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Tautomeric 6-oxoisocytidine (methanol solvate)

Dale C. Swenson,* Sanjib Bera and Vasu Nair

Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA

Correspondence e-mail: dale-swenson@uiowa.edu

Key indicators

Single-crystal X-ray study
T = 180 K
Mean σ(C–C) = 0.006 Å
Disorder in main residue
R factor = 0.052
wR factor = 0.128
Data-to-parameter ratio = 6.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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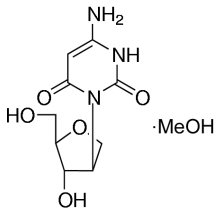
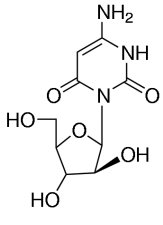
Ambiguity concerning the base structure of 6-oxoisocytidine methanol solvate {systematic name: 4-(*R*)-[4-amino-2,6-dioxopyrimidine-1-yl]-3(*S*)-hydroxy-2(*R*)-furanmethanol methanol solvate}, $C_{18}H_{18}N_{18}O_{18}\cdot CH_3OH$, is resolved by the crystal structure reported here. The 3-imine N site is protonated and forms a hydrogen bond with the 6-oxo carbonyl group of an adjacent molecule. The solid-state packing leads to the formation of sheets of molecules with the intervening space occupied by disordered methanol solvent molecules.

Comment

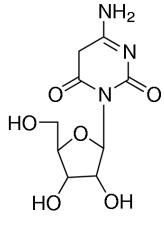
Isomeric nucleosides (or isonucleosides), a novel class of nucleosides, have attracted much interest recently because of their significant anti-HIV and anti-HSV activity, as well as their stability towards acidic and enzymatic deamination (Nair & Jahnke, 1995). For example, 4(*S*)-(6-amino-9*H*-purin-9-yl)-tetrahydro-1(*S*)-furanmethanol (IsoddA), an isomeric dideoxynucleoside synthesized in our laboratory, has antiviral activity against HIV-1 and HIV-2 (Nair *et al.*, 1995; Nair & Nuesca, 1992). In addition, it has been reported that the isodeoxynucleoside, IsodG, with guanine as the nucleobase, has activity against HSV-1 and HSV-2 (Kakefuda *et al.*, 1994). Our interest in isomeric nucleosides with new nucleobases led us to the synthesis of 6-oxoisocytidine, (I). However, in the literature, there is some ambiguity concerning the structure of the base moiety of 6-oxocytidine. Two different structures have been suggested for this base moiety in compounds (II) (Falco *et al.*, 1970) and (III) (Lipkin *et al.*, 1968). Thus, it was important, not only to synthesize compound (I) for antiviral studies, to establish unequivocally the structure of the target molecule by physicochemical techniques including single-crystal X-ray crystallography. The target nucleoside, (I), was synthesized from 5-iodoisocytidine *via* the anhydronucleoside intermediate.



(I)



(II)



(III)

The furanose ring adopts a C2′-envelope conformation. The envelope (O1′/C3′/C4′/C5′) is nearly perpendicular [dihedral angle = 89.5 (2)°] to the planar cytidine ring (N1/C2/N3/C4/C5/C6; r.m.s. deviation = 0.003 Å). The CH_2OH equatorial

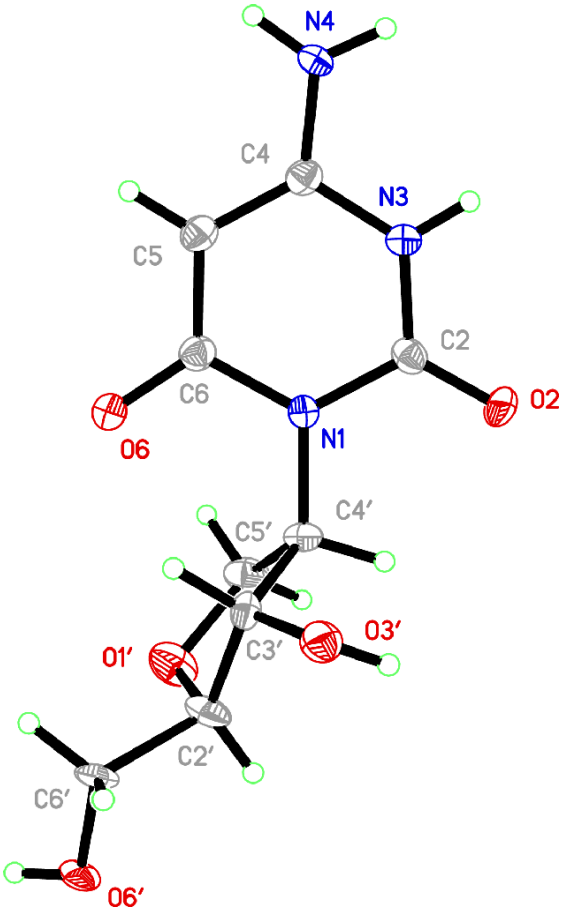


Figure 1
View of the title compound. Displacement ellipsoids are shown at the 35% probability level. Only one orientation of the disordered CH_2OH group is shown.

substituent at C2′ exhibits threefold disorder, with each of the C2′—C6′ *anti* conformers equally represented. [The C6′—O6′ orientation is *anti* to C2′—C3′ (site 1), C6′*B*—O6′*B* is *anti* to C2′—O1′ (site 2), and C6′*C*—O6′*C* is *anti* to C2′—H2′1 (site 3).]

The H3···O6 and H4*B*···O6 hydrogen bonds form ribbons of molecules parallel to the *b* axis. These ribbons stack parallel to the *a* axis to form sheets. The stacks are held together *via* π-stacking interactions [cytidine–cytidine^{i} = 3.419 Å and cytidine–cytidine^{ii} = 3.333 Å; symmetry codes: (i) $1-x, -y, \frac{1}{2}+z$; (ii) $2-x, -y, \frac{1}{2}+z$] and the H4*A*···O3′ hydrogen bond. The inter-sheet space [centered on the $(x, y, 0)$ and $(x, y, \frac{1}{2})$ planes] is occupied by disordered methanol of solvation. Four partially occupied [occ(C21—O21) = 0.333, occ(C21′–O21′) = 0.333, occ(C31—O31) = 0.166 and occ(C31′—O31′) = 0.166] sites are included in the structure. The O3′—H3′ hydroxyl group hydrogen bonds to the methanol O atom (for each of the disorder sites). There is a correlation between the location of the >C2′—CH_2OH substituent and the methanol disorder sites. For site 1, the methanol molecule is located at the C31—O31 and C31′—O31′ sites, for site 2 at the C21′—O21′ site, and for site 3 at the C21—O21 site. See Table 2 for the hydrogen-bonding geometries (including the disordered structure).

The conclusion from the X-ray data is supported by the high-field ^{13}C NMR spectrum.

Experimental

Compound (I): to a solution of 5-iodoisocytidine (0.36 g, 1 mmol) in DMSO/^{t}BuOH (1:1, 40 ml) was added ^{t}BuOK (0.45 g, 4 mmol). The reaction mixture was heated at 333 K for 24 h. The solution was neutralized with 0.5 *M* aqueous HCl, evaporated to dryness and purified over silica gel to give the anhydro derivative. The anhydro derivative was dissolved in 0.2 *M* $Ba(OH)_2$ (10 ml) and heated at 373 K for 1 h. The solution was neutralized with 0.5 *M* HCl and evaporated to dryness. The residue was purified over HPLC on C-18 reverse-phase column (H_2O/MeOH) to give (I) (0.04 g, 16%) as a white powder. Compound (I) was crystallized from MeOH (m.p. 454 K). ^{1}H NMR (DMSO-d_6, p.p.m.): 10.40 (*bs*, 1 H); ^{13}C NMR (DMSO-d_6, p.p.m.): 163.3, 153.8, 151.1, 85.0, 74.2, 71.2, 65.3, 61.9, 57.7; UV (MeOH): λ_{max} 266; HRMS (FAB): $(M + H)^+$ calculated for $C_9H_{14}N_3O_5$ 244.0933, found 244.0923.

Crystal data

$C_9H_{13}N_3O_5\cdot CH_4O$
M_r = 275.27
Orthorhombic, $C222_1$
a = 6.7571 (14) Å
b = 12.430 (3) Å
c = 28.880 (6) Å
V = 2425.7 (9) Å^3
Z = 8
D_x = 1.507 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4008 reflections
θ = 3.3–25.0°
μ = 0.13 mm^{-1}
T = 180 (2) K
Plate, colorless
0.13 × 0.11 × 0.03 mm

Data collection

Nonius KappaCCD diffractometer
CCD φ scans
Absorption correction: none
13 640 measured reflections
1237 independent reflections
1078 reflections with $I > 2\sigma(I)$
R_{int} = 0.058
θ_{max} = 25.0°
$h = -8 \rightarrow 8$
$k = -14 \rightarrow 14$
$l = -34 \rightarrow 34$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.128
S = 1.06
1231 reflections
206 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0581P)^2 + 4.8516P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.034
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.0091 (16)

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.399 (5)	C5—C6	1.396 (5)
N1—C6	1.417 (5)	O1′—C2′	1.423 (6)
N1—C4′	1.483 (5)	O1′—C5′	1.442 (6)
C2—N3	1.354 (5)	C3′—C2′	1.491 (7)
N3—C4	1.364 (5)	C3′—C4′	1.557 (7)
C4—N4	1.350 (5)	C4′—C5′	1.509 (7)
C4—C5	1.381 (6)		
C2—N1—C6	122.8 (3)	C2′—O1′—C5′	106.1 (4)
C2—N1—C4′	118.1 (3)	C2′—C3′—C4′	100.2 (4)
C6—N1—C4′	119.0 (3)	N1—C4′—C5′	115.5 (4)
N3—C2—N1	114.9 (3)	N1—C4′—C3′	115.3 (4)
C2—N3—C4	125.4 (3)	C5′—C4′—C3′	104.6 (3)
N3—C4—C5	119.7 (4)	O1′—C5′—C4′	107.3 (4)
C4—C5—C6	119.1 (4)	O1′—C2′—C3′	106.6 (4)
C5—C6—N1	118.1 (3)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O6^{i}	0.88	1.90	2.724 (4)	155
N4—H4A···O3′^{ii}	0.88	2.08	2.898 (5)	155
N4—H4B···O6^{i}	0.88	2.10	2.858 (5)	144
O6′—H6′···O31^{iii}	0.84	2.18	2.57 (3)	108
O6′—H6′···O31′^{iii}	0.84	2.30	2.85 (5)	123
O6′B—H6′B···O2^{iv}	0.84	2.05	2.793 (12)	147
O6′C—H6′C···N4^{v}	0.84	2.35	3.041 (10)	140
O6′C—H6′C···O1′	0.84	2.32	2.786 (12)	115
O3′—H3′···O21^{vi}	0.84	1.88	2.722 (12)	175
O3′—H3′···O21′^{vi}	0.84	2.11	2.936 (13)	170
O3′—H3′···O31^{vii}	0.84	1.72	2.55 (2)	168
O3′—H3′···O31′^{vii}	0.84	2.07	2.75 (15)	137
O21—H21···O1′^{viii}	0.84	2.02	2.856 (13)	173
O21′—H21′···O6′B	0.84	1.94	2.68 (2)	147
O31—H31···O1′^{ix}	0.84	2.11	2.851 (15)	146
O31′—H31′···O6′	0.84	2.22	2.81 (2)	128

Symmetry codes: (i) $\frac{3}{2}-x,\frac{1}{2}+y,\frac{1}{2}-z$; (ii) $1-x,y,\frac{1}{2}-z$; (iii) $\frac{1}{2}+x,\frac{1}{2}-y,1-z$; (iv) $x-\frac{1}{2},y-\frac{1}{2},z$; (v) $\frac{3}{2}-x,y-\frac{1}{2},\frac{1}{2}-z$; (vi) $\frac{1}{2}+x,\frac{1}{2}+y,z$; (vii) $x,1-y,1-z$; (viii) $x-1,y,z$; (ix) $x-\frac{1}{2},\frac{1}{2}-y,1-z$.

The CH_2OH substituent at C2′ is disordered, by rotation about the C2′—C6′ bond, over three orientations of equal occupancy (0.3333). In one orientation (C6′/H6′1/H6′2/O6′/H6′), the C—O bond is *anti* to the C2′—C3′ bond, another (C6′B/H6′3/H6′4/O6′B/H6′B) has the C—O bond *anti* to the C2′—O1′ bond, and the third (C6′C/H6′5/H6′6/O6′C/H6′C) has the C—O bond *anti* to the C2′—H2′1 bond. The occupancies of each refined to approximately 1/3, so each was fixed to 0.3333 for the final refinement cycles. The coordinates of H2′1 were allowed to refine with a U_{iso} value of $1.1U_{eq}$(C2′). The methanol molecule of solvation is also disordered and each orientation was refined as a rigid group (C—H = 0.99 Å, C—O = 1.45 Å and O—H = 0.84 Å, tetrahedral angles). One orientation (C21/H21A—C/O21/H21) was refined with occupancy 0.3333, as was the second (C21′/H21D—F/O21′/H21′). For these two orientations, the C and O atoms were refined with individual isotropic displacement parameters. The third orientation exhibited high thermal motion and was split into two groups (C31/H31A—C/O31/H31 and C31′/H31D—F/O31′/H31′) with occupancy 0.1666 and one isotropic displacement parameter for both C and both O atoms. All H atoms (except H2′1) were included with the riding model (or were part of a rigid group) with program defaults. The largest shift (0.034) occurred for the rotz parameter of the O31 rigid group. The average shift was 0.003. 433 Friedel pairs were merged for the final cycles of refinement. The absolute structure was assumed from the synthesis.

Data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1997); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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