on a boiling water bath for 1 hr. The solvent was evaporated and the residue was washed by 5% HCl solution. The precipitate was collected by filtration, washed with water, and recrystallized from MeOH to give amine derivatives (**6a**—**e**).

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Some Properties of Sulfanilamide Monohydrate

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The crystalline form taken by sulfanilamide monohydrate depends on the concentration of sulfanilamide in the aqueous solution from which it is crystallized. Apparent heats of solution are reported for the four (anhydrous) polymorphic forms of sulfanilamide.

Theoretical

The phenomena of polymorphism and hydrate formation in sulfanilamide have attracted considerable attention recently.[2-7] We would like to contribute some additional observations.

In contrast to previous investigators, we have found that the form taken by sulfanilamide monohydrate depends on the conditions of its crystallization. In addition, we have observed that the various polymorphs of sulfanilamide are not inevitably converted to the more stable β form when in contact with water at temperatures above the temperature at which transition from the monohydrate to the anhydrous form occurs.

Slow cooling of hot, aqueous sulfanilamide solutions containing 15%, 8%, and 5% of the solute usually produces crystals which, on filtration and storage in a vacuum desiccator over diluted sulfuric acid (density, 1.08g/ml, 96% relative humidity) exhibit differential thermal analysis (DTA) thermograms of the type represented in Figure 1 as α', β', and δ', respectively. While the DTA thermograms of these hydrated species appear to be quite similar, exhibiting peaks near 40° corresponding to the breaking of interactions between water molecules and the crystal lattice, and near 100°, corresponding to the vaporization of water from the sample tube, the DTA thermograms obtained following exposure of these crystals to the atmosphere are quite different. Exposure of the hydrates to air causes the crystals to lose moisture rapidly, and after a few days of such exposure, it is found that the α' crystals on dehydration exhibit an endothermic peak at 110°, characteristic of the α form of sulfanilamide, and an infrared spectrum which is also characteristic of this form.[3]

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[1] Location: *Iowa City, Iowa 52242, U.S.A.*
[2] M. Kuhnert-Brandstätter and S. Wunch, *Mikrochim. Acta*, 6, 1297 (1969).
[3] H.O. Lin and J.K. Guillory, *J. Pharm. Sci.*, 59, 972 (1970).
[4] A. Burger, *Sci. Pharm.*, 41, 290; 303 (1973).
[5] A. Burger, *Pharm. Ind.*, 35, 626 (1973).
[6] H.O. Lin, N.C. Baenziger, and J.K. Guillory, *J. Pharm. Sci.*, 63, 145 (1974).
[7] K. Sekiguchi, Y. Tsuda, and M. Kanke, *Chem. Pharm. Bull.* (Tokyo), 23, 1353 (1975).

Similarly, the β' and δ' forms, on dehydration, exhibit endothermic peaks in the DTA at 123° and 97°, respectively, characteristic of the β and δ forms. Infrared spectra of these species also correspond to the previously published spectra.[3]

The order with which these crystals precipitate from solution provides some additional evidence for the assignment of relative stabilities to the anhydrous polymorphic forms, since a form of Ostwald's rule[8] can be applied here. This rule, which applies to supersaturated solutions, states that the form which crystallizes out is not necessarily the most stable one, but the one which can be reached with the minimum loss of free energy.

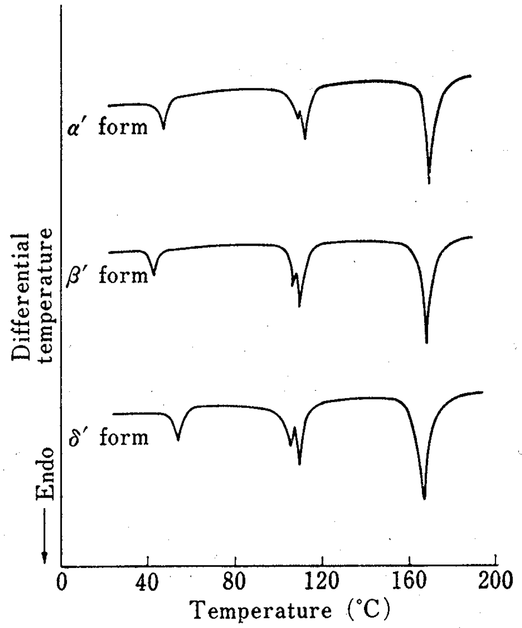

Fig. 1. DTA Thermograms for Polymorphs of Sulfanilamide Monohydrate

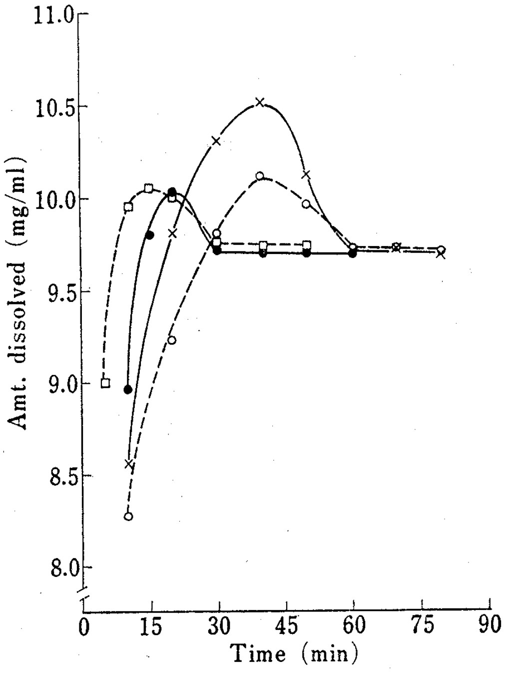

Fig. 2. Dissolution Profile for the Polymorphs of Sulfanilamide in Water using the Beaker Method at 37°

key: ○, α form; □: β form; ×: γ form; ●: δ form

Sekiguchi, *et al.*[7] have shown that dissolution of the anhydrous α form of sulfanilamide (Note: We[6] have designated this form as δ; Burger,[4] as Form III.) can be characterized by concentration *vs.* time plots which display maxima. These maxima are interpreted as saturation concentrations of the α form which, at temperatures above 38.3°, is converted to the less soluble anhydrous β form (Burger's Form II) of sulfanilamide. At 30° and 20°, the maxima are again interpreted as saturation solubilities of the α form, but in this instance, conversion is to the less soluble monohydrate.

Burger[5] has reached a similar conclusion, and has shown that, in some instances, at 20°, it is possible to obtain a dissolution plot for Form III which has two maxima. In our own studies,[9] at 37°, we observed only single peaks for each of the four anhydrous forms of sulfanilamide (See Figure 2).

Both Burger[5] and Sekiguchi, *et al.*[7] suggest that at temperatures between the transition temperature for conversion from the monohydrate to the hydrate form, and the temperature at which conversion from the β to the γ form occurs (According to Burger, II→I.) only the β form will crystallize out. We have found otherwise. In our experiments, we have observed

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8) W. Ostwald, *Z. physik. Chem.*, **22**, 306 (1897).

9) H.O. Lin, "Investigations of Physical Properties of Sulfanilamide Polymorphs," Ph. D. Dissertation, The University of Iowa, Iowa City, 1971, p. 65; *Dissertation Abstr.* B, 4703-B, March 1972.

TABLE I. Solubilities of Sulfanilamide Polymorphs and Sulfanilamide Monohydrate in Water (M × 10^2)

T, °C	Anhydrous polymorphs α form	 β form	 γ form	 δ form	Hydrate form
15					2.20
26					4.32
30	5.87[a)]	5.81[a)]	6.11[a)]	5.81[a)]	5.60
37	9.12	9.07	9.24	8.92	8.42
40	9.75	9.68	9.64	9.64	
50	14.35	14.19	14.30	14.33	

a) estimated from maxima in the dissolution plots

small, but measurable, differences in the equilibrium solubilities obtained for the four anhydrous modifications of sulfanilamide (See Table I). In addition, we have isolated the residue of crystals from the sample vials at the conclusion of solubility determinations, and have subjected these to DTA and to infrared analysis. As one might expect, there are some changes in the positions of the peaks in the DTA thermograms when these are compared to similar traces run on crystals which have not been in contact with water. But, in the case of the sediment obtained in the 40° solubility experiments, it was found that crystals of the α form continued to exhibit a transition at 106—107°, and those of the β form, at 124—128°, even after 36 hours of equilibration with water at 40°. Infrared spectra confirmed the fact that these species remained in their original forms.

The γ form, which does not undergo transition prior to fusion, does undergo partial conversion to a form exhibiting a peak in the DTA at 101° (possibly the α form), and the δ form undergoes partial conversion to the β form, since it exhibits peaks in DTA both at 107° and at 121°. Nevertheless, it must be concluded that sizeable amounts of the crystals in contact with water must remain in their original metastable forms.

In spite of the fact that partial conversion of the polymorphs does occur, it is interesting to note that reasonably linear plots of log C_s *vs.* $1/T$ can be obtained from the data in Table I. When these data are treated by least squares analysis, one obtains the heats of solution and the transition temperatures listed in Table II. Subtraction of the heats of solution for the anhydrous forms from the heat of solution of sulfanilamide monohydrate yields the heats of conversion from the monohydrate to the anhydrous forms that are shown. Data are not included for the γ form, because we were unable to obtain this form as a monohydrate under the conditions used in this study. The solubilities listed for the various anhydrous modifications at 30°, where these species are metastable with respect to hydrate formation, were obtained by estimation from maxima in the dissolution plots.

It should be noted that there is excellent agreement between the heat of dehydration shown in this table for the β form and the figure reported by Burger.[5)] Burger obtained a value of 2.36 kcal mole^{-1} and a transition temperature of 38°.

TABLE II. Apparent Heats of Solution and Related Data

Crystalline form	Apparent heat of solution kcal mol.$^{-1}$	Correlation coefficient	Apparent heat of transition, ΔH $S \cdot H_2O \rightarrow S$ kcal. mol^{-1}	Transition temperature
α	8.46	0.986	2.34	38°
β	8.44	0.985	2.36	36°
γ	8.03	0.987	—	—
δ	8.57	0.989	2.23	37°

Experimental

Preparation of Crystalline Forms——Techniques used for the preparation of the four anhydrous polymorphic forms of sulfanilamide have been described in a previous publication.[3] Sulfanilamide monohydrate was prepared by recrystallization from distilled water. Hot aqueous sulfanilamide solutions of various concentrations were prepared and cooled to room temperature. The crystals were collected by filtration and kept in a desiccator over diluted sulfuric acid (density=1.08 g/ml, 96% relative humidity). After a few days the samples were subjected to differential thermal analysis and to thermogravimetric analysis.

Characterization of Crystalline Forms——The Du Pont Model 900 Differential Thermal Analyzer was employed to distinguish between the polymorphic forms and the monohydrate. Samples were heated from room temperature to a temperature several degrees above fusion at a uniform heating rate of 10° per minute. Samples of approximately 2 mg were employed in ordinary glass capillary tubes, 2 mm in diameter. Nitrogen gas was flushed through the standard cell throughout the heating procedure, and cold junction thermocouples in an ice bath were used to establish the reference temperature. Other techniques, including infrared spectroscopy (with KBr pellets), and hot stage microscopy were used whenever results obtained by DTA were inconclusive.

Solubility Determinations——The solubility of each of the various crystalline forms of sulfanilamide was determined by analysis of aliquots of saturated solutions. An excess of crystals of each form over the amount required for saturation of the solvent was placed in a 20 ml vial, stoppered with a plastic screw cap, and the vial was rotated end-over-end in a constant temperature bath controlled to $\pm 0.1°$. Equilibrium was usually attained after 36 hours or less. The contents of the vial were permitted to settle for some time, and the supernatant liquid was filtered through sintered glass. After appropriate dilution, the sample was analyzed spectrophotometrically using a Beckman Model DU spectrophotometer. Two or more determinations were made at each temperature, and the mean of these determinations was taken as the solubility.

Dissolution Determinations——The method used for obtaining dissolution profiles for the polymorphs of sulfanilamide was a modification of the rotating disk technique developed by Levy and Sahli.[10] One-half inch flat-faced pellets (surface area, 1.27 cm^2) of pure sulfanilamide polymorphs were prepared using a Beckman Potassium Bromide Dye and a Pasadena Hydraulics, Inc. Press at a pressure of 12 tons. Pellets were mounted on glass holders at the end of 25 cm glass rods with the aid of epoxy glue, in such a manner that only one surface of the tablet was exposed to solvent. The other end of the glass rod was attached to a Cole-Palmer Model 4555-3 Controlled Speed Motor.

An appropriate amount of the dissolution medium was placed in a three-neck round bottom flask which was immersed in a constant temperature bath controlled to $\pm 0.1°$. After temperature equilibration was achieved, the pellet attached to the glass holder was immersed into the dissolution medium. The stirrer was set to revolve at a speed of 60 rpm. A suitable number of aliquots was removed from the flask at appropriate time intervals for analysis. An equal volume of fresh dissolution medium was replaced after sampling, so that the volume in the flask remained constant throughout the study. An appropriate correction was made in the concentration measurements. Two or more dissolution rate determinations were performed, and the average value was taken as the amount dissolved at a particular time. Maxima in the solubility *vs.* time plots were used to obtain estimates of the solubility of the anhydrous polymorphic forms at 30°, a temperature at which these forms are metastable with respect to hydrate formation.

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[10] G. Levy and B.A. Sahli, *J. Pharm. Sci.*, **51**, 58 (1962).