minimization of lone-pair–lone-pair interactions, which gives a shortened N—N bond.

Conclusion

The least-squares refinement of H parameters on high-order X-ray data shows that the data do contain information about the H atoms, but in this study the amount of data seems to be less than that needed for satisfactory refinement. The variation in the N—H bond lengths with the various minimum $\sin \theta/\lambda$ cut-off values follows the same trend as that seen in diformohydrazide: the N—H distances decrease with increasing $(\sin \theta/\lambda)_{\min}$ up to about 0.50 Å^{-1}, where the shortest bond lengths are found; a minimum cut-off of 0.75 Å^{-1} is necessary in order to obtain a reasonable mean N—H bond length.

The excellent agreement between the difference electron densities obtained for carbonohydrazide and diformohydrazide, where the differences follow the expected electronic variations, further support the usefulness of the $X - X_{HO}$ method for obtaining information about electron density deformations.

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Structural Studies of O-Cyclocytidine Derivatives. I. The Crystal and Molecular Structure of 6,2'-Anhydro-1-β-D-arabinofuranosyl-6-hydroxycytosine

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Abstract

The title compound, $C_9H_{11}N_3O_5$, crystallizes in the monoclinic system with space group $P2_1$, $Z = 2$ and unit-cell dimensions $a = 10.491$ (10), $b = 7.255$ (7), $c = 6.858$ (14) Å and $\beta = 103.55$ (10)°. The structure was solved by the direct interpretation of the three-dimensional Patterson function and refined by full-matrix and block-diagonal least-squares methods. The final R value was 0.051 for 740 independent reflections. The glycosyl torsion angle, χ_{CN}, is $111.4°$ (high anti) and the arabinose conformation is unusual C(4')-exo. The orientation of the C(5')–O(5') bond is gauche–gauche as found frequently in many nucleosides.

Introduction

The compound 1-β-D-arabinofuranosylcytosine (Ara-C) has been known to be effective as an inhibitor of DNA synthesis (Talley & Vaitkevicius, 1963) and it has been used for the medical treatment of leukemia and lymphoma. Furthermore, the Ara-C cyclo-derivative, 2,2'-anhydro-1-β-D-arabinofuranosylcytosine (2,2'-CC), possesses biological activity (Hoshi, Kanzawa, Kuretani, Saneyoshi & Arai, 1971) as a

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stronger inhibitor for cytidylate reductase and DNA polymerase than Ara-C. On the other hand, 6,2′-anhydro-1-β-D-arabinofuranosyl-6-hydroxycytosine (6,2′-CC), which has low activity (Kanai, Ichino, Hoshi, Kanzawa & Kuretani, 1972), is expected to have a conformation similar to that of 2,2′-CC (Brennan & Sundaralingam, 1973), except for a glycosidic torsion angle. Because of the additional cyclization by which the base ring is fused to the sugar ring, such molecules are under some strain, but the conformational freedom should be restricted and the molecular structures found in the crystalline state might be preserved in solution. Therefore, it seems very important to elucidate the detailed crystal and molecular structures of these cyclocompounds in order to compare the structural features with those of the related non-cyclocompounds, and they may be useful for the conformational studies by NMR and CD in solution. The preliminary structural result of 6,2′-CC has already been reported (Kashitani, Fujii & Tomita, 1976).

Experimental

The material was recrystallized from aqueous solution as a colorless plate. Weissenberg and precession photographs showed the crystal to be monoclinic with the space group $P2_1$. The density was measured by flotation in a chloroform–ethylene bromide mixture. The crystallographic data are shown in Table 1.

The intensities of 740 independent reflections within sin θ/λ < 0·55 Å^{-1} were measured on a fully automatic four-circle diffractometer with Cu $K\alpha$ radiation using the ω–2θ scan technique and adjusted to an absolute scale by Wilson's statistics. No absorption correction was made because of the small crystal dimensions (0·10 × 0·23 × 0·03 mm). All numerical calculations were carried out on an NEAC-2200-700 computer of the computation center of this university, with the programs of The Universal Crystallographic Computing System (1973).

Structure determination

The structure was solved by direct interpretation of the three-dimensional Patterson function; the peaks around the origin were immediately assigned by the vector sets as being due to the planar part of the molecule which

consists of eight non-hydrogen atoms of cytosine and three of the five-membered ring formed by the cyclization. The calculated minimum function based on this molecular portion revealed the proper positions of these eleven atoms in the crystal lattice, and the subsequent Fourier synthesis using the phase angles based on these atomic positions exhibited the peaks for the other six non-hydrogen atoms. The structure was refined by a full-matrix least-squares method with isotropic temperature factors for all the non-hydrogen atoms and then by a block-diagonal least-squares method with anisotropic temperature factors, and the R value was reduced to 0·081. At this stage, all H atoms could be located by a difference Fourier synthesis. The final refinement was carried out by a block-diagonal least-squares method with anisotropic temperature factors for all non-hydrogen atoms and with isotropic parameters for eleven H atoms. The final R value was reduced to 0·051.

Results and discussion

The atomic coordinates with their estimated standard deviations are given in Table 2.*

Table 2. *The final atomic coordinates of 6,2′-CC ($\times 10^4$ for non-hydrogen atoms; $\times 10^3$ for H) with their estimated standard deviations in parentheses*

	x	y	z
N(1)	906 (4)	70 (9)	3818 (6)
C(2)	−399 (5)	200 (12)	3875 (8)
N(3)	−1294 (4)	418 (9)	2138 (6)
C(4)	−892 (5)	518 (10)	438 (8)
C(5)	430 (5)	484 (11)	305 (8)
C(6)	1292 (5)	190 (10)	2077 (8)
O(2)	−677 (4)	108 (11)	5533 (6)
N(4)	−1838 (4)	627 (9)	−1289 (7)
O(2′)	2595 (3)	22 (8)	2376 (6)
C(1′)	1984 (6)	−319 (10)	5487 (9)
C(2′)	3143 (6)	−517 (10)	4449 (9)
C(3′)	4135 (5)	902 (9)	5543 (9)
C(4′)	3689 (5)	1216 (10)	7476 (9)
O(1′)	2280 (4)	1196 (7)	6818 (6)
O(3′)	5455 (3)	288 (8)	6021 (6)
C(5′)	4139 (6)	3013 (13)	8567 (11)
O(5′)	3780 (4)	4609 (7)	7430 (7)
H(N4)	−143 (6)	49 (12)	−254 (9)
H(N4′)	−278 (6)	66 (12)	−152 (9)
H(5)	75 (6)	50 (12)	−107 (9)
H(1′)	183 (7)	−149 (11)	637 (10)
H(2′)	358 (7)	−187 (12)	452 (10)
H(3′)	409 (6)	209 (11)	452 (10)
H(4′)	427 (6)	11 (13)	858 (9)
H(5′)	520 (6)	300 (10)	905 (9)
H(5′′)	372 (6)	316 (13)	995 (10)
H(O3′)	579 (6)	1 (13)	464 (9)
H(O5′)	301 (6)	521 (13)	770 (9)

Table 1. *Crystal data of 6,2′-CC*

$C_9H_{11}N_3O_5$	FW 241·11
Monoclinic	Space group $P2_1$
$a = 10\cdot491$ (10) Å	$Z = 2$
$b = 7\cdot255$ (7)	$F(000) = 252$
$c = 6\cdot858$ (14)	$V = 507\cdot45$ Å^3
$\beta = 103\cdot55$ (10)°	$D_m = 1\cdot571$ Mg m^{-3}
λ(Cu $K\alpha$) = 1·5418 Å	$D_x = 1\cdot578$
$\mu = 1\cdot13$ mm^{-1}	

The torsion angles in the sugar moiety and the deviations of individual atoms from the least-squares planes are listed in Tables 3 and 4 respectively.

(a) Bond lengths and angles

The bond lengths and angles are shown in Fig. 1, where the average standard deviations are about 0·009 Å for the bond lengths and 0·7° for the bond angles.

The cyclization between C(6) and O(2') causes little alteration in the bond lengths and angles of the base moiety, compared with those found in cytosine (Jeffrey

Table 3. Torsion angles (°)

Notation	Designation	Angle
χ	O(1')—C(1')—N(1)—C(6)	111·4
τ_0	C(4')—O(1')—C(1')—C(2')	−31·4
τ_1	O(1')—C(1')—C(2')—C(3')	6·2
τ_2	C(1')—C(2')—C(3')—C(4')	19·7
τ_3	C(2')—C(3')—C(4')—O(1')	−38·9
τ_4	C(3')—C(4')—O(1')—C(1')	44·3
ψ_{OO}	O(1')—C(4')—C(5')—O(5')	−59·4
ψ_{CO}	C(3')—C(4')—C(5')—O(5')	56·8

Table 4. Deviations (Å) of atoms from least-squares planes

X, Y and Z refer to the orthogonal coordinate system (Å) with X along a, Y along b and Z along c^*. An asterisk indicates atoms included in calculating the least-squares plane.

(a) Base

	(I)	(II)	(III)
N(1)	0·006*	0·010*	−0·055*
C(2)	−0·014*	0·098	−0·037*
N(3)	0·001*	0·248	0·041*
C(4)	0·021*	0·293	0·084*
C(5)	−0·024*	0·143	0·003*
C(6)	0·015*	0·047*	−0·021*
O(2)	−0·045	0·034	−0·093
N(4)	0·116	0·525	0·243
O(2')	0·038	−0·049*	−0·043*
C(1')	0·108	−0·038*	−0·021*
C(2')	0·252	0·042*	0·109*

Equations of the planes
(I) $-0·057X - 0·992Y - 0·116Z + 0·370 = 0·0$
(II) $-0·136X - 0·973Y - 0·185Z + 0·577 = 0·0$
(III) $-0·085X - 0·985Y - 0·153Z + 0·414 = 0·0$

(b) Sugar

	(I)	(II)
C(1')	−0·021*	−0·035*
C(2')	0·019*	0·035*
C(3')	0·155*	−0·023*
C(4')	−0·321*	−0·612
O(1')	0·228*	0·024*
O(3')	−0·651	−0·858
C(5')	0·141	−0·352
O(5')	1·526	0·995

Equations of the planes
(I) $-0·207X + 0·751Y - 0·627Z + 2·695 = 0·0$
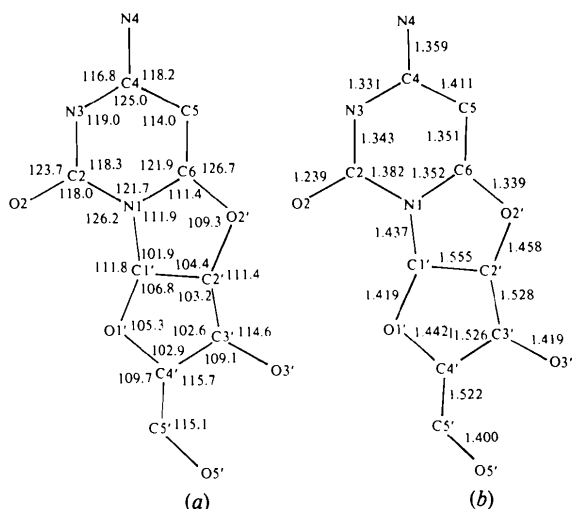(II) $-0·241X + 0·654Y - 0·717Z + 3·030 = 0·0$

Fig. 1. (a) Bond angles (°) and (b) bond lengths (Å). The average e.s.d.'s are about 0·009 Å for the bond lengths and 0·7° for the bond angles.

& Kinoshita, 1963) and cytidine derivatives (Furberg, Petersen & Rømming, 1965), but considerable changes are found in the sugar moiety. The C(6)—O(2') bond (1·339 Å) is significantly shorter than the normal C—O single bond (1·426 Å; Sutton, 1965), whereas the C(2')—O(2') bond (1·458 Å) is a little longer. These values correspond well with the C(2)—O(2') bond distances (1·335 and 1·344 Å) and C(2')—O(2') distances (1·461 and 1·462 Å), found in 2,2'-anhydro-1-β-D-arabinofuranosyluracil (2,2'-CU; Suck & Saenger, 1973; Delbaere & James, 1973) which has a similar fused-ring system. The shortening of the glycosidic N(1)—C(1') bond length (1·437 Å) is rather more significant than the corresponding distance (1·457 Å) of 2,2'-CU which is even shorter than the average value of the ribofuranose glycosidic linkage (1·476 Å; Voet & Rich, 1970). As we would expect, the cyclization also produces some changes in the bond angles around N(1), C(1') and C(2'), i.e. the angles N(1)—C(1')—C(2'), C(1')—C(2')—O(2') and C(1')—N(1)—C(6) are smaller by 13, 10 and 7°, respectively, than those found in Ara-C (Chwang & Sundaralingam, 1973; Tougard & Lefebvre-Soubeyran, 1974).

(b) Molecular conformation

The molecular conformation is shown in Fig. 2. The glycosyl torsion angle χ_{CN}, O(1')—C(1')—N(1)—C(6) (111·4°), in the high anti region, as expected differs by ca 180° from that found in 2,2'-CC (Brennan & Sundaralingam, 1973) or 2,2'-CU (Suck & Saenger, 1973; Delbaere & James, 1973). The nine-membered fused-ring system formed by the cyclization between C(6) and O(2') is essentially planar (Table 4). The

dihedral angle between the sugar plane [except C(4')] and the nine-membered ring plane is 60° and this indicates that the conformation of 6,2'-CC is flatter than that of 2,2'-CC (Brennan & Sundaralingam, 1973) having an angle of 71°. The sugar puckering exhibits a C(4')-*exo* conformation, where the C(4') atom is displaced by 0·61 Å from the least-squares plane formed by the remaining four atoms C(1'), C(2'), C(3') and O(1') (Table 4) and the torsion angle O(1')—C(1')—C(2')—C(3') is only 6·2° (Table 3). A similar sugar conformation is found in one molecule (*A*) of 2,2'-anhydro-2-hydroxy-1-β-D-arabinofuranosyl-4-pyridone (Hutcheon & James, 1977), but it is distinct from those in 2,2'-cyclopyrimidine nucleosides such as 2,2'-CC (Brennan & Sundaralingam, 1973) and 2,2'-CU (Suck & Saenger, 1973; Delbaere & James, 1973) which have the C(4')-*endo* and C(4')-*endo*,C(3')-*exo* conformations respectively. The C(5')—O(5') bond is in the *gauche–gauche* conformation [torsion angles O(5')—C(5')—C(4')—C(3') = 57°]. Because of the C(4')-*exo*
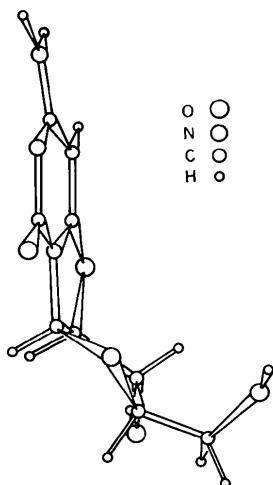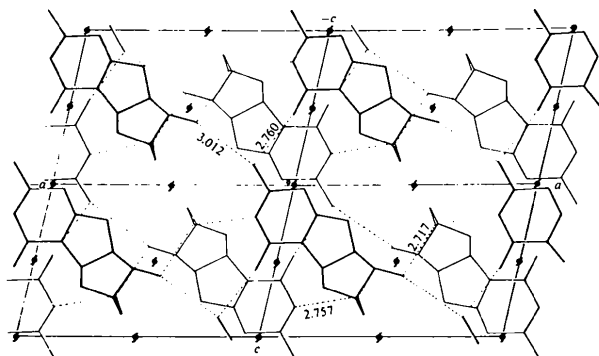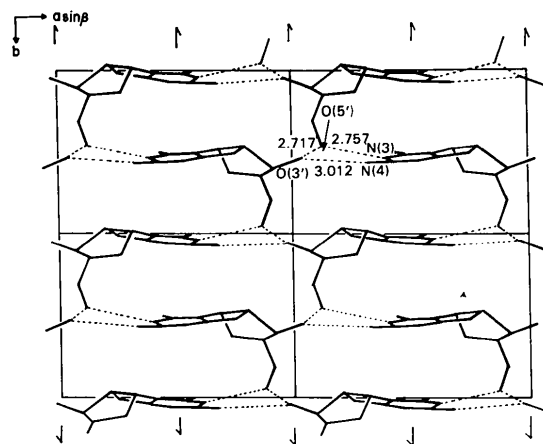

Fig. 4. The molecular packing and hydrogen bonding (dashed lines) viewed along the *c* axis.

Table 5. *Distances (Å) and angles (°) for the hydrogen bonds*

D–H···A		D···A	H···A	∠D–H···A
N(4)–H(N4)···O(2)	(X, Y, −1+Z)	2·760	1·72	174
N(4)–H(N4')···O(3')	(−1+X, Y, −1+Z)	3·012	2·21	140
O(5')–H(O5')···N(3)	(−X, 0·5+Y, 1−Z)	2·757	1·83	157
O(3')–H(O3')···O(5')	(1−X, −0·5+Y, 1−Z)	2·717	1·62	174

puckering, the molecule has no short contact between O(5') and any atoms in the base moiety, and also no intramolecular hydrogen bond, in contrast to Ara-C (Chwang & Sundaralingam, 1973; Tougard & Lefebvre-Soubeyran, 1974) which shows the C(2')-*endo* conformation and has an O(2')—H···O(5') hydrogen bond. In contrast to the case of 2,2'-CC, the 6,2'-CC molecule is electrically neutral, and no electrostatic interaction participates in the stabilization of the molecular structure.

(c) Molecular packing

Molecular packing is shown in Figs. 3 and 4 which represent the projections along the *b* and *c* axes, respectively.

The base planes are nearly parallel to the (010) plane of the crystal lattice, but no base stacking is observed (Fig. 3). There are eight hydrogen bonds as shown in Table 5, in which N(4) participates as a donor, O(2) as an acceptor and two hydroxyl atoms, O(3') and O(5'), as both donors and acceptors.

Fig. 2. The molecular conformation.

O	O
N	O
C	O
H	o

Fig. 3. The molecular packing and hydrogen bonding (dashed lines) viewed along the *b* axis.

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Structural Studies of *O*-Cyclocytidine Derivatives.
II. The Crystal and Molecular Structures of 2,2′-Anhydro-1-β-D-arabinofuranosyl-5-dimethylsulfonio-6-oxocytosine Chloride and 2,2′-Anhydro-1-{3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl}-5-chloro-6-oxocytosine and the Comparison with their Conformations in Aqueous Solution

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Abstract

The title compounds, 2,2′-anhydro-1-β-D-arabino-furanosyl-5-dimethylsulfonio-6-oxocytosine chloride [$C_{11}H_{16}N_3O_5S^+.Cl^-$, 5-S($CH_3$)$_2$-2,2′-CC] and 2,2′-anhydro-1-{3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl}-5-chloro-6-oxocytosine ($C_{13}H_{14}ClN_3O_7$, 5-Cl-2,2′-CC) crystallize in the orthorhombic system with space group $P2_12_12_1$ and the tetragonal system with space group $I4_1$, respectively. The unit-cell dimensions are $a = 11\cdot156$ (3), $b = 17\cdot403$ (10) and $c = 7\cdot355$ (8) Å for 5-S(CH_3)$_2$-2,2′-CC and $a = b = 20\cdot125$ (10) and $c = 7\cdot566$ (8) Å for 5-Cl-2,2′-CC. Both structures were solved by the heavy-atom method and refined to R values of 0·042 for 5-S(CH_3)$_2$-2,2′-CC and 0·066 for 5-Cl-2,2′-CC. The molecular geometries in both compounds are very similar; the glycosidic torsion angles, χ_{CN}, are 302·7° for 5-S(CH_3)$_2$-2,2′-CC and 291·1° for 5-Cl-2,2′-CC, sugar conformations are C(4′)-*endo*-O(1′)-*exo* and C(4′)-*endo*, respectively, and the orientations about the C(5′)—O(5′) bond are both *gauche–gauche*. The intramolecular short contacts between O(5′) and the N(1), C(2) and O(2′) atoms in the newly

introduced five-membered ring are observed. In connection with their NMR and CD results, it seems likely that both molecular structures found in the crystals are retained even in aqueous solution.

Introduction

5-S(CH_3)$_2$-2,2′-CC and 5-Cl-2,2′-CC (Fig. 1) were synthesized from AraC† (Kanai & Maruyama, 1976).

As described in the previous paper (Yamagata, Fujii, Kanai, Ogawa & Tomita, 1979), such a cyclo-nucleoside would be a suitable model for comparing the dihedral angles observed in the crystal structure with the corresponding angles calculated from the coupling constants of NMR by the use of the Karplus formula and also for studying the π–π* Cotton effects in the CD pattern, because of the rotational restriction around the base and the sugar moieties by cyclization.

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† Abbreviations: AraC: 1-β-D-arabinofuranosylcytosine; 2,2′-CC: 2,2′-anhydro-1-β-D-arabinofuranosylcytosine; AraU: 1-β-D-arabinofuranosyluracil; 2,2′-CU: 2,2′-anhydro-1-β-D-arabinofuranosyluracil; 2,2′-CP: 2,2′-anhydro-2-hydroxy-1-β-D-arabinofuranosyl-4-pyridone; 6,2′-CC: 6,2′-anhydro-1-β-D-arabinofuranosyl-6-hydroxycytosine; 2,2′-α-CxyloU: 2,2′-anhydro-1-α-D-xylofuranosyluracil.

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