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Thermodynamic Properties of Polymorphs of Tolbutamide[1]

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Thermodynamic values for two polymorphic forms of tolbutamide (form A and form B) were calculated on the basis of solubility determination and differential scanning calorimetry. The transition temperature and the heat of transition were estimated to be 93.3°C, and 230 cal/mol by the former method, and 98.5°C, and 255 cal/mol by the latter method. The dissolution rate was only slightly affected by the polymorphic form.

Keywords——tolbutamide polymorphism; solubility; transition temperature; thermodynamic parameters; dissolution rate

Simmons *et al.*[2] reported that tolbutamide had two polymorphic forms, which showed the same dissolution rate and bioavailability in beagle dogs.

On the other hand, Burger *et al.*[3] and Al-Saieq *et al.*[4] suggested the existence of four forms of tolbutamide. However, Leary *et al.*[5] reported differential scanning calorimetry (DSC), optical and X-ray crystallography data indicating that the stable forms which could be obtained corresponded to either form A or form B reported by Simmons. We have also obtained the crystalline forms of tolbutamide according to the procedures described by Simmons, Burger and Al-Saieq, and our results, obtained by infrared (IR) spectroscopy and X-ray diffractometry, were consistent with those of Leary *et al.* However, there are various kinds of polymorphs which cannot be characterized in relation to the preparative methods. For example, the thermodynamic properties of forms A and B of Simmons were not described expect for the transition temperature (113°C).

Therefore, a more detailed investigation seemed necessary. This paper deals with the thermodynamic properties of these polymorphs (forms A and B of Simmons) and the dissolution behavior studied by the stationary disk method.

Experimental

Materials——Tolbutamide polymorphs A and B were obtained by the method described by Simmons *et al.*[2] The particles of tolbtamide used for solubility and dissolution studies were those passing through a 100 mesh sieve (less than 149 μm).

Identification of the Polymorphs——Powder X-ray diffractometry and IR were employed in the manner described in the previous paper.[6]

Solubility Measurement——Using a dissolution cell simmilar to that described by Sekiguchi *et al.*,[7] an excess of tolbutamide was placed in 50 ml of HCl–KCl buffer solution (pH 2.0, $\mu=0.1$), which was maintained at 4°C, 10°C, 20°C, 30°C and 40°C by circulating constant temperature water in the outer vessel. Immediately after the addition, 400 rpm agitation was applied by means of a magnetic stirrer. Aliquots of the solution were taken at appropriate times, filtered through a membrane filter (pore size, 0.22 μm), and diluted, then the concentration of tolubutamide was determined according to the ultraviolet absorption method (229 nm).

Procedure for the Determination of the Dissolution Rate——The dissolution rate was determined by a stationary disk method, using the apparatus described in a previous paper.[8] Two hundred and fifty mg of the sample was compressed in a cylindrical die with a Shimadzu hydraulic press for KBr tablets for IR spectroscopy. It was comfirmed by X-ray diffractometry that no phase transition took place during the compression. The compressed disk was not ejected from the die, and the die cavity was stoppered. The die carrying the compressed disk was set on the dissolution apparatus so as to make the disk face the stirrer. Every experiment was done under the following conditions: HCl–KCl buffer solution (pH 2.0, $\mu=0.1$) as the

dissolution medium; at 30°C; 100 rpm stirrer velocity; 1.3 cm diameter disk of sample compressed under 200 kg/cm². Aliquots (2 ml) of the solution were taken at appropriate time intervals and diluted, then the concentration was determined from the UV absorption at 229 nm.

Differential Scanning Calorimetry (DSC)——This was done using a Shimadzu DSC-30M differential scanning calorimeter. In order to determine the heat of transition, indium (ΔH_n 28.4 J/g) was used as a standard sample.

Results and Discussion

The Dissolution Rate, Solubility Behavior and Thermodynamics of Transition

Tolbutamide forms A and B were stable and no change in crystalline form was observed through grinding and compression. The dissolution curves of forms A and B are shown in Fig. 1. Form B dissolved faster than form A, and the apparent dissolution rate was about 1.05 times than of form A.

By plotting the saturated concentration of each form according to van't Hoff's equation as shown in Fig. 2, the transition temperature was estimated from the intersection point of the two straight lines and the heat of transition was estimated from the difference in slope between these two straight lines. The results are shown in Table I.

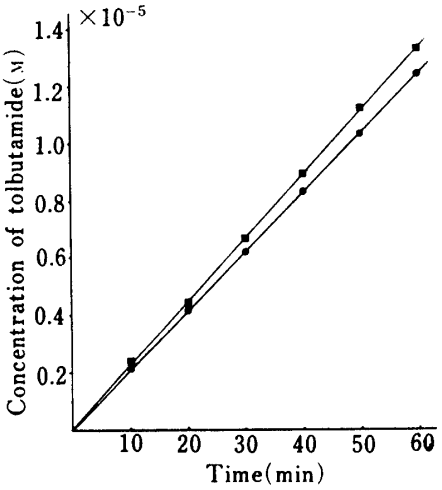

Fig. 1. Dissolution Rate Curves of Tolbutamide Polymorphs in pH 2.0 Buffer Solution at 30°C

●: form A, ■: form B.
Each value is the mean of five experimental runs. The standard deviation is ±8.1% at most.

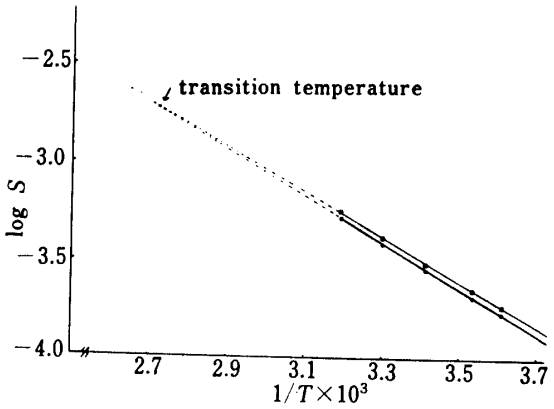

Fig. 2. The van't Hoff Plots for Tolbutamide Polymorphs A and B in pH 2.0 Buffer Solution

S: solubility ●: form A, ■: form B.
Each value is the mean of three experimental runs. The standard deviation of each value is negligibly small.

Table I. Thermodynamic Values calculated for Tolbutamide Polymorphs A and B

	Transition temperature (°C)	Heat of solution (kcal/mol)	Heat of transition (cal/mol)	G_{20}°C (cal/mol)
Form A	93.3	5.33	230	50.4
Form B		5.10		

The transition temperature was estimated as 93.3°C and the heat of transition was 230 cal/mol. The transition temperature of 93°C approximately corresponded to that of 98.5°C obtained by DSC. In addition, the heat of transition from form B to form A was determined

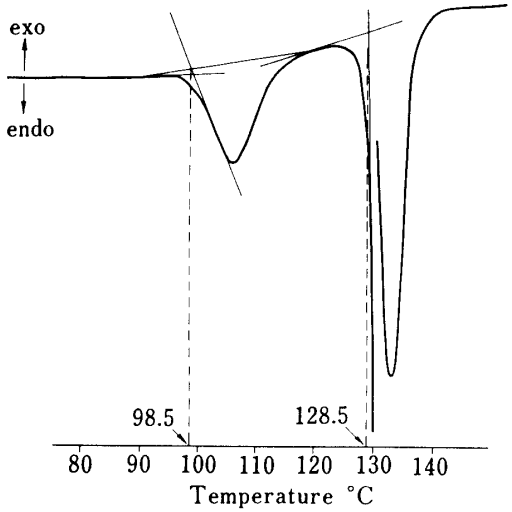

Chart 1. DSC–Thermograms of Tolbutamide Polymorphs B

The operating conditions were as follows; sample weight 14.36 mg; reference sample α-Al_2O_3; atmosphere N_2 40 ml/min; sensitivity ± 10 mJ/s; heating rate 10°C/min; thermocouple C–A; sample cell Al.

by integration of the peak area as shown in Chart 1. The estimated heat of transition was 255 cal/mol. This also agrees approximately with that obtained by the van't Hoff plots. It is clear that the difference in thermodynamic properties between forms A and B is small.

Aguiar and Zelmer[9] suggested that a large difference in free energy content of polymorphs, as was demonstrated in the case of chloramphenicol palmitate ($\Delta G = -774$ cal/mol), may significantly affect the absorption and resulting blood levels, and that a small difference, as was found with mefenamic acid ($\Delta G = -251$ cal/mol), may not affect the absorbability of the drug. Further, it was pointed out by Yokoyama *et al.*[10] that ΔG for the two polymorphs of acetohexamide in their study was only 89.9 cal/mol and this difference did not significantly affect the bioavailability. ΔG for the two polymorphs of tolbutamide in the present study was only 50.4 cal/mol. Thus, our thermodynamic results are consistent with the finding that the polymorphic form of tolbutamide does not affect the bioavailability in beagle dogs as reported by Simmons *et al.*

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References and Notes

1) This paper forms Part XXXIX of "Physico-chemical Approach to Biopharmaceutical Phenomena." The preceding paper, Part XXXVIII: H. Ueda and T. Nagai, *Chem. Pharm. Bull.*, **29**, 2710 (1981).
2) D.L. Simmons, R.J. Ranz, N.D. Gyanchandani, and P. Picotte, *Can. J. Pharm. Sci.*, **7**, 121 (1972).
3) A. Burger, *Sci. Pharm.*, **43**, 161 (1975).
4) S.S. Al-Saieq and G.S. Riley, *Pharm. Acta. Helv.* **56**, 125 (1981).
5) J.R. Leary, S.D. Ross, and M.J.K. Thomas, *Pharm. Weekblad. Sci. Ed.*, **3**, 62 (1981).
6) K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **25**, 2608 (1977).
7) K. Sekiguchi, E. Owada, and K. Ito, *Chem. Pharm. Bull.*, **15**, 873 (1967).
8) Y. Hamada, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **23**, 1205 (1975).
9) A.J. Aguiar and J.E. Zelmer, *J. Pharm. Sci.*, **58**, 983 (1969).
10) T. Yokoyama, T. Umeda, K. Kuroda, K. Sato, and Y. Takagishi, *Chem. Pharm. Bull.*, **27**, 1476 (1979)