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Hygroscopicity and Solubility of Noncrystalline Cephalexin[1]

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Noncrystalline cephalexin (NC) was prepared by freeze-drying of a saturated solution of the drug. The results of X-ray diffractometry and polarizing microscopy indicated that NC was in a noncrystalline state. The nuclear magnetic resonance spectrum and the thin-layer chromatography behavior of NC were identical with those of crystalline cephalexin (CC).

NC was stored under 0—95% relative humidity (RH) at 35°C for 2 weeks. It absorbed about 1 mol of water at 20—32% RH, and about 2 mol of water at 43—66% RH, but there was no change in the X-ray pattern. When NC was stored at 75—95% RH, however, it absorbed more than 2 mol of water, and X-ray diffraction peaks appeared. This result suggests that NC was transformed into a partly crystalline state under conditions of 75—95% RH. The decomposition point (Dp) was measured with a differential thermal analysis (DTA) instrument. The Dp values of NC and CC were 173°C and 190°C, respectively. The Dp of the partly crystalline solid formed from NC under conditions of 75—95% RH was about 183°C.

The solubility of NC in distilled water was examined by the equilibrium method. The amount of NC dissolved in distilled water at low temperatures reached a plateau, then decreased. This finding is due to the crystallization of NC. NC was about 6 times more soluble than CC solid at 10°C. The heat of solution for NC was calculated to be −3.24 kcal/mol from van't Hoff plots of log *Cs versus* $1/T$.

Keywords——cephalexin; freeze-drying; noncrystalline solid; noncrystalline state; hygroscopicity; solubility; thermal behavior; crystallization

Introduction

The solubility properties of a solid dosage form of a drug are influenced by its crystalline stat.[2] In the previous paper, the authors reported on the different crystalline phases of cephalexin[3] and their solubilities,[4] and described the effect of compression on the physicochemical properties of crystalline cephalexin (CC).[5] It was considered that CC was destroyed by the compression force and converted into a noncrystalline state. In the present paper, noncrystalline cephalexin (NC) was prepared by freeze-drying, and its hygroscopicity, stability in the solid state and solubility were studied.

Experimental

Materials——NC and CC used in the present study were prepared as follows.

(1) Crystalline Cephalexin (Phase IV): Phase IV was the monohydrate, which was obtained by recrystallization as described in the previous paper.[3]

(2) NC: 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.

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, filter Ni, voltage 20 kV, current 20 mA.

Infrared (IR) Spectra——IR spectra were recorded as mulls in Nujol using a infrared spectrophotometer (IR-2; Nihon Bunko Co., Ltd.).

Thermal Measurement——Thermal behavior was measured with a differential thermal analysis (DTA) instrument (DT-20B; Shimadzu Seisakusho Co., Ltd.). The measurement conditions were as follows: heating

TABLE I. Properties of Crystalline and Noncrystalline Cephalexin

	Noncrystalline solid	Crystalline solid (phase IV)
Apparent specific volume (1) Loose	176.8 cm^3/g	3.2 cm^3/g
(2) Tapped	154.9 cm^3/g	1.5 cm^3/g
TLC[a]	1 spot (Rf=0.33)	1 spot (Rf=0.33)
Crystallinity[b]	Noncrystalline form	Crystalline form

a) Solvent system, acetonitrile: water=3:1; Kieselgel 60 (Merck).
b) X-Ray diffractometry and polarized microscopy.

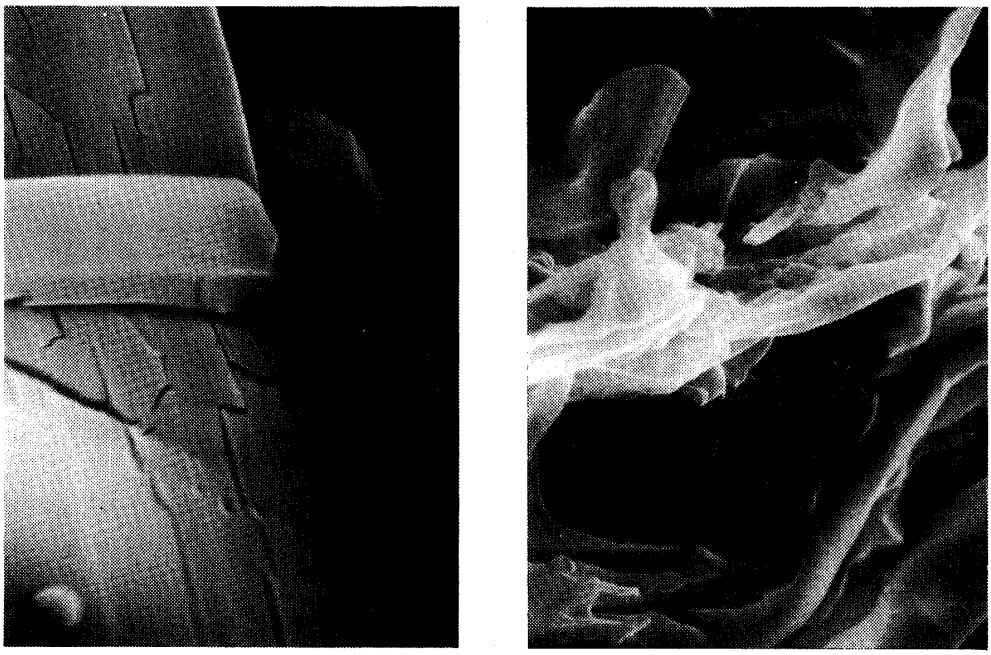

Fig. 1. Scanning Electron Microphotographs of Cephalexin

rate, 10 °C/min; N_2 gas flow, 30 ml/min.

Measurement of Water Content——The samples were stored in saturated salt solutions of various relative humidity (RH) values in desiccators (0—95% RH) at 35±1 °C, and the water content was determined by measuring the weight.

Nuclear Magnetic Resonance (NMR) Spectrum——The solvent used was deuterium oxide containing a small amount of trifluoroacetic acid to enhance solubility. The spectrum was recorded on an NMR instrument (FX-100; Nihon Denshi Co., Ltd.).

Scanning Electron Microscopy——A scanning electron microscope (HHS-2; Hitachi Seisakusho Co., Ltd.) was used at an accelerating voltage of 20 kV.

Solubility Measurement——Measurements of concentration were done in the manner reported previously.[4] The sample solution was immediately filtered through a 0.45 μm membrane filter (Millipore, HAWPO 01300), and the filtrate was suitably diluted for spectrophotometric assay at 262 nm.

Polarizing Microscopy——A polarizing microscope (Olympus Model POS) was used.

Results and Discussion

Table I shows the properties of NC prepared by freeze-drying of a saturated solution of cephalexin. The tapped apparent specific volume of NC was about 100 times larger than that of CC. NC easily acquires a static charge.

There was no decomposition during the preparation of NC, because the thin-layer chro-

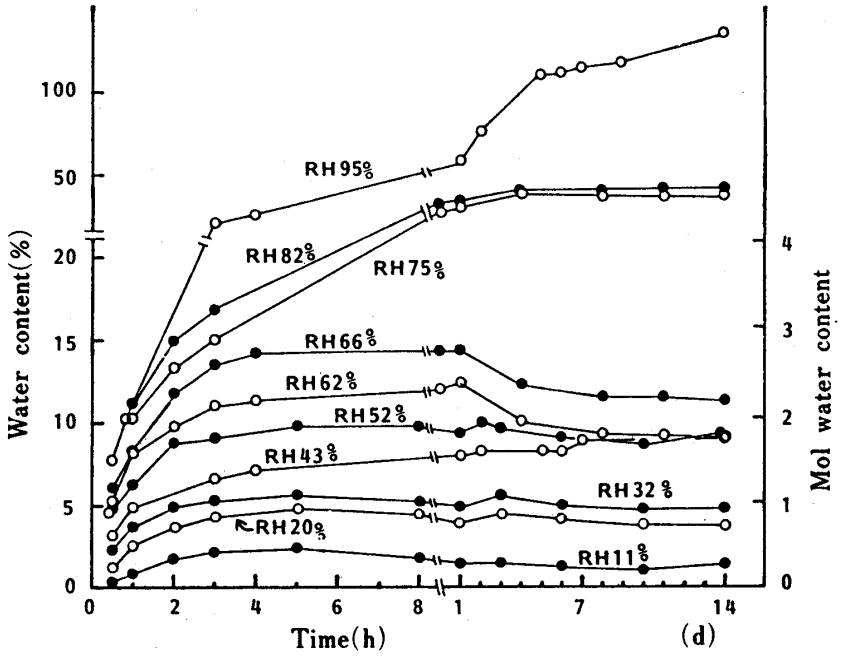

Fig. 2. Moisture Absorption Curves of NC at Various Values of Relative Humidity at 35°C

matography (TLC) behavior and the NMR data of NC were identical with those of CC.

No definite peaks were apparent in the X-ray diffraction pattern of NC, and it also showed no polarization. These results suggest that NC is in a noncrystalline state.

Figure 1 shows scanning electron photomicrographs of the surfaces of NC and CC. The photographs reveal distinct differences in the surface characteristics of the solids, that is, the latter consists of plate crystals, while NC is a disordered form.

Hygroscopicity

Figure 2 shows the moisture absorption curves of NC at various RH values at 35°C. The water content of NC increased as the RH was increased. The moisture absorption curves of NC at 62 and 66% RH reached a plateau at about 24h, and then declined gradually.

Figure 3 shows the water content–RH diagram after storage for 2 weeks at various RH values at 35°C. The water content of NC at 20 and 32% RH was about 1 mol of water, and that at 43—66% RH was about 2 mol of water. The water content of NC at 75—95% RH was much larger than that of NC at 66% RH.

Effect of Humidity on the Solid State Stability of NC

Figure 4 shows the change of the X-ray diffraction patterns of NC after storage for 2 weeks at various RH values at 35°C. The X-ray diffraction patterns of NC at up to 66% RH showed no diffraction peaks, as exemplified in Fig. 4-d). The X-ray diffraction patterns of NC at 75—95% RH showed several diffraction peaks, and the X-ray diffraction patterns were similar to that of CC, as shown in Fig. 4-b), and c). This result suggests that NC which had absorbed up to 2 mol of water remained in the noncrystalline state, and when NC absorbed more than 2 mol of water, crystallization occurred.

Figure 5 shows the changes of the IR spectra of NC after storage for 2 weeks at various RH values at 35°C. The IR spectra of NC was characterized by bands at 3130 cm^{-1}, 1760 cm^{-1} and 1555 cm^{-1} (Fig. 5-e)). The bands at 1750 cm^{-1} 1580 cm^{-1} of CC were due to the β-lactam $\nu_{C=O}$ and the carbonyl $\nu_{C=O}$, respectively (Fig. 5-a)). The IR spectra of NC at up to 66% RH were identical with that of NC except for the band at 3400 cm^{-1} due to the hydroxyl group (Fig. 5-d), and e)). The IR spectra of NC at 75—95% RH showed increased intensity at

3400 cm^{-1}, and the bands due to the β-lactam $\nu_{C=O}$ and the carbonyl group $\nu_{C=O}$ appeared at 1750 cm^{-1} and at about 1600 cm^{-1}, respectively. The spectra of NC at 75% RH was similar to that of CC, as shown in Fig. 5-a), and c). This result suggests that NC crystallized when it was stored at more than 75% RH.

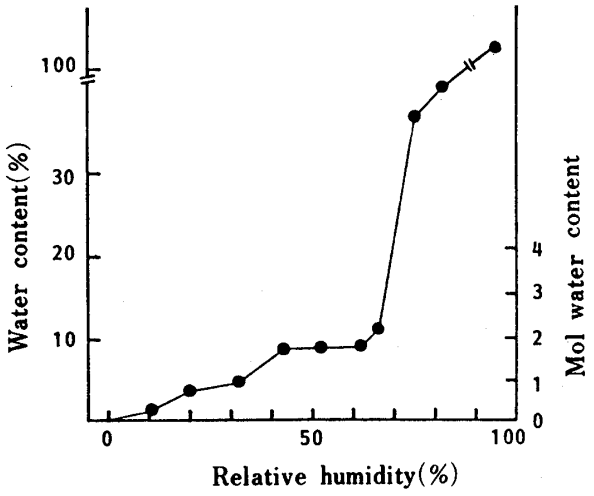

Fig. 3. Change of Water Content of NC at Various Levels of Relative Humidity at 35 °C

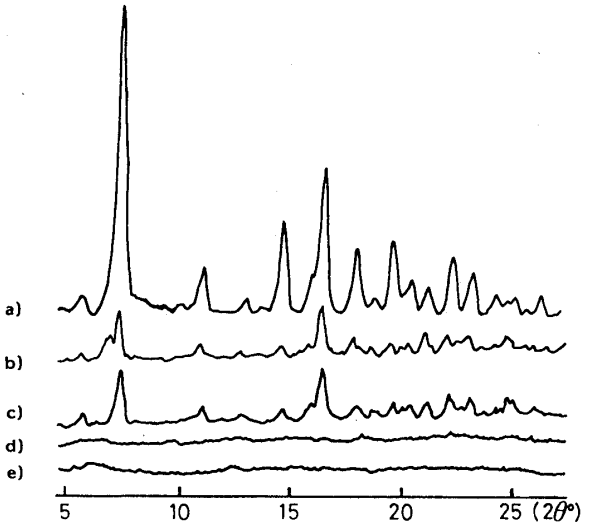

Fig. 4. Change of X-Ray Diffraction Patterns of NC at Various Levels of Relative Humidity at 35 °C

a) CC, b) NC at 95% RH, c) NC at 75% RH, d) NC at 66% RH, e) NC.

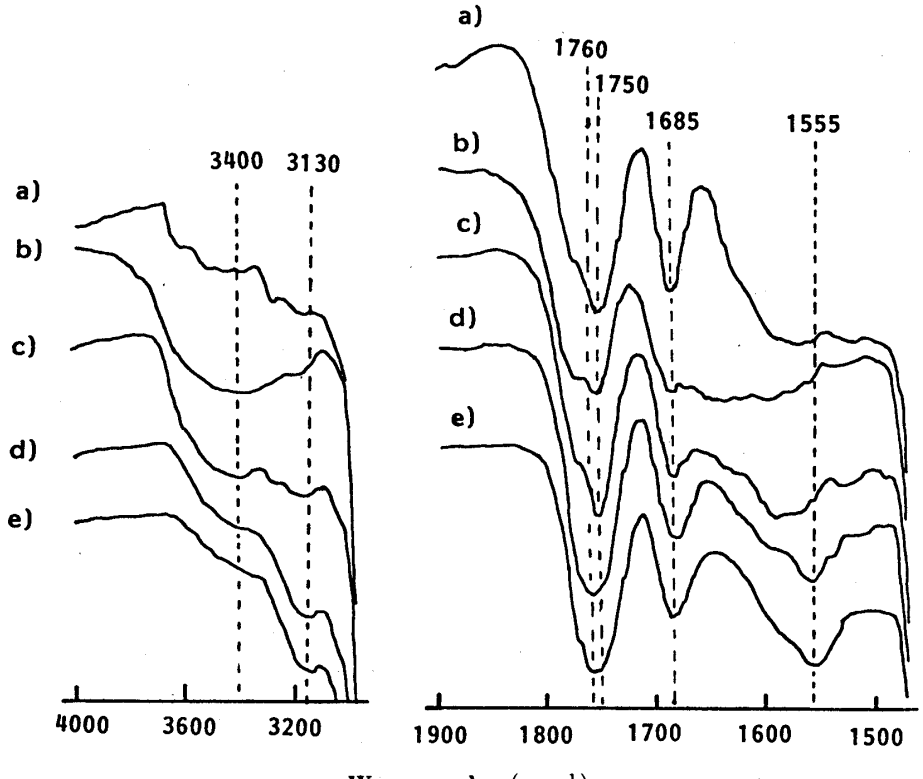

Fig. 5. Change of IR Spectra (4000—3200 cm^{-1} and 1900—1500 cm^{-1}) of NC at Various Levels of Relative Humidity at 35 °C

a) CC, b) NC at 95% RH, c) NC at 75% RH, d) NC at 66% RH, e) NC.

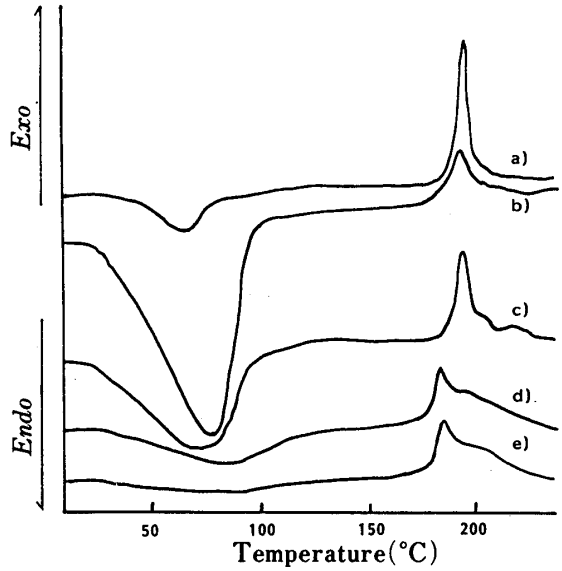

Fig. 6. Change of DTA Curves of NC at Various Levels of Relative Humidity at 35 °C

a) CC, b) NC at 95% RH, c) NC at 75% RH, d) NC at 66% RH, e) NC.

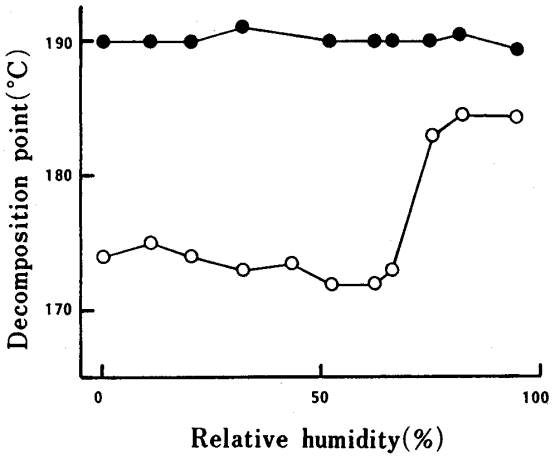

Fig. 7. Change of Decomposition Point of NC and CC under Various Levels of Relative Humidity at 35 °C as determined by DTA

NC; —○—, CC; —●—.

Figure 6 shows DTA curves of NC after storage for 2 weeks at various RH values at 35 °C. The DTA curve of CC showed an endothermic peak at about 50 °C due to dehydration of 1 mol of crystal water[3] and an exothermic peak at about 190 °C due to decomposition of cephalexin (Fig. 6-a)), while that of NC showed a broad endothermic peak at about 80 °C due to dehydration and an exothermic peak at about 173 °C due to decomposition (Fig. 6-e)). Nakagawa *et al.*[6] described the effects of grinding and drying on the solid state stability of sodium prasterone sulfate. The activation energy of a more disordered sample produced by grinding or drying was smaller than that of the intact sample, that is, the sample became more unstable. We previously reported that cephalexin was not transformed into the noncrystalline state by the removal of crystal water, but retained the crystal structure. However, the decomposition point (Dp) of NC which was obtained by freeze-drying was about 17 °C lower than that of CC, that is, NC was more unstable than CC. The DTA curve of NC at 66% RH showed an exothermic peak at about 173 °C due to decomposition, whereas those at 75—95% RH showed an exothermic peak at about 183 °C, as shown in Fig. 6-b), and c).

Figure 7 shows a Dp–RH diagram. The Dp of NC at up to 66% RH was about 173 °C, but at 75—95% RH, the Dp was about 183 °C. This result suggests that NC partly crystallized when it was stored at more than 75% RH, that is, NC changed to a more stable form under conditions of high humidity. However, the Dp of the solid crystallized from NC was about 5 °C lower than that of CC. The X-ray diffraction peaks of this solid obtained from NC under high humidity were broader than those of CC (Fig. 4-a), b) and c)). Therefore, this solid probably consists of both crystalline and noncrystalline regions.

The changes of the water content, the X-ray diffraction patterns, IR spectra and DTA curves were all consistent with the above view.

The Solubility of NC

Figure 8 shows the concentration–time curves of NC and CC after storage for 2 weeks at 43% RH at 35 °C. The concentration–time curves of NC at 10, 15 and 20 °C reached a plateau, and then declined. This finding is considered to be due to the crystallization of NC. The concentration–time curve of NC at 10 °C showed high concentrations for about 5 h

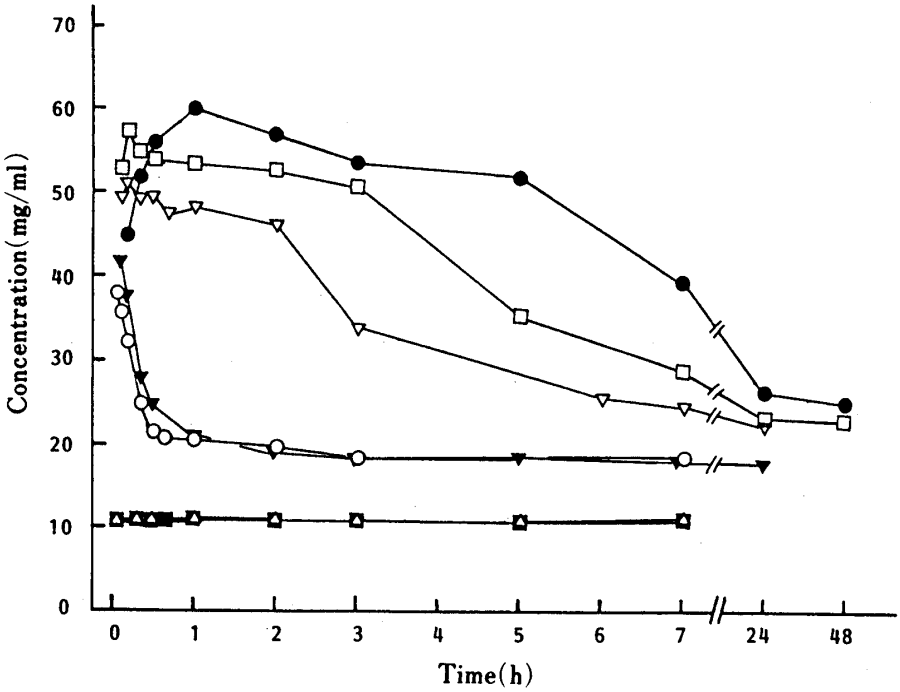

Fig. 8. Concentration–Time Curves for NC and CC in Water at Various Temperatures

NC at 10°C; —●—, CC at 10°C; —■—,
NC at 15°C; —□—, CC at 35°C; —△—,
NC at 20°C; —▽—,
NC at 25°C; —▼—,
NC at 35°C; —○—.

(Fig. 8), because NC crystallized slowly at low temperature. Therefore it was assumed that the solubilities (*Cs*) of NC corresponded to the initial plateau values of the concentration–time curves at 10, 15 and 20°C. The solubilities of NC at 10, 15 and 20°C were determined to be 59.9 mg/ml, 54.4 mg/ml and 49.2 mg/ml, respectively. The concentration–time curves of CC at 10, 15, 20, 25 and 35°C were almost the same. These results suggest that NC is more soluble than CC at various temperatures, as shown in Fig. 8. The partly crystallized solid obtained from NC was about twice as soluble as CC at 25 and 35°C.

Figure 9 shows van't Hoff plots for the solubilities of NC and CC. The plot for NC gave a good straight line. The value of the heat of solution for NC was calculated from the slope of the plot and was determined to be −3.24 kcal/mol.

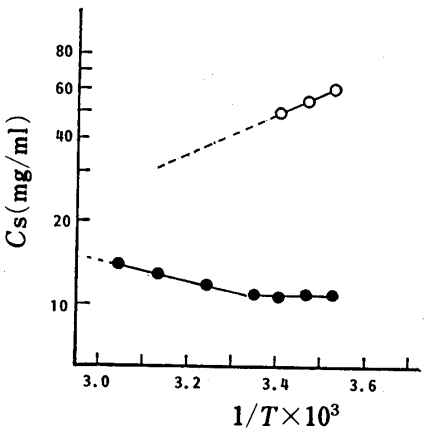

Fig. 9. Plots of Solubility Values for NC and CC

NC; —○—, CC; —●—.

The X-ray diffraction pattern of the solid residue which crystallized from NC in water was identical with that of phase II (dihydrate),[3] and that of the solid dried at 35°C was identical with that of phase IV. However, the X-ray diffraction peaks of the solid residue which crystallized from NC at 10°C were broader than those of CC, and its Dp was 183.5°C, 6.5°C lower than that of CC. This suggests that the solid residue which crystallized from NC consists of both crystalline and noncrystalline regions. Thus, the materials crystallized from NC at 10, 15 and 20°C contain considerable amounts of noncrystalline solid. In the previous

paper,[4] the solubilities of the solid residues which were transformed from the phase III–1/2 hydrate and the phase V–hydrate were reported to be much larger than that of CC at the same temperature, and the X-ray diffraction peaks of the solid residues were broader than those of CC. This finding may be in accord with the results of the present paper.

Conclusions

1. NC which was obtained by freeze-drying remained in the noncrystalline state under conditions of 0—66% RH at 35 °C.
2. NC was about 6 times more soluble than CC in distilled water at 10 °C.

References and Notes

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