Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 342 (2007) 131–138
Carbohydrate RESEARCH

Note

Solubility and crystal structure of *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate ('D-fructose-L-histidine')

Valeri V. Mossine,[a,*] Charles L. Barnes[b] and 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*

Received 5 October 2006; received in revised form 7 November 2006; accepted 9 November 2006
Available online 16 November 2006

Abstract—Within a set of food-related Amadori compounds, crystalline *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate (Fru-L-His × H_2O) has an unusually low solubility in water, which we determined as 0.21 g/100 g at 25 °C. The majority of the other fructose-amino acid conjugates have solubilities exceeding 100 g/100 g in water at this temperature. We report the crystal structure data on Fru-L-His × H_2O. The conformation of the carbohydrate is the normal $^2C_5$ pyranose chair. Bond lengths and valence angles compare well with the average values from a number of pyranose structures. All hydroxyl and carboxyl oxygen atoms, all nitrogen atoms and the water molecule are involved in an extensive hydrogen bonding, which forms a network of infinite chains with small antidromic rings.

Keywords: Amadori compound; Solubility; Crystal structure; Fructose-amino acid; D-Fructose-L-histidine

Condensation reactions between aldose sugars and primary or secondary amines, followed by the nucleophile-catalyzed Amadori rearrangement, result in the formation of 1-amino-1-deoxy-2-ketoses.[1] These compounds have been detected mostly in dried and stored foods[2,3] where they are believed to act as precursors of aroma, taste, and color compounds.[4,5] Amadori rearrangement has been shown to be an important in vivo reaction, possibly participating in undesired protein cross-linking and lipid oxidation in diabetes and aging.[6,7] In clinics, the evaluation of the extent of this reaction between blood glucose and hemoglobin or plasma proteins is widely used for monitoring diabetic patients.[8,9] Amadori compounds derived from amino acids have recently attracted attention as potential antioxidants,[10] analgesics,[11] and antitumor agents.[12,13]

As a part of our studies on antimetastatic and antitumor effects of amino glycoconjugates, we have synthesized a set of *N*-(1-deoxy-D-fructos-1-yl)-amino acids. These compounds are generally highly soluble in water and do not easily crystallize, if ever. We have noticed, however, that D-fructose-L-histidine is an exception to this rule and possesses an exceedingly low solubility in water at pH 6–7. To consider this anomaly in more detail, we estimated and compared solubilities of D-fructose-amino acids at 25 °C in unbuffered water (Table 1). It follows from data presented in Table 1 that relative solubilities of the Amadori compounds at 25 °C generally correlate with relative solubilities of the respective parent amino acids: compare the sequence **S**(Fru-L-His) ≪ **S**(Fru-L-Tyr) < **S**(Fru-L-Asp) < **S**(Fru-L-Trp) < **S**(Fru-L-Phe) < **S**(Fru-L-Ile) < **S**(Fru-Gly) < **S**(Fru-L-Pro) and the order of the literature values for amino acids **S**(Tyr) ≪ **S**(Asp) < **S**(Trp) < **S**(Phe) < **S**(Ile) < **S**(His) < **S**(Gly) < **S**(Pro). As expected, protonation of the imidazole ring in Fru-L-His significantly increased its (Fru-L-His × HCl in Table 1) solubility in water. The value of **S**(Fru-L-His) increases with the temperature, as shown in Figure 1. Remarkably, seemingly small structural changes to Fru-L-His, such as stereo orientation of a hydroxyl group of the ketose part (in D-tagatose-L-histidine) or side chain of the amino acid (in D-fructose-D-histidine) led to a dramatic solubility increase,

* Corresponding author. Tel.: +1 573 882 2608; e-mail: MossineV@missouri.edu

0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2006.11.011

Table 1. Solubilities of *N*-(1-deoxy-D-fructos-1-yl)amino acids in water at 25 °C

Compd	**S**, g/100g H_2O
[c]Fru-γAbu × 1/4(CH_3OH + C_3H_7OH + $2H_2O$)	>100 (97)
Fru-βAla	9.1 ± 0.2 (72)
Fru-L-Ala	51 ± 1 (16.7)
[c]Fru-L-Arg × (CH_3COOH + C_3H_7OH + H_2O)	>100 (19)
Fru-L-Asn × CH_3OH	>100 (2.5)
Fru-L-Asp	13.2 ± 0.1 (0.50)
[c]Fru-L-Gln × 1.5H_2O	>100 (4.2)
[c]Fru-L-Glp × nH_2O	>100
[c]Fru-L-Glu × nH_2O	>100 (1.1)
Fru-Gly	107 ± 4 (25.0)
$(Fru)_2$-Gly × 5H_2O	12.2 ± 0.1
[c]Fru-D-His × nH_2O	>100 (4.2)
Fru-L-His × H_2O	0.21 ± 0.01 (4.2)
Fru-L-His × HCl	51.8 ± 0.4 (18)
[c]Tag-L-His × nH_2O	>100 (4.2)
Fru-L-Hyp × H_2O	>100 (36.1)
Fru-L-Ile × 1/2H_2O	94 ± 4 (4.1)
Fru-L-Leu × 1/4(C_4H_9OH + 3H_2O)	>100 (2.4)
N_εFru-N_αFm-L-Lys × H_2O	>100
[c]N_α,$N_\varepsilon$$(Fru)_2$-L-Lys × (HCl + 2$H_2O$)	>100
[c]Fru-L-Met × 1/4(C_3H_7OH + 2H_2O)	>100 (5.6)
Fru-L-Phe × H_2O	29 ± 1 (3.0)
Fru-L-Pro × 1/2CH_3OH	124 ± 5 (162)
Fru-L-Ser × CH_3OH	>100 (41.9)
Fru-L-Thr × CH_3OH	>100 (9.8)
Fru-L-Trp × 2CH_3OH	14.7 ± 0.8 (1.14)
Fru-L-Tyr × H_2O	3.8 ± 0.1 (0.045)
Fru-L-Val	>100 (8.9)

The literature solubilities of parent amino acids[a] are given in parentheses.[b]

[a] Some amino acid abbreviations: γAbu, γ-aminobutyric acid; Glp, pyroglutamic acid; Hyp, hydroxyproline; N_αFm-L-Lys, N_α-formyl-L-lysine.

[b] The solubility of parent D-fructose is 800 g/100 g water.[14]

[c] Amorphous solid.

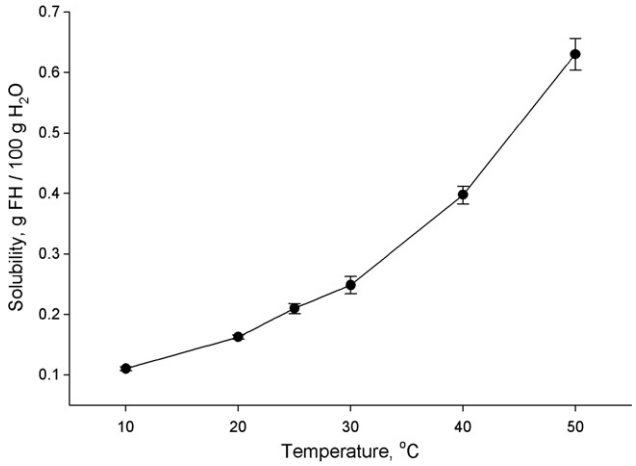

Figure 1. A solubility curve for Fru-L-His × H_2O in pure water.

estimated as more than 100 g/100 g water, for the respective compounds as compared to Fru-L-His. Obviously, the likely explanation for this observation must be related to the structure of the crystal lattice in Fru-L-His × H_2O. Unfortunately, crystalline fructose-amino acids do not have definite melting points that could be used for the comparison of the crystal material stability, due to their gradual and accelerating degradation at elevated temperatures.

However, we have succeeded with the separation of Fru-L-His × H_2O crystals suitable for X-ray diffraction study. In this report, we present X-ray analysis data on crystalline *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate. Calculated bond distances, valence angles and torsion angles are compared with the corresponding values for β-D-fructopyranose and *N*-(1-deoxy-β-D-fructopyranos-1-yl)-glycine, which are structurally similar to the sugar portion of the Amadori compound, and to L-histidine—a structural analog for the amino acid portion of the molecule.

The resulting ORTEP view of the molecule and numbering of atoms are shown in Figure 2. The molecule of D-fructose-L-histidine is a conjugate of 1-deoxy-D-fructose and the amino acid via its α-amino group. The amino acid portion is in the zwitterionic form with a positively charged tetrahedral secondary ammonium nitrogen and a negatively charged deprotonated carboxyl group. The β-D-pyranose ring of the crystalline Amadori compound exists in the $^2C_5$ or 1C(D) chair conformation, with puckering parameters[15] of $Q = 0.5497$ Å, $\theta = 176.16°$, and $\phi = 170.71°$. This conformation has the lowest energy, 11.46 kcal/mol,[16] among all possible fructose tautomers and was reported for the major component of an equilibrium mixture of the tautomeric forms of Amadori compounds, including Fru-L-His, in aqueous solutions, based on ^1H and ^{13}C NMR measurements.[17–19] In crystalline forms of Fru-Gly[20] and D-fructose,[21,22] the pyranose rings assume the same conformations.

Bond distances

Bond distances (Table 4) in the sugar part of Fru-L-His are similar (in e.s.d. range) to the corresponding values for Fru-Gly,[20] β-D-fructose,[21,22] and to the average values for a number of crystalline pyranose structures.[23]

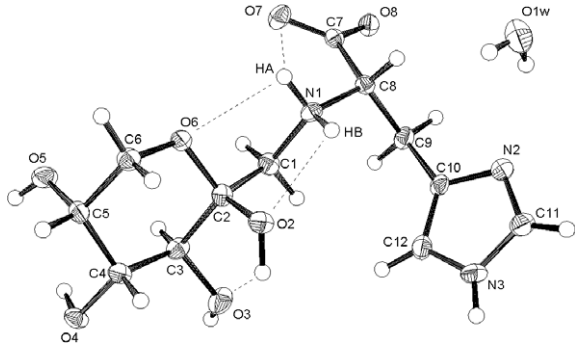

Figure 2. Atomic numbering and thermal ellipsoids (50% probability) for molecular conformation of crystalline *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate. Intramolecular hydrogen bonds are shown as dotted lines.

The mean values of C–C and C–O bond lengths in the β-D-fructopyranosyl portion of Fru-L-His (1.522 and 1.421 Å correspondingly) agree well with the corresponding values for β-pyranoses. Differences were observed with respect to the carboxylate bond lengths for D-fructose-L-histidine and its glycine analog. For Fru-L-His, one of the bonds, C7–O8, is much longer than the other, while, for Fru-Gly, both are approximately equal. The elongation of one of the two carboxyl bonds in Fru-L-His, also seen in the monoclinic L-histidine,[24] may be attributed to participation of O8 in strong hydrogen bonding, as shown below.

Valence angles

The values of the fructopyranose valence angles for Fru-L-His, Fru-Gly, and β-D-fructose 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.[22] All other valence angles in the β-D-fructopyranosyl rings are close to the average values[23] of 110–111° for a tetrahedral structure. The corresponding valence angles for crystalline histidine[24] and the amino acid portion of Fru-L-His (Table 4) show a great deal of similarity, as well. A small dissymmetry seen in carboxyl groups in both Fru-L-His, Fru-Gly, and L-His may be ascribed due to participation of the groups in strong hydrogen bonding.

Torsion angles

The endocyclic torsion angles of Fru-L-His (Table 4) differ from the corresponding angles for Fru-Gly and β-D-fructose by not more than 5° and range from 49.9° to 61.7°. The pyranose ring of Fru-Gly appears to be the closest conformationally to the 'standard' pyranosides,[23] which show C–C–C–C (ring) torsion angles to be 53–54°, C–C–C–O (ring) at 55–56°, and C–C–O–C at 59–60°. Its puckering parameter $\theta = 177.73°$ is closer to the theoretical[16] value of $\theta = 179.0°$ than θ values in Fru-L-His × H_2O or any other known crystalline β-D-fructopyranose.

The exocyclic angles around ring bonds in Fru-L-His (Table 4) appear to be close to the corresponding torsion angles of Fru-Gly[20] and β-D-fructose.[21,22] However, both Amadori compounds show closer ranges and smaller mean deviations from 'ideal' 180° (devs 5.6°, 4.7°, and 6.0° for Fru-L-His, Fru-Gly and Fru) or 60° (devs 3.6°, 4.3°, and 5.8°, respectively) of values for these torsion angles as compared to the respective values in the crystalline β-D-fructopyranose.

The three structures evidently differ in the corresponding torsion angles around C1–C2 bond (Table 4). Fru-L-His has the *gauche–trans* conformation, similar to the one found in β-D-fructose–calcium chloride complex.[21] Fru-Gly has the *trans–gauche* conformation (distorted by 15° relative to a staggered conformation),[20] while the *gauche–gauche* relationship around C1–C2 was found in crystalline anhydrous β-D-fructose.[22] The rare shifted *trans–gauche* (*-tg*) conformation in Fru-Gly is apparently due to extensive intramolecular hydrogen bonding which stabilized the amino acid portion of the molecule relative to the fructopyranose part. In Fru-L-His and β-D-fructose, the conformations around C1–C2 bond are more relaxed. The relative orientation of the imidazole ring in the amino acid part of Fru-L-His is similar to that found in crystalline DL-histidine[25] rather than in monoclinic and orthorombic forms of L-histidine.[24] In the latter, N2 is oriented towards the ammonium group, with an assistance by the respective intramolecular hydrogen bond. The conformation around C9–C10 is more relaxed in the crystalline histidines, as compared to Fru-L-His.

Hydrogen bonding

Because D-fructose-L-histidine monohydrate displayed a solubility, which is significantly lower than those of fructose, histidine, or any other fructose-amino acid, we assumed that this compound may have an extensive system of hydrogen bonding.

In the crystal structure of *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate we have found fifteen pairs of heteroatom contacts which form the intra- and intermolecular hydrogen bonding network (Table 5). All hydroxyl groups, ammonium and imidazole groups, and the water molecule, act as hydrogen donors such that all X–H (X = N or O) hydrogen atoms are allocated to the network. In accordance with updated geometric criteria for hydrogen bonds (for ∠(D–H···A) >90° and H···A distances <3 Å, respectively, a contact can be assumed to be a hydrogen bond)[26] we consider O4–H···O8 and O1W–H1···O3 as weak hydrogen bonds. All oxygen atoms participate in the hydrogen bonding as acceptors, including the ring O6 and anomeric O2. This trend is not common for carbohydrate structures.[27] However, in the reference structure of Fru-Gly, both atoms do participate as the acceptors. Each of the two carboxyl oxygen atoms participate in hydrogen bonding, but unequally: O7 is involved in two contacts, while O8 acts four times as acceptor. The interactions involving hydrogens O2–H, O4–H, and N1–HA are of the asymmetrical bifurcated[28,29] type: because the interactions O2–H···O3, O4–H···O8, and N1–HA···O2 have H···X distances close to or exceed the 2.40 Å criterion, these H-bonds should be considered as weak. The second ammonium hydrogen, N1–HB, is involved in a four-center hydrogen bond, with N1–HB···O4 being a major component of the bond. This type of H-bonding is rarely seen in the literature; however, it is also present in Fru-Gly.[20] One of the water hydrogen atoms, H1W, is involved in a symmetrical bifurcated hydrogen bonding, with long H···O distances that qualify the H-bonding as weak.

Intramolecular hydrogen bonding in the crystalline Fru-L-His is represented by a system of four contacts which involve the above mentioned multicentered types

at O2–H, N1–HA, and N1–HB, as well as acceptors, carboxylate O7 and pyranose ring O6 (Fig. 2). The participation of the ammonium hydrogens as bridges between the amino acid carboxylate group and the fructopyranose oxygen atoms, most commonly O2, appears to be a common feature among fructose-α-amino acids. Thus, it is present in an extensive intramolecular hydrogen bonding pattern found in Fru-Gly, with three contacts that involve hydroxyl groups O2 and O3, the ammonium group, and the carboxylate and which apparently are retained in aqueous solution of Fru-Gly, as suggested on the basis of the NMR data.[19] In the NMR spectra of virtually all fructosyl-α-amino acids in D_2O, the resonance signals of the two protons at C1 are split, pointing at their non-equivalence.[18,19] 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. Other known crystalline structures of amino acid-derived Amadori compounds, namely $(Fru)_2$-Gly × $5H_2O$[30] and Fru-L-Pro × H_2O,[31] show similar intramolecular H-bonding patterns, as well.

In the hydrogen bonded network of the crystalline Fru-L-His × H_2O (Figs. 3 and 4), the strongest intermolecular hydrogen bonds involve donors on the pyranosyl moiety for acceptors on the amino acid portion and vice versa. This arrangement determines the packing of the molecules (Fig. 3), which form infinite one-molecule-thick layers along the *xz* plane with identically oriented molecules linked by N1–HA···O8 and N3–H···O5 interactions. These layers are then cross-linked to the anti-parallel layers via the N–HB···O4, O3–H···N2, O4–H···O7, O4–H···O8, and O5–H···O8 intermolecular hydrogen bonds. The water molecules, which are oriented similarly throughout the crystal, serve as bridges between Fru-L-His molecules both within and between the layers.

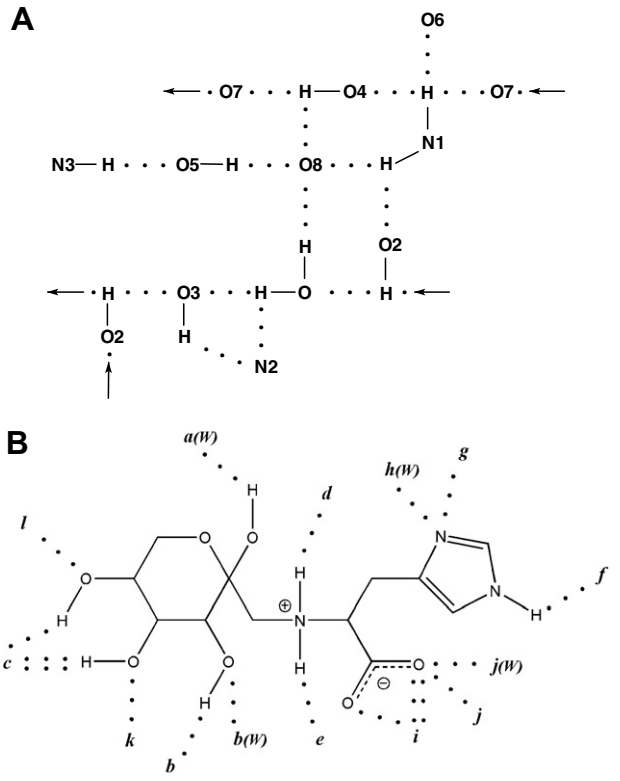

Figure 4. Schematic representation of hydrogen bonding in crystalline *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate. (A) Hydrogen-bond pattern occurring in the crystal structure of Fru-L-His × H_2O. (B) Symmetries of the neighboring molecules hydrogen-bonded to a molecule of D-fructose-L-histidine in crystalline Fru-L-His × H_2O. Symmetry codes: $^{i}-x+2, y+1/2, -z$; $^{j}x+1, y, z$; $^{k}-x+1, y-1/2, -z$; $^{l}x, y, z-1$; see Table 5 for $^{a-h}$.

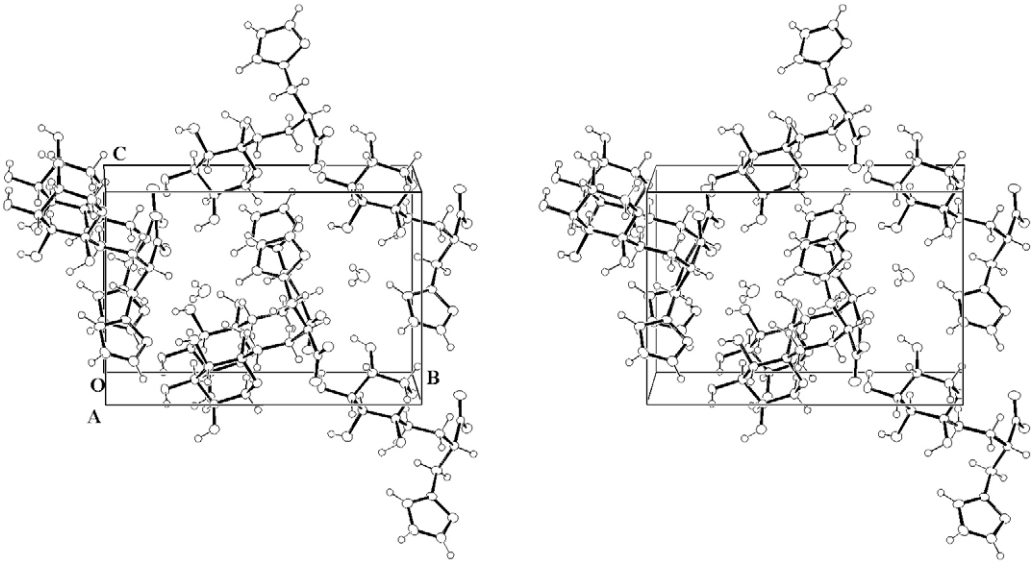

Figure 3. A stereoview on the crystal packing in *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate.

Taken together, the intra- and intermolecular hydrogen bonds form a three-dimensional network of two infinite chains. One is defined with water, hydroxyl groups O2–H and O3–H and imidazole N2 atoms forming the backbone (Fig. 4A). This backbone chain incorporates four-member antidromic rings involving water, O3–H hydroxyl group and N2. The second infinite chain is formed by carboxylate O7, ammonium N1–HB, and the O4–H hydroxyl group. Both of the backbone chains run in parallel, along crystallographic axis x, and are connected by a system of two fused antidromic rings, as shown in Figure 4A. The short side chains are attached to the fused rings at O8 and terminated at imidazole N3.

When compared to the structural analog D-fructose-glycine, the D-fructose-L-histidine molecules in the crystalline monohydrate are involved in significantly more extensive hydrogen bonded network, with water playing a consolidating role in it. A molecule of Fru-L-His is connected to fourteen other molecules in the crystal structure, employing 18 intermolecular hydrogen bonds (Fig. 4B), while Fru-Gly is hydrogen bonded to only ten neighbors, with 12 intermolecular heteroatom contacts.[20] Such a difference in the crystal structures of Fru-L-His × H_2O and Fru-Gly may contribute to the difference in stabilities of crystal lattices of these compounds and, ultimately, to the observed difference in their solubilities in water.

Table 2. Crystal data, structure determination and refinement data for *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate

Empirical formula	$C_{12}H_{19}N_3O_7 \times H_2O$
Formula weight	335.32
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	
a (Å)	5.5473(6)
b (Å)	14.0385(15)
c (Å)	9.4293(10)
β (°)	104.517(2)
U (Å^3)	710.87(13)
Z	2
Crystal size	0.35 × 0.15 × 0.05 mm
Calculated density (g cm^{-3})	1.567
μ (cm^{-1})	1.32
$F(000)$	356
Radiation Mo Kα, graphite monochromator	$\lambda = 0.71073$ Å
Diffractometer	Enraf–Nonius CAD4
Temperature (K)	173 ± 2
Data collection range	$2.23° < \theta < 27.13°$
Limiting indices	$-7 \leqslant h \leqslant 7$, $-16 \leqslant k \leqslant 18$, $-11 \leqslant l \leqslant 12$
No. of observed/unique data	5093/1624 [$R_{int} = 0.0390$]
Completeness to $\theta = 27.13°$	99.1%
Absorption correction	Semi-empirical from equivalents
Max/min transmission	0.99/0.81
Refinement method	Full-matrix least-squares on F^2
No. of restraints/parameters	1/223
R indices (all data)	$R_1 = 0.0571$, $wR_2 = 0.0771$
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0409$, $wR_2 = 0.0724$
Goodness of fit on F^2	1.055
Absolute structure parameter	0 (10)
Largest difference peak and hole (e Å^{-3})	0.212 and −0.201

1. Experimental

1.1. Reagents

D-Fructose-amino acids were from a collection previously prepared in our laboratory using published

Table 3. Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate

Atom	x	y	z	U_{eq}
N1	8218(4)	5846(2)	2676(3)	17(1)
C1	8707(6)	4827(2)	2379(3)	20(1)
O2	4551(4)	4479(2)	2502(2)	21(1)
N2	9403(5)	6308(2)	6934(3)	24(1)
C2	6265(6)	4358(2)	1631(3)	18(1)
O3	7342(5)	2826(2)	2663(3)	30(1)
N3	7466(5)	4971(2)	7170(3)	24(1)
C3	6617(6)	3305(2)	1296(3)	20(1)
O4	4595(4)	1936(2)	−100(2)	22(1)
C4	4233(6)	2891(2)	317(4)	19(1)
O5	4812(4)	3512(2)	−1981(3)	27(1)
C5	3205(6)	3524(2)	−1018(3)	19(1)
O6	5378(4)	4871(2)	316(2)	19(1)
C6	3019(6)	4547(2)	−552(3)	20(1)
O7	11,415(4)	6609(2)	1317(2)	24(1)
C7	12,193(6)	6659(2)	2670(3)	17(1)
O8	14,317(4)	6937(2)	3383(2)	21(1)
C8	10,387(5)	6389(2)	3607(3)	16(1)
O1W	6934(6)	8219(2)	5651(4)	36(1)
C9	11,643(6)	5859(3)	5009(3)	20(1)
C10	9932(6)	5635(2)	5981(3)	18(1)
C11	7931(6)	5874(3)	7633(3)	24(1)
C12	8732(6)	4816(3)	6120(4)	23(1)
H1NA	6930	5866	3129	20
H1NB	7692	6156	1793	20
H2NA	9468	4494	3310	24
H2NB	9878	4790	1742	24
H3N	6524	4557	7483	28
H3	7985	3249	783	24
H4	2961	2875	904	23
H5	1517	3291	−1550	23
H6A	2480	4955	−1431	24
H6B	1756	4596	23	24
H8	9712	6996	3905	19
H9A	12,343	5255	4744	24
H9B	13,047	6249	5571	24
H11	7282	6163	8370	28
H12	8761	4243	5589	27
H2O	4532	3868	2983	34(11)
H3O	8510(110)	2340(40)	2730(60)	83(19)
H4O	6115	1971	−556	70(15)
H5O	5086	2996	−2373	79(19)
H1W	8020(140)	7870(50)	6180(80)	110(30)
H2W	5960(110)	7900(50)	5170(70)	90(20)

U_{eq} is defined as 1/3 of the trace of the orthogonalized U_{ij} tensor.

Table 4. Bond distances (Å) and angles (°) for crystalline *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate

Bond distances	
C1–C2	1.512(4)
C2–C3	1.534(5)
C3–C4	1.525(4)
C4–C5	1.529(4)
C5–O5	1.423(4)
O6–C2	1.411(4)
C1–N1	1.497(4)
C2–O2	1.414(4)
C3–O3	1.419(4)
C4–O4	1.426(4)
C5–C6	1.512(5)
C6–O6	1.433(4)
N1–C8	1.506(4)
C7–C8	1.540(4)
C7–O7	1.242(4)
C7–O8	1.263(4)
C8–C9	1.524(4)
C9–C10	1.508(4)
C10–N2	1.385(4)
N2–C11	1.320(4)
C11–N3	1.345(5)
N3–C12	1.367(4)
C12–C10	1.351(5)
Exocyclic torsion angles	
N1–C1–C2–C3	−179.7(2)
N1–C1–C2–O2	−55.2(3)
N1–C1–C2–O6	+60.7(3)
C1–C2–C3–C4	−170.3(2)
C1–C2–C3–O3	+67.4(3)
O6–C2–C3–O3	−176.1(2)
O2–C2–C3–O3	−55.6(3)
O2–C2–C3–C4	+66.7(3)
O3–C3–C4–O4	−65.4(3)
C2–C3–C4–O4	+175.2(2)
O3–C3–C4–C5	+169.2(3)
C3–C4–C5–O5	+68.1(3)
O4–C4–C5–C6	−175.8(2)
O4–C4–C5–O5	−57.1(3)
O5–C5–C6–O6	−66.1(3)
C6–O6–C2–O2	−62.0(3)
C6–O6–C2–C1	−178.7(2)
C2–C1–N1–C8	+171.7(2)
Endocyclic torsion angles	
O6–C2–C3–C4	−53.8(3)
C2–C3–C4–C5	+49.9(3)
C3–C4–C5–C6	−50.6(3)
C4–C5–C6–O6	+54.7(3)
C5–C6–O6–C2	−61.7(3)
C6–O6–C2–C3	+60.7(3)
Valence angles	
N1–C1–C2	108.7(2)
C1–C2–C3	111.7(3)
O2–C2–C3	112.0(3)
O2–C2–C1	109.3(2)
O2–C2–O6	108.2(2)
C1–C2–O6	105.2(3)
O6–C2–C3	110.2(2)
C2–C3–C4	110.8(3)
C2–C3–O3	106.9(3)
O3–C3–C4	112.0(3)
C3–C4–C5	111.4(3)
O4–C4–C5	111.6(3)
O4–C4–C3	111.4(2)
C4–C5–C6	110.6(3)
C4–C5–O5	110.7(3)
O5–C5–C6	107.2(3)
C5–C6–O6	110.4(2)
C6–O6–C2	114.0(2)
C1–N1–C8	115.9(2)
C8–C7–O7	117.8(3)
C8–C7–O8	115.2(3)
O7–C7–O8	127.0(3)
C7–C8–C9	113.4(2)
C7–C8–N1	109.3(2)
N1–C8–C9	112.6(3)
C8–C9–C10	114.1(3)
C9–C10–N2	121.3(3)
C9–C10–C12	129.6(3)
C10–N2–C11	105.5(3)
N2–C11–N3	111.5(3)
C11–N3–C12	107.0(3)
N3–C12–C10	106.9(3)
Histidine torsion angles	
C1–N1–C8–C7	+77.0(3)
C1–N1–C8–C9	−49.8(3)
O7–C7–C8–N1	+16.1(4)
O8–C7–C8–N1	−165.9(3)
O7–C7–C8–C9	+142.5(3)
O8–C7–C8–C9	−39.5(4)
C7–C8–C9–C10	+176.9(3)
N1–C8–C9–C10	−58.5(4)
C8–C9–C10–C12	+99.0(4)
C8–C9–C10–N2	−82.1(4)
C9–C10–N2–C11	−178.3(3)
C12–C10–N2–C11	+0.8(4)
C10–N2–C11–N3	−0.8(4)
N2–C11–N3–C12	+0.5(4)
C11–N3–C12–C10	+0.1(4)
N3–C12–C10–C9	+178.5(3)
N3–C12–C10–N2	−0.6(4)

general methods.[12,19,30] Their purity was confirmed chromatographically immediately before and after the solubility experiments.

1.2. Solubility determination

The solubilities of D-fructose-amino acids were determined in unbuffered doubly distilled water. Typically, the crystalline Fru-L-His × H_2O in 2–3-fold excess over expected solubility at a given temperature was suspended in 4 mL water in the Whatman UniPrep filter chamber, and the chamber was closed with the 0.45 μm PTFE filtering plunger. The samples were slowly stirred at a set temperature for 12 h. After this time, the plunger was depressed into the chamber and the filtrate taken for the analysis. The solubilities of other fructosyl-amino acids were determined at 25 °C only and the equilibration was done in capped glass tubes, with 100–200 μL of the stirred suspensions in

Table 5. Hydrogen-bonding network in *N*-(1-deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate

D–H···A	D···A (Å)	D–H (Å)	H···A (Å)	∠(D–H···A) (°)
O2–H2O···O1W[a]	2.749	0.97	1.92	142.1
O2–H2O···O3	2.773	0.97	2.21	115.4
O3–H3O···N2[b]	2.757	0.93	1.84	171.3
O4–H4O···O7[c]	2.775	1.04	1.77	160.7
O4–H4O···O8[c]	3.299	1.04	2.62	123.0
O5–H5O···O8[c]	2.682	0.85	1.84	174.6
N1–H1NA···O2	2.772	0.92	2.34	108.2
N1–H1NA···O8[d]	2.862	0.92	2.14	134.3
N1–H1NB···O4[e]	2.963	0.92	2.08	159.5
N1–H1NB···O6	2.748	0.92	2.44	99.7
N1–H1NB···O7	2.660	0.92	2.31	102.1
N3–H3N···O5[f]	2.756	0.88	1.89	170.1
O1W–H1W···O3[g]	3.223	0.84	2.53	140.5
O1W–H1W···N2[h]	3.115	0.84	2.37	148.5
O1W–H2W···O8[d]	2.892	0.76	2.18	158.1

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

water. The sample suspensions were filtered using external polyethylene 45 μm Filter-Tips (LabSciences Inc., Reno, NV) into 200 μL pipettor tips. Determination of D-fructose-amino acid content in the weighed filtrates was carried out spectrophotometrically, with 0.5 mM NitroBlue Tetrazolium (NBT) redox indicator dye in 0.1 M carbonate buffer, pH 10.3. Typically, 25 μL of pre-diluted samples and standard solutions of a respective D-fructose-amino acid were mixed with 250 μL NBT in 96-well plates and left in the dark at room temperature. After 0.5–2 h, the optical densities in wells with the standards and samples were measured at 530 nm. All values were obtained from triplicate or quadruplicate measurements.

1.3. Single-crystal X-ray diffraction study

N-(1-Deoxy-β-D-fructopyranos-1-yl)-L-histidine monohydrate was crystallized from an aqueous solution overnight at room temperature. 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[32] and refined by full-matrix least squares techniques with the SHELXL-97[33] suite of programs, with the help of X-Seed.[34] Data were corrected for Lorentz and polarization effects, but not for absorption. Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydroxyl and secondary 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. Positional and thermal parameters are listed in Table 3.

Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC 622419. 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).

Acknowledgements

This work was supported, in part, by the Prostate Cancer Foundation and the University of Missouri Experiment Station Chemistry Laboratories.

References

1. Paulsen, H.; Pflughaupt, K.-W. In *The Carbohydrates*; Pigman, W., Horton, D., Eds.; Chemistry and Biochemistry; Academic Press: NY, 1980; Vol. IB, pp 881–927.
2. Eichner, K.; Reutter, M.; Wittmann, R. *ACS Symp. Ser.* **1994**, *543*, 42–54 (Thermally Generated Flavors).
3. Guyomarc'h, F.; Warin, F.; Muir, D. D.; Leaver, J. *Int. Dairy J.* **2000**, *10*, 863–872.
4. Yaylayan, V. A. *Food Sci. Technol. Res.* **2003**, *9*, 1–6.
5. Mills, F. D.; Baker, B. G.; Hodge, J. E. *J. Agric. Food Chem.* **1969**, *17*, 723–727.
6. Miyazawa, T.; Oak, J.-H.; Nakagawa, K. *Ann. N.Y. Acad. Sci.* **2005**, *1043*, 280–283.
7. Monnier, V. M.; Sell, D. R.; Genuth, S. *Ann. N.Y. Acad. Sci.* **2005**, *1043*, 567–581.
8. Bry, L.; Chen, P. C.; Sacks, D. B. *Clin. Chem.* **2001**, *47*, 153–163.
9. Narbonne, H.; Renacco, E.; Pradel, V.; Portugal, H.; Vialettes, B. *Diabetes Metab.* **2001**, *27*, 598–603.
10. Ryu, K.; Ide, N.; Matsuura, H.; Itakura, Y. *J. Nutr.* **2001**, *131*, 972S–976S.
11. Vértesy, L.; Fehlhaber, H.-W.; Kögler, H.; Schindler, P. *Liebigs Ann. Chem.* **1996**, 121–126.
12. Glinsky, G. V.; Mossine, V. V.; Price, J. E.; Bielenberg, D.; Glinsky, V. V.; Ananthaswamy, H.; Feather, M. S. *Clin. Exp. Metastasis* **1996**, *14*, 253–267.
13. Glinsky, V. V.; Glinsky, G. V.; Glinskii, O. V.; Huxley, V. H.; Turk, J. R.; Mossine, V. V.; Deutscher, S. L.; Pienta, K. J.; Quinn, T. P. *Cancer Res.* **2003**, *63*, 3805–3811.
14. Young, F. E.; Jones, F. T.; Lewis, H. J. *J. Phys. Chem.* **1952**, *56*, 1093–1096.
15. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1357.
16. French, A. D.; Dowd, M. K.; Reilly, P. J. *J. Mol. Struct.* **1997**, *395–396*, 271–287.
17. Altena, J. H.; van den Ouweland, G. A. M.; Teunis, C. J.; Tjan, S. B. *Carbohydr. Res.* **1981**, *92*, 37–49.
18. Röper, H.; Röper, S.; Heyns, K.; Meyer, B. *Carbohydr. Res.* **1983**, *116*, 183–195.
19. Mossine, V. V.; Glinsky, G. V.; Feather, M. S. *Carbohydr. Res.* **1994**, *262*, 257–270.
20. Mossine, V. V.; Glinsky, G. V.; Barnes, C. L.; Feather, M. S. *Carbohydr. Res.* **1995**, *266*, 5–14.

21. Craig, D. C.; Stephenson, N. C.; Stevens, J. D. *Cryst. Struct. Commun.* **1974**, *3*, 277–281.
22. Kanters, J. A.; Roelofsen, G.; Alblas, B. P.; Meinders, I. *Acta Crystallogr., Sect. B* **1977**, *33*, 665–672.
23. Jeffrey, G. A.; Taylor, R. *J. Comput. Chem.* **1980**, *1*, 99–109.
24. Madden, J. J.; McGandy, E. L.; Seeman, N. C.; Harding, M. M.; Hoy, A. *Acta Crystallogr., Sect. B* **1972**, *28*, 2382–2389.
25. Edington, P.; Harding, M. M. *Acta Crystallogr., Sect. B* **1974**, *30*, 204–206.
26. Jeffrey, G. A. *Cryst. Rev.* **2003**, *9*, 135–176.
27. Jeffrey, G. A.; Lewis, L. *Carbohydr. Res.* **1978**, *60*, 179–182.
28. Parthasarathy, R. *Acta Crystallogr., Sect. B* **1969**, *25*, 509–518.
29. Takagi, S.; Jeffrey, G. A. *Acta Crystallogr., Sect. B* **1977**, *33*, 3510–3515.
30. Mossine, V. V.; Barnes, C. L.; Glinsky, G. V.; Feather, M. S. *Carbohydr. Lett.* **1995**, *1*, 355–362.
31. Mossine, V. V.; Barnes, C. L.; Mawhinney, T. P. *J. Chem. Crystallogr.*, submitted for publication.
32. Sheldrick, G. M. SHELXS-97, *Crystal Structure Solution*; University of Göttingen, 1997.
33. Sheldrick, G. M. SHELXS-97, *Crystal Structure Refinement*; University of Göttingen, 1997.
34. Barbour, L. *J. Supramol. Chem.* **2001**, *1*, 189–191.