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6-Aza-2′-deoxy-2′-arabinofluorouridine, a 2′-deoxyribonucleoside with an N-sugar conformation in the solid state and in solution

Frank Seela,[a]* Padmaja Chittepu,[a] Junlin He[a] and Henning Eickmeier[b]

[a]Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastraße 7, 49069 Osnabrück, Germany, and [b]Anorganische Chemie II, Institut für Chemie, Universität Osnabrück, Barbarastraße 7, 49069 Osnabrück, Germany
Correspondence e-mail: frank.seela@uni-osnabrueck.de

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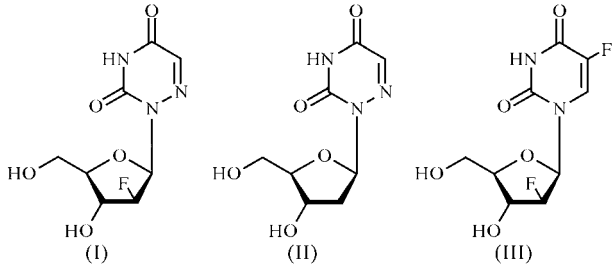
In the title compound, 2-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione, $C_8H_{10}FN_3O_5$, the torsion angle of the N-glycosylic bond is *anti* [χ = −125.37 (13)°]. The furanose moiety adopts the N-type sugar pucker ($^3T_2$), with P = 359.2° and τ_m = 31.4°. The conformation around the C4′—C5′ bond is antiperiplanar (*trans*), with a torsion angle γ of 177.00 (11)°. A network is formed *via* hydrogen bonds from the nucleobases to the sugar residues, as well as through hydrogen bonds between the sugar moieties.

Comment

About 0.07% of the Earth's crust consists of fluorine. Naturally occurring organofluorine compounds are known to be rare and only 13 have been discovered, including molecules like fluorothreonine (Sanda *et al.*, 1986) and nucleocidin (Morton *et al.*, 1969; Thomas *et al.*, 1956). Recently, 5-fluorouracil derivatives were isolated from the sponge *Phakellia fusca* (Xu *et al.*, 2003).

Fluorine-substituted analogues of the components of nucleic acid have become established as antiviral, antitumour and antifungal agents. Compounds of this class contain an F atom at the C2′ position of the sugar moiety. This modification strongly influences the physical, chemical and biological properties without perturbing the molecular geometry. Thus, the compounds 2′-fluoro-5-methyl-1-β-D-arabinofuranosyluracil (FMAU; Watanabe *et al.*, 1979), and 2′-fluoro-5-iodo-1-β-D-arabinofuranosyluracil (FIAU) and 2′-fluoro-5-iodo-1-β-D-arabinofuranosylcytosine (FIAC; Watanabe *et al.*, 1983, 1984), are potent and selective inhibitors of *Herpes simplex* virus types 1 and 2, *Varicella zoster* virus and cytomegalovirus, while 2′,2′-difluorocytidine *gem*-citabine (Hertel *et al.*, 1988) shows anticancer activity. The 2′-fluoro substituent also shifts the conformational equilibrium of the sugar moiety of a nucleoside, based on its configuration (Guschlbauer & Jankowski, 1980; Berger *et al.*, 1998; Ikeda *et al.*, 1998; Thibaudeau *et al.*, 1998). The incorporation of 2′-fluoro-arabino nucleosides into oligonucleotide duplexes enhances their susceptibility to RNase H cleavage, which makes them useful for antisense therapeutics (Damha *et al.*, 1998; Ikeda *et al.*, 1998; Yazbeck *et al.*, 2002). We report here the single-crystal X-ray structure of the title compound, (I). The absolute configuration of this molecule is β-D, established from the absolute configuration of the sugar moiety used in the synthesis. The synthesis will be described elsewhere (Seela *et al.*, 2004).



From the crystal structure of (I), it can be established that the torsion angle of the glycosylic bond is in the *anti* range, with χ = −125.37 (13)° (Fig. 1 and Table 1). Compound (III) has an *anti* orientation of the base with respect to the sugar ring [χ = −158.6 (3)°; Hempel *et al.*, 1999], while nucleoside (II), without a 2′-fluoro substituent, adopts an *anti* conformation which is very close to *syn* [χ = −93.9 (3)°; Seela & Chittepu, 2004]. The intramolecular repulsion between the 2′-fluoro substituent and the ring N atom adjacent to the glycosylation position (N6) is responsible for a significant change in the conformation of (I) compared with (II) (Freskos, 1989).

The sugar moiety of (I) shows pseudorotation parameters (Rao *et al.*, 1981) of P = 359.2° and τ_m = 31.4° with an N-type sugar pucker (C2′-*exo* and C3′-*endo*, $^3T_2$), while (III) adopts a twisted conformation ($^0T_1$) with a pseudorotation phase angle P = 101.6 (2) and an amplitude τ_m = 43.2 (1)°. The sugar conformation of nucleoside (II) is C2′-*endo*–C3′-*exo* ($^2T_3$) (S-type sugar). The orientation around the C4′—C5′ bond of (I)

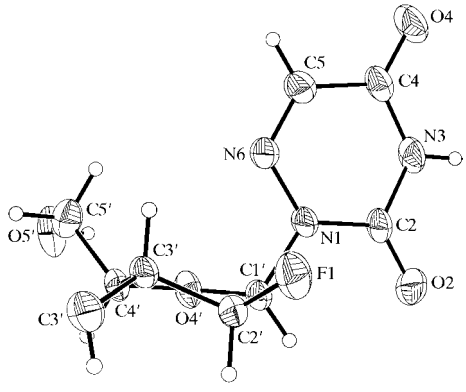


Figure 1
A perspective view of the nucleoside moiety of (I). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

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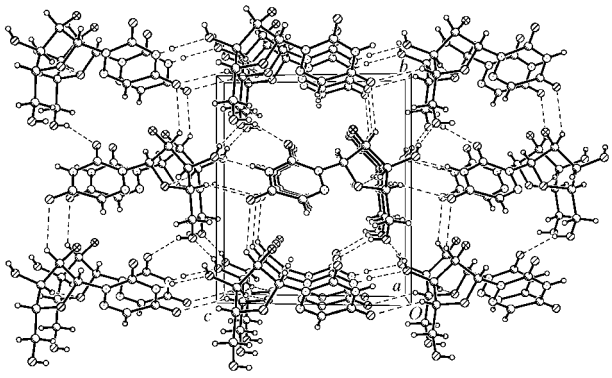

Figure 2
The crystal packing of (I), showing the intermolecular hydrogen-bonding network (dashed lines).

is antiperiplanar (*trans*), with a torsion angle γ (O5′—C5′—C4′—C3′) of 177.00 (11)°. The presence of the 2′-fluoro substituent affects the sugar ring bond lengths and angles when compared with those of (II). The C1′—O4′ bond length in (I) is about 0.04 Å shorter than the C4′—O4′ bond. The F2′—C2′ distance is similar to the C—F bonds found in other 2′-fluoroarabinonucleosides (Birnbaum *et al.*, 1982) and 2′-fluororibonucleosides (Suck *et al.*, 1974; Hakoshima *et al.*, 1981).

The sugar conformation of (I) in aqueous solution was also determined, from the ^{1}H NMR coupling constants measured in D_2O, using the program *PSEUROT*6.3 (Van Wijk *et al.*, 1999). This program calculates the best fits of three $^3J_{H,H}$ and two $^3J_{H,F}$ experimental coupling constants to the five conformational parameters, namely the phase angles (P_S and P_N) and puckering amplitudes (ψ_S and ψ_N) of the S- and N-conformers, and the population of the S-type conformer (X_S; $X_S + X_N = 1$). The input contained the following coupling constants: ^3J(H1′,H2′), ^3J(H2′,H3′), ^3J(H3′,H4′), ^3J(H1′,F) and ^3J(H3′,F). The program reveals that (I) exists as 100% N-type with two regions [$1 - P_N = 14.8°$ (^3E, C3′-*endo*), 77%; $2 - P_N = 288.0°$ ($^1T_0$, C1′-*endo*–O4′-*exo*), 23%], very different from the non-fluorinated nucleoside, (II), for which the solution conformation is only 58% N-type. This unusual N-conformation of (I) is due to the combined influence of the *gauche* effect of the 2′-fluoro atom and the anomeric effect of the nucleobase with the N atom next to the glycosylation site.

The structure of (I) is stabilized by several intermolecular hydrogen bonds (N3—H3···O3′, O3′—H3′···O5′ and O5′—H5′···O2; Table 2), as well as by a stacking interaction of the bases (nucleobase distance = 4.93 Å; Fig. 2).

The (100% N-type) sugar conformation observed for (I) has been previously reported for 8-aza-7-deazapurine 2′-deoxy 2′-fluoroarabinonucleosides (He *et al.*, 2003). These unusual conformational properties of the sugar moiety are the result of the F atom in the *arabino* configuration and a nucleobase N atom next to the glycosylation site. The non-fluorinated compound, (II), exhibits the S-conformation in the solid state and an almost equal population of N- and S-conformers in solution.

Experimental

Nucleoside (I) (see scheme) was prepared by the stereoselective glycosylation of silylated 6-azauracil with 3,5-di-*O*-benzyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide in the presence of CuI according to Freskos (1989), followed by deprotection of the sugar moiety with 0.1 *N* NaOMe in methanol. Suitable crystals (m.p. 438 K) were grown from a solution in dichloromethane–methanol (9:1). For the diffraction experiment, a single crystal of (I) was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_8H_{10}FN_3O_5$
M_r = 247.19
Monoclinic, $P2_1$
a = 4.9302 (9) Å
b = 10.993 (2) Å
c = 9.4360 (16) Å
β = 98.62 (2)°
V = 505.65 (16) Å^3
Z = 2
D_x = 1.624 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 47 reflections
θ = 5.3–17.3°
μ = 0.15 mm^{-1}
T = 293 (2) K
Block, colourless
0.4 × 0.3 × 0.3 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2574 measured reflections
1832 independent reflections
1769 reflections with $I > 2\sigma(I)$
R_{int} = 0.022
θ_{max} = 32.0°
$h = -7 \rightarrow 1$
$k = -16 \rightarrow 1$
$l = -14 \rightarrow 14$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.094
S = 1.05
1832 reflections
164 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0646P)^2 + 0.023P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.083 (12)

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.3793 (15)	C4—C5	1.4645 (19)
N1—C1′	1.4649 (16)	C5—N6	1.2829 (17)
F1—C2′	1.3929 (16)	C1′—O4′	1.4058 (18)
N3—C4	1.376 (2)	O4′—C4′	1.4486 (14)
O4′—C1′—C2′	105.34 (10)	F1—C2′—C1′	111.73 (10)
F1—C2′—C3′	112.82 (10)	C3′—C2′—C1′	105.11 (11)
N6—N1—C2—O2	179.01 (15)	F1—C2′—C3′—O3′	−84.17 (14)
N1—C2—N3—C4	2.9 (2)	N1—C1′—O4′—C4′	−111.35 (11)
N3—C4—C5—N6	0.0 (2)	C2′—C1′—O4′—C4′	10.18 (13)
C4—C5—N6—N1	1.1 (2)	C1′—O4′—C4′—C3′	9.68 (13)
C2—N1—N6—C5	−0.2 (2)	C2′—C3′—C4′—O4′	−25.17 (12)
C2—N1—C1′—O4′	−125.48 (13)	O3′—C3′—C4′—C5′	92.60 (14)
O4′—C1′—C2′—F1	−148.96 (11)	O4′—C4′—C5′—O5′	58.56 (15)
N1—C1′—C2′—F1	−29.03 (16)	C3′—C4′—C5′—O5′	176.95 (11)

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O3′^{i}	0.861 (13)	2.027 (13)	2.8817 (16)	172 (2)
O3′—H3′···O5′^{ii}	0.82 (2)	1.94 (2)	2.7330 (18)	163 (3)
O5′—H5′···O2^{iii}	0.82 (2)	2.08 (2)	2.8344 (16)	153 (4)

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

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 refinement. The known configuration of the parent molecule was used to define the enantiomer of the final nucleoside. All H atoms were initially found in a difference Fourier synthesis. In order to maximize the data-to-parameter ratio, H atoms bonded to C atoms were placed in geometrically idealized positions (C—H = 0.93–0.98 Å) and constrained to ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C)$. The positions of the H atoms on O and N atoms were refined and their $U_{iso}(H)$ values were constrained to $1.2U_{eq}(N,O)$. The distances O3′—H3′, O5′—H5′ and N3—H3 were restrained using DFIX (Sheldrick, 1997).

Data collection and cell refinement: *XSCANS* (Siemens, 1996); data reduction: *SHELXTL* (Sheldrick, 1997); program(s) used to solve and refine structure: *SHELXTL*; 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: SX1151). Services for accessing these data are described at the back of the journal.

References

Berger, I., Tereshko, V., Ikeda, H., Marquez, V. E. & Egli, M. (1998). *Nucleic Acids Res.* **26**, 2473–2480.

Birnbaum, G. I., Cygler, M., Watanabe, K. A. & Fox, J. J. (1982). *J. Am. Chem. Soc.* **104**, 7626–7630.

Damha, M. J., Wilds, C. J., Noronha, A., Brukner, I., Borkow, G., Arion, D. & Parniak, M. A. (1998). *J. Am. Chem. Soc.* **120**, 12976–12977.

Freskos, Y. N. (1989). *Nucleosides Nucleotides*, **8**, 549–555.

Guschlbauer, W. & Jankowski, K. (1980). *Nucleic Acids Res.* **8**, 1421–1433.

Hakoshima, T., Omori, H., Tomita, K., Miki, H. & Ikehara, M. (1981). *Nucleic Acids Res.* **9**, 711–729.

He, J., Eickmeier, H. & Seela, F. (2003). *Acta Cryst.* C**59**, o406–o408.

Hempel, A., Camerman, N., Grierson, J., Mastropaolo, D. & Camerman, A. (1999). *Acta Cryst.* C**55**, 632–633.

Hertel, L. W., Kroin, J. S., Misner, J. W. & Tustin, J. M. (1988). *J. Org. Chem.* **53**, 2406–2409.

Ikeda, H., Fernandez, R., Wilk, A., Barchi, J. J. Jr, Huang, X. & Marquez, V. E. (1998). *Nucleic Acids Res.* **26**, 2237–2244.

Morton, G. O., Lancaster, J. E., Van Lear, G. E., Fulmor, W. & Meyer, W. E. (1969). *J. Am. Chem. Soc.* **91**, 1535–1537.

Rao, S. T., Westhof, E. & Sundaralingam, M. (1981). *Acta Cryst.* A**37**, 421–425.

Sanda, M., Miyceno, T., Iwadare, S., Williamson, J. M., Arison, B. H., Smith, J. L., Douglas, A. W., Leisch, J. W. & Inamine, E. (1986). *J. Antibiot.* **39**, 259–265.

Seela, F. & Chittepu, P. (2004). In preparation.

Seela, F., Chittepu, P. & He, J. (2004). In preparation.

Sheldrick, G. M. (1997). *SHELXTL.* Release 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.

Siemens (1996). *XSCANS.* Version 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Spek, A. L. (1999). *PLATON.* University of Utrecht, The Netherlands. 32-Bit Windows implentation by L. J. Farrugia, University of Glasgow, Scotland.

Suck, D., Saenger, W., Main, P., Germain, G. & Declercq, J.-P. (1974). *Biochim. Biophys. Acta*, **361**, 257–265.

Thibaudeau, C., Plavec, J. & Chattopadhyaya, J. (1998). *J. Org. Chem.* **63**, 4967–4984.

Thomas, S. O., Singleton, V. L., Lowery, J. A., Sharpe, R. W., Pruess, L. M., Porter, J. N., Mowat, J. H. & Bohonos, N. (1956). *Antibiot. Annu.* pp. 716–721.

Van Wijk, L., Haasnoot, C. A. G., de Leeuw, F. A. A. M., Huckriede, B. D., Westra Hoekzema, A. J. A. & Altona, C. (1999). *PSEUROT*6.3. Leiden Institute of Chemistry, Leiden University, The Netherlands.

Watanabe, K. A., Reichman, U., Hirota, K., Lopez, C. & Fox, J. J. (1979). *J. Med. Chem.* **22**, 21–24.

Watanabe, K. A., Su, T.-L., Klein, R. S., Chu, C. K., Matsuda, A., Chun, M.-W., Lopez, C. & Fox, J. J. (1983). *J. Med. Chem.* **26**, 152–156.

Watanabe, K. A., Su, T.-L., Reichman, U., Greenberg, N., Lopez, C. & Fox, J. J. (1984). *J. Med. Chem.* **27**, 91–94.

Xu, X.-H., Yao, G.-M., Li, Y.-M., Lu, J.-H., Lin, C.-J., Wang, X. & Kong, C.-H. (2003). *J. Nat. Prod.* **66**, 285–288.

Yazbeck, D. R., Min, K.-L. & Damha, M. J. (2002). *Nucleic Acids Res.* **30**, 3015–3025.