[Chem. Pharm. Bull.
18(11)2290—2296(1970)]

UDC 547.745.03 : 615.31.011.3.073

Dissolution Kinetics of Polyvinylpyrrolidone of Various Molecular Weights[1,2]

Hisashi Nogami, Tsuneji Nagai,[3a] and Akira Kondo[3b]

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received June 4, 1970)

Dissolution studies of fractionated polyvinylpyrrolidone (PVP) in acetone–water (4:1) were carried out according to the rotating disk method.

It was considered from the anomalous viscosity that PVP of low molecular weight (below 10000) behaved as an polyelectrolyte.

Three stages of dissolution were observed with the lapse of time, *i.e.*, the initial, the main and the final ones, as described in a previous paper. The initial stage was shortened with the decrease in molecular weight.

Analyzing the dissolution rate of PVP of the main stage, the dissolution rate constant, K_T, was expressed as a function of the molecular weight, M, and the absolute temperature, T, as follows:

$$K_T = a\cdot\exp[[-\ln\{a/(K_T)_X\}]\cdot M/M_X]\cdot\exp\{-b(1-M/M_X)/RT\}$$

where R is the gas constant; $(K_T)_X$ and M_X are the converging dissolution rate constant and the converging molecular weight, respectively, of the plots of log K_T at various temperatures against M; a and b are theoretically the frequency factor and the activation energy, respectively, at $M=0$.

The decrease in viscosity of acetone–water (4:1) with addition of PVP was considered due to the destruction of structure and it was concluded that the destruction of acetone–water structure by the dissolved molecule might be an important factor affecting the dissolution rate constant, K_T.

In a previous paper,[4] the dissolution of polyvinylpyrrolidone (PVP) was investigated in acetone–water (4:1) system by the rotating disk method to make an approach to understanding of general dissolution behaviors of synthetic polymers available in pharmaceutical preparations, and there were found three stages of dissolution with the lapse of time, *i.e.*, the initial, the main and the final ones, only the main one being explained according to Noyes–Nernst equation.

The present paper is concerned with the findings obtained by the dissolution studies of fractionated PVP regarding the relationships among the dissolution rate constant, the molecular weight, the activation energy of dissolution and the viscosity of PVP in solution.

Experimental

Materials——Polyvinylpyrrolidone (PVP) marketed as "PVP-K30" by Gokyo Sangyo Co. Ltd. was fractionated into ten by the gel filtration method using Sephadex G-100, and then every fraction in a given volume of solution was lyophilized. The weight distribution with respect to the fraction number is shown in Fig. 1. The mean molecular weight of every fraction was estimated from the viscosity according to the equation:[5] $[\eta]=1.4\times10^{-4}\times M^{0.7}$ where $[\eta]$ and M are the intrinsic viscosity in water at 25° and the mo-

---

[1] This paper forms Part XIV of "Physico-chemical Approach to Biopharmaceutical Phenomena." Preceding paper, Part XIII: H. Nogami, T. Nagai, and T. Sonobe, *Chem. Pharm. Bull.* (Tokyo), **18**, **2101** (1970).

[2] A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April **1969**.

[3] Location: *Hongo, Tokyo*; *a*) To whom communications should be directed; *b*) Fellow from *Pharmaceutical Research Laboratory, Kyowa Hakko Co. Ltd., Fuji Plant, Nagaizumi-machi, Shunto-gun, Shizuoka.*

[4] H. Nogami, T. Nagai, and A. Kondo, *Chem. Pharm. Bull.* (Tokyo), **18**, **1185** (1969).

[5] W. Scholton, *Makromol. Chem.*, **7**, 209 (1952).

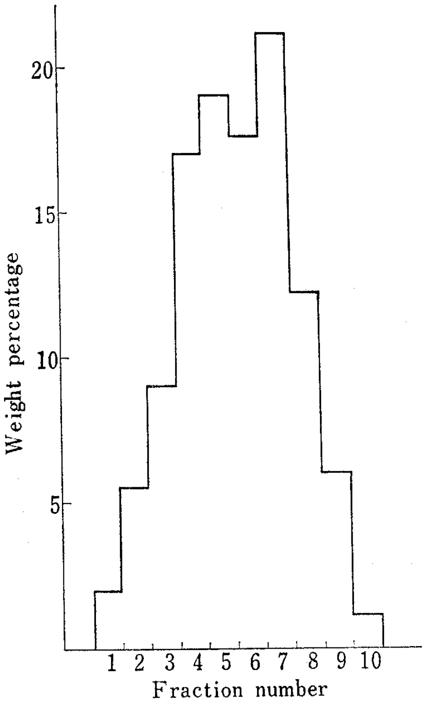

Fig. 1. Weight Distribution with Respect to the Fraction Number of PVP–K30 without Refractionation

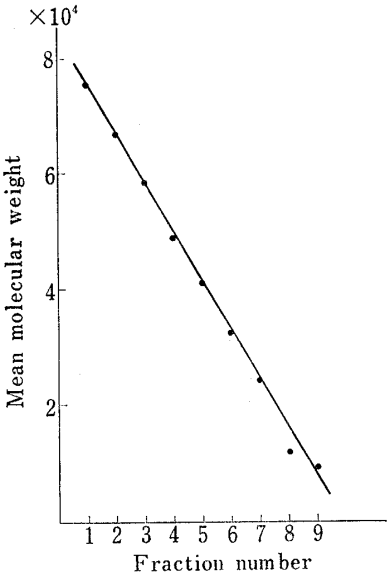

Fig. 2. Mean Molecular Weight with Respect to the Fraction Number of PVP–K30 without Refractionation

Table I. Mean Molecular Weight, M, and Mean Molecular Absorbance, UV λ^{H_2O} mμ (ε), of the Samples of PVP

Sample	M	193(ε)	210(ε)
F-1	9.8×10^4	9.56×10^{-8}	5.53×10^{-7}
F-3	5.8×10^4	8.77×10^{-8}	2.64×10^{-7}
F-5	3.8×10^4	7.98×10^{-8}	1.59×10^{-7}
F-7	2.4×10^4	6.32×10^{-8}	8.04×10^{-6}

lecular weight, respectively. The plot of M against the fraction number is shown in Fig. 2. Fig. 1 and 2 show the fractionation was done well. The above fractions No. 1, 3, 5 and 7 were refractionated and No. 1 was done once more to use as the samples, the respective molecular weights being shown in Table I.

Apparatus and Procedure for Dissolution Studies of PVP in Actone-Water (4:1)——These were the same as in the previous paper.[4)]

Quantitative Determination of the Dissolved Amount of PVP——This was done according to ultraviolet absorption method in the same way as in the previous paper,[4)] using a Hitachi 124 spectrophotometer. The optical density was recognized to follow Lambert-Beer rule in the measuring conditions. The molecular absorbances of the samples at 193 mμ and 210 mμ are shown in Table I.

Measurement of Viscosity——This was done by a Ubellode viscometer.

Result and Discussion

Anomalous Viscosity of Low Molecular Weight Fractions of Polyvinylpyrrolidone (PVP) in Water

Upon estimating the molecular weights shown in Table I from the viscosity, there was found an anomalous increase on the plots of η_{sp}/c against c in low concentration of low molecular fractions No. 8 and 9, as shown in Fig. 3, where η_{sp} is the specific viscosity and c the

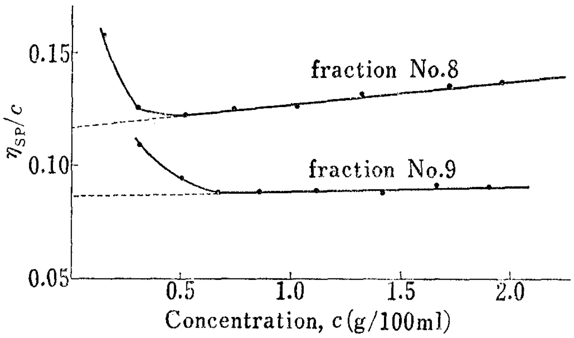

Fig. 3. Plots of η_{sp}/c against c of Fractions No. 8 and 9 of PVP–K30 without Refractionation, where η_{sp} the Specific Viscosity and c the Concentration in Water at 25°

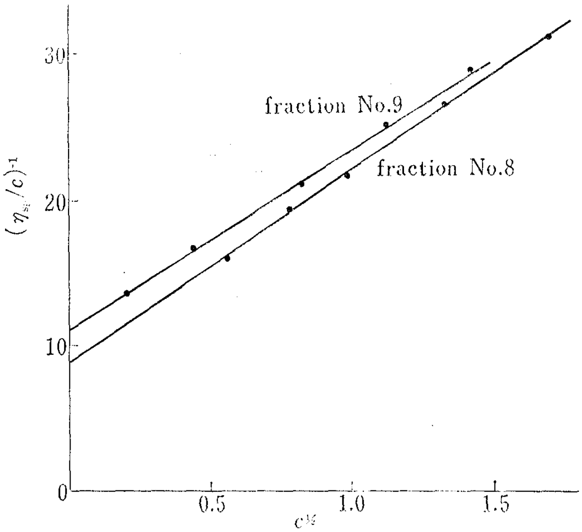

Fig. 4. Plots according to Fuoss' Equation of Fractions No. 8 and 9 of PVP–K30 without Refractionation, where the η_{sp} Specific Vicosity and c the Concentration in Water at 25°

concentration of PVP in water at 25°. Then, plotting $(\eta_{sp}/c)^{-1}$ against $c^{1/2}$ according to Fuoss' experimental equation[6]: $\eta_{sp}/c=A/(1+Bc^{1/2})$ where A and B are constant, which is concerned with the viscosity of dilute solution of polyelectrolytes, the straight lines were obtained for fractions No. 8 and 9, as shown in Fig. 4. Therefore, it is considered that PVP of low molecular weight (below 10000) behaves as a polyelectrolyte. The dissolution rate of polyelectrolyte should be analyzed on the consideration of factors affecting electric charges of the solute molecules, such as pH and ionic strength of solution.[7] Aside from these factors, the fractions of higher molecular weight than the above two were used to the dissolution studies in the present paper.

Dissolution Rates of the Respective Fractions of PVP

Fig. 5 shows the dissolution curves of the respective fractions of PVP, which were formed of three stages, *i.e.*, the initial, the main and the final ones, as was discussed in the previous paper.[4] It was shown that the initial stage was shortened with the decrease in molecular weight. This result seemed reasonable, because the initial stage was considered to be concerned with the swelling process of PVP inducing the steady dissolution,[4] which usually is not observed in the cases of low molecular weight compounds.[8,9]

Following the method described in previous papers,[4,8] the main stage of the dissolution curve of PVP in acetone–water (4:1) was analyzed according to Noyes–Nernst equation (1).

$$\frac{dc}{dt}=K(C_0-C)=\frac{S}{V}K_\mathrm{T}(C_0-C)=\frac{S}{V}\cdot\frac{D}{\delta}(C_0-C) \tag{1}$$

where C is the concentration at the time t, C_0 the saturated concentration, k the rate constant, K_T the dissolution rate constant, D the diffusion constant, and δ the diffusion layer thickness.

From the integrated form of equation (1), the following equations are obtained.

$$C_2=\exp(-k\cdot\Delta \mathrm{t})\cdot \mathrm{C}_1+\{1-\exp(-k\cdot\Delta t)\}C_0 \tag{2}$$

---

[6] R.M. Fuoss and U.P. Strauss, *Annals N.Y. Acad. Sci.*, **51**, 836 (1949); *idem*, *J. Polymer Sci.*, 3, 246 (1948).
[7] M. Hayashi, T. Nagai, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **18**, 2350 (1970).
[8] H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **14**, 329 (1966).
[9] *a*) H. Nogami, T. Nagai, E. Fukuoka, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 23 (1969); *b*) H. Nogami, T. Nagai, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 499 (1969).

$$\ln(C_2-C_1)=-kt_1+\ln[\{1-\exp(-k\cdot\Delta t)\}\cdot C_0] \tag{3}$$

where C_1 is the concentration at the time t_1 and C_2 the concentration after a given time Δt, *i.e.*, at the time $(t_1+\Delta t)$.

In the same way as in previous papers,[4,8] the saturated concentration, C_0, and the rate constant, k, of the main stage of dissolution were obtained according to equations (2) and (3), respectively. Then, the dissolution rate constant, K_T, and the activation energy of dissolution, ΔE, were obtained from k and from the temperature dependence of K_T, respectively, as shown in Table II.

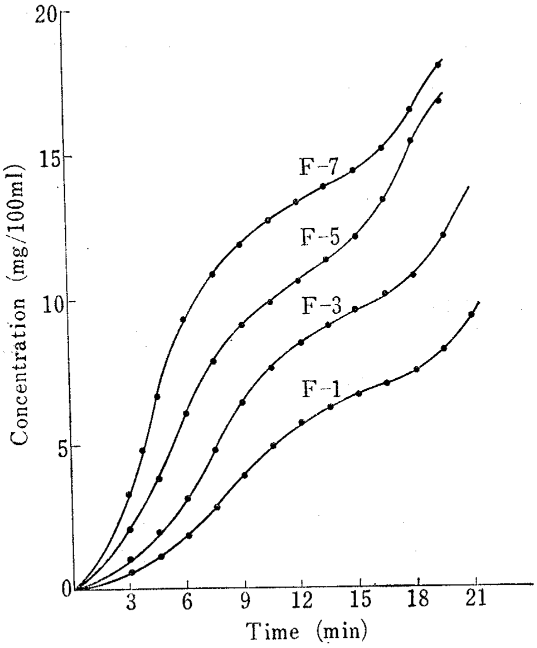

Fig. 5. Dissolusion Curves of Different Samples of PVP in 200 ml of Acetone–Water (4:1) at 20° from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

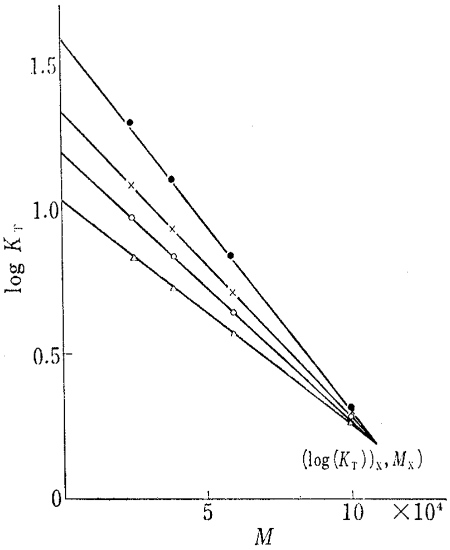

Fig. 6. Relationship between Dissolution Rate Constant, K_T, and Molecular Weight, M, of PVP

—●—: 25° —×—: 15°
—○—: 20° —△—: 10°

Table II. Rate Constant, k, Dissolution Rate Constant, K_T, Saturated Concentration, C_0, and Activation Energy of Dissolution, ΔE, of Different Samples of PVP in 200 ml of Acetone–Water (4:1) from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

Sample	Temperature (°C)	$k\times10^2$ (min^{-1})	K_T (cm/min)	C_0 (mg/100 ml)	ΔE (kcal/mole)
F-1	10	2.61	1.66	6.8	0.61
	15	2.87	1.83	6.8	
	25	3.26	2.01	7.8	
F-3	10	5.98	3.81	8.9	2.28
	15	6.99	4.45	8.9	
	25	10.53	6.76	9.8	
F-5	10	7.42	5.36	9.8	3.05
	15	10.61	6.76	10.8	
	25	19.11	12.17	11.9	
F-7	10	10.77	6.86	12.5	3.66
	15	14.49	9.23	13.6	
	25	31.19	19.87	14.3	

Relationships among Dissolution Rate Constant, Molecular Weight, Activation Energy of Dissolution and Viscosity of PVP in Solution

General Equation to Express the Dissolution Rate Constant, K_T, as a Function of the Molecular Weight, M, and the Absolute Temperature, T——Plotting the data of K_T against M, a linear relationship was found between log K_T and M at a given temperature, as shown in Fig. 6, to which the following equation may be given.

$$\ln K_T = \ln m - nM$$

$$K_T = m\cdot\exp(-nM) \qquad (4)$$

where m and n are the parameters. The straight lines at the respective temperatures in Fig. 6 approached a certain point, *i.e.*, log $K_T=0.2$ around $M=1.1\times10^5$. In this paper, the values of K_T and M at this convergence will be represented as $(K_T)_X$ and M_X, respectively.

Next, plotting the activation energy of dissolution, $\varDelta E$, against M, the value of M at $\varDelta E=0$ also was around $M_X=1.1\times10^5$, as shown in Fig. 7, and the straight line may be expressed by

$$\varDelta E = b(1-M/M_X) \qquad (5)$$

where b is the parameter, actually being 4.5 kcal/mole.

It is expressed theoretically from equations (4) and (5) that $K_T=m$ and $\varDelta E=b$ at $M=0$. Thus, the following expression is given by Arrhenius' equation.

$$m = a\cdot\exp(-b/RT) \qquad (6)$$

where a is the parameter, R the gas constant, and T the absolute temperature.

The slope of the straight line in Fig. 6 corresponds to the parameter, n. Accordingly,

$$n = \{\ln m - \ln(K_T)_X\}/M_X \qquad (7)$$

Substituting equation (6), equation (7) is rewritten as

$$n = [\ln\{a/(K_T)_X\} - b/RT]/M_X \qquad (8)$$

Combining equations (4), (6) and (8), finally the dissolution rate constant, K_T is expressed as

$$K_T = a\cdot\exp[[-\ln\{a/(K_T)_X\}]\cdot M/M_X]\cdot\exp\{-b(1-M/M_X)/RT\} \qquad (9)$$

The terms $a\cdot\exp[[-\ln\{a/(K_T)_X\}]\cdot M/M_X]$ and $-b(1-M/M_X)$ correspond to the frequency factor and the activation energy, respectively, in Arrhenius' equation, both being influenced by the molecular weight of PVP. Therefore, as expressed in equation (6), the parameters a and b mean theoretically the frequency factor and the activation energy, respectively, at $M=0$.

Discussion of the Dissolution Rate Constant, K_T, in Relation to the Viscosity of PVP Solution——It is expressed that $K_T=D/\delta$, as shown in equation (1). Both D and δ are not independent of the viscosity of solution. Therefore, it is significant to discuss the dissolution rate constant, K_T, on the basis of the viscosity of PVP in the same solvent as in dissolution studies, *i.e.*, in acetone–water (4:1).

The relative viscosity, η_r, of PVP F-5 as an example was plotted against the concentration, as shown in Fig. 8, decreasing with the increase in concentration.

From the result in Fig. 9 showing the structural viscosity of acetone–water system, it was considered that a structure was formed in acetone–water (4:1) which might be destructed with the addition of PVP, as was demonstrated by the resultant decrease in η_r shown in

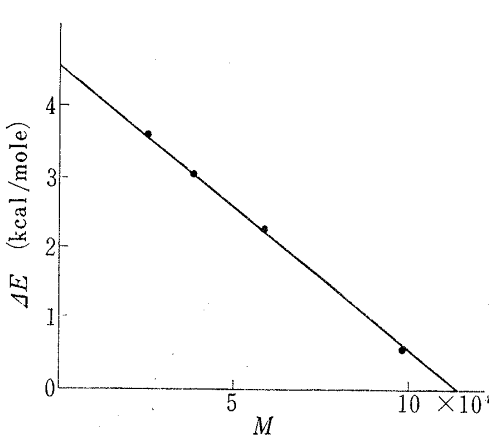

Fig. 7. Relationship between Activation Energy of Dissolution, ΔE, and Molecular Weight, M, of PVP

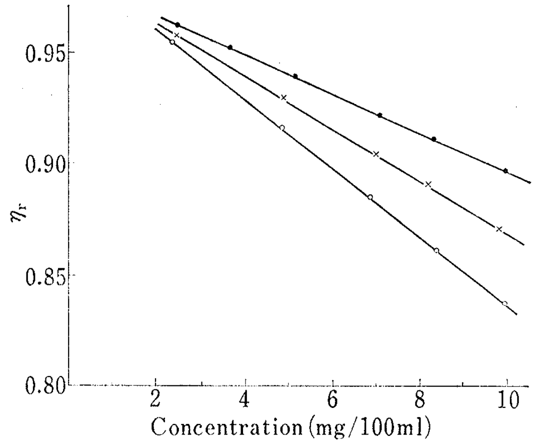

Fig. 8. Relative Viscosity, η_r of PVP F-5 plotted against Concentration in Acetone–Water (4:1)

—●—: 25°, —×—: 15°, —○—: 10°

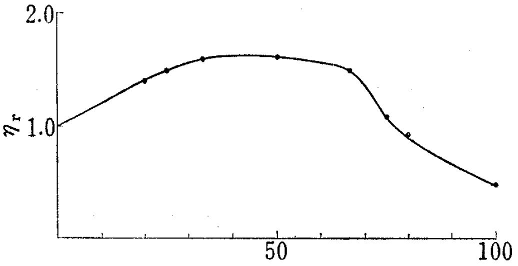

Fig. 9 Relative Viscosity, η_r, of 10 mg/100 ml of PVP F-3 in Acetone–Water System at 25°

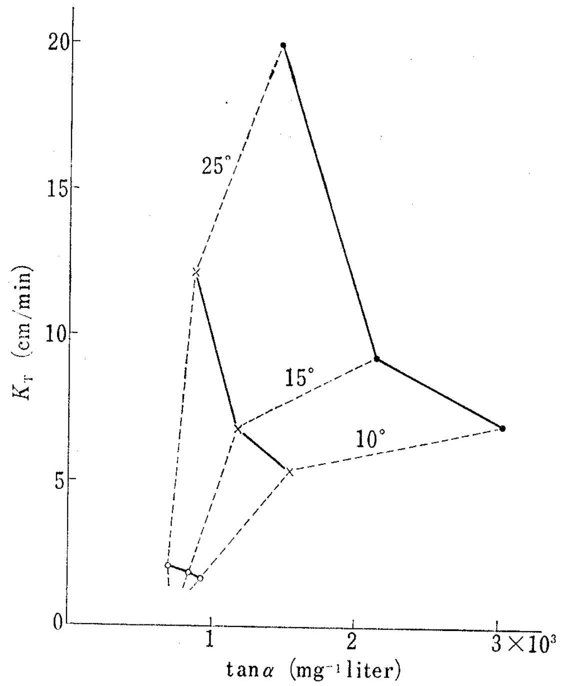

Fig. 10. Relationship between Dissolution Rate Constant, K_T, and Viscosity Depressing Activity in Acetone–Water (4:1), tan α, of Different Samples of PVP at Different Temperatures

—○—: F-1, —×—: F-5 —●—: F-7,

Fig. 8.[10] Therefore, the slope, tanα, of the plot of η_r against the concentration of PVP in Fig. 8 seemed to correspond to the viscosity depressing activity or the destructing activity, which decreased with the increase in temperature. From the result that the acetone–water structure might be destructed with the addition of PVP, the size of PVP molecule in solution seemed to be smaller than that of the acetone–water structure, and the decrease in the destructing activity with the increases in molecular weight of PVP and in temperature was considered to have relation to the changes in hydrophobicity of PVP and in interaction of acetone–water.[11]

Fig. 10 shows the relationship between the dissolution rate constant, K_T, and the viscosity depressing activity, tanα, *i.e.*, the slope of the plot in Fig. 8. The dependence of K_T on tanα decreased with the increase in molecular weight of PVP. This result was considered

---

10) J.A. Rupley, *J. Phys. Chem.*, **68**, 2002 (1964).
11) H. Nogami, T. Nagai, and H. Umeyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 328 (1970).

to have relation to the results that log K_T approached a certain point ($\log(K_T)_X$, M_X) in Fig. 6 and that $\varDelta E$ became zero at $M=M_X$ in Fig. 7, upon the increase in molecular weight of PVP.

Actually, plotting the molecular weight, M, against tanα, the plots seemed to approach a certain molecular weight, as shown in Fig. 11.

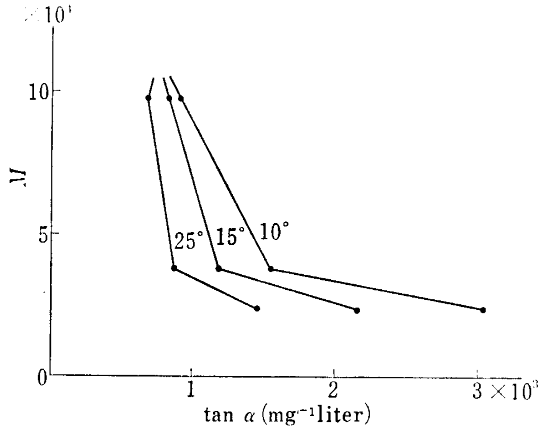

Fig. 11. Relationship between Molecular Weight, M, and Viscosity Depressing Activity in Acetone–Water (4:1), tan α, of PVP at Differene Temperatures

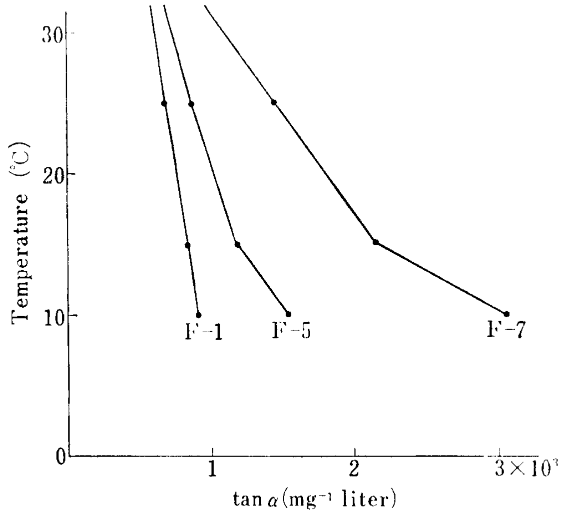

Fig. 12. Relationships between Temperature and Viscosity Depressing Activity in Acetone–Water (4:1), tan α, of Different Samples of PVP

In a similar way, the plots of the temperature against tanα also seemed to approach a certain temperature, as shown in Fig. 12.

It was concluded that the destruction of acetone–water structure by the dissolved PVP molecule might be an important factor affecting the dissolution rate constant, K_T. However, it may be difficult for the present to give a quantitative relationship between K_T and tanα, because the latter was observed in the condition independent of dissolution rate studies.