Acta Crystallographica Section E
Structure Reports
Online

ISSN 1600-5368

Pyrimethaminium sulfosalicylate monohydrate

Madhukar Hemamalini,[a] Packianathan Thomas Muthiah,[a]* Balasubramanian Sridhar[b] and Ramaswamy Karunanandam Rajaram[c]

[a]School of Chemistry, Bharathidasan University, Tiruchirappalli 620 024, Tamil Nadu, India, [b]Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India, and [c]School of Physics, Madurai Kamaraj University, Madurai 675 021, Tamil Nadu, India

Correspondence e-mail:
tommtrichy@yahoo.co.in

Received 8 April 2005
Accepted 19 April 2005
Online 27 April 2005

Key indicators

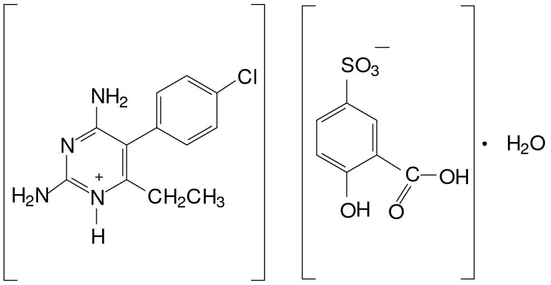
Single-crystal X-ray study
T = 273 K
Mean *σ*(C–C) = 0.004 Å
R factor = 0.036
wR factor = 0.106
Data-to-parameter ratio = 12.9

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

In the crystal structure of the title compound, 2,4-diamino-5-(4-chlorophenyl)-6-ethylpyrimidin-1-ium 3-carboxy-4-hydroxybenzenesulfonate monohydrate, $C_{12}H_{14}ClN_4^+\cdot C_7H_5O_6S^-\cdot H_2O$, the asymmetric unit contains two crystallographically independent protonated pyrimethamine (PMN) molecules, a pair of sulfosalicylate anions and two water molecules. Both the PMN molecules are protonated at one of the pyrimidine N atoms. The component species interact through numerous intermolecular N—H···O, N—H···N and O—H···O hydrogen bonds and C—H···O interactions.

Comment

Pyrimethamine [2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine], PMN, is a well known antifolate drug used in the treatment of malaria. In the chemotherapy of malaria and neoplastic diseases, substituted 2,4-diaminopyrimidines are widely employed as metabolic inhibitors of pathways leading to the synthesis of proteins and nucleic acid (Hitchings & Burchall, 1965). The present study has been undertaken as part of our research programme to explore hydrogen-bonding patterns involved in aminopyrimidine–carboxylate interactions.



(I)

The crystal structures of pyrimethamine (Sethuraman & Muthiah, 2002) and some of its complexes, for example, pyrimethamine hydrogen maleate, hydrogen succinate, hydrogen phthalate and fumarate (Sethuraman *et al.*, 2003), and pyrimethamine hydrogen glutarate and formate (Stanley *et al.*, 2002), have been reported from our laboratory. The crystal structures of 3-carboxy-4-hydroxybenzene sulfonic acid (sulfosalicylic acid) with Mn, Co, Ni, Zn and Cu have been reported in the literature (Ma *et al.*, 2003*a*,*b*,*c*,*d*,*e*). In the present paper, the conformation and hydrogen-bonding patterns of pyrimethamine sulfosalicylate monohydrate (PMNSSA), (I), are discussed.

In the structure of (I), the asymmetric unit contains two pyrimethamine (PMNH) cations, two sulfosalicylate anions

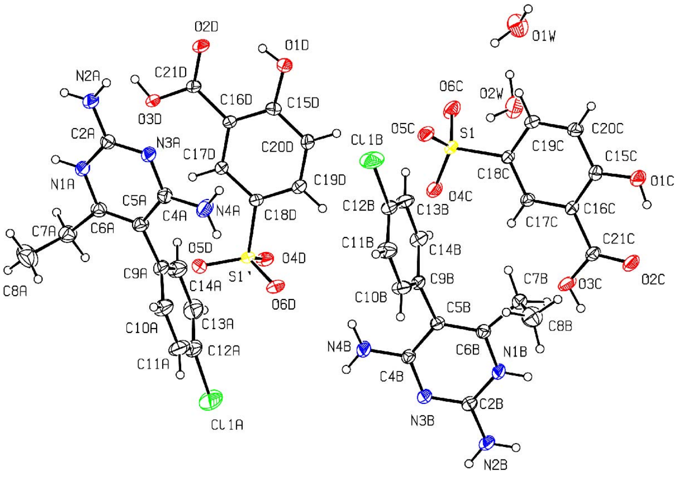


Figure 1
The asymmetric unit of (I), showing 50% probability displacement ellipsoids (arbitrary spheres for the H atoms).

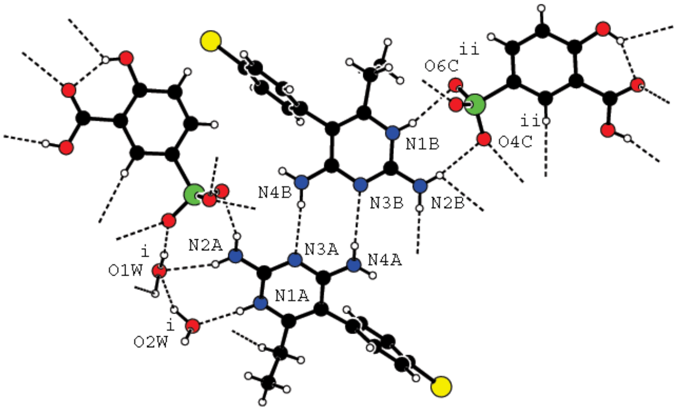


Figure 2
A view of fork-like hydrogen-bonding interactions (dashed lines) in (I). [Symmetry codes: (i) 1 + x, y, z, (ii) $x - \frac{1}{2}, \frac{1}{2} - y, z - \frac{1}{2}$.]

and two water molecules (Fig. 1). Both the PMN molecules are protonated at pyrimidine N atoms (N1*A* and N1*B*), as evident from the increase in the ring angle at N1*A* [C2*A*—N1*A*—C6*A* = 121.9 (2)°] and N1*B* [C2*B*—N1*B*—C6*B* = 122.2 (2)°] compared with 116.3 (2)° (molecule *A*) and 116.1 (2)° (molecule *B*) in neutral PMN (Sethuraman & Muthiah, 2002). The bond lengths and angles involving the two crystallographically independent PMNH cations agree with one another and with other PMNH cations reported in the literature (Stanley *et al.*, 2002).

The key conformational features of the PMN cations are described by two angles. The first is the dihedral angle between the 2,4-diaminopyrimidine and the *p*-chlorophenyl mean planes. The second is the torsion angle that represents the deviation of the ethyl group from the pyrimidine plane. The dihedral angles between the pyrimidine and benzene rings are 74.48 (14)° (cation *A*) and 80.26 (4)° (cation *B*). These values are close to the value observed in computer modelling studies on dihydrofolate reductase DHFR–PMN complexes (Sansom *et al.*, 1989). The C5*A*—C6*A*—C7*A*—C8*A* and C5*B*—C6*B*—C7*B*—C8*B* torsion angles are 104.8 (3) and 94.9 (3)°, respectively. The C—C bond lengths connecting the pyrimidine and benzene rings are 1.497 (3) Å (C5*A*—C9*A*) and 1.499 (3) Å (C5*B*—C9*B*), respectively, which agree closely with those observed in the crystal structure of metoprine (1.495 Å in molecule *A* and 1.478 Å in molecule *B*) (De *et al.*, 1989).

The geometries of the hydrogen-bonding interactions in (I) are given in Table 1. Two types of fork-like interactions are observed involving the PMNH cations, *viz.* one between cation *A* (N1*A* and N2*A*/H) and two water molecules (O1*W* and O2*W*) through a pair of N—H···O hydrogen bonds, and another between the sulfonate group (O4*C* and O6*C*) (anion *C*) and a PMN cation *via* a pair of N—H···O hydrogen bonds. This configuration can be designated by graph-set notation $R_2^2(8)$ (Etter, 1990; Bernstein *et al.*, 1995) (Fig. 2).

The sulfonic acid group is involved in forming fork-like interactions rather than the carboxyl group. A similar type of interaction has also been observed in trimethoprim sulfonate salts (Baskar Raj *et al.*, 2003). Cation *A* is linked to cation *B* through a pair of N4—H···N3 hydrogen bonds, involving the 4-amino group and the pyrimidine N3 atom. Each sulfosalicylate (anions *C* and *D*) self-assembles into chains along the *c* axis *via* O—H···O interactions involving the –OH group of the carboxyl group (O3*C* and O3*D*) and one of the sulfonate O atoms (O5*C* and O4*D*). Both these chains, which run in an alternate fashion, are linked *via* C—H···O and O—H···O hydrogen bonds, leading to the formation of a sheet-like structure, as shown in Fig. 3. There is intramolecular hydrogen bonding between the –OH and –COOH groups in sulfosalicylate anions. Additionally, π–π interactions between the aromatic rings are observed. The pyrimidine rings of the PMNH cations *A* form stacking interactions with the benzene rings of the sulfosalicylate anions (anions *C*), with a perpendicular separation of 3.573 Å, a centroid-to centroid distance of 3.9516 (15) Å and a slip angle (the angle between the centroid vector and the normal to the plane) of 21.1°. A similar type of stacking is also observed in the PMNH cation *B* to sulfosalicylate anion *D* interaction, with a perpendicular seperation of 3.174 Å, a centroid-to-centroid distance of 3.7735 (15) Å and a slip angle of 16.2°. These are typical aromatic stacking values (Hunter, 1994).

Experimental

A hot ethanol solution of pyrimethamine (62 mg, obtained as a gift sample from Shah Pharma Chem., India) and sulfosalicylic acid (110 mg, Merck) were mixed in a 1:1 molar ratio and warmed for half an hour over a water bath. On slow evaporation, block-shaped crystals of (I) were obtained.

Crystal data

$C_{12}H_{14}ClN_4^{+}\cdot C_7H_5O_6S^{-}\cdot H_2O$
M_r = 484.92
Monoclinic, $P2_1/n$
a = 15.2350 (15) Å
b = 19.3290 (12) Å
c = 15.8750 (14) Å
β = 113.960 (6)°
V = 4272.0 (7) Å^3
Z = 8
D_x = 1.508 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 25 reflections
θ = 11.3–13.8°
μ = 0.33 mm^{-1}
T = 273 K
Block, colourless
0.30 × 0.25 × 0.12 mm

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Data collection

Enraf–Nonius MACH-3 single-crystal diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{\rm min} = 0.939$, $T_{\rm max} = 0.959$
8317 measured reflections
7493 independent reflections
4891 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.013$
$\theta_{\rm max} = 25.0^\circ$
$h = -18 \rightarrow 16$
$k = -1 \rightarrow 22$
$l = -1 \rightarrow 18$
3 standard reflections
frequency: 60 min
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.106$
$S = 1.01$
7493 reflections
583 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0512P)^2 + 1.7056P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} = 0.041$
$\Delta\rho_{\rm max} = 0.20$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.30$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1A—H1A···O2$W^{\rm i}$	0.86	1.95	2.803 (3)	176
N1B—H1B···O6$C^{\rm ii}$	0.86	2.21	3.048 (3)	164
O1C—H1C···O2C	0.82	1.91	2.628 (3)	146
O1C—H1C···O5$D^{\rm iii}$	0.82	2.42	2.973 (3)	125
O1D—H1D···O2D	0.82	1.86	2.575 (3)	145
O1D—H1D···O4$C^{\rm iv}$	0.82	2.38	2.953 (2)	127
N2A—H2A···O6$D^{\rm iv}$	0.86	2.12	2.946 (3)	160
N2A—H2B···O1$W^{\rm i}$	0.86	2.20	2.989 (3)	152
O3C—H3C···O5$C^{\rm ii}$	0.82	1.77	2.576 (3)	166
O3D—H3D···O4$D^{\rm iv}$	0.82	1.93	2.747 (2)	176
N4A—H4A···N3$B^{\rm iv}$	0.86	2.40	3.216 (3)	158
O1W—H11W···O5$D^{\rm v}$	0.90	1.91	2.794 (3)	167
O1W—H12W···O6C	0.90	2.31	3.124 (3)	151
N2B—H21A···O4$D^{\rm ii}$	0.86	2.22	3.029 (3)	156
O2W—H21W···O6C	0.98	1.91	2.811 (3)	152
N2B—H22B···O2$D^{\rm vi}$	0.86	2.47	2.901 (3)	112
N2B—H22B···O4$C^{\rm ii}$	0.86	2.26	3.096 (3)	164
O2W—H22W···O1W	0.98	2.50	2.991 (3)	110
N4B—H41A···N3$A^{\rm ii}$	0.86	2.29	3.080 (3)	152
C7A—H7B···O6$D^{\rm vii}$	0.97	2.56	3.507 (3)	164
C13B—H13B···O5C	0.93	2.40	3.176 (3)	141
C17C—H17C···O4C	0.93	2.51	2.897 (3)	105
C17C—H17C···O1$D^{\rm ii}$	0.93	2.50	3.429 (3)	177
C17D—H17D···O1$C^{\rm i}$	0.93	2.40	3.325 (3)	175
C19C—H19C···O2$C^{\rm iv}$	0.93	2.57	3.477 (3)	166

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

The H atoms of the aromatic groups were positioned geometrically and those of the water molecule were positioned from difference Fourier maps. All H atoms were treated as riding. The C—H, O—H and N—H bond lengths are 0.93–0.97 Å, 0.82–0.98 Å and 0.86 Å, respectively. The constraint $U_{\rm iso}({\rm H}) = 1.2U_{\rm eq}$(carrier) was applied in all cases.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

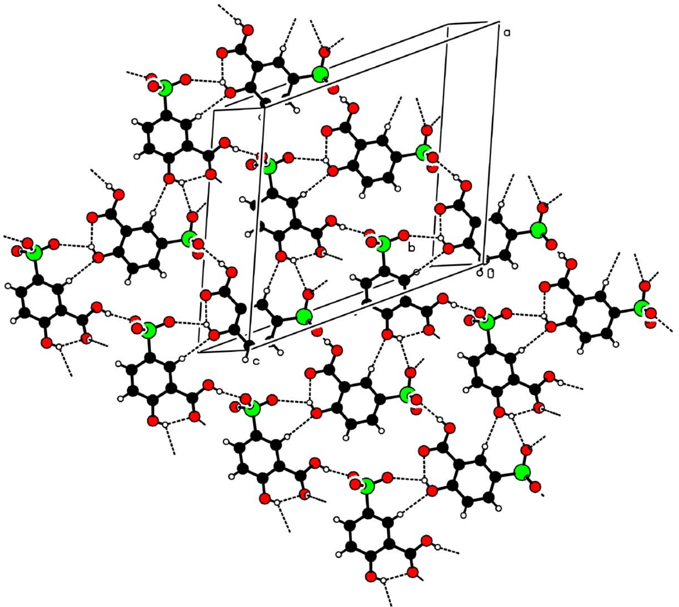

Figure 3
Hydrogen-bonding (dashed lines) patterns of compound (I).

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]. RKR thanks the Department of Science and Technology, Government of India, for establishing a Single-Crystal Diffractometer Facility at the School of Physics, Madurai Kamaraj University, Madurai, through the FIST programme.

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