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Dissolution Behavior of Solid Drugs. V.[1] Determination of the Transition Temperature and Heat of Transition between Barbital Polymorphs by Initial Dissolution Rate Measurements

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Transition temperature and heat of transition between barbital forms I and II were found to be 93° and 210 cal/mole, respectively, measuring their initial dissolution rates by the method reported in the previous paper. The latter value is reasonably close to the value of 330 ± 15 cal/mole obtained by differential scanning calorimetry (DSC). The data obtained in this study indicates that forms I and II are enantiotropic contrary to such a statement appeared in literature as they are monotropic. Furthermore, it was found that there is little difference in solubility values of barbital forms I and II.

The existence of at least three kinds of barbital polymorphs, forms I, II, and IV has been reported.[3–10] However, a little confusion was found among data by different authors. Further, in spite of the importance of the drug as a hypnotic, only one dissolution study covering two of its polymorphs is evident in the literature.[3]

In the present work, three kinds of barbital polymorphs[11] were obtained by recrystallization from different solvents. Thermal analysis by differential scanning calorimetry (DSC), infrared spectrophotometry (IR), and X-ray diffraction analysis were performed with all of the three crystals for identification. Then, using forms I and II, dissolution rates and solubilities were measured at various temperatures in order to determine the transition temperature, heat of transition and their solubility values. Data thus obtained were compared each other, and the most likely values or ranges of these thermodynamic constants were estimated.

Experimental

Materials——Preparation of barbital polymorphs by sublimation or by heat conversion was found inadequate, because the products were often contaminated with, or easily converted into other crystal forms. However, each one of the three forms was isolated by the following procedures.

Form I: Obtained from aqueous or acetone solution of commercial product of J.P. VIII grade by implanting freshly solidified pieces of fused barbital; or crystallized by freeze-drying the dioxane solution containing about 10% of barbital.

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[1] Part IV: K. Sekiguchi, K. Shirotani, and M. Kanke, *Yakugaku Zasshi*, **95**, 195 (1975).

[2] Location: *9-1, Shirokane, 5-chome, Minato-ku, Tokyo.*

[3] H. Nogami, T. Nagai, E. Fukuoka, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 23 (1969).

[4] A. Köfler, *Mikrochem.*, **33**, 4 (1947).

[5] T. Huang, *Acta Pharm. Intern.*, **2**, 95 (1951).

[6] B. Cleverley and P.P. Williams, *Tetrahedron*, **7**, 277 (1959).

[7] M. Brandstätter-Kuhnert and M. Aepkers, *Mikrochim. Acta*, **6**, 1055 (1962).

[8] T. Oba and R. Koyama, *Eisei Shikensho Hokoku*, **84**, 4 (1966).

[9] B.M. Craven, E.A. Vizzini, and M.M. Rodrigues, *Acta Cryst.*, **B25**, 1978 (1969).

[10] B.M. Craven and E.A. Vizzini, *Acta Cryst.*, **B27**, 1917 (1971).

[11] These three polymorphs were named as I, II, and IV in accordance with Craven's notation.[9,10] Although another form was detected in the present study, it was not separated in a pure state and further investigation will be necessary to find its characteristics.

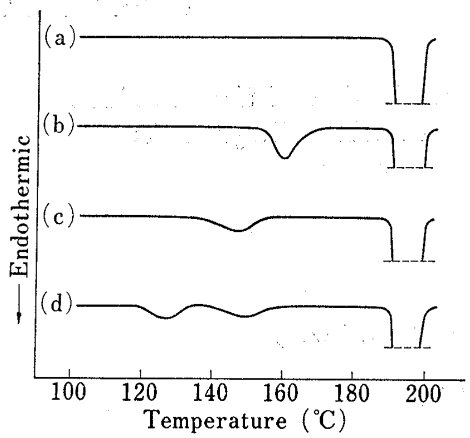

Fig. 1. DSC Curves of Barbital Polymorphs

Curve	Form	Sample wt. (mg)	Heating rate (°C/min)	Sensitivity (mcal/sec)
(a)	Form I	9.419	16	16
(b)	Form II	9.660	16	8
(c)	Form II, after compression	7.341	16	8
(d)	Form IV	9.461	8	8

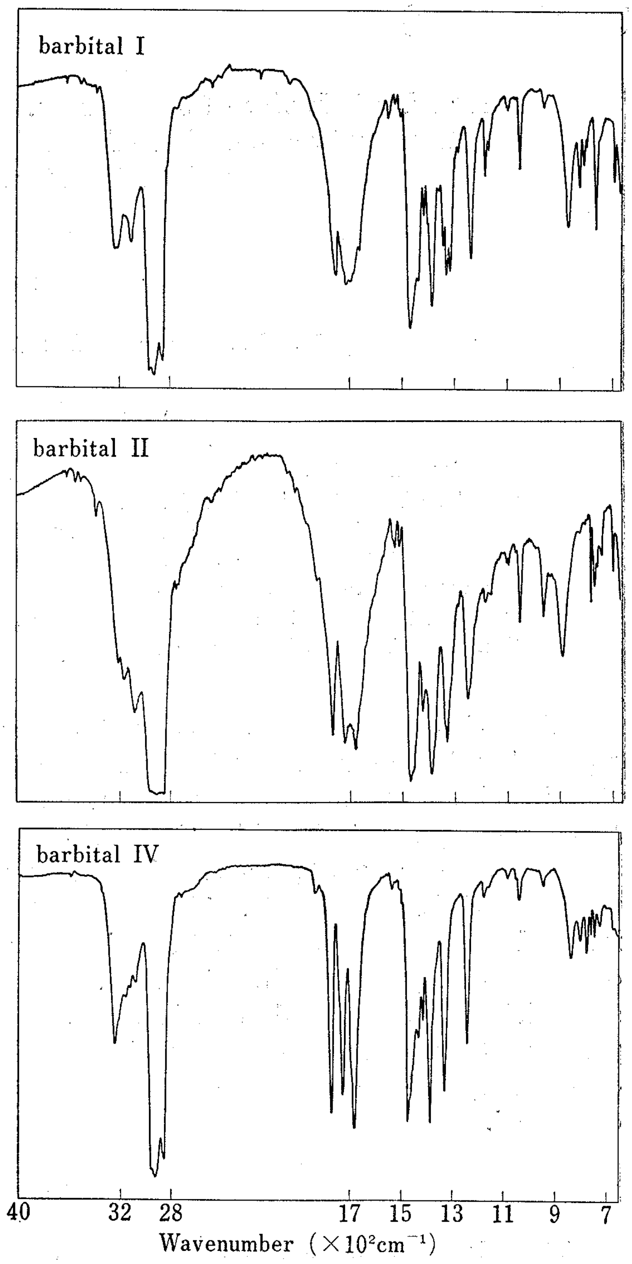

Fig. 2. Infrared Spectra of Barbital Forms I, II, and IV; Nujol Mull

Form II: Obtained from hot aqueous solution by slow cooling.

Form IV: Crystallized slowly from aqueous 0.1 N NH_3 solution.

Commercial products: Products of J.P. VIII grade manufactured by Iwaki Seiyaku, Co., Ltd. and Sanko Seiyaku Kogyo, Co., Ltd.

Preparation of Sample Disks——Sample disks were prepared in the same manner as described previously.[12] The diameter of the die was 10 mm, and a compression force of 3 tons (3.8 tons/cm^2) was applied to approximately 300 mg of sample powder for 1 minute.

Characterization of Polymorphic Forms——Polymorphic forms of the isolated crystals or of the disk surface before and after dissolution rate experiments were characterized by DSC, IR, and X-ray diffractometry. The DSC apparatus used was a Perkin-Elmer DSC-1B Differential Scanning Calorimeter. Measurement conditions adopted for this purpose were: heating rate, 8—16°/min; sensitivity, 8—16 mcal/sec; sample weight, 7—10 mg in a liquid sample pan. On DSC measurement, each polymorph except form I showed one or two transition peaks as shown in Fig. 1. IR spectra both by nujol mull and KBr disk methods were taken with a Jasco IRA-1 Grating Infrared Spectrophotometer (Fig. 2 and 3). The instrument used for X-ray diffraction analysis was a JEOL JDX-7F X-ray diffraction analyzer. Characteristic X-ray patterns are shown in Fig. 4.

Dissolution Rate Measurements——The apparatus and procedure for the dissolution rate measurement were essentially similar to those described in the previous paper.[12] The dissolution medium of 250.0 g of redistilled water was agitated with a magnetic stirring apparatus at a speed of 300 rpm, and was circulated by a pump at a constant flow rate of 300 ml/min through the cell of a Hitachi Perkin-Elmer 139 spectrophotometer. A sample disk was fixed on a glass holder and immersed into the medium previously stabilized at the desired temperature within a range of ±0.1°. Absorbance at a wavelength of 210 or 265 nm was recorded by a TOA EPR-3T recorder. Linear relationship between concentration and absorbance was confirmed beforehand in the absorbance range from 0 to about 0.5 at both wavelengths.

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12) K. Sekiguchi, M. Kanke, Y. Tsuda, K. Ishida, and Y. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1592 (1973).

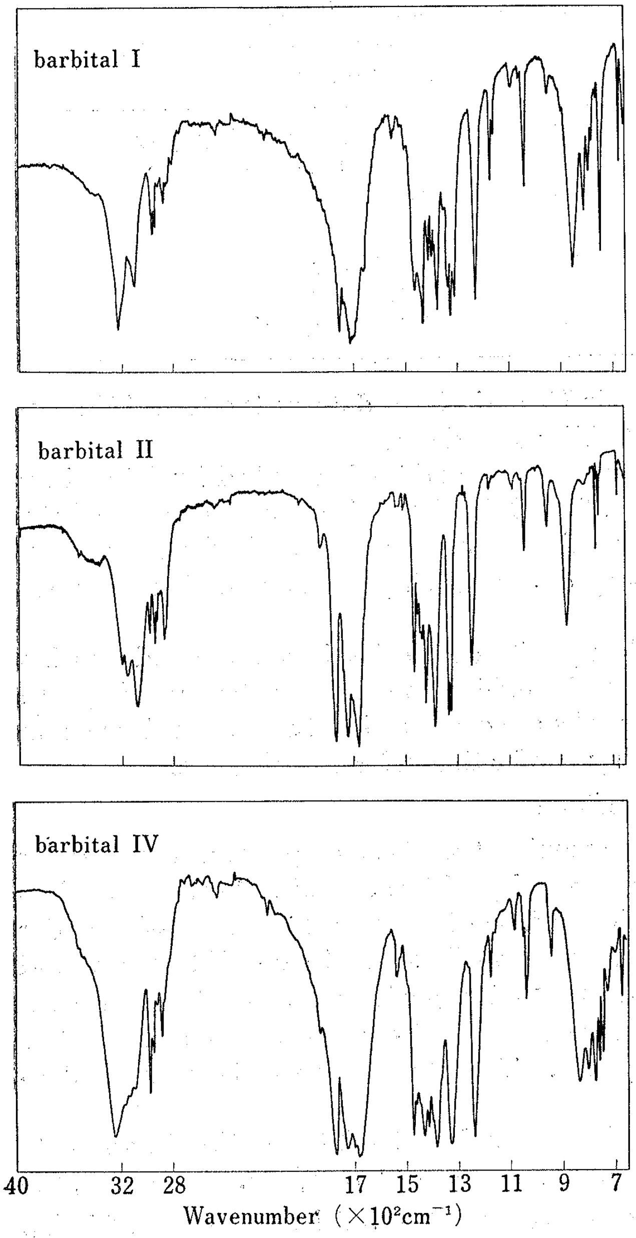

Fig. 3. Infrared Spectra of Barbital Forms I, II, and IV; KBr Disk

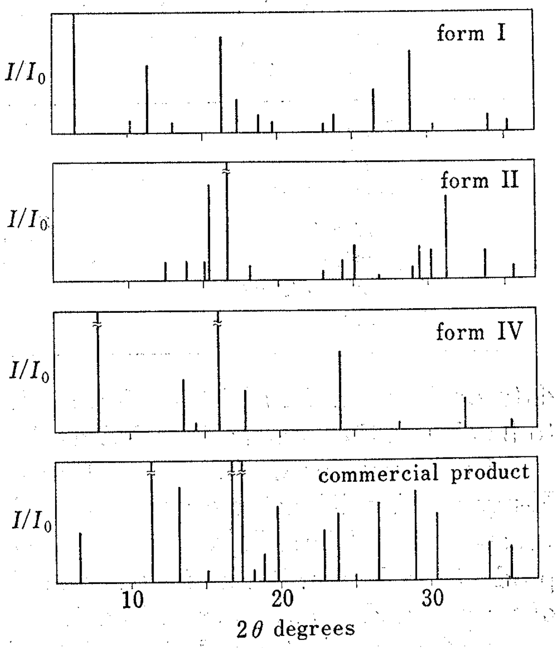

Fig. 4. X-Ray Diffraction Patterns of Barbital Polymorphs and a Comercial Product

Determination of Transition Temperature and Heat of Transition by DSC——The apparatus was the same as the one used for characterization. The following conditions were adopted: 1) Measurements of transition temperature: sample, barbital form II, finely powdered; sample weight, 12—18 mg; sample pan, for solid; sensitivity, 4 and 8 mcal/sec; heating rate, 1—64°/min. 2) Measurements of heat of transition: sample, form II, powdered; sample weight, about 10—12 mg, weighed down to three places of decimals; sample pan, for liquid; sensitivity 4 and 8 mcal/sec; heating rate, 8—16°/min.

Conventional Solubility Measurements——About twice the amount of sample crystals required to make a saturated solution was placed in 80 g of redistilled water in a jacketed cell similar to that used for dissolution rate measurements, and agitated at 600 rpm at temperatures of 20°, 25°, 30°, 35°, 37°, and 45° controlled within ±0.1°. At appropriate time intervals, small amounts of the solution were taken by filtering through a 0.45 μ membrane filter (Millipore HAWP 01300). An aliquot of each sample solution was weighed and diluted for spectrophotometric assay. By plotting concentration *versus* time, solubility equilibrium was determined at each temperature.

Results and Discussion

Comparison of Barbital Polymorphs obtained by the Present Work with Those reported in Literature

Polymorphic forms hitherto reported are listed in Table I. In comparing the IR spectra of Oba, *et al.*[8] with those by the authors or by others, forms A and B are closely similar to form II. The spectrum of C is identical to Craven's[9] or authors' form IV, while D is equal to form I. Among the four polymorphs reported by Huang,[5] his preparations of forms III and IV are, as Huang himself recognized, contaminated by form II. Similarly, Nogami, *et al.*[3] presented

Table I. Comparison of Barbital Polymorphs reported in Literature

Investigator	Notation				Characterization
Köfler[4)]	I	II	III	IV	hot-stage crystallography
Huang[5)]	I	II	III	IV	X-ray, hot-stage
Cleverley, *et al.*[6)]	I	II		IV	IR
Oba, *et al.*[8)]	D	A, B		C	IR
Nogami, *et al.*[3)]	I	II		III	IR, X-ray
Craven, *et al.*[9,10)]	I	II		IV	IR, X-ray
Authors	I	II		IV	IR, X-ray, DSC

data on forms I, II, and their form III, but their IR and X-ray data of the form III seem to be almost the same as form IV, as Craven, *et al.*[10)] pointed out.

In the present work, purity of crystals of forms I, II, and IV is certified by IR and by X-ray powder diffractometry as shown in Fig. 2, 3, and 4. Crystals of form IV showed the IR spectrum of form II, when they are ground hard in an agate mortar. As for commercial products in Japan, it was found from their X-ray data that they are more or less mixtures of forms I and II as shown in Fig. 4.

DSC curves of forms I, II, and IV differ clearly with each other in number and position of the transition peaks (Fig. 1). Crystals of form IV exhibit two peaks before melting. In this case, the first and the second endothermic peaks are confirmed to be the transition from form IV to II and form II to I, respectively, by conducting IR measurements.

Effect of Compression Force on Polymorphic Transition

For dissolution study, it was necessary to examine the effect of pressure required for disk formation on polymorphic transition. In comformity with the results of other investigators, no change was observed in DSC, IR, and X-ray data of form I after compression under the pressure of 3.8 tons/cm². Similarly, crystals of form II showed same IR spectra and X-ray patterns before and after compression up to 4.5 tons/cm². However, the transition peak from form II to I appeared about 10° lower on the DSC curve with the sample after compression as compared with the original crystals. The peak shift will be attributed to lattice defects produced by pressure.

In the case of form IV, transition to form II occurred by hard trituration in an agate mortar, although the form was even stable at a pressure force of 5 tons/cm². Therefore, the transition from form IV to II will be caused not by the pressure but by the heat of friction during grinding.

Determination of Transition Temperature and Heat of Transition by Dissolution Rate Measurements

The relationship between log (dE/dt) and $1/T$ obtained from initial dissolution rate are shown in Fig. 5. From these data, the transition temperature is estimated to be 93°, as indicated by the intersection of the two fitted lines, and the heat of transition is calculated to be 210 cal/mole by taking the difference between the heats of dissolution for both forms. The crystals on the disk surface showed identical characteristic DSC, IR and X-ray patterns before and after dissolution rate measurements.

Determination of Heat of Transition by DSC

Using liquid sample pans, the heat of transition between forms II and I was found to be 330±15 cal/mole from the peak area in the DSC curve. In order to determine the transition temperature, analysis was done with crystals of form II at various heating rates. The apparent transition temperatures thus obtained were plotted against heating rates, and the curve is extrapolated to 0°/min, as shown in Fig. 6. However, even with such trials, it was impossible to determine the accurate transition temperature.

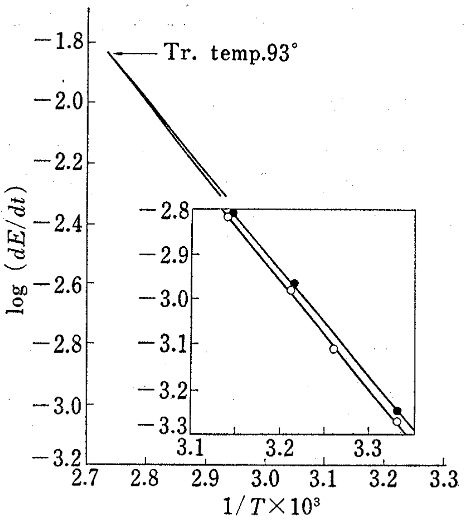

Fig. 5. Plots of log (*dE*/*dt*) against $1/T$ for Barbital Forms I and II in Water

●: Form I ○: Form II

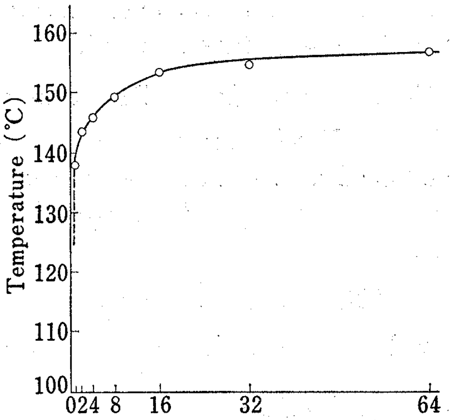

Fig. 6. Effect of DSC Heating Rate on Apparent Transition Temperature of Barbital (II→I)

sample weight: 12—18 mg
sensitivity: 4—8 mcal/sec
heating rate: 1—64°/min

Determination of Solubilities

The conventional solubility equilibrium method was employed to determine the solubilities of forms I and II at various temperatures and the transition point between them. Although IR spectra of the solid residue of both forms showed no apparent change of polymorphic transition during and after each experimental run, there is little statistically significant difference in solubility values between two forms as shown in columns 2 and 4 of Table II.

Table II. Solubility Data for Barbital Forms I and II in Water (g/100 g)

Temp. (°C)	Form I		Form II	
	Exptl.	Calcd.[a]	Exptl.	Theoretical[b]
20	0.706	0.733	0.696	0.682
25		0.831	0.787	0.778
30	0.877	0.939	0.858	0.884
35	0.960	1.055	0.964	0.999
37		1.105	1.055	1.049
45		1.320	1.300	1.264

a) calculated from dissolution rates
b) determined by the method of least squares from experimental data

Conclusion

In this work, the data obtained were examined in detail by comparing with those previously reported in literature and the following conclusions were reached.

(1) Type of Polymorphic Form

The three forms of barbital, forms I, II, and IV are certainly independent polymorphs. From the temperatures and the total area of transition peaks in the DSC curves, it is thought that enantiotropic relations exist between forms II and I and between IV and II. The order of stability was found to be IV>II>I at room temperature. Although Huang stated that transition of barbital from form II to I was monotropic,[5] his suggestion is doubtlessly incorrect, because he was based on a wrong definition of monotropy, and presumably because he could not discriminate between the endothermic and exothermic heat effects due to phase transition by the use of the hot-stage method.

(2) Significance of the Initial Dissolution Rate Measurements

By initial dissolution rate measurements, the transition point between polymorphs is determined easily. Because the principle of the method is based on the lag of polymorphic transition, it has many advantages over others in that it is simple, reliable, and widely applicable.

(3) Effect of Barbital Polymorphs on Drug Action

Minor difference in dissolution rate and in solubility of forms I and II at physiological temperature range was noticed by the authors, and all the commercial products examined in this study were found to be mixtures of the two forms. Therefore, there will be no practical influence on the hypnotic or sedative action of barbital, and its polymorphs will not be considered as an important factor in formulating solid dosage forms.

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