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2-Amino-8-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)imidazo[1,2-*a*][1,3,5]-triazin-4(8*H*)-one monohydrate, a 2′-deoxyguanosine analogue with an altered Watson–Crick recognition site

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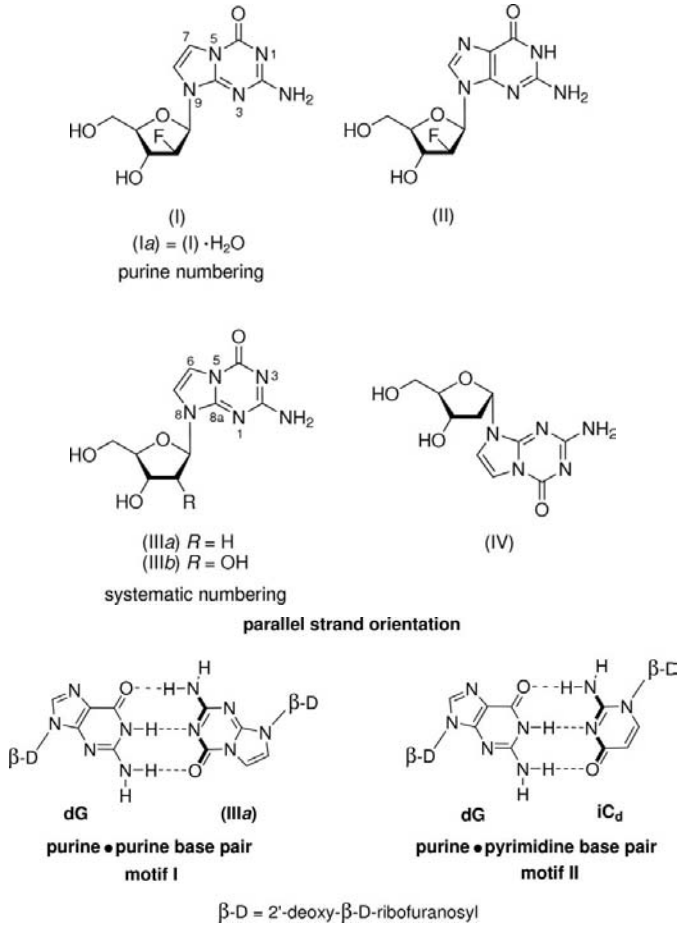
The title compound, $C_{10}H_{12}FN_5O_4\cdot H_2O$, shows an *anti* glycosyl orientation [χ = −123.1 (2)°]. The 2-deoxy-2-fluoroarabinofuranosyl moiety exhibits a major C2′-*endo* sugar puckering (*S*-type, C2′-*endo*–C1′-*exo*, $^2T_1$), with P = 156.9 (2)° and τ_m = 36.8 (1)°, while in solution a predominantly *N* conformation of the sugar moiety is observed. The conformation around the exocyclic C4′—C5′ bond is −*sc* (*trans*, *gauche*), with γ = −78.3 (2)°. Both nucleoside and solvent molecules participate in the formation of a three-dimensional hydrogen-bonding pattern *via* intermolecular N—H···O and O—H···O hydrogen bonds; the N atoms of the heterocyclic moiety and the F substituent do not take part in hydrogen bonding.

Comment

Among base-modified nucleosides, 5-aza-7-deazapurine (imidazo[1,2-*a*][1,3,5]triazine) compounds are of considerable interest as they form orthogonal base pairs (purine numbering is used throughout this discussion). 2-Amino-8-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)imidazo[1,2-*a*][1,3,5]triazin-4(8*H*)-one (5-aza-7-deaza-2′-deoxy-2′-fluoroguanosine), (I), is a fluorinated analogue of 5-aza-7-deaza-2′-deoxyguanosine, (III*a*), which can be considered a structural analogue of both 2′-deoxyguanosine (dG) and 7-deaza-2′-deoxyguanosine (see scheme) (Rosemeyer & Seela, 1987). Compound (III*a*) shows an altered Watson–Crick recognition site due to the absence of the H atom at N1, and is therefore the purine counterfeit of 2′-deoxyisocytidine (iC_d; see scheme, motif II) (Seela & Melenewski, 1999; Seela & Rosemeyer, 2002). Compound (III*a*) (β-D-anomer) forms a parallel-stranded duplex under neutral conditions when placed opposite dG. It was observed that this 'purine–purine' base pair (see scheme, motif I) is remarkably stable, thereby expanding the pairing modes of synthetic DNA (Seela & Melenewski, 1999). Parallel DNA can be generated either by changing the Watson–Crick recognition site of the nucleobase, as is the case for the above-mentioned 2′-deoxyisocytidine and compound (III*a*), or by changing the anomeric configuration from β-D to α-D (Morvan *et al.*, 1987; Seela & He, 2002). Base-pair motifs illustrating this point are shown in the scheme. Parallel-stranded DNA is not just a topic for synthetic biology applications but also demonstrates the polymorphic structures of DNA.



Recently, the 2′-deoxy-2′-fluoroarabino nucleoside of 5-aza-7-deazaguanosine, (I), has been synthesized and its conformational properties investigated in solution (Glaçon & Seela, 2004). The introduction of a 2′-arabinofluoro substituent has been found to confer potent antiviral activity which is enhanced compared with the unmodified counterparts (Pankiewicz, 2000). The presence of the F atom does not lead to significant steric perturbations in the shape of the molecule due to its small van der Waals radius (1.47 Å; Bondi, 1964). At the same time, an F atom is a substituent with the highest

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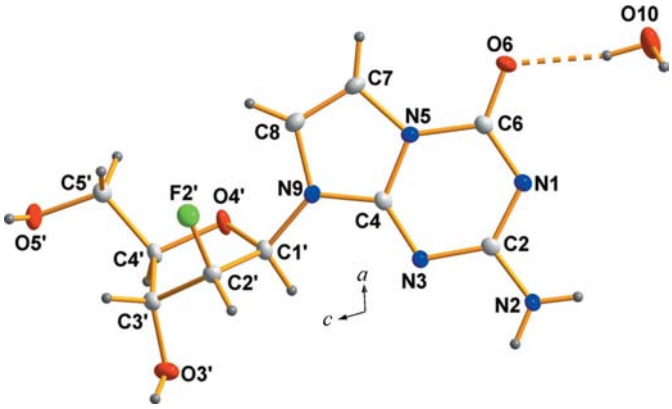

Figure 1
A perspective view of the molecule of (I*a*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates the hydrogen bond to the water molecule.

electronegativity (3.98, *versus* 3.44 for O). Therefore, its presence gives rise to essential changes in the electronic state and conformational behaviour of the pentofuranose ring.

We have now studied the conformation and hydrogen bonding of the monohydrate of (I), the title compound (I*a*), in the crystalline state and compared it with the related molecules of 5-aza-7-deazaguanosine, (III*b*) (Kojić-Prodić *et al.*, 1982), and the α-anomer of 5-aza-7-deaza-2′-deoxyguanosine, (IV) (Seela *et al.*, 2002). The three-dimensional structure of (I*a*) is shown in Fig. 1 and selected geometric parameters are listed in Table 1.

The 5-aza-7-deazapurine ring system of (I*a*) is nearly planar. The deviations of the ring atoms from the least-squares plane (N1/C2/N3/C4/N5/C6–C8/N9) range from −0.021 (2) (atom N5) to 0.018 (2) Å (atom N1), with an r.m.s. deviation of 0.014 Å. The C1′ substituent and atom O6 of (I*a*) lie 0.317 (3) and 0.041 (3) Å, respectively, above this plane, while atom N2 lies 0.074 (3) Å below it. The C2—N2 bond length of the amino group is 1.329 (2) Å, which is very close to the value observed for the amino group of the related 7-deaza-2′-deoxyguanosine [1.343 (4) Å; Seela *et al.*, 2005].

For purines, the orientation of the nucleobase relative to the sugar moiety (*syn*/*anti*) is defined by the torsion angle χ (O4′—C1′—N9—C4) (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). In the crystalline state of (I*a*), the glycosyl bond torsion angle is in the *anti* range, with $\chi = -123.1\ (2)^\circ$. The ribonucleoside (III*b*) also adopts an *anti* conformation (Kojić-Prodić *et al.*, 1982), while the 2′-deoxyribonucleoside α-anomer, (IV), adopts a high-*anti* conformation, with $\chi = 87.5\ (3)^\circ$ (Seela *et al.*, 2002). The glycosyl N9—C1′ bond in (I*a*) is 1.447 (2) Å, which is shorter than the corresponding bonds in both (III*b*) [1.462 (4) Å] and the α-anomer, (IV), lacking the 2′-fluoro substituent [1.461 (4) Å].

The conformation about the exocyclic C4′—C5′ bond, defined by the torsion angle γ (O5′—C5′—C4′—C3′), is $-78.3\ (2)^\circ$ for (I*a*), corresponding to a −*sc* (*trans*, *gauche*) conformation. This conformation was also observed for the hydroxy group of the α-anomer, (IV) (Seela *et al.*, 2002). In contrast, for ribonucleoside (III*b*) a −*gauche* conformation about the C4′—C5′ bond was reported, which corresponds to *ap* (*gauche*, *trans*) according to Saenger (1984). The F2′—C2′ length of (I*a*) is 1.398 (2) Å, similar to the C—F bonds found in other 2′-fluoro 'up' nucleosides (Birnbaum *et al.*, 1982; He *et al.*, 2003; Seela *et al.*, 2006) and 2′-fluoro 'down' nucleosides (Suck *et al.*, 1974; Hakoshima *et al.*, 1981). Moreover, the F2′—C2′ bond length is notably close to the C2′—O2′ distance observed in the parent compound, (III*b*) [1.400 (4) Å; Kojić-Prodić *et al.*, 1982].

The C2′-*endo* (south, *S*) and C3′-*endo* (north, *N*) puckerings are the most frequently observed sugar-ring conformations of nucleosides. The sugar moiety of (I*a*) shows an *S*-type conformation, with a major C2′-*endo* puckering (C2′-*endo*–C1′-*exo*, ${}^2T_1$) and a pseudorotation phase angle $P = 156.9\ (2)^\circ$, with the maximum amplitude $\tau_m = 36.8\ (1)^\circ$. Its conformation is close to that of the nonfluorinated ribonucleoside (III*b*) (*S*-type, C2′-*endo*, ${}^2E$, $P = 164.2^\circ$; Kojić-Prodić *et al.*, 1982). The 2′-deoxyribonucleoside α-anomer, (IV), also adopts an *S* sugar conformation, with $P = 177.43^\circ$ and $\tau_m = 30.5^\circ$ (C2′-*endo*–C3′-*exo*, ${}^2T_3$; Seela *et al.*, 2002).

In contrast with its behaviour in the solid state, the spatial conformation of the sugar moiety dynamically interconverts between north and south in solution. For fluorinated compound (I), this ratio was determined from the vicinal ${}^3J$(H,H) and ${}^3J$(H,F) coupling constants of ^{1}H NMR spectra measured in DMSO-d_6 containing one drop of D_2O, using the *PSEUROT6.3* program (Van Wijk *et al.*, 1999). The presence of the F atom shifts the sugar population of (I) towards the north conformation (54% *N*) compared with compound (III*a*) (37% *N*) (Glaçon & Seela, 2004). The same observation can also be made in the case of fluorinated (II) (50% *N*) and the unmodified 2′-deoxyguanosine (29% *N*) (Tennilä *et al.*, 2000). Thus, in solution, the presence of the F atom in an 'up' position (*arabino* configuration) enhances the population of the *N* conformers. It is interesting to note that the sugar conformation of compound (I) favours *N* puckering in solution, while in the crystalline state (I*a*) adopts an *S*-type sugar conformation.

The crystalline structure of nucleoside (I*a*) forms an infinite three-dimensional network which is stabilized by several intermolecular hydrogen bonds involving the nucleoside and water molecules (Table 2 and Figs. 2 and 3). If layers are selected perpendicular to the *b* axis, it can be seen that the nucleobases of (I*a*) stack into columns with alternating orientations.

Hydrogen bonds are formed within each layer as well as between adjacent layers. The nucleosides are linked by three intermolecular hydrogen bonds. Both H atoms of the amino group act as donors, forming hydrogen bonds with atom O6 of a neighbouring base moiety (N2—H2*B*···O6^{ii}) and atom O4′ of a neighbouring sugar residue (N2—H2*A*···O4′^{i}) (see Table 2 for symmetry codes and geometry). Moreover, adjacent sugar residues form strong hydrogen bonds (O3′—H3′O···O5′^{iii}). To connect molecules of adjacent layers, the water molecule acts as a donor (O10—H10*A*···O6 and O10—H10*B*···O3′^{i}) as well as an acceptor (O5′—H5′O···O10^{iv}), as

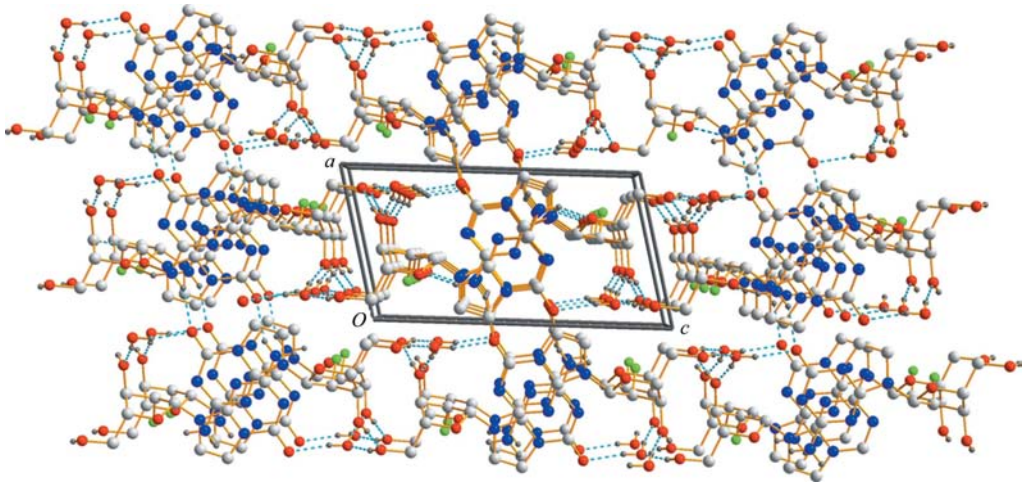

Figure 2
The crystal packing of the β-anomer, (I*a*), showing the intermolecular hydrogen-bonded network (dashed lines). The projection is parallel to the *ac* plane.

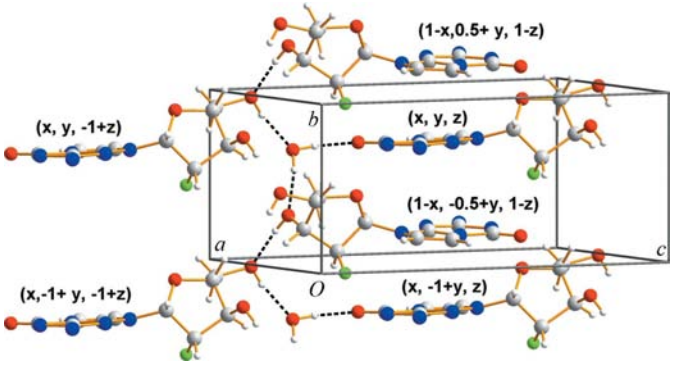

Figure 3
A detailed view of the hydrogen-bonded network (dashed lines) connecting the nucleoside and water molecules.

illustrated in Fig. 3. Neither the heterocyclic ring N atoms nor the F substituent take part in hydrogen bonding.

Earlier, we reported the crystal structure of the closely related α-anomer of 5-aza-7-deaza-2′-deoxyguanosine, (IV), albeit lacking the 2′-fluoro substituent (Seela *et al.*, 2002). Interestingly, compound (IV) crystallizes in the same space group (monoclinic, $P2_1$), with one water molecule in the asymmetric unit, as found for (I*a*) (Seela *et al.*, 2002). However, closer inspection of the crystal packing of (IV) reveals several differences from the molecular packing of (I*a*). In the crystal structure of (IV), the 5-aza-7-deazaguanine moieties form double layers and are arranged in a reverse orientation to each other (Seela *et al.*, 2002). A distance of 3.508 Å between nucleobases within a layer was calculated. Moreover, individual double layers are spatially displaced. In contrast, the 5-aza-7-deazaguanine moieties of (I*a*) form highly regular layers, with a distance of 3.354 Å between the nucleobases. As in (IV), the nucleobases of (I*a*) are alternating, although with different orientations of the sugar moieties, as shown in Fig. 2. In addition, the hydrogen-bonding network of the two compounds is different. Conspicuously, none of the heterocyclic ring N atoms of (I*a*) is involved in hydrogen bonding, which is in contrast with (IV), where atoms N1 and N3 function as acceptor sites (Seela *et al.*, 2002).

Experimental

Compound (I) was synthesized as reported previously (Glaçon & Seela, 2004). Slow crystallization from water afforded (I*a*) as colourless plates (decomposition above 503 K). For the diffraction experiment, a single crystal was mounted on a MiTeGen Micro-Mounts fibre in a thin smear of oil.

Crystal data

$C_{10}H_{12}FN_5O_4\cdot H_2O$
M_r = 303.26
Monoclinic, $P2_1$
a = 7.3752 (6) Å
b = 6.3516 (4) Å
c = 13.8654 (11) Å
β = 103.648 (4)°
V = 631.18 (8) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.14 mm^{-1}
T = 130 K
0.34 × 0.20 × 0.04 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2008)
T_{min} = 0.947, T_{max} = 0.995
20880 measured reflections
1813 independent reflections
1680 reflections with $I > 2\sigma(I)$
R_{int} = 0.041

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.079
S = 1.09
1813 reflections
192 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

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 an inconclusive value [0.3 (6)]. Therefore, Friedel equivalents (1512) 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, the H atoms were placed in geometrically idealized positions (C—H = 0.93–0.98 Å and N—H =

Table 1
Selected geometric parameters (Å, °).

N1—C6	1.333 (2)	N5—C7	1.401 (2)
N1—C2	1.356 (2)	N9—C1′	1.447 (2)
C2—N2	1.329 (2)	C2′—F2′	1.398 (2)
F2′—C2′—C1′	109.64 (15)	H10*A*—O10—H10*B*	104.5
F2′—C2′—C3′	108.70 (14)		
N2—C2—N3—C4	177.60 (18)	O4′—C1′—C2′—F2′	−78.78 (18)
C7—N5—C6—O6	0.8 (3)	N9—C1′—C2′—F2′	38.5 (2)
C4—N9—C1′—O4′	−123.1 (2)	O4′—C4′—C5′—O5′	164.03 (15)
C8—N9—C1′—O4′	40.3 (3)	C3′—C4′—C5′—O5′	−78.3 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2*A*···O4′^{i}	0.86	2.37	2.989 (2)	129
N2—H2*B*···O6^{ii}	0.86	2.06	2.8553 (19)	153
O3′—H3′O···O5′^{iii}	0.82	1.80	2.617 (2)	175
O5′—H5′O···O10^{iv}	0.82	1.82	2.624 (2)	168
O10—H10*A*···O6	0.87	1.92	2.7748 (19)	167
O10—H10*B*···O3′^{i}	0.87	1.93	2.792 (2)	169

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

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). The water H atoms were located in a difference map and their parameters were initially refined freely. Due to the low reflection/refined parameter ratio, the O—H distances were constrained to 0.87 Å, with U_{iso}(H) = 1.5U_{eq}(O), in the final cycle of refinement.

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* and *DIAMOND* (Brandenburg, 1999); 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: GD3329). Services for accessing these data are described at the back of the journal.

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