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A 2:1 sulfamethazine–theophylline cocrystal exhibiting two tautomers of sulfamethazine

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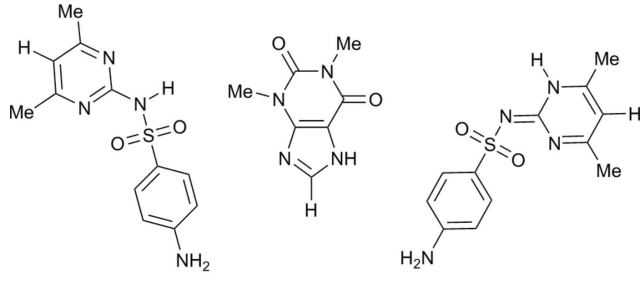
In the title cocrystal, 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide–4-amino-*N*-(4,6-dimethyl-1,2-dihydropyrimidin-2-ylidene)benzenesulfonamide–1,3-dimethyl-7*H*-purine-2,6-dione (1/1/1), $C_7H_8N_4O_2\cdot 2C_{12}H_{14}N_4O_2S$, two sulfamethazine molecules cocrystallize with a single molecule of theophylline. Each molecule of sulfamethazine forms a hydrogen-bonded ribbon along the *b* axis crosslinked by further hydrogen bonding. The two sulfamethazine molecules exhibit a hydrogen-shift isomerization so that the crystal structure contains both tautomeric forms. Calculation of their relative energies showed that the tautomer protonated at the chain N atom is considerably more stable than the one where an N atom in the aromatic ring is protonated. The latter, here observed for the first time, is stabilized through strong intermolecular interactions with the theophylline molecules.

Comment

Cocrystals have been increasingly recognized as an attractive alternative to solid forms of drug products (Vishweshwar *et al.*, 2006). The design of cocrystals containing an active pharmaceutical ingredient (API) with an excipient (Basavoju *et al.*, 2008) or another component (Childs & Hardcastle, 2007; Bucar *et al.*, 2007) can provide an opportunity to design drug-delivery systems at the molecular level. Further, it can improve the pharmaceutical properties of the API (Fernandez-Lopez *et al.*, 2001).

Theophylline is often used in the treatment of respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD) (Van Andel *et al.*, 1999). A derivative of xanthine, theophylline is both weakly acidic and weakly basic, with corresponding pK_a and pK_b values of 8.6 and 11.5, respectively (Cohen, 1975). Theophylline is expected to have a high potential for cocrystal formation due to the C═O and N—H sites in the molecule (Trask *et al.*, 2006). Indeed, Childs *et al.* (2007) have summarized the complexes formed between theophylline and both acids (*e.g.* oxalic acid, malonic acid, gentisic acid, sulfathiazole, acetaminophen, *etc.*) and bases (*e.g.* urea, benzylamine, phenobarbital, *etc.*). Sulfamethazine is a sulfonamide drug that has been used to treat bacterial diseases in human and veterinary medicine and to promote growth in cattle, sheep, pigs and poultry. Sulfamethazine is known to form cocrystals with aspirin, benzoic acid, trimethoprim and 4-aminosalicylic acid, among others (Caira, 1992, 2007; Caira *et al.*, 1995; Zhang *et al.*, 2007).

In this work, sulfamethazine and theophylline have been cocrystallized in a 2:1 ratio to yield a cocrystal, (I), containing theophylline (hereafter labelled THEO) and two tautomers of sulfamethazine (hereafter labelled S_{LET} for the low-energy tautomer and S_{HET} for the high-energy tautomer). Although observation of both tautomeric forms of a molecule in the solid state is still rare, it is more probable if the tautomers have similar energies. This is highlighted in a paper on tautomers in the Cambridge Structural Database (Cruz-Cabeza & Groom, 2011). In the case of sulfamethazine, however, this is the first time the high-energy tautomer has been observed. Sulfamethazine has been crystallized as a pure substance (Basak *et al.*, 1983; Tiwari *et al.*, 1984), as well as cocrystallizing with carboxylic acids and other solvates, but in every case it was the low-energy stable tautomer that was observed. The observation of both forms in the same structure is rare, especially because of the high energy difference between the two tautomers (see below).



S_{LET} THEO S_{HET}

(I)

The molecular structure of each component in (I) is shown in Fig. 1. The local structure of the theophylline molecule is unremarkable, yielding a planar molecule [mean deviation = 0.015 (3) Å]. The two sulfamethazine molecules differ in their geometry and, most importantly, in the position of one of the H atoms. All H atoms involved in hydrogen bonding were located in a difference map and allowed to refine. S_{HET} has the H atom on atom N17 of the ring, whereas S_{LET} has the H atom on atom N31 in the chain. As expected, this affects the bond distances (Table 1), most notably that the chain N atom has shorter bonds to both S and C atoms in S_{HET}. In contrast, the longer intra-ring bond from the bridgehead C atom C12 to the H-bearing N atom N17 in S_{HET} should be noted. Literature data for the structure of sulfamethazine, representative of the stable tautomer, have been included in the table for comparison. Also reported are the torsion angle and interplanar

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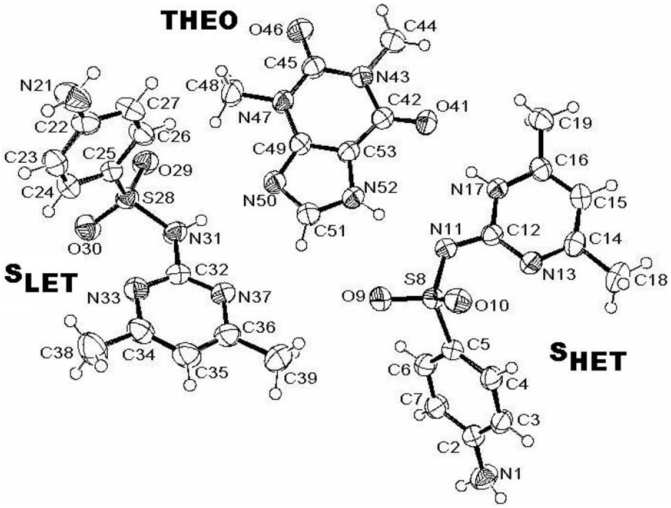

Figure 1
The molecular structures of the two interacting sulfamethazine tautomers (S_{LET} and S_{HET}) and one theophylline (THEO) molecule in the cocrystal, (I). Displacement ellipsoids are drawn at the 50% probability level. Disordered H atoms of methyl groups (C38, C44 and C48) have been omitted for clarity.

spacing but, although they differ between the low- and high-energy tautomers, no trends are observed compared with the published structures. The terminal NH_2 group also shows some small differences between the two tautomers of sulfamethazine. S_{HET} has a slightly pyramidyl shape at the terminal atom N1 [sum of internal angles = 347 (1)°], but S_{LET} is almost planar, with the sum of the internal angles for atom N21 being 358 (1)°.

The molecular packing of the cocrystal is presented in Figs. 2 and 3, and the geometry of the hydrogen-bonding interactions is given in Table 2. Fig. 2 is a view approximately down the *c* axis, showing two distinct ribbons of sulfamethazine (labelled S_{LET} and S_{HET}) extending along the *b* axis; S_{HET} tautomers are linked together by hydrogen bond N1—H1*B*···O10^{i} and S_{LET} are linked together *via* hydrogen bond N21—H21*A*···O30^{ii} (see Table 2 for symmetry codes). The two ribbons form an extended chain *via* a hydrogen bond between the amine and the sulfoxide of the same sulfamethazine. The theophylline forms a close interaction with S_{HET}, linked together by two hydrogen bonds, *viz.* N17—H17*A*···O41 and N52—H52*A*···N11, forming a nine-membered ring. There are three more hydrogen-bonding interactions, which are shown more clearly in Fig. 3. In this case, the view is approximately down the *b* axis. There are three hydrogen-bonding interactions involving THEO, the two discussed above forming the interaction with S_{HET}, and the other side of the theophylline being linked to S_{LET} *via* N31—H31*A*···N50^{iv}. The two ribbons are thus linked to each other through THEO, as well as being linked directly to each other through two other interactions. Ribbon S_{LET} connects directly to ribbon S_{HET} *via* N21—H21*B*···O10^{iii}. The final interaction is the weakest but the most interesting. Atom H1A does not participate in a conventional hydrogen bond but points towards the centroid (*Cg*) of aromatic ring C22–C27 of S_{LET} (Fig. 3). Thus, the acceptor is the electron density of an aromatic ring, essentially a very weak N—H···π interaction. This link between the two ribbons, the last in Table 2 (entry N1—H1*A*···*Cg*^{i}), is certainly a long interaction but still a fundamental part of the overall molecular packing scheme.

The S_{LET} tautomer (protonated at the chain N atom) was calculated by density functional theory (DFT) methods to be 33.2 kJ mol^{-1} more stable than the S_{HET} tautomer (protonated at the aromatic ring) at the B3LYP/6-311++G** level of theory and using a polarizable continuum model (see *Experimental*). This large tautomeric energy difference is probably due to the fact that, by protonating the aromatic N

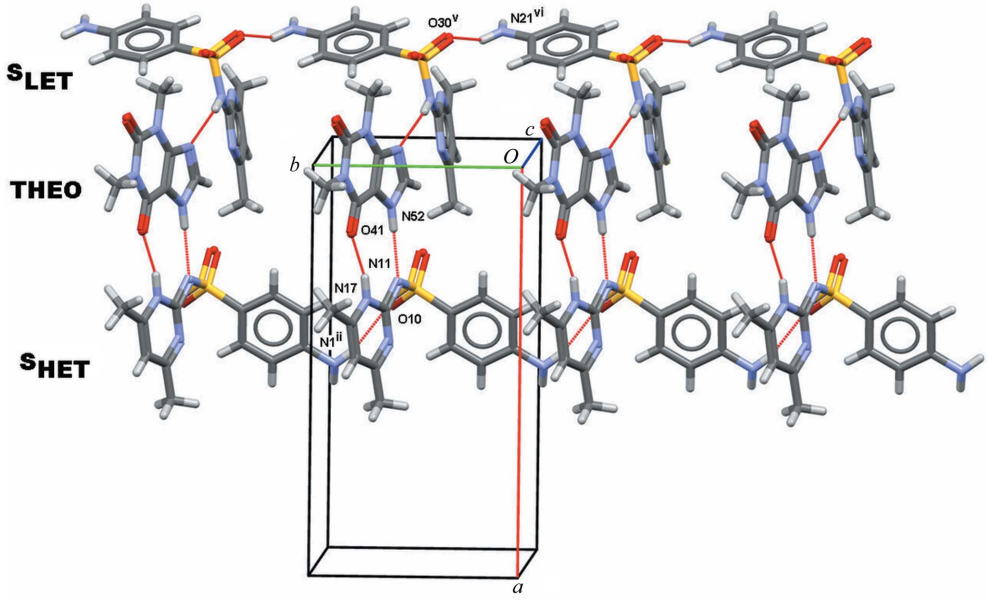

Figure 2
A molecular packing diagram, viewed approximately down the *c* axis, showing the ribbons of sulfamethazine (S_{LET} and S_{HET}) along the *b* axis. Atoms involved in hydrogen bonding are labelled and hydrogen bonds are indicated by thin lines. Disordered H atoms of methyl groups (C38, C44 and C48) have been omitted for clarity. [Symmetry codes: (ii) *x*, *y* + 1, *z*; (v) *x* − 1, *y*, *z*; (vi) *x* − 1, *y* − 1, *z*.]

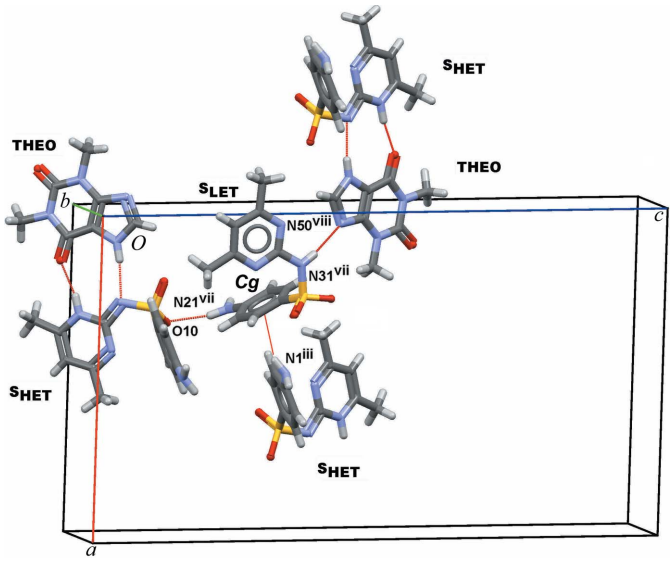

Figure 3
A molecular packing diagram, viewed approximately down the *b* axis, showing the hydrogen-bonding network linking the two ribbons of sulfamethazine together. Atoms involved in hydrogen bonding are labelled and hydrogen bonds are indicated by thin or dotted lines. Disordered H atoms of methyl groups (C38, C44 and C48) have been omitted for clarity. [Symmetry codes: (iii) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (vii) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (viii) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$.]

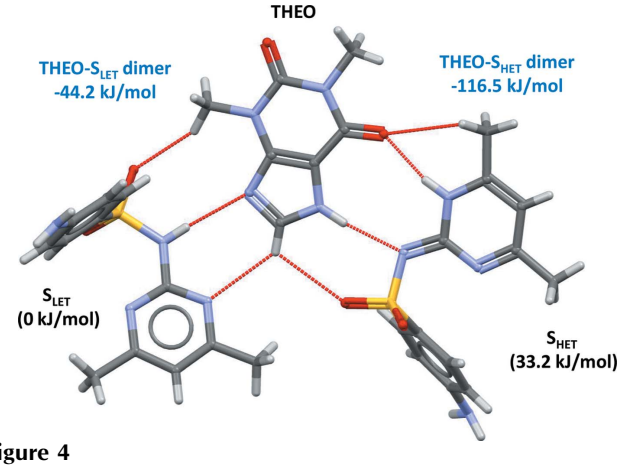

Figure 4
The relative molecular energies of the two tautomers (S_{LET} and S_{HET}) and the interaction energies of the THEO–S_{LET} and THEO–S_{HET} dimers.

atom, some aromaticity of the pyrimidine ring is lost. The observation of pairs of tautomers in the solid state with energy differences greater than 30 kJ mol^{-1} is still uncommon in crystal structures (Cruz-Cabeza & Groom, 2011). In fact, there are 16 crystal structures containing sulfamethazine in the Cambridge Structural Database (Version 5.32, November 2010; Allen, 2002) and all of them crystallize as the most stable S_{LET} tautomer. This energy penalty is compensated for by the much better interaction between S_{HET} and THEO (which involves two strong hydrogen bonds and two weak ones; Fig. 4). The *PIXEL* interaction energies for the THEO–S_{HET} and THEO–S_{LET} dimers were calculated to be −116.5 and −44.2 kJ mol^{-1}, respectively. Clearly, the interaction between S_{HET} and THEO and the extended hydrogen-bonding structure of (I) play an important role in the stabilization of the high-energy tautomer of sulfamethazine, reported here for the first time.

In summary, X-ray diffraction shows that a three-component adduct is formed in (I) between sulfamethazine and theophylline in a 2:1 ratio. In the cocrystal, extensive hydrogen bonding is observed, most notably involving the theophylline which forms significant hydrogen-bonding interactions to both the sulfamethazine tautomers. The strong interaction between theophylline and the high-energy S_{HET} tautomer of sulfamethazine, as verified by *PIXEL* calculations, has made the observation of the latter in the crystal structure possible for the first time.

Experimental

Sulfamethazine, theophylline and methanol were purchased from Sigma–Aldrich (Milwaukee, Wisconsin, USA) and were used without further purification. A mixture of sulfamethazine (0.056 g, 0.2 mmol) and theophylline (0.018 g, 0.1 mmol) was stirred in methanol (50 ml) with slight warming until dissolution was complete. The filtered solution was kept in a fume hood at room temperature and after several days, yellow crystals of (I) were obtained.

The relative stability of the two tautomers, S_{LET} and S_{HET}, was calculated using DFT methods with the program *GAUSSIAN03* (Frisch *et al.*, 2003). The X-ray molecular geometries for S_{LET} and S_{HET} were energy minimized in the gas phase at the B3LYP/6-311++G** level of theory, with the torsion angles constrained to the experimental values. The energy-minimized molecular geometries were then used for a single-point energy calculation at the same level of theory but using a polarizable continuum model (Cossi *et al.*, 2002) with a dielectric constant $\varepsilon = 3$, typical for organic crystals (Cooper *et al.*, 2008). With this simple model, we took into account the effect of the crystalline environment on the relative stability of the two tautomers.

For the calculation of the intermolecular interactions, we used the *PIXEL* method as part of the *OPIX* program developed by Gavezzotti (2003, 2007). We calculated the intermolecular interaction energies of the THEO–S_{LET} and THEO–S_{HET} dimers, as observed in the crystal structure (see Fig. 4). The geometry of the heavy atoms in the two dimers was taken from the crystal structure and H-atom positions were normalized using the program *Mercury* (Version 2.2; Macrae *et al.*, 2008). Electron densities were calculated using *GAUSSIAN03* at the MP2/6-31G** level of theory. The molecular electron density for each molecule was output in a three-dimensional grid with steps of 0.08 Å.

Crystal data

$C_7H_8N_4O_2\cdot 2C_{12}H_{14}N_4O_2S$
$M_r = 736.84$
Monoclinic, $P2_1/c$
$a = 15.8827$ (6) Å
$b = 8.1004$ (3) Å
$c = 27.7913$ (10) Å
$\beta = 91.835$ (2)°
$V = 3573.7$ (2) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.21$ mm^{-1}
$T = 293$ K
0.51 × 0.32 × 0.21 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2009)
$T_{min} = 0.900$, $T_{max} = 0.957$
46924 measured reflections
7364 independent reflections
5968 reflections with $I > 2\sigma(I)$
$R_{int} = 0.024$

Table 1
Selected bond distances and angles (Å, °).

	S—N	N—C	C—N[b]	C—S—N—C[c]	Interplanar angle
S_{HET}	1.6176 (15)	1.338 (2)	1.366 (2)	−68.34 (17)	62.9 (2)
S_{LET}	1.6424 (16)	1.401 (2)	1.331 (2)	61.43 (19)	86.0 (2)
Sulfamethazine[a]	1.632 (2)	1.412 (2)	1.343 (2)	−84.9 (2)	78.1 (2)

Reference: (*a*) Tiwari *et al.* (1984). Notes: (*b*) C12—N17 and C32—N37; (*c*) C5—S8—N11—C12 and C25—S28—N31—C32.

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.110$
$S = 1.03$
7364 reflections
487 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.29$ e Å^{-3}
$\Delta\rho_{min} = -0.41$ e Å^{-3}

Aromatic H atoms were positioned geometrically and refined using a riding model, with C—H = 0.93 Å and U_{iso}(H) = 1.2U_{eq}(C). Methyl H atoms were idealized with tetrahedral angles and refined as a rotating group, with C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C). Three of the methyl groups (C38, C44 and C48) were refined as idealized disordered methyl groups. The N-bound H atoms were located in a difference map and allowed to refine, with U_{iso}(H) = 1.2U_{eq}(C).

Data collection: *APEX2* (Bruker, 2009); cell refinement: *SAINT* (Bruker, 2009); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3166). Services for accessing these data are described at the back of the journal.

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

Cg is the centroid of the C22–C27 aromatic ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*B*···O10^{i}	0.87 (2)	2.25 (2)	3.097 (2)	163 (2)
N17—H17*A*···O41	0.88 (2)	1.92 (2)	2.780 (2)	165 (2)
N21—H21*A*···O30^{ii}	0.86 (2)	2.31 (2)	3.008 (2)	137 (2)
N21—H21*B*···O10^{iii}	0.87 (2)	2.17 (2)	3.017 (2)	167 (2)
N31—H31*A*···N50^{iv}	0.83 (2)	2.31 (2)	3.131 (2)	168 (2)
N52—H52*A*···N11	0.87 (2)	2.09 (2)	2.948 (2)	172 (2)
N1—H1*A*···*Cg*^{i}	0.88 (2)	2.97 (2)	3.755 (2)	149 (2)

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

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