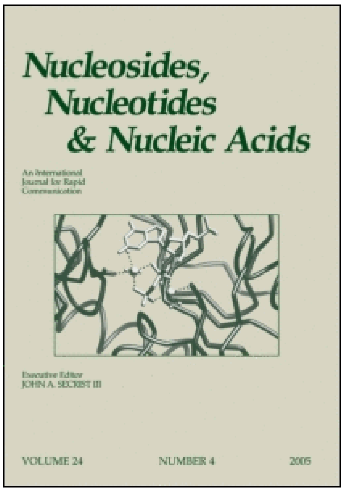

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# Structure of 2',3'-0-Isopropylidene-5-Bromouridine

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# STRUCTURE OF 2',3'-O-ISOPROPYLIDENE-5-BROMOURIDINE

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Abstract: The crystal and molecular structure of the title compound has been determined by the X-ray diffraction method. The crystals are orthorhombic, space group $P2_12_12_1$ (Z=4), with the unit cell dimensions a=5.244(2), b=14.916(6) and c=19.068(5) Å. The structure was solved by direct methods and refined up to the R value of 0.058 by the full matrix least-squares method. The glycosidic torsion angle is 13.5(11)° (anti conformation), the sugar puckering being C(3')-exo, C(4')-endo. The orientation of the C(5')-O(5') bond is gauche-gauche.

## INTRODUCTION

X-Ray, NMR and circular dichroism (CD) investigations on pyrimidine nucleoside structures have indicated that almost all the pyrimidine nucleosides have anti conformations (torsion angle $\chi$, C(6)-N(1)-C(1')-O(1');0-80°) around the glycosidic bond both in the solid state and in solution. However, studies of the nuclear Overhauser effects (NOE) and CD on 2',3'-O-isopropylidene pyrimidine nucleosides indicate that the molecules exist in syn conformation ( $\chi$; ≃240° ) in dimethylsulfoxide[1], 1,2-dichloroethane[2] or cyclohexane[3]. Therefore, it is of interest to elucidate the molecular structures of 2',3'-O-isopropylidene pyrimidine nucleosides in the solid state by

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the X-ray diffraction method. Until now, only the structure of 2',3'-O-isopropylideneuridine (i-U)[4] has been reported, and its glycosidic conformation is anti. We have now undertaken the X-ray structural analysis of 2',3'-O-isopropylidene-5-bromouridine (i-$Br^5U$) in order to compare the glycosidic conformation with those of the related compounds in solution or in the solid state.

## EXPERIMENTAL

i-$Br^5U$ was crystallized from an aqueous ethanol solution as colorless needles. X-Ray photographs showed the crystals to be orthorhombic with space group $P2_12_12_1$. The unit-cell dimensions were determined based on the $2\theta$ values of 24 reflections that were obtained in the measurement by a diffractometer. The range of the $2\theta$ values was between 35° and 55° (Cu $K\alpha$), and the calculation of the unit-cell dimensions were done by a least-squares procedure. The crystallographic data are summarized in TABLE 1.

The intensity data within $\sin\theta/\lambda=0.58$ $\mathring{A}^{-1}$ were collected on a Rigaku automatic four-circle diffractometer with Cu $K\alpha$ radiation and the $\omega$-$2\theta$ scan technique. The total number of reflections measured was 1407, of which 1215 had intensities greater than $3\sigma(F_o)$ and were used in the structure analysis. Intensities were corrected for the usual Lorentz and polarization factors, but due to the small size of the crystal (0.02x0.08x0.3 mm), an absorption correction was not applied.

The structure was solved by direct methods using the program MULTAN 78[5], and refined by the full matrix least-squares method with anisotropic temperature factors for all the nonhydrogen atoms. All the

TABLE 1. Crystal data

$C_{12}H_{15}N_2O_6Br$
orthorhombic
$a=5.244(2)$ $\mathring{A}$
$b=14.916(6)$
$c=19.068(5)$
$\lambda(\text{Cu } K\alpha)=1.54173$ $\mathring{A}$
$\mu(\text{Cu } K\alpha)=4.45$ $mm^{-1}$

FW 363.2
Space group $P2_12_12_1$
$Z=4$
$F(000)=736$
$V=1491.4(9)$ $\mathring{A}^3$
$Dm=1.613(2)$ Mg $m^{-3}$
$Dx=1.620$

hydrogen atoms could be located on a difference Fourier map. The final refinement including hydrogen atoms with isotropic temperature factors reduced the R value to 0.058. All the numerical calculations were carried out on an ACOS Series 77 NEAC ACOS 700 at the Crystallographic Research Center, Institute for Protein Research, Osaka University, using the programs of The Universal Crystallographic Computing System-Osaka (1979)[6]. Scattering factors used were those cited in International Tables for X-ray Crystallography (1974)[7].

## RESULTS AND DISCUSSION

Positional and thermal parameters are given in TABLE 2. Fig. 1 shows an ORTEP[8] stereographic representation of the molecular conformation of i-Br$^5$U, which is very similar to i-U[4]. The torsion angle about the glycosidic bond ($\chi$) is 13.5°, which corresponds to an anti conformation, not to a syn conformation as expected from NOE or CD studies(TABLE 3). However, only two crystallographic determinations are not sufficient to reach a conclusion that the anti conformation is predominant in 2',3'-O-isopropylidene pyrimidine nucleosides, because the conformation around the glycosidic bond might be influenced by the solvent used in crystallization: CD patterns of 2',3'-O-isopropylidene pyrimidine nucleosides in water or methanol show that their glycosidic conformations are anti, while the syn conformation might be found in solvents such as 1,2-dichloroethane, dimethylsulfoxide or cyclohexane.

The sugar conformation is C(3')-exo,C(4')-endo (P=211°, $\tau_m$=22°), similar to that in 2',3'-O-isopropylidene adenosine (i-A; P=215°, $\tau_m$=31)[10] or i-U (P=216°, $\tau_m$=24°)[4], but different from that found in typical nucleosides (C(2')-endo type, P=144-180°, or C(3')-endo type, P=0-36°). In TABLE 4 are listed the pseudorotation paramaters and glycosidic conformations for 2',3'-O-isopropylidene and the related 2',3'-cyclic nucleosides or nucleotides. It is seen that the sugar ring puckering of the nucleosides or nucleotides having an additional five-membered ring cis to the ribose about C(2')-C(3') shows a maximum amplitude smaller than that ($\tau_m$=38.7°)[11] of unmodified nucleosides or nucleotides but that there are several puckering conformations, i.e., planar , C(4')-exo type, C(2')-endo type, C(4')-endo,C(3')-exo type , or O(1')-endo type.

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

| atom | x | y | z | $B_{eq}$(Å$^2$)[b] |
|---|---|---|---|---|
| Br | -418(3) | 7964(1) | 8124(1) | 5.45(3) |
| N(1) | -2829(17) | 6898(5) | 6253(4) | 2.7(4) |
| C(2) | -1121(20) | 7236(6) | 5762(5) | 2.7(5) |
| N(3) | 481(18) | 7887(5) | 5990(4) | 2.9(4) |
| C(4) | 840(24) | 8152(6) | 6669(5) | 3.5(5) |
| C(5) | -741(23) | 7713(6) | 7173(5) | 3.1(4) |
| C(6) | -2598(21) | 7129(6) | 6960(5) | 2.9(5) |
| O(2) | -1148(13) | 6960(5) | 5155(3) | 2.7(3) |
| O(4) | 2521(19) | 8683(5) | 6813(4) | 5.3(4) |
| C(1') | -4920(19) | 6303(6) | 5985(4) | 2.3(4) |
| C(2') | -3943(20) | 5369(7) | 5782(5) | 2.6(5) |
| C(3') | -5787(22) | 4744(7) | 6158(5) | 3.1(5) |
| C(4') | -7093(21) | 5294(7) | 6721(5) | 3.0(5) |
| C(5') | -5971(23) | 5162(8) | 7449(5) | 3.8(5) |
| O(1') | -6796(13) | 6216(5) | 6501(3) | 2.8(3) |
| O(2') | -4477(16) | 5228(5) | 5045(3) | 3.7(4) |
| O(3') | -7596(15) | 4519(6) | 5634(4) | 4.0(4) |
| O(5') | -3256(16) | 5230(5) | 7430(4) | 4.5(4) |
| C(6') | -6297(26) | 4563(9) | 4977(6) | 4.7(7) |
| C(7') | -4857(39) | 3655(10) | 4872(8) | 7.9(10) |
| C(8') | -8206(30) | 4791(14) | 4426(7) | 7.9(10) |
| H(3)[c] | 189(27) | 808(9) | 557(6) | |
| H(6) | -382(27) | 681(8) | 729(6) | |
| H(1') | -558(28) | 658(8) | 561(6) | |
| H(2') | -182(29) | 523(9) | 591(6) | |
| H(3') | -511(30) | 418(8) | 631(6) | |
| H(4') | -925(28) | 531(8) | 680(6) | |
| H(5') | -704(28) | 568(8) | 773(6) | |
| H(5") | -674(27) | 452(8) | 757(7) | |
| H(O5') | -257(30) | 476(9) | 769(7) | |
| H(7'1) | -595(28) | 344(8) | 466(6) | |
| H(7'2) | -420(28) | 345(8) | 534(6) | |
| H(7'3) | -347(28) | 381(8) | 436(6) | |
| H(8'1) | -698(30) | 483(9) | 398(7) | |
| H(8'2) | -875(28) | 551(8) | 454(6) | |
| H(8'3) | -943(29) | 443(8) | 437(6) | |

[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 the hydrogen atoms are 5.0 Å$^2$.

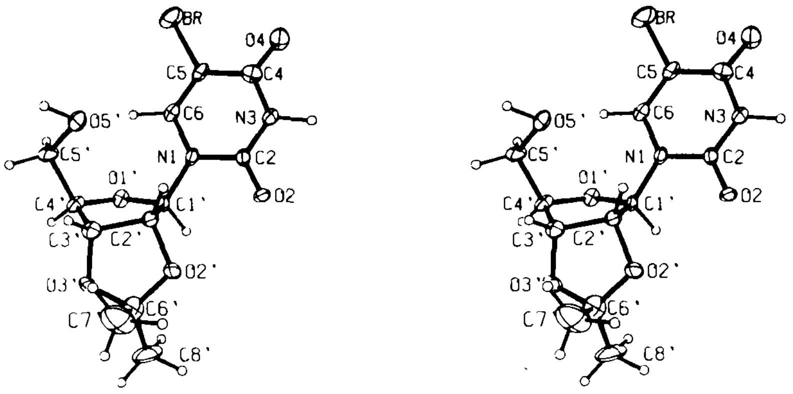

Fig. 1. Stereoview of the molecular conformation with atomic numberings.

TABLE 3. Torsion angles(°)

| | Designation | |
|---|---|---|
| $\chi$ | O(1')-C(1')-N(1)-C(6) | 13.5(11) |
| $\tau_0$ | C(1')-O(1')-C(1')-C(2') | 4.5(10) |
| $\tau_1$ | O(1')-C(1')-C(2')-C(3') | 8.7(10) |
| $\tau_2$ | C(1')-C(2')-C(3')-C(4') | -18.0(10) |
| $\tau_3$ | C(2')-C(3')-C(4')-O(1') | 21.0(10) |
| $\tau_4$ | C(3')-C(4')-O(1')-C(1') | -16.0(10) |
| $\psi_{OO}$ | O(1')-C(4')-C(5')-O(5') | -69.7(11) |
| $\psi_{CO}$ | C(3')-C(4')-C(5')-O(5') | 48.0(12) |
| $\lambda_0$ | O(2')-C(6')-O(3')-C(3') | -32.1(11) |
| $\lambda_1$ | C(6')-O(3')-C(3')-C(2') | 29.0(10) |
| $\lambda_2$ | O(3')-C(3')-C(2')-O(2') | -15.9(10) |
| $\lambda_3$ | C(3')-C(2')-O(2')-C(6') | -3.2(10) |
| $\lambda_4$ | C(2')-O(2')-C(6')-O(3') | 21.3(11) |

The conformation about C(4')-C(5') bond is the usual gauche-gauche.

The bond distances and angles (Figs 2 and 3) in i-Br$^5$U are in good agreement with those found in related nucleosides.

The packing of molecules viewed along the a axis is shown in Fig. 4. The i-Br$^5$U molecules are linked together through either an intermolecular hydrogen bond (N(3)-H---O(2); 2.819(10) Å) along the two fold screw axis parallel to the a axis or a hydrogen bond

TABLE 4. Conformational parameters[9] for 2',3'-O-isopropylidene and related nucleosides and nucleotides

| | P(°) | $\tau_m$(°) | χ | ref. |
|---|---|---|---|---|
| i-A(A) | planar | 4 | anti | 10 |
| i-Br$^8$A(A)$^a$ | planar | 2 | syn | 12 |
| 2',3'-cCMP•Na(B)$^b$ | planar | 2 | syn | 13 |
| i-CN$^6$U$^c$ | 51($_4$E) | 30 | syn | 14 |
| 2',3'-cCMP•Na(A) | 81($^0$T$_4$) | 35 | syn | 13 |
| i-mnm$^5$s$^2$U$^d$ | 125($_1$E) | 40 | anti | 15 |
| i-Br$^8$A(B) | 146($^2_1$T) | 27 | syn | 12 |
| i-Br$^8$I$^e$ | 157($^2$T$_1$) | 33 | syn | 16 |
| mmU$^f$ | 163($^2$E) | 23 | anti | 17 |
| 2',3'-cCMP$^g$ | 173($^2$T$_3$) | 29 | anti | 18 |
| i-Br$^5$U | 211($_3$T$^4$) | 21 | anti | this work |
| i-A(B) | 215($^4_3$T) | 31 | anti | 10 |
| i-U | 216($^4_3$T) | 24 | anti | 4 |
| 2',3'-cUMP$^h$ | 261($_0$T$^1$) | 23 | anti | 18 |

Abbreviations; $^a$2',3'-O-isopropylidene-8-bromoadenosine, $^b$sodium salt of cytidine 2',3'-cyclic phosphate, $^c$2',3'-O-isopropylidene-6-cyanouridine, $^d$2',3'-O-isopropylidene-5-methylaminomethyl-2-thiouridine, $^e$2-methyl-8-bromo-2',3'-O-isopropylideneinosine, $^f$2',3'-O-methoxymethyleneuridine, $^g$cytidine 2',3'-cyclic phosphate, $^h$triethylammonium salt of uridine 2',3'-cyclic phosphate.

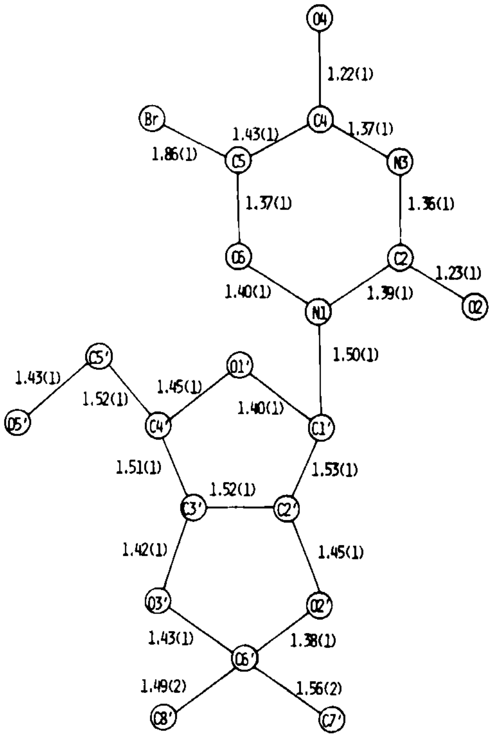

Fig. 2. Bond lengths (Å) with estimated standard deviations in parentheses.

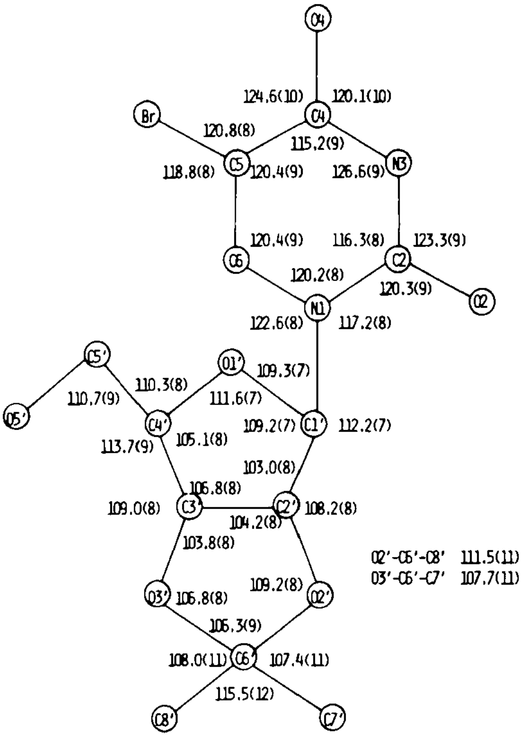

Fig. 3. Bond angles (°) with estimated standard deviations in parentheses.

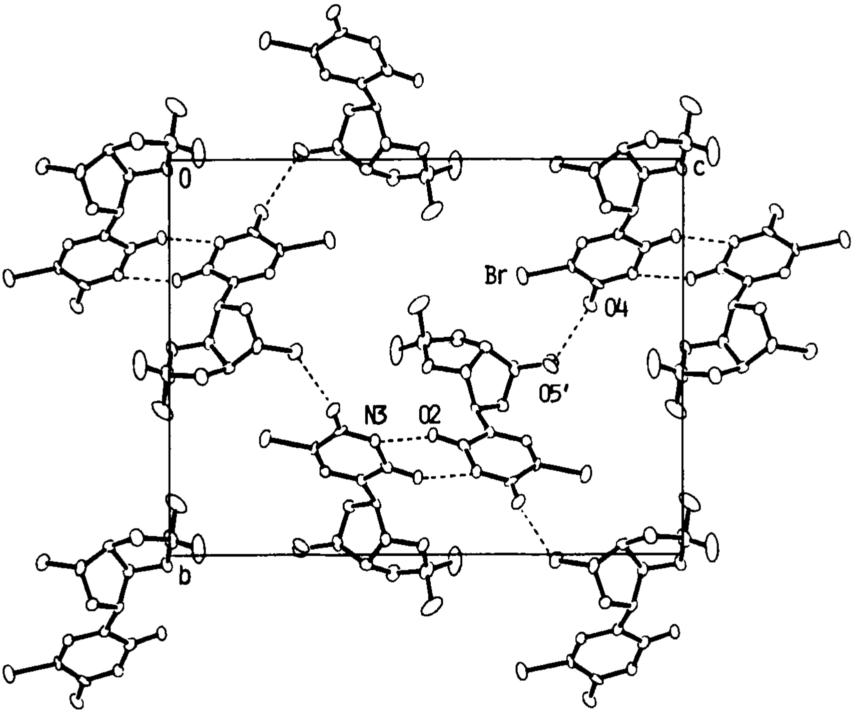

Fig. 4. Molecular packing along the a axis. Dashed lines indicate the hydrogen bonds.

(O(5')-H---O(4); 2.749(12) Å) along the two fold screw axis parallel to the b axis. The base stacking is not observed. The overall arrangement of i-Br$^5$U molecules in crystals is quite similar to that of i-U[4,19].

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