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Hydrogen-bonding patterns in trimethoprim trifluoroacetate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.059
wR factor = 0.188
Data-to-parameter ratio = 15.9

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

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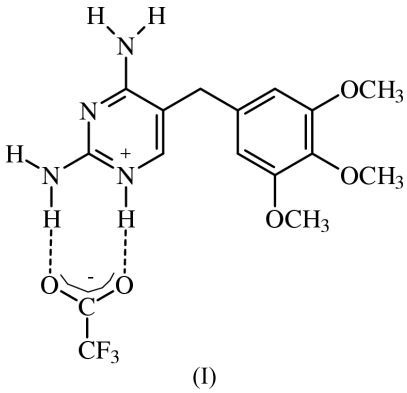
In the title compound, trimethoprim trifluoroacetate [or 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidin-1-ium trifluoroacetate], $C_{14}H_{19}N_4O_3^+\cdot C_2F_3O_2^-$, the trimethoprim molecule is protonated at N-1. The carboxylate group of the trifluoroacetate anion binds with the protonated pyrimidine ring of trimethoprim (TMP) by two nearly parallel N—H···O hydrogen bonds. This is reminiscent of the carboxylate–trimethoprim interaction observed in dihydrofolate reductase (DHFR)–trimethoprim complexes. The pyrimidine moieties of the trimethoprim cations are centrosymmetrically paired through a pair of N—H···N hydrogen bonds involving the 4-amino group and atom N3. The 2-amino group of one TMP motif and the 4-amino group of another motif (both of these motifs are members of a base pair) are bridged by one of the methoxy O atom of a third TMP motif, leading to a five-membered (excluding H atoms) hydrogen-bonded chelate. One of the H atoms of the 2-amino group is also involved in a bifurcated hydrogen bond involving two methoxy O atoms of a trimethoprim motif, leading to a five-membered (including the H atom) hydrogen-bonded chelate. The pyrimidine ring makes a dihedral angle of 83.69 (10)° with the phenyl ring in the trimethoprim cation. In the trifluoroacetate moiety, the average F—C bond distance is 1.261 Å and F—C—C and F—C—F bond angles are 114.7 and 103.7° respectively.

Comment

Trimethoprim (TMP) in its N1-protonated form inhibits the bacterial dihydrofolate reductase (DHFR). X-ray crystal structures of various DHFR complexes with TMP have been reported (Kuyper, 1989, 1990). The crystal structures of trimethoprim (Koetzle & Williams, 1976), trimethoprim acetate (Bryan *et al.*, 1987) and trimethoprim monobenzoate (Giuseppetti *et al.*, 1984) have been reported. The crystal structures of trimethoprim nitrate (Murugesan & Muthiah, 1997), trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001), trimethoprim hydrogen glutarate (Robert *et al.*, 2001), diaquadibromobis(trimethoprim)cadmium(II) monohydrate (Muthiah & Robert, 1999), trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001) and trimethoprim salicylate methanol solvate (Panneerselvam *et al.*, 2002) have been reported from our laboratory. Trifluoroacetic acid (TFA) is a very strong carboxylic acid, easily volatile, and used for protein purifications. Several trifluoroacetate salts and their crystal structures have been reported (Rodrigues *et al.*, 2001). The present study of the title compound, (I), has been undertaken to identify the hydrogen-bonding patterns in relation to other trimethoprim complexes.



(I)

In this crystal, TMP is protonated at N1 like other TMP complexes (Panneerselvam *et al.*, 2002). Hence, the internal angle at N1(C2—N1—C6) has increased to 116.7 (2)° compared with 115.46° in neutral TMP (Koetzle & Williams, 1976). The pyrimidine ring makes a dihedral angle 83.69 (10)° with the phenyl ring, the corresponding angle in trimethoprim perchlorate (Muthiah *et al.*, 2002) being 83.7 (3)°. In the trifluoroacetate moiety, the average F—C bond distance and F—C—C and F—C—F bond angles are 1.261 Å, 114.7° and 103.7°, respectively. These values agree with those in the crystal structures of dimethlyglycinium trifluoroacetate (Rodrigues *et al.*, 2001) and sarcosinium trifluoroacetate (Rodrigues *et al.*, 2000). An *ORTEP*-3 (Farrugia, 1997) view of (I) is shown in Fig. 1.

There are various modes of hydrogen-bonding patterns present in this structure. Fork-like interactions exist, involving carbonyl O atoms from trifluoroacetate (acting as H-atom acceptors), with the N1 and N2 amino H atoms (acting as H-atom donors) in the trimethoprim molecule. This type of carboxylate–TMP interaction has been observed in DHFR–TMP complexes and the crystal structures of trimethoprim acetate (Bryan *et al.*, 1987), trimethoprim salicylate methanol solvate (Panneerselvam *et al.*, 2002), trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001). There is a self base pair between the pyrimidine moieties through N4—H···N3 hydrogen bonds involving the N4 amino group and the N3 atom. These motifs (fork-like interaction and base pairing) are among the 20-most frequently observed bimolecular cyclic hydrogen-bonded motifs in organic crystal structures (Allen *et al.*, 1998). A similar type of base-pair has also been observed in trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001), trimethoprim acetate (Bryan *et al.*, 1987), trimethoprim perchlorate (Muthiah *et al.*, 2002), trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001) and trimethoprim salicylate methanol solvate (Panneerselvam *et al.*, 2002). The 2-amino group of one TMP motif and the 4-amino group of another motif (both of these motifs are members of a base-pair) are bridged by a methoxy oxygen (O1) of a third TMP motif, leading to a five membered (excluding H atoms) hydrogen-bonded chelate. As a result of combining base pairing and the hydrogen bonds involving methoxy oxygen (O1) atom, complementary *DADA* (*D* = donor and *A* = acceptor in hydrogen bonds) arrays of quadruple hydrogen-bonding patterns occur. This pattern is also reported in trimethoprim salicylate methanol solvate (Panneerselvam *et al.*, 2002). One of the H atoms of the 2-amino group is also involved in a bifurcated hydrogen bond, involving two methoxy O atoms of a trimethoprim motif, leading to a five-membered (including the H atom) hydrogen-bonded chelate. This type of bifurcated hydrogen bond has also been observed in the crystal structure of trimethoprim acetate (Bryan *et al.*, 1987). The overall structure of this crystal is stabilized by weak hydrogen bonds C8—H8*C*···F3 [3.457 (5) Å] and C9—H9*A*···O4 [3.282 (4) Å]. The hydrogen-bonding patterns are shown in Fig. 2. The bond lengths and angles are given in Table 1. The geometry of the hydrogen bonds is given in Table 2.

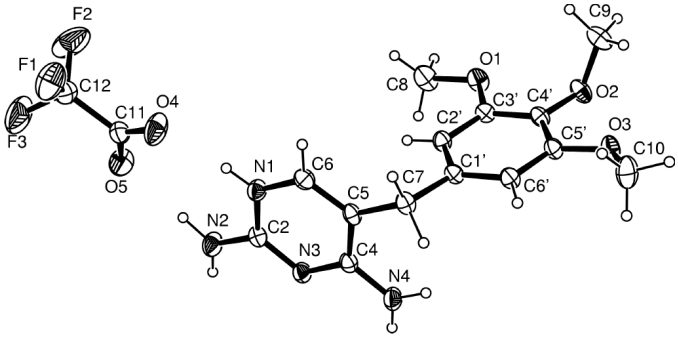


Figure 1
ORTEP diagram of the title compound, (I), showing 50% probability displacement ellipsoids

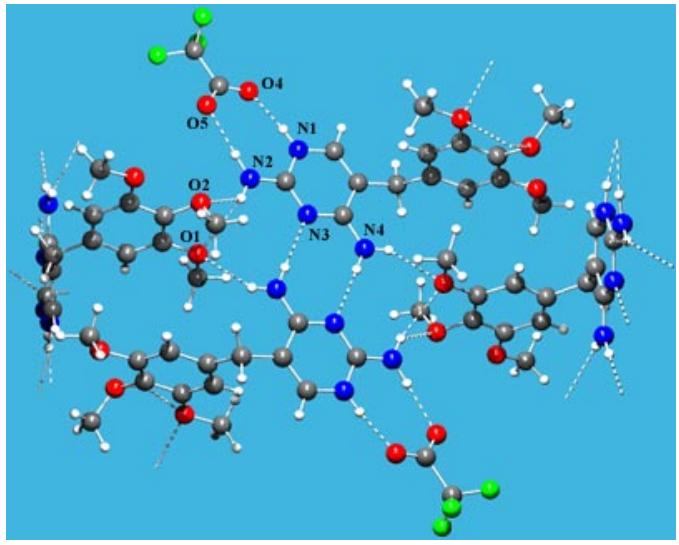


Figure 2
Hydrogen-bonding patterns of trimethoprim trifluoroacetate

Experimental

Trimethoprim (obtained as a gift from Shilpa Antibiotics Ltd) and trifluoroacetic acid (MERCK) were mixed in 1:1 molar ratio in water. The mixture was warmed for half an hour over a water bath. On slow cooling at room temperature, colourless needle-shaped crystals were formed.

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot C_2F_3O_2^-$
$M_r = 404.35$
Monoclinic, $P2_1/a$
$a = 10.380\ (2)$ Å
$b = 19.091\ (3)$ Å
$c = 9.947\ (2)$ Å
$\beta = 112.17\ (2)^\circ$
$V = 1825.4\ (6)$ Å^3
$Z = 4$
$D_x = 1.471$ Mg m^{-3}
Mo Kα radiation
Cell parameters from 25 reflections
$\theta = 2.1$–30.2°
$\mu = 0.13$ mm^{-1}
$T = 293\ (2)$ K
Needle, colourless
$0.31 \times 0.27 \times 0.16$ mm

Data collection

Bruker AXS SMART diffractometer with CCD
ω–2θ scans
Absorption correction: none
26370 measured reflections
5238 independent reflections
2610 reflections with $I > 2\sigma(I)$
$R_{int} = 0.050$
$\theta_{max} = 31.7^\circ$
$h = -13 \rightarrow 13$
$k = -27 \rightarrow 27$
$l = -14 \rightarrow 14$
1 standard reflection
every 100 reflections
frequency: 60 min
intensity decay: negligible

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.059$
$wR(F^2) = 0.188$
$S = 0.97$
5238 reflections
330 parameters
Only the coordinates of H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.1018P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.89$ e Å^{-3}
$\Delta\rho_{min} = -0.58$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0029 (15)

Table 1
Selected geometric parameters (Å, °).

F1—C12	1.276 (3)	O3—C10	1.378 (4)
F2—C12	1.305 (4)	O3—C5′	1.357 (3)
F3—C12	1.303 (4)	N1—C2	1.361 (3)
O4—C11	1.200 (4)	N1—C6	1.330 (3)
O5—C11	1.213 (3)	N2—C2	1.298 (3)
O1—C3′	1.357 (3)	N3—C2	1.390 (3)
O1—C8	1.407 (4)	N3—C4	1.310 (3)
O2—C4′	1.384 (3)	N4—C4	1.387 (3)
O2—C9	1.442 (4)		
C3′—O1—C8	116.4 (2)	N1—C2—N3	124.68 (19)
C4′—O2—C9	114.3 (2)	N2—C2—N3	120.9 (2)
C5′—O3—C10	116.3 (2)	N1—C2—N2	114.4 (2)
C2—N1—C6	116.7 (2)	O1—C3′—C4′	113.96 (19)
C2—N3—C4	118.64 (19)	O1—C3′—C2′	124.3 (2)
O5—C11—C12	118.4 (3)	N3—C4—N4	117.3 (2)
O4—C11—O5	125.8 (3)	N3—C4—C5	119.3 (2)
O4—C11—C12	115.8 (3)	N4—C4—C5	123.4 (2)
F1—C12—F2	102.8 (3)	O2—C4′—C3′	120.37 (19)
F3—C12—C11	113.6 (3)	O2—C4′—C5′	120.63 (19)
F1—C12—F3	99.7 (3)	O3—C5′—C6′	126.0 (2)
F1—C12—C11	114.9 (3)	O3—C5′—C4′	114.50 (19)
F2—C12—F3	108.7 (3)	N1—C6—C5	122.1 (2)
F2—C12—C11	115.6 (2)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O4^{i}	0.90 (3)	1.93 (3)	2.819 (3)	170 (3)
N2—H2A···O5^{i}	0.97 (4)	2.01 (4)	2.979 (4)	173 (3)
N2—H2B···O1^{ii}	0.87 (3)	2.41 (3)	3.172 (3)	146 (2)
N2—H2B···O2^{ii}	0.87 (3)	2.36 (3)	3.010 (3)	132 (3)
N4—H4A···N3^{iii}	0.88 (4)	2.24 (4)	3.126 (3)	179 (4)
N4—H4B···O1^{iv}	0.86 (3)	2.42 (3)	3.065 (3)	132 (2)
C8—H8C···F3^{v}	0.99 (4)	2.48 (4)	3.457 (5)	169 (3)
C9—H9A···O4^{vi}	0.93 (4)	2.53 (4)	3.282 (4)	138 (4)

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

H atoms were located from a difference Fourier map, and their coordinates and isotropic displacement parameters were refined

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: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *PLATON* (Spek, 1997).

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