Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

The 7-bromo derivative of 2-amino-2′-deoxytubercidin fluorinated at the sugar moiety

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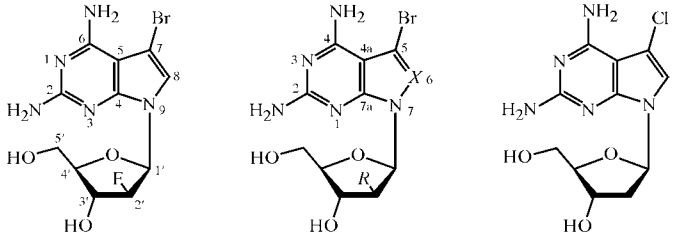
Received 20 April 2007
Accepted 4 June 2007
Online 22 September 2007

The title compound, 2,4-diamino-5-bromo-7-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine, $C_{11}H_{13}BrFN_5O_3$, shows two conformations of the exocyclic C4′—C5′ bond, with the torsion angle γ (O5′—C5′—C4′—C3′) being 170.1 (3)° for conformer 1 (occupancy 0.69) and 60.7 (7)° for conformer 2 (occupancy 0.31). The N-glycosylic bond exhibits an *anti* conformation, with χ = −114.8 (4)°. The sugar pucker is *N*-type (C3′-*endo*; $^3T_4$), with P = 23.3 (4)° and τ_m = 36.5 (2)°. The compound forms a three-dimensional network that is stabilized by several intermolecular hydrogen bonds (N—H···O, O—H···N and N—H···Br).

Comment

The introduction of halogens in components of nucleic acids generally leads to changes in their physical properties and biological activity. Among the various positions, the 7-position of the 7-deazapurine moiety (purine numbering is used throughout) and the 2′-position of the sugar residue are important modification sites (Seela, Chittepu *et al.*, 2005). A series of 7-substituted 7-deazapurines ribonucleosides and 2′-deoxyribonucleosides exhibit antiviral activity against various RNA and DNA viruses, including *Herpes simplex* virus types 1 and 2 (HSV-1 and HSV-2) (Bergstrom *et al.*, 1984; De Clercq *et al.*, 1986). The introduction of the 7-bromo substituent increases the polarizability of the nucleobase and enhances base-stacking interactions, thereby stabilizing the DNA duplex structure (Ramzaeva & Seela, 1996; Seela & Thomas, 1995). The 7-bromo substituent decreases the basicity of the title compound, (I) (pK_a = 4.77), compared with the non-halogenated compound (pK_a = 5.67), as indicated by the lower pK_a value. The nuleobase plays an important role in directing the conformation of the sugar moiety.

The introduction of an F atom instead of H into the 2′-position of the sugar moiety of nucleosides enhances the chemical stability and biological activity of nucleosides (Filler & Naqvi, 1979; Marquez *et al.*, 1990; Masood *et al.*, 1990). It leads to a minor change in the size of the molecule but strongly influences the *S*/*N* conformational equilibrium of the pentofuranose ring in solution (He *et al.*, 2003). In order to elucidate the combined influence of bromination at position 7 of 2-amino-2′-deoxytubercidin and the introduction of a 2′-fluoro substituent in the sugar residue, we have synthesized the title compound, 2-amino-7-deaza-7-bromo-2′-deoxy-2′-fluoroadenosine, (I), and subjected it to single-crystal X-ray analysis. The synthesis of the title compound was reported previously (Peng & Seela, 2004). The structure of (I) is shown in Fig. 1 and selected geometric parameters are summarized in Table 1.



The orientation of the base relative to the sugar moiety (*syn*/*anti*) is denoted by the torsion angle χ, which is defined as O4′—C1′—N9—C4 for purine nucleosides (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). The crystal structure of compound (I) exhibits a torsion angle χ of −114.8 (4)°, falling into the *anti* range. This value is close to those of compounds (II*a*) (see scheme) [χ = −105.0 (6)°; Seela, Sirivolu *et al.*, 2005] and (III) [χ = −102.5 (6)°; Seela *et al.*, 2006]. The length of the N-glycosylic bond of nucleoside (I) is 1.442 (5) Å, which is similar to compounds (II*a*) [1.447 (5) Å; Seela, Sirivolu *et al.*, 2005] and (III) [1.464 (6) Å; Seela *et al.*, 2006]. For the sugar moiety, two major twisted conformations are found, denoted north and south. The north (*N*) conformation refers to the C3′-*endo*–C2′-*exo* conformer, whereas the south (*S*) conformation represents the C2′-*endo*–C3′-*exo* conformer (Seela *et al.*, 2000). The sugar moiety of compound (I) shows an *N* conformation with a phase angle of pseudorotation P = 23.3 (4)° and the maximum amplitude of puckering τ_m = 36.5 (2)° (Altona & Sundaralingam, 1972), indicating that the sugar ring adopts an unsymmetrical twist (C3′-*endo*–C4′-*exo*; $^3T_4$). Nucleoside (III) shows the same sugar moiety structure as (I) (P = 19.6° and τ_m = 32.9°; Seela *et al.*, 2006), whereas compound (II*a*) exhibits differences in the *N* conformation [C3′-*endo*–C2′-*exo*, between $^3T_2$ and E_3, with P = 5.8 (5)° and τ_m = 30.0 (3)°; Seela, Sirivolu *et al.*, 2005].

In the crystal structure of (I), two conformations of the exocyclic C4′—C5′ bond were found, corresponding to occupancies of 0.69 of conformer 1 (Fig. 1*a*) and 0.31 of conformer 2 (Fig. 1*b*). The torsion angle γ is defined as O5′1—C5′—C4′—C3′ for conformer 1 and O5′2—C5′—C4′—C3′ for conformer 2. For conformer 1, this torsion angle is 170.1 (3)°, falling into

  DOI: 10.1107/S0108270107027138

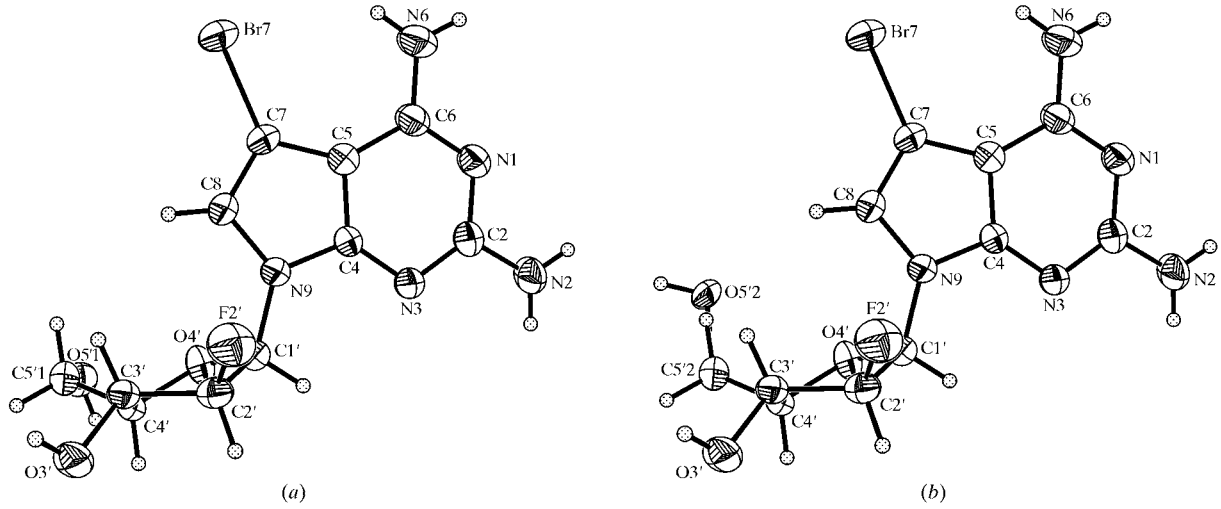


Figure 1
Perspective views of (*a*) conformer 1 (occupancy of 0.69) and (*b*) conformer 2 (occupancy 0f 0.31) of compound (I), showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary size.

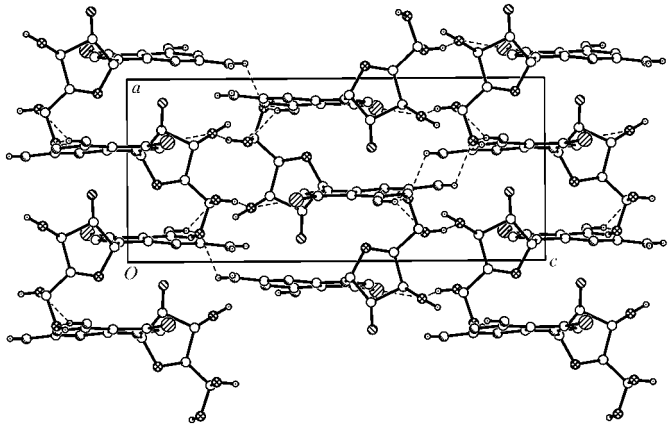


Figure 2
The crystal packing of (I), showing the intermolecular hydrogen-bonding network (projection parallel to the *b* axis). Only H atoms involved in hydrogen bonding are shown.

the +*ap* (*trans*) range. This is close to compounds (II*a*) [γ = 172.0 (4)°; Seela, Sirivolu *et al.*, 2005] and (III) [γ = 171.5 (4)°; Seela *et al.*, 2006]. In contrast, conformer 2 adopts a conformation with γ = 60.7 (7)°, representing a +synclinal (*gauche*) conformation. The base unit of (I) is essentially planar, with an r.m.s. deviation of 0.0201 Å and a maximum deviation of −0.0369 (3) Å for ring atom C2. The bromo substituent is located −0.0764 (5) Å below the 7-deazapurine plane on the same side as the 2-amino group [−0.0851 (6) Å], whereas the 6-amino group lies 0.0533 (7) Å above the plane.

In contrast with the behaviour in the solid state, the spatial conformation of the sugar moiety dynamically interconverts between north (*N*) and south (*S*) in solution. This ratio was determined from the vicinal ^3J(H,H) coupling constants of the ^{1}H NMR spectrum measured in D_2O, using the *PSEUROT* program (van Wijk & Altona, 1993). The populations in an aqueous solution of compound (I) are 0.63 *S* and 0.37 *N*, whereas for the non-fluorinated nucleoside, (II*c*), the populations are shifted towards *S* (0.71 *S* and 0.29 *N*; Peng & Seela, 2004). This shows that the introduction of an F atom in the *arabino* position of the sugar moiety enhances the population of the *N*-conformers. In contrast, the related 8-aza compound, (II*b*), incorporating an N atom instead of a C atom at position 8, exclusively forms the *N* conformation (He *et al.*, 2003).

Compound (I) forms a compact three-dimensional network, which is stabilized by hydrogen bonds and stacking interactions (Fig. 2 and Table 2). The nucleobases are arranged head-to-tail. The two conformers, 1 and 2, are linked through hydrogen bonds between neighbouring nucleobases and sugar residues. The N2 and N6 amino groups function as H-atom donors and atoms O5′ of both conformers act as H-atom acceptors (N2—H2*A*···O5′1, N2—H2*B*···O5′1 and N6—H6*A*···O5′2). Further hydrogen bonds connect neighbouring sugar residues and the exocyclic substituents of the nucleobase. Hydrogen bonds are formed between atoms N3 and H5′ of conformer 1 (O5′1—H5′1···N3), while atom H5′ of conformer 2 forms a hydrogen bond with atom O3′ (O5′2—H5′2···O3′). Both conformers form two further intermolecular hydrogen bonds (O3′—H3*A*···N1 and N6—H6*B*···Br7).

Experimental

Compound (I) was synthesized as described previously (Peng & Seela, 2004) and was crystallized from MeOH (m.p. 470 K). For the diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{11}H_{13}BrFN_5O_3$
M_r = 362.17
Orthorhombic, $P2_12_12_1$
a = 7.7618 (14) Å
b = 9.688 (2) Å
c = 17.707 (3) Å
V = 1331.6 (5) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 3.12 mm^{-1}
T = 293 (2) K
0.4 × 0.4 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
Absorption correction: ψ scan (*XSCANS*; Siemens, 1996)
T_{min} = 0.479, T_{max} = 0.791
(expected range = 0.325–0.536)
2872 measured reflections
2687 independent reflections
2221 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.106
S = 1.03
2687 reflections
205 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.60 e Å^{-3}
$\Delta\rho_{min}$ = −0.78 e Å^{-3}
Absolute structure: Flack (1983), with 460 Friedel pairs
Flack parameter: 0.005 (12)

Table 1
Selected geometric parameters (Å, °).

C2—N2	1.366 (5)	N9—C1′	1.442 (5)
C6—N6	1.342 (5)	C2′—F2′	1.386 (4)
C7—Br7	1.873 (3)	C5′1—O5′1	1.380 (7)
N1—C2—N2	115.7 (3)	N9—C1′—C2′	114.4 (3)
N6—C6—N1	118.6 (4)	F2′—C2′—C3′	111.7 (3)
C8—C7—Br7	125.0 (3)	F2′—C2′—C1′	111.9 (3)
C5—C7—Br7	127.1 (3)	O4′—C4′—C5′1	109.4 (3)
C4—N9—C1′	124.9 (3)	O5′1—C5′1—C4′	113.8 (3)
O4′—C1′—N9	109.1 (3)		
C6—N1—C2—N3	−3.3 (7)	C1′—C2′—C3′—C4′	33.1 (3)
C7—C5—C6—N6	2.6 (10)	C2′—C3′—C4′—O4′	−35.2 (3)
C6—C5—C7—Br7	0.0 (10)	C2′—C3′—C4′—C5′1	−154.8 (3)
C4—N9—C1′—O4′	−114.8 (4)	N9—C1′—O4′—C4′	−126.6 (3)
C8—N9—C1′—O4′	61.8 (5)	C2′—C1′—O4′—C4′	−3.3 (4)
O4′—C1′—C2′—F2′	−140.6 (3)	C5′1—C4′—O4′—C1′	147.5 (3)
N9—C1′—C2′—F2′	−20.8 (4)	C3′—C4′—O4′—C1′	24.8 (3)
O4′—C1′—C2′—C3′	−19.5 (3)	O4′—C4′—C5′1—O5′1	53.2 (5)
N9—C1′—C2′—C3′	100.3 (3)	C3′—C4′—C5′1—O5′1	170.1 (3)
F2′—C2′—C3′—O3′	−85.6 (4)	C3′—C4′—C5′2—O5′2	60.7 (7)

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2A···O5′1^{i}	0.86	2.62	3.290 (6)	136
N2—H2B···O5′1^{ii}	0.86	2.45	3.034 (6)	126
N6—H6A···O5′2^{iii}	0.86	2.12	2.857 (10)	143
N6—H6B···Br7	0.86	2.78	3.469 (4)	138
O3′—H3′A···N1^{iv}	0.82	2.04	2.857 (4)	175
O5′1—H5′1···N3^{v}	0.82	2.06	2.871 (5)	169
O5′2—H5′2···O3′^{vi}	0.82	2.23	2.714 (9)	118

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

The absolute configuration was obtained from the Flack (1983) parameter as well as from the defined configuration of the sugar halide used in the glycosylation reaction. All H atoms were found in a difference Fourier synthesis. In order to maximize the data-to-parameter ratio, the H atoms were placed in geometrically idealized positions, with C—H = 0.93–0.98 Å and N—H = 0.86 Å, and constrained to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C,N). The OH groups were refined as rigid groups allowed to rotate but not tip, with O—H = 0.82 Å and U_{iso}(H) = 1.5U_{eq}(O).

Atom O5′ shows a rather large displacement parameter. This resulted from two different positions (1 and 2) of atom O5′. It is in agreement with the bond lengths and angles. Consequently, two site-occupancy factors, $K1$ and $K2$, were introduced, with $K2 = 1 - K1$.

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*; 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: SF3039). Services for accessing these data are described at the back of the journal.

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