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2′-Deoxy-5-propynylcytidine: a nucleoside forming two solid-state conformations

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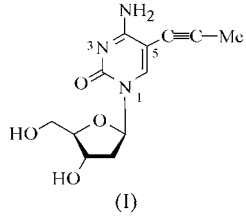
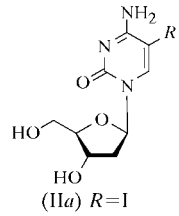
The title compound, 4-amino-1-(2-deoxy-β-D-erythropentofuranosyl)-5-(prop-1-ynyl)pyrimidin-2(1*H*)-one, $C_{12}H_{15}N_3O_4$, shows two conformations in the crystalline state which differ mainly in the glycosylic bond torsion angle and the sugar pucker. Both molecules exhibit an *anti* glycosylic bond conformation, with torsion angles $\chi = -135.0$ (2) and -156.4 (2)° for molecules 1 and 2, respectively. The sugar moieties show a twisted C2′-*endo* sugar pucker (S-type), with P = 173.3 and 192.5° for molecules 1 and 2, respectively. The crystal structure is characterized by a three-dimensional network that is stabilized by several intermolecular hydrogen bonds between the two conformers.

Comment

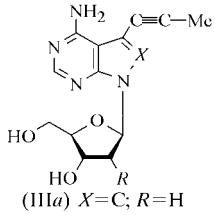
Advances in synthetic nucleic acid chemistry have led to a broad variety of structurally modified DNA constituents, including modifications on the nucleobase or the sugar moiety (Seela & Zulauf, 1998; Wang *et al.*, 2000). Their introduction into DNA oligonucleotides has provided modified nucleic acids with superior properties compared with their parent counterparts, *e.g.* increased duplex stability or mismatch recognition (Barnes & Turner, 2001; Froehler *et al.*, 1992; He & Seela, 2002). For pyrimidine nucleosides, the 5-position of the nucleobase is an appropriate place to introduce functional groups such as halogens or propynyl groups, as this site lies in the major groove of the DNA duplex (Ahmadian *et al.*, 1998). Modifications at this position are also well tolerated by RNA and DNA polymerases, which do not interact with the nucleobases in the major groove (Roychowdhury *et al.*, 2004). 5-Propynylated pyrimidine nucleosides have been shown to increase duplex and triplex stability significantly, which makes them useful tools for application in antisense technology or in primer probe interactions, as well as for the fabrication of novel DNA constructs (Froehler *et al.*, 1992; He & Seela, 2002; Seela & Budow, 2007; Seela, Budow & Leonard, 2007). The introduction of the propynyl group at the 5-position of cytosine lowers the pK_a value of the heterocycle from 4.5 to 3.3 (Robles *et al.*, 2002). Thus, the protonation of N3 requires more strongly acidic conditions than the unsubstituted species. The shift of the pK_a value has a significant influence on the formation of the tetrameric i-motif structure, which is well known to be formed by cytosine-rich oligonucleotides under weakly acidic conditions (pH 5; Guéron & Leroy, 2000). The self-assembly of oligonucleotides in which consecutive 2′-deoxycytidine stretches are replaced by 2′-deoxy-5-propynylcytidine residues in the i-motif structure is simply achieved under significantly stronger acidic conditions (pH 3.5). 2′-Deoxy-5-propynylcytidine, (I), has also been used for the construction of a novel colorimetric assay, which is based on DNA gold nanoparticle conjugates responding selectively to pH changes in a narrow pH range between 4 and 3 (Seela & Budow, 2007; Seela, Budow & Leonard, 2007). Consequently, we became interested in performing a single-crystal X-ray analysis of compound (I), which is reported here.



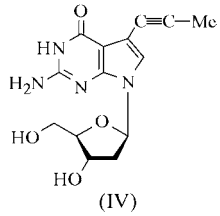
(I)
Systematic numbering



(II*a*) R=I
(II*b*) R=Me



(III*a*) X=C; R=H
(III*b*) X=N; R=OH



(IV)

This is the first X-ray structure of a propynylated 2′-deoxypyrimidine nucleoside. The X-ray structures of some purine-like propynyl nucleosides and ribonucleosides, such as 7-deaza-2′-deoxy-7-propynyladenosine, (III*a*) (Seela, Shaikh *et al.*, 2006), 8-aza-7-deaza-7-propynyladenosine, (III*b*) (Lin *et al.*, 2005), and 7-deaza-2′-deoxy-7-propynylguanosine, (IV) (Seela, Shaikh & Eickmeier, 2004), have been reported recently.

Compound (I) was synthesized from 2′-deoxy-5-iodocytidine, (IIa), and propyne gas using the palladium-catalyzed Sonogashira cross-coupling reaction (Hobbs, 1989; Froehler *et al.*, 1992; Seela, Budow & Leonard, 2007). Slow crystallization of 2′-deoxy-5-propynylcytidine from a mixture of dichloromethane and methanol (85:15) gave colourless crystals. The crystals consist of two forms of molecules which differ in their conformation. They are here denoted (I-1) and (I-2). Similar results have been found for crystals of 2′-deoxy-5-propynyluridine (Seela, Budow & Eickmeier, 2007) and 4-nitro-2*H*-indazole-N^2-ribonucleoside (Seela, Peng *et al.*, 2004). The

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three-dimensional structures of the two molecules of 2′-deoxy-5-propynylcytidine, *viz*. type 1, (I-1), and type 2, (I-2), are shown in Fig. 1, and selected geometric parameters are listed in Table 1. The glycosylic torsion angle in pyrimidine nucleosides is generally found to be *anti* and only in rare cases has the *syn* conformation been reported (Saenger, 1984). The orientation of the nucleobase relative to the sugar moiety (*syn*/*anti*) is defined by the torsion angle χ (O4′—C1′—N1—C2) (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983).

In the crystalline state of (I), both types of molecules, (I-1) and (I-2), adopt *anti* conformations for the glycosylic bond. For (I-1), the torsion angle of the glycosylic bond is χ = −135.0 (2)°, which is very similar to the torsion angle in 2′-deoxy-5-methylcytidine, (II*b*) (χ = −131.7°; Sato, 1988; Seela *et al.*, 2000). In comparison, the glycosylic bond torsion angle of (I-2) is χ = −156.4 (2)°.

The lengths of the N1—C1′ glycosylic bonds of (I-1) and (I-2) are very similar [1.475 (2) Å for (I-1) and 1.490 (2) Å for (I-2)], while the N1—C1′ bond of (II*b*) is slightly shorter [1.461 (3) Å; Sato, 1988].

The 2′-deoxyribofuranosyl moieties of (I-1) and (I-2) show an S-type conformation and exhibit a twisted C2′-*endo* sugar puckering. This is consistent with the preferred conformation of 2′-deoxyribonucleotides (Saenger, 1984). Molecule (I-1) shows a pseudorotational phase angle P = 173.3°, with the maximum amplitude τ_m = 37.5° referring to a major C2′-*endo* sugar puckering (C2′-*endo*–C3′-*exo*, $^2T_3$) (Rao *et al.*, 1981), and molecule (I-2) exhibits a minor 2′-*endo* sugar puckering (C3′-*exo*–C2′-*endo*, $_3T^2$), with P = 192.5° and τ_m = 34.2°. Compound (II*b*) also exhibits a similar sugar conformation (C2′-*endo*, ^2E, with P = 161.5° and τ_m = 37.9°; Sato, 1988; Seela *et al.*, 2000).

Both (I-1) and (I-2) display different conformations about the C4′—C5′ bond, which is defined by the torsion angle γ (O5′—C5′—C4′—C3′). For molecule (I-1), the torsion angle γ = 57.8 (3)°, representing a synclinal (+*gauche*) conformation, whereas in (I-2) the C4′—C5′ bond adopts an antiperiplanar (*trans*) conformation, with γ = 166.1 (2)°. The same antiperiplanar conformation of the exocyclic group has been reported for 2′-deoxy-5-methylcytidine, (II*b*) [γ = 178.7 (2)°; Sato, 1988].

The heterocyclic ring systems of (I-1) and (I-2) are nearly planar; the r.m.s. deviations of the ring atoms (N1/C2/N3/C4/C5/C6) from their calculated least-squares planes are 0.0074 and 0.0143 Å, respectively. In both molecules, the exocyclic groups lie on both sides of the pyrimidine ring system.

The propynyl groups of (I-1) and (I-2) form an almost linear and rigid residue [C151—C152—C153 = 179.3 (3)° for (I-1) and C251—C252—C253 = 178.7 (3)° for (I-2)]. In both mol-

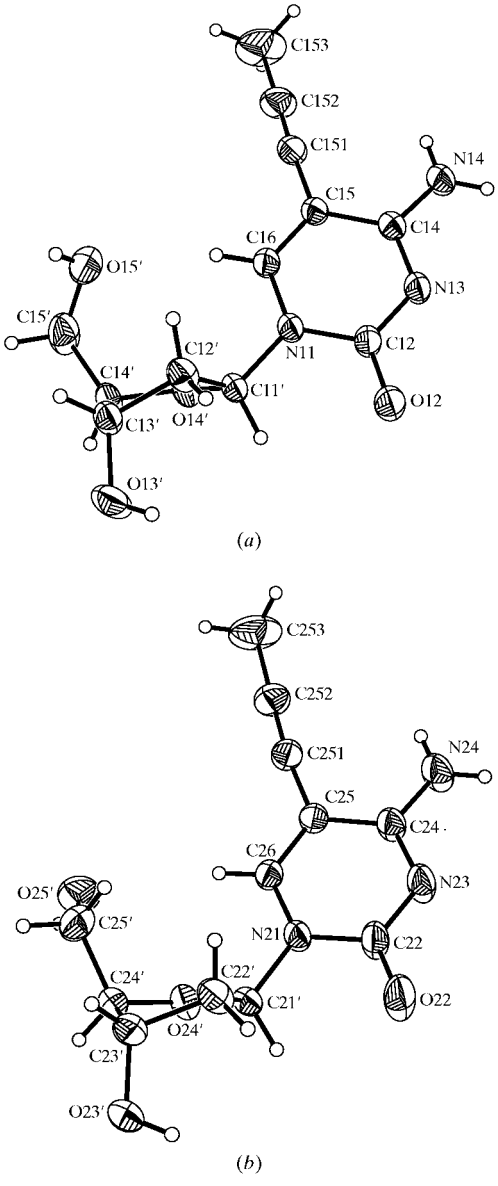

Figure 1
Perspective views of (*a*) molecule (I-1) and (*b*) molecule (I-2). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

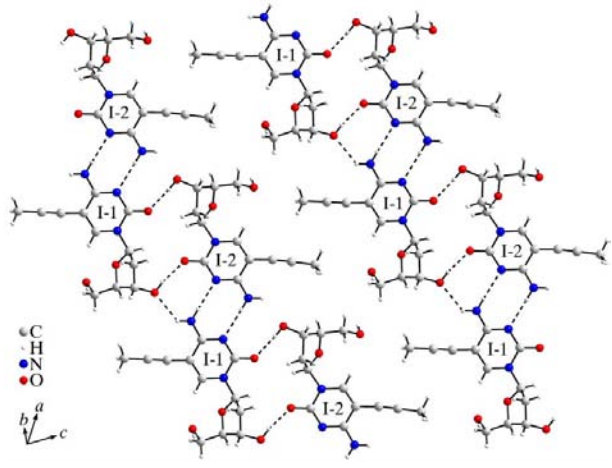

Figure 2
A ball-and-stick model of molecules (I-1) and (I-2) within one sheet of the crystal structure of (I), viewed perpendicular to the sheet of molecules. Intermolecular hydrogen bonds are represented by dashed lines.

ecules, the propynyl groups are inclined with respect to the pyrimidine ring plane. The angles of inclination have been calculated as the deviation of the propynyl group (atoms C151 and C251) from the normal to the pyrimidine plane (atoms C15 and C25). For molecule (I-1), the angle is 3.5°, which is within the range observed in 1-(β-D-arabinofuranosyl)-5-propynyluracil (3.7°; Cygler *et al.*, 1984). The angle of inclination of (I-2) is larger (4.4°) and similar to the angles found for 7-deaza-2′-deoxy-7-propynylguanosine, (IV) (4.6°; Seela, Shaikh & Eickmeier, 2004), and 8-aza-7-deaza-7-propynyladenosine, (III*b*) (4.0°; Lin *et al.*, 2005). Only in the case of 7-deaza-2′-deoxy-7-propynyladenosine, (III*a*), is the propynyl group in a nearly coplanar orientation with respect to the nucleobase moiety (1.6°; Seela, Shaikh *et al.*, 2006). The triple-bond length of (I-1) is 1.190 (3) Å and that for (I-2) is 1.183 (3) Å, which are both in the range of non-conjugated triple bonds (Cygler *et al.*, 1984).

In the crystal structure of nucleoside (I), molecules (I-1) and (I-2) are linked into sheets by several intermolecular hydrogen bonds (Table 2 and Fig. 2). These sheets are stabilized by two types of hydrogen bonds. Molecules of different conformation are linked through hydrogen bonds between neighbouring base and sugar units (O13′—H13′···O22^{iii} and N14—H14*A*···N23^{i}, and O23′—H23′···O12^{vii} and N24—H24*A*···N13^{v}; symmetry codes are given in Table 2). Two further hydrogen bonds between the sugar moieties and the nucleobases are found connecting molecules of identical conformation [N14—H14*B*···O13′^{ii} and O15′—H15′···N13^{iv} for (I-1), and N24—H24*B*···O23′^{vi} and O25′—H25′···N23^{viii} for (I-2); symmetry codes are given in Table 2]. The sheets are built up by alternating chains consisting of conformers (I-1) and (I-2). Each of these chains contains only one type of conformer, as shown in Fig. 2.

Experimental

Compound (I) was synthesized from (II*a*) according to literature procedures (Hobbs, 1989; Froehler *et al.*, 1992; Seela, Budow & Leonard, 2007) and was slowly crystallized from a mixture of dichoromethane and methanol (85:15) as colourless crystals [m.p. 481 K (decomposition)]. For the X-ray diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary using epoxy resin.

Crystal data

$C_{12}H_{15}N_3O_4$
M_r = 265.27
Triclinic, *P*1
a = 8.3908 (7) Å
b = 9.0698 (8) Å
c = 9.7303 (10) Å
α = 64.734 (5)°
β = 71.721 (10)°
γ = 88.198 (11)°
V = 631.33 (10) Å^3
Z = 2
D_x = 1.395 Mg m^{-3}
Mo *Kα* radiation
μ = 0.11 mm^{-1}
T = 293 (2) K
Block, colourless
0.3 × 0.2 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
ω/2θ scans
4107 measured reflections
3456 independent reflections
3173 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 30.0°
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.112
S = 1.05
3456 reflections
350 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0675P)^2 + 0.0502P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N11—C11′	1.475 (2)	N21—C21′	1.490 (2)
C15—C151	1.428 (3)	C25—C251	1.434 (3)
C151—C152	1.190 (3)	C251—C252	1.183 (3)
C16—N11—C11′	119.07 (16)	C26—N21—C21′	121.90 (16)
O12—C12—N13	121.98 (19)	O22—C22—N23	122.5 (2)
N14—C14—C15	120.15 (19)	N24—C24—C25	120.58 (19)
C151—C15—C14	120.82 (18)	C24—C25—C251	119.80 (18)
C152—C151—C15	174.7 (3)	C252—C251—C25	172.1 (3)
C151—C152—C153	179.3 (3)	C251—C252—C253	178.7 (3)
C11′—N11—C12—O12	−4.2 (3)	C21′—N21—C22—O22	−1.8 (4)
N14—C14—C15—C151	2.2 (3)	N24—C24—C25—C251	−3.3 (4)
C12—N11—C11′—O14′	−135.0 (2)	C22—N21—C21′—O24′	−156.4 (2)
C13′—C14′—C15′—O15′	57.8 (3)	C23′—C24′—C25′—O25′	166.1 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N14—H14*A*···N23^{i}	0.86	2.23	3.024 (3)	154
N14—H14*B*···O13′^{ii}	0.86	2.25	2.877 (3)	130
O13′—H13′···O22^{iii}	0.82	1.92	2.726 (3)	167
O15′—H15′···N13^{iv}	0.82	2.27	3.032 (3)	154
N24—H24*A*···N13^{v}	0.86	2.36	3.115 (3)	147
N24—H24*B*···O23′^{vi}	0.86	2.20	2.812 (3)	128
O23′—H23′···O12^{vii}	0.82	1.96	2.773 (3)	171
O25′—H25′···N23^{viii}	0.82	2.27	3.064 (4)	162

Symmetry codes: (i) $x+1, y+1, z$; (ii) $x+1, y+1, z-1$; (iii) $x, y, z+1$; (iv) $x-1, y, z$; (v) $x-1, y-1, z$; (vi) $x-1, y-1, z+1$; (vii) $x, y, z-1$; (viii) $x+1, y, z$.

In the absence of suitable anomalous scattering, Friedel equivalents could not be used to determine the absolute structure. Refinement of the Flack (1983) parameter led to an inconclusive value (Flack & Bernardinelli, 2000) [−0.2 (8)]. Therefore, Friedel equivalents (428) were merged before the final refinement. The known configuration of the parent molecule was used to define the enantiomer employed in the refined model. All H atoms were found in a difference Fourier synthesis. In order to maximize the data–parameter ratio, H atoms were placed in geometrically idealized positions, with C—H distances in the range 0.93–0.98 Å and N—H distances of 0.86 Å, and constrained to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C) or 1.2U_{eq}(N). The OH groups were refined as rigid groups allowed to rotate but not tip, with O—H distances of 0.82 Å and U_{iso}(H) = 1.5U_{eq}(O).

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 1997); program(s) used to solve structure: *SHELXTL*; program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL* and *DIAMOND* (Brandenburg, 1999); software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3048). Services for accessing these data are described at the back of the journal.

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