Crystal Structure of Methyl 4-Acetamido-4-cyano-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside

Miroslav Koóš[1]*****, **Bohumil Steiner**[1], **Ján Gajdoš**[1], **Vratislav Langer**[2], **Dalma Gyepesová**[3], **Ľubomír Smrčok**[3] **and Marián Ďurík**[3]

[1]Institute of Chemistry, Slovak Academy of Sciences, SK-84238 Bratislava, Slovak Republic
Tel.: (+421-7)-59410254, Fax: (+421-7)-59410222, E-mail: chemmiro@savba.sk
[2]Department of Inorganic Environmental Chemistry, Chalmers University of Technology, SE-41296 Göteborg, Sweden
[3]Institute of Inorganic Chemistry, Slovak Academy of Sciences, SK-84236 Bratislava, Slovak Republic

*Author to whom correspondence should be addressed.

Abstract: The detailed structure of methyl 4-acetamido-4-cyano-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside was established by X-ray analysis confirming *allo* configuration at C-4 and suggesting a $^4C_1$ conformation of the pyranose ring. The values of relevant torsion angles and calculated puckering parameters revealed a distortion into the direction of $^0H_5$, thus indicating a flattening at C-1 and C-4.

Keywords: Amino nitrile, methyl allopyranoside, amino sugar, X-ray analysis.

Introduction

With respect to biological and medicinal importance, amino sugars represent a significant group of organic compounds. To understand the mechanism of their biological activity, a lot of suitable synthetically prepared model compounds with well established structure are needed.

In our previous paper [1], we have described the preparation of two sugar amino nitriles – methyl 4-amino-4-cyano-4,6-dideoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**1**) and 4-amino-4-cyano-4,6-

dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (**2**) which are structurally related to naturally occurring biologically important Perosamine (**3**) (Figure 1). Because of the difficulties in unambiguous establishing the configuration at C-4 position of the pyranose ring (*allo* versus *gulo*) by NMR methods, suitable crystals of corresponding *N*-acetylated compounds **4** and **5** were subjected to X-ray analysis.
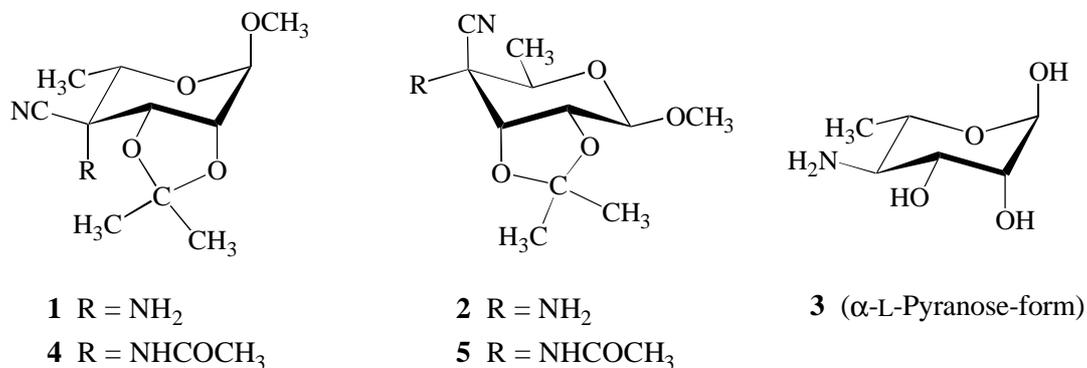

1 R = NH$_2$
4 R = NHCOCH$_3$

2 R = NH$_2$
5 R = NHCOCH$_3$

3 (α-L-Pyranose-form)

Figure 1.

Since the crystal and molecular structure determination of **4** by NMR and X-ray methods has already been published [1], we now wish to present the X-ray analysis of acetylated amino nitrile **5**.

Results and Discussion

Synthesis

The amino nitrile **2** was synthesized either from 4-uloses **6** or **7** using slightly modified Strecker reaction conditions (Scheme 1) or alternatively from cyanohydrin **8** (ammonia and ammonium chloride as reactants) as described in [1]. Subsequent acetylation (acetic anhydride, pyridine) afforded the title compound **5** [1].

Structure Elucidation

The title compound **5** was fully characterized by ^{1}H and ^{13}C NMR, EIMS, CIMS, [α]$_D$, TLC, mp and elemental analysis data [1]. The coupling constants $J_{1,2}$ of 6.9 Hz and $J_{2,3}$ of 5.2 Hz (in comparison with $J_{1,2}$ of 0 Hz and $J_{2,3}$ of 6.3 Hz reported for $^1C_4$ conformation of **4**) suggested an inversion of a $^1C_4$ to a $^4C_1$ conformation with an equatorial glycosidic methoxyl group and H-3, an axial H-5 and H-2 and favoured 2,3-*cis* stereochemistry for the isopropylidene group (similar base-catalyzed isomerizations with inversion at C-5 and unchanged configuration at C-3 were observed previously [2,3]) indicating the possibility of either β-D-*allo* or β-D-*gulo* configuration. Because the data obtained from NMR measurements were unsufficient, X-ray analysis was used to determine unambiguously correct actual configuration and simultaneously, conformation of the pyranose ring.

6 R = CH$_3$, R^1 = H
7 R = H, R^1 = CH$_3$
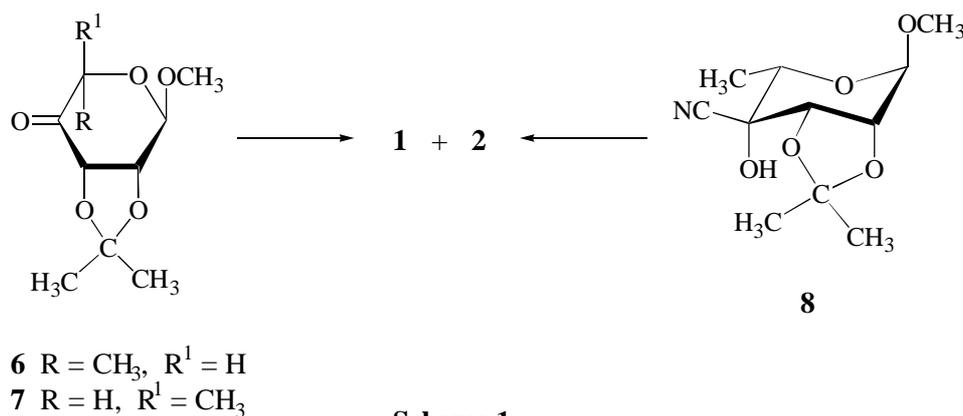
Scheme 1.

X-ray Analysis

   The suitable crystals were obtained by slow crystallization from a mixture of ethyl acetate–hexane (1:2, v/v) at room temperature. The relevant crystallographic data and structure refinement are given in Table 1. The bond lengths and bond angles are listed in Table 2. A list of selected torsion angles is given in Table 3. The final positional parameters are summarized in Table 4. Perspective view and the numbering of the atoms is depicted in Figure 2. The hydrogen atoms were refined isotropically in idealized positions riding on the atom to which they are attached.
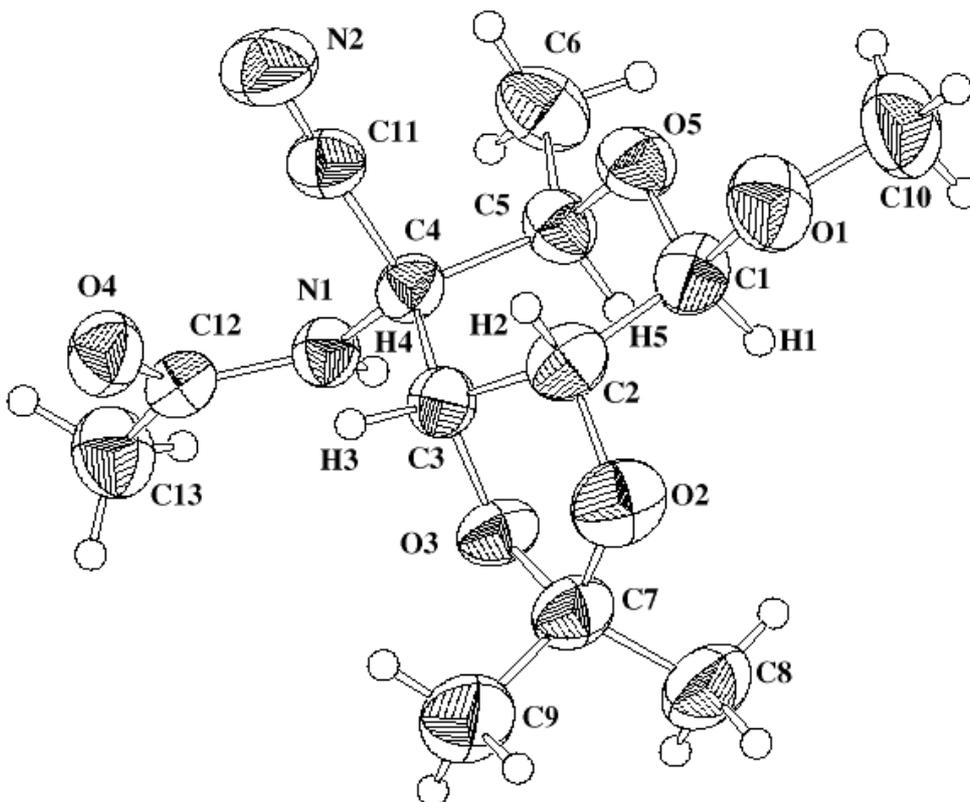
Figure 2. ZORTEP plot and atomic numbering of compound **5**.

The analysis of ring conformation by calculating puckering parameters [$Q = 0.544(4)$ Å, $\theta = 22.9(5)°$, $\varphi = 326.9(13)°$] according to Cremer and Pople [4] has shown that pyranose ring in **5** adopt a $^4C_1$ conformation which is slightly distorted into the direction of $^0H_5$ [5,6], thus indicating a flattening at C-1 and C-4.

The values of relevant torsion angles [O3–C3–C4–C11 = 170.0(3)°, C3–C4–C5–C6 = –177.8(4)°] clearly demonstrate an *allo* configuration respecting the above mentioned conformation of the pyranose ring. On the other hand, torsion angle O1–C1–C2–O2 = –84.7(4)° suggests a β-D-anomeric linkage. Additionally, the values of torsion angles H1–C1–C2–H2 = 156.2(5)° and H2–C2–C3–H3 = –35.0(7)° obtained from X-ray analysis are in good agreement with those obtained from ^1H NMR measurements. According to Karplus curve [7], observed vicinal coupling constants $J_{1,2} = 6.9$ Hz and $J_{2,3} = 5.2$ Hz correlate with dihedral angles of 154° and 36°, respectively.

Experimental

General

The relevant data of synthetic and analytical methods as well as instruments and materials used for the preparation and characterization of the title compound are presented in ref. [1]. Analytical sample of **5** was used for generation of suitable crystals.

X-ray Analysis

Crystal and experimental data for compound **5** are given in Table 1. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares technique. The choice of space group and hence the absolute configuration of the compound (1-R, 2-R, 3-R, 4-R, 5-R) was based on the fact that configuration on positions 1, 2, 3 and 5 of pyranose ring is known and could not change. The crystallographic computations were performed with Bruker SHELXTL [8]. The ZORTEP program [9] was used for the molecular graphics drawing.

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The corresponding deposition number is CCDC 140110. Copies of the data can be obtained free of charge on request to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408, Fax: +44-1223 336-033).

Table 1. Crystal and experimental data for compound **5**[a].

Empirical formula	$C_{13}H_{20}N_2O_5$
Formula weight	284.31
Temperature, T (K)	296(2)

Continuation of the Table 1.

Wavelength, λ (Å)	0.71073
Crystal system	Hexagonal
Space group	$P6_2$
Unit cell dimensions (Å)	$a = 15.6124(6)$ $\alpha = \beta = 90°$
	$b = 15.6124(6)$
	$c = 10.6318(6)$ $\gamma = 120°$
Unit-cell volume, V (Å^3)	2244.3(2)
Formula units per unit cell, Z	6
Calculated density, D_x (g cm^{-3})	1.262
Absorption coefficient, μ (mm^{-1})	0.097
F(000)	912
Crystal size (mm)	0.56 (max) 0.04 (min)
Diffractometer	Siemens SMART CCD
Theta range for data collection (°)	1.51—23.29
Index ranges	$-17 \leq h \leq 17, -17 \leq k \leq 15, -11 \leq l \leq 11$
Reflections collected	8776
Independent reflections [$I > 2\sigma(I)$]	2141 ($R_{int} = 0.044$)
Refinement method	Full-matrix least-squares on F^2
Data / parameters	2141 / 206
Goodness of fit (all)	1.013
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0490$, w$R2 = 0.1232$
R indices (all data)	$R1 = 0.0706$, w$R2 = 0.1443$
Largest diff. peak and hole	0.133 and -0.169 (e Å^{-3})

[a] Standard deviations in parentheses.

Table 2. Selected bond lengths [in Å] and bond angles [in °] for compound **5**[a].

C4–C11	1.495(7)	C4–N1	1.449(5)
C4–C3	1.540(5)	C4–C5	1.546(5)
C3–O3	1.414(5)	C3–C2	1.525(6)
C2–O2	1.422(5)	C2–C1	1.512(6)
C1–O1	1.377(5)	C1–O5	1.429(5)
O5–C5	1.412(5)	C5–C6	1.507(6)
O3–C7	1.428(5)	O2–C7	1.439(5)
C7–C8	1.494(7)	C7–C9	1.509(6)

Continuation of the Table 2.

O1–C10	1.449(6)	C11–N2	1.133(6)
N1–C12	1.334(5)	O4–C12	1.238(5)
C12–C13	1.490(6)	C11–C4–N1	110.9(3)
C11–C4–C3	107.2(3)	N1–C4–C3	111.9(3)
C11–C4–C5	107.9(3)	N1–C4–C5	109.5(3)
C3–C4–C5	109.3(3)	O3–C3–C2	102.0(3)
O3–C3–C4	108.3(3)	C2–C3–C4	115.7(3)
O2–C2–C1	110.8(3)	O2–C2–C3	102.5(3)
C1–C2–C3	114.1(3)	O1–C1–O5	108.0(3)
O1–C1–C2	108.4(3)	O5–C1–C2	111.5(3)
C5–O5–C1	111.9(3)	O5–C5–C4	107.5(3)
O5–C5–C6	107.9(3)	C4–C5–C6	114.5(4)
C3–O3–C7	106.2(3)	C7–O2–C2	108.7(3)
O2–C7–O3	105.8(3)	O2–C7–C8	110.2(4)
O3–C7–C8	108.6(4)	O2–C7–C9	108.5(4)
O3–C7–C9	110.4(4)	C8–C7–C9	113.1(4)
C1–O1–C10	113.7(4)	N2–C11–C4	176.5(5)
C12–N1–C4	124.7(3)	O4–C12–N1	120.7(4)
O4–C12–C13	121.8(4)	N1–C12–C13	117.4(4)

[a] Standard deviations in parentheses.

Table 3. Selected torsion angles [in °] for compound **5**[a].

C1–C2 – C3–C4	–32.8(5)
H1–C1–C2–H2	156.2(5)
H2–C2–C3–H3	–35.0(7)
C3–C4 – C5–O5	–57.9(4)
C3–C2 – O2–C7	20.3(5)
C3–C4 – C5–C6	–177.8(4)
O1–C1 – C2–O2	–84.7(4)
C10–O1 – C1–O5	–64.5(5)
C10–O1 – C1–C2	174.5(4)
C13–C12 – N1–C4	–178.9(4)
O4–C12 – N1–C4	3.2(7)
O2–C2 – C3–O3	–35.5(5)
O3–C3 – C4–C11	170.0(3)

[a] Standard deviations in parentheses.

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for compound **5**[a].

Atom	x	y	z	U(eq)
C4	2055(3)	4584(3)	2104(4)	40.0(9)
C3	1000(3)	3989(3)	1565(4)	41.3(9)
H3	584(3)	4240(3)	1904(4)	32(9)
C2	492(3)	2871(3)	1736(4)	49.9(11)
H2	119(3)	2682(3)	2527(4)	61(12)
C1	1188(3)	2462(3)	1702(4)	49.8(10)
H1	1345(3)	2398(3)	826(4)	35(9)
O5	2080(2)	3080(2)	2375(2)	50.3(8)
C5	2622(3)	4029(3)	1829(4)	45.5(10)
H5	2653(3)	3957(3)	917(4)	63(13)
O3	1058(2)	4084(2)	241(3)	46.9(7)
O2	−175(2)	2514(2)	702(3)	64.1(9)
C7	159(3)	3280(3)	−236(4)	52.6(11)
C9	−614(4)	3583(4)	−382(6)	77(2)
H9A	−391(10)	4110(16)	−985(21)	105(23)
H9B	−721(16)	3805(21)	414(8)	69(15)
H9C	−1221(7)	3028(7)	−669(28)	64(13)
C8	381(4)	2933(4)	−1438(5)	70.7(14)
H8A	671(19)	3471(7)	−2026(10)	71(15)
H8B	−220(5)	2405(14)	−1783(14)	74(14)
H8C	835(15)	2700(18)	−1277(6)	89(19)
O1	727(2)	1546(2)	2267(3)	67.8(9)
C10	1284(4)	1034(4)	2189(6)	81(2)
H10A	892(12)	374(11)	2512(35)	131(25)
H10B	1879(15)	1383(17)	2676(30)	113(24)
H10C	1451(25)	1004(26)	1327(7)	120(24)
C6	3657(3)	4519(4)	2355(5)	63.7(13)
H6A	4039(7)	5170(9)	2004(21)	69(14)
H6B	3960(8)	4133(12)	2143(24)	74(14)
H6C	3632(3)	4566(19)	3253(6)	95(19)
C11	1959(3)	4623(3)	3498(5)	46.1(10)
N2	1865(3)	4602(3)	4557(4)	69.1(11)
N1	2592(2)	5571(2)	1576(3)	40.1(8)
H4	3041(2)	5687(2)	1027(3)	63(15)
O4	1834(2)	6207(2)	2705(3)	57.6(8)
C12	2440(3)	6313(3)	1880(4)	44.5(9)
C13	3050(4)	7276(3)	1223(5)	63.2(13)
H13A	2642(9)	7384(19)	644(37)	184(42)
H13B	3575(24)	7261(15)	772(41)	138(27)
H13C	3325(32)	7801(5)	1830(7)	179(35)

[a] Standard deviations in parentheses.

References and Notes

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Samples Availability: Available from the authors.