H-2 trans diaxial relationship indicated by $J_{1,2}$ = 8.20 Hz (at 4.92 ppm). The assignments for all the protons in structures I, II and III (Tables 1 and 2) were firmly established by homonuclear decoupling experiments and corroborated by the very close match between the recorded and simulated spectra for the individual isomers.[16]

Table 1

^1H NMR Chemical Shift Values (PPM) From The Isomeric Forms of 1 in D_2O at 400 MHz

Proton	Isomers I	II	III
H-1	5.55 d	5.32 d	4.92 d
H-2	4.05 dd	4.10 dd	3.22 dd
H-3	4.59 dd	4.51 dd	3.61 dd
H-4	4.95 d	4.90 d	3.30 d
H-6	2.22 s	2.27 s	1.45 s

Table 2

^1H NMR Coupling Constant (Hz) From the Isomeric Forms of I in D_2O at 400 MHz

J(Hz)	Isomers I	II	III
J(1,2)	3.66	0.55	8.20
J(2,3)	2.70	1.65	9.30
J(3,4)	4.26	5.00	9.77

Relative percentages for the three isomers were determined by careful integration of the upfield methyl proton singlets; 36% for I, 28% for II and 36% for III. The C-6 proton signals from the two furanose forms I and II were conveniently differentiated by comparison of their integration value ratio with the integration value ratio of the readily assigned downfield C-1 anomeric protons.[16]

The fully decoupled ^{13}C NMR spectrum of the isomeric mixture (Fig. 3) contained eighteen lines, six for each of the three isomers. The three C-6 carbon signals were clustered in the up-

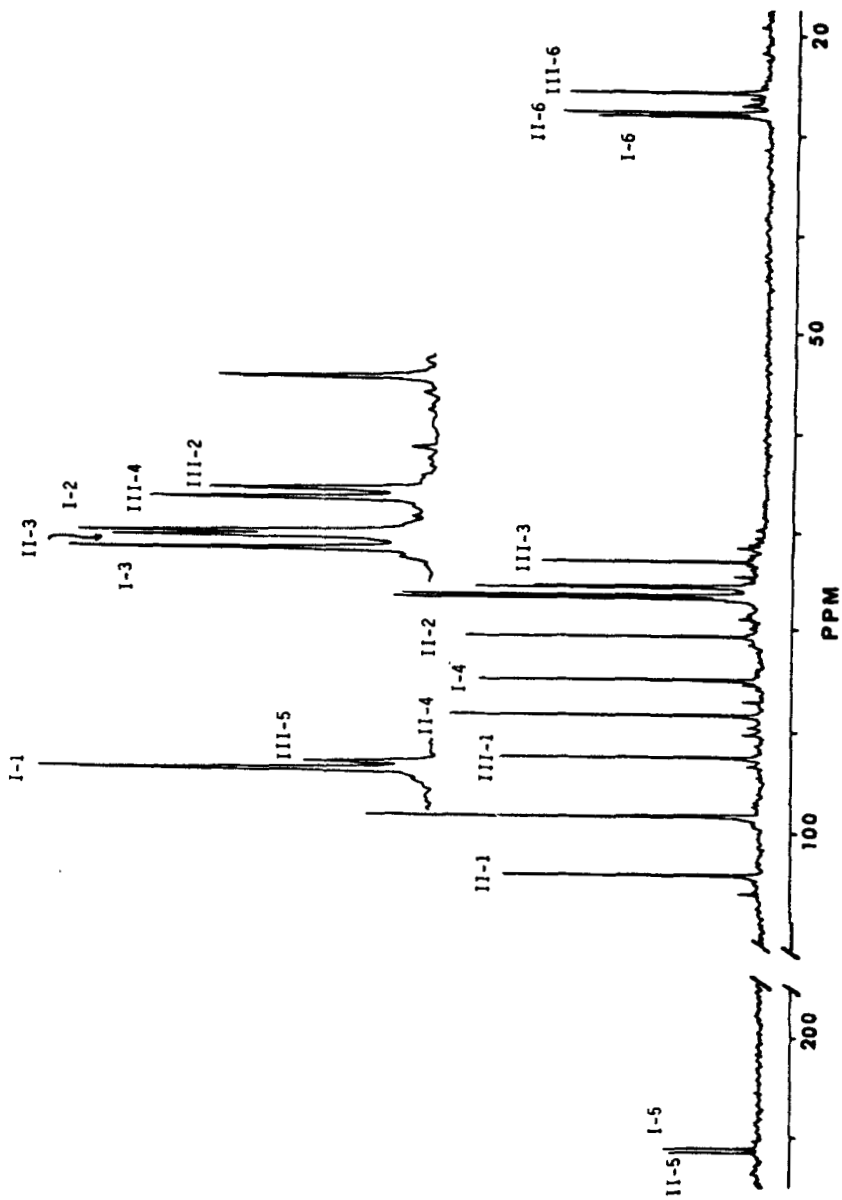


Fig. 3. Fully decoupled ^{13}C NMR spectrum (100.6 MHz) of 1 in water. Arabic numbers indicate carbon positions.

field region of the spectrum (24.5-28.0 ppm), the ring carbon signals falling between 73 and 104 ppm, and the two C-5 carbonyl carbons from I and II at 211.06 and 211.48 ppm. ^{13}C assignments were established by proton-carbon decoupling experiments. The carbon chemical shifts and assignments are summarized in Table 3.

In order to establish the configuration of the ketone anomeric carbon (C-5) of III, the C-6, H-4 three bond H-C-C-C coupling constant was measured from the undecoupled carbon spectrum. The value of this coupling constant was less than 0.5 Hz, and falls into the experimentally observed range of couplings (0-3.3 Hz) for a gauche relationship.[17,18] A larger coupling ($\sim$4-8 Hz) is expected from a trans-diaxial ($\sim$180°) geometry. Therefore, the C-5 methyl group of III is equatorial and the C-5 hydroxyl group is axial.

The high combined percentage (64%) of the hexofuranose ring forms I and II is an unusual result when compared to higher pyranose ring compositions from aldohexoses[4] and 2-hexuloses[7,8] in general, but in particular when compared to ring composition data from the parent molecules, 6-deoxy-D-glucose (2) and 1-deoxy-L-sorbose (3) (Table 4). In addition, the β-1 pyranose ring form dominates the aqueous isomeric compositions of 6-acetamido-6-deoxy-D-xylo-hexos-5-ulose (4)[20] and D-xylo-hexos-5-ulose (5),[21] molecules which can be considered as C-6 N-acetyl and hydroxy derivatives of 1.

To account for the high aldohexofuranose content of 1, we reexamined the known factors that influence simple aldohexose and 2-hexulose solution compositions. Among the 2-hexuloses it is the absence of an electron withdrawing substituent on C-1 that diminishes the acetal forming ability of the ketose carbonyl and increases the percentage of the free carbonyl form of the molecule (Table 4). A second important factor is that aldoses form acetals more readily than do ketoses. When these two factors work in concert, as they do in 1, the result is the high percentage of

Table 3

^{13}NMR Chemical Shift Values (PPM) From The Isomeric Forms of 1 in Water at 100.6 MHz

Carbon	Isomers I	II	III
1	98.309	103.951	92.455
2	76.891	76.621	75.410
3	76.530	80.655	73.042
4	84.872	88.269	75.559
5	211.055	211.480	98.157
6	27.968	27.604	24.541

Table 4

Isomeric Composition (%) of 1, 2, and 3 In Aqueous Solution

Compound	α p	β p	α f	β f	Carbonyl
6-deoxy-D-xylo-hexos-5-ulose (1, 23 °C)		36	36	28	64[a]
6-deoxy-D-glucose (2, 44 °C)[19]	36	64			
1-deoxy-L-sorbose (3, 27 °C)[11]	92			ca. 4	ca. 4

a. The carbonyl percentage is the sum of the α f and β f structure.

the furanoid structures observed (I and II), both of which are also free carbonyl (ketose) sugars. That the aldehyde carbonyl is more prone to acetal formation than is the ketone carbonyl is underscored by the total absence of the ketohexofuranose forms (Ic, Id, and Ie) in the isomeric mixture from 1. In keeping with what has been observed from aldohexose and 2-heptulose composition studies, we found neither free aldehyde structures nor hydrated carbonyl structures. Furthermore, as with the parent molecule 1-deoxy-L-sorbose (3), the pyranoid structure (III) derived from 1 has an axial OH and an equatorial CH_3 at the ketone anomeric carbon.

EXPERIMENTAL

The ^1H NMR spectra were obtained using Bruker (400 MHz) and Nicolet (300 MHz) spectrometers. The ^{13}C NMR spectra were recorded using the Bruker instrument (100.6 MHz) only. ^1H NMR spectra were measured in deuterium oxide solutions and ^{13}C NMR spectra in water. Proton chemical shifts are reported relative to tetramethysilane as an internal standard (0.00 ppm) and carbon chemical shifts relative to dioxane as an internal standard (67.8 ppm).

6-Deoxy-D-xylo-hexos-5-ulose (1). 6-Deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose[14] (4, 0.43 g, 2.1 mmol) in water (5 mL), and Biorad AG 50W-X2 H^+-form resin (6.5 g) was maintained without stirring at 55 °C for 16 h. The absence of starting material in the aqueous reaction mixture was indicated by silica gel thin layer chromatography (ethyl ether as the eluent).

An alternative hydrolysis procedure involved substituting Nafion® membrane squares of ca. 1 cm x 1 cm for the resin catalyst. Complete hydrolysis took place at room temperature in 24 h.

Removal of the resin or membrane by filtration, and the solvent by freeze-drying, yielded the product (1)[15] as a straw-colored gum. The product was prepared for ^1H NMR spectral measurements

by dissolving it in deuterium oxide, freeze-drying the deuterium oxide, and repeating the process once again.

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