Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

N—H···N hydrogen bonds in trimethoprim salicylate methanol solvate [trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine]

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.005 Å
H-atom completeness 86%
R factor = 0.063
wR factor = 0.216
Data-to-parameter ratio = 10.7

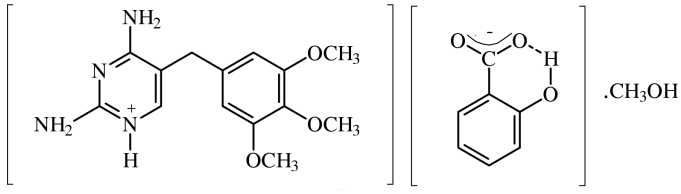
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

In the title compound, trimethoprim salicylate methanol solvate [3,4,5-trimethoxybenzyl)pyrimidin-1-ium salicylate methanol solvate], $C_{14}H_{19}N_4O_3^+\cdot C_7H_5O_3^-\cdot CH_4O$, the trimethoprim molecule is protonated at N1. The carboxylate group of the salicylate ion interacts with the protonated pyrimidine moiety of trimethoprim through a pair of nearly parallel N—H···O hydrogen bonds. This is reminiscent of the carboxylate–trimethoprim interaction observed in dihydrofolate reductase–trimethoprim complexes. The pyrimidine moieties of the trimethoprim cations are centrosymmetrically paired through a pair of N—H···N hydrogen bonds involving the 4-amino group and the unsubstituted pyrimidine N atom. The pyrimidine plane makes a dihedral angle of 89.5 (4)° with the phenyl ring in the trimethoprim cation.

Received 11 December 2001
Accepted 16 January 2002
Online 25 January 2002

Comment

Trimethoprim (TMP) is an antifolate drug. In its N1-protonated form, it inhibits its target, the bacterial dihydrofolate reductase (DHFR) (Hitching *et al.*, 1988). The crystal structures of DHFR from various sources complexed with antifolate drugs have also been reported in the literature. Salicylic acid is a widely used analgesic. The title compound, (I), has been investigated because of our interest in the hydrogen-bonding patterns of aminopyrimidine–carboxylate complexes and in the conformation of drugs. The crystal structures of trimethoprim nitrate (Murugesan & Muthiah, 1997), trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001), trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim glutarate (Jebamony *et al.*, 2001), diaquodibromobis(trimethoprim)cadmium(II) monohydrate (Muthiah & Robert, 1999), trimethoprim hydrogen maleate (Prabakaran, Robert *et al.*, 2001), trimethoprim perchlorate (Muthiah *et al.*, 2002), cytosinium hydrogen maleate (Balasubramanian *et al.*, 1996) and 5-fluorocytosinium salicylate (Prabakaran, Murugesan *et al.*, 2001) have been reported from our laboratory.



(I)

TMP is protonated at N1, as reported in various crystal structures containing TMP cations (Prabakaran, Robert *et al.*,

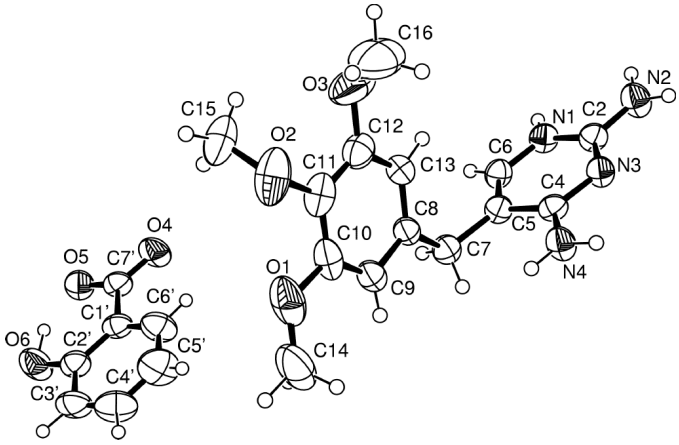


Figure 1
View of the title compound with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level (the methanol molecule has been omitted for clarity).

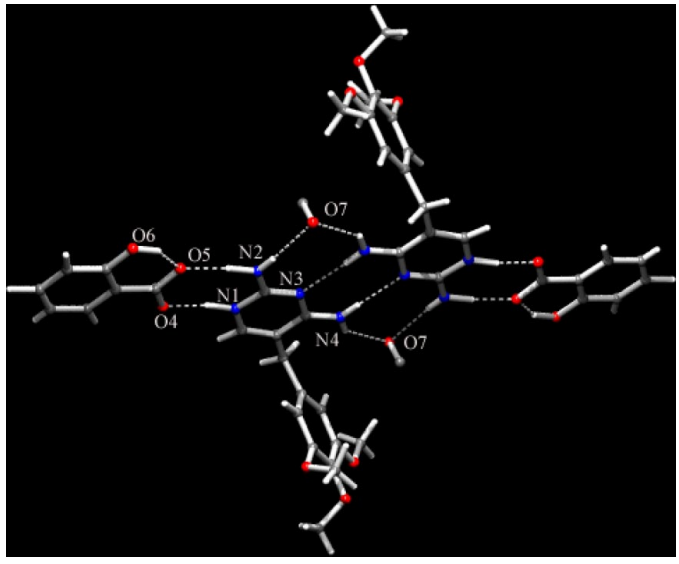


Figure 2
Hydrogen-bonding patterns in trimethoprim salicylate methanol solvate.

2001). This is evident from the increase in the ring angle at the site of protonation, namely N1. The internal angle at N1 (C2—N1—C6) has increased to 119.1 (2)°, compared with 115.46° in neutral TMP (Koetzle & Williams, 1976). The pyrimidine ring makes a dihedral angle of 89.5 (4)° with the phenyl ring, close to the value of 85.5 (2)° observed for trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001). The corresponding dihedral angle in trimethoprim salicylate monohydrate is 89.4 (2)°. The values of two torsion angles, *viz*. C4—C5—C7—C8 −74.6 (3)° and C5—C7—C8—C9 155.2 (2)°, are very close to those in trimethoprim perchlorate (Muthiah *et al.*, 2002) and trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001). The methanol molecule is disordered, as evident from the abnormal C1*A*—O7 bond length of 1.626 (12) Å, and the large displacement parameters of atoms C1*A* and O7. An *ORTEP*-3 (Farrugia, 1997) diagram of the anion and cation, with the atom-labelling scheme, is shown in Fig. 1.

The carboxylate group of the salicylate ion interacts with the protonated pyrimidine moiety of trimethoprim, through a pair of nearly parallel N—H···O hydrogen bonds. This is reminiscent of the carboxylate–TMP interaction observed in the DHFR–TMP complexes. This motif is one of the 20 most frequently observed bimolecular cyclic hydrogen-bonded motifs in organic crystal structures (Allen *et al.*, 1998). This motif has also been observed in the crystal structures of trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim hydrogen maleate (Prabakaran, Robert *et al.* 2001), and 5-fluorocytosinium salicylate (Prabakaran, Murugesan *et al.*, 2001). The typical intramolecular hydrogen bond (Jebamony & Muthiah, 1998) between the phenolic OH and the carboxylate group is also present in the salicylate moiety. The pyrimidine moieties of trimethoprim cations are centrosymmetrically paired through a pair of N—H···N hydrogen bonds involving the 4-amino group and the pyrimidine-N3 atom. This type of pairing has also been reported in trimethoprim hydrogen maleate (Prabakaran, Robert *et al.*, 2001), trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001) and trimethoprim perchlorate (Muthiah *et al.*, 2002). The 2-amino group of one member of the pair and the 4-amino group of the other member of the pair are bridged by the O atom of methanol, using a pair of N—H···O hydrogen bonds. Hence, as a result of the pairing and the involvement of the methanol O atom, complementary *DADA* (*D* = donor in hydrogen bonds, *A* = acceptor in hydrogen bonds) arrays of quadruple hydrogen-bonding patterns occur (Jebamony *et al.*, 2001). This is shown in Fig. 2.

Experimental

The title compound was prepared by mixing a hot methanolic solution of trimethoprim (obtained as a gift from Shilpa Antibiotics Ltd) with a hot methanolic solution of salicylic acid (Loba Chemie) in a 1:1 molar ratio. The mixture was cooled slowly and kept at room temperature. After a few days, needle-shaped colourless crystals were obtained.

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot C_7H_5O_3^-\cdot CH_4O$
M_r = 460.48
Triclinic, $P\overline{1}$
a = 10.0139 (19) Å
b = 10.2600 (19) Å
c = 11.984 (9) Å
α = 105.93 (3)°
β = 109.17 (5)°
γ = 92.50 (2)°
V = 1106.1 (10) Å^3
Z = 2
D_x = 1.383 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10–15°
μ = 0.10 mm^{-1}
T = 293 (2) K
Needle, colourless
0.30 × 0.30 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.97, T_{max} = 0.99
4377 measured reflections
3889 independent reflections
2855 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 25.0°
$h = -11 \rightarrow 11$
$k = -12 \rightarrow 12$
$l = -13 \rightarrow 14$
2 standard reflections
frequency: 60 min
intensity decay: negligible

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.063$	$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.216$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.65$	$\Delta\rho_{max} = 0.62$ e Å^{-3}
3889 reflections	$\Delta\rho_{min} = -0.38$ e Å^{-3}
365 parameters	

Table 1
Selected geometric parameters (Å, °).

O1—C10	1.365 (4)	O6—C2′	1.348 (4)
O1—C14	1.419 (6)	O7—C1*A*	1.626 (12)
O2—C11	1.391 (4)	N1—C6	1.357 (4)
O2—C15	1.431 (4)	N1—C2	1.353 (4)
O3—C12	1.396 (4)	N2—C2	1.330 (4)
O3—C16	1.333 (7)	N3—C2	1.331 (4)
O4—C7′	1.238 (4)	N3—C4	1.349 (3)
O5—C7′	1.278 (4)	N4—C4	1.330 (3)
C10—O1—C14	117.3 (3)	O1—C10—C11	114.9 (3)
C11—O2—C15	114.9 (3)	O1—C10—C9	124.7 (3)
C12—O3—C16	118.6 (4)	O2—C11—C12	121.7 (3)
C2—N1—C6	119.1 (2)	O2—C11—C10	119.4 (3)
C2—N3—C4	118.0 (2)	O3—C12—C11	121.2 (3)
N2—C2—N3	120.1 (3)	O3—C12—C13	118.0 (3)
N1—C2—N2	117.1 (3)	O6—C2′—C3′	118.2 (3)
N1—C2—N3	122.8 (3)	O6—C2′—C1′	122.2 (3)
N3—C4—C5	122.6 (2)	O4—C7′—C1′	119.2 (3)
N4—C4—C5	121.0 (2)	O5—C7′—C1′	116.7 (3)
N3—C4—N4	116.4 (2)	O4—C7′—O5	124.0 (3)
N1—C6—C5	122.4 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O4^{i}	1.04 (6)	1.68 (6)	2.696 (4)	165 (5)
N2—H2*A*···O7^{ii}	0.81 (4)	2.30 (4)	3.102 (5)	176 (5)
N2—H2*B*···O5^{i}	1.09 (4)	1.74 (4)	2.817 (4)	171 (2)
N4—H4*A*···N3^{ii}	0.86	2.16	3.019 (4)	174
N4—H4*B*···O7	0.86	2.20	2.926 (4)	142
O6—H6*A*···O5	1.06 (5)	1.52 (5)	2.499 (4)	151 (4)
C4′—H4′···O3^{iii}	1.04 (4)	2.38 (4)	3.364 (6)	156 (3)
C6—H6···O1^{iii}	0.91 (3)	2.53 (3)	3.436 (4)	175 (2)
C6′—H6′···O4	0.94 (3)	2.47 (4)	2.812 (4)	102 (3)
C15—H15*A*···O3	0.96	2.49	3.074 (5)	119

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

The following H atoms were positioned geometrically and kept fixed: H4*A*, H4*B*, H15*A*, H15*B*, H15*C*, H16*A*, H16*B* and H16*C*. All other H atoms were located from a difference Fourier map and were refined isotropically.

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*-3 (Farrugia, 1997); software used to prepare material for publication: *PLATON* (Spek, 1990).

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