Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

7-Deaza-2′-deoxy-7-propynylguanosine

Frank Seela,[a]* Khalil Shaikh[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

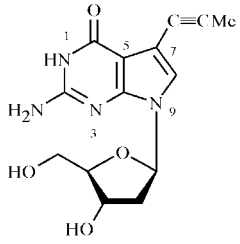
Received 25 March 2004
Accepted 12 May 2004
Online 22 June 2004

The title compound, $C_{14}H_{16}N_4O_4$, adopts the *anti* conformation at the glycosylic bond [χ −117.1 (5)°]. The sugar pucker of the 2′-deoxyribofuranosyl moiety is C2′-*endo*–C3′-*exo*, $^2T_3$ (*S*-type). The orientation of the exocyclic C4′—C5′ bond is +*sc* (*gauche*). The propynyl group is linear and coplanar with the nucleobase moiety. The structure of the compound is stabilized by several hydrogen bonds (N—H···O and O—H···O), leading to the formation of a multi-layered network. The nucleobases, as well as the propynyl groups, are stacked. This stacking might cause the extraordinary stability of DNA duplexes containing this compound.

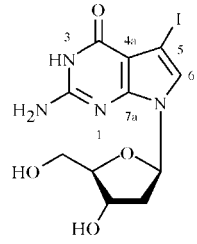
Comment

The incorporation of 7-deaza-2′-deoxyguanosine (Winkeler & Seela, 1983) and its 7-substituted derivatives (purine skeleton numbering is used throughout this discussion) into oligonucleotides results in the enhancement of DNA duplex stability (Seela & Driller, 1986; Ramzaeva & Seela, 1996). Oligonucleotide triplexes are also stabilized when 7-deaza-2′-deoxyguanosine is part of the triplet motif 7-deazaguanine–guanine-cytosine (Milligan *et al.*, 1993). Moreover, 7-deazapurine 2′,3′-dideoxynucleoside triphosphates carrying 7-alkynylamino groups linked to fluorescent reporter moieties are used for DNA sequencing (Prober *et al.*, 1987; Cocuzza, 1988; Hobbs, 1989).

The title compound, (I), is of importance because it enhances the stability of DNA–RNA duplexes (Buhr *et al.*, 1996), as well as of duplex DNA (Seela & Shaikh, 2004). The stability increase might be caused by the increase in hydrophobicity of the major groove and/or by the increase in polarizibility of the nucleobase. Hence, the potency of antisense oligonucleotides is improved (Lamm *et al.*, 1991; Uhlmann *et al.*, 2000). These favourable properties also find application in oligonucleotide diagnostics (Bailly & Waring, 1998). Our laboratory has shown that a propynyl group introduced into the 7-position of a 'purine' base exerts a stronger stabilizing effect on DNA duplexes (He & Seela, 2002) than one in the 5-position of a pyrimidine base (Froehler *et al.*, 1992; Wagner *et al.*, 1993). As, in both cases, the propynyl residues protrude into the limited space of the major groove of B-DNA, it was of interest to study the crystal structure of (I) and we present the results here.



(I)
Purine numbering



(II)
Systematic numbering

Compound (I) was synthesized from the 7-iodo nucleoside (II) (Ramzaeva & Seela, 1995) and propyne gas using the Pd-catalyst-assisted Sonogashira cross-coupling reaction (Hobbs, 1989; Robins *et al.*, 1990), and was crystallized from MeOH. The three-dimensional structure of (I), or 2-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one (systematic numbering; IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983), is shown in Fig. 1 and selected bond distances and angles are presented in Table 1. In the crystalline state, the orientation of the nucleobase relative to the sugar moiety is *anti* [χ −117.1 (5)°], which is similar to what was found for the 8-methyl derivative of 7-deaza-2′-deoxyguanosine (Seela *et al.*, 1997). The torsion angle χ (O4′—C1′—N9—C4) is defined by analogy with the purine system (Saenger, 1984).

The sugar ring of (I) is twisted, as shown by the torsion angles along C3′—C4′—O4′—C1′ [6.7 (5)°] and C4′—O4′—C1′—C2′ [−30.1 (5)°]. The pseudorotation angle *P* is 152.5°,

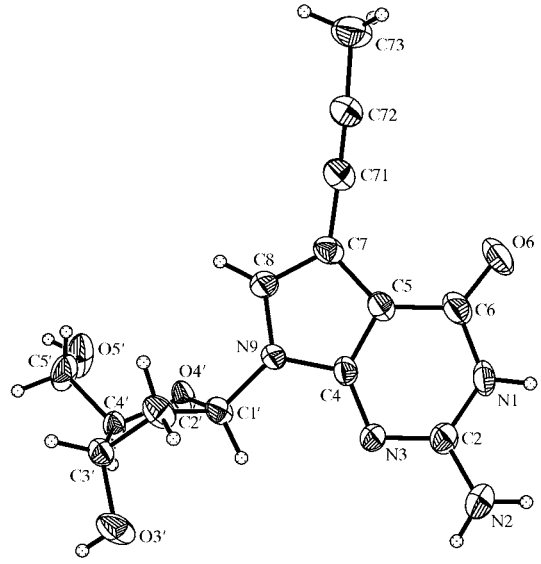


Figure 1
A perspective view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrarily radii.

 DOI: 10.1107/S0108270104011552

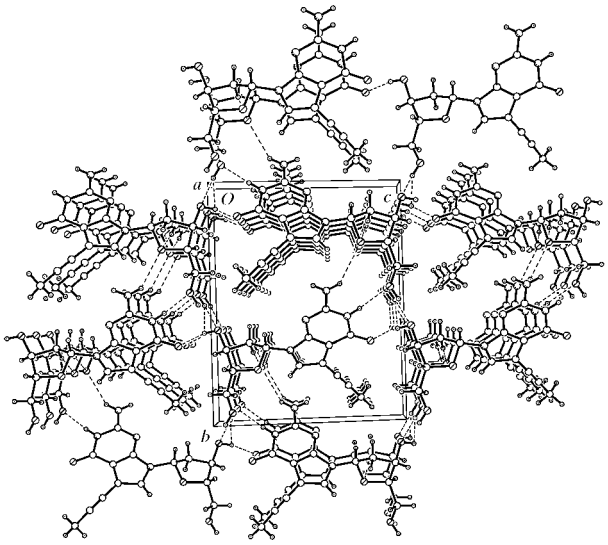


Figure 2
Details of the multi-layered network of (I), showing the hydrogen bonds within the monolayers and the stacking of the nucleobases and propynyl residues.

with an amplitude τ_m of 41.9°, indicating an *S*-type sugar pucker (2′-*endo*–3′-*exo*, $^2T_3$) (Rao *et al.*, 1981), which is also the favoured conformation in solution (71%). The conformational analysis was carried out on the basis of vicinal [^{1}H, ^{1}H] coupling constants using the *PSEUROT*6.3 program (Van Wijk *et al.*, 1999). The solid-state conformation about the C4′—C5′ bond is +*sc* (*gauche*) (Saenger, 1984).

The base moiety of (I) is nearly planar, the r.m.s. deviation of the ring atoms from their calculated least-squares planes being 0.025 Å [N1 −0.012 (4), C2 −0.036 (4), N3 0.010 (4), C4 0.026 (4), C5 −0.017 (5), C6 0.046 (4), C7 −0.024 (4), C8 −0.014 (4) and N9 0.019 (4) Å]. The O6 substituent of (I) lies 0.141 (8) Å above and the N atom of the 2-amino group −0.076 (8) Å below this plane. The linear propynyl group is in a coplanar orientation with respect to the nucleobase moiety.

The triple-bond length is 1.184 (7) Å, which corresponds to the usual length (Cygler *et al.*, 1984). Apparently, the C≡C bond is not in conjugation with the pyrrolo[2,3-*d*]pyrimidine heterocycle.

The structure of (I) is stabilized by several hydrogen bonds (N1—H1*A*···O5′, N2—H2*B*···O4′, O3′—H3′*A*···O6 and O5′—H5′*A*···O3′), leading to the formation of a multi-layered network. There are no hydrogen bonds between the layers. The bases are stacked, as are the propynyl residues (Fig. 2 and Table 2). This stacking of the nucleobases might cause the extraordinary stability of DNA duplexes containing (I).

Experimental

To a solution of (II) (500 mg, 1.28 mmol; Ramzaeva & Seela, 1995) in anhydrous dimethylformamide (4 ml), tetrakis(triphenylphosphine)-palladium(0) [$(PPh_3)_4Pd$; 116 mg, 0.1 mmol], CuI (68 mg, 0.36 mmol) and triethylamine (240 µl, 1.71 mmol) were added with stirring. The sealed suspension was saturated with propyne at 273 K and stirred at room temperature for 24 h. The solvent was evaporated *in vacuo*. The reaction mixture was dissolved in MeOH (2 ml), adsorbed on silica gel (2 g) and subjected to flash chromatography [silica gel 60, column 15 × 3 cm, eluant CH_2Cl_2–MeOH (95:5)]. Compound (I) was isolated from the main zone as a colourless solid (350 mg, yield 90%) and crystallized upon cooling from hot MeOH, yielding colourless crystals (m.p. < 483 K). UV (MeOH, nm): 236 (27 800), 271 (13 200). For the X-ray diffraction experiment, a single crystal of (I) was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{14}H_{16}N_4O_4$
M_r = 304.31
Monoclinic, $P2_1$
a = 4.799 (2) Å
b = 13.601 (3) Å
c = 11.014 (3) Å
β = 100.49 (3)°
V = 706.9 (4) Å^3
Z = 2
D_x = 1.430 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 36 reflections
θ = 3.0–15.1°
μ = 0.11 mm^{-1}
T = 293 (2) K
Plate, colourless
0.6 × 0.2 × 0.1 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2562 measured reflections
1772 independent reflections
1190 reflections with $I > 2\sigma(I)$
R_{int} = 0.040
θ_{max} = 28.0°
$h = -1 \rightarrow 6$
$k = -17 \rightarrow 1$
$l = -14 \rightarrow 14$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.063
$wR(F^2)$ = 0.172
S = 1.02
1772 reflections
206 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0971P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C7—C71	1.433 (7)	C72—C73	1.461 (8)
N9—C1′	1.447 (5)	C1′—O4′	1.452 (6)
C71—C72	1.184 (8)	C4′—O4′	1.454 (5)
N3—C4—N9	123.3 (4)	C71—C72—C73	177.0 (6)
N9—C4—C5	107.5 (4)	N9—C1′—O4′	108.3 (4)
C8—C7—C71	125.7 (5)	N9—C1′—C2′	115.6 (4)
C71—C7—C5	128.6 (4)	O4′—C4′—C5′	109.6 (4)
C8—N9—C4	108.6 (4)	O4′—C4′—C3′	106.9 (4)
C8—N9—C1′	127.5 (4)	C5′—C4′—C3′	113.6 (4)
C4—N9—C1′	123.9 (4)	C1′—O4′—C4′	107.5 (3)
C72—C71—C7	178.0 (6)	O5′—C5′—C4′	110.1 (5)
C2—N3—C4—N9	−177.6 (5)	C4—N9—C1′—C2′	126.4 (5)
C4—C5—C7—C71	177.2 (5)	N9—C1′—C2′—C3′	159.9 (4)
C6—C5—C7—C71	−7.3 (10)	C1′—C2′—C3′—C4′	−36.0 (5)
C7—C8—N9—C1′	−178.3 (5)	C2′—C3′—C4′—O4′	18.9 (5)
N3—C4—N9—C1′	−3.9 (7)	C2′—C3′—C4′—C5′	−102.1 (5)
C5—C4—N9—C1′	178.9 (4)	N9—C1′—O4′—C4′	−153.7 (4)
C8—N9—C1′—O4′	61.2 (7)	C2′—C1′—O4′—C4′	−30.1 (5)
C4—N9—C1′—O4′	−117.1 (5)	C5′—C4′—O4′—C1′	130.3 (5)
C8—N9—C1′—C2′	−55.3 (7)	C3′—C4′—O4′—C1′	6.7 (5)

In the absence of significant anomalous scattering, Friedel opposites could not be used to determine the absolute structure. Refinement of the Flack (1983) parameter led to an inconclusive value (Flack & Bernardinelli, 2000) for this parameter [−1 (3)]. Therefore,

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···O5′^{i}	0.86	2.10	2.946 (6)	170
N2—H2B···O4′^{i}	0.86	2.40	3.109 (6)	140
O3′—H3′A···O6^{ii}	0.82 (4)	1.80 (2)	2.600 (6)	164 (7)
O5′—H5′A···O3′^{iii}	0.82 (4)	1.95 (2)	2.727 (6)	159 (7)

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

Friedel equivalents were merged before the final refinement. In order to maximize the data/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 hydroxy H atoms were initially placed in their difference-map positions, and were then geometrically idealized and constrained to ride on their parent O atoms, although chemically equivalent O—H 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, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1139). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Bailly, C. & Waring, M. J. (1998). *Nucleic Acids Res.* **26**, 4309–4314.
Buhr, C. A., Wagner, R. W., Grant, D. & Froehler, B. C. (1996). *Nucleic Acids Res.* **24**, 2974–2980.
Cocuzza, A. J. (1988). *Tetrahedron Lett.* **29**, 4061–4064.
Cygler, M., Anderson, W. F., Giziewicz, J. & Robins, M. J. (1984). *Can. J. Chem.* **62**, 147–152.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
Froehler, B. C., Wadwani, S., Terhorst, T. J. & Gerrard, S. R. (1992). *Tetrahedron Lett.* **33**, 5307–5310.
He, J. & Seela, F. (2002). *Nucleic Acids Res.* **30**, 5485–5496.
Hobbs, F. W. Jr (1989). *J. Org. Chem.* **54**, 3420–3422.
IUPAC–IUB Joint Commission on Biochemical Nomenclature (1983). *Eur. J. Biochem.* **131**, 9–15.
Lamm, G. M., Blencowe, B. J., Sproat, B. S., Iribarren, A. M., Ryder, U. & Lamond, A. I. (1991). *Nucleic Acids Res.* **19**, 3193–3198.
Milligan, J. F., Krawczyk, S. H., Wadwani, S. & Matteucci, M. D. (1993). *Nucleic Acids Res.* **21**, 327–333.
Prober, J. M., Trainor, G. L., Dam, R. J., Hobbs, F. W., Robertson, C. W., Zagursky, R. J., Cocuzza, A. J., Jensen, M. A. & Baumeister, K. (1987). *Science*, **238**, 336–341.
Ramzaeva, N. & Seela, F. (1995). *Helv. Chim. Acta*, **78**, 1083–1090.
Ramzaeva, N. & Seela, F. (1996). *Helv. Chim. Acta*, **79**, 1549–1558.
Rao, S. T., Westhof, E. & Sundaralingam, M. (1981). *Acta Cryst.* A**37**, 421–425.
Robins, M. J., Vinayak, R. S. & Wood, S. G. (1990). *Tetrahedron Lett.* **31**, 3731–3734.
Saenger, W. (1984). *Principles of Nucleic Acid Structure*, edited by C. R. Cantor. New York: Springer–Verlag.
Seela, F. & Driller, H. (1986). *Nucleic Acids Res.* **14**, 2319–2332.
Seela, F., Rosemeyer, H., Zulauf, M., Chen, Y., Kastner, G. & Reuter, H. (1997). *Liebigs Ann. Chem.* pp. 2525–2530.
Seela, F. & Shaikh, K. (2004). Unpublished results.
Sheldrick, G. M. (1997). *SHELXTL.* Release 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Siemens (1996). *XSCANS*. Release 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Uhlmann, E., Peyman, A., Ryte, A., Schmidt, A. & Buddecke, E. (2000). *Methods Enzymol.* **313**, 268–284.
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.
Wagner, R. W., Matteucci, M. D., Lewis, J. G., Gutierrez, A. J., Moulds, C. & Froehler, B. C. (1993). *Science*, **260**, 1510–1513.
Winkeler, H.-D. & Seela, F. (1983). *J. Org. Chem.* **48**, 3119–3122.