Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

7-Iodo-8-aza-7-deaza-2′-deoxyadenosine and 7-bromo-8-aza-7-deaza-2′-deoxyadenosine

Frank Seela,[a]* Matthias Zulauf,[a] Hans Reuter[b] and Guido Kastner[b]

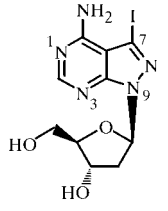
[a]Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, D-49069 Osnabrück, Germany, and [b]Anorganische Chemie II, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, D-49069 Osnabrück, Germany
Correspondence e-mail: fraseela@rz.uni-osnabrueck.de

Received 18 October 1999
Accepted 17 January 2000

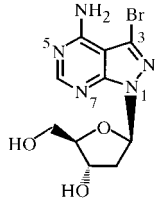
The isomorphous structures of the title molecules, 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3-iodo-1*H*-pyrazolo-[3,4-*d*]pyrimidine, (I), $C_{10}H_{12}IN_5O_3$, and 4-amino-3-bromo-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, (II), $C_{10}H_{12}BrN_5O_3$, have been determined. The sugar puckering of both compounds is C1′-*endo* (^1E). The *N*-glycosidic bond torsion angle χ^1 is in the high-*anti* range [−73.2 (4)° for (I) and −74.1 (4)° for (II)] and the crystal structure is stabilized by hydrogen bonds.

Comment

Oligonucleotides containing 7-iodo-8-aza-7-deaza-2′-deoxyadenosine, (I), or 7-bromo-8-aza-7-deaza-2′-deoxyadenosine, (II) (Seela & Zulauf, 1998), show enhanced stability of duplexes with antiparallel (aps) chain orientation (Seela *et al.*, 1997; Seela & Zulauf, 1999). Purine skeleton numbering is used throughout the following discussion. The X-ray structures of the related 7-bromo- and 7-iodo-8-aza-7-deazaguanine 2′-deoxynucleosides show that the steric and stereoelectronic effects of the nucleobase are responsible for the high-*anti* conformation of the base and also for the sugar-ring conformation (Seela, Becher *et al.*, 1999). In the light of this, it was of interest to evaluate the crystal structures of the



(I)
Purine numbering



(II)
Systematic numbering

7-halogeno-8-aza-7-deaza-2′-deoxyadenosines, (I) and (II), and compare them with that of the unsubstituted 8-aza-7-deaza-2′-deoxyadenosine (Seela, Zulauf *et al.*, 1999). Both compounds can now be prepared in a one-pot reaction with increased yield compared with the two-step procedure (Seela & Zulauf, 1998). Compounds (I) and (II) crystallize isomorphously.

The ribonucleoside 8-aza-7-deazaadenosine (8-azatubercidin) exhibits a C1′-*exo*–C2′-*endo* conformation (Sprang *et al.*, 1978), and for the unsubstituted 8-aza-7-deaza-2′-deoxy-4-adenosine a $^{2'}T_{3'}$ (*S*-type sugar) sugar-ring conformation was determined (Seela, Zulauf *et al.*, 1999). In contrast to this, an unusual C1′-*endo* ($^{1'}E$) sugar-ring conformation is observed for (I) and (II). This can be seen from the torsion angle ν_3 (C2′—C3′—C4′—O4′) of −2.8 (4)° for (I) and −3.8 (4)° for (II), implying an almost planar arrangement of these four atoms, with a deviation of C1′ from the least-squares planes of 0.488 (5) Å for (I) and 0.496 (5) Å for (II). The puckering amplitude τ_m and the pseudorotation phase angle *P* (Rao *et al.*, 1981) for (I) are τ_m = 34.8 (3)° and *P* = 309.4 (4)°, while for (II) τ_m = 35.0 (3)° and *P* = 310.9 (4)°.

The orientation of the base relative to the sugar (*syn*/*anti*) is defined by the torsion angle χ^1 (O4′—C1′—N9—C4) (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983); the preferred conformation around the *N*-glycosidic bond of a natural 2′-deoxynucleoside is usually in the *anti* range. It was shown that Coulomb repulsion between the non-bonding electron pairs of O4′ and N8 of 8-aza-tubercidin (Sprang *et al.*, 1978), formycin (Prusiner *et al.*, 1973) and 7-halogeno-8-aza-7-deaza-2′-deoxypurines (Seela, Becher *et al.*, 1999) forces the *N*-glycosidic conformation into the high-*anti* (−*sc*) range (Klyne & Prelog, 1960). Compounds (I) and (II) also adopt a high-*anti* conformation [χ^1 = −73.2 (4)° for (I) and −74.1 (4)° for (II)].

The halogeno substituents possess a stereoelectronic effect (Seela, Becher *et al.*, 1999; Rosemeyer *et al.*, 1997); as a result, the torsion angle χ^1 is significantly lower compared with that for 8-aza-7-deaza-2′-deoxyadenosine [χ^1 = −106.3 (2)°; Seela, Zulauf *et al.*, 1999] and the high-*anti* conformation is strengthened. Compared with (I) and (II), the 7-iodo-7-deaza-

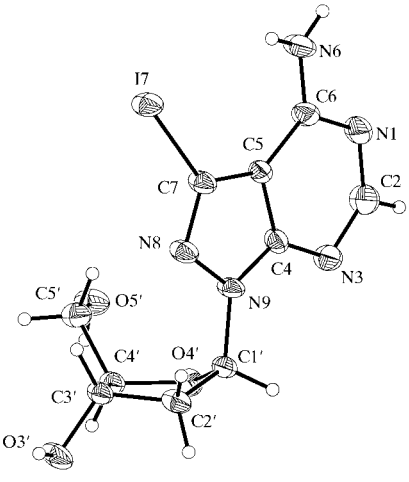


Figure 1
A perspective view of (I) showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of small arbitrary size.

2′-deoxyadenosine adopts a C3′-*exo* ($_{3'}E$) sugar conformation with an almost perfect *anti* orientation of the base [χ^1 = −147.1 (8)°; Seela *et al.*, 1996]. The high-*anti* conformation of (I) and (II) may be stabilized through van der Waals interactions resulting from the contact between N8 and C2′ or one of its H atoms [N—C = 2.761 (5) Å and N—H = 2.45 Å for (I); N—C = 2.777 (5) Å and N—H = 2.47 Å for (II)]. Similar interactions were also observed for 8-azaadenosine (Singh & Hodgson, 1974) and 8-azatubercidin (Sprang *et al.*, 1978).

Another intramolecular attraction was determined between the 7-halogeno substituent and one of the amino H atoms of (I) and (II). This hydrogen bond leads to a hindered rotation of the amino group. Therefore, two signals for the amino protons can be observed in the ^{1}H NMR spectra at ambient temperature. The proton signals become indistinguishable at a coalescence temperature of 340 K.

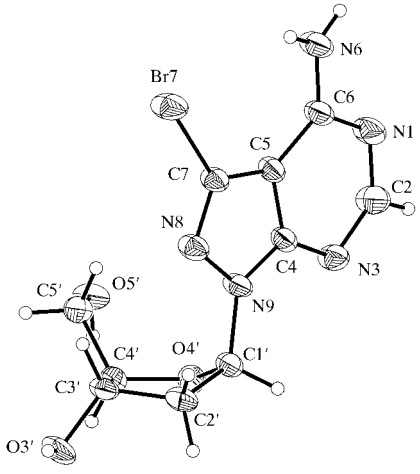


Figure 2
A perspective view of (II) showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of small arbitrary size.

The exocyclic angle N8—N9—C1′ is smaller than C4—N9—C1′, by 6.3 (4) for (I) and by 5.6 (4)° for (II), as observed for other nucleosides adopting the high-*anti* conformation (Sprang *et al.*, 1978; Prusiner *et al.*, 1973). The conformation about the C4′—C5′ bond of (I) and (II) is in the *trans* (+*ap*) range [γ = 175.4 (3)° for (I), 175.2 (3)° for (II)]. The halogeno substituents of (I) and (II) lead to a lengthening of the glycosidic bond, while the other bond lengths and torsion angles of (I) and (II) are similar to those of 8-aza-7-deaza-2′-deoxyadenosine (Seela, Zulauf *et al.*, 1999).

Intermolecular hydrogen bonds formed by (I) and (II) generate a three-dimensional network and provide additional crystal stabilization (Tables 2 and 4).

The 8-aza-7-deazaadenine base of (I) and (II) is planar. The deviations of the ring C and N atoms from the least-squares plane are in the range of −0.031 (5)–0.043 (3) Å for (I) and −0.037 (5)–0.045 (3) Å for (II). The bulky iodo substituent of (I) lies −0.091 (6) Å and the bromo substituent of (II) −0.084 (6) Å out of the heterocyclic plane. For comparison, the iodo atom of 7-iodo-7-deaza-2′-deoxyadenosine is located −0.135 (14) Å out of the plane (Seela *et al.*, 1996).

Experimental

Compound (I) was prepared from 1-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-3-iodo-4-methoxy-1*H*-pyrazolo[3,4-*d*]-pyrimidine (Seela & Zulauf, 1998; 500 mg, 0.8 mmol) by treatment with saturated NH_3/MeOH (150 ml, 3:1 *v*/*v*) for 5 h at 363 K in an autoclave. The solvent was evaporated and the residue purified by flash chromatography on silica gel (column 10 × 3 cm, methanol–dichloromethane 1:9). Crystallization from ^{i}PrOH yielded colourless needles (yield 138 mg, 46%) which showed identical ^{1}H and ^{13}C NMR data to those of a verified sample (Seela & Zulauf, 1998). Compound (II) was prepared from 3-bromo-1-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (Seela & Zulauf, 1998; 500 mg, 0.86 mmol) by treatment with saturated NH_3/MeOH (150 ml, 3:1 *v*/*v*) for 5 h at 363 K in an autoclave. The solvent was evaporated and the residue purified by flash chromatography on silica gel (column 10 × 3 cm, methanol–dichloromethane 1:9). Crystallization from ^{i}PrOH yielded colourless needles (yield 148 mg, 52%) which showed identical ^{1}H and ^{13}C NMR data to those of a verified sample (Seela & Zulauf, 1998).

Compound (I)

Crystal data

$C_{10}H_{12}IN_5O_3$
M_r = 377.15
Monoclinic, $P2_1$
a = 9.259 (3) Å
b = 7.2787 (10) Å
c = 9.767 (3) Å
β = 110.29 (2)°
V = 617.4 (3) Å^3
Z = 2
D_x = 2.029 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 40 reflections
θ = 5.08–17.82°
μ = 2.607 mm^{-1}
T = 293 (2) K
Needle, colourless
0.55 × 0.15 × 0.15 mm

Data collection

Siemens *P*4 diffractometer
2θ/ω scans
Absorption correction: ψ scan (*SHELXTL*; Sheldrick, 1997*a*)
T_{min} = 0.445, T_{max} = 0.704
3057 measured reflections
1455 independent reflections (plus 1239 Friedel-related reflections)
2668 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 27°
$h = -11 \rightarrow 11$
$k = -9 \rightarrow 9$
$l = -12 \rightarrow 12$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.026
$wR(F^2)$ = 0.069
S = 1.036
2694 reflections
174 parameters
Only H-atom *U*'s refined
$w = 1/[\sigma^2(F_o^2) + (0.0411P)^2 + 0.4360P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.63 e Å^{-3}
$\Delta\rho_{min}$ = −0.65 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997*b*)
Extinction coefficient: 0.0102 (11)
Absolute structure: Flack (1983)
Flack parameter = −0.01 (2)

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

N9—C1′	1.480 (4)		
C4—N9—C1′	127.5 (3)	N8—N9—C1′	121.2 (3)
C4—N9—C1′—O4′	−73.2 (4)	C2′—C1′—O4′—C4′	32.8 (3)
C2′—C3′—C4′—O4′	−2.8 (4)	C3′—C4′—O4′—C1′	−18.8 (3)
C3′—C4′—C5′—O5′	175.4 (3)	C3′—C4′—C5′—O5′	175.4 (3)
N8—N9—C1′—O4′	101.6 (4)	O3′—C3′—C4′—C5′	114.1 (3)
C1′—C2′—C3′—C4′	21.3 (4)	O4′—C4′—C5′—O5′	54.4 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
N6—H61···O5′^{i}	0.86	2.17	2.907 (4)	143.2
N6—H62···I7	0.86	2.91	3.610 (3)	139.7
O3′—H3′1···N1^{ii}	0.82	2.18	2.837 (4)	136.7
O5′—H5′···N3^{iii}	0.82	2.18	2.940 (4)	154.5

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

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

D—H···A	D—H	H···A	D···A	D—H···A
N6—H61···O5′^{i}	0.86	2.12	2.870 (4)	145.9
N6—H62···Br7	0.85	2.84	3.510 (3)	136.4
O3′—H3′1···N1^{ii}	0.82	2.21	2.828 (4)	131.9
O5′—H5′···N3^{iii}	0.82	2.08	2.890 (4)	171.9

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

Compound (II)

Crystal data

$C_{10}H_{12}BrN_5O_3$
$M_r = 330.16$
Monoclinic, $P2_1$
$a = 9.0930$ (9) Å
$b = 7.2595$ (10) Å
$c = 9.6369$ (19) Å
$\beta = 109.362$ (11)°
$V = 600.16$ (16) Å^3
$Z = 2$
$D_x = 1.827$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 35 reflections
$\theta = 4.74$–$16.32°$
$\mu = 3.438$ mm^{-1}
$T = 293$ (2) K
Needle, colourless
0.50 × 0.12 × 0.12 mm

Data collection

Siemens $P4$ diffractometer
$2\theta/\omega$ scans
Absorption correction: ψ scan (*SHELXTL*; Sheldrick, 1997*a*)
$T_{min} = 0.497$, $T_{max} = 0.662$
2959 measured reflections
1411 independent reflections (plus 1193 Friedel-related reflections)
2381 reflections with $I > 2\sigma(I)$
$R_{int} = 0.035$
$\theta_{max} = 27°$
$h = -11 \rightarrow 11$
$k = -9 \rightarrow 9$
$l = -12 \rightarrow 12$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.093$
$S = 1.052$
2604 reflections
174 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F_o^2) + (0.0529P)^2 + 0.2516P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.51$ e Å^{-3}
$\Delta\rho_{min} = -0.54$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997*b*)
Extinction coefficient: 0.0071 (17)
Absolute structure: Flack (1983)
Flack parameter = −0.014 (11)

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

N9—C1′	1.473 (4)		
C4—N9—C1′	127.1 (3)	N8—N9—C1′	121.5 (3)
C4—N9—C1′—O4′	−74.1 (4)	C2′—C1′—O4′—C4′	32.5 (3)
C2′—C3′—C4′—O4′	−3.8 (4)	C3′—C4′—O4′—C1′	−18.3 (3)
C3′—C4′—C5′—O5′	175.2 (3)	C3′—C4′—C5′—O5′	175.2 (3)
N8—N9—C1′—O4′	101.9 (4)	O3′—C3′—C4′—C5′	113.1 (3)
C1′—C2′—C3′—C4′	22.5 (4)	O4′—C4′—C5′—O5′	54.9 (4)

All H atoms were found in difference Fourier syntheses but were constructed in geometrically reasonable positions, with the exception of the amino H atoms. These were first refined with a common N—H distance and then fixed on the amino N atoms using a riding model. For all H atoms a common isotropic displacement parameter was refined. The absolute configurations were confidently proven by the diffraction experiment.

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 1997*a*); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*b*); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*b*); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1089). Services for accessing these data are described at the back of the journal.

References

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
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**, 1196–1202.
Rao, S. T., Westhof, E. & Sundaralingam, M. (1981). *Acta Cryst.* A**37**, 421–425.
Rosemeyer, H., Zulauf, M., Ramzaeva, N., Becher, G., Feiling, E., Mühlegger, K., Münster, I., Lohmann A. & Seela, F. (1997). *Nucleosides Nucleotides*, **16**, 821–828.
Seela, F., Becher, G., Rosemeyer, H., Reuter, H., Kastner, G. & Mikhailopulo, I. A. (1999). *Helv. Chim. Acta*, **82**, 105–124.
Seela, F., Ramzaeva, N. & Zulauf, M. (1997). *Nucleosides Nucleotides*, **16**, 963–966.
Seela, F. & Zulauf, M. (1998). *J. Chem. Soc. Perkin Trans.* 1, pp. 3233–3239.
Seela, F. & Zulauf, M. (1999). *J. Chem. Soc. Perkin Trans.* 1, pp. 479–488.
Seela, F., Zulauf, M., Kastner, G. & Reuter, H. (1999). *Acta Cryst.* C**55**, 1947–1950.
Seela, F., Zulauf, M., Rosemeyer, H. & Reuter, H. (1996). *J. Chem. Soc. Perkin Trans.* 2, pp. 2373–2376.
Sheldrick, G. M. (1997*a*). *SHELXTL*. Release 5.1. Bruker AXS Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1997*b*). *SHELXL*97 and *SHELXS*97. University of Göttingen, Germany.
Siemens (1996). *XSCANS*. Version 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Singh, P. & Hodgson, D. J. (1974). *J. Am. Chem. Soc.* **96**, 5276–5278.
Sprang, S., Scheller, R., Rohrer, D. & Sundaralingam, M. (1978). *J. Am. Chem. Soc.* **100**, 2867–2872.