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Hydrogen bonding patterns in trimethoprim sulfate trihydrate [trimethoprim = 2,4-diamino-5-(3,4,5-methoxybenzyl)pyrimidine]

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.036
wR factor = 0.092
Data-to-parameter ratio = 9.5

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

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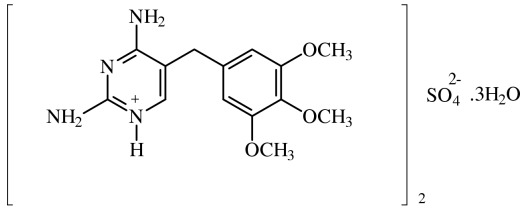
Trimethoprim sulfate trihydrate, $2C_{14}H_{19}N_4O_3^+\cdot SO_4^{2-}\cdot 3H_2O$ [$(TMPH^+)_2(SO_4)^{2-}\cdot 3H_2O$, $TMPH^+$ = 2,4-diamino-5-(3,4,5-methoxybenzyl)pyrimidin-1-ium], is an antibacterial agent. In its N1-protonated form, it inhibits the bacterial dihydrofolate reductase enzyme. The asymmetric unit contains two TMPH cations, a sulfate anion and three water molecules. The TMPH cations are each paired about their respective inversion centres *via* N—H···N hydrogen bonds. These pairs are further bridged by a network of hydrogen bonds involving the sulfate anion and water molecules. Both the TMPH cations make hydrogen bonds with water molecules through the 2-amino groups, reminiscent of TMP-dihydrofolate reductase complexes. The pyrimidine plane makes a dihedral angle of 75.89 (8)° with the phenyl ring in one TMPH cation, the corresponding angle in the other moiety being 69.96 (8)°.

Comment

Dihydrofolate reductase enzyme (DHFR) reduces dihydrofolate to tetrahydrofolate. Tetrahydrofolate is involved in the synthesis of methionine, which is essential for the living organism. Trimethoprim (TMP) has greater affinity for bacterial DHFR than for human DHFR. Antifolate drugs complexed with DHFR from various sources have been widely studied (Feeney, 2000). The crystal structure of TMP and its complexes, *e.g.* TMP (Koetzle & Williams, 1976), TMP monobenzoate (Giuseppetti *et al.*, 1984), TMP monobenzoate–benzoic acid (Bettinetti *et al.*, 1985), TMP acetate (Bryan *et al.*, 1987), TMP sulfadimidine 1:1 (Bettinetti & Sardone, 1997) and 1:2 (Sardone *et al.*, 1997) complexes have been reported in the literature.

Hydrogen-bonding patterns involving sulfonate and sulfate groups in biological systems and metal complexes are of current interest (Onoda *et al.*, 2001). In a sulfate-binding protein, the sulfate anion is bound mainly by seven hydrogen bonds. Five of them are from the main-chain peptide NH groups (Pflugrath & Quiocho, 1985; Pflugrath & Quiocho, 1988; Jacobson & Quiocho, 1988). The present study is aimed at understanding the conformation of TMP and the hydrogen-bonding networks involving the sulfate anion, water molecules and TMP cations. As part of structural investigations on drugs and their complexes carried out in our laboratory, we have already reported the structures of trimethoprim formate (Umadevi & Muthiah, 1994), trimethoprim perchlorate (Umadevi & Muthiah, 2001), trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim nitrate (Murugesan & Muthiah, 1997), the cadmium complex of TMP (Muthiah & Robert, 1999) and trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001).

In the crystal structure of trimethoprim sulfate trihydrate (TMPS), (I), the asymmetric unit contains two TMPH cations, a sulfate anion and three water molecules. An *ORTEP*II (Johnson, 1976) diagram of the asymmetric unit with the atom-labelling scheme is shown in Fig. 1.



(I)

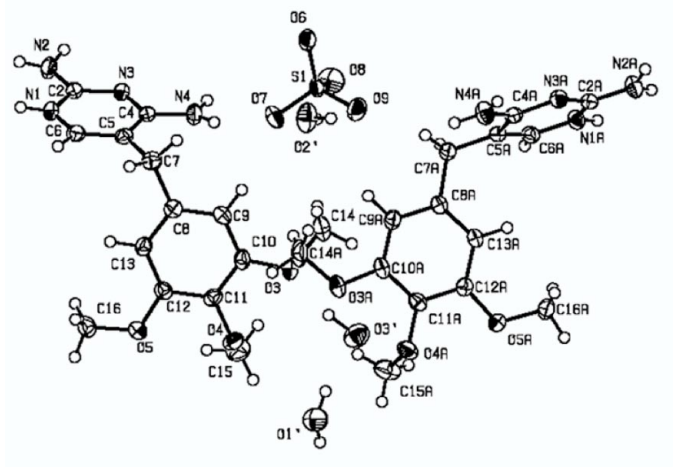


Figure 1
ORTEP diagram of the asymmetric unit of (I) showing 50% probability displacement ellipsoids.

The sulfate ion is tetrahedral in shape, as expected; the S—O distances range from 1.449 (4) to 1.481 (2) Å. Both the TMPH cations are protonated at N1. The internal angles at N1, C2—N1—C6 and C2*A*—N1*A*—C6*A* have increased to 119.9 (8) and 120.3 (1)°, respectively, from 115.46° in neutral TMP. The bond lengths and angles involving the two crystallographically independent TMPH cations agree with one another and with other TMPH cations reported in the literature (Prabakaran *et al.*, 2001). The conformation adopted by the trimethoprim moiety in this structure is described by the two torsion angles C4—C5—C7—C8 and C5—C7—C8—C9. In this structure, these torsion angles are −73.3 (2) and 120.6 (5)°, respectively, for molecule *A* and −94.5 (2) and 158.3 (7)° for molecule *B*. These values are in the range reported for TMP monobenzoate (Giuseppetti *et al.*, 1984) and TMP acetate (Bryan *et al.*, 1987). The pyrimidine ring makes a dihedral angle of 75.89 (8)° with the phenyl ring in molecule *A*, the corresponding angle in molecule *B* being 69.96 (8). These values are in the range reported for TMP monobenzoate (Giuseppetti *et al.*, 1984) and TMP formate (Umadevi & Muthiah, 1994).

Two kinds of TMP-pairing have been observed in this crystal structure. One TMPH cation is paired about the inversion centre through a pair of N2—H···N3 hydrogen bonds whereas the other TMPH cations (atom labels with suffix A) are paired about an inversion centre through a pair of N4*A*—H···N3*A* hydrogen bonds. The former mode of pairing has been already observed in TMP hydroxybenzoate dihydrate (Robert & Muthiah, 2001) and the latter mode has been noted in trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001). These pairs are further bridged by a network of hydrogen bonds involving water molecules and the sulfate ion. All of the sulfate-O atoms are involved in hydrogen bonding. Both the TMPH cations make hydrogen bonds with water molecules through the 2-amino groups, reminiscent of TMP–DHFR complexes. A view of the crystal packing is shown in Fig. 2.

Experimental

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

Crystal data

$2C_{14}H_{19}N_4O_3^+\cdot SO_4^-\cdot 3H_2O$	D_x = 1.438 Mg m^{-3}
M_r = 732.78	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 35 reflections
a = 7.229 (1) Å	θ = 3–70.8°
b = 23.242 (1) Å	μ = 0.17 mm^{-1}
c = 20.373 (1) Å	T = 293 (2) K
β = 98.59 (1)°	Needle, colourless
V = 3384.6 (5) Å^3	0.3 × 0.2 × 0.2 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 25.0°
ω–2θ scans	$h = 0 \rightarrow 8$
Absorption correction: none	$k = 0 \rightarrow 27$
6445 measured reflections	$l = -24 \rightarrow 23$
5951 independent reflections	4 standard reflections
5134 reflections with $I > 2\sigma(I)$	frequency: 60 min
R_{int} = 0.014	intensity decay: negligible

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0402P)^2 + 1.9477P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.036	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.092	$\Delta\rho_{max}$ = 0.40 e Å^{-3}
S = 1.06	$\Delta\rho_{min}$ = −0.34 e Å^{-3}
5951 reflections	
627 parameters	
All H-atom parameters refined	

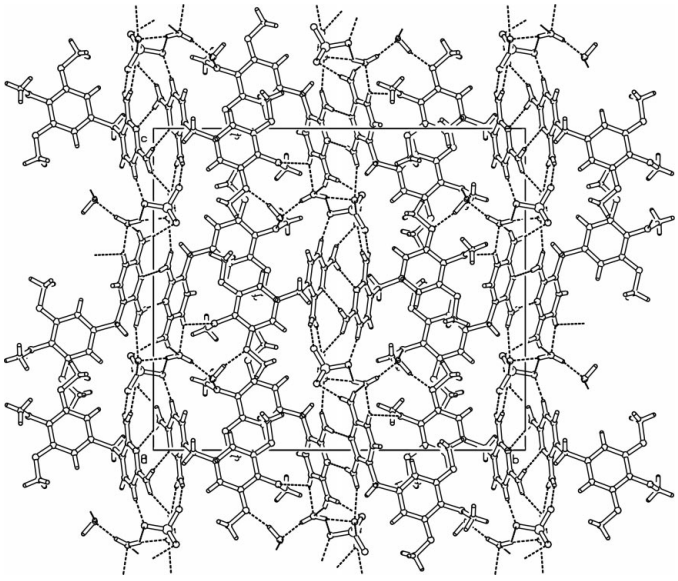


Figure 2
Hydrogen-bonding patterns of trimethoprim sulfate trihydrate

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O6^{i}	0.86 (2)	1.80 (2)	2.654 (2)	172 (2)
O1′—H1′···O3′	0.88 (2)	1.87 (2)	2.737 (2)	170.3 (18)
O1′—H2′···O6^{ii}	0.91 (3)	2.42 (3)	3.121 (2)	133 (3)
O1′—H2′···O8^{ii}	0.91 (3)	1.90 (3)	2.781 (2)	160 (3)
O2′—H3′···O9	0.72 (3)	2.33 (3)	3.045 (2)	169 (3)
O2′—H4′···O8^{iii}	0.89 (3)	2.03 (3)	2.900 (3)	167 (3)
O3′—H5′···O3	1.02 (4)	1.83 (4)	2.828 (2)	166 (3)
O3′—H6′···O4A^{iv}	1.05 (5)	1.76 (5)	2.778 (2)	162 (4)
N2A—H8···O1′^{v}	0.83 (2)	2.06 (2)	2.818 (3)	152 (2)
N4—H21···O2′^{iv}	0.87 (3)	2.15 (3)	2.974 (3)	157 (2)
N4A—H22···N3A^{vi}	0.91 (2)	2.25 (2)	3.155 (2)	173.1 (18)
N2A—H23···O9^{vii}	0.92 (3)	1.96 (3)	2.826 (2)	156 (2)
N4A—H27···O8^{iii}	0.90 (2)	2.24 (2)	3.105 (2)	161 (2)
N4—H30···O7	0.88 (2)	2.00 (2)	2.826 (2)	155 (2)
N1A—H37···O1′^{v}	0.85 (2)	2.00 (2)	2.778 (2)	152 (2)
N1A—H37···O4^{v}	0.85 (2)	2.58 (2)	3.090 (2)	120.1 (19)
N2—H40···N3^{viii}	0.86 (2)	2.23 (2)	3.080 (2)	176 (2)
N2—H41···O2′^{i}	0.85 (2)	2.33 (2)	3.038 (3)	140 (2)
C7A—H3···O8^{iii}	0.96 (2)	2.38 (2)	3.295 (3)	158.5 (17)
C6A—H7···O4^{v}	0.95 (2)	2.51 (2)	3.131 (2)	123.2 (14)
C6A—H7···O5^{v}	0.95 (2)	2.46 (2)	3.363 (2)	158.3 (17)
C9—H15···O7	0.93 (2)	2.31 (2)	3.131 (2)	146.7 (18)
C15—H33···O3A^{iv}	0.97 (2)	2.59 (2)	3.537 (3)	167 (2)

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

Table 1
Selected geometric parameters (Å, °).

S1—O9	1.4684 (15)	O5A—C16A	1.420 (2)
S1—O6	1.4812 (15)	O5A—C12A	1.365 (2)
S1—O7	1.4494 (15)	N1—C6	1.357 (3)
S1—O8	1.4716 (16)	N1—C2	1.346 (2)
O3—C14	1.439 (3)	N2—C2	1.334 (3)
O3—C10	1.372 (2)	N3—C2	1.333 (2)
O4—C11	1.381 (2)	N3—C4	1.346 (2)
O4—C15	1.439 (3)	N4—C4	1.327 (2)
O5—C12	1.372 (2)	N1A—C2A	1.358 (2)
O5—C16	1.428 (2)	N1A—C6A	1.357 (2)
O3A—C14A	1.423 (3)	N2A—C2A	1.322 (2)
O3A—C10A	1.364 (2)	N3A—C4A	1.350 (2)
O4A—C15A	1.428 (3)	N3A—C2A	1.334 (2)
O4A—C11A	1.384 (2)	N4A—C4A	1.326 (2)
O6—S1—O7	109.54 (8)	N4—C4—C5	121.42 (16)
O6—S1—O8	108.17 (9)	N1—C6—C5	122.09 (18)
O6—S1—O9	108.47 (8)	O3—C10—C11	116.06 (16)
O7—S1—O8	111.07 (9)	O3—C10—C9	123.42 (16)
O7—S1—O9	110.55 (8)	O4—C11—C12	120.96 (15)
O8—S1—O9	108.97 (9)	O4—C11—C10	119.77 (15)
C10—O3—C14	117.31 (16)	O5—C12—C13	124.72 (16)
C11—O4—C15	113.10 (14)	O5—C12—C11	115.02 (15)
C12—O5—C16	117.19 (15)	N2A—C2A—N3A	120.83 (16)
C10A—O3A—C14A	117.13 (16)	N1A—C2A—N3A	121.77 (15)
C11A—O4A—C15A	113.94 (15)	N1A—C2A—N2A	117.40 (16)
C12A—O5A—C16A	116.72 (15)	N4A—C4A—C5A	121.58 (15)
C2—N1—C6	119.88 (16)	N3A—C4A—C5A	121.89 (14)
C2—N3—C4	118.48 (16)	N3A—C4A—N4A	116.52 (14)
C2A—N1A—C6A	120.30 (15)	N1A—C6A—C5A	121.56 (18)
C2A—N3A—C4A	118.43 (14)	O3A—C10A—C11A	115.06 (16)
N2—C2—N3	118.93 (18)	O3A—C10A—C9A	124.56 (16)
N1—C2—N3	122.17 (18)	O4A—C11A—C12A	119.70 (16)
N1—C2—N2	118.90 (16)	O4A—C11A—C10A	120.62 (16)
N3—C4—C5	122.04 (15)	O5A—C12A—C11A	115.29 (16)
N3—C4—N4	116.55 (16)	O5A—C12A—C13A	124.71 (15)

H atoms were located from difference Fourier maps 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* (Johnson, 1976); software used to prepare material for publication: *PLATON* (Spek, 1997).

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