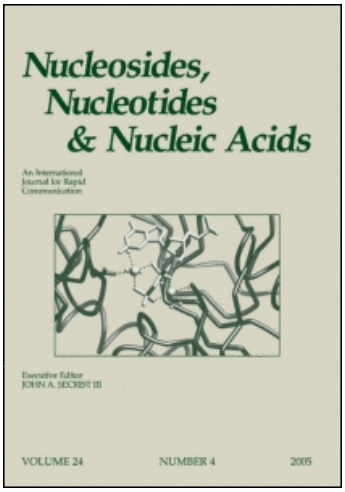

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STRUCTURE OF 2',3'-O-ISOPROPYLIDENE-6-CYANOURIDINE

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Abstract: The crystal and molecular structure of the title compound has been determined by the X-ray diffraction method. Crystals belong to the orthorhombic space group $P2_12_12_1$, and the cell dimensions are a=7.832(1), b=20.466(2) and c=9.159(1) A. The structure was solved by direct methods and refined by the full matrix least-squares method to R=0.070. The conformation about the glycosidic bond is syn probably because of the steric hindrance between the sugar moiety and the cyano group at the C(6) position of the base. The sugar puckering is C(4')-exo, and the orientation of C(5')-O(5') bond is gauche-trans.

INTRODUCTION

From studies by NOE and CD, 2',3'-O-isopropylidene pyrimidine nucleosides are expected to have the syn-conformations in solution[1-3]. However, as described in the previous paper[4], the molecular conformations of the two 2',3'-O-isopropylidene pyrimidine nucleosides so far reported are anti. Therefore, the structural features of 2',3'-O-isopropylidene pyrimidine nucleosides with the syn conformation are still obscure. Usually, the replacement of hydrogen at C(6) position of base with a bulky substituent leads to a nucleoside with a syn

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conformation because of the steric hindrance between the sugar moiety and the substituent. The title compound (i-CN^6U) was synthesized[5] for investigation of the effect of the cyano substituent on the overall conformation of the molecule in the solid state.

EXPERIMENTAL

Crystals of i-CN^6U were obtained from methanol solution by the vapor diffusion technique using ether as precipitant. X-Ray photographs showed the crystals to be orthorhombic with space group $P2_12_12_1$. The unit cell dimensions were determined by a least-squares procedure based on the 2θ values of 25 diffractometer-measured reflections in the range $35°<2\theta<55°$ (Cu Kα). The density was determined by the flotation method in a benzene/carbon tetrachloride mixture. The crystallographic data are summarized in TABLE 1.

Intensities of 1377 reflections within $\sin\theta/\lambda=0.58$ $\AA^{-1}$ were collected from a crystal of dimensions 0.07x0.12x0.3 mm on a Rigaku automatic four-circle diffractometer (Cu Kα). Of those, 1142 with $|F_o|>3\sigma|F_o|$ were used for the structure analysis. The data were corrected for Lorentz and polarization factors but not for absorption.

The structure was solved by direct methods using the program MULTAN 78[6], and refined by the full matrix least-squares method with anisotropic temperature factors for all the non-hydrogen atoms. All H atoms were located on a difference Fourier map. The final refinement including the H atoms with isotropic temperature factors reduced the R value to 0.070. All numerical calculation were carried out on an ACOS 700 Computer at the Crystallographic Research Center, Institute for Protein Research, Osaka University, using the

TABLE 1. Crystal data

$C_{13}H_{15}N_3O_6$	FW 309.28
orthorhombic	Space group $P2_12_12_1$
a=7.832(1) Å	Z=4
b=20.466(2)	F(000)=648
c=9.159(1)	V=1468.2(3) $Å^3$
λ(Cu Kα)=1.54173 Å	Dm=1.394(1) Mg m^{-3}
μ(Cu Kα)=0.97 mm^{-1}	Dx=1.394

TABLE 2. Final positional and thermal parameters with their estimated standard deviations[a].

atom	x	y	z	B_{eq} (Å^2)[b]
N(1)	4394(8)	4924(3)	8068(6)	2.7(2)
C(2)	3798(11)	5249(3)	6825(8)	3.2(3)
N(3)	4241(10)	5899(3)	6789(7)	3.8(3)
C(4)	5273(13)	6235(4)	7751(10)	4.5(4)
C(5)	5879(11)	5869(4)	8960(8)	3.3(4)
C(6)	5436(10)	5237(4)	9078(8)	3.1(3)
O(2)	2949(8)	4994(3)	5901(6)	4.2(3)
O(4)	5593(12)	6817(3)	7537(8)	7.4(4)
C(7)	6067(12)	4854(4)	10308(9)	4.0(4)
N(7)	6596(14)	4587(4)	11269(10)	7.5(6)
C(1')	4038(10)	4206(3)	8159(8)	2.7(3)
C(2')	2190(9)	4021(3)	7904(7)	2.5(3)
C(3')	2228(10)	3598(3)	6544(8)	2.7(3)
C(4')	4073(11)	3388(3)	6439(8)	3.0(4)
C(5')	4655(13)	3311(5)	4857(11)	5.7(5)
O(1')	5048(7)	3902(2)	7110(6)	3.7(2)
O(2')	1711(7)	3559(2)	9013(5)	2.8(2)
O(3')	1109(7)	3060(2)	6843(6)	3.4(2)
C(6')	508(10)	3132(4)	8349(9)	3.1(4)
C(7')	-1265(12)	3412(4)	8312(11)	4.4(4)
C(8')	608(13)	2467(4)	9112(10)	4.3(4)
H(3)[c]	467(11)	607(4)	600(9)	
H(5)	677(11)	616(4)	960(9)	
H(1')	433(11)	405(4)	931(9)	
H(2')	120(11)	442(4)	796(9)	
H(3')	190(11)	381(4)	538(9)	
H(4')	417(11)	300(4)	707(9)	
H(5')	453(11)	382(4)	401(9)	
H(5")	369(11)	306(4)	408(9)	
H(O5')	699(11)	269(4)	430(9)	
H(7'1)	-123(11)	391(4)	775(9)	
H(7'2)	-199(11)	309(4)	774(9)	
H(7'3)	-145(11)	352(4)	903(9)	
H(8'1)	172(11)	234(4)	892(9)	
H(8'2)	37(11)	258(4)	1024(10)	
H(8'3)	-39(11)	222(4)	866(9)	

[a]All values are multiplied by 10^4 for the nonhydrogen atoms and 10^3 for the hydrogen atoms. [b]The equivalent isotropic temperature factors for the nonhydrogen atoms were computed using the expression: $B_{eq}=3/4\Sigma_{ij}\beta_{ij}(a_i \cdot a_j)$. [c]The isotropic temperature factors for hydrogen atoms are 3.0 Å^2.

programs of The Universal Crystallographic Computing System-Osaka (1979)[7]. The atomic scattering factors used were those cited in International Tables for X-ray Crystallography (1974)[8].

RESULTS AND DISCUSSION

Final atomic parameters are given in TABLE 2. The molecular conformation of i-CN^{6}U is stereoscopically[9] shown in Fig.1. As expected, the conformation about the glycosidic bond is syn with the torsion angle χ, 257.4° (TABLE 3), which is similar to those found in pyrimidine nucleosides and nucleotides with the syn conformation (TABLE 4). The allowable χ range is remarkably narrow (ca. 20°), in comparison with those for the anti conformation (purine χ; 0-130°, pyrimidine χ; 0-80°) or the syn conformation found in purine nucleosides and nucleotides (χ; 210-280°)[10], probably because of the short contacts between the O(2) atom in the base and some atoms in the sugar moiety beyond the allowable χ range.

The sugar conformation is C(4')-exo, which is, as shown in TABLE 4, one of two typical sugar conformations (C(4')-exo type; P=35-51°, C(2')-endo type; P=139-169°) found in pyrimidine nucleosides and nucleotides with the syn conformation. The usual C(3')-endo conformation (P=18°) of pyrimidine nucleosides bears unacceptable short contacts between the O(2) atom and the sugar atoms when the χ angle is rotated up to the syn region. On the other hand, the intra-

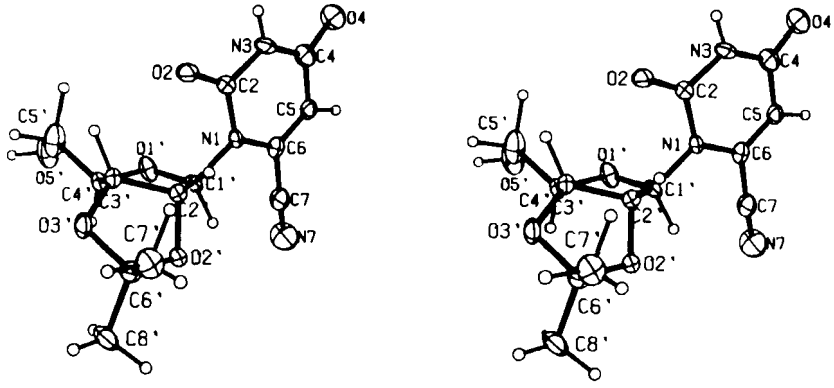

Fig. 1. Stereoview of the molecular conformation with atomic numberings.

TABLE 3. Torsion angles(°)

Designation		
χ	O(1')-C(1')-N(1)-C(6)	257.4(7)
τ_0	C(4')-O(1')-C(1')-C(2')	-16.1(7)
τ_1	O(1')-C(1')-C(2')-C(3')	-2.5(7)
τ_2	C(1')-C(2')-C(3')-C(4')	18.7(7)
τ_3	C(2')-C(3')-C(4')-O(1')	-28.6(7)
τ_4	C(3')-C(4')-O(1')-C(1')	28.3(7)
ψ_{OO}	O(1')-C(4')-C(5')-O(5')	65.2(8)
ψ_{CO}	C(3')-C(4')-C(5')-O(5')	-178.2(7)
λ_0	O(2')-C(6')-O(3')-C(3')	-19.5(7)
λ_1	C(6')-O(3')-C(3')-C(2')	-3.4(7)
λ_2	O(3')-C(3')-C(2')-O(2')	24.5(7)
λ_3	C(3')-C(2')-O(2')-C(6')	-37.4(6)
λ_4	C(2')-O(2')-C(6')-O(3')	36.0(7)

TABLE 4. Conformational parameters[20] for pyrimidine nucleosides and nucleotides in syn conformation.

	χ(°)	P(°)	τ_m(°)	C4'-C5'	hydrogen bond	ref.
2',3'-cCMP•Na(A)[a]	254	planar	2	gt	no	15
S^4U[b]	263	35	40	gg	no	11
2'-f,3',5'-ac_2dU[c]	252	39	35	tg	impossible	16
3',5'-cTMP deriv[d]	263	49	47	tg	impossible	17
3',5'-cUMP deriv[e]	251	50	47	tg	impossible	18
i-CN^6U	257	51	30	gt	no	this work
2',3'-cCMP•Na(B)	243	81	36	gg	no	15
m^6dU[f]	242	139	31	gg	yes	12
m_2-ribo-L(A)[g]	254	151	39	gg	yes	19
m^6U(A)[h]	251	155	35	gg	yes	13
m_2-ribo-L(B)	261	163	38	gg	yes	19
m^6U(B)	253	169	37	gt	no	13

Abbreviations; [a]sodium salt of cytidine 2',3'-cyclic phosphate, [b]4-thiouridine, [c]3',5'-O-diacetyl-2'-deoxy-2'-fluorouridine, [d]thymidine 3',5'-cyclic-N,N-dimethylphosphate, [e]2'-acetyluridine-3',5'-cyclic phosphate benzyl ester, [f]6-methyl-2'-deoxyuridine, [g]6,7-dimethyl-N-1--D-ribofuranosyllumazine, [h]6-methyluridine.

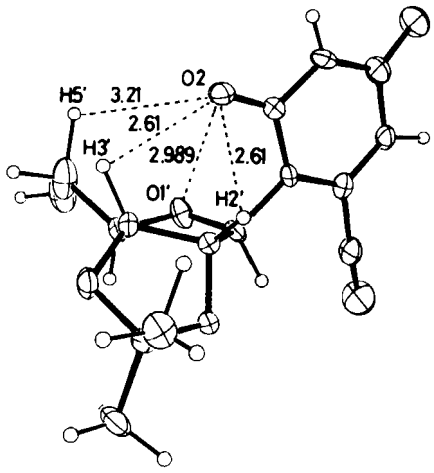

Fig. 2. The atomic distances (Å) from O(2) atom to some atoms of the ribose moiety in i-CN^6U.

molecular contacts when a pyrimidine nucleoside in the syn range takes the C(2')-endo or C(4')-exo,C(3')-endo conformation, for example, H(3')---O(2) (2.27 Å) in s^4U[11], H(2')---O(2) (2.30 Å) in m^6dU[12], H(2')---O(2) (2.29 Å) in m^6U(A) and H(2')---O(2) (2.26 Å) in m^6U(B)[12], are acceptable, and particularly in the present case, the C(4')-exo conformation is favorable to aviod such steric hindrance (see Fig. 2). Therefore, the sugar conformation in pyrimidine nucleosides with the syn conformation will adopt a C(4')-exo type including C(4')-exo,C(3')-endo twist type rather than a usual C(3')-endo type. It is interesting that 3',5'-cyclic nucleotides, with predominantly C(4')-exo sugar puckering and 2'-fluoro-2'-deoxynucleosides, with a strong preference for the C(4')-exo,C(3')-endo conformation[21] exist in the syn conformation with unmodified bases. The pyrimidine nucleosides having the C(2')-endo sugar puckering in the syn range generally have the gauche-gauche conformation about C(4')-C(5') bond, causing intramolecular O(5')-H---O(2) hydrogen bond formation, but i-CN^6U with C(4')-exo sugar puckering takes a gauche-trans conformation.

The bond lengths and angles are shown in Figs. 3 and 4. In spite of the substitution of a hydrogen with a cyano group at the C(6) position, the bond lengths and angles in the base moiety are in good agreement with those of the standard uracil skeleton[14]. The angle distorsions around the C(2') and C(3') atoms are commonly observed in 2',3'-O-isopropylidene nucleosides.

The molecular packing viewed along the a axis is shown in Fig. 5. The molecule is held together with three kinds of unusual hydrogen bonds, N(3)-H---O(2') (2.872 Å), O(5')-H---O(3') (2.863 Å) and

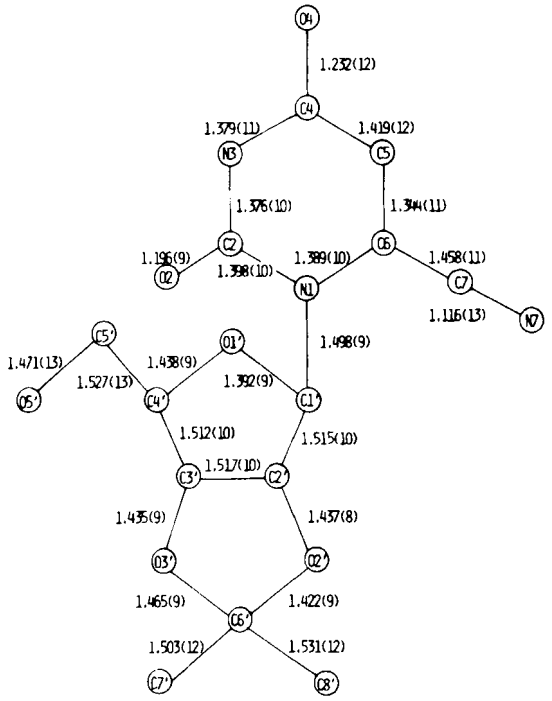

Fig. 3. Bond lengths (Å) with estimated standard deviations in parentheses.

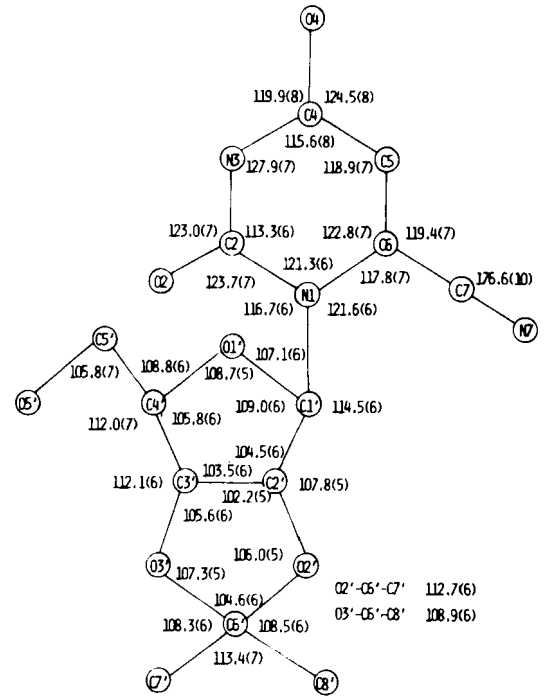

Fig. 4. Bond angles (°) with estimated standard deviations in parentheses.

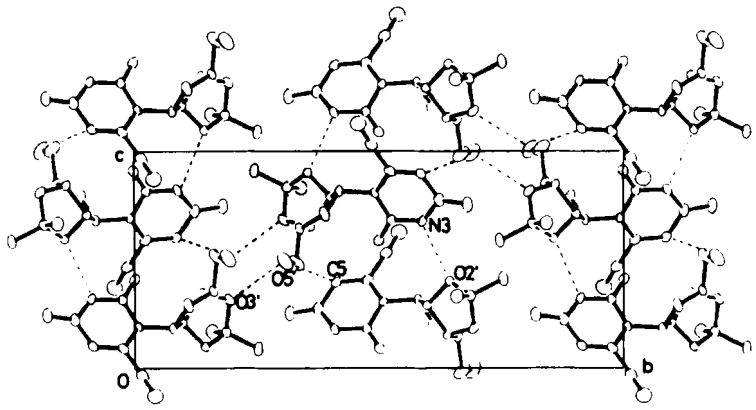

Fig. 5. Molecular packing along the a axis.
Dashed lines indicate the hydrogen bonds.

C(5)-H---O(5') (3.125 Å), where the oxygen atom of the ether bond and a hydrogen attached to a carbon atom in the pyrimidine ring are involved.

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