CRYSTAL AND MOLECULAR STRUCTURE OF 6,2'-ANHYDRO-1-β-D-ARABINO-FURANOSYLCYTOSINE

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SUMMARY:

The crystal and molecular structure of the title compound has been determined by X-ray diffraction method. The compound crystallizes in monoclinic system with the space group $P2_1$ and Z=2; the unit cell dimensions are a=10.491, b=7.255, c=6.858 A and β=103.55°. The structure was refined to an R-index of 0.051. The glycosyl torsion angle χ_{CN} is 111.4° (syn-anti) and the arabinose ring forms an exo-conformation, in which C(4') is displaced by 0.61 A out of the plane of remaining four atoms. The orientation of the C(5')-O(5') bond is the gauche-gauche as similar as that found frequently in many nucleosides.

INTRODUCTION:

The compound, ara-C,*) has been known to be effective for the inhibition of DNA synthesis,[1] and it has been used for the treatment of leukemia and lymphomas. Furthermore, the cyclonucleoside of ara-C derivatives, for instance, 2,2'-cyclo-C[2], possesses biological activity as a strong inhibitor for cytidylate reductase and DNA polymerase than its parent compound, ara-C. On the other hand, 6,2'-cyclo-C has a little activity,[3] of which conformation is expected to be similar to that of 2,2'-cyclo-C except a glycosidic torsion angle.[4] Because of these polycyclic molecules in which the base ring is fused to the sugar ring, the conformational freedom should be restricted and these molecular structures found in the crystalline state might be also preserved in solution. Therefore, it seems very important to elucidate the detailed crystal and molecular structure and compare its structural feature with that of related compounds.

*) Abbreviations: 6,2'-cyclo-C: 6,2'-anhydro-1-β-D-arabinofuranosylcytosine, 2,2'-cyclo-C: 2,2'-anhydro-1-β-D-arabinofuranosylcytosine, ara-C: 1-β-D-arabinofuranosylcytosine, ara-U: 1-β-D-arabinofuranosyluracil, 2,2'-cyclo-U: 2,2'-anhydro-1-β-D-arabinofuranosyluracil

EXPERIMENTAL:

The material 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 unit cell dimensions are a=10.491, b=7.255, c=6.858 Å, and β=103.55°. For the structure analysis, the intensities of 740 independent reflections ($2\theta_{max}$=116°) were measured on a full-automatic four-circle diffractometer (Rigaku Denki Co.) with Cu Kα radiation using the ω-2θ scan technique. The structure was solved by means of a three dimensional Patterson synthesis; the vector peaks around the origin was interpreted immediately using a planar model which consists of eight atoms of cytosine and three in the sugar moiety. The calculated minimum function based on this model revealed properly the position of the molecule in the crystal lattice. Refinement of the non-hydrogen atoms with anisotropic temperature factors and the hydrogen atoms with isotropic temperature parameters reduced an R-index to 0.051.

RESULT AND DISCUSSION:

The final atomic coordinates of all non-hydrogen atoms are given in Table 1. The bond distances and angles (see Fig.1(a)) in the base moiety show the similar features as that found in cytosine and cytidine derivatives. The cyclization between atoms C(6) and O(2') causes little alteration in the base conformation, but the considerable conformational changes were found in the sugar moiety and the newly formed five-membered ring. The C(6)-O(2') bond (1.339 Å) is significantly shorter than a normal C-O single bond (1.426 Å), whereas the C(2')-O(2') bond (1.458 Å) is a little longer than the average C-O single bond. The shortening of the glycosyl bond distance (1.437 Å) is also significant. As one would expect, the cyclization also produces some major changes in the angles around C(1') and C(2') of the arabinose moiety, i.e., the angles of N(1)-C(1')-C(2') and C(1')-C(2')-O(2') are apparently smaller by ca. 10° than those found in ara-C,

The molecular conformation is shown in Fig.1(b). The nine-membered fused ring system which are resulted by the cyclization between C(6) and O(2') is nearly planar. The dihedral angle between the sugar and the nine-membered ring planes is 60°. This value indicates that the conformation of 6,2'-cyclo-C is flatter than that of 2,2'-cyclo-C having the angle of 71°. The pucker-

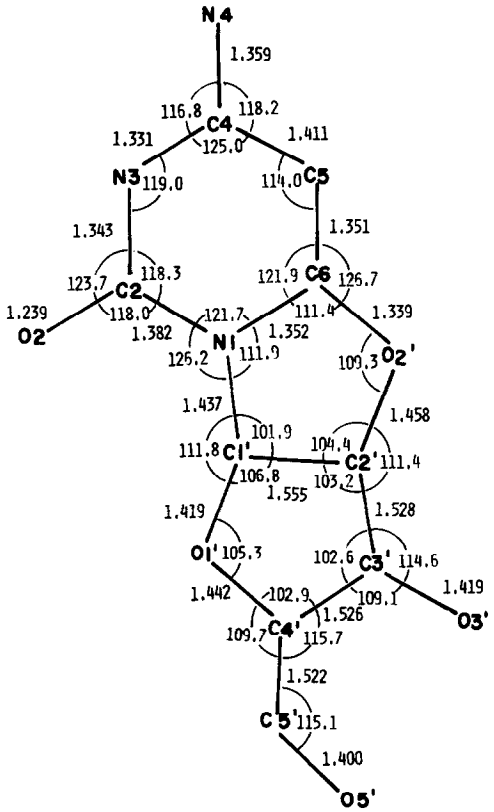

Fig.1(a)

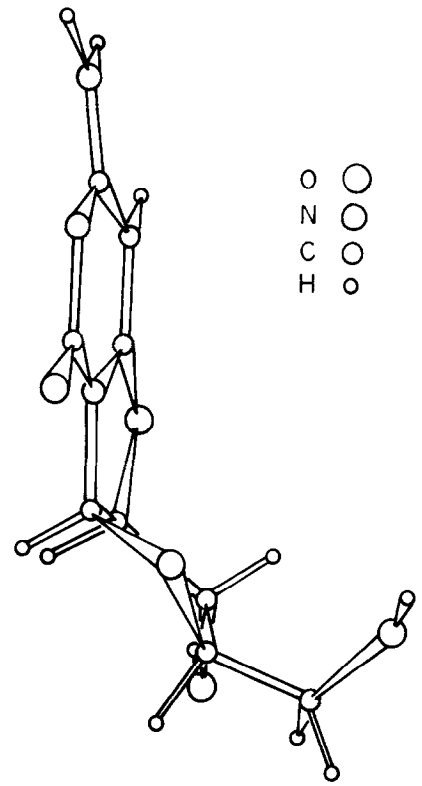

Fig.1(b)

ing of the sugar ring is somewhat different from those found in the other nucleosides. It exhibits a C(4') exo- conformation; the atom C(4') is displaced by 0.61 Å from the least-squares plane of remaining four atoms. This conformation is distinct from those in the 2,2'-cyclo-pyrimidine nucleosides, 2,2'-cyclo-C and 2,2'-cyclo-U,[5)6)] so far determined by X-ray method. The 2,2'-cyclization might render the sugar conformation to be a C(4')-endo or C(4')-endo-C(3')-exo. The orientation of the C(5')-O(5') bond is the gauche-gauche configuration (O(5')-C(5')-C(4')-C(3')=57° and O(5')-C(5')-C(4')-O(1')=-59°). Because of a C(4')-exo puckering, the molecule has no short contact between O(5') and any atom in the base moiety, and also no contact suitable for the intramolecular hydrogen bond, O(2')-H---O(5'), as found in ara-C[7)8)] or ara-U[9)] which have both a C(2')-endo-conformation. The 6,2'-cyclo-C molecule in this crystal is electrically neutral, and no electrostatic interaction participates for the stabilizing of

Table 1

Atom	X	Y	Z
N(1)	.0906(4)	.0070(9)	.3818(6)
C(2)	-.0399(5)	.0200(12)	.3875(8)
N(3)	-.1294(4)	.0418(9)	.2138(6)
C(4)	-.0892(5)	.0518(10)	.0438(8)
C(5)	.0430(5)	.0484(11)	.0305(8)
C(6)	.1292(5)	.0190(10)	.2077(8)
O(2)	-.0677(4)	.0108(11)	.5533(6)
O(6)	.2595(3)	.0022(8)	.2376(6)
N(4)	-.1838(4)	.0628(9)	-.1289(7)
C(1')	.1984(6)	-.0319(10)	.5487(9)
C(2')	.3143(6)	-.0517(10)	.4449(9)
C(3')	.4135(5)	.0902(9)	.5543(9)
C(4')	.3689(5)	.1216(10)	.7476(9)
O(1')	.2280(4)	.1196(7)	.6818(6)
O(3')	.5455(3)	.0288(8)	.6021(6)
C(5')	.4139(6)	.3013(13)	.8567(11)
O(5')	.3779(4)	.4609(7)	.7430(7)

molecular structure in contrary to the case of 2,2'-cyclo-C. A glycosidic torsion angle, χ_{CN}, which was defined by Sundaralingum, is 111.4°, and the orientation of the base in respect to the sugar ring is in the opposite direction to that of 2,2'-cyclo-pyrimidine nucleosides.

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