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Molecular and crystal structure and the Hirshfeld surface analysis of 1-amino-1-deoxy-α-D-sorbopyranose and 1-amino-1-deoxy-α-D-psicopyranose ("D-sorbosamine" and "D-psicosamine") derivatives

Valeri V. Mossine [a, *], Charles L. Barnes [b], Thomas P. Mawhinney [a]

[a] Department of Biochemistry, University of Missouri, Columbia, MO 65211, USA
[b] Department of Chemistry, University of Missouri, Columbia, MO 65211, USA

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ABSTRACT

Sorbosamine and psicosamine are the last two 1-amino-1-deoxy-hexuloses for which no structural data were available. We report on a ^{13}C NMR and a single crystal X-ray diffraction study of 1-deoxy-1-(*N*-methylphenylamino)-D-sorbose (**1**) and 1-deoxy-1-(*N*-methylphenylamino)-D-psicose (**2**). In solutions, both aminosugars are conformationally unstable and establish equilibria, with 90.7% α-pyranose, 3.8% α-furanose, 1.0% β-pyranose, 0.5% β-furanose, and 4.0% acyclic *keto* form for **1** and 32.4% α-furanose, 27.2% α-pyranose, 21.0% β-pyranose, 9.1% β-furanose, and 11.0% acyclic *keto* form for **2**. X-ray diffraction data provided detailed structural information on **1** and **2** in the α-pyranose form. Both molecules adopt the $^{5}C_{2}$ ring conformations, the bond distances and valence angles compare well with respective pyranose structures. All hydroxyl groups in crystal structures of both **1** and **2** participate in two-dimensional hydrogen bonding networks, the H-bonding pattern in **1** is dominated by co-crystallized water molecules. The Hirshfeld surface analysis revealed a significant contribution of non- or weakly polar interactions to the packing forces for both molecules, with crystal structure of **2** featuring short H···H contacts. Other structural features found in **2** are a significant planarity of the tertiary amino group (the pyramid heights are 0.127 Å in **2** vs 0.231 Å in **1**), a concomitant non-involvement of the amine nitrogen in heteroatom contacts, and a unique *anti-periplanar* conformation around the C1–C2 bond.

1. Introduction

1-Amino-1-deoxy-hexuloses have long been a subject of studies in food and health sciences, due to their roles as key intermediates of the Maillard reaction in foods and *in vivo* [1,2]. The overwhelming proportion of 1-amino-1-deoxy-hexulose derivatives found in organic matter are D-fructose-amino acid or –polypeptide conjugates, owing to the natural abundance of D-glucose, the source sugar, and amino acids in proteins and in the free form. A number of bacterial, fungal and mammalian enzymes [3,4], carbohydrate transporters [5,6], and lectins [7] can bind amino acids and proteins decorated with D-fructosamine and other naturally occurring and synthetic ketosamines, such as 1-amino-1-deoxy-D-tagatose or lactulosamine. One mammalian enzyme, fructosamine-3-kinase-related protein (FN3K-RP) [8], can specifically recognize 1-amino-1-deoxy-D-psicose, although this aminosugar has not been structurally characterized, so far. While the physiological significance of 1-amino-1-deoxy-hexuloses to humans is not understood, clinical analysis of blood fructosamine has been in extensive use for decades [9] and, more recently, a therapeutic and chemopreventive potential of this class of carbohydrates, both naturally occurring and synthetic, has been assessed [10].

As a part of our structure-activity studies of ketosamines, we have prepared *N*-methyl-*N*-phenyl derivatives of 1-amino-1-deoxy-D-sorbose and 1-amino-1-deoxy-D-psicose which were successfully crystallized and allowed, for the first time, to obtain an accurate description of their structures through X-ray diffraction studies.

2. Results and discussion

1-Deoxy-1-(*N*-methylphenylamino)-D-sorbose (**1**) and 1-deoxy-1-(*N*-methylphenylamino)-D-psicose (**2**) were synthesized starting with *N*-methylaniline and, respectively, D-gulose or D-allose and

* Corresponding author.
E-mail address: mossinev@missouri.edu (V.V. Mossine).

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following a conventional Amadori rearrangement reaction protocol. In aqueous solutions, both compounds establish isomerization equilibria (Fig. 1), with the α-pyranose being a predominant anomeric form in **1** and with comparable proportions of the α-furanose, α-pyranose and β-pyranose in **2** (Table 1). There is a notably high (4%) proportion of the acyclic *keto* tautomer in **1**, which exceeds the percentages of α- and β-furanose and β-pyranose anomers in the equilibrium. Even higher (11%) proportion of the acyclic tautomer was found in solution of **2**. Previously reported estimates for the population of the acyclic forms of sorbose and psicose in aqueous solutions did not exceed 0.3% (Table 1). On the other hand, enhanced formation of the acyclic forms was observed in D-fructosamine derivatives with hydrophobic amino substituents that are in close proximity to the carbonyl group and apparently contribute to a significant increase in the acyclic *keto* tautomer proportion [11]. A similar phenomenon was reported for 1-deoxy-sorbose and 1-deoxy-psicose (Table 1), as well.

Crystalline **1** exists exclusively in the α-pyranose form, as evidenced by solid-state ^{13}C NMR data (Fig. 2a, Supplementary Table S1) and the following X-ray diffraction study. Crystallization of **2** afforded a mixture of the α-pyranose and α-furanose anomers (Fig. 2b, Supplementary Table S1). Suitable for the X-ray diffraction study monocrystals contained only one anomer, the α-pyranose.

The ORTEP views of the molecules and numbering of the atoms are shown in Figs. 3 and 4. Both molecules can be viewed as conjugates of 1-deoxy-D-sorbose or 1-deoxy-D-psicose and *N*-methylaniline jointed *via* the amino nitrogen atom. The α-D-pyranose rings in crystalline **1** and **2** exist in the $^5C_2$ chair conformation, with puckering parameters [19] for the α-D-sorbopyranose in **1**: $Q = 0.5830$ Å, $\theta = 2.01°$, and $\varphi = 265.02°$ and for the α-D-psicopyranose in **2**: $Q = 0.5632$ Å, $\theta = 3.60°$, and $\varphi = 249.24°$. The related $^2C_5$ α-L-sorbopyranose [12,20] and $^5C_2$ 1-deoxy-α-D-sorbopyranose [14,15] conformations exist as the major or the only structure in both solution equilibria and in crystalline state. These conformations are mirror equivalents and are very close to the sugar ring structure found in **1**. In contrast, two publications [16,17] on crystal structures of D-psicose report the $^2C_5$ β-D-psicopyranose conformers. Experimental determination of the 1-deoxy-α-D-psicopyranose conformation in solution was not conclusive [14], but modelling studies predicted a predominance of the $^5C_2$ and $^2C_5$ conformers, in the 5/1 ratio [21].

Bond distances and valence angles (Supplementary Table S3) in the carbohydrate parts of **1** and **2** compare well to the corresponding values found in α-L-sorbose [12], 1-deoxy-α-D-sorbose [15], β-D-psicose [16,17], three *N*-alkyl-*N*-phenyl derivatives of 1-amino-1-deoxy-D-fructose [11,22], and to the average values for a number of crystalline pyranose structures [23]. Noticeable features include the elongated C1–C2 and shortened N1–C7 bonds in **2**. The endocyclic torsions (Supplementary Table S4) do not differ significantly from the "standard" pyranoside torsions [23] with C–C–C–C (ring) at ~54°, C–C–C–O (ring) - at ~56°, and C–C–O–C - at ~60°. The exocyclic torsion angles O–C–C–O and O–C–C–C, which are located around the ring C–C bonds and involve at least one exocyclic oxygen atom, are close to the "ideal" 60° or 180°, as well.

One obviously outstanding feature of structure in **2** is found in the *anti-periplanar* disposition of N1 and O2 around the C1–C2 bond. In twenty known, so far, structures of 1-deoxy-1-amino-hexulopyranoses, the anomeric oxygen O2 and the amino N1 are invariably located in the *syn* disposition, possibly due to a stabilizing effect of the intramolecular hydrogen bond between the amino group and the pyranose ring O6, anomeric O2–H, or the exocyclic O3–H hydroxyl groups. Accordingly, short intramolecular heteroatom contacts around the amino group are a common feature of the H-bonding schemes in crystalline Amadori compounds. In 1-amino-1-deoxy-ketose derivatives with an uncharged amino group, the neighboring hydroxyl groups act as donors for the amine nitrogen acceptor, such as in **1** (Table 2, Fig. 3). When the amino group is protonated and charged, the ammonium group donates its hydrogen(s) to multicentered intramolecular H-bonding, with the anomeric O2, the ring O6, and/or exocyclic O3 acting as acceptors [24,25]. Remarkably, the amino nitrogen atom in **2** does not participate in any heteroatom contact. On the other hand, the mutual disposition geometry of N1 and H–C3 in **2** is such that this contact can be considered a weak C–H···N hydrogen bond (Supplementary Table S5). In addition, there are two weak intramolecular C–H···O contacts, namely C12–H···O3 and C13–HB···O6. These contacts and crystal packing forces could cooperate in stabilization of the unusual geometry in **2**, as discussed in further detail below.

Crystal packing and the intermolecular hydrogen bonds in the crystalline **1** are shown in Fig. 5a. The intermolecular H-bonding is localized in "hydrophilic" layers oriented along the crystallographic *ab* plane. Within the layers, a system of intermolecular heteroatom contacts (5 out of 6, see Table 2) is dominated by water molecules which thus serve as main nodes of the H-bonding network in **1**. A simplified graphical representation of the network is shown in

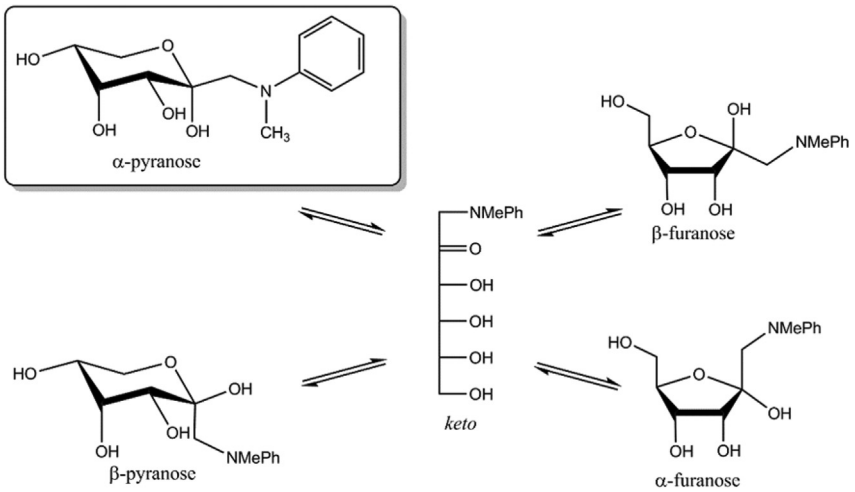

Fig. 1. Tautomeric equilibria in solutions of 1-amino-1-deoxy-hexuloses, exemplified here for 1-deoxy-1-(*N*-methylphenylamino)-D-psicose (**2**). See the Graphical Abstract for 1-deoxy-1-(*N*-methylphenylamino)-D-sorbose (**1**) drawing and Fig. 3 and 4 for ORTEP views of the α-pyranose conformations of **1** and **2**.