[Chem. Pharm. Bull. 33(11)5028—5035(1985)]

Water Content and Dehydration Behavior of Crystalline Caffeine Hydrate[1)]

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(Received March 27, 1985)

The polymorphic transition of anhydrous caffeine was investigated by differential scanning calorimetry (DSC) and X-ray powder diffractometry. The water content of caffeine hydrate was determined by means of thermogravimetry, a phase diagram of the water–caffeine system, and a water vapor sorption experiment. All the results indicated that caffeine hydrate does not exist as a monohydrate, but contains 0.8 mol of water per mol of caffeine. Some thermodynamic parameters including the enthalpies of transition, fusion, and dehydration were determined by DSC of two anhydrous polymorphs and the hydrated form. The effect of dehydration on the micromeritic properties of caffeine was studied by electron microscopy and BET gas adsorption analysis.

Keywords——caffeine hydrate; dehydration; anhydrous caffeine; polymorph; thermal behavior; phase diagram; specific surface area; water vapor sorption

It is stated in the drug monographs of the Pharmacopoeia of Japan Tenth Edition (JP X)[2)] that caffeine hydrate contains 1 mol of water per mol of caffeine. However, our preliminary experiments, in which the weight decrease curve of wet caffeine hydrate was measured at room temperature, indicated that the monohydrate does not exist.

About the four decades ago, Waters and Beal found that the stable hydrate of caffeine at high relative humidities contains 5/6 mol of water per mol of caffeine.[3)] More recently, Sutor investigated the hydrate crystallographically and obtained very interesting results.[4)] Further, Bothe and Cammenga studied the dehydration kinetics of caffeine by thermal analysis.[5)] All of these authors indicated the existence of a hydrate containing less water than the monohydrate.

The present paper deals with the water of crystallization of caffeine hydrate. Dehydration and hydration of caffeine were studied by differential scanning calorimetry, thermogravimetry and water vapor sorption measurements. The micromeritic properties of caffeine were also investigated.

Experimental

Materials——Caffeine hydrate was prepared as follows. Anhydrous caffeine (JP X) dissolved in hot distilled water was left overnight at room temperature. Caffeine hydrate recrystallized out in long, silky needles, which were collected by filtration, and adhering water was soaked up with filter papers. These wet crystals were placed in a tared glass dish and weighed at suitable intervals with a chemical balance. The moisture in the chamber of the balance was removed by silica gels. A weight decrease curve obtained at 25 ± 1 °C is shown in Fig. 1. Since free water would be eliminated more rapidly than combined water, it was reasonably considered that the first plateau appearing after 300—600 min would correspond to the net weight of pure caffeine hydrate without the adhering water. The subsequent gradual decrease and the second plateau after 8 d are attributable to the dehydration of combined water and the weight of anhydrous caffeine, respectively. The weight difference between two plateaus was equivalent to 0.803 mol of water. In this report, caffeine retaining the crystalline state corresponding to the first plateau is referred

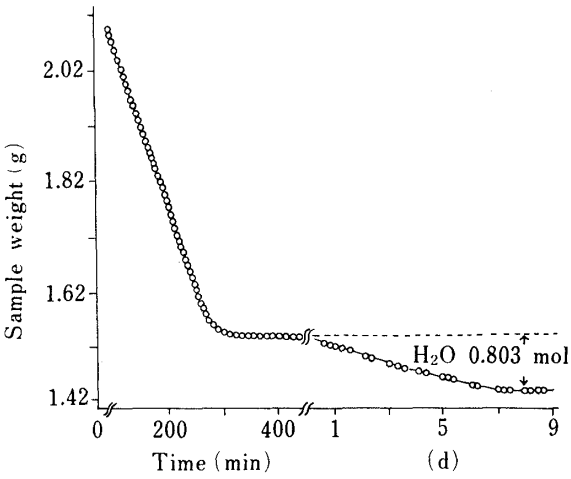


Fig. 1. Weight Decrease Curve of Caffeine Hydrate at 25±1 °C

to as caffeine hydrate. As caffeine hydrate effloresces under atmospheric conditions, it was stored in a constant humidity desiccator containing a saturated calcium sulfate solution with its precipitate, the relative humidity of which was approximately 97% at 25 °C. Under these conditions, caffeine hydrate was stable throughout the experiments.

Differential Scanning Calorimetry (DSC)——A Daini Seikosha DSC-20 differential scanning calorimeter was used. The heating rate usually employed was 1 or 5 °C/min. The DSC apparatus was calibrated with distilled water (0 °C; 6.01 kJ/mol), indium (156.6 °C; 3.3 kJ/mol), and tin (231.9 °C; 7.07 kJ/mol). The samples had a mass of 8—10 mg and were weighed on a microbalance to ±0.01 mg. The reference material was calcined α-Al_2O_3, and dry nitrogen was allowed to flow at a rate of 50 ml/min. For the measurements under closed conditions, the samples were encapsulated in gas-tight (hermetic) containers which could withstand a pressure of 50 atm. For the measurements below room temperature, the furnace was cooled with a cryogenic cover filled with liquid N_2.

Thermogravimetry (TG)——A Perkin-Elmer TGS-1 thermobalance was used. The sample weights were 3—10 mg and the heating rate was 4 °C/min.

Infrared (IR) Spectroscopy——IR spectra were measured by the Nujol mull method with a Jasco IRA-1 grating infrared spectrometer.

X-Ray Powder Diffractometry——A JDX-7F X-ray diffraction analyzer from Japan Electron Optics Laboratory Co., Ltd. was used (Ni filter, CuK_α radiation, $\lambda = 1.542$ Å).

Scanning Electron Microscopy——The surface appearance of caffeine hydrate and anhydrous caffeine was observed using a scanning electron microscope (MINI SEM model MSM-4, Hitachi-Akashi Co., Ltd.).

Microscopic Observation——Microscopic observations of crystals during dehydration under atmospheric conditions were made using a microscope (model-FH, Olympus Optical Co., Ltd.).

Measurements of Specific Surface Area and Water Vapor Sorption——The specific surface area of caffeine and the weight increase of anhydrous caffeine due to hydrate formation were determined using a BET gas adsorption and water vapor sorption apparatus (model P-850, Shibata Chemical Apparatus Mfg. Co., Ltd.). In the measurements of specific surface areas, the sample weights were 0.9—7 g and the adsorbed gas was N_2. The apparatus for water vapor sorption consisted of a quartz spring balance (sensitivity 10.55 mg/mm) and a flask from which water vapor is supplied. The apparatus was maintained at a constant temperature by an air bath system. Anhydrous caffeine (about 1.0 g, precisely weighed) was placed in a quartz bucket (1.25 g) forming a powder bed roughly 2 mm deep. After the apparatus had been evacuated, the pumping system was valved off. Then, by introducing water vapor into the apparatus, the sample was exposed to 97% relative humidity. The elongations of the quartz spring were read with a cathetometer at suitable intervals, and the readings were converted into weight values from a calibration curve previously determined.

Results and Discussion

DSC of Caffeine

Anhydrous caffeine form II was prepared by drying the wet hydrate in a silica gel desiccator followed by heating at 80 °C for several hours to eliminate remaining minute amounts of water. As shown in Fig. 2 (a), the DSC curve has two endothermic peaks. The first one around 150 °C is broad and can be ascribed to the transition into a new crystal form (form I). The transition was confirmed from the alteration of the X-ray powder diffraction patterns. The enthalpy of transition was 3.7±0.2 kJ/mol; this value agrees with those of other

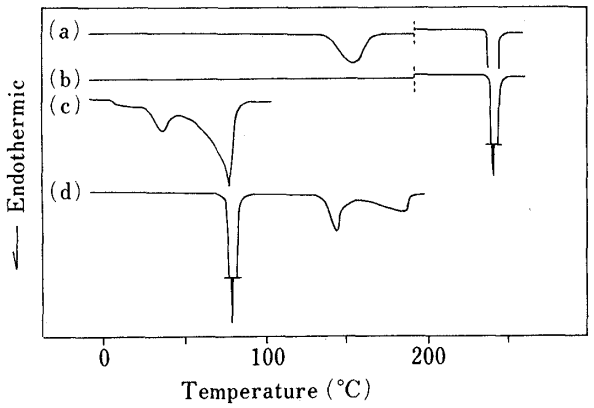


Fig. 2. DSC Curves of Caffeine (Heating Rate: 5 °C/min)

(a) Anhydrous caffeine (form II) under closed conditions: sample weight, 9.300 mg. (b) Anhydrous caffeine (form I) under closed conditions: sample weight, 9.321 mg. (c) Caffeine hydrate under open conditions: sample weight, 5.214 mg. (d) Caffeine hydrate under closed conditions: sample weight, 11.076 mg.

The dotted lines on curves (a) and (b) represent the change of sensitivity from 10 to 40 mJ/s.

investigators.[6] The second peak at 236.0 °C was due to melting of form I and the enthalpy of fusion was 21.5±0.5 kJ/mol.

Form I was prepared by heating form II at 180 °C for 10 h in a thick glass test tube which could withstand a pressure of 20 atm. The DSC curve showed no transition peak but gave a fusion peak (Fig. 2 (b)).

Curve (c) is the DSC pattern of caffeine hydrate under open conditions. A broad endothermic peak owing to the dehydration and the subsequent evaporation of eliminated water was observed. The whole area of this peak corresponds to the heat value of 41.8±1.1 kJ/mol. Since the heat of evaporation of water which was measured under the same DSC conditions was 38.9±0.4 kJ/mol, the difference between the two values may be approximately equal to the enthalpy of dehydration. Taking into account that the hydrate contains 0.8 mol of water per molecule, the calculated enthalpy of dehydration is 10.7 kJ/mol. Our preliminary vapor pressure studies indicated that the heat of dehydration of caffeine hydrate is 41.2 kJ/mol, and this value agreed with the results of DSC.

Curve (d) is the DSC pattern of caffeine hydrate under closed conditions. Because of the absence of free water, a melting peak of ice around 0 °C does not appear. The sharp peak at 79—80 °C is attributable to the peritectic reaction of the hydrate, and the enthalpy of dehydration was apparently 7.96±0.16 kJ/mol. As Bothe and Cammenga pointed out,[7] this value contains the heat of evaporation of a part of the water into the void space in the hermetic container, the heat of dissolution of some caffeine into the rest of the water, and the heat of transition to a metastable anhydrous caffeine.[8] Therefore, the value obtained directly from the peak area would be somewhat overestimated. The endothermic peaks at 142—143 °C and at 184—185 °C are due to the transition from form II to form I and the melting of form I, respectively.

X-Ray Diffraction of Caffeine

The X-ray powder diffraction patterns of the two polymorphs and the hydrate of caffeine are in Fig. 3. All of the patterns are different and characteristic.

IR Spectra of Caffeine

The IR spectra of the two polymorphs of anhydrous caffeine are indistinguishable, as shown in Fig. 4. The hydrate possesses a broad absorption in the region of 3000—3600 cm^{-1} which is due to the hydrogen bonding of water molecules.

TG and Water Vapor Sorption of Caffeine

To investigate the water content of the hydrate in detail, dynamic TG was performed as follows: the wet hydrate crystals were left in a TG furnace at 25 °C until a constant weight was reached, and then the furnace was heated at the rate of 4 °C/min to 90 °C. The weight

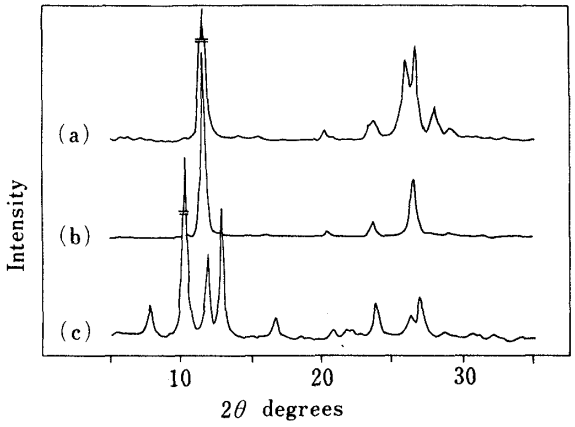


Fig. 3. X-Ray Powder Diffraction Patterns of Caffeine

(a) Anhydrous form II. (b) Anhydrous form I. (c) Hydrate.

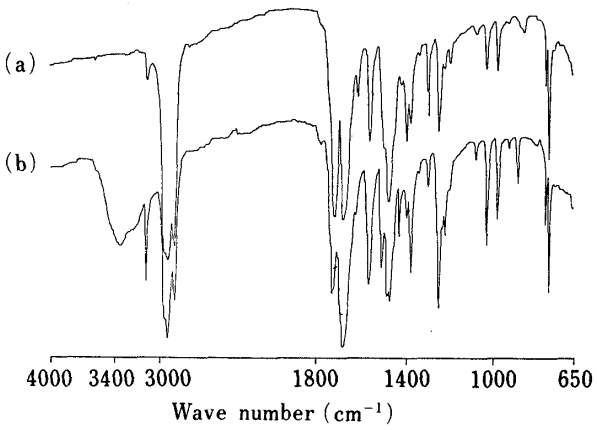


Fig. 4. IR Spectra of Caffeine (Nujol Mull)

(a) Anhydrous form. (b) Hydrate.

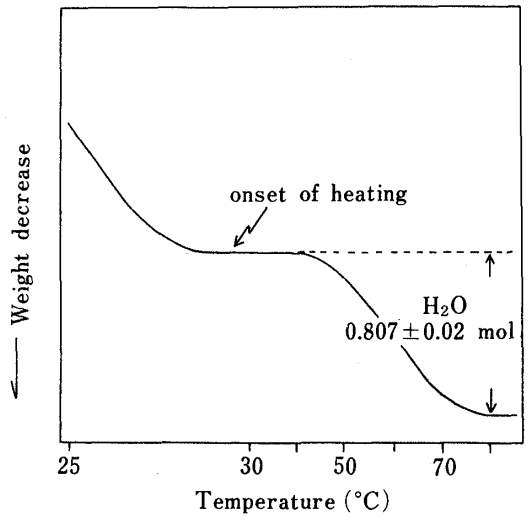


Fig. 5. Dynamic TG Curve of Dehydration of Wet Crystalline Caffeine Hydrate (Heating Rate: 4 °C/min)

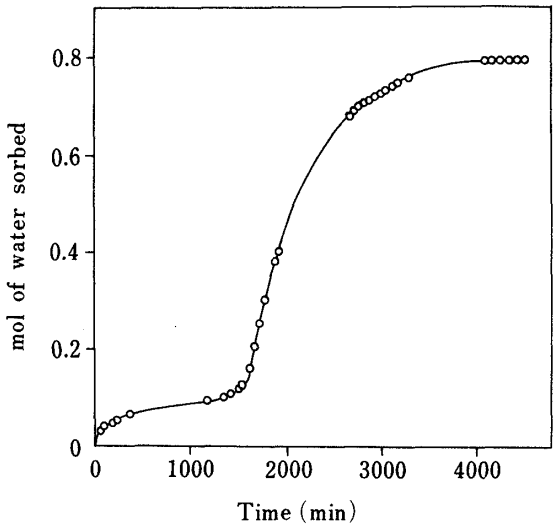


Fig. 6. Sorption of Water Vapor on Anhydrous Caffeine at 25±1 °C (Relative Humidity: 97%)

difference between the two plateaus in Fig. 5 corresponded to 0.807±0.02 mol of water. This value agreed very well with the result obtained by using a chemical balance (see Fig. 1).

The water vapor sorption on anhydrous caffeine, having a specific surface area of 1.12 m^2/g, was measured. Figure 6 shows plots of the mol numbers of sorbed water against time. After an initial long induction period, the water vapor sorption proceeds fairly rapidly and soon attains an equilibrium state. The difference between the initial and final length of the spring is equivalent to 0.802 mol of water. Both of the results indicate that caffeine hydrate possesses 0.8 mol of water of crystallization.

Phase Diagram of the Caffeine–Water System

Using the DSC gas-tight containers, the phase diagram of the caffeine–water system was constructed. The powder of anhydrous caffeine and water corresponding to each composition were precisely weighed into a container, and an aluminum cover was mounted on it. The container was sealed with a caulker and transferred to a DSC furnace maintained at 25 °C. The furnace was cooled to −60 °C with liquid N_2, and shortly thereafter, the sample solidified

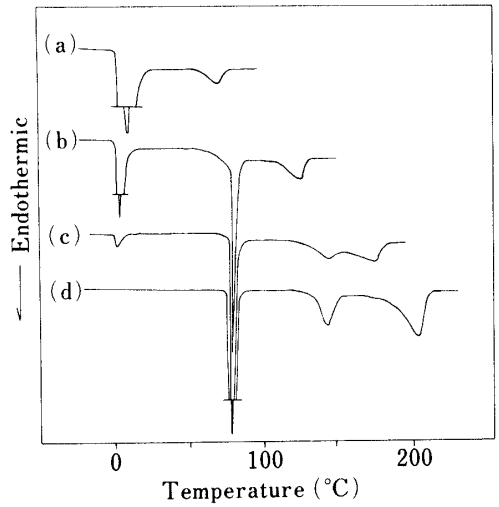


Fig. 7. DSC Curves of the Caffeine–Water System (Heating Rate: 5 °C/min)

(a) Caffeine 3.34 mol%: total sample weight, 18.764 mg. (b) 21.24 mol%: 10.305 mg. (c) 50.54 mol%: 8.530 mg. (d) 68.69 mol%: 8.254 mg.

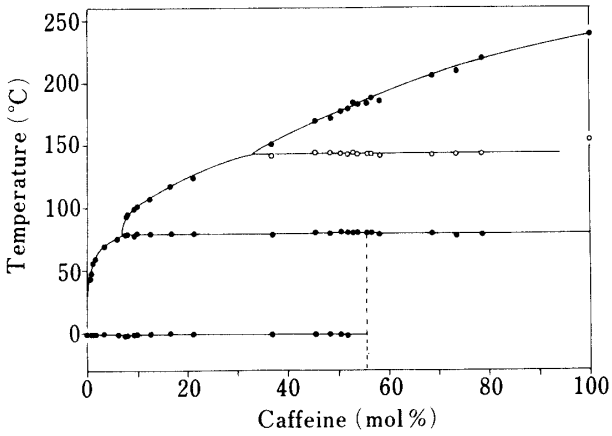


Fig. 8. Phase Diagram of the Caffeine–Water System

The dotted line corresponds to the composition of caffeine hydrate. ○, polymorphic transition point; ●, eutectic, peritectic, or melting point.

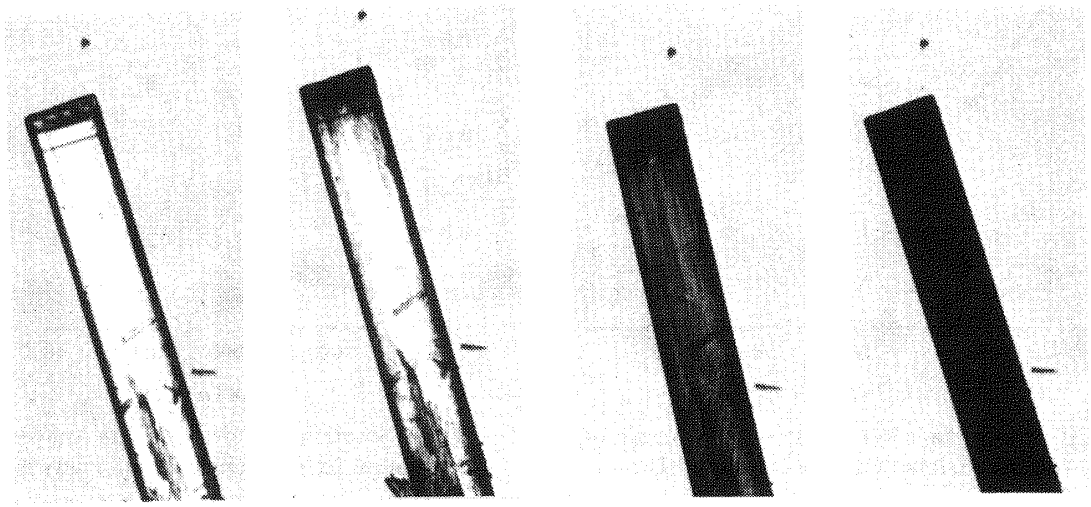
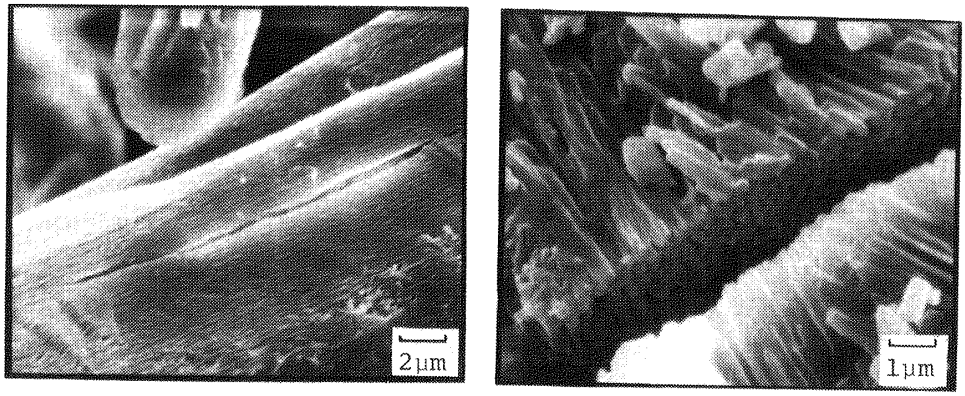


Fig. 9. Dehydration of a Crystal of Caffeine Hydrate in Air at Room Temperature

(a) Immediately after standing in air. (b) After 2 h in air. (c) After 3 h in air. (d) After 24 h in air.

completely. Subsequently, the furnace was heated at a rate of 5 °C/min until the contents fused completely. The container was removed from the furnace and was allowed to stand at room temperature. After a week, the DSC measurement of the same sample was run again according to the above-mentioned procedures. Typical DSC patterns obtained in this manner are illustrated in Fig. 7. Excluding the peak due to the polymorphic transition of caffeine which appears at 142—143 °C, two or three peaks generally appeared. The lowest peak at 0 °C and the middle one at 79—80 °C are due to the eutectic and peritectic reactions, respectively; while the highest peak is ascribed to the melting of the hydrate (Fig. 7 (a)) or anhydrous caffeine (Fig. 7 (b) (c) (d)) depending on the composition of the sample.

The phase diagram was satisfactorily obtained as shown in Fig. 8 by connecting the temperatures corresponding to each phase reaction. The composition equivalent to the



(a) (b)

Fig. 10. Scanning Electron Micrographs of Caffeine
(a) Caffeine hydrate, 5000×. (b) Caffeine after dehydration, 10000×.

hydrate is equal to 55.56 mol% of caffeine. The eutectic peak at 0 °C still appears at a composition of a little more than 50 mol%. This suggests that the hydrate is not composed of equimolecular caffeine and water, but is richer in caffeine in molecular ratio. However, when the caffeine content exceeds 52 mol%, no eutectic peak is perceptible; this can be reasonably ascribed to the sensitivity of the instruments. In other words, it seems certain from the shape of the phase diagram in Fig. 8 that these samples contain negligibly small amounts of the eutectic mixture (cryohydrate); accordingly, the endothermic heat effect due to the eutectic fusion might be included in the slight change of the base line slope. From the above results, it is concluded that caffeine does not form the formerly believed monohydrate, but forms one containing 0.8 mol of water of crystallization.

Microscopic Observations

The dehydration behavior of a crystal of caffeine hydrate was observed microscopically in air at room temperature. As shown in Fig. 9, the dehydration takes place predominantly in the long axis. According to X-ray crystallography carried out by Sutor,[4] and Gerdil and Marsh,[9] there are tunnels of water molecules approximately parallel to the *c* axis (the long direction). The anisotropic behavior in the dehydration[10] and the ease of efflorescence are probably due to the preferential escape of the water molecules along this axis.

Figure 10 shows electron microphotographs of the hydrate and anhydrous caffeine. The smooth surface of the hydrate is in contrast to the rough surface having many deep cavities of anhydrous caffeine. These cavities run along the long direction of the crystal.

Specific Surface Area of Caffeine

The specific surface areas of the hydrate and anhydrous caffeine were measured with a BET gas adsorption apparatus. Since the hydrate effloresces in air, the content of water was determined after each measurement. More than 0.75 mol of water remained in all of the samples. The surface areas are shown in Table I. The slow recrystallization from a relatively low concentration produces large crystals such as sample (3). Anhydrous caffeine obtained by dehydration under various conditions, briefly described in the table, has a greater surface area than the corresponding hydrate. The large surface area of freeze-dried caffeine may be due to the formation of fine crystals during rapid freezing, dehydration during drying, and/or formation of a metastable simple eutectic mixture. The X-ray diffraction pattern of the freeze-dried powder coincided with the pattern of polymorph II.

In order to elucidate the limit of the increment of specific surface area, the effect of repeated hydration and dehydration was studied using samples (2) and (3) in Table I.

TABLE I. Specific Surface Areas of Caffeine Samples

Sample	Conditions for dehydration	Specific surface area (m^2/g)
Hydrate-(1)		0.89
Hydrate-(2)		0.98
Hydrate-(3)		0.48
Anhydrous-(1)	a) 20—25 °C (in silica gel desiccator), atmospheric	1.08
	b) 60 °C for 6 h, approx. 30 mmHg	0.94
Anhydrous-(2)	20—25 °C, atmospheric	1.98
Anhydrous-(3)	20—25 °C (in silica gel desiccator), atmospheric	0.74
Freeze-dried		7.39

Caffeine hydrate was recrystallized from aqueous solution with the following concentrations. sample (1), 14.3 w/v%; sample (2), 4.0 w/v%; sample (3), 3.0 w/v%.

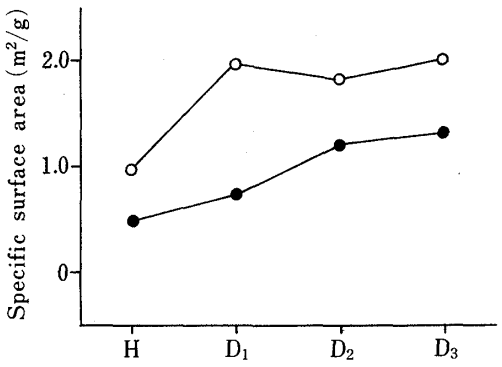


Fig. 11. Effect of Repeated Hydration and Dehydration on the Specific Surface Area of Caffeine

H, caffeine hydrate; D, dehydrated caffeine. ○, sample (2); ●, sample (3).

Sekiguchi *et al.*[11] investigated the effect of repeated solvation and desolvation on the particle size of griseofulvin and its chloroformate, and found that one cycle of the method produces effectively pulverized griseofulvin. The ordinate in Fig. 11 is specific surface area and H and D on the abscissa are the hydrate and dehydrated caffeine, respectively. Sample D_1 was obtained according to the method described in Table I. Sample D_2 was prepared by dehydration of the regenerated hydrate formed by water vapor sorption for several days. Sample D_3 was prepared by a further repetition of these procedures. In the course of these procedures, no mechanical forces (such as trituration) were applied. With repetition of hydration–dehydration cycles, the surface area increases initially, but soon approaches the asymptotic value. This result may be ascribed in part to liquid formation (*e.g.* by capillary condensation) during the hydration process.

References and Notes

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