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Acyclic Tautomers in Crystalline Carbohydrates: The Keto Forms of 1-Deoxy-1-carboxymethylamino-D-2-pentuloses (Pentulose-glycines)

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Acyclic intermediates are of fundamental importance for a large segment of carbohydrate chemistry and biochemistry relating to transformations at the carbonyl/anomeric carbon.[1,2] That the acyclic carbonyl tautomer is a principal reactive form in numerous redox-,[1a] isomerization-,[1b,c] addition-,[1d] condensation-,[1e,f] degradation-,[1a] and other reactions of carbohydrates has long been recognized.[2] Recently, extensive structural studies on mechanisms of carbohydrate transformations by such important classes of enzymes as aldose/ketose reductases[3] and aldo/keto isomerases[4] have confirmed that acyclic sugar forms are reactive intermediates at the active site of these and other[5] enzymes.

Equilibrated solutions of aldoses or ketoses generally contain only a very low fraction of the polyhydroxyaldehyde or -ketone,[6] and crystallization of unprotected sugars, as a rule, yields the most stable cyclic pyranose or, in some cases, furanose isomer. Ab initio calculations[7] for acyclic sugars would be resource-consuming, due to a large number of conformations possible. Thus, a detailed structural description of the acyclic carbonyl tautomers of carbohydrates is nearly nonexistent.

There are, however, a few indications that nonprotected reducing sugars able to crystallize spontaneously in the acyclic form might be found within the group of *N*-(1-deoxy-2-ketos-1-yl)amines, also referred to as ketosamines or Amadori compounds. The latter have long been of an interest in the area of food chemistry.[1c,8] In the last two decades, implications of ketosamines in aging, diabetes, renal disease, and so forth, attracted the attention of clinical chemists,[9] and their potential use as anticancer drugs is being investigated.[10] The keto form for some crystalline ketosamines has been suggested on the basis of IR spectral data.[8a] We have previously reported on *N*,*N*-di-(1-deoxy-D-fructos-1-yl)glycine which adopts a unique hemiketal form where one of the carbohydrate residues is acyclic.[11]

Here we present NMR and X-ray diffraction data on acyclic tautomeric forms of *N*-(1-deoxy-D-*erythro*-2-pentulos-1-yl)- and *N*-(1-deoxy-D-*threo*-2-pentulos-1-yl)glycines (ribulose-glycine, **1**, and xylulose-glycine, **2**). Both **1** and **2** tautomerize in D_2O, as evidenced by NMR spectral data, with the β-furanose as the major form (52 and 39% respectively), followed by the α-furanose (28 and 34%) and the acyclic keto tautomer (20 and 27%). Crystalline **1** and **2** were obtained from the syrups at 4 °C. Only **2** afforded crystals suitable for single-crystal diffraction studies.

In the solid state ^{13}C NMR spectra (Figure 1) of powdered, crystalline **1** and **2**, all seven expected carbon resonances are detected.[12] In both spectra, the signals at 206 ppm can be unambiguously assigned to the carbonyl resonances, while no peaks were detected in the region of 90−110 ppm, indicating that both compounds in crystalline state exist exclusively as keto tautomers.

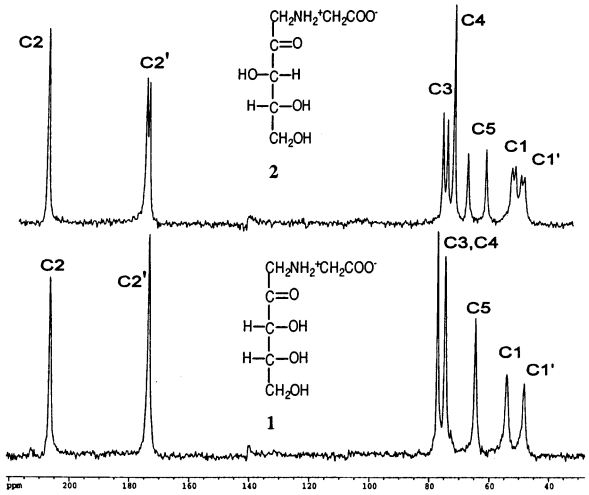

Figure 1. Solid-state ^{13}C NMR spectra of D-ribulose-glycine (**1**) and D-xylulose-glycine (**2**). See Figure 2 for atom numbering.

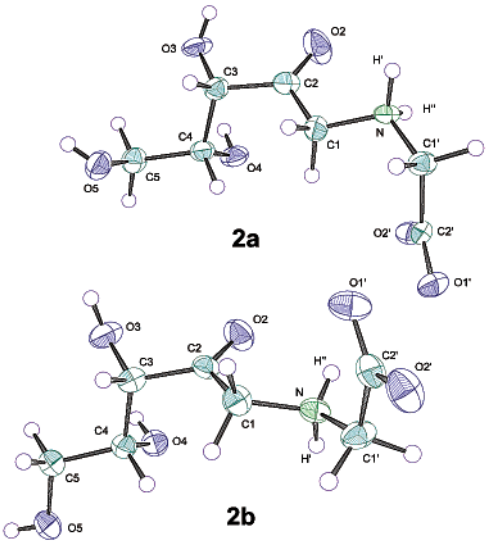

Figure 2. Molecular structures of conformers in crystalline D-xylulose-glycine.

In the spectrum of **2**, however, all but the C2 and C4 carbon signals are split, suggesting two conformationally unequal molecules. This was confirmed by a crystal structure determination. There are two crystallographically independent molecules of xylulose-glycine in the crystal of **2**. ORTEP views of the molecules **2a** and **2b** are shown in Figure 2. In both molecules, the carbohydrate portions exist in the acyclic keto form with bent carbon chain conformations.

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Table 1. Selected Bond Distances (Å) and Angles (deg) in Conformers of D-Xylulose-glycine

	2a	2b		2a	2b
C1−C2	1.495(4)	1.517(4)	C1−C2−C3	116.3(2)	114.4(2)
C2−C3	1.520(4)	1.520(5)	C2−C3−C4	109.6(2)	109.5(2)
C3−C4	1.531(4)	1.531(4)	C1−C2−O2	121.0(3)	121.1(3)
C4−C5	1.524(4)	1.522(5)	O2−C2−C3	122.6(3)	124.6(3)
C2−O2	1.207(4)	1.205(4)	N−C1−C2−O2	6.8(4)	−24.9(4)
C3−O3	1.408(4)	1.411(4)	O2−C2−C3−O3	−0.9(4)	−19.1(4)
C4−O4	1.417(4)	1.422(4)	C1−C2−C3−C4	−62.1(3)	−81.5(3)
C5−O5	1.420(4)	1.416(4)	C3−C4−C5−O5	−66.0(3)	−172.3(2)

The amino acid portions of both molecules are in the expected zwitterion form of a glycine *N*-derivative.

As demonstrated in Table 1, the C−C bond distances in the sugar portion of **2** are close to the corresponding values for alditols[13a] (mean of 1.520 Å), except for the C1−C2 bond in **2a**, which at 1.495 Å is significantly shorter. The mean values of hydroxyl C−O bond lengths in **2** (1.414 and 1.418 Å for **2a** and **2b** respectively) are shorter than corresponding bonds in alditols and rather closer to the average values[13b] found in a number of pyranoses. The C−C(OH)−C valence angles are somewhat closer to tetrahedral values than the respective angles in alditols.[13a] Overall, we found no significant differences between values of valence angles in **2a**, **2b** and the corresponding mean values in alditols or relevant glycine *N*-derivatives.

Of 16 torsion angles calculated for **2** (including atoms C, N, O only) only four have comparable values in the molecules **2a** and **2b**. All of these are located around the C3−C4 bond, thus making this portion of xylulose-glycine molecule the most conservative conformationally. The major conformational differences between **2a** and **2b** stem from the relative positions of hydroxyl oxygen O5 (Table 1) and the carboxyl group with respect to the rest of the molecule. Interestingly, a large fragment of molecule **2a** is virtually flat and includes atoms O3, C3, C2, O2, C1, N, C1′, with only small (1−7°) distortions from staggered/eclipsed conformation in related torsion angles (Table 1). The corresponding arrangement of the same atoms in molecule **2b** appears to be skewed (10−25° distortion from the staggered/eclipsed positions) with respect to that in **2a**. A similar spatial arrangement for the carbohydrate fragment was found for the acyclic D-xylose/D-xylulose intermediate in the active site of xylose isomerase.[14] In the enzyme complex, however, the periplanar disposition for O1, O2, and O4 of acyclic D-xylose/D-xylulose is stabilized by coordination with two metal ions, typically Mg^{2+} or Mn^{2+}. In addition, the probable solution conformations for D-xylulose were deduced from careful NMR studies[12] and are also in agreement with those found for the sugar portions of **2a** and **2b**.

In the crystal structure of **2,** the intermolecular hydrogen-bonding pattern consists of infinite ammonium carboxylate chains, with two finite branches that involve carbohydrate hydroxyl groups and are attached to the carboxylate acceptor atoms. There are no intramolecular hydrogen bonds in **2** and no evidence for the involvement of the carbonyl O2 in hydrogen bonding.

In conclusion, this work provides the first reported accurate structural data on a pentulose keto tautomer and might be of use in relevant mechanistic, structural, and computational studies of carbohydrates, for example modeling the D-xylose isomerase.[15]

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Supporting Information Available: Synthesis and characterization data for **1** and **2** (PDF). X-ray structural data for **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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