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Dissolution Behavior of Solid Drugs. VI.[1] Determination of Transition Temperatures of Various Physical Forms of Sulfanilamide by Initial Dissolution Rate Measurements[2]

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The initial dissolution rate measurement method was applied to physical forms of sulfanilamide, two polymorphs and a hydrate. As the result, the transition temperatures and the heats of transition between the metastable α- and the stable β-forms, and between the β- and the hydrated forms were determined to be $-119°$, 0.17 kcal/mole, and 38.3°, 1.74 kcal/mole, respectively.

At the same time, thermal behaviors and solubilities of all the known forms of sulfanilamide including the above three were investigated by other methods such as differential scanning calorimetry and conventional solubility measurement. Data obtained agree well with those by dissolution study, though direct solubility determination of the metastable α-form was impossible because of rapid conversion to the β- or to the hydrated form. Thus, the total relation among these physical forms could be more clearly understood by combining all these data, and the supposition proposed previously that the α-form was monotropic with respect to the β-polymorph was denied completely.

A number of studies on physical forms of sulfanilamide have been reported. McLachlan[4] exhibited crystallographic pictures of four polymorphic forms of sulfanilamide, β-, δ-, ε-, and ν-forms, while Watanabe, *et al.*[5] confirmed, more previously, the existence of three polymorphic forms of the sulfonamide and designated them as α-, β-, and γ-forms. These three forms might be essentially the same as McLachlan's ν, δ-, and ε-forms, respectively, judging from the lattice constants described in each literature. In addition, Watanabe, *et al.* investigated physicochemical properties of α- and β-forms, especially their thermal behaviors by X-ray powder diffraction method, hot-stage polarizing microscopy, and measurement of heat of solution using a copper calorimeter. They observed that the transition from α- to β-form began to occur at about 40° on standing, and proceeded remarkably at about 90°, although both forms were practically stable at room temperature. Based on their results, they also mentioned that α-form of sulfanilamide was monotropic with respect to the β-form. However, the experimental evidences presented were not enough to draw such a conclusion that the two polymorphs were monotropic. Moreover, the values of heat of solution reported by them were too small due to a mistake in their calculation.

In the present study, transition temperatures and heats of transition between α- and β-forms, and also between the hydrate and β-form of sulfanilamide were determined by the initial dissolution rate measurements as described in the previous paper.[1] The results were discussed and compared with data by the differential scanning calorimetry (DSC), conventional solubility measurement, and the hot-stage polarizing microscopy.

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1) Part V: K. Sekiguchi, M. Kanke, N. Nakamura, and Y. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **23**, 1347 (1975).

2) Presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1973.

3) Location: *9-1, Shirokane 5-chome, Minato-ku, Tokyo.*

4) D. McLachlan, "X-ray Crystal Structure," McGraw-Hill, Inc., New York, 1957, p. 138.

5) A. Watanabe and H. Kamio, *Yakugaku Zasshi*, **63**, 501 (1943).

Experimental

Materials——1) α-Form of Sulfanilamide (α-S): Obtained by crystallization of commercial product of J.P. VIII grade from isoamyl, *n*-amyl or *n*-butyl alcohol, by holding the warm solution at room temperature or cooling it immediately.

2) β-Form of Sulfanilamide (β-S): Crystallized from methyl or ethyl alcohol by gradual cooling of its warm solution to room temperature and maintaining for two to three days.[5]

3) γ-Form of Sulfanilamide (γ-S): Obtained by saturating sulfanilamide in isoamyl alcohol at approximately 120° and allowing it to cool slowly to room temperature.[5] This form is stable at highest range of temperature. mp 163—166°.

4) δ-Form of Sulfanilamide (δ-S)[6]: Obtained from isoamyl or *n*-butyl alcohol solution. Although the conditions for crystallization were nearly the same as for γ-S, it often happened that this form of sulfanilamide crystallized out instead of γ-S. This form is not stable even in solid state and changes gradually into β-S.

5) Hydrated Form of Sulfanilamide: Isolated by cooling the warm saturated aqueous solution rapidly and maintaining below 15°.

Characterization of Various Physical Forms——Several methods were used in characterizing these physical forms. These were: Hot-stage polarizing microscopy, using a Ernst Leitz Microscope Model 350 with

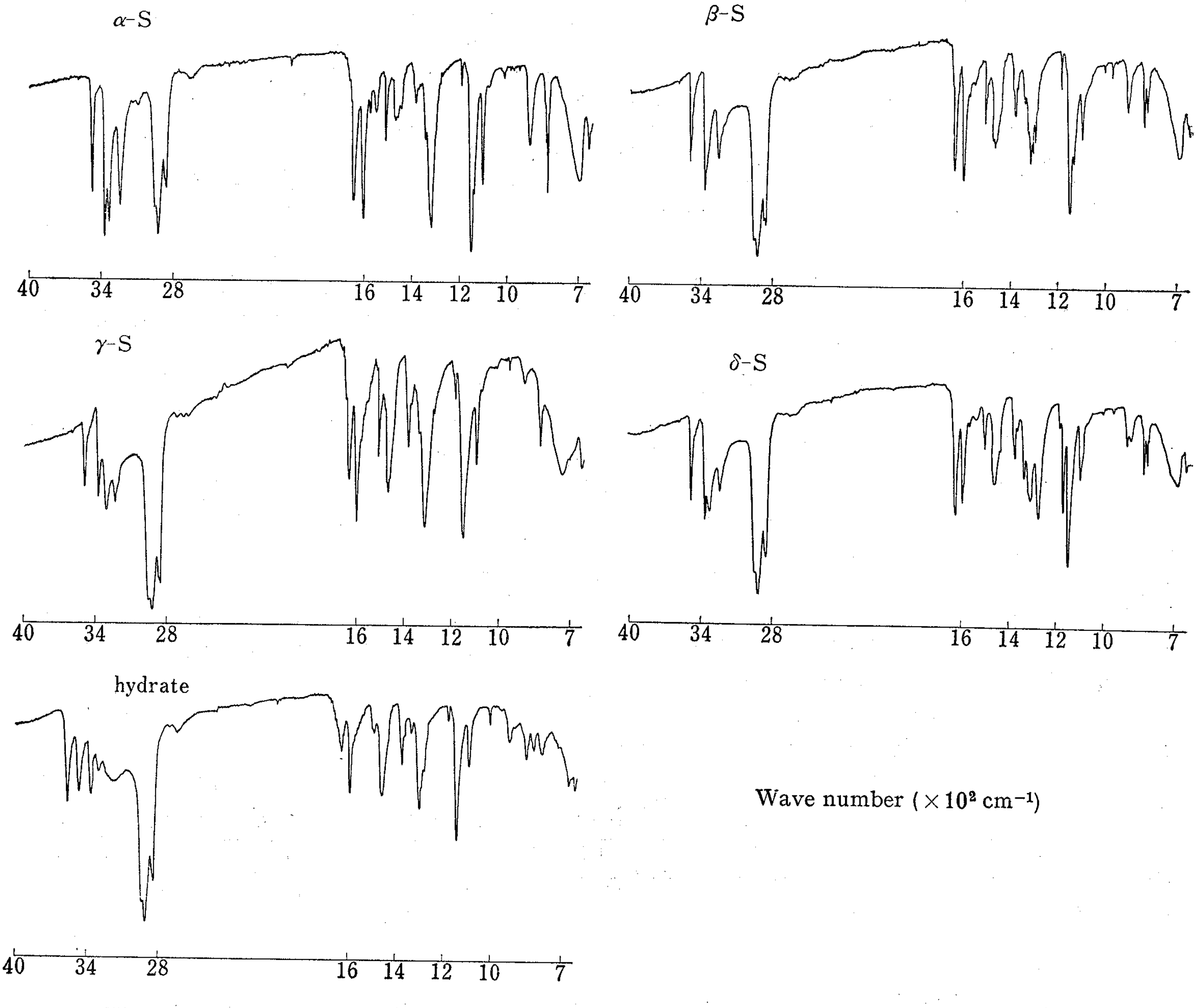

Fig. 1. Infrared Absorption Spectra of Various Physical Forms of Sulfanilamide (nujol mull)

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[6] For α-, β-, and γ-forms, the notation by Watanabe, *et al.* was adopted. However, since the fourth one is omitted in their study, we designated it as the δ-polymorph. This form is thought to be equal to McLachlan's β-form by the reason mentioned in the text.

both a polarizing equipment and a hot-stage; Infrared (IR) spectrophotometry, using a Jasco IRA-1 Grating Infrared Spectrophotometer; X-ray diffraction analysis, using a Rigaku Geigerflex 2030 X-ray Powder Diffraction Analyzer (Ni filter, Cu-Kα ray $\lambda = 1.542\text{Å}$); and DSC, using a Perkin-Elmer DSC-1B Differential Scanning Calorimeter.[7] Characteristic patterns for each form obtained by these methods are shown in

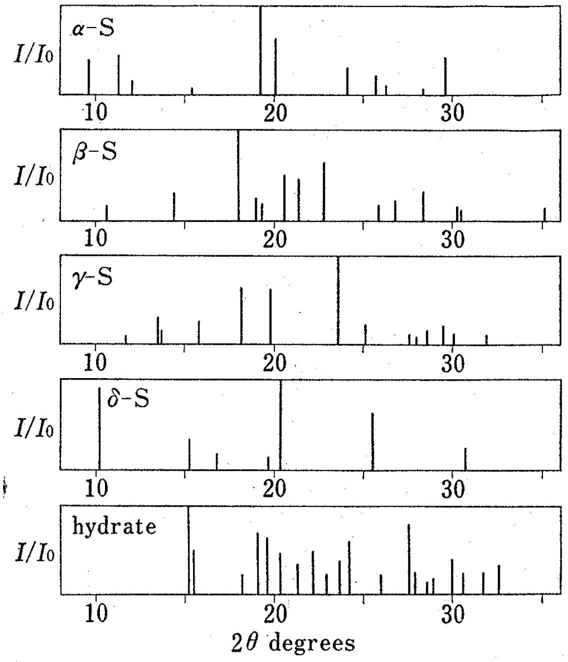

Fig. 2. X-Ray Diffraction Patterns of Various Physical Forms of Sulfanilamide

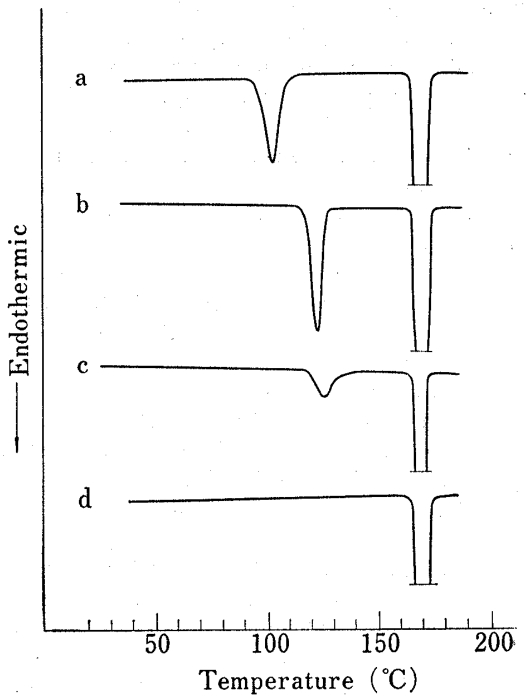

Fig. 3. DSC Curves of Various Polymorphs of Sulfanilamide using Solid Sample Pans

a : α-S, 18.543 mg, 16°/min
b : β-S, 18.473 mg, 16°/min
c : δ-S, 14.765 mg, 16°/min
d : γ-S, 19.0 mg, 16°/min

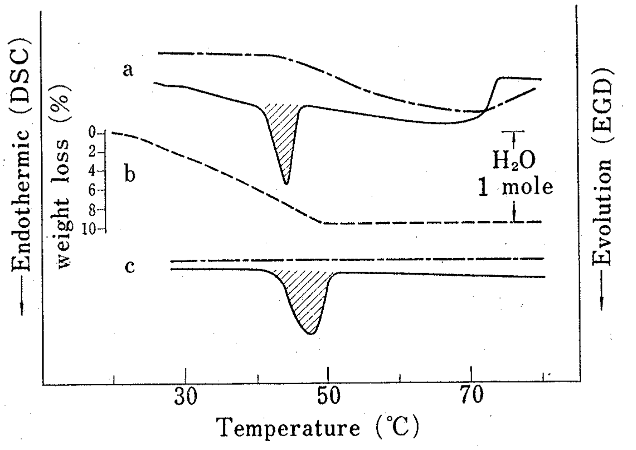

Fig. 4. Thermograms of Sulfanilamide Hydrate
——— : DSC curve, —-—- : EGD curve,
--------- : TG curve

a : solid sample pan, 7.079 mg, 8°/min
b : 2.305 mg, weight loss 0.220 mg, 8°/min
c : liquid sample pan, 6.381 mg, 8°/min

Table I. Comparison between 2θ Values of δ-S by X-Ray Powder Diffraction Analysis and Those calculated from the Crystallographic Data[a] of McLachlan's β-Form

δ-S 2θ Value	McLachlan's β-form	
	2θ Value	Miller index
5.1	5.05	[001]
10.2	10.12	[002]
15.3	15.28	[102]
16.8	16.78	[020]
19.7	19.64	[022]
20.4	20.35	[120]
25.55	25.50	[123]
30.75	30.70	[006]
36.0	35.98	[232]
41.4	41.40	[240]
46.8	46.79	[236]

a) a=7.745 b=10.56 c=17.475

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[7] In some cases, evolved gas detection (EGD) was done simultaneously.

Figs. 1,2,3, and 4. In Table I, 2θ values of δ-S by powder diffraction analysis and those calculated from the crystallographic data of McLachlan's β-form are given. It is evident from these data that the two forms coincide with each other.

Determination of the Combining Ratio of the Hydrate——Molecular ratio of water contained in the hydrate of sulfanilamide was determined both by weight loss on drying and by thermogravimetry, using a Perkin-Elmer TGS-1 Thermogravimeter. In each case, the weight loss indicates that precisely one mole of crystal water is contained in the hydrate (Fig. 4).

Dissolution Rate Measurements——Measurements of initial dissolution rates were done by the similar manner as reported previously.[1] A disk with the diameter of 10 mm was prepared by applying pressure of 3 tons for 5 minutes to approximately 300 mg of the sample powder placed in an evacuable die. In the dissolution measurement cell, 250.0 g of distilled water was agitated by a magnetic stirrer at a constant speed of 600 rpm and was circulated through the flow cell attached to a UV-spectrophotometer (Type: Hitachi 139) by means of a pump at a fixed flow rate of 330 ml per minute. When the temperature of the dissolution medium attained to the desired value, the disk mounted on a disk holder with paraffin (mp about 65°) was placed into the medium and the change of absorbance which corresponds to the amount dissolved was recorded automatically at a wave length of 258 nm by a recorder (TOA EPR-3T) attached to the spectrophotometer through a log converter (TOA PB-70A). From the curve thus obtained, dE/dt value could be decided. The exposed surface of the disk were characterized by IR and DSC before and after measurements.

Solubility Determination——A sufficient amount of sample powder was placed in 50 g of distilled water in the same type of cell as the one used in the dissolution experiment and stirred at 600 rpm at a desired temperature. At appropriate time intervals, solution samples were taken by glass syringes until the concentration attained equilibrium. The sample solutions were immediately filtered through a 0.45 μ membrane filter (Sartorius GMBH 11306) in order to remove suspended particles of the solid residue. The filtrates were then weighed and diluted for spectrophotometric assay at a wavelength of 225 nm.

Determination of the Transition Temperature and the Heat of Transition by DSC——The apparatus was the same as the one used for identification. Temperature corrections were made by an Indium cell provided for calibration by the manufacturer, and the following experimental conditions were adopted:

1) Measurement of Transition Temperature: a) Sample: Except the hydrate, each sample was finely powdered. b) Sample Weight: 13—28 mg, accurately weighed in the chemical balance. c) Sample Pan: Solid sample pan. d) Heating rate: 0.5—64°/min.

2) Measurement of Heat of Transition: a) Sample Weight: 7—22 mg of α-, β-, and δ-S, and 7—9 mg of the hydrate, accurately weighed down to 0.01 mg by a semimicro-balance. b) Sample Pan: For the three polymorphs, a solid sample pan was used, while both solid and liquid pans were employed for the hydrate. c) Heating Rate: 8°/min and 16°/min. d) Peak Area: The area under a transition peak was measured either by a planimeter or by weighing the piece cut from the photocopy of the DSC peak.

Results and Discussion

The Transition Temperature and the Heat of Transition by Dissolution Rate Measurements

Fig. 5 shows the initial dissolution of α-, β-S, and the hydrate measured at various temperatures. By plotting these dE/dt values against reciprocal of the absolute temperatures, a straight line for each physical form was obtained by the method of least squares as shown in Fig. 6. The slope of the line represents the heat of dissolution of each form and the intersections of these lines exhibit transition temperatures. Also, the heat of transition can be calculated by taking the difference between the heats of dissolution for two forms. Thus, the transition temperature and the heat of transition between α- and β-S, and between β-S and the hydrate are estimated to be −119° and 0.17 kcal/mole, and 38.3° and 1.74 kcal/mole, respectively.

According to the definition of monotropy, the transition temperature between α- and β-S does indicate that the transition is not monotropic but enantiotropic. However, it can be considered from a practical point of view that α-S is always metastable at ordinary temperature range as compared with the β-S and the transition can take place in only one direction, since the transition point lies at extremely low temperature.

After each run, the surface of the disk was characterized to find whether any transition had occurred or not. Although β-S was unchanged at all experimental temperatures, it was found that α-S shows rapid conversion to β-S. The fact is indicated by the presence of inflection points in the absorbance-time curves for α-S after some time of dissolution and the slopes

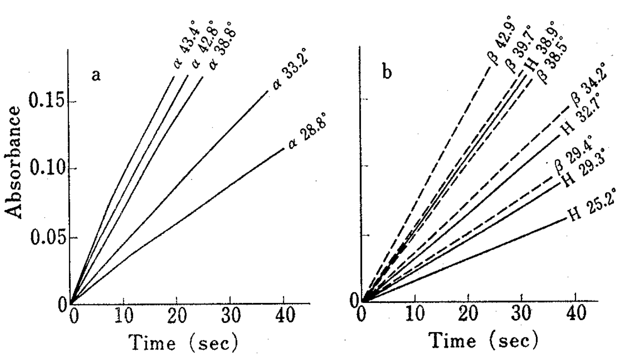

Fig. 5. Curves representing the Initial Dissolution Rates of Various Physical Forms of Sulfanilamide at Various Temperatures by Automatic Recording

a) α-form *b*) -------- : β-form, ——— : hydrate

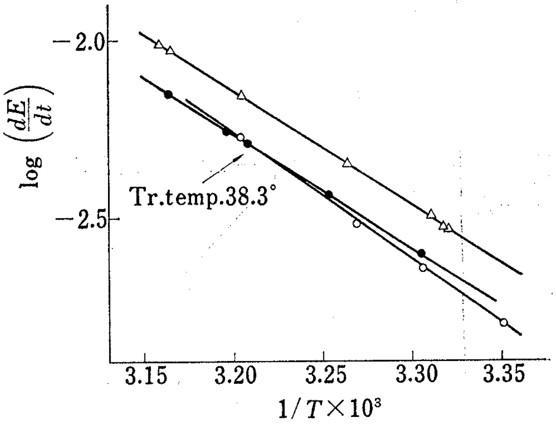

Fig. 6. Plots of log (dE/dt) against $1/T$ for α-, β-, and the Hydrated Forms of Sulfanilamide in Water

△ : α-form, ● : β-form, ○ : hydrate

above these points approach to those for β-S as shown in Fig. 5a and 5b. Nevertheless, the linearity found in the beginning of dissolution of α-S will no doubt represent that the disk dissolves in its original form due to delay of transition. Similarly, in the case of the hydrate, conversion to β-S often observed above the transition temperature of 38.3° several minutes after dissolution.

The Transition Temperature and the Heat of Transition by Solubility Determination

The solubilities of the β-form and the hydrate of sulfanilamide in each stable temperature range were determined by the conventional equilibrium method. The van't Hoff plots for these data are shown in Fig. 7. From the slope of the straight line, the heat of solution for each form is calculated at 8.96 kcal/mole for β-S and 10.71 kcal/mole for the hydrate, respectively. Consequently, the heat of transition from the hydrate to the anhydrous β-S should be 1.75 kcal/mole from the difference between the two heats of solution. Also, the transition temperature is found to be 35.8° from the intersection of two lines.

Kienle, *et al.*[8] reported previously about the solubility of sulfanilamide and estimated that the transition temperature and the heat of dehydration were 37° and 1.810 kcal/mole, respectively. These values are in good agreement with those obtained in the present study. Although the authors confirmed the existence of a monohydrate both by dilatometry and by vapor pressure measurement, they paid no regard for the presence of polymorphs. However, the anhydrous form they used must be β-S judging from the procedure adopted for its preparation and from their solubility data.

Estimation of the Metastable Solubilities

Because α-S is metastable at ordinary temperatures and converts rapidly to either β-S or the hydrate, it was impossible to determine its solubilities by the conventional equilibrium method, as shown in Fig. 8. Hence, solubility estimation for the metastable α-S was made by the following equation reported previously,[9] where Cs and

$$Cs' = Cs \times \frac{dE'/dt}{dE/dt}$$

Cs', and dE/dt and $dE'/\mathrm{d}t$ are solubilities and dissolution rates for the stable and metastable forms, respectively. In Table II, the solubilities for the metastable α-S and the maximum

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[8] R.H. Kienle and J.M. Sayward, *J. Am. Chem. Soc.*, **64**, 2464 (1942).

[9] M. Kanke and K. Sekiguchi, *Chem. Pharm. Bull.* (Tokyo), **21**, 878 (1973).

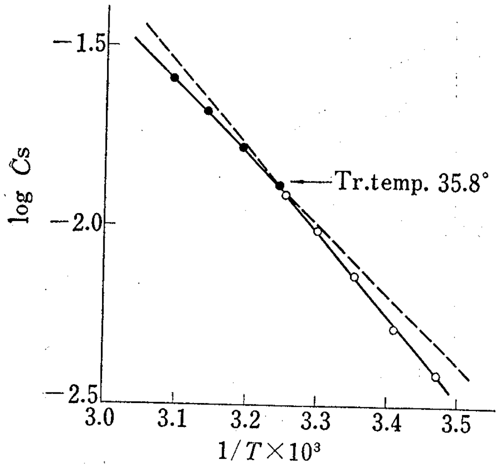

Fig. 7. The van't Hoff Plots of Solubility Values for β- and the Hydrated Forms of Sulfanilamide in Water

● : β-form, ○ : hydrate

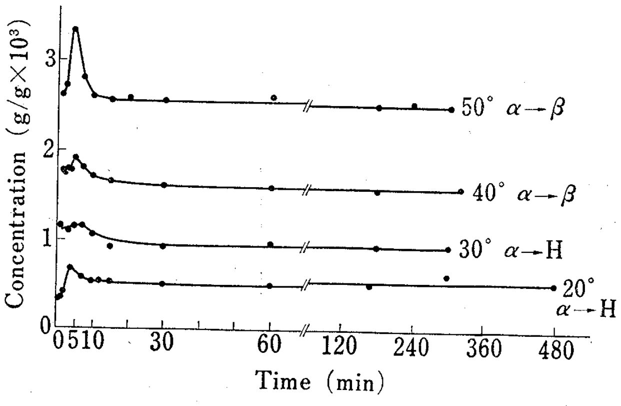

Fig. 8. Concentration-Time Curves for α-Form of Sulfanilamide in Water at Various Temperatures

The kinds of physical forms appeared after conversion are noted in the figure.

Table II. Solubilities for α- and β-Forms of Sulfanilamide in Water

Temp. (°C)	β-S Exptl. soly., g/g×10²	α-S Calcd.[a] soly., g/g×10²	Max. conc. obt'd[b] exptly., g/g×10²
20	0.615[c]	0.803	0.68
25	0.799[c]	1.048	0.93
30	1.024[c]	1.350	1.15
35	1.299	1.720	1.49
40	1.639	2.181	1.90
45	2.069	2.765	2.17
50	2.562	3.437	3.33

a) calculated from the equation $Cs' = Cs \times \frac{dE'/dt}{dE/dt}$

b) Maximum concentrations attained during dissolution of α-S.

c) These figures are the ones by extrapolating the experimental solubilities at temperatures above the transition point of the hydrated form.

Table III. Solubilities for β- and the Hydrated Forms of Sulfanilamide in Water at Various Temperatures

Temp. (°C)	Exptl. soly., g/g×10²		Calcd.[a] metastable soly., g/g×10²	
	β-S	Hydrate[b]	β-S	Hydrate[b]
15	0.471[c]	0.386	0.485	
20	0.615[c]	0.520	0.620	
25	0.799[c]	0.726	0.823	
30	1.024[c]	0.970	1.048	
35	1.299	1.291[c]		1.339
40	1.639	1.709[c]		1.664
45	2.069	2.237[c]		2.195
50	2.562	2.897[c]		2.836

a) calculated from the equation, $Cs' = Cs \times \frac{dE'/dt}{dE/dt}$

b) The amounts of the hydrate are expressed as those of anhydrous sulfanilamide.

c) These figures are the ones by extrapolating the experimental solubilities of β-S and the hydrate above and below the transition temperature.

concentrations attained during its dissolution processes are given. It is clear that the former values are always considerably larger than those of the latter.

In the same manner, solubilities of both β-S and the hydrate in the metastable temperature regions are calculated and compared with those obtained by extrapolation of the actual solubility curves in Fig. 7. Close agreement between these values will indicate the validity of estimation from dissolution rates (Table III).

Activation Energy for Dissolution

The activation energy for dissolution is calculated by subtracting the heat of solution from the heat of dissolution. From slopes of the lines in Figs. 6 and 7, the heats of dissolution and of solution for β-S and the hydrate are determined to be 14.56 and 16.29 kcal/mole, and 8.96 and 10.71 kcal/mole. Therefore, the values of Ea for both forms become 5.59 and 5.58 kcal/mole, respectively. In the previous paper,[9] the authors mentioned that polymorphic forms of the same substance should have the same Ea, so long as the dissolution is diffusion controlled. Agreement of the above two values demonstrates that the same is true of the anhydrous and hydrated forms of one substance and that the molecular species in solution are equal in either form.

Thickness of the Diffusion Layer

Thickness of the diffusion layer δ was calculated by the following equations, as previously reported,[9] where K is

$$K = \frac{SD}{V\delta}$$

$$D = \frac{kT}{6\pi\mu r} \qquad \text{(Stokes-Einstein equation)}$$

the apparent dissolution rate constant determined experimentally, S is the surface area of the disk exposed to dissolution medium of water, V is the volume of the medium, D is the diffusion constant, k is the Boltzmann constant, T is the absolute temperature, μ is the viscosity of the dissolution medium (water in this case), and r is the radius of the molecule of sulfanilamide or its hydrate, respectively. The molecular radius was calculated from the molecular weight of each form and the weight and volume of the disk, by assuming that all the molecules are closely packed as spheres. Thus, the diffusion constants D for β-S and the hydrate are decided to be 6.704×10^{-6} cm^2/sec and 6.558×10^{-6} cm^2/sec, respectively at 25°. Hence, the thickness of the diffusion layer δ at the same temperature becomes 4.31×10^{-3} cm for β-S and 4.33×10^{-3} cm for the hydrate. The fact that the two diffusion constants resemble closely with each other will indicate that both forms dissolve into the bulk solution as the same kind of molecular species. It is also reasonable from the values of δ to conclude that the dissolution of β-S and the hydrate are diffusion controlled.

The Transition Temperature and the Heat of Transition by DSC

The polymorphic transition of an organic substance often retards considerably. In addition, the extent of delay appeared in DSC curve becomes larger with the increase in heating rate owing to the dynamic nature of DSC. For these reasons, the transition temperatures of both α- and β-forms of sulfanilamide were estimated by plotting the beginning temperature of transition against the heating rate and extrapolating the curve to the rate of zero (Fig. 9). Thus, the transition point from α- to γ-S and that from β- to γ-S were determined to be about 80° and 90°, respectively. In the case of δ-form, since measurement was done without extrapolation, the transition from δ- to γ-S at the heating rate of zero will occur at a temperature lower by ten degrees or so. However, if the DSC curves of the three forms are compared at the same rate of 16°/min, it is clear that the transition point for δ-S is the highest among the three.

Table IV. The Heat of Transition between Various Physical Forms of Sulfanilamide by Dissolution Rate and Solubility Measurements, and DSC

Method	Transition	Transition temperature (°C)	Heat of transition (kcal/mole)
Dissolution rate	α-S → β-S	−119	0.17
	hydrate → β-S	38.3	1.74
Solubility	hydrate → β-S	35.8	1.75
DSC	α-S → γ-S	about 80	$0.45_1 \pm 0.01$
	β-S → γ-S	about 90	$0.41_7 \pm 0.01$
	δ-S → γ-S		0.17 ± 0.01
	α-S → β-S		0.03_4[a]
	α-S → δ-S		0.28[a]
	β-S → δ-S		0.25[a]
	hydrate → β-S	about 40	2.0 ± 0.2
			2.7 ± 0.1[b]

a) These figures are the ones by mutual subtraction of the heats of transition from α-, β-, and δ-S to γ-S.
b) measured under closed condition

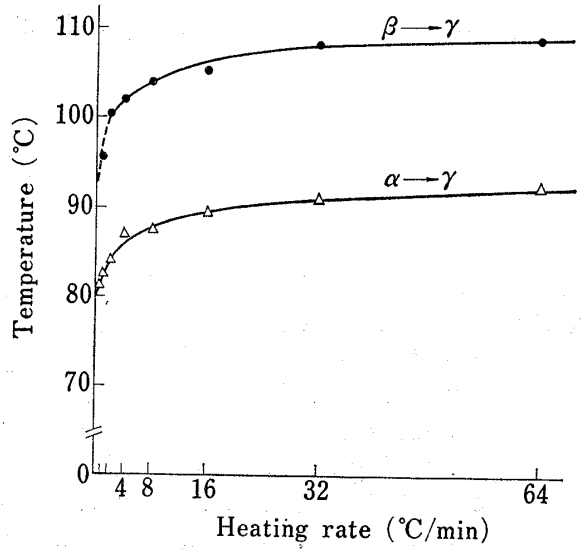

Fig. 9. Effect of Heating Rate of DSC on Transition Temperature of α- and β- Forms of Sulfanilamide

sample weight : 13—28 mg
sensitivity: 8—16 mcal/sec
heating rate : 0.5—64°/min

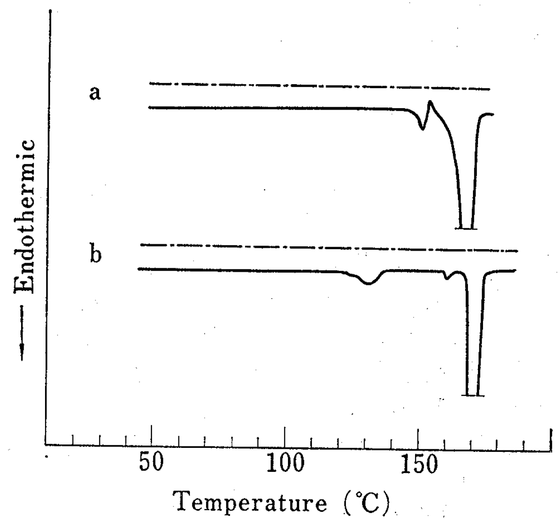

Fig. 10. Thermograms of α- and β-Forms of Sulfanilamide

—— :DSC curve, —·— :EGD curve
a: α-S crystallized from n-amyl alcohol, solid sample pan, 16°/min
b: β-S crystallized from ethyl alcohol, liquid sample pan, 3.82 mg, 16°/min

The heats of transition by DSC are listed in Table IV. They are the averages of at least five runs. In the case of the hydrate, the heats were determined by measuring areas of the shadowed portions of the DSC peaks under semiclosed and closed conditions in Fig. 4. On the other hand, the values for transition between α- and β-S, between α- and δ-S, and between β- and δ-S were obtained by mutual subtraction of the heats of transition from α-, β-, and δ-S to γ-S. In this connection, Lin, *et al.*[10] have recently measured the heats of transition from α- and β-S to γ-S by differential thermal analysis. Although they gave figures in kcal even down to three places of decimal, the data will not be so highly reliable because of the limited accuracy of the method for quantitative application.

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10) H.O. Lin and J.K. Guillory, *J. Pharm. Sci.*, **59**, 972 (1970).

The Metastable Melting Point by DSC and by Microscopic Thermal Analysis

As shown in Fig. 10(a), when DSC was performed with α-S crystals isolated from *n*-amyl alcohol, it very often happened that a chain of two endothermic and one exothermic peaks appeared above 146° in place of the two endothermic ones due to transition from α- to γ-S, and to melting of γ-S. In such a case, the second large endothermic peak became broader and shifted several degrees lower than that by melting of γ-S. Similarly, when the same crystals of α-S were applied to the microscopic thermal analysis using a hot-stage, some of them were noticed to be melted between 147° and 153° without showing any cracking attributable to the transition from α- to γ-S. Such a phenomenon was more clearly observed if the heating rate was increased to about 30°/min. From these facts, it is certain that the first pair of small peaks is assigned to the metastable melting of α-S and subsequent solidification to another polymorphic form.

When DSC under closed condition was done with the crystals of β-S obtained by crystallization from ethyl alcohol, three endothermic peaks appeared at 130°, 160°, and 168°, respectively (Fig. 10(b)). The first peak represents clearly the transition from β- to γ-S, while the third one just corresponds to the melting of γ-S. Although a conclusive evidence was not obtained by microscopic observation, the second small peak at 158—162° is thought to be due to melting of β-S crystals remained unchanged above its transition temperature. Therefore, the second large endothermic peak in Fig. 10(a) will be ascribed to the combined heat effects by successive melting of α-, β-, and γ-S.

Conclusion

As shown above, a thorough examination concerning various physical forms of sulfanilamide were made by dissolution rate measurements and by several other methods of analysis. Results thus obtained were compared with each other and the following conclusions were reached.

(1) The Transition Temperatures and the Heats of Transition by Various Methods

The transition temperatures and the heats of transition between α- and β-forms, and between β- and the hydrated forms of sulfanilamide were determined by dissolution study. At the same time, these thermodynamic constants were determined directly or indirectly by DSC and by conventional solubility measurements. The transition temperature between α- and β-S could not be determined by the latter two methods because of easy conversion of the metastable α-S in an aqueous solution or because of the difficulty to carry out measurements at extremely low temperatures. However, the heat of transition between α- and β-S could be obtained from DSC data by subtracting the heat of transition between α- and γ-S from that between β- and γ-S. The heats of transition between α- and δ-S, and between β- and δ-S were calculated in the same manner. Results thus obtained are summarized in Table IV. A satisfactory agreement is obtained among values of the heat of transition from the hydrate to β-S except that by DSC under closed condition. Because in the latter case, there will be remained some void space in the liquid sample pan, a positive error will be necessarily introduced due to evaporation of water from the solution formed by peritectic transition of the hydrate. Although the heat of transition between α- and β-S by the dissolution rate method is found to be five times larger than that by DSC, the absolute heat quantities of them are no more than 170 cal/mole and 34 cal/mole, respectively. Therefore, the discrepancy will be permissible, if the difference in accuracy, precision and applicability among methods and experimental conditions are taken into consideration.

(2) A Schematic Phase Diagram for α-, β-, and γ-Forms of Sulfanilamide

In addition to the transition temperatures among α-, β-, and γ-S, the stable or the metastable melting points of them were determined by DSC and by the hot-stage polarizing microscopy. The accuracy of these data are not the same; however, total relations among the three polymorphs will be obvious and be represented by a schematic pt-diagram in Fig. 11. From the diagram, the δ-form is omitted by the reason that more detailed studies are necessary in order to reveal its relations to other forms. However, it is supposed that the stability range for δ-S should be narrow from values of the transition temperature and the heat of transition between δ- and γ-S determined by DSC.

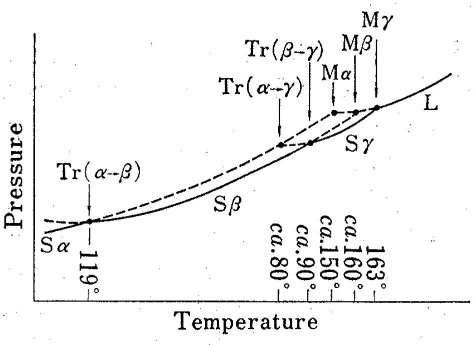

Fig. 11. Schematic pt-Diagram for α-, β-, and γ-Forms of Sulfanilamide

(3) The Concept of Monotropic Transition

In physical chemistry, the relation between two polymorphs are divided into two categories, enantiotropy and monotropy. But so far as the authors know, so-called monotropic forms in literature are all lacking of conclusive evidences to demonstrate that they are really monotropic. The most decisive criterion for monotropy is that the transition point between the two forms exists at a certain temperature above the melting points of both forms. However, the monotropic transition point has not yet been measured because it can not be realized actually. Even though the point is an imaginary one, it is theoretically possible to estimate it indirectly by several methods such as measurements of solubilities, dissolution rates and heats of solution at various temperatures. Among them, the most promising is the one by the initial dissolution rates, since the method utilize the delayed conversion of the metastable form effectively.

As is evident from the results above, the transition temperature between the metastable α- and the stable β-forms of sulfanilamide locates at a temperature much lower than the melting points of both forms. Therefore, the relation between these polymorphs belongs not to monotropy but to enantiotropy, and the supposition by Watanabe, *et al.* that they are monotropic is completely denied. The conclusion is further supported by the results of DSC that α-S shows a transition peak to γ-S at a temperature lower than the peak from β- to γ-S, and that the heat of transition between α- and γ-S is always less than the one between β- and γ-S. Although continued efforts will be required to accumulate experimental proofs, the present authors now have an opinion that the concept of monotropy might only be the product of the brain that has no actual meaning.

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