Acta Crystallographica Section E
Structure Reports
Online

ISSN 1600-5368

Hydrogen-bonding patterns in bis(trimethoprim) dipicolinate pentahydrate

Madhukar Hemamalini,[a] Packianathan Thomas Muthiah,[a]* Gabriele Bocelli[b] and Andrea Cantoni[b]

[a]School of Chemistry, Bharathidasan University, Tiruchirappalli 620 024, Tamil Nadu, India, and [b]IMEM-CNR, Parco Area delle Scienze 37a, I-43010 Fontanini-Parma, Italy

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

In the title compound, $2C_{14}H_{19}N_4O_3^{+}\cdot C_7H_3NO_4^{2-}\cdot 5H_2O$, the asymmetric unit contains two trimethoprim cations (*A* and *B*), a dipicolinate anion and five water molecules. One of the picolinate carboxylate groups interacts with cation *A* *via* a pair of N—H···O hydrogen bonds, forming a ring motif $R_2^2(8)$. A loop of O—H···O hydrogen bonds is formed between four water molecules and the two carboxylate groups to form a supramolecular chain along the *a* axis. Molecules *A* and *B* constitute a base pair *via* N—H···N hydrogen bonds, and these base pairs are cross-linked by N—H···O and C—H···O hydrogen bonds.

Received 21 April 2005
Accepted 27 June 2005
Online 6 July 2005

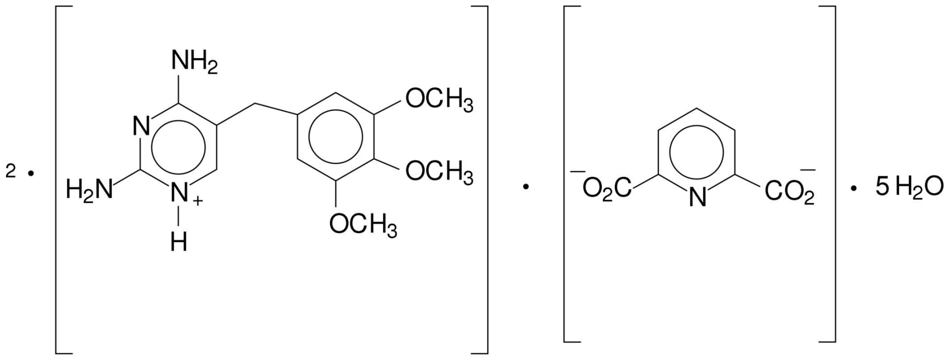
Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.057
wR factor = 0.160
Data-to-parameter ratio = 17.1

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

Comment

Trimethoprim [2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)-pyrimidine, TMP] is a well known antifolate drug. It selectively inhibits the bacterial dihydrofolate reductase (DHFR) enzyme. The present study was undertaken to explore the hydrogen-bonding patterns involving aminopyrimidine–carboxylate interactions. The crystal structure of dipicolinic acid (pyridine-2,6-dicarboxylic acid) has already been reported (Carranza Téllez *et al.*, 2002). Dipicolinic acid is a multi-chelating ligand capable of forming monomeric or polymeric complexes (Guerriero *et al.*, 1987; Kjell *et al.*, 1993; Abboud *et al.*, 1998).



(I)

In the crystal structure of trimethoprim dipicolinate pentahydrate (TMPDIP), (I), the asymmetric unit contains two trimethoprim cations (*A* and *B*), a dipicolinate anion and five water molecules. A diagram of the asymmetric unit with the atom-labelling scheme is shown in Fig. 1.

Both trimethoprim molecules are protonated at N1, as evident from the increase of the internal angle at N1 from 115.5 (5)° in neutral TMP (Koetzle & Williams, 1976) to 119.8 (2)° (cation *A*) and 120.0 (2)° (cation *B*) (Table 1) in (I).

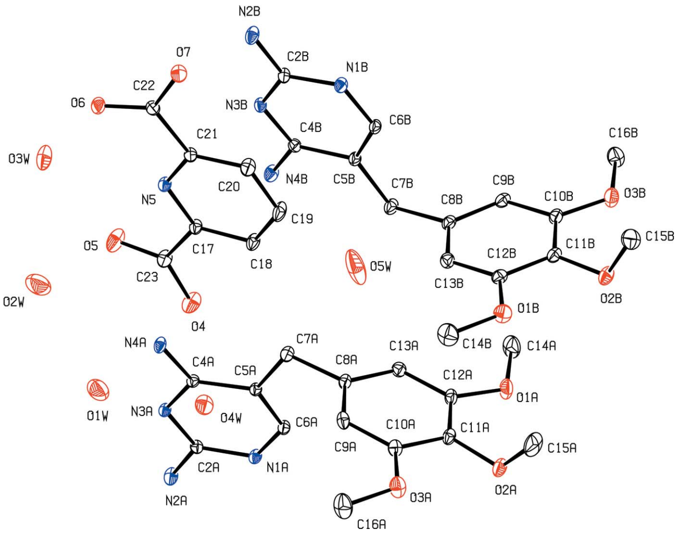


Figure 1
A view of (I), with the atom-labelling scheme and 50% probability displacement ellipsoids. H atoms have been omitted for clarity.

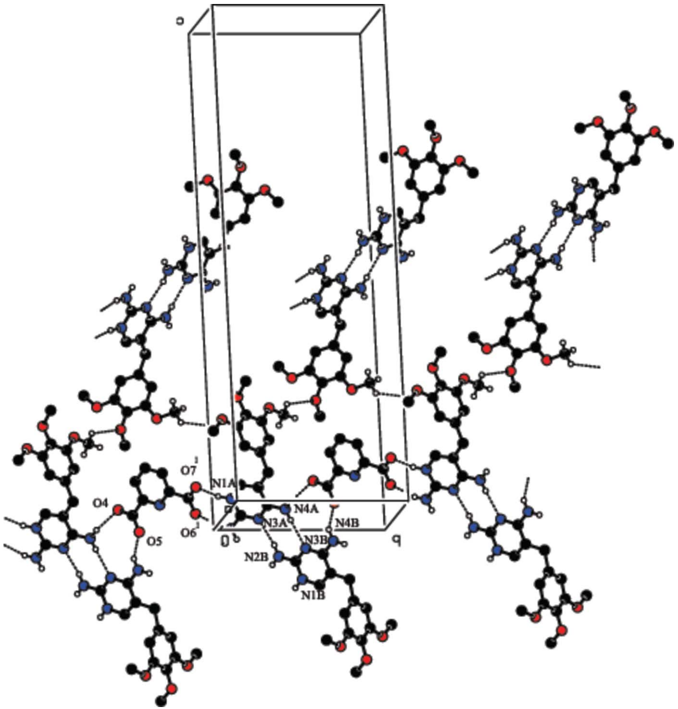


Figure 2
The hydrogen-bonding patterns (dashed lines) of (I). [Symmetry code: (i) $x - 1, y - 1, z$.]

The conformation of the trimethoprim cation is described by the two torsion angles, C4*A*—C5*A*—C7*A*—C8*A* and C5*A*—C7*A*—C8*A*—C9*A* [159.9 (2) and −90.8 (3)°] and C4*B*—C5*B*—C7*B*—C8*B* and C5*B*—C7*B*—C8*B*—C9*B* [−169.7 (2) and −100.7 (3)°] for cations *A* and *B*, respectively. The benzene ring makes dihedral angles of 77.55 (12) (cation *A*) and 82.28 (12)° (cation *B*) with the corresponding pyrimidine plane. These values agree closely with the range of values observed in previously reported compounds (Giuseppetti *et al.*, 1984).

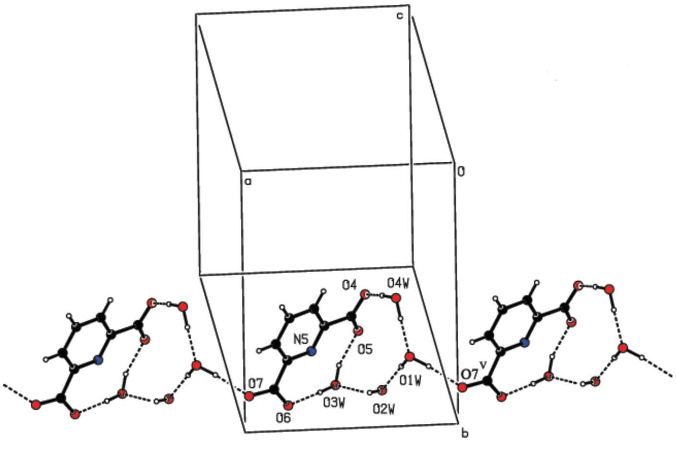


Figure 3
A view of the O—H⋯O hydrogen bonds (dashed lines) in (I). [Symmetry code: (v) $x - 1, y, z$.]

The C—O—C (aromatic) angles at the methoxy groups differ significantly. This difference is also observed in the crystal structure of neutral trimethoprim and can be attributed to the close approaches involving the atoms of the three methoxy groups (Koetzle & Williams, 1976).

The geometries of the hydrogen-bonding interactions in (I) are given in Table 2. One of the carboxylate groups (C22/O6/O7) interacts with cation *A via* a pair of N—H⋯O hydrogen bonds, forming an $R_2^2(8)$ ring motif (Etter, 1990; Bernstein *et al.*, 1995). This motif is present in the DHFR–trimethoprim complex (Kuyper, 1989).

Cations *A* and *B* constitute a base pair *via* N4*A*—H⋯N3*B* and N2*B*—H⋯N3*A* hydrogen bonds. The two 4-amino groups of cations *A* and *B* are further bridged by the carboxylate group *via* an N—H⋯O hydrogen bond, forming an $R_3^3(10)$ ring, as shown in Fig. 2. A loop of O—H⋯O hydrogen bonds is formed between four water molecules and the carboxylate groups, to form a supramolecular chain along the *a* axis (Fig. 3). There are also C—H⋯O hydrogen bonds involving the methoxy groups, but these are not discussed in detail here.

Experimental

Trimethoprim (145 mg; obtained as a gift sample from Shilpa Antibiotics Ltd) and dipicolinic acid (41 mg; Merck) were mixed in a 2:1 molar ratio in hot ethanol (50 ml) and warmed for 30 min over a water bath. On slow evaporation, blocks of crystals of (I) were obtained.

Crystal data

$2C_{14}H_{19}N_4O_3^{+}\cdot C_7H_3NO_4^{2-}\cdot 5H_2O$
$M_r = 837.85$
Monoclinic, $P2_1/n$
$a = 9.713$ (2) Å
$b = 12.025$ (3) Å
$c = 35.703$ (3) Å
$\beta = 94.23$ (3)°
$V = 4158.7$ (14) Å^3
$Z = 4$

$D_x = 1.338$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 3.1$–27.0°
$\mu = 0.11$ mm^{-1}
$T = 293$ K
Block, colourless
0.38 × 0.26 × 0.19 mm

Data collection

Philips PW1100 diffractometer
ω scans
Absorption correction: refined from ΔF (*SHELXA*; Sheldrick, 1997)
$T_{\min} = 0.961$, $T_{\max} = 0.980$
9210 measured reflections
9074 independent reflections
4170 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.023$
$\theta_{\max} = 27.0°$
$h = -12 \rightarrow 12$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 45$
1 standard reflection every 100 reflections intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.057$
$wR(F^2) = 0.160$
$S = 0.96$
9074 reflections
532 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0728P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.33$ e Å^{-3}
$\Delta\rho_{\min} = -0.35$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0032 (5)

Table 1
Selected geometric parameters (Å, °).

O1*A*—C12*A*	1.370 (3)	O2*B*—C11*B*	1.375 (3)
O1*A*—C14*A*	1.411 (4)	O3*B*—C10*B*	1.365 (3)
O2*A*—C11*A*	1.378 (3)	O3*B*—C16*B*	1.414 (4)
O2*A*—C15*A*	1.390 (4)	N1*B*—C2*B*	1.357 (3)
O3*A*—C10*A*	1.358 (3)	N1*B*—C6*B*	1.356 (3)
O3*A*—C16*A*	1.416 (5)	N2*B*—C2*B*	1.320 (3)
N1*A*—C2*A*	1.346 (3)	N3*B*—C2*B*	1.329 (3)
N1*A*—C6*A*	1.367 (3)	N3*B*—C4*B*	1.346 (3)
N2*A*—C2*A*	1.336 (3)	N4*B*—C4*B*	1.328 (3)
N3*A*—C4*A*	1.350 (3)	O4—C23	1.248 (3)
N3*A*—C2*A*	1.330 (3)	O5—C23	1.231 (4)
N4*A*—C4*A*	1.320 (3)	O6—C22	1.251 (3)
O1*B*—C12*B*	1.362 (3)	O7—C22	1.257 (3)
O1*B*—C14*B*	1.421 (4)	N5—C21	1.338 (3)
O2*B*—C15*B*	1.422 (4)	N5—C17	1.336 (3)
C12*A*—O1*A*—C14*A*	118.2 (2)	N2*B*—C2*B*—N3*B*	120.3 (2)
C11*A*—O2*A*—C15*A*	117.0 (2)	N1*B*—C2*B*—N2*B*	117.7 (2)
C10*A*—O3*A*—C16*A*	117.9 (2)	N4*B*—C4*B*—C5*B*	119.8 (2)
C2*A*—N1*A*—C6*A*	119.8 (2)	N3*B*—C4*B*—C5*B*	122.4 (2)
C2*A*—N3*A*—C4*A*	118.3 (2)	N3*B*—C4*B*—N4*B*	117.8 (2)
N1*A*—C2*A*—N3*A*	122.2 (2)	N1*B*—C6*B*—C5*B*	122.1 (2)
N2*A*—C2*A*—N3*A*	120.6 (2)	O3*B*—C10*B*—C9*B*	124.4 (2)
N1*A*—C2*A*—N2*A*	117.2 (2)	O3*B*—C10*B*—C11*B*	115.6 (2)
N3*A*—C4*A*—C5*A*	122.2 (2)	O2*B*—C11*B*—C12*B*	119.6 (2)
N4*A*—C4*A*—C5*A*	121.0 (2)	O2*B*—C11*B*—C10*B*	120.5 (2)
N3*A*—C4*A*—N4*A*	116.8 (2)	O1*B*—C12*B*—C13*B*	125.3 (2)
N1*A*—C6*A*—C5*A*	122.1 (2)	O1*B*—C12*B*—C11*B*	115.1 (2)
O3*A*—C10*A*—C9*A*	124.6 (2)	C17—N5—C21	118.9 (2)
O3*A*—C10*A*—C11*A*	115.7 (2)	N5—C17—C18	121.9 (2)
O2*A*—C11*A*—C10*A*	120.0 (2)	N5—C17—C23	116.9 (2)
O2*A*—C11*A*—C12*A*	120.1 (2)	N5—C21—C20	121.9 (2)
O1*A*—C12*A*—C13*A*	124.1 (2)	N5—C21—C22	116.3 (2)
O1*A*—C12*A*—C11*A*	115.3 (2)	O7—C22—C21	117.1 (2)
C12*B*—O1*B*—C14*B*	117.8 (2)	O6—C22—C21	118.9 (2)
C11*B*—O2*B*—C15*B*	115.6 (2)	O6—C22—O7	123.9 (2)
C10*B*—O3*B*—C16*B*	118.2 (2)	O4—C23—C17	116.1 (2)
C2*B*—N1*B*—C6*B*	120.0 (2)	O4—C23—O5	125.2 (3)
C2*B*—N3*B*—C4*B*	118.1 (2)	O5—C23—C17	118.7 (3)
N1*B*—C2*B*—N3*B*	122.0 (2)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1*A*···O7$^{\rm i}$	0.99	1.75	2.730 (3)	168
N1*B*—H1*B*···O4*W*$^{\rm ii}$	0.92	1.81	2.728 (3)	176
N2*A*—H2*A*···O2*W*$^{\rm iii}$	0.86	2.52	3.138 (4)	129
N2*A*—H2*B*···O6$^{\rm i}$	0.86	2.05	2.892 (3)	165
N4*A*—H4*A*···N3*B*$^{\rm iv}$	0.86	2.26	3.113 (3)	174
N4*A*—H4*B*···O4	0.86	2.09	2.900 (3)	156
O1*W*—H11···O7$^{\rm v}$	0.97	1.82	2.754 (4)	160
O1*W*—H12···O2*W*	0.98	1.76	2.712 (5)	165
O2*W*—H21···O3*W*	0.98	2.20	3.139 (4)	160
N2*B*—H21*A*···N3*A*$^{\rm iv}$	0.86	2.16	3.009 (3)	170
O2*W*—H22···O5*W*$^{\rm vi}$	0.86	2.51	2.976 (5)	114
N2*B*—H22*B*···O1*W*$^{\rm ii}$	0.86	2.50	3.265 (4)	149
O3*W*—H31···O6	0.95	1.90	2.854 (3)	178
O3*W*—H31···N5	0.95	2.52	2.898 (3)	104
O3*W*—H32···O5	0.94	1.85	2.759 (4)	162
O3*W*—H32···N5	0.94	2.40	2.898 (3)	113
O4*W*—H41···O1*W*	0.95	1.81	2.738 (3)	165
N4*B*—H41*A*···O5$^{\rm iv}$	0.86	2.05	2.798 (3)	145
O4*W*—H42···O4	0.97	1.79	2.733 (3)	164
O5*W*—H51···O6$^{\rm vii}$	0.93	2.00	2.821 (4)	146
O5*W*—H52···O3*W*$^{\rm iv}$	0.96	1.69	2.594 (4)	155
C7*A*—H7*B*···O4	0.97	2.27	3.176 (3)	155
C13*A*—H13*A*···O5*W*	0.93	2.52	3.384 (4)	154
C16*A*—H16*A*···O2*A*$^{\rm viii}$	0.96	2.38	3.061 (4)	128

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

The H atoms of the aromatic groups were positioned geometrically and those of the water molecule were located in difference Fourier maps. All H atoms were treated as riding, with C—H, O—H and N—H bond lengths of 0.93–0.97 Å, 0.86–0.97 Å and 0.86–0.99 Å, respectively, and with $U_{\rm iso}({\rm H}) = 1.2U_{\rm eq}$(parent).

Data collection: *FEBO* (Belletti, 1996); cell refinement: *MolEN* (Fair, 1990); data reduction: *MolEN*; 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*.

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].

References

Abboud, K. A., Xu, C. & Drago, R. S. (1998). *Acta Cryst.* C**54**, 1270–1273.

Belletti, D. (1996). *FEBO*. Internal Report 1-96. Centro di Studio per la Strutturistica Diffractometrica del CNR, Parma, Italy.

Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.

Carranza Téllez, V., Gaytan, B. S., Bernes, S. & Vergara, E. G. (2002). *Acta Cryst.* C**58**, o228–o230.

Etter, M. C. (1990). *Acc. Chem. Res.* **23**, 120–126.

Fair, C. K. (1990). *MolEN*. Enraf-Nonius, Delft, The Netherlands.

Giuseppetti, G., Tadini, C., Bettinetti, G. P., Giordano, F. & La Manna, A. (1984). *Acta Cryst.* C**40**, 650–653.

Guerriero, P., Casellato, U., Sitran, S., Vigato, P. A. & Graziano, R. (1987). *Inorg. Chim. Acta*, **133**, 337–345.

Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Kjell, H., Martin, L., Goran, S. & Jorgen, A. (1993). *Acta Chem. Scand.* **47**, 449–455.

Koetzle, T. F. & Williams, G. J. B. (1976). *J. Am. Chem. Soc.* **98**, 2074–2078.

o2370 Hemamalini *et al.* • $2C_{14}H_{19}N_4O_3^{+}\cdot C_7H_3NO_4^{2-}\cdot 5H_2O$ *Acta Cryst.* (2005). E**61**, o2368–o2371

Kuyper, L. F. (1989). *Computer-Aided Drug Design: Methods and Applications*, edited by T. J. Perun & C. L. Propst, ch. 9, pp. 327–370. New York: Marcel Dekker Inc.

Sheldrick, G. M. (1997). *SHELXS97*, *SHELXL97* and *SHELXA*. University of Göttingen, Germany.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.