Kinetic Study on the Isothermal Transition of Bromovalerylurea Polymorphs in the Solid State at High Temperature

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The kinetics of the solid-state isothermal transition of bromovalerylurea polymorphic forms (I, II and III) at high temperature were investigated by means of differential scanning calorimetry. Kinetic analysis according to the method of Hancock and Sharp indicated that the transition of form I to form II follows the one-dimensional diffusion mechanism. The activation energy for this transition calculated from the Arrhenius plots was 826.2 kJ/mol. On the other hand, it was found that the transition of form III to form I conforms with the mechanism of random nucleation and two-dimensional growth of nuclei (Avrami-Erofeev equation). This activation energy was estimated to be 185.2 kJ/mol. It was concluded that the mechanism and the value of activation energy were both different between the two kinds of isothermal transitions of bromovalerylurea polymorphic forms.

Keywords—bromovalerylurea polymorphism; isothermal transition; kinetic analysis; differential scanning calorimetry; X-ray powder diffractometry

In the previous papers,2–4 we investigated the kinetics and mechanisms of the isothermal transition of polymorphic forms in the solid state. It was confirmed that the kinetics and mechanisms of the isothermal transition were different among drugs and among polymorphic forms of the same drug.

Watanabe5 reported that bromovalerylurea had two polymorphic forms (forms I and II). Furthermore, Kiwada et al.6 found a new polymorphic form (form III) of bromovalerylurea, and reported that form II was the most stable and form III was the most unstable at higher temperature.

This paper is concerned with the kinetics of the isothermal transition of bromovalerylurea polymorphic forms (forms I, II and III) in the solid state at high temperature, based on differential scanning calorimetry.7,8

Experimental

Materials—Bromovalerylurea was a commercial product (Lot No. 2761EN) of JP X grade (Nihon Shinyaku Co., Ltd.). All other chemicals were reagent-grade commercial products.

Preparation of Polymorphic Forms—1) Form I: Form I was prepared by the method of Watanabe5 as follows. Bromovalerylurea (5 g) was dissolved in 200 ml of methanol at 64–65 °C and recrystallized at room temperature. The resulting crystals were collected by filtration and dried at 30 °C in a vacuum.

2) Form II: Form II was obtained by heating form I at about 130 °C for 1 h under a flow of dried nitrogen gas.

3) Form III: Form III was obtained by a modification of the method of Kiwada et al.6 as follows. Form I (10 g) was dissolved in 40 ml of methanol at 64–65 °C and maintained in a freezer at −20 °C for about 1 week. The resulting crystals were collected by filtration and dried at 30 °C in a vacuum.

Forms I, II and III thus obtained were passed through a 200 or 300 mesh sieve. All crystalline forms were stored at 4 °C in a desiccator and then used for experiments.

Identification of Polymorphic Forms—Each polymorphic form passed through a 200 mesh sieve was identified...
by X-ray powder diffractionometry (Rigaku Denki, Miniflex, Ni-filter, Cu-Kα radiation, 35 kV, 20 mA). The X-ray powder diffraction patterns of the three polymorphic forms were in agreement with those reported by Kiwada et al., respectively.

**Thermal Analysis**—Thermal analysis was carried out with a differential scanning calorimeter (DSC; Perkin-Elmer, model DSC-2C) and a thermogravimeter (TG; Perkin-Elmer, model TGS-2).

**Preparation of Calibration Curve for Form I or Form III by DSC**—Known quantities of form I (passed through a 200 mesh sieve) or form III (passed through a 300 mesh sieve) were accurately weighed into aluminum pans. Thermograms of these samples were run at a heating rate of 5 °C/min (for form I) or 20 °C/min (for form III) with a sensitivity of 4.2 mJ/s (for form I) or 8.4 mJ/s (for form III). Dry nitrogen gas was passed at 20 ml/min during all DSC experiments. The area under the transition peak of form I to form II at 130 °C (Fig. 1a) or that of form III to form I at 111 °C (Fig. 1c) was measured in units of μV·s with a Chromatopac (Shimadzu, C-RIA). As can be seen in Fig. 2, each calibration curve gave a straight line (form I, r = 0.996; form III, r = 0.997).

**Kinetic Study of Isothermal Transition**—Form I or form III (5 ± 0.5 mg) was accurately weighed into aluminum pans. The samples were then placed at selected constant temperatures (± 0.1 °C) for a suitable period in the analyzer unit of the DSC. Thermograms for each sample were run under the same conditions as described in the case of preparation of the calibration curves, and the area under the transition peak was measured. The residual fractions (1 − x) of form I or form III 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

DSC and TG Curves of Polymorphic Forms

The DSC and TG curves (heating rate: forms I and II, 5°C/min; form III, 20°C/min) of the three polymorphic forms are shown in Fig. 1.

Form I gave a characteristic thermogram with two endothermic peaks; one at 130°C corresponded to the solid-state transition of form I to form II, and the other at 152°C was attributed to fusion accompanied with decomposition of form II (Fig. 1a). Form II showed only one endothermic peak at 152°C due to fusion accompanied with decomposition (Fig. 1b). Form III exhibited a small endothermic peak at 111°C, attributable to transition of form III to form I, and sharp endo- and exothermic peaks at about 144—148°C corresponding to fusion of form I and recrystallization to form II, with a large endothermic peak at 153°C due to fusion accompanied with decomposition of form II (Fig. 1c). In this case, the X-ray powder diffraction pattern of form I obtained by recrystallization from methanol was identical with that of form I obtained on transition of form III by heating. The polymorphic transformation pathway of the metastable form III during heating was III → I → II, without direct transition of form III to form II.

None of the polymorphic forms showed any decrease in weight until the melting point during heating.

The Isothermal Transition of Form I to Form II

Figure 3 shows the isothermal transition curves of form I to form II at 117, 118, 119 and 120°C. The four curves were all exponential and this isothermal transition appeared to be temperature-dependent.

The kinetic analysis of the isothermal transition of form I to form II was carried out according to the method of Hancock and Sharp,9 and the m value for this transition was estimated, based on Eq.1:

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

(1)

where \( m \) is the intrinsic value for various theoretical equations of solid-state decomposition, \( \alpha \)
is the fraction of transition, \( t \) is the heating time and \( B \) is a constant. The relationship between the theoretical equations and the \( m \) value was discussed in the previous paper.\(^4\)

The \( m \) value for the isothermal transition of form I to form II was estimated to be 0.62 ± 0.04 (mean ± S.D.; \( n = 4 \)), as shown in Fig. 4. These results suggest that this transition proceeds by the one-dimensional diffusion mechanism \((\alpha^2 = k \cdot t, m = 0.62)^{8-10}\) The plots of \( \alpha^2 \) against \( t \) at any temperature were linear, as shown in Fig. 5. The apparent transition rate constant \((k)\) at 120°C calculated from the slope of the straight line (Fig. 5) was about 7 times higher than that at 117°C.

From the results of observation with a scanning electron microscope, it was found that the crystalline shapes during the isothermal transition of form I to form II apparently changed, as shown in Fig. 6; the leaflet (parallelogramic) crystals of form I were transformed into needle crystals of form II. These results correspond well with the thermomicroscopic observations reported by Kiwada et al.\(^6\)

The Isothermal Transition of Form III to Form I

The isothermal transition curves of form III to form I at 75, 77.5, 80 and 82.5°C are shown in Fig. 7. It was confirmed, by means of X-ray powder diffractometry, that form III did not directly transform to form II during heating at the temperatures described above. The transition rates were relatively lower at the earlier period of transition and then increased rapidly at any temperature.
Fig. 7. Residual Fraction of Form III during the Isothermal Transition to Form I of Bromovalerylurea

- ○, 75 °C
- •, 77.5 °C
- △, 80 °C
- ▲, 82.5 °C

Fig. 8. Plots of $\ln[-\ln(1-\alpha)]$ versus $\ln t$ for the Isothermal Transition of Form III to Form I of Bromovalerylurea ($\alpha=0.15-0.5$)

- ○, 75 °C ($m=1.84$, $r=0.984$)
- •, 77.5 °C ($m=1.80$, $r=0.981$)
- △, 80 °C ($m=2.69$, $r=0.994$)
- ▲, 82.5 °C ($m=2.03$, $r=0.988$)

Fig. 9. Plots of $[-\ln(1-\alpha)]^{1/2}$ versus $t$ for the Isothermal Transition of Form III to Form I of Bromovalerylurea

- ○, 75 °C ($r=0.980$)
- •, 77.5 °C ($r=0.988$)
- △, 80 °C ($r=0.996$)
- ▲, 82.5 °C ($r=0.979$)

Fig. 10. Scanning Electron Microphotographs of Bromovalerylurea Crystals during the Isothermal Transition of Form III to Form I at 82.5 °C

(a) form III before heating ($\times 1500$), (b) after 40 min ($\times 1500$).
As shown in Fig. 8, the m value for the isothermal transition of form III to form I was calculated to be 2.09 ± 0.41 (mean ± S.D.; n = 4) according to the same method as described previously. Accordingly, this transition may conform with the mechanism of random nucleation and two-dimensional growth of nuclei (Avrami–Erofeev equation, \([- \ln(1 - \alpha)]^{1/2} = k \cdot t; m = 2.00\)).\(^9\) The plots of \([- \ln(1 - \alpha)]^{1/2}\) against t at four temperatures showed good linearity (Fig. 9). The value of k at 82.5°C was about 4 times that at 75°C. This transition mechanism is similar to that of carbamazepine polymorphic form I to form III\(^2\) and benoxaprofen polymorphic form I to form II.\(^1\)

Figure 10 shows scanning electron microphotographs of bromovalerylurea crystals during the isothermal transition of form III to form I at 82.5°C. It was confirmed that the columnar crystals of form III were transformed into smaller parallelogramic crystals of form I. In this case, the occurrence and growth of nuclei of form I within a crystal of form III were not clearly observed on scanning electron microphotographs.

**Activation Energy for Isothermal Transitions**

The activation energy for the isothermal transition of form I to form II was calculated to be 826.2 kJ/mol from the slope of the Arrhenius plots, as shown in Fig. 11. This value appeared to be very high. This high activation energy may be related to the energy required to unpack the crystal structure, which is very rigid. More research is needed to explain the high value of this activation energy.

On the other hand, the activation energy for the isothermal transition of form III to form I was calculated to be 185.2 kJ/mol in the same manner as described above (Fig. 11). The activation energy for the isothermal transition of form I to form II was thus about 4 times higher than that of form III to form I. It was concluded that the mechanism and the value of activation energy were both different between the two kinds of isothermal transitions of bromovalerylurea polymorphic forms.

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**References and Notes**

917 (1986).


