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A New Pattern of Hydrogen Bonding between Perpendicular Bases in the Crystal Structure of 5-Nitro-6-methyluracil*

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Crystals of 5-nitro-6-methyluracil are monoclinic, $a = 5.612(1)$, $b = 9.521(3)$, $c = 13.116(2)$ Å, $\beta = 102.37(3)^\circ$, space group $P2_1/c$ with $Z = 4$. The structure was determined from three-dimensional diffractometer data by the multiresolution technique and refined by the least-squares method to an R of 0.062. The pattern of hydrogen bonding [N(3)–H(N3) \cdots O(2) (2.853 Å) and N(1)–H(N1) \cdots O(4) (2.856 Å)] is different from that for uracil; this difference is presumably caused by the substitutions at the 5 and 6 positions of uracil. A pair of molecules related by a center of inversion are 'self-paired' by two N(3)–H(N3) \cdots O(2) bonds. On the other hand, the molecules related by the N(1)–H(N1) \cdots O(4) hydrogen bonds are nearly perpendicular (81°) to each other and form a linear chain. The nitro group is disordered with the major fraction (0.84) twisted by $\pm 41.4^\circ$ with respect to the plane of uracil and the minor fraction (0.16) twisted by $\mp 37.0^\circ$. Our analysis provides a structural basis for the interpretation of ESR and ENDOR spectra by Box, Potienko & Budzinski [*J. Chem. Phys.* (1976), in the press].

Introduction

Crystal structure studies on a series of derivatives of uracil have been undertaken in our laboratory with a view to investigate the influence of different substituents on uracil on its hydrogen-bonding pattern.

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The structure of 5-nitro-6-methyluracil (hereinafter referred to as 5N6MU) was determined as part of the above scheme, as well as to correlate the results of crystal-structure analysis with electron and nuclear spin resonance studies at this Institute (Box, Potienko & Budzinski, 1976). The crystal structure of another derivative of uracil, 6-methyl-5,6-dihydrouracil, has also been elucidated in our laboratory and published separately (Kou & Parthasarathy, 1977).

Experimental

Crystals of 5N6MU, suitable for X-ray work, were kindly supplied to us by Dr H. Box of this Institute. The crystals are monoclinic and the space group is $P2_1/c$. The unit cell and other crystallographic data are given in Table 1.

Complete intensity data were collected to the limit of $2\theta = 165^\circ$ with Cu $K\alpha$ radiation. The stationary-crystal-stationary-counter technique (Furnas & Har-ker, 1955) was employed for obtaining the intensities with a 5° take-off angle; 1529 reflections were measured of which 126 had their intensities less than twice the background in that ($\sin \theta/\lambda$) range, and were given zero weight during the refinement. The crystal used for the data collection had the dimensions $0.38 \times 0.35 \times 0.33$ mm and was mounted with \mathbf{a}^* along the φ axis of the goniostat. The difference in absorption as a function of φ (Furnas, 1957) was measured for the axial reflections and was used for correcting approximately the anisotropy of absorption. This correction

was less than 10% for most of the reflections, reaching a maximum of 17% for some of them. The data were processed in the usual way.†

Phase determination and refinement of the structure

The structure was determined by the multi-solution technique (Germain, Main & Woolfson, 1971) and refined by several cycles of least squares, with the block-diagonal approximation employed. An electron-density difference map ($R = 0.11$, all H atoms refined) showed two peaks which could be interpreted as two oxygens [OD(5a) and OD(5b)] belonging to a different orientation of the nitro group with a small occupancy. Additional cycles of refinement (with fixed occupancies for the nitro groups based on their electron densities) led to the final R value 0.062 for the 1390 observed reflections. At this stage, some 13 reflections had very poor agreement between their $|F_o|$'s and $|F_c|$'s ($|F_c|$ being greater than $|F_o|$). These are listed in Table 2(a).‡ In order to decide on the source of these discrepancies (errors in measurement or extinction), a complete set of data was re-collected from another crystal (with twice the volume) in another orientation. We found that these data also refined in a similar way, yielding an $R = 0.065$. However, the discrepancies in the set of reflec-

Table 1. *Crystal data for 5-nitro-6-methyluracil*

Color: pale yellow	
Space group: $P2_1/c$	
$Z = 4$	$a = 5.612(1) \text{ \AA}$
$\mu(\text{Cu } K\alpha) = 7.8 \text{ cm}^{-1}$	$b = 9.521(3)$
$D_o = 1.66 \text{ g cm}^{-3}$	$c = 13.116(2)$
$D_c = 1.68 \text{ g cm}^{-3}$	$\beta = 102.37(3)^\circ$
$t = 22 \pm 3^\circ\text{C}$	$\lambda(\text{Cu } K\alpha_1) = 1.54051 \text{ \AA}$

† Reflections with indices hkl and $\bar{h}\bar{k}l$ have, interestingly, the same value of $\sin \theta$. This equality occurs because $|c^*|$ happens to be equal to $1/2a^* \cos \beta^*$. This accidental relation is only geometrical; the corresponding intensities are not equal to each other.

‡ See deposition footnote on p. 1751.

Table 3. *Final atomic parameters for 5-nitro-6-methyluracil, with e.s.d.'s in parentheses*

Positional parameters are expressed as fractions of the lattice translations. Thermal parameters are given by the expression $T = \exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$.

	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
O(2)	0.3704 (4)	0.0613 (3)	0.3797 (1)	0.0325 (7)	0.0133 (3)	0.0033 (1)	0.0155 (7)	0.0047 (4)	-0.0010 (3)
O(4)	0.1201 (4)	0.1761 (3)	0.6740 (1)	0.0344 (7)	0.0146 (3)	0.0025 (7)	0.0096 (8)	0.0049 (4)	0.0014 (3)
O(5a)†	-0.4804 (4)	0.3509 (3)	0.5212 (2)	0.0222 (7)	0.0113 (3)	0.0074 (2)	-0.0006 (8)	0.0086 (6)	-0.0024 (4)
O(5b)†	-0.1779 (6)	0.4118 (4)	0.6437 (2)	0.0458 (12)	0.0186 (5)	0.0049 (2)	0.0154 (12)	0.0013 (7)	-0.0091 (5)
OD(5a)*	-0.231 (3)	0.493 (1)	0.545 (1)	0.051 (6)	0.005 (1)	0.011 (1)	-0.009 (4)	0.024 (5)	-0.003 (2)
OD(5b)*	-0.330 (3)	0.315 (2)	0.629 (1)	0.049 (6)	0.018 (2)	0.006 (1)	0.001 (6)	0.027 (4)	0.005 (2)
N(1)	0.0479 (4)	0.2077 (3)	0.3658 (2)	0.0252 (7)	0.0101 (3)	0.0022 (1)	0.0042 (7)	0.0031 (4)	0.0007 (3)
N(3)	0.2274 (4)	0.1112 (2)	0.5255 (2)	0.0237 (7)	0.0083 (2)	0.0027 (1)	0.0038 (7)	0.0021 (4)	0.0010 (3)
N(C5)	-0.2577 (4)	0.3533 (3)	0.5629 (2)	0.0290 (8)	0.0096 (3)	0.0039 (1)	0.0042 (8)	0.0057 (5)	-0.0004 (3)
C(2)	0.2267 (5)	0.1228 (3)	0.4210 (2)	0.0238 (8)	0.0085 (3)	0.0026 (1)	0.0020 (8)	0.0021 (5)	-0.0007 (3)
C(4)	0.0087 (5)	0.1888 (3)	0.5795 (2)	0.0222 (8)	0.0082 (3)	0.0028 (1)	-0.0015 (8)	0.0033 (5)	0.0001 (3)
C(5)	-0.0953 (5)	0.2742 (3)	0.5131 (2)	0.0222 (8)	0.0077 (3)	0.0031 (1)	-0.0008 (7)	0.0040 (5)	-0.0002 (3)
C(6)	-0.1138 (4)	0.2819 (3)	0.4078 (2)	0.0206 (7)	0.0084 (3)	0.0032 (1)	-0.0004 (7)	0.0025 (5)	0.0007 (3)
C(M6)	-0.2930 (6)	0.3670 (4)	0.3325 (2)	0.0296 (10)	0.0135 (4)	0.0038 (2)	0.0110 (10)	0.0046 (6)	0.0037 (4)

	x	y	z	B		x	y	z	B
H(N1)	0.061 (6)	0.226 (4)	0.300 (3)	3.9 (7)	Hb(CM6)	-0.372 (8)	0.447 (5)	0.368 (4)	6.8 (11)
H(N3)	0.348 (6)	0.064 (3)	0.566 (2)	3.0 (6)	Hc(CM6)	-0.214 (8)	0.397 (5)	0.281 (3)	5.8 (10)
Ha(CM6)	-0.444 (9)	0.321 (6)	0.313 (4)	7.7 (10)					

* These atoms have a fixed occupancy factor of 0.84.

† These atoms carry an occupancy factor of 0.16.

tions in Table 2(a) still persisted. The crystal was repeatedly dipped in liquid nitrogen and warmed to lessen extinction effects (Lonsdale, 1947), and these reflections were remeasured. The result of these experiments (Table 2b)* showed a surprising decrease in intensity instead of an increase. The decrease in intensity due to the liquid nitrogen treatment for these selected reflections seems to be real and not an artefact. One possible explanation is that the repeated cooling and warming up 'annealed' the structure and changed the occupancy of the two nitro groups, but no particular combination of the occupancies reduced the differences between the observed and calculated structure factors for these reflections. Omission of these reflections yielded flat difference electron-density maps. Inclusion of these reflections gave rise to diffuse peaks in the difference maps with peak heights of the order of $0.6 \text{ e } \text{Å}^{-3}$ in the vicinity of the nitro groups, but these peaks made no stereochemical sense. It is possible that this crystal contains, in addition to the major conformers, a small percentage of different conformers of 5N6MU molecules with their nitro groups twisted by varying amounts. A detailed investigation of the nature of the disorder and the reduction in the intensity of these reflections will require data collection at different temperatures. Consequently, we decided to point out this problem here, but to omit these reflections from further consideration in our present study.

The refinement was considered to be complete, and the final atomic and thermal parameters and their

estimated standard deviations are given in Table 3.* The observations were weighted with the differential synthesis weights ($1/f_c$ where f_c is the scattering factor of the C atom) and the refinement was carried out by minimizing $\sum \{w|F_o| - (1/k)|F_c|\}^2$. Atomic scattering factors for C, N, O and H atoms were taken from Stewart, Davidson & Simpson (1965). The final reliability index is 0.062 [omitting the 13 reflections of Table 2(a)] and 0.097 for all the observed 1529 reflections.

The bond lengths and angles in the molecule are given in Fig. 1. The average (except for the disordered nitro group) of the e.s.d.'s in bond lengths is 0.003 Å (non-hydrogens) and 0.04 Å (involving one H atom); the corresponding e.s.d.'s in bond angles are 0.2 and 4.1° respectively.

Bond lengths and angles

The bond lengths and angles in the uracil moiety are somewhat similar to those observed in 5-nitrouracil (Craven, 1967) but differ from those observed in uracil (Stewart & Jensen, 1967). These differences are in the C(4)—O(4), C(4)—C(5) and C(5)—C(6) bond distances, and in all the ring angles except at C(2) and N(3), indicating the effect of the nitro substituent on the uracil ring (see, also, Craven, 1967). The C(5)—N(C5) bond in the present structure is longer by 0.016 Å , as compared with 5-nitrouracil; also, the N—O distances in the nitro group differ in these two structures.

The effect of thermal libration on bond distances was studied with the method (and program) of Schomaker & Trueblood (1968). The corrections to the bonds for thermal libration are about 0.01 Å for all the bonds (about three times the e.s.d.'s in bonds) and are significant except for the disordered group.

Conformation and disorder of the nitro group

In 5-nitrouracil (Craven, 1967), the nitro group is in the plane of the uracil ring; the torsion angle O(5b)—N(C5)—C(5)—C(4) (the numbering of the 5-nitrouracil structure has been changed to agree with our notation) is $\mp 4.2^\circ$. The introduction of the 6-methyl substituent in the present structure causes the nitro group to take up a disordered arrangement with two orientations for the nitro group (torsion angles ± 41.4 and $\mp 37.0^\circ$). The lack of coplanarity of the nitro and uracil moieties in 5-nitro-6-methyluracil decreases the p_z — p_z overlap of

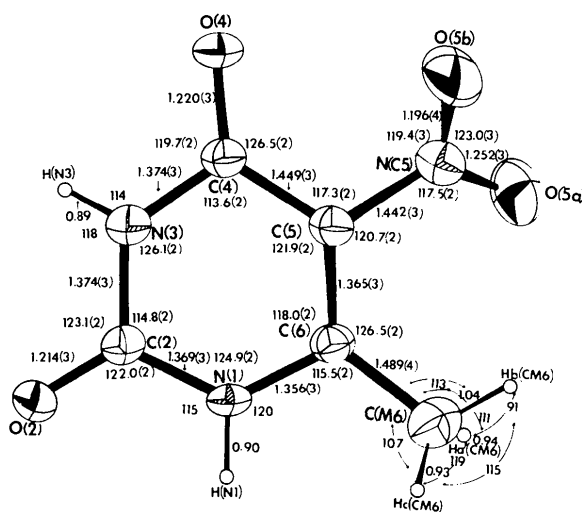


Fig. 1. Bond distances (Å) and angles ($^\circ$) in the molecule (major fraction). The distances and angles in the nitro group corresponding to the minor fraction are: N(C5)—OD(5a) $1.37(1)$, N(C5)—OD(5b) $1.10(2)$ Å, C(5)—N(C5)—OD(5a) $110(1)^\circ$; C(5)—N(C5)—OD(5b) $124(1)$, OD(5a)—N(C5)—OD(5b) $122(1)^\circ$.

* A list of structure factors, Table 2(a) and (b) and a table of least-squares planes and atomic deviations have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32321 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

the orbitals on C(5) and N(C5), resulting in a slightly longer C(5)—N(C5) distance of 1.443 Å, as compared with 1.427 Å in 5-nitrouracil. While the reason for the twisting of the nitro group about C(5)—N(C5) is appar-

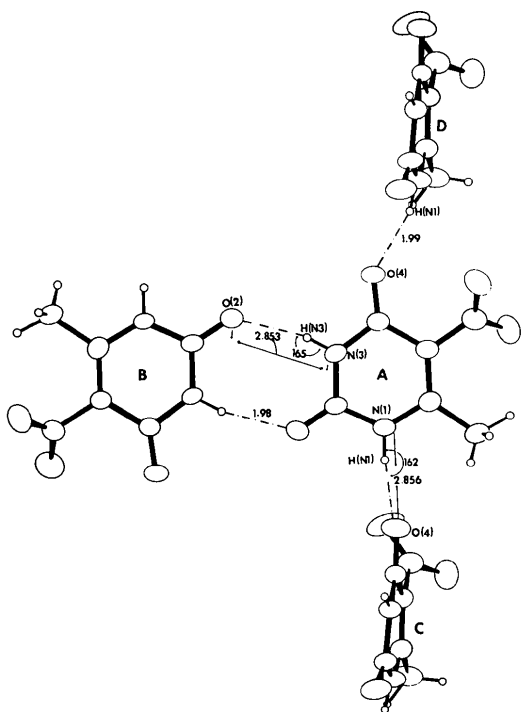


Fig. 2. Schematic diagram illustrating the hydrogen bonding in the structure. Molecules *A*, *B*, *C* and *D* correspond to equivalent positions x, y, z ; $1 - x, y, 1 - z$; $x, \frac{1}{2} - y, z - \frac{1}{2}$; and $x, \frac{1}{2} - y, \frac{1}{2} + z$ respectively.

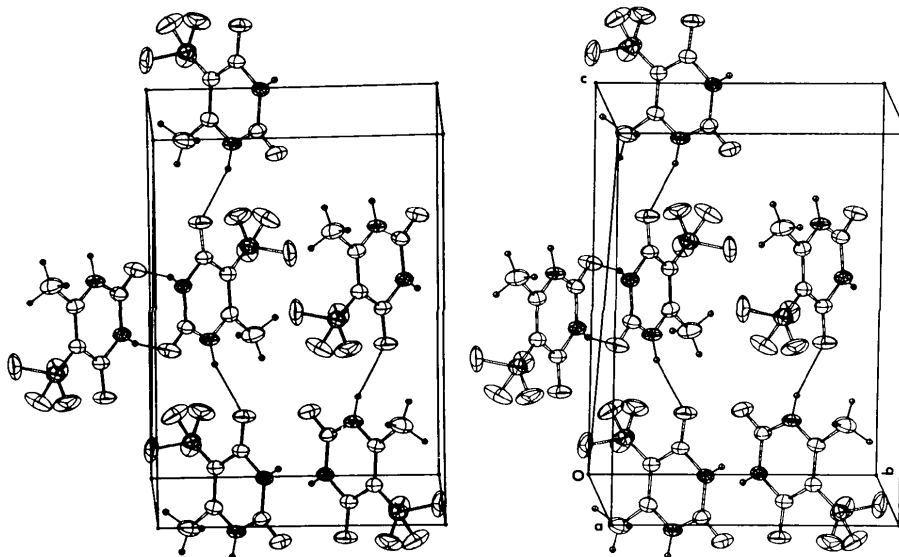


Fig. 3. A stereoscopic view of the molecular packing.

Table 4. *Hydrogen-bond distances (Å) and angles (°)*

Superscripts refer to the following symmetry-related positions: (i) $x, \frac{1}{2} - y, z - \frac{1}{2}$; (ii) $1 - x, y, 1 - z$.

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$N(1)-H(N1) \cdots O(4^i)$	0.90 (3)	1.98 (3)	2.856 (3)	162 (3)
$N(3)-H(N3) \cdots O(2^{ii})$	0.89 (3)	1.98 (3)	2.853 (3)	165 (3)

ent, it is not clear why there is a large difference between the occupancies of the two nitro groups (0.84 compared to 0.16). Also, it is not clear why the two N—O distances are unequal in 5-nitro-6-methyluracil compared with the nearly equal N—O distances in 5-nitrouracil.

The pyrimidine ring is slightly non-planar with the atoms C(2), N(3), and C(4) deviating from the least-squares plane through the base by -0.026 , 0.047 and -0.033 Å respectively.*

Hydrogen bonding and packing

An important feature of the structure is the existence of a hydrogen-bonding scheme different from that of uracil and 5-nitrouracil (Fig. 2, Table 4). The two neighboring molecules *C* and *D* (Fig. 2) are nearly perpendicular (81°) to the reference molecule *A* to which they are hydrogen-bonded. Such an unusual stereochemistry of hydrogen bonding in which the hydrogen-bonded nucleic-acid bases are almost perpendicular to one another has not been observed in other crystal

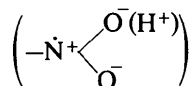
* See previous footnote.

structures of nucleic-acid bases, although in some nucleosides (see Hawkinson & Coulter, 1971) a similar arrangement has been noted. There is hardly any stacking of the molecules. A stereoscopic view of the packing is shown in Fig. 3.

Correlation of the structure with magnetic resonance spectra

The ESR spectra of irradiated single crystals of 5-nitro-6-methyluracil have been studied by Snipes & Benson (1968), Sagstuen, Melo & Henriksen (1972), Sagstuen (1973), Benson & Lorenz (1974) and more recently by Box, Potienko & Budzinski (1976). Sagstuen, Melo & Henriksen (1972) have also carried out preliminary crystallographic studies of the unit cell and space group of 5-nitro-6-methyluracil, which agree closely with our results. Part of Sagstuen's analysis of the ESR spectra of 5-nitro-6-methyluracil was dependent on his model for the crystal structure and hydrogen bonding of this molecule. The model proposed by him for the hydrogen bonding in 5-nitro-6-methyluracil is based on the structure of uracil and 5-nitrouracil; it consists of a pair of N(3)—H...O(4) hydrogen bonds across centers of inversion. This model is clearly incorrect in view of our crystal structure analysis.

Our investigation provides structural evidence for the interpretation of several important features of the ESR and ENDOR measurements of Box, Potienko & Budzinski (1976). These workers observed only one conformation of the reduction product:



though there are molecules with two different orientations of nitro groups in the structure. The observed direction of the minimum g value, after transformation from the \mathbf{a}^* , \mathbf{b} , \mathbf{c} axes used by Box *et al.* (1976) to the \mathbf{a} , \mathbf{b} , \mathbf{c}^* axes used by us, is given by the direction cosines (0.130, 0.801, -0.582); this direction is nearly along the normal to the nitro group (0.250, 0.818, -0.518) of the major conformer that seems to trap the electron selectively. A doublet splitting was observed in the hyperfine spectrum of the reduction product in non-deuterated crystals, but not in deuterated crystals, indicating the influence of an exchangeable H atom whose proton neutralizes the reduced anion. The origin of this neighboring proton is indicated by the direction of maximum hyperfine coupling to the proton of the neutral reduction product (for a discussion, see Box, Potienko & Budzinski, 1976). This direction in the \mathbf{a} , \mathbf{b} , \mathbf{c}^* frame is given by the direction cosines (0.337, 0.007, 0.941), pointing to HN(1) of molecule *D* (Fig. 2); HN(1) makes a contact of 2.57 Å to O(5b) along the direction (0.348, 0.504, 0.790) which corresponds reasonably to the direction of maximum hyperfine coupling to the proton of the neutral reduction product.

The oxidation product was identified by Box *et al.* (1976) as a cation obtained by removal of an electron from the uracil ring by measuring the hyperfine tensor coupling the spin density on N(1) with the proton of HN(1) and comparing its principal-axes directions with the molecular orientation in the crystal. The direction (-0.292, 0.164, 0.942) of minimum magnitude of coupling corresponds to the N(1)—H(N1) direction (\mathbf{V}_1 , -0.292, 0.183, 0.938), the direction (-0.559, 0.769, -0.307) of the intermediate coupling parallels the normal to the plane of uracil (\mathbf{V}_2 , -0.628, 0.764, -0.145) and the direction of the maximum coupling (0.775, 0.616, 0.133) is along $\mathbf{V}_1 \times \mathbf{V}_2$ (0.743, 0.631, 0.109) according to expectations.

We are grateful to Dr D. Harker for valuable and stimulating discussions, to Dr H. C. Box for having kindly provided us with a single crystal for our analysis and also for having communicated to us some of the results of ESR and ENDOR studies, and to Mrs N. Winiewicz for her excellent technical help at all stages of this investigation. The following computing programs were used: *BDL-6* (a modified version of Gantzel, Sparks and Trueblood's ACA program No. 317), a generalized program for Fourier summation by Dr S. T. Rao and *ORTEP* by Dr C. K. Johnson. This work was supported by a grant CA16844 from the National Cancer Institute, National Institutes of Health.

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