Acta Cryst. (1977). B33, 3704-3707

Crystal Structure and Conformation of 3-Deaza-4-deoxyuridine

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(Received 12 April 1977; accepted 21 May 1977)

 $C_{10}H_{13}O_5N$ is orthorhombic, space group $P2_12_12_1$, with $a = 25 \cdot 18$, $b = 7 \cdot 127$, $c = 5 \cdot 715$ Å, Z = 4. The structure was refined to R = 0.049 for 749 counter reflexions. Features of the nucleoside include an orientation of the base at the glycosidic bond N(1)-C(1') in the *anti* range (53.5°), a ribosyl moiety in the C(2')-endo conformation and a gauche-gauche arrangement of C(4')-C(5'). The packing is characterized by a staggered arrangement of the bases and a clear separation of hydrophobic and hydrophilic regions. Comparison with other pyrimidine nucleosides suggests an interrelationship between the puckering of the ribose and the orientation of the base, which has its structural basis in the formation of the intramolecular interaction C(6)-H...O(5').

The secondary and tertiary structures of nucleic acids are mainly determined by the stereochemistry of the monomeric building blocks. The influence of modifications in the base moiety on the stereochemistry of nucleic acids has not yet been clarified. Therefore, as part of our studies on the structures of pyrimidine nucleosides, some of which occur in tRNA, we have solved the crystal structure of 3-deaza-4-deoxyuridine $(1-\beta-D-ribofuranosyl-2-pyridone)$, which is the least polar nucleoside of this series. This nucleoside, furthermore, represents a model compound, which shows the space filling of a pyrimidine nucleoside, but has no ability to form Watson-Crick-type hydrogen bonds with adenosine.



Table 1. Crystal data

Molecular formula C₁₀H₁₃O₅N

$$\begin{split} M_r &= 227 & & Z = 4 \\ Space group P2_1 2_1 2_1 & & Z = 4 \\ b &= 7 \cdot 127 \ (3) & & \rho_o = 1 \cdot 46 \ \text{g cm}^{-3} \ \text{(flotation)} \\ c &= 5 \cdot 715 \ (5) & & \rho_c = 1 \cdot 470 \\ V &= 1025 \cdot 7 \ \text{Å}^3 & & \mu = 9 \cdot 1 \ \text{cm}^{-1} \end{split}$$

known procedure (Vorbrüggen & Krolikiewicz, 1975). Crystals were grown as light-brown orthorhombic blocks from methanol and were identical with those obtained from water. The systematic absences h00, 0k0and 00l for odd indices determine the space group as $P2_12_12_1$. Crystal data are summarized in Table 1. Intensities were collected on a Stoe two-circle diffractometer (Cu K α radiation) equipped with a graphite monochromator; the crystal was orientated along c. In this way 906 symmetry-independent reflexions (hk0-4) with $\theta \le 60^\circ$ were measured in the $\theta-2\theta$ scan mode. The data were corrected for background and for Lorentz and polarization factors, but not for absorption. 749 reflexions had $|E| > 3\sigma_{E_1}$

Structure determination and refinement

The structure was solved with SHELX-76 (Sheldrick, 1976) which uses scattering factors from International Tables for X-ray Crystallography (1974).

Isotropic refinement with unit weights reduced R to 0.138, which dropped to 0.091 with anisotropic

Experimental

 $1-\beta$ -D-Ribofuranosyl-2-pyridone was synthesized by a

Table 2. Positional parameters and their estimated standard deviations

	x	У	Z
N(1)	0.1068(1)	-0.0297 (5)	0.5700 (7)
C(2)	0.1029 (2)	-0·1669 (8)	0.735(1)
O(2)	0.1401 (1)	-0.1952 (7)	0.8762 (8)
C(3)	0.0536 (2)	-0.2684(9)	0·740 (1)
C(4)	0.0154(2)	-0.2347(8)	0.584 (1)
C(5)	0.0223(2)	-0·1000 (8)	0.414 (1)
C(6)	0.0677 (2)	0.0005 (7)	0.4067 (9)
C(1')	0.1545 (2)	0.0905 (7)	0.5672 (9)
C(2')	0.1885 (2)	0.0715 (7)	0.3483 (9)
C(3')	0.2127 (2)	0.2679 (8)	0.3261 (8)
C(4′)	0.1695 (2)	0.3944 (7)	0.422 (1)
O(1')	0.1368 (1)	0.2796 (5)	0.5746 (6)
O(2')	0.2246 (1)	-0.0771 (5)	0.3834 (6)
O(3′)	0.2584(1)	0.2857 (5)	0.4785 (6)
C(5')	0.1341 (2)	0.4817 (9)	0.240(1)
O(5′)	0.1136 (1)	0.3457 (6)	0.0800 (9)
H(C3)	0.055 (2)	-0.338 (7)	0.89(1)
H(C4)	-0·019 (2)	-0.316 (7)	0.570 (9)
H(C5)	-0.005 (2)	-0.075 (7)	0.280 (9)
H(C6)	0.076 (2)	0.099 (7)	0.296 (9)
H(C1')	0.177 (2)	0.062 (7)	0.71(1)
H(C2')	0.166 (2)	0.052 (7)	0.21(1)
H(C3')	0.225 (2)	0.303 (7)	0.152(9)
H(C4')	0.184 (2)	0.478 (8)	0.504 (9)
H(O2')	0.238 (2)	-0.082 (9)	0.28(1)
H(O3')	0.286 (2)	0.243 (8)	0.388 (9)
H(C5')	0.106 (2)	0.537 (8)	0.33 (1)
H′(C5′)	0.152 (2)	0.563 (9)	0.20(1)
H(O5')	0.142 (2)	0.343 (8)	-0.01(1)

temperature factors. At this stage 10 of the 13 H atoms were located by a difference synthesis. Weights $w = 1/\sigma(|F|)^2$ were introduced and further refinement with fixed H temperature factors yielded the positions of the three remaining H atoms and finally converged at an R of 0.049.* None of the positional parameters of the heavy atoms shifted more than 0.07 σ in the last cycle. Positional parameters are listed in Table 2.

Results

Structure of the base

The bond lengths of the base (Fig. 1) agree satisfactorily with those of 2-pyridone (Penfold, 1953) showing a mean deviation of 0.023 Å. As expected, the greatest differences are around N(1). The part of the base which is turned away from the ribose, O(2)-C(2)-C(3)-C(4), correlates well with 2pyridone, whereas the other part shows only moderate agreement. The direction of the deviations of the angles from 120° is the same for all values when compared with 2-pyridone, but the amount of the deviation is always smaller. The pyridone ring is nearly planar with a standard deviation of the ring atoms of 0.014 Å (Table 3). O(2) deviates 0.040 Å from the best plane

Table 3. Least-squares planes through the base and the ribose moiety

The plane equations in crystal space are of the form lx + my + nz = p. Atoms which define the planes are marked by an asterisk.

		Deviation from plane (Å)
Base	NT(1) *	0.022
m = -0.4032 m = -0.6782	$C(2)^*$	-0·023
n = 0.6144	O(2)	-0.040
p = -0.7515	C(3)*	0.006
	C(4)*	0.009
	C(5)*	-0.008
	C(6)*	-0.008
	C(1')	0.109
Ribose		
l = 0.5871	C(1')*	-0.014
m = -0.1959	C(2')	-0.520
n = 0.7855	C(3′)*	0.013
p = 4.9703	C(4')*	- 0 .021
	O(1')*	0.022



Fig. 1. The bond lengths (Å), bond angles (°) and dihedral angles (°) of 3-deaza-4-deoxyuridine ($\sigma_{\chi\chi} = 0.007$ Å, $\sigma_{\chi\chi\chi} = 0.4^{\circ}$, X = C, O, N).

^{*} Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32790 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

whereas C(2) is planar trigonal; the same feature is found in 2-pyridone. Of all substituents, C(1') shows the greatest deviation from the base plane (0.109 Å) and is situated on the opposite side of the ring from O(2).

Structure of the ribose

The ribose has a C(2')-endo conformation (Fig. 2) with C(1'), C(3'), C(4') and O(1') in the plane ($\sigma = 0.018$ Å) while C(2') deviates by 0.52 Å (Table 3). C(1')-O(1') is 0.032 Å shorter than C(4')-O(1'), as is nearly always found in nucleoside structures. The orientation at N(1)-C(1') is anti with a dihedral angle C(6)-N(1)-C(1')-O(1') of 53.5°. The base is held in this conformation by the characteristic intramolecular interaction H(C6)...O(5') (Table 4). C(5')-O(5') is gauche to C(3')-C(4') and to O(1')-C(4') with dihedral angles of 50.7 and -68.7° (Figs. 1 and 2).

Packing of the molecules

Views down c (Fig. 3) and b (Fig. 4) illustrate the crystal structure, which is determined by the three



Fig. 2. The structural representation of 3-deaza-4-deoxyuridine with the thermal ellipsoids of the heavy atoms.

Table 4. List of intermolecular hydrogen bonds, including the characteristic intramolecular $C(6)-H\cdots$ O(5') interaction

$\mathbf{H}\cdots \mathbf{Y}(\mathbf{\dot{A}})$	$X \cdots Y$ (Å)	$\angle X - H \cdots Y(\circ)$
2.315	2.783	122.2
1.892	2.701	145.7
2.329	2.985	123-1
2.353	3.297	165.8
	$H \cdots Y(\dot{A})$ 2.315 1.892 2.329 2.353	$\begin{array}{ccc} H \cdots Y \left(\dot{A} \right) & X \cdots Y \left(\dot{A} \right) \\ \hline 2 \cdot 315 & 2 \cdot 783 \\ 1 \cdot 892 & 2 \cdot 701 \\ 2 \cdot 329 & 2 \cdot 985 \\ 2 \cdot 353 & 3 \cdot 297 \end{array}$



Fig. 3. A view down **c** with **a** horizontal and **b** vertical. The individual base stacks are designated with letters. They are related by the following symmetry operations: $A \leftrightarrow B$: screw axis parallel to **b**: $A \leftrightarrow C$: screw axis parallel to **a**: $A \leftrightarrow D$: screw axis parallel to **c**.



Fig. 4. A view down **b** with **a** horizontal and **c** vertical (for the definition of the letters A, B, C and D see Fig. 3).



Fig. 5. A view parallel to the base stack B with the bases A perpendicular to it (see Fig. 4).

screw axes. The three-dimensional structure can be divided into layers parallel to the bc plane showing the sequence: base-ribose-vribose-base-vibose etc., with adjacent ribose moieties connected by hydrogen bonds (Table 4). The bases are stacked along \mathbf{c} at a distance of 3.51 Å. They are located not directly one upon another but show a staggered arrangement with only a small $O(2) \cdots H(C6)$ overlap. The stacked bases A (Fig. 4) are nearly perpendicular (94.6°) to the six-membered rings of the adjacent base stack B, and the same is true for the bases C and D. This feature is illustrated in Fig. 5 which shows a view parallel to the planes of the bases B. C(3) (3.58), H(C3) (2.74) and H(C4) (3.21 Å) of the bases A have the smallest distances from the best planes of B.

Discussion

The structure of 3-deaza-4-deoxyuridine is similar to that of comparable nucleosides. For example, 3-deazauridine (Schwalbe & Saenger, 1973), 5-chlorouridine (Hawkinson & Coulter, 1971) and 5-hydroxyuridine (Thewalt & Bugg, 1973) also exhibit the C(2')-endo conformation of the ribose with C(6)-N(1)-C(1')-O(1')dihedral angles of 52.3, 51.4 and 42.1°. 3-Deaza-4deoxyuridine (53.5°) fits into this group. On the other hand, uridine (Green, Rosenstein, Shiono, Abraham, Trus & Marsh, 1975), 5-methyluridine (Hunt & Subramanian, 1969), 5-nitrouridine (Egert, Lindner, Hillen & Gassen, 1977) and 2-thiouridine (Hawkinson, 1977) exist in the C(3')-endo conformation with dihedral angles about the glycosidic bond of 18.3 (24.3), 29.4, 25.6 and 17°. From these values it is evident that there is a relation between the puckering of the ribose and the orientation of the base. This could be explained by the formation of the intramolecular interaction $C(6)-H\cdots O(5')$ (Saenger, 1973). This characteristic hydrogen bonding, which seems to stabilize the orientation of the glycosidic bond, occurs, for example, in 3-deaza-4-deoxyuridine, uridine, 3deazauridine, 5-chlorouridine, 5-methyluridine and 5nitrouridine. The formation of a C(6)-H···O(5') interaction requires a greater C(6)-N(1)-C(1')-O(1')dihedral angle in C(2')-endo than in C(3')-endo puckering.

The packing of the molecules is comparable with that of other nucleosides. The separation of hydrophobic and hydrophilic regions is a principle which is always realized. Alternating layers of bases and sugars as in 3deaza-4-deoxyuridine are found, for example, in 2thiouridine, 5-hydroxyuridine and 6-methyluridine (Suck & Saenger, 1972). Also, the interaction between the bases fits with the known structures of pyrimidine nucleosides because an extensive base stacking has never been found, but the bases only partially overlap as in uridine or 2-thiouridine. Hydrophilic interactions, for example hydrogen bonds, seem to mainly determine the crystal structure and are optimized at the expense of the base stacking. Indeed, it is questionable whether conclusions concerning the conformation of nucleic acids are valid from the crystalline structures of their building blocks.

The calculations were carried out at the Rechenzentrum der Technischen Hochschule Darmstadt. The work was supported by the Fonds der Chemischen Industrie.

References

- EGERT, E., LINDNER, H. J., HILLEN, W. & GASSEN, H. G. (1977). Nucleic Acids Res. 4, 929–937.
- GREEN, E. A., ROSENSTEIN, R. D., SHIONO, R., ABRAHAM, D. J., TRUS, B. L. & MARSH, R. E. (1975). Acta Cryst. B31, 102–107.
- HAWKINSON, S. W. (1977). Acta Cryst. B33, 80-85.
- HAWKINSON, S. W. & COULTER, C. L. (1971). Acta Cryst. B27, 34–42.
- HUNT, D. J. & SUBRAMANIAN, E. (1969). Acta Cryst. B25, 2144–2152.
- International Tables for X-ray Crystallography (1974). Vol. IV, pp. 99–102. Birmingham: Kynoch Press.
- PENFOLD, B. R. (1953). Acta Cryst. 6, 599-600.
- SAENGER, W. (1973). Angew. Chem. 85, 680-690.
- SCHWALBE, C. H. & SAENGER, W. (1973). Acta Cryst. B29, 61-69.
- SHELDRICK, G. M. (1976). Unpublished.
- SUCK, D. & SAENGER, W. (1972). J. Amer. Chem. Soc. 94, 6520–6526.
- THEWALT, Y. & BUGG, C. E. (1973). Acta Cryst. B29, 1393-1398.
- VORBRÜGGEN, H. & KROLIKIEWICZ, K. (1975). Angew. Chem. 87, 417.