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Crystal and Molecular Structure of a Purine Arabinonucleoside, 9-β-D-Arabinofuranosyladenine Hydrochloride*

BY ALICE KU CHWANG AND M. SUNDARALINGAM†

Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin, Madison, Wisconsin 53706, *U.S.A.*

AND S. HANESSIAN

Department of Chemistry, University of Montreal, Montreal, Canada

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The crystals of 9-β-D-arabinofuranosyladenine hydrochloride (ara-A.HCl), $C_{10}H_{14}N_5O_4Cl$, have space group $P2_1$, with $a=6{\cdot}475$, $b=15{\cdot}587$, $c=7{\cdot}510$ Å and $\beta=121{\cdot}6°$; $Z=2$. The crystal structure was solved by the multi-solution tangent method and refined by full-matrix least-squares calculations to a final R index of 0·031 for 862 reflections. The molecule has the *anti* conformation about the glycosyl bond with $\chi=29{\cdot}7°$. The arabinose ring is $^3T_2$ puckered and the conformation about the exocyclic C(4′)–C(5′) bond is *gauche–gauche*, the torsion angles O(1′)–C(4′)–C(5′)–O(5′) and C(3′)–C(4′)–C(5′)–O(5′) are $-62{\cdot}3°$ and 55·1° respectively. These conformational features are similar to one of the most common conformations [C(3′)-*endo-anti-gg*] found in the ribo and 2′-deoxyribo nucleosides. The shortest intramolecular contact (2·77 Å) between the base and sugar is O(2′)···N(9). The adenine base is protonated at N(1), which in turn is hydrogen bonded to a neighboring arabinose O(3′) atom. Intermolecular O(2′)···O(5′) hydrogen bonds link the adjacent molecules along the c axis. Adenine rings of adjacent unit cells lie in sheets and are linked by hydrogen bonds between the amino group and the ring nitrogen N(3). The chloride ion is in a cavity formed by three nucleosides, to which it is hydrogen bonded through the arabinose O(3′), O(5′) and the amino nitrogen N(6).

Introduction

9-β-D-Arabinofuranosyladenine (ara-A) was first synthesized by Lee, Benitez, Goodman & Baker (1960) and later was discovered as a naturally occurring nucleoside from the culture filtrates of *S. antibioticus* (Parke, Davis & Co., 1967). It has been established that both ara-A and the synthetic 1-β-D-arabinofuranosylcytosine (ara-C) inhibit the growth of tumor cells and DNA synthesis (Suhadolnik, 1970; Cohen, 1966). The antitumor effects of ara-A and ara-C are decreased by their enzymatic deamination *in vivo* to the biologically inactive catabolites, arabinofuranosylhypoxanthine (LePage & Junga, 1965) and 1-β-D-arabinofuranosyluracil (ara-U) (Papac, Creasey, Calibresi & Welch, 1965; Camiener & Smith, 1965) respectively. Thus, the activity of ara-A and ara-C as inhibitors is related to the levels of deaminase in tumor tissues. Studies have indicated that the mechanism of the inhibition of the replication of DNA involves the direct interaction of the triphosphorylated derivatives of ara-A or ara-C with the DNA polymerase to produce an inactive enzyme (York & LePage, 1966; Furth & Cohen, 1967). Furthermore, ara-A (Miller, Dixon, Ehrlich, Sloan & McLean, 1968) and its derivatives (Hanessian, 1973) are known to exhibit antiviral activity against DNA viruses (Schabel, 1968).

Six arabinoside crystal structures containing pyrimidine bases have been reported: ara-C (Chwang & Sundaralingam, 1973; Lefebvre-Soubeyran, Tougard & Champetier, 1973; Tougard & Lefebvre-Soubeyran, 1974), ara-C.HCl (Sherfinski & Marsh, 1973), 1-β-D-arabinofuranosyluracil (ara-U) (Tollin, Wilson & Young, 1973), 1-β-D-arabinofuranosyl-4-thiouracil (4-thio-ara-U) (Saenger, 1972), 1-β-D-arabinofuranosyl-5-bromouracil (5-Br-ara-U) (Tougard, 1969, 1973*a*) and 1-β-D-arabinofuranosylthymine (ara-T) (Tougard, 1973*b*). However, to date there have been no detailed structural data reported on a purine arabinonucleoside. Here, we report the molecular structure and conformation of ara-A.HCl and compare them with those of the analogous ribonucleosides. The crystal structure of the neutral compound itself (ara-A) has been determined (Bunick & Voet, 1973).

Experimental

Crystals of ara-A.HCl (Pfanstiehl Labs, Waukegan, Illinois) were obtained by slow evaporation from a solution of equal volume of toluene and ethanol, that had been adjusted to *p*H 2–3 with a trace of HCl. Preliminary film data showed that the crystals are monoclinic, space group $P2_1$. Lattice constants were obtained from a least-squares fit of 12 centered reflections on a Picker FACS-1 diffractometer. The density was measured by flotation in a solution of carbon tetrachloride and cyclohexane. The crystallographic data are given in Table 1. Intensity data from the

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† To whom correspondence should be addressed.

hkl–$\bar{h}kl$ quadrant were collected on a crystal of dimensions 0·10 × 0·20 × 0·30 mm with the θ–2θ scan technique at a scan rate of 2° min^{-1} and a scan width of 2·0° in 2θ. Backgrounds were counted for 10 s at the beginning and the end of each scan. Three standard reflections 024, 280, 331 were measured periodically. These showed no significant change during data collection. In the range of measurement (2θ max = 115°) 862 reflections were greater than 1·5 times their standard deviations, and were used in the structural analysis after being corrected for the usual Lorentz and polarization effects.

Table 1. *Crystal data of 9-β-D-arabinofuranosyladenine hydrochloride*

	$(C_{10}H_{14}N_5O_4)^+Cl^-$
F.W.	303·71
Space group	$P2_1$
Unit-cell dimensions	a = 6·475 (3) Å
	b = 15·587 (3)
	c = 7·510 (3)
	β = 121·62° (0·02°)
Z	2
D_m	1·55 g cm^{-3}
D_x	1·562 g cm^{-3}
μ for Cu $K\alpha$	24·24 cm^{-1}
Total reflections ($2\theta_{max}$ = 115°)	901
Observed reflections	862

Structure determination and refinement

The structure was solved by direct methods with the program *MULTAN* (Main, Germain & Woolfson, 1970). An E map based on the phases of 227 reflections revealed the positions of 20 atoms, which gave an R value, where $R = \sum||F_o| - |F_c||/\sum|F_o|$, of 0·21. These coordinates were then refined by two cycles of isotropic full-matrix least-squares refinement to an R = 0·07. A difference electron density map was then calculated from which the positions of 14 hydrogen atoms were obtained. These coordinates were fixed with isotropic temperature factors of 3·0 Å^2. Four cycles of anisotropic refinement on the heavy atoms alone reduced the R value to 0·031.* The average shift/σ ratio in the parameters was 0·05. The weighting scheme used was $1/\sqrt{w} = 3·46 - 0·044F_{obs}$ for F_{obs} less than 25·5, $1/\sqrt{w}$ = 2·34 for F_{obs} greater than 25·5 and less than 79·0; and $1/\sqrt{w} = 1·25 + 0·0138F_{obs}$ for F_{obs} larger than 79·0. The scattering factors for C, O, N and Cl were those from Cromer & Waber (1965), and that for H was from Stewart, Davidson & Simpson (1965).

Results

The atomic positional and thermal parameters, with their e.s.d.'s are listed in Table 2. The bond distances and angles are given in Fig. 1. The average estimated standard deviations of bond lengths and angles involving the heavy atoms are 0·008 Å and 0·4° respectively.

Discussion

Bond distances and angles

Base: The dimensions of the N(1) protonated adenosine moiety in this structure are in good agreement with those found in a number of other N(1) protonated systems; *viz.*, 5′-AMP (Kraut & Jensen, 1963; Lin & Sundaralingam, 1973), 3′-AMP (Sundar-

* The structure-factor table has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30505 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Positional and thermal parameters of atoms in ara-A*.HCl

Positional parameters of nonhydrogen atoms have been multiplied by 10^4. Positional parameters of hydrogen atoms have been multiplied by 10^3. Anisotropic thermal parameters have been multiplied by 10^4. Anisotropic temperature factor is of the form $\exp[-(\beta_{11}h^2 + \ldots + 2\beta_{12}hk + \ldots)]$. Standard deviations in parentheses refer to the least significant digits.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	2387 (7)	4081 (3)	3819 (6)	147 (14)	26 (2)	110 (11)	13 (4)	55 (11)	−10 (4)
C(2)	4543 (9)	3959 (4)	5601 (8)	186 (20)	32 (3)	127 (14)	10 (6)	58 (14)	−24 (5)
N(3)	6334 (7)	3504 (3)	5760 (6)	147 (15)	32 (2)	105 (11)	12 (5)	31 (10)	−14 (4)
C(4)	5761 (8)	3168 (3)	3888 (7)	124 (16)	20 (2)	124 (13)	7 (5)	63 (13)	1 (4)
C(5)	3615 (9)	3253 (3)	1999 (7)	141 (15)	15 (2)	108 (11)	2 (5)	52 (11)	−1 (4)
C(6)	1775 (8)	3743 (3)	1949 (8)	130 (18)	19 (2)	118 (13)	2 (5)	48 (13)	2 (4)
N(6)	−412 (8)	3878 (3)	267 (7)	175 (16)	34 (2)	89 (11)	28 (5)	24 (11)	−4 (4)
N(7)	3682 (7)	2823 (3)	425 (6)	185 (15)	23 (2)	101 (10)	7 (4)	56 (11)	−5 (3)
C(8)	5865 (9)	2483 (4)	1390 (7)	200 (18)	26 (2)	87 (11)	3 (6)	53 (12)	−3 (4)
N(9)	7222 (7)	2682 (3)	3490 (6)	140 (14)	27 (2)	108 (10)	11 (4)	60 (10)	0 (4)
C(1′)	9687 (8)	2386 (4)	5059 (7)	99 (16)	30 (2)	115 (11)	2 (5)	44 (11)	−2 (5)
O(1′)	10965 (6)	2238 (2)	4030 (5)	201 (12)	19 (2)	177 (10)	−1 (3)	127 (10)	1 (3)
C(2′)	9697 (8)	1533 (4)	6068 (7)	85 (15)	33 (3)	92 (11)	0 (5)	27 (11)	−1 (4)
O(2′)	7635 (6)	1412 (3)	6235 (6)	151 (13)	57 (2)	135 (10)	6 (4)	81 (10)	20 (4)
C(3′)	9818 (8)	889 (3)	4610 (7)	131 (15)	22 (2)	86 (12)	−5 (5)	36 (11)	5 (4)
O(3′)	10606 (5)	50 (3)	5452 (5)	173 (12)	22 (1)	148 (9)	−7 (4)	48 (8)	11 (4)
C(4′)	11546 (8)	1327 (3)	4119 (8)	130 (17)	18 (2)	143 (13)	5 (4)	81 (13)	1 (4)
C(5′)	11341 (10)	1060 (4)	2100 (9)	232 (19)	23 (2)	204 (15)	3 (6)	136 (15)	2 (5)
O(5′)	8940 (7)	1150 (3)	284 (6)	301 (15)	33 (2)	130 (9)	−17 (4)	117 (10)	0 (3)
Cl	4786 (2)	0 (0)	−149 (2)	196 (4)	35 (0)	131 (3)	−13 (1)	57 (3)	4 (1)

Table 2 (*cont.*)

	x	*y*	*z*	*B*
H(1)	133	442	388	3·0
H(2)	427	417	675	3·0
H(61)	−163	423	38	3·0
H(62)	−84	362	−111	3·0
H(8)	629	216	55	3·0
H(1′)	1065	282	626	3·0
H(2′)	1139	161	749	3·0
H(O2′)	859	132	795	3·0
H(3′)	804	83	337	3·0
H(O3′)	1213	−1	680	3·0
H(4′)	1337	112	537	3·0
H(5′1)	1199	51	223	3·0
H(5′2)	1214	149	191	3·0
H(O5′)	817	63	32	3·0

alingam, 1966) adenosine.HCl (Shikata, Ueki & Mitsui, 1973) (see also Rao & Sundaralingam, 1970; Voet & Rich, 1970).

Arabinose moiety: The geometry of the arabinose ring shows some important differences from those of the ribose rings in nucleosides (Sundaralingam & Jensen, 1965; Sundaralingam, 1973; Saenger & Eckstein, 1970; Arnott & Hukins, 1972) which arise mainly from the different configuration of the hydroxyl group O(2′)H. For example the valence angle C(1′)–C(2′)–O(2′) in ara-A.HCl is about 6° larger than the values found for the C(3′)-*endo* ribose rings (Sundaralingam, 1973). The inversion at the C(2′) atom also brings the base N(9) atom and the hydroxyl group O(2′)H to within 2·77 Å thereby markedly reducing the glycosyl angle range for the base compared with a ribonucleoside. Other short contacts between O(2′) and the base are O(2′)···N(3), 3·34 Å and O(2′)···C(4) 3·14 Å. The exocyclic O(5′) atom and the base C(8)–H group have the following contact distances: O(5′)···C(8) = 3·27 Å and H···O(5′) = 2·41 Å. The ring C(1′)–O(1′) and C(4′)–O(1′) bond distances in ara-A.HCl are also significantly different as has been observed in the ribose rings of nucleosides and nucleotides (Sundaralingam, 1965, 1968; Sundaralingam & Jensen, 1965).

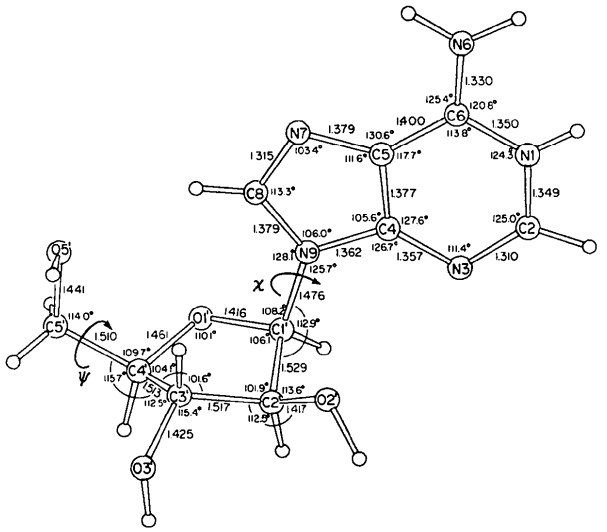

Fig. 1. Bond lengths and bond angles in ara-A.HCl. The glycosyl torsion angle $\chi = O(1')$–$C(1')$–$N(9)$–$C(8)$ and the exocyclic torsion angle about the C(4′)–C(5′) bond $\psi = O(5')$–$C(5')$–$C(4')$–$C(3')$.

Molecular conformation

Glycosyl torsion angle: The glycosyl torsion angle defined by the atoms O(1′)–C(1′)–N(9)–C(8) (Sundaralingam, 1969) is 29·7° which corresponds to the *anti* conformation. As mentioned above, the O(2′)H group tends to restrict the base to the *anti* conformation and theoretical energy calculations have shown that the favored range of *anti* angles is shifted towards higher values for the arabinosides than the ribosides (Yathindra & Sundaralingam, 1974).

Planarity of the base: The deviations of the atoms from the least-squares plane of the base are shown in Table 3. The largest deviations are those of the amino nitrogen N(6) (0·023 Å) and the arabinose ring atom C(1′) (0·036 Å).

Table 3. *Deviations of the atoms from the least-squares plane of the base*

N(1)	0·011*	N(6)	−0·023
C(2)	0·002*	N(7)	−0·001*
N(3)	−0·010*	C(8)	−0·001*
C(4)	−0·007*	N(9)	0·015*
C(5)	−0·006*	C(1′)	−0·036
C(6)	−0·002*	RMS	0·008
		ΔSTD	0·004

Atoms used in fitting the least-squares plane are denoted by asterisks. The equation of the plane is $0{\cdot}5372X + 0{\cdot}8200Y - 0{\cdot}1975Z = 4{\cdot}7461$ where X, Y, Z are referred to the orthogonal axes a, b, c^* directions in Å.

Conformation of the arabinose moiety: The atoms C(3′) and C(2′) are displaced by 0·474 and 0·162 Å respectively on opposite sides of the plane C(1′)–O(1′)–C(4′). Thus the arabinose ring has the $^3T_2$ [C(3′)-*endo*, C(2′)-*exo*] conformation, which is also one of the preferred modes of puckering of the ribose ring (Sundaralingam, 1965, 1969; Altona & Sundaralingam, 1972). The furanose ring torsion angles and the glycosyl and exocyclic C(4′)–C(5′) bond torsion angles in ara-A.HCl are compared with those of the corresponding ribonucleosides, adenosine.HCl (Shikata, Ueki & Mitsui, 1973) and adenosine (Lai & Marsh, 1972) in Table 4. The glycosyl conformation is *anti* in all these structures. The ψ angle in ara-A.HCl is similar to that of adenosine.HCl (*gauche–gauche*) but different from adenosine (*gauche–trans*) itself. This angle, in fact, exhibits considerable flexibility in nucleosides (Sundaralingam, 1965, 1969, 1973; Shefter & Trueblood, 1965). On the other hand the puckering of the furanose ring in ara-A.HCl [C(3′)-*endo*] is similar to adenosine, while in adenosine.HCl the puckering is C(2′)-*endo*. The phase angles of pseudorotation (**P**) and the max-

imum amplitude of puckering (τ_m) (Altona & Sundaralingam, 1972, 1973) of the furanose rings for the three nucleosides are also given in Table 4.

Table 4. *Comparison of the conformational parameters of arabinosyladenosine*.HCl *and the corresponding adenosine*.HCl *and adenosine*

	Ara-A.HCl	Adenosine.HCl	Adenosine
χ	29·7°	43·1°	9·9°
$\psi_{C3'O5'}$	55·1	60·9	176·9
	gg	*gg*	*gt*
$\varphi_{O1'O5'}$	−62·3	−59·3	60·1
Sugar pucker	$^3T_2$	$^2T_3$	$^3T_2$
P	9·3	168·8	7·0
τ_m	40·2	40·18	36·8
τ_0	6·4	−20·1	7·4
τ_1	−28·7	36·8	−27·3
τ_2	39·1	−38·4	35·7
τ_3	−36·0	27·9	−32·5
τ_4	18·8	−5·1	16·0

The torsion angles O(2')–C(2')–C(3')–O(3') and O(2')–C(2')–C(1')–N(9) are −76·8 and −31·7° respectively for ara-A.HCl while these angles for adenosine.HCl and adenosine are −47·2, −81·5 and 45·36, −153·72° respectively. The 5'-hydroxyl group of ara-A.HCl is rotated through an unusual torsion angle; *viz.*, H–O(5')–C(5')–C(4') = 83° rather than in the usual *anti* range. This is due to the hydrogen bonding of O(5')H to a neighboring chloride ion. The hydroxyl group O(3')–H is *anti* to the C(3')–H(3') bond while the O(2')–H group is *cis* to the C(2')–H(2') bond. The relevant torsion angles H(O3')–O(3')–C(3')–H(3') and H(O2')–O(2')–C(2')–H(2') are −168·2° and −9·9°, respectively.

Molecular packing and hydrogen bonding

The hydrogen-bonding distances and angles are shown in Fig. 2. The two shortest hydrogen bonds are between O(3') and the protonated ring nitrogen N(1), and between O(2') and O(5'). The Cl^- ion is hydrogen bonded to the amino nitrogen N(6) and the arabinose hydroxyl groups O(3')H and O(5')H of three different nucleoside molecules. It lies roughly in the plane formed by the atoms to which it is hydrogen bonded. There are also two contacts of 3·45 and 3·57 Å respectively between the Cl^- ion and the base atoms C(5) and N(7) of a fourth nucleoside molecule. The bases are linked along the (101) diagonal in adjacent unit cells to form an infinite ribbon by the only interbase hydrogen bond, N(6)H···N(3). Adjacent molecules along the *c* axis are also linked into an infinite chain by the hydrogen bonds involving the hydroxyl groups O(5') and O(2'). The arabinose ring oxygen O(1') exhibits two contacts less than 3·10 Å, one to C(6) (3·01 Å) and the other to N(1) (3·05 Å). Both of these involve adjacent bases.

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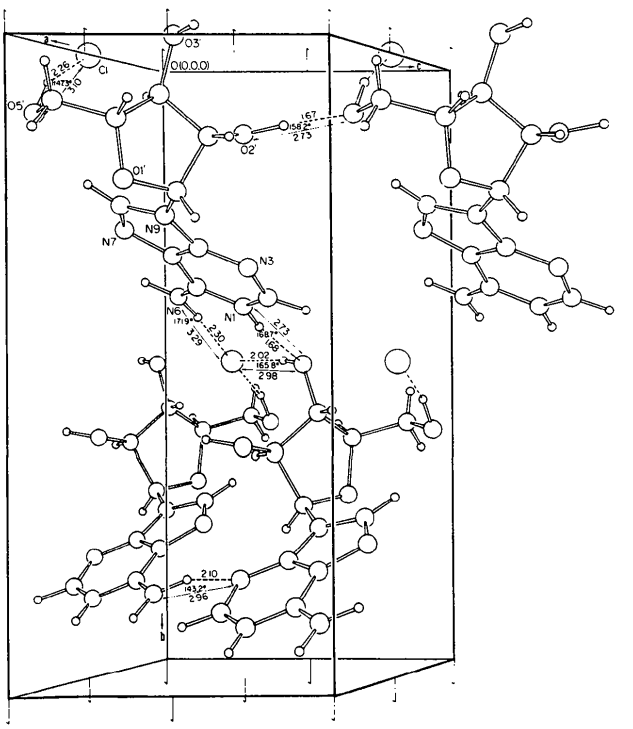

Fig. 2. A parallel projection of the crystal structure showing the packing and the hydrogen-bonding scheme.

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Stereochemistry of Anticholinergic Agents. V.* Crystal and Molecular Structure of Thiphenamil Hydrochloride

BY J. J. GUY AND T. A. HAMOR

Chemistry Department, The University, Birmingham B15 2TT, England

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Thiphenamil hydrochloride, *S*-(2-diethylaminoethyl) diphenylthioacetate hydrochloride, crystallizes as the monohydrate from butanone in the monoclinic space group $P2_1/c$ with $a=19{\cdot}41$ (1), $b=7{\cdot}52$ (1), $c=14{\cdot}78$ (1) Å, $\beta=103{\cdot}90$ (5)° and $Z=4$. The structure was determined by Patterson and Fourier methods from three-dimensional X-ray counter data and refined by least-squares calculations to R 5·5% for 2233 observed amplitudes. Estimated standard deviations for bond lengths, bond angles and torsion angles average 0·006 Å, 0·3°, and 0·5°. In the thiphenamil cation, the acetylthiocholine-like moiety has the C–C(=O)–S–C grouping antiplanar, C(=O)–S–C–C, synclinal, and S–C–C–N^+, antiplanar. The C(=O)–S and S–C bond lengths are 1·780 (4) and 1·814 (4) Å. The molecular geometry is compared with those of related anticholinergic and cholinergic molecules.

Introduction

Certain derivatives of acetylcholine incorporating ring substituents in the acyl group and larger groups on the nitrogen atom act as atropine-like antagonists of acetylcholine at the parasympathetic post-ganglionic (muscarinic) receptor (Triggle, 1965). The crystal structures of a number of these compounds have been determined and their conformations compared (Guy & Hamor, 1974*a*). We now present the results of a crystal structure analysis of *S*-(2-diethylaminoethyl) diphenylthioacetate hydrochloride (thiphenamil hydrochloride), the thiolester analogue of the anticholinergic adiphenine hydrochloride, the structure of which has already been described (Guy & Hamor, 1973). Thiphenamil has an anticholinergic activity *ca* 20% of

* Part IV: Guy & Hamor (1974*a*).