Kinetics of Polymorphic Transformation of Sulfathiazole Form I

ELIE G. SHAMI*, PETER D. BERNARDO, ELISABETH S. RATTIE, and LOUIS J. RAVIN▲

Abstract □ A quantitative method is presented which utilizes differential scanning calorimetry for the determination of sulfathiazole Form I in the presence of sulfathiazole Form II. Data are included which demonstrate that the method can be utilized to follow the rate of transformation of Form I to Form II. The kinetics for this transition have been described as being somewhat analogous to diffusion-controlled crystal growth from solution. An activation energy of 56 kcal./mole was calculated for the system. This value was in agreement with the activation energy obtained using a differential thermal method.

Keyphrases □ Sulfathiazole Form I—quantitative method for determining Form I in presence of Form II, kinetics of polymorphic transformation, differential scanning calorimetry □ Transformation kinetics—sulfathiazole Form I and Form II, quantitative differential scanning calorimetric method □ Differential scanning calorimetry—determination of polymorphic transformation of sulfathiazole Form I in presence of Form II, kinetics

The thermal behavior of sulfathiazole has been studied by a number of workers (1–3). Most describe methods for preparing various forms and their subsequent characterization. Moustafa and Carless (4) reported the use of differential scanning calorimetry to estimate the amount of sulfathiazole Form I in the presence of sulfathiazole Form II. They also observed a rapid change of Form I to Form II above the transition temperature and essentially no change below the transition temperature. This paper reports the quantitative determination of sulfathiazole Form I in the presence of sulfathiazole Form II and the use of this quantitative procedure to follow the kinetics of transformation of sulfathiazole Form I to sulfathiazole Form II.

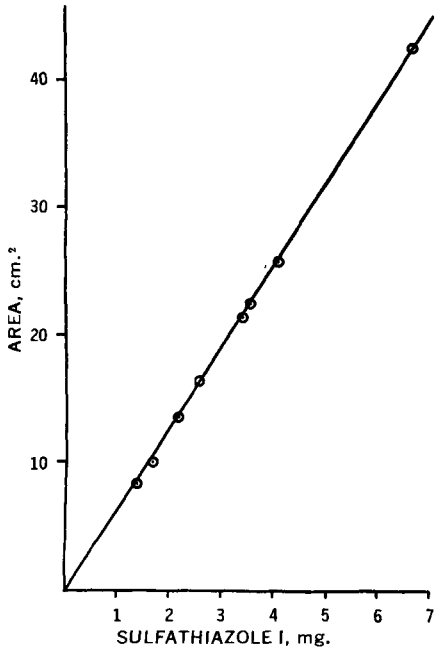

Figure 1—*Calibration curve for sulfathiazole Form I [rate of heating, 40°/min.; sensitivity range, 4; chart speed, 10.2 cm. (4 in.)/min.].*

Table I—Determination of Form I in Presence of Form II by Differential Scanning Calorimetry

Mixture	Percent Form I Theoretical	Percent Form I Found[a]	Percent Error
A	51.5	50.1 ± 0.7	−2.7
B	68.5	68.9 ± 0.4	+0.6
C	74.0	74.8 ± 0.6	+1.0
D	20.2	21.4 ± 0.7	+5.9

[a] Average of four determinations.

EXPERIMENTAL

Materials—Sulfathiazole Form I was prepared by slow recrystallization from an acetone–chloroform solvent system. Sulfathiazole Form II was prepared by heating Form I to 180°. IR analysis was used to identify the presence of both forms.

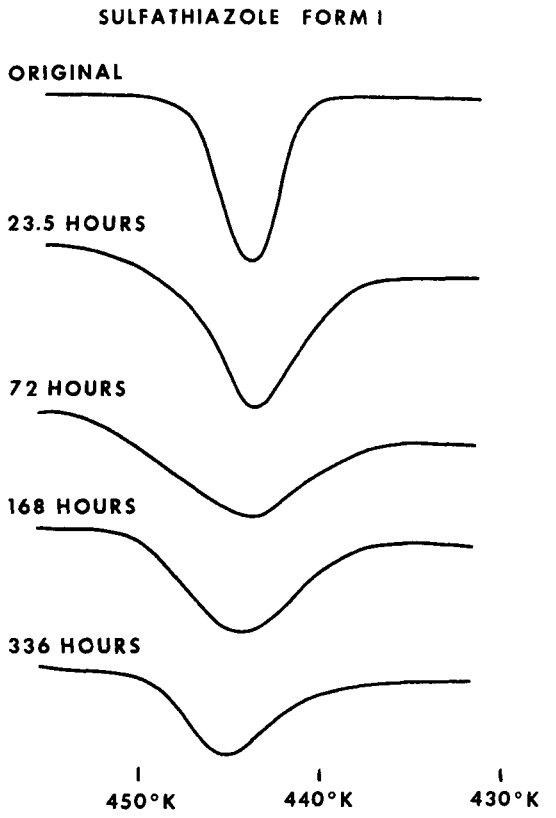

Figure 2—*Plot illustrating the change in transition endotherm with time for sulfathiazole Form I at 415°K.*

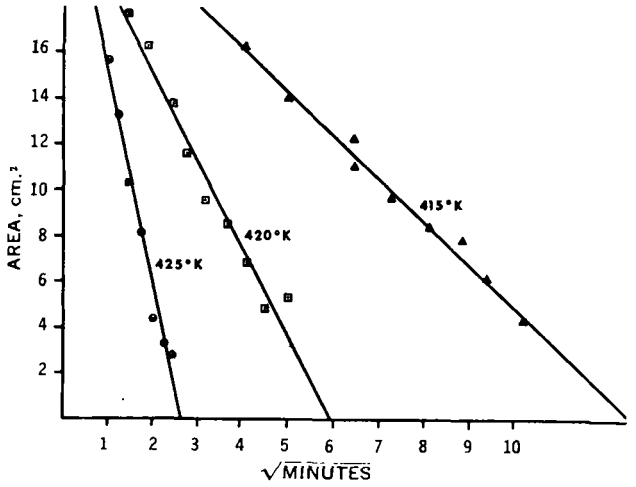

Figure 3—*Plot illustrating the rate of transformation of sulfathiazole Form I at several temperatures.*

Apparatus—A differential scanning calorimeter[1] with a recorder attachment[2] and an effluent analyzer was used. Samples of indium (purity 99.99%) were used to calibrate the instrument. The areas under the transition endotherms were measured with a planimeter[3].

Determination of Standard Curve—Known quantities of sulfathiazole Form I, previously treated to minimize the effect due to particle size, were accurately weighed. Thermograms of these samples were run using a heating rate of 40°/min. at a sensitivity range of 4 and a chart speed of 10.2 cm. (4 in.)/min. Nitrogen gas was flowing at a rate of 15 ml./min. during the experiment. These conditions were used for all differential scanning calorimetry determinations. The area under the transition endotherm was determined.

Utility of Standard Curve—Known quantities of sulfathiazole Forms I and II were intimately mixed in a mortar. Samples weighing from 4 to 9 mg. were accurately weighed into aluminum pans. Thermograms of these samples were run, and the areas under the transition endotherms were determined.

Kinetic Experiment—Pure sulfathiazole Form I, 3.0 ± 0.1 mg., was weighed into aluminum pans. The samples were then placed in the analyzer unit of the differential scanning calorimeter at selected constant temperatures (425, 420, 415, and 395°K.) for various time intervals. Thermograms for each sample were run as previously described. The area under the transition endotherms was determined. The amount of Form I remaining was calculated utilizing the thermal constant from the standard curve.

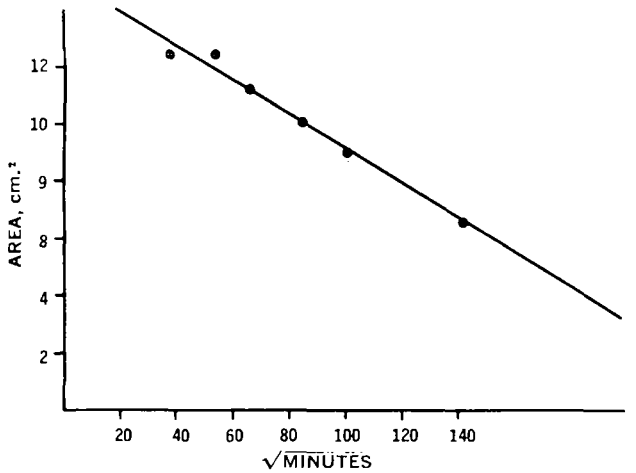

Figure 4—*Plot illustrating the rate of transformation of sulfathiazole Form I at 395°K.*

[1] Perkin-Elmer model DSC-1-B.
[2] Serva-riter II.
[3] Keuffel & Esser.

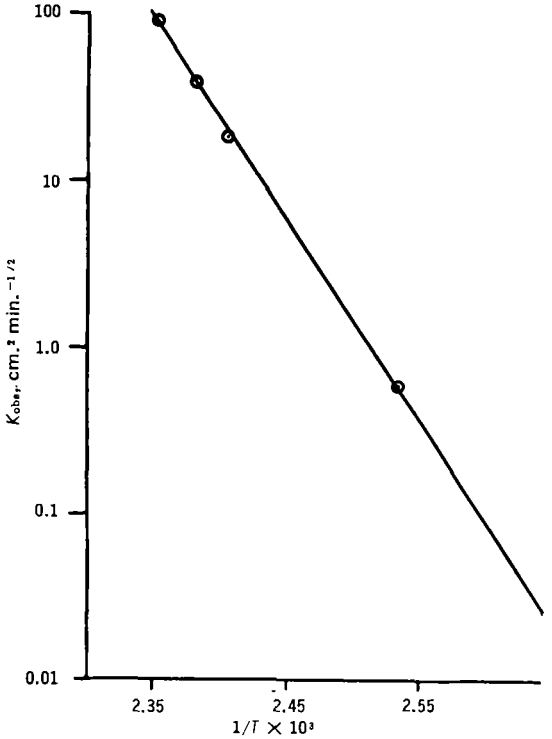

Figure 5—*Typical Arrhenius-type plot showing the temperature dependency for the transition of sulfathiazole Form I to sulfathiazole Form II.*

Effect of Heating Rate—Samples of sulfathiazole Form I were run on the differential scanning calorimeter at heating rates of 5, 10, 20, and 40°/min. The maximum transition temperature was determined by drawing a linear segment from each end of the transition endotherm and then drawing a line perpendicular from the baseline through the intercept at the height of the transition endotherm.

RESULTS AND DISCUSSION

Figure 1 illustrates a linear relationship between the amount of sulfathiazole Form I and the peak area of the transition endotherm. This relationship was utilized to quantitate the amount of Form I in a sample. Accordingly, by using the value for the slope of this line from the standard curve (6.1186 cm.²/mg.), analysis of unknown samples could be made. To verify this, mixtures of the stable and metastable (Forms I and II) sulfathiazole were prepared,

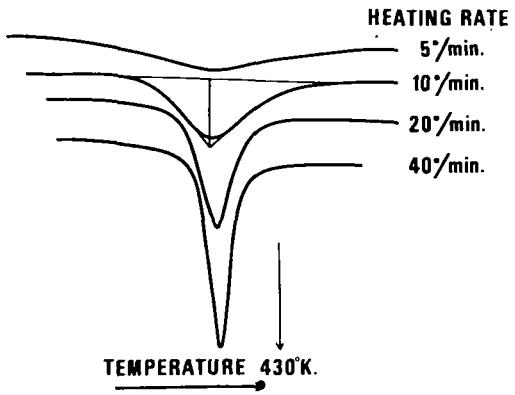

Figure 6—*Effect of heating rate on the peak maximum temperature for the transition endotherm. The method for determining the peak maximum temperature is shown for the 10°/min. trial.*

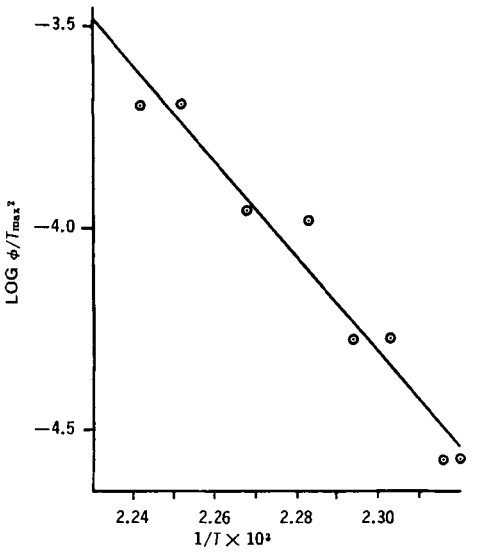

Figure 7—*Plot showing the relationship of heating rate and peak maximum temperature for the transition endotherm in determining the thermodynamic activation energy.*

in which the amount of Form I in the mixtures varied from 20 to 74%. The results of this experiment are shown in Table I. Excellent agreement was found between the experimental and theoretical values. These data show a higher degree of accuracy than was found in the work of Moustafa and Carless (4).

The kinetics of the transformation of sulfathiazole Form I were studied at 395, 415, 420, and 425°K. Figure 2 depicts the change in the transition endotherm as a function of time at 415°K. The fact that the transition endotherm is changing with time indicates that Form I is slowly disappearing. Figures 3 and 4 illustrate the data obtained in the kinetic studies in which a linear relationship resulted when the area of the transition endotherm was plotted *versus* the square root of time. These results suggest that the transition is analogous to the diffusion-controlled crystal growth from solution (5). Reaction rates were determined for the rates of conversion. A typical Arrhenius-type plot of the data is presented in Fig. 5. From these data the apparent heat of activation was determined to be approximately 56 kcal./mole. To verify this, the thermodynamic activation energy for the transition of Form I to Form II was determined by an alternate method (6). Similar to the work of Himuro *et al.* (7), the peak maximum temperature for the transition endotherm was measured at various heating rates. The data are illustrated in Fig. 6. As expected, the peak maximum temperature decreased as the heating rate decreased. Utilizing the following equation of Kissinger (6):

$$\frac{d(\ln \phi/Tm^2)}{d(1/T_m)} = -E/R \qquad \text{(Eq. 1)}$$

where ϕ is the heating rate, and T_m is the peak maximum temperature for transition, a plot of ln ϕ/Tm^2 *versus* $1/T_m$ should yield a straight line with a slope of $-E/R$. This is illustrated in Fig. 7. The energy of activation as determined by this method was approximately 57 kcal./mole. The value is in good agreement with the results obtained isothermally. The data presented in this study suggest that the differential scanning calorimeter can be utilized as a quantitative analytical tool to follow the kinetic transformation of polymorphic materials.

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Acetyldigoxin and Acetyldigitoxin from *Digitalis lanata*

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Abstract □ This paper describes the ready separation of acetyldigoxin from acetyldigitoxin when these secondary glycosides are isolated in combination from *Digitalis lanata*, fresh or dried, containing the maximum amounts of the native glycosides. The initial primary extract used 35% aqueous methanol and enzyme-favoring conditions. Final separation of the two acetyl glycosides was effected by partitioning between 12.5% aqueous methanol and benzene or toluene.

Keyphrases □ Acetyldigoxin—separation from acetyldigitoxin in *Digitalis lanata* extracts □ Acetyldigitoxin—separation from acetyldigoxin in *Digitalis lanata* extracts □ *Digitalis lanata* extracts—separation of acetyldigoxin from acetyldigitoxin

Previous reports described the preparation of acetyldigoxin (1) from *Digitalis lanata* and acetyldigitoxin (2) from *Digitalis siberica* and *Digitalis mertonensis*. In the case of *D. lanata*, an aqueous primary extract of the fresh leaves was used; in the case of *D. siberica* and *D. mertonensis*, 35% aqueous methanol was used to prepare a primary extract from either the fresh or dried leaves. Solubility characteristics of the acetyl glycosides,