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Dehydration of Cephalexin Hydrates[1]

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The dehydration processes of cephalexin phases IV, II, III-1/2 H_2O, V-H_2O and the noncrystalline solid dihydrate (NC-2H_2O) were studied by means of various thermal kinetic analyses using differential thermal analysis (DTA) and differential scanning calorimetry (DSC) instruments. The activation energy and mechanism of dehydration were determined by using approximate thermal kinetic analyses according to Kissinger's and Barton's methods, as well as the nonisothermal kinetic method of Criado and the isothermal DSC method.

The dehydrations of phase IV and NC-2H_2O were first-order reactions as determined by all methods. The dehydration of phase III-1/2 H_2O followed first-order kinetics under nonisothermal conditions and two-dimensional diffusion kinetics under isothermal conditions. The dehydration of phase V-H_2O followed three-dimensional diffusion kinetics under nonisothermal conditions, and 1/2 order kinetics under isothermal conditions. The dehydration mechanisms of phases III-1/2 H_2O and V-H_2O, obtained by allowing organic desolvates to absorb water, depended on the heating conditions.

Phase transition induced by the dehydration was measured by X-ray diffractometry. Phases IV, III-1/2 H_2O and V-H_2O were transformed into phases I, III and V, respectively, by dehydration at 130°C. Phase II was transformed into phase IV after heating at 40°C. NC-2H_2O remained in an amorphous state at 130°C.

Keywords——cephalexin; hydrate; dehydration mechanism; activation energy; latent heat; thermal kinetic analysis

Introduction

Recently, solvates and hydrates of organic solid drugs have attracted the interest of many investigators, but there are few reports on the use of thermal kinetic analyses to investigate solvates or hydrates.[2] Kissinger[3] reported an approximate kinetic method using a differential thermal analysis (DTA) instrument, while Criado *et al.*[4] reported a nonisothermal kinetic method using a thermogravimetry (TG) instrument. Shirotani and Sekiguchi[5] developed an isothermal kinetic method using a TG instrument and used it to study cortisone acetate organic solvates.

In previous papers,[6-8] the authors reported on the different crystalline phases of cephalexin and their solubilities. In the present paper, the dehydration behavior of cephalexin hydrates was studied by various thermal kinetic methods. The nature of the dehydration mechanisms under isothermal and nonisothermal conditions, the dehydration point (D_p), the latent heat and the activation energy were determined by using DTA and differential scanning calorimetry (DSC) instruments.

Experimental

Materials——Cephalexin hydrates used in the present study were prepared as follows.

(1) **Phase IV (Monohydrate)**——Phase IV was obtained by recrystallization as described in the previous paper.[6]

(2) **Phase II (Dihydrate)**——Phase II was obtained by storage of phase IV under 95% relative humidity (RH) in a desiccator containing K_2SO_4 saturated solution at 35°C for 2 weeks.

(3) **Phase III-1/2 Hydrate**——Phase III-1/2 hydrate (III-1/2 H_2O) was obtained from phase III (demethanolate) by storage under 43% RH at 35°C for 2 weeks, as described in the previous paper.[6]

(4) **Phase V Hydrate**——Phase V hydrate (V–H_2O) and phase V–xH_2O samples were obtained by storage of phase V (deacetonitrilate) under 11% and 43% RH at 35°C for 2 weeks, as described in the previous paper.[6]

(5) **The Noncrystalline Solid Dihydrate (NC-$2H_2O$)**——Phase IV cephalexin (1.5 g) was dissolved in 100 ml of distilled water. The undissolved drug was filtered off, then 0.5 g of charcoal powder was added. The mixture was stirred for about 30 min, then filtered, and the saturated solution was lyophilized. The resulting product, NC, was dried in a P_2O_5 desiccator under a vacuum overnight at room temperature. NC–$2H_2O$ was obtained by storage of NC under 43% RH at 35°C for 2 weeks.

X-Ray Diffraction——The X-ray diffraction patterns were obtained with an X-ray diffractometer (Type JDX-7E; Nihon Denshi Co., Ltd.). The measurement conditions were as follows: target Cu (K_α), filter Ni, voltage 20 kV, current 20 mA.

Thermal Measurement——The DTA curves were measured with a DTA instrument (DT-20B; Shimadzu Seisakusho Co., Ltd.). The DSC curves were measured with a DSC instrument (SC-20B; Shimadzu Seisakusho Co., Ltd.). The measurement conditions were as follows: sample weight, about 3 mg (DTA) or about 5 mg (DSC); sample cell, an aluminium crimp cell having a cell cover with five holes for stainless steel hypodermic needles (JIS cord H) for gas flow; N_2 gas flow, 30 ml/min.

Results and Discussion

Dehydration Point and DTA Curve

Fig. 1 shows the DTA curves of phases IV, II, III-1/2 H_2O, V-H_2O and NC-$2H_2O$. The curve of phase IV showed an endothermic peak due to dehydration of 1 mol of crystal water. The curve of phase II showed two endothermic peaks at about 40°C and about 70°C, as shown in Fig. 1-(B), and this finding suggests that phase II contains two kinds of crystal water. The curve of phase III-1/2 H_2O showed a broad endothermic peak due to dehydration of 1/2 mol of water. The curve of phase V–H_2O showed an endothermic peak due to dehydration. The curve of NC-$2H_2O$ showed a broad endothermic peak due to dehydration of 2 mol of water.

Fig. 2 shows the effect of heating rate in DTA on the D_p of cephalexin hydrates. The D_p was measured in the manner shown in Fig. 3. The D_p values were estimated by extrapolating the curves in Fig. 2 to zero heating rate. The D_p values of phases II, IV, III-1/2H_2O, V-H_2O and NC-$2H_2O$ were about 25, 39, 28, 45 and 13°C, respectively. The D_p values of phases II, III-1/2 H_2O and NC-$2H_2O$ were lower than those of phases IV and V-H_2O, that is, the former phases were easier to dehydrate than the latter.

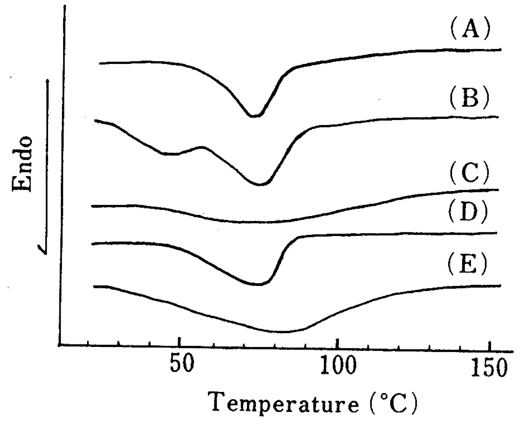

Fig. 1. The DTA Curves of Cephalexin Hydrates

(A) ,phase IV; (B), phase II; (C) phase III-1/2 H_2O; (D), phase V-H_2O; (E) NC-$2H_2O$. (Heating rate; 10°C/min).

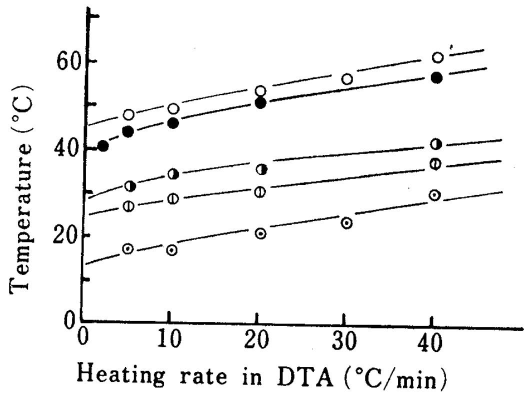

Fig. 2. Effect of Heating Rate in DTA on the Dehydration Points of Cephalexin Hydrates

●, phase IV; ⦶, phase II; ◑, phase III-1/2 H_2O; ○, phase V-H_2O; ⊙, NC-$2H_2O$.

Approximate Thermal Kinetic Analysis of the Dehydrations

(1) **Kissinger's Method**[3]——Kissinger assumed that the thermal decomposition of clay minerals obeyed first-order kinetics, and derived an approximate equation for the activation

energy. Further, Kissinger reported that the relationship between the shape index S of the DTA curve and n of Eq. 1 is given by Eq. 2.

$$dx/dt=k\,(1-x)^n \qquad \text{Eq. 1}$$

$$n=1.26\,S^{1/2} \qquad \text{Eq. 2}$$

where k is the rate constant, x is the fractional decomposition, and n is the reaction order of the decomposition.

Fig. 3 shows how the shape index (S) and T_m are determined, where T_m is the temperature of the DTA peak maximum. Table I shows the shape index and reaction order of the cephalexin hydrates (mean values measured at heating rates of 5—40°C/min from Fig. 1,(A)—(E)). The standard deviation (S.D.) values of S and n of phase III-1/2 H_2O were larger than those of the others, because DTA peaks of phase III-1/2 H_2O were very broad. The dehydrations of phases IV, III-1/2 H_2O and NC-2H_2O were first-order reactions, and that of phase V-H_2O was a 2/3 order reaction.

Fig. 4 shows Kissinger's plots for phases IV, II, III-1/2 H_2O, V-H_2O and NC-2H_2O, where ϕ is heating rate. Each plot gave a good straight line, and the activation energy of dehydration was calculated from the slope by the least-squares method. The activation energies obtained are shown in Table V.

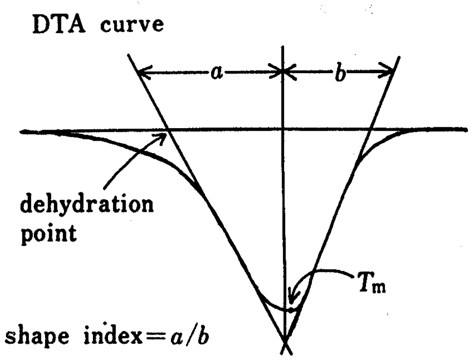

Fig. 3. Method for Measuring the Degree of Asymmetry in a DTA Peak

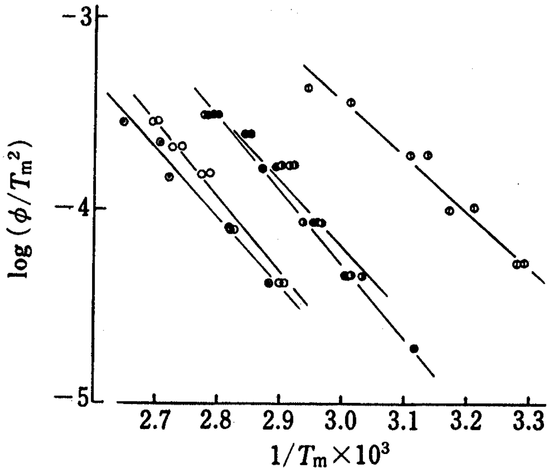

Fig. 4. Kissingers Plots for the Thermal Dehydration of Cephalexin Hydrates by DTA

●, phase IV; ⦶, phase II; ◑, phase III-1/2 H_2O; ○, phase V-H_2O; ⊙, NC-2H_2O.

Table I. Shape Index and the Order of Reaction determined by Kissinger's Method

Sample	N[a]	Shape index (S)	S.D.	Reaction order[b] (n)	S.D.
Phase IV	11	0.656	0.102	1.017	0.077
PhaseIII-1/2 H_2O	9	0.635	0.139	0.998	0.112
Phase V-H_2O 11% RH	10	0.256	0.048	0.635	0.058
Phase V-xH_2O 43% RH	10	0.302	0.074	0.687	0.086
NC-H_2O	5	0.599	0.072	0.974	0.059

a) Number of measurements (heating rate; 5—40°C/min).
b) $n=1.26\,S^{1/2}$; mean value of the measurements.

(2) **Barton's Method**——Barton[9] assumed that the glass transition of a polymer was a first-order reaction, and derived an approximate equation relating the temperature corresponding to any fixed fractional degree of transition to the heating rate.

Fig. 5 shows the effect of heating rate on the DSC curves of phase IV. Fig. 6 shows Barton's plots for phases IV, III-1/2 H_2O, V-H_2O and NC-2H_2O, where T is the temperature of half-life of the dehydration obtained by means of latent heat measurement. Each plot gave a good straight line, and the activation energies were calculated from the slope by the least-squares method. The activation energies are listed in Table V.

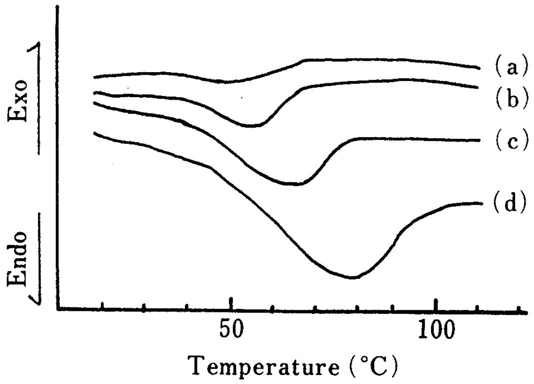

Fig. 5. Effect of Heating Rate on the DSC Curves of Phase IV

(a), 2.5°C/min; (b), 5°C/min; (c), 10°C/min; (d), 20°C/min.

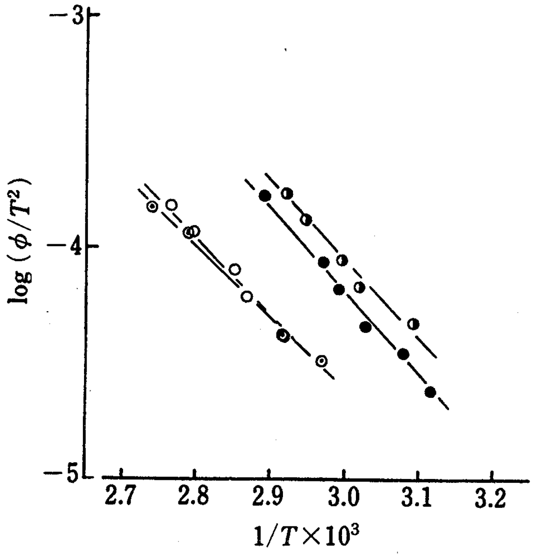

Fig. 6. Barton's Plots for the Thermal Dehydration of Cephalexin Hydrates studied by DSC

●, phase IV, ◐, phase III-1/2 H_2O; ○, phase V- H_2O; ⊙, NC-2H_2O.

Nonisothermal Kinetic Analysis of the Dehydrations

Criado *et al.*[4] summarized various kinetic equations for the most common mechanisms believed to operate in solid-state decomposition, as shown in Table II.

TABLE II. Kinetic Equations for the Most Common Mechanisms believed to operate in Solid-state Decomposition

Symbol	$f(x)$	$g(x)$	Mechanism
R_2	$(1-x)^{1/2}$	$2(1-(1-x)^{1/2})$	One-half order mechanism
R_3	$(1-x)^{2/3}$	$3(1-(1-x)^{1/3})$	Two-thirds order mechanism
F_1	$(1-x)$	$-\ln(1-x)$	First-order mechanism
A_2	$2(-\ln(1-x)^{1/2})(1-x)$	$(-\ln(1-x))^{1/2}$	Two-dimensional growth of nuclei (Avrami equation)
A_3	$3(-\ln(1-x)^{2/3})(1-x)$	$(-\ln(1-x))^{1/3}$	Three-dimensional growth of nuclei (Avrami equation)
D_1	$1/2x$	x^2	One-dimensional diffusion
D_2	$1/(-\ln(1-x))$	$(1-x)\ln(1-x)+x$	Two-dimensional diffusion
D_3	$3(1-x)^{2/3}/2(1-(1-x)^{1/3})$	$(1-(1-x)^{1/3})^2$	Three-dimensional diffusion (Jander equation)
D_4	$3/2((1-x)^{-1/3}-1)$	$(1-2x/3)-(1-x)^{2/3}$	Three-dimensional diffusion (Ginstiling–Brounshtein equation)

The kinetic equation of decomposition of a hydrate involves a function $f(x)$, and its integrated form is function $g(x)$, where x is the fraction of dehydrate at time t. The rate of decomposition is expressed generally as

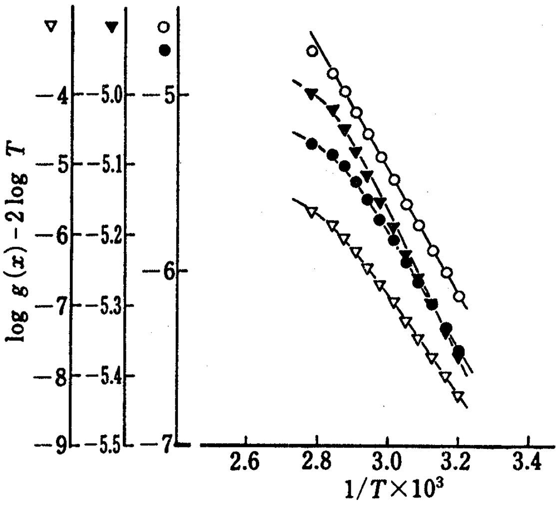

Fig. 7. Criado's Plots for DSC of Phase IV

(Heating rate; 10°C/min)
●, R_2; ○, F_1; ▼, A_3; ▽, D_3.

$$dx/dt = kf(x) \qquad \text{Eq. 3}$$

where k is the rate constant.

The Arrhenius equation gives

$$k = A \exp(-E/RT) \qquad \text{Eq. 4}$$

where $\boldsymbol{R}$ is the gas constant, A is the frequency factor and E is the activation energy of dehydration. Further, at a constant heating rate,

$$a = dT/dt \qquad \text{Eq. 5}$$

Now, from Eqs. 3, 4 and 5.

$$\int_0^x dx/f(x) = (A/a)\int_0^T \exp(-E/\boldsymbol{R}T)dT \qquad \text{Eq. 6}$$

The integrated form of Eq. 6 was obtained by Coats *et al.*,[10] and, taking logs, we have

$$\ln g(x) - 2\ln T = \ln(A\boldsymbol{R}/Ea) - E/\boldsymbol{R}T \qquad \text{Eq. 7}$$

Thus, the activation energy can be obtained from the slope of a plot of ($\ln g(x)$—$2 \ln T$) against $1/T$, which should be linear.

Fig. 7 shows Criado's plots for phase IV. The correlation coefficients of Criado's plots of various functions $g(x)$ and heating rate are shown in Table III. The dehydrations of phases IV, III-1/2 H_2O and NC-2H_2O obeyed first-order kinetics under nonisothermal conditions, except for that NC-2H_2O at the heating rate of 20°C/min. The dehydration of phase V-H_2O appeared to be a three-dimentional diffusion reaction under nonisothermal conditions.

TABLE III. Correlation Coefficients of Criado's Plots (Constant Heating Rate)

Sample	Heating rate (°C/min)	R_2	R_3	F_1	A_2	A_3	D_1	D_2	D_3	D_4
Phase IV	5	0.9969	0.9985	0.9994[a)]	0.9994[b)]	0.9993	0.9895	0.9946	0.9986	0.9963
	10	0.9927	0.9952	0.9984[a)]	0.9980[b)]	0.9975	0.9846	0.9904	0.9957	0.9924
	15	0.9944	0.9966	0.9989[a)]	0.9986[b)]	0.9982	0.9869	0.9923	0.9970	0.9942
	20	0.9898	0.9932	0.9978[a)]	0.9971[b)]	0.9961	0.9792	0.9868	0.9941	0.9896
Phase III-1/2 H_2O	5	0.9436	0.9527	0.9684[a)]	0.9621	0.9540	0.9221	0.9387	0.9568[b)]	0.9451
	10	0.9709	0.9784	0.9891[a)]	0.9857[b)]	0.9806	0.9507	0.9661	0.9620	0.9719
	15	0.9831	0.9882	0.9951[a)]	0.9930[b)]	0.9894	0.9818	0.9798	0.9902	0.9839
	20	0.9720	0.9782	0.9878[a)]	0.9832[b)]	0.9759	0.9571	0.9694	0.9814	0.9738
Phase V-H_2O	5	0.9975	0.9975	0.9957	0.9949	0.9939	0.9942	0.9970	0.9978[a)]	0.9975[b)]
	10	0.9971[b)]	0.9970	0.9942	0.9930	0.9914	0.9936	0.9967	0.9973[a)]	0.9286
	15	0.9970	0.9981[b)]	0.9980	0.9976	0.9969	0.9910	0.9956	0.9984[a)]	0.9968
	20	0.9980	0.9985[b)]	0.9979	0.9974	0.9967	0.9944	0.9973	0.9987[a)]	0.9980
NC-2H_2O	5	0.9824	0.9868	0.9937[a)]	0.9919[b)]	0.9894	0.9701	0.9793	0.9884	0.9826
	10	0.9936	0.9961	0.9989[a)]	0.9985[b)]	0.9979	0.9848	0.9912	0.9966	0.9934
	15	0.9959	0.9978	0.9995[a)]	0.9993[b)]	0.9991	0.9885	0.9939	0.9981	0.9957
	20	0.9972	0.9987	0.9988[b)]	0.9983	0.9977	0.9900	0.9954	0.9990[a)]	0.9970

a) Most linear $g(x)$. *b*) Next-best $g(x)$.

The activation energy of dehydration was calculated from the slope of the most linear Criado's plot by the least-squares method, and the results are shown in Table V.

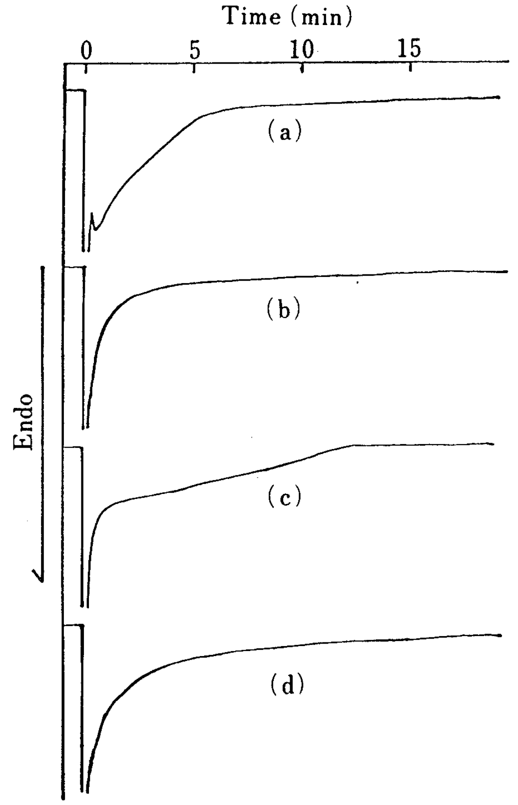

Fig. 8. Isothermal DSC Curves for Dehydration of Cephalexin Hydrates at 60°C

(a), phase IV; (b), phase III-1/2 H_2O; (c), phase V-H_2O; (d); NC-$2H_2O$.

Isothermal Kinetic Analysis of the Dehydrations

Shirotani and Sekiguchi[5] studied the desorption of solvates and the activation energy by calculating the function $g(x)$ in Table II from isothermal TG data.

An isothermal condition is better than a non-isothermal condition for measuring the activation energy of dehydration, because the results are simpler to interpret. We therefore measured the isothermal DSC of cephalexin hydrates. Fig. 8 shows the isothermal DSC curves of phases IV, III-1/2 H_2O, V-H_2O and NC-$2H_2O$ at 60°C. The fractional dehydration x was calculated by measuring the latent heat (x=0.10—0.90). From the values of x, the function $g(x)$ in Table II was calculated and the curves in Fig. 9 were obtained by plotting $g(x)$ against time t. Table IV shows the mean correlation coefficients of these plots.

The dehydrations of phase IV and NC-$2H_2O$ were first-order reactions, that of phase V-H_2O was a 1/2 order reaction, and that of phase III-1/2 H_2O was a two dimensional diffusion reaction. The rate constants k for dehydration of the four hydrates can be determined from the slopes of the plots with the function $g(x)$ giving the highest correlation coefficient (best linearity).

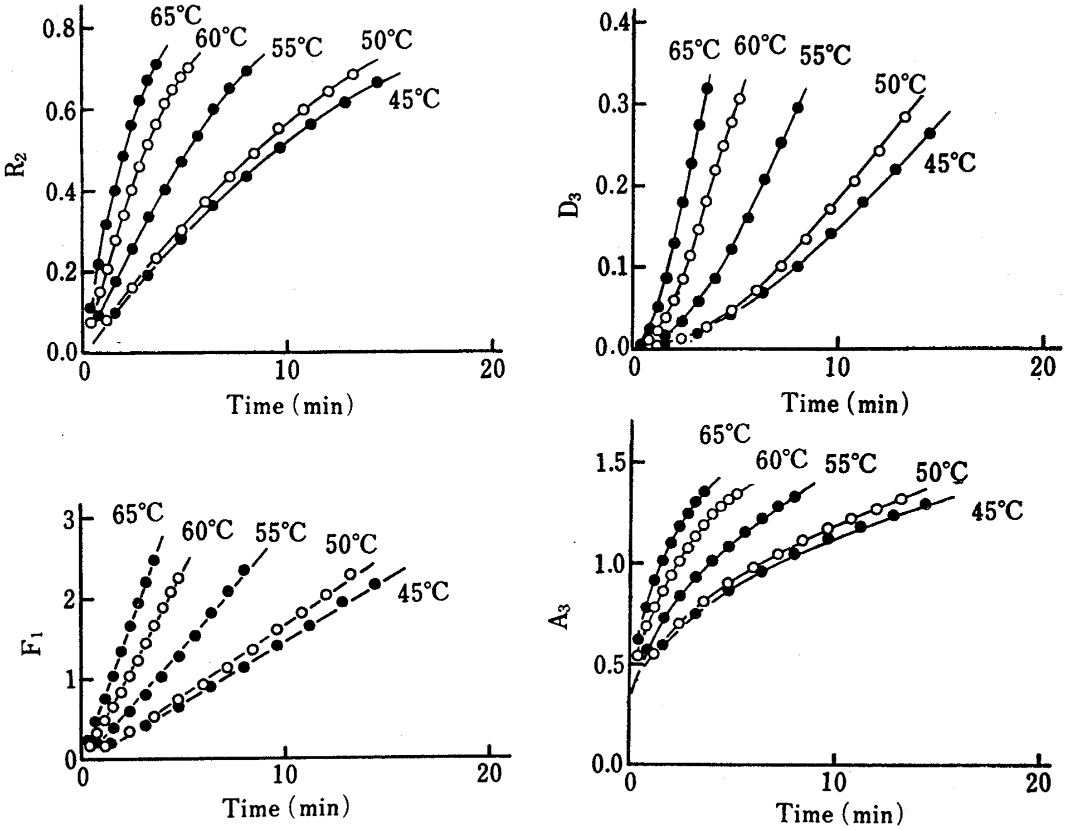

Fig. 9. Dependence of the Function $g(x)$ on Time for the Isothermal Dehydration of Phase IV

TABLE IV. Mean Correlation Coefficients of Plots of $g(x)$ against Time under Isothermal Conditions

Sample		R_2	R_3	F_1	A_2	A_3	D_1	D_2	D_3	D_4
Phase IV	r	0.9935	0.9976[b]	0.9991[a]	0.9928	0.9833	0.9932	0.9967	0.9879	0.9961
(n=5)	S.D.	0.0024	0.0013	0.0007	0.0016	0.0037	0.0026	0.0016	0.0033	0.0017
Phase III-	r	0.9885	0.9942	0.9986[b]	0.9826	0.9766	0.9978	0.9990[a]	0.9934	0.9980
1/2 H_2O (n=4)	S.D.	0.0097	0.0029	0.0011	0.0049	0.0067	0.0016	0.0012	0.0039	0.0020
Phase V-	r	0.9996[a]	0.9977	0.9863	0.9988[b]	0.9945	0.9968	0.9833	0.9567	0.9749
H_2O (n=4)	S.D.	0.0004	0.0016	0.0035	0.0004	0.0012	0.0020	0.0064	0.0098	0.0075
NC-$2H_2O$	r	0.9929	0.9972	0.9992[a]	0.9910	0.9823	0.9956	0.9991[b]	0.9894	0.9977
(n=4)	S.D.	0.0024	0.0014	0.0005	0.0020	0.0028	0.0025	0.0005	0.0034	0.0014

r : Mean correlation coefficients of the plots of $g(x)$ against time t.
n : Number of measurements.
a): Most linear $g(x)$. b): Next-best $g(x)$.

TABLE V. Latent Heat and Activation Energy Values determined by the Various Kinetic Methods for Cephalexin Hydrates

Sample	Transformed phase[a]	Latent heat (n=3) (kcal/mol)	Activation energy					
			Kissinger's method (kcal/mol)	Barton's method (kcal/mol)	Criado's[b] method (kcal/mol)	The most linear $g(x)$	Isothermal method (kcal/mol)	The most linear $g(x)$
Phase IV	Phase I	7.13	17.02	16.97	15.67	F_1	17.41	F_1
Phase II	Phase IV[c]	15.33[d]	11.74	—	—	—	—	—
Phase III-1/2H_2O	Phase III	7.56	15.92	14.90	11.38	F_1	13.63	D_2
Phase V-H_2O 11% RH	Phase V	7.31	17.61	16.59	25.12	D_3	15.10	R_2
Phase V-xH_2O 43% RH	Phase V	7.29	17.32	—	—	—	—	—
NC-$2H_2O$	NC	13.11	15.99	13.60	12.50	F_1	14.00[e]	F_1

a) Transition was identified by X-ray diffractometry after drying at 130°C for 10 min.
b) Heating rate, 10°C/min. c) Drying at 40°C. d) Phase II ⟶ phase I. e) NC-$2H_2O$ ⟶ NC-H_2O.

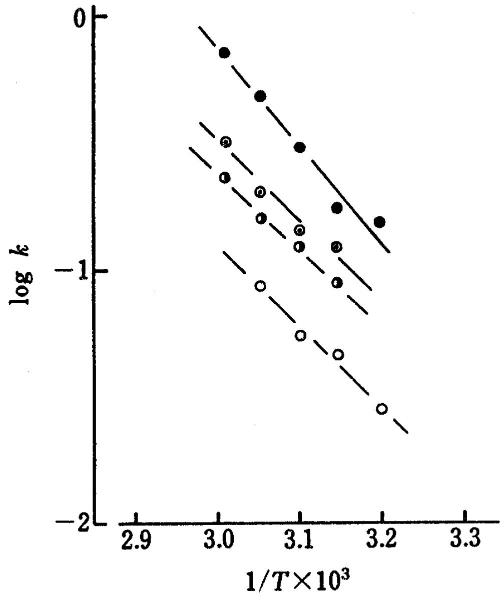

Fig. 10. Plots of log k against $1/T$ for the Thermal Dehydration of Cephalexin Hydrates (Isothermal DSC)

●, phase IV; ◑, phase III-1/2 H_2O; ○, phase V-H_2O; ⊙, NC-$2H_2O$.

The activation energies of the dehydration of phases IV, III-1/2 H_2O, V-H_2O and NC-$2H_2O$ were calculated from the slopes of the Arrhenius plots (Fig. 10) by the least-squares method, and the results are shown in Table V.

Phase Transition of Cephalexin Hydrates Caused by the Dehydration

A sample fixed on an X-ray holder was heated at 130°C for 10 min, and the X-ray diffraction patterns were measured under a current of dry air. The results are shown in Table V. Phase IV was transformed into the anhydride phase I[6] after heating at 130°C. Phase II was transformed into phase IV after heating at 40°C. These results suggest that phase II was transformed into phase I through phase IV. Phases III-1/2 H_2O and V-H_2O were transformed into phases III and V, respectively, after heating at 130°C. The X-ray diffraction pattern of NC-$2H_2O$ which had been heated at 130°C showed no peaks, and this result suggests that NC under these conditions remained in the amorphous state.

The latent heats of phases IV, III-1/2 H_2O and V-H_2O determined by the isothermal method at 50°C were 98.3, 103.0 and 106.0% of those determined by the nonisothermal method, respectively. However, the latent heats of NC-$2H_2O$ determined at 50, 55, 60 and 65°C by the isothermal method were 50.5, 46.0, 47.8 and 48.2% of that found by the nonisothermal method at the heating rate of 10°C/min. The weight losses of phases IV, III-1/2 H_2O and V-H_2O on heating at 50°C were 1.10, 0.39 and 0.99 mol of water, respectively. However, the weight loss of NC–$2H_2O$ on heating at 65°C for 30 min was 0.91 mol of water. These results suggest that phases IV, III-1/2 H_2O and V-H_2O, respectively, transformed into phase I, III and V under the isothermal conditions (50—65°C), and NC-$2H_2O$ transformed into NC-H_2O.

When the measured samples were stored under 43% RH overnight at 35°C, the X-ray diffraction patterns of phases I, III and V became identical with those of phases IV, III-1/2 H_2O and V-H_2O, respectively. These results suggest that the dehydrations of phases IV, III-1/2 H_2O and V-H_2O and NC-$2H_2O$ are reversible reactions.

Latent Heat and Activation Energy Values determined by the Various Kinetic Methods

The latent heat of dehydration was measured by DSC at the heating rate of 10°C/min, and averaged over 3 runs. Table V shows the latent heats of cephalexin hydrates, the dehydration mechanisms and activation energies as determined by Kissinger's, Barton's Criado's and the isothermal methods. The activation energy is per mol of absorbed water.

The dehydration mechanism of phase IV was a first-order reaction as determined by Kissinger's (Table I) and Criado's methods, as well as the isothermal method, and its activation energy was about 16 kcal/mol.

The latent heat of phase II was about twice that of phase IV, since phase II is a dihydrate form. By Kissinger's method, the activation energies of phases II and IV are 11.74 and 17.02 kcal/mol, and D_p of phases II and IV are about 25°C and about 39°C, respectively. These results suggest that phase II absorbed 2 kinds of water.

The latent heat of dehydration of 1 mol of water from phase III-1/2 H_2O is about twice that of phase IV, and the D_p of the former is about 11°C lower than that of the latter. The activation energy of phase III-1/2 H_2O is smaller than that of phase IV by every kinetic method. The dehydration of phase III-1/2 H_2O was a first-order rection as determined by Kissinger's and Criado's methods, and a two-dimensional diffusion reaction as determined by the isothermal method. These results suggest that the water of phase III-1/2 H_2O is different from that of phase IV, and the dehydration mechanism of phase III-1/2 H_2O depends on the heating conditions.

As reported in the previous paper,[6] phase V absorbed 1 mol of water at 11% RH, and about 2 mol of water at 95% RH, and the amount of absorbed water was proportional to RH at 11—95% RH.

The activation energies determined by Kissinger's method and the latent heats of phase V-H_2O (11% RH) and phase V-xH_2O (43% RH) were almost the same, that is, phase V-H_2O is stable under these storage RH conditions. The activation energies of phase V-H_2O as determined by Kissinger's and Barton's methods are almost the same. Criado's method gave an activation energy of 25.12 kcal/mol, while the isothermal method gave an activation energy of 15.10 kcal/mol. The activation energy of phase V-H_2O appears to depend on the heating conditions.

The dehydration mechanism of phase V-H_2O was a 2/3 order reaction by Kissinger's method, a 1/2 order reaction by the isothermal method, and a three dimensional diffusion reaction by Criado's method under nonisothermal conditions. These results suggest that the dehydration mechanism of phase V-H_2O depends on the heating conditions.

The latent heat of NC-$2H_2O$ was about twice that of phase IV, since it contained 2 mol of water, and the D_p was about 13°C, the lowest in all the samples. In the nonisothermal method, the water of NC-$2H_2O$ all behaves similarly, but under isothermal conditions (50—

65°C) NC-$2H_2O$ is transformed into NC-H_2O, that is, two types of water were distinguishable. In the previous paper,8) the water contents of NC were reported to be 1 mol at 20—32% RH, and 2 mol at 43—66% RH. In all methods, the activation energy of NC-$2H_2O$ was about 20% smaller than that of phase IV. The dehydration mechanism is first-order by all methods. Therefore, the reaction is not dependent on heating conditions. The DTA curves of NC-$2H_2O$ showed an exothermic peak (Fig. 1-(E)), and NC-$2H_2O$ is in an amorphous state. These results suggest that NC-$2H_2O$ is a molecular compound consisting of 1 mol of cephalexin and 2 mol of water, and the bond between NC and water is weaker than in the case of phase IV.

The present results show that the dehydrations of phases IV and NC-$2H_2O$ (which was recrystallized or lyophilized from aqueous solution) followed first-order kinetics. On the other hand, phases III-1/2 H_2O and V-H_2O which had been recrystallized from organic solvents and allowed to absorb water after desolvation6) showed dehydration behavior that was dependent on the heating conditions. This suggests that the dehydration mechanism is rather complex in these cases. This result suggests the behavior of its water is uncommon dehydration.

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References and Notes

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