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# The Dissolution Properties and Physico-chemical Properties of Polymorphic Forms of (α-Bromoisovaleryl)urea[1]

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The dissolution properties and physico-chemical properties of three polymorphic forms of (α-bromoisovaleryl)urea are reported. Form II transformed to form I rapidly in water at 37°C, but this transition was delayed by 0.25% gelatin. The solubility of form II was 50% higher than that form I. The transition temperatures of form II to form I, and form III to form I were 70.2°C and 11.4°C, respectively, as determined by measurements of dissolution rates and solubilities. The enthalpy values, $\Delta H_{sol}$ and $\Delta H_{diss}$, of the polymorphs were calculated. The thermodynamic values of form II and form III for the conversion to form I were calculated from these values, *i.e.* heats of transition ($\Delta H_{trans}$), differences of free energy at 37°C ($\Delta G_T$), differences of entropy at 37°C ($\Delta S_T$), and entropy changes at transition temperatures ($\Delta S_{trans}$). The differences of free energy, which may affect the bioavailabilities of polymorphs, and the $\Delta S_{trans}$ values were found to be fairly small.

**Keywords**——polymorph; (α-bromoisovaleryl)urea; solubility; dissolution rate; enthalpy; entropy; free energy

## Introduction

It was reported in 1938 by Watanabe that (α-bromoisovaleryl)urea had two polymorphic forms (form I and form II).[2] The third polymorphic form of (α-bromoisovaleryl)urea (form III) was reported by the authors in 1980.[3] In the previous report, the methods for preparation, as well as the infrared absorption, X-ray diffraction, and transition properties, of the three polymorphs were presented.

It has been recognized that the variation in the dissolution behavior of polymorphs is an important factor affecting the bioavailabilities of solid pharmaceuticals.[4–8] Thus, the dissolution properties of the polymorphic forms of (α-bromoisovaleryl)urea in water with or without gelatin at 37°C, and the solubilities and dissolution rates at various temperatures were studied. The results are reported in this paper. Furthermore, from these dissolution data, various physico-chemical parameters of the polymorphic forms were calculated.

## Experimental

**Materials**——Polymorphs of (α-bromoisovaleryl)urea (form I, form II, and form III) were prepared as described in the previous paper,[3] and identified by X-ray diffractometry. Gelatin was purchased from DIFCO Laboratories (Detroit, U.S.A.). (α-Bromo-*n*-caproyl)urea was used as an internal standard for gas–liquid chromatography (GLC). This compound was synthesized by the authors from *n*-caproic acid, bromine, and urea by the method reported for the synthesis of (α-bromoisovaleryl)urea by Nishizaki *et al.*[9] The identify of the product was confirmed by comparing its infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS) with those of an authentic commercial sample of (α-bromoisovaleryl)urea. The materials used for GLC with a flame ionization detector (FID) were of reagent grade, and those for GLC with an electron capture detector (ECD) were of specially prepared reagent grade for pesticide residue analysis (Kanto Chem. Co., Inc., Tokyo).

**Procedure**——Solubility Study: Two hundred ml of water was stirred with a Teflon plate (3.5 × 6 cm) at 150 rpm in a double-walled beaker (600 ml)[6] at 6°, 20°, 37°, and 50°C. Excess powdered (α-bromoisovaleryl)urea (about 2 g, 100—170 mesh) was added to the water. In the case of the study with gelatin, the powdered drug was suspended in 10 ml of 5% gelatin solution, and immediately added to 190 ml of

water. After appropriate time intervals, about 1 ml of sample solution was taken up and filtered through a membrane filter (Millipore, 0.45 μm). A half ml of ethyl acetate and 2.0 ml of internal standard solution in ethyl acetate (0.5 mg/ml) were added to 0.5 ml of the filtrate. The mixture was shaken for 10 min and centrifuged for 10 min. Two ml of the upper layer was concentrated, and 0.2 ml of acetone was added to the residue. Two μl of this acetone solution was used for GLC–FID (Shimadzu Seisakusho Ltd., Kyoto, type GC-5A). A typical chromatogram is shown in Fig. 1.

Dissolution Rate Study: A disk of (α-bromoisovaleryl)urea 1.3 cm in diameter was prepared by compressing 200 mg of powdered drug under a pressure of 125 kg/cm². The preparation of the disk sample did not affect the crystalline form of the compound as determined by X-ray diffraction. The disk was stuck on a glass plate with double-sided tape (Seltac®, Nichiban Co. Ltd., Tokyo) and then placed in the dissolution medium (200 ml) in the beaker used in the solubility study. One hundred μl of sample solution was taken up at appropriate times, and the concentration was determined by GLC–ECD according to the ECD method for determination of blood concentration, described elsewhere [10]

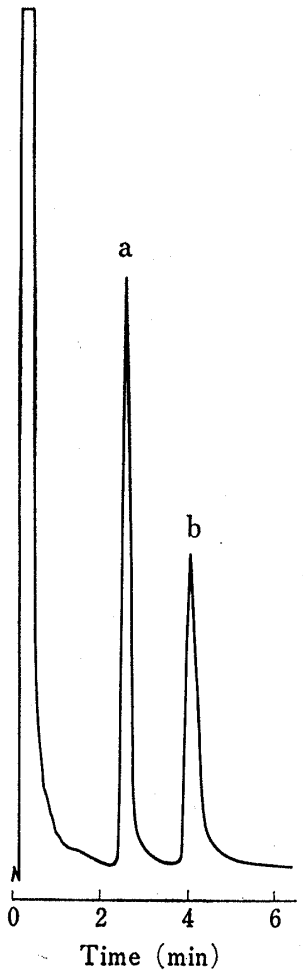


Fig. 1. Gas Chromatogram of (α-Bromoisovaleryl)urea

Condisions: detector, FID; column, 5% PEG 20 M/Chromosorb G AW DMCS (60—80 mesh, 3 mm × 1 m); column temp., 175°C; detector temp., 200°C; flow rates, $N_2$ 80 ml/min, $H_2$ 45 ml/min, air 0.9 l/min; sens., 100 MΩ; range, 0.16 V.

Peak; a: (α-bromoisovaleryl) urea, 20 μg, b: (α-bromo-*n*-caproyl) urea (IS), 20 μg.

## Results and Discussion

### Dissolution Curves in Water with or without Gelatin

Dissolution curves in water at 37°C are shown in Fig. 2. The dissolution curve of form III was similar to that of form I. The X-ray diffraction patterns showed no change after the experiments with form I and form III. On the other hand, the dissolution curve of form II showed a peak followed by a lower plateau level. It is suggested that form II transformed to form I during the dissolution experiment. After the dissolution experiment with form II, the remaining crystals showed the X-ray diffraction pattern of form I.

Figure 3 shows the results obtained in the dissolution experiment with gelatin solution. The transformation of form II to form I was not observed during this experiment and the plateau level of form II, which was considered to be the saturated concentration of form II, was higher than that of form I or form III. It was considered that gelatin delayed the transformation of form II to form I, in accord with the results obtained by Higuchi *et al.*[11] and Kuroda *et al.*[12] on sulfathiazole, and by Miyazaki *et al.*[13] on chlortetracycline hydrochloride.

### Solubilities at Various Temperatures

The dissolution patterns of form I and form III are shown in Fig. 4. Table I shows the values of apparent solubility at various temperatures. No change of crystalline form was observed during the dissolution experiment at any temperature. Higher solubilities were observed with Form III at all the temperatures except at 6°C. Very similar solubility values were obtained at 6°C, so it is assumed that the transition temperature between form I and

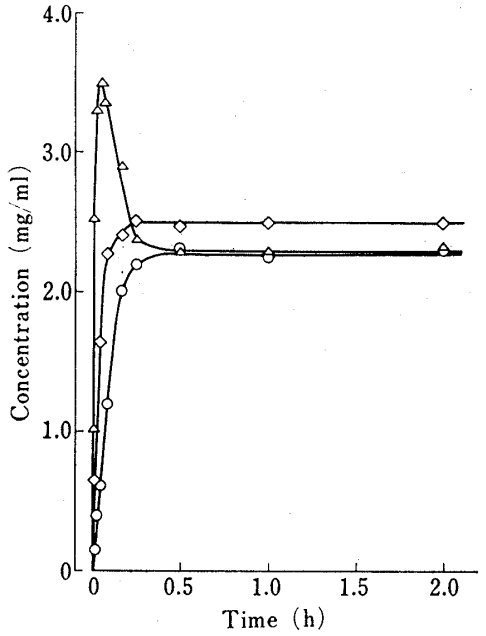


Fig. 2. Dissolution Curves of Polymorphs of (α-Bromoisovaleryl)urea in Water at 37°C

○: form I, △: form II, ◇: form III.

form III is about 6°C. Since form II is transformed rapidly to form I in water as described above, it is impossible to determine its solubility.

## Dissolution Rate Study

The initial dissolution properties of form I and form II in the disk method at various temperatures are shown in Fig. 5. The experiments were carried out over a short period (2 min) to avoid the transformation of form II to form I, which was very fast, as described above. It is considered that this period is too short to transform and to saturate for form II on the basis of the results obtained in the solubility experiments shown in Fig. 2 and Fig. 3. Since form III is very fragile, it was impossible to prepare a disk. From the slopes of these curves, the dissolution rates were calculated by least-squares analysis, and the results are shown in Table II. Form II dissolved faster than form I at these temperatures.

## Calculation of Thermodynamic Parameters

The heat of solution ($\Delta H_{sol}$) can be calculated from the saturated concentration at various temperatures by means of van't Hoff plots, as follows,[14]

$$\frac{d \ln C_s}{dT} = \frac{\Delta H_{sol}}{RT^2} \quad (1)$$

where $C_s$ is the saturated concentration, $R$ is the gas constant, and $T$ is absolute temperature.

The heat of dissolution ($\Delta H_{diss}$) can be calculated from the dissolution rates at various temperatures in the same manner as follows,[15]

$$\frac{dC}{dT} = K e^{-\Delta H_{diss}/RT} \quad (2)$$

where $C$ is concentration and $K$ is a constant. Eq. 1 and Eq. 2 can be transformed as follows,[16]

$$\log C_s = -\frac{\Delta H_{sol}}{2.303RT} + \text{const.} \quad (3)$$

$$\log\left(\frac{dC}{dT}\right) = -\frac{\Delta H_{diss}}{2.303RT} + \text{const.} \quad (4)$$

These two enthalpy values ($\Delta H_{sol}$ and $\Delta H_{diss}$) are related as follows,[15,16]

$$\Delta H_{diss} = \Delta H_{sol} + E_a \quad (5)$$

where $E_a$ is the activation energy of diffusion, which is considered to be equal in all polymorphic forms under constant dissolution conditions.[16] It can be obtained by calculation from the experiments with form I as follows,

$$E_a = \Delta H^{I}_{diss} - \Delta H^{I}_{sol} \quad (6)$$

In the present experiments, it is difficult to obtain both $\Delta H^{II}_{sol}$ and $\Delta H^{III}_{diss}$ for the reasons described above, that is, the rapid transformation for form II and the fragility of form

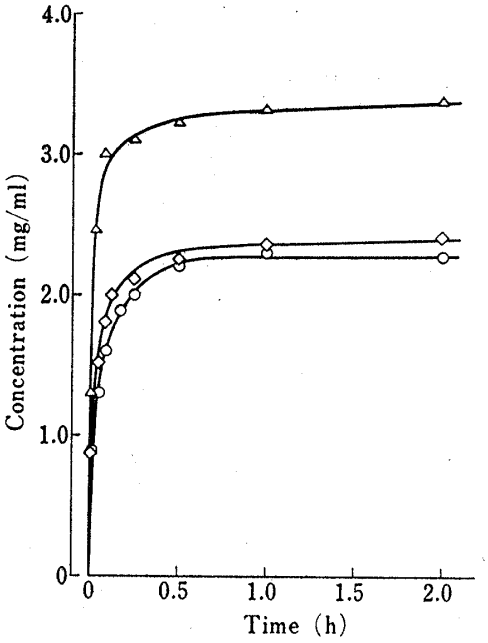


Fig. 3. Dissolution Curves of Polymorphs of (α-Bromoisovaleryl)urea in Water containing Gelatin at 37°C

○: form I, △: form II, ◇: form III.

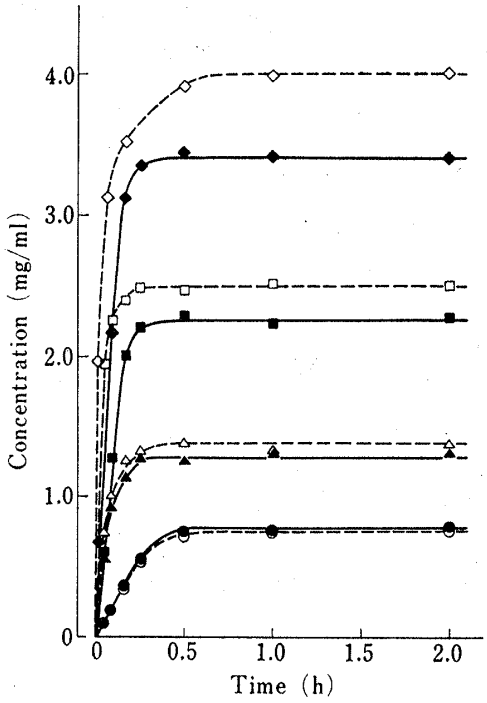


Fig. 4. Solubility Curves of Form I and Form III of (α-Bromoisovaleryl)urea in Water at Various Temperatures

——: form I, ----: form III.
●○: 6°C, ▲△: 20°C, ■□: 37°C, ◆◇: 50°C.

TABLE I. Solubility Data for Form I and Form III of (α-Bromoisovaleryl)urea in Water at Various Temperatures

| Temp. (°C) | Solubility (mmol/l) | |
|---|---|---|
| | Form I | Form III |
| 6 | 3.5 | 3.4 |
| 20 | 5.7 | 6.1 |
| 37 | 10.1 | 11.1 |
| 50 | 15.3 | 17.9 |

III. Therefore they were calculated by using $E_a$, $\Delta H^{III}_{sol}$, and $\Delta H^{II}_{diss}$ as follows,

$$\Delta H^{II}_{sol} = \Delta H^{II}_{diss} - E_a \quad (7)$$

$$\Delta H^{III}_{diss} = \Delta H^{III}_{sol} + E_a \quad (8)$$

Van't Hoff type plots of solubilities and dissolution rates are shown in Fig. 6 and Fig. 7, respectively. Linear relationships were obtained in both cases.

From the slopes of the straight lines, $\Delta H_{sol}$ values of form I and form III and $\Delta H_{diss}$ values of form I and form II were obtained. The values of $\Delta H^{II}_{sol}$, $\Delta H^{III}_{diss}$, and $E_a$ were calculated from the observed values as described above. These values are listed in Table III. The obtained value for $E_a$ (3.87 kcal/mol) is reasonable compared with those for other compounds reported by Wadke *et al.*[15]

Transition temperatures ($T_{trans}$) were also obtained from the intersection points in Fig. 6 and Fig. 7 as 70.2°C ($T^{I,II}_{trans}$) and 11.4°C ($T^{I,III}_{trans}$) for form II to form I and for form III to form I, respectively. The value of $T^{I,II}_{trans}$ obtained in this experiment was lower than that obtained by the heating stage method (about 96°C) reported by Watanabe *et al.*[17]

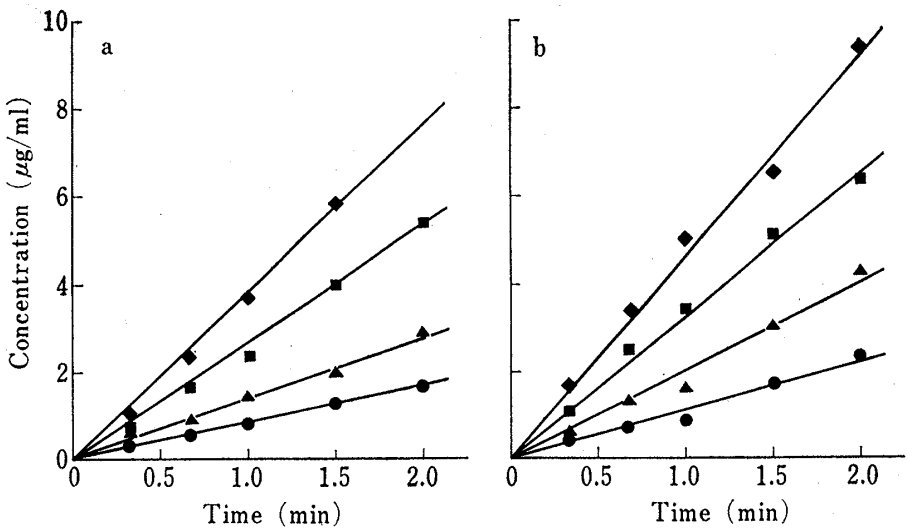


Fig. 5. Initial Dissolution Rates of Form I and Form II of (α-Bromoisovaleryl)urea in Water at Various Temperatures

a: form I. b: form II.
●: 10°C, ▲: 20°C, ■: 30°C, ◆: 37°C.

TABLE II. Dissolution Rates for Form I and Form II of (α-Bromoisovaleryl)urea in Water at Various Temperatures

| Temp. (°C) | Dissolution rate (μg/ml/min/disk) | |
|---|---|---|
| | Form I | Form II |
| 10 | 0.87 | 1.11 |
| 20 | 1.40 | 2.14 |
| 30 | 2.73 | 3.20 |
| 37 | 3.90 | 4.51 |

It is assumed that this discrepancy is due to the difference of the methods. On the other hand, the value of $T_{trans}^{I,III}$ obtained in this experiment was 11.4°C, and this value is reasonable in the light of the information obtained in the previous study on the preparation of form III.

Under conditions of constant temperature and pressure, the free energy difference, $\Delta G_T^{I,II}$ between form I and form II at an absolute temperature ($T$) is given by the following equation,[15]

$$\Delta G_T^{I,II} = RT \ln\left(\frac{R_{diss}^{II}}{R_{diss}^{I}}\right) \tag{9}$$

where $R_{diss}^{I}$ and $R_{diss}^{II}$ are the dissolution rates of form I and form II, respectively. On the other hand, $\Delta G_T^{I,III}$ is given as follows,[18]

$$\Delta G_T^{I,III} = RT \ln\left(\frac{C_s^{III}}{C_s^{I}}\right) \tag{10}$$

where $C_s^{I}$ and $C_s^{III}$ are the solubilities of form I and form III, respectively.

At an absolute temperature ($T$), the entropy values $\Delta S_T$ for the transitions of form II to form I and form III to form I can be calculated as follows,[18]

$$\Delta S_T^{I,II} = \frac{\Delta H_{trans}^{I,II} - \Delta G_T}{T} \tag{11}$$

$$\Delta S_T^{I,III} = \frac{\Delta H_{trans}^{I,III} - \Delta G_T}{T} \tag{12}$$

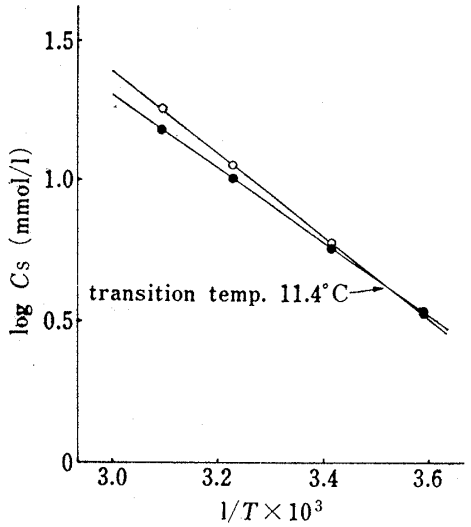


Fig. 6. The van't Hoff Plots of Solubility Values of Form I and Form III of (α-Bromoisovaleryl)urea in Water

●: form I. ○: form III.

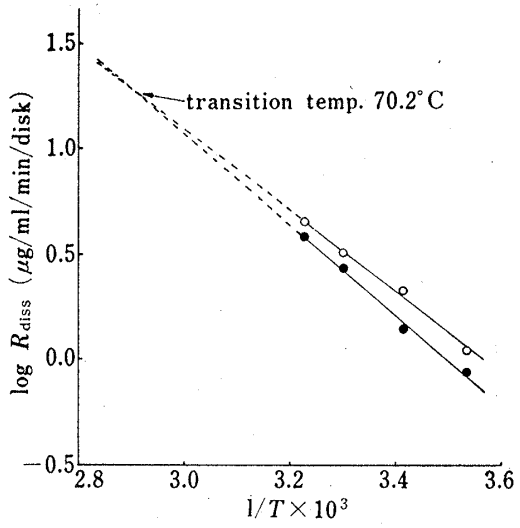


Fig. 7. Plots of log ($R_{diss}$) against $1/T$ for Form I and Form II of (α-Bromoisovaleryl)urea in Water

●: form I. ○: form II.

TABLE III. Enthalpy Values of (α-Bromoisovaleryl)urea Polymorphs

| | $\Delta H_{sol}$ (kcal/mol) | $\Delta H_{diss}$ (kcal/mol) | $E_a$ (kcal/mol) |
|---|---|---|---|
| Form I | 6.06 | 9.93 | 3.87[a)] |
| Form II | 4.99[b)] | 8.86 | — |
| Form III | 6.77 | 10.64[c)] | — |

a) Calculated from equation (6) in the text.
b) Calculated from equation (7) in the text.
c) Calculated from equation (8) in the text.

where $H^{I,II}_{trans}$ and $H^{I,III}_{trans}$ are heats of transition from form II to form I and form III to form I, respectively, and can be calculated as follows,[18)]

$$\Delta H^{I,II}_{trans} = \Delta H^{II}_{sol} - \Delta H^{I}_{sol} \quad (13)$$

At the transition temperature, the free energy difference, $\Delta G$, is equal to zero and the entropy change, $\Delta S_{trans}$, can be calculated by using Eq. 11 and Eq. 12, neglecting the $\Delta G_T$ term. The calculated thermodynamic values are listed in Table IV. The obtained $\Delta G_T$ values of form II and form III for conversion to form I at 37°C were −88.4 and −57.2 cal/mol, respectively. These values between the polymorphs of (α-bromoisovaleryl)urea are a little different from the value of chloramphenicol palmitate (−774 cal/mol) reported by Aguiar *et al.*[18)]

TABLE IV. Thermodynamic Values of Form II and Form III of (α-Bromoisovaleryl)urea Polymorphs calculated for the Conversion to Form I

| | Trans. temp. (°C) | $\Delta H_{trans}$ (kcal/mol) | $\Delta G_T$ at 37°C (cal/mol) | $\Delta S_T$ at 37°C (e.s.u.) | $\Delta S_{trans}$ (e.s.u.) |
|---|---|---|---|---|---|
| Form II | 70.2 | −1.07 | −88.4 | −3.17 | −3.12 |
| Form III | 11.4 | +0.71 | −57.2 | +2.47 | +2.50 |

In conclusion, the following results were obtained regarding the dissolution properties and physico-chemical properties of the polymorphic forms of (α-bromoisovaleryl)urea. i) Form II transformed rapidly to form I in water at 37°C, but this trans formation was delayed by the presence of 0.25% gelatin. ii) The transition temperatures of form II to form I and form III to form I were 70.2 and 11.4°C as determined from the dissolution rates and the solubilities, respectively. iii) The solubility of form II was about 50% higher than that of form I in water with gelatin at 37°C and the apparent dissolution rate of form II was about 30% higher than that of form I at 37°C. iv) The differences of free energies between form I and form II, and form I and form III were fairly small at 37°C.

It is suspected that polymorphs which have a small difference of free energy might show essentially no difference of bioavailability *in vivo*, in view of the report of Aguiar *et al.*[18] On the other hand, another report[12] has argued against this view. In our next study, experiments will be carried out to clarify this point and also to determine the effect of solubilities and dissolution rates on the absorption rates of bioavailabilities.

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## References and Notes

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