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δ-Sulfanilamide

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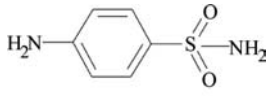
The δ polymorph of sulfanilamide (or 4-aminobenzenesulfonamide), $C_6H_8N_2O_2S$, displays an overall three-dimensional hydrogen-bonded network that is dominated by a two-dimensional substructure with $R_2^2(8)$ rings; these result from dimeric N—H···O interactions between adjacent sulfonamide groups. This study shows how the polymorphism of sulfanilamide is linked to its versatile hydrogen-bonding capabilities.

Comment

The antibacterial activity of sulfanilamide, (I), was first recognized in 1936 (Buttle *et al.*, 1936). This followed the introduction of prontosil as an antibacterial agent (Domagk, 1935), the activity of which depends on its conversion to sulfanilamide. The use of sulfanilamide was eclipsed by its prodrugs, the more effective sulfadrugs, shortly afterwards. The sulfadrugs are remarkably polymorphic. We are aware of only sulfadiazine amongst the commercial antibacterial sulfonamides as being monomorphic. We have previously reported new structures of polymorphs of sulfathiazole (Hughes *et al.*, 1999) and sulfapyridine (Gelbrich *et al.*, 2007).



(I)

The polymorphism of sulfanilamide was extensively but sporadically investigated over a number of years (Burger, 1973). There are three well known polymorphs, usually designated α (space group *Pbca*), β ($P2_1/c$) and γ ($P2_1/c$). The crystal structures of these have been determined (Alléaume & Decap, 1965*a*,*b*; O'Connor & Maslen, 1965; O'Connell & Maslen, 1967), as well as that of an elusive hydrate (Alléaume & Decap, 1968). The thermodynamic relationships between these polymorphs is still uncertain (Portieri *et al.*, 2004). There have been several accounts of the existence of other polymorphs, although no structures of these have been reported (McLachlan, 1957; Lin & Guillory, 1970; Lin *et al.*, 1974; Sekiguchi *et al.*, 1975; Portieri *et al.*, 2004).

During an investigation of the polymorphism, transformation and solvate forming propensities of the sulfadrugs (Bingham *et al.*, 2001), we prepared several solvates of sulfanilamide by crystallization from both common and uncommon liquids. The structure of an isolated crystal from the preparation of the diethyl suberate solvate of sulfanilamide proved to be that of a new polymorph, here named δ-sulfanilamide. The data collection took place many months after the crystallization and isolation. It therefore appears to be a form of higher kinetic stability than the α and γ forms, both of which revert to the β form, which is the thermodynamically stable form at room temperature, over a period of several months.

δ-Sulfanilamide crystallizes in the space group *Pbca* with one independent molecule. The geometric parameters of the molecule, which is shown in Fig. 1, are unexceptional. The sulfonamide (s) and aniline (a) NH_2 groups provide hydrogen-bond donor functionalities, while the O and N atoms are potential hydrogen-bond acceptor sites. Atom O1 accepts two hydrogen bonds from (s)NH_2 groups of two neighbouring molecules. Thus, dimers with a central $R_2^2(8)$ ring (Bernstein *et al.*, 1995) are formed, and four such dimers are joined together by $R_6^4(16)$ rings. Both ring types are centrosymmetric. The resulting extended two-dimensional hydrogen-bonded structure, illustrated in Fig. 2(*a*), lies parallel to the *ab* plane. It consists of two antiparallel sublayers of molecules, enabling close head-to-head contacts of their respective sulfonamide units (Fig. 2*b*), while the two sets of aniline units point in opposite directions away from the central hydrogen-bonded sheet. Antiparallel aniline fragments originating from two adjacent (s)NH···O(s)-bonded planes form a common stack. This enables the (a)NH_2 groups to engage in a second set of interactions with the sulfonamide groups of a neighbouring plane, *viz.* (a)NH···O(s), using the sulfonyl O atom that is not employed in the primary contacts, and (a)NH···N(s). The extended two-dimensional structure shown in Fig. 2(*c*) arises from these two secondary interactions in addition to the dimeric (s)NH···O(s) contacts. The two (a)NH···*A* interactions involving the aniline NH_2 group are secondary in the sense that their H···*A* distances (> 2.5 Å) are considerably longer than the (s)NH···O(s) bonds (Table 1). Together, primary and secondary NH···*A* bonds generate an overall three-dimensional framework of hydrogen-bonded sulfanilamide molecules.

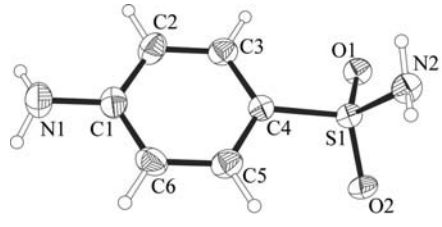


Figure 1
The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

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A recurring feature of all four forms of (I) is the presence of (s)NH···O(s)-bonded chains enabled by head-to-head contacts of adjacent sulfonyl groups, which always result in (s)NH···O(s)-bonded planes, and neighbouring planes of this type are always separated by antiparallel stacked aniline fragments. Fig. 3(*a*) illustrates the toplogy of the (s)NH···O(s)-bonded planes in form δ, which is based on dimeric $R_2^2(8)$ rings. The same dimer is also present in forms α and γ, which adopt a common topolgy (Fig. 3*b*), where each of the two sulfonyl O atoms is engaged in one (s)NH···O(s) bond, in contrast to polymorph δ where just one O atom is employed twice. The β polymorph also contains an extended two-dimensional structure arising from (s)NH···O(s) bonds, but it

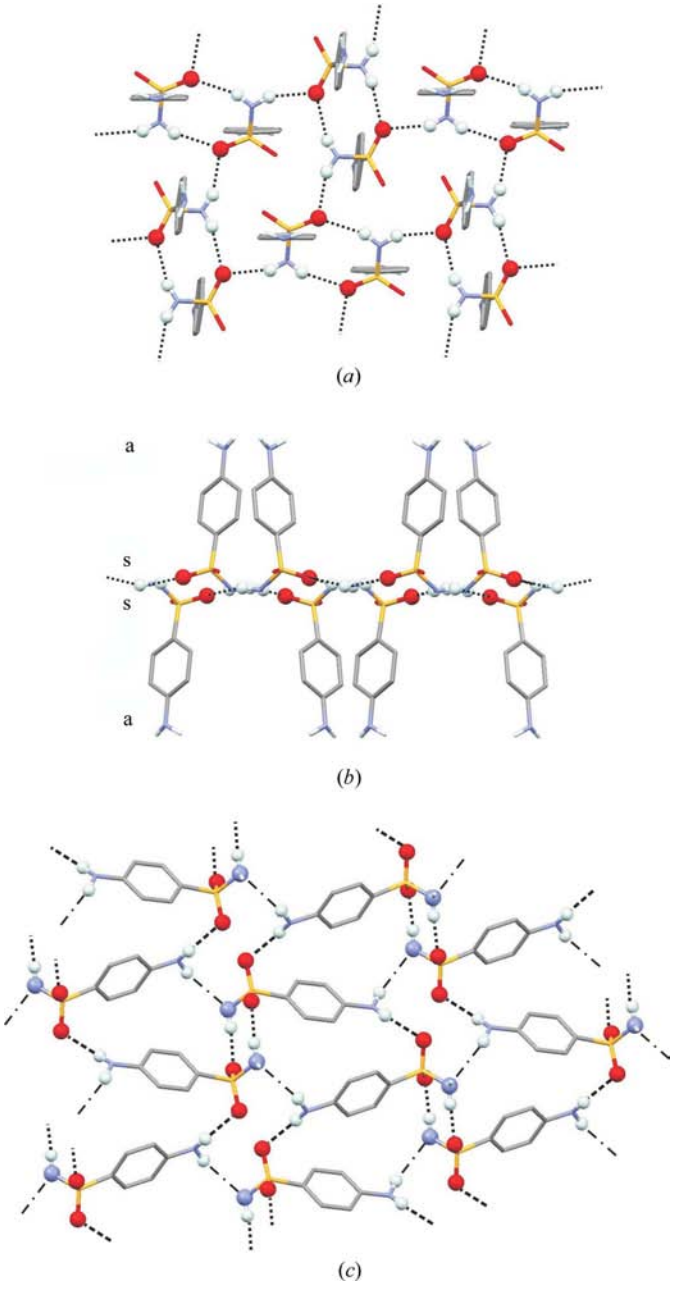

Figure 2
Details of the three-dimensional hydrogen-bonding network of δ-sulfanilamide, with atoms participating in the drawn hydrogen bonds represented as spheres. (*a*) The two-dimensional structure arising from the primary (s)NH···O(s) interactions between sulfonamide groups. (*b*) The same hydrogen-bonded sheet rotated by 90°, showing the two groups of molecules with their sulfonamide groups aligned head-to-head. (*c*) The two-dimensional structure arising from secondary hydrogen bonds in combination with primary dimers. Key: dot–dashed lines (a)NH···N(s), dashed lines (a)NH···O(s) and dotted lines (s)NH···O(s) dimers.

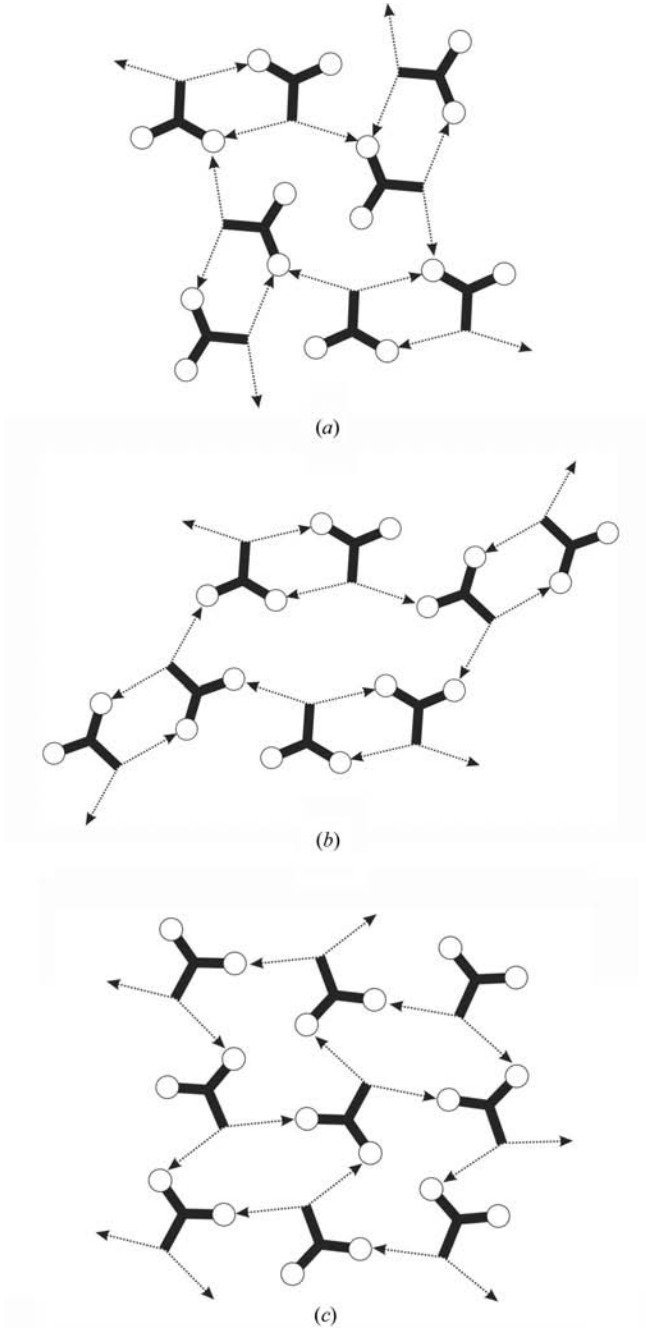

Figure 3
The topology of the extended two-dimensional structures arising from (s)NH···O(s) interactions in modifications of sulfanilamide. Molecules are represented by their sulfonamide groups (arrows denote NH···O bonds and circles represent O atoms): (*a*) $R_2^2(8)$ dimers fused with $R_6^4(16)$ rings in form δ (see also Fig. 2*a*); (*b*) $R_2^2(8)$ dimers fused with $R_6^6(20)$ rings in forms α and γ; (*c*) fused $R_4^4(16)$ and $R_4^4(24)$ rings in form β.

is not composed of dimers and the characteristic $R_2^2(8)$ rings are absent from this structure (Fig. 3*c*). This is also the only one of the four modifications without a hierarchy of shorter (s)NH···O(s) and longer (a)NH···*A* bonds.

Using the *XPac* program (Gelbrich & Hursthouse, 2005), the packing of the sulfanilamide molecules in the four polymorphs was analyzed. It was found that the (s)NH···O(s)-bonded dimer present in the α, γ and δ forms is the only packing fragment that occurs in more than one of these structures. Beyond these individual dimeric units, the common two-dimensional topology of α and γ (Fig. 3*b*) translates into two different spatial arrangements of sulfanilamide molecules. The comparison of molecular volumes determined at 150 K (188.0 Å^3 for α, 184.6 Å^3 for β, 187.1 Å^3 for γ and 188.4 Å^3 for δ; Hursthouse *et al.*, 1999*a*,*b*, 1998) shows that the stable β form is also the polymorph with the highest density. The occurrence of the other three forms may be attributed to a competing aggregation preference of sulfanilamide molecules for (s)NH···O(s)-bonded dimers.

Experimental

Sulfanilamide (1 g) was dissolved in diethyl suberate (6 g) at about 423 K. The crystals obtained on cooling were identified as the diethyl suberate solvate of sulfanilamide by the change of the carbonyl stretching frequency from 1734 cm^{-1} in diethyl suberate to 1743 cm^{-1} in the crystals. However, a crystal chosen for single-crystal diffraction proved to be a novel polymorph of sulfanilamide, reported here. No other crystal of this polymorph could be found in the preparation, or in subsequent preparations.

Crystal data

$C_6H_8N_2O_2S$
M_r = 172.20
Orthorhombic, *Pbca*
a = 9.7056 (19) Å
b = 8.6794 (17) Å
c = 17.890 (4) Å
V = 1507.0 (5) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.38 mm^{-1}
T = 150 (2) K
0.20 × 0.20 × 0.15 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.928, T_{max} = 0.939
4580 measured reflections
1346 independent reflections
978 reflections with $I > 2\sigma(I)$
R_{int} = 0.061

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.106
S = 1.00
1346 reflections
121 parameters
4 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.39 e Å^{-3}

All H atoms were identified in a difference map. Benzyl H atoms were positioned geometrically (C—H = 0.95 Å). H atoms attached to N atoms were refined with restrained distances [N—H = 0.88 (2) Å]. The U_{iso} parameters of all H atoms were refined freely.

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).

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H3N···O1^{i}	0.872 (17)	2.21 (2)	2.985 (3)	148 (2)
N2—H4N···O1^{ii}	0.863 (18)	2.20 (2)	3.022 (3)	159 (3)
N1—H1N···N2^{iii}	0.877 (18)	2.58 (2)	3.372 (4)	151 (3)
N1—H2N···O2^{iv}	0.885 (18)	2.51 (2)	3.388 (4)	173 (3)

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

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3211). Services for accessing these data are described at the back of the journal.

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