Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Hydrogen-bonding patterns in trimethoprim tetrafluoroborate

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.002 Å
Disorder in solvent or counterion
R factor = 0.049
wR factor = 0.132
Data-to-parameter ratio = 14.9

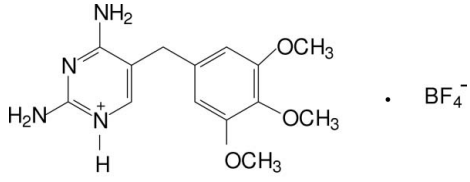
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 3 October 2005
Accepted 8 November 2005
Online 16 November 2005

In the title compound [systematic name: 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidinium tetrafluoroborate], $C_{14}H_{19}N_4O_3^+\cdot BF_4^-$, the trimethoprim (TMP) molecule is protonated at one of the pyrimidine N atoms. The protonated N atom and 2-amine group of the TMP cation interact with the tetrafluoroborate anion through a pair of N—H···F hydrogen bonds [graph set $R_2^2(8)$]. The inversion-related TMP cations are linked through a pair of N—H···N hydrogen bonds. The 2-amine group of one TMP cation and the 4-amine group of another cation are bridged by a methoxy O atom, *via* N—H···O hydrogen bonds.

Comment

Trimethoprim [2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)-pyrimidine or TMP] is a well known antifolate drug. It is a potent inhibitor of bacterial dihydrofolate reductase (DHFR) but is less effective against human DHFR. The drug (TMP) in its N1-protonated form inhibits DHFR. The crystal structure of trimethoprim (Koetzle & Williams, 1976) and its complexes, for example, trimethoprim monobenzoate benzoic acid (Bettinetti *et al.*, 1985) and trimethoprim acetate (Bryan *et al.*, 1987), have been reported in the literature. The present study has been undertaken to explore the hydrogen-bonding patterns involving the TMP cation in a variety of environments. The crystal structures of TMP sulfate trihydrate (Muthiah *et al.*, 2001), TMP nitrate (Murugesan & Muthiah, 1997) and TMP carboxylates (Stanley *et al.*, 2005) have also been reported from our laboratory.



(I)

The asymmetric unit of (I) contains a protonated trimethoprim (TMP) cation and a tetrafluoroborate anion (FLUB) (Fig. 1). The trimethoprim molecule is protonated at atom N1 of the pyrimidine moiety, which is evident from the increase in the internal angle at protonated N1 [C2—N1—C6 = 120.15 (13)°] compared with that at unprotonated atom N3 [C2—N3—C4 = 118.36 (14)°]. The dihedral angle between the pyrimidine and benzene planes is 84.27 (7)°; the corresponding angle in trimethoprim perchlorate is 83.7 (2)° (Muthiah *et al.*, 2002). The conformation of the trimethoprim cation is described by the two torsion angles C4—C5—C7—C8 and C5—C7—C8—C9, which are 77.84 (19) and

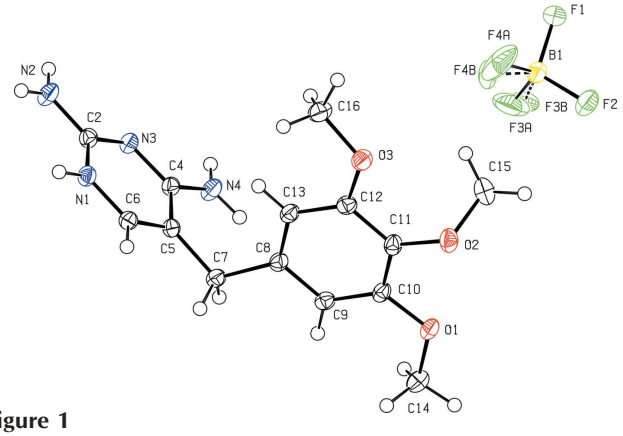


Figure 1
A view of (I), with the atom-labelling scheme and 50% probability displacement ellipsoids.

−158.03 (14)°, respectively. The distorted tetrahedral BF_4 ion has typical B—F distances.

Atoms F2 and F1 act as acceptors in N—H···F interactions (Table 2) with the protonated pyrimidine N1 and 2-amine group of the TMP cation, leading to the formation of a fork-like hydrogen-bonding pattern with graph-set notation $R_2^2(8)$ (Etter, 1990; Bernstein *et al.*, 1995). The $R_2^2(8)$ motif is frequently observed in aminopyrimidine carboxylate salts (Lynch & Jones, 2004). Here the tetrafluoroborate anion mimics the role of the carboxylate group. The TMP cations are paired centrosymmetrically through N4—H4*A*···N3^{iii} and N3···H4*A*^{iii}—N4^{iii} hydrogen bonds (symmetry codes are given in Table 2). The 2-amine group of one TMP cation and the 4-amine group of another cation (both of these cations being members of a base pair) are bridged by methoxy atom O1, using a pair of N—H···O hydrogen bonds, leading to a complementary *DADA* (*D* = donor in hydrogen bonds, *A* = acceptor in hydrogen bonds) array of quadruple hydrogen bonds (Fig. 2). This pattern is similar to that reported in TMP nitrate (Murugesan & Muthiah, 1997), TMP trifluoroacetate (Francis *et al.*, 2002), and TMP salicylate methanol solvate (Panneerselvam *et al.*, 2002). The hydrogen-bonding parameters are listed in Table 2.

Experimental

Hot aqueous solutions of trimethoprim (145 mg; obtained as a gift sample from Shilpa Antibiotics Ltd) and tetrafluoroboric acid (220 mg of 40% solution; Aldrich) were mixed in a 1:2 molar ratio. The resulting solution was warmed over a water bath for a few minutes and then kept at room temperature for crystallization. After a few days, block-shaped colourless crystals of (I) were obtained.

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot BF_4^-$
M_r = 378.14
Triclinic, $P\overline{1}$
a = 9.4105 (3) Å
b = 9.5397 (2) Å
c = 10.1276 (4) Å
α = 88.564 (2)°
β = 73.253 (2)°
γ = 72.304 (2)°
V = 827.48 (5) Å^3
Z = 2
D_x = 1.518 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3811 reflections
θ = 3.0–27.6°
μ = 0.14 mm^{-1}
T = 120 (2) K
Block, colourless
0.18 × 0.16 × 0.09 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
φ and ω scans
Absorption correction: none
18185 measured reflections
3811 independent reflections
3193 reflections with $I > 2\sigma(I)$
R_{int} = 0.041
θ_{max} = 27.6°
$h = -12 \rightarrow 12$
$k = -12 \rightarrow 12$
$l = -13 \rightarrow 13$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.132
S = 1.15
3811 reflections
255 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0644P)^2 + 0.2497P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.61 e Å^{-3}
$\Delta\rho_{min}$ = −0.52 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.133 (9)

Table 1
Selected geometric parameters (Å, °).

O1—C10	1.377 (2)	N1—C2	1.356 (2)
O1—C14	1.443 (2)	N1—C6	1.364 (2)
O2—C11	1.3802 (19)	N2—C2	1.330 (2)
O2—C15	1.435 (2)	N3—C2	1.331 (2)
O3—C16	1.435 (2)	N3—C4	1.347 (2)
O3—C12	1.368 (2)	N4—C4	1.322 (2)
C10—O1—C14	116.47 (12)	N4—C4—C5	120.69 (15)
C11—O2—C15	114.69 (13)	N3—C4—N4	117.24 (15)
C12—O3—C16	116.53 (12)	N1—C6—C5	121.27 (15)
C2—N1—C6	120.15 (13)	O1—C10—C9	123.88 (15)
C2—N3—C4	118.36 (14)	O1—C10—C11	115.49 (14)
N2—C2—N3	119.35 (15)	O2—C11—C12	121.87 (15)
N1—C2—N2	118.59 (14)	O2—C11—C10	118.96 (15)
N1—C2—N3	122.06 (15)	O3—C12—C11	115.08 (14)
N3—C4—C5	122.06 (14)	O3—C12—C13	124.55 (15)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···F2^{i}	0.88	1.97	2.8445 (17)	177
N2—H2*A*···O1^{ii}	0.88	2.10	2.9345 (18)	158
N2—H2*B*···F1^{i}	0.88	2.01	2.8851 (17)	174
N4—H4*A*···N3^{iii}	0.88	2.29	3.121 (2)	158
N4—H4*B*···O1^{iv}	0.88	2.36	2.9210 (18)	122
C6—H6···O2^{v}	0.95	2.50	3.171 (2)	128
C9—H9···F3*A*^{iv}	0.95	2.38	2.995 (9)	122
C14—H14*B*···F4*A*^{vi}	0.98	2.50	3.414 (10)	155
C15—H15*C*···O3	0.98	2.46	3.022 (2)	116

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

All H atoms were placed in idealized locations and were refined using a riding model, with C—H = 0.95–0.99 Å, N—H = 0.88 Å and U_{iso}(H) = 1.2U_{eq}(C,N). Two of the F atoms in the BF_4 group are disordered over two positions, and the occupancy factors for the disordered positions F3*A*/F3*B* and F4*A*/F4*B* were refined to 0.60 (2)/0.40 (2). Similarity restraints were applied to distances involving disordered atoms.

Data collection: *COLLECT* (Hooft, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure:

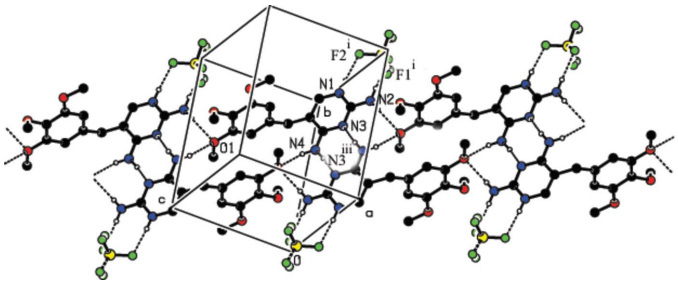


Figure 2
The hydrogen-bonding (dashed lines) patterns of (I). [Symmetry codes: (i) $x, 1 + y, z - 1$; (iii) $1 - x, 1 - y, -z$.]

SHELXL97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

MH thanks the Council of Scientific and Industrial Research (CSIR), India, for the award of a Senior Research Fellowship (SRF) [reference No. 9/475(123)/2004-EMR-I]. DL thanks the EPSRC National Crystallography Service (Southampton, England) for X-ray data collection.

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