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Hydrogen-bonding patterns in trimethoprim perchlorate [trimethoprim = 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine]

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.002 Å
R factor = 0.048
wR factor = 0.168
Data-to-parameter ratio = 21.4

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

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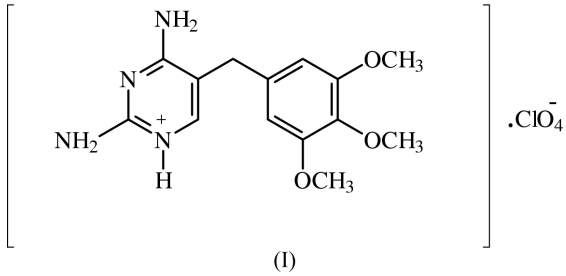
In the title crystal, trimethoprim perchlorate [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidin-1-ium perchlorate], $C_{14}H_{19}N_4O_3^+\cdot ClO_4^-$, the trimethoprim molecule is protonated at N1. The perchlorate ion makes double hydrogen bonds of type N—H···O with the 2-amino group and the protonated N1 atom of the trimethoprim cation, reminiscent of the fork-like interactions of the carboxylate group with the trimethoprim (TMP) cation observed in the dihydrofolate reductase–trimethoprim complex. The pyrimidine moieties of trimethoprim cations are centrosymmetrically paired through a pair of N—H···N hydrogen bonds involving the 4-amino group and the pyrimidinium-N atom. The two pairs of TMP cations are linked by N—H···O hydrogen bonds to form a supramolecular ladder-like structure. The pyrimidine plane makes a dihedral angle of 83.72 (8)° with the phenyl ring in the TMP cation.

Comment

Trimethoprim (TMP) is a well known antifolate drug, which selectively inhibits the bacterial species of the enzyme dihydrofolate reductase (DHFR) (Hitching *et al.*, 1988). This enzyme is found in bacteria and mammals. TMP and other antifolate drugs complexed with DHFR from various sources have been widely studied and are of current interest (Feeney, 2000). The N1-protonated diaminopyrimidine ring of TMP binds deep inside the enzyme cleft through several hydrogen bonds. The crystal structures of TMP and its complexes have been reported in the literature (Koetzle & Williams, 1976; Giuseppetti *et al.*, 1984; Bryan *et al.*, 1987; Bettinetti & Sardone, 1997).



(I)

As part of structural investigations on drugs and their complexes in a variety of molecular environments carried out in our laboratory, we have reported the structures of trimethoprim formate (Umadevi & Muthiah, 1994), trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim nitrate (Murugesan & Muthiah, 1997), trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001), trimethoprim glutarate (Robert *et al.*, 2001) and trimethoprim

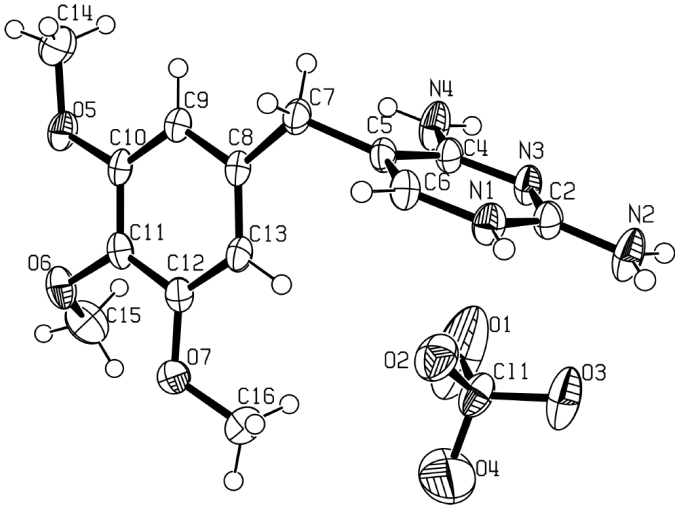


Figure 1
View of the title compound with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

sulfate trihydrate (Muthiah *et al.*, 2001). The present study has been aimed at understanding the conformation and hydrogen-bonding interactions in trimethoprim perchlorate, (I).

In the crystal structure of trimethoprim perchlorate (TMPP), the perchlorate ion is tetrahedral in shape, as expected, with Cl—O distances ranging from 1.372 (2) to 1.431 (2) Å (Yokota *et al.*, 1999). Small deviations from ideal values can be attributed to the relatively high displacement parameters of the atoms in the perchlorate anion. The TMP is protonated at N1, as reported in various crystal structures containing TMP cations (Prabakaran *et al.*, 2001). This is evident from the increase in the ring angle at the site of protonation, namely N1. The internal angle at N1, C2—N1—C6 has increased to 120.10 (14)°, compared with 115.46° in neutral TMP (Koetzle & Williams, 1976). The conformation of the TMP molecule is described by two torsion angles, *viz.* C4—C5—C7—C8 of 78.4 (2) and C5—C7—C8—C9 of −157.51 (1)°. These values are in the range reported for TMP sulfate trihydrate (Muthiah *et al.*, 2001). The pyrimidine ring makes a dihedral angle of 83.72 (8)° with the phenyl ring, which is close to the value of 85.5 (2)° observed for trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001). An *ORTEP*III (Farrugia, 1997) diagram of the molecule with the atom-labelling scheme is shown in Fig. 1.

The TMP cation and the perchlorate anion are linked by hydrogen bonds N1—H···O2 (of perchlorate ion) and N2—H···O3 (of the same perchlorate ion). This is reminiscent of the fork-like interaction of the carboxylate group (of Asp27 of the enzyme) with the TMP cation (Kuyper, 1990). 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 the pyrimidinium N3 atom. This type of pairing has also been reported in trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001) and

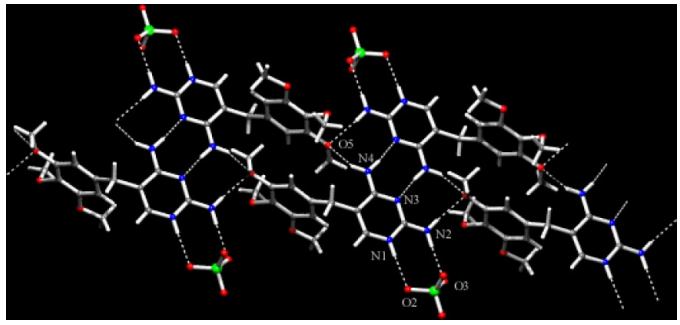


Figure 2
Hydrogen bonding-patterns in trimethoprim perchlorate

trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001). The two pairs of TMP cations are linked by N2—H···O5 and N4—H···O5 hydrogen bonds to form a supramolecular ladder-like structure. These interactions are shown in Fig. 2. In addition, C—H···O hydrogen bonds also stabilize the crystal structure.

Experimental

Trimethoprim perchlorate was prepared by dissolving trimethoprim (obtained as a gift from Shilpa Antibiotics Ltd) in hot methanol, followed by addition of dilute perchloric acid. On cooling, colourless crystals were formed.

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot ClO_4^-$
M_r = 390.78
Triclinic, $P\overline{1}$
a = 9.672 (2) Å
b = 10.219 (1) Å
c = 9.651 (2) Å
α = 91.19 (1)°
β = 107.18 (1)°
γ = 72.44 (2)°
V = 866.4 (3) Å^3
Z = 2
D_x = 1.498 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 3.1–30.2°
μ = 0.27 mm^{-1}
T = 293 (2) K
Block, colourless
0.3 × 0.3 × 0.2 mm

Data collection

Siemens AED diffractometer
ω–2θ scans
5105 measured reflections
5105 independent reflections
3593 reflections with $I > 2\sigma(I)$
θ_{max} = 30.2°
$h = -13 \rightarrow 13$
$k = -14 \rightarrow 14$
$l = 0 \rightarrow 13$
4 standard reflections
frequency: 60 min
intensity decay: negligible

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.168
S = 1.13
5105 reflections
238 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.50 e Å^{-3}
$\Delta\rho_{min}$ = −0.55 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

Cl1—O1	1.372 (2)	O7—C12	1.362 (2)
Cl1—O2	1.4309 (19)	O7—C16	1.424 (3)
Cl1—O3	1.4284 (19)	N1—C2	1.352 (2)
Cl1—O4	1.411 (3)	N1—C6	1.361 (2)
O5—C10	1.374 (2)	N2—C2	1.327 (3)
O5—C14	1.439 (3)	N3—C2	1.330 (2)
O6—C11	1.376 (2)	N3—C4	1.344 (2)
O6—C15	1.421 (3)	N4—C4	1.326 (2)
O1—Cl1—O2	110.64 (15)	N1—C2—N2	118.24 (15)
O1—Cl1—O3	110.85 (14)	N1—C2—N3	122.18 (16)
O1—Cl1—O4	111.12 (19)	N3—C4—C5	122.30 (14)
O2—Cl1—O3	109.32 (11)	N4—C4—C5	120.80 (16)
O2—Cl1—O4	106.33 (16)	N3—C4—N4	116.90 (15)
O3—Cl1—O4	108.45 (15)	N1—C6—C5	121.47 (16)
C10—O5—C14	117.13 (14)	O5—C10—C9	123.48 (16)
C11—O6—C15	115.22 (15)	O5—C10—C11	116.05 (14)
C12—O7—C16	117.66 (15)	O6—C11—C12	121.61 (17)
C2—N1—C6	120.10 (14)	O6—C11—C10	118.89 (16)
C2—N3—C4	118.22 (14)	O7—C12—C11	115.34 (15)
N2—C2—N3	119.58 (16)	O7—C12—C13	124.40 (17)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3^{i}	0.86	2.07	2.929 (2)	177
N2—H2*A*···O5^{ii}	0.86	2.14	2.958 (2)	160
N2—H2*B*···O2^{i}	0.86	2.10	2.958 (2)	175
N4—H4*A*···N3^{iii}	0.86	2.34	3.155 (2)	158
N4—H4*B*···O5^{iv}	0.86	2.39	2.958 (2)	124
C6—H6···O6^{v}	0.93	2.56	3.230 (2)	129
C9—H9···O4^{vi}	0.93	2.56	3.154 (4)	122
C15—H15*C*···O7	0.96	2.50	3.017 (3)	114

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

After checking their presence in a difference map, the H-atoms were geometrically fixed and allowed to ride on their parent atoms.

Data collection: *AED* (Belletti *et al.*, 1993); cell refinement: *AED*; data reduction: *AED*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Farrugia, 1997); software used to prepare material for publication: *PLATON* (Spek, 1997).

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