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The Interaction between Water and Cephalexin in the Crystalline and Noncrystalline States[1)]

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Solid cephalexin (CEX) has been obtained as crystals, the noncrystalline solid (NC) produced by freeze-drying and the noncrystalline solid (GNC) produced by grinding in a centrifugal mill for 4 h. Each product formed an anhydride, monohydrate and dihydrate. The interaction between water and CEX in the crystalline and noncrystalline states was studied by the infrared (IR) spectral method and the thermal kinetic analytical method (Criado method) using differential scanning calorimetry.

In the IR spectrum of CEX, the hydroxyl ν_{OH} band was observed at 3400 cm^{-1}, the amido ν_{NH} band at 3100 cm^{-1}, the amine $\nu_{NH_3^+}$ band at 2600 cm^{-1}, the β-lactam $\nu_{C=O}$ band at 1760 cm^{-1}, the amido $\nu_{C=O}$ band at 1680 cm^{-1}, and the carboxylate $\nu_{CO_2^-}$ band at 1600 cm^{-1}. The IR spectral intensity ratios were calculated from the peak heights of the bands with respect to the band at 1280 cm^{-1} as an internal standard peak. The changes of the IR spectral intensity ratios with increasing water content led us to the following conclusions. In the crystalline monohydrate (phase IV), the first water molecule interacted with the amine and carboxylate groups of different molecules in the crystal of CEX. In the crystalline dihydrate (phase II), the second water molecule interacted with NH and C=O of the amido group of CEX. In NC–H_2O, the water molecule is adsorbed at the carboxylate group of CEX, while in NC–$2H_2O$, the second water molecule is adsorbed at the amine group.

The dehydrations of phase IV, GNC–H_2O, GNC–$2H_2O$ and NC–$2H_2O$ followed first-order kinetics and the activation energies (E) were 15.67, 14.83, 14.58 and 12.50 kcal/mol, respectively, while that of NC–H_2O followed three-dimensional diffusion kinetics and its E value was 15.81 kcal/mol. The E of phase II (second water molecule) was 11.74 kcal/mol as determined by the Kissinger method.

These results suggest that the binding energies between the various forms of CEX and water reflect the characteristics of the groups of the CEX molecule to which water is actually bound in each case.

Keywords——cephalexin; hydrate; molecular interaction; adsorption site; dehydration; IR spectral method; thermal kinetic method

In the previous paper, we described several polymorphs and noncrystalline forms of cephalexin (CEX). These were phases I (anhydride), IV′ (anhydride), IV (monohydrate) and II (dihydrate) as crystalline CEX,[2)] and the noncrystalline solid (NC) obtained by the freeze-drying method[3)] and that (GNC) obtained by centrifugal mill grinding,[4)] both of which formed an anhydride, monohydrate and dihydrate.[3,5)] Nakai *et al.* also reported on the state of ground mixtures of drugs with microcrystalline cellulose using an infrared (IR) spectral method.[6)]

In the present work, the interaction between the CEX molecule and adsorbed water, and the site of adsorption, were studied by investigating the relation between the water content and IR spectrum of various solid CEX powders. The dehydration of the hydrates was studied by thermal kinetic analysis, and the relation between the thermal dynamic parameters and the site of adsorption of water was investigated.

Experimental

Materials

Crystalline CEX——Phase IV (monohydrate) was obtained by recrystallization of bulk powder as described in the previous paper.[5] Phase I (anhydride) was obtained by drying of phase IV in a P_2O_5 desiccator at 130 °C. Phase IV′ (anhydride) was obtained by drying of phase IV in a P_2O_5 desiccator at 35 °C. Phase II (dihydrate) was obtained by storage of phase IV at 95% relative humidity (RH) in a desiccator at 35 °C.

Noncrystalline CEX——NC was obtained from a saturated solution of CEX by freeze-drying as in the previous paper,[6] and the monohydrate (NC–H_2O) and the dihydrate (NC–$2H_2O$) were obtained by storage in 20 and 62% RH desiccators at 35 °C, respectively. GNC was obtained from phase IV ground for 4 h in a centrifugal mill, and the monohydrate (GNC–H_2O) and the dihydrate (GNC–$2H_2O$) were obtained by storage in 20 and 62% RH desiccators at 35 °C, respectively.

Measurement of Physicochemical Properties

X-Ray Diffraction——The X-ray diffraction profiles were obtained with an X-ray diffractometer (type JDX-7E; Nihon Denshi Co., Ltd.). The measurement conditions were as follows; target Cu(Kα), filter Ni, voltage 20 kV, current 10 mA.

IR Spectra——The spectra were measured as Nujol mulls using an IR spectrophotometer (IR-2; Nihon Bunko Co., Ltd.). The concentrations of mulls were adjusted to give almost the same absorption intensities of key bands at each measurement. The values of wave number were corrected on the basis of those of a polystyrene film standard.

Thermal Analysis——The thermal behavior was measured with differential thermal analysis (DTA) and differential scanning calorimeter (DSC) instruments (DT-20B and SC-20B; Shimadzu Seisakusho Co., Ltd.), and the measurement conditions were as follows: sample weight, about 3 mg (DTA) or about 5 mg (DSC); sample cell, an aluminum cell having a cell cover with five holes for stainless hypodermic needles (JIS cord H) for gas flow; N_2 flow, 30 ml/min; heating rate, 10 °C/min. The latent heat of dehydration was measured by using DSC and averaged over 3 runs. The fractional dehydration x was calculated from the values of latent heat measured by the DSC method, as in the previous paper.[10]

Results and Discussion

IR Spectrum and Adsorption Site of Water

Water Content of Crystalline and Noncrystalline CEX Powders——Figure 1 shows the water content–RH plots for phase IV, GNC and NC, taken from the previous papers.[2,3,5] The water content of phase IV was about 1 mol/mol at 20—75% RH, and was about 2 mol/mol at 95% RH. The water content of NC was about 1 mol/mol at 20—32% RH, and was about 2 mol/mol at 43—66% RH. The water content of GNC was about 1 mol/mol at 20% RH, and was about 2 mol/mol at 52—82% RH, but was proportional to the value of RH and was not stoichiometrical.

Change of X-Ray Diffraction Profile of CEX Powder Caused by Humidity Change——The X-ray diffraction profiles of the six kinds of CEX powders were reported in the previous papers.[2-4] Phases I, II, IV and phase IV′ (crystalline forms of CEX) showed characteristic X-ray diffraction profiles, but GNC obtained by grinding and NC obtained by freeze-drying showed no diffraction peaks. These results suggested that the latter two solids were in noncrystalline states. NC and GNC remained in a noncrystalline state during storage at less than 66 and 82% RH at 35 °C, respectively.

Change of IR Spectra of CEX Powders Caused by Humidity Change——Marrell[7] assigned the IR bands of CEX as follows; the band at 3500—3000 cm^{-1} is due to the hydroxyl ν_{OH} and the amido ν_{NH}. The bands at 2600 cm^{-1}, at 1760 cm^{-1}, and at 1690 cm^{-1} are due to the amine $\nu_{NH_3^+}$, the β-lactam $\nu_{C=O}$ and the amido $\nu_{C=O}$, respectively. The broad band at 1600 cm^{-1} is due to the carboxylate $\nu_{CO_2^-}$.

Figure 2 shows the IR spectra of crystalline CEX powders. Phase I showed peaks at 1698 and 1667 cm^{-1}, but phase IV′ showed only the peak at 1680 cm^{-1}. It can be presumed that the carboxyl group of phase I forms an intramolecular hydrogen bond, because the IR spectral band of the carboxylate $\nu_{CO_2^-}$ forming the hydrogen bond is at 1650—1680 cm^{-1},[8] and the IR spectral band shifts to higher frequency when the group involved forms a bend-type hydrogen

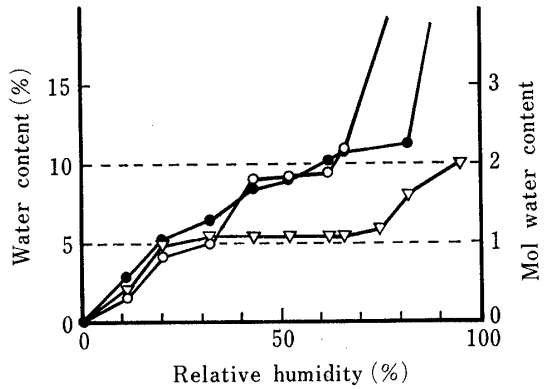

Fig. 1. Change of Water Content of CEX at Various Levels of Relative Humidity at 35 °C

▽, intact crystal (phase IV); ○, NC; ●, GNC.

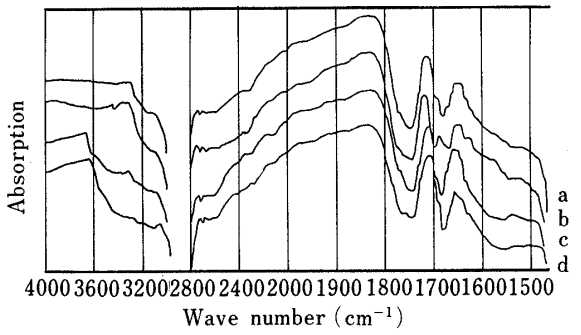

Fig. 2. IR Spectra of Crystalline CEX

a, phase IV′; b, phase I; c, phase IV; d, phase II.

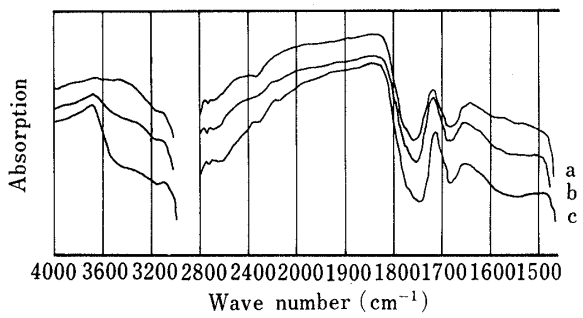

Fig. 3. IR Spectra of GNC

a, GNC; b, GNC–H_2O; c, GNC–$2H_2O$.

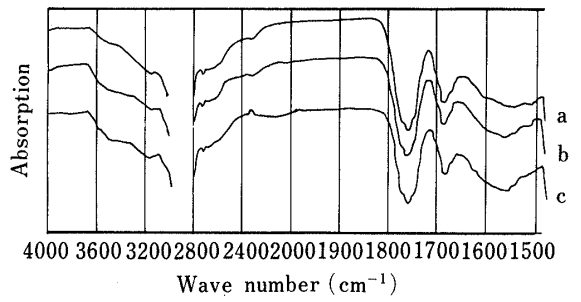

Fig. 4. IR Spectra of NC

a, NC; b, NC–H_2O; c, NC–$2H_2O$.

TABLE I. IR Spectral Bands of CEX

Sample	Hydroxyl ν_{OH} cm^{-1}	Amido ν_{NH} cm^{-1}	Amine $\nu_{NH_3^+}$ cm^{-1}	β-Lactam $\nu_{C=O}$ cm^{-1}	Amido $\nu_{C=O}$ cm^{-1}	Carboxyl $\nu_{C=O}$ cm^{-1}
Phase IV′	—	3120	2600	1746	1680	1540
Phase I	—	3120	2600	1746	1698, 1667	1545
Phase IV	3400	3120	2600	1748	1680	1560
Phase II	3400	3120	2600	1746, 1765 sh	1680	1550
GNC	—	3160	2600	1760	1685	1550
GNC–H_2O	3400	3160	2600	1755	1685	1550
GNC–$2H_2O$	3400	3160	2600	1747	1685	1550
NC	—	3140	2600	1762	1683	1560
NC–H_2O	3400	3140	2600	1760	1683	1560
NC–$2H_2O$	3400	3140	2600, 2100	1758	1683	1565

bond.[9] The IR spectral intensities in these band regions changed with increasing water content. Figure 3 shows the IR spectra of GNC; it can be seen that the IR spectral intensities changed with increasing water content. In the case of NC (Fig. 4), the IR spectral intensity of NC changed with increasing water content, and a new broad band at 2100 cm^{-1} appeared in the IR spectrum of NC–$2H_2O$.

The IR spectral data for CEX powders are summarized in Table I.

Relation between IR Spectral Intensity Ratio and RH——In order to estimate IR spectral

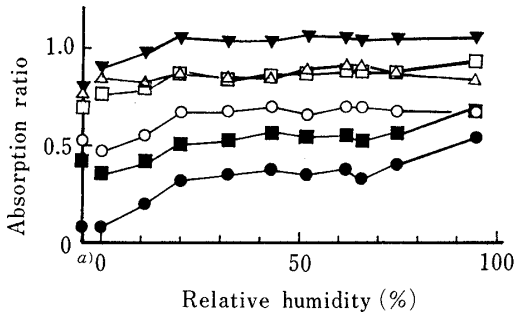

Fig. 5. Change of IR Spectral Absorption Ratios of Crystalline CEX Hydrates

●, hydroxyl stretch; ■, amido NH stretch; ○, NH_3^+ stretch; △, β-lactam stretch; □, amido C=O stretch; ▼, carboxylate stretch.
a) In a P_2O_5 desiccator at 130 °C.

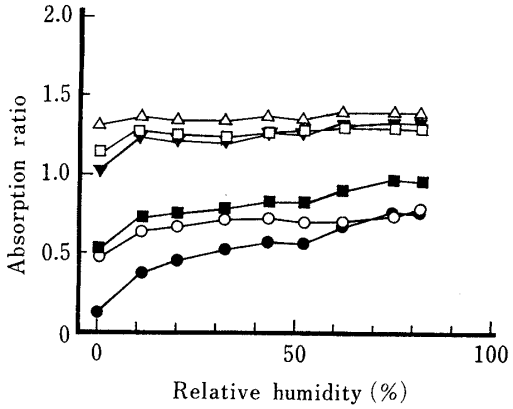

Fig. 6. Change of IR Spectral Adsorption Ratios of GNC

●, hydroxyl stretch, ■, amido NH stretch; ○, NH_3^+ stretch; △, β-lactam stretch; □, amido C=O stretch; ▼, carboxylate stretch.

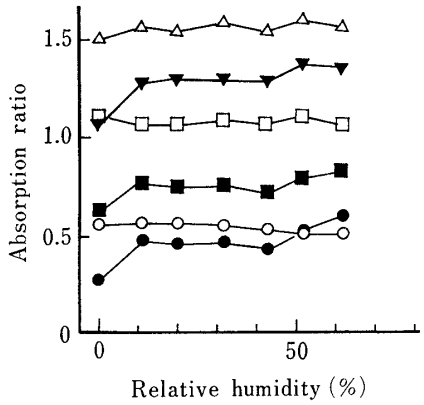

Fig. 7. Change of IR Spectral Absorption Ratios of NC

●, hydroxyl stretch; ■, amido NH stretch; ○, NH_3^+ stretch; △, β-lactam stretch; □, amido C=O stretch; ▼, carboxylate stretch.

intensity, the peak heights of the key bands were measured from base lines drawn between the minima at about 850 and 1850 cm^{-1}, and at about 1850 and 3700 cm^{-1}, and the IR spectral intensity ratios were calculated from the peak heights with respect to that of the band at 1280 cm^{-1} as an internal standard, which was essentially invariant.

Figure 5 shows the relation between the IR spectral intensity ratio of crystalline CEX and RH. The intensity ratios of the hydroxyl ν_{OH} and the amido ν_{NH} and $\nu_{C=O}$ increased at 20% RH, stayed approximately constant at 20—75%, RH, and increased at 95% RH, and the intensity ratios were approximately proportional to the water content. The intensity ratios of the amine $\nu_{NH_3^+}$ and the carboxylate $\nu_{CO_2^-}$ increased at 20% RH, and stayed approximately constant at more than 20% RH. However, the intensity ratio of β-lactam $\nu_{C=O}$ was constant throughout.

Figure 6 shows the relation between the IR spectral intensity ratios of GNC and RH. The intensity ratios of the amine $\nu_{NH_3^+}$ and the amido $\nu_{C=O}$ increased at 11% RH, and stayed approximately constant at 11—82% RH. However, the intensity ratio of the β-lactam $\nu_{C=O}$ was constant throughout.

Figure 7 shows the relation between the IR spectral intensity ratios of NC and RH. The intensity ratios of the hydroxyl ν_{OH} increased at 11% RH, stayed approximately constant at 11—43% RH, increased at 52% RH, and stayed approximately constant at 52—62% RH. The intensity ratios of the carboxylate $\nu_{CO_2^-}$ and the amido ν_{NH} increased at 11% RH, and stayed approximately constant at 11—62% RH. The intensity ratio of the amine $\nu_{NH_3^+}$ was constant

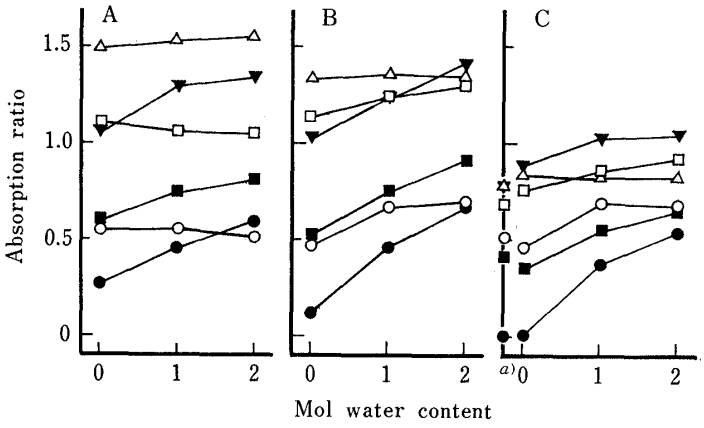

Fig. 8. Change of IR Spectral Absorption Ratios of CEX Hydrates

A, NC; B, GNC; C, crystal.
●, hydroxyl stretch; ■, amido NH stretch; ○, NH_3^+ stretch; △, β-lactam stretch; □, amido C=O stretch; ▼, carboxylate stretch.
a) In a P_2O_5 desiccator at 130 °C.

at 0—43% RH, and decreased slightly at 43—62% RH. However, the intensity ratios of the amido $\nu_{C=O}$ and the β-lactam $\nu_{C=O}$ were constant throughout.

Adsorption Site of Water——Figure 8 shows the relation between the IR spectral intensity ratios of NC, GNC and crystalline CEX and the water content. In NC, the intensity ratios of the hydroxyl ν_{OH}, the amido ν_{NH} and the carboxylate $\nu_{CO_2^-}$ for NC–H_2O were larger than those of NC, though the band of the amido ν_{NH} overlapped with that of the hydroxyl ν_{OH}. The intensity ratio of the amido $\nu_{C=O}$ for NC–$2H_2O$ was larger than that for NC–H_2O, and that of the amine $\nu_{NH_3^+}$ for NC–$2H_2O$ was smaller than that for NC–H_2O. A new broad band appeared at 2100 cm^{-1} in the IR spectrum of NC–$2H_2O$. The band due to amine $\nu_{NH_3^+}$ of an ionic amino acid is at 2080—2140 cm^{-1},[8] and the IR spectral band shifts to lower frequency when the group involved forms a straight-type hydrogen bond,[9] so it appears that the second water molecule interacts with the amine group, and the band of the amine group at 2600 cm^{-1} shifts to 2100 cm^{-1}. CEX molecules of NC are disordered because it is a noncrystalline state, and therefore the orientation of intermolecular interactions is at random and the net effect is negligible.

These results suggest that in NC, the first water molecule is adsorbed at the carboxylate group of CEX, and the second water molecule is adsorbed at the amine group, as shown in Fig. 9(a).

In crystalline CEX, when phases I and IV′ were transformed into phase IV by adsorbing 1 mol of water, the intensity ratios of the carboxylate $\nu_{C=O}$, the amine $\nu_{NH_3^+}$, the amido $\nu_{C=O}$ and the amido ν_{NH} increased. It seems that the first water molecule interacted with the amine and carboxylate groups of different molecules in the crystal of CEX, as shown in Fig. 9(b). When phase IV was transformed into phase II by adsorbing 1 mol of water, the intensity ratios of the amido $\nu_{C=O}$ and ν_{NH} increased, so the second water molecule presumably interacted with the amido NH and C=O groups.

When GNC adsorbed 1 mol of water, the intensity ratios of the amido ν_{NH} and $\nu_{C=O}$, the amine $\nu_{NH_3^+}$ and the carboxylate $\nu_{CO_2^-}$ increased, and when GNC–H_2O adsorbed 1 mol of water, the intensity ratios of the amido ν_{NH} and $\nu_{C=O}$, and the carboxylate $\nu_{CO_2^-}$ increased. These results suggest that adsorption of water by GNC showed intermediate behavior between those of crystalline CEX and NC. Therefore GNC is IR-spectrally different from NC, even though both products are X-ray diffractometrically in the same noncrystalline state.

Relation between IR Spectral Intensity Ratio and State of Hydration of CEX——Figure 10 shows the relations between the IR spectral intensity ratios of various CEX powders and the states of hydration. At each level of water content, the intensity ratios of the crystal, GNC and NC were different from each other, and the differences were especially marked for the β-lactam $\nu_{C=O}$. In the previous paper,[4] the IR spectral intensity ratios of the β-lactam $\nu_{C=O}$ and the carboxylate $\nu_{CO_2^-}$ were used to calculate the degree of crystallinity of ground CEX, but

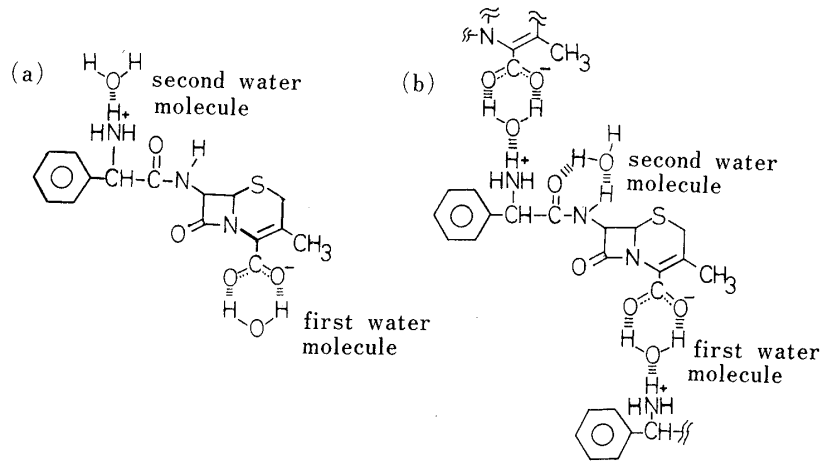

Fig. 9. Models of Water Adsorption Sites of Crystalline and Noncrystalline CEX
(a), NC obtained by freeze-drying; (b), crystalline CEX.

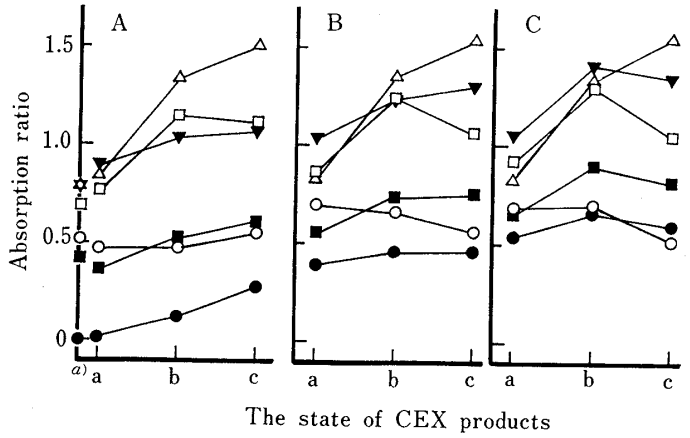

Fig. 10. Change of IR Spectral Absorption Ratios with the Hydration State of CEX Products

A, anhydride; B, monohydrate; C, dihydrate.
●, hydroxyl stretch; ■, amido NH stretch; ○, NH_3^+ stretch; △, β-lactam stretch; □, amido C=O stretch; ▼, carboxylate stretch.
a) Crystal (phase I); a, crystal; b, GNC; c, NC.

the degree of crystallinity determined by the IR spectral method was different from that determined by the X-ray diffraction internal standard method for grinding times between 2 and 4 h, since NC and phase IV were utilized as standard samples.[4] This confirms that, even though NC and GNC are X-ray diffractometrically in the same noncrystalline state, the two products are IR spectrometrically different.

Dehydration of Crystalline and Noncrystalline CEX Hydrates

Thermal Behavior of Crystalline and Noncrystalline CEX Hydrates——Figure 11 shows the DTA curves for CEX hydrates. In the case of crystalline CEX, the DTA curves for phase I and IV′ showed an exothermic peak due to decomposition at about 190 °C. The curve for phase IV showed an endothermic peak due to dehydration (1 mol of water) at about 70 °C, and an exothermic peak due to decomposition at about 190 °C. The curve for phase II showed two endothermic peaks due to dehydration (2 mol of water) at about 40 and 70 °C, and an exothermic peak due to decomposition at about 190 °C.

The DTA curve for GNC showed an exothermic peak due to decomposition at about 160 °C. The curve for GNC–H_2O showed a broad endothermic preak due to dehydration (1 mol of water) at 30—110 °C and an exothermic peak due to decomposition at about 160 °C. The curve for GNC–$2H_2O$ showed an endothermic broad peak due to dehydration (2 mol of water) at 30—110 °C and an exothermic peak due to decomposition at about 160 °C.

The DTA curve for NC showed an exothermic peak due to decomposition at about 175 °C. The curves for NC–H_2O and NC–$2H_2O$ showed an endothermic peak due to

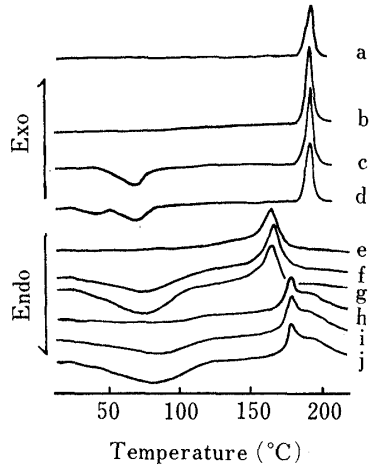

Fig. 11. DTA Curves of CEX Powders

a, phase I; b, phase IV'; c, phase IV; d, phase II; e, GNC; f, GNC–H_2O; g, GNC–$2H_2O$; h, NC; i, NC–H_2O; j, NC–$2H_2O$.

dehydration (1 and 2 mol of water, respectively) at about 20—120 °C and an exothermic peak due to decomposition at about 175 °C.

These results suggest that phase II adsorbs two kinds of water, one weakly bonding with CEX and the other strongly bonding, and consequently the DTA curve showed two endothermic peaks. On the other hand, the 2 mol of water adsorbed by GNC and NC behave similarly (or identically) in dehydration, so that the DTA curves showed one endothermic peak.

Thermal Kinetic Analysis of Crystalline and Noncrystalline CEX Hydrates——The dehydration of crystalline and noncrystalline CEX hydrates was studied by means of DSC by the nonisothermal kinetic method. The fractional dehydration was calculated by measuring the latent heat (H). Criado *et al.*[11] derived the so-called Criado equation (Eq. 1) based on 9 kinetic equations[10] for solid state dehydration:

$$\ln g(x) - 2\ln T = \ln(AR/Ea) - E/RT \qquad (1)$$

where $g(x)$ is the model equation, x is the fractional dehydration, A is the frequency factor, R is the gas constant, a is the heating rate, E is the activation energy and T is temperature (Kelvin).

It assumed that the water of GNC–$2H_2O$ and NC–$2H_2O$ is of a single kind, since the DSC curves of each showed one endothermic peak.

Figure 12 shows the most linear Criado plots for the crystalline and noncrystalline CEX hydrates, obtained by the least-squares method. Table II lists the thermal kinetic parameters obtained from the Criado plots and the latent heat (H) of the dehydration.

The dehydration of phase IV followed first-order kinetics (F_1), and its E value was 15.67 kcal/mol. The dehydration of GNC–H_2O followed F_1 kinetics; its E value was smaller than that of phase IV, and its A was about 1/10 of that of phase IV. The dehydration of NC–H_2O followed three-dimensional diffusion kinetics (Ginsting–Brounshtein) (D_4); its E value and that of phase IV were almost the same, but its A was about 1/100 of that of phase IV, and its H was about 30% smaller than that of phase IV. The E of the second molecule of water of phase II was 11.74 kcal/mol as determined by the Kissinger method,[12] being smaller than that of phase IV.

The dehydration of GNC–$2H_2O$ followed F_1 kinetics; its E and A were approximately equal to those of GNC–H_2O, respectively. This suggests that the thermal behavior of the first water molecule of GNC–$2H_2O$ was similar to that of the second water, so that the DSC and DTA curves showed one endothermic peak.

The dehydration of NC–H_2O followed D_4 kinetics; its E and H were smaller than those

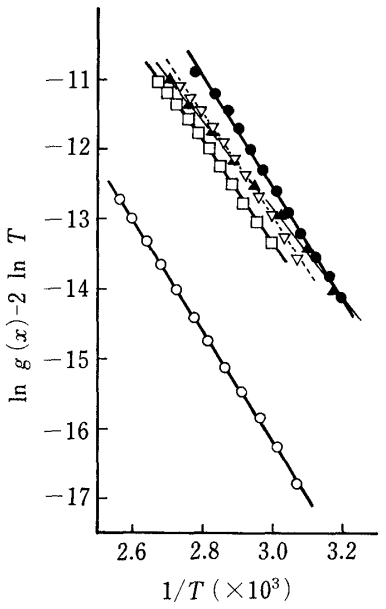

Fig. 12. Criado Plots for Nonisothermal Dehydration of NC, GNC and Crystals

●, phase IV (crystalline monohydrate); □, GNC–H_2O; ▽, GNC-$2H_2O$: ○, NC–H_2O; ▲, NC–$2H_2O$.

TABLE II. Thermodynamic Parameters of Dehydration for CEX Hydrates

Sample	Transformed phase	Latent heat (kcal/mol $\pm\delta$)	The most linear model	Activation energy (kcal/mol)	Frequency factor (min^{-1})
Phase IV	Phase I	7.13 ±0.20	F_1	15.67	5.432×10^9
GNC–H_2O	GNC	8.31 ±0.43	F_1	14.83	5.984×10^8
NC–H_2O	NC	5.07 ±0.24	D_4	15.81	6.331×10^7
Phase II	Phase IV	15.33[a] ±0.52	—	11.74[b]	—
GNC–$2H_2O$	GNC	16.62 ±0.62	F_1	14.58	5.962×10^8
NC–$2H_2O$	NC	13.11 ±0.46	F_1	12.50	2.530×10^7

δ=standard deviation ($n=3$). *a*) Phase II→phase I. *b*) Kissinger method.

of phase IV or GNC–H_2O, and its DTA and DSC peaks showed a very broad endothermic peak. However, the dehydration of NC–$2H_2O$ followed a different kinetic model from that of NC–H_2O, and the water content of NC showed stoichiometric values at various RH levels, as shown in Fig. 1. Therefore, it seems that the behavior of the second water molecule of NC–$2H_2O$ is different from that of NC–H_2O.

Relation between Water Adsorption Site of CEX Hydrate and Dehydration—— Adsorption sites of crystalline and noncrystalline CEX hydrates were studied using the IR spectral method (Fig. 9), and the thermal dynamic parameters of dehydration (Table II). Since the water of phase IV is adsorbed between the polar carboxylate and the polar amine groups of two CEX molecules *via* hydrogen bonds, the E and H values for its dehydration were large. Since the second water molecule of phase II is adsorbed at the small polar amido NH and C=O groups of one CEX molecule, the E and dehydration point were smaller than those of the water of phase IV. Therefore, the DTA showed double peaks for the dehydration (2 mol of water).

Since the water of NC–H_2O is adsorbed at the polar carboxylate group through a hydrogen bond, its dehydration followed D_4 kinetics, and was different from that of phase IV. Since the second water molecule of NC–$2H_2O$ is adsorbed at the polar amine *via* a hydrogen bond, its dehydration (F_1) was different from that of NC–H_2O. Therefore, the water content of NC was stoichiometric at various RH values.

The adsorbed water of GNC showed intermediate behavior between that of crystalline CEX and that of NC based on the IR spectral result, but the thermal analytical result showed behavior similar to that of crystalline CEX, even through GNC is in the noncrystalline state. Nakai[13] also investigated the relation between adsorbed water in noncrystalline drugs and hydrogen bonding. Taken together, the results suggest that the binding energy between CEX and water reflects the characteristics of the binding groups involved.

Conclusions

(1) In crystalline CEX, the first water molecule of phase II is adsorbed intermolecularly between the amine and the carboxylate groups of different CEX molecules, while the second water is adsorbed at the amido NH and C=O groups.

(2) In NC obtained by the freeze-drying method, the first water molecule of NC–$2H_2O$ is adsorbed at the carboxylate group of CEX, and the second water molecule is adsorbed at the amine group.

(3) The results suggest that there is a relation between the thermal dynamic paramters of dehydration for CEX in various solid states and the characteristics of the water-binding groups.

(4) The IR spectral results and the dehydration behavior as determined by the thermal kinetic method of GNC obtained by grinding were different from those of NC obtained by freeze-drying, even though both products were X-ray diffractometrically in the noncrystalline state.

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References and Notes

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