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The regioisomeric 1*H*(2*H*)-pyrazolo[3,4-*d*]pyrimidine N^1- and N^2-(2′-deoxy-β-D-ribofuranosides)

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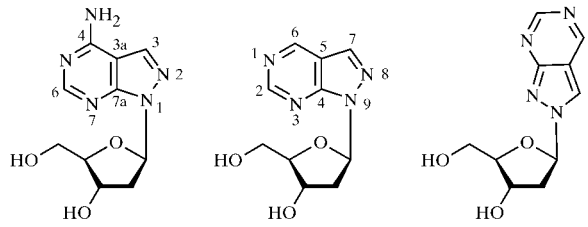
In the title regioisomeric nucleosides, alternatively called 1-(2-deoxy-β-D-*erythro*-furanosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{10}H_{12}N_4O_3$, (II), and 2-(2-deoxy-β-D-*erythro*-furanosyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{10}H_{12}N_4O_3$, (III), the conformations of the glycosylic bonds are *anti* [−100.4 (2)° for (II) and 15.0 (2)° for (III)]. Both nucleosides adopt an S-type sugar pucker, which is C2′-*endo*-C3′-*exo* ($^2T_3$) for (II) and 3′-*exo* (between $_3E$ and $^4T_3$) for (III).

Comment

During a search for more stable 'dA-dT' base pairs, various 3-substituted pyrazolo[3,4-*d*]pyrimidine 2′-deoxyribonucleosides (7-substituted 8-aza-7-deazapurine 2′-deoxyribonucleosides) were studied as analogues of 2′-deoxyadenosine and were incorporated in oligonucleotides (systematic numbering is used throughout the paper). The interchange of the five-membered ring atoms and the presence of substituents (Br or I) on the 3-position of the modified purine bases exert an influence on the base-pair stability (Seela, Becher & Zulauf, 1999; He & Seela, 2002*a*). Common 2′-deoxyribonucleosides tend to adopt an *anti* conformation. The orientation of the base relative to the sugar (*syn*/*anti*) is defined by the torsion angle χ (O4′—C1′—N9—C4) (purine numbering; IUPAC–IUB Joint Commision on Biochemical Nomenclature, 1983). 2′-Deoxyadenosine shows an *anti* conformation, with a torsion angle χ (O4′—C1′—N1—C7a) of −165.1° (Sato, 1984), while that of pyrazolo[3,4-*d*]pyrimidin-4-amine 2′-deoxyribonucleoside (8-aza-7-deaza-2′-deoxyadenosine), (I), is between an *anti* and a high-*anti* conformation [χ = −106.3 (2)°; Seela, Zulauf *et al.*, 1999]. Further substitution (Br or I) at the 3-position drives the conformation to high-*anti* [for the 3-bromo derivative, χ = −74.1 (4)°, while for the 3-iodo derivative, χ = −73.2 (4)°; Seela *et al.*, 2000]. The steric and stereo-electronic effects of the nucleobases are thought to be responsible for this change.



To the best of our knowledge, there is no reported crystal structure of a pyrazolo[3,4-*d*]pyrimidin-2-yl 2′-deoxyribonucleoside. Here, the X-ray crystallographic analyses of a pair of N^1- and N^2-glycosylated pyrazolo[3,4-*d*]pyrimidines, *viz*. (II) and (III), respectively, are described. Both nucleosides have the same β-D configuration. According to the systematic numbering for compound (II), the torsion angle χ is defined by O4′—C1′—N1—C7a. The definition of an *anti* base orientation about the glycosylic bond of the N^2-nucleoside, (III), is arbitrarily ascribed to the torsion angle O4′—C1′—N2—C3 of 180°, according to Seela & Debelak (2000).

From the crystal structure of compound (II) (Fig. 1), the conformation of the glycosylic bond is between the *anti* and high-*anti* values [χ = −100.4 (2)°], and is very close to that of compound (I) (Seela, Zulauf *et al.*, 1999). Compound (III) adopts an *anti* conformation, with χ = 15.0 (2)°. The glycosylic bond between atoms N2 and C1′ of compound (III) is 0.034 Å longer than that between atoms N1 and C1′ of compound (II).

Both nucleosides show an S-type sugar conformation, but with different ring puckering. The sugar conformation of nucleoisde (II) is C2′-*endo*-C3′-*exo* ($^2T_3$), with pseudo-rotation parameters (Rao *et al.*, 1981) P = 185.6 (2)° and τ_m = 40.3 (1)°, while the sugar part of nucleoside (III) has a 3′-*exo* conformation (between $_3E$ and $^4T_3$), with pseudo-rotation parameters P = 203.3 (1)° and τ_m = 37.0 (1)°. These two nucleosides have the same *ap* (*g*−) conformation about the C4′—C5′ bond; the values of γ (C3′—C4′—C5′—O5′) are 177.97 (18) and 175.73 (13)° for (II) and (III), respectively. This means that the base and the hydroxymethyl group undergo the same disrotatory motion so that the Coulombic repulsion between atoms N2 and O5′ or between atoms N1 and O4′ is minimized (Seela, Becher *et al.*, 1999). Similarly, nucleoside (I) adopts the C2′-*endo*-C3′-*exo*-type (S-type) sugar puckering, but with a −*ap* conformation around the C4′—C5′ bond [γ = −178.73 (16)°; Seela, Zulauf *et al.*, 1999], while 2′-deoxyadenosine has a C3′-*endo* conformation (Sato, 1984). These results have an influence on the stability of oligonucleotide duplexes (He & Seela, 2002*a*).

The base moieties of (II) and (III) are nearly planar. The r.m.s. deviations of the ring atoms (N1/N2/C3/C3a/C4/N5/C6/N7/C7a) from their calculated least-squares planes are 0.018 and 0.013 Å, respectively, with the maximum deviations being 0.028 (2) (N1) and 0.019 (1) Å (C3a). Atom C1′ is displaced from this plane by 0.033 (2) and 0.139 (1) Å in (II) and (III),

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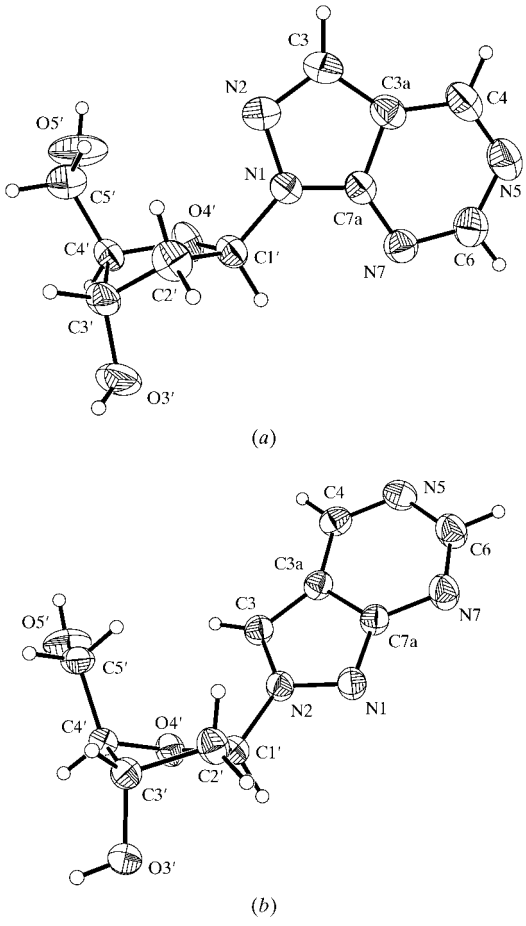

Figure 1
Perspective views of nucleosides (*a*) (II) and (*b*) (III). Displacement ellipsoids for non-H atoms are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

respectively. The bases are strongly stacked in both crystal structures.

Structures (II) and (III), which differ only in the glycosylation positions (N1 *versus* N2), each form two different types of hydrogen bonds. Structure (II) is stabilized by intermolecular hydrogen bonds between O3′—H and O4′($2-x$, $y-\frac{1}{2}$, $\frac{3}{2}-z$) of two sugar moieties and between O5′—OH of the sugar moiety and N7($1+x$, y, z) of an adjacent nucleobase unit. These interactions link the molecules into an infinite two-dimensional network in which the bases are stacked and tilted with respect to each other. In contrast, structure (III) is stabilized exclusively by hydrogen bonds between the bases and sugar units [O3′—H with N7($1-x$, $\frac{1}{2}+y$, $2-z$) and O5′—H with N5($2-x$, $\frac{1}{2}+y$, $1-z$)]. These interactions link the molecules into an infinite two-dimensional network, with piles of stacked bases tilted only slightly with respect to each other.

Experimental

Nucleoside (II) (Seela & Steker, 1984) was prepared by the glycosylation reaction of pyrazolo[3,4-*d*]pyrimidine with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-furanosyl chloride (Hoffer, 1960), followed by deprotection of the sugar moiety (He & Seela, 2002*b*); m.p.: 421 K; R_F (silica-gel thin-layer chromatography): 0.22 (CH_2Cl_2/CH_3OH, 9:1). Suitable crystals were grown from a solution in methanol. Nucleoside (III) was obtained as the minor product from the above glycosylation reaction followed by deprotection of the sugar moiety; m.p.: 427 K; R_F (silica-gel thin-layer chromatography): 0.13 (CH_2Cl_2/CH_3OH, 9:1). Suitable crystals were grown from a solution in acetone.

Compound (II)

Crystal data

$C_{10}H_{12}N_4O_3$
$M_r = 236.24$
Orthorhombic, $P2_12_12_1$
$a = 6.9306\ (8)$ Å
$b = 11.1084\ (15)$ Å
$c = 13.7591\ (11)$ Å
$V = 1059.3\ (2)$ Å^3
$Z = 4$
$D_x = 1.481$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 40 reflections
$\theta = 6.9$–$12.5°$
$\mu = 0.11$ mm^{-1}
$T = 293\ (2)$ K
Transparent needle, colourless
0.58 × 0.28 × 0.28 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2375 measured reflections
1784 independent reflections
1474 reflections with $I > 2\sigma(I)$
$R_{int} = 0.021$
$\theta_{max} = 30.0°$
$h = -1 \rightarrow 9$
$k = -15 \rightarrow 1$
$l = -19 \rightarrow 1$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.105$
$S = 1.03$
1784 reflections
164 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0518P)^2 + 0.1719P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.21$ e Å^{-3}
$\Delta\rho_{min} = -0.18$ e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.023 (3)

Table 1
Selected geometric parameters (Å, °) for (II).

N1—C1′	1.448 (2)		
C7a—N1—C1′	128.04 (18)	N2—N1—C1′	120.69 (17)
C7a—N1—N2—C3	−0.8 (3)	C1′—C2′—C3′—O3′	76.1 (2)
C1′—N1—N2—C3	−175.5 (2)	C1′—C2′—C3′—C4′	−39.3 (2)
C4—C3a—C7a—N7	−1.4 (3)	C2′—C3′—C4′—O4′	35.0 (2)
C3—C3a—C7a—N7	179.51 (19)	O3′—C3′—C4′—C5′	157.48 (17)
C7a—N1—C1′—O4′	−100.4 (2)	N1—C1′—O4′—C4′	−133.65 (17)
N2—N1—C1′—O4′	73.3 (2)	C5′—C4′—O4′—C1′	105.76 (19)
C7a—N1—C1′—C2′	139.9 (2)	C3′—C4′—O4′—C1′	−16.6 (2)
O4′—C1′—C2′—C3′	30.5 (2)	O4′—C4′—C5′—O5′	60.9 (2)
N1—C1′—C2′—C3′	152.21 (19)	C3′—C4′—C5′—O5′	177.97 (18)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3′—H3′O···O4′^{i}	0.80 (2)	2.16 (2)	2.871 (2)	149 (3)
O5′—H5′O···N7^{ii}	0.80 (2)	2.04 (2)	2.828 (3)	168 (3)

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

Table 3
Selected geometric parameters (Å, °) for (III).

N2—C1′	1.4817 (18)		
C7a—N1—N2	102.79 (12)	N1—N2—C1′	116.08 (12)
C3—N2—C1′	128.25 (13)		
C7a—N1—N2—C3	0.14 (17)	C1′—C2′—C3′—O3′	84.82 (15)
C7a—N1—N2—C1′	−175.41 (12)	C1′—C2′—C3′—C4′	−33.24 (15)
C3—C3a—C7a—N7	−179.60 (14)	C2′—C3′—C4′—O4′	36.04 (14)
C3—N2—C1′—O4′	15.0 (2)	O3′—C3′—C4′—C5′	159.99 (12)
N1—N2—C1′—O4′	−170.15 (12)	C2′—C1′—O4′—C4′	3.33 (14)
N1—N2—C1′—C2′	70.59 (16)	O4′—C4′—C5′—O5′	58.82 (17)
O4′—C1′—C2′—C3′	19.55 (15)	C3′—C4′—C5′—O5′	175.73 (13)
N2—C1′—C2′—C3′	139.15 (12)		

Compound (III)

Crystal data

$C_{10}H_{12}N_4O_3$
M_r = 236.24
Monoclinic, $P2_1$
a = 4.9396 (7) Å
b = 13.1528 (14) Å
c = 8.1780 (12) Å
β = 102.772 (9)°
V = 518.17 (12) Å^3
Z = 2
D_x = 1.514 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 47 reflections
θ = 4.5–16.1°
μ = 0.12 mm^{-1}
T = 293 (2) K
Transparent block, yellow
0.57 × 0.57 × 0.48 mm

Data collection

Bruker $P4$ diffractometer
$2\theta/\omega$ scans
2202 measured reflections
1562 independent reflections
1524 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 30.0°
$h = -6 \rightarrow 1$
$k = -1 \rightarrow 18$
$l = -11 \rightarrow 11$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.092
S = 1.07
1562 reflections
164 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0637P)^2 + 0.0228P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.026 (9)

Table 4
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
O3′—H3′O···N7^{i}	0.842 (15)	1.992 (15)	2.832 (2)	175 (2)
O5′—H5′O···N5^{ii}	0.842 (15)	1.972 (15)	2.8011 (19)	168.0 (17)

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

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 inconclusive values (Flack & Bernadinelli, 2000) [−0.2 (16) for (II) and 0.4 (10) for (III)]. Therefore, the Friedel equivalents [416 for (II) and 119 for (III)] were merged before the final refinements. The known configuration of the parent molecule was used to define the enantiomer employed in the refined model. All H atoms were initially found in a difference Fourier synthesis. In order to maximize the data-to-parameter ratio, the 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. The hydroxy H atoms were initially placed in difference-map positions, then geometrically idealized and constrained to ride on their parent O atoms, although the chemically equivalent O—H bond lengths were allowed to refine while being constrained to be equal. An overall isotropic displacement parameter was refined for all H atoms.

For both compounds, 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*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1143). Services for accessing these data are described at the back of the journal.

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