Similar sulfonamides with different crystal structures: sulfasymazine and sulfatriazine

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The crystal structures of 4-amino-N-(4,6-diethyl-1,3,5-triazin-2-yl)benzenesulfonamide, $C_{13}H_{17}N_5O_2S$, and 4-amino-N-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzenesulfonamide, $C_{11}H_{13}N_5O_4S$, also known as sulfasymazine and sulfatriazine, respectively, are dominated by hydrogen-bond interactions. All three potential hydrogen-bond donors are employed in each case, resulting in a three-dimensional network for sulfasymazine, while an entirely different hydrogen-bonded layer structure is obtained for sulfatriazine. This study demonstrates the versatile nature of the hydrogen-bonding capabilities in sulfonamides, even in structurally very similar molecules.

Comment

Structurally related compounds may form isomorphous crystal structures. For example, a series of 23 isostructural 4,4'-disubstituted benzenesulfonamidobenzenes have been identified (Gelbrich *et al.*, 2007). Sulfasymazine, (I), and sulfatriazine, (II), are closely related historical drugs of the sulfonamide family with antibacterial properties (Frisk & Hultman, 1965; Nabert-Bock, 1958). These compounds differ only in the nature of *R*, but their crystal structures display very different packing arrangements despite the fact that the O atoms in the methoxy substituents of (II) do not take part in hydrogen bonding.

(I) *R* = Et
(II) *R* = OMe
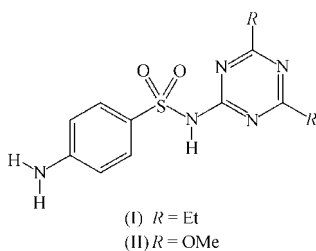
As can be seen in Figs. 1 and 2, the molecules of (I) and (II) adopt slightly different conformations. The S1—N2—C7—N3 torsion angle is 8.4 (3)° in sulfasymazine and 39.7 (3)° in

sulfatriazine, and the methoxy and ethyl substituents adopt different conformations relative to the triazine ring. It is well known that the low-energy conformations differ for ethyl and methoxy substituents on benzene rings, with ethyl substituents preferentially lying out of the plane (with a minimum energy when the C_{ar}—C_{ar}—C_{Et}—C_{Et} torsion angle is 90°) and methoxy substituents preferentially lying in-plane (Cinacchi & Prampolini, 2003). The N4—C8—C10—C11 and N4—C9—C12—C13 torsion angles in sulfasymazine are 128.1 (2) and 93.2 (2)°, respectively, whereas the equivalent torsion angles in sulfatriazine, N4—C8—O3—C10 and N4—C9—O4—C11, are 179.4 (2) and 1.2 (3)°, respectively; thus, the methoxy and ethyl groups adopt approximately the low-energy conformation expected for each compound.

Both compounds have three potential hydrogen-bond donors, all of which are employed in both structures. In sulfasymazine, (I), one of the amine H atoms is involved in a bifurcated hydrogen bond to both an N atom in the triazine ring and an O atom of the sulfone group. The crystal structure consists of an infinite three-dimensional hydrogen-bonded network, where each molecule is connected to five others. The two NH···N interactions result in layers which contain dimers
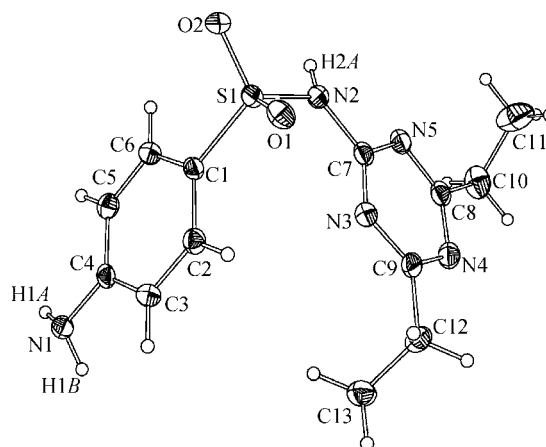

Figure 1
The molecular geometry of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level, with H atoms shown as spheres of arbitrary size.

Figure 2
The molecular geometry of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level, with H atoms shown as spheres of arbitrary size.
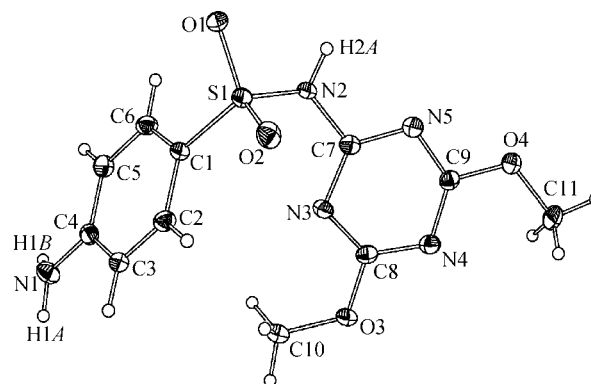
with a central $R_2^2(24)$ ring, and four such rings are linked into a larger ring, the graph-set notation (Bernstein *et al.*, 1995) of which is $R_6^6(32)$ (Fig. 3*a*). Each layer is connected to those above and below it by $NH_2\cdots O_2S$ hydrogen bonding (Fig. 3*b*) with rather long H···O distances (see Table 1). This type of hydrogen bonding, where each of the H atoms in the NH_2 group is hydrogen bonded to an O atom in the same sulfone group, is not novel but is unusual. In the Cambridge Structural Database (Version 5.29 of 2007; Allen, 2002), this feature is found in only one other N1-substituted sulfonamide, a 1:1 cocrystal of sulfadimidine with aspirin (Caira, 1992). A simplified hydrogen-bonding diagram of the overall three-dimensional hydrogen-bonded network is shown in Fig. 3(*c*), where each molecule has been collapsed to a point and hydrogen bonds are represented by arrows (which point to the hydrogen-bond acceptor). The rings are offset such that atom N3 lies directly above the centre of the other ring, and atoms
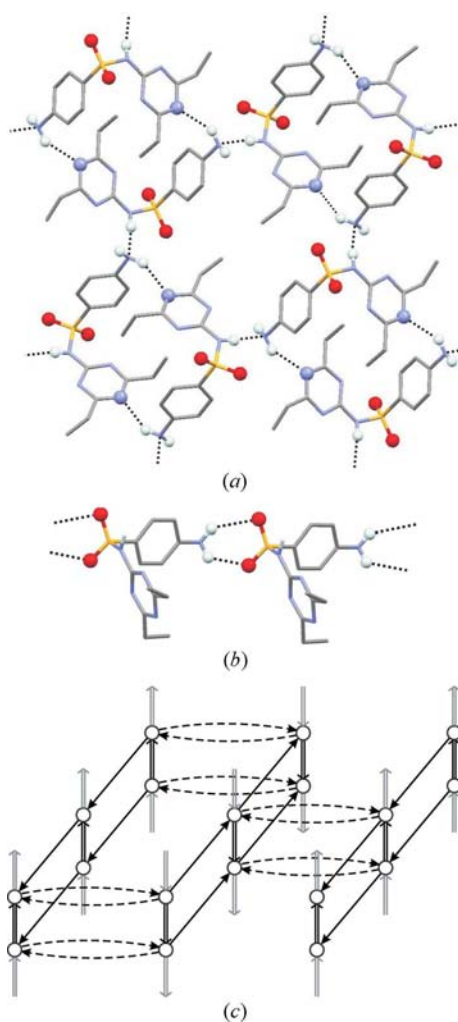
C9 and C7 eclipse one another. The shortest hydrogen bond in the structure is that between the amide H atom and amine N atom, at 2.029 (18) Å.

Sulfatriazine, (II), on the other hand, exhibits a two-dimensional hydrogen-bonding pattern which is composed of two layers of molecules. Each layer (Fig. 4*a*) consists of $R_4^4(26)$ rings that result from two interactions, both involving the NH_2 group as a hydrogen-bond donor, namely $HNH\cdots O{=}S$ and $HNH\cdots N_{triazine}$. The sulfonamide units of each layer are linked by dimeric $SNH\cdots O{=}S$ contacts to those of the other layer, resulting in $R_2^2(8)$ and $R_4^4(24)$ rings (Fig. 4*b*). A visualization of the overall double-layer topology, where each molecule of (II) is hydrogen bonded to five other molecules, is given in Fig. 4(*c*). The triazine rings, which are aligned parallel to each other on the outer faces of the double layer, slot together with the triazine rings of the adjacent double layer. The triazine rings do not, however, exhibit any π stacking; the

(a)

(b)

(c)

Figure 3
The hydrogen-bonded network of (I). (*a*) A detail of the two-dimensional structure arising from NH···N interactions, namely four $R_2^2(24)$ rings linked by a central $R_6^6(32)$ ring. (*b*) An $NH_2\cdots O_2S$ hydrogen-bonded chain with $R_2^2(6)$ rings. (*c*) The topology of the overall three-dimensional hydrogen-bonding network. Key: single solid arrow = NH···NH$_2$; double solid arrow = NH$_2\cdots$O$_2$S (two hydrogen bonds); dashed arrow = HNH···N$_{triazine}$.
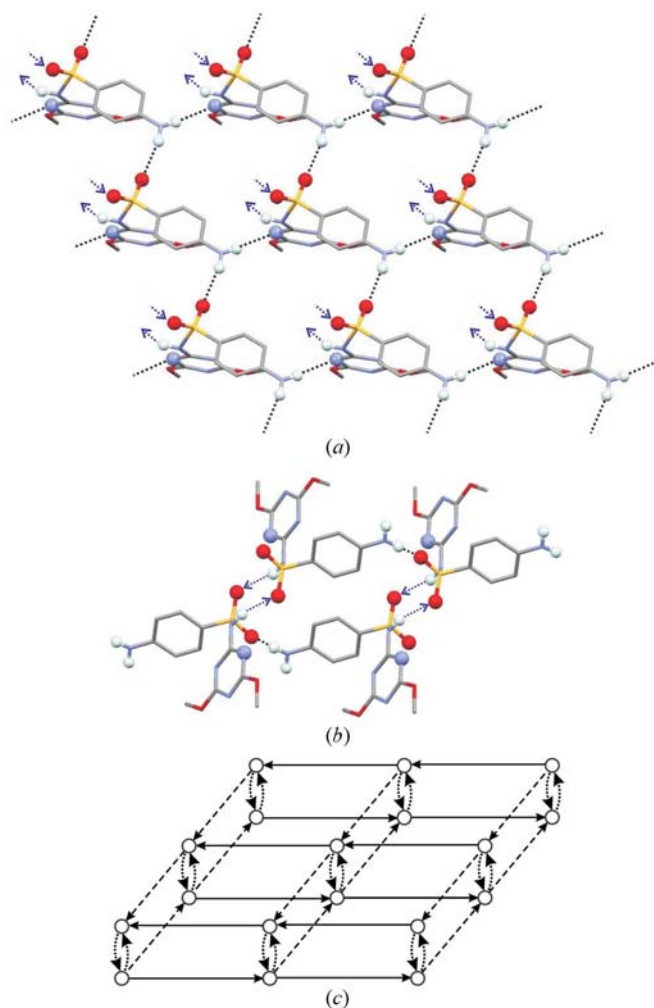

(a)

(b)

(c)

Figure 4
The hydrogen-bonded network of (II). (*a*) A single hydrogen-bonded layer held together by $R_4^4(26)$ rings. The hanging bonds marked with arrows indicate the dimeric link to the second layer. (*b*) Two pairs of molecules (top and bottom) belonging to different layers and connected by two dimeric $R_2^2(8)$ rings and one $R_4^4(24)$ ring. (*c*) The topology of the overall three-dimensional hydrogen-bonding network in (II). Key: solid arrow = HNH···O$=$S; dashed arrow = HNH···N$_{triazine}$; dotted arrow = SNH···O$=$S.

rings are offset by more than the width of a triazine ring. The sulfonamide dimer formed by the mutual donation of the amide H atom to the sulfonamide O atom of the other molecule is also seen in at least four other crystal structures of sulfonamides (Rambaud *et al.*, 1985; Giuseppetti *et al.*, 1977; Patel *et al.*, 1983; Liu *et al.*, 1994), plus a series of isomorphous crystal structures of 23 related sulfonamides (Gelbrich *et al.*, 2007).

Polymorphism in sulfonamides is a well known phenomenon, and one reason for this is the number of possible combinations between potential hydrogen-bond donor and acceptor groups. Thermomicroscopic analysis of pure sulfasymazine showed the substance to melt without change at 461–463 K. Sulfatriazine showed decomposition upon melting at 442 K, also without previous transformation. However, for sulfatriazine, two crystal morphologies with different melting points have been observed, namely needles and rods (405–408 K), and rhombuses and prisms (431–439 K) (Kuhnert-Brandstätter *et al.*, 1970), in addition to the monohydrate which is present in the commercial product. From hot-stage microscopy experiments we have confirmed the existence of needles that melt at 412 K, but we did not obtain single crystals of this form. Thus, the possibility of isostructural polymorphs of (I) and (II) cannot be discounted, although this would probably require the energy of a higher conformation of either the methoxy or the ethyl groups being overcome.

Experimental

Sulfasymazine was supplied by Lederle (now Wyeth–Lederle Pharma). Single crystals suitable for diffraction were prepared by slowly cooling a saturated acetonitrile solution of the commercial product. Sulfatriazine monohydrate was supplied by Stickstoffwerke Linz; single crystals of anhydrous sulfatriazine were prepared by dissolving sulfatriazine monohydrate in acetonitrile and allowing the solution to evaporate slowly to dryness.

Compound (I)

Crystal data

$C_{13}H_{17}N_5O_2S$	$V = 1444.42$ (6) Å^3
$M_r = 307.38$	$Z = 4$
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation
$a = 9.3257$ (2) Å	$\mu = 0.24$ mm^{-1}
$b = 16.7918$ (4) Å	$T = 120$ (2) K
$c = 9.8600$ (2) Å	$0.20 \times 0.20 \times 0.20$ mm
$\beta = 110.693$ (1)°	

Data collection

Bruker–Nonius KappaCCD diffractometer	17818 measured reflections
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2007)	2805 independent reflections
	2342 reflections with $I > 2\sigma(I)$
$T_{min} = 0.932$, $T_{max} = 0.954$	$R_{int} = 0.054$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.042$	H atoms treated by a mixture of
$wR(F^2) = 0.114$	independent and constrained
$S = 1.01$	refinement
2805 reflections	$\Delta\rho_{max} = 0.84$ e Å^{-3}
204 parameters	$\Delta\rho_{min} = -0.57$ e Å^{-3}
3 restraints	

Table 1
Hydrogen-bond geometry (Å, °) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1—H1A⋯O2^i	0.884 (17)	2.64 (2)	3.298 (2)	132 (2)
N1—H1B⋯N4^{ii}	0.883 (16)	2.329 (19)	3.121 (2)	149 (2)
N1—H1B⋯O1^i	0.883 (16)	2.52 (2)	3.098 (2)	124.0 (19)
N2—H2⋯N1^{iii}	0.869 (17)	2.029 (18)	2.891 (2)	171 (2)

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

Compound (II)

Crystal data

$C_{11}H_{13}N_5O_4S$	$\gamma = 109.255$ (2)°
$M_r = 311.32$	$V = 667.06$ (5) Å^3
Triclinic, $P\bar{1}$	$Z = 2$
$a = 8.1566$ (3) Å	Mo $K\alpha$ radiation
$b = 8.6577$ (4) Å	$\mu = 0.27$ mm^{-1}
$c = 10.5410$ (4) Å	$T = 120$ (2) K
$\alpha = 97.180$ (3)°	$0.30 \times 0.20 \times 0.20$ mm
$\beta = 103.374$ (2)°	

Data collection

Bruker–Nonius KappaCCD diffractometer	7268 measured reflections
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2007)	2448 independent reflections
	2122 reflections with $I > 2\sigma(I)$
$T_{min} = 0.914$, $T_{max} = 0.948$	$R_{int} = 0.072$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.052$	H atoms treated by a mixture of
$wR(F^2) = 0.157$	independent and constrained
$S = 1.09$	refinement
2448 reflections	$\Delta\rho_{max} = 0.43$ e Å^{-3}
203 parameters	$\Delta\rho_{min} = -0.61$ e Å^{-3}
3 restraints	

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

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1—H1A⋯N5^i	0.876 (18)	2.336 (19)	3.206 (3)	172 (3)
N1—H1B⋯O2^{ii}	0.869 (17)	2.19 (2)	2.998 (3)	154 (3)
N2—H2⋯O1^{iii}	0.861 (18)	2.11 (2)	2.899 (2)	152 (3)

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

All H atoms were identified in a difference map. Methyl H atoms were idealized and included as rigid groups allowed to rotate but not to tip (C—H = 0.98 Å). The H atoms of CH$_2$ (C—H = 0.99 Å) and benzene (C—H = 0.95 Å) groups were positioned geometrically. The U_{iso}(H) parameters were set at $1.5U_{eq}$(C) for methyl H atoms and $1.2U_{eq}$(C) for other C-bound H atoms. H atoms attached to N atoms were refined with restrained distances [N—H = 0.88 (2) Å] and their U_{iso}(H) parameters were refined freely.

For both compounds, data collection: *COLLECT* (Hooft, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* (Bruker, 1998) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *publCIF* (Westrip, 2008).

organic compounds

Supplementary data for this paper are available from the IUCr electronic archives (Reference: EM3013). Services for accessing these data are described at the back of the journal.

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