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X-Ray Analysis of the Molecular Compound of Homosulfanilamide and Sulfathiazole

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The solid state structure of a 1:1 homosulfanilamide: Sulfathiazole adduct was determined by single crystal X-ray diffraction. The results showed that the acidic proton of sulfathiazole is abstracted by the aminomethyl group of homosulfanilamide to form a salt. Intramolecular hydrogen bonds are also involved in the stabilization of this "molecular compound".

Sekiguchi, Owada and Ito have studied[2] the physico-pharmaceutical properties of the "molecular compound" of homosulfanilamide (HS) and sulfathiazole (ST). On the basis of their studies it was concluded that the HS component exists as the ammonium cation and that ST exists as the deprotonated anion. Hydrogen bonding between the two molecular entities was not felt to play an important role in this complex. Since the sulfathiazole-sulfanilamide complex has been shown to exist as a hydrogen bonded adduct in solution[3] and in the solid state,[4] it was deemed worthwhile to carry out a X-ray structural study on this molecular complex to fully illustrate the nature of the forces between the molecular species of this complex.

Experimental

Crystals of the complex were obtained by slow evaporation of an ethanol solution containing equimolar amounts of the respective components. The material crystallizes in the triclinic system with the following unit cell constants: $a=12.106$ (1) Å, $b=10.421$ (2) Å, $c=8.284$ (2) Å, $\alpha=102.98$ (3)°, $\beta=90.03$ (4)°, and $\gamma=107.72$ (2)°. The measured density of 1.499 gm/cm^3 compares well with the value of 1.515 gm/cm^3 calculated using a molecular weight of 441.56 and assuming two molecular adducts per unit cell. Statistical analysis of the intensity data indicated that the crystal is centrosymmetric. It was assumed throughout the study that the space group is $P\bar{1}$; successful refinement of the structure confirmed this assumption.

Intensity data were collected by the stationary crystal stationary counter technique on a General Electric XRD-6 diffractometer using Ni-Co balanced filters for Cu Kα radiation. In the range of measurement (0° to 110° in 2 θ) 2267 unique reflections out of 2306 had intensities significantly greater than their respective backgrounds. The data were corrected for Lorentz and polarization factors, α_1—α_2 splitting, and absorption. The absorption correction was based on the anisotropy of transmission of the X-ray beam as a function of the angle ϕ for a reflection at $\chi=90°$.

The structure was solved by "direct methods" through application of the Sayre relationships.[5] A program by Long[6] was used to determine the phases of 231 reflections with $|Eo|\geq 1.5$. An E-Fourier map calculated with the most consistent set of signs for the 231 reflections revealed the positions of all 21 nonhydrogen atoms. The 14 hydrogens were located in subsequent difference electron density maps. The structure was refined by the least squares method using a block diagonal approximation to the normal equations. The weighting scheme used in the final cycles of refinement was $w^{-1}=1.444-0.089\ |Fo|+0.004\ |Fo|^2$, such that the average weighted difference squared ($w\Delta F$) is approximately constant over the whole range of observed structure factors. The unobserved data were given zero weight. With the nonhydrogen

1) Location: *Buffalo, N.Y., 14214, U.S.A.*
2) K. Sekiguchi, E. Owada, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **15**, 873 (1967).
3) K. Sekiguchi and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **13**, 405 (1965).
4) E. Shefter and P. Sackman, *J. Pharm. Sci.*, **60**, 282 (1971).
5) D. Sayre, *Acta Cryst.*, **5**, 60 (1952).
6) R.E. Long and Ph. D. Thesis, University of California, Los Angeles (1965).

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atoms having anisotropic temperature factors and the hydrogen atoms isotropic ones, the final weighted and unweighted R factors are 0.087 and 0.068, respectively.

The final positional and thermal parameters together with their estimated standard deviations are given in Tables I and II. The estimated standard deviations were calculated from the inverses of the full normal equation blocks.

TABLE I. Positional and Thermal Parameters With Their Respective Estimated Standard Deviations (In Parentheses) $\times 10^4$

Temperature Factor $= \exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)]$

Atom	x/a	y/b	z/c	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
				ST					
S1	−1965(1)	−4441(1)	1543(2)	68(1)	78(2)	112(2)	85(2)	36(3)	37(3)
S2	−4179(1)	−6166(2)	3111(2)	62(1)	141(2)	148(3)	50(3)	−6(3)	105(4)
O1	−2771(4)	−5480(4)	243(5)	96(4)	82(5)	114(7)	87(7)	−11(8)	−8(9)
O2	− 792(4)	−3865(4)	1031(5)	73(4)	125(6)	164(8)	112(8)	86(9)	84(11)
N1	−3660(5)	404(5)	3299(7)	97(5)	91(6)	228(12)	116(10)	−16(12)	−3(14)
N2	−1780(4)	−4988(5)	3116(6)	58(4)	75(5)	138(8)	66(8)	4(9)	66(11)
N3	−2607(4)	−5890(5)	5319(6)	85(5)	86(6)	109(8)	70(9)	−12(10)	42(11)
C1	−3345(5)	− 785(6)	2984(7)	60(5)	79(7)	126(10)	66(9)	54(11)	53(13)
C2	−2371(5)	− 834(6)	3826(7)	73(5)	70(7)	121(10)	55(10)	0(11)	−29(13)
C3	−1968(5)	−1953(6)	3410(7)	65(5)	92(7)	119(10)	69(10)	−6(11)	66(13)
C4	−2553(5)	−3077(5)	2157(6)	64(5)	56(6)	95(9)	58(9)	36(10)	33(11)
C5	−3546(5)	−3057(6)	1339(7)	54(5)	81(7)	114(9)	57(9)	−6(10)	20(13)
C6	−3927(5)	−1929(6)	1744(7)	54(5)	99(7)	126(10)	74(10)	4(11)	70(14)
C7	−2724(5)	−5617(5)	3882(6)	74(5)	59(6)	93(9)	79(9)	−2(10)	13(12)
C8	−3669(6)	−6501(6)	5873(8)	100(6)	93(8)	131(11)	83(11)	50(13)	66(14)
C9	−4598(6)	−6701(7)	4906(8)	78(6)	132(9)	152(11)	68(12)	78(13)	122(16)
				HS					
S	2820(2)	−808(2)	1598(2)	144(2)	124(2)	174(3)	191(4)	−109(4)	−67(4)
O1	4005(5)	4(7)	1863(10)	133(7)	215(10)	600(23)	262(14)	−350(20)	−331(24)
O2	2358(7)	−1742(6)	2631(7)	364(12)	227(10)	165(10)	464(19)	72(17)	172(16)
N1	597(5)	4573(6)	2519(6)	93(5)	154(8)	130(9)	179(11)	−32(11)	−14(13)
N2	2517(5)	−1715(5)	−290(6)	136(6)	90(6)	118(9)	112(10)	23(12)	4(12)
C1	88(6)	3225(7)	2882(9)	74(6)	124(9)	234(15)	103(12)	−1(15)	−19(18)
C2	802(5)	2243(6)	2404(7)	57(5)	105(8)	124(10)	87(10)	−12(11)	13(14)
C3	1985(5)	2688(6)	2271(8)	68(5)	87(7)	165(12)	66(10)	19(12)	25(14)
C4	2588(5)	1752(6)	1955(8)	67(5)	104(8)	147(11)	88(11)	3(12)	7(15)
C5	2013(5)	356(6)	1789(7)	97(6)	77(7)	104(10)	107(11)	−28(12)	−3(13)
C6	835(6)	−94(6)	1864(8)	89(6)	83(8)	190(13)	41(11)	−48(14)	34(16)
C7	236(6)	858(7)	2167(8)	64(6)	129(9)	174(13)	42(11)	−13(13)	2(17)

TABLE II. Hydrogen Atom Parameters with Standard Deviations (in Parentheses)

Atom	$x/a \times 10^3$	$y/b \times 10^3$	$z/c \times 10^3$	Biso (Å²)
		ST		
H1(N1)	−435(6)	21(7)	305(8)	5.6(1.6)
H2(N1)	−342(5)	78(5)	394(7)	3.5(1.2)
H (C2)	−203(5)	−31(5)	446(7)	3.3(1.2)
H (C3)	−133(5)	−203(6)	405(7)	4.5(1.4)
H (C5)	−389(5)	−389(6)	52(8)	4.9(1.4)
H (C6)	−452(5)	−200(5)	131(7)	3.3(1.2)
H (C8)	−373(5)	−673(6)	683(7)	4.6(1.4)
H (C9)	−526(6)	−688(6)	506(8)	5.1(1.5)

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		HS		
H1(N1)	126(5)	514(6)	310(7)	4.1(1.3)
H2(N1)	5(6)	505(7)	242(9)	6.3(1.6)
H3(N1)	93(8)	446(9)	168(11)	9.5(2.4)
H1(N2)	259(6)	−243(7)	−31(8)	5.3(1.5)
H2(N2)	281(6)	−144(7)	−89(8)	5.4(1.6)
H1(C1)	−55(4)	288(5)	222(6)	3.0(1.1)
H2(C1)	−2(7)	357(8)	421(10)	8.2(2.1)
H (C3)	234(7)	384(8)	244(10)	7.3(1.9)
H (C4)	325(6)	210(7)	175(9)	6.5(1.8)
H (C6)	42(5)	−80(6)	177(7)	3.9(1.3)
H (C7)	−54(5)	52(6)	197(7)	4.2(1.3)

Discussion of Result

Intramolecular Bonding

The intramolecular bond distances and angles of the sulfathiazole (ST) and homosulfanilamide (HS) components are shown in Figures 1 and 2, respectively. The estimated standard deviations for the bond lengths and angles are in general 0.005 Å and 0.2° for those bonds involving sulfur, and 0.008 A and 0.5° for those involving the other non-hydrogen atoms. The errors in the parameters involving hydrogen atoms are about ten times as large as those of the non-hydrogen atoms.

Sulfathiazole

There are significant differences in the bonding parameters of the ST entity of this complex as compared with the parameters found for ST in other solid state complexes.[4] The most striking disparity results from the transfer of the hydrogen atom attached to N3 of ST to the basic aminomethyl group of HS in this complex. This deprotonation results in changes of the electronic structure of ST, as reflected in comparative differences of the intramolecular parameters of ST in the complexes of ST-sulfanilamide,[4] ST-theophylline,[4] and ST-HS (see Table III). The C7-N3 and S1-N2 bond lengths are shorter and the N2-C7 and S1-O distances longer, with concommitantly smaller N2-C7-S2 and O1-S1-O2 bond angles in the ST-HB complex. Similar changes in the $-SO_2-N<$ portion of dibenzene sulfonamide have been shown[7] to occur upon deprotonation, suggesting a greater d_π—p_π interaction in in the S1-N2 bond.

Sulfathiazole in both the sulfanilamide and theophylline complexes is present in the imido tautomeric form with the proton attached to N3 and has essentially identical bonding parameters in these complexes. While the N3-C7 and C7-N2 bond distances of ST in these complexes are equal (see Table III), in the ST-HS complex the N3-C7 bond distance is shorter by 0.065 Å than the C7-N2 bond. The alteration in the electronic structure on loss of the pro-

Table III. Comparison of ST Bonding Parameters Found In Several Complexes

Bond	ST-Anion	ST-Sulfanilamide	ST-Theophylline
N3-C7	1.302 Å	1.327 Å	1.322 Å
C7-N2	1.367	1.327	1.320
N2-S1	1.577	1.602	1.610
S1-O1	1.455	1.441	1.434
S1-O2	1.468	1.440	1.438
N2-C7-S2	126.3°	129.3°	130.1°
O1-S1-O2	114.6	117.6	118.5

7) F.A. Cotton and P.F. Stokely, *J. Am. Chem. Soc.*, **92**, 294 (1970).

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ton indicates that the negative charge is localized primarily on N3 with some delocalization to N2. This is further evidenced by the presence of a strong hydrogen bond to N3 and a somewhat weaker one to N2.

Sulfathiazole is capable of a variety of conformational states by means of rotation about three bonds: C4-S1, S1-N2, and N2-C7.[4] Table IV compares the acute torsion angles about these bonds for the three ST complexes. The small variation in values is in all probability due to the differences in packing forces for each complex. Molecular models suggest that these conformations represent the most sterically favorable conformations.

TABLE IV. Conformation Parameters

——Torsion Angles (°)[a]——

Compound	N2-S1-C4-C3	C4-S1-N2-C7	S1-N2-C7-S2
ST anion	56	66	12
ST-sulfanilamide	52	80	7
ST-theophylline	87	85	6
HS cation	73[b]		
Sulfanilamide-ST	79		
Sulfanilamide (α form)	59		
Sulfanilamide (β form)	71		
Sulfanilamide hydrate	90		

a) Calculated in the manner described by Shefter and Sackman (3).
b) In the case of HS the atoms involved in this conformation angle are N2-S1-C5-C4.

Homosulfanilamide

In general, the intramolecular bonding parameters of HS agree well with the corresponding values for sulfanilamide in the ST complex[4] and in the various crystalline modifications of sulfanilamide studied.[8–10]

The presence of the methylene carbon between the amino group and the benzene ring prevents delocalization of the nitrogen lone pair of electrons into the *pi* ring. This results in an increased basicity of the amino group in HS relative to sulfanilamide. It is this greater

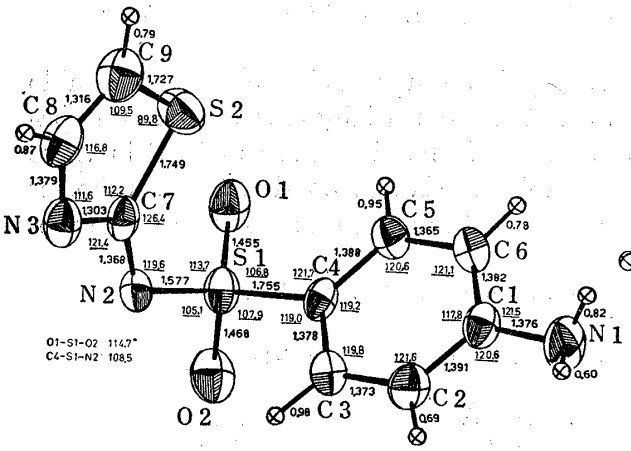

Fig. 1. Bond Distances and Angles for Sulfathiazole

Thermal ellipsoids are drawn at the 50% probability level in this figure and all subsequent illustrations.

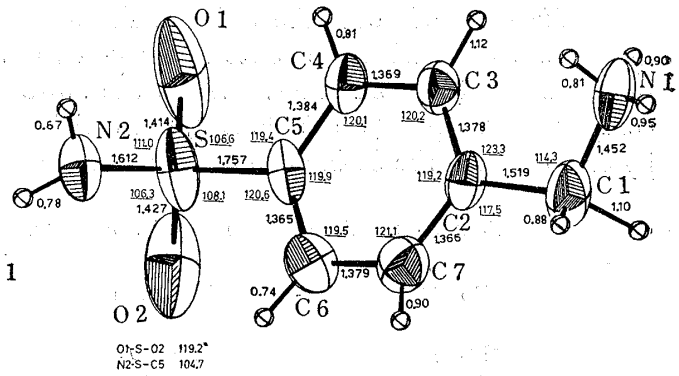

Fig. 2. Bonding Parameters for Homosulfanilamide

8) M. Alleaume and J. Decap, *Acta Cryst.*, **B24**, 214 (1968).
9) B.H. O'Connor and E.N. Maslen, *Acta Cryst.*, **18**, 363 (1965).
10) A.M. O'Connell and E.N. Maslen, *Acta Cryst.*, **22**, 134 (1967).

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basicity that enables the HS amino group to abstract the acidic proton from ST to form a salt. In the case of sulfanilamide complexed with ST, the proton is not removed.

The S-O lengths of HS are significantly shorter than those of the ST component. This can result from a decreased *pi* overlap between S and N2 in HS relative to ST and also in part due to the greater thermal motion of the oxygen atoms of HS (see Figure 1).

The conformation about the C5-S of HS is compared with values from various other sulfas in Table IV. The torsion angles all fall within the synclinal range (60±30°) which is the preferred steric conformation.

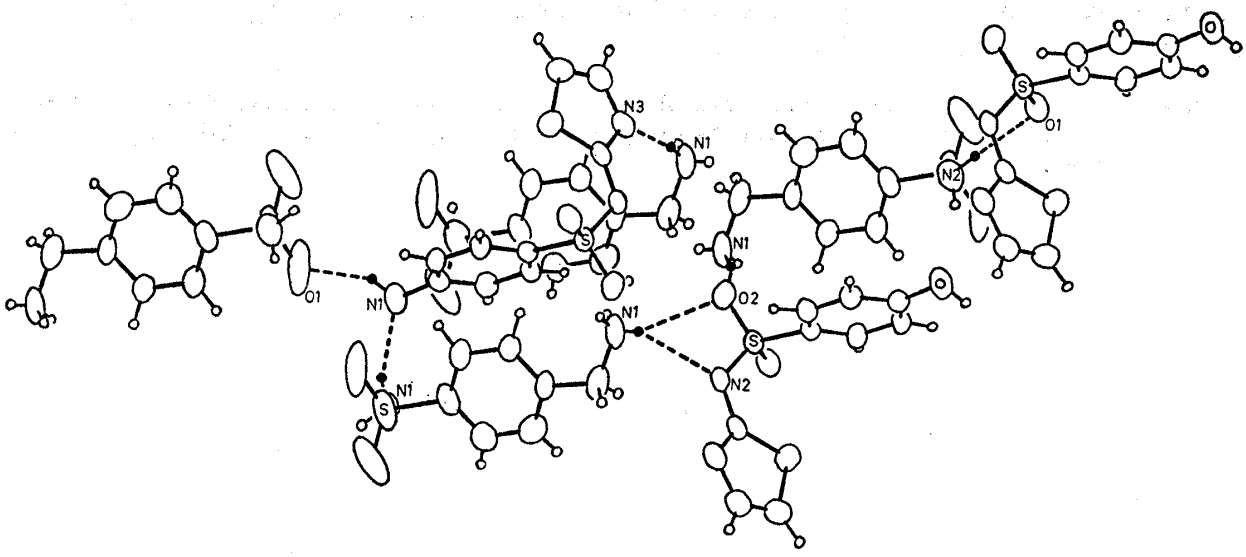

Fig. 3. Hydrogen Bonds found in the Crystal Structure of the HS–ST complex

Table V. Intermolecular Hydrogen Bond Parameters

Acceptors	Donors	Parameters	
O1 HS	H1(N1) ST	H···O1	2.15 Å
		N···O1	2.940 Å
		N1-H···O1	164°
O1 ST	H2(N2) HS	H···O1	2.26 Å
		N2···O1	3.041 Å
		N2-H···O1	177°
O2 ST	H1(N1) HS	H···O2	2.18 Å
		N1···O2	2.895 Å
		N1-H···O2	147°
O2 ST	H2(N1) HS[a)]	H···O2	2.22 Å
		N1···O2	3.073 Å
		N1-H···O2	152°
N2 ST	H2(N1) HS[a)]	H···N2	2.29 Å
		N1···N2	3.093 Å
		N1-H···N2	140°
N3 ST	H3(N1) HS	H···N3	1.94 Å
		N1···N3	2.806 Å
		N1-H···N3	163°
N1 ST	H2(N2) HS	H···N1	2.55 Å
		N2···N1	3.222 Å
		N2-H···N1	172°

a) bifurcated hydrogen interaction

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Intermolecular Bonding

Hydrogen bonding is the dominant interaction between the two sulfonamides in this solid complex. The hydrogen bonds involving the charged portions of the molecules (N1(HS) and N3(ST)) are stronger than those between other portions of the two molecules. The strongest interaction thus is between N3(ST) and N1(HS).

In Figure 3 the various hydrogen bridges found in this complex are illustrated. The parameters describing these intermolecular linkages are given in Table V.

The ST molecules in the theophylline and sulfanilamide complexes form cyclic hydrogen bonded dimers, involving the imide linkage. The deprotonation makes this dimeric arrangement for ST impossible in this complex. It should also be pointed out that in general the intermolecular hydrogen linkages in the ST-sulfanilamide complex are significantly weaker than those found in the HS-ST complex.

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