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6-Methyl-5,6-dihydrouracil, a Highly Disordered Structure

BY WILLIAM W. H. KOU AND R. PARTHASARATHY*

*Center for Crystallographic Research, Roswell Park Memorial Institute,
Buffalo, New York 14263, USA*

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Abstract. $C_5H_8N_2O_2$, monoclinic, $C2$ (with the molecules highly disordered in such a way that an approximate mirror is introduced normal to the b axis; $C2/m$ approximately describes the crystal structure), $a = 10.532(3)$, $b = 6.447(2)$, $c = 9.183(2)$ Å, $\beta = 101.55(3)^\circ$, $Z = 4$, $D_o = 1.39$, $D_c = 1.39$ g cm $^{-3}$, $R = 0.08$. Because of the disorder and ambiguities in the results of least-squares analysis in this structure, the y coordinates of the atoms are indeterminate. The molecules are self-paired across twofold axes by pairs of $N(1) \cdots O(2)$ (2.88 Å) and $N(3) \cdots O(4)$ (2.88 Å) hydrogen bonds. The orientation of the g tensor of the products of radiation damage in the crystal is correlated with the orientation of the molecules in the crystal structure.

Introduction. Transfer-ribonucleic acid molecules contain a variety of modified bases, one of which is dihydrouracil which occurs in a special loop region. The title compound (Fig. 1) (hereafter referred to as 6mhura) is an analog of the naturally occurring 5,6-dihydrouracil. The present investigation was undertaken to study the influence of different substituents upon the hydrogen-bonding pattern of uracil, and also to correlate the results of the crystal structure analysis with ENDOR studies by our colleague Dr H. Box and his co-workers.

Crystals of 6mhura (Sigma Chemical Company)

were obtained by slow evaporation from water solution. Intensity data to the limit $2\theta = 120^\circ$ (little scattering was observed beyond this range) for $Cu K\alpha$ were obtained from a crystal of size $0.65 \times 0.35 \times 0.15$ mm by the stationary crystal-stationary counter technique, with a 5° take-off angle. Of the 770 reflections measured, 186 intensities were less than twice the background in that range and were given zero weight during the refinement. The difference in absorption as a function of the φ angle (Furnas, 1957) was measured for the axial 600 reflection and was used for correcting

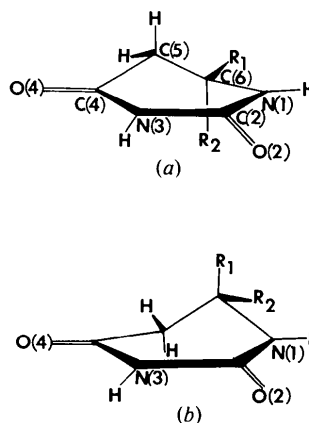


Fig. 1. $R_1 = H$, $R_2 = C(Me)$ yields the (*S*) isomer; $R_1 = C(Me)$, $R_2 = H$ yields the (*R*) isomer. For each isomer, two modes of pucker, (a) and (b), are possible.

* To whom correspondence should be addressed.

approximately the anisotropy of absorption; the correction for some reflections ranged up to 30%. The intensities were processed in the usual way.

The systematically absent reflections ($h + k$ odd in hkl) indicate three possible space groups, namely $C2$, Cm and $C2/m$. The concentration of peaks in the Harker sections ($u0w$) and ($u\frac{1}{2}w$) indicate $C2$, but the intensity statistics suggest $C2/m$. To a first approximation, the molecule may be considered planar; initially the space group $C2/m$ was chosen and a structural model was obtained with *MULTAN* (Germain, Main & Woolfson, 1970). The atomic and thermal parameters were refined by the least-squares method with a block-diagonal approximation, minimizing $\sum w||F_o| - (1/k)|F_c||^2$, where k is a scale factor and w is the weight ($w = 1/f_c$ where f_c is the scattering factor of the C atom). Atomic scattering factors for the C, N and O atoms were taken from *International Tables for X-ray Crystallography* (1962).

Since the only way to fit the structure in $C2/m$ is to impose a molecular mirror plane coincident with the crystallographic mirror plane, the six nonhydrogen atoms [N(1), C(2), O(2), N(3), C(4) and O(4)] which were obtained from the E map of the multiresolution phase determination were used as the trial model of the structure, with their y coordinates fixed at zero. An electron density difference map revealed the locations of C(5), C(6) and C(m) (with their y coordinates slightly different from zero). Since the peak for C(m) was nearly in the plane of the molecule, conformers with axial orientation (Fig. 1) for the methyl were not considered any further. The use of these nine atoms as a trial model yielded an R value of 0.18 for a refinement with isotropic thermal parameters, but the refinement would not proceed any further even with aniso-

tropic thermal parameters. For refining the structure further, the space group $C2$ was used; the molecular coordinates from $C2/m$ were used and they were allowed to refine without imposing mirror symmetry. Six cycles of least-squares refinement in $C2$ reduced R to 0.10 (with anisotropic thermal parameters). Since there are two enantiomers [$C(m)$ is equatorial regardless of the pucker], two sets of half-weight atoms were generated from the $C2$ coordinates. One set of 'half-atoms' corresponds to x, y, z , and the other set to x, \bar{y}, z ; three cycles of least-squares refinement reduced R to 0.08. It is important to emphasize at this stage that the y coordinates of the individual atoms of the molecules are indeterminate owing to the disorder and also to ambiguities in the results of least-squares analysis in special cases (for a discussion, see Parthasarathy, Sime & Speakman, 1969). Consequently, it should not be regarded that the space group for this structure has been established as $C2$. We felt that the quality of the data did not justify more complicated models of refinement; consequently the refinement was terminated and the refined parameters are reported in Table 1.* Similar difficulties were experienced in the refinement of the structure of dihydrothymine (Furberg & Jensen, 1968).

The eighteen half-atoms are away from the plane $y = 0$ by distances ranging from 0.03 to 0.15 Å. Since there are nine atoms and two positions for each atom, $2^9 = 512$ 'molecules' are theoretically possible, but stereochemical considerations eliminate most of these from further considerations. Two 'best' choices of

* A list of structure factors and Table 2 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32302 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. Atomic coordinates and thermal parameters ($\times 10^3$, except $\beta_{11} \times 10^4$)

| Type | Weight | x | y | z | β_{11} | β_{22} | β_{33} | β_{12} | β_{13} | β_{23} |
|---|--------|---------|---------|---------|--------------|--------------|--------------|--------------|--------------|--------------|
| Temperature factor: $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$. | | | | | | | | | | |
| N(1) | 0.5 | 143 (1) | 24 (3) | 638 (1) | 63 (8) | 32 (6) | 8 (1) | 1 (4) | 4 (1) | -3 (5) |
| 2N(1) | 0.5 | 143 (1) | -31 (4) | 640 (1) | 84 (8) | 17 (4) | 10 (1) | 2 (5) | 9 (2) | -1 (5) |
| O(2) | 0.5 | 135 (1) | 12 (5) | 391 (1) | 78 (7) | 36 (6) | 10 (1) | 3 (6) | 5 (1) | 6 (7) |
| 2O(2) | 0.5 | 137 (1) | -33 (4) | 392 (1) | 78 (7) | 23 (5) | 10 (1) | -1 (4) | 7 (1) | -1 (4) |
| N(3) | 0.5 | 332 (1) | 25 (2) | 545 (1) | 64 (8) | 17 (5) | 11 (1) | -1 (3) | 7 (2) | 1 (4) |
| 2N(3) | 0.5 | 334 (1) | -28 (4) | 546 (1) | 76 (8) | 11 (3) | 12 (1) | -2 (4) | 7 (2) | -2 (5) |
| O(4) | 0.5 | 531 (1) | 7 (8) | 696 (1) | 58 (7) | 59 (7) | 14 (1) | 3 (8) | 4 (1) | -14 (12) |
| 2O(4) | 0.5 | 529 (1) | -24 (6) | 696 (1) | 72 (7) | 41 (6) | 14 (1) | 0 (7) | 7 (1) | 3 (9) |
| C(2) | 0.5 | 198 (1) | 22 (3) | 520 (1) | 72 (9) | 20 (5) | 10 (1) | -2 (4) | 7 (2) | 0 (5) |
| 2C(2) | 0.5 | 195 (1) | -25 (4) | 517 (1) | 77 (9) | 9 (3) | 13 (1) | 1 (5) | 8 (2) | 5 (6) |
| C(4) | 0.5 | 412 (1) | 11 (8) | 682 (1) | 77 (10) | 30 (7) | 11 (1) | -1 (7) | 5 (2) | 4 (9) |
| 2C(4) | 0.5 | 412 (1) | -32 (6) | 680 (1) | 81 (10) | 21 (7) | 11 (1) | 1 (5) | 4 (2) | 6 (6) |
| C(5) | 0.5 | 346 (1) | -37 (9) | 812 (2) | 91 (12) | 50 (13) | 13 (2) | 1 (8) | 9 (2) | 4 (10) |
| 2C(5) | 0.5 | 347 (1) | 55 (4) | 810 (2) | 67 (11) | 67 (14) | 9 (2) | -1 (6) | 5 (2) | 3 (7) |
| C(6) | 0.5 | 216 (1) | 67 (3) | 786 (2) | 63 (10) | 46 (7) | 10 (2) | 4 (4) | 6 (2) | -2 (5) |
| 2C(6) | 0.5 | 219 (1) | -64 (3) | 787 (1) | 91 (12) | 44 (11) | 8 (1) | 5 (5) | 7 (2) | 3 (5) |
| C(m) | 0.5 | 137 (1) | 6 (14) | 902 (1) | 106 (14) | 79 (13) | 9 (1) | -18 (16) | 11 (2) | -11 (19) |
| 2C(m) | 0.5 | 137 (1) | -30 (8) | 902 (2) | 112 (13) | 37 (9) | 11 (1) | 10 (8) | 12 (2) | 0 (9) |

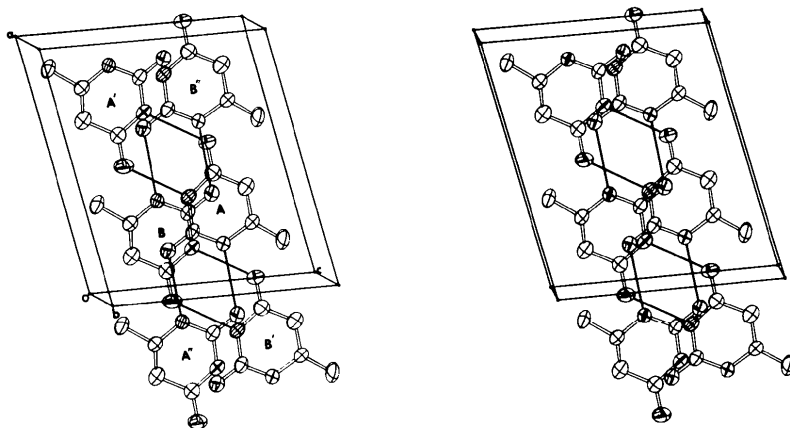


Fig. 2. A stereo view of the packing and hydrogen bonding of the molecules (only one isomer is shown in this diagram).

representative models for the molecule were chosen from the possibilities by inspection of the bond lengths, bond angles, and torsion angles, and by comparing them with those of uracil (Stewart & Jensen, 1967), dihydrouracil (Rohrer & Sundaralingam, 1970), N^1 -(N -methylcarbamoyl)- N^3 -methyl-5,6-dihydrouracil (Parthasarathy, Ohrt, Dutta & Chheda, 1973), dihydrothymine (Furberg & Jensen, 1968), and dihydrouridine (Sundaralingam, Rao & Abola, 1971). The bond distances and angles in the two models that agree best with the above structures are given in Table 2.†

Discussion. The packing viewed along **b** (Fig. 2) shows the formation around diad axes of $N(3)-H \cdots O(4)$ hydrogen-bonded (2.88 Å) cyclic dimers of molecules A and A'' and $N(1)-H \cdots O(2)$ hydrogen-bonded (2.88 Å) dimers of molecules A and A'' . A is the reference molecule to which A' and A'' are related by $1-x, y, 1-z$ and $\bar{x}, y, 1-z$ respectively. In another layer at $y \sim \frac{1}{2}$, the molecules $B(\frac{1}{2}-x, \frac{1}{2}+y, 1-z)$, $B'(-\frac{1}{2}+x, \frac{1}{2}+y, z)$ and $B''(\frac{1}{2}+x, \frac{1}{2}+y, z)$ are hydrogen-bonded in a similar way. There is hardly any stacking of the rings.

From ENDOR studies (Budzinski & Box, 1975) on single crystals of 6-methyl-5,6-dihydrouracil X-irradiated at 4.2 K, the direction cosines for the maximum g value of the **g** tensor [for the oxidation product with the unpaired electron localized in a $2p$ orbital on $N(1)$] are found to be $(-0.269, 0.000, 0.963)$ in the **a, b, c*** frame of reference. Theory shows that the direction of the maximum value of the **g** tensor is perpendicular to the direction (\mathbf{V}_1) of the $N(1)-H$ bond and to \mathbf{V}_3 , the vector defining the plane of the molecule (Box & Budzinski, 1973). This expectation is verified for this structure also. The direction (\mathbf{V}_1) (0.984, 0.000, 0.178)

of the $N(1)-H$ bond was taken to be equal to that of the $N(3)-C(2)$ bond, and \mathbf{V}_2 to be along **b**; hence the direction of $\mathbf{V}_1 \times \mathbf{V}_2$ $(-0.178, 0.000, 0.984)$ is nearly along the direction of the maximum value of the **g** tensor.

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† See previous footnote.