The Crystal and Molecular Strucure of Arabinofuranosyladenine Hydrochloride[1]

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(Received May 11, 1974)

Crystals of arabinofuranosyladenine hydrochloride are monoclinic, space group $P2_1$, with $a=6.47$, $b=15.56$, $c=6.87$ Å, and $\beta=111.6°$. Intensity data were collected on a four-circle diffractometer with Mo-Kα radiation. The structure was solved by means of Patterson and Fourier methods and refined using block-diagonal least-squares technique. The final *R*-factor for 1681 observed reflections is 4.5%. The sugar conformation is C3′-*endo* and the C(5′)–O(5′) bond is *gauche* to both C(4′)–O(1′) and C(4′)–C(3′). The torsional angle about the glycosidic C–N bond is *anti*, with $\chi_{CN}=29.2°$. The hydrogen-bond scheme is similar to those found in several salts of nucleosides and deoxynucleosides.

9-β-D-Arabinofuranosyladenine (ara-A), first synthesized by Lee *et al.* in 1960,[2] is active against a broad spectrum of DNA virus[3] and inhibits the DNA polymerase.[4] Consequently the conformation of this molecule has been of great interest in comparison with other structurally related nucleosides. In this paper, we describe the molecular and crystal structure of ara-A monohydrochloride (ara-A HCl) with particular attention focussed on conformational aspects and intermolecular interactions of the ara-A cation in the crystalline state.

Experimental

Crystals of ara-A HCl[5] were prepared in our laboratories, and recrystallized from water, in a suitable form for X-ray structure analysis. Crystal dimensions of this salt are; $a=6.47\pm0.02$, $b=15.56\pm0.03$, $c=6.87\pm0.02$ Å, and $\beta=111.6\pm0.3°$ and the space group belongs to $P2_1$. The density was measured by the floatation method in a mixed solution of tetrachloromethane and cyclohexane and found to be 1.544 g/cm^3, while the calculated value is 1.558 g/cm^3 (if $Z=2$).

A total of 1681 independent reflections were collected on a Rigaku automatic four-circle diffractometer using Zr-filtered Mo-Kα radiation and measured up to $2\theta=60°$ in the θ-2θ scan mode. All data were corrected for the Lorenz and polarization factors but not for absorption.

Determination and Refinement of the Structure

The parameters of the chlorine anion could be obtained from a three-dimensional sharpened Patterson map. After several applications of successive Fourier syntheses a trial structure of the arabinoside emerged except for the hydrogen atoms. The initial refinement for the positional and thermal parameters was carried out by a block-diagonal least-squares technique. Four cycles of this computation dropped the *R*-factor to 8.1%. Then the difference Fourier synthesis was calculated to obtain the hydrogen atoms. These atoms were revealed at reasonable positions. Four more cycles of the least-squares refinement using anisotoropic temperature for the heavy atoms and isotropic factors

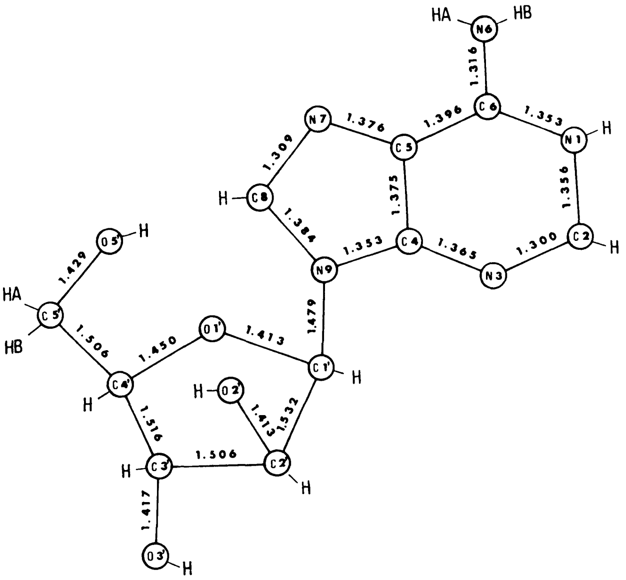


Fig. 2. Bond distances in the arabinofuranosyladenine cation.

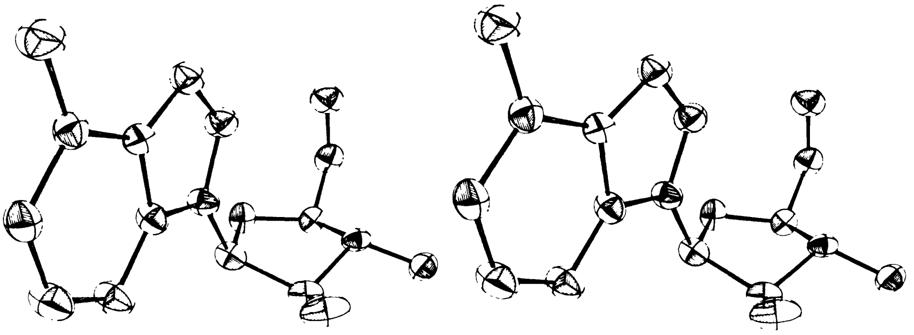


Fig. 1. A stereographic illustration of the arabinofuranosyladenine cation.

for the hydrogen atoms were made. The final *R*-factor was 4.5% for all observed reflections. Tables 1, 2, and 3 list the positional and thermal parameters, while the observed and calculated structure factors are given in Table 4.[6] A stereographic illustration of the ara-A cation computed by the ORTEP program[7] using these parameters is exhibited in Fig. 1. Bond distances and angles are shown in Figs. 2 and 3 and Table 5.

TABLE 1. POSITIONAL PARAMETERS OF THE NON-HYDROGEN ATOMS, WITH THEIR ESTIMATED STANDARD DEVIATIONS IN PARENTHESES

All parameters have been multiplied by 10^4.

	x/a	y/b	z/c
Cl	68(2)	−3(1)	−143(2)
N(1)	6441(6)	4092(2)	3824(5)
C(2)	6046(8)	3955(3)	5605(7)
N(3)	4428(7)	3504(3)	5773(6)
C(4)	3115(7)	3167(3)	3889(6)
C(5)	3393(7)	3254(3)	2009(6)
C(6)	5179(7)	3745(3)	1958(6)
N(6)	5670(7)	3889(3)	290(6)
N(7)	1751(6)	2825(2)	439(5)
C(8)	510(7)	2492(3)	1381(6)
N(9)	1266(6)	2684(2)	3495(5)
C(1′)	369(6)	2384(3)	5069(6)
C(2′)	1375(7)	1528(3)	6078(6)
C(3′)	−188(6)	880(3)	4624(6)
C(4′)	−2414(6)	1330(3)	4114(6)
C(5′)	−4244(8)	1061(3)	2112(7)
O(1′)	−1932(5)	2236(2)	4030(5)
O(2′)	3599(5)	1415(3)	6237(5)
O(3′)	−155(5)	50(2)	5444(9)
O(5′)	−3674(6)	1157(2)	301(5)

TABLE 2. THERMAL PARAMETERS OF THE NON-HYDROGEN ATOMS WITH THEIR ESTIMATED STANDARD DEVIATIONS

All parameters have been multiplied by 10^4. The thermal parameters are of the form

$T=\exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+2B_{12}hk+2B_{13}hl+2B_{23}kl)]$.

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	212(3)	39(0)	140(2)	19(1)	74(2)	5(1)
N(1)	162(10)	23(1)	146(8)	−19(3)	50(8)	−6(3)
C(2)	192(13)	35(2)	127(10)	−20(4)	66(9)	−20(4)
N(3)	177(11)	34(2)	132(8)	−23(4)	73(8)	−14(3)
C(4)	146(11)	22(2)	123(8)	−6(3)	59(8)	−8(3)
C(5)	153(11)	20(2)	110(8)	−3(3)	47(8)	1(3)
C(6)	136(11)	20(2)	123(8)	−6(3)	37(8)	1(3)
N(6)	212(12)	38(2)	137(9)	−35(4)	82(9)	−6(3)
N(7)	175(10)	26(2)	126(8)	−13(3)	47(9)	−2(3)
C(8)	152(11)	27(2)	126(9)	−12(4)	25(8)	2(4)
N(9)	123(9)	26(2)	110(7)	−14(3)	38(6)	−5(3)
C(1′)	132(11)	28(2)	138(8)	−8(4)	69(8)	−8(4)
C(2′)	117(10)	34(2)	112(9)	−1(4)	43(8)	2(3)
C(3′)	107(10)	27(2)	95(8)	11(3)	26(7)	4(3)
C(4′)	102(9)	24(2)	145(9)	4(3)	51(8)	4(3)
C(5′)	138(11)	30(2)	187(11)	0(4)	31(9)	6(4)
O(1′)	111(7)	22(1)	190(8)	3(3)	46(6)	0(3)
O(2′)	104(8)	57(2)	146(7)	12(3)	24(6)	14(3)
O(3′)	215(9)	28(1)	148(7)	21(3)	77(6)	11(3)
O(5′)	179(9)	40(2)	154(8)	18(3)	14(7)	−3(3)

TABLE 3. POSITIONAL AND ISOTROPIC THERMAL PARAMETERS OF THE HYDROGEN ATOMS, WITH THEIR ESTIMATED STANDARD DEVIATIONS IN PARENTHESES

	x/a	y/b	z/c	B
HN(1)	0.734(9)	0.452(3)	0.357(8)	3.5(1.2)
HC(2)	0.718(8)	0.416(3)	0.681(7)	2.7(1.1)
HAN(6)	0.489(10)	0.357(4)	−0.112(8)	4.2(1.3)
HBN(6)	0.696(9)	0.410(3)	0.038(8)	3.6(1.2)
HC(8)	−0.075(8)	0.220(3)	0.091(7)	3.5(1.2)
HC(1′)	0.041(8)	0.285(3)	0.614(7)	3.2(1.5)
HC(2′)	0.124(9)	0.166(4)	0.752(8)	3.7(1.2)
HC(3′)	0.024(8)	0.088(3)	0.319(7)	3.0(1.1)
HC(4′)	−0.279(8)	0.123(3)	0.534(7)	2.9(1.1)
HAC(5′)	−0.457(8)	0.047(3)	0.233(7)	2.7(1.1)
HBC(5′)	−0.563(9)	0.141(4)	0.168(8)	3.6(1.2)
HO(2′)	0.425(10)	0.160(4)	0.779(8)	4.8(1.4)
HO(3′)	−0.005(9)	0.007(4)	0.668(7)	4.2(1.2)
HO(5′)	−0.298(8)	0.080(3)	0.021(7)	3.0(1.1)

TABLE 5. BOND LENGTHS AND ANGLES, WITH THEIR ESTIMATED STANDARD DEVIATIONS IN PARENTHESES

Atoms	Length, Å	Atoms	Angle, deg.
N(1)–C(2)	1.356(7)	C(2)–N(1)–C(6)	123.0(4)
N(1)–C(6)	1.353(5)	N(1)–C(2)–N(3)	126.2(4)
C(2)–N(3)	1.300(7)	C(2)–N(3)–C(4)	111.3(4)
N(3)–C(4)	1.365(5)	N(3)–C(4)–C(5)	127.0(4)
C(4)–C(5)	1.375(7)	N(3)–C(4)–N(9)	126.8(4)
C(4)–N(9)	1.353(6)	C(5)–C(4)–N(9)	106.2(3)
C(5)–C(6)	1.396(7)	C(4)–C(5)–C(6)	118.2(4)
C(5)–N(7)	1.376(5)	C(4)–C(5)–N(7)	111.0(4)
N(7)–C(8)	1.309(7)	C(6)–C(5)–N(7)	130.8(4)
C(8)–N(9)	1.384(5)	N(1)–C(6)–C(5)	114.3(4)
C(6)–N(6)	1.316(7)	N(1)–C(6)–N(6)	120.1(4)
N(9)–C(1′)	1.479(6)	C(5)–C(6)–N(6)	125.6(4)
		C(5)–N(7)–C(8)	104.0(4)
C(1′)–C(2′)	1.532(7)	N(7)–C(8)–N(9)	112.9(4)
C(1′)–O(1′)	1.413(5)	C(4)–N(9)–C(8)	106.0(4)
C(2′)–C(3′)	1.506(6)	C(4)–N(9)–C(1)′	125.8(3)
C(2′)–O(2′)	1.413(6)	C(8)–N(9)–C(1′)	128.1(4)
C(3′)–C(4′)	1.516(6)		
C(3′)–O(3′)	1.417(6)	N(9)–C(1′)–O(1′)	107.8(3)
C(4′)–C(5′)	1.506(5)	N(9)–C(1′)–C(2′)	113.0(4)
C(4′)–O(1′)	1.450(5)	O(1′)–C(1′)–C(2′)	106.3(4)
C(5′)–O(5′)	1.429(7)	C(1′)–C(2′)–C(3′)	101.8(3)
		C(1′)–C(2′)–O(2′)	113.2(4)
N(1)–H	0.94(6)	C(3′)–C(2′)–O(2′)	112.6(4)
C(2)–H	0.93(4)	C(2′)–C(3′)–C(4′)	101.7(4)
N(6)–HA	1.04(5)	C(2′)–C(3′)–O(3′)	115.9(3)
N(6)–HB	0.87(6)	C(4′)–C(3′)–O(3′)	112.5(4)
C(8)–H	0.88(5)	C(3′)–C(4′)–O(1′)	104.5(3)
C(1′)–H	1.02(5)	C(3′)–C(4′)–C(5′)	116.5(4)
C(2′)–H	1.04(6)	O(1′)–C(4′)–C(5′)	110.0(3)
C(3′)–H	1.12(6)	C(4′)–C(5′)–O(5′)	113.5(4)
C(4′)–H	0.97(6)	C(4′)–O(1′)–C(1′)	109.9(3)
C(5′)–HA	0.96(5)		
C(5′)–HB	1.00(5)		
O(2′)–H	1.03(5)		
O(3′)–H	0.83(6)		
O(5′)–H	0.73(5)		

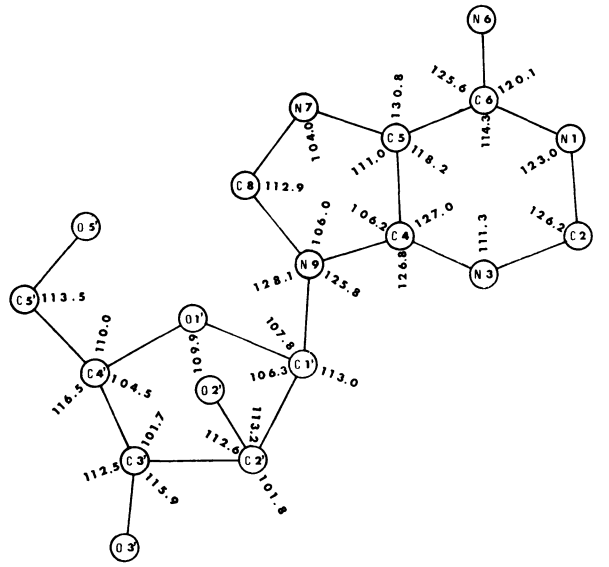
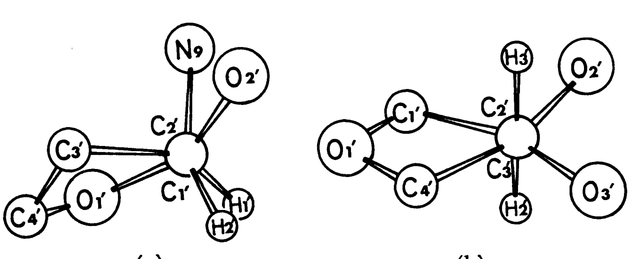


Fig. 3. Bond angles in the arabinofuranosyladenine cation.

Description and Discussion of the Structure

The conformational aspects of the ara-A cation are similar to those usually found in nucleosides and nucleotides. The puckering of this sugar residue is C3'-*endo* in which the atom C(3') is displaced by 0.60 Å from the least-squares plane as constructed in relation to the remaining four atoms in the furanose ring and on the same side as C(5').[8] The torsional angles about the exocyclic C(4')-C(5') bond denoted as ϕ_{OO} and ϕ_{OC} by Shefter and Trueblood[9] are 62.4 and 56.3° respectively, rendering the *gauche-gauche* conformation. The other torsional angle about the glycosidic bond, C(1')-N(9), is *anti* and that of C(8)-N(9)-C(1')-O(1'), χ_{CN},[10] is 29.2°.

The only difference in the molecular features between the ara-A cation and the adenosine cation is the configuration at the carbon atom C(2'); with respect to the furanose ring, the relationship between the OH group and the H atom at C(2') is reversed. The arrangements of atoms around the C(2')-C(1') and C(3')-C(2') bonds are represented in Figs. 4(a) and (b), respectively. The O(2')H group is in the *cis* position N(9) relative to the C(2')-C(1') bond, while oriented *gauche* to O(3') in relation to the C(3')-C(2') bond. Therefore, the torsional angle of O(2')-C(2')-C(1')-N(9), 31.7°, in the ara-A cation becomes smaller than those of 153.7° in adenosine[11] (C3'-*endo*) and 81.5° in the adenosine cation[12] (C2'-*endo*). And there are some short intramolecular non-bonded distances. They are shown in Fig. 5. With respect to the arrangement of atoms around the C(3')-C(2') bond, the O(3')-C(3')-C(2')-O(2') torsional angle of 77.6° in the ara-A cation is larger than those of 45.3° in adenosine and 47.2° in the adenosine cation. In Table 6, these angles are listed.



(a) (b)

Fig. 4. Views down (a) the C(2')-C(1') bond and (b) the C(3')-C(2') bond.

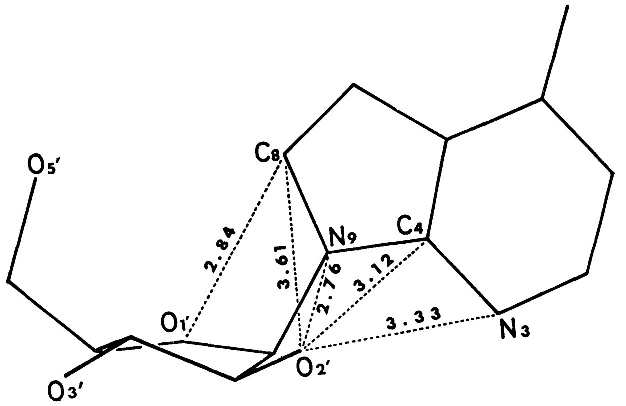


Fig. 5. Intramolecular short nonbonded contacts (Å).

TABLE 6. TORSIONAL ANGLES IN THE ARA-A CATION AND RELATED COMPOUNDS

Puckering of sugar	ara-A cation[a)] C3'-*endo*	Adenosine[b)] C3'-*endo*	adenosine cation[c)] C2'-*endo*
N(9)-C(1')-C(2')-O(2')	31.7°	153.7°	81.5°
N(9)-C(1')-C(2')-C(3')	89.5	92.4	153.7
O(1')-C(1')-C(2')-O(2')	149.7	86.6	161.6
O(1')-C(1')-C(2')-C(3')	28.5	27.3	36.8
O(2')-C(2')-C(3')-O(3')	77.6	45.3	47.2
O(2')-C(2')-C(3')-C(4')	160.1	79.3	162.6
C(1')-C(2')-C(3')-O(3')	160.9	160.4	77.0
C(1')-C(2')-C(3')-C(4')	38.6	35.8	38.4

a) This study b) Ref. 11 c) Ref. 12

The positioning of the O(2') atom seems to affect the bond lengths of C(2')-C(3') and N(9)-C(1') in arabinosyl nucleoside. The C(2')-C(3') bond length of 1.506 Å is shorter than those in adenosine, 1.528 Å, and in the adenosine cation, 1.529 Å, but close to arabinofuranosyl-4-thiouracil[13] (ara-S^4-U, C3'-*endo*), 1.508 Å. The bond length of N(9)-C(1') in the ara-A cation, 1.479 Å, is slightly longer than those in adenosine, 1.466 Å, and the adenosine cation, 1.460 Å. This tendency is seen in other arabinoside derivatives which are 1.481 Å (ara-S^4-U), 1.48 Å (ara-T,[14] C1' *exo*-O1' *endo*), 1.471 Å (ara-U,[15] C2' *endo*-C1' *exo*), and 1.475 Å (ara-C HCl,[16] C2'-*endo*).

As in adenosine hydrochloride, the ring of the base residue is protonated at the N(1) atom. No particular differences can be observed in the overall base residue from those found in other salts[17] regardless of the configuration of the arabinofuranosyl residue.

Figure 6 displays the crystal structure of ara-A HCl projected along the a-axis where the hydrogen-bonds

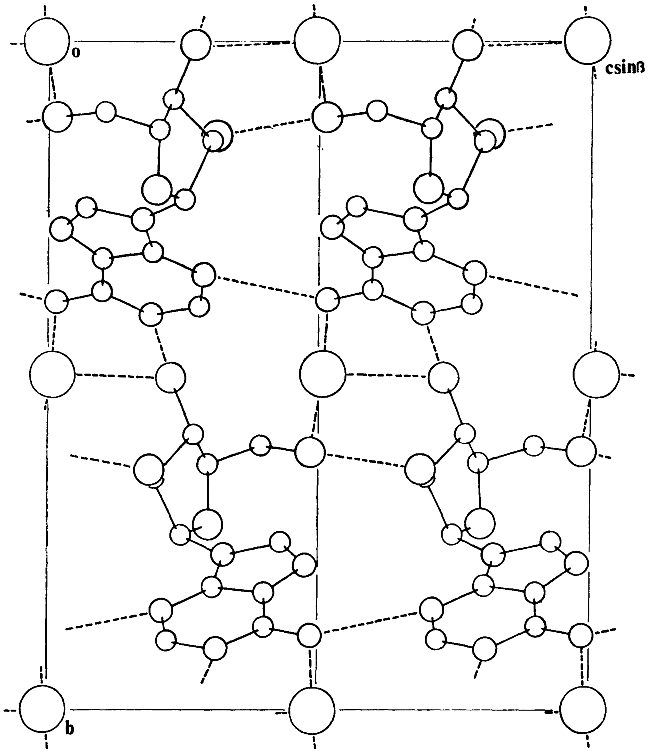


Fig. 6. A projection of the structure viewed down the a-axis. Hydrogen bonds are shown as broken lines.

are indicated by broken lines. Between the cation molecules, there is one hydrogen-bond related by the twofold screw axis and two hydrogen-bonds related by the translational operation. The N(1) atom hydrogen-bonds to O(3′) of the cation at $(1-x,\ 1/2+y,\ 1-z)$ in which the N(1) atom acts as a proton-donor, with a N(1)—O(3′) distance of 2.713 Å. The N(6) atom donates one of two hydrogen atoms to N(3) of another cation at $(x,\ y,\ -1+z)$ and O(2′) donates its proton to O(5′) at $(1+x,\ y,\ 1+z)$ forming usual hydrogen bond distances of 2.966 and 2.728 Å respectively. The chloride anion accepts three hydrogen atoms from O(3′), O(5′), and N(6) with distances of 2.983, 3.124, and 3.284 Å, respectively. Details of the hydrogen-bond distances and angles are given in Table 7.

Table 7. Hydrogen-bond distances and angles, D–H···A

D–H	A	Distance D–A	Distance H···A	Angle D–H···A
N(1)–H	O(3′)(a)	2.713Å	1.89Å	145°
N(6)–HA	N(3)(b)	2.966	2.05	147
N(6)–HB	Cl^-(c)	3.284	2.43	165
O(2′)–H	O(5′)(d)	2.728	1.88	137
O(3′)–H	Cl^-(e)	2.983	2.16	174
O(5′)–H	Cl^-(f)	3.124	2.42	162

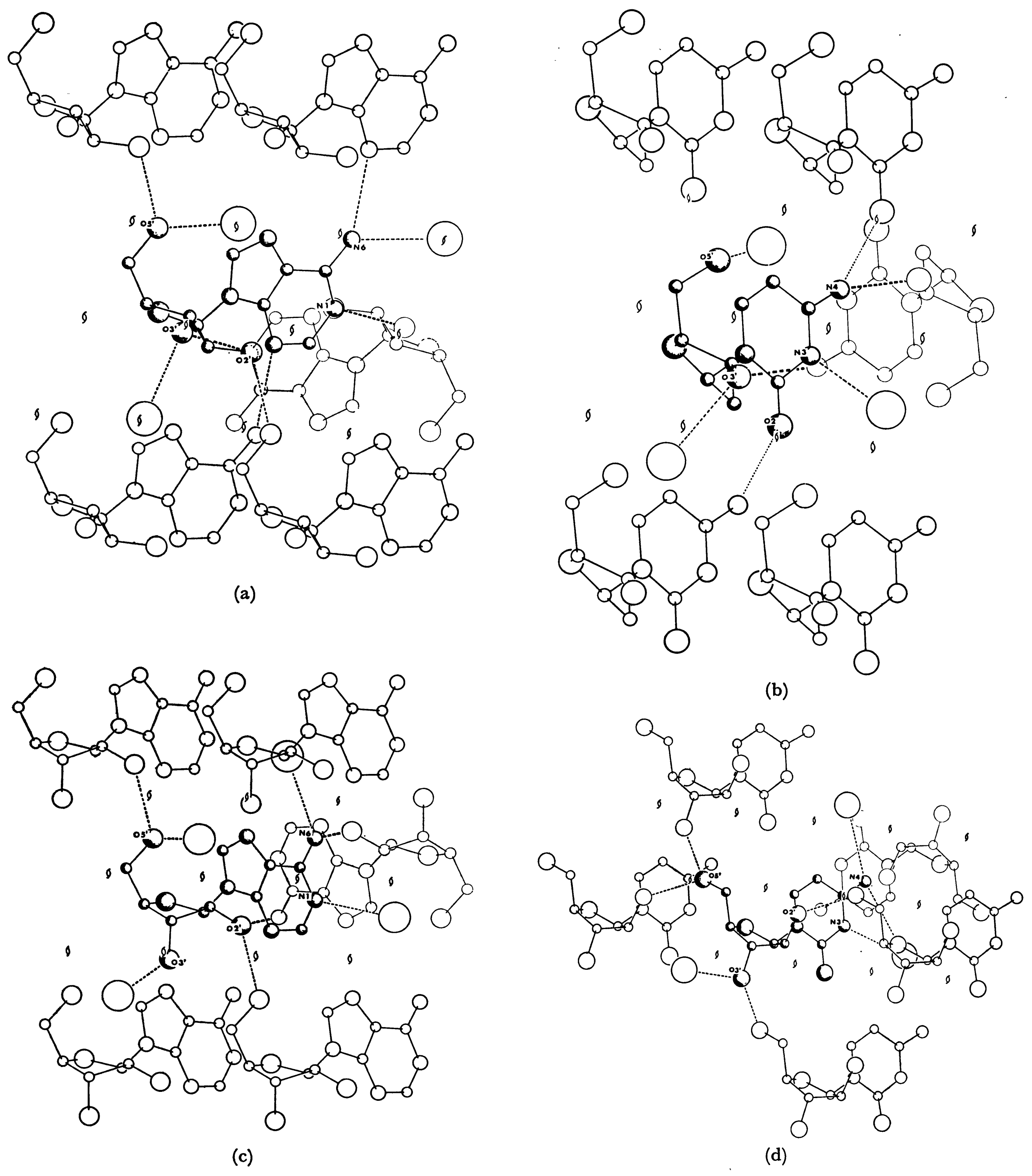
a) at $1-x,\ 1/2+y,\ 1-z$. b) at $x, y,\ -1+z$. c) at $1-x,\ 1/2+y,\ -z$. d) at $1+x, y,\ 1+z$. e) at $x, y,\ 1+z$. f) at x, y, z.

In order to make a comparison of the hydrogen-bond scheme of ara-A HCl with those of the other HCl salts of nucleoside derivatives, the projections of the crystal structures viewed along the b-axis of ara-A HCl, deoxycytidine hydrochloride (DC HCl),[18] adenosine hydrochloride (A HCl),[12] and arabinofuranosylcytosine hydrochloride (ara-C HCl)[16] are exhibited in Figs. 7(a), (b), (c), and (d). The space group of each crystal is $P2_1$. In these illustrations, the hydrogen-bonds formed between the cations related by a twofold screw axis are drawn by the bold broken lines, and the others are by the normal broken ones. The short intermolecular contacts in the DC HCl assumed to be weak hydrogen-bonds are represented by dotted lines. The noteworthy point in these figures is that some parts in the hydrogen-bond schemes closely resemble each other. In the molecular packings of these crystals, the hydrogen-bonds oriented in a similar manner are listed in the same row of Table 8. Each O(3′)H hydroxy group in all salts donates the hydrogen atom to the chlorine anion in a similar fashion and O(2′)—O(5′) hydrogen-bonds are formed in similar directions except the DC cation, which has no O(2′)H group. On the other hand, in the first three cations in Table 8, the hydrogen-bonds are formed between the cations related by a screw axis. They are N(1)H—O(3′) in the ara-A cation, N(4)H—O(3′) in the DC cation, and N(6)H—O(2′) in the A cation. One of the cations in ara-C HCl does not make hydrogen-bond to the other neighbouring cation related by a screw axis, and no hydrogen-bond forms between O(5′) and Cl^-. The combination of hydrogen-bonds in these molecules distinguishes the molecular arrangement of ara-C HCl from the remain-

Table 8. The hydrogen bonding schemes in various hydrochlorides
Each row shows the hydrogen-bonds oriented in similar directions.

	ara-A HCl[a)]	DC HCl[b)]	A HCl[c)]	ara-C HCl[d)]
The hydrogen bond related by screw axis	N(1)H···O(3′)	N(4)HB···O(3′)	N(6)HB···O(2′)	
Hydrogen bonds related by translation	N(6)HA···N(3)	N(4)HA···O(2)		
	O(2′)H···O(5′)		O(2′)H···O(5′)	O(2′)H···O(5′)
				O(5′)H···O(3′)
Other hydrogen bonds	O(3′)H···Cl^-	O(3′)H···Cl^-	O(3′)H···Cl^-	O(3′)H···Cl^-
	O(5′)H···Cl^-	O(5′)H···Cl^-	O(5′)H···Cl^-	
	N(6)HB···Cl^-			
		N(3)H···Cl^-	N(1)H···Cl^-	N(3)H···Cl^-
			N(6)HA···Cl^-	N(4)HA···Cl^-
				N(4)HB···Cl^-

a) arabinofuranosyladenine hydrochloride (This study). b) deoxycytidine hydrochloride (Ref. 18).
c) adenosine hydrochloride (Ref. 12). c) arabinofuranosylcytosine hydrochloride (Ref. 16).



(a)

(b)

(c)

(d)

Fig. 7. The crystal structures projected down the b-axis of (a) arabinofuranosyladenine hydrochloride, (b) deoxycytidine hydrochloride, (c) adenosine hydrochloride, and (d) arabinofuranosylcytosine hydrochloride, being drawn from the published parameters. The bold broken lines indicate the hydrogen-bonds related by the acrew axis and the normal broken ones indicate other hydrogen-bonds. The dotted lines indicate weak hydrogen-bonds. Note that the hydrogen-bond schemes in the former three crystals resemble each other.

ing three compounds. The hydrogen-bond net-works of these salts resemble each other in taking an overall view of the crystal structures as shown in Figs. 7(a), (b), and (c). This can be interpreted as indicating that the hydrogen-bond schemes of these nucleoside salts are broadly divided into two categories, one is in ara-C HCl and the other is in the rest of three compounds, thus far.

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