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Hydrogen-bonded supramolecular ribbons in the antifolate drug pyrimethamine

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.054
wR factor = 0.142
Data-to-parameter ratio = 11.8

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

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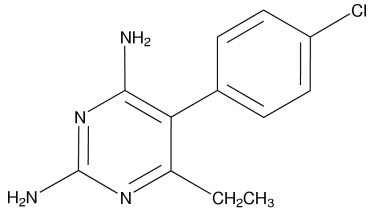
In the crystal structure of pyrimethamine [2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine], $C_{12}H_{13}ClN_4$, the asymmetric unit contains two crystallographically independent pyrimethamine molecules (*A* and *B*), differing in their conformations. The dihedral angle between the pyrimidine and the substituted phenyl plane is 74.4 (1)° in molecule *A* and 82.4 (1)° in molecule *B*. Molecule *A* is linked with molecule *B* through a pair of N—H···N hydrogen bonds on one side and through another pair of N—H···N hydrogen bonds on the other side. Thus, there is a supramolecular ribbon, consisting of *A* and *B* molecules arranged in an alternating manner. Two such ribbons are connected centrosymmetrically through a pair of N—H···Cl bonds. These *ABAB* pairs and *BABA* interconnections lead to a supramolecular sheet-like structure.

Comment

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). The target of these drugs is the enzyme dihydrofolate reductase, to which they bind more tenaciously than does the substrate (folic acid). Pyrimethamine [2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine], (I), is a popular antifolate drug used in the treatment of malaria. The present study has been carried out to gain an understanding of the conformation and the hydrogen-bonding patterns present in the crystal structure of pyrimethamine.



(I)

In the crystal structure of (I), the asymmetric unit contains two crystallographically independent pyrimethamine molecules, *A* and *B*. An *ORTEP*II (Johnson, 1976) view of the molecules, with the atom-labeling scheme, is shown in Fig. 1. There is no significant difference in the bond lengths and angles between the two molecules and there is good agreement between these values and the corresponding values in the crystal structure of 2,4-diamino-5-(3,4-dichlorophenyl)-6-methylpyrimidine (metoprine) (De *et al.*, 1989), which also crystallizes with the same $P\overline{1}$ space group, and with the

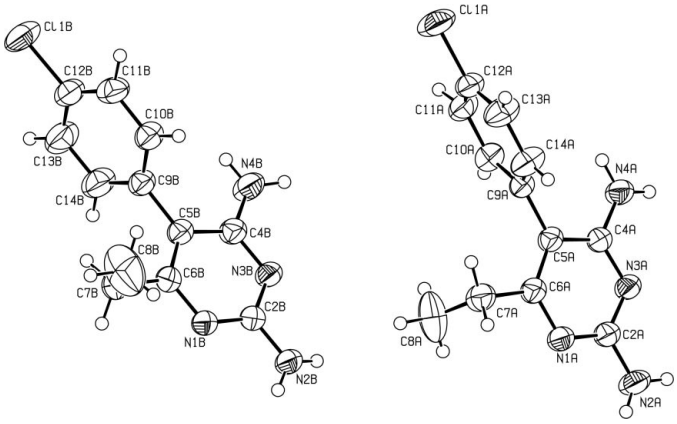


Figure 1
View of the title compound, showing the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

asymmetric unit containing two independent molecules. Selected bond lengths and angles are given in Table 1.

In the crystal structure, the conformations of the pyrimethamine molecules are described by the following two angles. The first is the dihedral angle between the 2,4-diaminopyrimidine and *p*-chlorophenyl rings, which represents the twist of the phenyl ring from the pyrimidine plane. The second is the torsion angle C5—C6—C7—C8, which represents the deviation of the ethyl group from the benzene plane. The dihedral angle between the pyrimidine plane and phenyl ring is found to be 74.4 (1)° in molecule *A* and 82.4 (1)° in molecule *B*. Thus, the phenyl ring avoids coplanarity with the pyrimidine ring and attains a position approximately perpendicular to it. The same observation has been made in the modeling studies on dihydrofolate reductase–pyrimethamine complexes (Sansom *et al.*, 1989). A similar observation has also been made in the crystal structure of metoprine, where the dihedral angle values are 78.1 (molecule *A*) and 91.6° (molecule *B*) (De *et al.*, 1989). The torsion angle C5*A*—C6*A*—C7*A*—C8*A* in molecule *A* is 97.8 (3)° and the angle C5*B*—C6*B*—C7*B*—C8*B* in molecule *B* is −97.2 (3)°. Modeling studies of dihydrofolate reductase–pyrimethamine complexes indicate that this dihedral angle plays an important role in the proper docking of the drug molecule in the active site of the enzyme and that the change in the torsion angle representing the orientation of the ethyl group does not affect the overall binding energy of the enzyme–drug complex (Sansom *et al.*, 1989). The bond connecting the pyrimidine and phenyl rings, namely C5—C9 [(C5*A*—C9*A* = 1.491 (3) Å in molecule *A* and C5*B*—C9*B* = 1.492 (3) Å in molecule *B*], shows partial double-bond nature, characteristic of these ring systems. These values are in close agreement 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).

Two kinds of base pairing are observed in the crystal structure of pyrimethamine. Molecule *A* is paired with molecule *B* on one side through a pair of N2—H···N1 hydrogen bonds (Table 2), involving the 2-amino group and the pyrimidine N1 atom and, on the other side, it is paired with another molecule of *B* through a pair of N4—H···N3 hydrogen bonds (Table 2), involving the 4-amino group and the pyrimidine N3 atom. These hydrogen-bonded *ABAB* pairs lead to a supramolecular ribbon structure. This pattern is shown in Fig. 2. The same type of ribbon motif has also been observed in the crystal structure of metoprine (De *et al.*, 1989) and trimethoprim (Koetzle & Williams, 1976). However, in trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine] (TMP), the basic building motif is only one kind of TMP molecule, whereas in pyrimethamine and metoprine, it is a pair of conformationally different moieties. The supramolecular ribbons are interconnected by a pair of N4—H···Cl hydrogen bonds (Table 2), the *A* molecule of one ribbon being connected to the *B* molecule of the other. Thus, the two kinds of base pairing, *via* N—H···N hydrogen bonds and their interconnection through N—H···Cl hydrogen bonds, lead to a supramolecular sheet-like structure. A similar N—H···Cl bond interconnection between two ribbon motifs has also been observed in the crystal structure of metoprine (De *et al.*, 1989). This pattern is shown in Fig. 3. The hydrogen-bonding geometry is given in Table 2.

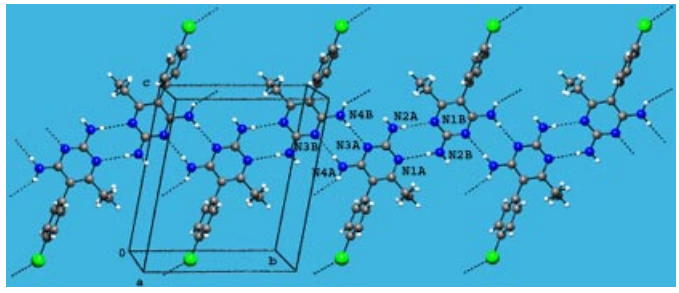


Figure 2
Hydrogen-bonded supramolecular ribbon-like motif in (I).

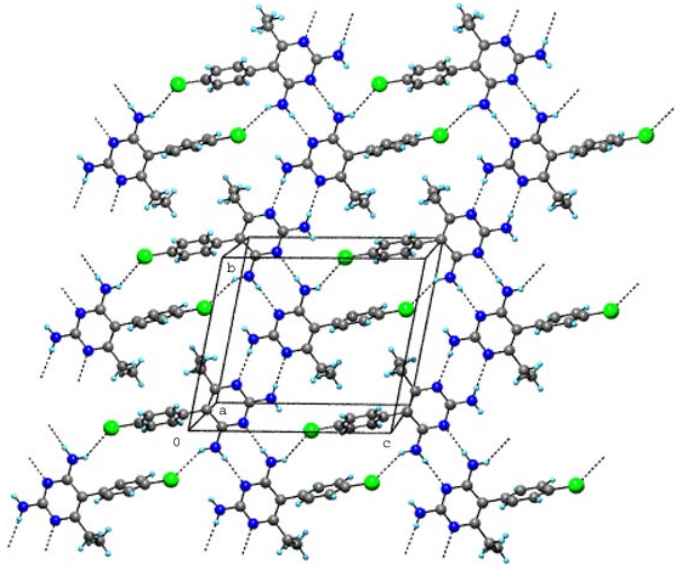


Figure 3
Supramolecular sheet-like motif in (I). Sheet formation is through N—H···N and N—H···Cl hydrogen bonds.

Thus, the supramolecular structure of pyrimethamine contains three kinds of hydrogen-bonding ring motifs, two similar smaller rings containing eight atoms each and one larger ring containing several atoms. Apart from a pair of H atoms involved in hydrogen-bond formation, the first ring consists of a pair of N1/C2/N2 atoms, the second ring consists of a pair of N3/C4/N4 atoms and the third ring consists of a pair of N4/C4/C5/Cl atoms and phenyl group. It is interesting to note that there is a difference in the hydrogen-bonding modes between the 2-amino and the 4-amino groups of the pyrimethamine molecule. In the 2-amino group, only one of the H atoms is involved in hydrogen-bond formation along the ribbon (N2—H···N1 hydrogen bond). However, in the 4-amino group, both the H atoms are involved in hydrogen-bond formation, one linearly along the ribbon (N4—H···N3 hydrogen bond) and the other laterally with the neighboring ribbon (N4—H···Cl hydrogen bond).

Experimental

Pyrimethamine (obtained as a gift sample from Lupin Laboratories Ltd, India) was dissolved in hot methanol. The solution was allowed to cool slowly and kept at room temperature. After a few days, colorless block-shaped crystals were obtained.

Crystal data

$C_{12}H_{13}ClN_4$
M_r = 248.71
Triclinic, $P\overline{1}$
a = 9.5854 (15) Å
b = 10.8061 (17) Å
c = 12.484 (2) Å
α = 79.059 (13)°
β = 89.440 (15)°
γ = 82.372 (14)°
V = 1258.2 (4) Å^3
Z = 4
D_x = 1.313 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10–15°
μ = 0.29 mm^{-1}
T = 293 (2) K
Transparent block, colorless
0.32 × 0.19 × 0.19 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.936, T_{max} = 0.974
4724 measured reflections
4437 independent reflections
4035 reflections with $I > 2\sigma(I)$
R_{int} = 0.030
θ_{max} = 25.3°
$h = 0 \rightarrow 11$
$k = -12 \rightarrow 12$
$l = -14 \rightarrow 14$
3 standard reflections
frequency: 60 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.142
S = 1.16
4437 reflections
376 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0673P)^2 + 0.5352P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.37 e Å^{-3}
$\Delta\rho_{min}$ = −0.40 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

Cl1*A*—C12*A*	1.742 (2)	N4*A*—C4*A*	1.340 (3)
Cl1*B*—C12*B*	1.748 (2)	N1*B*—C2*B*	1.336 (3)
N1*A*—C6*A*	1.349 (3)	N1*B*—C6*B*	1.353 (3)
N1*A*—C2*A*	1.338 (3)	N2*B*—C2*B*	1.350 (3)
N2*A*—C2*A*	1.355 (3)	N3*B*—C4*B*	1.338 (3)
N3*A*—C2*A*	1.338 (3)	N3*B*—C2*B*	1.335 (3)
N3*A*—C4*A*	1.339 (3)	N4*B*—C4*B*	1.342 (3)
C2*A*—N1*A*—C6*A*	116.25 (18)	Cl1*A*—C12*A*—C13*A*	118.3 (2)
C2*A*—N3*A*—C4*A*	116.38 (17)	Cl1*A*—C12*A*—C11*A*	120.21 (19)
C2*B*—N1*B*—C6*B*	116.09 (18)	N1*B*—C2*B*—N2*B*	116.46 (19)
C2*B*—N3*B*—C4*B*	116.47 (17)	N1*B*—C2*B*—N3*B*	126.64 (18)
N1*A*—C2*A*—N3*A*	126.55 (18)	N2*B*—C2*B*—N3*B*	116.89 (19)
N1*A*—C2*A*—N2*A*	116.6 (2)	N3*B*—C4*B*—N4*B*	117.1 (2)
N2*A*—C2*A*—N3*A*	116.88 (19)	N3*B*—C4*B*—C5*B*	122.03 (19)
N4*A*—C4A—C5*A*	120.95 (18)	N4*B*—C4*B*—C5*B*	120.8 (2)
N3*A*—C4*A*—C5*A*	122.03 (19)	N1*B*—C6*B*—C5*B*	122.57 (19)
N3*A*—C4*A*—N4*A*	117.01 (18)	N1*B*—C6*B*—C7*B*	115.13 (19)
N1*A*—C6*A*—C5*A*	122.71 (18)	Cl1*B*—C12*B*—C11*B*	119.3 (2)
N1*A*—C6*A*—C7*A*	114.76 (18)	Cl1*B*—C12*B*—C13*B*	119.0 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2*A*—H22*A*···N1*B*^{i}	0.83 (3)	2.24 (3)	3.068 (3)	176 (3)
N2*B*—H22*B*···N1*A*^{i}	0.81 (3)	2.22 (3)	3.027 (3)	174 (3)
N4*A*—H41*A*···Cl1*B*^{ii}	0.89 (3)	2.72 (3)	3.472 (2)	143 (2)
N4*B*—H41*B*···Cl1*A*^{ii}	0.85 (4)	2.67 (3)	3.393 (2)	143 (3)
N4*A*—H42*A*···N3*B*^{iii}	0.88 (3)	2.16 (3)	3.027 (3)	172 (3)
N4*B*—H42*B*···N3*A*^{iii}	0.90 (3)	2.16 (3)	3.060 (3)	178 (3)

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

In both molecules *A* and *B*, the ethyl H atoms were fixed geometrically and refined using a riding model. All other H atoms were located from a difference Fourier map and were refined isotropically.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *MolEN* (Fair, 1990); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *PLATON* (Spek, 1997).

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