Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

3-Bromo-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidine-4,6-diamine: a nucleoside which strongly enhances DNA duplex stability

Frank Seela,[a]* Venkata Ramana Sirivolu,[a] Junlin He[a] and Henning Eickmeier[b]

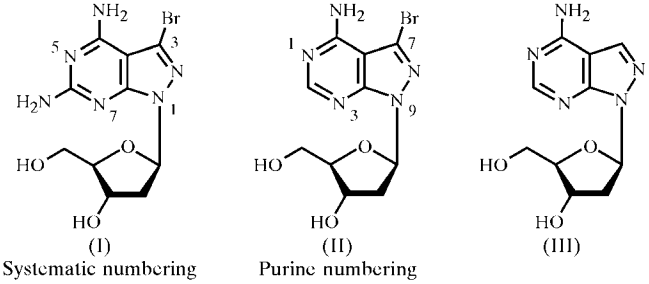
[a]Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastraße 7, 49069 Osnabrück, Germany, and [b]Anorganische Chemie II, Institut für Chemie, Universität Osnabrück, Barbarastraße 7, 49069 Osnabrück, Germany
Correspondence e-mail: frank.seela@uni-osnabrueck.de

Received 14 October 2004
Accepted 3 December 2004
Online 15 January 2005

The title compound, $C_{10}H_{13}BrN_6O_3$, exhibits an *anti* glycosylic bond conformation, with an O—C—N—C torsion angle of −105.0 (6)°. The pseudorotation phase angle and the amplitude [P = 5.8 (5)° and τ_m = 30.0 (3)°, respectively] indicate N-type sugar puckering ($^3T_2$).

Comment

The title compound, (I) (Seela & Becher, 2001), can substitute 2′-deoxyadenosine within dA–dT base pairs, thereby stabilizing DNA duplexes strongly. Moreover, it leads to a harmonization of the 'dA'–dT *versus* the dG–dC base pair stability (He & Seela, 2002*a*,*b*). This special property is suggested to result from two structural modifications of the base: firstly, the additional 6-amine group, which can form an extra hydrogen bond within the base pair, and secondly, the 3-bromo substituent, which increases the polarizability of the base, thereby increasing base stacking interactions. (Systematic numbering is used throughout the manuscript.) In the following, we describe the single-crystal X-ray structure of (I) and compare its structural properties with those of (II) and (III).



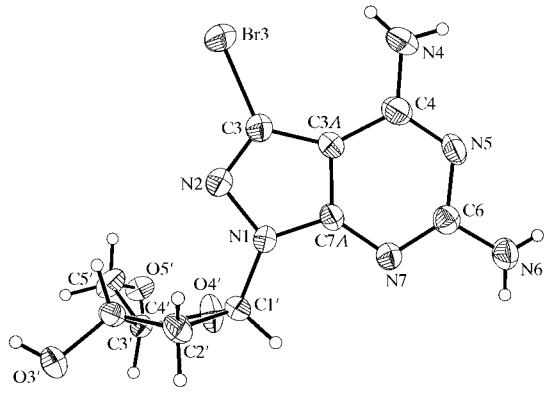


Figure 1
A perspective view of (I). Displacement ellipsoids for non-H atoms are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

Nucleoside (I) (Fig. 1) exhibits a torsion angle χ(O4′—C1′—N1—C7*A*) of −105.0 (6)°. This torsion angle is defined in analogy to the torsion angle χ of purines (O4′—C1′—N9—C4) (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). The torsion angle of compound (I) falls into a range between *anti* and high-*anti*, while compound (II) exhibits a high-*anti* torsion angle (χ = −74.6°; Seela *et al.*, 2000); compound (III) adopts the same *anti* conformation as (I) (χ = −106.3°; Seela, Zulauf *et al.*, 1999), which is the preferred conformation of natural purine 2′-deoxyribonucleosides (Rosemeyer *et al.*, 1997). It has been shown that Coulombic repulsion between the non-bonding electron pairs of atoms O4′ and N8 of 8-azatubercidin (Sprang *et al.*, 1978), formycin (Prusiner *et al.*, 1973) and 7-halogenated 8-aza-7-deazapurine 2′-deoxyribonucleosides (Seela, Becher *et al.*, 1999, and references therein; Seela & Zulauf, 1998) forces the N-glycosylic conformation into the high-*anti* (−*sc*) range (Klyne & Prelog, 1960).

The nucleobase of compound (I) is nearly planar. The r.m.s. deviation of ring atoms N1–C7*A* from their calculated least-squares plane is 0.0178 Å; atom N4 has the maximum deviation [0.04 (1) Å] and lies above the plane, whereas the N atom of the 6-amine group [0.078 (6) Å] lies below this plane. Atoms C1′ and Br3 are also coplanar, with deviations of −0.018 (7) and −0.079 (6) Å, respectively. The bond lengths are in the normal range. The C4′—O4′ bond is 0.025 Å longer than the O4′—C1′ bond (Table 1), because atom O4′ is conjugated with the nucleobase through atom C1′.

The two amine groups of (I) are involved in hydrogen bonding with atom O5′ of the sugar moiety, as shown in Table 2.

From numerous X-ray structures, it is known that the sugar moieties in natural nucleosides adopt predominantly two distinct conformations, *viz*. north (N) and south (S). The structures are dynamically interconverted in solution; however, ribonucleosides prefer the N conformation, while 2′-deoxyribonucleosides are predominantly in the S state. The

 DOI: 10.1107/S0108270104032123

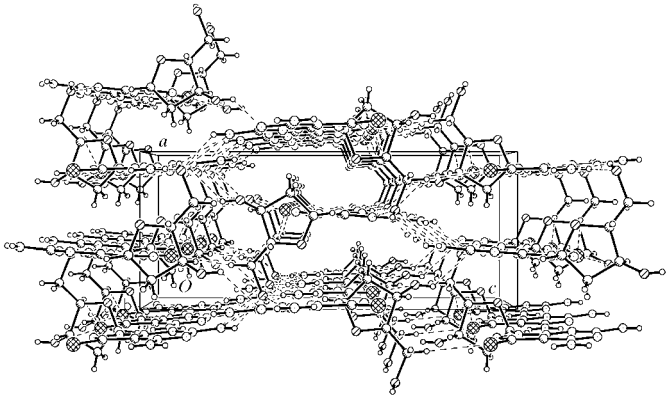


Figure 2
The crystal packing of the multilayered network of (I), showing intermolecular hydrogen bonding.

sugar conformation of nucleosides is also influenced by the base moiety.

The pseudorotation phase angle and the amplitude of (I) [P = 5.8 (5)° with τ_m = 30.0 (3)°] demonstrate N-type sugar puckering (3′-*endo*–2′-*exo*, $^3T_2$). The sugar ring is twisted, as shown by the C3′—C4′—O4′—C1′ [ν_4 = 12.6 (4)°] and C2′—C1′—O4′—C4′ [ν_0 = 6.4 (5)°] torsion angles. Nucleoside (II) has P = 310.9 (4)° and τ_m = 35.0 (3)°, with a C1′-*endo* (^1E) sugar ring conformation. Such an N conformation is uncommon for 2′-deoxyribonucleosides. In contrast to the above two nucleosides, compound (III) exhibits a C2′-*endo*–C3′-*exo* conformation ($^2T_3$, S-type sugar), which is the common sugar conformation of 2′-deoxyribonucleosides.

The population in aqueous solution of the two major conformers of nucleoside (I) is 37% N and 63% S, very close to that of (II) (39% N and 61% S; Seela & Zulauf, 1998). This ratio was determined from the vicinal ^3J(H,H) coupling constants of the ^{1}H NMR spectra measured in D_2O, using the *PSEUROT* program (van Wijk & Altona, 1993).

Compound (I) forms a three-dimensional network, which is stabilized by hydrogen bonds and by stacking interactions of the heterocyclic base moieties (Fig. 2 and Table 2). The H atoms of the N4 and N6 amino groups interact *via* hydrogen bonds with the O atom of the 5′-hydroxy group of the same neighbouring nucleoside molecule. Intermolecular O3′—H3′···N5 and O5′—H5′···N7 hydrogen bonds also exist. The halogen substituents form a weak intramolecular hydrogen bond with the other H atom of the N4 amino group (3.481 Å) and an intermolecular interaction with atom C4′ of the sugar moiety (3.724 Å). The sugar rings are approximately perpendicular to the nucleobase plane.

Experimental

Compound (I) was prepared according to the method described by Seela & Becher (2001). UV (MeOH): λ_{max} 228 (30900), 260 (8100), 262 (8200), 278 (7800) with a pK_a value of 3.3 at 242 nm. Suitable crystals were grown 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

$C_{10}H_{13}BrN_6O_3$
M_r = 345.17
Orthorhombic, $P2_12_12_1$
a = 7.5939 (10) Å
b = 9.2822 (18) Å
c = 18.164 (2) Å
V = 1280.3 (3) Å^3
Z = 4
D_x = 1.791 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 42 reflections
θ = 5.0–12.5°
μ = 3.23 mm^{-1}
T = 293 (2) K
Transparent plate, light brown
0.32 × 0.28 × 0.14 mm

Data collection

Bruker $P4$ diffractometer
$2\theta/\omega$ scans
Absorption correction: empirical (*SHELXTL*; Sheldrick,1997)
T_{min} = 0.316, T_{max} = 0.519
4231 measured reflections
3682 independent reflections
2568 reflections with $I > 2\sigma(I)$
R_{int} = 0.042
θ_{max} = 30.0°
$h = -10 \rightarrow 10$
$k = -13 \rightarrow 13$
$l = -25 \rightarrow 25$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.139
S = 1.07
3682 reflections
199 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0688P)^2 + 0.0128P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.89 e Å^{-3}
Absolute structure: Flack (1983), 1536 Friedel pairs
Flack parameter = 0.020 (16)

Table 1
Selected geometric parameters (Å, °).

N1—C1′	1.447 (5)	N6—C6	1.355 (6)
C3—Br3	1.868 (4)	C1′—O4′	1.408 (5)
N4—C4	1.340 (6)	C4′—O4′	1.433 (5)
C7*A*—N1—C1′	129.4 (4)	N6—C6—N5	115.0 (4)
N2—N1—C1′	119.5 (3)	O4′—C1′—N1	109.9 (4)
N2—C3—Br3	120.3 (3)	N1—C1′—C2′	113.1 (4)
C3*A*—C3—Br3	126.8 (3)	O4′—C4′—C5′	110.8 (4)
N5—C4—N4	119.6 (4)	C1′—O4′—C4′	111.8 (3)
C7*A*—N1—N2—C3	−0.7 (6)	C1′—C2′—C3′—C4′	29.2 (4)
C1′—N1—N2—C3	−177.2 (5)	C2′—C3′—C4′—O4′	−25.9 (4)
Br3—C3—C3*A*—C4	3.4 (11)	C2′—C3′—C4′—C5′	−147.2 (4)
C4—N5—C6—N6	178.0 (5)	N1—C1′—O4′—C4′	−116.6 (4)
C4—C3*A*—C7*A*—N7	−3.9 (9)	C2′—C1′—O4′—C4′	6.4 (5)
C7*A*—N1—C1′—O4′	−105.0 (6)	C5′—C4′—O4′—C1′	135.0 (4)
N2—N1—C1′—O4′	70.7 (6)	C3′—C4′—O4′—C1′	12.6 (4)
N1—C1′—C2′—C3′	98.1 (4)	C3′—C4′—C5′—O5′	172.0 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H4*A*···O5′^{i}	0.82 (5)	2.28 (4)	2.989 (5)	146 (6)
N6—H6*B*···O5′^{ii}	0.82 (5)	2.12 (5)	2.933 (5)	167 (6)
O3′—H3′···N5^{iii}	0.82 (3)	2.27 (2)	3.053 (5)	159 (6)
O5′—H5′···N7^{iv}	0.82 (2)	1.98 (3)	2.803 (5)	177.0 (17)

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

All H atoms were initially found in a difference Fourier synthesis. In order to maximize the data/parameter ratio, H atoms bonded to C atoms were placed in geometrically idealized positions (C—H = 0.97

and 0.98 Å) and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C)]. The hydroxy and N-bound H atoms were initially placed in their difference-map positions, and then geometrically idealized and constrained to ride on their parent atoms, although the chemically equivalent bond lengths were allowed to refine while being constrained to be equal.

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* and *PLATON* (Spek, 1999).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1785). Services for accessing these data are described at the back of the journal.

References

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
He, J. & Seela, F. (2002*a*). *Tetrahedron*, **58**, 4535–4542.
He, J. & Seela, F. (2002*b*). *Helv. Chim. Acta*, **85**, 1340–1354.
IUPAC–IUB Joint Commission on Biochemical Nomenclature (1983). *Eur. J. Biochem.* **131**, 9–15.
Klyne, W. & Prelog, V. (1960). *Experientia*, **16**, 521–523.
Prusiner, P., Brennan, T. & Sundaralingam, M. (1973). *Biochemistry*, **12**, 1196–1201.
Rosemeyer, H., Ramzaeva, N., Zulauf, M., Thomas, H., Chen, Y., Mittelbach, C. & Seela, F. (1997). *Nucleosides Nucleotides*, **16**, 1447–1451.
Seela, F. & Becher, G. (2001). *Nucleic Acids Res.* **29**, 2069–2078.
Seela, F., Becher, G., Rosemeyer, H., Reuter, H., Kastner, G. & Mikhailopulo, I. A. (1999). *Helv. Chim. Acta*, **82**, 105–124.
Seela, F. & Zulauf, M. (1998). *J. Chem. Soc. Perkin Trans.* 1, pp. 3233–3239.
Seela, F., Zulauf, M., Reuter, H. & Kastner, G. (2000). *Acta Cryst.* C**56**, 489–491.
Seela, F., Zulauf, M., Reuter, H. & Kastner, G. (1999). *Acta Cryst.* C**55**, 1947–1950.
Sheldrick, G. M. (1997). *SHELXTL.* Release 5.1. Bruker AXS Inc., Madison, Wisconsin, USA.
Siemens (1996). *XSCANS.* Release 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Spek, A. L. (1999). *PLATON for Windows*. Utrecht University, The Netherlands. (32-Bit Windows implementation by L. J. Farrugia, University of Glasgow, Scotland.)
Sprang, S., Rohrer, D., Scheller, R. & Sundaralingam, M. (1978). *J. Am. Chem. Soc.* **100**, 2867–2872.
Wijk, J. van & Altona, C. (1993). *PSEUROT*. Version 6.2 of July 1993. University of Leiden, The Netherlands.