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N—H···O and O—H···O hydrogen bonds in crystal engineering: trimethoprim hydrogen glutarate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.048
wR factor = 0.140
Data-to-parameter ratio = 8.8

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

In the title compound, $C_{14}H_{19}N_4O_3^+\cdot C_5H_7O_4^-$, trimethoprim (TMP) is protonated. In the glutarate anion, one of the two carboxylic acid groups is deprotonated while the other exists as —COOH. The carboxyl group of the hydrogen glutarate ion makes a hydrogen-bonding pattern with N—H groups of the trimethoprim cation which is similar to the carboxylate group (of Asp-27 of DHFR)-trimethoprim cation interaction observed in trimethoprim–DHFR complexes. Two TMP cations and two hydrogen glutarate anions are arranged about an inversion center so that complementary DDAA arrays of quadruple hydrogen-bonding patterns are formed. The hydrogen glutarate ion bridges the 2-amino and 4-amino groups of TMP. There are also carboxyl–carboxylate hydrogen-bonding interactions involving a head-to-tail arrangement of hydrogen glutarate ions which leads to hydrogen-bonded supramolecular ribbons.

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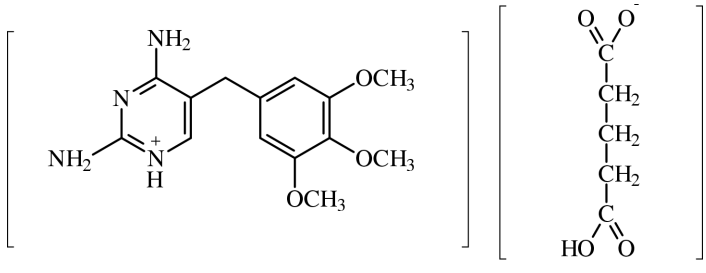
Comment

Trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine] is a well known antifolate drug. It is a potent inhibitor of bacterial dihydrofolate reductase (DHFR) but is less effective against human DHFR. The present study has been undertaken as a part of our research program to explore the hydrogen-bonding patterns involving aminopyrimidines–carboxyl(ate) interactions. Such systems offer a network of O—H···O, N—H···O and N—H···N hydrogen bonds which can be exploited for crystal engineering (Kuduva *et al.*, 2001). The crystal structures of trimethoprim acetate (Bryan *et al.*, 1987), trimethoprim monobenzoate (Giuseppetti *et al.*, 1984), trimethoprim monobenzoate–benzoic acid (1/1), form I (Giuseppetti *et al.*, 1988), trimethoprim monobenzoate–benzoic acid (1/1), form II (Bettinetti *et al.*, 1985), dichlorobis(trimethoprim)zinc(II) and dichloro(trimethoprim) cadmium(II) methanol solvate (Simo *et al.*, 2000) are known.



(I)

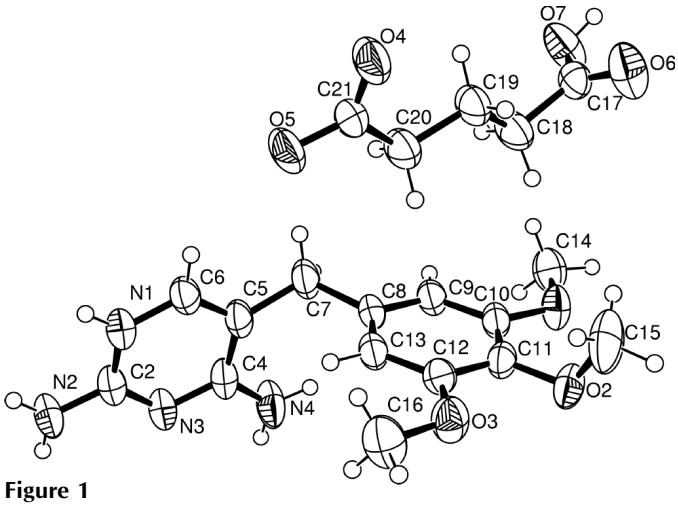


Figure 1
An *ORTEP*II (Johnson, 1977) view of the title molecule with displacement ellipsoids at the 50% probability level.

We have reported earlier the hydrogen-bonding patterns in the crystal structures of trimethoprim formate (Umadevi & Muthiah, 1994), trimethoprim perchlorate (Umadevi, 1997), trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996), trimethoprim nitrate (Murugesan & Muthiah, 1997), dibromodiaquabis(trimethoprim)cadmium(II) monohydrate (Muthiah & Robert,1999), trimethoprim maleate (Prabakaran *et al.*, 2001) and cytosinium hydrogen maleate (Balasubramanian *et al.*, 1996).

The title drug, (I), is protonated at N1, as evident from the increase of the internal angle at N1 from 115.46 (5)° in TMP (Koetzle & Williams, 1976) to 120.61 (16)° in the present study. The conformation of the trimethoprim cation is described by the two torsion angles τ_1(C4—C5—C7—C8) of −72.8 (3) and τ_1(C5—C7—C8—C9) of 148.4 (2)°. The phenyl ring makes a dihedral angle of 85.64 (9)° with the pyrimidine plane. This is in agreement with the range of previously reported values, *viz.* 93.8 (1)° for trimethoprim nitrate (Murugesan & Muthiah, 1997) and 93.2 (1)° for trimethoprim maleate (Prabakaran *et al.*, 2001).

The backbone conformation of the hydrogen glutarate anion can be described by the two torsion angles C17—C18—C19—C20 of 172.29 (19) and C18—C19—C20—C21 of −172.7 (2)°. As evident from the torsion angles, the backbone is in a fully extended conformation (Saraswathi *et al.*, 2001). Of the two carboxyl groups, one is deprotonated while the other is not.

The geometries of the hydrogen-bonding interactions are given in Table 2. The carboxyl group of the hydrogen glutarate ion makes a fork-like hydrogen-bonding pattern with N1—H and N2—H 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, 1989, 1990). Two TMP cations and two hydrogen glutarate anions are arranged about an inversion center so that the complementary *DDAA* arrays of quadruple hydrogen-bonding patterns are formed (*D* stands for hydrogen-bond donor and *A* stands for hydrogen-bond acceptor in an array) (Sijbesma *et al.*, 1997). This pattern is shown in Fig. 2.

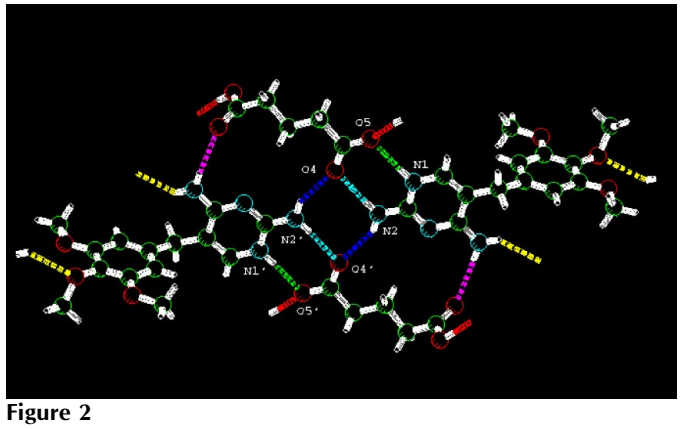


Figure 2
View of the complementary *DDAA* arrays of quadruple hydrogen-bonding patterns.

The N4—H and N2—H amino groups of the TMP cation are hydrogen bonded to the carboxyl and carboxylate ends, respectively, of the same hydrogen glutarate ion. Thus, the hydrogen glutarate ion bridges the 2-amino and 4-amino groups of TMP. The 2-amino group also forms a hydrogen bond with the O atom of the carboxylate group, whereas in the drug–enzyme complex, this amino group is hydrogen bonded to a water molecule (Kuyper, 1989, 1990). Another H atom at N4 makes a hydrogen bond with the methoxy-O atom of a neighboring molecule. The carboxyl group (O4—H) of the hydrogen glutarate ion is hydrogen bonded to the carboxylate group (O7) of the neighboring hydrogen glutarate ion. This type of carboxyl–carboxylate interaction has been observed in the crystal structures of many acid salts and proteins (Sawyer & James, 1982). This head-to-tail arrangement of the hydrogen glutarate ions leads to hydrogen-bonded supramolecular ribbons (Sarasvathi *et al.*, 2001) (Fig. 3).

Thus, in the crystal structure of trimethoprim hydrogen glutarate, the following three well established hydrogen-bonded motifs are simultaneously present: (i) fork-like interaction of a carboxylate moiety with protonated aminopyrimidine, (ii) the complementary DDAA arrays of quadruple hydrogen bonding, and (iii) carboxyl–carboxylate interactions leading to supramolecular ribbons.

Experimental

Trimethoprim (obtained as a gift from Shilpa Antibiotics Ltd.) and glutaric acid (E-Merck Ltd, India) in 1:1 molar ratio were dissolved in warm water and crystallized by slow evaporation.

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot C_5H_7O_4^-$
M_r = 422.44
Triclinic, $P\overline{1}$
a = 12.017 (2) Å
b = 10.090 (3) Å
c = 8.804 (4) Å
α = 84.430 (3)°
β = 94.900 (3)°
γ = 104.590 (3)°
V = 1026.1 (6) Å^3
Z = 2
D_x = 1.367 Mg m^{-3}
Cu Kα radiation
Cell parameters from 40 reflections
θ = 3.8–70.9°
μ = 0.89 mm^{-1}
T = 293 (2) K
Thin plate, pale yellow
0.25 × 0.22 × 0.19 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
3203 measured reflections
3203 independent reflections
3201 reflections with $I > 2\sigma(I)$
$\theta_{max} = 70.9°$
$h = -14 \rightarrow 14$
$k = -12 \rightarrow 12$
$l = 0 \rightarrow 10$
1 standard reflection
frequency: 100 min
intensity decay: negligible

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.048$
$wR(F^2) = 0.140$
$S = 1.11$
3203 reflections
363 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.0866P)^2 + 0.1793P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.21$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C10	1.364 (2)	O6—C17	1.196 (3)
O1—C14	1.411 (3)	O7—C17	1.296 (3)
O2—C11	1.385 (2)	N1—C6	1.368 (2)
O2—C15	1.421 (3)	N1—C2	1.359 (3)
O3—C12	1.362 (3)	N2—C2	1.338 (2)
O3—C16	1.417 (3)	N3—C2	1.321 (3)
O4—C21	1.239 (3)	N3—C4	1.350 (2)
O5—C21	1.272 (2)	N4—C4	1.317 (3)
C10—O1—C14	116.40 (16)	O1—C10—C11	115.66 (17)
C11—O2—C15	113.33 (19)	O1—C10—C9	124.08 (17)
C12—O3—C16	117.51 (17)	O2—C11—C10	120.07 (16)
C2—N1—C6	120.61 (16)	O2—C11—C12	120.57 (17)
C2—N3—C4	117.39 (17)	O3—C12—C11	114.75 (17)
N2—C2—N3	119.60 (18)	O3—C12—C13	125.00 (16)
N1—C2—N3	122.10 (16)	O6—C17—O7	121.99 (18)
N1—C2—N2	118.30 (17)	O6—C17—C18	125.14 (19)
N3—C4—C5	123.49 (17)	O7—C17—C18	112.85 (18)
N3—C4—N4	115.62 (18)	O4—C21—C20	119.42 (16)
N4—C4—C5	120.87 (17)	O5—C21—C20	116.42 (17)
N1—C6—C5	121.36 (18)	O4—C21—O5	124.11 (18)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O5^{i}	0.86	1.86	2.720 (3)	174
N2—H2*A*···O4^{ii}	0.86	2.13	2.890 (3)	148
N2—H2*B*···O4^{i}	0.86	1.94	2.798 (3)	173
N4—H4*A*···O6^{ii}	0.86	2.21	3.037 (3)	162
N4—H4*B*···O2^{iii}	0.86	2.40	3.053 (3)	134
O7—H7···O5^{iv}	0.82	1.82	2.616 (3)	164
C6—H6···O7^{v}	0.93	2.59	3.109 (3)	115
C16—H16*B*···O6^{vi}	0.96	2.40	3.355 (4)	173

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

Data collection: *MolEN* (Fair, 1990); cell refinement: *MolEN*; data reduction: *MolEN*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1977) and *PLATON* (Spek, 1997); software used to prepare material for publication: *PLATON*.

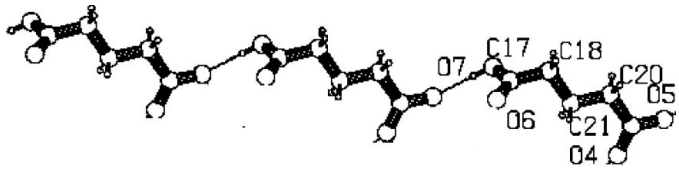


Figure 3
Arrangement of hydrogen-bonded supramolecular ribbons of hydrogen glutarate ions.

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