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Crystal Structure of 5-Iodouracil

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Crystals of 5-iodouracil are monoclinic, space group $P2_1$, with $a=14{\cdot}210$ (1), $b=4{\cdot}458$ (1), $c=4{\cdot}899$ (3) Å, and $\beta=92{\cdot}31$ (1)°. There are two formula units per cell. Observed and calculated densities are 2·54 and 2·548 g cm^{-3}, respectively. Intensity data for 591 reflections were collected on an automatic diffractometer. The structural parameters were refined by full-matrix least-squares calculations to an R index of 0·044. The molecules form planar, hydrogen-bonded ribbons, which are stacked with an inter-ribbon spacing of 3·15 Å and an I···C(6) distance of 3·76 Å that is slightly shorter than a normal van der Waals contact.

Introduction

Like other 5-halogenated uracil derivatives, 5-iodouracil is an antimetabolite that is incorporated into nucleic acids. Past crystallographic studies have indicated that halogen substituents affect solid state base-stacking patterns, and have suggested that stacking interactions involving the halogen substituents may contribute to the unusual physical and biological properties of nucleic acids which contain halogenated pyrimidines (Bugg, Thomas, Sundaralingam & Rao, 1971; Bugg & Sternglanz, 1974; Sternglanz & Bugg, 1975). We determined the crystal structure of 5-iodouracil to obtain additional information about the crystallographic stacking patterns of halogenated bases.

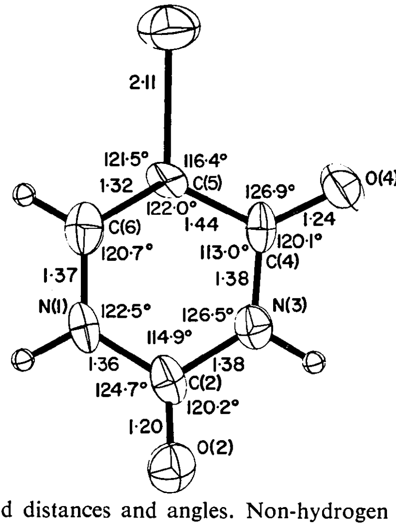

Fig. 1. Bond distances and angles. Non-hydrogen atoms are represented by thermal ellipsoids scaled to include 50% probability. Hydrogen atoms are represented by spheres of 0·1 Å radius. Bond lengths and bond angles are given; estimated standard deviations of bond lengths are about 0·018 Å, except for the C(5)–I bond length, which has an estimated standard deviation of 0·013 Å. Estimated standard deviations of bond angles are about 0·9°. This drawing, and that in Fig. 2, were prepared by using the program *ORTEP* (Johnson, 1965).

Experimental

Needle-shaped crystals were grown by slowly evaporating an aqueous solution of 5-iodouracil. The space group is $P2_1$ as indicated by the systematic absence of $0k0$ reflections when k is odd. Cell constants were obtained by least-squares analysis of 2θ values for 12 high-angle reflections (Cu $K\alpha_1$, $\lambda=1{\cdot}54051$ Å) measured on the diffractometer. The density was measured by flotation in a benzene–1,1,2,2-tetrabromoethane mixture.

A crystal fragment with approximate dimensions 0·03 × 0·08 × 0·22 mm was mounted on a Picker FACS-1 diffractometer with its b axis slightly inclined to the φ axis of the goniostat. Three-dimensional X-ray intensity data for the 591 symmetry-independent reflections with $2\theta<128°$ were obtained with the diffractometer (nickel-filtered copper radiation, a scintillation counter, and a θ–2θ scanning technique). The scanning speed was 1° min^{-1} and a 20 s background measurement was performed at each terminus of the scans. Three strong reflections ($\bar{1}01$, $\bar{1}11$, and 020) which were monitored periodically exhibited no significant variation of intensity during data collection. Those reflections with scan counts below background levels were given their calculated negative intensity values and were retained in all subsequent calculations. Intensities were assigned variances, $\sigma^2(I)$, according to counting statistics plus a correctional term $(0{\cdot}03S)^2$, S being the scan count. The intensities and their variances were corrected for Lorentz and polarization effects, and absorption corrections were applied by using the computer program *ORABS* (Wehe, Busing & Levy, 1962). The calculated linear absorption coefficient is $\mu=408{\cdot}1$ cm^{-1}; the transmission factors ranged from 0·06 to 0·31. The data were scaled by a Wilson (1942) plot.

Solution and refinement

We arrived at a suitable trial structure by the heavy-atom method. Coordinates and anisotropic temperature parameters for the non-hydrogen atoms and Zachariasen's (1963) isotropic extinction parameter g [as formulated by Coppens & Hamilton (1970)] were refined by a modified version of the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962; Busing, 1971). The quantity minimized was $\sum w(F_o^2 - F_c^2/k^2)^2$, where k is a scale factor and the weight w is equal to $1/\sigma^2(F_o^2)$. Scattering factors for the non-hydrogen atoms were from *International Tables for X-ray Crystallography* (1962), and anomalous dispersion correction factors for these atoms were from Cromer & Liberman (1970). Scattering factors for the hydrogen atoms were from Stewart, Davidson & Simpson (1965). Coordinates for the three hydrogen atoms were calculated by assuming trigonal bonding with N–H and C–H bond distances of 0·95 Å. Hydrogen atoms were assigned isotropic temperature factors of 3·0 Å^2 and were included in structure-factor calculations but not in the least-squares refinement. During the last cycle of refinement, no parameter shifted more than one-tenth of its estimated standard deviation. The final R index $\{\sum||F_o|-|F_c||/\sum|F_o|\}$ is 0·044; the goodness-of-fit $\{[\sum w(F_o^2-F_c^2)^2/(m-s)]^{1/2}$, where m is the number of reflections used and s is the number of parameters refined$\}$ is 2·52; and the weighted R index, $\{\sum w(F_o^2-F_c^2)^2/\sum wF_o^4\}^{1/2}$, is 0·108. The coordinates were inverted through the origin and the alternate enantiomeric structure was also refined; this enantiomer refined to only $R=0{\cdot}049$, goodness-of-fit $=2{\cdot}72$, weighted R index $=0{\cdot}117$. We have assumed that the first model with $R=0{\cdot}044$ is the correct one and all subsequent discussion of structural properties will be based on the results of that refinement. A final three-dimensional difference Fourier map showed several peaks and troughs near the iodine atom ranging up to 1·3 e Å^{-3} in magnitude; the fluctuations elsewhere in the map did not exceed 0·7 e Å^{-3} in magnitude.

Results and discussion

Table 1 lists the atomic parameters and their estimated standard deviations. Estimated errors in positional parameters are about 0·001 Å for the iodine atom and 0·013 Å for the other non-hydrogen atoms.* Fig. 1 shows bond lengths, bond angles, and thermal ellipsoids of 5-iodouracil. The molecule is not planar: C(2) deviates by 0·034 Å from a least-squares plane through the six atoms of the pyrimidine ring, the oxygen substituents deviate by about 0·040 Å and the iodine atom by 0·095 Å. Fig. 2 shows the crystal-packing and hydrogen-bonding scheme. The molecules form sets of planar hydrogen-bonded ribbons that run in the [011] and [0$\bar{1}$1] directions. Within these ribbons, adjacent bases are joined by N(1)–H···O(4) hydrogen bonds [N(1)···O(4) = 2·90 Å, H(N1)···O(4) = 2·17 Å, N(1)–H(N1)···O(4) = 132°]. The sets of ribbons run almost perpendicular to each other and are joined by N(3)–H···O(2) hydrogen bonds [N(3)···O(2) = 2·78 Å, H(N3)···O(2) = 1·84 Å, N(3)–H(N3)···O(2) = 167°]. The iodine atoms are clustered together in sheets that lie parallel to the *bc* plane; the shortest I···I contact is 4·22 Å. Ribbons of bases are stacked with an inter-ribbon spacing of 3·15 Å. Fig. 3 shows the stacking pattern, as viewed perpendicular to the plane of the ribbons. As is commonly found in crystal structures of pyrimidines (Bugg *et al.*, 1971), the stacking pattern is characterized by minimal base overlap, and one of the carbonyl oxygen atoms is positioned practically over the center of an adjacent pyrimidine ring. In contrast to the stacking patterns in most other crystal structures of halogenated uracil derivatives (Bugg & Sternglanz, 1974, and references therein), the iodine atom is not positioned directly over the pyrimidine ring of a neighboring base. However, the intimate halogen–base contacts that appear to dominate the stacking patterns of halogenated bases recur in the 5-iodouracil structure, where the iodine atom forms a close contact with atom C(6) of an adjacent pyrimidine ring; the I···C(6) distance of 3·76 Å is the only stacking interaction that is shorter than a normal (Pauling, 1960) van der Waals distance. As reviewed earlier

Table 1. *Atomic parameters and their estimated standard deviations*

Values for non-hydrogen atoms have been multiplied by 10^4. Hydrogen-atom positional parameters have been multiplied by 10^3. Anisotropic temperature factors are in the form: $T=\exp(-\beta_{11}h^2-\beta_{22}k^2-\beta_{33}l^2-2\beta_{12}hk-2\beta_{13}hl-2\beta_{23}kl)$. Isotropic temperature factors are given in Å^2. The refined value for the isotropic extinction parameter is 0·006 (2).

	x	y	z	β_{11} (or B)	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
I	955 (1)	2500	2506 (2)	39 (1)	563 (7)	817 (7)	−7 (3)	5 (1)	−33 (10)
N(1)	3488 (7)	7388 (54)	4716 (18)	50 (5)	247 (64)	208 (31)	22 (26)	−7 (9)	−76 (64)
C(2)	4146 (9)	6572 (31)	2913 (22)	54 (8)	223 (71)	165 (45)	−7 (16)	−1 (15)	15 (38)
O(2)	4937 (6)	7532 (53)	2921 (15)	51 (4)	430 (49)	319 (32)	−8 (37)	23 (9)	43 (82)
N(3)	3869 (7)	4306 (28)	1124 (18)	41 (5)	320 (61)	231 (37)	−2 (16)	6 (11)	−18 (48)
C(4)	2990 (8)	3019 (46)	873 (23)	48 (5)	226 (111)	219 (41)	28 (23)	14 (12)	−42 (61)
O(4)	2828 (7)	1037 (28)	−855 (20)	57 (5)	477 (62)	317 (39)	−40 (16)	−3 (12)	−121 (48)
C(5)	2337 (7)	4232 (27)	2764 (23)	35 (6)	40 (55)	371 (51)	−23 (15)	12 (13)	30 (50)
C(6)	2596 (10)	6219 (37)	4631 (25)	50 (7)	410 (76)	243 (51)	32 (21)	2 (15)	−23 (54)
H(N1)	365	879	611	3·0					
H(N3)	434	358	−6	3·0					
H(C6)	216	686	592	3·0					

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30855 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

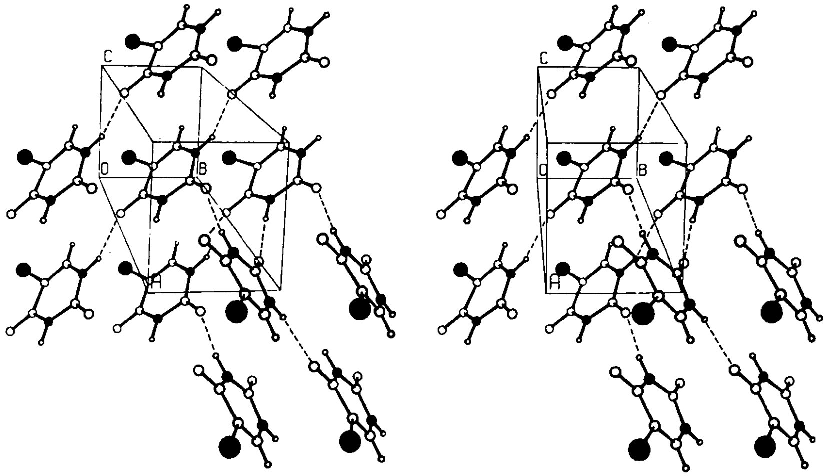

Fig. 2. Stereo drawing of the crystal packing and the hydrogen-bonding scheme. Ring nitrogen atoms are represented by small solid spheres, iodine atoms by large solid spheres. Hydrogen bonds are depicts by dashed lines.

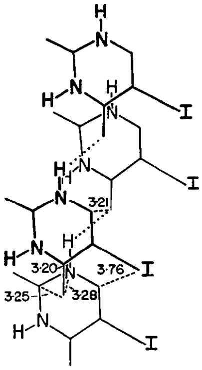

Fig. 3. Base stacking pattern of hydrogen-bonded ribbons viewed perpendicular to the base planes. Hydrogen bonds are depicted as dotted lines. Close interatomic contacts are shown by dashed lines and given in Å.

(Bugg *et al.*, 1971; Bugg, 1972; Bugg & Sternglanz, 1974; Sternglanz & Bugg, 1974), halogen interactions of this type may affect the stacking properties of uracil derivatives in aqueous and biological systems. They may partially account for the enchanced thermal stabilities of helical polynucleotides that contain 5-halogenated pyrimidine residues, for the mutagenic effects of 5-halogenated uracil derivatives that are incorporated into nucleic acids, and for the observation that, in aqueous solution, 5-halogenated uracil nucleosides stack more extensively than either thymidine or uridine.

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