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Aminopyrimidine–carboxyl(ate) interactions in trimethoprim maleate, an antifolate drug

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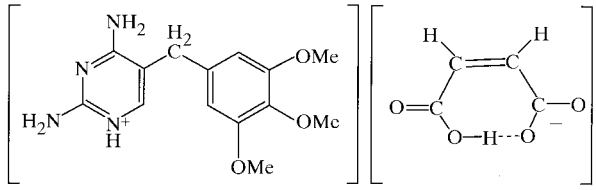
In the title cocrystal, trimethoprim maleate [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidin-1-ium maleate], $C_{14}H_{19}N_4O_3^+\cdot C_4H_3O_4^-$, the trimethoprim molecule is protonated at N1. The carboxyl group of the maleate ion makes a specific double hydrogen bond of type N—H···O with the 2-amino group and the protonated N1 atom of the trimethoprim cation which is similar to the carboxylate–trimethoprim cation interaction observed in the complex of dihydrofolate reductase with trimethoprim. 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 pyridinium N3 atom of a symmetry-related molecule. One of the O atoms at the maleate carboxylate group bridges the 2-amino and 4-amino groups on either side of the paired trimethoprim cations. The other O atom of the carboxylate group forms an intramolecular O—H···O hydrogen bond with the carboxyl group. These characteristic hydrogen bonds result in infinite two-dimensional aggregation of rings into a supramolecular ladder, which is further crosslinked through weak C—H···O interactions with methoxy groups of neighbouring trimethoprim molecules to form a layered structure.

Comment

Dihydrofolate reductase (DHFR) is an essential cellular enzyme as it is involved in several biosynthetic processes, as well as being the target for antifolate drugs such as trimethoprim (TMP). Drug–receptor complexes of DHFR from various sources with antifolate drugs have been widely studied and are of current interest (Feeney, 2000). TMP is very effective as it has differential affinity for bacterial DHFR *versus* human DHFR. The drug in its N1-protonated form inhibits DHFR. The crystal structures of trimethoprim and its complexes, for example, trimethoprim (Koetzle & Williams, 1976), trimethoprim monobenzoate (Giuseppetti *et al.*, 1984), trimethoprim monobenzoate–benzoic acid 1:1 complex (Bettinetti *et al.*, 1985), trimethoprim acetate (Bryan *et al.*, 1987), trimethoprim sulfametrole (Giuseppetti *et al.*, 1994), and trimethoprim sulfadimidine 1:1 (Bettinetti & Sardone, 1997) and 1:2 (Sardone *et al.*, 1997) complexes have been reported in the literature. The crystal structures of maleic acid complexed with L-histidine and L-lysine (Pratap *et al.*, 2000), and with DL- and L-arginine (Ravishankar *et al.*, 1998) have been studied recently for their aggregation modes and interaction patterns from the hydrogen bonding point of view. As part of structural investigations on drugs and their complexes carried out in our laboratory, we have already determined the structures of trimethoprim formate (Umadevi & Muthiah, 1994), trimethoprim perchlorate (Umadevi & Muthiah, 2001), trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996) and trimethoprim nitrate (Murugesan & Muthiah, 1997). The present study has been aimed at understanding the conformation, hydrogen bonding and specificity of trimethoprim–carboxyl(ate) interactions in trimethoprim maleate, (I).



(I)

The TMP molecule is protonated at N1, as is evident from the increase in the ring angle at N1 from 115.46 (5)° in neutral trimethoprim to 121.5 (4)° in the present work. The conformation of the TMP molecule is described by two torsion angles, *i.e.* C4—C5—C7—C1′ of −70.0 (5)° and C5—C7—C1′—C2′ of 144.2 (4)°. The pyrimidine ring makes a dihedral angle of 93.2 (1)° with the phenyl ring, which is close to the value of 93.8 (1)° observed for trimethoprim nitrate (Murugesan & Muthiah, 1997). An *ORTEP*II (Johnson, 1976) diagram of the molecule with the atom-labelling scheme is shown in Fig. 1.

The drug TMP in its protonated form interacts with the carboxyl and carboxylate moieties of maleate ions. The carboxyl-group hydrogen bonding in protein structures has also been well established (Ramanadham *et al.*, 1993). The carboxyl group of the maleate ion makes a specific double hydrogen bond of type N—H···O with the 2-amino group and the protonated N1 atom of the TMP cation which is similar to the carboxylate–trimethoprim cation interaction observed in DHFR–TMP complexes (Kuyper, 1990). The least-squares planes passing through the carboxylate group and the pyrimidine ring involved in the specific hydrogen-bond interaction make an angle of 17.3 (6)°. The pyrimidine moieties of trimethoprim cations are centrosymmetrically paired through a couple of N—H···N hydrogen bonds involving the 4-amino

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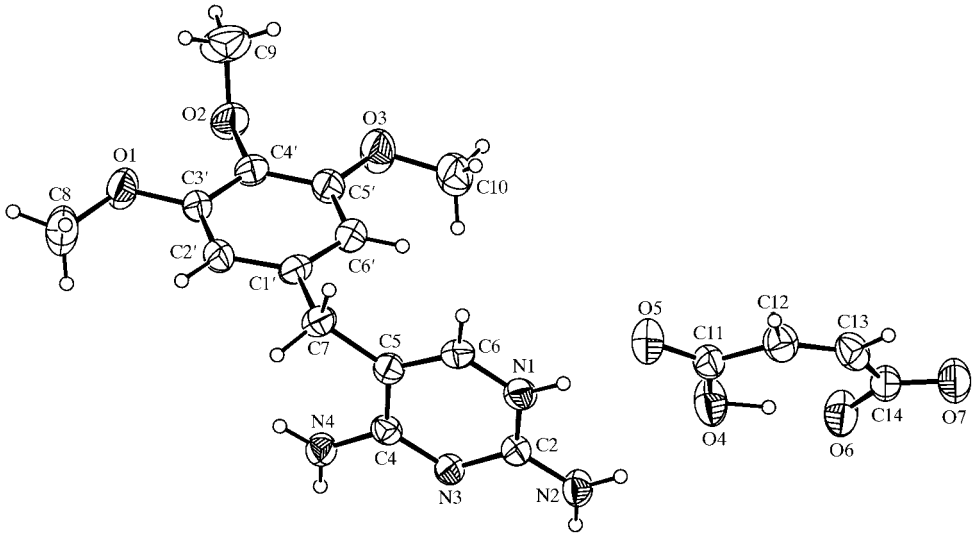

Figure 1
*ORTEP*II (Johnson, 1976) diagram of (I) with the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

group and the N3 atom. The specific double hydrogen bonds between the TMP and maleate ions, as well as two N—H···N hydrogen bonds in the paired pyrimidine moieties, form eight-membered hydrogen-bonded rings with a graph-set motif of $R_2^2(8)$ (Etter, 1990; Bernstein *et al.*, 1995). One of the O atoms (O7) at the carboxylate group of the maleate ions bridges the 2-amino and 4-amino groups on either side of the paired TMP cations, forming hydrogen-bonded ring motifs with graph-set $R_3^2(8)$. The other O atom (O6) of the carboxylate group of the maleate ion forms an intramolecular O—H···O hydrogen bond with the O4 atom of the carboxyl group.

The hydrogen-bonding patterns formed upon the association of aminopyrimidine moieties of TMP molecules *via* self-pairing and carboxylate bridging resemble those of water-mediated *GG* pairing observed in the crystal structure of guanine hydrochloride dihydrate in the GG_4^2 mode (Jeffrey & Saenger, 1991). Both structures have a direct base-pairing through two N—H···N hydrogen bonds with an $R_2^2(8)$ motif,

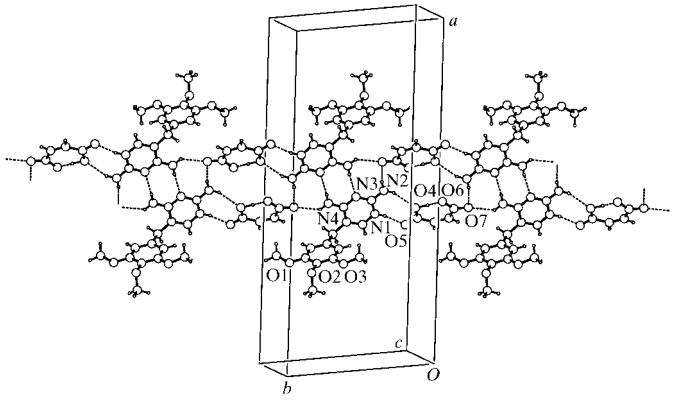

Figure 2
Hydrogen-bonded supramolecular ladder containing alternate TMP and maleate ions.

which is embedded by two O-mediated hydrogen-bonded rings of graph-set $R_3^2(8)$. The characteristic hydrogen-bonded rings observed in the structure aggregate into a supramolecular ladder consisting of a pair of chains, each of which is built up of alternate TMP and maleate ions (Fig. 2). As can be seen in Fig. 2, two maleate ions are interconnected by paired TMP molecules and *vice versa*. The ladders are further cross-linked through weak C—H···O interactions with methoxy groups of neighbouring TMP molecules to form a layered structure. The geometrical parameters of the hydrogen-bond interactions are given in Table 2.

Experimental

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

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot C_4H_3O_4^-$
M_r = 406.40
Monoclinic, $P2_1/n$
a = 28.485 (2) Å
b = 12.964 (3) Å
c = 5.413 (2) Å
β = 93.27 (3)°
V = 1995.7 (9) Å^3
Z = 4
D_x = 1.353 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 40 reflections
θ = 6.82–21.34°
μ = 0.89 mm^{-1}
T = 293 K
Plate, pale yellow
0.31 × 0.26 × 0.17 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.757, T_{max} = 0.863
4200 measured reflections
3796 independent reflections
1522 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 69.96°
$h = -10 \rightarrow 34$
$k = -14 \rightarrow 15$
$l = -6 \rightarrow 6$
3 standard reflections
frequency: 60 min
intensity decay: negligible

Refinement

Refinement on F^2
$R(F)$ = 0.065
$wR(F^2)$ = 0.257
S = 0.911
3796 reflections
278 parameters
H-atom refinement: see below
$w = 1/[\sigma^2(F_o^2) + (0.1407P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0017 (5)

The hydroxy H4 atom (bonded to O4) was refined isotropically. All other H atoms were treated as riding, with N—H and C—H distances of 0.86 and 0.93–0.97 Å, respectively.

Table 1
Selected geometric parameters (Å).

O1—C3′	1.373 (6)	O6—C14	1.295 (7)
O1—C8	1.432 (7)	O7—C14	1.217 (7)
O2—C4′	1.389 (6)	N1—C6	1.356 (6)
O2—C9	1.401 (6)	N1—C2	1.340 (6)
O3—C5′	1.366 (6)	N2—C2	1.309 (6)
O3—C10	1.409 (7)	N3—C2	1.352 (6)
O4—C11	1.276 (7)	N3—C4	1.355 (5)
O5—C11	1.244 (6)	N4—C4	1.326 (6)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O5	0.86	1.90	2.747 (6)	168
N2—H2*A*···O4	0.86	2.13	2.936 (6)	155
N2—H2*B*···O7^{i}	0.86	2.20	3.041 (6)	166
O4—H4···O6	1.06 (6)	1.36 (6)	2.423 (6)	174 (6)
N4—H4*A*···N3^{ii}	0.86	2.13	2.985 (5)	172
N4—H4*B*···O7^{iii}	0.859	2.14	2.829 (6)	137
C10—H10*C*···O1^{iv}	0.96	2.59	3.355 (8)	137

Symmetry codes: (i) $-x, -1-y, 2-z$; (ii) $-x, -y, 1-z$; (iii) $x, 1+y, z-1$; (iv) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{3}{2}-z$.

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: *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: OA1113). Services for accessing these data are described at the back of the journal.

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