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Crystal and Molecular Structure of β -5-Isopropyl-2'-deoxyuridine

BY M. CZUGLER, A. KÁLMÁN, J. T. SÁGI, A. SZABOLCS AND L. ÖTVÖS

Central Research Institute of Chemistry, Hungarian Academy of Sciences, Budapest, POB 17, H-1525, Hungary

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Abstract

$C_{12}H_{18}N_2O_5$ is monoclinic, space group $P2_1$, with $a = 7.999$ (1), $b = 16.266$ (6), $c = 4.855$ (3) Å, $\beta = 94.34$ (8)°, $Z = 2$. The final $R = 0.061$ for 992 counter reflexions. C(8) of the isopropyl moiety lies in the best plane of the pyrimidine ring while C(7) and C(9) are displaced by 0.22 and 1.59 Å. The glycosidic torsion angle O(1')–C(1')–N(1)–C(6) is 64.4° (*anti* conformation). The sugar ring has the usual C(2')-*endo* conformation. The arrangement about C(4')–C(5') is such that O(5') is oriented *gauche-gauche* (g^+) with respect to O(1') and C(3').

Introduction

The polymerization of a series of 5-alkyl-substituted 2'-deoxyuridine triphosphates by *Escherichia coli* DNA polymerase-I enzyme has recently been studied in our laboratory (Sági, Szabolcs, Szemző & Ötvös, 1977). A decreased reaction rate of the title compound with respect to that of the other derivatives has been thought to be correlated with some steric effect of the isopropyl moiety. In order to shed light on this question, the conformations of the title compound and β -5-ethyl-2'-

deoxyuridine have been determined in the crystalline state. Our structure determinations form part of the series of X-ray analyses of 5-substituted 2'-deoxyuridines (Barr, Hamor & Walker, 1978; and references herein) studied as potential antiviral and antitumor agents (Torrence, Spencer, Bobst, Descamps & De Clercq, 1978).

Experimental

The title compound and other 5-alkyl-2'-deoxyuridine derivatives studied in enzymatic reactions (Sági *et al.*, 1977) were synthesized in our laboratory (Szabolcs, Sági & Ötvös, 1975; Ötvös, Szabolcs, Sági & Szemző, 1975). Cell dimensions were determined from Weissenberg and precession photographs. Intensities were measured on a Stoe–Güttinger two-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation (Kálmán, Simon, Schawartz & Horváth, 1974). 1002 reflexions were scanned, of which 992 with $I - 2.5\sigma(I) \geq 0$ were used in the analysis. No absorption correction was made.

Crystal data

$C_{12}H_{18}N_2O_5$, $M_r = 270.29$, monoclinic, $a = 7.999$ (1), $b = 16.266$ (6), $c = 4.855$ (3) Å, $\beta =$
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94.34 (8)°, $U = 629.9 \text{ \AA}^3$, $Z = 2$, $D_c = 1.425 \text{ Mg m}^{-3}$, $F(000) = 288$; systematic absences: $0k0$, k odd; space group $P2_1$, Cu $K\alpha$ radiation, $\lambda = 1.5418 \text{ \AA}$.

Structure determination

The structure was solved by direct methods with 140 normalized structure factors having $E \geq 1.40$. An E map computed from a phase set with the second best consistency gave the positions of 17 of the 19 non-hydrogen atoms. The missing two atoms were located from a difference synthesis. Blocked-full-matrix least-squares refinement of positional and vibrational parameters (anisotropic for non-hydrogen and an overall isotropic temperature factor $\bar{u} = 0.057 \text{ \AA}^2$ for H atoms) converged to a final R of 0.061 for 992 reflexions $\{R_w = \sum w^{1/2} \Delta / \sum w^{1/2} |F_o| = 0.072$ with the final weighting scheme $w = 1/[\sigma^2(F_o) + 0.00642F_o^2]\}$. The H atoms belonging to OH moieties were located in a difference map and were kept fixed at the last stage of refinement. The positions of the other 16 H atoms were generated from assumed geometries with C–H and N–H distances constrained to 1.08 and 0.94 Å. A bonded-H-atom scattering factor was employed (Stewart, Davidson & Simpson, 1965) with complex neutral scattering factors for the remaining atoms (Cromer & Mann, 1968; Cromer & Liberman, 1970). The calculations were performed with *SHELX* (Sheldrick, 1976). The atomic coordinates are given in Table 1.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34327 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion

The shape of the molecule is illustrated in Fig. 1, which also shows the numbering of the atoms. Bond lengths and angles are in Table 2 and the results of least-squares-plane calculations in Table 3. Selected torsion angles together with relevant data from the literature are summarized in Table 4.

Stereochemistry and conformation of the molecule

Bond lengths and angles agree with corresponding values in 5-vinyl-2'-deoxyuridine (Hamor, O'Leary & Walker, 1978), 5-ethynyl-2'-deoxyuridine (Barr, Hamor & Walker, 1978), sodium uridine-5'-*O*-methylphosphate-methanol (Hoogendorp & Romers, 1978) and related compounds. Accordingly, the effect of the vinyl and ethynyl moieties on the electronic structure of the pyrimidine ring is shown by the bond distances and angles at C(5).

(a) *The deoxyribose residue.* The mean-plane calculations (Table 3) and the corresponding torsion

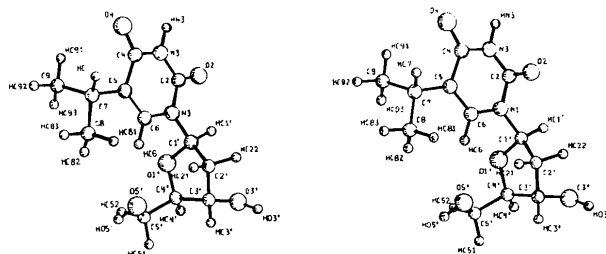


Fig. 1. A stereoscopic drawing of the title compound showing the atomic numbering.

Table 1. Fractional atomic coordinates ($\times 10^4$) and e.s.d.'s

Owing to constrained refinements, the e.s.d.'s of the H atoms are identical to those given for the corresponding non-H atoms.

	x	y	z		x	y	z
N(1)	8465 (3)	5129 (2)	2199 (4)	H(N3)	8231	7062	1703
C(2)	8855 (4)	5903 (2)	1250 (6)	H(C6)	6808	4392	4420
N(3)	7975 (3)	6530 (2)	2300 (5)	H(C81)	5593	4481	8594
C(4)	6730 (3)	6471 (2)	4159 (5)	H(C82)	4280	4245	5618
C(5)	6203 (3)	5635 (2)	4741 (5)	H(C83)	3409	4631	8587
C(6)	7120 (4)	5012 (2)	3844 (6)	H(C91)	3247	6394	3821
C(7)	4673 (3)	5523 (2)	6318 (6)	H(C92)	2036	5747	5800
C(8)	4474 (4)	4659 (4)	7351 (6)	H(C93)	2907	5361	2830
C(9)	3103 (4)	5774 (3)	4565 (7)	H(C7)	4847	5919	8101
O(2)	9903 (4)	6025 (2)	−425 (6)	H(C1')	10455	4682	402
O(4)	6141 (3)	7105 (2)	5047 (5)	H(C21)	9301	3856	5383
C(1')	9401 (3)	4427	1375 (5)	H(C22)	11348	4067	4460
O(1')	8315 (3)	3924 (2)	−348 (4)	H(C3')	10155	2540	3778
C(2')	10109 (4)	3869 (2)	3700 (6)	H(C4')	8972	2746	−1657
C(3')	10168 (4)	3043 (3)	2326 (5)	H(C51)	7334	1998	1265
C(4')	8661 (4)	3075 (2)	167 (6)	H(C52)	6063	2762	−406
C(5')	7105 (4)	2651 (3)	1096 (6)	H(O5')	5806	2655	3982
O(5')	6722 (3)	2958 (2)	3663 (5)	H(O3')	12558	2813	1951
O(3')	11649 (3)	2974 (2)	877 (5)				

angles (Table 4) indicate that the sugar ring has the *S*-type C(2')-endo conformation with C(2') as the flap of an (approximate) envelope; this can also be seen from the lowest asymmetry parameter $\Delta C_s^{(2')} = 3.4^\circ$

Table 2. Bond distances (Å) and angles ($^\circ$)

N(1)–C(1')	1.438 (4)	C(7)–C(9)	1.519 (4)
N(1)–C(2)	1.384 (5)	O(1')–C(4')	1.426 (5)
N(1)–C(6)	1.401 (4)	C(1')–O(1')	1.420 (3)
C(2)–N(3)	1.361 (5)	C(1')–C(2')	1.524 (4)
C(2)–O(2)	1.227 (4)	C(2')–C(3')	1.502 (6)
N(3)–C(4)	1.397 (4)	C(3')–C(4')	1.537 (4)
C(4)–C(5)	1.458 (6)	C(3')–O(3')	1.427 (4)
C(4)–O(4)	1.226 (5)	C(4')–C(5')	1.521 (5)
C(5)–C(6)	1.342 (5)	C(5')–O(5')	1.398 (4)
C(5)–C(7)	1.503 (4)	O(5')–H(O5')	0.906 (4)
C(7)–C(8)	1.504 (7)	O(3')–H(O3')	0.901 (3)
C(2)–N(1)–C(6)	121.0 (3)	C(8)–C(7)–C(9)	109.6 (3)
C(2)–N(1)–C(1')	119.6 (3)	N(1)–C(6)–C(5)	123.0 (4)
C(1')–N(1)–C(6)	119.3 (3)	N(1)–C(1')–O(1')	108.3 (3)
N(1)–C(2)–N(3)	114.9 (3)	N(1)–C(1')–C(2')	116.1 (3)
N(1)–C(2)–O(2)	123.4 (4)	O(1')–C(1')–C(2')	105.6 (2)
O(2)–C(2)–N(3)	121.7 (4)	C(1')–C(2')–C(3')	103.1 (2)
C(2)–N(3)–C(4)	127.2 (4)	C(2')–C(3')–C(4')	102.9 (3)
N(3)–C(4)–O(4)	118.7 (4)	C(2')–C(3')–O(3')	110.1 (3)
N(3)–C(4)–C(5)	114.9 (4)	O(3')–C(3')–C(4')	107.7 (2)
O(4)–C(4)–C(5)	126.3 (3)	O(1')–C(4')–C(3')	106.5 (3)
C(4)–C(5)–C(6)	117.9 (3)	O(1')–C(4')–C(5')	109.8 (3)
C(4)–C(5)–C(7)	118.0 (3)	C(3')–C(4')–C(5')	113.6 (3)
C(6)–C(5)–C(7)	124.1 (4)	C(4')–C(5')–O(5')	110.0 (4)
C(5)–C(7)–C(8)	113.2 (3)	C(1')–O(1')–C(4')	110.6 (2)
C(5)–C(7)–C(9)	110.6 (3)		

Table 3. Mean-plane calculations

Deviations are in Å; atoms whose deviations are marked by an asterisk define the plane. X, Y, Z refer to the orthogonal axial system; weighted r.m.s.d.'s are 0.043 Å for *a* and 0.013 Å for *d*.

Plane	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>
N(1)	0.050 (3)*	0.005 (9)*	0.007*	
C(2)	–0.039 (4)*	–0.014 (8)*	–0.006*	
N(3)	–0.018 (3)*	0.021 (9)*	–0.002*	
C(4)	0.062 (3)*	–0.018 (9)*	0.009*	
C(5)	–0.054 (4)*	0.009 (8)*	–0.009*	
C(6)	–0.001 (4)*	–0.003 (9)*	0.001*	
O(2)	–0.140 (4)	0.009 (9)	0.010	
O(4)	0.164 (4)	–0.072 (8)	0.027	
C(7)	–0.218 (3)	0.002 (10)	–0.025	
C(8)	–0.015 (5)	–0.173 (10)	0.177	
C(9)	–1.585 (5)	–	–	
C(1')	0.131 (3)	0.076 (9)	0.027	0.010 (3)*
C(2')				0.509 (3)
C(3')				–0.009 (3)*
C(4')				0.016 (4)*
O(1')				–0.016 (3)*
C(5')				1.241 (4)

Plane *a*: $0.6556X + 0.0566Y + 0.7530Z = 5.2666$.

Plane *b*: 5-ethyl-2'-deoxyuridine (M. Czugler, A. Kálmán & J. T. Sági, unpublished work).

Plane *c*: 5-vinyl-2'-deoxyuridine (Hamor *et al.*, 1978).

Plane *d* (deoxyribose ring):

$$-0.6355X - 0.0220Y + 0.7718Z = -4.8578.$$

(Duax, Weeks & Rohrer, 1976) and the pseudo-rotation phase angle of 169.9° with the maximum amplitude of puckering $\phi_m = 33.9^\circ$ [if ϕ_o is assigned to the rotation about O(1')–C(4') (Altona, Geise & Romers, 1968)]. The conformation about C(4')–C(5') is *gauche-gauche* (g^+) (Sundaralingam, 1973), as revealed by the torsion angles O(1')–C(4')–C(5')–O(5') = 66.4° and C(3')–C(4')–C(5')–O(5') = 53.0° . A similar arrangement has been reported in sodium uridine-5'-*O*-methylphosphate-methanol (Hoogendorp & Romers, 1978) and 5-iodo-2'-deoxyuridine (Cameran & Trotter, 1965). The glycosidic torsion angle $\chi = 64.4^\circ$ falls in the part of the *anti* range found most frequently for C(2')-endo β -pyrimidine nucleosides. A similar χ (63.3°) was observed in 5-iodo-2'-deoxyuridine (Cameran & Trotter, 1965). In sodium uridine-5'-*O*-methylphosphate-methanol (Hoogendorp & Romers, 1978) χ is 79.1° while in 5-ethynyl-2'-deoxyuridine (Barr, Hamor & Walker, 1978) it is only 18.6° . The angle between the best planes of the sugar ring (for four atoms) and the pyrimidine base (for six atoms) is 80.6° .

(b) *The pyrimidine base.* The pyrimidine ring is less planar than in 5-vinyl-2'-deoxyuridine (Hamor, O'Leary & Walker, 1978) and 5-ethyl-2'-deoxyuridine (refinement in progress) (Table 3). C(1'), O(2), O(4) and C(7) are out of the best plane of the base by 0.13–0.22 Å. Nevertheless, the synperiplanar conformation of C(7)–C(8) about C(5)–C(7) resembles those in 5-vinyl- and 5-ethyl-2'-deoxyuridines. Accordingly, the other methyl group of the isopropyl moiety should protrude significantly from the least-squares plane of the base (1.59 Å). If this asymmetric conformation of the isopropyl moiety is sustained in solution, even to some extent, then the protruding methyl group can hinder the development of base-stacking of the natural DNA chain. The disturbing effect of such a protruding methyl group in the formation of a DNA chain has been modeled as shown in Fig. 2. This hypothesis based on the molecular conformation observed in the crystal-

Table 4. Selected torsion angles ($^\circ$) of the title compound (I, mean e.s.d. 0.8°) compared with those of sodium uridine-5'-*O*-methylphosphate-methanol (II) (Hoogendorp & Romers, 1978).

		(I)	(II)
τ_0	C(4')–O(1')–C(1')–C(2')	–17.8	–19.8
τ_1	O(1')–C(1')–C(2')–C(3')	31.5	34.3
τ_2	C(1')–C(2')–C(3')–C(4')	–32.2	–34.9
τ_3	C(2')–C(3')–C(4')–O(1')	22.6	24.6
τ_4	C(3')–C(4')–O(1')–C(1')	–3.0	–3.0
ψ'	O(3')–C(3')–C(4')–C(5')	145.3	148.2
ψ	C(3')–C(4')–C(5')–O(5')	53.0	52.8
	C(4')–C(5')–O(5')–X	–179.0	173.4
		(X = H)	(X = P)
χ	O(1')–C(1')–N(1)–C(6)	64.4	79.1
	C(8)–C(7)–C(5)–C(6)	12.8	–

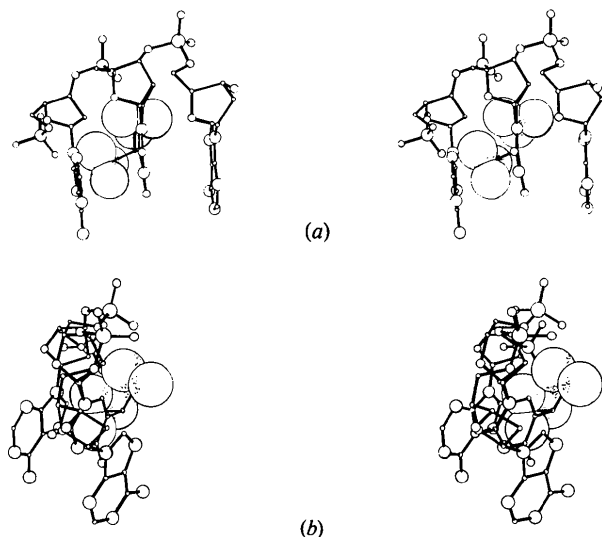


Fig. 2. Projections of a hypothetical adenylyl-(3'→5')-5-isopropyl-2'-deoxyuridylyl-(3'→5')-adenosine segment of a single strand of *B*-DNA. The pyrimidine base of the title compound was fitted by least squares to that of the *B*-DNA model computed from the coordinates of Arnott, Dover & Wonacott (1969). H atoms of the terminal methyl groups are drawn with their van der Waals radii. Projection (a) is viewed along the C(2)···C(5) direction of the central base, while projection (b) is drawn along the sugar-phosphate backbone.

line state may explain the limited incorporation of the corresponding 5'-triphosphate ester of the title compound in enzymatic DNA synthesis (Žmudzka, Nowak & Sági, 1979).

(c) *The overall conformation.* The title compound has an *anti*, *gauche-gauche* (g^+) C(2')-*endo* envelope conformation. It resembles that in sodium uridine-5'-*O*-methylphosphate-methanol (Hoogendorp & Romers, 1978) (Table 4).

Table 5. *Hydrogen-bond parameters of the title compound*

A···H—D	A···D	A···H	A···H—D
O(4)···H(O5')—O(5') ⁱ	2.789 (7) Å	1.887 (7) Å	173 (5)°
O(4)···H(O3')—O(3') ⁱⁱ	2.917 (8)	2.074 (7)	155 (6)
O(3')···H(N3)—N(3) ⁱⁱⁱ	2.838 (9)	1.949 (8)	157 (5)

Symmetry code (unlabelled atoms refer to the original molecule)

- (i) $1 - x, \frac{1}{2} + y, 1 - z$ (iii) $2 - x, \frac{1}{2} + y, -z$
(ii) $2 - x, \frac{1}{2} + y, 1 - z$

Hydrogen bonding

The non-bonded contacts less than the sum of the van der Waals radii indicate three hydrogen bonds in which all the H atoms linked to O and N are involved (Table 5). O(3') takes part in two helices formed around the screw axes $2_1(1, y, \frac{1}{2})$ and $2_1(1, y, 0)$, partly as donor, partly as acceptor. O(4) is involved in two helices built up around the screw axes $2_1(1, y, \frac{1}{2})$ and $2_1(\frac{1}{2}, y, \frac{1}{2})$ as acceptor.

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