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50. Keiji Ito*1 and Keiji Sekiguchi*2 : Studies on the Molecular Compound of Organic Medicinals. III.*3 The Structure of the Molecular Compound of Sulfanilamide and Sulfathiazole.*4

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In order to elucidate the nature of bonding in the molecular compound of sulfanilamide and sulfathiazole, infrared absorption measurements were carried out with the compound, its components including the two polymorphic modifications of sulfathiazole and their deuterated products. Also, thermodynamic calcultions were done with the solubility data at various temperatures.

On careful comparison of the spectra, it is suggested that in the compound the sulfonamido group of each component combines together by two hydrogen bonds to form a ring structure and that each *p*-amino group exists freely. The heat and the entropy change of the molecular compound formation in aqueous solution which are calculated at −8.3 kcal./mole and −21.3 cal./mole/deg., respectively, are thought to be too large to expect a linear combination of the components by one hydrogen bond but are adequate for the ring structure containing two hydrogen bonds. Thus, the same conclusion is reached both from the spectral evidences and from the thermodynamic calculations.

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Previously, it was confirmed by solubility and thermal analysis that sulfanilamide and sulfathiazole form a one-to-one molecular compound.[1] Also, the infrared spectrum of the compound was found to be different from that of the corresponding mechanical mixture.

In the present paper, the authors investigate the nature of bonding between the component sulfonamides in the molecular compound by infrared absorption measurements and by thermodynamic calculations of the solubility data.

Experimental

Materials——Polymorphic modifications of sulfanilamide and sulfathiazole were prepared by the methods of Watanabe[2] and Grove,[3] respectively.

Infrared Absorption Measurement——Apparatus : Koken DS-301 IR-spectrophotometer. KBr disc method. Polystyrene film was adopted for the frequency calibration; however, since a NaCl prism was used wave numbers in the ν-NH region are not strictly correct. Deuteration was done in the mixture of D_2O and acetone.

Solubility Measurement——Experimental conditions at 20 and 30° were the same as those reported in the previous paper[1] except that the molecular compound was added 0.6 and 0.8 g. per 100 ml. of distilled water, respectively.

Results and Discussion

Infrared Absorption Spectra——Infrared spectra of the molecular compound, components and their deuterated products are given in Fig. 1 in which those for α-

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*3 Part II : This Bulletin, **14**, 255 (1966).
*4 A part of this work was presented at the Hokkaido Branch Meeting of Pharmaceutical Society of Japan, June, 1961.

1) K. Sekiguchi, K. Ito : This Bulletin, **13**, 405 (1965).
2) A. Watanabe, H. Kamio : Yakugaku Zasshi, **62**, 501 (1942).
3) D. C. Grove, G. L. Keenan : J. Am. Chem. Soc., **63**, 97 (1941).

and γ-sulfanilamide are omitted because the spectral differences between the three polymorphic forms are comparatively few.

Generally, it is recognized that in dilute CCl_4 solution para-substituted aromatic amines give two bands at 3500~3450 and at 3400~3380 cm^{-1} due to asymmetric and

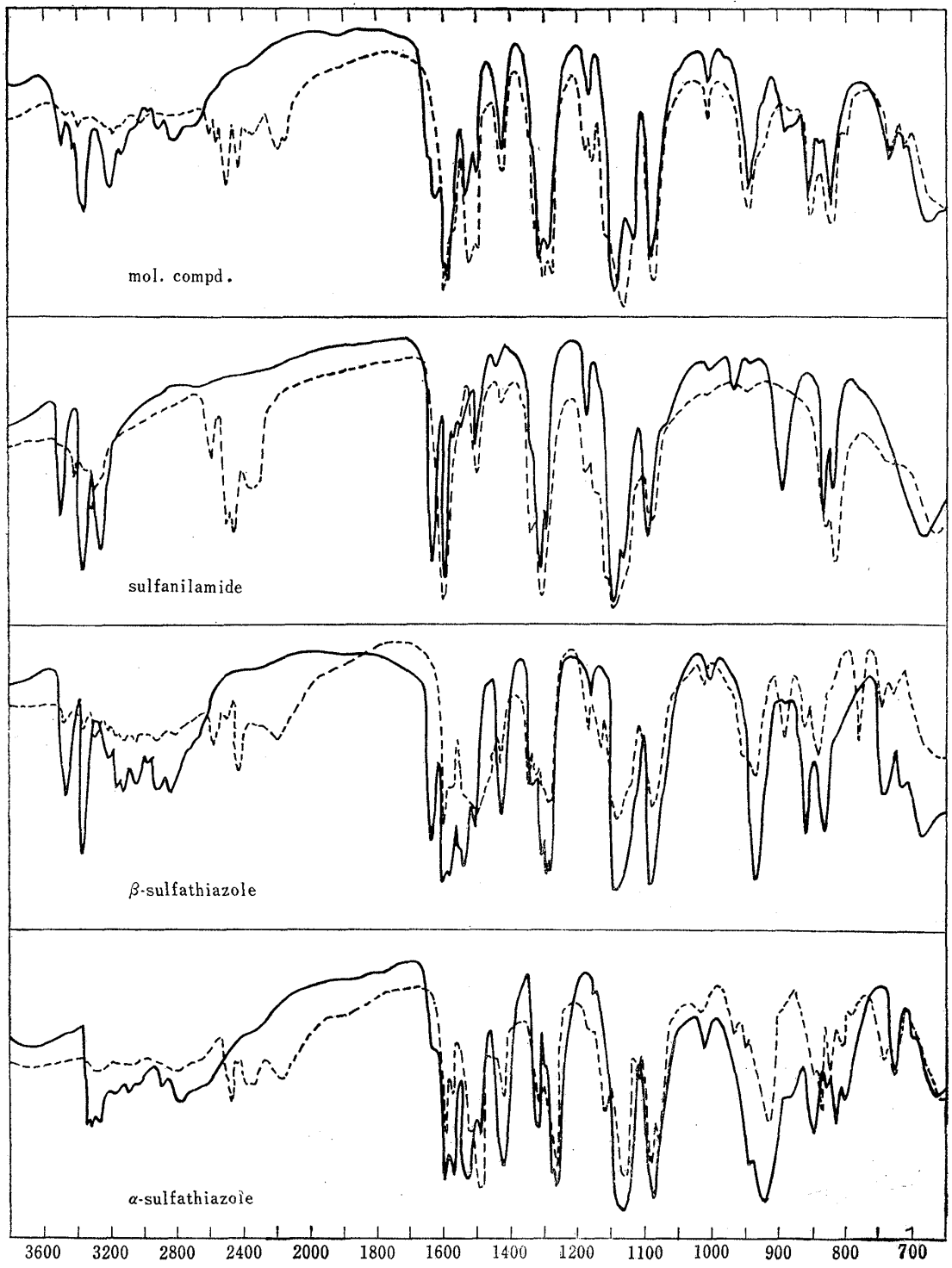


Fig. 1. Infrared (IR) Spectra of the Sulfanilamide-Sulfathiazole Molecular Compound and Its Components including the Polymorphic Forms of Sulfathiazole (solid lines) and of the N-Deuterated Compounds (broken lines) in Potassium Bromide Disc

Spectrum of sulfanilamide is the one obtained with β-form of the polymorphic forms (α,β and γ[2]), among which there is no remarkable difference in IR spectrun.

symmetric ν-NH absorptions.[4,5] Thus, among the three bands of sulfanilamide in the region 3500~3200 cm^{-1}, the first two at 3500 and 3380 cm^{-1} arise from ν-NH of *p*-amino group, and the third one at 3260 cm^{-1} is assigned to ν-NH for sulfonamido group. (Both α- and γ-sulfanilamide give additional bands near 3340 cm^{-1}.). Based on their positions and shapes, Baxter, *et al.*[6] concluded that the *p*-amino group of sulfanilamide is comparatively free from association even in solid state, while the sulfonamido group combines each other by hydrogen bonding as in (I). The same hydrogen bonded dimeric structure was also proposed by Scheele,[7] by Chaplin[8] and by Févre[9] from molecular weight and dielectric constant determinations.

$$\begin{array}{l} -SO_2\cdots\cdots HN- \\ \quad\vert \qquad\quad \vert \\ -NH\cdots\cdots O_2S- \end{array}$$
I

In the case of sulfathiazole, different spectra are observed between the two polymorphic modifications especially in the region above (and it is considered that these differences will afford helpful clues to solve the structure of the molecular compound). β-Sulfathiazole gives two sharp bands at 3460 and 3360 cm^{-1} and a series of bands in 3200~2600 cm^{-1}. The former two are assigned to the free NH_2 stretching mode. The latters are considered to be mainly attributed to ν-NH of the associated sulfonamido group, though definite assignment of each band is difficult. In this connection, the associated ν-NH and ν-SO absorptions (1290 and 1143 cm^{-1}) of β-sulfathiazole arise at a little lower wave numbers than the corresponding ones of mono-substituted sulfonamides measured by Baxter[6] and by Momose.[10] These differences can be explained by the increase in the strength of association in β-sulfathiazole. In the α-modification, the peak at 3460 cm^{-1} disappears and a new band appears at about 100 cm^{-1} lower wave numbers. Such a shift which has not been observed in other N^1-substituted sulfonamides,[11] will indicate that the *p*-amino group of α-form acts as the proton donor in the association.

If, in the molecular compound, either or both of the *p*-amino groups of the components contributes to the bonding between them, a similar shift in ν-NH absorption to that observed with α-sulfathiazole would be expected; however, since no such shift occurs, the two amino groups will not be restrained by the molecular compound formation. On the other hand, the ν-NH absorptions of sulfonamido groups appears not at 3260 cm^{-1} but in the range 3200~2600 cm^{-1}. It is therefore supposed that the compound formation is ascribed to the interaction between the two sulfonamido groups of sulfanilamide and sulfathiazole and that the interaction will be stronger than the dimeric association of sulfanilamide.

The δ-NH_2 absorption of each component arises in the range 1640~1630 cm^{-1}, while the corresponding one of the deuterated product moves to 1180~1160 cm^{-1}. Similarly, bands at 1638 and 1620 cm^{-1} of the molecular compound disappear by deuteration and shift to the same region; accordingly, they are clearly assigned to the same deformation frequencies. Although in α-sulfathiazole in which the *p*-amino group forms hydrogen bond the δ-NH_2 absorption shows decrease in intensity as compared with the strong one of the β-modification, a shift to higher frequency was not observed.

The two bands of sulfathiazole near 1570 and 1530 cm^{-1} are regarded as being typical of the thiazole structure.[12] By deuteration, they shift to some extent. In

4) S. Califano, R. Moccia : Gazz. chim. ital., **87**, 805 (1957).
5) L. J. Bellamy, R. L. Williams : Spectrochim. Acta, **9**, 341 (1957).
6) J. N. Baxter, J. Cymerman-Craig, J. B. Willis : J. Chem. Soc., **1955**, 669.
7) W. Scheele, A. Hartmann : Kolloid-Z., **131**, 126 (1953).
8) H. O. Chaplin, L. Hunter : J. Chem. Soc., **1937**, 1114.
9) R. J. W. LeFèvre, H. Vine : *Ibid.*, **1938**, 1790.
10) T. Momose, Y. Ueda, T. Shoji, H. Yano : This Bulletin, **6**, 669 (1958).
11) Nihon-Yakkyokuho Dai-I-bu Kaisetsusho, Appendix, 13 (1962), Hirokawa-shoten.
12) H. M. Randall, *et al.* : "Infrared Determination of Organic Structures," Van Nostrand (1949).

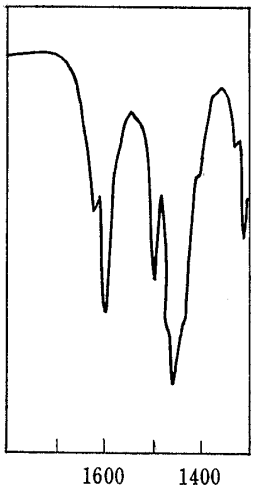


Fig. 2. Infrared Spectrum of Sulfathiazole-Na in Potassium Bromide Disc

the Na salt of sulfathiazole, these bands disappear completely, as shown in Fig. 2. Since the same characteristic absorptions appear in the molecular compound at 1589 and 1532 cm^{-1}, an ionic structure as $(sulfanilamide)^+$ $(sulfathiazole)^-$ will contribute nothing to the compound formation.

In some literature,[11] the bands in the range of 1650~1630 and 1580~1560 cm^{-1} measured for sulfathiazole, sulfadiazine and sulfamerazine were ascribed to ν-C=N and δ-NH_2 absorptions, respectively. However, the assignments are thought to be unreasonable because it is difficult to explain the spectral changes of the deuterated products of the three sulfonamides shown in Fig. 1 and 3. Also, these are inconsistent with the results by Califano, *et al.*[4] and with findings on conjugation of heterocyclic compounds.[13,14]

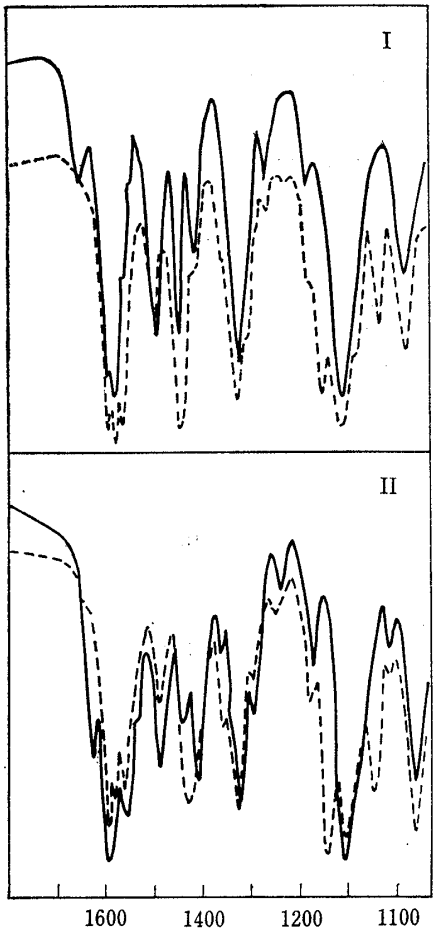
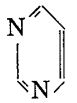


Fig. 3. Infrared Spectra of Sulfadiazine and Sulfamerazine (solid lines) and the N-Deuterated Compounds (broken lines) in Potassium Bromide Disc

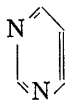
I : sulfadiazine; δN^4H_2 1650 cm^{-1}



ring vib. 1580

sulfadiazine-d; δN^4D_2 1178

II : sulfamerazine; δN^4H_2 1630



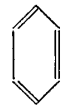
ring vib. 1565

sulfamerazine-d; δN^4D_2 1175

Characteristic absorptions of the aromatic ring near 1600 and 1500 cm^{-1} of the molecular compound and the components show no change in frequency by deuteration. The three peaks measured for the compound at 1310, 1288 and 1145 cm^{-1} are assigned to the ν-SO absorptions. They are nearly the same in positions as the corresponding ones of sulfanilamide and β-sulfathiazole and are more simplified in shapes. Since the α-modification of sulfathiazole gives ν-SO absorptions at a little lower frequencies, it may be considered that in the compound the oxygen atoms of $-SO_2-$groups of both components will take part only in the dimeric ring association as proton acceptors, but not in the hydrogen bonding with *p*-amino group.

13) E. R. Blout, M. Fields : J. Am. Chem. Soc., **72**, 479 (1950).
14) C. L. Angyal, R. L. Werner : J. Chem. Soc., **1952**, 2911.

Table I. Observed Infrared Absorption Frequencies in cm^{-1}

Molecular compound of sulfanilamide and sulfathiazole	Sulfanilamide	Sulfathiazole β-form	Sulfathiazole α-form	Assignment[a]
near 3500 3440 3380[b] 3360	near 3500 3380	near 3460 3360	near 3340 3320 3280	ν(N⁴H)
3200～2600	3260	3200～2600	3200～2600	ν(N¹H)
1638[b] 1620	1638	1633	1630[b]	δ(N⁴H₂)
1589 1532		1575 1536	1570 1527	 ring vib.
1595[b] 1503	1598 1502	1594 1503	1595 1496	 〃
1310 1288	1324[b] 1315 1296	1307 1290 1282	1280 1270	ν_{as}(SO)
1145	1148	1143	1138	ν_{s}(SO)
	Deuterated compound			
2600～2000	2600～2300	2600～2000	2500～2000	ν(ND)
1178	1175	1163	1161	δ(N⁴D₂)

a) ν: stretching, δ: deformation, as: asymmetrical, s: symmetrical
b) shoulder

As a whole, the infrared spectrum of the molecular compound is in many respects common to those of sulfanilamide and β-sulfathiazole (Table I). One but none the less important difference between the compound and sulfanilamide lies in the fact that the 3260 cm^{-1} band of the latter is absent in the former. Thus, from these spectral evidences, it can be concluded that in the molecular compound the components are combined by hydrogen bonds between the two sulfonamido groups to form a ring structure similar to those found in the association of solid sulfanilamide and β-sulfathiazole. Further, it is supposed that the hydrogen bonds are stronger than those involved in the dimeric association of sulfanilamide. In this connection, Sheinker[15] and Uno[16] reported that the solid sulfathiazole takes the imido structure; however, the sample materials of these authors are likely to be limited to the α-modification when their spectra are compared with those in Fig. 1. For this reason, the discussion above is done by assuming that sulfathiazole has the amido structure. Even if the β-modification exists predominantly in the imido form, no important change in the conclusion will occur.

Thermodynamic Calculations——Formation constants of the molecular compound in aqueous solutions at 20° and at 30° calculated in the same manner as in the previous paper[1] are given in Table II with those at 25° and at 35°. It was found that the stable solubility equilibrium was attained after 15 hours at 20°, while at 30° after about 9 hours. A plot of logarithm of the formation constant versus $1/T$ gives a straight line (Fig. 4) so that the heat of formation is determined from the slope. Free energy and entropy changes are also calculated and the whole results are summarized in Table III.

15) Yu. N. Sheinker, *et al.*: J. Phys. Chem. U. S. S. R., **31**, 1745 (1957).
16) T. Uno, *et al.*: This Bulletin, **11**, 704 (1963).

Table II. The Formation Constants for the Molecular Compound in Water Solution

Temp. (°C)	Molar concn. × 10^3					Formation constant $K^{a)}$
	Obsd. concn.		Free S [S]$^{a)}$	Free T [T]$^{a)}$	[ST]$^{a)}$	
	Total S	Total T				
20	3.795	1.567	3.622	1.394	0.173	34.3
25	4.942	2.068	4.711	1.837	0.231	26.7
30	6.308	2.720	5.988	2.400	0.320	22.3
35	8.115	3.534	7.703	3.122	0.412	17.1

S, T and ST represent sulfanilamide, sulfathiazole and the molecular compound, respectively.
a) [T]=soly. of sulfathiazole in water [ST]=total T−[T] [S]=total S−[ST]

$$K=\frac{[ST]}{[S][T]}$$

Since the heat of formation is exothermic to the extent of 8.3 kcal./mole, it is supposed that in one molecule of the molecular compound two hydrogen bonds are involved. The dimeric association of sulfanilamide was reported by Baxter, *et al.*[6] to be stronger than that of benzenesulfonamide, but is thought to be weaker from the above interpretation of the spectral data than the interaction in the molecular compound. Since the heat of association of benzenesulfonamide was estimated to be 6.5 kcal./mole,[7] the value of the heat of formation of the compound will be appropriate. The absolute value of the negative entropy change is considered to be too large to expect a linear combination of components when it is compared with those obtained in the studies of "complex formation" by Higuchi, *et al.*[17] and by Samejima[18]; accordingly, a ring structure will exist by which a further decrease in the freedom of movement will take place.

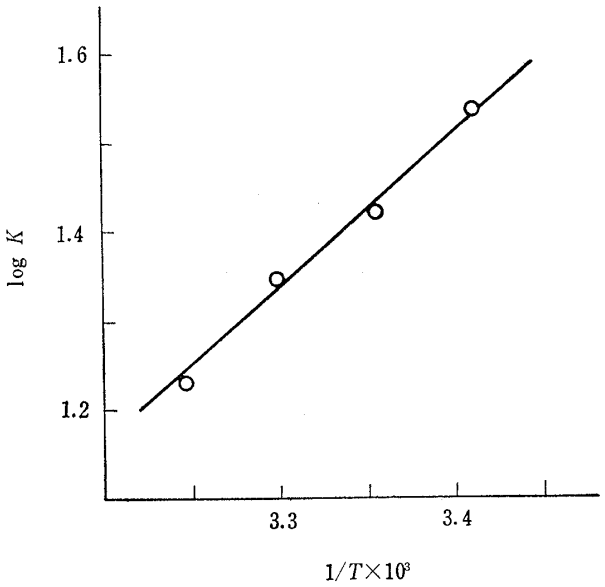


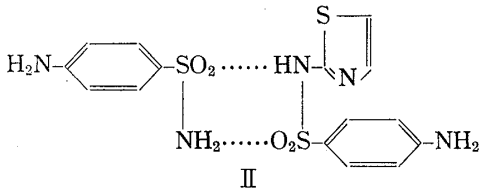
Fig. 4. Log K plotted against the Reciprocal of Absolute Temperature

Table III. Thermodynamic Values of the Interaction between Sulfanilamide and Sulfathiazole in Water Solution

Temp. (°C)	K	$\Delta H^{a)}$ cal./mole	$\Delta F^{\circ b)}$ cal./mole	$\Delta S^{c)}$ cal./mole/deg.
20	34.3	−8300	−2060	−21.3
25	26.7		−1950	−21.3
30	22.3		−1870	−21.2
35	17.1		−1740	−21.3

a) heat of formation for the mol. compd. calcd. from the slope of the line log K vs $1/T$ (Fig. 4): $\Delta H=-\text{slope}\times 2.303R$
b) free energy change: $\Delta F^{\circ}=-RT\ln K$
c) entropy change: $\Delta S=(\Delta H-\Delta F^{\circ})/T$

17) T. Higuchi, D. A. Zuck: J. Am. Pharm. Assoc., **42**, 138 (1953).
18) M. Samejima: Yakugaku Zasshi, **80**, 99 (1960).



II

Thus, from the spectral evidences as well as from the thermodynamic values, the same conclusion is reached that in the structure of the molecular compound two hydrogen bonds will be involved as shown in (II).