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Crystal Forms of Calcium D(+)-Pantothenate

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Calcium D(+)-pantothenate crystallized from various solvents was proved to have three polymorphs (α-, β-, and γ-form), an amorphous form and a solvate which contained 4 molecules of methanol and 1 molecule of water of crystallization. It was also found that the solvate was changed to the amorphous form by drying, to α-form on standing in a closed container at temperatures above 30° and to the monohydrate on standing in atmosphere. The data of X-ray powder diffraction, infrared spectroscopy and dissolution behavior are presented for the identification of these various forms.

Various kinds of crystals of calcium D(+)-pantothenate have been prepared by several investigators.[2-5] However, the physical properties of these crystals have not been investigated in detail and the data of different authors are at variance.

In the present study, various crystals of calcium D(+)-pantothenate obtained by recrystallization from different solvents were examined by thermal analysis, X-ray diffraction analysis, infrared spectrophotometry and dissolution-rate measurements for characterization of the crystals.

As the results, calcium D(+)-pantothenate was found to have three polymorphs (α-, β- and γ-form), an amorphous from and a solvate which contained 4 molecules of methanol and 1 molecule of water of crystallization. It was also found that the solvate was changed to the amorphous form by drying at 50—100°, to α-form on standing in a closed container at temperatures above 30° and to the monohydrate on standing in atmosphere.

Experimental

Materials——Calcium D(+)-pantothenate used for preparation of the various crystal forms was the amorphous form which was prepared by drying at 50—100° under an infrared (IR) lamp the solvate recrystallized from 90% aqueous methanol at 0°. Solvents used in this experiment were reagent grade.

Instruments——Thermal analysis was carried out using TG-DTA (Rigaku Denki CAT. No. 8021). Measurement conditions adopted for this purpose were; heating rate, 1°/min; senstivity of amplifier, ±50 μV; standard sample, Al_2O_3; atmosphere, air; weight, 100—150 mg. The X-ray diffraction patterns were obtained with a Rigakudenki X-ray diffractometer Type 2012 with; target, Cu; filter, Ni; voltage, 35 kV; current, 20 mA; count range, 2000 c.p.s; time constant, 1 sec; scanning speed 2°/min; divergency, 1°; receiving slit, 0.15 mm. IR spectra were taken with a Hitachi Grating Infrared Spectrophotometer Model 215 using nujol mull. The gas-liquid chromatography was carried out with a Shimadzu Gas Chromatograph Model GC-4BM equipped with a hydrogen flame ionization detector and a glass column (2.0 m × 3.0 mm) packed with Porapak. Q (80—100 mesh).

Preparation of Crystals——The amorphous form was dissolved in a suitable volume of appropriate solvent and allowed to stand for 5 hour—2 days at a constant temperature. The deposited crystals were filtered and dried at room temperature *in vacuo*. The water contents of the aqueous solvents used were less than 25%.

Hygroscopic Equilibrium——Saturated salts solutions were used in order to obtain constant relative humidities. Changes in weight and water content of the samples were measured periodically. Water content was determined by the Karl-Fisher method.

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1) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
2) E.T. Stiller, S.A. Harris, J. Finkelstein, J.C. Keresztesy, and K. Folkers, *J. Am. Chem. Soc.*, **62**, 1785 (1940).
3) H. Levy, J. Weijlard, and E.T. Stiller, *J. Am. Chem. Soc.*, **63**, 2846 (1941).
4) S. Funabashi and K. Michi, *Bull. Inst. Phys. Chem. Research.* (Japan), **22**, 681 (1943).
5) K. Masutani, S. Tazaki, H. Hotta, A. Kitaide, and I. Sakiyoku, Japan Patent 40-2330 (1965).

Rate of Dissolution——A weighed sample of the various crystals, approximately two times the concentration necessary to saturate the solution, was added in 200 ml of methanol maintained at 30°±0.1° with stirring. Periodically 10—20 ml aliquots of the solution were withdrawn and immediately filtered through 11 G 4 glass filter. The concentration was determined by the titration of Ca with 0.05 mol. EDTA.

Results and Discussion

α-Form

The crystals obtained from methanol, methyl cellosolve and aqueous methanol at temperatures above 30° appear as fluffy needles under a microscope, and the crystals obtained from ethanol at temperatures below 20° are needles.

It was found that these crystals were identical each other by X-ray diffraction patterns and IR spectra. These crystals are named α-form.

Levy, *et al.*$^{3)}$ Funabashi, *et al.*$^{4)}$ described methods for the preparation of a methanol solvate. Levy's methanol solvate obtained from 99.5% methanol at room temperature was needles which had a melting point of 195—196°, and Funabashi's methanol solvate obtained from methanol at room temperature was prisms which had a melting point of 153.5—154.0°. As far as we followed their procedures for preparation of methanol solvates, the reported crystals could not be obtained. However, we obtained a solvate which contained methanol and water of crystallization from aqueous methanol at low temperatures as described later. The crystal form of this solvate are closely similar to that of Funabashi's methanol solvate.

β-Form

The crystals obtained from ethanol at temperatures below 20° are α-form, but the crystals obtained at temperatures above 35° are microcrystalline. At temperatures between 20° to 35°, the mixed crystals of α-form and microcrystals are obtained. The crystals obtained from aqueous ethanol are needles similar to α-form obtained from ethanol. The X-ray diffraction patterns and IR spectra showed that the needles and the microcrystals are identical, but differ from α-form. From the results of thermal analysis and gas-liquid chromatography, these crystals proved to be not solvated.

These crystals are named β-form.

γ-Form

The crystals obtained from isopropanol or aqueous isopropanol, were found to comprize two kinds of crystals, α-form and the crystals differed from α-form or β-form by comparison of their X-ray diffraction patterns and IR spectra. In this case, α-form tends to be prevailed by rapid crystallization, while the latter tends to be obtained by slow crystallization. Both crystalline forms appear as needles or long coloumns and are indistinguishable under a microscope. The latter form was found to be nonsolvated by thermal analysis and gas-liquid chromatography.

These crystals are named γ-form.

Levy, *et al.*$^{3)}$ have reported that the crystals obtained from isopropanol were fine needles which contained 1/2 molecule of isopropanol of crystallization. As far as we investigated the crystals obtained from isopropanol or aqueous isopropanol under various conditions, an isopropanol solvate was not obtained.

Amorphous Form

The microcrystalline powders are precipitated from the methanol solution by addition of acetone, ether, ethyl acetate, *etc.* These powders proved to be amorphous form by X-ray diffraction analysis.

All forms described above had a melting point of 193—197°.

D-PC·4MeOH·1H$_2$O

The crystals obtained from aqueous methanol at low temperatures are hygroscopic prisms which have a melting point of 61—62°. Although these crystals have been prepared by Masutani, *et al.*,[5] no physical data have been reported. These crystals were presumed to be a solvate because the melting point was lower than that of the other crystals. Therefore the composition of solvents of crystallization was examined by gas-liquid chromatography, the Karl-Fisher method, weight loss on drying, elemental analysis and thermal analysis, and it was revealed that the crystals were a solvate which contained 4 molecules of methanol and 1 molecule of water of crystallization.

These crystals are hereinafter abbreviated as D-PC·4MeOH·1H_2O.

The TG–DTA (thermogravimetry-differential thermal analysis) curve of D-PC·4MeOH·1H_2O is illustrated in Fig. 3(a). The thermogram of D-PC·4MeOH·1H_2O shows three endothermic changes and three weight losses at the same temperatures; the first change at about 65° and the second change at about 80° correspond to the liberation of the solvents of crystallization and the third change at about 185° corresponds to decomposition. The TG curve suggests that the liberation of the solvents proceeds through two steps; at first 2 molecules of methanol liberate and next 2 molecules of methanol and 1 molecule of water liverate.

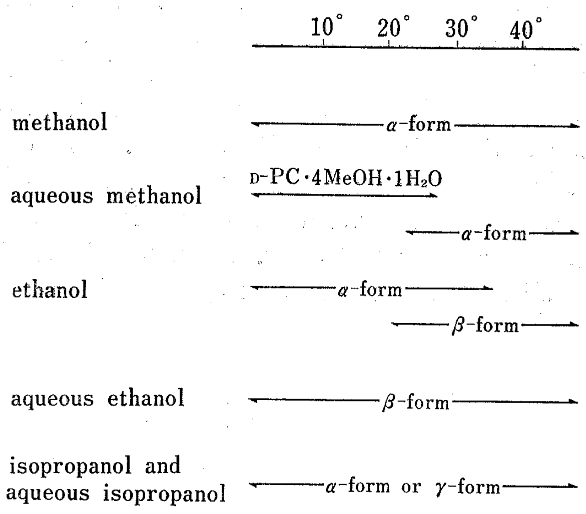


Fig. 1. The Crystal Forms of Calcium D(+)-Pantothenate Obtained from Lower Alcohols and Aqueous Lower Alcohols

The crystals obtained from methanol, ethanol, isopropanol and the corresponding aqueous alcohols in this studies described above are summarized in Fig. 1.

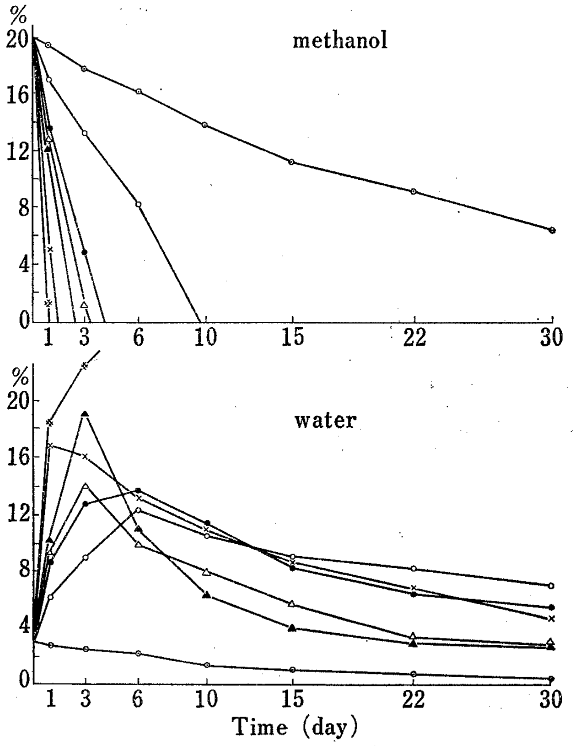


Fig. 2. Changes of Water and Methanol Contents in D-PC·4MeOH·1H_2O under Constant Relative Humidities at 20°

⊙—⊙: 0%, ○—○: 20%, ●—●: 35%, △—△: 54%, ▲—▲: 75%, ×—×: 81%, ♯—♯: 95%

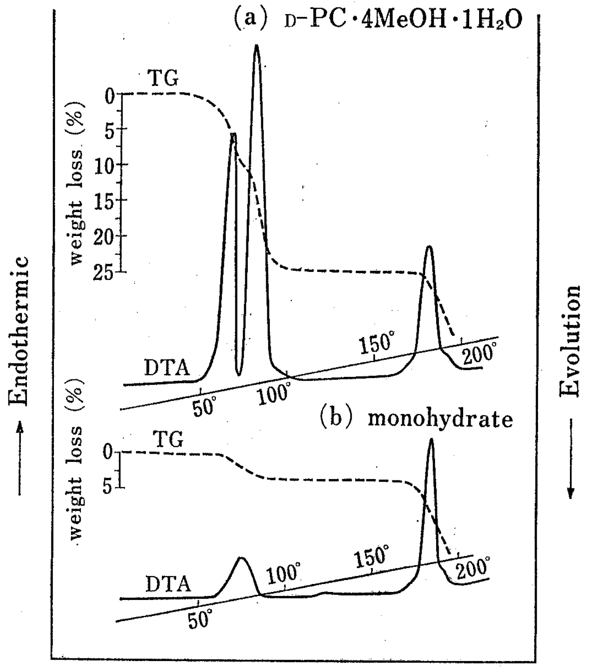
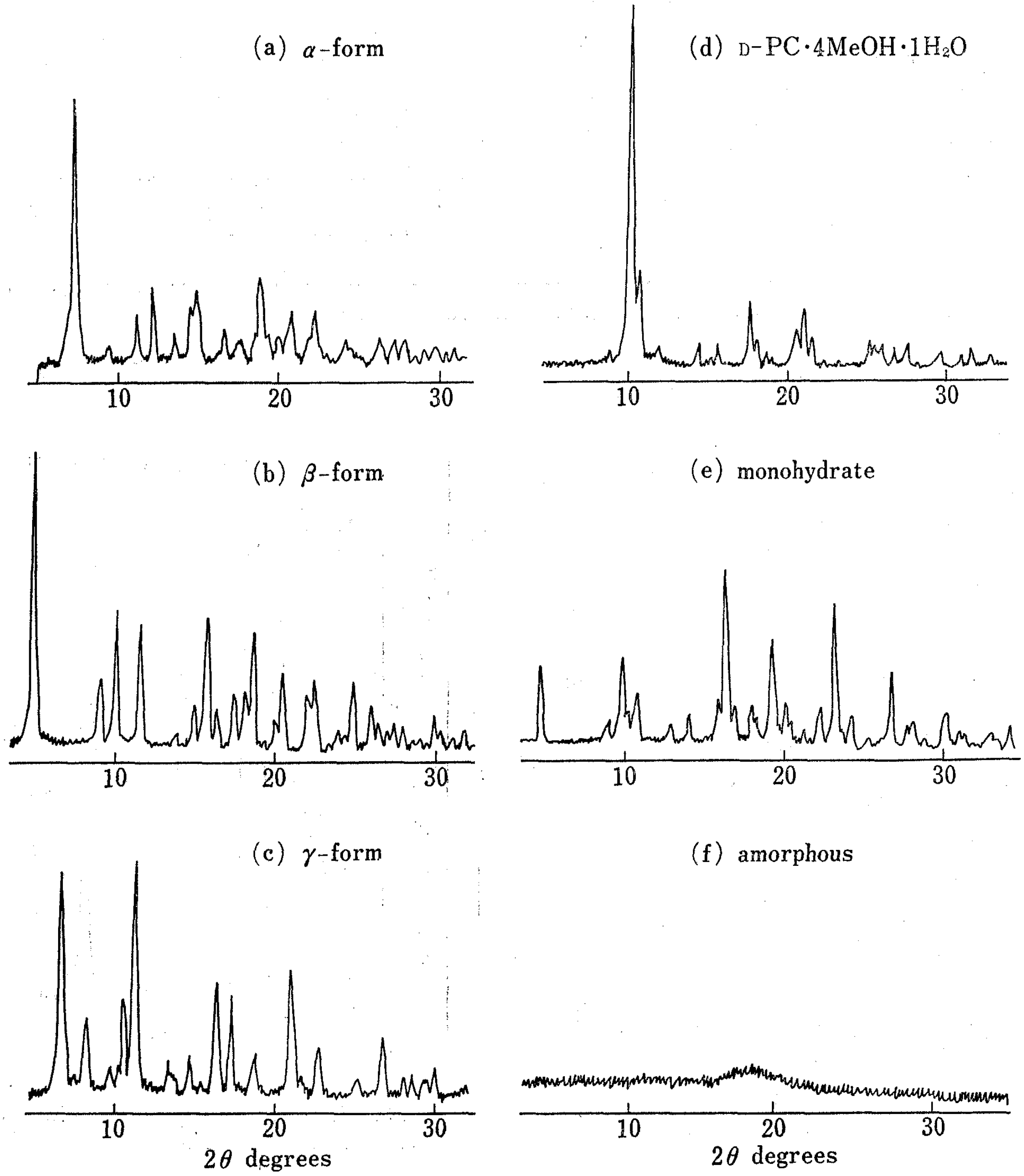


Fig. 3. TG-DTA Curves of D-PC·4MeOH·1H_2O and Monohydrate

Conversion of D-PC·4MeOH·1H$_2$O

The solvents of crystallization of D-PC·4MeOH·1H$_2$O are liberated by drying at 50—100°. From the result of X-ray diffraction analysis, the nonsolvated form obtained was found to be amorphous form.

D-PC·4MeOH·1H$_2$O is converted to α-form by standing in a closed container for a few days at temperatures above 30°. However, by standing in atomsphere, the water content of this crystals increases and the methanol of crystallization liberates. In order to examine stability of the methanol of crystallization and hygroscopic degrees of D-PC·4MeOH·1H$_2$O, the changes in methanol and water content of this crystals were measured periodically under constant relative humidities at 20°. The experimental results obtained are shown in Fig. 2. It was found from the data that methanol of crystallization was labile under high humidities, and the water content under relative humidities of 20—81% increased in the beginning and decreased after 1—6 days. The rate of increase of the water content is fast under high humidity conditions, but the rate of decrease is fast under moderate humidity conditions (54—75%).


(a) α-form

(d) D-PC·4MeOH·1H$_2$O

(b) β-form

(e) monohydrate

(c) γ-form

(f) amorphous

Fig. 4. X-Ray Diffraction Patterns of Calcium D(+)-Pantothenate Crystal Forms

The water content at equilibrium becomes 3.6—3.8%, which agrees with the theoretical water content of monohydrate (3.62%).

The TG–DTA curves of the crystals obtained at equilibrium are shown in Fig. 3(b). The thermogram of these crystals shows an endothermic change and weight loss of 3.6% at about 75° suggesting the presence of 1 molecule of water. From the result of the thermal analysis, it was revealed that this crystals were monohydrate.

D-PC·4MeOH·$1H_2O$ was also found to be converted to monohydrate by standing at 37° under relative humidities of 20—80%.

D-PC·4MeOH·$1H_2O$ is hygroscopic, but monohydrate is nonhygroscopic.

X-Ray Diffraction and IR Spectroscopy

The X-ray diffraction patterns and the IR spectra for the various forms are shown in Fig. 4 and Fig. 5. These distinguishing patterns and spectra can be utilized for the identification of the various forms and offer the possibility for the analysis of the various forms in mixtures.

Dissolution Rate Studies

The dissolution behavior of the various crystal forms in methanol at 30° is shown in Fig. 6. These plots show the concentration attained in solution for each crystal form as a function

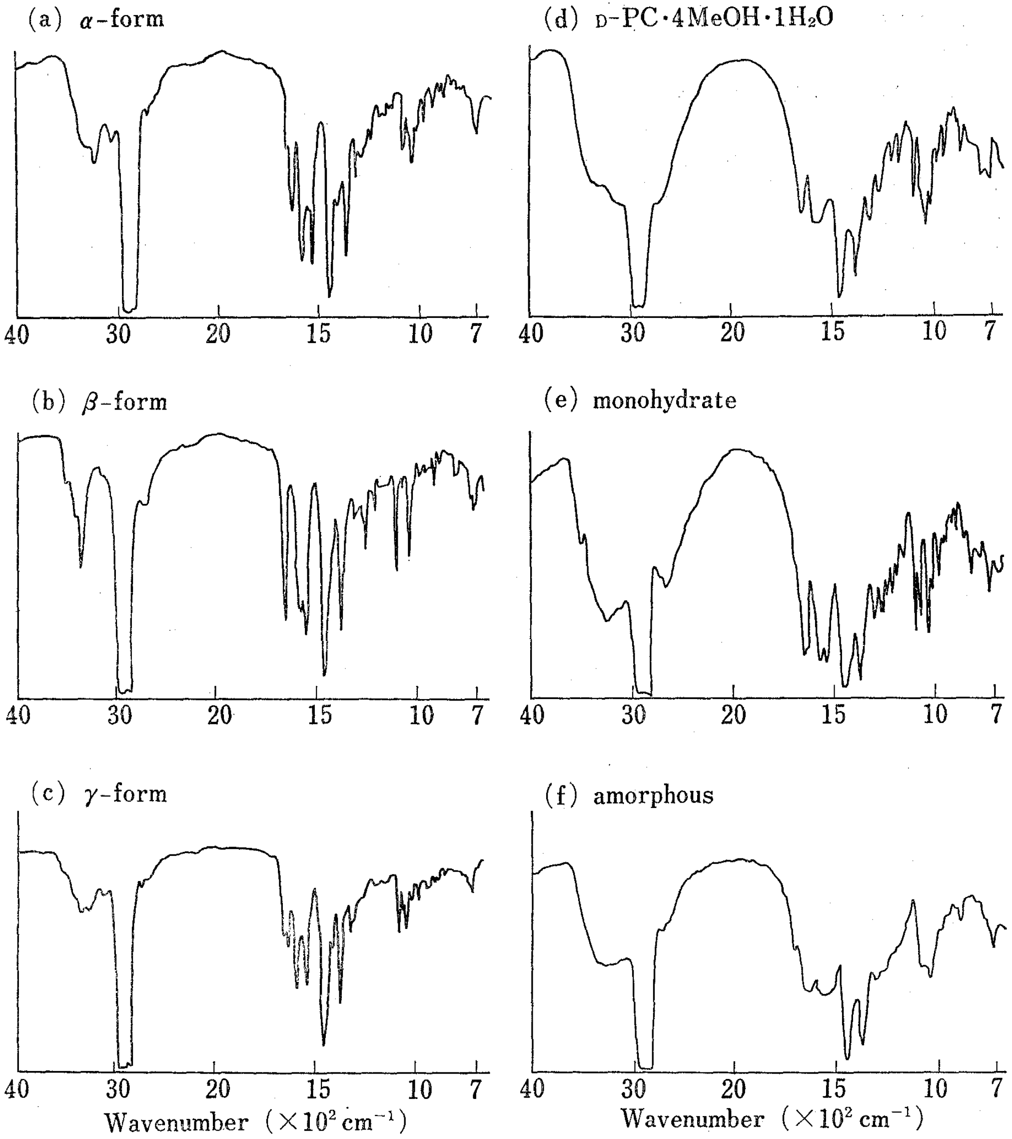


Fig. 5. Infrared Spectra of Calcium D(+)-Pantothenate Crystal Forms

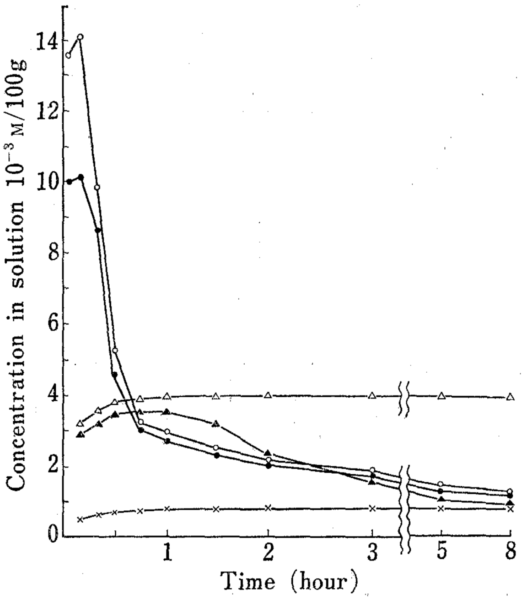


Fig. 6. Dissolution Behaviors of the Crystal Forms of Calcium D(+)-Pantothenate in Methanol at 30°

×—×: α-form, △—△: β-form, ▲—▲: γ-form, ○—○: D-PC·4MeOH·$1H_2O$, ●—●: monohydrate

of time in the presence of an excess of the solid phase and under essentially constant agitation. It is apparent from the data that the initial rates of dissolution of the two solvates were very much greater than those for the three nonsolvated crystal form, and that α-form is the most stable form at this stage because it has the lowest saturation concentration among the all crystal forms. The dissolution curves for D-PC·4MeOH·$1H_2O$, monohydrate and γ-form show that after attainment of the maximum concentration values, the concentration levels decrease. The limiting values of these concentrations were found to be the solubility of α-form. The complete reversion to α-form at this stage was confirmed by X-ray diffraction analysis and IR spectrophotometry of crystals isolated after the lowest plateau levels were reached. β-Form is not transformed to α-form within 8 hours at this stage.

It was found that the dissolution behavior could be also utilized for the identification of the various forms.

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