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2′,3′-Didehydro-3′-deoxythymidine *N*-methyl-2-pyrrolidone solvate (D4T·NMPO)

Davide Viterbo,[a]* Marco Milanesio,[b] Ramón Pomés Hernández,[c] Chryslaine Rodríguez Tanty,[d] Ivan Colás González,[d] Marquiza Sablón Carrazana[d] and Julio Duque Rodríguez[c]

[a]Dipartimento di Scienze e Tecnologie Avanzate, Università del Piemonte Orientale 'A. Avogadro', Corso T. Borsalino 54, I-15100 Alessandria, Italy, [b]Dipartimento di Chimica IFM, Università di Torino, Via P. Giuria 7, I-10125 Torino, Italy, [c]X-ray Laboratory, National Center for Scientific Research, PO Box 6880, Havana, Cuba, and [d]Laboratory of Organic Synthesis, National Center for Scientific Research, PO Box 6880, Havana, Cuba
Correspondence e-mail: viterbo@ch.unito.it

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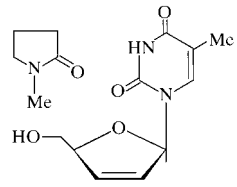
The title compound, 1-(2′,3′-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine 1-methyl-2-pyrrolidone solvate, $C_{10}H_{12}N_2O_4{\cdot}C_5H_9NO$, is an NMPO solvate of the anti-AIDS agent D4T. In its crystal structure, both the pyrimidine and the furanose rings are planar and approximately perpendicular [82.1 (4)°]. The value of the torsion angle defining the orientation of the thymine with respect to the joined furane, $\chi = -100.8\,(4)^\circ$, and that of the torsion angle giving the orientation of the hydroxyl group linked to the furane ring, $\gamma = 52.9\,(5)^\circ$, show that the glycosylic link adopts the so-called high-*anti* conformation and the 5′-hydroxyl group is in the *+sc* position. The NMPO solvate is linked to the nucleoside through a fairly strong hydrogen bond.

Comment

Many chemotherapeutic compounds (Huryn & Okabe, 1992) have been evaluated since AIDS (acquired immuno deficiency syndrome) appeared in the world and became one of the most important epidemic diseases in modern times (De Clercq & Balzarini, 1995). Nucleoside analogues, particularly those belonging to the 2′,3′-*O*-dideoxynucleoside and 2′,3′-*O*-didehydro-2′,3′-*O*-dideoxynucleoside family (Chu *et al.*, 1989; Herdewijn *et al.*, 1987), have shown high effectiveness in the treatment of AIDS, inhibiting the human immunodeficiency virus (HIV) reverse transcriptase after their anabolic activation to 5′-triphosphate derivatives by cellular kinases.

2′,3′-Didehydro-3′-deoxythymidine (stavudine or D4T) is a potent and selective antiviral agent that is currently in clinical trials for the treatment of AIDS (Baba *et al.*, 1987). D4T was originally synthesized by Horwitz *et al.* (1966) and recently different groups have developed different synthetic routes in order to obtain an easy procedure with high yield (Negron *et al.*, 1994; Bonaffé *et al.*, 1996). Skonezny *et al.* (1994) have developed a simple and gentle procedure for obtaining D4T, which included a novel purification step where D4T was isolated with *N*-methylpyrrolidone as solvate, D4T·NMPO.



D4T·NMPO

The structural study of this complex was undertaken in order to gain further information on the geometry of D4T and on its link with NMPO, which is the final step of the adopted synthetic procedure. The structures of two crystal phases of D4T alone have already been solved (Gurskaya *et al.*, 1991; Harte *et al.*, 1991; Van Roey *et al.*, 1993) together with those of other 2′,3′-didehydro-2′,3′-deoxynucleotides (D4N) (Birnbaum *et al.*, 1989; Van Roey *et al.*, 1993; Pugazhenthi *et al.*, 1994).

A view of the molecular adduct is shown in Fig. 1, where the numbering scheme is consistent with that adopted in the above references. Bond distances and angles of D4T in our solvate do not show any relevant deviation from the literature values.

Three parameters may be used to describe the most important conformational features of a nucleoside molecule (Saenger, 1984): the torsion angle χ = C2—N1—C1′—O4′ for the geometry of the glycosylic link, the furanose ring puckering and the orientation of the 5′-hydroxyl group in terms of the torsion angle γ = C3′—C4′—C5′—O5′. The values of $\chi = -100.8\,(4)$ and of $\gamma = 52.9\,(5)^\circ$ in our compound show that the glycosylic link adopts the so called high-*anti* conformation and the 5′-hydroxyl group is in the *+sc* (synclinal) position, as found in a number of other D4N molecules (Van Roey *et al.*, 1993). The value of γ is largely determined by the type of hydrogen bond in which O5′ is engaged: indeed in 2′,3′-didehydro-2′,3′-deoxy-5-hydroxymethyluridine (D4HMUrd) (Pugazhenthi *et al.*, 1994), where O5′ acts only as a hydrogen-bond acceptor, the 5′-hydroxyl group adopts the *ap* (antiperiplanar) conformation, while the *+sc* conformation is found when O5′ acts as donor.

The furanose ring is significantly planar, with an r.m.s. deviation of the five-atom plane of 0.003 Å and O4′ at −0.009 (2) Å from the plane of the other four atoms. A similar flat ring was found in one of the two independent molecules of 2′,3′-didehydro-2′,3′-deoxyuridine (D4U) (Van Roey *et al.*, 1993) and in a 4′-C-branched derivative of D4U (Yamaguchi *et al.*, 1992). The pyrimidine ring is also planar, but with a larger r.m.s. deviation [0.006 Å, with C2 at −0.011 (2) Å and N3 at 0.009 (2) Å from the plane]. The dihedral angle between the pyrimidine and the furanose planes is 82.1 (4)°.

The geometry of the NMPO molecule is not well defined because it is affected by some disorder, as indicated by the

high values of the atomic displacement parameters of some of the atoms.

The two moieties of our adduct are held together by a fairly strong O5′—H5′···O* hydrogen bond, with O5′···O* = 2.663 (4), H5′···O* = 1.88 Å and an angle at H5′ of 159°. O5′ is also involved as acceptor in a medium strength intermolecular N3—H3···O5′($1 - x$, $y - \frac{1}{2}$, $\frac{1}{2} - z$) hydrogen bond, with N3···O5′ = 2.853 (4), H3···O5′ = 2.01 Å and an angle at H3 of 166°.

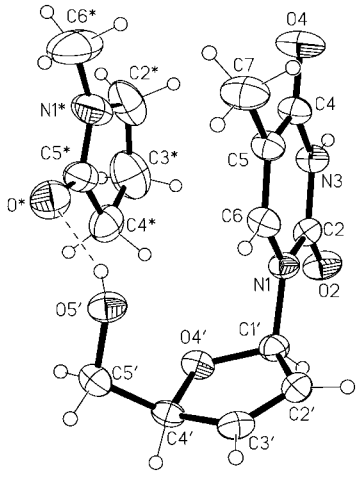


Figure 1
Drawing of the molecule of the title compound showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level

Experimental

The D4T·NMPO complex was synthesized from thymidine by several reaction steps. The initial step involved the mesylation of the 3′ and 5′ hydroxyl groups of thymidine. The bis-mesylthymidine was heated with aqueous sodium hydroxide (30%) to give 3′,5′-anhydrothymidine, then treated with potassium hydroxide in isopropyl alcohol to produce D4T, which was then isolated as the D4T·NMPO complex.

Crystal data

$C_{10}H_{12}N_2O_4·C_5H_9NO$
M_r = 323.35
Orthorhombic, $P2_12_12_1$
a = 7.471 (1) Å
b = 13.988 (1) Å
c = 15.739 (2) Å
V = 1644.8 (3) Å^3
Z = 4
D_x = 1.306 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 30 reflections
θ = 12–26°
μ = 0.099 mm^{-1}
T = 293 (2) K
Prism, colourless
0.65 × 0.50 × 0.35 mm

Data collection

Siemens four-circle diffractometer
ω scans
2807 measured reflections
2619 independent reflections
1674 reflections with $I > 2\sigma(I)$
R_{int} = 0.013
θ_{max} = 27.48°
$h = -9 \rightarrow 1$
$k = -18 \rightarrow 1$
$l = -20 \rightarrow 1$
2 standard reflections
every 98 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.155
S = 0.998
2619 reflections
211 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0936P)^2 + 0.0334P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.006
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.41 e Å^{-3}
Absolute configuration: the absolute configuration was assumed to agree with the known chirality of D4T (Gurskaya *et al.*, 1991; Harte *et al.*, 1991; Van Roey *et al.*, 1993)

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*/*IRIS* (Sheldrick, 1990) and *MOLDRAW* (Ugliengo *et al.*, 1993); software used to prepare material for publication: *PARST* (Nardelli, 1995), *PARSTCIF* (Nardelli, 1991) and *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1454). Services for accessing these data are described at the back of the journal.

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