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Dissolution Kinetics of Barbital Polymorphs[1,2]

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The dissolution rate constants of barbital polymorphs in water were measured by rotating disk method. The phase transition took place by compression during preparing of the disk. Combining the Levich equation and the concept of consecutive process first proposed by Berthoud, the rate constant of interfacial chemical reaction and that of transport process were obtained separately, and the diffusion coefficient also was calculated. These values were reasonable compared with data found in many references and the theoretical diffusion coefficient calculated according to the Wilke and Othmer equations.

The activation energies of transport process and chemical reactionwere obtained from the temperature dependence. Furthermore, the solubility data obtained by the finite differences diagram method affordedthe heat of transition, transition temperature and entropy change between Phase I and Phase III.

Numerous studies have been made on the dissolution phenomena since Noyes–Nernst theory was established in 1904. Recently, a number of works have been reported on the influence of solid phase characteristics on the dissolution rate of polymorphic organic medicinals from the standpoint that the drug availability varies with the rate of release or dissolution.[4-6]

Wurster and Taylor[6] found that the dissolution behavior of three crystalline forms of prednisolone could be described by consecutive processes involving a reaction at the interface and transport away from the interface.

In the present paper, the dissolution rate constants of barbital polymorphs were obtained by rotating disk method reported in a previous paper[7] to discuss the factors controlling the dissolution process.

Analyzing the rate constants, it was found that the dissolution of phase I does not accord with Levich's equation.[7-9] This means that the phenomenon may not be fully interpreted by the diffusion mechanism only. Here, a consecutive process may give an explanation for the phenomenon to be considered.

General Concept

It is considered that the molecules originated from different crystalline forms exist in the same state in the solution and thus have the same diffusion coefficient. Therefore, if the dissolution of every crystalline form coincide with the diffusion model[10] the same dissolution

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[1] This paper forms Part XXIV of "Studies on Powdered Preparations." Preceding paper, Part XXIII: H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **16**, 2263 (1968).

[2] Presented at the 87th Annual Meeting of Pharmaceutical Society of Japan, Kyoto, April 1967.

[3] Location: *Hongo, Tokyo.*

[4] E. Sheftner and T. Higuchi, *J. Pharm. Sci.*, **52**, 781 (1963).

[5] G. Milosovich, *J. Pharm. Sci.*, **53**, 484 (1964).

[6] D.E. Wurster and P.W. Taylor, *J. Pharm. Sci.*, **54**, 670 (1965).

[7] H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **14**, 329 (1966).

[8] V.G. Levich, "Physicochemical Hydrodynamics," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1962.

[9] V.G. Levich, *Acta Physicochem.*, U.R.S.S., **17**, 257 (1942).

[10] W. Nernst, *Z. Physik. Chem.*, **47**, 52 (1904).

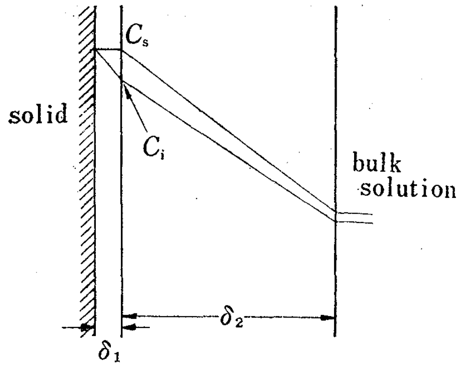

Fig. 1. Schematic Diagram of Concentration Profile on the Dissolution Process of Solid

C_s: saturated concn.
C_i: effective concn.
δ_1: thickness of effective or saturated concn. layer
δ_2: thickness of diffusion layer

rate constant should be given by Levich's equation, because his theory is based on the diffusion mechanism. If the above relationship is not satisfied under certain conditions, the interfacial reaction has to be taken into consideration for the overall dissolution rate studies though the system is included in "one phase system in non-reactive media." Thus, a consideration of consecutive process causing a double layer to exist for the material transport may be helpful in analyzing the dissolution rate.

The concentration profile diagram is shown schematically in Fig. 1 to account for the consecutive process of the dissolution of solid.[6]

Regarding the dissolution as a chemical reaction at the interface, the rate may be expressed by the following equation:

$$\frac{dC_i}{dt}=\frac{S_r}{V}K_r(C_s-C_i) \qquad (1)$$

where S_r is the solid surface area available for attack of water, V is the volume of solution and K_r is the rate constant of chemical reaction per unit area in unit volume. The intrinsic surface area available for attack is not obtained but the apparent surface area can be substituted for the above mentioned area.[11] The rate of transport through the diffusion layer into bulk solution is given by Fick's first law as follows by assuming the concentration gradient to be constant:

$$\frac{dC}{dt}=\frac{S_t}{V}K_t(C_i-C) \qquad (2)$$

where S_t is the surface area of diffusion layer, C is the concentration at the time t and K_t is the rate constant of transport process. Then, if a steady-state concentration for C_i is assumed and S_r is equal to S_t, C_i is represented as

$$C_i=\frac{K_rC_s+K_tC}{K_r+K_t} \qquad (3)$$

Substituting equation (3) into equation (2),

$$\frac{dC}{dt}=\frac{S}{V}\cdot\frac{K_rK_t}{K_r+K_t}(C_s-C) \qquad (4)$$

Then

$$\frac{K_rK_t}{K_r+K_t}=K_{app} \qquad (5)$$

where K_{app} is the apparent rate constant per unit area in unit volume. Equation (4) apparently is in accordance with the Noyes-Nernst equation. This concept concerning an intermediate concentration, C_i, was originally proposed by Berthoud.[12]

Generally, the rate of concentration change at a given point in the solution is expressed by the rate components of isotropic transport at that point. The rate components, produced

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[11] D.P. Gregory and A.C. Riddiford, *J. Chem. Soc.*, **1956**, 3756.
[12] A. Berthoud, *J. Chem. Phys.*, **10**, 633 (1912).
[13] W.G. Cochran, *Proc. Camb. Phil. Soc.*, **30**, 365 (1934).

with the disk which rotates at a constant angular velocity, follow the Navier–Stokes and continuity equation,[8] the solution of which was given by reducing the fluid motion equation to a simple form.[13] Using the solution, the thickness of diffusion layer, δ, was obtained by Levich[8,9] as

$$\delta = 1.612 \times D^{1/3} \times \nu^{1/6} \times \omega^{-1/2} \qquad (6)$$

where D is the diffusion coefficient, ν is the kinematic viscosity and ω is the angular velocity of rotation.

The term "δ" in equation (6) corresponds to the above described δ_2. Therefore, the rate constant of diffusion, K_t, is

$$K_t = 0.620 \times D^{2/3} \times \nu^{-1/6} \times \omega^{1/2} \qquad (7)$$

The rate constant of diffusion and the apparent rate constant can be represented by D/δ_2 and $D/(\delta_1+\delta_2)$ respectively. Considering $\delta_2 \gg \delta_1$, it can be assumed that D/δ_2 is closely equal to $D/(\delta_1+\delta_2)$. Therefore, combining equation (7) and (5)

$$1/K_{app} = 1.612 \times D^{-2/3} \times \nu^{1/6} \times \omega^{-1/2} + 1/K_r \qquad (8)$$

According to equation (8), the plots of $1/K_{app}$ against $\omega^{-1/2}$ shows a straight line at a slope of $1.612 \times D^{-2/3} \times \nu^{1/6}$ with a intercept of $1/K_r$. Under a limit condition of $K_r \rightarrow \infty$, equation (4) and (8) become the Noyes–Nernst equation, Levich equation, respectively. Moreover, in the theoretical assumption of $\omega \rightarrow \infty$, no diffusion layer will apparently exist at the surface of solid and K_{app}approaches K_r.[14] Consequently, K_r and K_t may be obtained at the same time, provided the experimental conditions are kept suitable.

Experimental

Materials—Commercial barbital J.P. was used for preparation of the samples. Four crystalline forms of barbital examined by X-ray pattern method have been reported by T.Y. Huang and B. Cleverley.[15,16] In the present paper, barbital polymorphs I and III were used. Phase I was obtained by evaporating the alcohol solution of barbital to dryness or by compressing phase II which was prepared by slow crystallization from a hot water. Phase III was prepared by cooling a weak alkaline saturated solution in hot water quite rapidly without shaking.

Apparatus and Procedure——Rotating disk method, as described in the previous paper,[7] was employed. Every experiment was carried out under the following conditions: the distilled water of 50 ml at 37, 30, 20 and 10°; the rotating velocity of disk at 300, 200 and 100 rpm; the disk of 3 cm diameter compressed under 1, 2, 3, 4 and 5 ton/cm^2 for 30 minutes. The disks were prepared with the punch surface unlubricated since it was reported that the disk lubricated showed a lag time in dissolution rate.[5,6] The polymorphic forms of the disk were characterized by X-ray diffraction and Infrared (IR) absorption method. For the X-ray diffractometry by Cu-k_α radiation, a special holder, as shown in Fig. 2, was used to fix the disk on the sample stand of a Toshiba X-ray Diffractometer Model ADX-102. IR absorption was measured by a Japan Spectroscopic IR Spectrophotometer Model IR-S using mull samples.

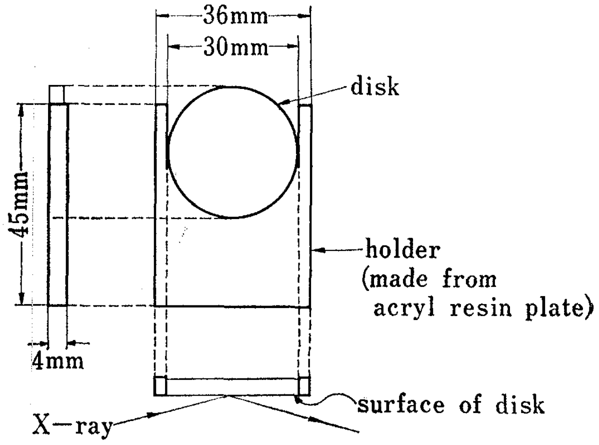

Fig. 2. Holder to Support a Compressed Disk

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[14] Allowing the increment of the angular velocity, the diffusion layer becomes thinner but the length really approaches constant (about 10^{-4} cm).

[15] Tso-Yueh Huang, *Acta Pharm. Intern.*, **11**, 95 (1951).

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

The concentration of barbital was determined by ultraviolet (UV) absorption method using a Hitachi Perkin–Elmer 139 UV–VS spectrophotometer. The optical density was obtained at 212 mμ after appropriate dilution with water and at 238 mμ after dilution with borate buffer of pH 9.6.

Results and Discussions

Barbital has at least three different crystalline forms. The powder or slug sample of respective form was compressed under previously described conditions. The state of a system of one component, that is a pure substance, is completely determined by two variable, the temperature and the pressure. Then, one component can exist in different crystalline forms in the two ways described as "enantiotropy" and "monotropy." The various polymorphic forms differ in density, crystal structure, heat of formation and other physical properties. Accordingly, when the sample was compressed to make a disk or sphere for the dissolution rate studies, the transformation of phase has properly to be taken into account. No publication, however, has been found describing such a change of phase. In this study phase II was gradually transformed to phase I when it was compressed under higher pressure and at more than 3 ton/cm^2 the transformation was complete. Therefore, it was diffi-

Table I. The Influence of Various Compressional Pressures on the Apparent Dissolution Rate Constant and Density of Barbital Polymorphs in Water at 30°, 300 rpm

Pressure (ton/cm^2)	Phase I		Phase III	
	Density (g/cm^3)	$K_{app}\times 10$ (cm/min)	Density (g/cm^3)	$K_{app}\times 10$ (cm/min)
1	1.24	1.70	1.24	1.99
2	1.26	1.65	1.24	2.09
3	1.24	1.68	1.23	2.02
4	1.24	1.67	1.22	1.99
5	1.25	1.68	1.26	2.08

Table II. X–Ray Diffraction Patterns of Barbital Polymorphs using Cu–$K\alpha$ Radiation

Phase I		Phase II		Phase III	
$d^{a)}$	$I^{b)}$	$d^{a)}$	$I^{b)}$	$d^{a)}$	$I^{b)}$
11.19	39	11.19	6	10.91	100
11.05	56	7.13	11	6.46	25
8.75	5	6.41	8	5.79	15
7.83	100	5.75	9	5.50	55
7.25	8	5.30	100	5.34	5
6.81	10	4.92	19	4.98	20
6.51	12	4.67	6	4.79	6
5.51	31	4.25	20	4.15	7
5.40	21	3.86	3	3.67	19
5.30	30	3.67	3	3.63	24
5.09	78	3.56	10	3.18	5
4.50	16	3.05	3	2.82	6
3.73	10	2.97	4	2.79	6
3.53	25	2.87	17	2.76	7
3.36	18	2.66	11	2.52	5
3.08	25				

a) interplanar distance in Å b) relative intensity cult to get a compressed disk of pure phase II. This phenomenon, however, may have been caused by the heat evolved as a result of compression. In the previous paper,[7] it was reported that there was no remarkable effect of the compressional pressure on the density of disk and on the dissolution rate constant of sulfadiazine. In the cases of phase I and III of barbital in this study also a similar result was given as shown in Table I. Therefore, the dissolution rate is considered to depend on the apparent geometrical surface area of disk. The infrared mull spectra of three forms are presented in Fig. 3. Table II gives the X-ray diffraction data. Either of these methods was useful to characterize the respective forms. Practically, when tablets were compressed for the pharmaceutical purpose, some possibility of transformation or phase transition should be considered in this regard.

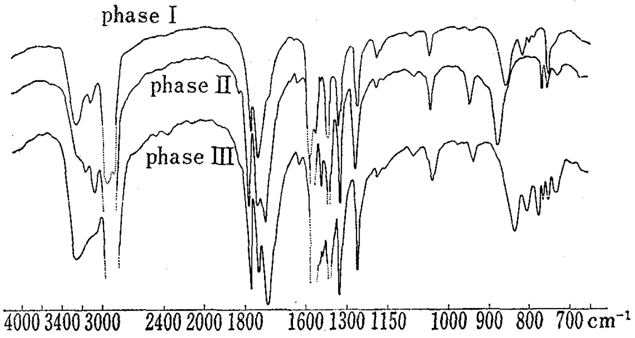

Fig. 3. Infrared Absorption Spectra of Barbital Polymorphs in Nujol

Dependence of Rate Constant on Rotating Velocity and Temperature

In previous papers,[7,17] it was found that the slope of the plot of log (C_2–C_1) against t_1 corresponded to the dissolution rate constant, where C_1 is the concentration at time t_1 and C_2 is the concentration after a given time Δt, *i.e*, ($t_1+\Delta t$). The slope did not change with the progress of dissolution of sulfadiazine and benzoic acid derivatives in water. However, in the case of phase I of barbital in this study, the slope changed slightly with the time, as shown in Fig. 4. A possible explanation for this might be as follows. When a steady-state concentration for C_i is assumed, the dissolution rate follows equation (4). If the dissolution process gets away from such a steady-state after some period because the rate of interfacial reaction gets faster than the rate of diffusion, C_i approaches C_s and the saturated condition is finally satisfied in the layer. After then, the dissolution rate follows the typical Noyes–Nernst equation as

$$\frac{dC}{dt}=K_t(C_s-C) \qquad (9)$$

Therefore, K_{app} means $K_r \cdot K_t/(K_r+K_t)$ before such a changing point and K_t after that point. Accordingly, if a flexional point was found on the plot of log (C_2—C_1) against t_1, it might correspond to a time to reach saturation in the layer. The apperance of such a fixional point, however, might be due to many other factors such as crystallization of stable phase on the surface and slight change of apparent surface area. The circumstances were so much complicated that it

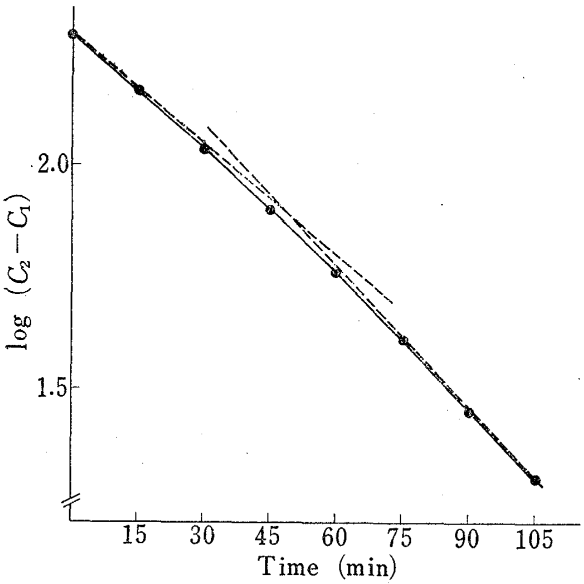

Fig. 4. Typical Example of the Relationship between log (C_2-C_1) and Time t_1 on the Dissolution of Barbital Phase I in Water

Temp.: 30°
rotating velocity: 200 rpm
C_1: concentration at time t_1 (mg/100 ml)
C_2: concentration at time t_1+15 min

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[17] H. Nogami, T. Nagai, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **14**, 351 (1966).

was difficult to examine the relationship between the dissolution rate constant and the proceeding of dissolution. Consequently, in the case of phase I the initial dissolution rate was considered to be more reasonable to discuss how the rate of interfacial reaction had influence on the overall dissolution rate. The dependence of K_{app} on rotating velocity of disk at various temperature was shown in Table III. As the pure disk of phase II was not obtained, this phase was not employed. The plots of K_{app} against angular velocity gave a straight line as shown in Fig. 5.

Table III. Apparent Dissolution Rate Constants, K_{app}, of Phase I and Phase III ($K_{app} \times 10$ (cm/min))

	Temp. (°C)	Rotating velocity of disk (rpm)			
		600	300	200	100
Phase I	37	4.00	2.55	2.07	1.32
	30	—	1.68	1.41	1.08
	20	—	1.17	1.00	0.75
	10	—	0.95	0.81	0.62
Phase III	37	3.34	2.31	1.79	1.23
	30	—	2.02	1.67	1.18
	20	—	1.52	1.27	0.89
	10	—	1.27	1.05	0.75

The extrapolation of slope of phase III passed through the origin, being in accordance with Levich's equation (7), but that of phase I did not. This fact indicates that the dissolution behavior of phase I into water can not be explained by diffusion model, becuase diffusion coefficient, D, should be identical for the different crystalline forms of barbital at the same temperature. The dissolution of phase III coincided with the transport-controlled one. Then, plotting $1/K_{app}$ against $\omega^{-1/2}$ by equation (8), a linear relationship were obtained as shown in Fig. 6.

Accordingly, it was proved that the diffusion coefficient was the same in either case because two straight line in Fig. 6 had the same slope. The diffusion coefficient and the rate constant of interfacial chemical reaction, K_r, were calculated by the method of least squares.

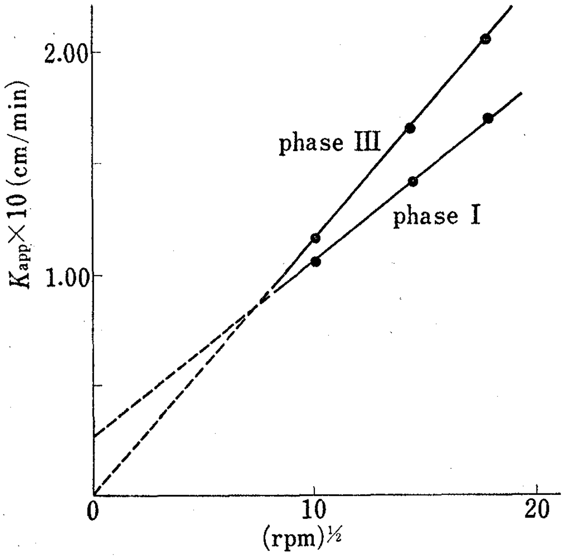

Fig. 5. Dependence of Apparent Dissolution Rate Constant, K_{app}, of Barbital Polymorphs in Water on the Rotating Velocity of Disk at 30°

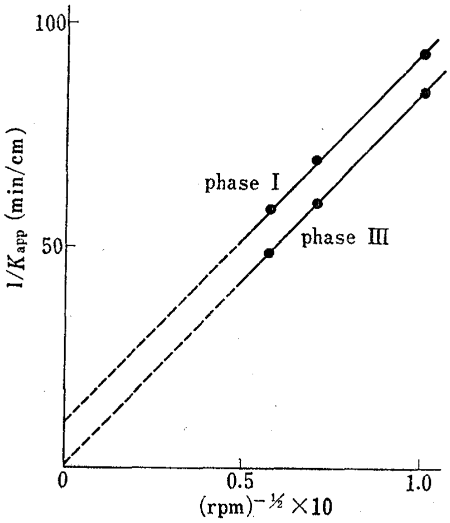

Fig. 6. Plots of the Reciprocal of Apparent Dissolution Rate Constant, $1/K_{app}$, *vs.* That of Square Root of Rotating Velocity at 30°

The distinct difference between the rate constant of interfacial chemical reaction of phase I and that of phase III was recognized at various temperatures. The transport rate constant of each form, K_t, was calculated by using equation (5) and the respective values were almost invariable. The results showed the same tendency at 10, 20° as shown in Table IV.

TABLE IV. Rate Constants of Interfacial Chemical Reaction, K_r, and of Transport Process, K_t, Diffusion Coefficients, D, and Diffusion Layer Thicknesses, δ, of Phase I and Phase III at Various Temperatures and Rotating Velocities in Water

Species and temp. (°C)		Rotating velocity (rpm)	$K_r \times 10$ (cm/min)	$K_t \times 10$ (cm/min)	$D \times 10^6$ (cm²/sec)	$\delta \times 10^3$ (cm)
Phase I	30	300	8.62	2.09	10.4	2.99
		200	8.62	1.69	10.4	3.69
		100	8.62	1.23	10.4	5.09
	20	300	4.88	1.54	6.35	2.45
		200	4.88	1.26	6.35	3.00
		100	4.88	0.87	6.35	4.26
	10	300	3.12	1.36	5.32	2.33
		200	3.12	1.09	5.32	2.91
		100	3.12	0.78	5.32	4.10
Phase III	30	300	83.3	2.07	9.48	2.75
		200	83.3	1.70	9.48	3.36
		100	83.3	1.20	9.48	4.75
	20	300	37.0	1.59	6.46	2.45
		200	37.0	1.32	6.46	2.95
		100	37.0	0.91	6.46	4.28
	10	300	18.2	1.37	5.49	2.41
		200	18.2	1.11	5.49	2.97
		100	18.2	0.78	5.49	4.20

The values of the diffusion coefficient and of diffusion layer thickness seem to be reasonable compared with data which have been reported for the transport–controlled dissolution. Simultaneously, the diffusion coefficient at various temperatures were obtained theoretically according to equation of Wilke,[18] Othmer[19] using the factors of molecular volume, viscosity and temperature. These results are satisfactorily close to the observed values as shown in Table V. Diffusion coefficients at 37° were not obtained because the slopes of plots according to equation (8) bended slowly with the decrease of the square root of angular velocity.[20] Accordingly, K_r and K_t at 37° were not calculated. The inermediate concentration of the boundary layer, C_i, was calculated by equation (3) and shown in Table VI.

TABLE V. Comparison between the Observed Diffusion Coefficients and Theoretical Values

Temp. (°C)	Phase I	Phase III	Wilke method	Othmer method
	$D \times 10^6$ (cm²/sec)			
30	10.4	9.48	7.56	7.59
20	6.35	6.46	5.83	5.90
10	5.32	5.49	4.33	4.42

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[18] C.R. Wilke, *Chem. Eng. Progress*, **45**, 218 (1949).
[19] D.F. Othmer and M.S. Thakar, *Ind. Eng. Chem.*, **45**, 589 (1953).
[20] This effect will be reported in detail in a future publication.

Table VI. Calculated Concentration, C_i, of the Interface between δ_1 and δ_2 at 30° (mg/100 ml)

	Rotating velocity of disk (rpm)		
	300	200	100
Phase I	656	681	713
Phase III	756	759	763

The boundary of phase I is not saturated, but reaches about 90% saturation. Since the molecule exists in such a relatively high concentration at the interface, the concentration gradient gives a driving force controlling the overall dissolution rate. Much attention has been paid to transport process from solid surface in "one phase in non-reactive media" dissolution. However, besides in the reactive media system, the consideration of the double barrier will give a proper explanation for the divergence of dissolution rate constant.

Temperature dependence of transport rate constant and the rate constant of interfacial chemical reaction are shown in Table IV. The activation energies, E_a, of each process concerning two phases were calculated by the Arrhenius equation, as shown in Table VII. These results seem reasonable when the interfacial chemical reaction and the transport process are taken into consideration for the dissolution phenomena and suggest that phase III exists in a lower energy state at experimental temperatures. Moreover, K_r and E_a of phase III are larger than those of phase I. This fact might be due to the disagreement of frequency factor according to the Arrhenius equation influenced by compensation effect.

Table VII. Activation Energy, E_a, of Interfacial Chemical Reaction and of Transport Process

	Interfacial chemical reaction E_a (cal/mole)	Transport process E_a (cal/mole)
Phase I	9540	4390
Phase III	13270	4580

The Thermodynamic Relationships of The Polymorphic Forms obtained from Rate Studies

As shown in Table VIII, the saturated concentration of the polymorphic forms of barbital were determined at various temperatures by the finite differences diagram method.[7]

Table VIII. Saturated Concentration, C_o, of the Respective Phase according to Finite Differences Diagram Method

Temp. (°C)	Phase I C_o (mg/100 ml)	Rhase III C_o (mg/100 ml)
37	972	1020
30	815	775
20	628	523
10	472	350

The van't Hoff plots for these results yielded a linear relationship, respectively, and the heat of solution of both forms were calculated as 3800 cal/mole for phase I and 6090 cal/mole for phase III. The processes were endothermic reaction. The thermodynamic consideration of polymorphic forms was discussed by W.I. Higuchi, *et al.*[21] If the solubility ratio between

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21) W.I. Higuchi, P.K. Lau, T. Higuchi, and J.W. Shell, *J. Pharm. Sci.*, **52**, 150 (1963).

two forms is in accordance with Henry's law, it can be said that there is no interaction between solute and solvent. Therefore, the relation of the solubility ratio to the enthalpy of phase transition was given by the following equation:

$$\frac{\partial \ln (S_{\text{I}}/S_{\text{III}})}{\partial T} = \frac{\Delta H_{\text{I, III}}}{RT^2} \tag{10}$$

The left hand of equation (10) should be independent of the solvent. At the transition temperature, T_t, the solubilities of two phases will be equal, *i.e.*, $S_{\text{I}}=S_{\text{III}}$. Finally, at $T=T_t$

$$\Delta H_{\text{I, III}} = T_t \cdot \Delta S_{\text{I, III}} \tag{11}$$

The plot of the logarithm of $S_{\text{I}}/S_{\text{III}}$ against $1/T$ gave a straight line by integral formula of equation (10), as shown in Fig. 7. The heat of transition was calculated from this slope. The transition temperature was also obtained from the intersection between this plot and the line of $S_{\text{I}}/S_{\text{III}}=1$. The results are shown in Table IX.

Table IX. Thermodynamic Values for the Phase Transition

$\Delta H_{\text{I, III}}$ (cal/mole)	T_t (C°)	$\Delta S_{\text{I, III}}$ (e.u.)
−2030	34	−6.6

The solubility data were inferred from these obtained by rate studies but these thermodynamic values were reasonable compared with data found in other references.[5,21] It can not be proved whether the relation between phase I and phase III is monotropy or enanthiotropy from only these results obtained.

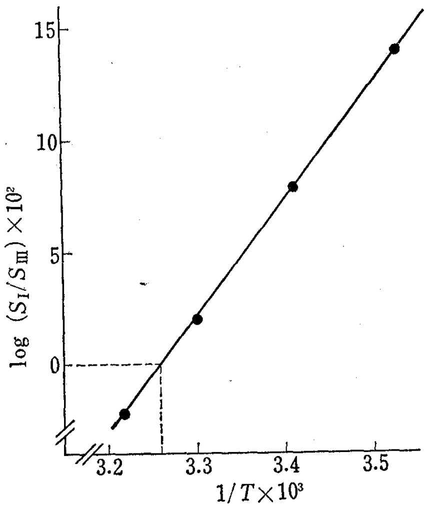

Fig. 7. Plot of Logarithm of Solubility Ratios against Reciprocal of Absolute Temperature

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