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Stavudine

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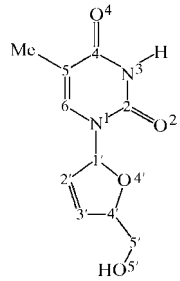
The crystal structure of the title compound (systematic name: 2′,3′-didehydro-2′,3′-deoxythymidine), $C_{10}H_{12}N_2O_4$, consists of two molecules in the asymmetric unit bound together by hydrogen bonds. The conformational geometry differentiates this form of stavudine from its two previously published polymorphs. In addition, a different hydrogen-bonding scheme is observed compared with the previous two structures. This polymorph is the thermodynamically most stable form of the antiviral drug, as evidenced by differential scanning calorimetry (DSC) and IR data.

Comment

Stavudine was one of numerous nucleosides first prepared nearly 40 years ago (Horwitz *et al.*, 1966). Stavudine (Zerit) has since proven itself a potent antiviral drug and is used for the treatment of HIV/AIDS (Canadian Pharmacists' Association, 2000). A plethora of nucleoside derivatives have been examined (Van Roey *et al.*, 1993) in an attempt to find the most biologically active complex. Stavudine showed exceptional promise and thus various solvates of stavudine (Skonezny *et al.*, 1995; Radatus & Murthy, 2003; Viterbo *et al.*, 2000) have been examined. In addition, the physico-chemical properties and thermodynamics of the hydrate and two polymorphs of the pure compound have been studied extensively (Gandhi *et al.*, 2000). Gandhi defined the two pure forms as Form I (the more stable polymorph) and Form II (a metastable polymorph), with the hydrate defined as Form III. Polymorph I of stavudine is the thermodynamically most stable form and is the marketed form.

Two crystallographic studies have already been carried out on stavudine. They have yielded a triclinic (Gurskaya *et al.*, 1991) and a monoclinc crystal (Harte *et al.*, 1991). Neither of these publications identified the polymorphic form of their single crystal in the course of their X-ray diffraction study. In an attempt to correlate the polymorph to the crystal structure, we used the techniques developed by Gandhi *et al.* (2000) to produce Forms I, II and III. DSC and solid-state FT–IR were used to confirm the polymorphic form before carrying out the X-ray diffraction experiment. Unfortunately, only Form I afforded X-ray-quality single crystals. To our surprise, Form I corresponded to an as yet unpublished orthorhombic form of stavudine. This paper presents the crystal structure of stavudine, (I), along with a comparison with the two previously published polymorphs, hereafter referred to as stavudine (H) and stavudine (G).



(I)

The chemical formula of stavudine and the preferred numbering scheme are shown in the scheme above. This discussion will compare the geometry of the three polymorphs and their hydrogen-bonding schemes. The structure of stavudine and its biological activity are typically described *via* three characteristic torsion angles, *viz.* χ (C2—N1—C1′—O4′), ν (N1—C1′—O4′—C4′) and γ (C3′—C4′—C5′—O5′). These torsion angles and some selected bond lengths are compared and contrasted for the three crystal structures. Similarly, the different hydrogen-bonding schemes are examined for the three polymorphs.

The present polymorph (Fig. 1) of stavudine consists of two crystallographically independent molecules, *A* and *B*. The two molecules are paired into dimers *via* intermolecular hydrogen bonds (N3*B*—H···O4*A* and N3*A*—H···O2*B*). Molecule *B* is disordered at the hydroxyl site and was modelled as a 0.72:0.28 mixture of CH_2OH atoms. The displacement parameters of the two methylene moieties and the two hydroxyl groups of the disorder were restrained to be identical. In addition, the bond lengths of the disordered region (C4′—C5′ and C5′—O5′) were restrained to be identical to the bond lengths in the well ordered molecule (*A*).

Table 1 contains the data for the present polymorph of stavudine, (I), along with data from Harte's determination, stavudine (H), and Gurskaya's determination, stavudine (G). The unit-cell data are represented, as well as selected conformational features used to describe the thymine–furanose geometry of stavudine. The most notable comparison of the three unit cells is that a simple doubling of the *a* axis can transform the monoclinic cell very nearly into the orthorhombic cell. However, despite the unit-cell similarities, the polymorphs are quite different, as a discussion of the geometry will show.

The majority of the geometry discussion hinges on rotation about the N1—C1′ bond, so it is reproduced in Table 1 along with the three torsion angles defined earlier. Stavudine (H) and stavudine (G) both have two molecules in the asymmetric unit, similar to what we observe in (I). Thus, there are six

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molecules to compare in our examination of the geometry. Stavudine (H) and stavudine (G) both show a short and a long N1—C1′ bond. (I), in contrast, possesses two much more similar but shorter N1—C1′ bonds. The χ torsion angles show the largest extremes, whereas both ν and γ vary little between the six configurations. In fact, there are four configurations, as molecule *B* of (I) is very similar to molecule *A* of stavudine (H). Similarly, molecule *B* of stavudine (H) is very similar to molecule *A* of stavudine (G). Finally, molecule *A* of (I) and molecule *B* of stavudine (G) both have different configurations again, as emphasized by the χ torsion angle.

Tables 2 and 3 contain the hydrogen-bonding data for the three polymorphs, *viz.* (I), stavudine (H) and stavudine (G). All three polymorphs form dimers of the two independent molecules, utilizing hydrogen bonding between the amide and carbonyl groups of the thymidine base. Stavudine (H) and stavudine (G) both have a symmetric interaction between atoms N3 and O2. (I), however, forms an asymmetric dimer between N3*A*—H···O2*B* and N3*B*—H···O4*A*. This is closer to what is expected, since it is typically atom O4 of the thymidine which is involved in the Watson–Crick interaction. These N—H···O bonds are all in the ranges 2.820 (4)–2.934 (3) Å and 168 (3)–174 (3)°.

Stavudine (G) continues its hydrogen bonding to form continuous layers with bonding between adjacent hydroxyl groups. Stavudine (H) has a different hydrogen-bonding pattern in that one of the hydroxyl H atoms bonds to an adjacent hydroxyl O atom, and that second hydroxyl O atom has its H atom in close contact with an adjacent furanyl O atom. This is counter to what Harte reports, since he claims two hydroxy–furanyl interactions, but his second *D*···*A* distance is too long [3.862 (5) Å] to be considered a hydrogen-bonding interaction. The present structure also shows this 'mixed' hydrogen-bonding interaction. The well resolved molecule *A* very clearly shows the hydroxyl H atom bonding to a neighbouring hydroxyl O atom of molecule *B*. Molecule *B*, due to its disordered –CH_2OH moiety, shows two hydrogen-bonding schemes. The major interaction (72%) sees the hydroxyl H atom bonding to a neighbouring hydroxyl O atom of molecule *A*. The minor component (28%) forms a hydrogen bond towards the furanyl O atom of an adjacent molecule *B*. The hydrogen bonding observed in the minor component is undoubtedly a constricted geometry, as evidenced by the very different value of γ (31°) from the remaining values (50.5–61.5°) in Table 1.

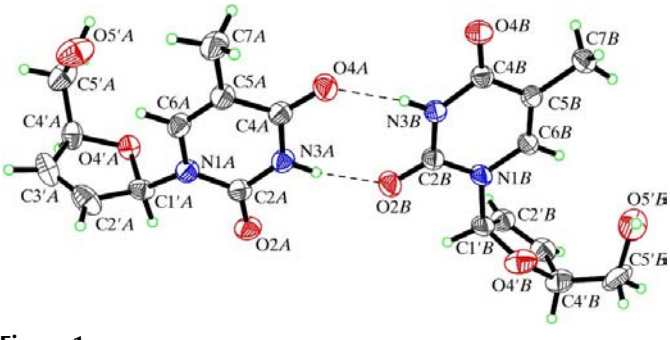

Figure 1
The structure of (I), showing 30% probability displacement ellipsoids and the atom-labelling scheme.

The two potential donor atoms and the four potential acceptor atoms allow for a varied number of hydrogen-bonding schemes in this versatile molecule (Table 3). Stavudine, in its three polymorphs, has shown three unique crystal structures to date. All three exist in the solid state as dimers formed by intermolecular hydrogen bonding between two crystallographically independent molecules. The extended hydrogen-bonding structure differs in all three incarnations of stavudine. Stavudine (G) shows a pure hydroxyl–hydroxyl extended network. Stavudine (H) shows a hydroxyl–furanyl and a hydroxyl–hydroxyl interaction. Finally, (I) shows a hydroxyl–hydroxyl interaction, and the disordered portion of the second molecule reveals both a hydroxyl–furanyl and a hydroxyl–hydroxyl hydrogen-bonding scheme.

Single crystals of the marketed form of stavudine, Form I, have been unequivocally characterized by IR and DSC in our laboratories. Furthermore, the single-crystal X-ray structure of polymorph I is presented here, 14 years after two other polymorphs were published. The geometry of the three polymorphs has been discussed herein, as has the hydrogen-bonding scheme. We will continue our attempts to grow single crystals of Form II to verify which, if either, of the two published structures corresponds to it.

Experimental

Stavudine at 99.5% purity was provided by Apotex PharmaChem Inc. Solvents were purchased from Sigma–Aldrich. Stavudine was dissolved in propan-2-ol at 323 K and the solution filtered to remove any insoluble particles. The clean filtrate was cooled to 298 K with a linear cooling profile (0.1 K min^{-1}) while agitating the solution to recrystallize the stavudine. The DSC and FT–IR analyses confirmed that pure Form I of stavudine was produced. To produce Form II, the purified Form I was dissolved in propan-2-ol at 321 K and cooled to 298 K over a period of 10 min (approximately linearly) without stirring. The final product was identified as pure Form II using DSC and FT–IR. Various solvents were tested using a slow evaporative crystallization technique. Approximately 3 ml of saturated solutions of (I) were prepared in various solvents (deionized water, methanol, methyl ethyl ketone, propan-2-ol and acetonitrile). For each solvent, five vials of equal concentration were prepared. The vials were placed in a nitrogen-filled oven at room temperature under slight vacuum for about one month. The only solvent that produced X-ray-quality single crystals was water. Interestingly, the single crystal turned out to be polymorph I and not the hydrate.

Crystal data

$C_{10}H_{12}N_2O_4$
M_r = 224.22
Orthorhombic, $P2_12_12_1$
a = 5.4230 (2) Å
b = 16.2077 (9) Å
c = 24.0104 (13) Å
V = 2110.38 (18) Å^3
Z = 8
D_x = 1.411 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20837 reflections
θ = 1.7–25.0°
μ = 0.11 mm^{-1}
T = 296 (2) K
Needle, colourless
0.80 × 0.25 × 0.17 mm

Table 1
A comparison of the unit-cell parameters and some selected geometric parameters (Å, °) for (I), stavudine (H) and stavudine (G).

	(I)		Stavudine (H)		Stavudine (G)	
System	Orthorhombic		Monoclinic		Triclinic	
Space group	$P2_12_12_1$		$P2_1$		$P1$	
a	5.4230 (2)		11.662 (1)		5.493 (1)	
b	16.2077 (9)		5.422 (1)		9.881 (1)	
c	24.0104 (13)		16.233 (3)		10.077 (1)	
α	90		90		105.04 (1)	
β	90		92.64 (1)		102.34 (1)	
γ	90		90		89.61 (1)	
R	5.86		3.6		3.4	
	Molecule		Molecule		Molecule	
	A	*B*	*A*	*B*	*A*	*B*
N1—C1	1.466 (6)	1.456 (5)	1.477 (3)	1.502 (3)	1.505 (3)	1.487 (4)
χ†	−102.1 (3)	−117.2 (4)	−118.0 (6)	−174.1 (5)	−172.6 (7)	−85.1 (6)
ν†	−129.0 (3)	−127.6 (3)	−130.5 (5)	−123.1 (5)	−125.6 (6)	−128.8 (6)
γ†	50.5 (6)	62.0 (13) 32 (5)‡	60.6 (8)	53.8 (7)	54.1 (8)	55.5 (7)

† Torsion angles are defined as follows: χ (C2—N1—C1′—O4′), ν (N1—C1′—O4′—C4′) and γ (C3′—C4′—C5′—O5′). ‡ The extra value for γ in (I) is due to disorder.

Table 2
Intermolecular hydrogen-bond parameters (Å, °) for stavudine (H) and stavudine (G).

See Table 3 for the corresponding data for (I).

	D	*A*	*D*···*A*	*D*—H···*A*
Stavudine (H)	N3*A*	O2*B*	2.934 (3)	170
	N3*B*	O2*A*	2.838 (2)	174
	O5′*B*	O4′*A*	3.074 (3)	179
	O5′*A*	O5′*B*	2.787 (3)	
	O5′*A*	O4′*B*	3.862 (5)	140
Stavudine (G)	N3*A*	O2*B*	2.844 (5)	174
	N3*B*	O2*A*	2.877 (5)	172
	O5′*A*	O5′*B*	2.982 (6)	142
	O5′*B*	O5′*A*	2.972 (6)	166

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)
T_{min} = 0.917, T_{max} = 0.981
13427 measured reflections
3680 independent reflections
2526 reflections with $I > 2\sigma(I)$
R_{int} = 0.130
θ_{max} = 25.0°
$h = -6 \rightarrow 6$
$k = -15 \rightarrow 19$
$l = -28 \rightarrow 28$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.168
S = 1.04
3680 reflections
296 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0965P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.028 (4)

H atoms were positioned geometrically and constrained as riding atoms, with C—H = 0.93 Å and U_{iso}(H) = 1.2U_{eq}(C), and N—H = 0.86 Å and U_{iso}(H) = 1.2U_{eq}(N) for aromatic H atoms, C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms, C—H = 0.97 Å and U_{iso}(H) = 1.2U_{eq}(C) for methylene H atoms, C—H = 0.98 Å and U_{iso}(H) = 1.2U_{eq}(C) for methyne H atoms, and O—H = 0.82 Å and U_{iso}(H) = 1.5U_{eq}(C) for hydroxyl H atoms. Restrained bond lengths were C4′*B*—C5′*B* = 1.476 Å, C4′*B*—C5′*C* = 1.476 Å, C5′*B*—O5′*B* = 1.402 Å and C5′*C*—O5′*C* = 1.402 Å. The absolute structure could not be determined reliably and the Friedel pairs were merged for the final refinement. The crystals were weakly diffracting and thus a large crystal was used to ensure data out to 50° in 2θ.

Table 3
Hydrogen-bond geometry (Å, °) for (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3*A*—H3*A*···O2*B*	0.86	1.98	2.823 (4)	168
N3*B*—H3*B*···O4*A*	0.86	2.04	2.890 (4)	172
O5′*A*—H5′*C*···O5′*C*^{i}	0.82	1.86	2.674 (13)	171
O5′*B*—H5′*F*···O5′*A*^{ii}	0.82	2.10	2.870 (6)	156
O5′*C*—H5′*I*···O4′*B*^{iii}	0.82	2.15	2.959 (14)	167

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

Data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 2001); software used to prepare material for publication: *SHELXTL/PC*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1230). Services for accessing these data are described at the back of the journal.

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