Effect of Crystal Packing on H-Bond Parameters: X-Ray Structure of the Sulfadimidine-*p*-Chlorobenzoic Acid Co-crystal

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The X-ray structure of the 1:1 co-crystal (**1**) between the antibacterial drug sulfadimidine (SD) and *p*-chlorobenzoic acid (PCL) is reported. Compound **1** crystallizes in the space group $P2_1/c$ with $a = 15.354(5)\text{\AA}$, $b = 14.433(4)\text{\AA}$, $c = 18.732(5)\text{\AA}$, $\beta = 94.540(5)^\circ$, and $Z = 8$. In the two independent co-crystal units, identical $R_2^2(8)$ hydrogen-bonded motifs occur, each involving the hydrogen bond $\text{SD}(-\text{SO}_2-\text{N}-\text{H})\cdots\text{O}=\text{C}(\text{PCL})$ and the hydrogen bond $\text{PCL}(\text{O}-\text{H})\cdots\text{N}(\text{SD pyrimidinyl})$. A significant inequality of the two $\text{N}\cdots\text{O}$ distances in the chemically identical $\text{N}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bonds indicates that such parameters can be strongly influenced by the crystal packing factors.

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Co-crystal formation is of significant current interest, especially in the context of pharmaceutical development.¹ The reaction between the antibacterial sulfadimidine [4-amino-*N*-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide] and a series of benzoic acid derivatives, both in the solid-state and in solution, yielded 1:1 co-crystals whose properties and solid-state reactions have recently been reviewed.² The title structure **1** (Fig. 1) is a representative member of this series, typified by the formation of the $R(8)$ hydrogen bonded motif between the co-crystallizing partners. An earlier attempt to correlate the $\text{N}-\text{H}\cdots\text{O}$ and $\text{O}-\text{H}\cdots\text{N}$ distances comprising this specific $R_2^2(8)$ system with $\text{p}K_a$ differences between the co-crystal partners was partially successful, but was based on the X-ray structures of a series of analogs that contained only one co-crystal molecule in the asymmetric unit.³ An examination of the title structure, however, with two molecules of the co-crystal in the asymmetric unit, allows possible effects of the crystal packing on the variability of the hydrogen bonded parameters to be distinguished.

Colorless crystals of **1** were grown by the slow evaporation of an acetonitrile solution containing an equimolar mixture of sulfadimidine and *p*-chlorobenzoic acid. As proven by PXRD

analysis, the identical phase could also be obtained by solid-state co-grinding of the components in a ball-mill for 10 min. Although sulfadimidine and *p*-chlorobenzoic acid yielded DSC fusion endotherms peaking at 197 and 243°C, respectively, **1** melted at 207°C. Co-crystal formation was also confirmed by shifts of the $\text{N}-\text{H}$ infrared stretching bands of pure sulfadimidine (3436, 3337, 3236 cm^{-1}) to significantly higher frequencies in the product (3469, 3376, 3256 cm^{-1}).

Intensity data were measured from a crystal of size $0.38 \times 0.38 \times 0.40$ mm at room temperature (294 ± 2 K), and were corrected for Lp and absorption effects. With $Z = 8$, the space group $P2_1/c$ requires the asymmetric unit to comprise two co-crystal units. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXL 97. All hydrogen atoms were located unequivocally in difference

Fig. 1 Chemical structure of the sulfadimidine-*p*-chlorobenzoic acid co-crystal.

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Table 1 Crystal and experimental data

CCDC deposition number	672462
Formula	$\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_2\text{S} \cdot \text{C}_7\text{H}_5\text{ClO}_2$
Formula weight	434.89
Crystal system	monoclinic
Space group	$P2_1/c$
Z	8
a	$15.354(5)\text{\AA}$
b	$14.433(5)\text{\AA}$
c	$18.732(5)\text{\AA}$
β	$94.540(5)^\circ$
V	$4138(2)\text{\AA}^3$
D_x	1.396 g cm^{-3}
No. of reflections used	7498
$2\theta_{\text{max}}$	50.0° with Mo K_α
R (3983 data, $I > 2\sigma(I)$)	0.0386
$(\Delta/\sigma)_{\text{max}}$ final cycle	0.001
$(\Delta\rho)_{\text{max}}$	$0.18\text{ e}\text{\AA}^{-3}$
$(\Delta\rho)_{\text{min}}$	$-0.22\text{ e}\text{\AA}^{-3}$
Measurement	Enraf-Nonius CAD4
Program system	Enraf-Nonius Structure Determination Package
Structure Determination	SHELXS-97
Refinement	full-matrix: SHELXL-97

Fig. 2 ORTEP drawing of the asymmetric unit at the 40% probability level.

Fourier maps and subsequently added at idealized positions in a riding model with U_{iso} set at 1.2 – 1.5 times those of their parent atoms. All methyl H atoms were found to be disordered over two orientations, and were modeled accordingly. All non-H atoms were treated anisotropically. Crystal data and refinement details are listed in Table 1.

The two crystallographically independent co-crystal units A, B (Fig. 2) display the same type of molecular association, namely complementary hydrogen bonding between the carboxyl group of the acid molecule and the amido N atom and a pyrimidinyl N atom of sulfadimidine, giving rise to the $R_2^2(8)$ motif, which is common to the co-crystal series.² The bond lengths and bond angles for the independent sulfadimidine molecules are virtually identical (Table 2), but the primary torsion angles listed indicate their significantly different conformations. In both of the acid molecules, the $-COOH$ group is nearly coplanar with the phenyl ring.

The hydrogen-bonding parameters in the $R_2^2(8)$ system are of primary interest here. In co-crystal unit A, the hydrogen bond $N-H\cdots O$ has $N\cdots O = 2.846(3)\text{\AA}$ and the $O-H\cdots N$ bond has $O\cdots N = 2.666(3)\text{\AA}$. The corresponding distances in the co-crystal unit B are $N\cdots O = 2.797(3)\text{\AA}$ and $O\cdots N = 2.670(3)\text{\AA}$. Therefore, in this co-crystal, while there is no significant difference between the $O\cdots N$ distances, the $N\cdots O$ distances in units A and B differ by $\sim 12\sigma$ ($\sigma =$ combined e.s.d.). Since the latter hydrogen bonds are chemically identical, this significant difference can only be attributed to packing effects in the crystal, which also result in different conformations of the drug molecule in units A and B (It should be added that the four distances cited above are unaffected by the mode of N-H hydrogen atom modelling employed, *i.e.* free H atom refinement, or the idealised trigonal geometry applied based on ΔF map evidence).

The above finding is sufficient evidence to indicate that hydrogen-bonded distances, as measures of strengths of interactions between binding partners in co-crystals, may be governed not only by inherent differences in the nature of the co-crystallizing partner molecules (as reflected in *e.g.* pK_a differences), but also by crystal packing. In an earlier study, it was in fact pointed out that for a series of seven sulfadimidine co-crystal analogs in this series, with acid partner pK_a values spanning the range of 2.89 – 6.97, the $N\cdots O$ and $O\cdots N$ distances spanned the respective ranges of 2.779(3) – 2.841(4) and 2.639(3) – 2.724(4) $\text{\AA}$. In this series, the maximum and

Table 2 Selected bond distances ($\text{\AA}$), angles ($^\circ$) and torsion angles ($^\circ$)

S8 - O9	1.424(2)	S37 - O39	1.424(1)
S8 - O10	1.429(2)	S37 - O38	1.427(2)
S8 - N11	1.639(2)	S37 - N40	1.637(1)
N13 - C14	1.345(3)	N42 - C43	1.341(3)
N17 - C16	1.341(3)	N46 - C45	1.345(3)
C12 - N13	1.320(3)	C41 - N42	1.325(3)
C12 - N17	1.336(3)	C41 - N46	1.339(3)
C4 - N7	1.361(3)	C33 - N36	1.355(4)
C26 - O27	1.305(3)	C55 - O56	1.309(3)
C26 - O28	1.216(3)	C55 - O57	1.215(3)
C23 - C129	1.733(2)	C52 - C158	1.729(3)
C12 - N13 - C14	116.1(2)	C41 - N42 - C43	116.1(2)
C12 - N17 - C16	116.5(2)	C41 - N46 - C45	116.4(2)
S8 - N11 - C12	127.7(2)	S37 - N40 - C41	124.7(1)
C1 - S8 - N11	107.5(1)	C30 - S37 - N40	106.6(1)
O9 - S8 - O10	118.9(1)	O38 - S37 - O39	118.1(1)
O27 - C26 - O28	123.4(2)	O56 - C55 - O57	123.3(2)
C2 - C1 - S8 - N11	-95.2(2)	C35 - C30 - S37 - N40	73.6(1)
C1 - S8 - N11 - C12	-68.3(2)	C30 - S37 - N40 - C41	56.1(1)
S8 - N11 - C12 - N13	0.0(3)	S37 - N40 - C41 - N42	16.2(2)
C21 - C20 - C26 - O28	3.4(4)	C50 - C49 - C55 - O57	-5.1(3)
C25 - C20 - C26 - O27	0.4(4)	C54 - C49 - C55 - O56	-3.7(3)

minimum $N\cdots O$ distances in the $N-H\cdots O$ hydrogen bonds thus differ by $\sim 12\sigma$. This, we note, is of the same order as the difference between the two independent $N\cdots O$ distances reported here for co-crystal **1**, clearly showing that the subtle influence that partner pK_a differences may confer on them may be overshadowed by gross differences resulting from packing effects. It follows that, unless such co-crystals display a strong measure of crystal isostructurality,⁴ conformational and/or crystal packing differences can render the type of attempted correlation referred to earlier meaningless.³

The crystal of **1** is stabilised by four additional intermolecular $N-H\cdots O$ hydrogen bonds involving the $-NH_2$ functions of sulfadimidine as donors, and sulfonyl or acid carbonyl oxygen atoms as acceptors. (One of these, $N7-H7B\cdots O39$, linking units A and B, is shown in Fig. 2). The $N\cdots O$ distance range for these H-bonds is 3.006(3) – 3.281(3) $\text{\AA}$. The shortest π -stacking interaction in the crystal of **1**, 3.648(2) $\text{\AA}$, is that between the phenyl ring of a *p*-chlorobenzoic acid molecule and a pyrimidine ring of a sulfadimidine molecule.

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