

The Structure of Cordycepin

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Abstract. $C_{10}H_{13}N_5O_3$, $P2_1$, $a = 4.589(4)$, $b = 7.497(5)$, $c = 16.073(10)$ Å, $\beta = 85.06(10)^\circ$, $V = 550.80$ Å³, $Z = 2$, $d_c = 1.514$ Mg m⁻³, $R = 0.072$ for 1013 reflexions. The molecule is in the *anti* conformation, the sugar ring pucker is C(3')-*endo* and the conformation about C(4')–C(5') is *gauche-trans*.

Introduction. The mould *Cordyceps militaris* secretes a substance which inhibits the growth of several bacteria (Cunningham, Hutchinson, Manson & Spring, 1951; Rottman & Guarino, 1964), increases the survival time of mice with Ehrlich ascites tumours (Jagger, Kredich & Guarino, 1961) and inhibits the growth of human tumour cells in culture (Rich, Meyers, Weinbaum, Cory & Suhadolnik, 1965). This substance, called cordycepin, is the nucleoside antibiotic 3'-deoxyadenosine (Fig. 1). Its mode of action is by inhibition of RNA synthesis. It is incorporated as 3'-deoxyadenosine triphosphate at the 3' end of the RNA molecule and this prevents further elongation (Suhadolnik, 1979).

From the structural point of view it was of interest to compare the conformation of cordycepin with other nucleosides, in particular 2'-deoxyadenosine, adenosine and adenine arabinofuranoside.

Cordycepin was purchased from Calbiochem and crystals were obtained by evaporation from aqueous solution. Weissenberg photographs showed that the crystals were monoclinic, with systematic absences consistent with the space groups $P2_1$ and $P2_1/m$. The asymmetry of the molecule establishes the space group

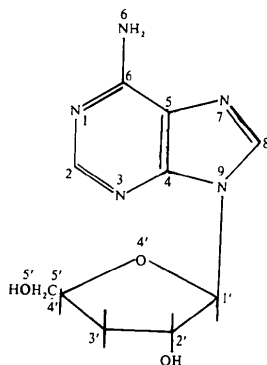


Fig. 1. Cordycepin molecule.

as $P2_1$. The intensities of 1333 unique reflexions in the range up to $2\theta = 55^\circ$ were measured on a Stoe two-circle diffractometer with graphite-monochromatized Mo $K\alpha$ radiation. Of these, 1013 with $F_o > 3.5\sigma(F_o)$ were used for the structure analysis. Most of the data were obtained from a crystal mounted along b , on layer planes $k = 0$ to 7, although one layer plane from a crystal mounted along a was used for scaling. Difficulty in obtaining good crystals for other than b -axis data is responsible for the rather high e.s.d.'s in the y coordinates. Lorentz and polarization but no absorption corrections were applied.

The orientation of the plane of the purine base was determined by evaluating the $I(\theta, \varphi)$ function of Tollin & Cochran (1964), with the largest 300 sharpened reflexions and a disc radius of 4 Å. The azimuthal orientation of the purine base within the plane was determined from the Patterson section of orientation (θ, φ) and from an $I(\theta_1, \theta_2, \theta_3)$ rotation function (Munns, 1971). Both methods gave essentially identical results. The position of the adenine base relative to the symmetry axis was determined by evaluating the Q function (Tollin, 1966). The adenine atoms were used to calculate phases and to obtain an electron density map which revealed the positions of the sugar atoms.

The structure was refined by block-diagonal least squares. All structure factors were assigned unit weights and the non-hydrogen atom coordinates and individual isotropic temperature factors were refined. R dropped to 0.11. A difference map calculated at this stage contained peaks, most of which were interpretable as H atoms.

With fixed H atom coordinates and fixed isotropic temperature factors of 0.05, the positional and anisotropic thermal parameters of the non-hydrogen atoms were refined. R fell to 0.0715* and in the last cycle the shifts in the positional and thermal parameters were $< 0.18\sigma$ and 0.10σ , respectively.

* Lists of structure factors, anisotropic thermal parameters and H atom positional parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35323 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion. Coordinates of the non-hydrogen atoms are given in Table 1. Bond lengths and angles are listed in Tables 2 and 3.

The adenine base is essentially planar and the maximum deviation of a ring atom is 0.025 Å (Table 4). The bond lengths and angles are in good agreement

Table 1. *Fractional coordinates ($\times 10^4$) of the non-hydrogen atoms with e.s.d.'s*

	x	y	z
N(1)	3555 (15)	-2541 (39)	4355 (4)
C(2)	5736 (14)	-2844 (38)	3745 (5)
N(3)	6782 (14)	-1738 (40)	3153 (4)
C(4)	5557 (17)	-158 (39)	3231 (5)
C(5)	3311 (17)	332 (40)	3829 (4)
C(6)	2307 (18)	-958 (40)	4408 (4)
N(6)	168 (18)	-617 (40)	5000 (5)
N(7)	2562 (16)	2076 (39)	3713 (4)
C(8)	4290 (17)	2615 (39)	3076 (4)
N(9)	6155 (13)	1319 (38)	2761 (3)
C(1')	8464 (17)	1512 (40)	2068 (4)
C(2')	7369 (20)	898 (40)	1240 (5)
C(3')	6509 (18)	2615 (40)	868 (5)
C(4')	8552 (16)	3962 (40)	1185 (4)
O(4')	9206 (11)	3266 (38)	1994 (3)
O(2')	9786 (13)	144 (38)	738 (4)
C(5')	7421 (22)	5800 (40)	1300 (6)
O(5')	9464 (15)	6972 (39)	1602 (4)

Table 2. *Bond lengths (Å) for the non-hydrogen atoms with e.s.d.'s*

N(1)–C(2)	1.358 (10)	C(6)–N(6)	1.332 (10)
C(2)–N(3)	1.321 (11)	N(9)–C(1')	1.477 (8)
N(3)–C(4)	1.312 (11)	C(1')–C(2')	1.533 (12)
C(4)–C(5)	1.396 (10)	C(2')–C(3')	1.487 (13)
C(5)–C(6)	1.393 (12)	C(3')–C(4')	1.497 (12)
C(6)–N(1)	1.317 (12)	C(4')–O(4')	1.456 (8)
C(5)–N(7)	1.369 (12)	O(4')–C(1')	1.361 (11)
N(7)–C(8)	1.304 (9)	C(2')–O(2')	1.430 (10)
C(8)–N(9)	1.363 (10)	C(4')–C(5')	1.478 (13)
N(9)–C(4)	1.355 (11)	C(5')–O(5')	1.402 (12)

Table 3. *Bond angles (°) for the non-hydrogen atoms with e.s.d.'s*

C(6)–N(1)–C(2)	119.1 (7)	C(4)–N(9)–C(1')	126.7 (7)
N(1)–C(2)–N(3)	127.9 (9)	C(8)–N(9)–C(1')	126.7 (7)
C(2)–N(3)–C(4)	111.8 (7)	N(9)–C(1')–C(2')	111.0 (6)
N(3)–C(4)–C(5)	126.0 (8)	N(9)–C(1')–O(4')	108.6 (7)
C(4)–C(5)–C(6)	117.3 (8)	O(4')–C(1')–C(2')	108.2 (7)
C(5)–C(6)–N(1)	117.7 (7)	C(1')–C(2')–C(3')	102.0 (7)
N(3)–C(4)–N(9)	128.3 (7)	C(2')–C(3')–C(4')	104.6 (7)
C(6)–C(5)–N(7)	133.0 (8)	C(3')–C(4')–O(4')	104.2 (7)
C(5)–N(7)–C(8)	105.1 (7)	C(4')–O(4')–C(1')	110.8 (6)
N(7)–C(8)–N(9)	113.0 (7)	C(1')–C(2')–O(2')	108.2 (7)
C(8)–N(9)–C(4)	106.6 (6)	C(3')–C(2')–O(2')	109.6 (7)
N(9)–C(4)–C(5)	105.7 (7)	C(3')–C(4')–C(5')	116.6 (7)
C(4)–C(5)–N(7)	109.7 (7)	O(4')–C(4')–C(5')	108.6 (7)
N(1)–C(6)–N(6)	120.6 (8)	C(4')–C(5')–O(5')	112.9 (8)
C(5)–C(6)–N(6)	121.7 (9)		

Table 4. *Deviations (Å) of atoms from least-squares planes, and torsion angles (°)*

The e.s.d.'s are *ca* 0.01 Å and 0.8°. The atoms marked with an asterisk were used to calculate the mean planes. *X*, *Y* and *Z* are coordinates, in Å, relative to *a*, *b* and *c**.

(1) Purine ring

$$3.3724X + 2.1994Y + 10.8077Z - 5.3373 = 0$$

N(1)*	0.009	C(6)*	-0.006
C(2)*	0.019	N(6)*	-0.013
N(3)*	-0.025	N(7)*	-0.004
C(4)*	-0.006	C(8)*	0.009
C(5)*	-0.009	N(9)*	0.013
C(1')	0.085		

(2) Sugar ring

$$4.1457X - 1.7467Y - 4.5086Z - 2.3294 = 0$$

C(1')*	-0.017	O(4')*	0.018
C(2')*	0.010	O(2')	1.370
C(3')*	-0.479	C(5')	-0.852
C(4')*	-0.010	O(5')	-0.346

Torsion angles

O(4')–C(1')–N(9)–C(4)	205.6
O(5')–C(5')–C(4')–C(3')	180.0
O(5')–C(5')–C(4')–O(4')	62.4

with those found in related structures containing adenine (Voet & Rich, 1970).

The sugar ring is puckered so that C(3') is *endo*, *i.e.* lying out of the mean plane through the other sugar ring atoms on the same side as C(5') (Table 4). The orientation of C(5')–O(5') with respect to the sugar ring is *gauche* relative to C(4')–O(4') and *trans* relative to C(4')–C(3') (Table 5).

The torsion angle describing the rotation of the sugar ring about the glycosyl bond, $\chi_{\text{CN}}[\text{O}(4')\text{--C}(1')\text{--N}(9)\text{--C}(4)]$, is 205.6°. The molecule is thus in the *anti* conformation like the majority of nucleosides and nucleotides in the solid state. The torsion angle is similar to that in adenine arabinofuranoside, and slightly larger than those in 2'-deoxyadenosine and adenosine (Table 5).

The C(3')-*endo* sugar pucker is one of the favoured conformations found in nucleosides and nucleotides. The same kind of pucker is observed in adenosine and adenine arabinofuranoside, whereas that in 2'-deoxy-

Table 5. *A comparison of the conformational parameters of cordycepin with those of related nucleosides (angles in deg)*

	2'-dA	A	araA	3'-dA
$\chi_{\text{CN}}[\text{O}(4')\text{--C}(1')\text{--N}(9)\text{--C}(4)]$	182.7	188.6	204.8	205.6
$\theta[\text{O}(5')\text{--C}(5')\text{--C}(4')\text{--O}(4')]$	68.1	60.1	70.5	62.4
$\theta[\text{O}(5')\text{--C}(5')\text{--C}(4')\text{--C}(3')]$	186.9	176.9	55.1	180.0
Sugar pucker	C(3')- <i>exo</i>	C(3')- <i>endo</i>	C(3')- <i>endo</i>	C(3')- <i>endo</i>

2'-dA: 2'-deoxyadenosine (Watson, Sutor & Tollin, 1965); A: adenosine (Lai & Marsh, 1972); araA: adenine arabinofuranoside (Chwang & Sundaralingam, 1974); 3'-dA: 3'-deoxyadenosine (present study).

adenosine is the rather unusual C(3')-*exo* pucker (Table 5).

The *gauche-trans* conformation about C(4')-C(5'), although less favoured than the *gauche-gauche* when all nucleosides and nucleotides are considered, is observed also in 2'-deoxyadenosine, adenosine and the related adenosine analogue tubercidin (Stroud, 1973; Abola & Sundaralingam, 1973). Quantum-mechanical calculations of the preferred conformations of C(3')-*endo* nucleosides (Pullman & Saran, 1976) show that for an isolated molecule there is a global energy minimum corresponding to the *gauche-gauche* conformation, when the torsion angle C(4')-C(5')-O(5')-H is 180°. However, there is a local minimum for the *gauche-trans* conformation, only about 2.1 kJ mol⁻¹ above the global minimum, when the torsion angle involving the H atom is in the range 270-310°. In the present structure, the torsion angle is 242° which corresponds to an energy only slightly greater than 2.1 kJ mol⁻¹ above the global minimum. The energy calculations do not take into account any intermolecular interactions which may affect the conformation in the crystalline state.

The arrangement of the molecules in the crystal and the hydrogen-bonding scheme are shown in Fig. 2. Hydrogen-bond lengths and angles are listed in Table 6. All available H atoms participate in hydrogen bonding.

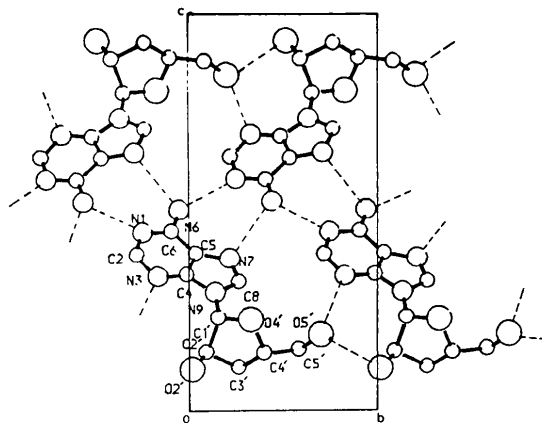


Fig. 2. A projection of the structure viewed along *a*.

Table 6. *Hydrogen-bond lengths (Å) and angles (°) with e.s.d.'s*

N(6)-H...N(1) ^a	3.001 (10)	C(6)-N(6)-N(1)	139.1 (8)
N(6)-H...N(7) ^b	2.897 (10)	C(6)-N(6)-N(7)	130.0 (8)
O(2')-H...O(5') ^c	2.751 (10)	C(2')-O(2')-O(5')	93.0 (8)
O(5')-H...N(3) ^d	2.852 (12)	C(5')-O(5')-N(3)	105.3 (8)

Symmetry code

(a)	-x, $\frac{1}{2} + y, 1 - z$	(c)	x, -1 + y, z
(b)	-x, $-\frac{1}{2} + y, 1 - z$	(d)	x, 1 + y, z

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