3'-Deoxy-2',3'-difluorothymidine, a Nucleoside Analogue

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Abstract

The title compound, 1-(2,3-dideoxy-2,3-difluoro-β-D-ribopentofuranosyl)thymine, $C_{10}H_{12}F_2N_2O_4$, consists of an almost planar heterocyclic base moiety oriented anti with respect to a puckered sugar moiety. The sugar pucker is $^2T_3$ and the N-glycosidic torsion angle is $-119.6(2)°$. The conformation of the O5' atom is +sc and the molecules are held together by a network of N—H···O and O—H···O hydrogen bonds.

Comment

A number of sugar-modified nucleosides display antiviral activity because of their ability to interfere with virally encoded enzymes. The enzymes catalyse those reactions which only occur in the virus-infected cells (Prusoff et al., 1984). The title compound, (I), is a structural analogue of AZT, which is licenced as an anti-AIDS drug for human use. The structural analysis of the title compound is a continuation of earlier work (Das, Mazumdar, Das, Talapatra, Scheiner & Schwalbe, 1993; Das, Mazumdar, Bertolasi & Van Aerschot, 1993) involving systematic conformational studies on modified nucleosides with the aim of understanding the structure–function relationships of possible anti-AIDS compounds.

(I)
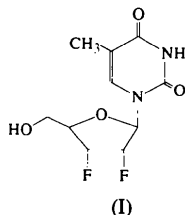
All bond lengths and angles are within the normal ranges (Allen et al., 1987). The heterocyclic base moiety is almost planar, with a maximum deviation of $-0.040(2)$ Å for the C4 atom. The N-glycosidic torsion angle χ (C2—N1—C1'—O4') has a value of $-119.6(2)°$ which corresponds to an anti orientation of the base moiety (Fig. 1). The sugar pucker is C2'-endo/C3'-exo ($^2T_3$), with a pseudorotation phase angle P of $169.8(1)°$ and a maximum puckering amplitude ψ of $36(1)°$. The conformation of the O5' atom with respect to the sugar moiety is defined by the torsion angle O5'—C5'—C4'—C3' (γ), which has a value of $49.3(3)°$ and indicates that O5' is +sc oriented. Although fluorine has a similar electronegative character to a hydroxyl group, it does not take part in the formation of hydrogen bonds.
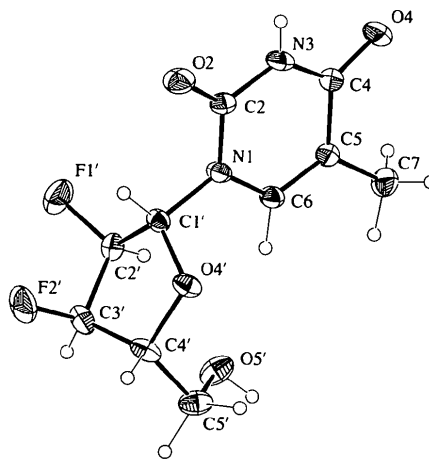

Fig. 1. An ORTEP (Johnson, 1965) plot of (I) with displacement ellipsoids for the non-H atoms drawn at the 30% probability level.
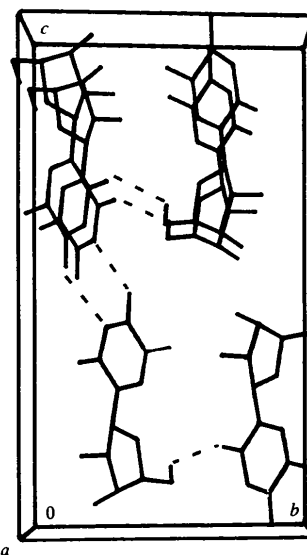

Fig. 2. A view of the unit-cell contents with hydrogen bonds shown by dashed lines.

In the crystal, molecules are held together by N—H···O and O—H···O hydrogen bonds and C—H···O contacts. The title compound has a close conformational similarity to one of the conformers of AZT which has two separate molecules in asymmetric unit, with χ angles of $-125.9\,(5)$ and $-172.0\,(5)°$ and a sugar pucker P of 171 (1) and 213 (1)° (Dyer, Low, Tollin, Wilson & Howie, 1988). Molecules are linked by a network of N—H···O and O—H···O hydrogen bonds (Fig. 2).

Experimental

Crystals of (I) were obtained from an acetone–hexane solution.

Crystal data

$C_{10}H_{12}F_2N_2O_4$	Mo $K\alpha$ radiation
$M_r = 262.21$	$\lambda = 0.71073$ Å
Orthorhombic	Cell parameters from 25
$P2_12_12_1$	reflections
$a = 4.837\,(1)$ Å	$\theta = 9-14°$
$b = 13.296\,(1)$ Å	$\mu = 0.127$ mm^{-1}
$c = 18.240\,(1)$ Å	$T = 293$ K
$V = 1173.1\,(3)$ Å^3	Needle
$Z = 4$	$0.50 \times 0.31 \times 0.19$ mm
$D_x = 1.485$ Mg m^{-3}	Colourless
$D_m = 1.478$ Mg m^{-3}	
D_m measured by flotation	
in an n-heptane/CCl$_4$	
solution	

Data collection

Enraf–Nonius CAD-4	$\theta_{max} = 30°$
diffractometer	$h = 0 \rightarrow 6$
$\omega/2\theta$ scans	$k = 0 \rightarrow 17$
Absorption correction:	$l = 0 \rightarrow 25$
none	3 standard reflections
1996 measured reflections	frequency: 30 min
1996 independent reflections	intensity decay: 0.5%
1578 observed reflections	
$[F > 6.0\sigma(F)]$	

Refinement

Refinement on F	$\Delta\rho_{max} = 0.25$ e Å^{-3}
$R = 0.037$	$\Delta\rho_{min} = -0.19$ e Å^{-3}
$wR = 0.042$	Extinction correction: none
$S = 1.428$	Atomic scattering factors
1578 reflections	from International Tables
211 parameters	for X-ray Crystallography
$w = 1/[\sigma^2(F) + 0.00074F^2]$	(1974, Vol. IV)
$(\Delta/\sigma)_{max} = 0.06$	

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
N1	0.4235 (4)	0.8200 (1)	0.2153 (1)	0.0339 (5)
C2	0.3391 (5)	0.7596 (1)	0.1585 (1)	0.0354 (6)
N3	0.4672 (5)	0.7787 (1)	0.0930 (1)	0.0412 (5)
C4	0.6710 (6)	0.8491 (1)	0.0798 (1)	0.0385 (6)
C5	0.7367 (5)	0.9152 (2)	0.1405 (1)	0.0349 (6)
C6	0.6120 (5)	0.8974 (1)	0.2047 (1)	0.0329 (5)
O2	0.1645 (4)	0.6937 (1)	0.1653 (1)	0.0518 (5)
O4	0.7810 (6)	0.8543 (1)	0.0191 (1)	0.0612 (7)
C7	0.9387 (6)	0.9991 (2)	0.1295 (2)	0.0488 (8)
C1'	0.3098 (4)	0.8026 (2)	0.2882 (1)	0.0329 (6)
C2'	0.5261 (5)	0.7829 (2)	0.3468 (1)	0.0369 (6)
C3'	0.3839 (6)	0.8192 (2)	0.4155 (1)	0.0427 (7)
C4'	0.2196 (5)	0.9091 (2)	0.3888 (1)	0.0386 (6)
O4'	0.1690 (5)	0.8907 (1)	0.3113 (1)	0.0372 (4)
C5'	0.3568 (5)	1.0090 (2)	0.3988 (1)	0.0469 (7)
O5'	0.6309 (4)	1.0021 (1)	0.3711 (1)	0.0514 (5)
F1'	0.5969 (4)	0.6826 (1)	0.3492 (1)	0.0656 (6)
F2'	0.1991 (5)	0.7442 (1)	0.4376 (1)	0.0721 (6)

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O4^i	0.78 (3)	2.07 (3)	2.849 (2)	179 (3)
O5'—H5'···O2^{ii}	0.84 (4)	1.99 (4)	2.812 (2)	166 (4)
C6—H6···O5'	0.97 (2)	2.40 (2)	3.340 (2)	163 (2)
C4'—H4'···O5'^{iii}	1.05 (3)	2.35 (3)	3.121 (3)	129 (2)

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

All H atoms were located from difference Fourier maps and included in the refinement with individual isotropic displacement parameters.

Data collection: CAD-4 Software (Enraf–Nonius, 1989). Cell refinement: CAD-4 Software. Program(s) used to solve structure: MULTAN80 (Main et al., 1980). Program(s) used to refine structure: SHELX76 (Sheldrick, 1976). Molecular graphics: ORTEP (Johnson, 1965). Software used to prepare material for publication: PARST (Nardelli, 1983).

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