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The Molecular Geometry of 2′,3′-Dideoxy-2′,3′-didehydroadenosine from an X-ray Crystal Structure Determination

By W. L. B. Hutcheon and M. N. G. James

Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2E1

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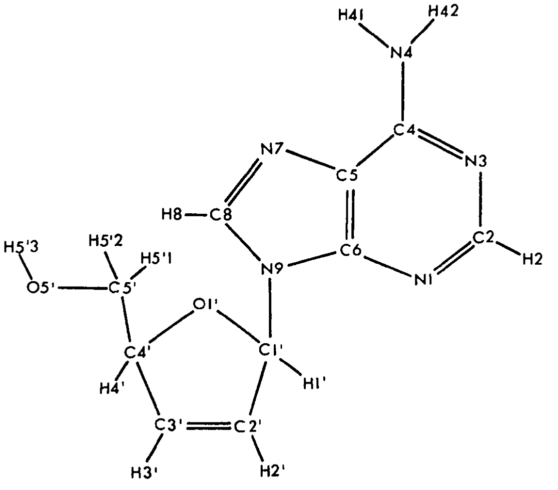
This paper describes the first determination of the molecular and crystal structures of a synthetic unsaturated furanosyl adenine nucleoside. The title compound, 2′,3′-dideoxy-2′,3′-didehydroadenosine (DDA), has the molecular formula $C_{10}N_5O_2H_{11}$ and crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell of dimensions: $a = 10{\cdot}035$ (2), $b = 13{\cdot}863$ (3) and $c = 7{\cdot}830$ (2) Å. The measured density of this crystalline form was 1·41 g cm^{-3} and the density calculated from the crystal data assuming $4(C_{10}N_5O_2H_{11})$ per cell is 1·42 g cm^{-3}. Intensity data (1860 reflexions) were measured on an automated four-circle diffractometer to $2\theta \le 60°$ using Mo $K\bar{\alpha}$ radiation. The structure was solved by symbolic addition and tangent refinement procedures but only after all triplets containing three reflexions from the same axial zone were removed from the $\sum_2$ listing. Full-matrix least-squares refinement of the atomic parameters converged to a conventional R index of 0·045. Bond lengths and angles in the adenine ring are within expected limits. The 2′,3′ double bond [length 1·317 (3) Å] distorts the geometry of the furanose ring which is best described in the envelope conformation, ^4E, with atom C(4′) 0·107 Å from the plane of the other four ring atoms. The crystal structure has base–base stacking of the adenine rings which are related by a 2_1 axis passing through the centres of these rings and resulting in a high degree of base overlap. In addition to the base stacking there is an intermolecular hydrogen bond from O(5′) to N(3) of the neighbouring 2_1 related adenine ring [O(5′)–N(3) = 2·744 (4) Å]. The stacks of 2_1 related molecules are connected by two additional hydrogen-bonding networks.

Introduction

Unsaturated furanosyl adenine nucleosides are of interest for a number of reasons. Angustmycin A is a nucleoside antibiotic which possesses significant antibacterial and antitumour activity and its chemical synthesis has been reported (McCarthy, Robins & Robins, 1968). This compound contains a C(4′)–C(5′) exocyclic double bond. Another antibiotic, blasticidin S, has been shown to consist of a 2′,3′ unsaturated pyranosyl derivative of cytosine (Otake, Takeuchi, Endo & Yonehara, 1965). A proposal that unsaturation at the 2′,3′ position in the ribofuranose ring is an intermediate in the biosynthesis of 2′-deoxyribonucleotides has appeared (Reichard, 1962). Further work however, has cast some doubt on this proposal and another mechanism in which the hydroxyl group on the 2′ carbon is replaced by a hydride ion has been proposed (Larsson, 1965). The first reported synthesis of a 2′,3′ unsaturated furanosyl purine has been described by McCarthy, Robins, Townsend & Robins (1966). Treatment of 3′-*O*-tosyl-2′-deoxyadenosine with sodium methoxide in dimethylformamide provides a direct synthesis of 2′,3′dideoxy-2′,3′-didehydroadenosine (DDA). The presence of the 2′,3′ double bond in the furanose ring places restrictions on the conformational flexibility of this ring. The ribofuranose nucleosides and nucleotides exhibit conformational restrictions about the glycosidic bond (φ_{CN}) and the C(4′)–C(5′) bond ($\varphi_{C4'-C5'}$) (Sundaralingam, 1969; Arnott, 1970). A recent analysis of the conformations of adenosine and guanosine (Kang, 1973) shows that sugar ring puckering is closely related to the conformationally allowed states for φ_{CN} and $\varphi_{C4'-C5'}$. In the present compound, DDA, the rotational barrier due to the ring puckering and the H2′ atom are removed. It is thus of interest to determine the molecular geometry of DDA and to examine the conformational angles φ_{CN} and $\varphi_{C4'-C5'}$ when these rotational barriers are obviated. The molecular structure and the atom numbering scheme used in this analysis are shown below.



Experimental

Suitable single crystals of DDA from acetone recrystallization were kindly supplied by Dr M. Robins of the Chemistry Department, University of Alberta. Preliminary oscillation and Weissenberg photographs showed *mmm* symmetry and systematic absences $h00$, $h=2n+1$; $0k0$, $k=2n+1$; $00l$, $l=2n+1$. The unit-cell dimensions were determined from accurately centred 2θ values of 12 reflexions in the range $35° < 2\theta < 45°$ ($\lambda = 0{\cdot}70926$ Å, Mo $K\alpha_1$) by the least-squares procedure described by Busing & Levy (1967). These values and other pertinent crystal data are contained in Table 1.

Table 1. *Crystal data for 2′3′-dideoxy-2′3′-didehydroadenosine*

Molecular formula		$C_{10}N_5O_2H_{11}$
M.W.		233·2
Crystal system		Orthorhombic
Space group		$P2_12_12_1$
Cell dimensions:	a	10·035 (2) Å
	b	13·863 (3)
	c	7·830 (2)
	V	1089·3 Å^3
d_{calc}		1·42 g cm^{-3}
d_{obs} (flotation in C_6H_5Cl and C_6H_5Br)		1·41 g cm^{-3}
$F(000)$		488 e
Crystal size		0·2 × 0·2 × 0·3 mm
Linear absorption coefficient (μMo $K\alpha$)		1·13 cm^{-1}
2θ range explored		$3° < 2\theta < 60°$
Total measurements		3565
Total unique reflexions		1860
Total reflexions [$I > 3\sigma(I)$]		1319 (71 %)
Temperature during data collection		22 ± 2°C

The intensity data were measured from a single crystal of DDA mounted with the c axis coincident with the spindle axis of a Picker FACS-1 diffractometer. Monochromated Mo $K\alpha$ radiation (48 kV, 16 mA) from a highly oriented graphite monochromator was used as the incident radiation. The reflexions were scanned in the θ–2θ mode with a scan speed of 2° min^{-1} and a basic peak width of 1·5° which was modified by 0·692 tan θ to allow for $\alpha_1\alpha_2$ splitting. Fixed position background counts were taken for 10 s at either end of the 2θ scan for each reflexion. Crystal decomposition and instrument stability were monitored by measuring three reflexions, 006, 2,10,0 and 651 after every 50 reflexions of the data run. No variation in the intensities of these three reflexions was observed. The intensity data were collected for the *hkl* and $\bar{h}kl$ octants and the equivalent reflexions subsequently merged to give 1860 unique measurements. The standard deviations of the intensities were computed from $\sigma(I) = (P + t^2B + k^2I^2)^{1/2}$, in which P is the total peak counts, B the total background count, t the ratio of time spent on the peak scan to total time on the background, $k = 0{\cdot}01$ and I the net intensity of the peak. Using the criterion $\sigma(I)/I < 0{\cdot}3$ a total of 1319 unique reflexions were used in the subsequent structure solution and refinement. The intensities were reduced to structure amplitudes by the application of the appropriate Lorentz and polarization factors for normal-beam equatorial geometry. The small value of the linear absorption coefficient (Table 1) and the small crystal size did not warrant absorption corrections.

Structure solution and refinement

The relative structure amplitudes were placed on absolute scale by the application of a scale factor of 0·25 derived from a Wilson statistical analysis. An overall isotropic temperature factor of 2·76 Å^2 was also derived from this analysis. The first attempt at a structure solution was done with the symbolic addition procedures of hand phasing (Karle & Karle, 1966). Initially a set of 30 reflexions was phased by hand and then expanded to include all reflexions with $|E| \geq 1{\cdot}5$ in tangent refinement (Karle & Hauptman, 1956). The resulting E map produced what appeared to be a fragment of a six-membered ring which could have been part of the adenine moiety. Further interpretation of this map was

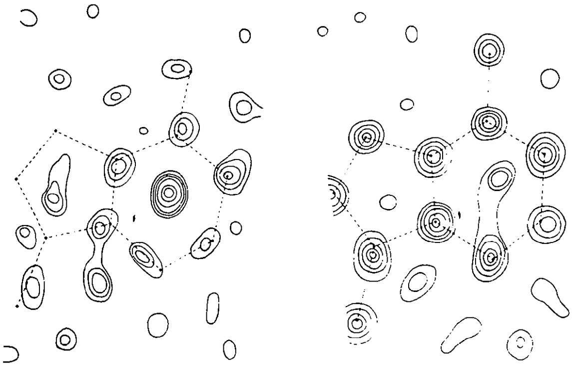

(*a*) (*b*)

Fig. 1. (*a*) Section of the E map containing the atoms of the adenine ring. The phases were derived as mentioned in the text and included the 'triple zero relations' in the $\sum_2$ search and tangent refinement. (*b*) Same section of the E map computed from tangent refinement omitting the 'triple zero relations'.

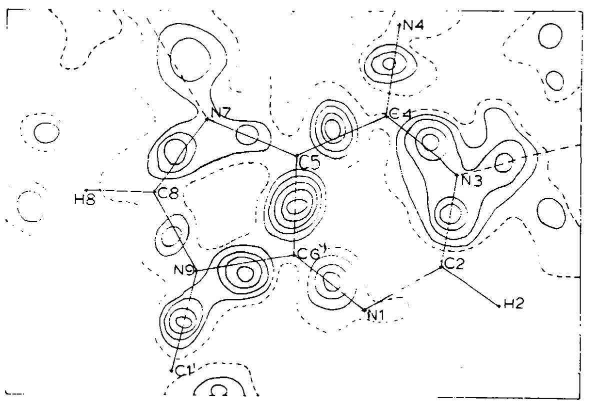


Fig. 2. The final difference map showing the section through the adenine ring. Contours are drawn at intervals of 0·05 e Å^{-3}. Negative contours shown using dotted lines. The chained lines show the direction of hydrogen bonding.

not possible. The tangent refinement was then repeated; in this cycle of phase determination all $\sum_2$ relations among three reflexions from the same (axial) zone were removed from the refinement (Karle, 1969; Delbaere & James, 1973). This procedure reduced the R_{Karle} value (Karle & Karle, 1966) from 0·27 to 0·19 and the 17 largest peaks on the resulting E map could be interpreted easily in terms of a plausible molecular model. Those sections through the adenine ring for each of the above mentioned E maps are shown in Fig. 1. In each map the final positions of the atoms are indicated. A comparison of these two maps shows vividly the importance of removing the 'triple zeros' especially in a structure such as this that contains a number of planar atomic groupings.

The atomic parameters taken from the second E map were refined initially with isotropic thermal motion parameters in three cycles of full-matrix least-squares calculations to an R index ($R=\sum||F_o|-k|F_c||/\sum|F_o|$) of 0·116. In this and subsequent least-squares cycles the function minimized was $\sum w(|F_o|-|F_c|)^2$; $\sqrt{w}=[2F_o/P+B+(0{\cdot}01I)^2]^{1/2}$. A difference map computed at this stage showed the positions of all hydrogen atoms in regions of positive density ranging from 0·4 to 0·8 e Å^{-3}. Four further cycles of full-matrix refinement, with the thermal motion of the non-hydrogen atoms described by anisotropic ellipsoids and the parameters of the hydrogen atoms included reduced the R index to 0·045 ($Rw\{\sum w(|F_o|-k|F_c|)^2/\sum w|F_o|^2\}^{1/2}=$ 0·066). The goodness of fit, $\{\sum w(|F_o|-k|F_c|)^2/(m-n)\}^{1/2}$, was 0·79. No atom parameter shifted by more than 0·17 of its associated standard deviation in the final cycle.

In the above computations the atomic form factors for C, N and O were those of Cromer & Mann (1968). The scattering curve for the hydrogen atoms was that

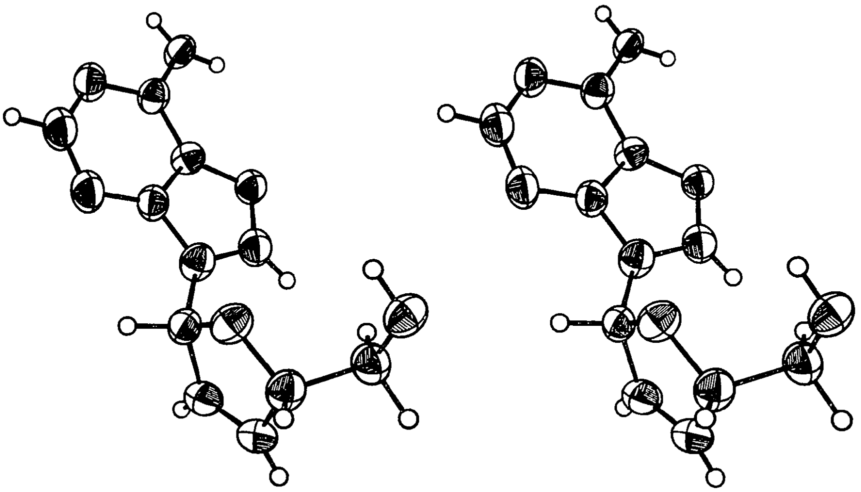


Fig. 3. Stereo drawing of DDA. Thermal ellipsoids show 50% probability.

Table 2. *Final atomic parameters and their standard deviations (in parentheses)*

The coordinates and temperature parameters of the non-hydrogen atoms have been multiplied by 10^4; the positional parameters for the hydrogen atoms by 10^3. The expression used for the anisotropic temperature factor is $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	3031 (2)	5727 (2)	4065 (6)	61 (2)	37 (1)	245 (9)	−9 (1)	18 (4)	12 (3)
C(2)	4178 (3)	5262 (3)	4124 (7)	56 (2)	42 (2)	237 (10)	−9 (2)	20 (4)	7 (4)
N(3)	4408 (2)	4317 (2)	4381 (6)	53 (2)	43 (1)	176 (8)	−2 (1)	15 (3)	5 (3)
C(4)	3361 (3)	3718 (2)	4604 (5)	51 (2)	35 (1)	134 (7)	−1 (1)	3 (3)	−5 (3)
N(4)	3585 (3)	2783 (2)	4885 (6)	54 (2)	33 (1)	231 (9)	4 (1)	9 (4)	10 (3)
C(5)	2074 (3)	4130 (2)	4557 (5)	48 (2)	31 (1)	126 (7)	−1 (1)	1 (3)	−2 (3)
C(6)	2011 (3)	5110 (2)	4286 (6)	54 (2)	33 (1)	143 (7)	1 (1)	14 (4)	6 (3)
N(7)	810 (2)	3739 (2)	4740 (5)	50 (2)	32 (1)	182 (7)	−4 (1)	6 (3)	−1 (2)
C(8)	16 (3)	4485 (2)	4575 (6)	52 (2)	39 (1)	169 (8)	−4 (1)	7 (4)	−7 (3)
N(9)	672 (2)	5336 (2)	4282 (5)	52 (2)	32 (1)	170 (7)	3 (1)	10 (3)	6 (2)
C(1′)	135 (3)	6321 (2)	4178 (6)	70 (2)	32 (1)	175 (8)	7 (2)	20 (4)	15 (3)
C(2′)	−1092 (4)	6404 (3)	3095 (7)	94 (4)	54 (2)	135 (8)	11 (2)	−2 (4)	26 (4)
C(3′)	−2080 (4)	6732 (3)	4037 (7)	76 (3)	54 (2)	176 (9)	19 (2)	2 (5)	28 (4)
C(4′)	−1657 (3)	6859 (2)	5848 (7)	67 (3)	32 (1)	179 (9)	10 (1)	7 (4)	1 (3)
O(1′)	−232 (2)	6658 (2)	5812 (5)	67 (2)	41 (1)	177 (7)	7 (1)	−2 (3)	−10 (2)
C(5′)	−2361 (4)	6157 (3)	7022 (6)	71 (3)	48 (2)	148 (8)	−5 (2)	7 (4)	−1 (3)
O(5′)	−1983 (3)	6243 (2)	8743 (4)	59 (2)	62 (2)	150 (6)	10 (2)	7 (3)	−8 (3)

Table 2 (*cont.*)

	x/*a*	*y*/*b*	*z*/*c*	*B*(Å^2)
H(2)	489 (5)	569 (3)	399 (8)	3·6 (10)
H(41)	294 (4)	245 (3)	500 (7)	2·7 (8)
H(42)	438 (6)	258 (4)	477 (9)	5·3 (13)
H(8)	−88 (3)	448 (3)	455 (6)	1·7 (6)
H(1′)	83 (6)	672 (4)	363 (8)	4·0 (11)
H(2′)	−109 (5)	627 (4)	199 (9)	4·1 (11)
H(3′)	−291 (6)	685 (4)	374 (8)	3·9 (10)
H(4′)	−171 (6)	750 (4)	636 (9)	4·5 (12)
H(5′1)	−337 (4)	635 (3)	702 (7)	2·5 (8)
H(5′2)	−215 (5)	551 (4)	661 (8)	3·8 (10)
H(5′3)	−123 (6)	603 (4)	879 (8)	3·5 (12)

given for the orbitally contracted model described by Mason & Robertson (1966). A final difference map is shown in Fig. 2 and there were no features greater than $\pm$0·27 e Å^{-3} present. The positive regions of difference electron density could be correlated with bonding electron density in the molecule which was not accounted for in the model.*

Results and discussion

The final positional and thermal parameters are contained in Table 2. The molecular conformation of the DDA molecule is shown by the stereoscopic drawing in Fig. 3. This drawing was made from the coordinates of the enantiomer that corresponds to the *β*-D-isomer, although in the present study the absolute configuration was not determined.

Fig. 4 contains the bond lengths and interbond angles for the DDA molecule. The e.s.d.'s in atomic positions were determined from the diagonal elements of the inverse matrix of the final least-squares cycle. The resulting e.s.d.'s in the derived bond lengths for the non-hydrogen atoms average 0·003 Å and for the bond angles involving these atoms 0·3°. Those e.s.d.'s for the molecular parameters involving hydrogen atoms are an order of magnitude larger (*i.e.* 0·03 Å and 3·0°).

(i) 2′,3′-*Dideoxy*-2′,3′-*didehydro*-*β*-D-*glycero-pentofuranose ring*

This compound represents the first structural study of an unsaturated pentofuranose ring and as expected the presence of the 2′,3′ double bond has a marked effect on the geometry of this ring.

The Csp^2–Csp^2 double bond has a length of 1·317 (3) Å and is significantly shorter than the normal C=C bond length of 1·335 (5) Å (Sutton, 1965). There is no apparent reason for this short bond but bonds of a similar length have been found in the butenolide moiety of gutierolide (1·316 Å) (Cruse, 1973) and in Δ-8,14-anhydrodigitoxigenin (1·317 Å) (Gilardi & Karle, 1970). The C(1′)–C(2′) and C(3′)–C(4′) bonds are similar to those of 1·493 Å in L-ascorbic acid (Azarnia, Berman & Rosenstein, 1972) and *d*-iso-ascorbic acid (Hvoslef, 1968). The carbon–oxygen bonds show the same pattern of unequal bond lengths [1·411 (3) Å and 1·457 (3) Å] found in many ribose rings (Sundaralingam & Jensen, 1965) and in butenolide moieties (Gilardi & Karle, 1970; Cruse, 1973).

The bond angles at C(2′) and C(3′) show a significant deviation from 120°. The values of 111·1° and 109·1° respectively [Fig. 4(*b*)] are similar to those in L-ascorbic acid (Hvoslef, 1968) and in the butenolide ring of ouabain (Cruse, 1973) and is due to ring cyclization.

(ii) *Torsion angles*

The conformation of the unsaturated pentofuranose ring is ^4E with four of the atoms [C(1′), C(2′), C(3′)

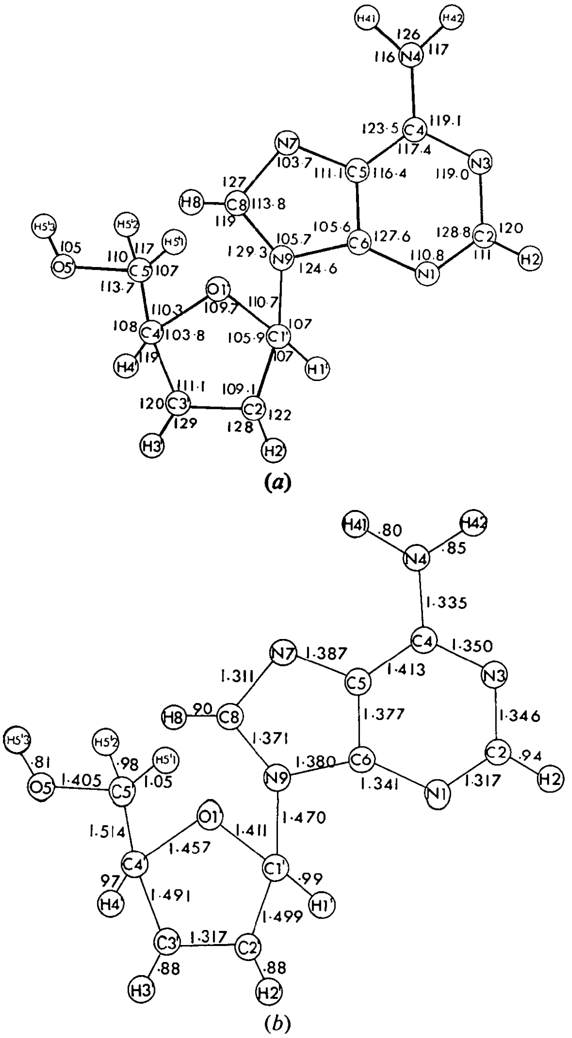


Fig. 4. (*a*) Bond lengths and (*b*) angles in DDA. Standard deviations in bond lengths are $\pm$0·003 Å, in bond angles $\pm$0·3°. Deviations are 10 times greater when a hydrogen atom is involved.

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* The structure factor tables have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30419 (10 pp.). Copies may be obtained from The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

and O(1′)] being planar (maximum deviation 0·006 Å, Table 3). The fifth atom C(4′) is 0·107 Å out of this plane and on the same side of the plane as atom C(5′). This deviation is much smaller than ~0·6 Å found in many ribofuranose rings (Sundaralingam, 1969).

Table 3. *Least-squares planes for the adenine and unsaturated pentofuranose rings*

Deviation of atoms from least-squares planes

$$px+qy+rz=s$$

Adenine		Pentofuranose ring	
N(1)*	−0·009 Å	C(1′)*	−0·006 Å
C(2)*	0·004	C(2′)*	0·006
N(3)*	0·000	C(3′)*	−0·004
C(4)*	0·000	O(1′)*	0·004
C(5)*	0·000	C(4′)	−0·107
C(6)*	0·004	H(2′)	0·021
N(7)*	−0·001	H(3′)	−0·036
C(8)*	−0·005	$p=$	2·5722
N(9)*	0·007	$q=$	12·9028
N(4)	−0·007	$r=$	2·0423
C(1′)	−0·105	$s=$	9·3828
H(41)	0·036	$\chi^2=$	3·60
H(42)	0·106		
$p=$	−0·4189		
$q=$	−2·2129		
$r=$	7·7227		
$s=$	3·2006		
$\chi^2=$	9·50		

* Atoms included in least-squares plane calculation.

The conformation about the C(4′)–C(5′) bond is *gauche–trans* ($\varphi_{OO}=62{\cdot}9°$, $\varphi_{OC}=-178{\cdot}3°$) rather than the preferred *gauche–gauche* (Sundaralingam & Jensen, 1965). A similar conformation is found in tubercidin (Abola & Sundaralingam, 1973) ($\varphi_{OO}=62{\cdot}0$, $\varphi_{OC}=-178{\cdot}3°$) and in *N*-(*β*-D-ribofuranosyl)imidazole (James & Matsushima, 1973) ($\varphi_{OO}=64{\cdot}3°$, $\varphi_{OC}=-179{\cdot}6°$). This conformation appears to be adopted to facilitate hydrogen bonding, noticeably that between O(5′) and N(3).

The torsion angle φ_{CN} C(8)–N(9)–C(1′)–O(1′) is +72·9° and has an *anti* conformation. This value of +72·9° is larger than normally found for purine nucleosides and nucleotides (Sundaralingam, 1969; Lai & Marsh, 1972) of 4° to 40°. Since H(2′) is now in the plane of the unsaturated pentofuranose ring rather than above it, there is little steric hindrance between H(2′) and H(8) [H(2′)–H(8) 3·20 (7) Å] allowing essentially free rotation about the N(9)–C(1′) bond. The conformation observed in this crystal structure is dictated more by hydrogen bonding than by steric hindrance of the adenine ring and the puckering of ribose ring.

(iii) *Adenine ring*

The bond angles and lengths in the adenine ring agree within experimental uncertainties with those found in earlier structures containing a neutral adenine ring (Lai & Marsh, 1972, and references cited therein). The nine non-hydrogen atoms of the adenine ring are coplanar ($\chi^2=9{\cdot}50$, Table 3) with the largest deviation from the plane being N(1) at 0·009 Å. The amino group nitrogen N(4) is within 3σ of the plane although its hydrogens are displaced out of the plane toward the hydrogen-bond acceptors O(5′) and N(7).

(iv) *Intermolecular hydrogen bonding and crystal packing*

The molecules stack in the crystal with a high degree of overlap of the adenine rings (Fig. 5). Each ring is related to others in the stack by a twofold screw axis passing through the adenine ring and approximately perpendicular to it. The rings are slightly tilted with

Table 4. *Hydrogen-bond distances and angles*

Type of bond	Distance (Å)			Angle	Symmetry
A–H···*B*	*A*···*B*	*A*–H	H···*B*	*A*–H···*B*	of acceptor
–N(4)–H(42)···N(7)	3·085 (4)	0·85 (3)	2·36 (6)	143°	$2_1\|\mathbf{a}$
–N(4)–H(41)···O(5′)	2·880 (5)	0·80 (3)	2·16 (5)	149	$2_1\|\mathbf{b}$
–O(5′)–H(5′3)···N(3)	2·744 (4)	0·81 (3)	1·95 (6)	166	$2_1\|\mathbf{c}$

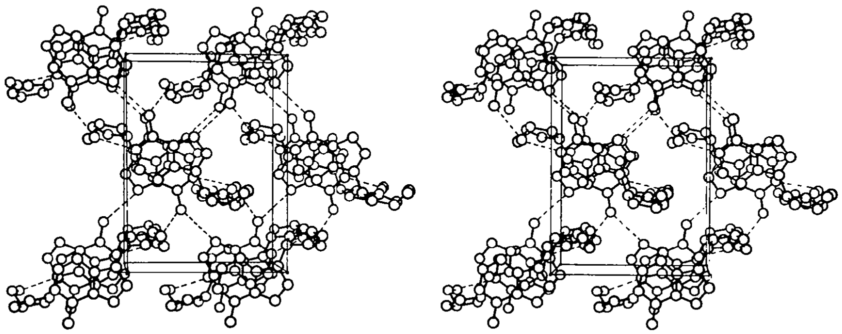

Fig. 5. Stereo drawing of the molecular packing in the cell. Hydrogen bonds are indicated by dotted lines. The view is down the *c* axis with the *a* axis horizontal and the *b* axis down the page.

respect to this axis (7·2°) and have an interbase separation of 3·91 Å. Using potential energy calculations, Motherwell & Isaacs (1972) predict an energy minimum when there is complete overlap of the purine rings. Usually steric hindrance and hydrogen bonding involving the sugar moieties of nucleosides and nucleotides prevent this complete overlap. In this structure however, the almost flat pentofuranose ring and the lack of hydroxyl groups at the 2′ and 3′ positions greatly reduce steric hindrance allowing a much greater overlap of the base rings. In addition to base–base interactions, there is hydrogen bonding between the molecules in the stack. A bond is formed between O(5′) of one molecule and N(3) of the adenine ring in the molecule directly below it in the stack (Table 4).

These columns are held together by two additional networks of hydrogen bonds. A bond is formed between N(4) and O(5′) of a symmetry-related ($2_1//b$) molecule. The oxygen atom O(5′) is thus both a hydrogen-bond donor and acceptor. Finally there is a third hydrogen-bond network between N(4) and N(7) of the molecules related by the 2_1 axis parallel to *a*. This packing is illustrated in Fig. 5, hydrogen bonds being designated by dotted lines. All the hydrogen bonds are bent (Table 4) ranging from 166° for N(3)···H(5′3)–O(5′) to 143° for N(4)–H(42)···N(7), a value slightly greater than the maximum deviation of 30° from linearity as suggested by Donohue (1968). All available nitrogens and oxygens, except O(1′) and N(1), are involved in hydrogen bonding.

A final point regarding the hydrogen bonding observed in this structure involves those hydrogen bonds to the adenine ring. In each adenine ring of the structure, atom N(4) acts as a hydrogen-bond donor in two cases and atom N(7) accepts a hydrogen bond. This bonding pattern for the adenine ring resembles that observed first by Hoogsteen (1963) and referred to as the Hoogsteen base-pairing. The Watson–Crick base-pairing involves the atoms N(3) and N(4) of adenine and this is also observed in the present structure with N(3) acting as an acceptor of a hydrogen bond from O(5′).

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Computations were done with the X-RAY 70 system of programs (Stewart, Kundell & Baldwin, 1970) modified by one of us (WLBH) to run on the Michigan Terminal System developed for the IBM 360/67 at the University of Alberta. Drawings were done using C. K. Johnson's program *ORTEP* (1965).

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