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The saccharide–hydrazide linkage: molecular and crystal structures of the semicarbazide derivatives of D-glucose, D-galactose, and D-xylose, including a 'forbidden' conformation of the galactose derivative

Charles R. Ojala,[a] Joanne M. Ostman,[a] William H. Ojala[b,*]

[a] *Department of Chemistry, Normandale Community College, Bloomington, MN 55431, USA*
[b] *Department of Chemistry, University of St. Thomas, 2115 Summit Avenue, St. Paul, MN 55105, USA*

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Abstract

The X-ray crystal structures of the semicarbazide derivatives of D-glucose, D-galactose, and D-xylose are described. All are glycopyranosyl derivatives in the solid state. The glucose semicarbazide crystallizes as a dihydrate. Two different conformations of the galactose semicarbazide are found, one having the *gg* side-chain orientation unfavorable for monosaccharides having the $^4C_1$-D-*galacto* configuration. In the two other known examples, this conformation is stabilized by an intramolecular hydrogen bond, but in the current structure, the hydrogen bonds involving the side chain are intermolecular. In these semicarbazides the N–N–C=O torsional angle is approximately 180°, in contrast to the angles of 0.60 and 13.9° in the two solid-state conformations of 2-benzoyl-1-(α-D-xylopyranosyl)hydrazine [Ernholt, B. V.; Thomsen, I. B.; Lohse, A.; Plesner, I. W.; Jensen, K. B.; Hazell, R. G.; Liang, X.; Jakobsen, A.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 278–287]. The water molecules and the carbonyl oxygen are heavily involved in H-bonding. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Semicarbazides; X-ray crystal structures; Monosaccharide dihydrates; Forbidden conformation; Hydrogen bonding; Saccharide–hydrazide linkage

1. Introduction

Oligosaccharides bearing a radioactive or fluorescent label allowing their detection at low concentration are probes useful in the study of carbohydrate biosynthesis and function. Previous studies have demonstrated the importance of hydrazide linkages as a means of connecting labeling agents such as biotin and related compounds to oligosaccharides of interest. Such studies have also called attention to the tautomerism that determines the detailed structure of these linkages, both cyclic and acyclic saccharide–hydrazide linkages being possible upon reaction of a carbohydrate with a hydrazide.[1,2] In a report[3] describing the production of biotinylated oligogalacturonates by reaction of the oligosaccharides with 6-(biotinoyl)aminohexanoic hydrazide (biotin-x-hydrazide), an intermediate open-chain hydrazone connecting the open-chain form of the reducing monosaccharide to the labeling agent was subjected to reduction with $NaCNBH_3$ to form the final, stable hydrazide link. In contrast, in a study[4] in which biotinyl-L-3-(2-naphthyl)alanine hydrazide and 6-(biotinyl)aminohexanoic hydrazide were compared as labeling agents, ^1H NMR studies of disaccharide model compounds bearing these labels showed that the reducing monosaccharides remained intact, assuming the closed ring form and the β-anomeric configuration. This investigation also demonstrated the sensitivity of lectin binding of the labeled oligosaccharides to the structure of the labeling agent itself, particularly with respect to how well the labeled oligosaccharide served as a glycoprotein mimic. The structure of the hydrazide thus can play a significant role in biomolecular recognition.

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* Corresponding author. Fax: + 1-651-962-5209.
E-mail address: whojala@stthomas.edu (W.H. Ojala).

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Table 1
Cremer–Pople puckering parameters and asymmetry parameters

	1	**2** [a]	**3**
Q (Å)	0.574(1)	0.561(1); 0.590(2)	0.565(1)
Θ (°)	5.8(1)	12.7(2); 5.3(2)	6.3(1)
Φ (°)	304.9(12)	319.5(7); 310.5(16)	320.1(14)
ΔC_S(C-1, C-4) (°)	9.77(10)	16.83(13); 8.95(12)	10.36(13)
ΔC_S(C-2, C-5) (°)	4.87(10)	8.52(12); 4.55(12)	5.97(13)
ΔC_S(C-3, O-5) (°)	5.15(10)	8.33(12); 4.40(12)	4.44(12)

[a] Two molecules in the asymmetric unit. For atom names of the second molecule, add 20 to the atom names of the first molecule.

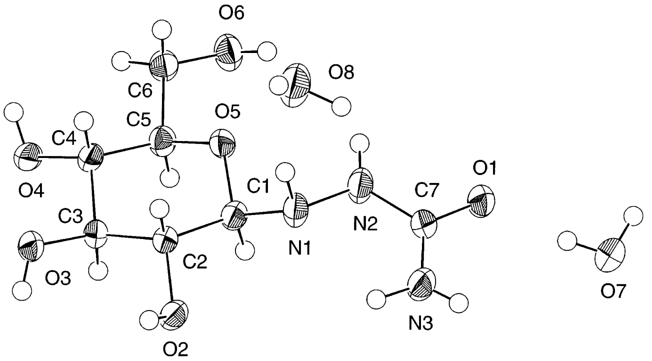

Fig. 1. ORTEPII[10] drawing of **1**, showing atom numbering. The ellipsoids are drawn at the 50% probability level.

We have been conducting a study of derivatives formed by the reaction of monosaccharides with nitrogenous bases, using X-ray crystallography to determine (as in the biotinylation studies cited previously) whether the derivative assumes the open-chain Schiff-base structure or the cyclic glycosylamine structure in the solid state. We are considering the suitability of these derivatives as small-molecule model systems for investigating molecular recognition in macromolecular systems such as glycoproteins; the occurrence of partic-

Table 2
Torsional angles (°)

Angle	**1**	**2** [a]	**3**
O-1–C-7–N-2–N-1	−179.3(2)	−173.7(2); 179.9(3)	177.6(3)
O-2–C-2–C-1–O-5	173.1(2)	167.0(2); 171.7(2)	173.0(3)
O-2–C-2–C-1–N-1	−68.5(2)	−72.3(3); −65.4(3)	−66.2(3)
O-2–C-2–C-3–O-3	67.4(2)	74.4(3); 66.5(3)	68.9(3)
O-2–C-2–C-3–C-4	−172.2(2)	−164.1(2); −171.1(2)	−171.8(2)
O-3–C-3–C-2–C-1	−171.5(2)	−164.9(2); −174.4(2)	−168.7(2)
O-3–C-3–C-4–O-4	−63.6(2)	51.8(3); 53.7(3)	−61.2(3)
O-3–C-3–C-4–C-5	175.4(2)	173.6(2); 177.2(2)	173.0(2)
O-4–C-4–C-3–C-2	175.2(2)	−72.4(3); −67.6(3)	177.6(3)
O-4–C-4–C-5–O-5	−179.3(2)	60.9(3); 61.2(3)	173.6(2)
O-4–C-4–C-5–C-6	62.3(2)	−58.9(3); −62.8(3)	
O-5–C-1–N-1–N-2	−58.8(2)	−62.3(3); −69.8(3)	−60.7(4)
O-5–C-1–C-2–C-3	52.2(2)	48.6(3); 54.4(3)	53.1(3)
O-5–C-5–C-4–C-3	−59.5(2)	−60.2(3); −60.5(3)	−59.4(3)
O-5–C-5–C-6–O-6	65.1(2)	61.7(3); −66.4(3)	
O-6–C-6–C-5–C-4	−175.6(2)	−178.5(2); 57.3(3)	
N-1–N-2–C-7–N-3	−0.6(4)	8.2(4); 3.1(4)	−2.7(4)
N-1–C-1–O-5–C-5	179.6(2)	177.9(2); 174.3(2)	179.1(3)
N-1–C-1–C-2–C-3	170.6(2)	169.2(2); 177.3(2)	174.0(3)
N-2–N-1–C-1–C-2	−178.1(2)	175.4(2); 166.5(2)	178.0(2)
C-1–O-5–C-5–C-4	64.8(2)	67.3(3); 64.6(3)	64.1(4)
C-1–O-5–C-5–C-6	−173.0(2)	−170.3(2); −166.2(2)	
C-1–N-1–N-2–C-7	−128.8(2)	−132.2(3); −120.2(3)	−112.5(3)
C-1–C-2–C-3–C-4	−51.1(2)	−43.4(3); −51.9(3)	−49.5(3)
C-2–C-1–O-5–C-5	−60.7(2)	−61.3(3); −62.1(3)	−60.2(3)
C-2–C-3–C-4–C-5	54.2(2)	49.4(3); 55.9(3)	51.8(3)
C-3–C-4–C-5–C-6	−177.9(2)	−180.0(2); 175.5(2)	

[a] Two molecules in the asymmetric unit. For atom names of the second molecule, add 20 to the atom names of the first molecule.

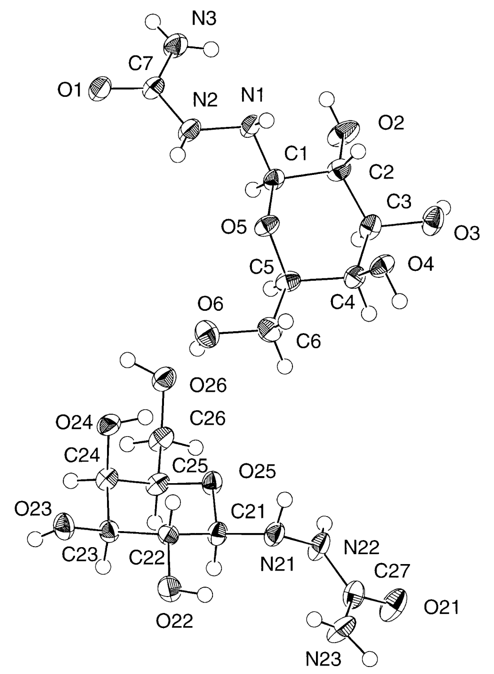

Fig. 2. ORTEPII[10] drawing of **2**, showing atom numbering. The ellipsoids are drawn at the 50% probability level.

ular intermolecular hydrogen bonding modes in different small-molecule crystal structures may indicate that these are interactions favorable enough to occur in macromolecular systems as well.[5] In a previous report,[6] we described the molecular and crystal structures of four mannose derivatives, including the one formed upon reaction of D-mannose with semicarbazide. The possibility had been raised in the earlier literature that the mannose and galactose semicarbazides might actually exist in open-chain semicarbazone form while the glucose and xylose semicarbazides were true semicarbazides existing in pyranose form. This inference was based on the fact that acetylation yielded the open-chain acetylated semicarbazones of mannose and galactose but the cyclic acetylated semicarbazides of glucose and xylose.[7,8] However, we found the crystalline mannose semicarbazide to be a glycopyranosyl derivative.

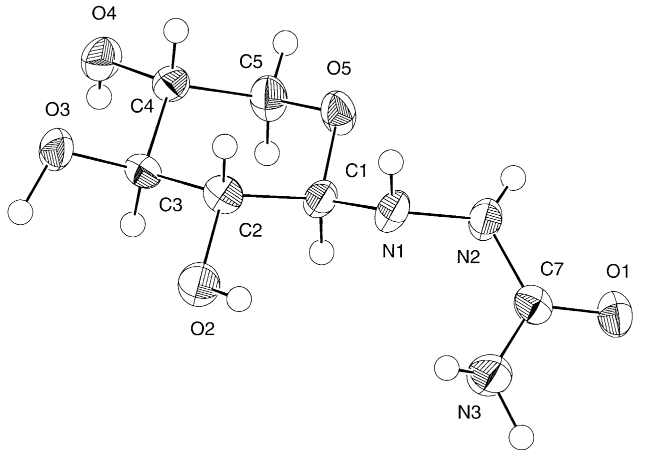

Fig. 3. ORTEPII[10] drawing of **3**, showing atom numbering. The ellipsoids are drawn at the 50% probability level.

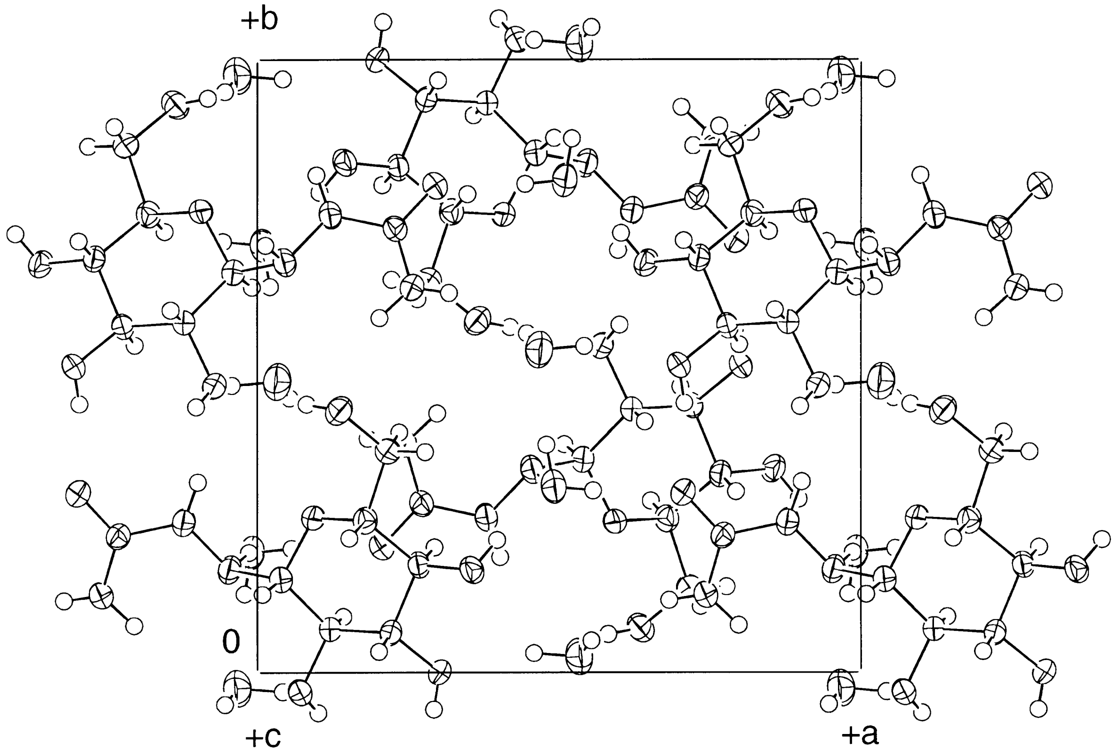

Fig. 4. Molecular packing in **1** viewed along the *c*-axis.

Table 3
Hydrogen bond parameters (Å, °)

Compound	D–H···A	D–H	H···A	D···A	D–H···A
1	O-2–H-20···O-4^{i}	0.83(3)	1.90(3)	2.716(2)	167(3)
	O-3–H-30···O-1^{ii}	0.81(3)	1.90(3)	2.703(3)	171(3)
	O-4–H-40···O-7^{iii}	0.85(3)	1.80(3)	2.640(3)	168(3)
	O-6–H-60···N-1^{iv}	0.83(3)	2.93(3)	3.284(3)	108(3)
	O-6–H-60···O-2^{iv}	0.83(3)	2.00(3)	2.800(2)	161(3)
	O-7–H-71···O-8^{v}	0.86(3)	1.93(3)	2.790(3)	174(3)
	O-7–H-72···O-1^{vi}	0.83(3)	1.89(3)	2.727(2)	176(3)
	O-8–H-81···O-3^{vii}	0.93	1.98	2.878(2)	164
	O-8–H-81···O-4^{vii}	0.93	2.70	3.276(3)	121
	O-8–H-82···O-6^{vi}	0.88(3)	2.04(3)	2.889(3)	161(3)
	N-1–H-91···O-7^{viii}	1.02(3)	2.25(3)	3.171(3)	150(2)
	N-2–H-92···O-2^{iv}	0.89(3)	2.34(3)	3.199(3)	161(3)
	N-3–H-93···O-8^{vii}	0.76(3)	2.38(3)	3.027(3)	143(3)
	N-3–H-94···O-6^{ii}	0.94(3)	2.09(3)	2.977(3)	157(2)
2	O-2–H-20···O-6^{ix}	0.87(3)	2.13(3)	2.992(3)	170(3)
	O-3–H-30···O-1^{ix}	0.81(3)	1.94(3)	2.728(3)	165(3)
	O-4–H-40···O-1^{x}	0.93(3)	1.69(3)	2.616(3)	177(3)
	O-6–H-60···O-26^{vi}	0.72(3)	1.98(3)	2.689(3)	172(4)
	O-22–H-220···O-23^{xi}	0.91(3)	1.97(3)	2.860(3)	166(3)
	O-22–H-220···O-24^{xi}	0.91(3)	2.74(3)	3.033(3)	100(3)
	O-23–H-230···O-4^{xii}	0.76(3)	1.93(3)	2.688(3)	178(4)
	O-24–H-240···O-6^{vi}	0.85(3)	2.35(3)	3.028(3)	137(3)
	O-26–H-260···O-21^{xiii}	0.94(3)	1.68(3)	2.607(3)	168(3)
	N-1–H-91···O-22^{xiv}	0.87(3)	2.15(3)	2.981(3)	160(3)
	N-2–H-92···O-2^{xv}	0.80(3)	2.20(3)	2.981(3)	166(3)
	N-3–H-93···O-4^{xiii}	0.79(3)	2.55(3)	3.155(3)	134(3)
	N-3–H-94···O-6^{ix}	0.82(3)	2.19(4)	2.917(4)	147(3)
	N-22–H-292···O-26^{xvi}	0.84(3)	2.26(3)	3.063(3)	159(3)
	N-23–H-293···O-24^{x}	0.95(3)	1.94(3)	2.877(3)	166(3)
	N-23–H-294···O-23^{xi}	0.91(3)	2.17(4)	3.054(3)	163(3)
3	O-2–H-20···O-1^{ix}	0.86(4)	2.36(3)	3.007(3)	132(3)
	O-3–H-30···O-1^{xvii}	1.01(4)	1.76(4)	2.749(3)	166(3)
	O-4–H-40···O-3^{xviii}	0.78(4)	2.06(4)	2.733(3)	144(4)
	N-1–H-91···O-1^{x}	0.82(3)	2.26(3)	3.054(4)	162(4)
	N-2–H-92···O-4^{xix}	0.81(3)	2.40(3)	3.207(4)	171(3)
	N-3–H-93···O-2^{xv}	0.98(4)	2.07(4)	2.951(4)	148(3)
	N-3–H-94···O-1^{ix}	0.78(4)	2.46(4)	3.112(4)	143(4)

Symmetry codes: (i) $1/2-x$, $-y$, $-1/2+z$; (ii) $1-x$, $1/2+y$, $1/2-z$; (iii) $-1+x$, y, z; (iv) $1-x$, $-1/2+y$, $1/2-z$; (v) $3/2-x$, $-1-y$, $-1/2+z$; (vi) xyz; (vii) $1/2+x$, $-1/2-y$, $1-z$; (viii) $-1/2+x$, $-1/2-y$, $-z$; (ix) $-1/2+x$, $-3/2-y$, $-1-z$; (x) x, y, $1+z$; (xi) $-1/2-x$, $-1-y$, $1/2+z$; (xii) $-1-x$, $1/2+y$, $-1/2-z$; (xiii) x, y, $-1+z$; (xiv) $-1-x$, $-1/2+y$, $-1/2-z$; (xv) $1/2+x$, $-3/2-y$, $-1-z$; (xvi) $-3/2-x$, $-1-y$, $1/2+z$; (xvii) $-1+x$, y, $1+z$; (xviii) $-3/2-x$, $-1-y$, $-1/2+z$; (xix) $-1/2-x$, $-1-y$, $-1/2+z$.

In an early study[9] of monosaccharide semicarbazides, Maquenne and Goodwin prepared and characterized several of these derivatives, including the mannose, glucose, galactose, and xylose derivatives. We now describe here the molecular and crystal structures of the semicarbazide derivatives of D-glucose, D-galactose, and D-xylose. All three derivatives assume glycopyranosyl form in the solid state. Like the mannose semicarbazide reported previously, the glucose semicarbazide is a dihydrate. The galactose semicarbazide has an unusual conformation at its primary hydroxyl side chain, a conformation observed in only two previously described galactose derivatives (see Section 2). All three compounds feature the saccharide–hydrazide linkage and offer a detailed view of its structure and geometry.

2. Results and discussion

Molecular geometry.—ORTEPII[10] drawings showing the atom numbering schemes and molecular conformations for the D-glucose semicarbazide **1**, the D-galactose semicarbazide **2**, and the D-xylose semicarbazide **3** are shown in Figs. 1–3. Compound **2** was found to have two independent molecules in the asymmetric unit. Molecular geometries are described by the Cremer–Pople puckering parameters[11–13] and ring asymmetry parameters[14] (obtained from the program PLATON-94[15]) listed in Table 1 and the torsional angles listed in Table 2. All three compounds (including both molecules of **2**) assume the $^4C_1$ chair conformation in the solid state and are β anomers, the semicarbazide group being equatorially disposed in all cases. The torsional angle about the C-1–N-1 bond places the N-1–N-2 bond anti with respect to C-1–C-2 and gauche with respect to C-1–O-5. This is the '*E*1' conformation known to be preferred by pyranosides;[16,17] its relationship to the exo-anomeric effect is the subject of a recent report.[18] In **1** and **3**, and in one of the molecules of **2**, the O-5–C-5 bond length is equal to the O-5–C-1 bond length within experimental error; in the other molecule of **2**, O-5–C-5 is slightly longer than O-5–C-1. In all of these semicarbazides, the N–N–C=O torsional angle is approximately 180°.

In **1**, the conformation of the C-6–O-6 side chain (in terms of the O-5–C-5–C-6–O-6 and C-4–C-5–C-6–O-6 torsional angles) is *gt*, and in one of the two molecules of **2** (the molecule assigned the lower set of atom numbers in the ORTEP figures), the C-6–O-6 side chain conformation is *gt* also. In the other molecule in **2** (the molecule with the higher set of atom numbers), the C-6–O-6 side chain conformation is *gg*. This conformation is generally considered 'forbidden' for molecules having the $^4C_1$-D-*galacto* configuration.[19] A search of the Cambridge Structural Database[20] (CSD Version 5.21, April 2001 release) on a six-membered ring composed of five carbon atoms and one oxygen atom and substituted with only the monosaccharide C-4 hydroxyl and C-6–O-6 side chain (overall fragment formula $C_6H_4O_3$), with no additional constraints, yielded 470 hits. Adding the constraint that the C-4–O-4 and C-6–O-6 vectors must lie within an angle of 60° of each other shortened the list of hits to seven, including only two galactose derivatives: 2-acetamido-2-deoxy-α-D-galactose[21,22] and planteose dihydrate (α-D-galactopyranosyl-(1→6)-β-D-fructofuranosyl α-D-glucopyranoside dihydrate)[23] which have O-5–C-5–C-6–O-6 angles of − 63.6(6) and − 49.1° and C-4–C-5–C-6–O-6 angles of 59.2(6) and 74.6°, respectively. In both of these compounds, what otherwise would be an unfavorable peri interaction is stabilized by an intramolecular hydrogen bond, O-4 being the donor atom in 2-acetamido-2-deoxy-α-D-galactose and O-6 being the donor atom in planteose dihydrate. We looked for evidence of an intramolecular hydrogen bond linking the corresponding atoms O-24 and O-26 in **2** but did not find it. The hydrogen atoms of both hydroxyl groups were located in difference maps and were refined to reasonable positions as part of intermolecular hydrogen bonds; no peaks suggesting an intramolecular hydrogen bond were found (Table 3). Although a definitive answer may depend upon a neutron diffraction study of this compound, the evidence obtained in our X-ray structure determination suggests that the combination of molecular packing forces and intermolecular hydrogen bonds present in **2** are sufficient to stabilize this unusual conformation.

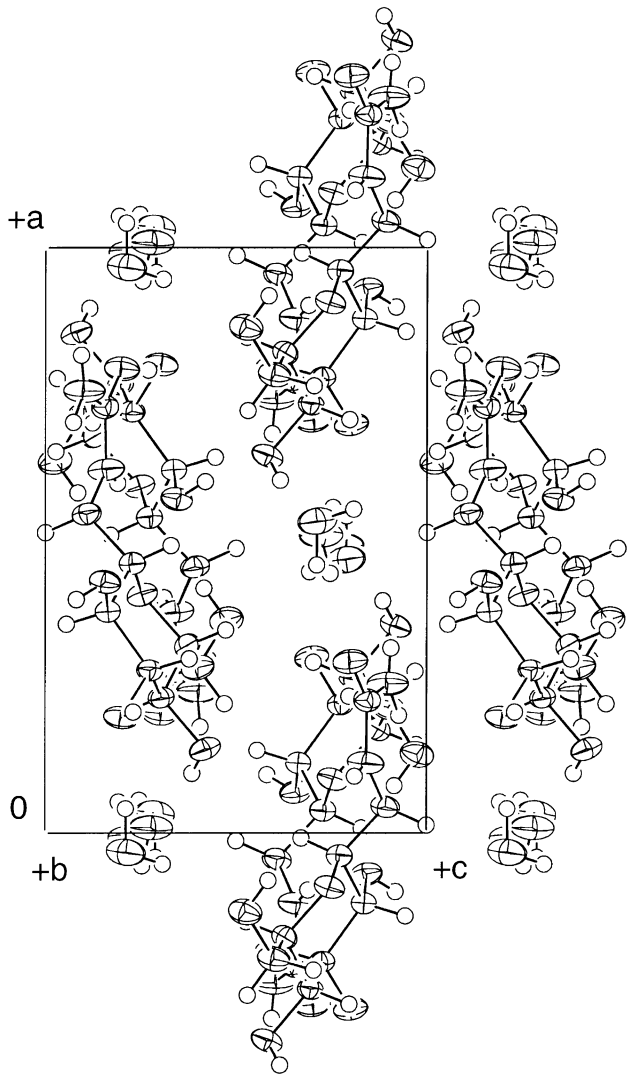

Fig. 5. Molecular packing in **1** viewed along the *b*-axis, showing water channels.

Packing arrangements and intermolecular interactions.—The packing arrangement in **1** is shown in Figs. 4 and 5. Like the mannose semicarbazide **4** described in an earlier report,[6] the glucose semicarbazide **1** is a

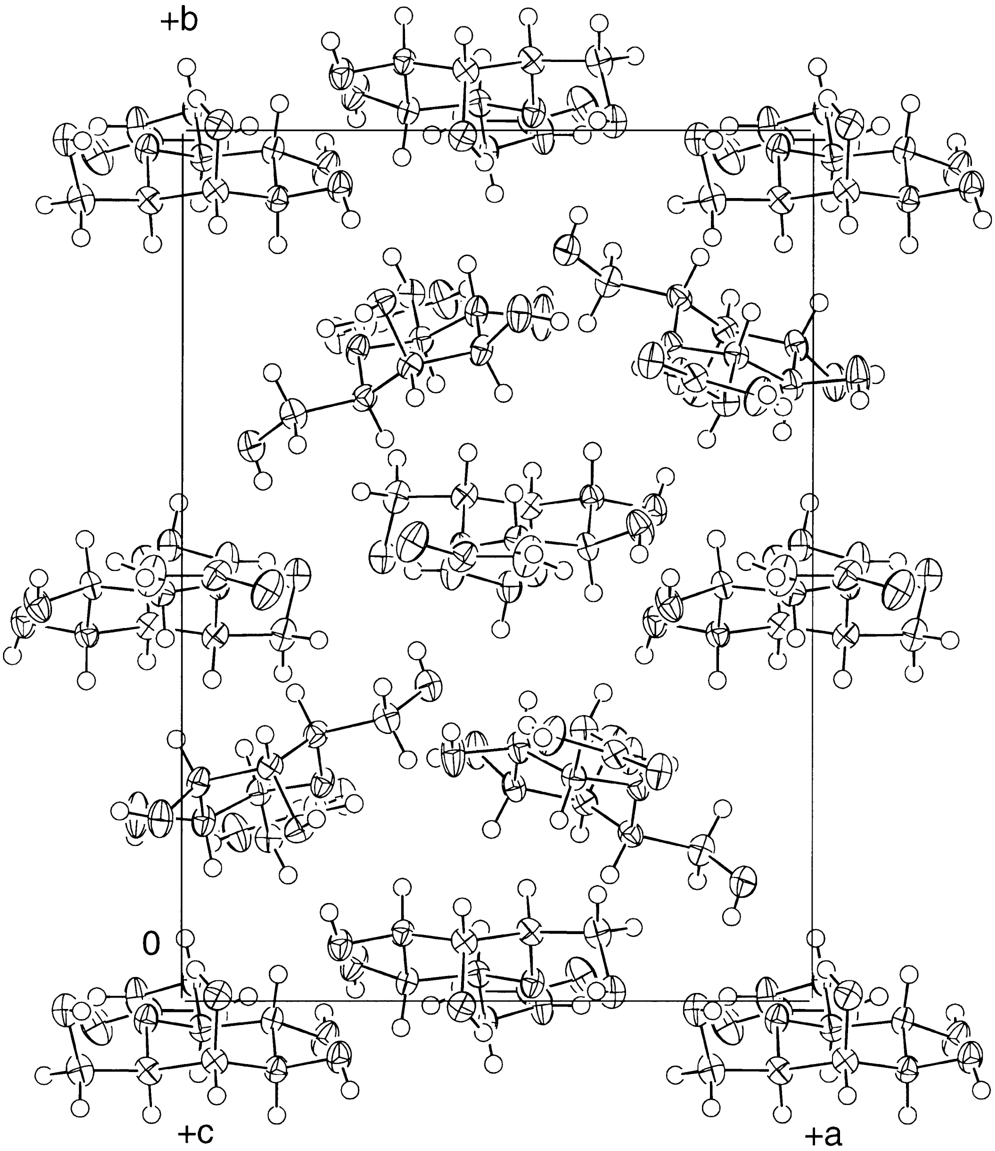

Fig. 6. Molecular packing in **2**.

dihydrate. In both **1** and **4** the carbonyl oxygen is connected to O-6 intramolecularly by a hydrogen-bonded bridge composed of two water molecules. All potential H-bond donors in **1** do in fact donate, although the interactions involving the N–H donors tend to be more distant than those involving the O–H donors. Only one of the potential acceptors, the ring oxygen O-5, fails to accept at least one hydrogen bond. The O-5 atom also plays no part in the hydrogen-bonding networks of **2**, **3**, or **4**. O-3 accepts only one H-bond in **1**, one donated by a water molecule. In contrast, the carbonyl oxygen, O-1, accepts two strong H-bonds, one from a water molecule and the other from O-3. The water molecules lie in well-defined channels (Fig. 5) that extend parallel to the *b*-axis. The loss of water, presumably through these channels, is apparent when crystals of **1** are heated to a temperature roughly 80° below their melting point[9] (see Section 3).

The packing arrangement in **2** is shown in Fig. 6. As in **1**, approaches involving the N–H groups as potential H-bond donors tend to be more distant than those involving the O–H groups. The two closest interactions between donor and acceptor atoms in **2** [2.607(3) and 2.616(3) Å] involve the carbonyl oxygen atoms O-1 and O-21 as acceptors and monosaccharide hydroxyl groups as donors. In **1**–**4**, water molecules and monosaccharide hydroxyl groups, rather than amide N–H hydrogen atoms, are hydrogen bonded to the carbonyl oxygen atoms, with the result that interactions of the hydrogen-bonded amide dimer type between semicarbazide groups are not observed. The shortest H-bonding contact in **2** is the O-26–H···O-21 contact of 2.607(3) Å between a primary hydroxyl oxygen atom and the carbonyl oxygen of a neighboring molecule, which may help stabilize the otherwise unfavorable *gg* conformation of the C-26–O-26 side chain.

The packing arrangement of **3**, shown in Fig. 7, follows the trends observed in the other monosaccharide semicarbazide structures discussed here. As previously, there are no hydrogen-bonded interactions of the amide dimer type. The ring oxygen O-5 does not participate in hydrogen bonding, even though the absence of a hydroxymethyl group on C-5 in this case would seem to make O-5 more accessible to H-bond donors. The hydrogen bonds to the carbonyl oxygen O-1 are among the shortest in the structure, and intermolecular contacts involving N–H donors are more distant. The N–N–C=O torsional angle of 177.6(3)° reflects an anti relationship between the N–N and C=O bonds in **3**, in interesting contrast to the corresponding torsional angle in a related structure, 2-benzoyl-1-(α-D-xylopyranosyl)hydrazine.[24] In the latter structure, which has two molecules in the asymmetric unit, the N–N–C=O torsional angles for the two molecules are 0.60 and 13.92°, placing the carbonyl oxygen in each molecule in position to participate in an intramolecular H-bond with O-2. Contacts to the carbonyl oxygen in **3**, on the other hand, are intermolecular rather than intramolecular. One of the H-bonding donors to the carbonyl oxygen in **3** is O-3, which is also the case in **1**, in **4**, and in one of the two molecules of **2**. Although it is true that O-3 is the only monosaccharide hydroxyl that has the same (equatorial) position from compound to compound in this series, this fact alone appears insufficient to explain the recurrence of an O-3–H···O-1 hydrogen bond from structure to structure. A contributing factor may be that the occurrence of this O-3–H···O-1 hydrogen bond in **1** and **2** is accompanied by a reciprocal interaction, an N-2–H···O-2 hydrogen bond from the molecule accepting the O-3–H···O-1 hydrogen bond. This defines a two-pronged hydrogen-bonding contact between the semicarbazide group of a given molecule and the O-2

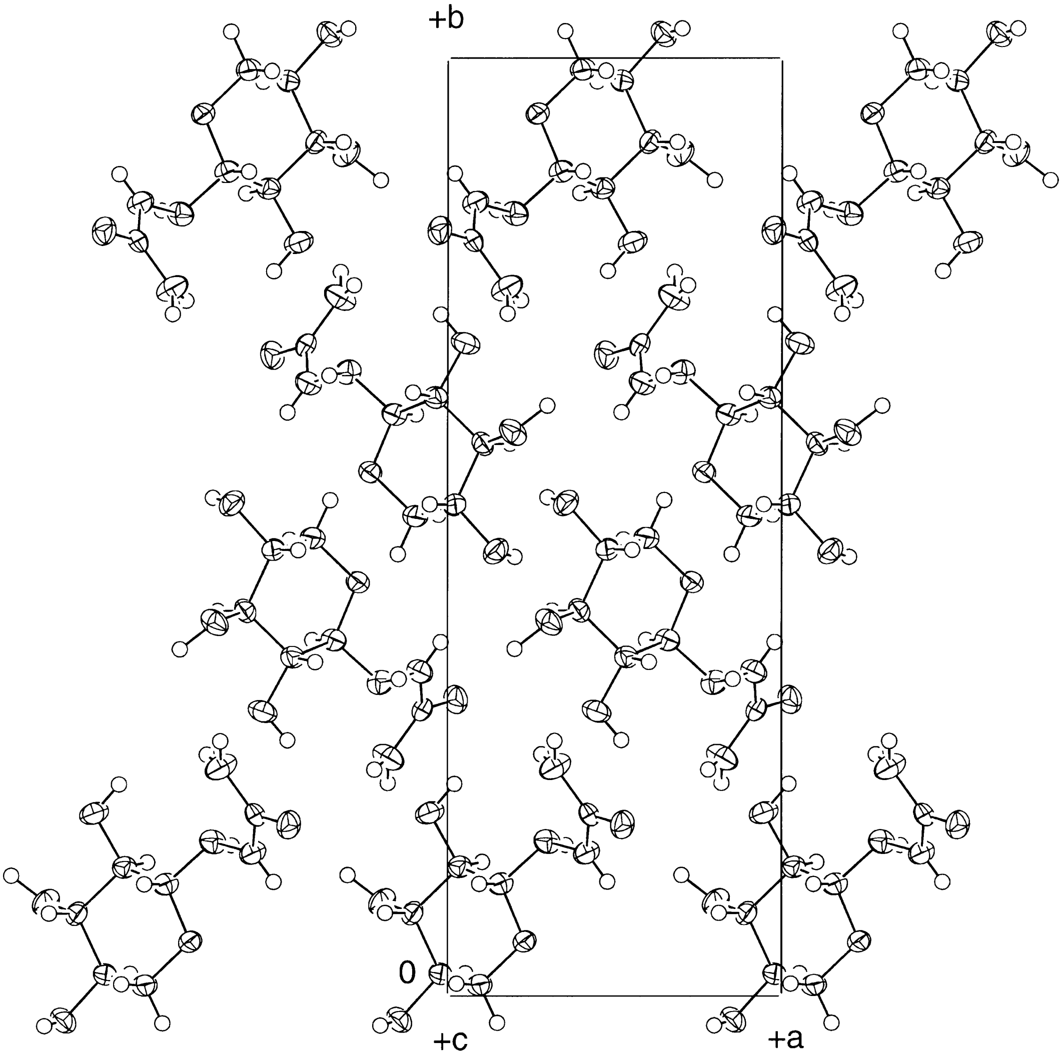

Fig. 7. Molecular packing in **3**.

Table 4
Crystal data, data collection parameters, and refinement results

	1	**2**	**3**
Formula	$C_7H_{15}N_3O_6 \cdot 2\ H_2O$	$C_7H_{15}N_3O_6$	$C_6H_{13}N_3O_5$
Formula weight	273.24	237.21	207.19
Crystal dimensions (mm)	$0.64 \times 0.36 \times 0.26$	$0.64 \times 0.32 \times 0.20$	$0.48 \times 0.40 \times 0.14$
Crystal system	orthorhombic	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	12.341(1)	12.276(2)	7.576(1)
b (Å)	12.476(1)	16.880(2)	21.167(1)
c (Å)	8.089(1)	9.920(2)	5.575(1)
V (Å^3)	1245.4(2)	2055.7(4)	894.0(2)
Z	4	8	4
D_{calc} (g cm^{-3})	1.457	1.533	1.539
F(000)	584	1008	440
μ (Cu K$_\alpha$) (cm^{-1})	11.58	11.11	11.61
$2\theta_{max}$ (°)	140.2	140.2	140.2
Measured reflections	2593	4148	2031
Unique reflections	1297	2075	1016
R_{int}	0.033	0.027	0.017
Observed reflections (no σ cutoff applied)	2188	3585	1650
Variables	197	338	149
Trans. coefficients	0.9343–1.0000	0.9559–1.0000	0.7890–1.0000
Secondary extinction[26]	1.40801×10^{-5}	8.54984×10^{-6}	1.28405×10^{-4}
Min/max in final difference map (e Å^{-3})	-0.23, 0.20	-0.29, 0.25	-0.35, 0.29
R; wR	0.056; 0.072	0.072; 0.077	0.077; 0.104

For all three structures: $T = 298$ K; diffractometer: Rigaku AFC6S; radiation: Cu K$_\alpha$; $\lambda = 1.54178$ Å; cell determination: 25 reflections, $45 < 2\theta < 50°$; data collection: MSC/AFC control software;[27] scan mode: $\omega/2\theta$; structure solution: SHELXS86;[28] structure refinement: TEXSAN software package;[29] decay correction: none for **1** or **2**; 3.07% for **3**; absorption corrections: psi scans;[30] figures: ORTEPII;[10] $R = \Sigma(F^2_{obs} - F^2_{calc})/\Sigma(F^2_{obs})$; $wR = [\Sigma\, w(F^2_{obs} - F^2_{calc})^2/\Sigma\, w(F^2_{obs})^2]^{1/2}$ where $w = 1/[\sigma(p)^2(F_{obs})] = 1/[\sigma^2(F_{obs}) + p^2F^2_{obs}/4]$; $R_{int} = \Sigma\Sigma/\langle F^2_i\rangle - F^2_{ij}/\!/\Sigma\, m\langle F^2_i\rangle$.

and O-3 hydroxyl groups of its neighbor. The O-2 and O-3 hydroxyls of **1** and **2** are both in equatorial positions; in **4**, in which O-2 is in an axial position, this two-pronged contact is absent. On the other hand, it is also absent from **3**, in which both O-2 and O-3 are equatorial as in **1** and **2**, and it occurs with only one of the two independent molecules of **2**. The two-pronged contact defined by O-3–H···O-1 and N-2–H···O-2 appears to be a favorable hydrogen-bonding motif, but it does not appear to be general and its occurrence is not readily predicted on the basis of monosaccharide stereochemistry alone.

A feature of these glycosylsemicarbazides that may be relevant to macromolecular systems is the occurrence of water molecules in two of the four structures we have examined. It has been pointed out that carbohydrates in general do not often form a variety of hydrates; this reluctance has been ascribed to the strong hydrogen-bonding patterns established by the carbohydrates themselves, patterns that usually exclude water molecules.[25] Although **2** and **3** are not hydrated, **1** and **4** are dihydrates. Hydrates (and polyhydrates) are more common among polysaccharides such as the planteose dihydrate structure discussed previously than among monosaccharides; among polysaccharides, the large size and irregular shape of the molecule presumably allows voids to exist in the crystal that can be filled by water molecules. Polyhydration of carbohydrates as small as **1**–**4** is less common. The fact that two of the four compounds in this single class of monosaccharide derivatives are not only hydrated but dihydrated is further evidence, along with the close water–carbonyl interactions already noted, that the hydrazide linkage can be expected to interact strongly with water in macromolecular systems. It is not unlikely that in these systems, hydrogen-bonding contacts between biomolecules and the hydrazide linkage, especially those contacts to the carbonyl group, will be water-mediated.

3. Experimental

Preparation of semicarbazides **1**–**3**.—Solutions of D-glucose, D-galactose, and D-xylose (0.5 g each) in EtOH (5 mL) were combined with solutions of semicarbazide hydrochloride (0.5 g) and NaOAc (0.75 g) in water (5 mL). The resulting solutions were heated for 5 min. Crystals of **1** were obtained by means of slow diffusion of EtOH into the reaction mixture, yielding colorless prisms, mp 176–179 °C (lit.[9] 197–198 °C) after apparent loss of solvent at 120–123 °C. Crystals of **2** were obtained as colorless prisms upon recrystallization of the crude product from 2-propanol–water, mp 185-190 °C (lit.[9] 200–202 °C). Crystals of **3** were obtained as colorless stout needles upon recrystallization of the crude product from EtOH–water, mp 170–172 °C (lit.[9] 202–204 °C). It was assumed that the discrepancies between the observed and literature melting points resulted from differences in heating rates, as the compounds tended to decompose upon heating.

X-ray crystal structure determinations.—A summary of the crystal data, data collection parameters, and refinement results is given in Table 4. In all three determinations, all non-hydrogen atoms were refined anisotropically, and hydrogen atoms bonded to carbon atoms were placed in calculated positions. Hydrogen atoms bonded to oxygen atoms or nitrogen atoms were refined (positional parameters only) except for H-81 (a water hydrogen atom) in **1**, which was left in its difference map position due to its failure to refine to a reasonable O–H bond distance.

4. Supplementary material

Full crystallographic details (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre for compounds **1**–**3** (CCDC 173839–173841). Copies of these data may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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