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Bis[2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidin-1-ium] DL-malate

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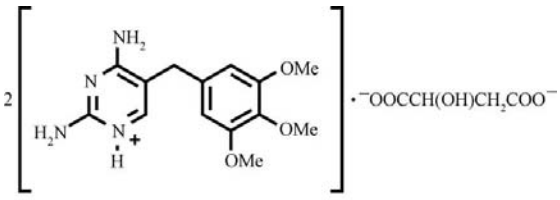
Racemic malic acid and trimethoprim [5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine] form a 1:2 salt (monoclinic, $P2_1/c$), $2C_{14}H_{19}N_4O_3^+\cdot C_4H_4O_5^{2-}$, in which the malate component is disordered across a centre of inversion. The crystal structure of the salt consists of protonated trimethoprim residues and a malate dianion. The carboxylate group of the malate ion interacts with the trimethoprim cation in a linear fashion through pairs of N—H···O hydrogen bonds to form a cyclic hydrogen-bonded motif. This is similar to the carboxylate–trimethoprim cation interaction observed earlier in the complex of dihydrofolate reductase with trimethoprim. The structure of the salt of trimethoprim with racemic DL-malic acid reported here is the first of its kind. The present study investigates the conformations and the hydrogen-bonding interactions, which are very important for biological functions. The pyrimidine plane makes a dihedral angle of 78.08 (7)° with the benzene ring of the trimethoprim cation. The cyclic hydrogen-bonded motif observed in this structure is self-organized, leading to novel types of hydrogen-bonding motifs in supramolecular patterns.

Comment

Trimethoprim (TMP) is a bacteriostatic antibiotic mainly used in the prophylaxis and treatment of urinary tract infections. It belongs to the class of chemotherapeutic agents known as dihydrofolate reductase inhibitors. Dihydrofolate reductase (DHFR) is an essential cellular enzyme involved in several biosynthetic processes as well as the target for antifolate drugs such as TMP. Antifolate drugs complexed with DHFR from various sources have been widely studied (Feeney, 2000). TMP has greater affinity towards bacterial DHFR than towards human DHFR. More than a dozen structures of TMP salts have been recorded in the Cambridge Structural Database (Version 5.29; Allen, 2002).

The role of malic acid (2-hydroxy-1,4-butanedioic acid) in supramolecular chemistry has not been widely studied although it is one of the simplest chiral dicarboxylic acids. Studies on the salts formed with primary amines and diamines using L-malic acid (Aakeröy & Nieuwenhuyzen, 1994, 1996) and racemic malic acid (Kaniskas, 1985; Farrell *et al.*, 2002) have been reported. The crystal structures of racemic malic acid adducted with aniline (Perpétuo & Janczak, 2003), melamine (Janczak & Perpétuo, 2003) and piperazine (Wang *et al.*, 2005) have been studied for their aggregation modes and hydrogen-bonding interactions.

The crystal structures of TMP salts formed with racemic compounds have not yet been explored. An earlier report reveals that, when both the components of a system are achiral, the adducts generally crystallize in centrosymmetric space groups. This may be due to the occurrence of inversion centres in molecular crystals (Brock & Dunitz, 1994). Even if one component is a racemic mixture of the two enantiomers of a chiral building block, similar considerations apply (Burchell *et al.*, 2000, 2001). The robustness and reliability of the self-complimentary DL-malic acid have also been used for crystal engineering (Pang *et al.*, 1997; Aakeröy *et al.*, 2000). The synthesis and structure determination of the title complex, (I), of TMP with DL-malic acid, which crystallizes in the centrosymmetric space group $P2_1/c$, have been carried out in order to investigate the conformations of the components and the hydrogen-bonding interactions, which are very important in determining the DHFR selectivity and biological functions.



(I)

The asymmetric unit of (I) (Fig. 1) contains one TMP cation and half of a malate dianion, with the full anion being disordered across a centre of inversion such that half of the sites accommodate molecules of D configuration and the other half accommodate molecules of L configuration. If a molecule of D-malic acid occupies any particular site then atom O6 is present and O6\$ is absent [the dollar (\$) symbol indicates the symmetry operation $(-x+1, -y+1, -z+1)$]; occupation by L-malic acid means that atom O6\$ is present and O6 is absent (Fig. 2). This is similar to the 1:1 adduct formed between 1,2-bis(4-pyridyl)ethene and racemic malic acid (Farrell *et al.*, 2002).

The TMP cations are protonated at atom N4, as confirmed by the increase in the internal C1—N4—C2 angle to 119.80 (18)° from the value of 115.46° found in neutral TMP (Koetzle & Williams, 1976). The bond lengths and angles of the TMP cation are comparable to those of previously reported TMP cations. The C—O—C angles at the methoxy groups differ significantly. This difference has also been 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).

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The conformation adopted by the trimethoprim molecule in this structure is described by torsion angles C4—C3—C5—C6 and C3—C5—C6—C11. These torsion angles are −81.2 (2) and −166.57 (19)°, respectively, which are comparable to previously reported values (Hemamalini *et al.*, 2003). The TMP conformation plays an important role in DHFR selectivity (Hitching *et al.*, 1988). The conformation adopted by the C—C—O—C methoxy groups in the trimethoprim molecule is similar to that in the related structure reported by Trilleras *et al.* (2005). Consistent with these different conformations, the pairs of exocyclic C—C—O angles at C8 and C10 differ widely, while the angles at C9 differ slightly (Table 1). These are typical of the angles found in planar methoxyarenes. An all-*trans* conformation is observed for the carbon skeleton of the malate anion [C15—C16—C16$—C15$ = 180° (see Fig. 1 for symmetry code); van der Sluis & Kroon, 1985, 1989]. The pyrimidine ring makes a dihedral angle of 78.08 (7)° with the benzene ring of the TMP cation, which is found to be within the range reported previously (Giuseppetti *et al.*, 1984; Muthiah *et al.*, 2001; Raj, Muthiah *et al.*, 2003; Raj, Sethuraman *et al.*, 2003).

In (I), the carboxylate group of the malate anion forms two nearly parallel N—H···O hydrogen bonds with the amine group and the protonated N4 atom of the TMP cation. This is reminiscent of the carboxylate interaction with the TMP cation in the DHFR–TMP complex (Kuyper, 1990). Similar specific double hydrogen bonds have been formed in almost all the structures of TMP–carboxylate complexes previously reported. This hydrogen-bonded motif formed as a result of the pair of N—H···O hydrogen bonds can be represented by the graph-set notation $R_2^2(8)$ (Etter, 1990; Bernstein *et al.*, 1995). It is one of the 24 recurrent hydrogen-bonded cyclic bimolecular motifs observed in organic crystal structures (Allen *et al.*, 1998). This motif is a well known supramolecular synthon in aminopyrimidine–carboxylate salts (Stanley *et al.*, 2005). It self-organizes in different ways to give different types of hydrogen-bonding patterns (Raj, Stanley *et al.*, 2003). An

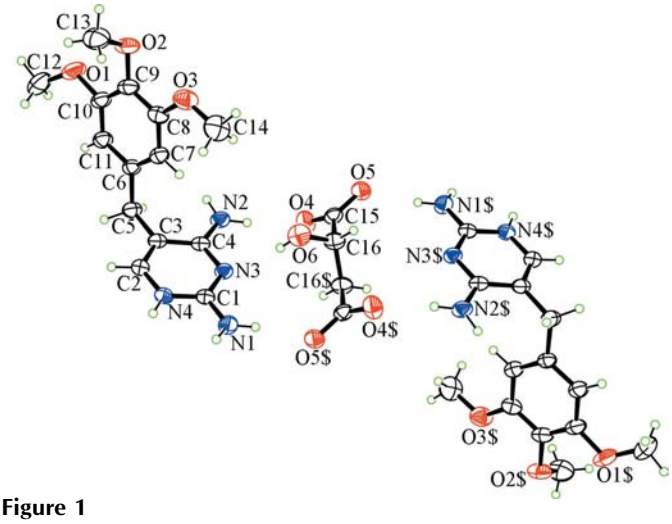

Figure 1
The molecular structure of (I), showing 40% probability displacement ellipsoids. Both D- and L-malic acid occupy the same site with centrosymmetric disorder. The dollar sign ($) denotes the symmetry operation (−*x* + 1, −*y* + 1, −*z* + 1). Atoms O6$, H6$ and H16*B* have been omitted for clarity.

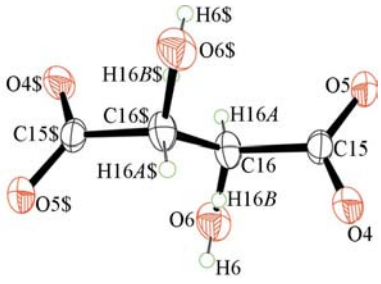

Figure 2
The malic acid component in (I), showing 30% probability displacement ellipsoids. It is disordered across a centre of inversion, so that if atom O6 is present (D-malic acid) then O6$ is absent, while if atom O6$ is present (L-malic acid), O6 is absent [the dollar sign ($) denotes the symmetry operation (−*x* + 1, −*y* + 1, −*z* + 1)].

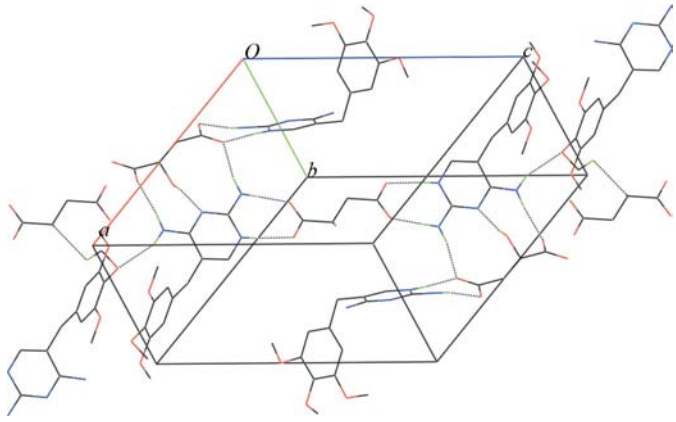

Figure 3
Part of the crystal structure of (I), showing the formation of an $R_2^2(8)$ hydrogen-bonded motif. For the sake of clarity, only H atoms involved in hydrogen bonding are shown. Dashed lines represent hydrogen bonds.

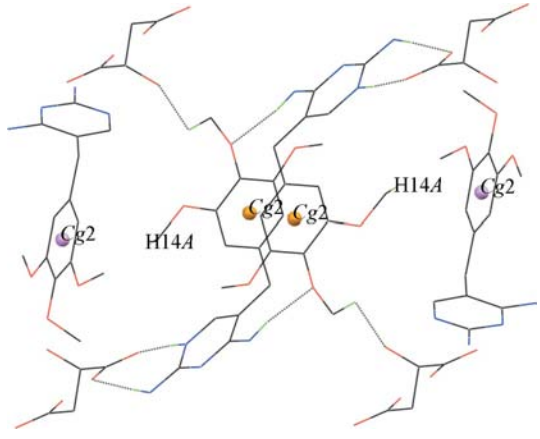

Figure 4
Part of the crystal structure of (I), showing the aromatic π–π and C—H···π(arene) interactions. Dashed lines represent hydrogen bonds. (*Cg*2 represents the centroid of the C6–C11 ring.)

intermolecular hydrogen bond between the hydroxy group of the anion (O6) and a ring N atom (N3) of the cation is observed. The geometries of the hydrogen-bonding interactions of (I) are given in Table 2. The amine groups of each TMP cation form intermolecular hydrogen bonds with the neighbouring carboxylate group of the malate dianion as well as with the methoxy group of neighbouring TMP cations. Part of the crystal structure of (I), showing the formation of an $R_2^2(8)$ hydrogen-bonded motif, is shown in Fig. 3. The parallel benzene rings at (x, y, z) and $(-x, -y+2, -z+1)$, which lie in different frameworks, are linked by aromatic π–π stacking interactions. They have an interplanar spacing of 3.427 Å and a centroid separation of 3.5605 (13) Å. The presence of this aromatic π–π interaction along with the C—H$\cdots\pi$(arene) interaction (Table 2) is illustrated in Fig. 4. These observed interactions together form an extensive three-dimensional hydrogen-bonded framework.

Experimental

Equimolar quantities of racemic malic acid and trimethoprim were dissolved in water. The solution was stirred well and set aside to crystallize. Colourless crystals of (I) suitable for X-ray diffraction analysis were obtained from the resulting solution after a week of slow evaporation.

Crystal data

$2C_{14}H_{19}N_4O_3^+\cdot C_4H_4O_5^{2-}$
M_r = 714.74
Monoclinic, $P2_1/c$
a = 12.9850 (3) Å
b = 9.3038 (2) Å
c = 15.6815 (3) Å
β = 111.065 (1)°
V = 1767.88 (7) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 293 K
0.30 × 0.20 × 0.20 mm

Data collection

Bruker Kappa-APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 1999)
T_{min} = 0.970, T_{max} = 0.980
16178 measured reflections
3108 independent reflections
2763 reflections with $I > 2\sigma(I)$
R_{int} = 0.020

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.115
S = 1.18
3108 reflections
265 parameters
3 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.33 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Table 1
Selected bond and torsion angles (°).

C10—O1—C12	118.5 (3)	O3—C8—C9	116.2 (2)
C9—O2—C13	112.76 (19)	O2—C9—C10	120.8 (2)
C8—O3—C14	117.6 (2)	O2—C9—C8	119.8 (2)
C1—N4—C2	119.80 (18)	O1—C10—C9	114.9 (2)
O3—C8—C7	124.0 (2)	O1—C10—C11	124.2 (2)
C12—O1—C10—C11	18.1 (4)	C14—O3—C8—C7	−0.6 (3)
C13—O2—C9—C8	−96.4 (3)		

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

*Cg*2 denotes the centroid of the C6–C11 ring.

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N1—H1*A*$\cdots$O4^{i}	0.91 (3)	1.91 (3)	2.810 (3)	173 (3)
N1—H1*B*$\cdots$O5^{ii}	0.89 (3)	1.93 (3)	2.798 (3)	165 (2)
N2—H2*A*$\cdots$O4	0.90 (3)	1.99 (3)	2.882 (3)	173 (3)
N2—H2*B*$\cdots$O2^{iii}	0.90 (3)	2.22 (3)	3.081 (3)	159 (2)
N4—H4$\cdots$O5^{i}	0.88 (3)	1.84 (3)	2.712 (2)	176 (3)
O6—H6$\cdots$N3	0.82	2.09	2.896 (5)	166
C13—H13*C*$\cdots$O6^{iv}	0.96	2.48	2.929 (4)	109
C14—H14*A*$\cdots$*Cg*2^{v}	0.96	2.97	3.546 (3)	119

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

The acid component is disordered about a crystallographic centre of inversion, so that atom O6 is equally disordered over two sites. The distances of atoms H16*A* and H16*B* (the latter is disordered with atom O6) from C16 were restrained to 0.930 (2) Å and the displacement parameters of these two H atoms were fixed as $1.2U_{eq}$ of the carrier C atom taken from the previous refinement. H atoms attached to N atoms were located in difference maps and then refined isotropically. All other H atoms were treated as riding atoms, with O—H distances of 0.82 Å and C—H distances of 0.93–0.97 Å, and with U_{iso}(H) = kU_{eq}(parent C), where k = 1.5 for the methyl H atoms and 1.2 for the remaining H atoms. U_{iso}(H6) was fixed at the same value as that used for H16*A* and H16*B*.

Data collection: *APEX2* (Bruker–Nonius, 2004); cell refinement: *APEX2* and *SAINT-Plus* (Bruker–Nonius, 2004); data reduction: *XPREP* in *SAINT-Plus*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3265). Services for accessing these data are described at the back of the journal.

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