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A Kinetic Study on the Isothermal Transition of Polymorphic Forms of Tolbutamide and Mefenamic Acid in the Solid State at High Temperatures[1)]

TSUNEO UMEDA,[a] NORIAKI OHNISHI,[a] TERUYOSHI YOKOYAMA,*[,a] TSUTOMU KURODA,[a] YOSHIAKI KITA,[a] KOJI KURODA,[a] ETSUKO TATSUMI,[b] and YOSHIHISA MATSUDA[b]

Hospital Pharmacy, Kobe University School of Medicine,[a] Kusunoki-cho, Chuo-ku, Kobe 650, Japan and Kobe Women's College of Pharmacy,[b] Motoyamakitamachi, Higashinada-ku, Kobe 658, Japan

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The kinetics of the isothermal transition of tolbutamide polymorphic forms (form B at 65, 70, 75 and 80 °C), as well as mefenamic acid (form I at 142.5, 145, 147.5 and 150 °C) were investigated by means of differential scanning calorimetry. Kinetic analysis according to the method of Hancock and Sharp indicated that the transition of form B to form A of tolbutamide proceeds by the mechanism of three-dimensional diffusion (Jander equation). The activation energy for this transition calculated from the slope of the Arrhenius plots was 37.3 kcal/mol. On the other hand, the transition of form I to form II of mefenamic acid appeared to follow the zero-order mechanism (Polany–Winger equation). The activation energy for this transition was calculated to be 86.4 kcal/mol.

Keywords——tolbutamide; mefenamic acid; polymorphism; isothermal transition; kinetic analysis; differential scanning calorimetry

The pharmaceutical implications of polymorphism have been reviewed by Haleblian and others,[2)] and the effects on physical stability, drug bioavailability and tableting are now recognized. However, only a few kinetic analyses of isothermal transition in the solid state have been reported.[3,4)]

In the previous paper,[1)] we investigated the kinetics and mechanism of the isothermal transition of carbamazepine polymorphs in the solid state by X-ray powder diffractometry, and reported that transition mechanisms were different among the polymorphic forms. This paper presents a kinetic analysis of the isothermal transition of the polymorphic forms of tolbutamide and mefenamic acid, based on differential scanning calorimetry.

Experimental

Materials——Tolbutamide used in this study was a commercial product of JP X grade (Hoechst Japan Co., Ltd.) and mefenamic acid (Lot No. 83022) was supplied by Warner Lambert Co., Ltd. All other chemicals were reagent grade commercial products.

Preparation of Polymorphic Forms——The polymorphic forms of tolbutamide (forms A and B) and mefenamic acid (forms I and II) were prepared according to the methods described by Simmons *et al.*[5)] and Aguiar *et al.*,[6)] respectively. The particle sizes of the polymorphic forms were in the range of 62—74 μm throughout this work. Form B of tolbutamide was stored at 5 °C and the other crystals were stored at room temperature.

Identification of Polymorphic Forms——Each polymorphic form was identified by using X-ray powder diffractometry (Rigaku Denki, Geigerflex, monochromator, Cu-*Kα* radiation, 40 kV, 10 mA), differential scanning calorimetry (DSC, Perkin–Elmer, model DSC-2C) and thermogravimetry (TG, Perkin–Elmer, model TGS-2). The X-ray powder diffraction patterns of the polymorphic forms of tolbutamide and mefenamic acid were in agreement with those reported by Simmons *et al.*[5)] and Aguiar *et al.*[6)] respectively.

In the DSC curves of forms A and B of tolbutamide, the latter crystal gave a characteristic thermogram with two endothermic peaks at 103 and 128 °C (heating rate; 20 °C/min) (Fig. 1). The smaller endothermic peak at 103 °C was attributable to the transition of form B to form A. The larger one at 128 °C corresponded to the melting point of form A. Form A showed only one endothermic peak corresponding to the melting point at 128 °C. These results were identical with those of Simmons *et al.*[5] and Ueda *et al.*[7] In the TG curves of forms A and B, no change in weight was observed.

As shown in Fig. 2, the DSC curves of form I of mefenamic acid showed two endothermic peaks at 179 and 230 °C (heating rate, 40 °C/min). These endothermic peaks corresponded to the transition of form I to form II and the melting point of form II, respectively. Form II gave only one endothermic peak corresponding to the melting point at 230 °C. In the TG curves of forms I and II, no change in weight was observed.

Preparations of Calibration Curves——Known quantities of form B of tolbutamide or form I of mefenamic acid were accurately weighed into aluminum pans. Thermograms of these samples were run at a heating rate of 20 °C/min (for form B) or 40 °C/min (for form I) with a sensitivity of 2 mcal/s. Dry nitrogen gas was passed at 20 ml/min during all DSC experiments. The area under the transition peak was measured as the value of $\mu V \cdot S$ with a Chromatopac (Shimadzu C-RIA). As shown in Fig. 3, each calibration curve gave a good straight line (tolbutamide, $r=0.999$; mefenamic acid, $r=0.997$).

In order to verify the utility of the calibration curves, mixtures of polymorphic forms were prepared, in which the amounts of form B or form I were determined from the appropriate calibration curve. As shown in Fig. 4, excellent

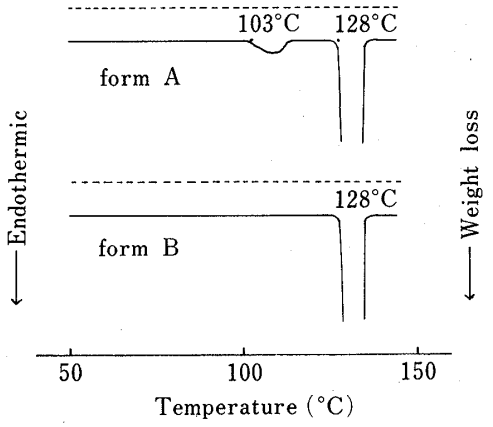

Fig. 1. DSC–TG Curves of Tolbutamide Polymorphs

——, DSC curves; ------, TG curves; heating rate, 20 °C/min.

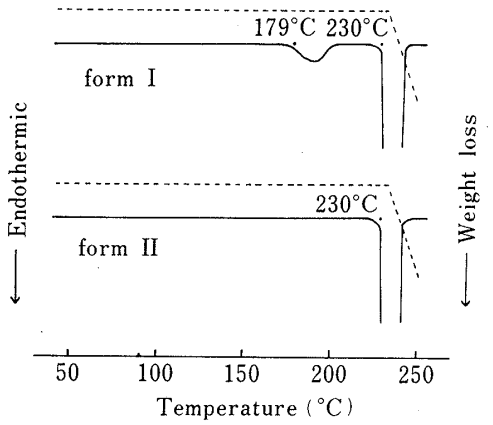

Fig. 2. DSC–TG Curves of Mefenamic Acid Polymorphs

——, DSC curves; ------, TG curves; heating rate, 40 °C/min.

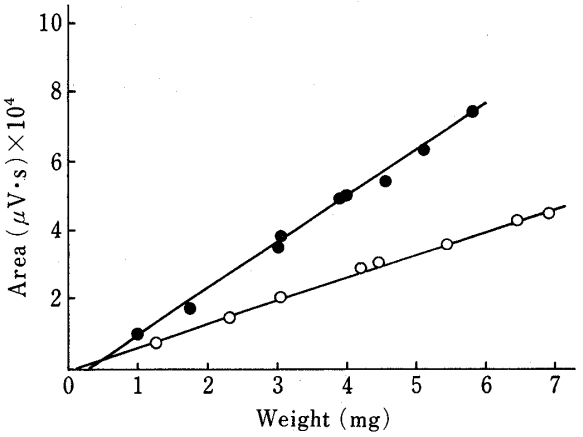

Fig. 3. Calibration Curves for Tolbutamide Form B and Mefenamic Acid Form I

○, tolbutamide form B ($r=0.999$), heating rate 20 °C/min; ●, mefenamic acid form I ($r=0.997$), heating rate 40 °C/min.

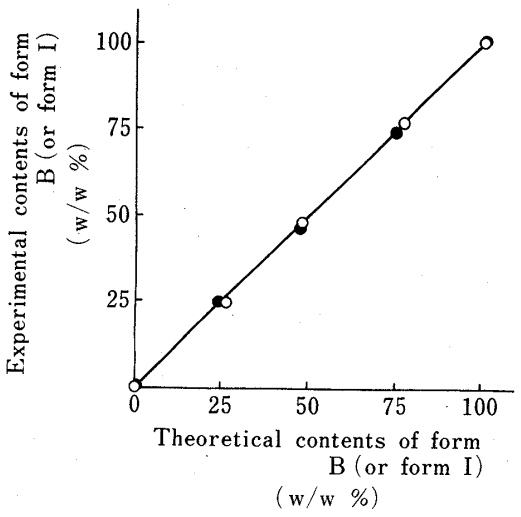

Fig. 4. Determination of Form B (or Form I) in the Presence of Form A (or Form II) by DSC

○, tolbutamide form A–form B mixture system; ●, mefenamic acid form I–form II mixture system.

agreement was obtained between the experimental and theoretical values.

Kinetic Studies of Isothermal Transition——Form B or form I (5 ± 0.5 mg) was weighed into aluminum pans. The samples were then kept at selected constant temperatures for a suitable period in the analyzer unit of the differential scanning calorimeter. Thermograms for each sample were run under the same conditions as described above and the area under the transition peak was measured. The residual amounts of form B or form I were calculated from the appropriate calibration curve.

Scanning Electron Microscopy——Changes of crystal shapes during the isothermal transition of polymorphic forms were observed with a scanning electron microscope (Nihon Denshi, JSM-T20).

Results and Discussion

The Isothermal Transition of Form B to Form A of Tolbutamide

Figure 5 shows the isothermal transition curves of form B to form A at 65, 70, 75 and 80 °C. It appeared that the transition rates were relatively higher at the earlier period of transition and then gradually decreased at any temperature.

Kinetic analysis of the isothermal transition of form B to form A was carried out according to the method of Hancock and Sharp.[8] In this method, the slope (m) estimated by plotting $\ln[-\ln(1-\alpha)]$ against $\ln t$ according to Eq. 1 is used in order to distinguish the reaction mechanisms:

$$\ln[-\ln(1-\alpha)] = \ln B + m \cdot \ln t \qquad (\alpha = 0.15—0.5) \qquad (1)$$

where α is the fraction of transition and B is a constant. The value of m is an intrinsic value determined from various theoretical equations for solid-state decomposition. The relationship between the theoretical equation and the value of m has been reported by Hancock and Sharp,[8] as summarized in Table I.

The value of m for the isothermal transition of form B to form A was estimated to be 0.51 ± 0.03 (mean $\pm$ S.D.; $n=4$) (Fig. 6). Accordingly, it appeared that this transition follows the three-dimensional diffusion mechanism (Jander equation).[9,10] The plots of $[1-(1-\alpha)^{1/3}]^2$ against time t at every temperature gave straight lines, as shown in Fig. 7.

However, little change in the crystal shape during the isothermal transition of form B was observed under the scanning electron microscope. That is to say, this transition appeared to proceed from the surface of crystals into the crystal entity without any change of the crystal shape.

The Isothermal Transition of Form I to Form II of Mefenamic Acid

The isothermal transition curves of form I to form II at 142.5, 145, 147.5 and 150 °C are shown in Fig. 8. Every plot showed good linearity, and the transition rate was a function of time only. The transition rate of form I to form II by heating was highly dependent on the

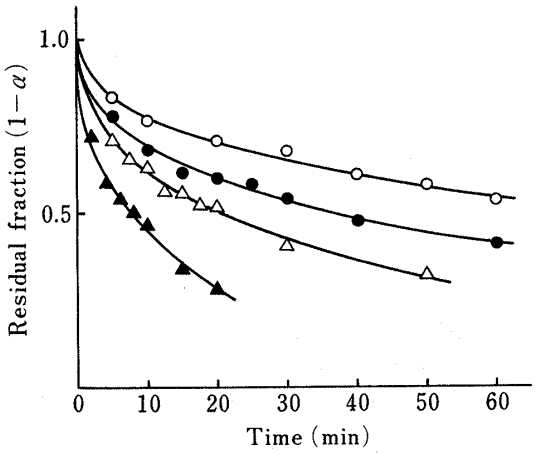

Fig. 5. Residual Fraction of Form B during the Isothermal Transition to Form A of Tolbutamide

○, 65 °C; ●, 70 °C; △, 75 °C; ▲, 80 °C.

TABLE I. Values of $m^{a)}$ for Solid-State Reaction Rate Equations

Equation	m	Mechanism
$\alpha=kt$	1.24	Zero-order mechanism (Polany–Winger equation)
$1-(1-\alpha)^{1/2}=kt$	1.11	Phase boundary reaction, cylindrical symmetry
$1-(1-\alpha)^{1/3}=kt$	1.07	Phase boundary reaction, spherical symmetry
$-\ln(1-\alpha)=kt$	1.00	Random nucleation, one nucleus on each particle
$[-\ln(1-\alpha)]^{1/2}=kt$	2.00	Random nucleation, two-dimensional growth of nuclei (Avrami–Erofeev equation)
$[-\ln(1-\alpha)]^{1/3}=kt$	3.00	Random nucleation, three-dimensional growth of nuclei (Avrami–Erofeev equation)
$\alpha^2=kt$	0.62	One-dimensional diffusion
$(1-\alpha)\ln(1-\alpha)+\alpha=kt$	0.57	Two-dimensional diffusion
$[1-(1-\alpha)^{1/3}]^2=kt$	0.54	Three-dimensional diffusion (Jander equation)
$(1-2\alpha/3)-(1-\alpha)^{2/3}=kt$	0.57	Three-dimensional diffusion (Ginstling–Brounshtein equation)

a) $\ln[-\ln(1-\alpha)]=\ln B+m\cdot\ln t$ ($\alpha=0.15$—0.50).

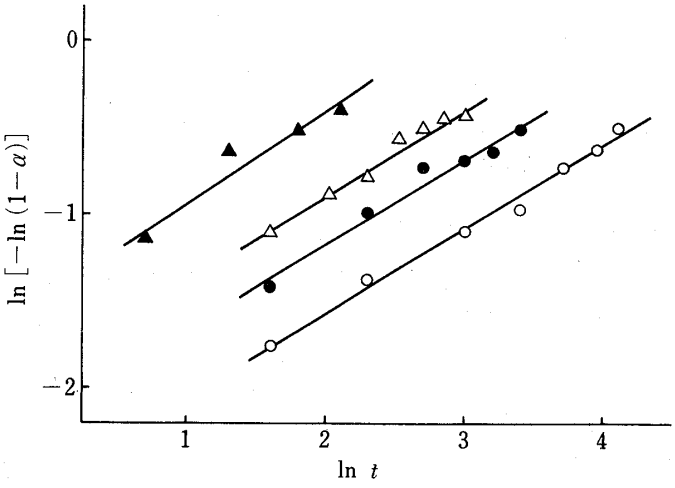

Fig. 6. Plots of $\ln[-\ln(1-\alpha)]$ *versus* $\ln t$ for the Isothermal Transition of Form B to Form A of Tolbutamide ($\alpha=0.15$—0.5)

○, 65 °C ($m=0.49$, $r=0.994$); ●, 70 °C ($m=0.49$, $r=0.984$); △, 75 °C ($m=0.50$, $r=0.987$); ▲, 80 °C ($m=0.55$, $r=0.983$).

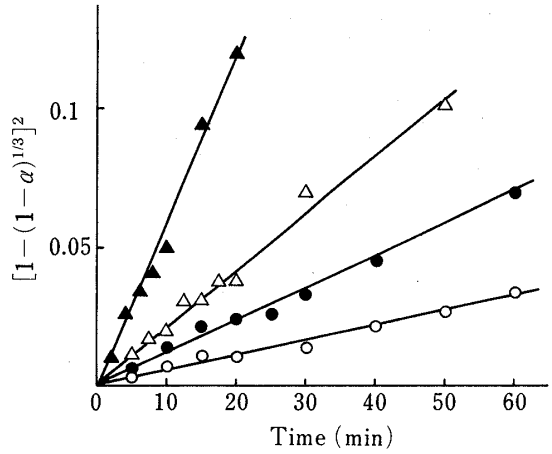

Fig. 7. Plots of $[1-(1-\alpha)^{1/3}]^2$ *versus* t for the Isothermal Transition of Form B to Form A of Tolbutamide

○, 65 °C ($r=0.994$); ●, 70 °C ($r=0.994$); △, 75 °C ($r=0.994$); ▲, 80 °C ($r=0.993$).

temperature, and the transition rate constant at 150 °C calculated from the slope of the straight line was about 6 times that at 142.5 °C.

As shown in Fig. 9, the value of m for the isothermal transition of form I to form II was calculated to be 1.29 ± 0.06 (mean $\pm$ S.D.; $n=4$) according to the method of Hancock and

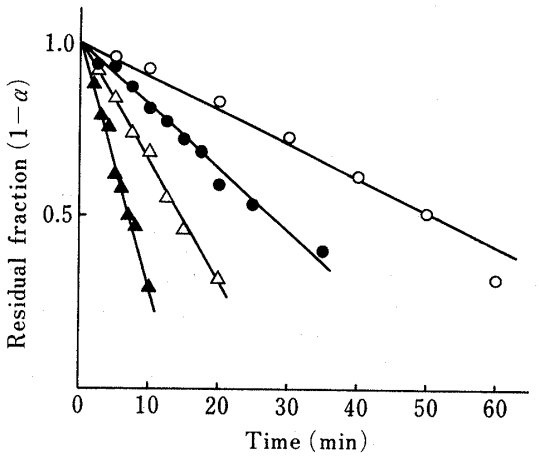

Fig. 8. Residual Fraction of Form I during the Isothermal Transition to Form II of Mefenamic Acid

○, 142.5 °C; ●, 145 °C; △, 147.5 °C; ▲, 150 °C.

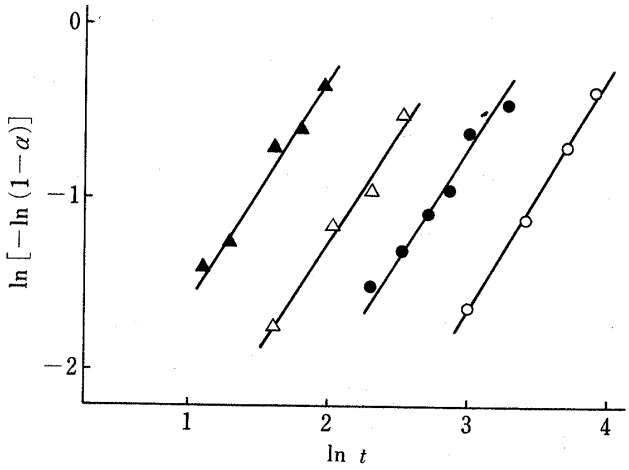

Fig. 9. Plots of $\ln[-\ln(1-\alpha)]$ *versus* $\ln t$ for the Isothermal Transition of Form I to Form II of Mefenamic Acid ($\alpha=0.15$—0.5)

○, 142.5 °C ($m=1.36$, $r=1.000$); ●, 145 °C ($m=1.21$, $r=0.990$); △, 147.5 °C ($m=1.27$, $r=0.990$); ▲, 150 °C ($m=1.30$, $r=0.974$).

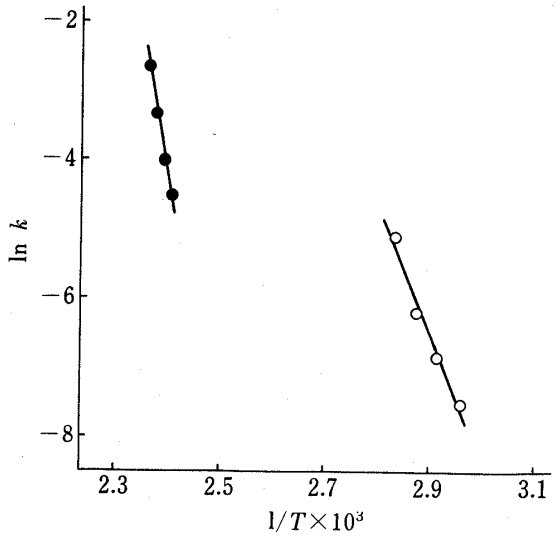

Fig. 10. Arrhenius Plots for the Isothermal Transition of Polymorphs of Tolbutamide and Mefenamic Acid

○, tolbutamide (form B→form A); ●, mefenamic acid (form I→form II).

Sharp.[8] Therefore, it was concluded that this transition proceeds in accordance with the zero-order mechanism (Polany–Winger equation).[11-13]

From the observations by scanning electron microscopy, the crystals of form I did not change in shape during the isothermal transition. Therefore, it seemed that the crystals reacted along one internal direction in proportion to time during this transition.[4]

Activation Energies for Isothermal Transition

The activation energy for the isothermal transition of form B to form A of tolbutamide was calculated to be 37.3 kcal/mol from the slope of the Arrhenius plots (Fig. 10). This value is similar to the activation energy (31.6 kcal/mol) for the transition of form II to form III of carbamazepine, which follows the diffusion mechanism.[1] This result suggests that the transition mechanism of tolbutamide is similar to that of carbamazepine.

On the other hand, the activation energy for the isothermal transition of form I to form II of mefenamic acid was calculated to be 86.4 kcal/mol in the same manner as described above (Fig. 10).

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References and Notes

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