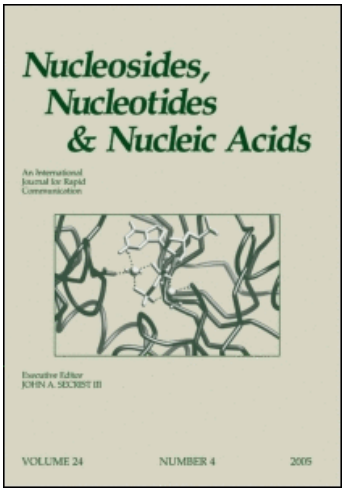

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Structure and Conformation of the Antiviral Agent 5-Methoxymethyl-2'-deoxyuridine

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STRUCTURE AND CONFORMATION OF THE ANTIVIRAL AGENT 5-METHOXYMETHYL-2'-DEOXYURIDINE

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Abstract - The three dimensional structure of the antiviral agent, 5-methoxymethyl-2'-deoxyuridine (MMdUrd) was determined by x-ray diffraction methods. MMdUrd crystallized in space group $P2_12_12_1$ of the orthorhombic system with $\underline{a}$ = 9.166(1)Å, $\underline{b}$ = 25.348(1)Å, $\underline{c}$ = 5.270(1)Å and Z = 4. The conformation of the glycosyl bond is anti (χ = 233.30), the deoxyribose ring has the C(2')-endo envelope conformation (^2E), the CH_2OH side chain has the g^+ conformation and the methoxy group at the C(5) position is on the same side of the pyrimidine plane as the O(4') oxygen. NMR spectroscopy was used to determine the conformation in solution. The spectra indicate that the sugar ring exists in a 60:40 equilibrium of the S- and N-states. The population of the three rotamers about the exocyclic C(4')-C(5') bond were estimated to be $g^+:t:g^-$::61%:31%:8%. The correlation of molecular conformation with antiviral activity is discussed.

INTRODUCTION

Pyrimidine nucleosides are useful therapeutic agents[1-6]. The biological effects elicited by these compounds are either due to the inhibition of key enzymes involved in

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nucleic acid biosynthesis, or due to the formation of fraudulent nucleic acids which are unable to function normally as a result of the incorporation of these pyrimidine antimetabolites[1-3,7,8]. For pyrimidine deoxyribonucleoside analogs, the nature of the C(5) substituent is an important factor in the determination of biological activity[1,2,4,6,9,10].

In the last ten years, several 5-substituted deoxyuridine derivatives with selective antiherpes activity have been reported[4-6,10-14]. In our laboratory, we have been evaluating antiviral activity of compounds related to 5-hydroxymethyl-2'-deoxyuridine (HMdUrd)[15-21]. This unique antimetabolite has been shown to replace 2'-deoxythymidine (dThd) in the DNA of certain lytic bacteriophages[22,23]. The rationale for the synthesis of compounds related to HMdUrd has been discussed previously[9]. HMdUrd is a potent cytotoxic agent[10,24,25], whereas its corresponding methyl derivative, 5-methoxymethyl-2'-deoxyuridine (MMdUrd) is a selective antiherpes agent[15-17,26,27]. Interestingly, higher ether homologues were devoid of antiviral activity as well as cytotoxicity[9,26]. The selective antiviral activity of MMdUrd results from its phosphorylation by virus-induced pyrimidine deoxyribonucleoside kinase (Viral-K)[28]. The nucleotide, after conversion to its corresponding triphosphate, is a selective competitive inhibitor of viral-induced DNA-dependent DNA polymerase[29]. Thus, insertion of a methyl group confers selectively of action against herpes simplex virus. Elongation of this side chain by only <u>one extra</u> CH_2 group (5-ethoxymethyl-2'-deoxyuridine) completely abolishes antiviral activity.

Three dimensional structural studies on nucleoside analogs with selective antiviral activity should provide useful information about the steric conformation required for pre-

ferential phosphorylation by Viral-K. The correlation of molecular conformation with biological activity should provide insight for rational development of antiviral drugs. In this paper, studies on the three dimensional structure of MMdUrd by X-ray crystallography and NMR spectroscopy are reported.

RESULTS AND DISCUSSION

X-ray structure

The data on the bond lengths and angles determined for MMdUrd are summarized in TABLES 1 and 2 and a stereoscopic view of the molecule is shown in FIG. 1. The bond angles in MMdUrd for C(2)-N(1)-C(1'), C(6)-N(1)-C(1') and N(1)-C(1')-O(4') are 117.3(2)°, 120.9(2)° and 108.4(2)°, respectively. These values are similar to those reported for dThd[30]. The corresponding values for HMdUrd are 118.7(4)°, 118.5(4)° and 104.7(4)°, respectively[31]. The selected torsion angles involving non-hydrogen atoms in MMdUrd are shown in TABLE 3. The conformation of the crystallographically-independent molecule about the glycosyl bond is anti and the glycosidic torsion angle O(4')-C(1')-N(1)-C(2), χ, has a value of 233.3°, which is within the normal range for pyrimidine-2'-deoxyribonucleosides with the anti conformation[32]. This value is similar to the torsion angle, χ = 236.4°, calculated for HMdUrd[31]. The conformation of the methoxy group can be expressed by the torsion angles C(5)-C(5,1)-O(5,2)-C(5,3), -114.2° and C(6)-C(5)-C(5,1)-O(5,2), -99.2°. For HMdUrd two possible values for the torsion angle C(6)-C(5)-C(5,1)-O(5,2), -78.4° and -2.5°, for the two disordered positions of O(5,2) have been reported by Birnbaum et al[31].

The deoxyribose ring has an envelope conformation in MMdUrd, dThd[30] and HMdUrd[31]. The conformations and the dis-

TABLE 1. Bond distances (Å)

N(1)-C(2)	1.392(3)*	C(5,1)-O(5,2)	1.438(3)
N(1)-C(6)	1.368(3)	O(5,2)-C(5,3)	1.414(5)
N(1)-C(1')	1.465(3)	C(1')-C(2')	1.512(4)
C(2)-O(2)	1.205(3)	C(1')-O(4')	1.429(3)
C(2)-N(3)	1.383(3)	C(2')-C(3')	1.507(4)
N(3)-C(4)	1.371(4)	C(3')-O(3')	1.435(3)
C(4)-O(4)	1.228(3)	C(3')-C(4')	1.527(4)
C(4)-C(5)	1.451(3)	C(4')-O(4')	1.452(3)
C(5)-C(5,1)	1.492(4)	C(4')-C(5')	1.505(4)
C(5)-C(6)	1.347(4)	C(5)-O(5')	1.408(4)

TABLE 2. Bond angles (deg)

C(2)-N(1)-C(6)	121.2(2)*	C(5,1)-O(5,2)-C(5,3)	113.1(3)
C(2)-N(1)-C(1')	117.3(2)	N(1)-C(6)-C(5)	123.7(2)
C(6)-N(1)-C(1')	120.9(2)	N(1)-C(1')-O(4')	108.4(2)
N(1)-C(2)-O(2)	123.4(2)	N(1)-C(1')-C(2')	114.8(2)
N(1)-C(2)-N(3)	114.2(2)	O(4')-C(1')-C(2')	105.5(2)
O(2)-C(2)-N(3)	122.4(2)	C(1')-O(4')-C(4')	108.6(2)
C(2)-N(3)-C(4)	127.5(2)	C(1')-C(2')-C(3')	101.4(2)
N(3)-C(4)-O(4)	120.3(2)	C(2')-C(3')-O(3')	106.8(2)
N(3)-C(4)-C(5)	115.1(2)	C(2')-C(3')-C(4')	103.1(2)
O(4)-C(4)-C(5)	124.6(2)	O(3')-C(3')-C(4')	111.6(2)
C(4)-C(5)-C(5,1)	120.1(2)	O(4')-C(4')-C(3')	106.2(2)
C(4)-C(5)-C(6)	118.1(2)	O(4')-C(4')-C(5')	108.8(2)
C(5,1)-C(5)-C(6)	121.7(2)	C(3')-C(4')-C(5')	115.1(2)
C(5)-C(5,1)-O(5,2)	113.1(3)	C(4')-C(5')-O(5')	110.9(3)

*Estimated standard deviation of the last digit is given in parentheses.

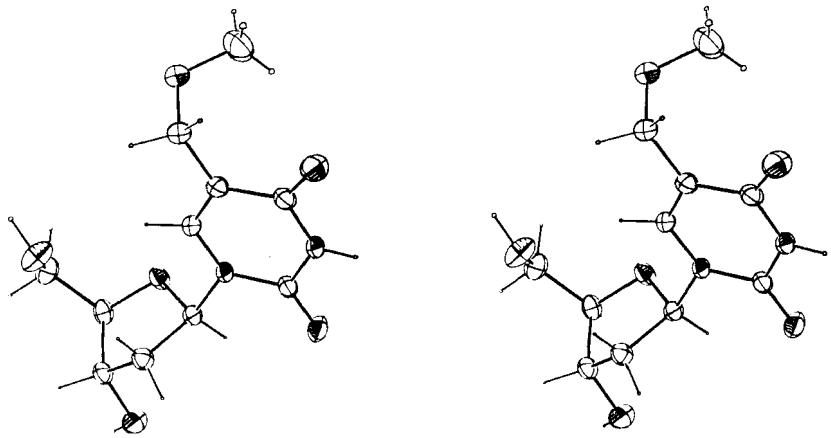

FIG. 1. Stereoscopic view of MMdUrd

TABLE 3. Selected torsion angles (deg)

C(1')-C(2')-C(3')-C(4')	-36.0
C(2')-C(3')-C(4')-O(4')	22.4
C(3')-C(4')-O(4')-C(1')	1.4
C(4')-O(4')-C(1')-C(2')	-24.8
O(4')-C(1')-C(2')-C(3')	38.0
O(5')-C(5')-C(4')-O(4')	-63.1
O(5')-C(5')-C(4')-C(3')	55.9
O(4')-C(1')-N(1)-C(2)	233.3
C(5)-C(5,1)-O(5,2)-C(5,3)	-114.2
C(6)-C(5)-C(5,1)-O(5,2)	-99.2
H(1')-C(1')-C(2')-H(2')	162
H(1')-C(1')-C(2')-H(2'')	36
H(2')-C(2')-C(3')-H(3')	-41
H(2'')-C(2')-C(3')-H(3')	82
H(3')-C(3')-C(4')-H(4')	-97
H(4')-C(4')-C(5')-H(5')	-62
H(4')-C(4')-C(5')-H(5'')	60

placements from the mean plane through the other four ring atoms are the following: C(2')-endo and 0.58Å for MMdUrd; C(3')-exo and 0.57Å for dThd; C(1')-exo and 0.42Å for HMdUrd. The values calculated for the two pseudorotational parameters for MMdUrd were P = 159.3° and τ_m = 39.6°[33].

A perspective drawing of the unit cell of MMdUrd is given in FIG. 2. There are two intermolecular hydrogen bonds per unit cell. The first is O(3')-H...O(4), the distances between O(4) and O(3'), H(03') are 2.803(3) and 2.08(3)Å respectively; the angle O(3')...O(4) is 154(3)°. The second hydrogen bond is O(5')-H...O(5,2), the distances between O(5,2) and O(5') and H(05') are 2.772(3) and 1.82(5)Å respectively; the angle O(5')-H...O(5,2) is 168(4)°. Birnbaum et al[31] reported an intramolecular hydrogen bond C(6)-H...O(4') in the crystal structure of HMdUrd with distances between O(4') and C(6) and H(6) of 2.786 and 2.27Å respectively. No such hydrogen bond was detected in MMdUrd.

NMR analysis

In order to correlate molecular conformation in aqueous solution with biological activity, the conformation of MMdUrd was also determined in D_2O by NMR spectroscopy. The ^1H and ^{13}C parameters are summarized in TABLES 4 and 5 respectively. The observed proton chemical shifts and coupling constants are similar to that of HMdUrd[31]. These results indicate that substitution of the hydroxy group in HMdUrd by a methoxy group has little effect on the conformation of the deoxyribofuranose ring in solution.

The conformation of the deoxyribose ring was determined by assuming an equilibrum between the N-state and the S-state shown in FIG. 3. Using the coupling constant values

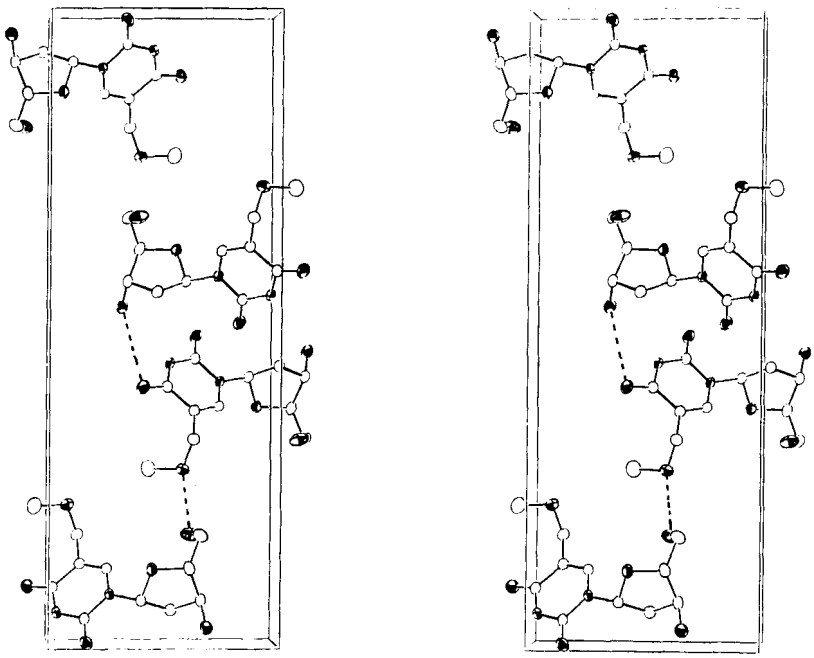

FIG. 2. Stereoscopic view of the packing of MMdUrd down the c axis of the unit cell.

for the N- and S-state calculated by the method of de Leeuw and Altona[34], the best fit with observed coupling constants was obtained with a 60% population in the S-state and 40% in the N-state (TABLE 4). These values are similar to the values reported for deoxyribonucleosides[32]. Thus, the pre ferred conformation for MMdUrd in solution is similar to the crystal structure as determined by X-ray analysis. Other investigators have proposed the possibility of an equilibrium between three conformational states[31]. However, at present, there is little evidence for the presence of minimum potential energy about the O(4')-endo conformation. Furthermore, it has been suggested that the pseudo-rotational barrier between the N-state and the S-state is con-

TABLE 4. Proton chemical shifts (ppm) and vicinal coupling constants (Hz) relative to internal TSP

Chemical Shifts		Coupling Constants		
			Obs.*	Calc.**
H(1')	6.27	$J_{1'2'}$	6.2	7.1
H(2')	2.37	$J_{1'2''}$	6.5	6.4
H(2'')	2.42	$J_{2'2''}$	-14.0	
H(3')	4.47	$J_{2'3'}$	6.1	5.8
H(4')	4.03	$J_{2''3'}$	4.4	4.9
H(5')	3.84	$J_{3'4'}$	4.0	4.2
H(5'')	3.76	$J_{4'5'}$	3.1	
H(6)	7.98	$J_{4'5''}$	4.6	
CH_2	4.23,4.25	$J_{5'5''}$	-12.2	
CH_3	3.36			

*Precision: 0.1-0.2 Hz.

**Calculations were performed assuming the phase angles, P = 18° for the S-state, P = 162° for the N-state and a puckering amplitude τ_m = 40°. The best fit with observed coupling constants was obtained with a 60% population in the S-state and 40% in the N-state.

TABLE 5. ^{13}C Chemical shifts (in ppm measured against a reference TMS capillary)

C(1')	85.50	C(2)	151.46
C(2')	38.94	C(4)	165.12
C(3')	70.28	C(5)	110.42
C(4')	86.76	C(6)	141.28
C(5')	60.99	CH_2	66.51
		CH_3	57.28

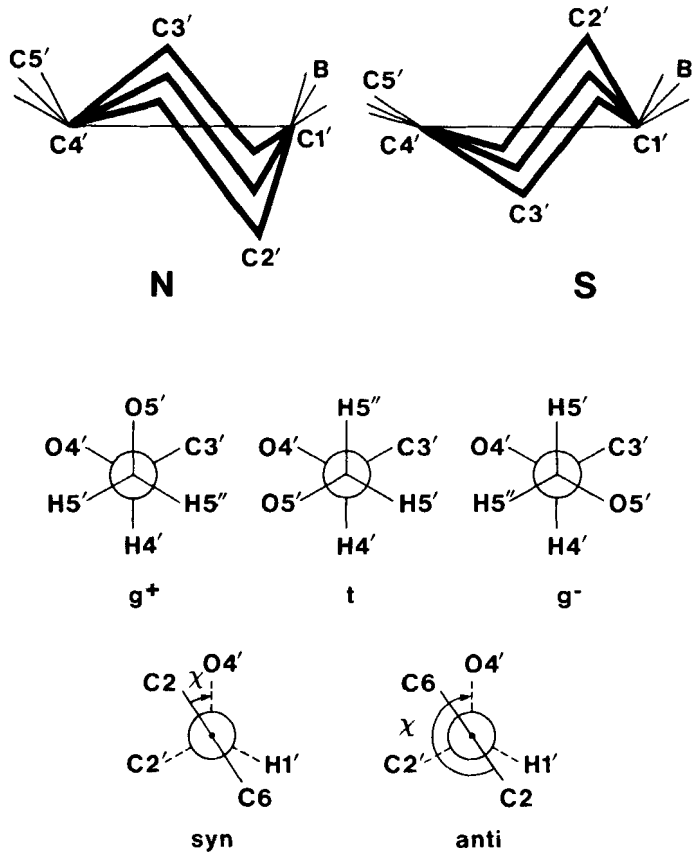

FIG. 3. Schematic drawing of the three major modes of conformational flexibility in pyrimidine-2'-deoxyribonucleosides. The χ convention[32], based on accepted chemical nomenclature, differs from the one frequently used where χ_{CN} was defined by O(4')-C(1')-N(1)-C(6):
$\chi = \chi_{CN} \pm 180$, viz. syn = 0 ± 90 and anti = 180 ± 90.

siderably lower in deoxyribonucleosides as compared to ribonucleosides[35]. Therefore, instead of assuming a three-point equilibrium, the averaging of coupling constants should be done over a wide range of pseudorotational states as suggested by Olson[35]. Unfortunately, reliable data on potential energy curves are not available for deoxy systems, thus

an approximation method of averaging was used. Nonetheless, the salient point is that the 60% population obtained for the S-state agrees, within a precision of 5%, with values reported for dThd, 5-ethyl-2'-deoxyuridine[36] and 5-hydroxymethyl-2'-deoxyuridine[31].

The population of the three rotamers (FIG. 3) about the exocyclic C(4')-C(5') bond was estimated from $J_{4'5'}$ and $J_{4'5''}$ data by the method of Haasnoot et al. because approximate methods using simple Σ relationships have a tendency to overestimate the population of the g^- state[37]. Accordingly, the g^+ mode contributes about 61% to the equilibrium mixture; while the t and g^- modes contribute 31% and 8% respectively. Thus the preferred conformation about the exocyclic C(4')-C(5') bond in solution is similar to that of the crystal structure (TABLE 3). In addition, these values also agree with the rotamer populations obtained when the same method of calculation is used on reported coupling constants for 5-substituted pyrimidine deoxynucleosides having the anti-glycosidic linkage[32]. To determine the conformation about the glycosidic bond the ^{13}C coupling constants were used. The $^3J_{C(2)-H(1')}$ value of 2.5 Hz observed for MMdUrd was similar to that of pyrimidine nucleosides having preference for the anti rotamer[32]. The anti-conformation was also inferred by comparison of ^1H and ^{13}C chemical shifts with reported values for syn and anti pyrimidine deoxyribonucleosides[38]. The two hydrogens in the methylene of the methoxymethyl side chain at C(5) have slightly different chemical shifts. In the crystal state, the methoxy group and O(4') oxygen of the deoxyfuranose ring are on the same side of the pyrimidine plane (FIG. 1). In contrast, HMdUrd has the same chemical shift for the two protons of the methylene group and in the solid state HMdUrd exhibits two conformations of

the hydroxymethyl group with little difference in energy between them[31]. These results suggest that there is a greater degree of rotational freedom about the exocyclic C(5)-C(5,1) bond in HMdUrd.

Conclusions

The differences in biological activity for dThd, HMdUrd, 5-ethyl-2'-deoxyuridine and MMdUrd are likely related to the nature of substituent at the 5-position of the pyrimidine ring because conformations with respect to the glycosidic linkage, the deoxyribofuranosyl ring and the exocyclic 5'-CH_2OH group are very similar. Attempts to correlate antiviral activity of 5-substituted-dUrd analogs to the electronic effect of the C(5) substituent revealed no systematic trend[31,39]. On the other hand, the selectivity of action of 5-substituted-dUrd compounds against herpes simplex virus appears to be related to the length of the side chain at C(5) of the pyrimidine ring. The optimum chain length of the substituent at the C(5) position seems to be three non hydrogen atoms for anti herpes activity. For example, 5-bromovinyl-2'-dUrd,[12] 5-propyl-2'-dUrd[13] and MMdUrd[15,16] are selective antiherpes agents. In contrast, 5-fluoro-dUrd[1], 5-iodo-dUrd[14], 5-trifluromethyl-dUrd[2] and HMdUrd[9,24,25] are cytotoxic agents. Since formation of nucleotide is an essential step for the biological activity of these antimetabolites, it appears that compounds which are readily phosphorylated by cytoplasmic dThd kinase exhibit cytotoxic activity, whereas selective antiherpes agents seem to be preferentially phosphorylated by the Viral-K[40]. The amino acid sequence of mammalian[41] and herpes simplex virus kinase[42] are significantly different, thus the conformation of their active centres should be different. This most

likely accounts for the substrate specificity of these anti-metabolites.

EXPERIMENTAL

MMdUrd, $C_{11}H_{16}O_6N_2$, was synthesized by the acid-catalyzed methylation of HMdUrd[16]. Initial crystallization trials with a saturated solution of MMdUrd in a mixture of ethyl acetate/cyclohexane produced very small crystals after a period of two years. Larger crystals were obtained by seeding the small crystals in freshly-prepared saturated solutions. The MMdUrd colorless crystals have space group $P2_12_12_1$ with $\underline{a}$ = 9.166(1)Å, $\underline{b}$ = 25.348(1)Å, $\underline{c}$ = 5.270(1)Å, Z = 4, observed density = 1.49g cm^{-3}, calculated density = 1.48g cm^{-3}. Quantitative data collection was done on an ENRAF-NONIUS CAD4F Diffractometer with an $\omega/2\theta$ scan and Ni-filtered copper radiation. Observational weights[43] for the reflections were derived from the formula: $W = (2I)^2/|Fo|^2 (T + (0.02I)^2 + r^2B)$, where I is the net intensity, $|Fo|$ is the observed structure amplitude, T is the total peak count, B is the sum of the background counts and r is the ratio of the peak-scan time to the total background - counting time (r = 2 for this data). The crystal was 0.125 x 0.025 x 0.075 mm in size and exhibited the forms {100}, {010}, and {001}. A total of 2242 reflections were collected out to Θ = 60°; 1002 unique reflections had Net I > $3\sigma(I)$ and the merging was 0.018 for 939 equivalent reflections, $R_I = (\sum_i |\bar{I}-I_i|)/\sum_i I_i$. The intensities were corrected for decay (maximum correction 1.10), for absorption (min./max. absorption correction = 1.01/1.07) and for Lorentz and polarization effects.

X-ray diffraction data collected on the MMdUrd crystal were processed by using the XRAY76 system[44]. The structure

was solved by employing the MULTAN80 package of computer programs[45]. Both figures of merit, ABSFOM & RESID were used to choose the best set of phases used in the structure determination. The values for ABSFOM and RESID were 1.0426 and 20.11, respectively.

The positions of the non-hydrogen atoms were determined from a calculated E map. Least-squares isotropic refinement gave an R value of 0.098. Anisotropic refinement was then carried out and gave an R value of 0.068. The positions of the hydrogen atoms were located by using a difference Fourier map. Finally, full-matrix least-squares refinement of anisotropic temperature factors for the non-hydrogen atoms and isotropic refinement for the hydrogen atoms converged to an R index of 0.027, $R = (\Sigma||F_o| - |F_c||/\Sigma|F_o|)$. The R_w was 0.030, $R_w = (\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$. The largest and average shift/error ratios for the parameters in the final cycle of refinement were 0.0127 and 0.0009, respectively. A stereoscopic representation of the molecule is shown in FIG. 1 and all final atomic coordinates are given in TABLE 6. The DEC2060 computer at the University of Saskatchewan was used to carry out all crystallographic computations. Preliminary report of this work has been published[46]. Supplementary material may be obtained from the publisher[47].

The NMR experiments were carried out using a Brucker CXP300 spectrometer. Spectra were recorded in the Fourier transform mode at 26°C. Solutions were made to a concentration of 0.2 M in D_2O. Chemical shifts were measured relative to internal trimethylsilyl propanesulfonic acid, sodium salt (TSP) for ^1H and relative to tetramethylsilane (TMS) in a concentric capillary for ^{13}C. ^1H NMR spectra were simulated with the aid of the LAOCOON III program and final coupling constants have a precision of 0.1-0.2 Hz.

TABLE 6. Atomic coordinates

ATOM	x/a	y/b	z/c	U or U^{eq} ($Å^2$)
N(1)	2648(2)*	845(1)	8640(5)	0.026
C(2)	1557(3)	468(1)	8920(5)	0.028
O(2)	1627(2)	107(1)	10404(4)	0.038
N(3)	375(2)	538(1)	7322(5)	0.028
C(4)	214(3)	912(1)	5461(6)	0.031
O(4)	-871(2)	910(1)	4094(5)	0.045
C(5)	1396(3)	1291(1)	5278(6)	0.029
C(5,1)	1315(3)	1731(1)	3403(6)	0.035
O(5,2)	857(2)	2222(1)	4514(5)	0.043
C(5,3)	-595(4)	2208(2)	5418(12)	0.067
C(6)	2552(3)	1230(1)	6830(5)	0.027
C(1')	3996(2)	767(1)	10086(6)	0.027
C(2')	5293(3)	594(1)	8521(6)	0.029
C(3')	6544(4)	768(1)	10177(6)	0.029
O(3')	6735(2)	366(1)	12069(4)	0.041
C(4')	5989(3)	1282(1)	11335(6)	0.030
O(4')	4408(2)	1260(1)	11185(4)	0.033
C(5')	6505(4)	1776(1)	10036(6)	0.041
O(5')	6148(3)	1768(1)	7438(5)	0.052
H(3)	-30(3)	29(1)	740(6)	0.042
H1(5,1)	230(3)	181(1)	296(6)	0.050
H2(5,1)	60(3)	163(1)	205(7)	0.043
H1(5,3)	-111(8)	222(2)	371(15)	0.181
H2(5,3)	-81(4)	253(2)	621(8)	0.079
H3(5,3)	-83(6)	195(2)	665(12)	0.137
H(6)	343(3)	144(1)	660(5)	0.031
H(1')	375(3)	52(1)	1136(6)	0.029
H(2')	534(3)	77(1)	705(6)	0.034
H(2'')	531(3)	21(1)	824(5)	0.034
H(3')	749(3)	82(1)	934(5)	0.029
H(4')	623(3)	129(1)	1305(6)	0.021
H(5')	760(4)	179(1)	1027(7)	0.061
H(5')	605(3)	211(1)	1071(6)	0.043
H(03')	740(3)	44(1)	1290(7)	0.042
H(05')	617(5)	213(2)	685(9)	0.092

$U_{eq} = (U_{11} + U_{22} + U_{33})/3$

*Estimated standard deviation of the last digit is given in parentheses. Nonhydrogen atoms x 10^4; hydrogen atoms x 10^3.

Calculations of coupling constants were performed assuming the phase angles P = 18° for the S-state, P = 162° for the N-state and a puckering amplitude τ_m = 40°.

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REFERENCES

1. C. Heidelberger in "Handbook of Experimental Pharmacology." Vol 38, Antineoplastic and Immunosuppressive Agents, Part II, A.C. Sartorelli and D.G. Johns, Eds. Springer Verlag, New York, N.Y. 1975, p. 192.
2. C. Heidelberger and D.H. King. Pharmac. Ther. 6, 427 (1979).
3. P. Calabresi and R.E. Parks, Jr. in "The Pharmacological Basis of Therapeutics," 6th Edition, A.G. Gilman, L.S. Goodman and A. Gilman, Eds. MacMillan Publishing Co, Inc., New York, N.Y. 1980, p. 1256.
4. E. DeClercq. Acta Microbiol. Acad. Sci. Hung. 28, 289 (1981).
5. E. DeClercq. Trends Pharmacol. Sci. 3, 492 (1982).
6. W.H. Prusoff and D.C. Ward. Biochem. Pharmacol. 25, 1233 (1976).
7. M.Y. Chu. Biochem. Pharmacol. 20, 2057 (1971).
8. W.B. Kremer. Ann. Int. Med. 82, 684 (1975).
9. J.B. Meldrum, V.S. Gupta and J.R. Saunders. Antimicrob. Agents Chemother. 6, 393 (1974).

10. G.T. Schiau, R.F. Schinazi, M.S. Chen and W.H. Prusoff. J. Med. Chem. 23, 127 (1980).

11. L.A. Babiuk, J.B. Meldrum, V.S. Gupta and B.T. Rouse. Antimicrob. Agents Chemother. 8, 643 (1975).

12. E. DeClercq, J. Descamps, P. De Somer, P.J. Barr, A.S. Jones and R.T. Walker. Proc. Natl. Acad. Sci. (USA) 76, 2947 (1979).

13. Y.C. Cheng, B.A. Domin, R.A. Sharma and M. Bobek. Antimicrob. Agents Chemother. 10, 119 (1976).

14. P.H. Fischer and W.H. Prusoff in "Handbook of Experimental Pharmacology." Vol. 61. P.E. Came and L.A. Caliguiri Eds. Springer-Verlag, New York, N.Y. 1982, p. 95.

15. N.K. Ayisi, V.S. Gupta, J.B. Meldrum, A.K. Taneja and L.A. Babiuk. Antimicrob. Agents Chemother. 17, 558 (1980).

16. V.S. Gupta. Drugs of the Future, 6, 32 (1981).

17. J.B. Meldrum, V.S. Gupta and L.A. Babiuk. Chemotherapy 26, 54 (1980).

18. N.K. Ayisi, J.B. Meldrum, A.L. Stuart and V.S. Gupta. Antiviral Res. 3, 161 (1983).

19. N.K. Ayisi, V.S. Gupta and L.A. Babiuk. Antiviral Res. 5, 13 (1985).

20. A.L. Stuart, N.K. Ayisi, G. Tourigny and V.S. Gupta. J. Pharm. Sci. 74, 246 (1985).

21. N.K. Ayisi, V.S. Gupta and L.A. Babiuk. Antiviral Res. (in press).

22. R.G. Kallen, M. Simon and J. Marmur. J. Mol. Biol. 5, 248 (1962).

23. S. Okubo, B. Strauss and M. Stodolsky. Virology 24, 552 (1964).

24. S. Waschke, J. Reefschalger, D. Barwolf and P. Langen. Nature, 255, 629 (1975).

25. J.B. Meldrum, V.S. Gupta, N.R. Lowes and A.R.P. Paterson. Toxicol. Appl. Pharmacol. 79, 423 (1985).

26. J.B. Meldrum, V.S. Gupta and C.E. Doige. Toxicol. Appl. Pharmacol. 53, 530 (1980).

27. N.K. Ayisi. In "Comparative Pharmacology and Toxicology of Selected Antiviral Drugs." Ph.D. thesis, University of Saskatchewan, Saskatoon, Canada. 1983.

28. G.A. Weinmaster. In "Investigation of Bovid Herpes Virus-1 Gene Products." M.Sc. thesis, University of Saskatchewan. 1981.

29. V.S. Gupta (unpublished results).

30. D.W. Young, P. Tollin, H.R. Wilson, Acta Crystallogr., Sect. B 25, 1423 (1969).

31. G.I. Birnbaum, R. Deslauriers, T.S. Lin, G.T. Shiau and W.H. Prusoff. J. Amer. Chem. Soc. 102, 4236 (1980).

32. D.B. Davies. Prog. Nucl. Magn. Reson. Spectr. 12, 136 (1978).

33. C. Altona and M. Sundaralingam. J. Amer. Chem. Soc. 94, 8205 (1972).

34. F.A.A.M. de Leeuw and C. Altona, J. Chem. Soc. Perkin II, 375 (1982).

35. W. Olson. J. Amer. Chem. Soc. 104, 270 (1982).

36. M. Remin, I. Ekiel and D. Shugar. Eur. J. Biochem. 53, 197 (1975).

37. C.A.G. Haasnoot, F.A.A.M. de Leeuw, H.P.M. de Leeuw and C. Altona. Rec. Trav. Chim. Phys. Bas. 98, 576 (1979).

38. J. Cadet, C. Taieb, M. Remin, W.P. Niemczura and F.E. Hruska. Biochem. Biophys. Acta, 608, 435 (1980).

39. E. DeClercq, J. Descamps, P.F. Torrence, E. Krajewska

and D. Shugar. Proc. Int. Congr. Chemother., Zurich, 10th, 352 (1978).

40. E. DeClercq and P.F. Torrence. J. Carb. Nucleo. Nucleoti. 5 (3), 187 (1978).
41. J.T. Kwoh and J.A. Engler. Nucleic Acid Res. 12, 3959 (1984).
42. H. Otsuka and S. Kit. Virology 135, 561 (1984).
43. F.R. Ahmed, S.R. Hall, M.E. Pippy and C.P. Huber. N.R.C. Crystallographic Programmes for the IBM/360 System, Accession Nos. 133-147. J. Appl. Crystallograph. 6, 309 (1973).
44. J.M. Stewart. The x-ray system of crystallographic computer programs. Computer Science Centre, University of Maryland, College Park, M.D. (1976).
45. P. Main, S.J. Fiske, S.E. Hall, L. Lessinger, G. Germain, J.P. DeClercq and M.M Wolfson. MULTAN-80. A System of Computer Programmes for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. University of York, England, 1980.
46. O.A.L. El-Kabbani, L.T.J. Delbaere and V.S. Gupta. Proc. Cand. Fed. Biol. Soc. 26, PA-259 (1983).
47. Anisotropic Thermal Parameters and Structure Amplitude Tables for MMdUrd can be obtained from the Journal Editorial Department, Marcel Dekker, Inc., 270 Madison Avenue, New York, N.Y., 10016.

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