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Formation of a new crystalline form of anhydrous β-maltose by ethanol-mediated crystal transformation

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ABSTRACT

β-Maltose monohydrate was transformed into an anhydrous form by ethanol-mediated method under several temperatures with agitation. A new stable anhydrous form of β-maltose ($M\beta_s$) was obtained, as substantiated by the X-ray diffraction patterns. $M\beta_s$ obtained by this method presented a fine porous structure, resulting in greater specific surface area compared to those of β-maltose monohydrate and anhydrous β-maltose obtained by vacuum drying ($M\beta_h$). The crystal transformation presumably consisted of two steps: dehydration reaction from the hydrous to amorphous forms and crystal formation from the amorphous forms to the noble anhydrous form. The kinetics of these reactions were determined by thermal analysis using Jander's equation and Arrhenius plots. The overall activation energies of the dehydration reaction and the formation of anhydrous maltose were evaluated to be 100 and 90 kJ/mol, respectively.

1. Introduction

Maltose is arguably one of the most important sugars used in the food industry.[1,2] It is a disaccharide formed from two units of glucose joined with an α(1→4)bond. It is found in germinating seeds such as barley as they break down their starch to use for growth. Anhydrous maltose and maltose monohydrate are commercialized worldwide mostly as 90% pure crystalline product for the food industry. In addition, maltose is used in pharmaceuticals as a raw material, for example in infusion in which it is sold as 99% purity or above as crystalline product. There are two anomers for maltose crystals: the α- and the β-forms, which have different crystal structures, melting points, solubility, and dissolution rates. In solution, one anomer can be converted into another by rearrangement of the position of the OH group in the open chain (anomerization). Maltose has three crystalline forms: anhydrous α-maltose,[3] β-maltose monohydrate,[4] and anhydrous β-maltose. Although they are anomers related via mutarotation, these forms can be regarded as polymorphs since there is a rapid interconversion between forms within solution. It is well recognized now that polymorphs, due to the difference in their potential energy levels, can have significant impact on the pharmaceutical behaviors of a compound, for example, stability, solubility, and bioavailability.

Some studies have been done about maltose crystal transformation. Hodge et al.[1] have studied the crystal transformation from β-maltose monohydrate to anhydrous maltose by vacuum drying, and observed that anhydrous maltose crystals produced actually contained α- and β-maltose in various proportions, depending on the drying conditions.[1] Without vacuum, for a single day process at 120 °C, anomerization occurred and anhydrous maltose with 73% α-maltose was obtained. Whereas, drying under vacuum at mild temperatures for long process times yielded an extremely hygroscopic and metastable form of anhydrous β-maltose. α-Maltose has unique properties such as high solubility and emulsifying capability.[5] Schmidt and Lammert[6] have investigated the physical aging of maltose glass prepared from β-maltose monohydrate. Yoshii et al.[5] investigated the crystal transformation from anhydrous α-maltose to β-maltose monohydrate. However, there have been few studies about the crystal transformation of maltose by means of a dehydrating solvent. The dehydration of sugar crystals by a solvent is considered as a soft dehydration method relative to the hard dehydration one by high-temperature drying. Nordhoff and Ulrich[7] have investigated the phase transformations from several hydrates of salts to their anhydrous forms in lower alcohols. Solvent-mediated transformation is affected by many factors such as temperature, initial supersaturation, agitation rate, solvent properties, impurities, etc.[8] Martins et al.[9] presented a method to obtain faceted tubular organic crystals of some organic compounds via a thermal gradient and Schuster et al.[10] reviewed the crystal

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transformation of sodium-2-ketogulonate monohydrate in methanol to form hollow needle-shaped anhydrate crystals. Recently, Ohashi et al.[11] elaborated a new dehydration method through which porous anhydrous trehalose crystals were formed in the drying medium of ethanol. In the case of lactose, soft or hard dehydration methods of α-lactose monohydrate (Lα-H_2O) can lead to hygroscopic ($L\alpha_h$) or stable anhydrous α-lactose ($L\alpha_s$).[12,13] Presently in the literature, little is known about the use of ethanol in the dehydration of sugar crystals, particularly the kinetic aspects and the consequences on the crystal size and shape. According to the phase transformation diagram of maltose, the transformation from pure β-maltose monohydrate (Mβ-H_2O) to anhydrous maltose by dehydration in ethanol can be expected, although nothing is hitherto known about the kinetics and mechanism of the reaction and as well the anomer ratio.

In this study, the as-received Mβ-H_2O crystals were dehydrated using ethanol and a new stable anhydrous β-maltose crystal form ($M\beta_s$) with fine pores was obtained. X-ray diffractometry was used to characterize the crystalline difference from the anhydrous β-maltose obtained by vacuum drying ($M\beta_h$). In order to elucidate the reaction mechanism of the overall crystal transformation, the evolution of water content in the sample was measured. Thermal analysis was performed and the reaction kinetics was analyzed by the Jander and the Arrhenius equations. The evolution of the surface structure and anomer ratio was also investigated using scanning electron microscopy and gas chromatography.

2. Experimental

2.1. Materials

The β-maltose monohydrate (99.3% purity, 96% β-form) was supplied with compliments by Hayashibara Co., Ltd (Okayama, Japan). The initial moisture content was measured to be 5.0 ± 0.1% using a Karl Fisher titrator (MKS-510, Kyoto Electronics Manufacturing Co., Ltd, Kyoto, Japan). Synthetic ethanol (99.5% purity) was obtained from Japan Alcohol Trading Co. Ltd (Tokyo, Japan). These reagents were used without any purification. Anhydrous β-maltose ($M\beta_h$) was also prepared by vacuum drying for structural comparison according to Hodge et al.,[1] by keeping the β-maltose monohydrate at 56 °C for 4 days under vacuum (ca. 10 Pa). Karl Fisher's Hydranal and Hayashi solvent FM were obtained from Riedel-de Haën (Sigma–Aldrich, Seelze, Germany) and Hayashi Pure Chemical Ind., Co., Ltd (Osaka, Japan), respectively.

2.2. Crystal transformation by ethanol dehydration

The experimental setup for crystal dehydration in ethanol is the same as the one used by Ohashi et al.[11] One liter of ethanol was poured into a glass reactor (2-L round bottomed separable flask) coupled with an agitation system (Heidon Three-one motor model BL 600, Shinto Scientific Co., Ltd, Tokyo, Japan) and heated to a predetermined temperature (45, 50, 55, 60, or 70 °C) in a water bath. The as-received Mβ-H_2O crystals with an average crystal length of over 100 μm were selected by sieving. About 100 g of these crystals were added into the reactor once the predetermined temperature was reached. The crystal transformation reaction was performed under an agitation of 170 rpm. Crystal slurry of about 50 mL was withdrawn at each predetermined sampling time using a vacuum aspirator and the sample was immediately centrifuge-filtered (Model H-112, Kokusan Co., Ltd, Saitama, Japan). The crystals were spread on a stainless steel sieve with an aperture size of 106 μm and kept at 60 °C for 40 min in a ventilated drying oven to remove the residual ethanol. After drying, measurement of moisture, thermal analysis, surface structure analysis, X-ray diffractometry, measurement of anomer content, specific surface area analysis, and pore size analysis was performed.

2.3. Measurement of moisture content

The Karl Fischer titrator, calibrated against 2 μL of water, was used to measure the water content of ethanol (5 μL) and maltose crystals (approximately 150 mg). The crystals were added to Hayashi solvent FM containing 26% methanol and <0.2 mg H_2O/mL. The ethanol and maltose samples were then titrated against a 5 mg/mL Hydranal composite solvent. For each sample, a triplicate measurement was done and the average value was presented.

2.4. Differential scanning calorimetry (DSC)

DSC was performed with EXSTAR 6000 DSC (DSC 6220, SII Nano Technology Inc., Tokyo, Japan) equipped with Muse Measurement software, version 3.7 (SII Nano Technology Inc.). Approximately 6 mg of the maltose sample was placed in a sealed aluminum pan and heated at the rate of 10 °C/min from 30 to 270 °C. Nitrogen was used as the purge gas at 30 mL/min. All measurements were repeated in triplicate.

2.5. Microstructural characterization of crystal surface

A scanning electron microscope (Model JSM 6060, JEOL Co., Ltd, Tokyo, Japan) was used to investigate the microstructural properties of the maltose crystals. The crystals were placed on a double-sided adhesive carbon tape (Nisshin EM Co., Ltd, Tokyo, Japan) adhered to a sample stub. All the samples were analyzed at an acceleration voltage of 2.0 kV without sputter coating.

2.6. X-ray diffractometry

Powder X-ray diffractometer (Model RINT-TTR III, Rigaku Co., Tokyo, Japan) was used to investigate the crystal structure. The maltose crystals were pounded in a mortar and filled in an aluminum plate sample holder for exposure to Cu-Kα radiation in the apparatus. Samples were scanned at a scanning speed of 2°/min over a diffraction angular range of 5°–30° at 50 kV/300 mA.

2.7. Determination of the anomer ratio

The α and β anomers of the maltose samples were quantified by gas chromatography as the trimethylsilyl (TMS) ester which had been prepared by the reaction with trimethylsilylimidazole (TMSI). About 20 mg of the maltose samples was dissolved in 1 mL of anhydrous pyridine by shaking for 10 min. Subsequently, 100 μL of the maltose pyridine solution was added into a 1-mL round-bottomed glass microtube (ϕ8 mm × 5 mm) containing the trimethylsilylating agent which had been prepared earlier by mixing 50 μL each of the constituent reagents in the order of TMSI, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), and trimethylchlorosilane (TMCS). Trimethylsilylation of the samples was performed at 60 °C for 30 min. After trimethylsilylation, 0.2 μL of the TMS derivatives were injected in duplicate into a gas chromatograph (GC-14A, Shimadzu Corporation, Kyoto, Japan) equipped with a glass column (2 mm i.d. × 3 m) packed with 2% Silicone OV-17/ChromosorbW (AW-DMCS, 80–100 mesh, Shinwa Chemical Industries, Ltd, Kyoto, Japan) and a flame ionization detector. The analytical conditions were as follows: column temperature, 210 °C; inlet temperature, 250 °C; detector temperature, 250 °C; carrier gas: N_2. The chromatograms were recorded and analyzed with a Chromatopac C-R8A (Shimadzu Corporation).