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2′-Deoxy-5-propynyluridine: a nucleoside with two conformations in the asymmetric unit

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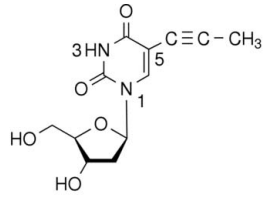
The title compound, 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)pyrimidin-2,4(1*H*,3*H*)-dione, $C_{12}H_{14}N_2O_5$, shows two conformations in the crystalline state: conformer 1 adopts a C2′-*endo* (close to ^2E; *S*-type) sugar pucker and an *anti* nucleobase orientation [$\chi = -134.04\ (19)^\circ$], while conformer 2 shows an *S* sugar pucker (twisted C2′-*endo*–C3′-*exo*), which is accompanied by a different *anti* base orientation [$\chi = -162.79\ (17)^\circ$]. Both molecules show a +*sc* (*gauche*, *gauche*) conformation at the exocyclic C4′—C5′ bond and a coplanar orientation of the propynyl group with respect to the pyrimidine ring. The extended structure is a three-dimensional hydrogen-bond network involving intermolecular N—H···O and O—H···O hydrogen bonds. Only O atoms function as H-atom acceptor sites.

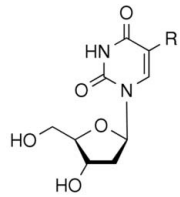
Comment

5-Propynylated pyrimidine nucleosides have been shown to increase duplex stability (Barnes & Turner, 2001; Froehler *et al.*, 1992; He & Seela, 2002) and can strengthen triplex formation (Gilbert & Feigon, 1999). This makes them useful for the development of polymer therapeutics by antisense or antigene technology with the aim of gene silencing (Manoharan, 2004; Praseuth *et al.*, 1999; Crooke, 2004). The structural changes caused by the incorporation of 2′-deoxy-5-propynyluridine, (I), instead of dT in duplex DNA increase base stacking and enhance the hydrophobic interactions between the side chains (He & Seela, 2002). The electron-withdrawing propynyl group at position 5 of pyrimidine nucleosides enforces hydrogen bonding, which is reflected by a decrease of the pK_a value from 9.3 (2′-deoxyuridine; Fox & Shugar, 1952) to 8.7 for 2′-deoxy-5-propynyluridine. As the 5-subsituent of a pyrimidine nucleoside lies in the major groove of the DNA duplex (Ahmadian *et al.*, 1998), it is tolerated by DNA polymerases when corresponding triphosphates are used (Roychowdhury *et al.*, 2004).

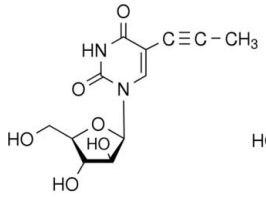


(I)

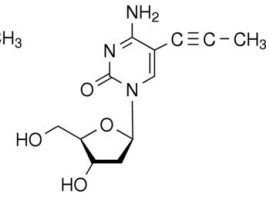
systematic numbering



(II*a*) R = H
(II*b*) R = I
(II*c*) R = —C≡CH



(III)



(IV)

This background prompted us to perform a single-crystal X-ray analysis of (I). Compound (I) was synthesized from 5-iodo-2′-deoxyuridine, (II*b*), and propyne gas, employing the palladium-catalyzed Sonogashira cross-coupling reaction (Hobbs, 1989; Froehler *et al.*, 1992). Slow crystallization of 5-propynyl-2′-deoxyuridine from methanol gave colourless crystals which were submitted to single-crystal X-ray analysis. The crystal structures of the closely related compounds 2′-deoxyuridine, (II*a*) (Rahman & Wilson, 1972), 2′-deoxy-5-ethynyluridine, (II*c*) (Barr *et al.*, 1978), 5-propynylarabinouridine, (III) (Cygler *et al.*, 1984), and 2′-deoxy-5-propynylcytidine, (IV) (Seela *et al.*, 2007), have been reported before and are now compared with the crystal structure of (I).

In the asymmetric unit of (I), two conformational states exist, which differ mainly in their conformation around the

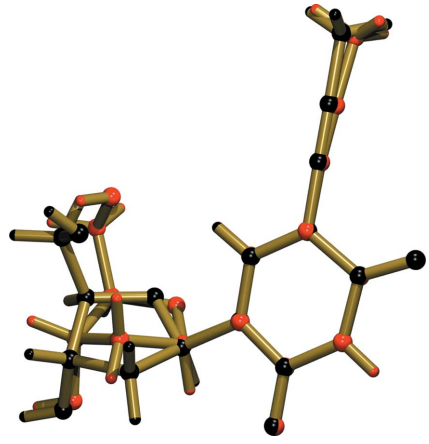


Figure 1
Overlay of molecules (I-1) and (I-2) [in the electronic version of the paper, (I-1) contains red balls and (I-2) contains black balls].

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N-glycosylic bond and the exocyclic C4′—C5′ bond, as demonstrated by Fig. 1. They are defined as conformers 1 and 2, denoted (I-1) and (I-2), respectively. Similar observations were made on the related crystals of (II*a*) and (IV). The three-dimensional structures of the molecules of (I-1) and (I-2), are shown in Fig. 2, and selected geometric parameters are listed in Table 1.

For pyrimidine nucleosides, 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). Commonly, an *anti* conformation at the N-glycosylic bond is observed for pyrimidine nucleosides, and only in rare cases has a *syn* conformation been reported (Saenger, 1984). Both molecules of (I) adopt an *anti* conformation with respect to the sugar ring. The glycosoylic bond torsion angles are χ = −134.04 (19)° for (I-1) and χ = −162.79 (17)° for (I-2). For the molecules of the parent unsubstituted 2′-deoxyuridine (II*a*), and the closely related (II*c*) and (III), *anti* conformations of the glycosylic bonds were reported, with χ within the range of values found for the molecules of (I) [χ = −153.65 and −156.54° for (II*a*), − 157.36° for (II*c*) and −153.65° for (III)].

The glycosylic N11—C11′ bond of (I-1) [1.473 (3) Å] is shorter than the corresponding bond length observed for (I-2) [N21—C21′ = 1.486 (2) Å]. These values are similar to the bond lengths found for the related molecules of (II*a*) (1.45 and 1.50 Å), (II*c*) [1.478 (3) Å] and (III) (1.485 Å), as well as for (IV) [1.475 (2) and 1.490 (2) Å].

The 2′-deoxyribofuranosyl moieties of (I-1) and (I-2) show an *S*-type sugar conformation, which is consistent with the preferred conformation of 2′-deoxyribonucleosides. Molecule (I-1) exhibits a pseudorotational phase angle P = 170.1 (2)°, with the maximum amplitude τ_m = 42.7 (1)°, which corresponds to a C2′-*endo* puckering (close to ^2E), and molecule (I-2) shows a twisted C2′-*endo*-C3′-*exo* ($^2T_3$) sugar conformation with P = 172.9 (2)° and τ_m = 36.2 (1)° (Rao *et al.*, 1981). The *S*-type sugar conformation of (I-1) and (I-2) observed in the crystalline state is consistent with the predominant *S* (71%) conformation of molecule (I) found in solution. This value is very close to the value observed for (II*a*) (70% *S*), indicating that the propynyl group introduced at position 5 of the pyrimidine moiety has almost no effect on the sugar conformation of (I). The sugar conformation of compound (I) in solution was determined from the vicinal ^3J(H,H) coupling constants of the ^{1}H NMR spectra measured in a dimethyl sulfoxide/D_2O mixture, applying the program *PSEUROT 6.3* (Van Wijk *et al.*, 1999). An *S* conformation with a 2′-*endo* sugar pucker was also observed in the crystalline state for (II*a*) and (II*c*).

The conformation about the exocyclic C4′—C5′ bond is defined by the torsion angle γ (O5′—C5′—C4′—C3′). For both molecules of (I), γ adopts a +synclinal (+*sc*, *gauche*, *gauche*) conformation, with γ = 62.6 (3)° for (I-1) and γ = 50.1 (3)° for (I-2). In the crystal structures of (II*a*) and (III), the torsion angle γ is within the same range (40–71°; +*sc*, *gauche*, *gauche*), whereas a −antiperiplanar (−*ap*, *gauche*, *trans*) conformation has been reported for the exocyclic group of (II*c*).

The heterocyclic ring systems of (I-1) and (I-2) are nearly planar. The r.m.s. deviations of the ring atoms from their calculated least-squares planes are 0.0154 and 0.0164 Å, respectively, with a maximum deviation of 0.0227 (14) Å for atom C14 of (I-1) and 0.0269 (13) Å for atom N21 of (I-2). In both molecules, the exocyclic groups lie above and below the heterocyclic plane of the pyrimidine ring system.

The propynyl groups of (I-1) and (I-2) are almost linear, with a C15*A*—C15*B*—C15*C* angle of 177.3 (2)° for (I-1) and a C25*A*—C25*B*—C25*C* angle of 178.5 (2)° for (I-2). In each molecule, the propynyl group is in a coplanar orientation with respect to the pyrimidine ring. The angles of inclination are close to 0° [0.4 (7)° for (I-1) and 0.8 (5)° for (I-2)]. Other nucleosides exhibit propynyl groups that are slightly inclined with respect to the nucleobase moiety. For the propynyl

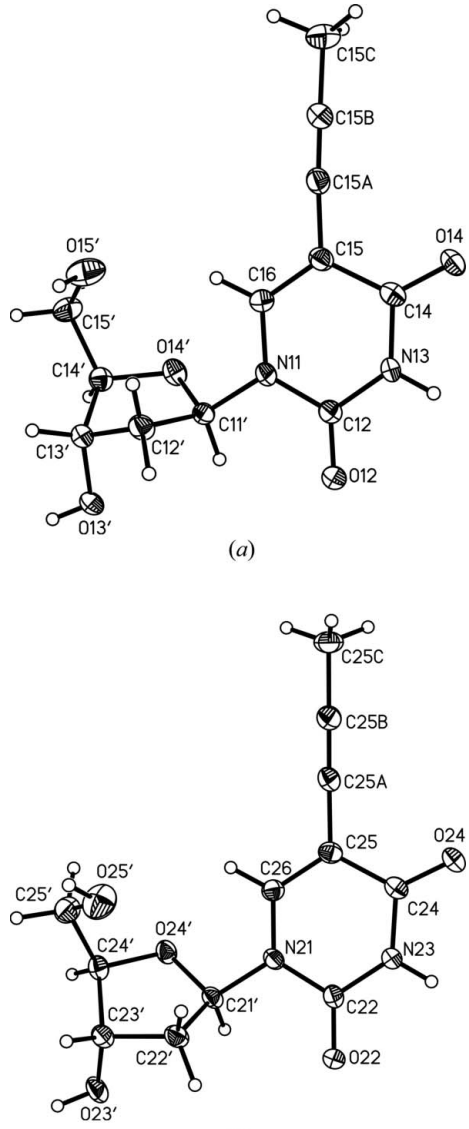

Figure 2
Perspective views of (*a*) molecule (I-1) and (*b*) molecule (I-2), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

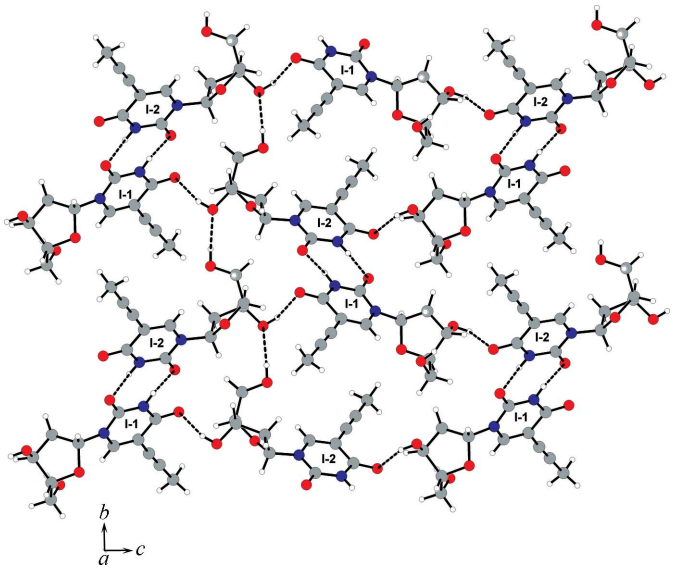

Figure 3
The crystal packing of (I), showing the intermolecular hydrogen-bonding network (projection parallel to the *a* axis).

groups of (III) and (IV-1), the angles of inclination are 3.7 and 3.5°, respectively, whereas for molecule (IV-2), the propynyl group is inclined by 4.4°.

In the crystal structure of nucleoside (I), molecules (I-1) and (I-2) are linked into an infinite three-dimensional network by several intermolecular hydrogen bonds (Table 2 and Fig. 3). Molecules of one conformation are linked to those of the other conformation resulting in an alternating arrangement of the conformers. Both molecules form identical hydrogen-bonding patterns (N13—H13···O22^{i}, O13′—H13*B*···O24^{ii}, O15′—H15···O13′^{iii}, N23—H23···O12^{iv}, O23′—H23*B*···O14^{v}, O25′—H25···O23′^{vi}; see Table 2 for symmetry codes and geometry); only O atoms act as acceptors in hydrogen bonding. Most probably as a result of 'hydrophobic interactions', the lipophilic propynyl groups of molecules (I-1) and (I-2) are arranged in proximal positions with respect to each other while maintaining an opposite chain orientation of the propynyl groups.

Experimental

Compound (I) was synthesized from 2′-deoxy-5-iodouridine (II*b*) and propyne gas according to literature procedures (Hobbs, 1989; Froehler *et al.*, 1992) and was crystallized slowly from methanol as colourless crystals (474 K). For the diffraction experiment, a single crystal was mounted on a MiTeGen MicroMounts fibre in a thin smear of oil.

Crystal data

$C_{12}H_{14}N_2O_5$
M_r = 266.25
Monoclinic, $P2_1$
a = 5.6201 (4) Å
b = 11.3645 (9) Å
c = 19.0281 (16) Å
β = 96.659 (4)°
V = 1207.12 (16) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.12 mm^{-1}
T = 130 K
0.32 × 0.23 × 0.15 mm

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2008)
T_{min} = 0.866, T_{max} = 0.932
22751 measured reflections
3046 independent reflections
2749 reflections with $I > I > 2\sigma(I)$
R_{int} = 0.032

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.088
S = 1.04
3046 reflections
363 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N11—C11′	1.473 (3)	N21—C21′	1.486 (2)
C15—C15*A*	1.431 (3)	C25—C25*A*	1.433 (3)
C15*A*—C15*B*	1.194 (3)	C25*A*—C25*B*	1.197 (3)
C15*B*—C15*C*	1.464 (3)	C25*B*—C25*C*	1.462 (3)
C15*B*—C15*A*—C15	175.8 (2)	C25*B*—C25*A*—C25	178.8 (2)
C15*A*—C15*B*—C15*C*	177.3 (2)	C25*A*—C25*B*—C25*C*	178.5 (2)
C12—N11—C11′—O14′	−134.04 (19)	C22—N21—C21′—O24′	−162.79 (17)
C13′—C14′—C15′—O15′	62.6 (3)	C23′—C24′—C25′—O25′	50.1 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N13—H13···O22^{i}	0.91 (3)	1.94 (3)	2.851 (2)	174 (2)
O13′—H13*B*···O24^{ii}	0.86 (3)	1.98 (4)	2.727 (2)	144 (3)
O15′—H15···O13′^{iii}	0.94 (4)	2.06 (4)	2.921 (3)	152 (3)
N23—H23···O12^{iv}	0.90 (3)	1.91 (3)	2.801 (2)	171 (2)
O23′—H23*B*···O14^{v}	0.79 (3)	2.01 (3)	2.760 (2)	158 (3)
O25′—H25···O23′^{vi}	0.80 (4)	2.04 (4)	2.824 (3)	166 (4)

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

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 inconclusive values for this parameter [0.3 (6)]. Therefore, Friedel equivalents (2617) 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 bonded to C atoms were placed in geometrically idealized positions, with C—H distances of 0.95–1.00 Å and U_{iso}(H) = xU_{eq}(C), where x = 1.5 for the methyl groups and 1.2 for the other H atoms. All H atoms bonded to O and N atoms were located in a difference Fourier map and allowed to refine freely. The refined O—H distances are in the range 0.79 (3)–0.94 (4) Å and the N—H distances are 0.90 (3) and 0.91 (3) Å.

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2009).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3346). Services for accessing these data are described at the back of the journal.

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