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The discrete role of chlorine substitutions in the conformation and supramolecular architecture of arylsulfonamides

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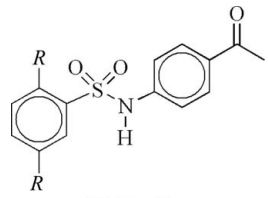
Two arylsulfonamide derivatives, *N*-(4-acetylphenyl)benzenesulfonamide, $C_{14}H_{13}NO_3S$, and *N*-(4-acetylphenyl)-2,5-dichlorobenzenesulfonamide, $C_{14}H_{11}Cl_2NO_3S$, differing by the absence or presence of two chloro substituents on one of the phenyl rings, were synthesized and characterized in order to establish structural relationships and the role of chloro substitution on the molecular conformation and crystal assembly. Both arylsulfonamides form inversion-related dimers through C—H$\cdots\pi$ and π–π interactions. These dimers pack in a similar way in the two structures. The substitution of two H atoms at the 2- and 5-positions of one phenyl ring by Cl atoms did not substantially alter the molecular conformation or the intermolecular architecture displayed by the unsubstituted sulfonamide. The structural information controlling the assembly of such compounds in their crystal phases is in the (phenyl)benzenesulfonamide molecular framework.

Comment

Compounds containing a sulfonamide group, $-SO_2NH$, are known to be powerful inhibitors of carbonic anhydrases. They are among the most widely used antibacterial agents, mainly due to their low cost, low toxicity and excellent activity against common bacterial diseases (Ozbek *et al.*, 2007). The sulfonamide group occurs in many biologically active compounds, including antimicrobial, antithyroid, antitumor and antimalarial drugs (Ozdemir *et al.*, 2009; Seo *et al.*, 2010; Dominguez *et al.*, 2005; Connor, 1998; Hanson *et al.*, 1999). In addition, several substituted aromatic and heterocyclic sulfonamides have been synthesized and evaluated for their potential therapeutic use as antiglaucoma agents (Remko *et al.*, 2010).

In this study, two arylsulfonamide derivatives, *N*-(4-acetylphenyl)benzenesulfonamide, (I), and *N*-(4-acetylphenyl)-2,5-dichlorobenzenesulfonamide, (II), differing in by the presence or absence of two chloro substituents on one of the phenyl rings, were synthesized and characterized by X-ray diffraction in order to establish structural relationships and the affect of chloro substitution on the molecular conformation and crystal assembly. Based on such knowledge, pharmacological profiles of these compounds could be further rationalized.



(I) R = H
(II) R = Cl

Despite the significant differences in the substitution patterns of the two compounds determined here, sulfonamides (I) and (II) exhibit similar intramolecular geometry (Fig. 1). A superposition of their molecular backbones shows the conformational similarity between the two compounds (Fig. 2), except for a slight rotation about the sulfamyl bridge bond axis (see below). As a practice in analyzing the intramolecular features of small molecules determined by X-ray diffraction, the geometric parameters of sulfonamides (I) and (II) were submitted to a *Mogul* check (Bruno *et al.*, 2004). All geometric values agree with those of other reported sulfonamide structures (*e.g.* Perlovich *et al.*, 2011; Martins *et al.*, 2009;

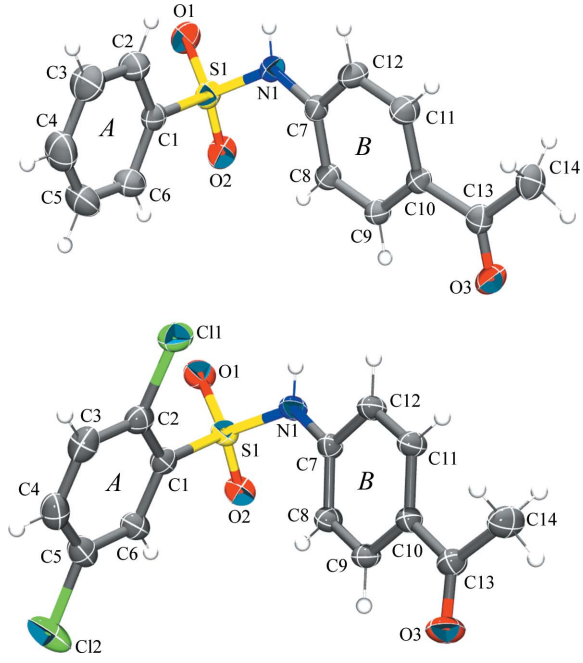


Figure 1
A view of the molecular structures of (I) (top) and (II) (bottom), showing the atom- and ring-labeling schemes. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

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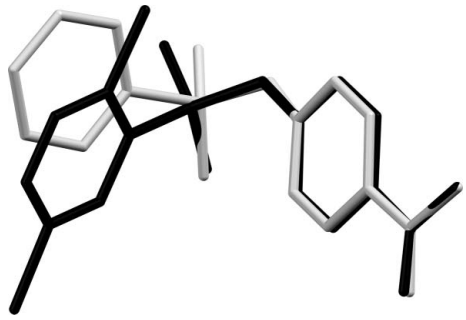

Figure 2
A superposition of sulfonamides (I) (grey) and (II) (black). H atoms have been omitted for clarity.

Drebushchak *et al.*, 2006, 2007). A near-90° angle between the planes of the two aromatic rings is a remarkable intramolecular feature observed in other related bioactive sulfonamides and was found in both (I) and (II). The planes through the benzene rings form a dihedral angle of 88.27 (8)° in (I) and 75.72 (8)° in (II) suggesting that their relationship is related to hindrance effects involving the two rings. However, the assignment of structural features as a result of only intermolecular forces is a very difficult exercise.

Not only are the molecular structures of sulfonamides (I) and (II) similar but so also are the supramolecular assemblies. In both structures, infinite one-dimensional chains are formed along the [010] direction by translation-related molecules (Fig. 3). Each chain is therefore composed of only one enantiomorph. In (I), these chains are created by a classical N1—H1···O3^{i} [symmetry code: (i) $x, y+1, z$] hydrogen bond and a nonclassical C9—H9···O1^{ii} [symmetry code: (ii) $x, y-1, z$] hydrogen bond, while the bifurcated acceptor N1—H1···O3^{i} and C12—H12···O3^{i} hydrogen-bond interactions connect such ribbons in (II). The geometric parameters of the hydrogen-bond interactions are shown in Tables 1 and 2. Enantiopure chains are stacked parallel to the direction [100] to create layers where the neighboring ribbon is composed of the same enantiomorph [in the case of the structure of sulfonamide (II)] or the other enantiomorph [in the case of the structure of sulfonamide (I)].

The hydrogen-bond patterns that assemble the chains differ between (I) and (II), as mentioned above. This can be viewed as a result of displacing molecules of (II) onto the (100) plane when compared to (I) (Fig. 4). Such a displacement is related to the formation of a halogen–π interaction between the 2_1-screw axis symmetry-related molecules of (II). The occurrence of this intermolecular contact is supported by the short distance between Cl2 and the centroid of ring *A* (*CgA*; atoms C1–C6) [3.528 (7) Å]. This halogen–π interaction Cl2···*CgA*^{iii} [symmetry code: (iii) $-x+1, y-\frac{1}{2}, -z-\frac{1}{2}$], along with the halogen–halogen contacts Cl1···Cl2^{iv} [3.453 (2) Å; symmetry code: (iv) $x, -y+\frac{3}{2}, z+\frac{1}{2}$] and Cl1···Cl1^{v} [3.581 (1) Å; symmetry code: (v) $-x+1, -y+2, -z$], occurring in (II), are the main differences between the crystal structures of the two sulfonamides.

Besides the three-dimensional connection of the [100]-stacked [010] chains along the *c* axis, these halogen–π and

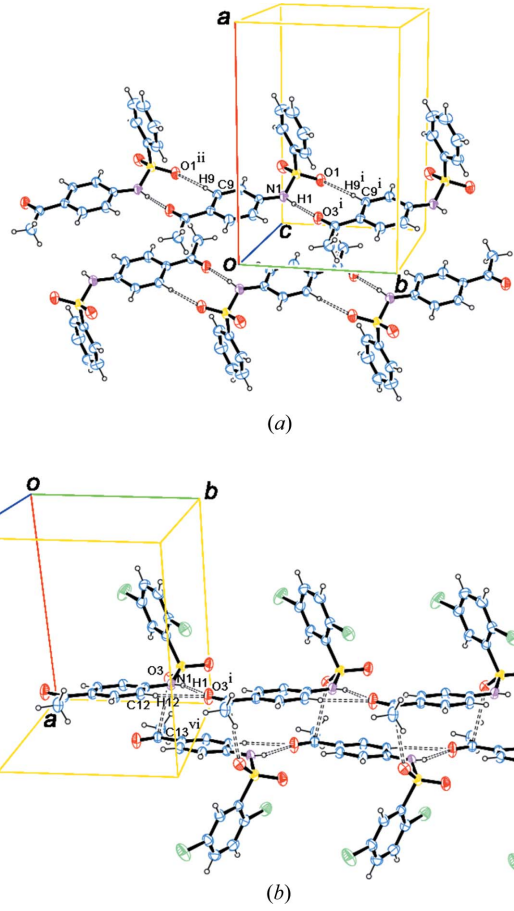

Figure 3
Infinite one-dimensional chains of (*a*) (I) and (*b*) (II), growing along the [010] direction. Classical N—H···O and nonclassical C—H···O hydrogen-bonding interactions are shown as dashed lines, as is the O···C dipole interaction in (*b*). [Symmetry codes: (i) $x, y+1, z$; (ii) $x, y-1, z$; (vi) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$.]

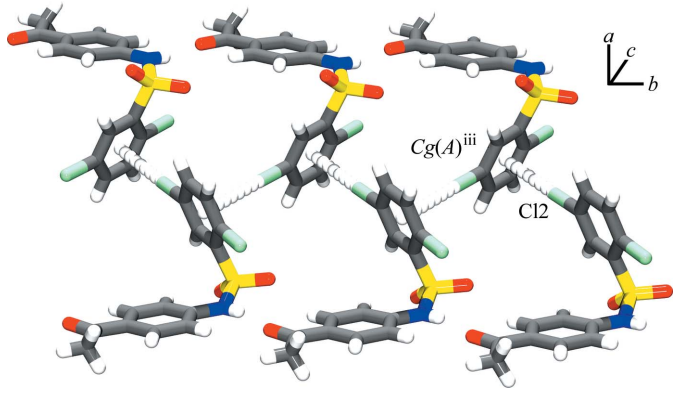

Figure 4
The halogen–π interaction occurring only in the structure of (II). [Symmetry code: (iii) $-x+1, y-\frac{1}{2}, -z-\frac{1}{2}$.]

halogen–halogen interactions, together with the dipole–dipole O2···C13^{vi} [3.223 (3) Å; symmetry code: (vi) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$] contact occurring between the sulfonyl and carbonyl groups of 2_1-screw axis symmetry-related molecules of (II) stacked parallel to the [100] direction, are responsible for the

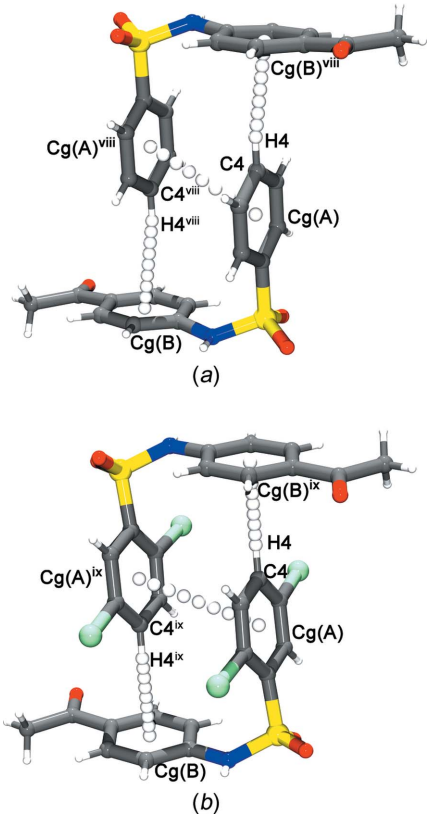

Figure 5
The C—H···π and π–π interactions in the structures of (*a*) (I) and (*b*) (II). [Symmetry codes: (viii) $-x+1, -y, -z+1$; (ix) $-x+1, -y+1, -z$.]

most significant conformational difference between the two compounds reported in this study: there is a conformational flexibility on the bridge connecting the benzene rings, which features a slight rotation about the N1—S1 bond axis of (II) if the sulfamyl group conformation of (I) is used as a reference. The values of the *X*—N1—S1—*Y* torsion angles (Table 3) deviate by approximately 15° between the two sulfonamides, which is in agreement with the rotation mentioned above.

No dipole–dipole O2···C13^{vi} interaction occurs in (I). In this structure, along the direction [010], the C5—H5···O1^{vii} [3.332 (3) Å; symmetry code: (vii) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$; Table 1] hydrogen bond also connects 2_1-screw axis symmetry-related molecules of (I) from different one-dimensional chains made up of the same enantiomorph.

Additionally, both structures are stabilized by C—H···π and π–π interactions, which generate inversion-related dimers. The contacts C4—H4···*CgB*^{viii} [2.87 Å; *CgB* is the centroid of the C7–C12 ring; symmetry code: (viii) $-x+1, -y, -z+1$] and *CgA*···*CgA*^{viii} [4.207 (7) Å] assemble these pairs of molecules in (I). Likewise, the contacts C4—H4···*CgB*^{ix} [2.64 Å; symmetry code: (ix) $-x+1, -y+1, -z$] and *CgA*···*CgA*^{ix} [4.010 (8) Å] play such a role in (II) (Fig. 5). These dimers can be considered as the building units of both crystal architectures, while their interaction patterns differ between the structures of (I) and (II). Contributing to the stabilization of the dimers of (II), there are two other halogen–halogen Cl1···Cl2^{ix} [3.852 (1) Å] contacts between inversion-related molecules kept in contact by the face-to-face and face-to-edge stacking interactions.

In conclusion, it was possible to characterize the existence of several classical and nonclassical hydrogen bonds and π–π stacking interactions contributing to the stabilization of the crystal packing of both compounds. Although the substitution of two H atoms at positions 2 and 5 of ring *A* by Cl atoms did not alter greatly the conformation and intermolecular architecture of the two sulfonamide analogs, despite halogen–π, halogen–halogen and dipole–dipole interactions present only in (II), it plays a discrete role in the conformation, which differs slightly from that of (I). This reveals that the structural information controlling the assembly of such compounds in their crystal phases is in the (phenyl)benzenesulfonamide molecular framework.

Experimental

Compounds (I) and (II) were obtained by equimolar coupling between phenylsulfonyl chloride or 2,5-dichlorophenylsulfonyl chloride and 4-aminoacetophenone in dichloromethane or acetone as solvent. The reactions were performed at 343 K for about 6 h. The precipitate was recrystallized from suitable solvents to obtain the single crystals used for analysis. The reaction yields were 54 and 55% for compounds (I) and (II), respectively.

Compound (I)

Crystal data

$C_{14}H_{13}NO_3S$
M_r = 275.31
Monoclinic, $P2_1/c$
a = 13.0007 (5) Å
b = 8.3615 (4) Å
c = 12.5179 (6) Å
β = 98.118 (3)°
V = 1347.13 (10) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 293 K
0.4 × 0.4 × 0.35 mm

Data collection

Nonius KappaCCD diffractometer
9368 measured reflections
3006 independent reflections
2214 reflections with $I > 2\sigma(I)$
R_{int} = 0.046

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3^{i}	0.85 (2)	2.03 (3)	2.879 (2)	173 (2)
C9—H9···O1^{ii}	0.93	2.56	3.486 (2)	172
C5—H5···O1^{vii}	0.93	2.42	3.332 (3)	165

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

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3^{i}	0.81 (3)	2.11 (3)	2.903 (2)	166 (2)
C12—H12···O3^{i}	0.93	2.64	3.388 (2)	137

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

Table 3
Selected torsion angles (°) of (I) and (II).

	(I)	(II)
C7—N1—S1—O1	−177.62 (17)	166.97 (17)
C7—N1—S1—O2	−48.6 (2)	−63.21 (19)
C7—N1—S1—C1	67.46 (19)	50.4 (2)

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.147	$\Delta\rho_{max}$ = 0.25 e Å^{-3}
S = 1.03	$\Delta\rho_{min}$ = −0.40 e Å^{-3}
3006 reflections	
177 parameters	

Compound (II)

Crystal data

$C_{14}H_{11}Cl_2NO_3S$	V = 1477.24 (5) Å^3
M_r = 344.2	Z = 4
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
a = 13.3622 (2) Å	μ = 0.59 mm^{-1}
b = 8.1542 (2) Å	T = 293 K
c = 15.6845 (3) Å	0.4 × 0.35 × 0.25 mm
β = 120.184 (1)°	

Data collection

Nonius KappaCCD diffractometer	2463 reflections with $I > 2\sigma(I)$
5653 measured reflections	R_{int} = 0.026
2972 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.049	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.144	$\Delta\rho_{max}$ = 0.39 e Å^{-3}
S = 1.08	$\Delta\rho_{min}$ = −0.51 e Å^{-3}
2972 reflections	
195 parameters	

All C—H H atoms were placed geometrically and refined using a riding model, with U_{iso}(H) = 1.2U_{eq}(C). The C—H distances were fixed at 0.96 Å for CH_3 groups and at 0.93 Å for aromatic groups. H1 bonded to N1 was found from a difference Fourier map and its positional parameters were refined freely, with U_{iso}(H) = 1.2U_{eq}(N).

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3150). Services for accessing these data are described at the back of the journal.

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