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Trimethoprim–hydrogen malonate (1/1)

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.002 Å
R factor = 0.054
wR factor = 0.155
Data-to-parameter ratio = 12.7

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

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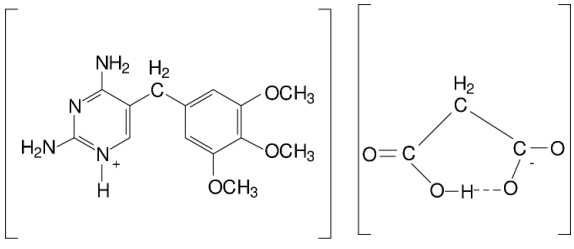
In the title compound, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidinium hydrogen malonate, $C_{14}H_{19}N_4O_3^+\cdot C_3H_3O_4^-$, the trimethoprim molecule is protonated at one of the pyrimidine N atoms. The carboxylate group of the hydrogen malonate ion accepts a pair of N—H···O hydrogen bonds from an adjacent trimethoprim molecule, which is similar to the carboxylate–trimethoprim cation interaction present in the complex of dihydrofolate reductase with trimethoprim. An O atom of the carboxyl group forms an intramolecular O—H···O hydrogen bond with the carboxylate group, leading to a folded conformation for the hydrogen malonate ion. Each hydrogen malonate ion bridges two diaminopyrimidine cations, *via* N—H···O and C—H···N hydrogen bonds, leading to a supramolecular ribbon made up of alternating cations and anions. Two such inversion-related ribbons are cross-linked by (amino)N—H···O(methoxy) hydrogen bonds, (pyrimidine)C—H···O(methoxy) hydrogen bonds and π–π stacking involving the benzene planes.

Comment

Trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine or TMP] is an antifolate drug. It is a potent inhibitor of bacterial dihydrofolate reductase (DHFR) but is less effective against human DHFR (Hitching *et al.*, 1988). The present study has been undertaken as part of our exploration of hydrogen-bonding patterns involving aminopyrimidine–carboxylate interactions. These types of interaction are very important for biological functions. For example, in the DHFR–trimethoprim complex, the protonated diaminopyrimidine ring of the drug makes a pair of N—H···O hydrogen bonds with the carboxylate group of the enzyme (Kuyper, 1990). The crystal structure of trimethoprim (Koetzle & Williams, 1976) and its complexes, for example, trimethoprim 5,5′-diethylbarbituric acid (Shimizu & Nishigaki, 1982), trimethoprim acetate (Bryan *et al.*, 1987) and trimethoprim sulfodimidine (Bettinetti & Sardone, 1997) have been reported in the literature.



(I)

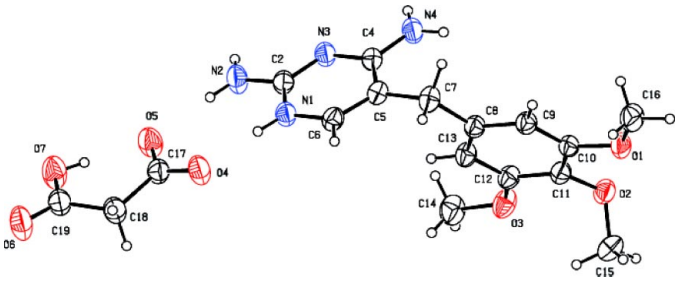


Figure 1
View of (I), with the atom labeling scheme, showing 50% probability displacement ellipsoids (arbitrary spheres for the H atoms).

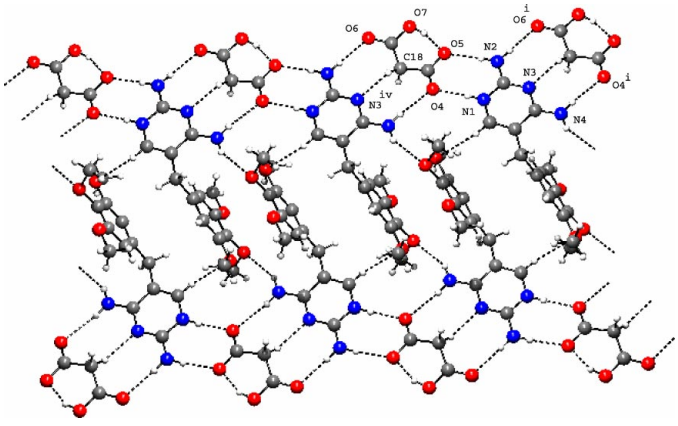


Figure 2
Hydrogen-bonding patterns (dashed lines) in (I) [symmetry codes: (i) x, $y-1$, z; (iv) x, $1+y$, z].

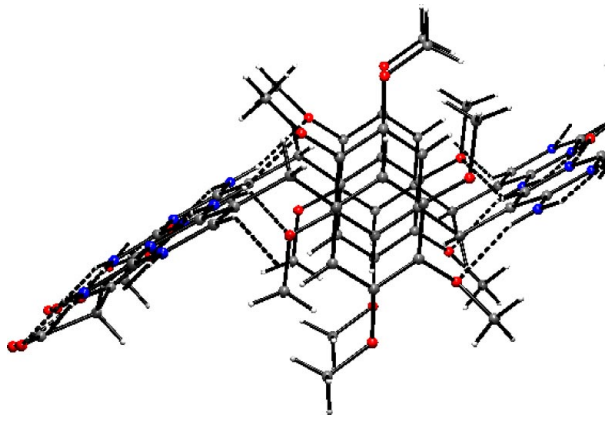


Figure 3
A view of the aromatic stacking interactions in (I). Dashed lines indicate hydrogen bonds.

We are applying crystal engineering techniques to diaminopyrimidine–carboxylate salts (Sethuraman *et al.*, 2003). We have already reported the structures of TMP hydrogen maleate (Prabakaran *et al.*, 2001), TMP hydrogen glutarate (Robert *et al.*, 2001), TMP formate (Umadevi *et al.*, 2002), TMP trifluoroacetate (Francis *et al.*, 2002), TMP terephthalate terephthalic acid (Hemamalini *et al.*, 2003), TMP sorbate dihydrate and TMP *o*-nitrobenzoate (Baskar Raj *et al.*, 2003). We present here the conformation and hydrogen-bonding patterns observed in the 1:1 adduct of trimethoprim and hydrogen malonate, (I) (Fig. 1).

The asymmetric unit of (I) contains a protonated trimethoprim cation and a hydrogen malonate anion. The trimethoprim is protonated at atom N1 of the pyrimidine moiety, which is evident from the increase in the internal angle at N1 (C2—N1—C6) from 115.46 (5)° in neutral trimethoprim (Koetzle & Williams, 1976) to 118.94 (16)° in the present study. This increase of the internal angle has also been observed in many TMP–carboxylate salts (Robert *et al.*, 2001). The dihedral angle between the pyrimidine and benzene planes is 71.72 (8)°, which is within the reported range 69.96 (8)–89.5 (2)° for related compounds (Giuseppetti *et al.*, 1984; Muthiah *et al.*, 2001).

The conformation of the trimethoprim cation is described by the two torsion angles C4—C5—C7—C8 and C5—C7—C8—C9, which are −66.7 (2) and 165.84 (17)°, respectively. This TMP conformation plays a very important role in DHFR selectivity (Hitching *et al.*, 1988). The carboxylate group O atoms (O4 and O5) of the hydrogen malonate ion act as acceptors in a fork-like hydrogen-bonding pattern [with graph-set notation $R_2^2(8)$] with the protonated pyrimidine nitrogen (N1) and 2-amino group of the trimethoprim cation, which is similar to the carboxylate group (of ASP-27 of DHFR) trimethoprim cation interaction observed in trimethoprim–DHFR complexes (Kuyper, 1990). This pattern is one of the 24 most frequently observed cyclic hydrogen-bonded motifs in organic crystal structures (Allen *et al.*, 1988).

Each hydrogen malonate ion bridges two diaminopyrimidine cations *via* N—H···O hydrogen bonds and C—H···N interactions (Table 1), leading to a supramolecular ribbon made up of the cations and the anions occurring alternately. Two such inversion-related ribbons are crosslinked by (amino)N—H···O (of methoxy O2) hydrogen bonds, (pyrimidine)C—H···O (of methoxy O1) hydrogen bonds (Table 1) and π–π stacking between benzene planes (Fig. 2). The centroid-to-centroid and interplanar distances are 4.089 (11) and 3.533 Å, respectively, and the slip angle (the angle between the centroid vector and the normal to the plane) is 30.24°. These values are consistent with those reported for other aromatic π–π stacking interactions (Hunter, 1994) and are shown in Fig. 3. Atom O7 of the carboxyl group of the hydrogen malonate anions forms an intramolecular O—H···O hydrogen bond with the O atom of the carboxylate group (O5) [with graph-set notation $S(6)$; Etter, 1990; Bernstein *et al.*, 1995], leading to a folded conformation. A similar intramolecular hydrogen bond has been observed in the crystal structures of benzylammonium hydrogen malonate and 4-picolinium hydrogen malonate (Djinović *et al.*, 1990). The dihedral angle between the carboxyl plane and the carboxylate plane of the hydrogen malonate ion is 18.80 (16)°. The torsion angles involving the hydrogen malonate ion also confirm the folded conformation.

Experimental

Hot aqueous solutions of trimethoprim (0.0745 g) and malonic acid (0.026 g) were mixed in a 1:1 molar ratio. The resulting solution was warmed over a water bath for 30 min and then kept at room

temperature for crystallization. After a few days, plate-shaped crystals of (I) were obtained.

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot C_3H_3O_4^-$
M_r = 394.39
Triclinic, $P\overline{1}$
a = 8.4851 (2) Å
b = 8.6566 (2) Å
c = 13.6425 (3) Å
α = 106.360 (3)°
β = 91.712 (2)°
γ = 92.950 (3)°
V = 959.08 (4) Å^3
Z = 2
D_x = 1.366 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 50 reflections
θ = 2.1–28.1°
μ = 0.91 mm^{-1}
T = 293 K
Thick plate, colorless
0.68 × 0.65 × 0.35 mm

Data collection

Bruker $P4$ diffractometer
ω scans
Absorption correction: refined from ΔF (*SHELXA*; Bruker, 2001)
T_{min} = 0.549, T_{max} = 0.726
3484 measured reflections
3268 independent reflections
3029 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 68.9°
$h = 0 \rightarrow 10$
$k = -10 \rightarrow 9$
$l = -16 \rightarrow 16$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.156
S = 1.07
3268 reflections
258 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0825P)^2 + 0.208P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.016 (2)

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O4	0.86	1.85	2.708 (2)	178
N2—H2A···O6^{i}	0.86	2.30	3.129 (3)	163
N2—H2B···O5	0.86	1.96	2.822 (2)	176
N4—H4A···O4^{i}	0.86	2.39	3.229 (2)	164
N4—H4B···O2^{ii}	0.86	2.40	3.182 (2)	151
O7—H7···O5	0.82	1.78	2.515 (3)	148
C6—H6···O1^{iii}	0.93	2.54	3.331 (2)	143
C15—H15B···O3	0.96	2.49	3.035 (3)	116
C18—H18B···N3^{iv}	0.97	2.33	3.228 (3)	154

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

All H atoms were located in difference Fourier maps and were relocated in idealized positions and refined as riding on their carrier atoms. The C—H, N—H and O—H bond lengths are 0.92–0.97, 0.86 and 0.82 Å, respectively. The constraint U_{iso}(H) = 1.2U_{eq}(carrier) or 1.5U_{eq}(methyl carrier) was applied as appropriate.

Data collection: *XSCANS* (Bruker, 2001); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Bruker, 2001); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

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