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Hydrogen-Bonding Patterns in Trimethoprim Nitrate, an Antifolate Drug

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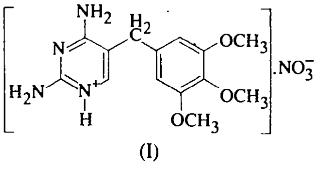
Abstract

In the crystal structure of trimethoprim nitrate [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidin-1-ium nitrate], $C_{14}H_{19}N_4O_3^+.NO_3^-$, the trimethoprim moiety is protonated at the N1 atom. The nitrate anion forms a fork-like hydrogen-bonded pattern with the trimethoprim cation which is similar to the carboxylate–trimethoprim cation interaction observed in the trimethoprim cation–dihydrofolate reductase complex. The pyrimidine ring makes a dihedral angle of 93.8 (1)° with the phenyl ring.

Comment

Trimethoprim is a widely used antibacterial agent (Finland, Kass & Plat, 1982). It is very effective since it has differential affinity for bacterial DHFR (dihydrofolate reductase) *versus* human DHFR. The drug in its N1-protonated form inhibits DHFR. The present study was undertaken in order to understand the conformation and hydrogen-bonding patterns of the protonated trimethoprim moiety in a variety of crystalline and molecular environments. Crystal structures of trimethoprim acetate (Haltiwanger, 1971), trimethoprim monobenzoate (Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1984) and trimethoprim monobenzoate–benzoic acid 1:1 complex (Bettinetti, Giordano, La Manna, Giuseppetti & Tadini, 1985) are known. As part of our work on trimethoprim, we have recently solved the crystal structures of trimethoprim formate (Umadevi & Muthiah, 1994), trimethoprim perchlorate (Umadevi & Muthiah, 1996) and trimethoprim salicylate monohydrate (Murugesan & Muthiah, 1996). The title drug, (I), is protonated at N1, as is evident from the increase in the ring angle at N1 from 115.46 (5)° in trimethoprim (Koetzle & Williams, 1976) to 119.8 (2)° in the present study. An *ORTEP* (Johnson, 1965) view of the molecule is given in Fig. 1.



(I)

The conformation of the trimethoprim cation is described by the two torsion angles C4—C5—C7—C1′ of 77.1 (3)° and C5—C7—C1′–C2′ of −158.8 (2)°. The phenyl ring makes a dihedral angle of 93.8 (1)° with the pyrimidine plane. This value is in agreement with an angle of 96.0 (1)° reported for trimethoprim monobenzoate (Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1984).

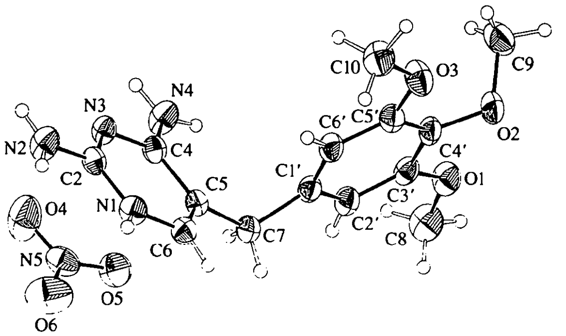


Fig. 1. An *ORTEP* (Johnson, 1965) view of the title molecule with displacement ellipsoids at the 50% probability level.

The geometry of the hydrogen bonds are given in Table 2. The nitrate anion forms a fork-like hydrogen-bonded pattern with the trimethoprim cation which is similar to the carboxylate–trimethoprim cation interaction observed in the trimethoprim cation–dihydrofolate reductase complex (Kuyper, 1989, 1990). The amino group at C2 also forms a hydrogen bond with the O atom of one of the methoxy groups of a neighboring molecule, whereas in the drug–enzyme complex, this amino group is hydrogen bonded to a water molecule (Kuyper, 1989, 1990).

Experimental

Trimethoprim (obtained as a gift from Shilpa Antibiotics Ltd) was dissolved in dilute nitric acid and crystallized from the mother liquor.

Crystal data

$C_{14}H_{19}N_4O_3^+.NO_3^-$
$M_r = 353.34$
Triclinic
$P\bar{1}$
$a = 8.4247\ (7)$ Å
$b = 9.4820\ (10)$ Å
$c = 10.6340\ (10)$ Å
$\alpha = 93.565\ (10)°$
$\beta = 104.462\ (9)°$
$\gamma = 101.452\ (8)°$
$V = 800.57\ (13)$ Å^3
$Z = 2$
$D_x = 1.466$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.7107$ Å
Cell parameters from 25 reflections
$\theta = 10–20°$
$\mu = 0.116$ mm^{-1}
$T = 293\ (2)$ K
Block
1.0 × 0.6 × 0.4 mm
Light yellow

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Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
3732 measured reflections
3487 independent reflections
2740 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.0131$
$\theta_{\rm max} = 26.91°$
$h = 0 \rightarrow 10$
$k = -12 \rightarrow 11$
$l = -13 \rightarrow 13$
3 standard reflections
frequency: 60 min
intensity decay: negligible

Refinement

Refinement on F^2
$R(F) = 0.0503$
$wR(F^2) = 0.1297$
$S = 1.134$
3487 reflections
302 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0507P)^2 + 0.3918P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} = 0.034$
$\Delta\rho_{\rm max} = 0.218$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.274$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

N1—C2	1.354 (3)	C4—C5	1.435 (3)
N1—C6	1.364 (3)	C5—C6	1.343 (3)
C2—N3	1.326 (2)	C5—C7	1.500 (3)
C2—N2	1.329 (3)	C7—C1′	1.518 (3)
N3—C4	1.347 (2)	C3′—O1	1.377 (2)
C4—N4	1.322 (2)	O1—C8	1.425 (3)
C2—N1—C6	119.8 (2)	N3—C4—C5	122.2 (2)
N3—C2—N2	120.3 (2)	C6—C5—C4	115.9 (2)
N3—C2—N1	122.4 (2)	C6—C5—C7	121.7 (2)
N2—C2—N1	117.3 (2)	C5—C7—C1′	117.9 (2)
C2—N3—C4	118.1 (2)	O1—C3′—C2′	123.8 (2)
N4—C4—N3	116.9 (2)	C3′—O1—C8	117.7 (2)
N4—C4—C5	120.9 (2)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O5	0.89 (3)	1.91 (3)	2.798 (2)	175 (3)
N2—H2A···O4	0.93 (3)	1.91 (3)	2.827 (3)	171 (2)
N2—H2B···O1$^{\rm i}$	0.85 (3)	2.21 (3)	2.979 (2)	150 (3)

Symmetry code: (i) $1 + x, y, 1 + z$.

H atoms were located from a difference Fourier map and their coordinates and isotropic displacement parameters were refined.

Data collection: *MolEN* (Fair, 1990). Cell refinement: *MolEN*. Data reduction: *MolEN*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1965). Software used to prepare material for publication: *SHELXL*93 and *PARST* (Nardelli, 1983).

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Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: VJ1045). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1-(2-Fluorophenyl)- and 1-(3-Fluorophenyl)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole

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Abstract

In the solid-state structures of the title compounds, $C_{15}H_{11}FN_2S$, with 2-fluorophenyl and 3-fluorophenyl substituents, the thiazole ring shows the typical envelope conformation, while the benzimidazole system is planar.

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