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Reevaluation of solubility of tolbutamide and polymorphic transformation from Form I to unknown crystal form

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ABSTRACT

Thermodynamic stability order of tolbutamide between polymorphs was evaluated using calorimetry and spectroscopic analysis. The heat of solution (ΔH) of Forms I–III measurements were carried out in dimethylsulfoxide between 298.2 K and 319.2 K. It was found that the ΔH of Forms II and III was increased nearly parallel with a temperature rise. However, change of the ΔH of Form I with a temperature rise was not in correspondence with that of other forms. Solubility data confirmed the change in ΔH of Form I around 308.2 K. XRD–DSC measurement of Form I detected a polymorphic transformation (Form $I^L \rightarrow$ unknown form) at 311 K. Obtained data suggested that the new crystal form (Form I^H) would exist above 311 K, and the order of thermodynamic stability was "Form III < Form I^L < Form II" below the transition temperature, on the other hand, the order was changed in "Form I^L and Form I^H < Form III < Form II" above the transition temperature. The crystal structure of Form I^H was determined by measurement of PXRD pattern on BL19B2 at SPring-8, and the change in the solid-state NMR spectrum confirmed the transformation of the crystal structure of Form I^L.

1. Introduction

Interest in the solid-state properties of drugs has grown tremendously in recent decades, especially in the pharmaceutical industry. The polymorphic form of a drug substance can have a profound impact on a spectrum of aspects, such as biological action, production, formulation and intellectual property protection. The relative stability of polymorphs depends on their free energies, such that a more stable polymorph has a lower free energy. Under a defined set of experimental conditions only one polymorph has the lowest free energy. This polymorph is the thermodynamically stable form and the other polymorph is termed a metastable form. The metastable form is sometimes desirable on account of its special properties, such as higher bioavailability, better behavior during grinding and compression, or lower hygroscopicity. However, a metastable form has a thermodynamic tendency to reduce its free energy by transforming into the stable form. Such a polymorphic transformation is often detrimental to the efficacy of the formulation. The extent of polymorphic transition depends on the processing conditions and the relative stability of the polymorphs.

Tolbutamide as shown in Fig. 1 is a hypoglycemic agent used clinically to treat insulin-dependent diabetic patients (Thomas and Ikeda, 1966). Four polymorphic forms (the Burger's Forms I–IV) have been reported and characterized (Leary et al., 1981; Simmons et al., 1972; Burger, 1975; Kimura et al., 1999). Forms I–III are known to crystallize from solvents and keep its crystal form at a room temperature, and Form IV is known to be prepared by the spray-drying and transfer to Form II stored under high humidity condition (Kimura et al., 1999; Chakravarty et al., 2005; Sonoda et al., 2006). It is recognized that Form IV is unstable form and difficult to crystallize from solvents. In the polymorphs, Form I is the most stable form around a melting point because of Forms II and III transition to Form I within heating (Kimura et al., 1999; Rowe and Anderson, 1984). The knowledge in the thermodynamic stability around a room temperature is critical information for the crystallization process in manufacturing. Because crystallization processes are generally operated around a room temperature, and a product is also stored around the room temperature. The thermodynamic stability of four polymorphs have been reported, however, there are some discrepancy in the data for Forms I and III around room temperature. It is known that Form I is the most stable polymorph heating over 384.5 K, and the order of thermodynamic stability is "Form III < Form II < Form I". However, the solubility of Form III at room temperature is higher than that of

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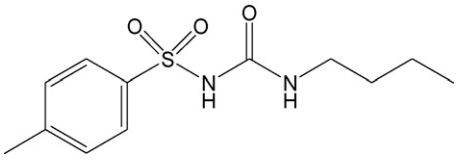

Fig. 1. Chemical structure of tolbutamide.

Form I, suggesting that the thermodynamic stability order should be "Form II < Form I < Form III". The conflict among the stability order would be caused by lack of knowledge. The aim of this study is to clarify the stability order of tolbutamide between polymorphs using thermodynamic and spectroscopic tools.

2. Experimental

2.1. Materials

Tolbutamide (Form I, purity > 99.0%, Sigma–Aldrich, Japan) and solvents (Wako Pure Chemical Industries, Ltd., Japan) used were reagent grade.

2.2. Preparation of tolbutamide polymorphs

Preparation of Form I: tolbutamide (10 g) was dissolved in CH_2Cl_2 (20 mL) at *ca.* 30 °C, then n-heptane (80 mL) was added dropwise in the solution maintained at *ca.* 30 °C. This suspension was cooled to *ca.* 0 °C. The crystals were collected by filtration and then dried under vacuum at room temperature.

Preparation of Form II: tolbutamide (22 g) was stirred in ethanol (70 mL) at *ca.* 40 °C, then the crystals maintained at *ca.* 40 °C in suspension was transferred to Form II for a few hours. This suspension was cooled to *ca.* 25 °C. The crystals were collected by filtration and then dried under vacuum at room temperature.

Preparation of Form III: tolbutamide (20 g) was dissolved in ethanol (100 mL) at *ca.* 50 °C, then the solution was rapidly cooled to *ca.* 0 °C. The Form III crystals were nucleated below 25 °C. The crystals were collected by filtration and then dried under vacuum at room temperature.

2.3. PXRD measurement

The powder Xray diffraction (PXRD) pattern was recorded on a Bruker AXS D8 Discover (Karlsruhe, Germany) at a voltage of 40 kV, a current of 40 mA with a Cu-Kα source (1.54 Å). And the recorded data was analyzed with GADDS system.

2.4. DSC

The DSC analysis was carried out using a PerkinElmer DSC-7 thermal analyzer (Norwalk, CT) with a data analysis system (PerkinElmer PYRIS Ver.3.81). The operating conditions of measurements were a scanning rate of 10 K/min and a sample weight of *ca.* 4 mg. The heat of fusion was calibrated with indium and pure water.

2.5. Microcalorimetery

The microcalorimetric analysis was carried out using a twin type heat conduction microcalorimeter Tokyo-Riko MMC-5111U (Tokyo, Japan). The microcalorimeter had attached break-ampoule-type attachments and a reaction vessel coated with Teflon. Twenty-five ml of dimethylsulfoxide was used as solvent, because tolbutamide of 200 mg dissolves readily in the solvent. Measurements were carried out at 298.2–319.2 K. *****The solvent in the reaction vessels was stirred at 60 rpm. Integral enthalpies were determined by comparing the observed area under the calorimetric curve with that for the heat evolved by a calibration heater.

2.6. XRD–DSC measurement

The Rigaku XRD–DSC II (Tokyo, Japan) for simultaneous measurement system of XRD and DSC was used for the measurement of the change in the crystalline state of samples. The operating conditions of XRD were a voltage of 50 kV, a current of 40 mA, and a Cu-Kα source (1.54 Å). The DSC was measured at a scanning rate of 0.5 K/min under N_2 atmosphere.

2.7. Solid-state ^{13}C NMR measurement

The solid-state NMR measurement was performed on a Bruker AVANCE 300 MHz digital NMR (Faellanden, Switzerland) with a cross polarization/magic angle spinning (CP/MAS). The operating conditions were a ^1H frequency of 300.13 MHz, a ^{13}C frequency of 75.48 MHz of ^1H frequency, a MAS speed of 5 kHz, a contact time of 2 ms and a recycling delay of 4 s. All spectra were calibrated with glycine (carbonyl ^{13}C at 176.03 ppm). The chemical shift of tolbutamide was assigned with the report of Kimura et al. (1999).

2.8. Solubility studies

The solubility of Forms I and III was not able to measure directly, because their crystal form transfered to Form II which was the most stable crystal form under 384.5 K within the ethanol solution (shown in Fig. 3). Therefore, The solubility of Forms I–III in 25 (v/v)% ethanol solution were led to apply the Noyes–Whitney equation to the Form II solubility and the dissolution rate of each forms. The Noyes–Whitney equation is written as

$$\frac{dC}{dt} = \frac{DS}{\delta V}(C_S - C) \quad (1)$$

where dC/dt is the rate of dissolution of the compound, D is the diffusion coefficient of the molecule, δ is the diffusion layer thickness, S is the surface area of the solid, V is the volume of the dissolution medium, C is the concentration of the dissolved solid in the solution and C_S is the solubility of the dissolved solid in the solution. In an initial dissolution condition $C_S \gg C$, Eq. (1) is expressed by

$$\frac{dC}{dt} = \frac{DS}{\delta V}C_S \quad (2)$$

If the D, δ, S, and V are independent of elapsed time, integration yields

$$C = \frac{DS}{\delta V}C_S t \quad (3)$$

where t is the elapsed time. If the D, δ, S, and V are constant, a difference in solubility of each polymorphs C_S is given by the ratio of each slope from C vs t. Consequently, it is known the solubility of metastable polymorph to measure the solubility of the stable polymorph (Shefter and Higuchi, 1963).

The solubility sample of Form II was prepared to be slurried the Form II crystals with 25 (v/v)% ethanol solution at a constant temperature for several hours, because Form II crystals were most stable in the mixed solvent. Then the sample was filtrated in a flask with membrane filter. The weighted sample (between 1 g and 2 g) was diluted with mobile phase (20 mL). And this sample was charged in HPLC (10 μL) and assayed to calculate with the working curve. The HPLC was used on Shimadzu HPLC system (Kyoto, Japan) composed with a detector of SPD-6AV, a pump of LC-6A, a column oven of CTO-6A, an injector of SIL-6B, a system controller of SCL-6B, an integrator C-R6A. The operating conditions were a mobile

phase of acetonitrile/0.05 M NaH_2PO_4 solution (45:55, v/v), a flow rate of 1.6 mL/min, a detection at 230 nm and a column of SHISEIDO CAPCELL PAK C_{18} (5 μm, Φ 4.6 mm × 150 mm).

The dissolution rate was measured by a stationary disk method in 25 (v/v)% ethanol solution at a constant temperature. The operating condition was a solution volume of 500 mL, a sample weight of *ca.* 70 mg and a tableting pressure of 1 ton/cm^2. A sample solution was withdrawn with pump at 2 min intervals and analyzed automatically with UV spectrophotometer Jasco V-530 (Tokyo, Japan). Initial dissolution rate was calculated from the data less than 5 min. After the dissolution rate measurements of individual polymorphs, the surfaces of remaining samples were evaluated by XRD measurements, and no physical transformation of polymorphic forms was confirmed during the solubility study.

2.9. PXRD measurement on BL19B2 (SPring-8)

A few gram of Form I was adequately ground with a pestle in an agate mortar and packed into Lindemann glass capillary with 0.3 mm diameter. The sample was mounted on the Debye–Scherrer camera (BL19B2 at SPring-8). Capillary spinner (180 rpm) was used to avoid prefferred orientation problem. The camera with radius of 286.5 mm has an Imaging Plate on the 2θ arm as a detector. The diffraction pattern was recorded in the 2θ range 0–75°. X-ray powder diffraction data were collected using a wavelength of 1.19781(2) Å. The exposure time was 20 min for one diffraction image.

2.10. Crystal structural analysis

Indexing of the powder diffraction patterns of tolbutamide was carried out using the program DICVOL04 (Boultif and Louer, 2004) and X-Cell (Material studio 4.2 accerlys) (Neuman, 2003). The Pawley refinement (Pawley, 1981) was used by DASH (CCDC) (David et al., 2001) to fit the peak profiles and extract the peak intensities. The method of simulated annealing was used by DASH for structure determination. A molecular connectivity model for Form I^H was taken from Form I^L. Rietveld refinements were carried out using the program RIETAN-FP (Izumi and Ikeda, 2000).

3. Results and discussion

3.1. Characterization of tolbutamide polymorphs

Each of the prepared crystals had a distinct PXRD pattern as shown in Fig. 2. These PXRD patterns have characteristic X-ray diffraction peaks due to each polymorphs (Forms I–III) reported by Kimura et al. (1999). It was confirmed that the prepared crystals are each of the polymorphs Forms I–III.

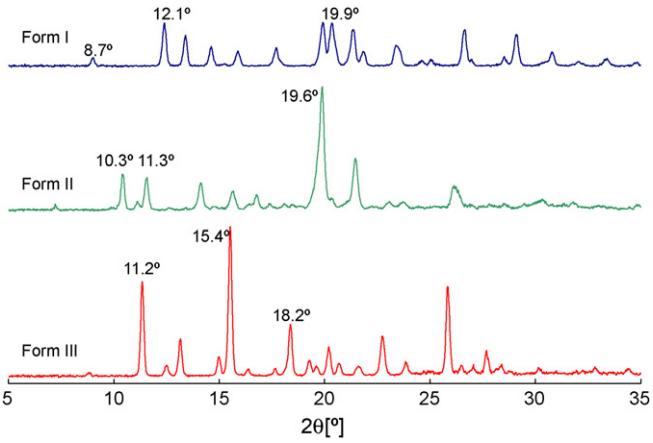

Fig. 2. PXRD patterns of tolbutamide polymorphs.

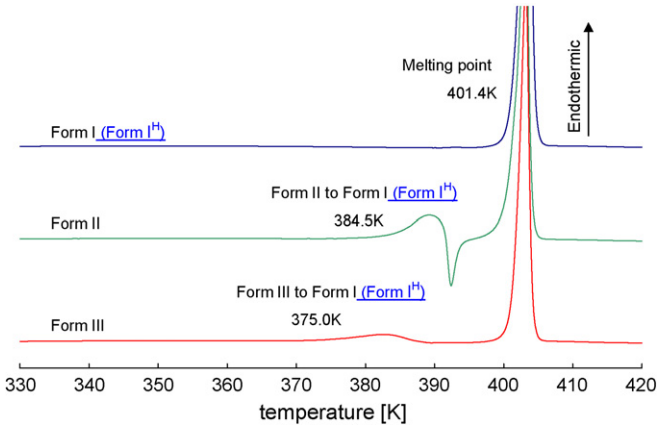

Fig. 3. DSC curves of tolbutamide polymorphs.

The DSC curves of polymorphs were shown in Fig. 3. On the DSC curve, Form I had a melting point at 401.4 K, and the polymorphic transition from Forms II to I was observed at 384.5 K. Polymorphic transition from Form III to I was also observed at 375.0 K. Forms II and III were transferred to Form I with heating and finally melted as Form I. However, the transition temperature of Form II was differed among the reports (Kimura et al., 1999; Ochiai and Ozao, 1992). Kimura et al. reported that the transition temperature of Form II was lower than that of Form III, the crystallinity and crystal size distribution which were affected by the crystallization condition, in fact, the former sample was crystallized from the slurry in EtOH, on the other hand, the latter sample was prepared by transformation from Form IV stored at 333.2 K, 75% RH. As mentioned previously, the order of thermodynamic stability is "Form III < Form II < Form I". However, the solubility of Form III at room temperature is higher than that of Form I. It is necessary to measure the heat of solution and solubility for the clarification of the polymorph's stability.

3.2. Heat of solution (ΔH) of tolbutamide polymorphs

The heat of solution (ΔH) of Forms I–III measurements were carried out in 25 mL of dimethylsulfoxide between 298.2 K and 319.2 K. The measured ΔH were shown in Fig. 4. As a result, it was found that Form II was the most stable crystal form in polymorphs. And the ΔH

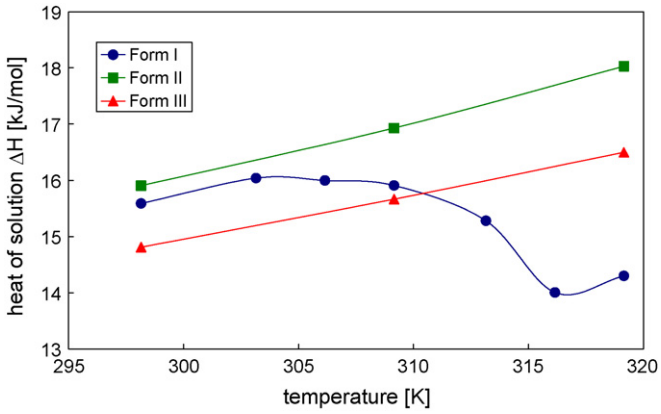

Fig. 4. ΔH of tolbutamide polymorphs.

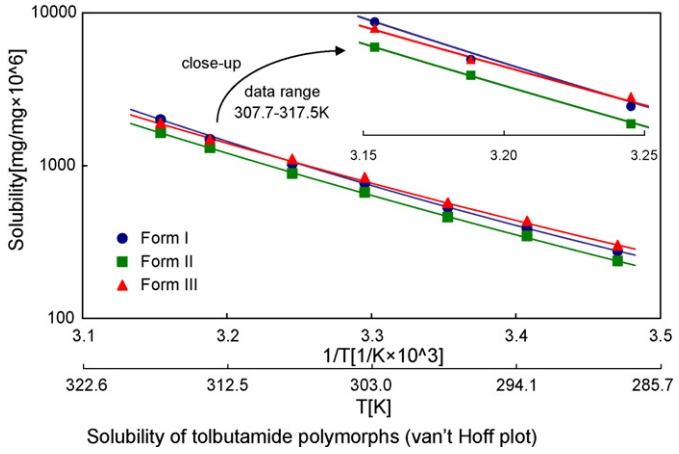

Fig. 5. Solubility of tolbutamide polymorphs (van't Hoff plot).

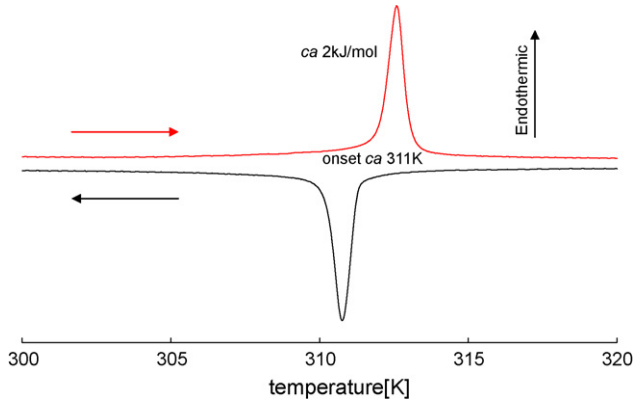

Fig. 6. DSC curve of the reversible peak of Form I.

of Forms II and III was increased nearly parallel with a temperature rise. However, the change in the ΔH of Form I with a temperature rise was not in correspondence with that of other forms. The ΔH of Form I was decreased around 303.2 K and the ΔH value was lower than that of Form III above this temperature. It was suggested that the thermodynamic character of tolubutamide was changed in the order of stability between Forms I and III in this temperature region. In consideration with this phenomenon, a crystal structure transition would occur around this temperature, and it was expected that the Form I crystal would be transferred to different structure with heating.

3.3. Solubility of tolbutamide polymorphs

The solubility of Forms I–III in 25 (v/v)% ethanol solution were led to apply the Noyes–Whitney equation to the Form II solubility and the dissolution rate of each forms. The solubility data calculated by the van't Hoff analysis between 288.2 K and 317.1 K was shown in Fig. 5. The plot was turned down because of a temperature dependence of ΔH (Rowe and Anderson, 1984). It was found that Form II was the most stable crystal form in polymorphs, and the solubility of Forms II and III were increased nearly parallel with a temperature rise. On the other hand, the solubility of Form I was decreased to less than the solubility of Form III over 308.2 K.The temperature dependency in the solubility was in accordance with the change of ΔH. Therefore, the change in ΔH of Form I with a temperature rise was confirmed.

3.4. Transition behavior of Form I

On the DSC curve of Form I (Fig. 6), a sharp endothermic peak between 309.15 K and 313.15 K was found and this peak was recognized in a reversible fashion (Traue et al., 1987; Giron, 1995; Kawakami and Ida, 2005). The enthalpy of this peak was a small value of *ca* 2 kJ/mol. The temperature range of this change was in accordance with the range expected crystal structure transition from the temperature dependency of Form I. Therefore, Form I was measured with XRD–DSC whether the reversible peak has an impact on the crystal structure. Fig. 7 shows the PXRD patterns at below and above temperature of the peak. It was found that XRD pattern was changed at the peak temperature. Accordingly, it was demonstrated that Form I was transferred to unknown crystal form with heating over 311 K. In this study, the new crystal was named "Form I^H" and the crystal known as "Form I" was called "Form I^L".

3.5. Crystal structure of Form I^H

The PXRD of Form I^H for crystal structure analysis was measured on BL19B2 at SPring-8. The sample was heated to 363.2 K in order to transfer from Forms I^L to I^H. The powder X-ray diffraction pattern of Form I^H was indexed in a monoclinic unit cell with indexing figure of merit $M(20) = 53.3$, $F(20) = 139.0$. Since the unit cell was similar to that of Form I^L, the same space group of $Pna2_1$ was assigned. The best SA solution gave profile χ^2 305.77 and intensity χ^2 62.55. Restrained Rietveld refinement was carried out, $a = 20.8095(4)$ Å, $b = 7.9323(2)$ Å, $c = 9.0610(2)$ Å, $V = 1495.67(5)$ Å^3, $R_{wp} = 0.0560$, $R_p = 0.0378$, $R_I = 0.0458$ and 2θ range 5.00–60.00° (Fig. 8). Molecular structure and the torsion angles of Forms I^L and I^H are shown in Fig. 9. The molecular packing of Form I^H has isomorphic structure of Form I^L. The conformation change of terminal butyl group (as indicated by ellipsoid in Fig. 9b and d) was observed. Additionally, the torsion angle around S–N bond (as indicated by torsion angle 6 in Fig. 9d) was changed.

The chemical shifts (δ) of Forms I^L and I^H in the NMR spectra were measured with ^{13}C NMR at 300.7 K and 330.7 K (Ueda and Nagai, 1981; Meejoo et al., 2003). The measured spectra were shown in Fig. 10. These ^{13}C NMR signals were assigned according to the report (Kimura et al., 1999) and the δ were listed in Table 1. Fig. 11 shows the ^{13}C CP/MAS spectra of Forms I^L and I^H. As shown in Fig. 11, the most representative peak shifts were arisen C1 and the butyl side chain (from C9 to C12). These phenomena were affected with the unit cell of Forms I^L and I^H. The unit cell of Forms I^L and I^H was shown in Table 2 (Donaldson et al., 1981). The butyl side chain has the most representative change in the unit cell. And the peak shift of C1 was considered due to its change. The peak shift

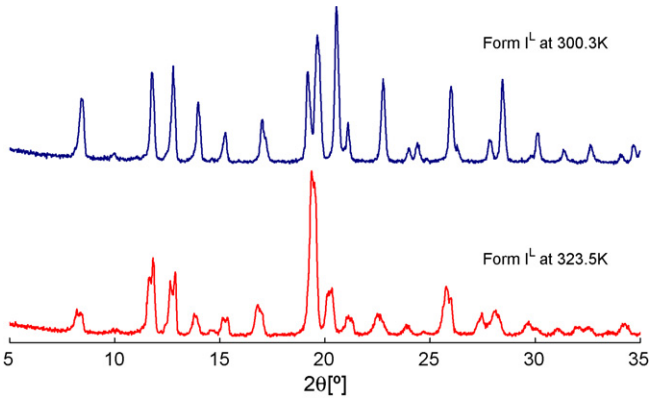

Fig. 7. PXRD patterns of Form I below and above endothermic peak.

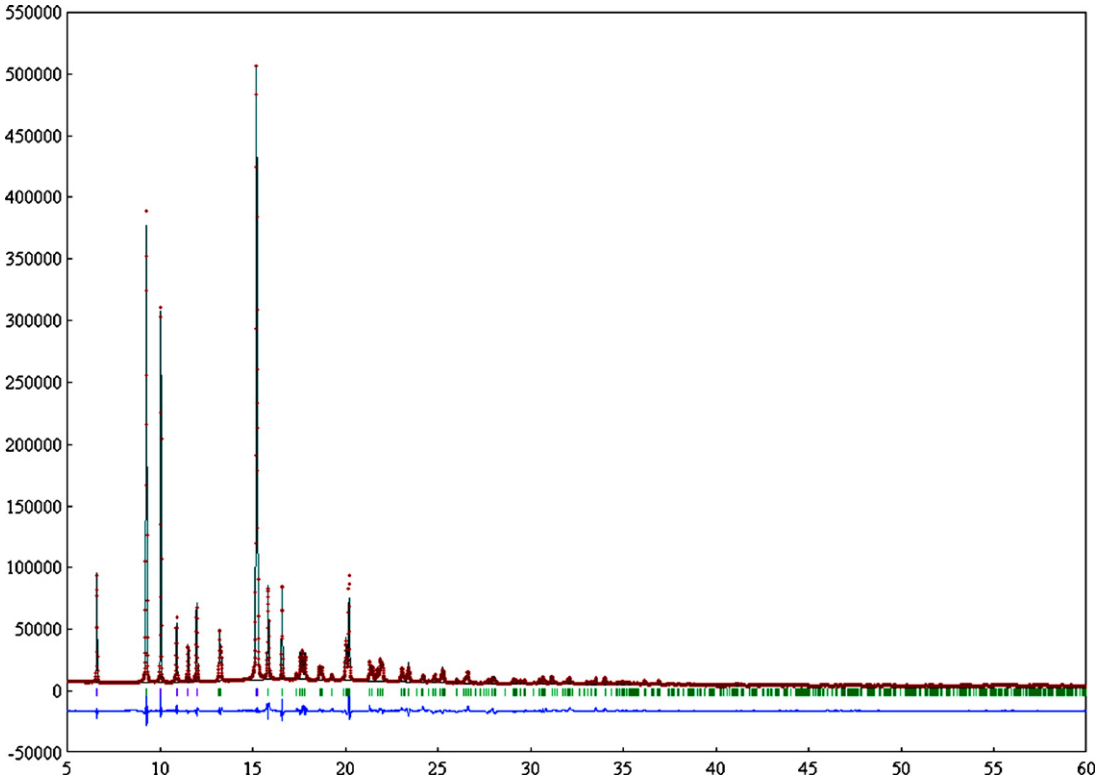

Fig. 8. Final Rietveld plot of Form I^H.

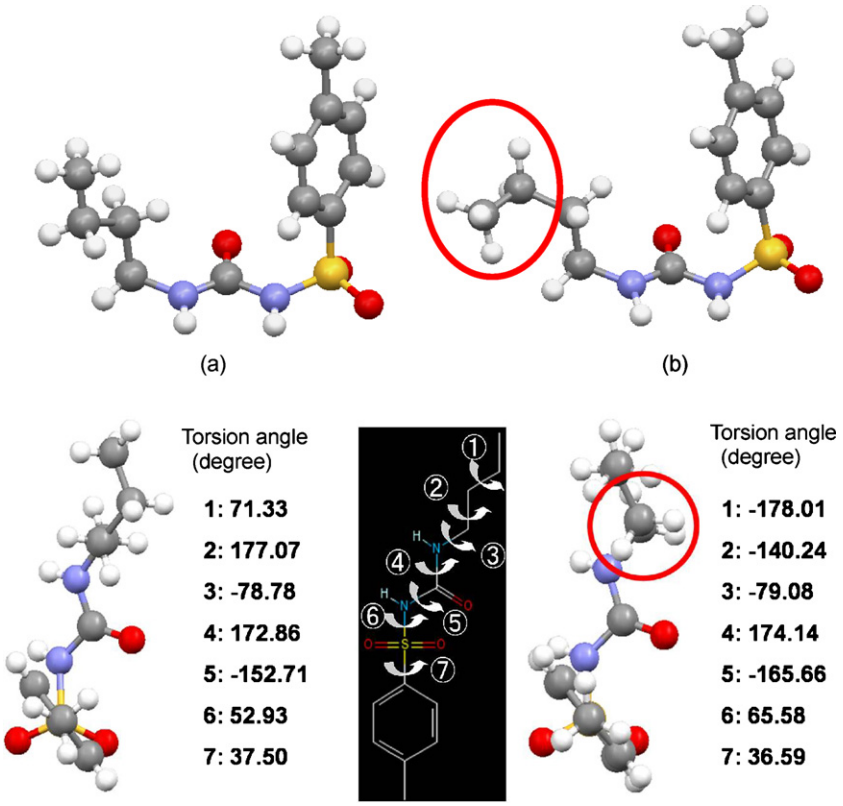

Fig. 9. Molecular structures and torsion angles of tolbutamide in Forms I^L and I^H. Molecular structure of tolbutamide in (a) Form I^L and (b) Form I^H and torsion angles of tolbutamide in (c) Form I^L and (d) Form I^H.

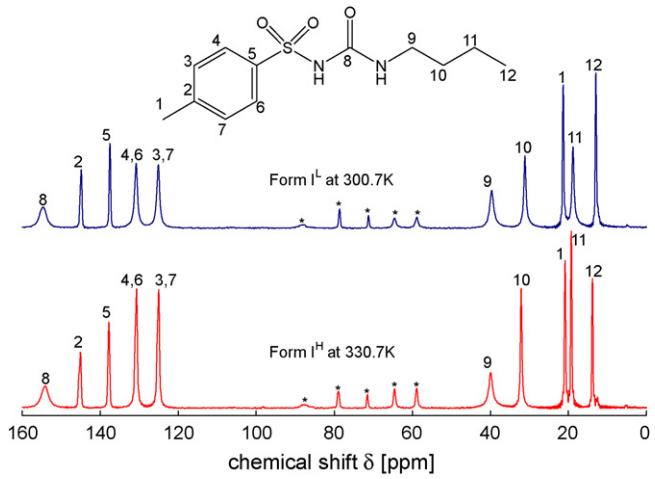

Fig. 10. ^{13}C CP/MAS spectra of Forms I^{L} and I^{H}. (*) Represents spinning side bands.

Table 1
^{13}C NMR chemical shift δ of Forms I^{L} and I^{H}.

Carbon	Crystal form		Peak shift $\Delta\delta$
	Form I^{L} (300.7 K)	Form I^{H} (330.7 K)	
1	021.4	020.9	0.5
2	144.9	145.1	0.2
3,7	125.1	125.1	0.0
4,6	130.8	130.7	0.1
5	137.5	137.8	0.3
8	154.6	154.2	0.4
9	039.8	040.0	0.2
10	031.2	032.2	1.0
11	018.9	019.3	0.4
12	013.1	013.9	0.8

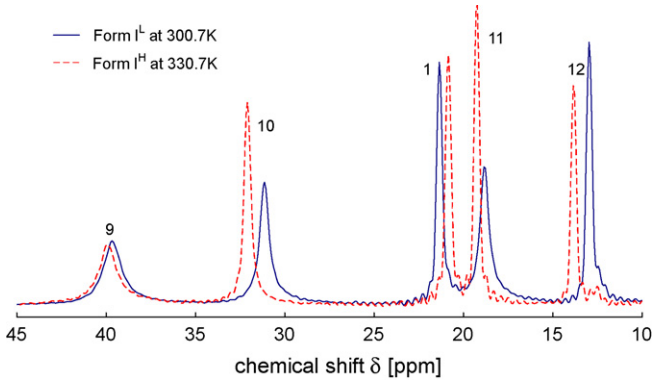

Fig. 11. ^{13}C CP/MAS spectra of Forms I^{L} and I^{H} (overlaid I^{L} and I^{H} spectra).

Table 2
Crystal data of Forms I^{L} and I^{H}.

	Crystal form	
	Form I^{L}	Form I^{H}
Crystal system	Orthorhombic	Orthorhombic
Space group	$Pna2_1$	$Pna2_1$
Unit-cell dimensions		
a (Å)	20.223(11)	20.8095(4)
b (Å)	7.831(9)	7.9323(2)
c (Å)	9.090(10)	9.0610(2)
V (Å^3)	1439.550	1494.67(5)

Data for Form I^{L} are quoted from known structure (Donaldson et al., 1981).

values $\Delta\delta$ of C1 and the butyl side chain listed in Table 1 were also larger than that of the other carbons. These phenomena were demonstrated that the changes of crystal structure are caused by the torsional change around S–N bond.

4. Conclusion

In this study, we could find the unknown crystal form, Form I^{H} that transformed from Form I (Form I^{L}) with heating. The crystal structure of Form I^{H} was confirmed by measurement of PXRD pattern on BL19B2 at SPring-8. From the result of thermal measurements of Forms I^{H} and I^{L}, the stability of tolbutamide polymorphs were cleared around a room temperature without thermodynamic discrepancy. The order of stability was changed from "Form III < Form I^{L} < Form II" below the transition temperature to "Form I^{L} and Form I^{H} < Form III < Form II" above the transition temperature.

These results would be very useful for confirming the robustness of process control for polymorph manufacturing and the design of crystallization process. Particularly, ΔH behavior was a one of the most effective method of the energetic stability for precision.

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