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Redetermination of 5-fluorocytosine monohydrate

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Key indicators

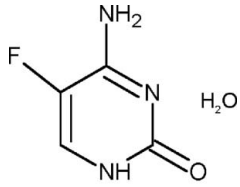
Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.002 Å
R factor = 0.055
wR factor = 0.165
Data-to-parameter ratio = 17.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, 4-amino-5-fluoro-2-hydroxypyrimidine monohydrate, $C_4H_4FN_3O\cdot H_2O$, with two molecules of each comprising the asymmetric unit, has been redetermined, providing a significant increase in the precision of the geometric parameters.

Comment

The rational design of supramolecular structures can be realised through crystal engineering based on relatively weak intermolecular forces (Desiraju, 1995). Among these forces, hydrogen bonding is by far the most common. In addition, owing to the paramount importance of the hydrogen bond in biological structures (Jeffrey & Saenger, 1991), the number of investigations on hydrogen bonding has grown enormously.



(I)

For these reasons, we have been attracted to the study of crystalline adducts of DNA/RNA pyrimidine bases which can mimic, when coupled with amino derivatives of aromatic *N*-heterocycles *via* multiple hydrogen bonds, the base-pairing of nucleic acids (Brunetti *et al.*, 2000, 2002; Portalone *et al.*, 1999, 2002; Portalone & Colapietro, 2004*a*,*b*).

5-Fluorocytosine (5FCytos), an antifungal agent often used in association with amphotericin B, has been reported to induce, in combination with cytosine deaminase, apoptosis in human malignant glioma cells (Kurozumi *et al.*, 2004). As a DNA/RNA pyrimidine base, it represents a good candidate to be associated in the crystalline phase with carefully selected molecules having multiple hydrogen-bond sites. Consequently, since from the Cambridge Structural Database (Version of May 2005; Allen, 2002) the only published structure determination of this compound was the monohydrate by Louis *et al.* (1982), with a relatively high R value (0.076), $5FCytos\cdot H_2O$, (I), has been reinvestigated. The current determination provides a significant increase in the precision of the geometric parameters, *viz.* σ(C—C) = 0.0014–0.0016 Å *cf.* 0.006–0.010 Å in the original report (Louis *et al.*, 1982). A different choice of the unit cell from that previously published has been made (Watkin, 1994).

The asymmetric unit of (I) comprises two almost coplanar 5FCytos aminooxo tautomers and two water molecules as

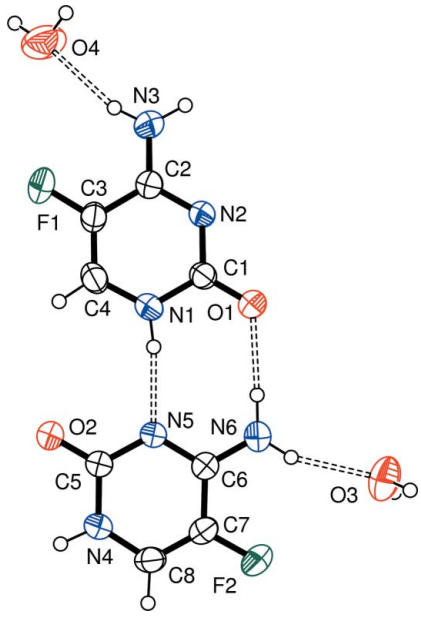


Figure 1
The asymmetric unit of (I). Displacements ellipsoids are drawn at the 50% probability level. Dashed lines indicate hydrogen bonds.

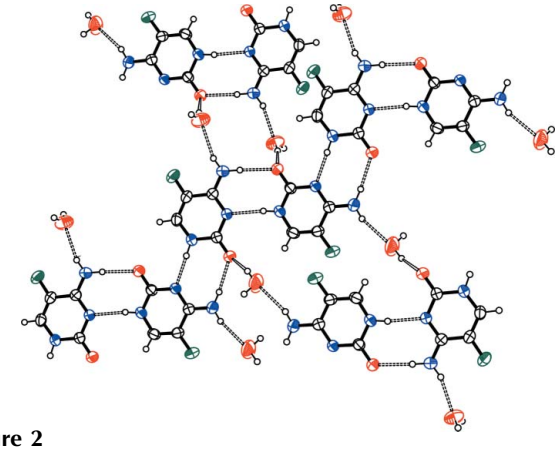


Figure 2
The hydrogen-bonding scheme (dashed lines) in (I). Displacements ellipsoids are drawn at the 50% probability level.

shown in Fig. 1. The corresponding bond lengths and angles of the two independent molecules are equal within experimental error (Table 1). A comparison of the molecular geometry of the cytosine ring with that reported for cytosine monohydrate (Weber *et al.*, 1980) shows that the only differences are in the immediate vicinity of the F substituent: the C—C bond lengths are shortened by ∼0.010 (1) Å and the C2—C3—C4 angle is widened by 3.0 (1)°. These observations are ascribed to substitution in the ring.

Consistent with the earlier study (Louis *et al.*, 1982), in the crystal structure the hydrogen-bonding scheme involves all H-atom donor/acceptor sites as summarized in Table 2. The 5FCytos molecules are connected into dimers *via* N—H···O and N—H···N hydrogen bonds, forming ribbons parallel to the *bc* plane (Fig. 2). Each hydrogen-bonded dimer forms an eight-membered ring with graph-set motif $R_2^2(8)$ (Etter *et al.*, 1990; Bernstein *et al.*, 1995). Similarly, each of the independent

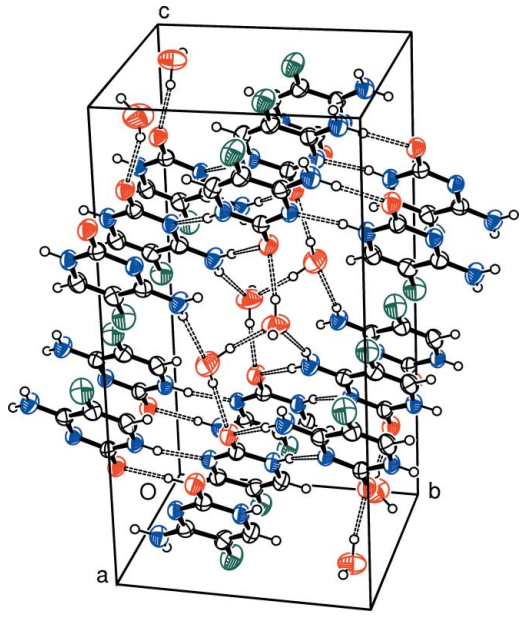


Figure 3
The packing of (I), highlighting the role water plays in stabilizing the crystal structure. Displacement ellipsoids are drawn at the 50% probability level. Dashed lines indicate hydrogen bonds.

water molecules shows a similar hydrogen-bonding scheme involving four contacts. Thus, each water molecule acts as a hydrogen-bond donor and acceptor to a pair of 5FCytos molecules, as well as to two water molecules (Fig. 3).

Experimental

The title compound (Fluka, 99% purity) was recrystallized without further purification from water by slow evaporation of the solvent.

Crystal data

$C_4H_4FN_3O\cdot H_2O$
M_r = 147.12
Monoclinic, $P2_1/c$
a = 7.5142 (11) Å
b = 9.4241 (16) Å
c = 17.692 (6) Å
β = 99.16 (2)°
V = 1236.9 (5) Å^3
Z = 8
D_x = 1.580 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 15 reflections
θ = 15–21°
μ = 0.15 mm^{-1}
T = 298 (2) K
Block, colourless
0.30 × 0.20 × 0.20 mm

Data collection

Huber CS four-circle diffractometer
ω scans
Absorption correction: none
6074 measured reflections
3447 independent reflections
2944 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 30.0°
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 13$
$l = -24 \rightarrow 24$
3 standard reflections
every 97 reflections
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.055
$wR(F^2)$ = 0.165
S = 1.05
3447 reflections
193 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0976P)^2 + 0.1585P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

F1—C3	1.3421 (13)	F2—C7	1.3452 (13)
O1—C1	1.2504 (14)	O2—C5	1.2474 (13)
N1—C4	1.3562 (15)	N4—C8	1.3619 (15)
N1—C1	1.3722 (13)	N4—C5	1.3763 (13)
N2—C2	1.3322 (13)	N5—C6	1.3349 (13)
N2—C1	1.3591 (13)	N5—C5	1.3601 (13)
N3—C2	1.3299 (14)	N6—C6	1.3269 (14)
C2—C3	1.4243 (14)	C6—C7	1.4270 (14)
C3—C4	1.3417 (16)	C7—C8	1.3401 (16)
C4—N1—C1	121.94 (9)	C8—N4—C5	121.90 (9)
C2—N2—C1	120.27 (8)	C6—N5—C5	120.48 (8)
O1—C1—N2	121.05 (9)	O2—C5—N5	121.41 (9)
O1—C1—N1	119.63 (9)	O2—C5—N4	119.37 (9)
N2—C1—N1	119.31 (10)	N5—C5—N4	119.21 (9)
N3—C2—N2	119.68 (9)	N6—C6—N5	119.50 (9)
N3—C2—C3	120.43 (10)	N6—C6—C7	120.87 (10)
N2—C2—C3	119.90 (9)	N5—C6—C7	119.63 (9)
C4—C3—F1	122.19 (10)	C8—C7—F2	122.23 (9)
C4—C3—C2	119.80 (10)	C8—C7—C6	120.14 (10)
F1—C3—C2	118.02 (10)	F2—C7—C6	117.62 (9)
C3—C4—N1	118.77 (9)	C7—C8—N4	118.62 (9)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···N5	0.88	1.96	2.8313 (13)	171
N3—H2···O2^{i}	0.91	2.03	2.9402 (14)	173
N3—H3···O4	0.85	2.29	3.0858 (18)	156
N4—H5···N2^{ii}	0.92	1.94	2.8548 (13)	173
N6—H6···O1	0.92	2.01	2.9260 (14)	176
N6—H7···O3	0.87	2.15	2.9810 (18)	161
O3—H9···O4^{iii}	0.80	2.19	2.987 (2)	174
O3—H10···O1^{iv}	0.88	1.90	2.7739 (16)	171
O4—H11···O2^{v}	0.86	1.95	2.7483 (17)	152
O4—H12···O3^{vi}	0.96	1.93	2.8492 (19)	158

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

All H atoms were found in a difference map and were refined as riding in their as-found relative positions, with independently refined U_{iso} values; C—H distances lie in the range 0.93–0.95 Å, N—H = 0.85–0.92 Å and O—H = 0.80–0.97 Å.

Data collection: *XCS* (Colapietro *et al.*, 1992); cell refinement: *XCS*; data reduction: *XCS*; program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Altomare, A., Burla, M. C., Camalli, M., Cascarano, G. L., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Brunetti, B., Piacente, V. & Portalone, G. (2000). *J. Chem. Eng. Data*, **45**, 242–246.
Brunetti, B., Piacente, V. & Portalone, G. (2002). *J. Chem. Eng. Data*, **47**, 17–19.
Colapietro, M., Cappuccio, G., Marciante, C., Pifferi, A., Spagna, R. & Helliwell, J. R. (1992). *J. Appl. Cryst.* **25**, 192–194.
Desiraju, G. R. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 2311–2326.
Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* B**46**, 256–262.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Jeffrey, G. A. & Saenger, W. (1991). *Hydrogen Bonding in Biological Structures*, pp. 247–268. Berlin, Heidelberg: Springer-Verlag.
Kurozumi, K., Tamiya, T., Ono, Y., Otsuka, S., Kambara, H., Adachi, Y., Ichikawa, T., Hamada, H. & Ohmoto, T. (2004). *J. Neuro-Oncol.* **66**, 117–127.
Louis, T., Low, J. N., & Tollin, P. (1982). *Cryst. Struct. Commun.* **11**, 1059–1064.
Portalone, G., Ballirano, P. & Maras, A. (2002). *J. Mol. Struct.* **608**, 35–39.
Portalone, G., Bencivenni, L., Colapietro, M., Pieretti, A. & Ramondo, F. (1999). *Acta Chem. Scand.* **53**, 57–68.
Portalone, G. & Colapietro, M. (2004*a*). *Acta Cryst.* E**60**, o1165–o1166.
Portalone, G. & Colapietro, M. (2004*b*). *J. Chem. Crystallogr.* **34**, 609–612.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Watkin, D. J. (1994). *Acta Cryst.* A**50**, 411–437.
Weber, H. P., Craven, B. M. & McMullan, R. K. (1980). *Acta Cryst.* B**36**, 645–649.