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108. Keiji Sekiguchi,*1 Eiji Owada, and Keiji Ito*2 : Studies on the Molecular Compounds of Organic Medicinals. Ⅳ.*3,4 Physico-pharmaceutical Properties of the Molecular Compound of Homosulfanilamide and Sulfathiazole.

(*College of Pharmaceutical Sciences, Kitasato Memorial University*1 *and Faculty of Pharmaceutical Sciences, Hokkaido University*2)

In order to obtain wider knowledges on the physico-pharmaceutical properties of the molecular compounds of organic medicinals, the dissolution behaviors, solubility equilibrium and the nature of the bonding between components were investigated with the compound of homosulfanilamide and sulfathiazole.

When the molecular compound was dissolved, the stable equilibrium, not the metastable one was rapidly attained. On the contrary, much differences in dissolution behaviors were observed with the corresponding physical mixture and the equilibrium was not reached even after 24 hours due to deposition of the compound on sulfathiazole particles.

From the phase diagram constructed, it was confirmed that the system belongs to the type where the formed compound is not decomposed by water. By applying the solubility product principle, formation constants at various temperatures were obtained and the changes of enthalpy, free energy and entropy for the molecular compound formation in solution were calculated.

It was supposed from these thermodynamic constants and the data of IR and electric conductance measurements that in the compound, the bonding between homosulfanilamide and sulfathiazole is caused by ionic interaction.

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In order to find possible applications of the molecular compounds, it is important to make clear various physico-pharmaceutical properties of them; however, no investigation was hitherto published concerning to the dissolution behaviors except the one by the authors on the compound of sulfanilamide and sulfathiazole.[1] In the present paper, further investigations were done on the dissolution behaviors, solubility equilibria and the mode of combination of the compound formed between homosulfanilamide and sulfathiazole. Thus, wider knowledges on the properties of the molecular compounds were obtained.

Experimentals

Materials——Recrystallized homosulfanilamide from H_2O, m.p. 153°. Sulfathiazole was of J. P. grade and was determined to be the stable modification at room temperature (α-form) by solubility and IR measurements.

Preparation of the Molecular Compound——An equimolar mixture of homosulfanilamide and sulfathiazole was nearly saturated. On cooling, the molecular compound was crystallized out in good yield. m.p. 169°.*5 *Anal.* Calcd. for $C_{16}H_{19}O_4N_5S$: C, 43.52; H, 4.34; N, 15.86. Found : C, 43.64; H, 4.30; N, 15.65. For dissolution experiments, the crystals were sieved to 60~150 mesh.

Preparation of the Mechanical Mixture——The particle size of each sulfonamide was arranged from 60 to 150 mesh. They were mixed in equimolar ratio.

Determination of Homosulfanilamide and Sulfathiazole——An aliquot of the sample solution was evaporated to dryness and the residue was completely dried at about 60° for 24 hours. The total amount of the components dissolved was determined by gravimetry. For the determination of homosulfanilamide,

*1 Shirokane-Sankocho, Shiba, Minato-ku, Tokyo (関口慶二).
*2 Kita-15-jo, Nishi-7-chome, Sapporo, Hokkaido (大和田栄治, 伊藤圭二).
*3 Part Ⅲ. This Bulletin, **15**, 422 (1967).
*4 Partly presented at the 20th Annual Meeting of the Pharmaceutical Society of Japan, April 6, 1965.
*5 Five degrees higher than the one reported by T. Naito, *et al.* : Yakugaku Zasshi, **73**, 663 (1953).
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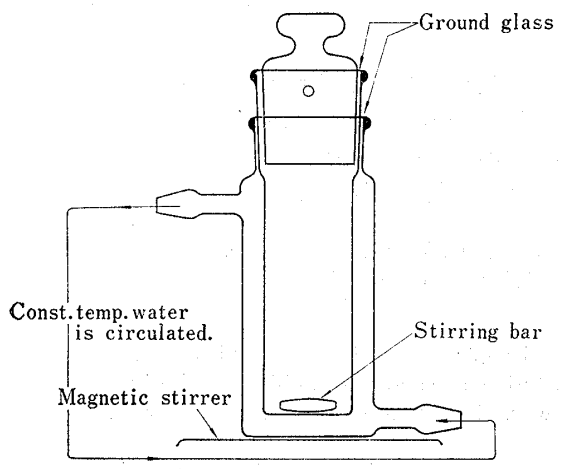

Fig. 1. A Special Type of Glass Thermospacer for the Solubility Study

another aliquot was titrated with 0.1*N*-HCl S. S. after proper dilution. Preliminary tests were done with solutions containing known amounts of both components and it was confirmed that the presence of sulfathiazole does not interfere the titration.

Procedure for Dissolution Study——A certain excess of the sample material was weighed accurately in the inner vessel of the special type of the dissolution cell (Fig. 1). After setting into the jacket, the cell was connected to a thermostat with a circulating device and was maintained at 15, 25 or 35°(±0.05°). To this was added 50 ml. of distilled water or solutions containing varying amounts of either component, which was previously kept at the experimental temperature. Immediately after addition, vigorous stirring was applied by a magnetic stirrer. At certain time intervals, aliquot portions of the solution were removed by a pipette equipped with a filter, and the concentration of solutes were determined. The solid residue was identified by IR measurement.

IR Spectrum and Electric Conductance Measurements——Koken DS 301 IR-Spectrometer (NaCl prism), KBr disc method; Digital Conductivity Meter Toa Electronics Model CM.

Results and Discussion

Dissolution Behaviors of the Molecular Compound and the Mixture——The process to the solubility equilibrium of the molecular compound in water at 25° differs considerably from that of the corresponding mechanical mixture (Fig. 2). By the compound, equilibrium is very quickly attained and is thought to be the stable one since equimolar and constant concentrations of the components are maintained for 24 hours. The increased solubility of sulfathiazole amounts to about seven times the intrinsic one of the sulfonamide.

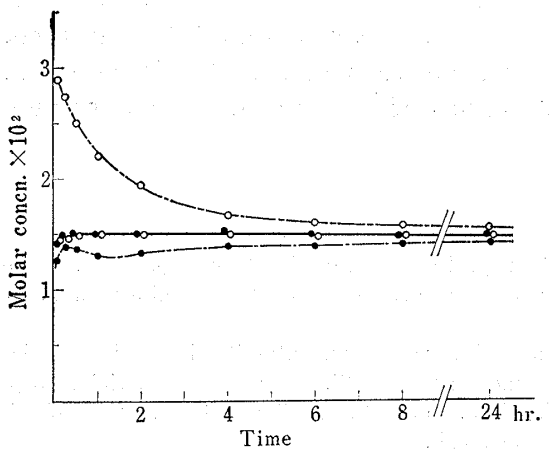

Fig. 2. Dissolution Curves for the Molecular Compound of Homosulfanilamide and Sulfathiazole (solid line) and the Corresponding Mechanical Mixture (chain lines) at 25°

sample amount: each 0.7 g. per 50 ml. of water
particle size: each 60~150 mesh
open circles: total concentrations of homosulfanilamide
closed circles: total concentrations of sulfathiazole

In the case of the mechanical mixture, the concentration of homosulfanilamide rises quickly and then decreases gradually while the curve for sulfathiazole shows a small peak and a subsequent shallow valley in the initial period of dissolution, similarly as observed with the mixture of sulfanilamide and sulfathiazole.[1] The fact indicates that formation of the compound in solution is rapid but its deposition occurs gradually even with vigorous agitation. Although the difference in concentrations of both components becomes gradually smaller, they never become equal until the end of the experiment. This will be natural because the diffusion of each component from the inside or the outside of the sulfathiazole particles is hindered progressively by the increase in thickness of the layer of the compound formed onto them. Thus, the solubility equilibrium can not practically be reached with the mechanical mixture. Almost the same differences in dissolution behaviors are observed at 15 and 35°.

Calculation of the Concentration of the Molecular Compound——Since no tendency of showing the metastable solubility by the compound, it forms a congruently saturated solution. In such a case, the concentration of the non-dissociated compound can not be calculated by the method applied to the incongruently saturated solution such as the one of sulfanilamide and sulfathiazole.[2] Further, the procedure adopted by Higuchi[3] will not give the correct value by the difficulty of attainment of solubility equilibrium. However, if the solubility product principle is applicable to the saturated solution of the organic molecular compound, the free compound concentration will be calculated according to the method reported in the previous paper.[2]

When the compound dissociates into its components in an aqueous solution, the dissociation constant K' is given by

$$K' = \frac{[Hs][T]}{[HsT]}, \qquad (1)$$

where $[Hs]$, $[T]$ and $[HsT]$ represent concentrations of free homosulfanilamide, sulfathiazole and the compound, respectively. If at saturation, the concentration of the free compound, $[HsT]_{satd.}$ is constant, it follows that

$$[Hs][T] = K'[HsT]_{satd.} = L, \qquad (2)$$

in which L is the solubility product.

When a sufficient excess of the molecular compound is added to the solution containing a varying amount of homosulfanilamide, the concentrations of free components

Table I. Solubilities of the Molecular Compound in Aqueous Homosulfanilamide Solutions at 25°

Molar concn. $\times 10^2$			$\times 10^2$	$\times 10^4$
Original cocn. of homosulfanilamide	$\Sigma(Hs)$	$\Sigma(T)$	$\Sigma(Hs)+\Sigma(T)$	$\Sigma(Hs)+\Sigma(T)$
0	1.492	1.531	3.023	2.284
0.138	1.579	1.422	3.001	2.245
0.354	1.688	1.379	3.067	2.328
0.537	1.875	1.363	3.238	2.556
0.808	2.077	1.281	3.358	2.661
1.087	2.355	1.285	3.640	3.026
1.500	2.724	1.245	3.969	3.391
1.745	2.959	1.265	4.224	3.743
1.997	3.197	1.226	4.423	3.920
2.238	3.421	1.226	4.647	4.194
2.502	3.705	1.234	4.939	4.572
2.954	4.130	1.198	5.328	4.948
3.242	4.437	1.198	5.635	5.316
3.504	4.653	1.218	5.871	5.667
3.998	5.132	1.195	6.327	6.133
4.469	5.584	1.155	6.739	6.450

$\Sigma(Hs)$ and $\Sigma(T)$ represent total concns. of homosulfanilamide and sulfathiazole, respectively.

Experiments were carried out by adding 0.7 g. of the compound into 50 ml. of homosulfanilamide soln. of which concn. was varied systematically. After stirring for 6 hrs., the satd. soln. was analyzed.

2) K. Ito, K. Sekiguchi : This Bulletin, **14**, 255 (1966).
3) T. Higuchi, D. A. Zuck : J. Am. Pharm. Assoc., **42**, 138 (1953), etc.

at eqilibrium are given by

$$[Hs]=\sum(Hs)-[HsT]_{satd.} \quad (3)$$

$$[T]=\sum(T)-[HsT]_{satd.} \quad (4)$$

where $\sum(Hs)$ and $\sum(T)$ are the total concentrations of both components. Thus, from (2), (3) and (4), it follows that

$$\sum(Hs)\times\sum(T)=[HsT]_{satd.}\{\sum(Hs)+\sum(T)\}+L-[HsT]^2_{satd.} \quad (5)$$

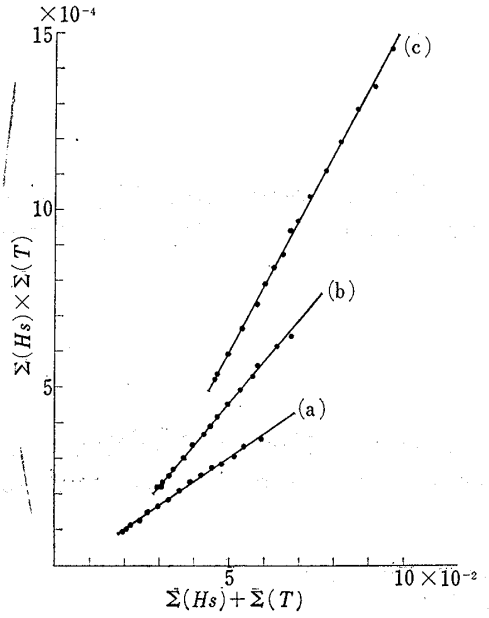

Fig. 3. Plot of $\sum(Hs)\times\sum(T)$ against $\sum(Hs)+\sum(T)$: Slopes of these lines give $[HsT]_{satd.}$

(a) : at 15°
(b) : at 25°
(c) : at 35°

By plotting the product of $\sum(Hs)$ and $\sum(T)$ against the sum, a straight line will be obtained so long as the solublity product principle is applicable to this system. From the slope of the line, the concentration of the non-dissociated compound will be determined.

As is seen in Table I and Fig. 3, the experimental data indicate the validity of assumption, and the saturated concentrations of the compound at 15, 25 and 35° are estimated from the slopes of the lines drawn by the method of least squares. Thus, $[Hs]$ and $[T]$ are determined, and the formation constant ($K=1/K'$) at each temperature can be calculated as given in Table II. Much larger values of these constants as compared with those for the compound of sulfanilamide and sulfathiazole will suggest that the introduction of $-CH_2-$ to $-NH_2$ of sulfanilamide will cause considerable change in the mode of combination of components.

Logarithmic plots of concentrations of both the free and the dissociated molecular compound against reciprocals of absolute temperatures are given in Fig. 4. The linear relations will also indicate the applicability of the theory.

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

Temp. (°C)	Molar concn. × 10²		Formation constant
	$[HsT]_{sat.}$	$[Hs]$ or $[T]$	
15	0.692	0.285	852
25	1.162	0.352	938
35	1.849	0.434	982

Hs, *T* and *HsT* represent homosulfanilamide, sulfathiazole and the molecular compound, respectively.

Phase Diagram of the System——The solubility changes of each one of the components in the presence of another are examined at 25°. Combining the results with those in Table I, the ternary phase diagram for the system of homosulfanilamide, sulfathiazole and water is constructed as shown in Fig. 5. The lines a-c, b-d and c-d represent saturation curves for sulfathiazole, homosulfanilamide and the compound, respectively.

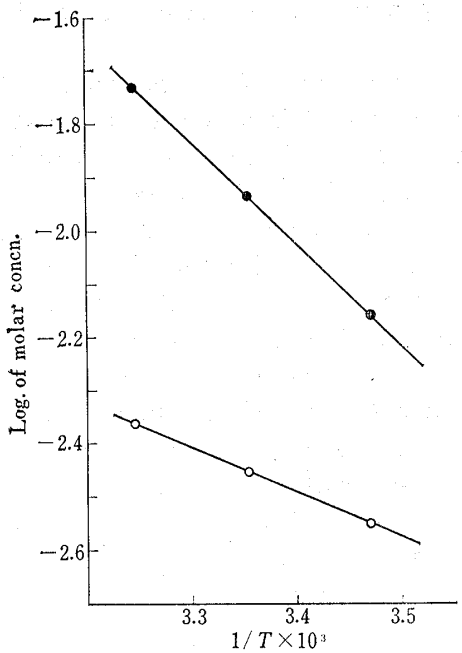

Fig. 4. The Relation between Tempetature and the Concentration of the Molecular Compound (closed circles) and Free Homosulfanilamide or Free Sulfathiazole (open circles) in the Aqueous Solution Molecular Compound

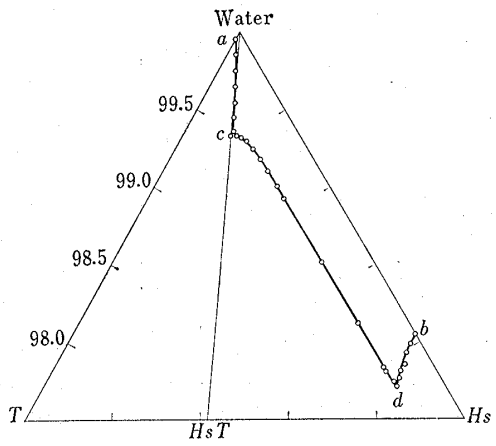

Fig. 5. Phase Diagram for the System of Homosulfanilamide, Sulfathiazole and Water at 25°

points *a* and *b*: solubilities of sulfathiazole and homosulfanilamide, respectively
c: composition of the satd soln. of the mol. compd. in pure water.

Mode of Combination of Components in the Molecular Compound——When the logarithum of the formation constant is plotted against the reciprocal of the absolute temperature, a straight line is obtained; from the slope the heat of formation of the molecular compound is given. Also, the free energy and entropy changes are calculated as shown in Table Ⅲ.

The results of IR measurements are represented in Fig. 7. The spectrum of the compound bears a better resemblance to the superimposed spectrum for homosulfanilamide hydrochloride and the Na salt of sulfathiazole than to the one for both free sulfonamides. For example, the band of the hydrochloride near 3200 cm^{-1} which is characteristic of ammonium salt (ν-NH) appears in the molecular compound. Also, in the compound the two typical absorptions for sulfathiazole in 1500～1600 cm^{-1} range disappear, whereas, the 1220 cm^{-1} band for the Na salt appears at the same wave number. Thus, it is supposed that the combination will not be attributed to the hydrogen bonding but to the ionic interaction between components as found in the complex of PAS and

Tabel Ⅲ. Thermodynamic Values for the Molecular Compound Formation in Water Solution

Temp. (°C)	ΔH cal/mole	$\Delta F°$ cal/mole	ΔS cal/mole deg
15		−3860	17.8
25	1260	−4060	17.8
35		−4220	17.8

ΔH, $\Delta F°$ and ΔS represent heat of formation, free energy change and entropy change for the mol. compd. formation in water soln., respectively.

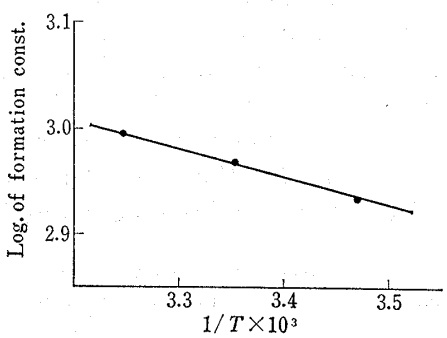

Fig. 6. The Relation between Temperature and the Formation Constant

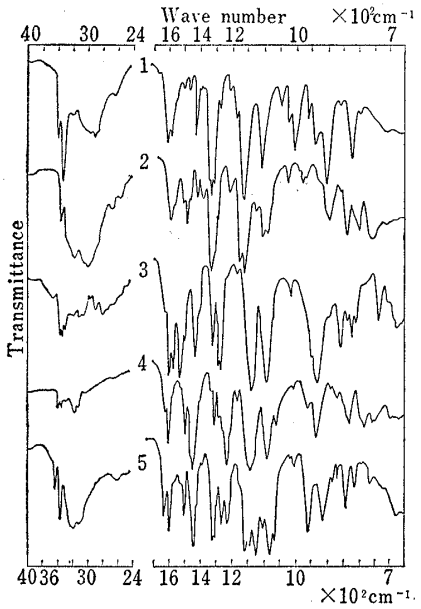

Fig. 7. Infrared Absorption Spectra of the Molecular Compound and Its Components (KBr disk)

1: Homosulfanilamide
2: Homosulfanilamide hydrochloride
3: Sulfathiazele
4: Sulfathiazole sodium
5: Mol. compd. of homosulfanilamide and sulfathiazole

INAH[4] or in the products between amines and orotic acid.[5]

The electric conductance of the aqueous solution of the molecular compound is much greater than that of the compound of sulfanilamide and sulfathiazole as given in Table Ⅳ. The difference will suggest that in the latter, the dissociated components exist as free molecules while in the former they take ionic forms. Since separation of the water of hydration will be accompanied with the compound formation, it is natural that the entropy change is positive(Table Ⅲ).

When the concentrations of the molecular forms of both components are negligibly lower than those of ionic ones, the above results afford no contradiction to the application of the solubility product principle, provided that the above treatments are followed by changing $[Hs]$ and $[T]$ into $[Hs^+]$ and $[T^-]$, respectively.

Table Ⅳ. Conductance Measurements of Molecular Compounds in Water[a] at 25°

Mol. compd.	Molar concn. $\times 10^3$	Spec. cond. (℧/cm) $\times 10^6$
Homosulfanilamide Sulfathiazole	1.5	71.0
Sulfanilamide Sulfathiazole	1.5	4.1

a) Spec. cond. of distilld water used as solvent was 4.0×10^{-6} ℧/cm.

Conclusion

It was hitherto believed that in an aqueous solution, a salt or a salt-like molecule dissociates completely into ions, and the presence of the non-dissociated species was almost ignored. However, Nakagawa has emphasized the pharmaceutical importance of such non-dissociated salts or ion-pairs in connection with his investigation on the interaction between nitrophenols and amines.[6] Since the approaches described above are different from that by Nakagawa, the presence of such species in solution is definitely confirmed.

In this connection, the term "molecular compound" adopted by the authors has a wide meaning. If the bond between components has not a covalent nature, the interaction is irrespective as to the kind of bonding forces such as hydrogen bond, van der Waals or charge transfer force, ionic interaction and those found in clathrates and inclusion compounds. The fundamental difference between the "molecular compound" and the "complex" used by Higuchi and other researchers in U.S.A. lies in the fact that the former must be separated as an independent solid phase while in the latter, separation of the solid "complex" is not always necessary; therefore, the definition of the "molecular compound" is more limitted but is less vague.

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4) J. A. Reinstein, T. Higuchi: J. Am. Pharm. Assoc., **47**, 749 (1958).
5) H. Nakatani, M. Nishikawa, E. Mizuta: Yakugaku Zasshi, **84**, 1051 (1964).
6) H. Nogami, F. Nakagawa: This Bulletin, **6**, 571 (1958); F. Nakagawa: Yakuzaigaku **27**, 73 (1967).