Structural Studies on Molecular Complexes V: Crystal Structures of Sulfathiazole–Sulfanilamide and Sulfathiazole–Theophylline Complexes

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Abstract □ The crystal structures of two sulfathiazole complexes, one involving theophylline and the other sulfanilamide, were determined by X-ray diffraction methods. The complexes are 1:1 adducts held together by hydrogen bonding. The hydrogen-bonding schemes in the two complexes are quite different. In the theophylline complex the aromatic amino group of sulfathiazole is involved in the principal intermolecular hydrogen bonds; whereas in the sulfanilamide complex, one of the sulfathiazole oxygens is the dominant participant. Sulfathiazole is present in both structures in the imido-configuration rather than the amido-form.

Keyphrases □ Molecular complexes—crystal structures □ Crystal structures—sulfathiazole–sulfanilamide, sulfathiazole–theophylline complexes □ Complexes, sulfathiazole with sulfanilamide and theophylline—crystal structure □ X-ray diffraction—analysis

The binding of sulfonamides to serum proteins has been extensively studied (1). The affinity of a sulfonamide for the serum proteins is an exceedingly important factor for dosage formulation, since the unbound material is responsible for the bacteriostatic activity (2). The principal protein nemesis in this regard is serum albumin. There appears to be one primary binding site in bovine serum albumin for sulfonamides (3); this site interacts with the *p*-aminobenzene sulfonamide moiety. Details of this interaction on a molecular level have yet to be elucidated.

Sulfonamides have also been reported to form association complexes with a variety of smaller molecules. Higuchi and Lach (4) described the interaction of sulfathiazole with a xanthine. A crystalline sulfathiazole–sulfanilamide complex was isolated and studied by Sekiguchi and Ito (5–7). Since the molecular basis(es) for the complex formation in such simple systems could be related to the principal driving force(s) for the sulfa–protein interactions and possibly for the antibacterial activity of these molecules which is a result of their interaction with a "bioreceptor," structural studies on some of these complexes were initiated.

The first sulfonamide complexes for which crystallographic studies were undertaken were sulfathiazole–theophylline (1:1) and sulfathiazole–sulfanilamide (1:1). These data are reported here.

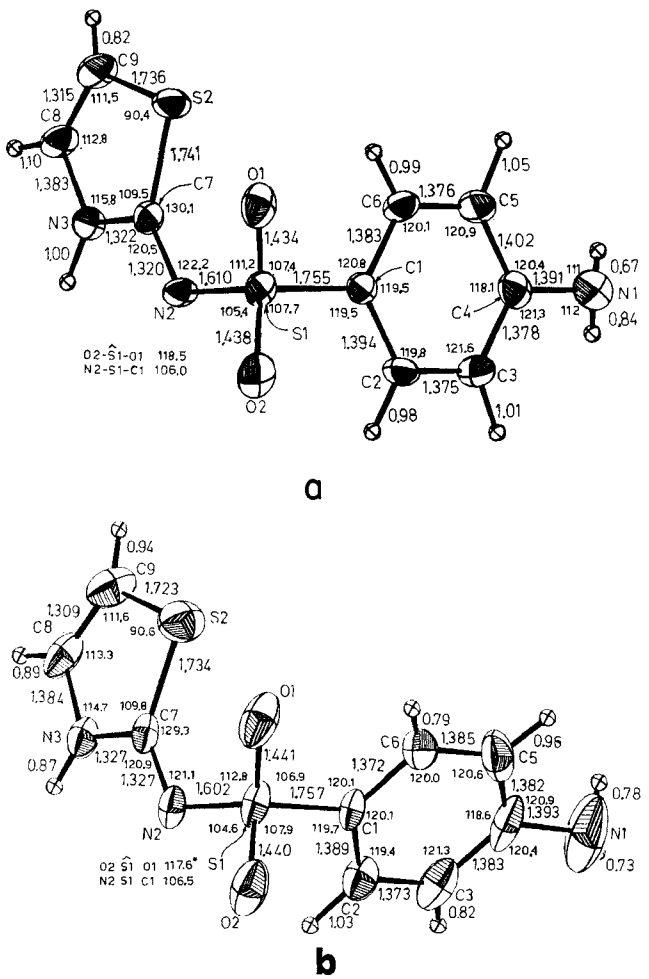


Figure 1—*Intramolecular bond lengths and angles of sulfathiazole found in the theophylline (a) and sulfanilamide (b) complexes. The thermal ellipses for the nonhydrogen atoms are drawn at the 50% probability level in this and all subsequent figures.*

EXPERIMENTAL

Colorless monoclinic prisms of the two complexes were obtained by slow evaporation of alcoholic solutions containing the respective chemical components. The following crystallographic data were measured for these crystals:

Sulfathiazole–Theophylline (1:1)		Sulfathiazole–Sulfanilamide (1:1)
11.020 (0.001) Å	*a*	9.135 (0.001) Å
9.010 (0.001) Å	*b*	5.379 (0.001) Å
20.186 (0.002) Å	*c*	36.633 (0.004) Å
113.68 (0.01)°	*β*	91.17 (0.02)°
1.57 g. cm.$^{-3}$	Density (measured by flotation)	1.47 g. cm.$^{-3}$
1.575 g. cm.$^{-3}$	Density (calculated)	1.431 g. cm.$^{-3}$
4	Z	4
$P2_1/c$	Space group	$P2_1/c$

Data Collection and Structure Determination—Intensity data on the complexes were collected by the stationary crystal-stationary counter technique on a General Electric single crystal orienter, using Cu Kα radiation. Monochromatization was approximately achieved by use of balanced Ross filters (Ni *versus* Co). The crystals, mounted for data collection, were 0.2 × 0.2 × 0.4 mm. for the sulfathiazole–theophylline complex and 0.1 × 0.2 × 0.3 mm. for the sulfanilamide–sulfathiazole complex. Of the 3086 independent reflections measured for the sulfanilamide-containing complex

Table I—Positional and Thermal Parameters[a] with Their Respective Standard Deviations (in Parentheses) × 10^4 for Nonhydrogen Atoms of Both Complexes

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
				Sulfathiazole–Theophylline Sulfathiazole					
S(1)	310(1)	2797(1)	1365(1)	65(1)	31(1)	16.1(.3)	−2(2)	20(1)	7(1)
S(2)	245(1)	6281(1)	1856(1)	108(2)	50(1)	14.6(.3)	9(2)	34(1)	−7(1)
O(1)	−245(3)	3151(4)	1878(2)	77(4)	85(5)	22 (7)	30(7)	41(3)	34(4)
O(2)	−212(4)	1544(4)	896(2)	83(4)	32(4)	29 (1)	−26(6)	4(4)	−8(4)
N(1)	6112(4)	1978(5)	2925(2)	78(5)	111(7)	19 (1)	21(9)	22(4)	−9(5)
N(2)	190(4)	4179(4)	837(2)	87(4)	32(4)	14 (1)	0(7)	32(4)	−3(4)
N(3)	230(4)	6672(4)	621(2)	97(5)	32(4)	13 (1)	4(7)	29(4)	10(4)
C(1)	2013(5)	2499(5)	1853(2)	68(5)	33(5)	12 (1)	1(8)	16(4)	3(4)
C(2)	2701(5)	1594(5)	1562(2)	84(5)	56(6)	12 (1)	4(9)	22(4)	−15(5)
C(3)	4051(5)	1449(6)	1915(3)	73(5)	76(6)	16 (1)	24(9)	36(5)	−6(5)
C(4)	4753(5)	2180(5)	2555(3)	68(5)	59(6)	15 (1)	0(9)	23(4)	12(5)
C(5)	4045(5)	3043(5)	2856(3)	89(6)	45(6)	17 (2)	−7(9)	15(5)	−17(5)
C(6)	2694(5)	3211(5)	2505(3)	74(5)	46(6)	18 (1)	9(9)	32(5)	−9(5)
C(7)	218(4)	5568(5)	1049(2)	58(5)	46(5)	14 (1)	8(8)	14(4)	1(4)
C(8)	249(5)	8083(5)	894(3)	99(6)	35(5)	20 (2)	2(9)	39(5)	−5(5)
C(9)	281(6)	8075(5)	1552(3)	119(7)	32(6)	23 (2)	2(10)	36(6)	−11(5)
				Theophylline					
N(1)	6727(4)	1315(4)	452(2)	63(4)	45(5)	20 (2)	12(7)	79(4)	1(4)
C(2)	6729(5)	2084(6)	1053(3)	61(5)	74(7)	21 (2)	10(9)	28(5)	11(5)
N(3)	6703(4)	3603(5)	1016(2)	90(5)	72(5)	16 (1)	12(8)	31(4)	−16(4)
C(4)	6710(5)	4292(5)	416(3)	64(5)	51(6)	19 (2)	6(8)	18(4)	7(5)
C(5)	6717(5)	3520(6)	−162(3)	70(5)	73(6)	15 (1)	−2(9)	21(4)	4(5)
C(6)	6756(5)	1932(6)	−171(3)	64(5)	73(6)	15 (1)	13(9)	6(4)	−2(5)
N(7)	6719(5)	4568(5)	−656(2)	102(5)	103(7)	21 (1)	12(10)	41(5)	28(5)
C(8)	6702(7)	5865(7)	−359(3)	130(8)	78(7)	31 (2)	−1(13)	26(7)	36(7)
N(9)	6702(5)	5785(5)	297(3)	120(6)	64(6)	26 (2)	8(9)	34(5)	6(5)
O(10)	6813(4)	1159(4)	−660(2)	112(5)	115(6)	16 (1)	36(8)	34(4)	−25(4)
C(11)	6801(6)	−320(6)	514(3)	121(7)	51(7)	33 (2)	11(11)	38(6)	11(6)
O(12)	6740(4)	1431(4)	1581(2)	116(5)	108(5)	22 (1)	30(8)	65(4)	32(4)
C(13)	6773(7)	4476(6)	1643(3)	143(8)	105(8)	23 (2)	30(13)	50(6)	−34(6)
				Sulfathiazole–Sulfanilamide Sulfathiazole					
S(1)	−1527(1)	4479(2)	4509.5(.2)	121(1)	209(3)	2.7 (.1)	−30(3)	−6.9(.4)	−6(1)
S(2)	−3737(1)	2867(2)	5154.4(.3)	119(1)	323(4)	7.2 (.1)	121(4)	13(1)	23(1)
O(2)	−164(3)	5219(6)	4352(1)	147(4)	429(12)	4.5 (.2)	−225(12)	−5(1)	16(3)
O(1)	−2452(4)	6407(5)	4651(1)	222(5)	217(9)	4.4 (.2)	100(11)	−6(2)	−9(2)
N(1)	−4880(6)	−660(11)	3334(1)	247(8)	868(29)	6.4 (.3)	−571(27)	−27(3)	5(5)
N(2)	−1072(3)	2453(6)	4812(1)	97(4)	276(11)	2.9 (.2)	1(10)	−7(1)	11(2)
N(3)	−1685(3)	−133(5)	5287(1)	103(4)	237(10)	3.2 (.2)	17(10)	−3(1)	7(2)
C(1)	−2558(4)	2899(6)	4173(1)	93(4)	207(11)	2.4 (.2)	−13(11)	−6(1)	9(2)
C(2)	−2003(4)	753(7)	4017(1)	119(5)	225(12)	4.1 (.2)	15(13)	−1(2)	3(3)
C(3)	−2791(5)	418(7)	3744(1)	168(6)	260(13)	4.1 (.2)	−95(15)	3(2)	−9(3)
C(4)	−4128(5)	497(8)	3622(1)	151(6)	441(18)	2.6 (.2)	−284(17)	−6(2)	10(3)
C(5)	−4659(4)	2647(10)	3777(1)	88(5)	630(23)	5.5 (.3)	−86(17)	−11(2)	57(4)
C(6)	−3876(4)	3843(8)	4052(1)	96(4)	336(14)	4.6 (.2)	64(13)	−1(2)	14(3)
C(7)	−2010(4)	1723(6)	5062(1)	88(4)	216(11)	2.7 (.2)	0(11)	−7(1)	4(2)
C(9)	−3947(5)	657(8)	5490(1)	135(5)	320(15)	6.2 (.3)	11(15)	22(2)	5(4)
C(8)	−2779(5)	−736(7)	5528(1)	149(5)	265(3)	3.3 (.2)	−4(14)	9(2)	11(3)
				Sulfanilamide					
S	1461(1)	4936(2)	3371.9(.2)	82(1)	298(3)	4.4 (.1)	−10(3)	−7.8(.4)	−7(1)
O(1)	2659(3)	5710(6)	3148(1)	79(3)	492(13)	5.9 (.2)	−75(10)	−2(1)	−23(3)
O(2)	1419(3)	2423(5)	3494(1)	130(4)	297(11)	9.3 (.3)	48(10)	−26(2)	10(3)
N(1)	−3841(4)	6795(7)	2460(1)	116(4)	456(16)	6.1 (.3)	−17(13)	−16(2)	20(3)
N(2)	1543(4)	6638(7)	3733(1)	135(14)	389(14)	4.0 (.2)	−73(13)	−3(2)	−4(3)
C(1)	−152(4)	5558(6)	3122(1)	83(4)	240(12)	3.5 (.2)	−12(11)	−6(1)	−2(3)
C(2)	−1317(4)	3931(7)	3130(1)	102(4)	250(13)	5.1 (.3)	−55(12)	−4(2)	25(3)
C(3)	−2542(4)	4338(8)	2911(1)	91(4)	341(15)	6.8 (.3)	−99(14)	−9(2)	18(4)
C(4)	−2626(4)	6374(7)	2681(1)	93(4)	319(14)	3.4 (.2)	31(12)	−3(2)	−3(3)
C(5)	−1467(4)	8064(7)	2686(1)	114(5)	269(13)	4.3 (.2)	12(13)	0(2)	17(3)
C(6)	−235(4)	7655(7)	2901(7)	95(4)	240(12)	4.8 (.2)	−60(12)	2(2)	5(3)

[a] Temperature factors expressed in the form $\exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$.

(*two theta* limit 130°), 2675 had counts significantly larger than their respective backgrounds. For the theophylline complex, 2580 reflections of the 2718 measured (*two theta* limit 120°) had observable intensities. The intensities were converted to structure factor amplitudes ($|\mathbf{F}|$) by applying corrections for Lorentz-polarization effects, $\alpha_1 - \alpha_2$ splitting, and absorption. The structure factors were placed on an absolute scale by Wilson's method.

The two structures were solved by application of the Sayre relationship (8). The procedure described by Long (9) was utilized to determine the phases of 398 normalized structure factors ($|\mathbf{E}|$), with $\mathbf{E}_{hkl} \geq 1.5$ for the sulfanilamide–sulfathiazole complex, and of 270 reflections with $\mathbf{E}_{hkl} \geq 1.65$ for the theophylline complex. The positions of all the nonhydrogen atoms were recognizable in the E-maps (10) computed with these phases.

Table II—Hydrogen Atom Parameters with Standard Deviations (in Parentheses)

Atom	$x \times 10^3$	$y \times 10^3$	$z \times 10^3$	Biso
		Sulfathiazole–Theophylline Sulfathiazole		
H(N1)1	640(8)	254(9)	315(4)	7.1(1.9) Å²
H(N1)2	648(6)	191(7)	263(3)	4.2(1.3)
H(N3)	28(5)	653(5)	14(3)	2.2(1.0)
H(C2)	237(8)	124(9)	106(4)	7.1(1.9)
H(C3)	462(5)	99(6)	164(3)	2.9(1.1)
H(C5)	440(5)	352(6)	338(3)	2.4(1.0)
H(C6)	210(6)	370(7)	270(3)	3.8(1.3)
H(C8)	34(7)	899(9)	55(4)	6.6(1.8)
H(C9)	38(4)	879(5)	182(2)	1.9(1.0)
		Theophylline		
H(N7)	665(6)	426(7)	−111(3)	4.7(1.4)
H(C8)	656(5)	678(6)	−66(3)	3.1(1.1)
H(C11)1	771(7)	−60(9)	71(4)	6.1(1.8)
H(C13)1	748(9)	391(11)	219(5)	9.8(2.6)
H(C13)2	596(7)	428(8)	178(4)	5.8(1.6)
H(C13)3	669(5)	544(6)	152(3)	3.2(1.1)
H(C11)2	640	−60	80	–[a]
H(C11)3	610	−90	10	–[a]
		Sulfathiazole–Sulfanilamide Sulfathiazole		
H(N1)1	−492(7)	194(13)	327(2)	9.9(1.8)
H(N1)2	−568(5)	−47(10)	339(1)	5.9(1.2)
H(N3)	86(5)	94(9)	471(1)	5.0(1.1)
H(C2)	−101(4)	3(8)	409(1)	3.8(0.9)
H(C3)	−242(4)	−169(8)	366(1)	3.7(0.9)
H(C5)	−553(5)	338(9)	367(1)	5.3(1.1)
H(C6)	−420(4)	501(7)	415(1)	3.3(0.8)
H(C9)	−489(5)	413(9)	558(1)	4.3(1.1)
H(C8)	−259(4)	−191(8)	569(1)	3.5(0.8)
		Sulfanilamide		
H(N1)1	−443(4)	549(8)	245(1)	4.0(0.9)
H(N1)2	−374(5)	761(9)	230(1)	4.8(1.0)
H(N2)1	99(4)	619(7)	390(1)	3.0(0.8)
H(N2)2	157(5)	796(9)	366(1)	4.8(1.0)
H(C2)	−129(4)	262(6)	325(1)	2.3(0.7)
H(C3)	−337(6)	343(12)	295(2)	7.8(1.5)
H(C5)	−152(5)	955(9)	257(1)	5.7(1.1)
H(C6)	53(4)	878(8)	288(1)	3.7(0.8)

[a] Position found in difference electron density map.

The structures were refined by least squares, employing a block diagonal approximation. During the final stages of refinement, difference electron density maps enabled the hydrogen atoms to be located. All but two were refined by least squares. The Cruickshank-type weighting schemes (11) used in the final cycles of refinement were

$$\sigma^2(|F|) = 1.44 - 0.089|F| + 0.0044|F|^2 \quad \text{(Eq. 1)}$$

for sulfanilamide–sulfathiazole, and

$$\sigma^2(|F|) = 1.39 - 0.078|F| + 0.0078|F|^2 \quad \text{(Eq. 2)}$$

for theophylline–sulfathiazole, with the unobserved reflections being given zero weight. The final R values (conventional reliability index $R = \Sigma\,||F_o| - |F_c||/\Sigma\,|F_o|$) were 0.068 (0.070 for all data) and 0.054 (0.080 including "unobserved" data) for the theophylline- and sulfanilamide-containing complexes, respectively. The atomic coordinates and thermal parameters for the complexes are presented in Tables I and II.[1]

The X-ray scattering factors used throughout these calculations were taken from the "International Tables for X-ray Crystallography" (12) with the exception of hydrogen. The form factors published by Stewart *et al.* (13) for hydrogen were utilized.

[1] A tabulation of the structure factors can be obtained from either the authors or the Health Sciences Library of the State University of New York at Buffalo.

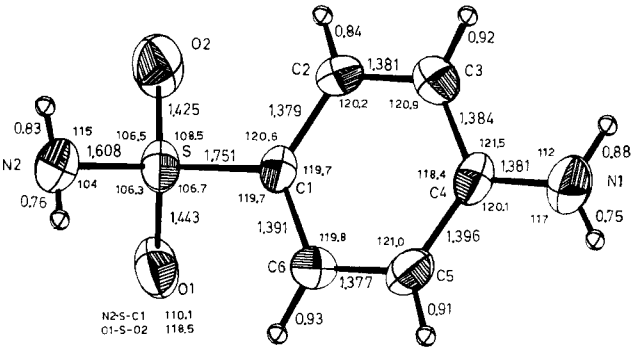


Figure 2—*Bonding parameters observed for sulfanilamide.*

The bond lengths and angles obtained for the molecular entities comprising the two complexes are shown in Figs. 1–3. The uncertainties associated with these parameters are in general about 0.004 Å and 0.2° for bonds and angles involving a sulfur and 0.007 Å and 0.5° for the other nonhydrogen bonds. The errors in the hydrogen positions are such that their bonding parameters are about 10 times as great as those for the nonhydrogen atoms. The high error associated with the hydrogens is not unusual in X-ray structures, especially those containing "heavy" atoms such as sulfur in these structures. For this reason, only those angles involving hydrogens pertinent to the discussion are presented.

DISCUSSION

Sulfathiazole—The sulfathiazole molecules in each complex have similar intramolecular bonding parameters; none of the differences is significant at the $p = 0.001$ level. The bond lengths and angles of the *para*-aminosulfonamide portion of the molecule are in good agreement with these values reported for sulfanilamide (14–17).

The sulfathiazole molecules are present in the imidotautomeric form in both complexes, *i.e.*, the proton is attached to N(3) rather than N(2). The preference of sulfathiazole for the imido-configuration over the amido-form was previously shown by IR studies (18) on this compound. The C(7)—N(3) and C(7)—N(2) bonds have essentially equivalent amounts of double bond character [bond order p is approximately 0.75 when calculated using the formula of Liquori and Vaciago (19)]. Therefore, Formula II would be a better representation of this linkage than I.

Sulfathiazole is capable of attaining a variety of conformation states by rotation about three bonds: C(1)—S(1), S(1)—N(2), and C(7)—N(2). A particular atomic constellation of sulfathiazole can thus be specified by three torsion angles. The three dihedral angles specified are ϕ C(1)—S(1)—N(2)—C(7), ϕ S(1)—N(2)—C(7)—S(2), and either ϕ C(6)—C(1)—S(1)—N(2) or ϕ C(2)—C(1)—S(1)—N(2), the choice being the acute angle. By choosing the smaller of the latter two dihedral angles, the ambiguity resulting

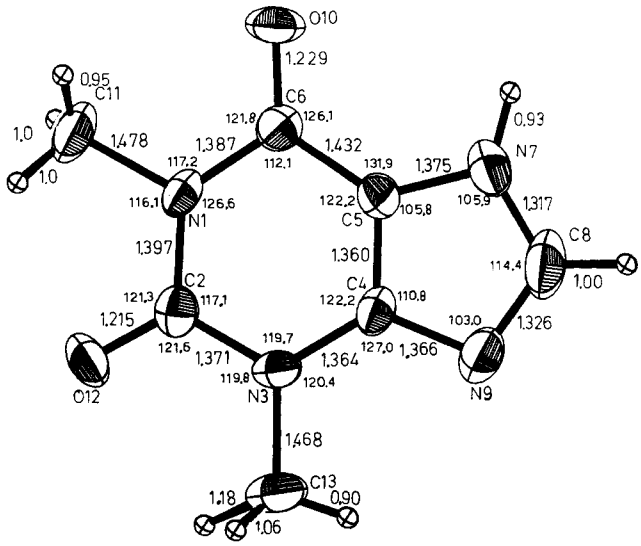
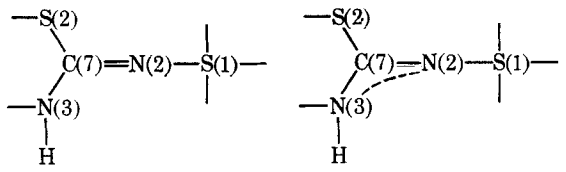


Figure 3—*Bond lengths and angles calculated for theophylline.*

Table III—Conformational Parameters[a]

	Torsion Angles°					
	Sulfathiazole		Sulfanilamide			
	Sulfanilamide Complex	Theophylline Complex	Sulfathiazole Complex	α-Form[b]	β-Form[c]	Hydrate[d]
N(2)—S(1)—C(2)[C(6)]	−52	−87	79	59	71	90
C(1)—S(1)—N(2)—C(7)	−80	−85				
S(1)—N(2)—C(7)—S(2)	−7	−6				

[a] Calculated in the manner prescribed by Klyne and Prelog (24). [b] Reference 15. [c] Reference 16. [d] Reference 14.



I II

from the twofold symmetry of the *p*-aminophenyl residue is resolved. The values obtained for the two sulfathiazole complexes are listed in Table III. The major conformational difference between the sulfathiazoles of the two complexes is the twist of the benzene ring about the C(1)—S(1) bond. Intermolecular packing forces (which are quite different in the two complexes) in all probability influence this conformation. The amide linkage of each sulfathiazole is hydrogen bonded in the same manner; this accounts for the similarity in the other two torsion angles.

The planarity of the benzene and thiazole ring is shown in Table IV. In both complexes, N(1) and S(1) are displaced from the plane of the phenyl ring by small but significant amounts. In the sulfanilamide-containing complex, N(2) is displaced significantly from the thiazole ring; such is not the case in the theophylline complex. These discrepancies are consequences of the intermolecular packing differences.

Sulfanilamide—The intramolecular bond parameters of sulfanilamide in the complexed state correspond quite well with those reported for various crystalline modifications of this molecule (14–17). A comparison of the conformation of sulfanilamide [rotation about the C(1)—S bond] in the various modifications and in the complex can be found in Table III. A molecular model (CPK model) of this compound indicates that there is no highly significant steric hindrance to rotation about this bond, but that torsion angles in the synclinal range (60 ± 30°) should be preferred. The observed angles for sulfanilamide and sulfathiazole all fall in the most favorable range.

Theophylline—In general, the bonding parameters for this molecule in the sulfathiazole–theophylline complex, 5-chlorosalicylic acid–theophylline complex (20), and theophylline monohydrate (21) are similar. The atoms comprising the purine ring in the sulfa complex are essentially coplanar (Table IV), as is the case in theophylline monohydrate. In the 5-chlorosalicylic acid–theophylline complex, "polarization bonding" was implicated as an intermolecular packing force, which resulted in a distinct distortion of the purine ring. Such forces do not appear to be operative in this crystalline complex.

Intermolecular Bonds—Hydrogen bonding appears to be the predominant intermolecular force responsible for the formation of these complexes. The hydrogen bonds in the two structures are illustrated in Figs. 4 and 5.

Although the two hydrogen-bonding schemes are distinctly different, one hydrogen interaction is common to both complexes. This involves the N(3)—H(N3)...N(2) hydrogen bridges between sulfathiazole molecules, which is fairly strong for an N—H...N interaction (22). The centrosymmetric nature of this bond results in a dimeric arrangement of the sulfathiazole molecules.

Theophylline Complex (Fig. 4)—The aromatic amino group [N(1)] is the only functional group of the sulfa that directly participates in the complexation. N(7) of theophylline donates its proton to the sulfa N(1), and the carbonyl oxygen [O(12)] of theophylline accepts an N(1) proton. Although the H(N1)...O(10) length of 2.54 Å is somewhat greater than the accepted maximum for a

Table IV—Displacements from Some Least-Squares Planes[a]

Atoms Comprising Least-Squares Plane	Sulfathiazole–Theophylline			Atoms Comprising Least-Squares Plane	Sulfathiazole–Sulfanilamide		
	Δ, Å	Other Atoms	Δ, Å		Δ, Å	Other Atoms	Δ, Å
	Sulfathiazole					**Sulfathiazole**	
C(1)	−0.012	S(1)	−0.143	C(1)	0.004	S(1)	−0.062
C(2)	0.008	N(1)	0.039	C(2)	−0.002	N(1)	−0.053
C(3)	0.006	O(1)	0.445	C(3)	−0.002	O(2)	−1.280
C(4)	−0.017	O(2)	0.388	C(4)	0.004	O(1)	0.135
C(5)	0.013	N(2)	−1.718	C(5)	−0.003	N(2)	1.103
C(6)	0.001			C(6)	−0.001		
C(7)	0.001	N(2)	0.002	C(7)	−0.012	N(2)	−0.042
S(2)	−0.004	S(1)	0.135	S(2)	0.011	S(1)	−0.232
C(8)	−0.008	H(N3)	0.06	C(8)	0.004	H(N3)	0.03
C(9)	0.008	H(C8)	0.08	C(9)	−0.011	H(C8)	0.06
N(3)	0.004	H(C9)	0.08	N(3)	0.007	H(C9)	−0.19
	Theophylline					**Sulfanilamide**	
N(1)	−0.011	O(10)	0.058	C(1)	0.023	S	−0.090
C(2)	0.006	C(11)	0.048	C(2)	0.034	O(1)	−0.947
N(3)	−0.005	O(12)	0.019	C(3)	0.022	O(2)	−0.449
C(4)	0.001	C(13)	0.084	C(5)	−0.001	N(1)	−0.021
C(5)	−0.008	H(N7)	−0.07	C(6)	0.043	N(2)	1.348
C(6)	0.015	H(C8)	−0.14		0.039		
N(7)	−0.003						
C(8)	−0.002						
N(9)	0.007						

[a] The least-squares planes were calculated according to the method of Schomaker *et al.* (25).

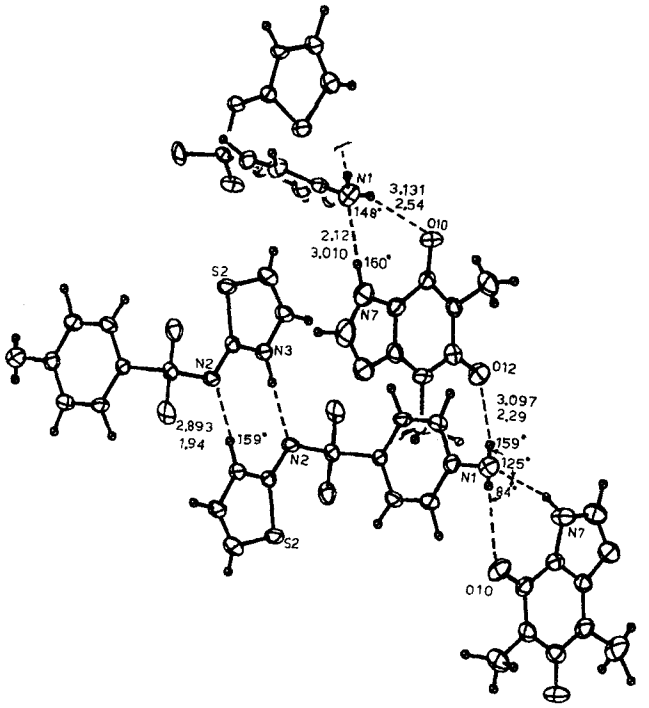


Figure 4—*A general view of the hydrogen bonding (dashed lines) in the theophylline-sulfathiazole complex.*

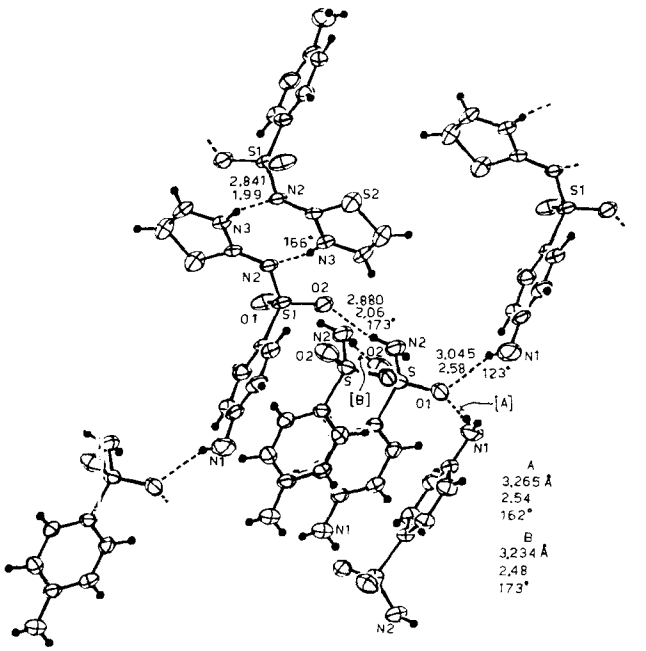


Figure 5—*The proposed hydrogen-bonding scheme (dashed lines) for the crystalline sulfanilamide-sulfathiazole complex, projected down a noncrystallographic axis.*

hydrogen bond [2.4 Å has been proposed as the upper limit for the H to O distance when hydrogen bonding is taking place (23)], the error in the hydrogen position makes it quite conceivable that this is indeed a hydrogen bond and not just a close contact. A consideration of the angles about N(1) and O(10) and the short N(1) — H bond lends credence to the proposed hydrogen-bonding scheme.

The hydrogen bonding about the amino group of sulfathiazole is no doubt responsible to a great extent for the distortion of this functional group from trigonal symmetry. Similar distortions were observed in β-sulfanilamide (16).

Sulfanilamide Complex (Fig. 5)—The relatively high uncertainty in the hydrogen positional parameters puts some doubt on the strength of the proposed hydrogen interactions; but as in the case of the theophylline complex, other molecular parameters were considered in developing the hydrogen-bonding scheme illustrated. The principle intermolecular bond (*i.e.*, greatest strength) between the two molecular entities is the donation of an N(2) hydrogen of sulfanilamide to O(2) of sulfathiazole. Another bridge between the two molecules, but much weaker in strength, involves the acceptance by the sulfanilamide oxygen [H(N1)]. The N to O distance in this hydrogen bond is over 0.16 Å longer than the other interspecies hydrogen bond.

The sulfanilamide molecules are weakly hydrogen bonded to one another through two N—H...O hydrogen bonds. Their N to O lengths (3.234 and 3.265 Å) fall in the upper range of such interactions (22); thus they can be considered extremely weak.

Ito and Sekiguchi (7) proposed a molecular structure for this complex that is quite different from the observed arrangement. The intermolecular bonding found in this crystal structure is consistent with the spectral data used to derive their model.

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