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2-Amino-7-chloro-2′-deoxytubercidin

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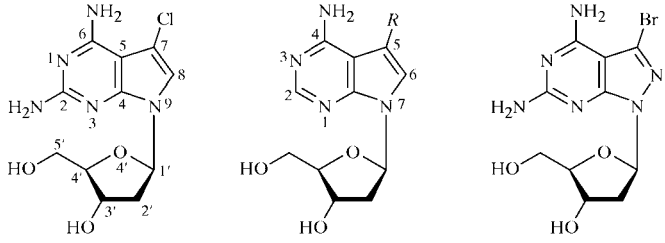
In 4-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine, $C_{11}H_{14}ClN_5O_3$, the conformation of the N-glycosylic bond is between *anti* and high-*anti* [$\chi = -102.5\ (6)^\circ$]. The 2′-deoxyribofuranosyl unit adopts the C3′-*endo*-C4′-*exo* ($^3T_4$) sugar pucker (N-type) with $P = 19.6^\circ$ and $\tau_m = 32.9^\circ$ [terminology: Saenger (1989). *Landolt-Börnstein New Series*, Vol. 1, *Nucleic Acids*, Subvol. a, edited by O. Madelung, pp. 1–21. Berlin: Springer-Verlag]. The orientation of the exocyclic C4′—C5′ bond is +*ap* (*trans*) with a torsion angle $\gamma = 171.5\ (4)^\circ$. The compound forms a three-dimensional network that is stabilized by four intermolecular hydrogen bonds (N—H···O and O—H···N) and one intramolecular hydrogen bond (N—H···Cl).

Comment

Purine-2,6-diamine 2′-deoxyribonucleosides have attracted attention because of their abilities to form tridentate base pairs with dT (Chollet & Kawashima, 1988; Lamm *et al.*, 1991; Bailly & Waring, 1998) (purine numbering is used throughout the manuscript; IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). 2-Amino-2′-deoxytubercidin was found to generate a stable base pair not only with 2′-deoxythymidine but also with 2′-deoxycytidine; this process causes mutagenic events (Okamoto *et al.*, 2002). This capability results from the strong basicity of 2-amino-2′-deoxytubercidin protonated in neutral or weakly acid medium, which is underlined by the pK_a value (5.71). The introduction of 7-halogen substituents, as in the title compound, (I), decreases the basicity to a pK_a of 4.86 (Peng *et al.*, 2006). Hybridization experiments show that nucleoside (I) exhibits better mismatch discrimination than 2-amino-2′-deoxytubercidin and also enhances the stability of duplex DNA (B-DNA) with antiparallel (aps) chain orientation as well as parallel (ps) chain orientation (Peng *et al.*, 2006). The stabilizing effect of 7-substituted 7-deazapurines is different from that of 8-substituted purine nucleosides, the latter showing a *syn* conformation of the N-glycosylic bond, which destabilizes B-DNA (Tavale & Sobell, 1970; Kanaya *et al.*, 1984; Sugiyama *et al.*, 1996). It is therefore of interest to study the structure of (I) in the solid state. Up to now, there has been no reported crystal structure of a 7-deazapurin-2,6-diamine 2′-deoxyribonucleoside. The structure of (I) is described here.



(I) (II*a*) *R*=H (II*b*) *R*=I (III)
Purine numbering Systematic numbering

The structure of (I) is shown in Fig. 1 and selected geometric parameters are summarized in Table 1. The space group ($P2_12_12_1$) is identical to that of 2′-deoxytubercidin, (II*a*) (Zabel *et al.*, 1987), but different from that of its 7-iodo derivative (II*b*) ($P2_1$) (Seela *et al.*, 1996).

The orientation of the base relative to the sugar (*syn*/*anti*) is defined by the torsion angle γ (O4′—C1′—N9—C4). For the 'purine' 2′-deoxyribonucleosides, the preferred conformation around the N-glycosylic bond is in the *anti* range (Saenger, 1989; Sato, 1984). It was reported that the 7-substituents of 8-aza-7-deaza-2′-deoxyadenosines drive the conformation to high-*anti* (Seela *et al.*, 1999, 2000). 7-Deazapurin-2,6-diamine nucleoside (I) adopts a high-*anti* conformation with $\gamma = -102.5\ (6)^\circ$, which is similar to that of 8-aza-7-bromo-7-deazapurin-2,6-diamine 2′-deoxyribonucleoside (III) [$\gamma = -105.0\ (6)^\circ$; Seela *et al.*, 2005].

For (I), the phase angle of pseudorotation (P) (Altona & Sundaralingam, 1972) is 19.6° and the maximum amplitude of puckering (τ_m) is 32.9°, which is unusual for a 2′-deoxyribonucleoside. This indicates that the sugar ring has C3′-*endo* conformation ($^3T_4$) and its pucker can also be described as N (Saenger, 1989). This is similar to the 8-aza-7-deazapurin-2,6-

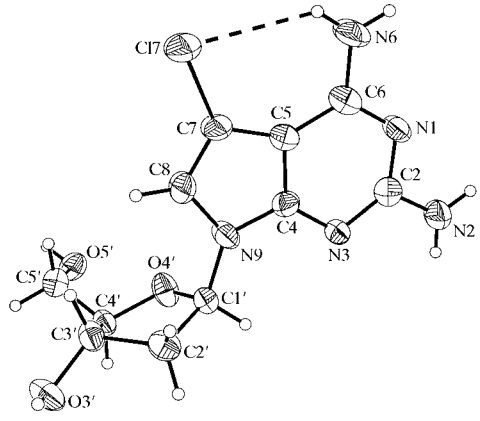


Figure 1
A perspective view of nucleoside (I) showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary size.

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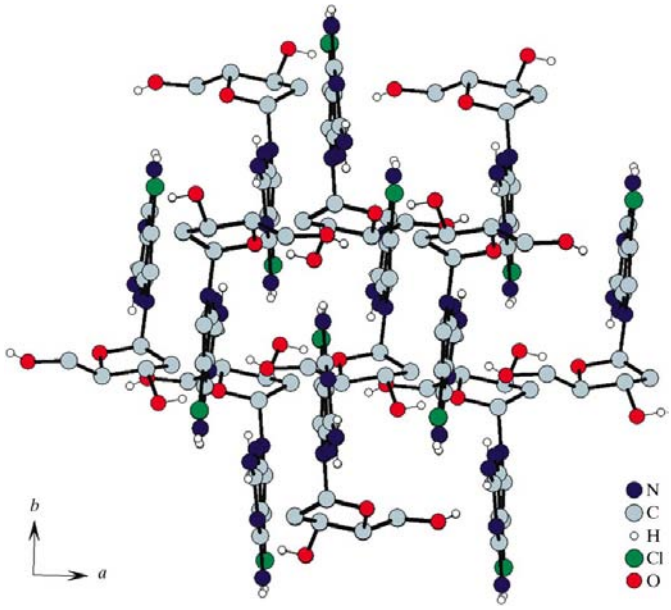

Figure 2
Ball-and-stick model of nucleoside (I) chains. Successive nucleobases on the same side of the chain are at a distance of 7.636 (2) Å.

diamine compound (III) (Seela *et al.*, 2005) but different from that of the parent 2′-deoxytubercidin, which adopts an S-type sugar pucker with $P = 186.6°$ (Zabel *et al.*, 1987). In contrast to the behaviour in the solid state, nucleoside (I) shows two populations in solution with N (28%) and S (72%) pucker (Seela & Peng, 2004). The conformation around the C4′—C5′ bond of (I) is in the *+ap* (*trans*) range (Saenger, 1989), with a torsion angle γ (C3′—C4′—C5′—O5′) of 171.5 (4)°.

The base unit of (I) is essentially planar. The chloro substituent is located −0.078 (7) Å out of the 7-deazapurine plane. The exocyclic N atom of the 2-amino group lies 0.083 (6) Å below and that of the 6-amino group 0.060 (8) Å above the plane.

Compound (I) forms a compact three-dimensional network, which is stabilized by four intermolecular hydrogen bonds and one intramolecular hydrogen bond formed between the H atom of the 6-amino group and the Cl atom (N6—H6*B*···Cl7; Table 2). The H6*B*···Cl7 contact distance is much shorter than the sum of the van der Waals radii (2.95 Å; Bondi, 1964). Fig. 2 shows a ball-and-stick model of nucleoside (I) with a chain-like arrangement in the crystal structure. The sugar moieties of the neighbouring chain are positioned in an antiparallel orientation. The adjacent heterocyclic bases of nucleosides within a chain are directed to opposite sides. The distance between successive nucleobases on the same side of the chain is 7.636 (2) Å, which is much longer than the average base pair distance in B-DNA (3.5 Å). Thus, no base stacking is observed in the crystal structure.

Experimental

Compound (I) was synthesized as described by Seela & Peng (2004) and crystallized from MeOH (m.p. 483 K). Crystals suitable for single-crystal X-ray diffraction were selected directly from the sample as prepared.

Crystal data

$C_{11}H_{14}ClN_5O_3$
$M_r = 299.72$
Orthorhombic, $P2_12_12_1$
$a = 7.637$ (2) Å
$b = 9.4576$ (17) Å
$c = 17.632$ (4) Å
$V = 1273.4$ (5) Å^3
$Z = 4$
$D_x = 1.563$ Mg m^{-3}
Mo $K\alpha$ radiation
$\mu = 0.32$ mm^{-1}
$T = 293$ (2) K
Block, colourless
0.5 × 0.4 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2586 measured reflections
1952 independent reflections
1068 reflections with $I > 2\sigma(I)$
$R_{int} = 0.057$
$\theta_{max} = 29.0°$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.060$
$wR(F^2) = 0.145$
$S = 1.00$
1952 reflections
187 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0543P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.30$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C2—N2	1.360 (7)	N9—C1′	1.464 (6)
C6—N6	1.345 (6)	C1′—O4′	1.432 (6)
C7—Cl7	1.729 (5)	C4′—O4′	1.432 (5)
N2—C2—N1	115.3 (5)	C8—N9—C1′	125.0 (4)
N1—C6—N6	119.0 (5)	O4′—C1′—N9	108.9 (4)
C8—C7—Cl7	126.0 (4)	N9—C1′—C2′	113.8 (4)
C5—C7—Cl7	125.6 (4)	O4′—C4′—C5′	109.2 (4)
C4—N9—C1′	126.8 (4)	C1′—O4′—C4′	110.5 (4)
N2—C2—N3—C4	−177.8 (5)	C2′—C3′—C4′—O4′	−31.5 (5)
C7—C5—C6—N6	0.2 (13)	C2′—C3′—C4′—C5′	−151.5 (4)
C6—C5—C7—Cl7	3.1 (13)	C3′—C4′—C5′—O5′	171.5 (4)
C7—C8—N9—C1′	−174.3 (6)	N9—C1′—O4′—C4′	−123.6 (4)
C4—N9—C1′—O4′	−102.5 (6)	C2′—C1′—O4′—C4′	−0.7 (5)
C8—N9—C1′—O4′	69.9 (7)	C5′—C4′—O4′—C1′	143.6 (4)
N9—C1′—C2′—C3′	100.4 (5)	C3′—C4′—O4′—C1′	20.6 (5)
C1′—C2′—C3′—C4′	30.5 (5)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2*B*···O5′^{i}	0.86	2.23	2.937 (5)	139
N6—H6*A*···O5′^{ii}	0.86	2.38	3.117 (6)	145
N6—H6*B*···Cl7	0.86	2.68	3.353 (5)	136
O3′—H3′*B*···N1^{iii}	0.82 (4)	2.11 (4)	2.930 (6)	179 (5)
O5′—H5′*C*···N3^{iv}	0.82 (3)	1.99 (3)	2.798 (5)	172 (5)

Symmetry codes: (i) $-x+\frac{1}{2}, -y+2, z-\frac{1}{2}$; (ii) $x+\frac{1}{2}, -y+\frac{5}{2}, -z$; (iii) $-x+\frac{3}{2}, -y+2, z+\frac{1}{2}$; (iv) $x-\frac{1}{2}, -y+\frac{3}{2}, -z$.

Refinement of the Flack (1983) parameter led to inconclusive values. Therefore, Friedel equivalents 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. The H-atom

coordinates of the OH groups were refined freely starting from difference map positions. The isotropic displacement parameter was constrained [U_{iso}(H) = 1.5U_{eq}(O)]. In order to maximize the data/parameter ratio, all other H atoms were placed in geometrically idealized positions (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) values of 1.2U_{eq}(C,N).

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* and *DIAMOND* (Brandenburg, 1999); 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: FA3032). Services for accessing these data are described at the back of the journal.

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