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Intermolecular N–H···O hydrogen-bonding interactions in 5-fluorocytosinium salicylate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.034
wR factor = 0.103
Data-to-parameter ratio = 11.2

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

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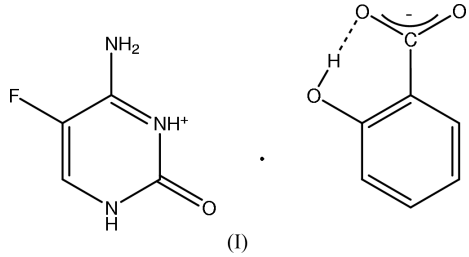
The title compound, $C_4H_5FN_3O^+\cdot C_7H_5O_3^-$, exists as a hydrogen-bonded heterodimer of 5-fluorocytosinium and salicylate ions which are connected through a pair of nearly parallel specific N—H···O hydrogen bonds. The heterodimer self-assembles *via* intermolecular N—H···O hydrogen bonds to form linear, as well as helical, hydrogen-bonded supramolecular chains that are interwoven into a three-dimensional network structure.

Comment

The potential importance of hydrogen bonding in the structure and function of biomolecules has been well established (Jeffrey & Saenger, 1991). Particularly, N—H···O hydrogen bonds are most predominant in determining the formation of secondary structure elements in proteins, base-pairing in nucleic acids and their biomolecular interactions. Model studies on complexes between nucleic acid bases and amino acids reveal some elementary stereochemical patterns, including N—H···O-type interactions, which are helpful for understanding the protein–nucleic acid recognition. Cytosine (C) base has been the subject of several investigations aiming



(I)

to study the relative stabilities of tautomeric forms (Kobayashi, 1998), hydration effects and hydrogen bonding (Sivanesan *et al.*, 2000). The structures of nucleotide complexes, especially cytosine along with amino acids, were extensively studied (Ohki *et al.*, 1974, 1975, 1976; Takenaka *et al.*, 1980). As we have been interested in hydrogen bonding patterns involving aminopyrimidine–carboxylate interactions, we have recently determined the crystal structures of cytosinium hydrogen maleate (Balasubramanian *et al.*, 1996), trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim formate (Umadevi & Muthiah, 1994) and trimethoprim maleate (Prabakaran *et al.*, 2001). For the present work, we have chosen salicylic acid to interact with 5-fluorocytosine. Salicylic acid, a well known analgesic, and its complexes with a few drug molecules such as antipyrine (Singh & Vijayan, 1974) and sulfadimidine (Patel *et al.*, 1988) were already reported in the literature. We present herein the crystal structure of 5-fluorocytosinium salicylate, (I), which

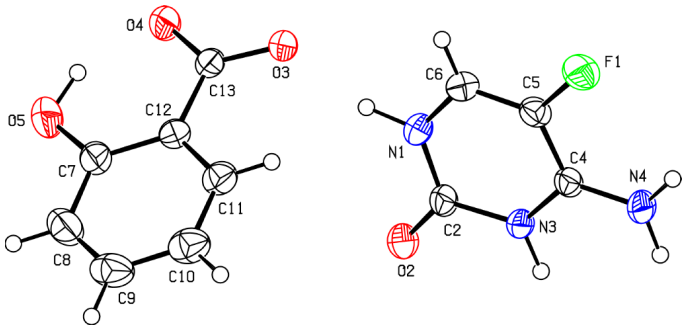


Figure 1
ORTEP diagram (*PLATON*; Spek, 1997) of (I) with the atom-labeling scheme. Displacement ellipsoids are drawn at the 30% probability level.

exhibits an extensive network of intermolecular N—H···O hydrogen bonds.

A view of the molecular structure with the atom-labelling scheme is shown in Fig. 1. The 5-fluorocytosine molecule is protonated at N3 leading to widening of the corresponding internal angle from 120.8 (5) to 124.6 (1)° compared with neutral 5-fluorocytosine (Louis *et al.*, 1982). There is an intramolecular N—H···F hydrogen bond between the N4-amino group and the F atom of the 5-fluorocytosinium cation, and the hydrogen-bonding parameters (Table 2) agree with those values (2.41 Å and 96°) noted for 5-fluorocytosine monohydrate (Louis *et al.*, 1982). There is also an intramolecular O—H···O hydrogen bond involving the phenolic OH and carboxylate groups, which is commonly observed in the salicylic moiety. The pyrimidine ring of the 5-fluorocytosinium cation makes a dihedral angle of 65.7 (1)° with the phenyl ring of the salicylate anion in the asymmetric unit of (I).

In the crystal, the carboxylate group of the salicylate anion makes a pair of nearly parallel specific hydrogen bonds of the type N—H···O through the N3 and N4 atoms of the 5-fluorocytosinium cation, forming a hydrogen-bonded heterodimer of the 5-fluorocytosinium and salicylate ions. Each hydrogen-bonded heterodimer forms an eight-membered ring with a graph-set motif of $R_2^2(8)$ (Etter, 1990; Bernstein *et al.*, 1995). The least-squares planes passing through the carboxylate group of the salicylate anion and the pyrimidine ring of the 5-fluorocytosinium cation at $(\frac{1}{2} - x, y - 1\frac{1}{2}, \frac{3}{2} - z)$ involved in the specific hydrogen-bond interaction make an angle of 9.4 (2)°. The neighbouring 5-fluorocytosinium cations in the heterodimers interact through N4—H···O2 hydrogen bonds to form a linear hydrogen-bonded supramolecular chain (Fig. 2). This type of cytosine–cytosine interaction through an N4—H···O2 hydrogen bond was previously proposed for a single stranded poly(C) nucleotide based on an NMR study (Broido & Kearns, 1982). It is interesting to note that 5-fluorocytosinium cations are neither paired nor stacked as usually expected, but self-assemble into infinite chains by intermolecular N—H···O hydrogen bonds. Such a self-assembly *via* intermolecular N—H···O and N—H···N hydrogen bonds has been recently reported for enaminonic (Bertolasi *et al.*, 1998) and pyrazole (Bertolasi *et al.*, 1999) derivatives, respectively. The hydrogen-bonded heterodimers

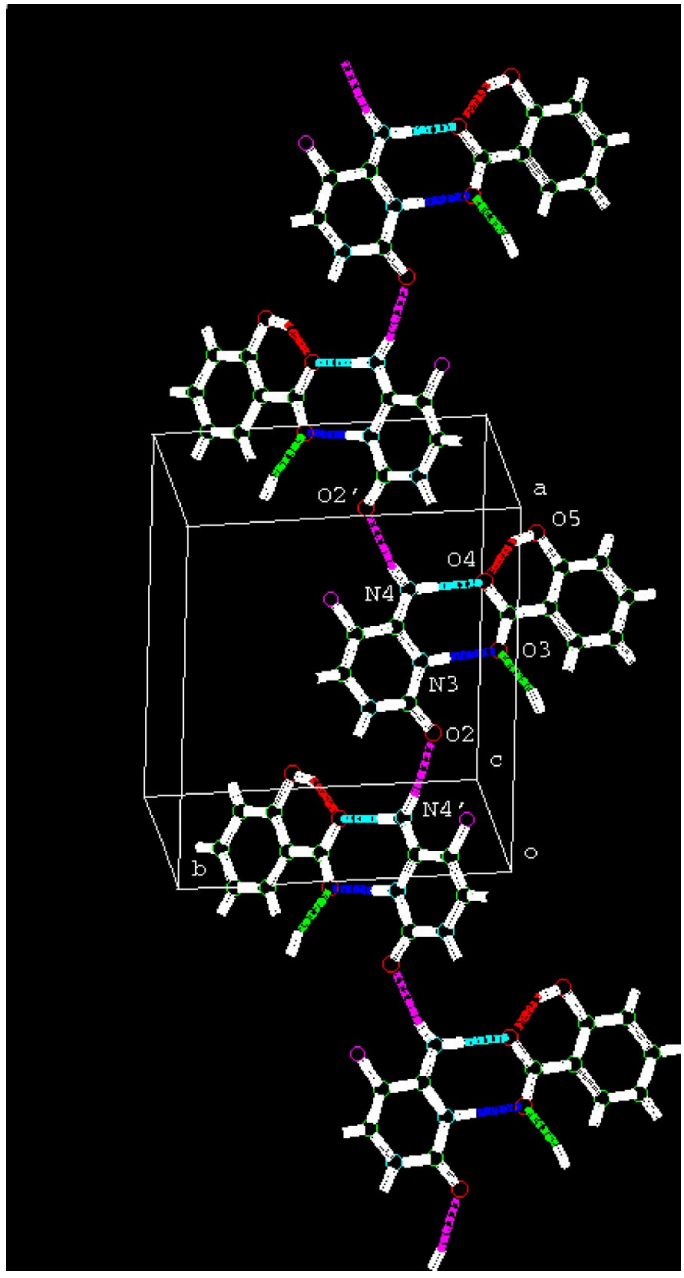


Figure 2
Hydrogen-bonded heterodimers of 5-fluorocytosinium and salicylate ions self-assemble into a linear chain through N4—H···O2′ interactions (similarly coloured hydrogen bonds are crystallographically equivalent) (*RPluto*; Cambridge Structural Database, 2000).

themselves also form a helical chain with a pitch length equivalent to *b* through intermolecular N1—H···O3 hydrogen bonds involving aminopyrimidine–carboxylate interactions (Fig. 3). Since the acceptor atom O3 links the helical chain and simultaneously participates in the specific hydrogen bond, it acts as a bifurcated acceptor. Thus, the hydrogen-bonding patterns observed in (I) are elegantly characterized by supramolecular linear and helical chains built up of heterodimers of 5-fluorocytosinium and salicylate ions. Indeed, these chains are interwoven into a three-dimensional

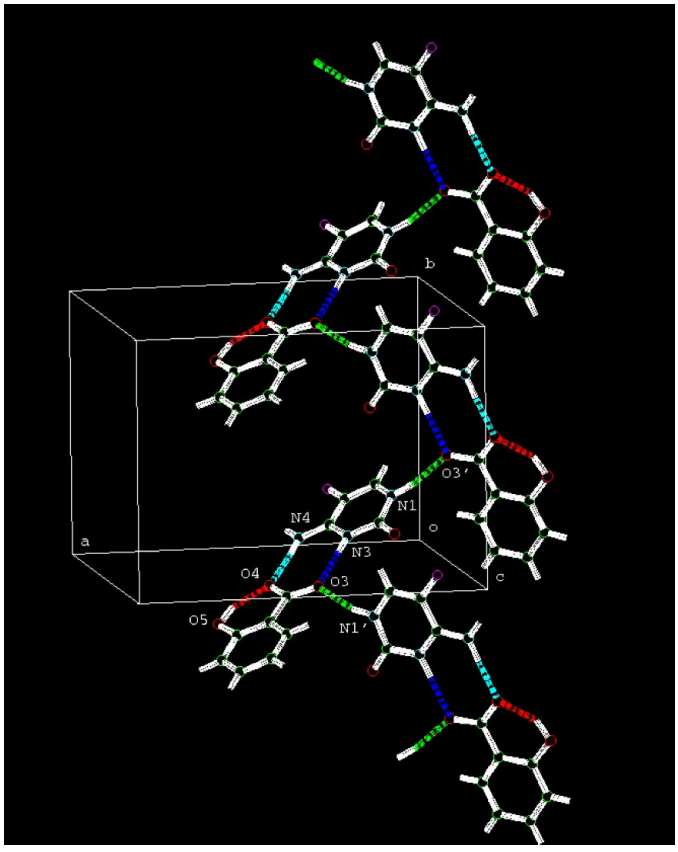


Figure 3
Hydrogen-bonded heterodimers of 5-fluorocytosinium and salicylate ions self-assemble into a helical chain through N1—H···O3′ interactions (similarly coloured hydrogen bonds are crystallographically equivalent) (*RPluto*; Cambridge Structural Database, 2000).

hydrogen-bonding network to form an intricate structure (Fig. 4).

Experimental

Hot aqueous solutions of 5-fluorocytosine and salicylic acid (received from Hoffmann La Roche, Basel and Loba Chemie Pvt. Ltd, respectively) were mixed in a 1:1 molar ratio. Crystals of (I) were grown from the solution by slow evaporation at room temperature.

Crystal data

$C_4H_5FN_3O^+\cdot C_7H_5O_3^-$
M_r = 267.22
Monoclinic, $P2_1/n$
a = 13.509 (5) Å
b = 10.519 (3) Å
c = 8.099 (2) Å
β = 101.540 (15)°
V = 1127.6 (6) Å^3
Z = 4
D_x = 1.574 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 2.0–25.0°
μ = 1.15 mm^{-1}
T = 293 K
Needle, colourless
0.26 × 0.23 × 0.17 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
2289 measured reflections
2141 independent reflections
1631 reflections with $I > 2\sigma(I)$
R_{int} = 0.010
θ_{max} = 70.0°
$h = -16 \rightarrow 14$
$k = -11 \rightarrow 12$
$l = -2 \rightarrow 9$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.103
S = 1.02
2141 reflections
192 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1407P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0066 (7)

Table 1
Selected geometric parameters (Å, °).

F1—C5	1.348 (2)	N1—C6	1.366 (2)
O3—C13	1.266 (2)	N1—C2	1.371 (2)
O4—C13	1.266 (2)	N3—C2	1.386 (2)
O5—C7	1.357 (2)	N3—C4	1.358 (2)
O2—C2	1.223 (2)	N4—C4	1.306 (2)
C2—N1—C6	122.98 (13)	O2—C2—N1	123.37 (14)
C2—N3—C4	124.65 (13)	O2—C2—N3	121.41 (14)
O5—C7—C8	118.03 (17)	N3—C4—N4	120.57 (13)
O5—C7—C12	122.20 (17)	N3—C4—C5	116.17 (13)
O4—C13—C12	117.82 (14)	N4—C4—C5	123.26 (14)
O3—C13—O4	122.28 (14)	F1—C5—C4	116.93 (13)
O3—C13—C12	119.88 (14)	F1—C5—C6	122.14 (14)
N1—C2—N3	115.22 (13)	N1—C6—C5	119.85 (15)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O3	0.98	1.76	2.7151 (19)	166
N3—H3···O3^{i}	0.95	1.82	2.7719 (19)	179
N4—H4A···O4^{i}	0.97 (2)	1.78 (2)	2.748 (2)	175 (2)
N4—H4B···F1	0.902 (18)	2.437 (19)	2.751 (2)	100.7 (15)
N4—H4B···O2^{ii}	0.902 (18)	1.994 (19)	2.880 (2)	167.0 (18)
O5—H5···O4	0.95 (3)	1.68 (3)	2.544 (2)	149 (3)

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

H atoms attached to C atoms were treated as riding, with an average C—H distance of 0.93 Å. All other H atoms were located from difference Fourier maps and refined isotropically. The H1 and H3 atoms attached to N1 and N3 were drifting and so their coordinates were fixed during the final refinements.

Data collection: *MolEN* (Fair, 1990); cell refinement: *MolEN*; data reduction: *MolEN*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1997) and *RPluto* (Cambridge Structural Database, 2000); software used to prepare material for publication: *PLATON* (Spek, 1997).

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References

Balasubramanian, T., Muthiah, P. T. & Robinson, W. T. (1996). *Bull. Chem. Soc. Jpn*, **69**, 2919–2922.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.

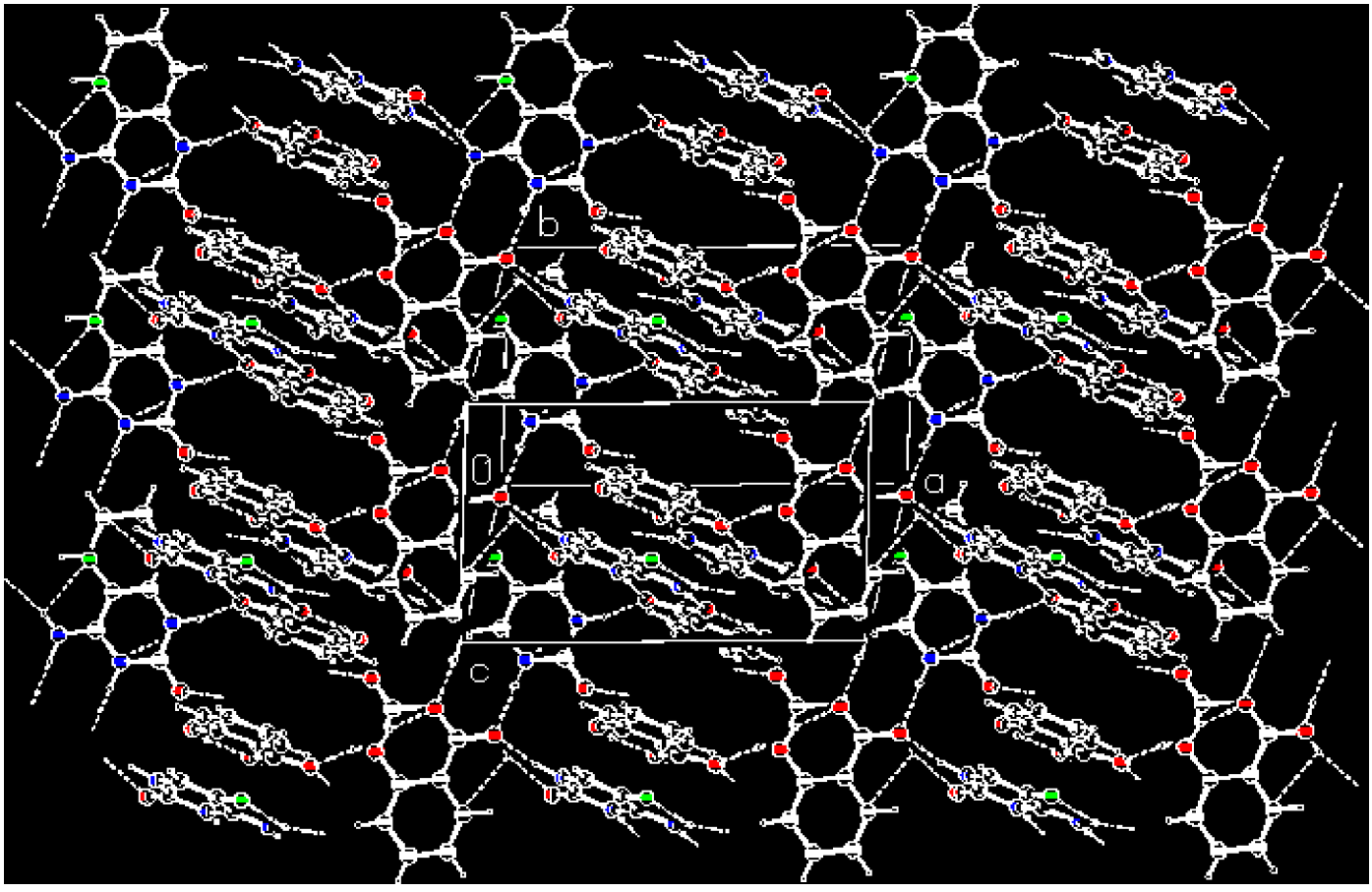

Figure 4
Crystal-packing diagram along the (001) plane illustrating the interweaving of linear and helical hydrogen-bonded chains leading to an intricate three-dimensional structure (*PLATON*; Spek, 1997).

Bertolasi, V., Gilli, P., Ferretti, V. & Gilli, G. (1998). *Acta Cryst.* B**54**, 50–65.
Bertolasi, V., Gilli, P., Ferretti, V., Gilli, G. & Fernandez-Castano, C. (1999). *Acta Cryst.* B**55**, 985–993.
Broido, M. S. & Kearns, D. R. (1982). *J. Am. Chem. Soc.* **104**, 5207–5216.
Cambridge Structural Database (2000). *RPluto*, http://www.ccdc.cam.ac.uk/prods/rpluto. Crystallographic Data Centre, 12 Union Road, Cambridge, England.
Etter, M. C. (1990). *Acc. Chem. Res.* **23**, 120–126.
Fair, C. K. (1990). *MolEN.* Enraf–Nonius, Delft, The Netherlands.
Jeffrey, G. A. & Saenger, W. (1991). *An Introduction to Hydrogen Bonding*, pp. 245–250. Berlin: Springer Verlag.
Kobayashi, R. (1998). *J. Phys. Chem. A*, **102**, 10813–10817.
Louis, T., Low, J. N. & Tollin, P. (1982). *Cryst. Struct. Commun.* **11**, 1059–1064.
Murugesan, S. & Muthiah, P. T. (1996). Academy Discussion Meeting on Frontiers in Structural Chemistry, IIT, Chennai, India. Abstract No. 3.4.
Ohki, M., Takenaka, A., Shimanouchi, H. & Sasada, Y. (1974). *Chem. Lett.* **6**, 551–554.
Ohki, M., Takenaka, A., Shimanouchi, H. & Sasada, Y. (1975). *Bull. Chem. Soc. Jpn*, **48**, 848–852.
Ohki, M., Takenaka, A., Shimanouchi, H. & Sasada, Y. (1976). *Bull. Chem. Soc. Jpn*, **49**, 3493–3497.
Patel, U., Haridas, M. & Singh, T. P. (1988). *Acta Cryst.* C**44**, 1264–1267.
Prabakaran, P., Robert, J. J., Muthiah, P. T., Bocelli, G. & Righi, L. (2001). *Acta Cryst.* C**57**, 459–461.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. Univeristy of Göttingen, Germany.
Singh, T. P. & Vijayan, M. (1974). *Acta Cryst.* B**30**, 557–562.
Sivanesan, D., Babu, K., Gadre, S. R., Subramanian, V. & Ramasami, T. (2000). *J. Phys. Chem. A*, **104**, 10887–10894.
Spek, A. L. (1997). *PLATON.* Utrecht University, The Netherlands.
Takenaka, A., Ohki, M. & Sasada, Y. (1980). *Bull. Chem. Soc. Jpn*, **53**, 2724–2730.
Umadevi, B. & Muthiah, P. T. (1994). 4th Eurasia Conference on Chemical Sciences, Kuala Lumpur, Malaysia. Abstracts, p. 74.