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Crystal structure of methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranoside. Stabilization of the crystal lattice by a double network of N–H···O, O–H···N and O–H···O interactions

Aleksandra Dąbrowska, Dagmara Jacewicz, Artur Sikorski and Lech Chmurzyński*

Faculty of Chemistry, University of Gdańsk, Sobieskiego 18/19, 80-952 Gdańsk, Poland

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Abstract—The structure, conformation and configuration of methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranoside were investigated by ^{1}H NMR, ^{13}C NMR and IR spectroscopy, as well as by optical rotation. The crystal structure was confirmed by single-crystal X-ray crystallographic analysis at 293 K and $R = 0.0434$ based on 910 independent reflections. The crystal belongs to the monoclinic system, space group of $P2_1$ with cell dimensions $a = 6.050(1)$ Å, $b = 7.284(1)$ Å, $c = 10.289(2)$ Å, $\beta = 104.69(3)°$, $D_c = 1.341$ Mg cm^{-3} and $V = 438.9(1)$ Å^3 for $Z = 2$. Furthermore, the molecule has a typical $^{4}C_1$ chair conformation. Hydrogen bonds between sugar molecules are responsible for stabilizing the crystal lattice.

Keywords: Methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranoside; Single-crystal X-ray structure; Conformation and configuration; Hydrogen bonding; Weak interactions

1. Introduction

Solid-state organization of carbohydrates is governed generally by hydrogen-bonding interactions in well-defined geometrical arrangements in the crystal lattice.[1] The presence of highly directional O–H···O hydrogen-bonding networks is an inbuilt feature of the hydroxyl groups abundant sugar pyranoses.[2] Although there are several crystal structure reports available on either partially or fully protected derivatives of pyranosides, the generality of noncovalent interactions responsible for the stability of crystalline lattice sugar derivatives remains to be understood in detail. The roles of weak interactions are becoming increasingly important to understand the packing forces in the crystalline lattice of carbohydrates.

In our previous paper, we reported the crystal structure of methyl 3-amino-2,3-dideoxy-α-D-*arabino*-hexopyranoside.[3] We have performed the single-crystal X-ray structural analysis of its β-anomer. We observe an elaborate network of N–H···O and O–H···N interactions that stabilize the molecules in the solid state. The details of the structural analysis are presented herein.

2. Experimental

2.1. Materials and methods

The synthetic methods for the prepared substances are given in Refs. 4 and 5. TLC was carried out on Silica Gel 60 F_{254} aluminum plates (E. Merck). Melting points were determined using a Büchi 510 apparatus. Optical rotations were measured using Hilgel–Watts polarimeter in 1-dm tubes at the D line of sodium and room temperature. IR spectra were recorded as Nujol mulls with a Bruker IFS 66 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured using a Varian Mercury spectrometer at 400 MHz in CD_3OD with Me_4Si as the internal standard. Field desorption mass spectra (FDMS) were recorded using a Varian Matt 711

* Corresponding author. Tel.: +48 58 345 04 04; fax: +48 58 345 04 72; e-mail: lech@chem.univ.gda.pl

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spectrometer. Elemental analyses were conducted with a Carlo Erba EA1108 elemental analyzer.

2.2. Preparation of single crystals for X-ray measurements

Methyl 3-azido-2,3-dideoxy-β-D-*arabino*-hexopyranoside[4,5] (0.5 g, 2.5 mM) was dissolved in 20 mL of dry MeOH; the reaction mixture was stirred and argon gas was bubbled through it for 15 min. After this time, the reaction mixture was hydrogenated at rt for 1 h with 22 mg of 10% Pd/C. Then, the catalyst was filtered off, and the filtrate was evaporated in vacuo to give the crude product. Approximately 0.5–1.0 wt.% of crude product was dissolved in 2:1 mixture of *n*-heptane and EtOAc (distilled) at about 50 °C. The sample tube was slowly cooled to room temperature and stored for 3–5 days. When no crystallization was observed after this time, the cap of the reagent tube was slightly opened to allow slow evaporation. Single crystals were obtained typically within two weeks. After recrystallization, methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranoside was isolated in yields of up to 85% (0.38 g); mp 141.5–143 °C; $[\alpha]_D^{20}$ −65 (*c* 0.1 CH_3OH); R_f 0.29 (MeOH); IR: *ν* [cm^{-1}] 3400, 3348, 3304 (ν-NH-amine), 2968, 2940. 2917 (νOH), 2815 (ν-acetal), 1591 (δ-NH-amine), 1423 (δ-OCH_3), 1111, 947 (ν-C–O–C); ^1H NMR (CD_3OD): δ [ppm] 1.353 (m, 1H, $J_{2a,2e}$ 12.4, $J_{2a,3}$ 12.4 Hz, H-2_a), 2.019 (dq, 1H, $J_{2e,3}$ 4.8 Hz, H-2_e), 2.709 (m, 1H, $J_{3,4}$ 9.2 Hz, H-3), 3.038 (t, 1H, $J_{4,5}$ 9.6 Hz, H-4), 3.21 (m, 1H, $J_{5,6}$ 6.0, $J_{5,6'}$ 2.4 Hz, H-5), 3.47 (s, 3H, OCH_3), 3.675 (dd, 1H, $J_{6,6'}$ 12.0 Hz, H-11A), 3.856 (dd, 1H, H-11B), 4.471 (dd, 1H, $J_{1,2a}$ 9.6, $J_{1,2e}$ 2.0 Hz, H-1); ^{13}C NMR (CD_3OD): δ [ppm] 39.574 (C-2), 54.135 (C-3), 56.87 (C-8), 63.204 (C-11), 73.788 (C-4), 79.319 (C-5), 102.904 (C-1); *m*/*z* (EI) 177 (M^+, 45%); Calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; N, 7.9. Found: C, 47.41; H, 8.59; N, 7.79.

2.3. Crystal structure determination and analysis

Diffraction data were collected at room temperature (293 K) on a KUMA KM-4 diffractometer[6] with Mo Kα radiation ($\lambda = 0.71073$ Å) using the $2\Theta/\omega$ scan mode. All H atoms were placed geometrically and refined using a riding model with C–H = 0.96 Å, O–H = 0.82 Å, N–H = 0.86 Å and $U_{iso}(H) = 1.2U_{eq}(C)$ (C–H = 0.96 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ in the case of the methyl H atoms). The crystal structure was refined to $R_1 = 0.0793$ (910 reflections) and $R_1 = 0.0434$ (810 reflections with $F_0 > 2\sigma(F_0)$) by full-matrix least-squares method using the program SHELX-97[7,8] based on 110 parameters. Atom numbering scheme and molecular packing in the crystal are illustrated in Figures 1 and 2, respectively.[9] The coordinates of atoms and their isotropic temperature factors are collected in Table 2, and a selection of the crystal's important geometric parameters is given in Table 3.

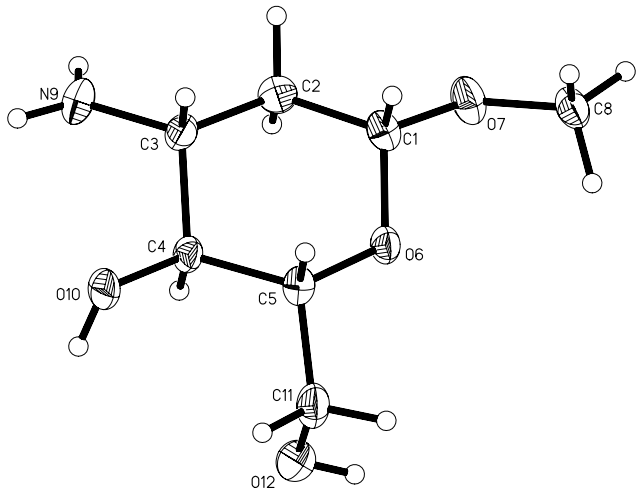

Figure 1. Structure of title compound showing 50% probability displacements for ellipsoids (H atoms as circles).

3. Results and discussion

Synthesis of the title compound was carried out by the reduction of its 3-azido precursor with methanol in the presence of Pd/C activators to afford the desired 3-amino-2,3-dideoxysugar in 85% yield. Single crystals suitable for analysis were obtained upon slow evaporation of a solution of the β anomer in *n*-heptane–EtOAc. The configuration and conformation of the methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranoside were established on the basis of ^1H, ^{13}C NMR and IR spectroscopy and optical data. It has been reported that in spite of the complexity of ^1H NMR spectra in carbohydrates, the peak position for the anomeric proton is often readily identified and can provide useful diagnostic information.[10] The H-1 signal of the β anomer appeared at a lower δ value (4.47 ppm) than the analogous proton of the α anomer[3] owing to the axial orientation of H-1. Two different values of coupling constants $J_{1,2a}$ 9.6 Hz and $J_{1,2e}$ 2.0 Hz, as well as negative value of the optical rotation, indicated the β-configuration for the molecule. Furthermore, the strong coupling of H-3 and axially oriented H-2 ($J_{2a,3}$ 12.4 Hz) indicated an axial orientation for the H-3 proton and consequently the D-*arabino* structure. The values of coupling constants, $J_{3,4}$–$J_{4,5}$ 9.2–9.6 Hz also confirmed the D-*arabino* structure. All the above findings were in accordance with the predicted $^4C_1$ conformation.

Noteworthy is the influence of the type of the substituent and configuration of the sugar on the chemical shifts of the H-3 protons in the ^1H NMR spectra. A comparison analysis of these substituents[3,4] showed that their deshielding influence on the H-3 proton increased

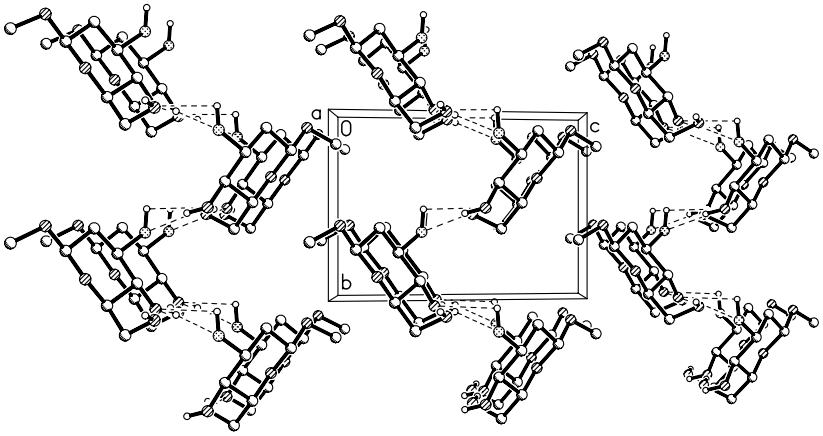

Figure 2. Molecular packing in unit cell (view along *a*-axis). Hydrogen bonds are drawn in dashed lines. H atoms not involved in hydrogen bonds have been removed.

in the following order: $-NH_2$ in β (δ 2.71), $-NH_2$ in α (δ 3.00), $-N_3$ in β (δ 3.32), $-N_3$ in α (δ 3.95). These findings are in accordance with stereoelectronic interactions that determine ^{1}H NMR spectral positions.

Crystal and X-ray diffraction data are given in Table 1. The molecular structure of methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranoside is shown in Figure 1. The coordinates of atoms and their isotropic temperature factors are collected in Table 2. All bond lengths and valence and torsion angles are in proximity of the ideal values. Some selected values are shown in Table 3.

The title compound crystallizes in the $P2_1$ space group and differs significantly when compared to its α anomer.[3] The differences are related to the structure of the sugar unit where the intermolecular contacts are important in the overall arrangement of molecules in their crystal states.

An analysis of the C–C bond lengths within the pyranose ring shows that they are in the range between 1.488 and 1.544 Å (Table 3). Amongst the bonds within the pyranose ring, exocyclic C-1–O-7 1.377(5) Å is found to be the shortest. C-5–O-6 and O-6–C-1 are 1.437(5) and 1.411(5) Å, respectively. The shortening of C-1–O-7 compared to O-6–C-1 indicates a significant anomeric effect.

The Cremer–Pople puckering parameters[11,12] $Q = 0.566(5)$ Å, $\Theta = 1.8(5)^\circ$ and the relevant dihedral angles are indicative of almost perfect $^4C_1$ conformation for the six-membered pyranoside ring (O-6–C-1–C-2–C-3–C-4–C-5). The packing arrangements are shown in Figure 2 (view along *a*-axis) and Fig. 3 (view along *b*-axis). The torsion angles O-6–C-5–C-11–O-12 of $-67.5(4)^0$ and C-4–C-5–C-11–O-12 of $53.6(5)^0$ indicate the *gauche–gauche* orientation of the primary hydroxy group with respect to the ring oxygen, as well as the C-4 hydroxyl group. On the other hand, the torsion angles of O-6–C-1–O-7–C-8 of $-72.4(5)^0$ and C-2–C-1–O-7–C-8 of $166.2(4)^0$ show that the anomeric substituent has *gauche–trans* orientation with respect to the pyranose ring.

Table 1. Crystal data and structure refinement

Empirical formula	$C_7H_{15}NO_4$
Formula weight	177.20
Temperature (K)	293(2)
Radiation wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	6.050(1)
b (Å)	7.284(1)
c (Å)	10.289(2)
β (°)	104.69(3)
V (Å^3)	438.60(13)
Z	2
Calculated density (Mg m^{-3})	1.342
Absorption coefficient (mm^{-1})	0.109
F(000)	192
Crystal size (mm)	$0.3 \times 0.3 \times 0.4$
Θ range for data collection (°)	2.05–25.25
Limiting indices	$-7 \leqslant h \leqslant 7$, $0 \leqslant k \leqslant 8$, $0 \leqslant l \leqslant 12$
Reflections collected/unique	910/863 [$R_{int} = 0.0368$]
Completeness to $2\Theta = 50.50$ (%)	100
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	863/1/113
Goodness-of-fit on F^2	1.006
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.043$ $wR_2 = 0.120$
R indices (all data)	$R_1 = 0.079$ $wR_2 = 0.142$
Absolute structure parameter	3(3)
Extinction coefficient	0.13(3)
Largest diff. peak and hole (e A^{-3})	0.339 and −0.159

Data on intermolecular interactions, that is, N–H···O, O–H···N and O–H···O hydrogen bonds are presented in Table 4. Intermolecular hydrogen bonds extend from 2.7 Å for O–H···N and O–H···O to

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for non-hydrogen atoms

Atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{eq}
C-1	3209(8)	2232(6)	−1237(4)	42(1)
C-2	4509(8)	1164(8)	−2054(5)	49(1)
C-3	5881(7)	2414(8)	−2711(4)	45(1)
C-4	4316(6)	3847(6)	−3529(4)	38(1)
C-5	3010(7)	4868(6)	−2638(4)	40(1)
O-6	1790(5)	3560(4)	−2037(3)	41(1)
O-7	1883(6)	1044(4)	−717(3)	55(1)
C-8	1005(9)	1835(7)	311(5)	52(1)
N-9	7056(6)	1384(7)	−3560(4)	56(1)
O-10	5619(5)	5142(6)	−4045(3)	54(1)
C-11	1335(8)	6221(8)	−3404(5)	53(1)
O-12	−167(5)	5469(7)	−4509(3)	67(1)

U_{eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

3.1 Å for N–H···O bonds. When viewed along the *a*-axis, each molecule in the crystal lattice interacts with another symmetry-related molecule by these hydrogen bonds. These two types of hydrogen bonds, specifically

Table 4. Hydrogen-bond distances and angles with H···A < *r*(Å) + 2.00 Å and D–H···A > 110°[a]

D–H···A	D–H	H···A	D···A	D–H···A
N-9–H-8B···O-12[i]	0.86	2.55	3.135(6)	126
O-10–H-10A···N-9[ii]	0.82	1.93	2.736(5)	168
O-12–H-12A···O-10[iii]	0.82	1.92	2.721(5)	166

[a] Symmetry codes: (i) [−*x* + 1, *y* − 1/2, −*z* − 1], (ii) [−*x* + 1, *y* + 1/2, −z − 1], (iii) [*x* − 1, *y*, *z*]. D and A denote donor and acceptor, respectively.

Table 3. Selected bond lengths (Å), valence and torsion angles (°)

Bond lengths		Valence angles		Torsion angles	
C-1–O-7	1.377(5)	O-7–C-1–O-6	109.2(3)	O-7–C-1–C-2–C-3	176.7(3)
C-1–O-6	1.411(5)	O-6–C-1–C-2	110.8(4)	O-6–C-1–C-2–C-3	56.3(5)
C-1–C-2	1.505(6)	O-7–C-1–C-2	109.3(4)	C-1–C-2–C-3–N-9	−177.2(4)
C-2–C-3	1.503(7)	C-1–C-2–C-3	111.4(4)	C-1–C-2–C-3–C-4	−54.7(5)
C-3–N-9	1.465(6)	C-2–C-3–N-9	111.4(4)	N-9–C-3–C-4–O-10	−62.8(5)
C-3–C-4	1.513(6)	C-3–C-4–N-9	110.6(4)	C-2–C-3–C-4–O-10	174.2(4)
C-4–O-10	1.416(5)	C-2–C-3–C-4	109.2(4)	N-9–C-3–C-4–C-5	177.6(4)
C-4–C-5	1.544(5)	O-10–C-4–C-3	109.8(3)	C-2–C-3–C-4–C-5	54.6(5)
C-5–O-6	1.437(5)	O-10–C-4–C-5	108.6(4)	O-10–C-4–C-5–O-6	−176.4(3)
C-5–C-11	1.488(7)	C-3–C-4–C-5	110.2(3)	C-3–C-4–C-5–O-6	−56.1(5)
O-7–C-8	1.421(5)	O-6–C-5–C-11	108.2(3)	O-10–C-4–C-5–C-11	63.1(5)
C-11–O-12	1.376(6)	O-6–C-5–C-4	109.4(3)	C-3–C-4–C-5–C-11	−176.6(4)
		C-4–C-5–C-11	112.8(3)	O-7–C-1–O-6–C-5	−179.6(3)
		C-1–O-6–C-5	113.8(3)	C-2–C-1–O-6–C-5	−59.1(5)
		C-1–O-7–C-8	113.5(3)	C-11–C-5–O-6–C-1	−177.8(4)
		O-12–C-11–C-5	113.0(5)	C-4–C-5–O-6–C-1	59.0(5)
				O-6–C-1–O-7–C-8	−72.4(5)
				C-2–C-1–O-7–C-8	166.2(4)
				O-6–C-5–C-11–O-12	−67.5(4)
				C-4–C-5–C-11–O-12	53.6(5)

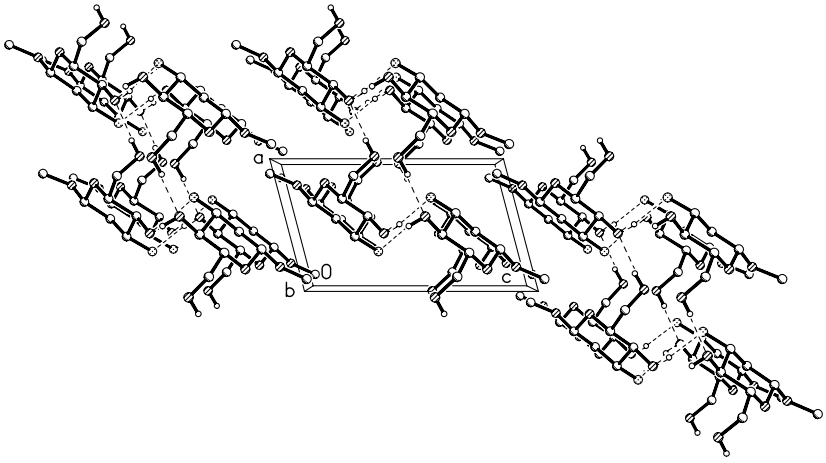

Figure 3. Molecular packing in unit cell (view along *b*-axis). The dashed lines represent hydrogen bonds. H atoms not involved in hydrogen bonds have been removed.

N-9–H-8B···O-12 and O-10–H-10A···N-9, form a zigzag chain, which runs down along the *b*-axis (Fig. 2). The remaining O–H···O bond, that is, O-12–H-12A···O-10, forms an infinite chain connecting molecules and is roughly perpendicular to the above two interactions. Consequently, these hydrogen bonds form rings between crystal layers along the *b*-axis in the unit cell.

4. Supplementary data

Full crystallographic details, excluding structure features, have been deposited (deposition No. CCDC 244335) with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (tel.: +44-1223-336408; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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