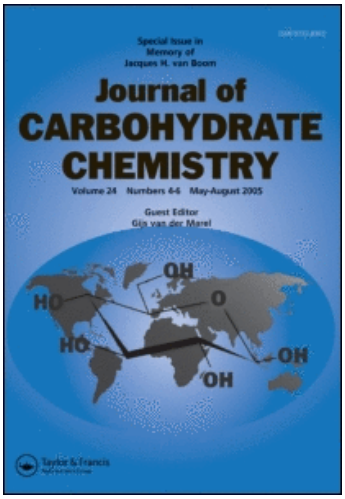


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

The Structure of *N*-(1-Deoxy-β-D-fructopyranos-1-yl)-L-proline Monohydrate ("D-Fructose-L-proline") and *N*-(1,6-Dideoxy-α-L-fructofuranos-1-yl)-L-proline ("L-Rhamnulose-L-proline")

Valeri V. Mossine[a]; Charles L. Barnes[b]; Thomas P. Mawhinney[a]
[a] Department of Biochemistry, University of Missouri, Columbia, MO, USA [b] Department of Chemistry, University of Missouri, Columbia, MO, USA

To cite this Article Mossine, Valeri V. , Barnes, Charles L. and Mawhinney, Thomas P.(2007) 'The Structure of *N*-(1-Deoxy-β-D-fructopyranos-1-yl)-L-proline Monohydrate ("D-Fructose-L-proline") and *N*-(1,6-Dideoxy-α-L-fructofuranos-1-yl)-L-proline ("L-Rhamnulose-L-proline")', Journal of Carbohydrate Chemistry, 26: 4, 249 — 266
To link to this Article: DOI: 10.1080/07328300701410718
URL: http://dx.doi.org/10.1080/07328300701410718

Journal of Carbohydrate Chemistry, 26:249–266, 2007

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300701410718

The Structure of *N*-(1-Deoxy-β-D-fructopyranos-1-yl)-L-proline Monohydrate ("D-Fructose-L-proline") and *N*-(1,6-Dideoxy-α-L-fructofuranos-1-yl)-L-proline ("L-Rhamnulose-L-proline")

Valeri V. Mossine

Department of Biochemistry, University of Missouri, Columbia, MO, USA

Charles L. Barnes

Department of Chemistry, University of Missouri, Columbia, MO, USA

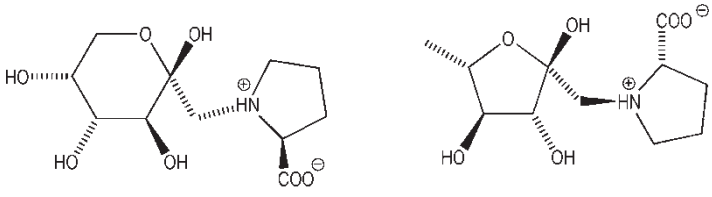
Thomas P. Mawhinney

Department of Biochemistry, University of Missouri, Columbia, MO, USA

D-Fructose-L-proline is an important food-related precursor for thermally generated aromas. We report the crystal structure analysis of *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-proline monohydrate **(1)** and its analog, *N*-(1,6-dideoxy-α-L-fructofuranos-1-yl)-L-proline ("L-rhamnulose-L-proline") **(2)**. The carbohydrate rings adopt the normal $^{2}C_{5}$ pyranose chair conformation in **1** and the ^{5}E furanose envelope conformation in **2**. Bond lengths and valence angles in **1** and **2** compare well with the average values from related pyranose and furanose structures. All hydroxyl and carboxyl oxygen atoms, ammonium groups, and the water molecule in **1** are involved in an extensive hydrogen bonding, which forms a system of infinite chains with attached side chains.

Received December 2, 2006; accepted April 4, 2007.
Address correspondence to Valeri V. Mossine, Department of Biochemistry, University of Missouri, Columbia, MO 65211, USA. E-mail: mossinev@missouri.edu

The hydrogen bonding network in **2** is an infinite three-dimensional network and is represented by separate short finite and infinite chains.



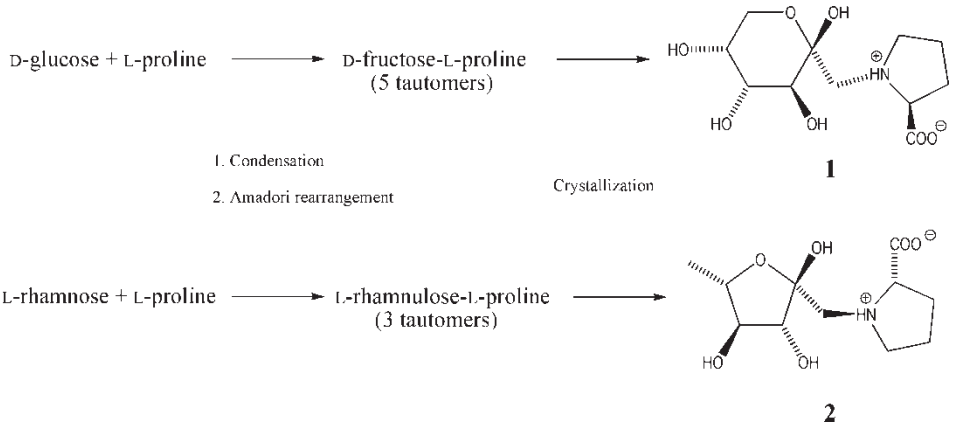
1 **2**

Keywords Amadori compound, Crystal structure, Fructose-amino acid, D-Fructose-L-proline, Rhamnulose-amino acid, L-Rhamnulose-L-proline

INTRODUCTION

The Maillard reaction is a term including a broad array of reactions originating from initial interactions between carbohydrates and amines, usually amino acids and proteins, which take place in foods upon their dehydrating and heating, and which, to a large extent, define organoleptic properties of the processed foods. Condensation reactions between aldose sugars and primary or secondary amines, followed by the nucleophile-catalyzed Amadori rearrangement, result in formation of 1-amino-1-deoxy-2-ketoses.[1] These compounds have been detected mostly in dried and stored[2,3] foods where they are believed to act as precursors of aroma, taste, and color compounds.[4,5] It has been established that the nature of both amino acid and reducing sugar determines the pattern of volatile products responsible for the generation of specific aromas in the reaction.

Proline is one of the most important amino acids in the field of the food-related Maillard reaction studies, due to its proven contribution to the largely attractive character of aromas of roasted foods produced in reactions of this amino acid with monosaccharides, primarily D-glucose. The Amadori rearrangement product of the reaction between L-proline and D-glucose (Sch. 1), D-fructose-L-proline, has been found in white vine,[6] Licorice root,[7] cured tobacco,[8] dried apricots and peaches,[2,9] malts, and beer.[10] Upon pyrolysis, D-fructose-L-proline produces a variety of volatile products[4,11–14] with characteristic caramel to nut-like aromas[15] and which are largely similar to the volatiles detected in proline-rich products, as well as D-glucose/L-proline model systems upon thermal treatment. This property of L-proline made it attractive in the food and tobacco industry as a means of improving the flavor of some products. For example, D-fructose-L-proline has long been



Scheme 1

considered as an ingredient for improving the flavor of tobacco.[7] On the other hand, replacement of D-glucose with other sugars, L-rhamnose in particular, was noted as a way to a further improvement of thermally generated aromas in foods.[16] The Amadori compound from L-rhamnose/L-proline reaction (Sch. 1), L-rhamnulose-L-proline, has been prepared,[17] and its thermal degradation products were studied as well.[18]

While a number of researchers used solid Amadori compounds in attempts to model the Maillard reaction, care should be taken when considering mechanistic aspects of the reaction pathways. As derivatives of reducing sugars, Amadori compounds in solutions establish an equilibrium between acyclic, pyranose, and furanose tautomeric forms, which would be expected to display different reactivity in the model reactions. Therefore, accurate structural information about solid 1-ketosamines is needed. To date, structures of only five Amadori compounds derived from amino acids have been characterized precisely, using X-ray diffraction methods (Table 1), and only two of

Table 1: Reported crystal structures of ketose-amino acids (Amadori compounds).

	Compound	Carbohydrate tautomer	Ref.
1.	D-Fructose-glycine	β-D-Fructopyranose	(19)
2.	Di-D-fructose-glycine	β-D-Fructopyranose and acyclic hemiketal	(20)
3.	D-Xylulose-glycine	Acyclic D-xylulose	(21)
4.	D-Fructose-L-histidine	β-D-Fructopyranose	(22)
5.	2,3:4,5-Di-*O*-isopropylidene-D-fructose-L-tyrosine benzyl ester	β-D-Fructopyranose	(23)
6.	D-Fructose-L-proline	β-D-Fructopyranose	This work
7.	L-Rhamnulose-L-proline	α-L-6-Deoxy-fructofuranose	This work

them represent truly food-relevant compounds, namely D-fructose-glycine and D-fructose-L-histidine.

In this report, we present X-ray diffraction data analysis on two L-proline-derived Amadori compounds, crystalline *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-proline monohydrate **(1)** and *N*-(1,6-dideoxy-α-L-fructofuranos-1-yl)-L-proline ("L-rhamnulose-L-proline") **(2).** The ring conformation, calculated bond distances, valence, and torsion angles in the sugar portion of **1** are compared with corresponding values for β-D-fructopyranose and *N*-(1-deoxy-β-D-fructopyranos-1-yl)-amino acids, while the respective parameters of **2** are compared to those in the isostructural fragments of crystalline L-rhamnulose-dibenzylamine and some α-furanoses; the amino acid portions of **1** and **2** are compared to crystalline proline and *N*-methylproline structures.

EXPERIMENTAL

The proline Amadori compounds were from a collection previously prepared in our laboratory using published general methods.[15,17]

N-(1-Deoxy-β-D-fructopyranos-1-yl)-L-proline monohydrate was crystallized from a saturated aqueous solution of D-fructose-L-proline over 2 weeks at 4°C, while *N*-(1,6-dideoxy-α-L-fructofuranos-1-yl)-L-proline formed crystals from a methanol/acetone (1:1) solution of L-rhamnulose-L-proline overnight at rt. The crystals were obtained as colorless prisms.

Crystal data and experimental details of the crystallographic studies are given in Table 2. The crystal structure was solved with the direct methods program SHELXS-97[24] and refined by full-matrix least squares techniques with the SHELXL-97[25] suite of programs, with the help of X-Seed.[26] Data were corrected for Lorentz and polarization effects and for absorption. Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydroxyl and ternary ammonium hydrogen atoms were located in difference Fourier maps and were refined with fixed isotropic thermal parameters. The remaining H-atoms were placed at calculated positions and included in the refinement using a riding model.

RESULTS AND DISCUSSION

The ORTEP view and atom numbering of the molecules **1** and **2** are shown in Figures 1 and 2, respectively. Both **1** and **2** may be considered as conjugates of an amino sugar and an amino acid jointed via the common amino group. The amino sugar is a 1-amino-1-deoxy-D-fructose in **1** and 1-amino-1,6-dideoxy-L-fructose in **2**, and the amino acid is L-proline in the zwitterion form with a positively charged tetrahedral ternary ammonium nitrogen and a negatively charged deprotonated carboxyl group.

Table 2: Crystal data, structure determination, and refinement data for **1** and **2**.

	1	**2**
Empirical formula	$C_{11}H_{19}NO_7 \times H_2O$	$C_{11}H_{19}NO_6$
Formula weight	295.29	261.27
Crystal system, space group	Monoclinic, $P2_1$	Orthorhombic, $P2_12_12_1$
Unit cell dimensions		
a(Å)	10.1799(6)	7.7096(4)
b(Å)	5.3993(3)	11.322(2)
c(Å)	12.6754(7)	15.307(3)
β(°)	104.722(1)	
U(Å^3)	673.82(7)	1336.2(4)
Z	2	4
Crystal size, mm	$0.5 \times 0.3 \times 0.1$	$0.4 \times 0.1 \times 0.1$
Calculated density (g · cm^{-3})	1.455	1.299
μ(cm^{-1})	1.24	1.06
F(000)	316	560
Diffractometer	Enraf-Nonius CAD4	
Radiation MoKα, graphite monochromator		$\lambda = 0.71073$Å
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Temperature (K)	173 ± 2	173 ± 2
Data collection range	$1.66 < \theta < 27.15°$	$2.24 < \theta < 27.12°$
Limiting indices	$-11 \le h \le 13$, $-6 \le k \le 6$, $-16 \le l \le 16$	$-8 \le h \le 9$, $-14 \le k \le 14$, $-19 \le l \le 19$
No. of observed/unique data	4844/1632 ($R_{int} = 0.0196$)	9314/1711 ($R_{int} = 0.0088$)
Completeness to $\theta = 27.15°$	98.7%	99.8%
Max/min transmission	0.99/0.72	0.99/0.74
No. of restraints/parameters	1/209	0/176
R indices (all data)	$R_1 = 0.0311$, $wR_2 = 0.0761$	$R_1 = 0.1049$, $wR_2 = 0.1630$
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0292$, $wR_2 = 0.0748$	$R_1 = 0.0639$, $wR_2 = 0.1442$
Goodness of fit on F^2	1.056	1.041
Absolute structure parameter	0 (10)	0 (10)
Largest difference peak and hole (e Å^{-3})	0.220 and −0.160	0.264 and −0.277

Ring Conformations

The β-D-pyranose ring of the crystalline **1** exists in the $^2C_5$ or 1C(D) chair conformation, with puckering parameters[27] $Q = 0.5511$ Å, $\theta = 173.68°$, and $\varphi = 133.00°$. This conformation has the lowest energy[28] among all possible fructose tautomers and is the major component of an equilibrium mixture of the tautomeric forms of 1-amino-1-deoxy-D-fructose derivatives, including

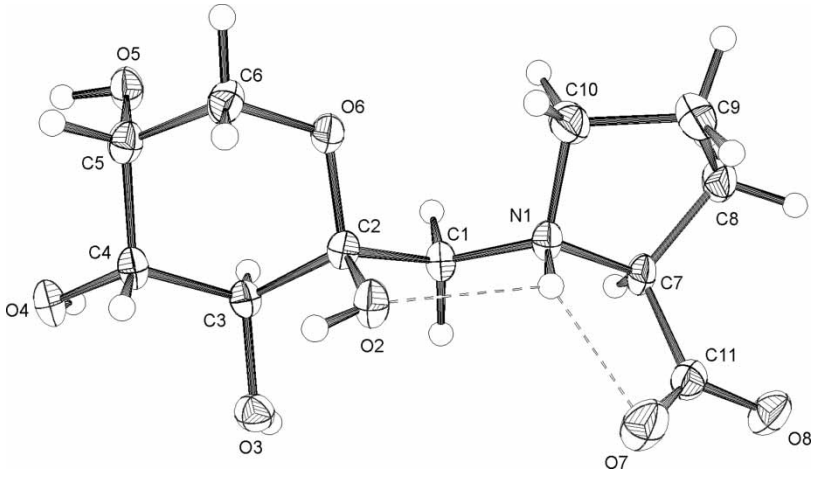


Figure 1: Atomic numbering and thermal ellipsoids (50% probability) for molecular conformation of crystalline *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-proline monohydrate. Intramolecular hydrogen bonds are shown as dotted lines.

D-fructose-L-proline, in aqueous solutions, as evidenced by the ^{1}H and ^{13}C NMR data.[29–31] In crystalline forms of D-fructose-glycine,[19] D-fructose-L-histidine,[22] and D-fructose,[32,33] the pyranose rings assume the same conformations.

L-Rhamnulose-L-proline crystallized in form of the α-anomer, with the furanose ring in the ^{5}E conformation. Puckering parameters for the α-furanose ring in **2** are $Q = 0.3986$ Å and $\varphi = 148.45^{\circ}$, and the pseudorotational parameters[34] are $P = 240.6^{\circ}$, with $\tau_m = 43.4^{\circ}$ for the C3-C4 bond. In contrast, crystalline L-rhamnulose-dibenzylamine[35] was obtained from a diethyl ether/petroleum ether mixture as the β-anomer, with the fructofuranose ring in the $^{3}T_2$ conformation. Both anomers equally populate the tautomeric equilibrium that establishes in the aqueous solution of L-rhamnulose-L-proline, according to the NMR measurements,[17] and both conformations fit well into the calculated energy minima for the respective furanose anomeric configurations.[28] Data on X-ray diffraction studies of α-fructofuranose structures are scarce in the literature, mostly related to fructose anhydrides, and do not compare well. For example, in crystalline peracetylated α-D-fructofuranose-β-D-fructofuranose 1,2′:2,6′ dianhydride, the α-furanose ring is in energetically unfavorable E_2 conformation,[36] possibly due to sterical constraints imposed by the rest of the molecule. However, in another reported crystalline 3,4,3′,4′-tetra-*O*-acetyl-6,6′-di(triphenylmethy)-α-D-fructofuranose-β-D-fructofuranose 1,2′:2,1′ dianhydride, the α-furanose ring is in E_5 conformation.[37] Diánez et al. have reported the only known structure of an Amadori glycoside, allyl 1-deoxy-1-[(1-methyl-2-benzoylvinyl)-amino]-α-D-fructofuranoside.[38] The carbohydrate ring in this molecule has

an unsymmetrical twist conformation $^{3}T_{2}$, which relates to the secondary energy minimum on the conformation-energy surface for α-furanoses.[28] In a crystal of 1-cyclohexylamino-1,6-dideoxy-α-D-tagatofuranose-6-*C*-sulfonic acid,[39] the sugar ring of this Amadori compound assumes a conformation intermediate between E_5 and $^{4}T_{5}$; it is also in the same energy minimum as the conformation of **2**. In crystalline methyl α-D-arabinofuranoside,[40] which is a configurational equivalent to the carbohydrate ring in **2**, the ring conformation is E_4 and thus is a mirror image of the ring form ^{5}E in **2**.

Therefore, it can be concluded that in both **1** and **2**, the sugar rings adopt conformations that are energetically favorable and were previously observed experimentally for the respective ring configurations. To the best of our knowledge, **2** represents the first crystal structure of a reducing ketose derivative in the α-fructofuranose configuration.

The pyrrolidine ring of the proline in **1** is in a C_s-C^{γ}-*endo* (envelope on C9) conformation, while in **2** it adopts a C_2-C^{γ}-*endo* (half-chair, twisted on C8-C9) conformation. Puckering parameters for the pyrrolidine ring in **1** are $Q = 0.4317$ Å and $\varphi = 113.00^{\circ}$, and the pseudorotational parameters are $P = 275.4^{\circ}$, with $\tau_m = 44.8^{\circ}$ for the N1-C7 bond. In **2** they are $Q = 0.4177$ Å, $\varphi = 90.37^{\circ}$, and $P = 253.0^{\circ}$, with $\tau_m = 43.6^{\circ}$ for the N1-C7 bond. For the comparison, the envelope ring conformations close to that in **1** have been reported for proline residues in some crystalline peptides,[41] while the twisted ring conformation in **2** is closer to those found in crystals of L-proline,[42] DL-proline,[43] and small peptides.[41] In contrast, the pyrrolidine ring in *N*-methyl-L-proline (hygric acid) monohydrate[44] or hydrochloride[45] accepts rare C_2-N-*endo* conformations.

Bond Distances

Bond distances in the fructopyranose part of **1** (Table 3) are similar (in e.s.d. range) to the corresponding values for β-D-fructose[32,33] and D-fructose-amino acids[19,22] and to the average values for a number of crystalline pyranose structures.[28,46] The mean values of C-C and C-O bond lengths in the β-D-fructopyranosyl portion of **1** (1.527 Å and 1.424 Å correspondingly) agree well with the corresponding values for β-pyranoses. The 1,6-dideoxy-α-L-fructofuranose in **2** also has no significant deviations in the mean bond distances (1.523 Å and 1.421 Å correspondingly) from those determined for the β-fructopyranose in **1**, the β-fructofuranose in L-rhamnulose-dibenzylamine,[35] and the averaged values for furanose structures.[40,47] In the proline part of both **1** and **2**, the N1-C7 bond (Table 3) is about 0.04 Å longer than respective bonds in a number of known proline structures,[41,43,45,48] while the rest of the bond lengths compare well. Differences were observed with respect to the carboxyl-oxygen bond lengths for **1** and **2**. For **1**, one of the bonds is longer than the other, while, for **2**, both are approximately equal

Table 3: Bond distances (Å) and angles (°) for crystalline **1** and **2**.

	1	**2**		**1**	**2**
Bond distances			*Valence angles*		
C1-C2	1.532(4)	1.511(6)	N1-C1-C2	111.8(2)	115.1(4)
C2-C3	1.539(5)	1.536(6)	C1-C2-C3	108.0(3)	114.7(3)
C3-C4	1.528(4)	1.527(6)	O2-C2-C3	114.4(3)	108.6(4)
C4-C5	1.532(4)	1.518(6)	O2-C2-C1	107.0(2)	107.8(4)
C5-C6	1.505(5)	1.524(6)	O2-C2-O5		110.5(3)
O5-C2		1.433(5)	O2-C2-O6	111.2(2)	
O6-C2	1.425(4)		C1-C2-O5		109.3(4)
C1-N1	1.485(4)	1.489(6)	C1-C2-O6	105.9(3)	
C2-O2	1.405(4)	1.405(5)	O5-C2-C3		105.8(4)
C3-O3	1.418(4)	1.428(5)	O6-C2-C3	110.0(2)	
C4-O4	1.421(4)	1.409(5)	C2-C3-C4	112.6(3)	104.3(3)
C5-O5	1.436(4)	1.428(6)	C2-C3-O3	109.9(3)	109.2(4)
C6-O6	1.438(4)		O3-C3-C4	109.5(3)	113.6(4)
N1-C7	1.526(4)	1.524(5)	C3-C4-C5	111.3(3)	102.2(3)
C7-C8	1.529(4)	1.520(6)	O4-C4-C3	111.0(2)	114.6(4)
C7-C11	1.535(4)	1.543(6)	O4-C4-C5	111.4(3)	111.9(4)
C11-O6		1.248(5)	C4-C5-C6	109.3(3)	114.4(4)
C11-O7	1.235(4)	1.258(5)	C4-C5-O5	110.8(3)	103.1(4)
C11-O8	1.262(4)		O5-C5-C6	109.3(3)	109.5(4)
C8-C9	1.519(4)	1.514(8)	C5-C6-O6	110.9(2)	
C9-C10	1.517(4)	1.491(7)	C5-O5-C2		106.4(3)
C10-N1	1.506(4)	1.509(6)	C6-O6-C2	113.5(2)	
			N1-C7-C11	106.7(3)	107.5(3)
Exocyclic torsion angles			C8-C7-C11	113.7(2)	113.9(4)
N1-C1-C2-C3	−166.5(2)	+66.3(5)	C8-C7-N1	104.8(1)	103.9(3)
N1-C1-C2-O2	−42.9(3)	−172.6(4)	C7-C8-C9	104.1(2)	103.0(4)
N1-C1-C2-O5		−52.3(5)	C8-C9-C10	101.7(3)	102.0(4)
N1-C1-C2-O6	+75.8(3)		N1-C10-C9	102.8(3)	106.0(4)
C1-C2-C3-C4	−165.6(2)	−124.6(4)	C7-C11-O6		116.7(4)
C1-C2-C3-O3	+72.0(3)	−2.9(5)	C7-C11-O7	118.2(3)	116.0(4)
O5-C2-C3-O3		+117.7(4)	C7-C11-O8	114.4(3)	
O6-C2-C3-O3	−173.0(2)		O6-C11-O7		127.4(4)
O2-C2-C3-C4	+75.4(3)	+114.6(4)	O7-C11-O8	127.3(3)	
O2-C2-C3-O3	−47.1(3)	−123.6(4)	C10-N1-C7	106.8(3)	106.3(3)
C2-C3-C4-O4	+173.0(2)	−142.0(4)	C10-N1-C1	116.2(3)	112.2(4)
O3-C3-C4-O4	−64.4(3)	+99.2(5)	C1-N1-C7	114.1(2)	115.6(3)
O3-C3-C4-C5	+171.1(3)	−139.6(4)			
C3-C4-C5-C6		+157.7(4)	*Proline torsion angles*		
C3-C4-C5-O5	+69.2(3)		C1-N1-C7-C11	−105.0(3)	−126.6(4)
O4-C4-C5-C6	−175.6(2)	−79.3(5)	C1-N1-C7-C8	+134.1(3)	+112.3(4)
O4-C4-C5-O5	−55.1(3)	+162.0(4)	C1-N1-C10-C9	−158.3(4)	−141.5(4)
O5-C5-C6-O6	−63.4(3)		O6-C11-C7-N1		0.0(5)
C5-O5-C2-C1		+153.6(4)	O7-C11-C7-N1	+3.6(3)	−179.0(4)
C5-O5-C2-O2		−87.9(4)	O8-C11-C7-N1	−176.3(3)	
C6-C5-O5-C2		−165.4(4)	O6-C11-C7-C8		+114.5(4)
C6-O6-C2-C1	+174.7(2)		O7-C11-C7-C8	+118.7(4)	−64.4(5)
C6-O6-C2-O2	−69.4(3)		O8-C11-C7-C8	−61.3(3)	
C2-C1-N1-C7	+167.3(2)	+84.5(4)	N1-C7-C8-C9	+22.9(4)	+34.7(5)

(*continued*)

Table 3: Continued.

	1	2		1	2
C2-C1-N1-C10	−67.8(2)	−153.4(4)	C11-C7-C8-C9	−93.3(4)	−81.9(5)
			C7-C8-C9-C10	−41.2(4)	−43.6(5)
Endocyclic torsion angles			C8-C9-C10-N1	+43.5(4)	+35.7(5)
C2-C3-C4-C5	+48.4(3)	−20.8(4)	C9-C10-N1-C7	−29.7(4)	−14.3(5)
C3-C4-C5-C6	−51.2(3)		C10-N1-C7-C8	+4.2(3)	−12.9(5)
C4-C5-C6-O6	+58.0(3)		C10-N1-C7-C11	+125.2(4)	+108.2(4)
C5-C6-O6-C2	−63.8(3)				
C6-O6-C2-C3	+58.3(3)				
O6-C2-C3-C4	−50.6(3)				
C3-C4-C5-O5		+38.9(4)			
C4-C5-O5-C2		−43.3(4)			
C5-O5-C2-C3		+29.5(4)			
O5-C2-C3-C4		−4.0(4)			

(Table 3). The elongation of one of the two carboxyl bonds in **1**, also seen in L- and DL-proline structures,[42,43,48] may be ascribed to an unequal participation of the carboxylate oxygen atoms in hydrogen bonding, as discussed below.

Valence Angles

The values of the fructopyranose valence angles for **1** (Table 3), D-fructose-glycine,[19] and β-D-fructose[33] differ more than 2° for the O-C-C angle type where O = O2, O3, and O5. These heteroatoms are involved in strong hydrogen bonding, both in the D-fructose-amino acids and in β-D-fructopyranose.[33] Most of valence angles of the β-D-fructopyranosyl rings in these molecules are close to the average values[46] of 110° to 111° for a tetrahedral structure. The ring bond angles in **2** are significantly, 4° to 9°, smaller than respective angles in **1**, due to steric constraints in the furanose ring. However, the angle values for **2** compare well, with the exception of the C2-C3-O3 angle, within 3°, with respective values in L-rhamnulose-dibenzylamine[35] and the averaged values for furanosides.[40,47] There is also a great deal of similarity in the valence angles for reported proline structures and the amino acid portion of the Amadori compounds **1** and **2** (Table 3). The carboxyl group in **1** shows a small dissymmetry due to unequal participation of the oxygens in hydrogen bonding (see below).

Torsion Angles

The endocyclic pyranose torsion angles of **1** (Table 3) differ from the corresponding angles for β-D-fructose[33] and D-fructose-glycine[19] by 1.5° to 6° and

fall into the range from 48.4° to 63.8°, which is significantly broader than that observed for the reference structures. Consequently, the pyranose ring conformation in **1** is more significantly deviated from the "standard" pyranosides,[46] which show C-C-C-C(ring) torsion angles to be 53°, C-C-C-O(ring) at 56° to 57°, and C-C-O-C at 60° to 64°, as compared to β-D-fructose and D-fructose-glycine.

The values of the exocyclic angles around ring bonds in **1** are close to the corresponding torsion angles of β-D-fructose and D-fructose-glycine. However, the pyranose structure in **1** shows greater deviation in range and means from "ideal" 180° or 60° of values for these torsion angles, specifically 165.6° to 175.6° (172.2°) and 47.1° to 75.4° (64.5°), as compared to the reference β-D-fructopyranosyl rings.

The endocyclic furanose torsion angles of **2** (Table 3) may be compared to the corresponding angles for 3,4,3′,4′-tetra-*O*-acetyl-6,6′-di(triphenylmethy)-α-D-fructofuranose-β-D-fructofuranose 1,2′:2,1′ dianhydride[37] and methyl α-D-arabinofuranoside,[49] which are configurationally and conformationally close to the enveloped ring in **2**. Indeed, the average difference between the respective angles in **2** and methyl α-D-arabinofuranoside is 1.3°, and this difference is even lower, only 0.4°, between the bond torsions in **2** and the fructose dianhydride. Similarly, the values of the exocyclic angles around ring bonds in **2** are close to the corresponding values of torsion angles in the reference α-furanosyl rings, with the average difference nearing 4°.

The conformation around the C1-C2 bond in crystalline Amadori compounds is of interest, since in ^{1}H NMR spectra of virtually all D-fructose-α-amino acids in D_2O, the resonance signals of the two protons at C1 are split, pointing at their nonequivalence.[29–31] This indicates that in the timeframe of the NMR experiment, rotation around C2-C1 and C1-N1 bonds is restricted, most likely due to the multicentered intramolecular hydrogen bonding. D-Fructose-L-proline has the *gauche-trans* conformation, distorted by 15° relative to a staggered position. The undistorted *gt* conformation was observed in the β-D-fructose-calcium chloride complex[32] and D-fructose-L-histidine.[22] In contrast, the *gauche-gauche* relationship around C1-C2 was found in crystalline anhydrous β-D-fructose,[33] and the *trans-gauche* conformation, also shifted by 15°, we observed in D-fructose-glycine.[19] In crystalline **2**, the conformation around C2-C1 is *gg* and is more relaxed (distorted by 7°) than in **1**. For the comparison, in other known furanose structures of Amadori compounds, there is the *tg* arrangement in allyl 1-deoxy-1-[(1-methyl-2-benzoylvinyl)amino]-α-D-fructofuranoside,[38] *gt* (distorted by 21°) in L-rhamnulose-dibenzylamine,[35] and *gg* in 1-cyclohexylamino-1,6-dideoxy-α-D-tagatofuranose-6-*C*-sulfonic acid.[39]

Torsion angles in the amino acid portions of **1** and **2** do not differ more than 25°: the most significant conformational difference between the proline residues is observed around the N1-C7 bond (Table 3). The carboxylate C11 carbons are in *trans* configuration relative to the carbohydrate C1 atoms and

are in eclipsed, *anti*-synclinal conformation around the N1-C7 bond (distorted by 45° and 53° relative to the staggered structure in, correspondingly, **1** and **2**); the respective *trans* configurations were found around N-Cα bonds in crystalline *N*-methyl-L-proline[44,45] as well.

Hydrogen Bonding and Crystal Structure

In the crystal structure of **1** we have found eight pairs of heteroatom contacts (distance <3.20 Å), which form the intra- and intermolecular hydrogen bonding network (Table 4). All hydroxyl groups and the ammonium group act as hydrogen donors, while the water molecule allocates two hydrogen atoms to the network. The water and all hydroxyl oxygen atoms participate in the hydrogen bonding as acceptors, including the anomeric O2. The participation of anomeric or ring oxygen atoms in H-bonding as acceptors is not common for carbohydrate structures.[50] However, in the reference structures of D-fructose-glycine[19] and D-fructose-L-histidine,[22] both atoms do participate as the acceptors, while in crystalline β-D-fructose, the anomeric O2 atom appears to be the acceptor in two hydrogen bonds.[33] Each of the two carboxyl oxygen atoms participates in hydrogen bonding, but unequally: O8 is involved in two contacts, while O7 acts only once as an acceptor. The interaction involving the ammonium hydrogen is of the asymmetrical bifurcated[51] type: it involves donors from a carbohydrate hydroxyl and amino acid carboxylate groups of the molecule.

Table 4: Hydrogen-bonding network in *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-proline monohydrate **(1)** and *N*-(1,6-dideoxy-α-L-fructofuranos-1-yl)-L-proline **(2)**.

D-H...A	D...A(Å)	D-H(Å)	H...A(Å)	∠(D-H...A)(°)
Hydrogen bonding in **1**				
O2-H2O...O5[a]	2.971	0.80	2.20	164
O3-H3O...O8[b]	2.594	0.85	1.76	170
O4-H4O...O1W[c]	2.740	0.86	1.88	178
O5-H5O...O4[d]	2.759	0.86	1.91	169
N1-H1 N...O2	2.686	0.86	2.29	109
N1-H1 N...O7	2.586	0.86	1.99	125
O1W-H1W...O8[e]	2.782	0.90	1.89	169
O1W-H2W...O3[f]	2.754	0.80	1.96	168
Hydrogen bonding in **2**				
O2-H2O...O7[g]	2.853	0.82	2.06	164
O3-H3O...O6[h]	2.706	0.77	1.94	174
O4-H4O...O7[h]	2.780	0.98	1.82	165
N1-H1 N...O6	2.584	0.93	2.01	119
N1-H1 N...O3	2.803	0.93	2.23	119

Symmetry codes: [a] x,y + 1,z; [b] − x + 1,y − (1/2), − z + 1; [c] x,y − 1,z; [d] − x,y − (1/2), − z; [e] − x + 1,y + (1/2), − z + 1; [f] x,y,z; [g] − x + 1,y − (1/2), − z + (1/2); [h] x − (1/2), − y + (1/2), − z + 1.

This type of hydrogen bonding appears to be a common feature for all known D-fructose-amino acid structures.[19,20,22]

The hydrogen bonding in **2** is less extensive than that found in **1**, due to one oxygen atom less in the molecule and the lack of cocrystallized water. There are only five types of hydrogen bonds in crystalline **2** (Table 4). All three hydroxyl groups and the ammonium group donate the hydrogens into the H-bonding network. However, only three oxygens, the carbohydrate O3 and the carboxylate O6 and O7, act as the acceptors. The negatively charged carboxylate group thus acts as an acceptor in four out of five types of hydrogen bonding in crystalline **2**. The ammonium hydrogen is involved in a symmetrical bifurcated bond, which, as in **1**, involves acceptors of both carbohydrate and carboxylate origin.

Intramolecular hydrogen bonding in crystalline **1** is represented by the above-mentioned bifurcated type for the ammonium hydrogen, which bridges the anomeric (O2) and the amino acid (O8) oxygen atoms forming two conjugated pseudocycles: one six-membered with sugar atoms and another five-membered with amino acid atoms, as shown in Figure 1. In a similar fashion, the intramolecular bonding in **2** is organized around the ammonium group, which is hydrogen-bonded to the carbohydrate O3 and carboxylate O6 (Fig. 3). This type of three-centered hydrogen bonding may contribute to the stabilization of specific torsions around C1-C2 in the Amadori compounds and may serve as an explanation for the observed restricted rotation around the C1-C2 bond in aqueous solutions, as mentioned above. In contrast, when the amino group cannot form H-bonded conjugation between the carbohydrate and the aglycon, such as in D-fructose-ω-amino acids[29,31] or in Amadori compounds derived from aromatic/aliphatic amines,[52] there is a free rotation around C1-C2 in water (but not in organic solvent!) regardless of presence of intermolecular H-interactions between the amino group and the sugar in the solid state.

In the crystal structure of **1**, the D-fructose-L-proline molecules are packed such that both the pyranose and the pyrrolidine ring planes are approximately oriented along the crystallographic ***xz*** plane and are stacked along the axis ***y***. In the hydrogen-bonded network of crystalline **1**, the water molecules determine half of all intermolecular contacts and act as bridges between D-fructose-L-proline molecules, both within and between the stacks (Fig. 2). The intermolecular hydrogen bonding forms two-molecule-thick layers, which are infinite along {1 0 1} and {0 1 0}. Within the layers, the stacks are held together by water and O2-H···O5 bonds. These stacks are then cross-linked via strong O3-H···O8 and O5-H···O4 intermolecular hydrogen bonds, as well as water molecules. The layers apparently interact through van-der-Waals forces. Taken together, the intra- and intermolecular hydrogen bonds in **1** form a system of antidromic infinite chains that coil along the ***y*** axis. Small homodromic finite chains are attached to these via the water molecule, as shown in Scheme 2.

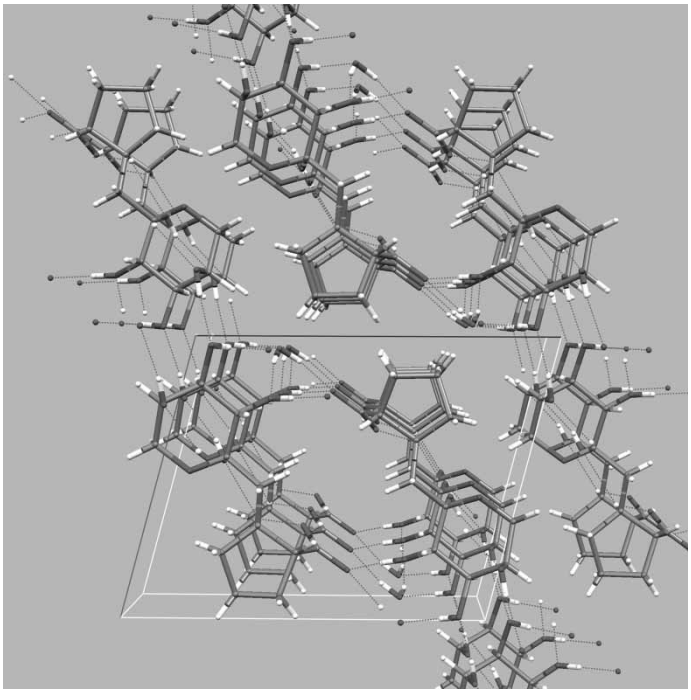


Figure 2: A prospective view along axis ***y*** on the crystal packing and hydrogen bonding in *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-proline monohydrate. Color code for the axes: ***x,*** red; ***y,*** green; ***z,*** blue.

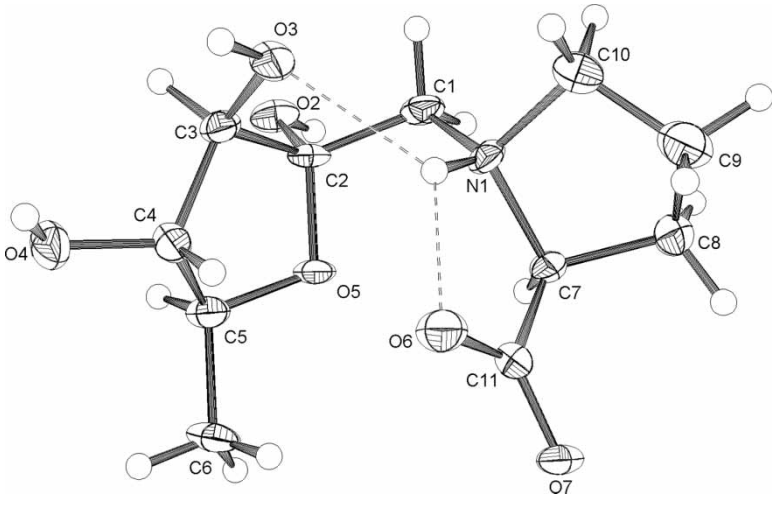


Figure 3: Atomic numbering and thermal ellipsoids (50% probability) for molecular conformation of crystalline *N*-(1,6-dideoxy-α-L-fructopyranos-1-yl)-L-proline.

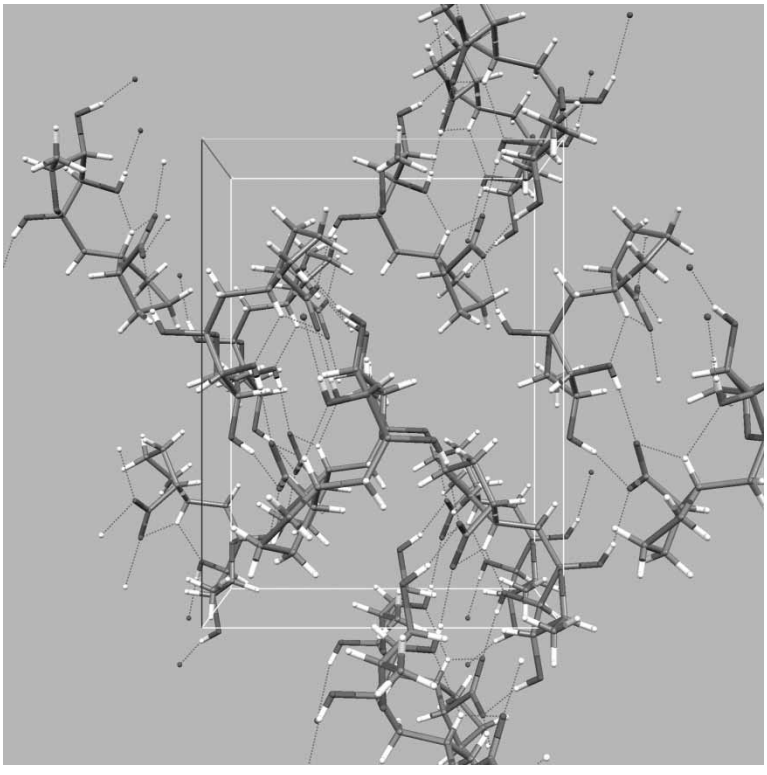
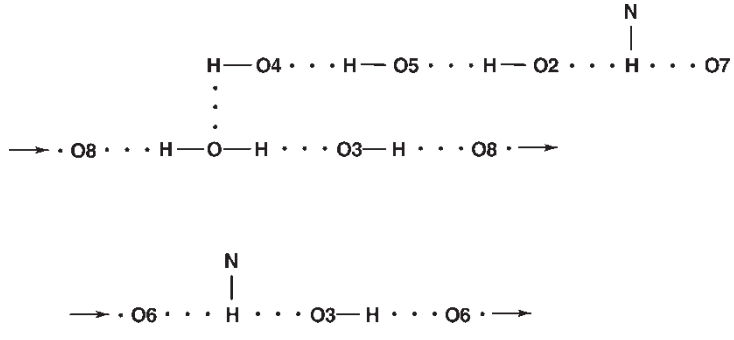


Figure 4: A prospective view along axis ***x*** on the crystal packing and hydrogen bonding in *N*-(1,6-dideoxy-α-L-fructopyranos-1-yl)-L-proline.

The crystal structure in **2** is an infinite three-dimensional network. Intermolecular hydrogen bonds connect molecules of **2** in all directions and throughout the crystal. Together with the intramolecular hydrogen bonds in **2**, they form a system of antidromic infinite chains (Fig. 4, Scheme 2), which coil along the ***x*** axis. In addition, there are short three-centered bonds



Scheme 2: Infinite patterns of hydrogen bonding in **1** (top) and **2** (bottom).

O4-H···O7···H-O2 in the crystal of **2**. The comprehensive character of the hydrogen bonding network and a lack of a cosolvent in crystalline **2** may contribute to a greater thermal stability of solid L-rhamnulose-L-proline as compared to D-fructose-L-proline (reported[17,53] melting points are ~119°C and ~145°C for **1** and **2**, respectively), despite the greater total number of hydrogen bonds in **1**, and though **1** has a greater density than **2**.

SUPPLEMENTARY DATA

Complete crystallographic data for **1** and **2** have been deposited with the Cambridge Crystallographic Data Centre, CCDC 631528 and 631529, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

REFERENCES

[1] Paulsen, H.; Pflughaupt, K.-W. Glycosylamines. In *The Carbohydrates. Chemistry and Biochemistry*; Pigman, W. and Horton, D., Eds.; Academic Press: New York, 1980, Vol. IB, pp. 881–927.

[2] Anet, E.F.L.J.; Reynolds, T.M. Chemistry of nonenzymic browning. I. Reactions between amino acids, organic acids, and sugars in freeze-dried apricots and peaches. Aust. J. Chem. **1957**, *10*, 182–192.

[3] Guyomarc'h, F.; Warin, F.; Muir, D.D.; Leaver, J. Lactosylation of milk proteins during the manufacture and storage of skim milk powders. Int. Dairy J. **2000**, *10*, 863–872.

[4] Vernin, G.; Debrauwer, L.; Vernin, G.M.F.; Zamkotsian, R.-M.; Metzger, J.; Larice, J.L.; Párkányi, C. Heterocycles by thermal degradation of Amadori intermediates. In *Off-Flavors in Foods and Beverages*; Charalambous, G.; Amsterdam, Ed.; Elsevier 1992, pp. 567–623.

[5] Yaylayan, V.A. Recent advances in the chemistry of Strecker degradation and Amadori rearrangement: implications to aroma and color formation. Food Sci. Technol. Res. **2003**, *9*, 1–6.

[6] Hashiba, H. Isolation and identification of Amadori compounds from miso, white wine and sake. Agric. Biol. Chem. **1978**, *42*, 1727–1731.

[7] Nishi, H.; Morishita, I. Components of Licorice root used for tobacco flavoring. I. Fractionation of the substances in Licorice root effective in improving the tobacco smoking quality. Nippon Nogei Kagaku Kaishi **1971**, *45*, 507–512.

[8] Tomita, H.; Noguchi, M.; Tamaki, E. Chemical studies on ninhydrin-positive compounds in cured tobacco leaves. Part II. Isolation of 1-deoxy-1-L-prolino-D-fructose. Agric. Biol. Chem. **1965**, *29*, 515–519.

[9] Davidek, T.; Kraehenbuehl, K.; Devaud, S.; Robert, F.; Blank, I. Analysis of Amadori compounds by high-performance cation exchange chromatography coupled to tandem mass spectrometry. Anal. Chem. **2005**, *77*, 140–147.

[10] Wittmann, R.; Eichner, K. Detection of Maillard products in malts, beers, and brewing colorants. Z. Lebensmitt. Untersuch.-Forsch. **1989**, *188*, 212–220.

[11] Yaylayan, V.A.; Sporns, P. Novel mechanisms for the decomposition of 1-(amino acid)-1-deoxy-D-fructoses (Amadori compounds): a mass spectrometric approach. Food Chem. **1987**, *26*, 283–305.

[12] Shigematsu, H.; Shibata, S.; Kurata, T.; Kato, H.; Fujimaki, M. Thermal degradation products of several Amadori compounds. Agric. Biol. Chem. **1977**, *41*, 2377–2385.

[13] Huyghues-Despointes, A.; Yaylayan, V.A.; Keyhani, A. Pyrolysis GC/MS analysis of 1-[(2′-carboxyl)pyrrolidinyl]-1-deoxy-D-fructose (Amadori-proline). J. Agric. Food Chem. **1994**, *42*, 2519–2524.

[14] Debrauwer, L.; Vernin, G.; Metzger, J.; Sioufi, A.M.; Larice, J.L. Kinetics of formation and thermal degradation of the fructose-proline Amadori intermediate (glucose + proline). Bull. Soc. Chim. Fr. **1991**, *128*, 244–254.

[15] Mills, F.D.; Hodge, J.E. Amadori compounds: vacuum thermolysis of 1-deoxy-1-L-prolino-D-fructose. Carbohydr. Res. **1976**, *51*, 9–21.

[16] Shaw, J.J.; Burris, D.; Ho, C.T. Response surface methodology in flavor research - reaction of rhamnose and proline. Perfumer Flavorist **1990**, *15*, 60–66.

[17] Doornbos, T.; van den Ouweland, G.A.M.; Tjan, S.B. Amadori compounds, derived from 6-deoxy sugars, as flavour precursors. Progr. Food Nutr. Sci. **1981**, *5*, 57–63.

[18] Coleman, W.M., III; Chung, H.L. Pyrolysis GC/MS analysi of Amadori compounds derived from selected amino acids with glucose and rhamnose. J. Anal. Appl. Pyrolysis **2002**, *63*, 349–366.

[19] Mossine, V.V.; Glinsky, G.V.; Barnes, C.L.; Feather, M.S. Crystal structure of an Amadori compounds, *N*-(1-deoxy-β-D-fructopyranos-1-yl)-glycine ("D-fructose-glycine"). Carbohydr. Res. **1995**, *266*, 5–14.

[20] Mossine, V.V.; Barnes, C.L.; Glinsky, G.V.; Feather, M.S. Interaction between two C1-X-C1′ branched ketoses: observation of an unprecedented crystalline *spiro*-bicyclic hemiketal tautomer of *N,N*-di(1-deoxy-D-fructos-1-yl)-glycine ("difructose glycine") having open chain carbohydrate. Carbohydr. Lett. **1995**, *1*, 355–362.

[21] Mossine, V.V.; Barnes, C.L.; Feather, M.S.; Mawhinney, T.P. Acyclic tautomers in crystalline carbohydrates: the keto forms of1-deoxy-1-carboxymethylamino-D-2-pentuloses (pentulose-glycines). J. Am. Chem. Soc. **2002**, *124*, 15178–15179.

[22] Mossine, V.V.; Barnes, C.L.; Mawhinney, T.P. Solubility and crystal structure of *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate ("D-fructose-L-histidine"). Carbohydr. Res. **2007**, *342*, 131–138.

[23] Kojic-Prodic, B.; Milinkovic, V.; Kidric, J.; Pristovsek, P.; Horvat, S.; Jakas, A. Synthesis and conformational analysis of the Amadori compound *N*-(2,3:4,5-di-*O*-isopropylidene-1-deoxy-β-D-fructopyranos-1-yl)-L-tyrosine benzyl ester. Carbohydr. Res. **1995**, *279*, 21–39.

[24] Sheldrick, G.M. *SHELXS-97, Crystal Structure Solution*; University of Göttingen, 1997.

[25] Sheldrick, G.M. *SHELXL-97, Crystal Structure Refinement*; University of Göttingen, 1997.

[26] Barbour, L. X-Seed—a software tool for supramolecular crystallography. J. Supramol. Chem. **2001**, *1*, 189–191.

[27] Cremer, D.; Pople, J.A. A general definition of ring puckering coordinates. J. Amer. Chem. Soc. **1975**, *97*, 1354–1357.

[28] French, A.D.; Dowd, M.K.; Reilly, P.J. MM3 modeling of fructose ring shapes and hydrogen bonding. J. Mol. Struct. (Theochem) **1997**, *395–396*, 271–287.

[29] Altena, J.H.; van den Ouweland, G.A.M.; Teunis, C.J.; Tjan, S.B. Analysis of the MHz, p.m.r. spectra of some products of the Amadori and Heyns rearrangements. Carbohydr. Res. **1981**, *92*, 37–49.

[30] Röper, H.; Röper, S.; Heyns, K.; Meyer, B. N.m.r. spectroscopy of N-(l-deoxy-D-fructos-l-yl)-L-amino acids ("fructose-amino acids"). Carbohydr. Res. **1983**, 116, 183–195.

[31] Mossine, V.V.; Glinsky, G.V.; Feather, M.S. The preparation and characterization of some Amadori compounds (1-amino-1-deoxy-D-fructose derivatives) derived from a series of aliphatic ω-amino acids. Carbohydr. Res. **1994**, *262*, 257–270.

[32] Craig, D.C.; Stephenson, N.C.; Stevens, J.D. β-D-Fructopyranose · calcium chloride dihydrate. Cryst. Struct. Commun. **1974**, *3*, 277–281.

[33] Kanters, J.A.; Roelofsen, G.; Alblas, B.P.; Meinders, I. The crystal and molecular structure of β-D-fructose, with emphasis on anomeric effect and hydrogen-bond interactions. Acta Crystallogr. **1977**, *B33*, 665–672.

[34] Rao, S.T.; Westhof, E.; Sundaralingam, M. Exact method for the calculation of pseudorotation parameters P, τ_m and their errors. A comparison of the Altona-Sundaralingam and Cremer-Pople treatment of puckering of five-membered rings. Acta Cryst. **1981**, *A37*, 421–425.

[35] Harding, C.C.; Watkin, D.J.; Hotchkiss, D.J.; Cook, J.M.D.; Fleet, G.W.J. 1-Amino-*N,N*-dibenzyl-1,6-dideoxy-β-L-fructofuranose. Acta Cryst. **2005**, *E61*, o995–o997.

[36] Manley-Harris, M.; Nicholson, B.K.; Thomson, R.A. The structure of hexa-*O*-acetyl-α-D-fructofuranose-β-D-fructofuranose 1,2′:2,6′ dianhydride. J. Carbohydr. Chem. **2003**, *22*, 1–8.

[37] Shalaby, A.; Fronczek, F.R.; Younathan, E.S. The configuration and conformation of di-D-fructose anhydride. I. The crystal and molecular structure of 3,4,3′,4′-tetra-*O*-acetyl-6,6′-di(triphenylmethyl)-di-D-fructose anhydride. I. Carbohydr. Res. **1994**, *265*, 207–214.

[38] Diánez, M.J.; López-Castro, A.; Márquez, R. Structure of allyl 1-deoxy-1-[(1-methyl-2-benzoylvinyl)amino]-α-D-fructofuranoside. Acta Cryst. **1988**, *C44*, 657–660.

[39] Fernándes-Bolaños, J.G.; Ulgar, V.; Maya, I.; Fuentes, J.; Diánez, M.J.; Estrada, M.D.; López-Castro, A.; Pérez-Garrido, S. Synthesis of new *C*-sulfosugars and *C*-sulfoalditols: Amadori rearrangement of 6-*C*-sulfo-D-fucose. Tetrahedron Asymm. **2003**, *14*, 1009–1018.

[40] Evdokimov, A.; Gilboa, A.J.; Koetzle, T.F.; Klooster, W.T.; Schultz, A.J.; Mason, S.A.; Albinati, A.; Frolow, F. Structures of furanosides: geometrical analysis of low-temperature X-ray and neutron crystal structures of five crystalline methyl pentofuranosides. Acta Cryst. **2001**, *B57*, 213–220.

[41] Ashida, T.; Kakudo, M. Conformations of prolyl residues in oligopeptides. Bull. Chem. Soc. Japan **1974**, *47*, 1129–1133.

[42] Kayushina, R.L.; Vainshtein, B.K. Structure determination of L-proline by X-ray diffraction. Kristallografiya **1965**, *10*, 834–844.

[43] Myung, S.; Pink, M.; Baik, M.-H.; Clemmer, D.E. DL-Proline. Acta Cryst. **2005**, *C61*, o506–o508.

[44] Toscano, R.A.; Enríquez, R.G.; Reynolds, W.F.; Magos, G.A.; Gnecco, D. L-1-Methylproline monohydrate. Acta Cryst. **1997**, *C53*, 1690–1692.

[45] Jones, G.P.; Naidu, B.P.; Paleg, L.G. Hygric acid (I) and stahydrine (II) as their hydrochlorides. Acta Cryst. **1988**, *C44*, 1669–1671.

[46] Jeffrey, G.A.; Taylor, R. The application of molecular mechanics to the structures of carbohydrates. J. Comput. Chem. **1980**, *1*, 99–109.

[47] Serianni, A.S.; Chipman, D.M. Furanose ring conformation: the application of ab initio molecular orbital calculations to the structure and dynamics of erythrofuranose and threofuranose rings. J. Am. Chem. Soc. **1987**, *109*, 5297–5303.

[48] Janczak, J.; Luger, P. L-Proline monohydrate at 100 K. Acta Cryst. **1997**, *C53*, 1954–1956.

[49] Evdokimov, A.; Kalb, A.J.; Koetzle, T.F.; Klooster, W.T.; Martin, J.M.L. Structures of furanosides: density functional calculations and high-resolution X-ray and neutron diffraction crystal structures. J. Phys. Chem. A **1999**, *103*, 744–753.

[50] Jeffrey, G.A.; Lewis, L. Cooperative aspects of hydrogen bonding in carbohydrates. Carbohydr. Res. **1978**, *60*, 179–182.

[51] Parthasarathy, R. The crystal structure of glycylglycine hydrochloride. Acta Cryst. **1969**, *B25*, 509–518.

[52] Tjan, S.B.; van den Ouweland, G.A.M. PMR investigation into the structure of some *N*-substituted 1-amino-l-deoxy-D-fructoses (Amadori rearrangement products). Evidence for a preferential conformation in solution. Tetrahedron **1974**, *30*, 2891–2897.

[53] Heyns, K.; Paulsen, H.; Schroeder, H. Interaction of ketohexoses with secondary amino acids and amines. Tetrahedron **1961**, *13*, 247–257.