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8-Aza-7-deaza-2′-deoxy-2-(methylsulfanyl)adenosine

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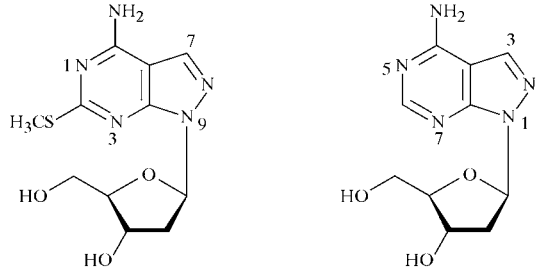
In the title compound, 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{11}H_{16}N_5O_3S$, the conformation of the glycosidic bond is between *anti* and high *anti*. The 2′-deoxyribofuranosyl moiety adopts the C3′-*exo*–C4′-*endo* conformation ($_3T^4$, S-type sugar pucker), and the conformation at the exocyclic C—C bond is +*sc* (+*gauche*). The exocyclic 6-amine group and the 2-methylsulfanyl group lie on different sides of the heterocyclic ring system. The molecules form a three-dimensional hydrogen-bonded network that is stabilized by O—H···N, N—H···O and C—H···O hydrogen bonds.

Comment

Extensive studies have been performed on modified nucleosides as analogues of natural DNA constituents. In this context, 8-aza-7-deaza-2′-deoxyadenosine [4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine; purine numbering is used throughout the manuscript], (II), is an ideal substitute for 2′-deoxyadenosine (Seela & Steker, 1985; Seela & Kaiser, 1988; Seela *et al.*, 1999). The thermal stability of DNA does not change even with multiple incorporations of (II)–dT base pairs in place of dA–dT pairs (dA is deoxyadenine and dT is deoxythymine; Seela & Kaiser, 1988; Seela *et al.*, 2000). Moreover, the introduction of chloro, bromo, iodo, propynyl and hexynyl substituents at the 7-position of (II) results in a significant stabilization of the duplex DNA. Because of the size and nature of these 7-substituents, they were found to be well accommodated into the major groove of B-DNA (Seela *et al.*, 2000, 2004; Seela & Zulauf, 1999; He & Seela, 2002). In contrast, the 2-substituents of purine residues are located in the minor groove of B-DNA and are limited by their narrow size. Recently, we studied DNA duplexes containing 2-chloro-8-aza-7-deaza-2′-deoxyadenosine, and found that they showed a destabilization compared with duplexes lacking the 2-chloro group (He & Seela, 2003). The consideration of the even bulkier methylsulfanyl group for the modification at the 2-position was prompted by the fact that this group is of particular biological importance in nature. The 2-(methylsulfanyl)adenosine analogues are constituents of tRNA and stabilize anticodon–anticodon interactions in the single-stranded state through increased stacking interactions (Esberg & Björk, 1995; Kierzek & Kierzek, 2003).



The present paper reports the single-crystal X-ray structure of the title compound, (I).

The canonical 2′-deoxyadenosine unit shows an *anti* conformation. The orientation of the base relative to the sugar moiety (*syn*/*anti*) of purine nucleosides is defined by the torsion angle χ (O4′—C1′—N9—C4) (purine numbering; IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). In the crystal structure of (I) (Fig. 1 and Table 1), the conformation of the glycosyl bond is between *anti* and high *anti* [χ = −105.9 (4)°], and is stabilized by an intramolecular hydrogen bond between the nucleobase and the sugar moiety (O5′—H5′···N8). The torsion angle of (I) is nearly identical to that of the related compound (II) [χ = −106.3 (2)°; Seela *et al.*, 1999]. The glycosylic bond length in (I) [N9—C1′ = 1.453 (3) Å] is only slightly longer than that in (II) [1.442 (2) Å].

The other major conformational parameter of interest is the puckering of the 2′-deoxyribofuranosyl moiety. The 2′-deoxyribonucleosides usually prefer the S-type (C2′-*endo*) sugar

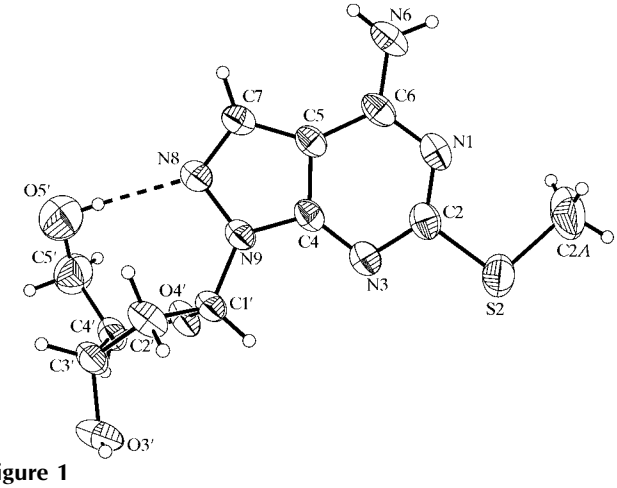


Figure 1
A perspective view of (I), showing the atomic numbering scheme. Displacement ellipsoids of non-H atoms are drawn at the 50% probability level. The intramolecular hydrogen bond is shown as a dashed line.

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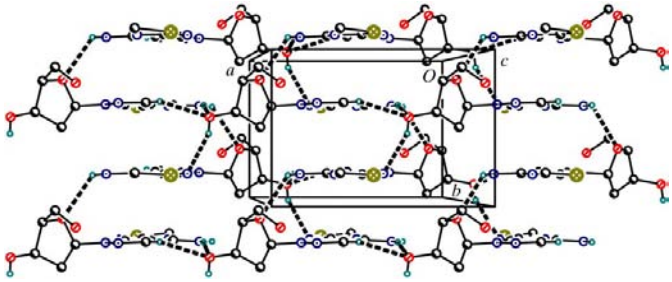

Figure 2
The intermolecular hydrogen-bond network and crystal packing of compound (I), viewed approximately perpendicular to the *xy* plane. Hydrogen bonds are indicated by dashed lines. H atoms not involved in hydrogen bonds have been omitted for clarity.

pucker (Saenger, 1984). This is also observed for compound (I), but it adopts an unusual unsymmetrical C3′-*exo*–C4′-*endo* ($_3T^4$) conformation with a pseudorotation phase angle, *P*, of 204.7 (4)° and a puckering amplitude, τ_m, of 28.0 (2)° (Rao & Sundaralingam, 1981). In contrast to this observation, an unsymmetrical C2′-*endo*–C3′-*exo* ($^2T_3$) sugar-ring conformation [*P* = 182.2 (2)° and τ_m = 41.2 (1)°] was found for (II).

The conformation around the C4′—C5′ bond of (I) is +*sc* (+*gauche*), with a dihedral angle, γ, of 41.9 (5)°, whereas in (II), the C4′—C5′ bond adopts a −*ap* (*trans*) conformation [γ = −178.7 (16)°].

The base moiety of nucleoside (I) is nearly planar, but the exocyclic substituents deviate from the plane. The r.m.s. deviation of the ring atoms N1, C2, N3, C4–C7, N8 and N9 from their least-squares plane is 0.0173 Å, with a maximum deviation of 0.030 (2) Å for atom N9. Atoms N6 and S2 of the exocyclic substituents show only minor deviations from this plane [0.079 (5) for N6 and −0.045 (3) Å for S2] and are therefore situated on opposite sides of the heterocyclic ring system. Atom C1′ of the sugar moiety is localized 0.104 (5) Å above the plane, on the same side of the nucleobase as atom N6 of the exocyclic NH_2 group.

The N3═C2—S2—C2*A* torsion angle is 175.2 (4)°, corresponding to a '*trans*' conformation around the C2—S2 bond. As a consequence, in base pairing the bulky 2-methylsulfanyl group of (I) leads to a steric clash with the 2-oxo group of dT, resulting in duplex destabilization.

In the three-dimensional hydrogen-bonded network of compound (I), the molecules are stacked head-to-tail. The intermolecular distance between the planes of neighbouring heterocycles is about 3.41 (4) Å and therefore in the range of B-DNA. The crystal structure is stabilized by several intermolecular hydrogen bonds with the H atoms of the exocyclic amine group as donors and atoms O4′ and O3′ of adjacent sugar moieties as acceptors (Table 2). The heterocyclic ring atom N3 is a hydrogen-bond acceptor for the neighbouring sugar moiety (N3^{iii}···H3′—O3′; symmetry code as in Table 2). A hydrogen bond between atom O3′ of the sugar moiety and atom H7 (Table 2) connects the nucleobase of one molecule with the sugar unit of another. These interactions link the molecules to form thick layers parallel to the *xy* plane (Fig. 2).

Experimental

The synthesis of nucleoside (I) has recently been reported (Seela *et al.*, 2005). The melting point of (I) is 499 K. Suitable crystals were obtained from a solution in methanol. For the diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{11}H_{15}N_5O_3S$
M_r = 297.34
Monoclinic, $P2_1$
a = 9.4470 (16) Å
b = 6.6805 (9) Å
c = 10.6102 (17) Å
β = 98.563 (9)°
V = 662.15 (18) Å^3
Z = 2
D_x = 1.491 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 38 reflections
θ = 5.4–12.8°
μ = 0.26 mm^{-1}
T = 293 (2) K
Needle, colourless translucent
0.4 × 0.3 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
2θ/ω scans
3965 measured reflections
1900 independent reflections
1785 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 29.0°
$h = -12 \rightarrow 12$
$k = -9 \rightarrow 9$
$l = -14 \rightarrow 14$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.163
S = 1.04
1900 reflections
184 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1183P)^2 + 0.1165P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.63 e Å^{-3}
$\Delta\rho_{min}$ = −0.42 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C2—S2	1.758 (3)	N8—N9	1.377 (3)
S2—C2*A*	1.803 (5)	N9—C1′	1.453 (3)
N1—C2—N3	130.1 (3)	N3—C2—S2	111.8 (2)
N1—C2—S2	118.1 (2)	C2—S2—C2*A*	102.7 (2)
N1—C2—S2—C2*A*	−4.4 (4)	C4—N9—C1′—C2’	134.4 (4)
N3—C2—S2—C2*A*	175.2 (4)	N8—N9—C1′—C2′	−44.7 (4)
C4—N9—C1′—O4′	−105.9 (4)	O4′—C4′—C5′—O5′	−76.9 (5)
N8—N9—C1′—O4′	75.1 (4)	C3′—C4′—C5′—O5′	41.9 (5)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H6*A*···O4′^{i}	0.86	2.54	3.110 (4)	124
N6—H6*B*···O3′^{ii}	0.86	2.05	2.879 (5)	161
O3′—H3′···N3^{iii}	0.82	2.40	3.164 (5)	155
O5′—H5′···N8	0.82	2.08	2.895 (5)	176
C7—H7···O3′^{ii}	0.93	2.48	3.229 (3)	138

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

In the absence of suitable anomalous scattering, Friedel equivalents could not be used to determine the absolute structure. Therefore, Friedel equivalents were merged before the final refinements. The known configuration of the parent molecule was used to define

the enantiomer of the final model. All H atoms were initially found in a difference Fourier synthesis. In order to maximize the data/parameter ratio, the H atoms were placed in geometrically idealized positions (C—H = 0.93–0.98 Å, O—H = 0.82 Å and N—H = 0.86 Å) and constrained to ride on their parent atoms with U_{iso}(H) values of $1.2U_{eq}$(C), $1.2U_{eq}$(N) and $1.5U_{eq}$(O).

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 1997*b*); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997*a*); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 1999).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1745). Services for accessing these data are described at the back of the journal.

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