

Molecular complexes of sulfonamides. 3. Structure of 5-methoxysulfadiazine (Form II) and its 1:1 complex with acetylsalicylic acid

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Received August 11, 1994

The X-ray structure of the biologically most active polymorph (Form II) of 5-methoxysulfadiazine (**1**) and that of the 1:1 complex between this sulfonamide and acetylsalicylic acid (**2**) are reported. The polymorph **1** is monoclinic, space group $P2_1/c$ with $a = 13.086(2)\text{Å}$, $b = 5.583(1)\text{Å}$, $c = 17.222(3)\text{Å}$, $\beta = 99.98(1)^\circ$, $Z = 4$ and occurs as centrosymmetric hydrogen bonded ($\text{N}-\text{H}\cdots\text{N}$) dimers in the crystal. This arrangement differs from that observed in other polymorphs of the drug. Complex **2** is triclinic, $P\bar{1}$, $a = 8.102(1)\text{Å}$, $b = 12.033(1)\text{Å}$, $c = 12.170(2)\text{Å}$, $\alpha = 111.67(1)^\circ$, $\beta = 93.77(1)^\circ$, $\gamma = 103.82(1)^\circ$, $Z = 2$. Complexation involves linear intermolecular hydrogen bonds, $\text{N}-\text{H}\cdots\text{O}=\text{C}$ and $\text{N}\cdots\text{O}-\text{H}$, between the amide group and pyrimidinyl N atom of the sulfonamide and the carboxylic group of the acetylsalicylic acid. On complexation to form **2**, neither molecular component undergoes any major structural change.

KEY WORDS: Key Words: Molecular complexes, sulfonamides, acetylsalicylic acid.

Introduction

In earlier parts of this series we described the structures of 1:1 complexes between sulfadimidine [4-amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide] and various aromatic carboxylic acid derivatives including 2- and 4-aminobenzoic acids,¹ 4-aminosalicylic acid (p-aminosalicylic acid or PAS) and acetylsalicylic acid (aspirin).² These studies have been extended to an investigation of the complexing behaviour of the related drug 5-methoxysulfadiazine [4-amino-N-(5-methoxy-2-pyrimidinyl)benzenesulfonamide] (hereinafter SMD). Only one molecular complex containing SMD has been structurally characterized.³ Various aspects of the polymorphism of this drug have also been reported during the last 25 years, including the identification of various polymorphs,⁴⁻⁷ their interconversion,^{8,9} and the X-ray crystal structures of two polymorphs designated Forms I and III.¹⁰

Reaction between SMD and aspirin produces a 1:1

molecular complex, analogous to that formed between sulfadimidine and aspirin. However, in our attempt to obtain a complex between SMD and PAS, large single crystals of a polymorph of SMD were obtained instead. We identified these as Form II, the biologically most active form of the sulfonamide,⁸ which when prepared by the usual method involving recrystallization from ethanol by rapid cooling to -12°C , is obtained as small particles with little or no geometrical form.⁵ This probably accounts for the fact that the crystal structure of this important polymorphic species has not hitherto been determined.

We report here the crystal structures of (**1**) SMD Form II and (**2**) the 1:1 complex between SMD and aspirin. The results allow several useful comparisons: the conformation and hydrogen bonding scheme for SMD in Form II with corresponding features in Forms I and III, the conformations of uncomplexed SMD and SMD complexed with aspirin, and finally the structures of the SMD-aspirin complex and its sulfadimidine analog. A possible reason for the crystallization of SMD Form II during the attempted preparation of a SMD-PAS complex is also discussed.

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Experimental

Crystal preparation

SMD was purchased from Aldrich-Chemie, Steinheim. X-ray powder diffraction analysis of the unground material matched the published pattern for Form I.⁵ A solution containing 0.05 g of SMD in 6 cm³ CH₃CN was mixed with a solution containing 0.027 g PAS in 2 cm³ CH₃CN and the mixture heated to 323K with stirring for 10 min. On evaporation, the residue consisted of unreacted PAS and several large columnar crystals. The latter were tentatively identified as SMD Form II from the resemblance between the unit cell data obtained photographically with those reported in the literature.⁵ Confirmation of this assignment was obtained after the single crystal X-ray analysis had been performed, by calculating the XRD pattern and finding that it corresponded with that published for Form II.⁵ A solution made by mixing 0.05 g SMD in 6 cm³ CH₃CN and 0.032 g aspirin in 1.5 cm³ CH₃CN and heating to 323K with stirring for ten minutes yielded, after slow evaporation, yellow prismatic crystals of (2) the 1:1 SMD-aspirin complex. Preliminary unit cell data for 2 differed from those reported for the starting materials, confirming that a compound had been formed. The 1:1 complex stoichiometry was confirmed by single crystal X-ray analysis.

Single crystal X-ray analyses

Analogous procedures were used for the crystal structure determinations. Preliminary unit cell dimensions and space group data were obtained from precession photographs. Intensity data were collected on an Enraf-Nonius CAD4 diffractometer with MoK α -radiation ($\lambda = 0.71069$ Å). Accurate cell parameters were determined by the least-squares analysis of accurate setting angles in the θ -range 16–17°. Reflections in the θ -range 1–25° were collected by the ω -2 θ scan mode using a variable scan speed depending on I and $\sigma(I)$ with a maximum time of 40 s per reflection. A variable scan width ω of $(0.85 + 0.35 \tan \theta)^\circ$ and a variable aperture width of $(1.12 + 1.05 \tan \theta)$ mm were used. Intensity control was performed every hour and orientation control every 200 measured reflections. Both data sets were corrected for Lp-effects and for absorption¹¹ using the program EAC of the Enraf-Nonius Structure Determination Package.¹² Data-collection parameters and details of structure refinements are listed in Table 1. Intensity statistics indicated that $P\bar{1}$ is the correct space group for the complex 2. The structures were solved by direct methods using program SHELX86¹³ and

Table 1. Crystal data, details of data-collection and refinement

	1	2
Formula	C ₁₁ H ₁₂ N ₄ O ₃ S	C ₁₁ H ₁₂ N ₄ O ₃ S · C ₉ H ₈ O ₄
$M_r/\text{g mol}^{-1}$	280.3	460.5
$a/\text{\AA}$	13.086(2)	8.102(1)
$b/\text{\AA}$	5.583(1)	12.033(1)
$c/\text{\AA}$	17.222(3)	12.170(2)
$\alpha/^\circ$	90.0	111.67(1)
$\beta/^\circ$	99.98(1)	93.77(1)
$\gamma/^\circ$	90.0	103.82(1)
$V/\text{\AA}^3$	1239.2(4)	1055.0(3)
Z	4	2
Space group	$P2_1/c$	$P\bar{1}$
$\mu(\text{MoK}\alpha)/\text{cm}^{-1}$	2.59	1.94
$F(000)$	584	480
$D_r/\text{g cm}^{-3}$	1.502	1.450
Crystal size/mm	$0.28 \times 0.34 \times 0.41$	$0.28 \times 0.34 \times 0.34$
Index range	–15, 15; 0, 6; 0, 20	–9, 9; –14, 14; 0, 14
Standard intensity variation/%	+0.5	+1.4
Absorption correction factor range	0.9899, 1.0000	0.9934, 0.9992
Reflections measured	2519	3896
Unique reflections	2064	3391
R_{int}	0.015	0.033
Observed reflections, $I > 2\sigma(I)$	1905	2971
L S variables	188	315
Mean shift/error	0.01	0.01
Weighting scheme	$[\sigma^2(F_o)]^{-1}$	$[\sigma^2(F_o)]^{-1}$
R	0.041	0.037
R_w	0.041	0.038
S	3.918	2.764
Final $\Delta\rho/e\text{\AA}^{-3}$, min, max	–0.42, 0.27	–0.34, 0.20

refined by full-matrix least-squares using SHELX76¹⁴ and minimizing $\Sigma w(|F_o| - |kF_c|)^2$. All H atoms were located in difference Fourier maps. Those attached to O or N atoms were allowed to refine freely while the rest were added in idealized positions with C–H 1.00 Å. Anisotropic thermal parameters were employed for non-H atoms and common variable U_{iso} values were assigned to H atoms in different chemical groups. The latter refined in the ranges 0.046–0.090 Å² and 0.054–0.103 Å² for 1 and 2, respectively. Complex neutral atomic scattering factors¹⁵ were used. Program PARST¹⁶ was used for geometrical calculations and PLUTO¹⁷ for molecular drawings. Fractional atomic coordinates and equivalent isotropic thermal parameters ($U_{\text{eq}} = (1/3)\Sigma_i \Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$) for nonhydrogen atoms are listed in Tables 2 and 3. Hydrogen atom positions, U_{ij} values, torsion angles and structure factor tables have been submitted to this journal.

Table 2. Fractional atomic coordinates ($\times 10^4$, $\times 10^5$ for S) and equivalent isotropic thermal parameters ($\text{\AA}^2 \times 10^3$) with esd's in parentheses for **1**

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U</i> _{eq}
S(1)	25849(5)	15494(13)	53683(4)	32(0)
O(1)	2719(1)	−309(4)	5956(1)	41(1)
O(2)	2815(1)	3961(4)	5618(1)	42(1)
O(3)	−929(2)	7023(5)	2829(2)	91(1)
N(1)	1366(2)	1251(5)	4966(1)	38(1)
N(2)	1266(2)	4468(5)	4087(1)	45(1)
N(3)	−230(2)	2321(4)	4293(1)	36(1)
N(4)	5198(2)	−813(5)	2997(2)	43(1)
C(1)	3314(2)	862(5)	4639(1)	29(1)
C(2)	3182(2)	−1305(5)	4242(2)	35(1)
C(3)	3802(2)	−1851(5)	3695(2)	36(1)
C(4)	4581(2)	−293(5)	3559(1)	33(1)
C(5)	4718(2)	1858(5)	3970(2)	35(1)
C(6)	4086(2)	2441(5)	4506(2)	33(1)
C(7)	783(2)	2775(5)	4425(2)	33(1)
C(8)	655(2)	5834(6)	3570(2)	56(1)
C(9)	−401(2)	5520(6)	3380(2)	48(1)
C(10)	−820(2)	3714(6)	3759(2)	42(1)
C(11)	−1984(2)	6628(8)	2570(2)	63(1)

Results and discussion

Bond lengths and bond angles for **1** and **2** are listed in Tables 4 and 5; hydrogen bond data appear in Table 6.

Table 3. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\text{\AA}^2 \times 10^3$) with esd's in parentheses for **2**

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U</i> _{eq}
S(1)	4639(1)	6152(1)	7383(1)	41(0)
O(1)	5298(2)	5604(1)	8117(2)	58(1)
O(2)	5398(2)	6082(2)	6334(2)	54(1)
O(3)	4496(2)	11363(2)	7004(2)	63(1)
O(4)	7540(2)	8323(1)	10275(2)	60(1)
O(5)	8275(2)	10339(2)	10656(2)	53(1)
O(6)	8774(2)	7613(1)	11933(1)	46(1)
O(7)	10542(2)	7135(2)	10606(2)	69(1)
N(1)	4967(2)	7608(2)	8311(2)	40(1)
N(2)	3853(2)	8292(2)	6936(2)	42(1)
N(3)	5859(2)	9694(2)	8688(2)	36(1)
N(4)	−2830(3)	3783(2)	5784(2)	55(1)
C(1)	2413(3)	5522(2)	6949(2)	37(1)
C(2)	1249(3)	5968(2)	7648(2)	43(1)
C(3)	−485(3)	5384(2)	7267(2)	47(1)
C(4)	−1096(3)	4349(2)	6181(2)	41(1)
C(5)	99(3)	3893(2)	5508(2)	44(1)
C(6)	1826(3)	4477(2)	5878(2)	43(1)
C(7)	4886(3)	8568(2)	7950(2)	34(1)

Table 3. Continued

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U</i> _{eq}
C(8)	3779(3)	9253(2)	6664(2)	49(1)
C(9)	4702(3)	10468(2)	7372(2)	42(1)
C(10)	5761(3)	10652(2)	8398(2)	39(1)
C(11)	5323(4)	12623(2)	7795(3)	65(1)
C(12)	9642(3)	9713(2)	11990(2)	39(1)
C(13)	9810(3)	8844(2)	12460(2)	42(1)
C(14)	10914(3)	9184(3)	13510(2)	54(1)
C(15)	11906(3)	10401(3)	14102(2)	60(1)
C(16)	11796(3)	11278(2)	13653(2)	52(1)
C(17)	10668(3)	10944(2)	12607(2)	46(1)
C(18)	8400(3)	9374(2)	10887(2)	41(1)
C(19)	9230(3)	6832(2)	10946(2)	46(1)
C(20)	7886(3)	5605(2)	10391(3)	58(1)

Table 4. Bond lengths ($\text{\AA}$) with esd's in parentheses

	1	2
S(1)—O(1)	1.439(2)	1.435(3)
S(1)—O(2)	1.430(2)	1.437(3)
S(1)—N(1)	1.634(2)	1.641(2)
S(1)—C(1)	1.746(2)	1.741(2)
O(3)—C(9)	1.362(4)	1.349(4)
O(3)—C(11)	1.393(4)	1.424(3)
N(1)—C(7)	1.388(4)	1.392(4)
N(2)—C(7)	1.326(4)	1.329(3)
N(2)—C(8)	1.329(4)	1.327(4)
N(3)—C(7)	1.330(4)	1.327(3)
N(3)—C(10)	1.342(4)	1.342(4)
N(4)—C(4)	1.394(4)	1.372(3)
O(1)—C(2)	1.386(4)	1.383(4)
C(1)—C(6)	1.389(4)	1.389(3)
C(2)—C(3)	1.381(5)	1.373(3)
C(3)—C(4)	1.390(4)	1.395(3)
C(4)—C(5)	1.390(4)	1.391(4)
C(5)—C(6)	1.381(5)	1.367(3)
C(8)—C(9)	1.375(4)	1.379(3)
C(9)—C(10)	1.367(5)	1.382(4)

Acetylsalicylic acid moiety in **2**

O(4)—C(18)	1.206(2)
O(5)—C(18)	1.316(4)
O(6)—C(13)	1.394(2)
O(6)—C(19)	1.361(3)
O(7)—C(19)	1.191(3)
C(12)—C(13)	1.392(4)
C(12)—C(17)	1.399(3)
C(12)—C(18)	1.484(3)
C(13)—C(14)	1.374(3)
C(14)—C(15)	1.376(4)
C(15)—C(16)	1.373(5)
C(16)—C(17)	1.382(3)
C(19)—C(20)	1.490(3)

Table 5. Bond angles (°) with esd's in parentheses

	1	2		1	2
N(1)–S(1)–C(1)	106.7(1)	106.3(1)	O(3)–C(9)–C(8)	117.1(3)	117.6(2)
O(2)–S(1)–C(1)	108.1(1)	108.6(1)	C(8)–C(9)–C(10)	116.8(3)	116.4(2)
O(2)–S(1)–N(1)	111.3(1)	110.8(2)	O(3)–C(9)–C(10)	126.2(3)	126.1(2)
O(1)–S(1)–C(1)	109.4(1)	110.5(1)	N(3)–C(10)–C(9)	121.6(3)	121.3(2)
O(1)–S(1)–N(1)	102.5(1)	103.4(1)			
O(1)–S(1)–O(2)	118.3(1)	116.7(1)			
C(9)–O(3)–C(11)	118.7(3)	117.1(2)	Acetylsalicylic acid moiety in 2		
S(1)–N(1)–C(7)	127.2(2)	124.1(2)	C(13)–O(6)–C(19)	117.1(2)	
C(7)–N(2)–C(8)	115.2(3)	115.7(2)	C(17)–C(12)–C(18)	120.1(2)	
C(7)–N(3)–C(10)	116.4(3)	117.0(2)	C(13)–C(12)–C(18)	122.1(2)	
S(1)–C(1)–C(6)	118.9(2)	116.8(2)	C(13)–C(12)–C(17)	117.8(2)	
S(1)–C(1)–C(2)	120.6(2)	123.1(2)	O(6)–C(13)–C(12)	121.3(2)	
C(2)–C(1)–C(6)	120.3(2)	119.9(2)	C(12)–C(13)–C(14)	121.4(3)	
C(1)–C(2)–C(3)	119.5(3)	119.6(2)	O(6)–C(13)–C(14)	117.1(2)	
C(2)–C(3)–C(4)	120.8(3)	121.1(2)	C(13)–C(14)–C(15)	119.7(3)	
N(4)–C(4)–C(3)	121.1(2)	121.2(2)	C(14)–C(15)–C(16)	120.4(2)	
C(3)–C(4)–C(5)	119.3(2)	118.4(2)	C(15)–C(16)–C(17)	120.0(2)	
N(4)–C(4)–C(5)	119.6(2)	120.5(2)	C(12)–C(17)–C(16)	120.6(2)	
C(4)–C(5)–C(6)	120.3(3)	120.7(2)	O(5)–C(18)–C(12)	113.6(2)	
C(1)–C(6)–C(5)	119.8(3)	120.2(2)	O(4)–C(18)–C(12)	123.8(2)	
N(2)–C(7)–N(3)	126.7(3)	126.3(3)	O(4)–C(18)–O(5)	122.6(2)	
N(1)–C(7)–N(3)	114.4(3)	115.2(2)	O(6)–C(19)–O(7)	122.3(2)	
N(1)–C(7)–N(2)	118.9(3)	118.5(2)	O(7)–C(19)–C(20)	126.9(3)	
N(2)–C(8)–C(9)	123.3(3)	123.4(2)	O(6)–C(19)–C(20)	110.9(2)	

Table 6. Hydrogen bond data with esd's in parentheses

D–H···A	D–H(Å)	D···A(Å)	H···A(Å)	D–H···A(°)
Compound 1				
N(1)–H(1)···N(3) ⁱ	0.86(3)	2.911(4)	2.05(3)	176(3)
N(4)–H(41)···N(4) ⁱⁱ	0.85(4)	3.269(4)	2.48(4)	156(3)
N(4)–H(42)···O(1) ⁱⁱⁱ	0.92(3)	3.061(3)	2.22(3)	152(3)
(i) = –x, –y, 1 – z; (ii) = 1 – x, –1/2 + y, 1/2 – z; (iii) = 1 – x, –y, 1 – z				
Compound 2				
O(5)–H(51)···N(3)	0.86(3)	2.730(3)	1.87(3)	178(3)
N(1)–H(1)···O(4)	0.92(2)	2.787(3)	1.87(2)	178(2)
N(4)–H(41)···O(2) ⁱ	0.91(3)	3.290(4)	2.48(3)	149(2)
N(4)–H(42)···O(2) ⁱⁱ	0.88(3)	3.281(4)	2.72(3)	123(2)
N(4)–H(42)···N(2) ⁱⁱⁱ	0.88(3)	3.230(3)	2.38(2)	162(3)
(i) = –1 + x, y, z; (ii) = –x, 1 – y, 1 – z				

Polymorphism of SMD

The nomenclature used here to designate different polymorphs of SMD is that of Bettinetti *et al.*⁵ The molecular conformation adopted in **1** (SMD Form II) is shown in Fig. 1. Bond lengths and bond angles for **1**

(Tables 4 and 5) are generally in excellent agreement with those reported for SMD Forms I and III.¹⁰ The overall conformation of **1** is described by the torsion angles τ_1 C(6)–C(1)–S(1)–N(1) 130.1(2)°, τ_2 C(1)–S(1)–N(1)–C(7) – 73.5(3)°, and τ_3 S(1)–N(1)–C(7)–N(2) 11.6(4)°, which differ signif-

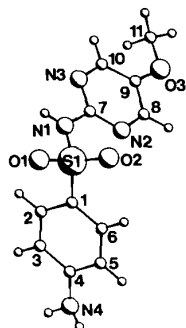


Fig. 1. Conformation of the SMD molecule in 1, (SMD Form II).

icantly from those observed in the other known polymorphs of SMD. This is due to the different hydrogen bonding arrangements occurring in Forms I, II, and III. In each polymorph, SMD forms dimeric hydrogen bonded motifs (non-centrosymmetric in Form I, centrosymmetric in Forms II and III). These motifs, shown schematically in Fig. 2, involve different combinations of $N-H \cdots O$ and $N-H \cdots N$ hydrogen bonds. It has long been recognized that the tendency for sulfonamides to form polymorphs is due to the variety of hydrogen bonding possibilities afforded by the presence of the sulfonyl ($S=O$), amide ($N-H$) and pyrimidinyl (N) functions.^{18,19} The SMD dimer reported here for 1 contains two identical $N-H \cdots N$ hydrogen bonds and also occurs in three solvates of SMD.²⁰ The crystal packing in 1 is shown in Fig. 3. A distinctive feature for this polymorph is the formation of a hydrogen bond $N(4)-H \cdots N(4')$ which links the amino groups of screw-related molecules. Repetition of this interaction by the 2_1 -axis (parallel to the short unit cell b -axis) generates an infinite chain ($\cdots N-H \cdots N-H \cdots$) in which each N atom is both hydrogen bond donor and acceptor. There is significant pyramidization at $N(4)$ as a result of this interaction (Fig. 1).

We have confirmed by X-ray powder diffractometry that the raw material used in our experiments is SMD Form I. We have also noted that when this form is recrystallized from acetonitrile, the same form results. However, in attempting to prepare a complex between SMD and PAS in acetonitrile, no complexation occurred and the unreacted SMD consisted of Form II, whose structure is described above. These observations do not explain the failure of SMD and PAS to complex under the conditions described, but it can be inferred that the presence of PAS induces crystallization of SMD Form II rather than Form I. A possible explanation is that the growth of nuclei of Form I are inhibited by pref-

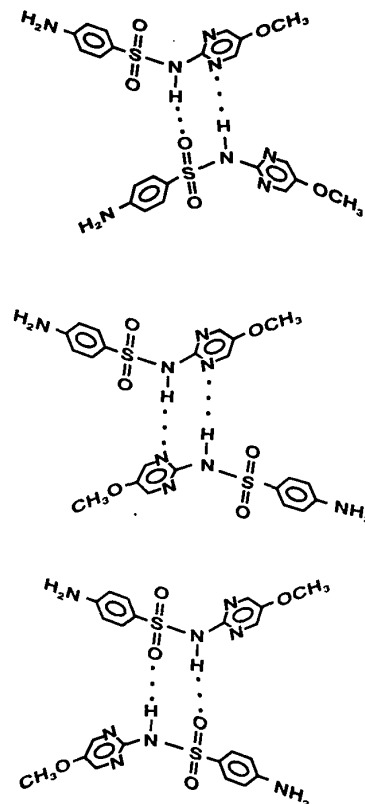


Fig. 2. Hydrogen bonded dimers in SMD polymorphs. Top: Form I¹⁰; Middle: Form II (present study), Bottom: Form III.¹⁰

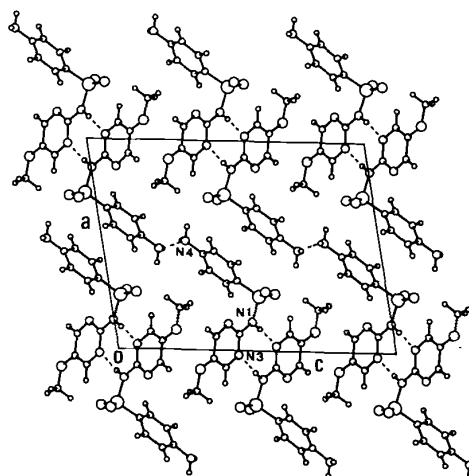


Fig. 3. [010] projection of the structure of 1 showing principal hydrogen bonds (dashed lines).

erential surface adsorption of PAS, thus favoring the crystallization of a different polymorph. Further experiments are necessary to confirm this hypothesis. Such a mechanism is likely, however, since Ebian *et al.*,⁹ who studied the effect of additives on the interconversion of SMD crystal forms, have shown that molecules which are structurally related to SMD (e.g., *p*-aminobenzoic acid) retard the transformation of Form II to Form III in aqueous suspension by their ability to fit onto growing sites on nuclei of Form III. Attempts are being made to obtain a complex between SMD and PAS using different conditions from those described above.

Structure of the complex 2

The structure of complex **2** is shown in Fig. 4. The carboxylic acid group of the aspirin molecule engages in complementary hydrogen bonding with the SMD amide group and pyrimidinyl N atom. This mode of complexation is identical to that previously reported for complexes of the related drug sulfadimidine with substituted aromatic acids, and in particular, with acetylsalicylic acid.² There are no significant changes in bond lengths and bond angles in SMD upon complexation (Tables 4 and 5). The torsion angles for SMD (defined above) in the complex are τ_1 157.9(2)°, τ_2 -78.4(2)°, and τ_3 28.9(3)°. Molecular parameters for the aspirin molecule are identical to those for aspirin in its 1:1 complex with sulfadimidine² and the carbonyl group of the -COOH function is again syn-planar to the acetoxy group. The intramolecular N-H...O and N...H-O hydrogen bonds in **2** are identical in length to those in the sulfadimidine complex but are more linear in **2**. Table 6 lists these and other hydrogen bond data for **2**.

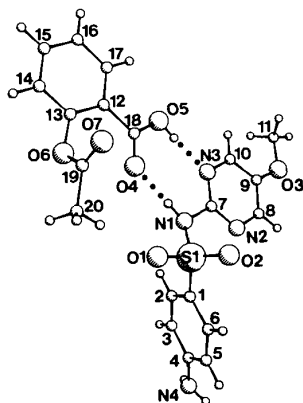


Fig. 4. Structure of the complex **2**.

Complexation by solid-solid reaction

Thus far, all of the 1:1 sulfonamide-aromatic carboxylic acid complexes reported in this series have been recovered from reactions occurring in solution, using either acetonitrile or ethanol as common solvent for the reacting components. However, we have recently obtained evidence for complex formation on co-grinding the solid reactants in a 1:1 molar ratio. These results will be published shortly.

Appendix

Hydrogen atom positions, anisotropic thermal parameters, torsion angles and structure factor tables for: **1** 5-methoxysulfadiazine (polymorphic Form II) and **2** 1:1 complex between 5-methoxysulfadiazine and acetylsalicylic acid.

Acknowledgments

Financial assistance from the FRD, Pretoria, and the University of Cape Town are gratefully acknowledged.

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