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# 5-Fluorouracil and thymine form a crystalline solid solution

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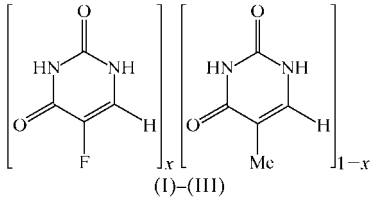
The crystal structure of a 5-fluorouracil–thymine [5-fluoropyrimidine-2,4(1*H*,3*H*)-dione–5-methylpyrimidine-2,4(1*H*,3*H*)-dione, $C_4H_3FN_2O_2\cdot C_5H_6N_2O_2$] solid solution has been determined. Both of the crystallographically independent sites can accommodate either 5-fluorouracil or thymine molecules, leading to occupational disorder [$C_{5-x}H_{6-3x}F_xN_2O_2\cdot C_{5-y}H_{6-3x}F_yN_2O_2$, with $x = 0.52$ and $y = 0.7$ for determination (I), $x = 0.55$ and $y = 0.69$ for (II), and $x = 0.67$ and $y = 0.76$ for (III)]. The 5-fluorouracil–thymine ratio in the crystal structure is influenced by the 5-fluorouracil–thymine ratio in the crystallization solution, though it does not exactly mirror it. The crystal structure comprises interpenetrating hydrogen-bonded nets, containing four independent hydrogen bonds.

## Comment

F atoms and methyl groups have been identified as being capable of replacing one another in a molecule to produce isomorphic crystal structures because of their similar size, shape and van der Waals interactions (Kuhnert-Brandstatter, 1982). Attempts were made to exploit this interchangeability as part of an ongoing study into the crystalline solid state of 5-fluorouracil (Hulme *et al.*, 2005; Hamad *et al.*, 2006), with the aim of growing 5-fluorouracil crystals isostructural with thymine (Portalone *et al.*, 1999) or thymine crystals isostructural with 5-fluorouracil form 1 (Fallon, 1973). Instead of producing such isostructural cocrystals, an entirely new structure was discovered, grown from solution in 2,2,2-trifluoroethanol, containing 5-fluorouracil and thymine in a solid solution.




(I)–(III)

A cocrystal can be defined as a crystal structure containing two (or more) molecular species on separate crystallographic sites with a fixed stoichiometric ratio in the crystal structure, in contrast with a solid solution, which exhibits 'a homogeneous crystalline phase in which some of the constituent molecules are substituted by foreign molecules that possess sufficient similarity that the lattice dimensions are changed only slightly' (Datta & Grant, 2004). In the structure reported here, both of the crystallographically independent sites (Fig. 1) can be occupied by either 5-fluorouracil or thymine molecules, giving non-integer occupancies for both molecules at each site and leading to the description of this structure as a solid solution rather than a cocrystal.

The structure adopts the monoclinic space group *C*2/*c*. The crystal structure, denoted (I), of a crystal grown from a 1:1 solution of 5-fluorouracil and thymine, with the structure determined at 150 K, is reported; two further structure determinations are reported to exemplify the features of this

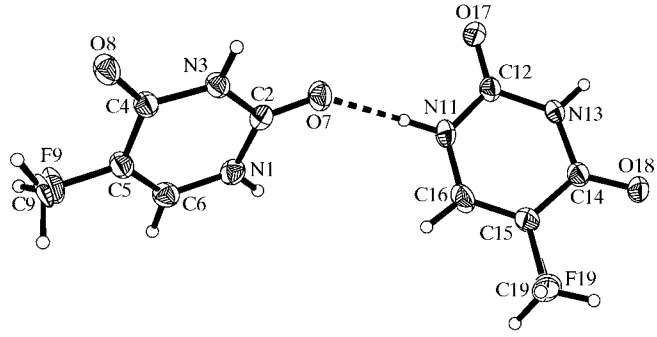



**Figure 1**
The asymmetric unit of the title cocrystal. Displacement ellipsoids are drawn at the 50% probability level. H atoms are shown as spheres (only one component of the disordered methyl groups is shown). The dashed line indicates the intermolecular hydrogen bond.

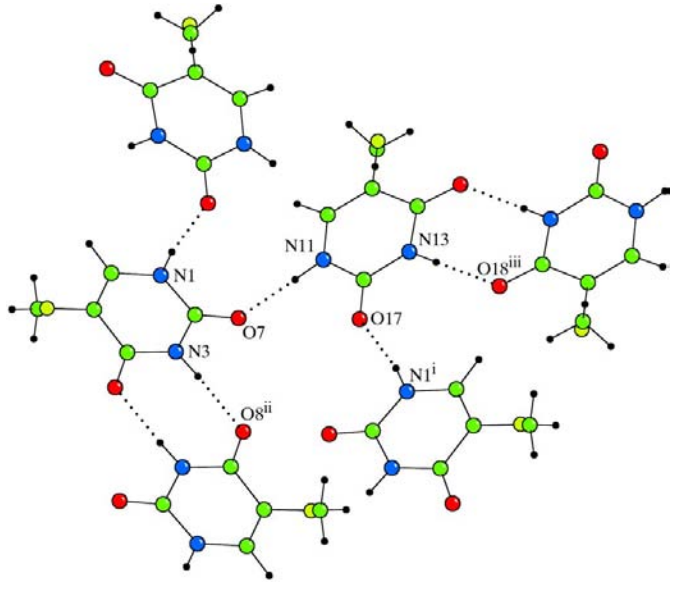



**Figure 2**
The hydrogen bonding present in the crystal structure. Hydrogen bonds are shown as dotted lines. [Symmetry codes: (i) $-x+\frac{3}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x+1, -y+2, -z+1$; (iii) $-x+\frac{3}{2}, -y+\frac{1}{2}, -z+2$.]

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system. (II) denotes the crystal structure determination of a crystal grown from a 1:1 solution at 298 K and (III) denotes the crystal structure determination of a crystal grown from a 2:1 solution of 5-fluorouracil and thymine at 150 K. Structure (I) will be used exclusively for the purposes of the discussion of the crystal structure, with the other two determinations used to highlight features of the solid solution structure.

The only difference between 5-fluorouracil and thymine is the substituent bonded to the 5-position in the molecular structure, and hence the only sign of the occupational disorder is the F:Me ratio at the 9- and 19-positions in the crystal structure. Both (I) and (II) were grown from 1:1 5-fluorouracil/thymine crystallization solutions and have similar F:Me ratios at the 9- and 19-postions [for (I), 0.52 (1):0.48 (1) for the 9-position and 0.70 (1):0.30 (1) for the 19-position; for (II), 0.55 (1):0.45 (1) for the 9-position and 0.69 (2):0.31 (2) for the 19-position]. This result indicates that the 5-fluorouracil/thymine ratio in the crystals is not simply a statistical distribution throughout the crystal but depends on the ratio in the crystallization solution. This fact is exemplified by the distinct preference for incorporating F at the 19-position, even though the original crystallization solution contained a 1:1 ratio. Structure (III) was grown from a 2:1 solution and has a higher proportion of F at both positions [0.66 (1):0.34 (1) for the 9-position and 0.76 (1):0.24 (1) for the 19-position]. It can be concluded that altering the 5-fluorouracil/thymine ratio in the crystallization solution will alter the ratio at each of the crystallographically independent sites. Refinements of (I) as either fully 5-fluorouracil or fully thymine did not prove satisfactory, yielding unacceptable displacement parameters at the 9- and 19-positions, and higher than expected $R$ factors, thus confirming the disordered model.

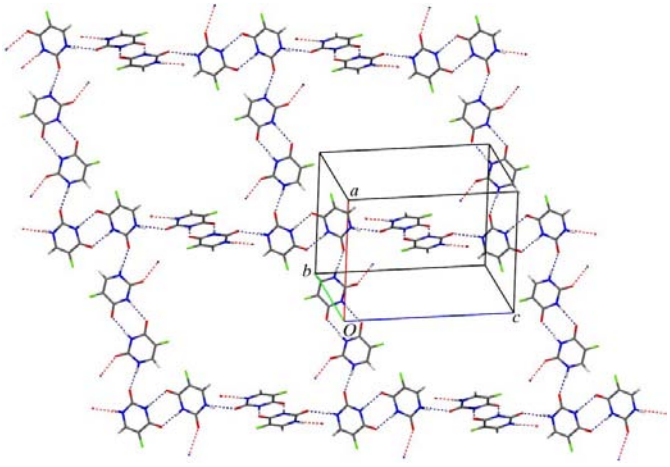


**Figure 3**
Four adjacent rings from a single net. Hydrogen bonds are shown as dotted lines.

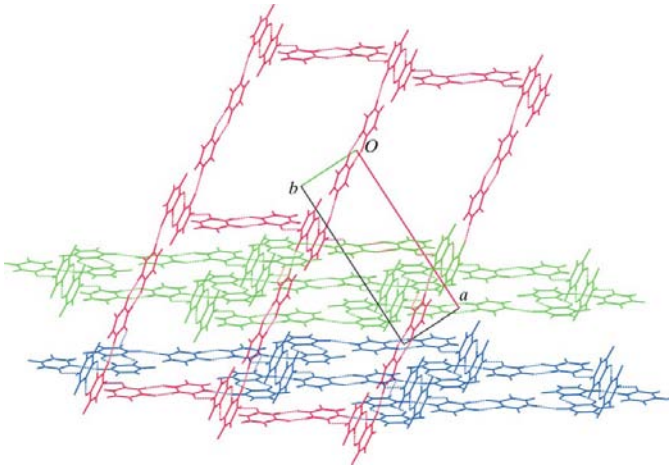


**Figure 4**
A view of three nets parallel to the $c$ axis, with two nets parallel to one another and intersecting the third net. Separate nets are shown as single colours. Hydrogen bonds are shown as dotted lines.

Structure (II), measured at room temperature, shows thermal expansion in the $a$ axis of approximately 0.5 Å (2.6%) compared with structure (I), determined at 150 K. No significant change is evident in either of the other cell axes or the $\beta$ angle. The unit cell was determined at 298 K for the crystal used for (III) at 150 K, and a similar expansion in the $a$ axis was observed [$a$ = 19.704 (11) Å at 298 K and $a$ = 19.235 (3) Å at 150 K].

It should be noted that crystals with this structure could not be grown from solutions with 5-fluorouracil/thymine ratios of 3:1 or 1:2, and attempts to grow pure 5-fluorouracil crystals with this structure from seeded solutions also failed. This implies that the two compounds have a limited solubility range in this solid solution.

The crystal structure contains four independent N—H···O hydrogen bonds, and all hydrogen-bond donors and acceptors are used (Table 1–3). Two $R_2^2(8)$ hydrogen-bonded dimers are present (Bernstein *et al.*, 1995), with one dimer composed of two N3—H3···O8($-x+1, -y+2, -z+1$) hydrogen bonds and the other dimer composed of two N13—H13···O18($-x+\frac{3}{2}, -y+\frac{1}{2}, -z+2$) hydrogen bonds. Along with the dimers, two single $D_1^1(2)$ hydrogen bonds participate in the overall hydrogen-bond network (Fig. 2), *viz.* N1—H1···O17($-x+\frac{3}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$) and N11—H11···O7.

The hydrogen bonds build a two-dimensional net, with the constituent rings of the net made up of 14 molecules in an approximately rectangular conformation. Of the 14 molecules, 12 are involved in six dimers joined by $R_2^2(8)$ hydrogen-bonded rings, and these dimers are connected together by single hydrogen bonds. The two remaining molecules are at diagonally opposite corners of the rectangle; along with the two single hydrogen bonds that incorporate each of these molecules into the ring, each participates in a dimer with the second molecule part of the adjacent ring. These interactions hence produce the two-dimensional net motif (Fig. 3).

Two subsets of nets are observed; within each subset, the planes of the nets are parallel to one another, but each of the subsets is parallel to different Miller planes, *viz.* [$\bar{5}11$] and [$\overline{5}11$]. The two subsets interpenetrate to give the overall three-dimensional hydrogen-bonded motif (Fig. 4), with hydrogen bonding at the points of interpenetration of the nets *via* single hydrogen bonds only.

## Experimental

The crystals used for determinations (I) and (II) were produced from a saturated solution of 5-fluorouracil and thymine (1:1 molar ratio) in 2,2,2-trifluoroethanol by solvent evaporation. The crystal used for structure determination (III) was produced from a saturated solution of 5-fluorouracil and thymine (2:1 molar ratio) in 2,2,2-trifluoroethanol by solvent evaporation.

### Determination (I)

*Crystal data*

$C_{4.48}H_{4.45}F_{0.52}N_2O_2\cdot C_{4.30}H_{3.91}F_{0.70}N_2O_2$
$M_r = 257.07$
Monoclinic, $C2/c$
$a = 19.3785\ (15)$ Å
$b = 5.9918\ (5)$ Å
$c = 20.0293\ (15)$ Å
$\beta = 117.813\ (1)^\circ$
$V = 2057.0\ (3)$ Å$^3$
$Z = 8$
$D_x = 1.660$ Mg m$^{-3}$
Mo $K\alpha$ radiation
$\mu = 0.15$ mm$^{-1}$
$T = 150\ (2)$ K
Diamond tablet, colourless
$0.79 \times 0.22 \times 0.20$ mm

*Data collection*

Bruker SMART APEX diffractometer
$\omega$ scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min} = 0.893$, $T_{max} = 0.971$
8568 measured reflections
2459 independent reflections
2232 reflections with $I > 2\sigma(I)$
$R_{int} = 0.016$
$\theta_{max} = 28.3^\circ$

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.096$
$S = 1.06$
2459 reflections
207 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0452P)^2 + 1.6915P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.35$ e Å$^{-3}$
$\Delta\rho_{min} = -0.19$ e Å$^{-3}$

**Table 1**
Hydrogen-bond geometry (Å, °) for (I).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N1—H1···O17$^{i}$ | 0.894 (18) | 1.895 (18) | 2.7769 (15) | 168.4 (16) |
| N3—H3···O8$^{ii}$ | 0.901 (18) | 1.910 (18) | 2.8092 (14) | 175.2 (15) |
| N11—H11···O7 | 0.876 (19) | 1.96 (2) | 2.7892 (14) | 156.6 (16) |
| N13—H13···O18$^{iii}$ | 0.875 (18) | 1.956 (18) | 2.8291 (14) | 176.1 (16) |

Symmetry codes: (i) $-x+\frac{3}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x+1, -y+2, -z+1$; (iii) $-x+\frac{3}{2}, -y+\frac{1}{2}, -z+2$.

### Determination (II)

*Crystal data*

$C_{4.45}H_{4.36}F_{0.55}N_2O_2\cdot C_{4.31}H_{3.94}F_{0.69}N_2O_2$
$M_r = 257.13$
Monoclinic, $C2/c$
$a = 19.856\ (11)$ Å
$b = 5.946\ (3)$ Å
$c = 20.073\ (11)$ Å
$\beta = 117.660\ (8)^\circ$
$V = 2099.0\ (19)$ Å$^3$
$Z = 8$
$D_x = 1.627$ Mg m$^{-3}$
Mo $K\alpha$ radiation
$\mu = 0.14$ mm$^{-1}$
$T = 298\ (2)$ K
Diamond tablet, colourless
$0.69 \times 0.20 \times 0.15$ mm

*Data collection*

Bruker SMART APEX diffractometer
$\omega$ scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min} = 0.907$, $T_{max} = 0.979$
8509 measured reflections
2492 independent reflections
1856 reflections with $I > 2\sigma(I)$
$R_{int} = 0.031$
$\theta_{max} = 28.4^\circ$

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.056$
$wR(F^2) = 0.138$
$S = 1.09$
2492 reflections
207 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0602P)^2 + 1.3663P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.24$ e Å$^{-3}$
$\Delta\rho_{min} = -0.19$ e Å$^{-3}$

**Table 2**
Hydrogen-bond geometry (Å, °) for (II).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N1—H1···O17$^{i}$ | 0.86 (3) | 1.94 (3) | 2.792 (3) | 171 (2) |
| N3—H3···O8$^{ii}$ | 0.88 (3) | 1.95 (3) | 2.831 (2) | 173 (2) |
| N11—H11···O7 | 0.89 (3) | 1.97 (3) | 2.805 (3) | 156 (2) |
| N13—H13···O18$^{iii}$ | 0.88 (2) | 1.98 (2) | 2.852 (3) | 175 (2) |

Symmetry codes: (i) $-x+\frac{3}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x+1, -y+2, -z+1$; (iii) $-x+\frac{3}{2}, -y+\frac{1}{2}, -z+2$.

### Determination (III)

*Crystal data*

$C_{4.33}H_{3.99}F_{0.67}N_2O_2\cdot C_{4.24}H_{3.73}F_{0.76}N_2O_2$
$M_r = 257.87$
Monoclinic, $C2/c$
$a = 19.235\ (3)$ Å
$b = 5.9683\ (8)$ Å
$c = 20.042\ (3)$ Å
$\beta = 118.216\ (2)^\circ$
$V = 2027.4\ (5)$ Å$^3$
$Z = 8$
$D_x = 1.690$ Mg m$^{-3}$
Mo $K\alpha$ radiation
$\mu = 0.15$ mm$^{-1}$
$T = 150\ (2)$ K
Colourless, diamond tablet
$0.45 \times 0.37 \times 0.34$ mm

*Data collection*

Bruker SMART APEX diffractometer
$\omega$ scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min} = 0.935$, $T_{max} = 0.950$
8306 measured reflections
2405 independent reflections
2147 reflections with $I > 2\sigma(I)$
$R_{int} = 0.030$
$\theta_{max} = 28.1^\circ$

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.110$
$S = 1.07$
2405 reflections
207 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0584P)^2 + 1.4434P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.30$ e Å$^{-3}$
$\Delta\rho_{min} = -0.25$ e Å$^{-3}$

**Table 3**
Hydrogen-bond geometry (Å, °) for (III).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N1—H1···O17$^{i}$ | 0.90 (2) | 1.90 (2) | 2.7790 (16) | 165.9 (18) |
| N3—H3···O8$^{ii}$ | 0.88 (2) | 1.93 (2) | 2.8054 (15) | 173.3 (17) |
| N11—H11···O7 | 0.84 (2) | 1.98 (2) | 2.7856 (16) | 159.7 (19) |
| N13—H13···O18$^{iii}$ | 0.87 (2) | 1.96 (2) | 2.8205 (15) | 174.1 (18) |

Symmetry codes: (i) $-x+\frac{3}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x+1, -y+2, -z+1$; (iii) $-x+\frac{3}{2}, -y+\frac{1}{2}, -z+2$.

In all three structures, the C5—C9 and C15—C19 bonds were restrained to 1.520 (2) Å, and the C5—F9 and C15—F19 bonds were restrained to 1.350 (2) Å. For each determination, all H atoms other

than the methyl H atoms were located in a difference map and were refined isotropically. In determinations (I) and (II), methyl H atoms were modelled as idealized disordered methyl groups over two sites offset by 60°. For determination (III), the C19 methyl group was modelled as an idealized disordered methyl group, and for the C9 methyl group the H atoms were located from a difference map and refined using a rigid rotor model. For structure determination (I), the refined C—H bond lengths are 0.948 (18) and 0.968 (17) Å, with all methyl C—H bond lengths fixed at 0.98 Å; the range of N—H bond lengths is 0.875 (18)–0.901 (18) Å. For structure determination (II), the C—H bond lengths are 0.95 (3) and 1.02 (3) Å, with all methyl C—H bond lengths fixed at 0.96 Å; the range of N—H bond lengths is 0.86 (3)–0.89 (3) Å. For structure determination (III), the C—H bond lengths are 0.950 (19) and 0.96 (2) Å, with all methyl C—H bond lengths fixed at 0.98 Å; the range of N—H bond lengths is 0.84 (2)–0.90 (2) Å.

For all determinations, data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics and software used to prepare material for publication: *CAMERON* (Watkin *et al.*, 1996) and *MERCURY* (Macrae *et al.*, 2006).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3013). Services for accessing these data are described at the back of the journal.

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