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Hydrogen-bonding patterns in pyrimethaminium dinitrate

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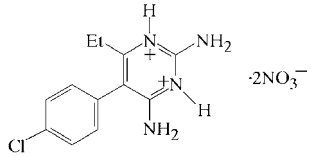
The title compound, 2,4-diamino-5-(4-chlorophenyl)-6-ethylpyrimidine-1,3-diium dinitrate, $C_{12}H_{15}ClN_4^{2+}\cdot 2NO_3^-$, contains two crystallographically independent pyrimethamine (PMN) molecules, which differ in the relative orientations of the pyrimidine and benzene rings and of the ethyl substitutents. In both pyrimethamine molecules, all the pyrimidine N atoms are protonated, unlike most related compounds, in which only one pyrimidine N atom is protonated. The two pyrimethamine moieties are bridged by a variety of N—H···O(nitrate) interactions, including some three-centre hydrogen bonds.

Comment

Pyrimethamine is an 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 acids (Hitchings & Burchall, 1965). Pyrimethamine acts against malarial parasites by selectively inhibiting their dihydrofolate reductase–thymidylate synthase (Sardarian *et al.*, 2003). Hydrogen bonding plays a key role in molecular recognition (Goswami & Ghosh, 1997) and crystal engineering (Goswami *et al.*, 1999). The design of a number of supramolecular nanoarchitectures, such as layers, ribbons, rosettes, rods, tapes, tubes, sheets and spheres, can be achieved through N—H···O and O—H···O hydrogen bonds (Vishweshwar *et al.*, 2002; Aitipamula *et al.*, 2002). The crystal structure of pyrimethamine (PMN) itself has been reported from our laboratory (Sethuraman & Muthiah, 2002). The crystal structures of trimethoprim nitrate (Murugesan & Muthiah, 1997), PMN hydrogen maleate, PMN hydrogen succinate, PMN hydrogen phthalate and PMN fumarate (Sethuraman *et al.*, 2003), and PMN hydrogen glutarate and PMN formate (Stanley *et al.*, 2002), have also been reported from our laboratory. In this paper, the conformation and hydrogen-bonding patterns of pyrimethamine dinitrate (PMNN), (I), are reported.

The asymmetric unit of (I) contains two pyrimethamine cations and four nitrate anions (Fig. 1). Both the PMN moieties are protonated at N1, N3, N1*A* and N3*A* of the pyrimidine moiety, which is evident from the increase in the internal angles C2—N1—C6, C2—N3—C4, C2*A*—N1*A*—C6*A* and C2*A*—N3*A*—C4*A* at the corresponding N atoms. The angles (Table 1) are larger than the values observed in neutral pyrimethamine [116.25 (18), 116.38 (17), 116.09 (18) and 116.47°, respectively; Sethuraman & Muthiah, 2002]. Usually, only one pyrimidine N atom (N1 or N1*A*) is protonated in the pyrimethamine molecule, but in (I) all the pyrimidine N atoms are protonated in both the pyrimethamine molecules.



(I)

The dihedral angle between the pyrimidine plane and the substituted phenyl plane is 82.5 (2)° in one molecule and 73.9 (2)° in the other. Similar dihedral angles are seen in the crystal structures of neutral pyrimethamine [74.4 (1)° in molecule *A* and 82.4 (1)° in molecule *B*; Sethuraman & Muthiah, 2002], 2,4-diamino-5-(3,4-dichlorophenyl)-6-methylpyrimidinium ethanesulfonate (71.1°; Cody, 1983) and metoprine (78.1° in molecule *A* and 91.6° in molecule *B*; De *et al.*, 1989). The two torsion angles (C5—C6—C7—C8 and C5*A*—C6*A*—C7*A*—C8*A*) of the PMN moieties are −107.7 (5) and −100.9 (5)°, respectively. These values are close to those observed in modelling studies of dihydrofolate reductase–

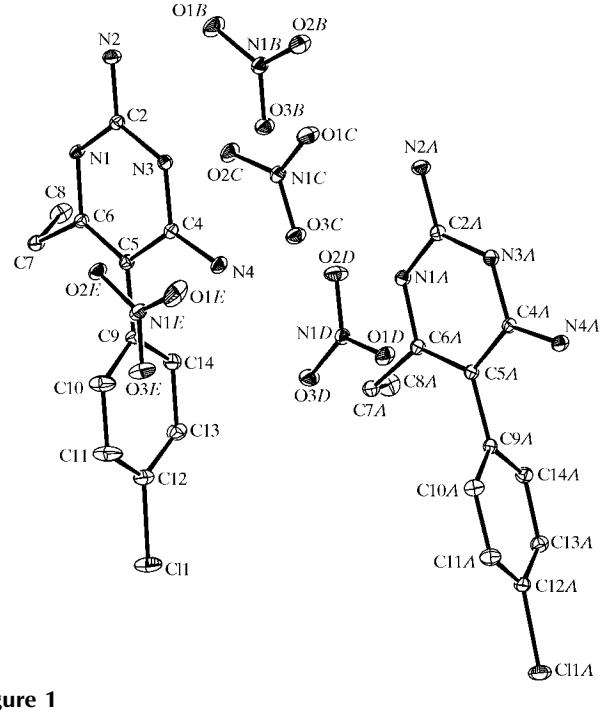


Figure 1
A view of the asymmetric unit of (I), showing 50% probability displacement ellipsoids and the atom-numbering scheme. H atoms have been omitted for clarity.

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pyrimethamine complexes, which indicates that these angles play an important role in the proper docking of the drug molecule in the active site of the enzyme (Sansom *et al.*, 1989). The lengths of the bonds connecting the pyrimidine and benzene rings (Table 1) are in close agreement with those reported for metoprine (De *et al.*, 1989). The different mutual arrangements of the *p*-chlorophenyl and ethyl substituents in the two independent molecules of (I) are illustrated in Fig. 2.

The protonated atom N1*A* and the 2-amino group are hydrogen bonded to the O atoms of the nitrate anion (O1*C* and O3*C*), leading to an eight-membered ring formed *via* N—H···O bonds (Fig. 3). The other protonation sites, atom N3*A* and the 4-amino group, are hydrogen bonded to the O atoms of the other nitrate anion (atoms O1*D* and O2*D*), forming a similar cyclic hydrogen-bonded ring. Both can be designated by graph-set notation $R_2^2(8)$ (Etter, 1990; Bernstein *et al.*, 1995). This type of interaction is similar to the carboxylate–trimethoprim interaction observed in the trimethoprim cation–dihydrofolate reductase complex (Kuyper, 1990) and to the cyclic hydrogen-bonded motif observed in many organic crystal structures (Allan *et al.*, 1998).

In the other pyrimethamine molecule, the protonated N atom (N1) of the pyrimidine ring forms a three-centre hydrogen bond with two O atoms of the nitrate ion (atoms O1*E* and O3*E*). The other protonated N atom (N3) forms a three-centre hydrogen bond, of similar type but weaker, with another nitrate ion (atoms O1*B* and O3*B*) (Table 2). The protonated N atom (N3), 2-amino group and 4-amino group

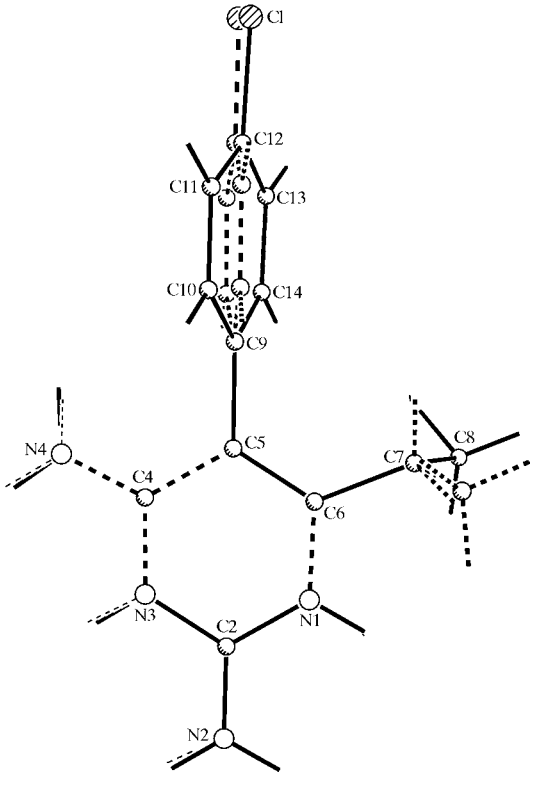

Figure 2
An orthogonal fit of the two PMN molecules in (I). The fitted atoms are those forming the pyrimidine moiety.

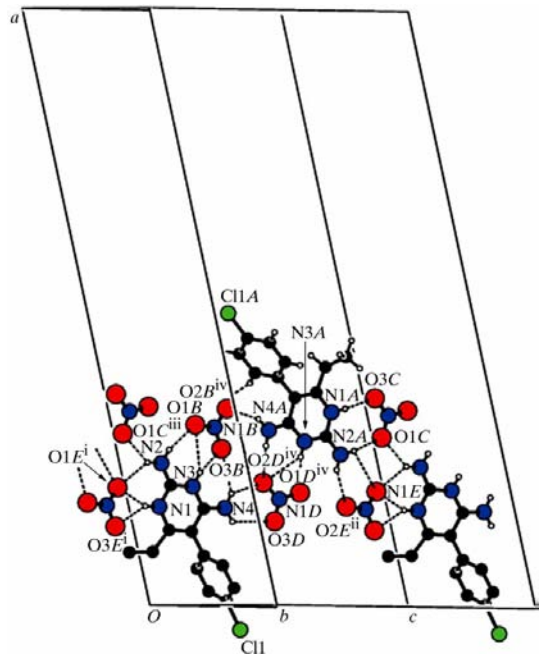

Figure 3
A view of the hydrogen-bonding patterns in compound (I) (for symmetry codes, see Table 2) along the *b* axis. For clarity, other cell content atoms and H atoms not involved in the bonding have been omitted.

are hydrogen bonded with two O atoms of the same nitrate ion (atoms O1*B* and O3*B*), forming both three-centre and bifurcated hydrogen bonds. The protonated N atom (donor; N1) and the 2-amino group form hydrogen bonds with the O atom of the nitrate ion (acceptor; O1*E*), leading to a six-membered ring which can be designated by graph-set notation $R_2^1(6)$ (Fig. 3). This type of packing is commonly observed in PMN hydrogen maleate, PMN hydrogen succinate and PMN hydrogenphthalate (Sethuraman *et al.*, 2003).

Experimental

To a hot methanol solution of pyrimethamine (62 mg, Shah Pharma Chemicals, India), a few drops of nitric acid were added. The solution was warmed over a water bath for a few minutes. The resultant solution was allowed to cool slowly at room temperature. Crystals of (I) appeared from the mother liquor after a few days.

Crystal data

$C_{12}H_{15}ClN_4^{2+}\cdot 2NO_3^-$
M_r = 374.75
Monoclinic, $C2/c$
a = 32.700 (7) Å
b = 12.926 (3) Å
c = 16.065 (3) Å
β = 104.73 (3)°
V = 6567 (3) Å^3
Z = 16
D_x = 1.516 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7379 reflections
θ = 3.4–25.7°
μ = 0.28 mm^{-1}
T = 295 (2) K
Prismatic, colourless
0.4 × 0.3 × 0.2 mm

Data collection

Kuma KM-4 CCD κ-geometry diffractometer
ω scans
Absorption correction: multi-scan (*XEMP*; Siemens, 1990)
T_{min} = 0.893, T_{max} = 0.952
27180 measured reflections
6490 independent reflections
3225 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 26.1°
$h = -21 \rightarrow 39$
$k = -15 \rightarrow 15$
$l = -19 \rightarrow 19$

Table 1
Selected geometric parameters (Å, °).

C5—C9	1.492 (6)	C5*A*—C9*A*	1.484 (5)
C2—N1—C6	122.9 (3)	O2*D*—N1*D*—O3*D*	120.6 (3)
C2—N3—C4	122.7 (3)	O1*E*—N1*E*—O3*E*	119.3 (4)
C2*A*—N1*A*—C6*A*	122.9 (3)	O1*E*—N1*E*—O2*E*	121.6 (4)
C2*A*—N3*A*—C4*A*	123.0 (3)	O2*E*—N1*E*—O3*E*	119.1 (4)
O1*D*—N1*D*—O2*D*	117.8 (4)	N1*A*—C6*A*—C5*A*	119.5 (4)
O1*D*—N1*D*—O3*D*	121.6 (4)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O1*E*^{i}	0.86	2.09	2.880 (5)	153
N1—H1···O3*E*^{i}	0.86	2.41	3.177 (6)	148
N1*A*—H1*A*···O3*C*	0.86	1.92	2.778 (4)	175
N2—H2···O1*B*	0.86	2.07	2.901 (5)	163
N2*A*—H2*A*···O2*E*^{ii}	0.86	2.03	2.794 (5)	148
N2*A*—H2*B*···O1*C*	0.86	1.93	2.784 (4)	171
N2—H3···O1*E*^{i}	0.86	2.33	3.056 (5)	142
N2—H3···O1*C*^{iii}	0.86	2.15	2.848 (5)	138
N3*A*—H3*A*···O1*D*^{iv}	0.86	1.92	2.765 (5)	167
N3—H4···O1*B*	0.86	2.58	3.290 (5)	141
N3—H4···O3*B*	0.86	1.88	2.722 (4)	164
N4*A*—H4*A*···O2*B*^{iv}	0.86	2.07	2.855 (5)	152
N4*A*—H4*B*···O2*D*^{iv}	0.86	1.98	2.813 (5)	164
N4—H5···O2*D*	0.86	2.17	2.832 (4)	134
N4—H5···O3*B*	0.86	2.46	3.154 (5)	139
N4—H6···O3*D*	0.86	2.51	3.050 (5)	121

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

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.059$
$wR(F^2) = 0.231$
$S = 1.03$
6490 reflections
451 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0399P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.46$ e Å^{-3}
$\Delta\rho_{min} = -0.64$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.00014 (3)

All H atoms were fixed geometrically and were refined using a riding model, with C—H = 0.92–0.96 Å, N—H = 0.85–0.86 Å and $U_{iso}(H) = 1.2U_{eq}(C,N)$.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2000); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2000); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976) and *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA1099). Services for accessing these data are described at the back of the journal.

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