

Structure of Ammonium 5-Fluoro-2'-deoxyuridine Cyclic 3',5'-Monophosphate Trihydrate, $C_9H_9FN_2O_7P^- \cdot NH_4^+ \cdot 3H_2O^\dagger$

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Abstract. $M_r = 379.24$, monoclinic, $P2_1$, $a = 10.796$ (1), $b = 6.245$ (1), $c = 12.411$ (1) Å, $\beta = 108.7$ (2)°, $V = 792.6$ (14) Å³, $D_x = 1.589$ (3) Mg m⁻³, $Z = 2$ (D_m could not be measured), $Cu K\alpha$, $\lambda = 1.5418$ Å, $\mu = 21.9$ cm⁻¹, $F(000) = 396$; measurement temperature: 295 (2) K; $R = 0.022$ for 1773 unique reflexions. The phase problem was solved by direct methods. The pyrimidine base assumes the *anti* conformation about the glycosidic C(1')–N(1) bond [$\chi = 50.3$ (3)°] while the ribose group exhibits an almost perfect half-chair conformation with a twofold axis which bisects C(1'). The ammonium cation situated in the neighbourhood O(7) [N...O = 2.832 (2) Å], together with the three water molecules and the N(3)–H(3) and C(6)–H(6) groups of the pyrimidine base, form 15 hydrogen bonds.

Introduction. The key role of cAMP and cGMP[‡] as bioregulators in living cells has been known for nearly a quarter of a century. To date, several hundred derivatives and analogues of naturally occurring cyclic nucleotides (especially of cAMP and cGMP) have been synthesized and evaluated biologically (Simon, Shuman & Robins, 1973; Miller 1977, 1981). Recently, 3',5'-cyclic monophosphates of pyrimidine nucleosides have also been isolated from leukaemia L-1210 cells (Bloch, 1974), rat-liver tissues (Bloch, 1975*a,b*) and bacterial culture fluids (Ishiyama, 1975). Knowledge of the biological function of pyrimidine nucleoside cyclic 3',5'-monophosphates is limited (Bloch, Dutschman & Maue, 1974; Noworytko, 1977), but perhaps herein lies a whole new area equal in importance to that of cAMP and cGMP (Robins, 1979); for example, cTMP has been reported as a possible mediator of insulin action (Kitabchi, Solomon & Brush, 1970). On the other hand, the cytostatic and antiviral activities of 5-fluorouracil and 5-fluoro-2'-deoxyuridine are also well-known (Bobek & Bloch, 1978; Torrence, De Clercq, Descamps, Huang & Witkop, 1979). Moreover 5-fluoro-2'-deoxyuridine 5'-phosphate was reported (De Clercq & Torrence, 1978; Renis, 1980; Smith,

Sidwell & Robins, 1980) to be a powerful inhibitor of TMP synthetase. Since there is a definite conformational component of the structure–activity relationship in nucleosides and cyclic 3',5'-nucleotide analogues (Miles, Miles & Eyring, 1979), it seemed worthwhile to determine the structure of the title compound.

Experimental. The compound was prepared and crystallized in our laboratories. Crystal size: 0.05 × 0.11 × 0.18 mm; diffractometer: Enraf–Nonius CAD-4 equipped with graphite monochromator; cell constants were determined by least squares using 25 reflexions collected in the range $h'_{\max} = 9$, $k'_{\max} = 5$, $l'_{\max} = 10$. Systematic absences: $k = 2n + 1$ in $0k0$. No absorption correction was applied, $2\theta_{\max} = 150^\circ$, $h_{\max} = 13$, $k_{\max} = 7$, $l_{\max} = 15$. Standard reflexions: 112, 321 (max. variation: 1.7%). Number of reflexions measured: 1822. Number of unique reflexions: 1773. Number of unobserved reflexions: 49 with $I < 1.0\sigma(I)$. The structure was solved by *MULTAN* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) using $E \geq 1.40$. The full-matrix least-squares procedure minimized $\sum w(\Delta F)^2$. 294 parameters were refined. Final $R = 0.022$, $R_w = 0.029$, $S = 3.07$, $w = [\sigma^2(F_o) + 0.25(pF_o)^2]^{-1}$ where $p = 0.01$. The maximum ratio of shift to error is 1.88 (for H atoms). Extinction coefficient: 9.82063×10^{-6} . All scattering factors including anomalous-dispersion corrections were taken from *International Tables for X-ray Crystallography* (1962). Program system applied: Enraf–Nonius SDP-34 with local modifications adapted to a PDP 11/34 minicomputer (64 K).

The *E* map computed from the best set with a low ABSFOM of 0.42 revealed the positions of 18 non-hydrogen atoms. A peak at $x = 0.47$, $y = 0.045$, $z = 0.41$ was assigned deliberately as the centre of the ammonium ion. In the first Fourier synthesis two more atoms could be located. The still missing C(2') atom of the sugar ring was then generated from the assumed geometry. The subsequent two cycles of structure factor and Fourier calculations combined with isotropic refinement of the heavy-atom positions revealed two additional water molecules. A third water molecule was found in a difference Fourier map ($R = 0.16$). Three cycles of anisotropic refinement reduced R to 0.12. At this stage six out of the nine H atoms of the nucleotide

† Dedicated to the memory of Mr Ernő Moravcsik, who died 2 February 1982.

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‡ cAMP is adenosine cyclic 3',5'-monophosphate; cGMP is guanosine cyclic 3',5'-monophosphate.

molecule and five of the water hydrogens were located in a second difference map. No H positions could be located, however, in the vicinity of the peak treated conditionally as NH_4^+ nitrogen [N(A)]. The missing H atoms of the nucleotide were then generated from assumed geometries and the anisotropic refinement of the non-hydrogen positions with fixed H coordinates improved R to 0.038. A search of the potential hydrogen bonds was then performed which showed that the peak regarded as the centre of the ammonium ion plays an acceptor role. Accordingly, the identity of the three water molecules and the NH_4^+ ion had to be revised. The third difference map computed from the heavy atom and the nucleotide H positions showed four peaks around the residual of the atom assigned formerly as $W(2)$. Moreover, two H atoms could now be found near the peak treated hitherto as N(A). The H atoms of $W(1)$ and $W(3)$ molecules were observed, however, approximately in those positions which had been revealed earlier. Thus, by exchanging the positions of the NH_4^+ ion and $W(2)$ molecule, R was reduced at once to 0.028 and all potential hydrogen-bond relationships were acceptable. Two additional cycles of anisotropic refinement of heavy-atom positions with fixed H-atom coordinates gave $R = 0.025$. In the following two cycles all H-atom positions were refined isotropically using a dampening factor of 0.666, whilst the heavy-atom positions, except those of O($W1$), O($W2$), O($W3$) and N(A), were kept fixed. This treatment resulted in, among other improvements, a better geometry for the ammonium tetrahedron.

Table 1. Fractional coordinates ($\times 10^5$ for P and $\times 10^4$ for the other atoms) and mean temperature factors for non-hydrogen atoms

E.s.d.'s are given in parentheses; $B_{\text{eq}} = 4[B_{11}B_{22}B_{33}/(a^*b^*c^*)]^{1/3}$.				
	x	y	z	$B_{\text{eq}}(\text{\AA}^2)$
P	81702 (4)	16000 (11)	64287 (3)	1.67 (1)
N(1)	6916 (1)	-683 (3)	1704 (1)	2.02 (4)
C(2)	7009 (2)	-680 (4)	619 (1)	1.96 (5)
N(3)	5821 (1)	-786 (3)	-250 (1)	2.03 (4)
C(4)	4590 (2)	-808 (3)	-144 (1)	2.01 (5)
C(5)	4622 (2)	-856 (4)	1023 (1)	2.07 (5)
C(6)	5722 (2)	-789 (4)	1886 (1)	2.16 (5)
O(2)	8046 (1)	-587 (3)	427 (1)	2.93 (4)
O(4)	3600 (1)	-794 (3)	-980 (1)	2.92 (4)
F	3452 (1)	-984 (3)	1197 (1)	3.36 (4)
C(1')	8109 (2)	-441 (4)	2678 (1)	2.29 (5)
C(2')	8234 (2)	1750 (4)	3273 (1)	2.37 (5)
C(3')	7936 (2)	1156 (3)	4349 (1)	1.70 (5)
C(4')	8506 (2)	-1074 (4)	4577 (1)	1.96 (5)
O(1')	8060 (1)	-2059 (3)	3488 (1)	2.57 (4)
O(3')	8496 (1)	2486 (2)	5327 (1)	1.89 (3)
C(5')	8086 (2)	-2187 (3)	5473 (2)	2.18 (5)
O(5')	8591 (1)	-871 (2)	6491 (1)	2.13 (3)
O(6)	6723 (1)	1717 (3)	6201 (1)	2.25 (3)
O(7)	9060 (1)	2670 (3)	7441 (1)	2.50 (4)
O($W1$)	841 (1)	9690 (3)	8984 (1)	3.05 (4)
O($W2$)	4712 (1)	448 (3)	4079 (1)	3.24 (4)
O($W3$)	3786 (1)	3563 (3)	2375 (1)	3.34 (4)
N(A)	1075 (1)	1341 (3)	1246 (1)	2.54 (4)

Table 2. Interatomic distances (\AA) and bond angles ($^\circ$) with their e.s.d.'s in parentheses

P-O(3')	1.615 (1)	C(2)-N(3)	1.388 (2)	C(1')-C(2')	1.540 (3)
P-O(5')	1.603 (1)	C(2)-O(2)	1.218 (2)	C(1')-O(1')	1.438 (2)
P-O(6)	1.498 (1)	N(3)-C(4)	1.377 (2)	C(2')-C(3')	1.516 (1)
P-O(7)	1.475 (1)	C(4)-C(5)	1.438 (1)	C(3')-C(4')	1.512 (3)
N(1)-C(2)	1.382 (1)	C(4)-O(4)	1.228 (2)	C(3')-O(3')	1.435 (2)
N(1)-C(6)	1.380 (2)	C(5)-C(6)	1.321 (2)	C(4')-O(1')	1.421 (2)
N(1)-C(1')	1.465 (2)	C(5)-F	1.350 (2)	C(4')-C(5')	1.499 (2)
				C(5')-O(5')	1.459 (2)
O(3')-P-O(5')	103.6 (1)	C(4)-C(5)-C(6)	122.8 (3)		
O(3')-P-O(6)	108.7 (1)	C(4)-C(5)-F	116.1 (3)		
O(3')-P-O(7)	107.9 (1)	C(6)-C(5)-F	121.1 (3)		
O(5')-P-O(6)	108.6 (1)	N(1)-C(6)-C(5)	120.9 (3)		
O(5')-P-O(7)	107.3 (1)	N(1)-C(1')-C(2')	114.0 (3)		
O(6)-P-O(7)	119.6 (1)	N(1)-C(1')-O(1')	106.5 (2)		
C(2)-N(1)-C(6)	121.5 (3)	C(2')-C(1')-O(1')	107.8 (3)		
C(2)-N(1)-C(1')	119.0 (2)	C(1')-C(2')-C(3')	101.2 (2)		
C(6)-N(1)-C(1')	119.4 (2)	C(2')-C(3')-C(4')	101.6 (2)		
N(1)-C(2)-N(3)	114.8 (3)	C(2')-C(3')-O(3')	116.9 (2)		
N(1)-C(2)-O(2)	123.3 (3)	C(4')-C(3')-O(3')	109.8 (2)		
N(3)-C(2)-O(2)	121.9 (3)	C(3')-C(4')-O(1')	103.1 (2)		
C(2)-N(3)-C(4)	127.3 (2)	C(3')-C(4')-C(5')	111.3 (3)		
N(3)-C(4)-C(5)	112.6 (3)	O(1')-C(4')-C(5')	114.4 (3)		
N(3)-C(4)-O(4)	121.6 (3)	C(1')-O(1')-C(4')	106.5 (2)		
C(5)-C(4)-O(4)	125.8 (3)	P-O(3')-C(3')	111.8 (2)		
		C(4')-C(5')-O(5')	105.3 (2)		
		P-O(5')-C(5')	118.6 (2)		

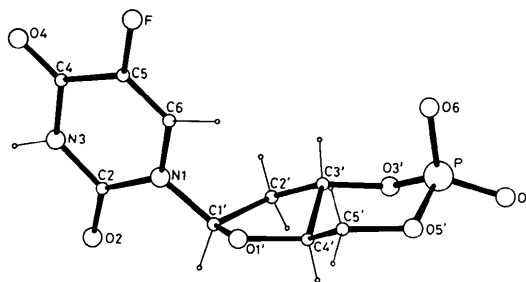


Fig. 1. A perspective view of the nucleotide molecule with atomic numbering. The H atoms are shown but not labelled.

Discussion. The final coordinates for the non-hydrogen atoms are given in Table 1.* The bond lengths and angles are listed in Table 2. A perspective view of the molecule showing the atomic numbering is depicted in Fig. 1.

Geometry. The bonding of the fairly planar pyrimidine ring [$-0.03590X + 0.99935Y - 0.01061Z = -0.69998$ with $\sigma(A) = 0.2627$, $\sigma(B) = 0.0473$, $\sigma(C) = 0$ and $\sigma(D) = 0.0157 \text{ \AA}$; max. dev.: $0.020 (2) \text{ \AA}$] agrees well with the corresponding values observed in 5-fluoro-2'-deoxyuridine (FUDR) (Harris & MacIntyre, 1964) but, of course, differs partly from that of thymidine (Young, Tollin & Wilson, 1969) and other 5-alkyl (5-ethyl: Czugler, Kálmán & Sági, unpublished work; 5-isopropyl: Czugler, Kálmán, Sági, Szabolcs & Ötvös, 1979; etc.) derivatives. Specifically the bond

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38400 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

angle C(4)–C(5)–C(6) is 5.7 (2)° greater than in the 5-alkyl analogues which can be attributed to the strong electron-withdrawing effect of F in agreement with the observations of Domenicano, Mazzeo & Vaciano (1976) for planar aromatic systems. This alteration is accompanied by a significant decrease of the bond angles at C(4) and C(6) and some visible shortening of C(4)–C(5) and C(5)–C(6) multiple bonds. The strain induced by the formation of the phosphate ring accounts for the altered bonding of the furanoside moiety. The shortening of C(4')–O(1') and the lengthening of C(1')–O(1') are particularly conspicuous.

The geometry of the phosphate ring does not differ basically from those reported up to now for cyclic 3',5'-phosphates (Sundaralingam, Haromy & Prusiner, 1982, and references therein). The mean of the four P–O distances whilst forming a rather distorted tetrahedron agrees well [1.547 (1) Å] with the expected value (Kálmán, 1971).

Conformation. Since the conformational parameters of 3',5'-cyclic nucleotides have recently been summarized by Sundaralingam, Haromy & Prusiner (1982) the relevant parameters of the title compound can be compared with them. Accordingly, the sugar ring exhibits a similar pucker to that of 5'-methylene-adenosine cyclic 3',5'-monophosphate (Sundaralingam & Abola, 1972). As shown by the lowest asymmetry factor, $fC_2 = 0.003$ Å (Kálmán, Czugler & Simon, 1982), inferred from the puckering parameters (Cremer & Pople, 1975) $Q = 0.422$ (3) Å, $\varphi = 306.5$ (4)°, the ribofuranose ring assumes an almost perfect half-chair conformation around a twofold axis which bisects C(1'). This form is quite near to a 3_4T pucker as defined by Altona & Sundaralingam (1972). The phosphate ring, as shown by the puckering parameters $Q = 0.596$ (3) Å, $\varphi = 215.0$ (20) and $\theta = 173.0$ (2)°, has a slightly flattened chair conformation with the sharpest pucker at the C(3')–C(4') *trans* junction [$\varphi' = 67.4$ (3)°]. One of the symmetry-independent molecules of uridine cyclic 3',5'-monophosphate (Coulter, 1969) possesses an amount of rotation about the glycosidic N(1)–C(1') bond ($\chi = 58.4^\circ$) closest to that of the title compound [50.3 (3)°] which falls in the *anti* range characteristic for the majority of pyrimidine nucleosides [cf. e.g. 5-alkyl-2'-deoxyuridines in Table 3 of Kálmán, Czugler & Simon (1982)]. The fact that 5-fluoro-2'-deoxyuridine displays a similar χ value (59.1°) suggests that the formation of the cyclophosphate ring has little effect on the conformation around the glycosidic linkage. It has an impact, however, on the orientation of N(1) relative to the sugar ring. Namely, in 5-fluoro-2'-deoxyuridine and in the 5-alkyl analogues it assumes a β -pseudo-equatorial position as shown by $\tau_1' = C(3')-C(2')-C(1')-N(1)$ falling in the range 145–160° (Kálmán, Czugler & Simon, 1982) while in the title compound, presumably due to the C_2 conformational symmetry of C(1'), it is pseudo-axial [$\tau_1' = 105.8$ (2)°].

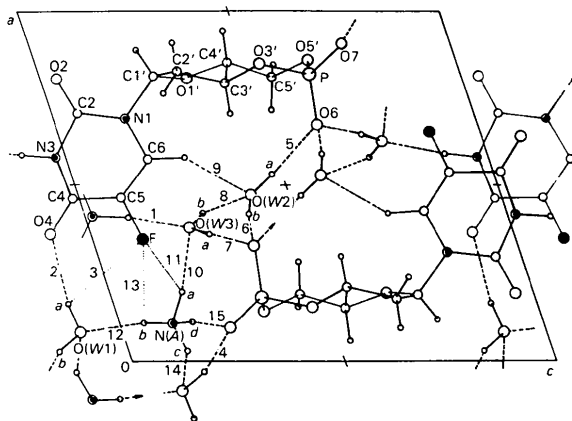


Fig. 2. Projection of crystal structure along [010] showing the network formed by 15 different D–H...A hydrogen bonds, numbered and labelled in accord with Table 3. (The H atoms taking part in the hydrogen bonds are distinguished by simple labels *a, b, c* and *d*.) These hydrogen bonds except 3, 11 and 13 which are made with F, and the three bifurcated H atoms, *Ha*, *Hb* and *H(W1)a*, are indicated by dashed lines. The two infinite hydrogen-bond helices formed around the twofold screw axes at $0, y, 0$ and $\frac{1}{2}, y, \frac{1}{2}$ are indicated by broken lines between *O(W1)* and *Hb*, and between *O(6)* and *H(W2)a*, respectively.

Hydrogen bonding. Analysis of non-bonded contacts less than the sum of the van der Waals radii taken from Allinger (1976) revealed 15 hydrogen bonds forming a three-dimensional network (Fig. 2) which is built up of 11 H atoms belonging to an N–H bond or a water molecule and furthermore to H(6). From this it follows that three H atoms should act as bifurcated donors. Their criteria have been recently summarized by Jeffrey (1982). In each case the bifurcated hydrogen bond employs the F atom on the second acceptor and an O atom as the primary acceptor resulting in a planar but asymmetric three-centred arrangement. Of the numerous van der Waals contacts involving F, only three listed in Table 3 could be regarded as hydrogen bonds if the van der Waals radii of Allinger (1976) for H and F are employed. One of them is still on the margin of the corrected (Hamilton & Ibers, 1968) F...H distance of 2.8 Å, indicating a weaker interaction than the other two in which *Ha* and *Hb* of the ammonium ion are taking part simultaneously. This presumably accounts for $Ha-N(A)-Hb = 111.6$ (38)° which is the second nearest to 109.5° in the distorted NH₄⁺ tetrahedron. Besides F, O(6) can also be regarded as a trifurcated acceptor. It links together H atoms of the symmetry-related *W(2)* molecules around the 2_1 ($\frac{1}{2}, y, \frac{1}{2}$) axis forming thus an infinite helix. The third H comes from *W(3)* situated a bit farther from the twofold axis. Four of the remaining five acceptor atoms, O(7), O(*W1*), O(*W2*) and O(*W3*), are bifurcated. O(7) maintains a strong hydrogen bond with the ammonium ion and a weaker one with the *W(1)* molecule, while O(*W1*) atoms form a second helix around 2_1 (0, *y*, 0) with the same symmetry-related NH₄⁺ ions *via* *Hb* and *Hc*

Table 3. Distances (Å) and angles (°) for the possible intermolecular hydrogen-bond contacts

No.	(xyz)	D...A	H...A	∠D-H...A	α†
1	N(3)—H(3)...O(W3)[1-x,y-½,-z]	2.832 (2)	1.89 (2)	168.8 (1.6)	65.7 (1.1)
2	O(W1)—H(W1)a*...O(4)[x,1+y,1+z]	2.980 (2)	2.12 (2)	177.6 (2.7)	
3	O(W1)—H(W1)a*...F[x,1+y,1+z]	3.272 (1)	2.84 (2)	112.8 (2.0)	
4	O(W1)—H(W1)b...O(7)[x-1,1+y,z]	2.910 (2)	2.12 (2)	161.5 (2.7)	
5	O(W2)—H(W2)a...O(6)[x,y,z]	2.935 (2)	2.09 (2)	164.1 (1.8)	81.3 (1.2)
6	O(W2)—H(W2)b...O(6)[1-x,y-½,1-z]	2.758 (2)	1.90 (3)	169.3 (2.1)	
7	O(W3)—H(W3)a...O(6)[x,y,z]	2.815 (2)	1.96 (4)	171.3 (3.1)	
8	O(W3)—H(W3)b...O(W2)[x,y,z]	2.811 (2)	1.97 (3)	158.9 (2.5)	
9	C(6)—H(6)...O(W2)[x,y,z]	3.331 (2)	2.42 (2)	147.5 (1.2)	87.4 (1.6)
10	N(A)—Ha*...O(W3)[x,y,z]	3.135 (2)	2.06 (2)	172.0 (1.8)	
11	N(A)—Ha*...F[x,y,z]	2.966 (2)	2.73 (3)	91.9 (2.7)	
12	N(A)—Hb*...O(W1)[x,y-1,z-1]	2.925 (2)	2.02 (3)	171.8 (2.1)	
13	N(A)—Hb*...F[x,y,z]	2.966 (2)	2.67 (2)	99.9 (2.5)	87.4 (1.6)
14	N(A)—Hc...O(W1)[-x,y-1,-z]	2.891 (2)	2.07 (3)	158.1 (3.1)	
15	N(A)—Hd...O(7)[1-x,y-½,1-z]	2.843 (2)	1.86 (3)	169.2 (2.0)	

* Bifurcated H atoms.

† Jeffrey (1982).

atoms. In addition to the OH...O bond donated by W(3), O(W2) also forms a medium strong CH...O contact (Jeffrey, 1982) with the C(6)—H(6) group. Finally, O(W3) is the acceptor of two NH...O bonds; the stronger is maintained by the N(3)—H(3) moiety, whilst the weaker comes from the ammonium ion *via* Ha. Thus each of the three water molecules is situated in the centre of a distorted tetrahedron formed by four hydrogen bonds. The remaining O(4) acts only as a single acceptor. It is worth noting that neither the three endocyclic O, nor O(2) takes part in these hydrogen bonds. Although each H...A and ∠DH...A parameter listed in Table 3 should be treated with caution, the mean parameters for the NH...O and OH...O bonds are worth mentioning:

	D—H	H...A	∠DH...A
NH...O	0.96 (2) Å	1.98 (3) Å	168.2 (2.1)°
OH...O	0.86 (3)	2.03 (3)	167.2 (2.5).

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