

The Crystal and Molecular Structure of 8,2'-Cycloadenosine Trihydrate

BY S. NEIDLE,* G. L. TAYLOR AND P. C. COWLING

Department of Biophysics, University of London, King's College, 26–29 Drury Lane, London WC2B 5RL, England

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Abstract

8,2'-Cycloadenosine, $C_{10}H_{11}N_5O_4 \cdot 3H_2O$, is a modified arabinosyladenosine nucleoside which has been cyclized at the C(8) and O(2') atoms. The trihydrate crystallizes in the orthorhombic space group $P2_12_12_1$, with $a = 8.680$ (2), $b = 5.991$ (2), $c = 27.203$ (4) Å, $Z = 4$. The structure was refined to $R = 0.0672$ for 1411 unique reflections, photographically recorded. The arabinofuranose ring has a flattened C(4')-endo-C(3')-exo pucker. The conformation about C(4')–C(5') is *gauche-gauche*, and that about the sugar–base bond is high *anti*. The crystal structure involves extensive base–base hydrogen bonding, N(1), N(6) and N(7) all being participants.

Introduction

Many arabinofuranosyl nucleosides act as antimetabolites, with potent antileukaemic and antiviral activity (Suhadolnik, 1970). Prominent among these is 9-β-D-arabinofuranosyladenine (ara-A). It has been found that 8,2'-O-cyclo-9-β-D-arabinofuranosyladenine (Fig. 1) (8,2'-cycloadenosine), which is obtainable in relatively large quantities, can be converted into ara-A in quantitative yield (Chattopadhyaya & Reese, 1977). The cyclonucleosides themselves possess biological activity, for example cyclo-ara-C is markedly active against leukaemic and other tumour cells (Hoshi, Kauzauna, Juretani, Saneyaski & Arai, 1971). 8,2'-Cycloadenosine is at present being screened for activity.

* To whom correspondence should be addressed.

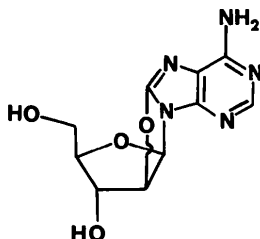


Fig. 1. 8,2'-Cycloadenosine.

The cyclonucleosides are also of interest in ORD and CD spectroscopic studies on nucleoside conformation, on account of the imposed restriction to rotational freedom about the glycosidic bond caused by the cyclization.

This study is the first to report the crystal structure of a purine cyclonucleoside, and continues our series on nucleoside and nucleotide conformation (Neidle, Kuhlbrandt & Achari, 1976; Neidle, Taylor & Robins, 1978; Neidle, Achari, Sheldrick, Reese & Bridson, 1978).

Experimental

The title compound readily formed large, colourless, elongated prisms from aqueous solution. They were unstable in air, so were kept sealed in a thin-walled quartz capillary tube with mother liquor. Photographs revealed that the crystals were orthorhombic. Systematic absences $h00: h = 2n + 1$; $0k0: k = 2n + 1$; and $00l: l = 2n + 1$ uniquely identified the space group as $P2_12_12_1$. Cell dimensions were obtained from two-circle diffractometer measurements.

Crystal data

$C_{10}H_{11}N_5O_4 \cdot 3H_2O$, $M_r = 319.2$, orthorhombic prisms elongated along **b**; $a = 8.680$ (2), $b = 5.991$ (2), $c = 27.203$ (4) Å, $V = 1414$ Å³, $D_m = 1.48$ (by flotation), $D_c = 1.499$ Mg m⁻³ for $Z = 4$, $F(000) = 552$, $\mu = 0.76$ mm⁻¹ for Cu $K\alpha$ radiation ($\lambda_\alpha = 1.54178$ Å); space group $P2_12_12_1$.

Intensities were collected photographically by the Weissenberg method with multi-film packs. The crystal was mounted about **b** and layers $h0l$ – $h5l$ were collected with timed exposures. Intensities were evaluated by the SRC Microdensitometer Service with an Optronics film scanner. 1411 unique reflections were obtained after scaling and merging 2876 measured reflections. The merging agreement index, R_{SYM} , was 0.0495.

Structure solution and refinement

The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971), employing magic integers

(Main, 1978). It was refined by full-matrix least squares with anisotropic temperature factors for the non-hydrogen atoms. H atoms were not located in a difference synthesis; where possible their positions were calculated from geometric considerations, and their contributions taken into account during the refinement. To avoid singularities during the simultaneous refinement of interlayer scale factors and anisotropic (U_{ij}) terms, U_{33} was constrained to equal the mean of U_{11} and U_{22} . The final R was 0.0672 and R_w was 0.0684, with weights $w = 1.0/(F_o + 0.0209F_o^2)$. Tables 1 and 2 list the final atomic parameters.*

Discussion

The molecular structure

Bond lengths and angles are shown in Fig. 2. The e.s.d.'s in lengths range from 0.008 to 0.011 Å and in

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34116 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Final positional parameters for the non-hydrogen atoms ($\times 10^4$), with e.s.d.'s in parentheses

	x	y	z
N(1)	11638 (7)	5400 (9)	4682 (2)
C(2)	11964 (10)	3550 (13)	4427 (3)
N(3)	11042 (7)	2046 (10)	4215 (2)
C(4)	9560 (7)	2654 (12)	4291 (2)
C(5)	9007 (8)	4484 (12)	4542 (2)
C(6)	10120 (9)	5925 (11)	4742 (2)
N(6)	14762 (7)	7209 (10)	5005 (2)
N(7)	7374 (7)	4757 (10)	4543 (2)
C(8)	7058 (8)	2791 (12)	4301 (2)
N(9)	8248 (7)	1527 (8)	4135 (2)
C(1')	7757 (7)	-364 (12)	3851 (2)
O(1')	8021 (6)	-185 (8)	3347 (2)
C(2')	5982 (8)	-225 (12)	3939 (2)
O(2')	5683 (6)	1897 (8)	4187 (2)
C(3')	5281 (8)	-206 (11)	3425 (2)
O(3')	4652 (6)	-2378 (8)	3318 (2)
C(4')	6624 (8)	313 (11)	3076 (2)
C(5')	6678 (12)	2712 (14)	2887 (3)
O(5')	6801 (6)	4282 (8)	3278 (2)
OW(1)	1527 (8)	2011 (11)	2807 (2)
OW(2)	9761 (7)	-4499 (10)	3102 (2)
OW(3)	11630 (7)	-1395 (10)	3537 (2)

Table 2. Calculated positional parameters ($\times 10^3$) for the H atoms assigned a temperature factor of 0.04 Å²

	x	y	z
H(C2)	1318	319	439
H(C1')	836	-187	395
H(C2')	553	-158	416
H(C3')	436	100	339
H(C4')	649	-69	275
H(C5'1)	564	305	268
H(C5'2)	766	289	265

angles from 0.3 to 0.7°. As shown in Fig. 3(a) and (b) the formation of the ether linkage between the sugar and the base results in an essentially planar fused three-ring system. Table 3 shows that, of the atoms in the fourth ring, C(2') deviates the most from this plane, by only 0.131 Å.

Bond lengths for the base are almost identical with those in ara-A (Bunick & Voet, 1974), as are the angles. The only exceptions are C(5)—N(7)—C(8), which is about 4° smaller, and N(7)—C(8)—N(9), which is about 4° larger than in ara-A. The formation of the C(8)—O(2') ether linkage has created major changes in the

Table 3. Deviations (Å) of atoms from least-squares planes

Adenine ring			Furanose ring		
N(1)	0.008	N(7)	-0.005	C(1')	0.000
C(2)	-0.006	C(8)	0.003	O(1')	0.000
N(3)	-0.005	N(9)	0.005	C(2')	0.000
C(4)	-0.005	*C(1')	-0.049	*C(3')	-0.154
C(5)	0.003	*C(2')	0.131	*C(4')	0.149
C(6)	-0.002	*O(2')	0.037	*C(5')	1.534
N(6)	-0.002				

* Atoms not included in the planes calculations.

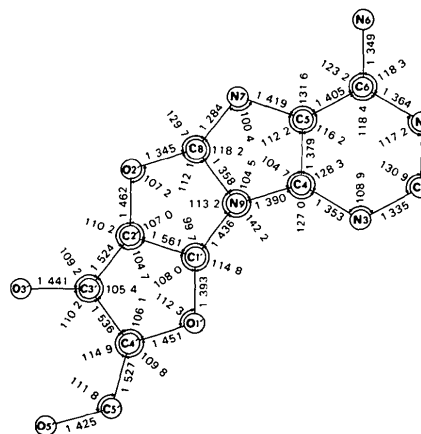


Fig. 2. Bond lengths (Å) and angles (°).

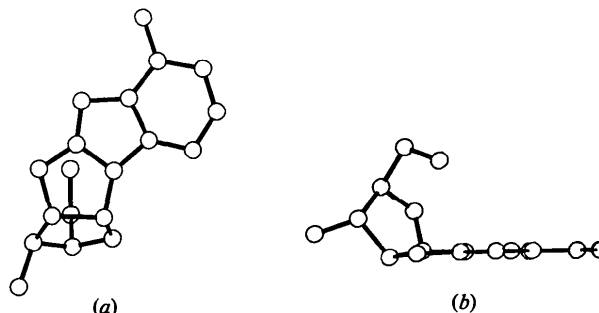


Fig. 3. Views of the cycloadenosine molecule (a) perpendicular to and (b) along the plane of the adenine base.

angles around N(9), C(1') and C(2') (Table 4). The only significant bond-length change is in C(2')–O(2') which is 0.05 Å longer in 8,2'-cycloadenosine than in ara-A. O(2')–C(8), 1.345 Å, shows considerable double-bond character.

The angle between the plane of the fused three-ring system [including C(1'), C(2') and O(2')] and the ribose ring is 115°; the corresponding angle in cycloctidine (Brennan & Sundaralingam, 1973) is 109°.

The glycosidic torsion angle χ (Table 5) is 107°, corresponding to a high *anti* conformation. Thus, the 8,2'-cyclization has restricted this angle to a much larger value than in either adenosine itself (Lai & Marsh, 1972) (10°) or ara-A (Bunick & Voet, 1974) (58°). Table 5 compares the major torsion angles with those found for related compounds.

The sugar pucker in 8,2'-cycloadenosine can be described as C(4')-*endo*–C(3')-*exo* (Table 3). This, or simple variants, appears to be the dominant conformation in the cyclonucleoside series and has also been observed in 2',3'-*O*-isopropylideneadenosine (Sprang, Rohrer & Sundaralingam, 1978). The sugar ring is almost flat, contrasting with the more pronounced

buckle of non-cyclonucleosides, where an out-of-plane atom commonly deviates by over 0.5 Å from the best plane of the other four. This is also reflected in the maximum amplitude of pucker (τ_m) which is only 18.9°, compared with an average of 39° for normal arabinose and ribose rings (Altona & Sundaralingam, 1972). However, Table 4 shows that the value of τ_m for 8,2'-cycloadenosine is low even for cyclonucleosides.

The C(4')-*endo* conformational restriction of the cyclonucleosides is a result of the inhibition of rotational freedom about C(1')–C(2') (τ_1) caused by cyclization. As a result, C(4') is the most mobile atom of the ring. Recent quantum-mechanical calculations (Levitt & Warshal, 1978) on the conformational flexibility of the furanose ring in DNA and RNA have shown that if τ_3 is constrained to follow a pseudorotational pathway and all other variables (*i.e.* atomic coordinates) are allowed to relax during energy minimization, then for values of the pseudorotation angle P between 240 and 300° [*i.e.* inclusive of the C(4')-*endo* conformer], the sugar ring becomes more planar. The results also show that this more planar C(4')-*endo* sugar conformation is not energetically less favoured than a conventional C(4')-*endo* conformation with a maximum pucker (τ_m) of around 40°.

The conformation about the exocyclic bond of the arabinose ring is almost perfectly *gauche-gauche* despite the fact that this results in close contacts between O(5') and the base C(8) of 2.93 Å, and between O(5') and O(1') of 2.88 Å.

Table 4. *A comparison of some bond angles (°) in 8,2'-cycloadenosine with those in ara-A (Bunick & Voet, 1974)*

	This study	Ara-A
C(8)–N(9)–C(1')	113.2	127.1
C(4)–N(9)–C(1')	142.2	126.0
N(9)–C(1')–C(2')	99.7	114.9
C(1')–C(2')–O(2')	107.0	114.7
N(9)–C(1')–O(1')	114.8	107.3

The crystal structure

Fig. 4 shows the hydrogen bonding involving the adenine bases. Each one links to two others, producing

Table 5. *Major torsion angles (°) for the cyclonucleosides*

	This study	Ara-A (a)	Ara-A HCl (b)	Cyclo-U (c) A	Cyclo-U (c) B	Cyclo-C (d)	Cyclopyridone A	Cyclopyridone B (e)	Range of τ_j values in cyclonucleosides
Glycosidic angle									
C(8)–N(9)–C(1')–O(1')	107.0	57.8	29.7	–65.5	–70.0	–61.4	–67.4	–68.0	
Arabinose ring									
C(4')–O(1')–C(1')–C(2') τ_0	6.4	–4.4	6.4	14.4	9.3	–	31.2	–14.5	45.7
O(1')–C(1')–C(2')–C(3') τ_1	6.0	–19.0	–28.7	4.2	12.9	–	–8.9	–2.9	21.8
C(1')–C(2')–C(3')–C(4') τ_2	–15.0	33.5	39.1	–19.7	–28.6	–	–14.6	17.5	46.1
C(2')–C(3')–C(4')–O(1') τ_3	18.9	–36.9	–36.0	28.3	34.5	–	33.5	–26.4	60.9
C(3')–C(4')–O(1')–C(1') τ_4	–16.1	26.2	18.8	–27.3	–27.7	–	–41.0	25.6	66.6
Pseudorotation angle P	217.5	25.2	9.3	227.3	213.6	233	248.6	49.7	
Maximum pucker τ_m	18.9 4T_3	37.0 3T_4	40.2 3T_2	29.0 4T_3	34.4 3T	– 4E	40.0 4T_0	27.1 ${}^4T^5$	
Exocyclic angles									
O(5')–C(5')–C(4')–O(1')	–60.2	62.1	–62.3	56.0	54.8	–69.8	69.5	169.9	
O(5')–C(5')–C(4')–C(3')	59.3	178.8	55.1	174.7	173.5	51.0	174.2	71.8	
	<i>gg</i>	<i>gt</i>	<i>gg</i>	<i>gt</i>	<i>gt</i>	<i>gt</i>	<i>gt</i>	<i>tg</i>	

References: (a) Bunick & Voet (1974). (b) Chwang, Sundaralingam & Hanessian (1974). (c) Delbaere & James (1973); Suck & Saenger (1973). (d) Brennan & Sundaralingam (1973). (e) Hutcheon & James (1977).

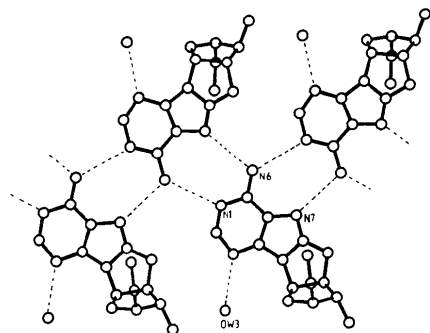


Fig. 4. The hydrogen bonding of the bases.

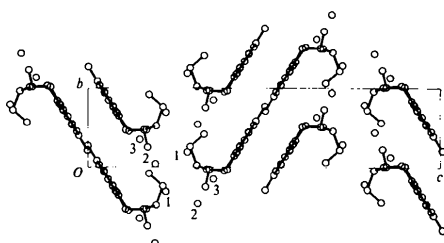
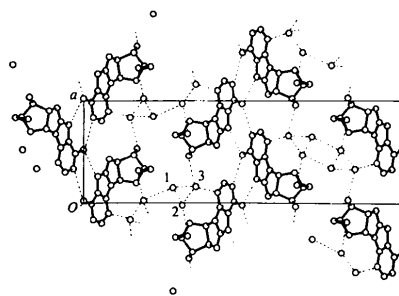
Fig. 5. Projection down *a* of the crystal structure; several water molecules are numbered.Fig. 6. Projection down *b* of the crystal structure.

Fig. 6 shows the projection down *b* of the crystal structure, revealing the extensive network of hydrogen bonds between waters, bases and O(2') and O(3') of the arabinose group. All the hydrogen-bond interactions are summarized in Table 6. The base-pair hydrogen bonds link molecules along *c*.

All the water molecules participate in their maximum number of hydrogen bonds. However, owing to our inability to locate H atoms, an unequivocal assignment of most of the donors and acceptors involving the water molecules cannot be performed.

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Table 6. *Hydrogen-bond distances (average e.s.d. 0.010 Å)*

Atom 1	Atom 2		Symmetry operation on atom 2
N(6)	N(1)	3.050 Å	$-\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$
N(6)	N(7)	3.034	$\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$
N(3)	OW(3)	2.814	x, y, z
O(3')	OW(3)	2.754	$-1 + x, y, z$
O(3')	O(5')	2.737	$x, -1 + y, z$
O(5')	OW(2)	2.713	$x, 1 + y, z$
OW(1)	OW(2)	2.714	$-1 + x, 1 + y, z$
OW(1)	OW(2)	2.860	$1 - x, \frac{1}{2} + y, \frac{1}{2} - z$
OW(1)	OW(3)	2.848	$-1 + x, y, z$
OW(2)	OW(3)	2.736	x, y, z

an infinite chain of base pairs. The adenine group utilizes not only N(1) and N(6) as donor and acceptor (Table 6) (as found in Watson-Crick adenine-thymine base pairs) but also N(6) and N(7), as in Hoosteen-like base-pairing. Identical mixed base-pairing arrangements have been frequently observed, for example in deoxyadenosine (Watson, Sutor & Tollin, 1965), 9-methyladenine (Stewart & Jensen, 1964) and 2'-*O*-methyladenosine (Prusiner & Sundaralingam, 1976), and appears to be an important mode of interaction between neutral adenine bases. The geometry found here accords well with that noted in these other structures. There is no twist between the planes of the interacting bases; the crystallographic symmetry necessitates this coplanarity (Fig. 5).

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The Structures of 4-Methoxy-2,6-dimethylbenzointrile *N*-Oxide (I), 4-Bromo-2,6-dimethylbenzointrile *N*-Oxide (II) and 2,4,6-Trimethylbenzointrile *N*-Oxide (III)

BY MOTOO SHIRO, MASUMI YAMAKAWA AND TANEKAZU KUBOTA

Shionogi Research Laboratory, Shionogi & Co. Ltd, Fukushima-ku, Osaka 553, Japan

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Abstract

The crystal structures of (I), (II) and (III) have been determined at 130 K (I) and 295 K (II, III). (I) is monoclinic, space group $P2_1/c$, $a = 8.36$ (1), $b = 12.76$ (2), $c = 9.01$ (1) Å, $\beta = 110.6$ (5)°, $Z = 4$. (II) is monoclinic, space group $P2_1/c$, $a = 8.942$ (1), $b = 7.040$ (1), $c = 16.966$ (2) Å, $\beta = 121.16$ (1)°, $Z = 4$. (III) is monoclinic, space group $C2/c$, $a = 8.771$ (1), $b = 15.124$ (3), $c = 7.070$ (1) Å, $\beta = 105.25$ (1)°, $Z = 4$. The structures were refined by the least-squares method to R indices of 0.071 (862 reflexions) for (I), 0.076 (974) for (II), and 0.163 (383) for (III). The details of the molecular structure of (III) were not obtained because of the disordered structure. The N–O dative bond lengths are 1.249 (7) and 1.237 (10) Å in (I) and (II), respectively, which are shorter than those in trimethylamine *N*-oxide (1.388 Å) and pyridine *N*-oxide derivatives (in the range of 1.28–1.30 Å). The bond $-C\equiv N\rightarrow O$ is considered to be linear, like those of fulminic acid and acetonitrile *N*-oxide. The hydrogen bonds between the O atom of the *N*-oxide group and the C atom in the benzene ring are weak compared with those found in crystals of pyridine *N*-oxide derivatives.

Introduction

Various physico-chemical studies of substituted benzonitrile *N*-oxides (Kubota, Yamakawa, Takasuka, Iwatani, Akazawa & Tanaka, 1967; Yamakawa, Kubota & Akazawa, 1967; Yamakawa, Kubota, Akazawa & Tanaka, 1968; Bastide, Maier & Kubota,

1976) have revealed that the $-C\equiv N\rightarrow O$ groups in benzonitrile *N*-oxides have the character of a partial triple bond, consisting of π and $\bar{\pi}$ systems (Fig. 1), and that the N–O dative bond lengths are, hence, shorter than those in aliphatic and aromatic amine *N*-oxides.

The structures of trimethylamine *N*-oxide (Caron, Palenik, Goldish & Donohue, 1964) and pyridine *N*-oxide derivatives were investigated, but no structures of benzonitrile *N*-oxides have been reported. The structure analyses of the three compounds were undertaken to confirm the electronic structure of benzonitrile *N*-oxide from a structural standpoint. The structure of (I) has been reported in a preliminary form by Shiro, Yamakawa & Kubota (1968).

Experimental

Crystals of each compound were obtained from a methanol solution. Crystal data are given in Table 1.

Three-dimensional intensity data for (I) were collected at 130 K on integral Weissenberg photographs with Ni-filtered Cu $K\alpha$ radiation ($h0l$ – $h6l$ and $0kl$ – $3kl$). Intensities were measured on a densitometer and those in the upper layer were corrected for spot size. Intensity

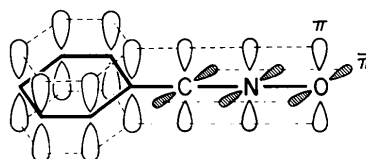


Fig. 1. Schematic π -resonance systems of benzonitrile *N*-oxide.