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A pseudo-quadruple hydrogen-bonding motif consisting of six N—H···O hydrogen bonds in trimethoprim formate

Balakrishnan Umadevi, Ponraj Prabakaran† and Packianathan Thomas Muthiah*

Department of Chemistry, Bharathidasan University, Tiruchirapalli 620 024, India
Correspondence e-mail: tommtrichy@yahoo.co.in

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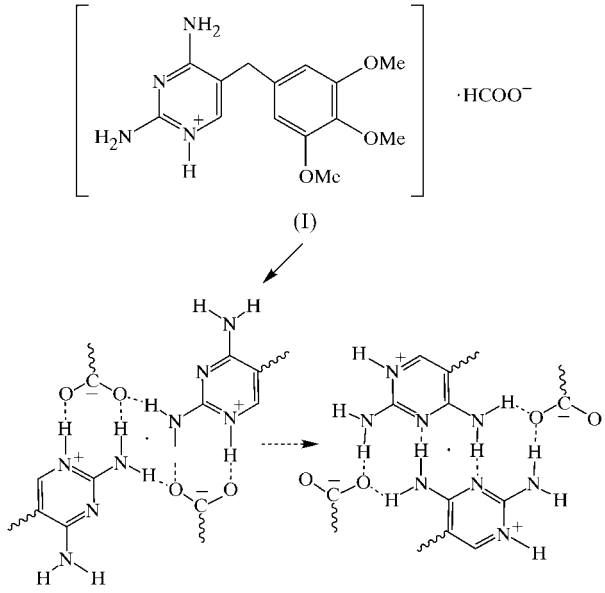
The title compound, trimethoprim (TMP) formate [systematic name: 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidin-1-ium formate], $C_{14}H_{19}N_4O_3^+\cdot CHO_2^-$, reveals a pseudo-quadruple hydrogen-bonding motif consisting of six N—H···O hydrogen bonds involving two unpaired TMP cations and two formate anions which are symmetrically disposed. The hydrogen-bonding motif is strikingly comparable with that observed in other TMP salts where the aminopyrimidine moieties of the TMP cations are centrosymmetrically paired. These conserved hydrogen-bonding motifs may serve as robust synthons in crystal engineering and design. The characteristic pseudo-quadruple hydrogen-bonding motif and other intermolecular hydrogen bonds operating in the crystal form a two-dimensional supramolecular sheet structure.

Comment

Trimethoprim (TMP) is a well known antifolate drug, which selectively inhibits the bacterial species of enzyme dihydrofolate reductase (DHFR) (Hitching *et al.*, 1988; Feeney, 2000). The drug in its N1-protonated form inhibits DHFR. In order to study the conformation and hydrogen-bonding patterns of the TMP molecule in various crystalline environments, we have investigated the crystal structures of trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim nitrate (Murugesan & Muthiah, 1997), trimethoprim hydrogen maleate (Prabakaran *et al.*, 2001), trimethoprim hydrogen glutarate (Robert *et al.*, 2001), trimethoprim sulfate trihydrate (Muthiah *et al.*, 2001), trimethoprim perchlorate (Muthiah *et al.*, 2002) and trimethoprim salicylate methanol solvate (Panneerselvam *et al.*, 2002). The crystal structures of TMP (Koetzle & Williams, 1976) and some of its salts, such as trimethoprim monobenzoate (Giuseppetti *et al.*, 1984), the trimethoprim monobenzoate–benzoic acid 1:1 complex (Bettinetti *et al.*, 1985), trimethoprim acetate (Bryan *et al.*, 1987), trimethoprim sulfametrole (Giuseppetti *et al.*, 1994), and the trimethoprim sulfadimidine 1:1 (Bettinetti & Sardone, 1997) and 1:2 (Sardone *et al.*, 1997) complexes, have also been reported in the literature. We present here the crystal structure of TMP formate, (I), and explore the hydrogen-bonding patterns in aminopyrimidine–carboxylate interactions.



(I)

An entry for (I) in the Cambridge Structural Database (CSD; Allen & Kennard, 1993), refcode TMPFOR, contains no atom coordinates. The structure of the molecule of (I) with the atom-labelling scheme is shown in Fig. 1. The TMP cation is protonated at N1, as is evident from the increase in the ring angle at N1, from 115.46 (5)° in neutral trimethoprim to 119.6 (2)° in (I). The conformation of the TMP cation is best described by two torsion angles, C4—C5—C7—C1′ of −70.2 (2)° and C5—C7—C1′—C2′ of 159.1 (2)°. The pyrimidine ring makes a dihedral angle of 82.3 (1)° with the phenyl ring, which is in agreement with the range of 70.0 (1)–96.0 (1)° reported for the related TMP salts mentioned above.

The carboxylate group of the formate anion forms two nearly parallel hydrogen bonds of the N—H···O type with the 2-amino group and the protonated N1 atom of the TMP cation, which is reminiscent of the carboxylate interaction with the TMP cation observed in the DHFR–TMP complex (Kuyper, 1990). Similar specific double hydrogen bonds have been noted in almost all the structures of TMP–carboxylate complexes which we have previously studied.

The aminopyrimidine moieties of the TMP cations are not paired, as routinely expected, but their 2-amino groups are connected by hydrogen bonds through two symmetry-related formate anions, which combines with the specific double hydrogen bonds to form a pseudo-quadruple hydrogen-bonding motif consisting of six intermolecular N—H···O hydrogen bonds (Fig. 2). This pseudo-quadruple hydrogen-bonding motif can be represented in the form of three fused

† Present address: RIKEN Tsukuba Institute, 3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan.

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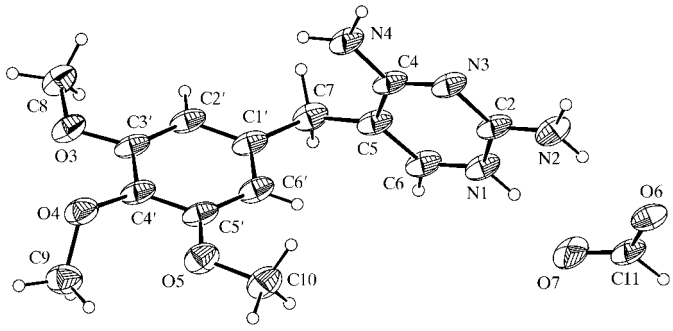

Figure 1
A view of the molecular structure of (I) with the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

$R_2^2(8)$, $R_4^2(8)$ and $R_2^2(8)$ rings, in order, using graph-set notation (Etter, 1990; Bernstein *et al.*, 1995) (see *Scheme* and Fig. 2).

This motif appears to be potentially recurrent, as we have recently found the same hydrogen-bonding pattern involving unpaired TMP cations in the structure of trimethoprim hydrogen glutarate (Robert *et al.*, 2001). However, all other TMP salts generally possess paired aminopyrimidine moieties of the TMP cations and consequently have a subtly different pseudo-quadruple hydrogen-bonding motif, with $R_3^2(8)$, $R_2^2(8)$ and $R_3^2(8)$ rings (see *Scheme*).

In the case of paired TMP cation–carboxylate interactions, it is interesting to note that the 2-amino and 4-amino groups of the diaminopyrimidine moieties of the TMP cations are bridged by an O atom of a carboxylate group (Prabakaran *et al.*, 2001), a methoxy group of TMP itself (Murugesan & Muthiah, 1997; Muthiah *et al.*, 2002), a methanol molecule (Panneerselvam *et al.*, 2002) or a water molecule (Muthiah *et al.*, 2001). Hence, the motif observed in all these TMP salts involving paired aminopyrimidine moieties can be effectively referred to as an O-mediated synthon. These conserved hydrogen-bonding motifs, also shown in (I), may serve as robust synthons in crystal engineering and design (Desiraju, 2001).

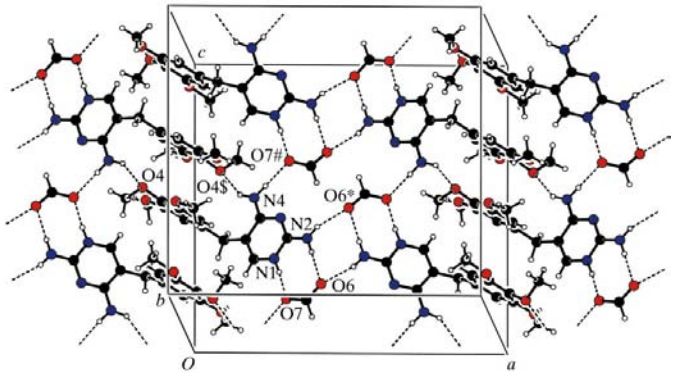

Figure 2
The two-dimensional supramolecular sheet structure of (I) formed by TMP and formate ions. The pseudo-quadruple hydrogen-bonding motifs consisting of three fused rings are depicted. Atoms labelled with an asterisk (*), hash (#) or dollar sign ($) are at the symmetry positions $(1-x, y, \frac{1}{2}-z)$, $(x, 1-y, z+\frac{1}{2})$ and $(-x, 1-y, 1-z)$, respectively.

In the present structure, the 4-amino group of the TMP cation also forms intermolecular hydrogen bonds with the carboxylate moiety of the formate anion, as well as with the methoxy group of a neighbouring TMP cation. The characteristic pseudo-quadruple hydrogen-bonding motif and other intermolecular hydrogen bonds operating in the crystal form a two-dimensional supramolecular sheet structure (Fig. 2).

Experimental

Trimethoprim (obtained as a gift from Shilpa Antibiotics Ltd) and formic acid, in a 1:1 ratio, were dissolved in warm water and crystallized from the mother liquor.

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot CHO_2^-$
$M_r = 336.35$
Monoclinic, $C2/c$
$a = 17.555$ (2) Å
$b = 11.708$ (2) Å
$c = 16.696$ (8) Å
$\beta = 92.43$ (3)°
$V = 3428.5$ (18) Å^3
$Z = 8$
$D_x = 1.303$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 40 reflections
$\theta = 5$–25°
$\mu = 0.83$ mm^{-1}
$T = 293$ K
Block, colourless
0.30 × 0.22 × 0.19 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
6169 measured reflections
3081 independent reflections
2824 reflections with $I > 2\sigma(I)$
$R_{int} = 0.047$
$\theta_{max} = 70°$
$h = -11 \rightarrow 21$
$k = -11 \rightarrow 14$
$l = -20 \rightarrow 19$
3 standard reflections
frequency: 60 min
intensity decay: negligible

Refinement

Refinement on F^2
$R(F) = 0.061$
$wR(F^2) = 0.166$
$S = 1.07$
3081 reflections
246 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0986P)^2 + 1.3308P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.33$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O3—C3′	1.367 (2)	O7—C11	1.244 (2)
O3—C8	1.416 (3)	N1—C2	1.353 (2)
O4—C4′	1.379 (2)	N1—C6	1.356 (2)
O4—C9	1.423 (3)	N2—C2	1.322 (2)
O5—C5′	1.363 (3)	N3—C2	1.335 (2)
O5—C10	1.422 (3)	N3—C4	1.341 (2)
O6—C11	1.229 (2)	N4—C4	1.321 (2)
C3′—O3—C8	117.91 (15)	N3—C4—N4	116.35 (14)
C4′—O4—C9	115.92 (15)	N3—C4—C5	122.38 (14)
C5′—O5—C10	117.91 (16)	N4—C4—C5	121.26 (15)
C2—N1—C6	119.58 (14)	O4—C4′—C3′	118.41 (15)
C2—N3—C4	118.22 (13)	O4—C4′—C5′	121.95 (17)
N1—C2—N3	122.33 (15)	O5—C5′—C6′	124.18 (16)
N2—C2—N3	119.87 (15)	O5—C5′—C4′	115.76 (15)
N1—C2—N2	117.80 (15)	N1—C6—C5	122.32 (15)
O3—C3′—C4′	115.04 (14)	O6—C11—O7	126.43 (16)
O3—C3′—C2′	124.43 (17)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O7	0.94 (3)	1.72 (3)	2.662 (2)	176 (2)
N2—H2A···O6^{i}	0.86	2.09	2.883 (2)	152
N2—H2B···O6	0.86	2.02	2.880 (2)	174
N4—H4A···O7^{ii}	0.86	2.05	2.860 (2)	158
N4—H4B···O4^{iii}	0.86	2.30	3.015 (2)	141
C2′—H2′···O6^{iv}	0.93	2.58	3.474 (3)	161
C6—H6···O3^{v}	0.93	2.53	3.452 (3)	174
C9—H9C···O5	0.96	2.47	2.938 (3)	110

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

All H atoms were treated as riding, with C—H distances in the range 0.93–0.97 Å and N—H distances of 0.86 Å, except for atom H1 attached to N1, the coordinates of which were refined, giving an N—H distance of 0.94 (3) Å.

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*II (Johnson, 1976) and *PLATON* (Spek, 1997); software used to prepare material for publication: *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1211). Services for accessing these data are described at the back of the journal.

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