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THE CRYSTAL AND MOLECULAR STRUCTURE OF 1-METHYL-5-BROMOURACIL AND SOME STRUCTURAL CONSIDERATIONS ON THE MUTATION MECHANISM

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A thymine analogue, 1-methyl-5-bromouracil, has been investigated by X-ray diffraction analysis. Its crystal structure is isomorphous with 1-methylthymine.

X-Ray diffraction studies for getting structural informations about base stacking and hydrogen bonding characteristics of 5-bromouracil are being performed in this laboratory to help understanding an induced mutagenic process at molecular level.

In previous papers[1-3], we described the crystal structures of the two forms of 1-ethyl-5-bromouracil in which the main structural difference is in the mode of hydrogen bond scheme. Also in the case of 1-methyl-5-bromouracil, two crystal forms have been obtained, but one of them is too thin for collecting the X-ray diffraction data and its structure is still unknown. The crystal structure reported here is that of the other crystal, the plate-like crystal, which is isomorphous with that of 1-methylthymine[4]. Crystal data for both compounds are given in Table 1.

Table 1. Crystal data

1-methyl-5-bromouracil	1-methylthymine[4]
monoclinic	monoclinic
a=7.26 Å b=12.29 Å	a=7.351 Å b=12.091 Å
c=7.65 Å β=89.5°	c=7.602 Å β=89.97°
$P2_1/c$ Z=4	$P2_1/c$ Z=4
ρ_o=2.00 gcm^{-3}	ρ_o=1.381 gcm^{-3}
ρ_c=1.99 gcm^{-3}	ρ_c=1.379 gcm^{-3}

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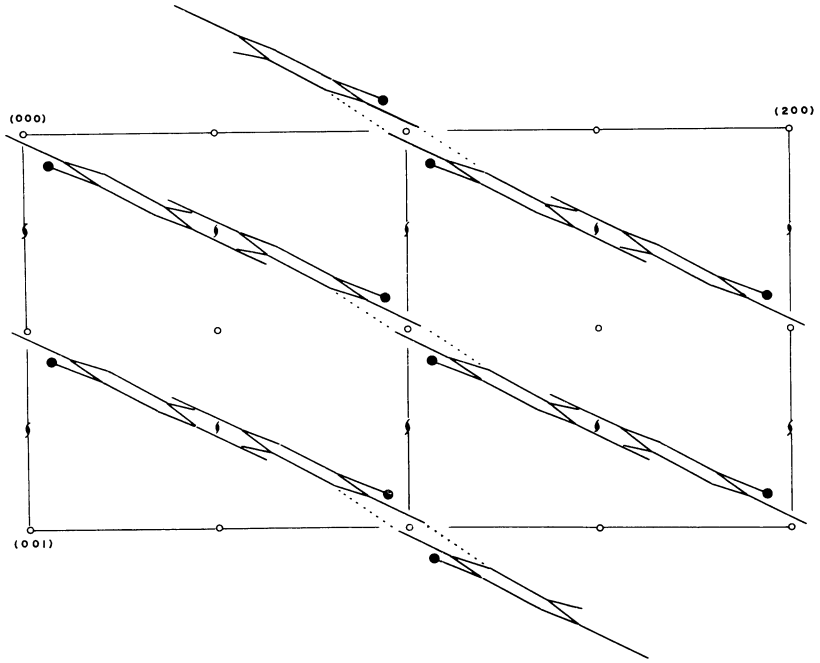

Fig. 1.
The crystal structure viewed down the b axis. Black circles represent bromine atoms.

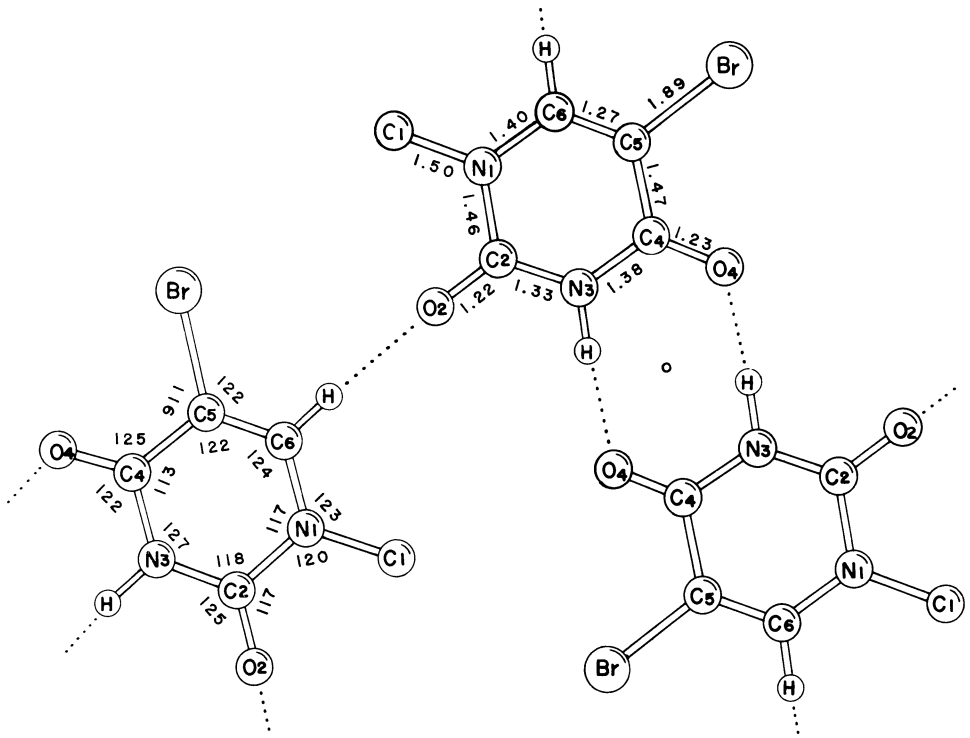

Fig. 2. Hydrogen-bonded arrangement of the molecules in a layer parallel to ($\bar{1}$ 0 2).

Three-dimensional intensity data were collected about the a and c axes with Cu-Kα radiation using a Weissenberg camera, and then estimated by visual comparison with a calibrated scale. 935 independent reflections were recorded as measurable intensities.

The positions of all non-hydrogen atoms were obtained from successive three-dimensional Fourier syntheses. Several cycles of least-squares refinement were carried out until the R-index was reduced to 0.12.

The pyrimidine ring lies almost on the ($\bar{1}$ 0 2) plane, forming a layered structure, in which these sheets are stacked to hold together by van der Waals interactions (Fig. 1). The bromine atoms are arranged to overlap with the adjacent pyrimidine rings at a distance of 3.57 Å. A similar bromine-base contact is found in the crystal structure of the form I of 1-ethyl-5-bromouracil[2]. In each layer, the molecules are joined together in pairs around a center of symmetry with two N-H---O hydrogen bonds connecting the N(3) atom with the carbonyl oxygen O(4) at a distance of 2.83 Å. On the other hand, C(6) atom probably participates in the C-H---O hydrogen bond to an adjacent base atom O(2) because of a short distance of 3.13 Å. Fig.2 shows the hydrogen bonded arrangement of the molecule in crystal.

Recently the crystal structures of 1-ethyl-5-bromouracil (form II)[3] and 1-ethylthymine[8] as well as 1-methyl-5-bromouracil and 1-methylthymine[4] have been found to be isomorphous by X-ray analysis in this laboratory. As mentioned in previous paper[2], an incorporation of 5-bromouracil into DNA in place of the normal thymine base probably reflects the structural similarity of 5-bromouracil and thymine, and may cause change in the mode of base-pairing[5], since it occasionally forms an unusual hydrogen bonding scheme: the hydrogen bond formed between N(3) and O(2) of 5-bromouracil in place of N(3) and O(4) are found in the crystal structures of 1-ethyl-5-bromouracil (form II)[3], the complex 9-ethyladenine - 1-methyl-5-bromouracil[6] and the complex adenosine - 5-bromouridine[7]. This may lead to mispairing in replication and result in mutation.

More precise structural consideration on the mutation mechanism is now under investigation

REFERENCES

1) H. Mizuno, N. Nakanishi, T. Fujiwara, K. Tomita, T. Tsukihara, T. Ashida and M. Kakudo, Biochem. Biophys. Res. Commun., 41, 1161 (1970).

2) H. Mizuno, T. Fujiwara and K. Tomita, Bull. Chem. Soc. Japan, 45, 905 (1972).

3) T. Tsukihara, T. Ashida and M. Kakudo, ibid., 45, 909 (1972).

4) K. Hoogsteen, Acta Cryst., 16, 28 (1963).

5) E. Freese, J. Mol. Biol., 1, 87 (1959).

6) L. Katz, K. Tomita and A. Rich, ibid., 21, 754 (1966).

7) A. E. V. Haschemeyer and H. M. Sobell, ibid., 18, 525 (1965).

8) H. Mizuno, Dissertation, Faculty of Pharm. Sci., Osaka Univ. (1972).

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