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Abstract. Transmission-type terahertz time-domain spectroscopy is applied to evaluate crystallized lactose particle of size below 30 μm, which is far too small compared to the wavelength of incident terahertz (THz)-wave. The THz-absorption spectrum of lactose is successfully deconvoluted by Lorentzian to two spectra with peaks at 17.1 cm^{-1} (0.53 THz) and 45.6 cm^{-1} (1.37 THz) derived from α-lactose monohydrate, and a spectrum at 39.7 cm^{-1} (1.19 THz) from anhydrous β-lactose after removal of the broad-band spectrum by polynomial cubic function. Lactose is mainly crystallized into α-lactose monohydrate from the supersaturated solution at room temperature with a small amount of anhydrous β-lactose below 4%. The absorption feature is dependent on the crystallized particle size and the integrated intensity ratio of the two absorptions due to α-lactose monohydrate is correlated in linear for the size. [DOI: 10.1117/1.OE.53.3.031203]

Subject terms: terahertz time-domain spectroscopy; α-lactose monohydrate; crystallized particle; terahertz absorption.

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1 Introduction

A terahertz (THz)-electromagnetic wave in the far infrared region is useful to characterize material properties based on the intra-vibration in relatively large organic molecules and/or the inter-molecular vibration incorporated hydrogen-bonding. The absorption feature of such organic material is significantly dependent on the molecular and crystal structures as demonstrated for L-phenylalanine comparing to L-tyrosine,[1] three different retinal isomers with polyene chain,[2] DL-alanine racemic compound comparing to D- and L-alanine,[3] and so on. Therefore, the lines peculiar to material can be recognized as the spectral fingerprint. To date, a lot of organic materials have been characterized by the spectral fingerprint which is useful not only for the qualitative analysis but also for the quantitative evaluation. For example, we previously demonstrated that the anomer content of lactose in the milled powder can be precisely determined by the integrated intensity ratio of THz-absorptions due to the α-form and the β-form crystals.[4] However, the crystallized particle size of organic materials has not been studied by THz-spectroscopy. In the case of saccharides, such as lactose used in food products, evaluation of the crystallized particle size is often required in sandiness which can be sensorically detected for sizes over 10 to 16 μm. In general, the size is evaluated by optical microscope or scanning electron microscope. Although such methods achieve a precise evaluation on the surface, the particle inside the products cannot be observed because the transmission length of the light or the electron is limited to regions within a submicrometer. In contrast, a THz-wave is notably absorbed in water but easily passed through most organic materials compared to UV–vis–infrared light or electron-beam. In concept, it is considered that the THz-imaging developed in some fields[5–7] is useful to disclose the shape of particle inside materials. However, it is not easy to perform the imaging of a particle with a size below 20 μm, which is far too small compared to the wavelength of a THz-wave around 1 THz. On the other hand, if the THz-absorption is dependent on size, THz-spectroscopy is useful to estimate a particle with such a small size.

In this article, transmission-type terahertz time-domain spectroscopy (THz-TDS) is applied to evaluate a lactose powder, which consists of crystallized particles with a size below 30 μm, and precise analysis on the absorption feature is performed to estimate the particle size.

2 Experimental

A transmission-type THz-TDS system was used to characterize lactose-powders. A detailed configuration of the system was shown elsewhere.[4] In this system, a femto-second fiber laser (peak wavelength at 782 nm, half-width of 87 fs, repetition rate of 48 MHz) was used as a pump light and a probe light after being split in two ways by a half-mirror. The pump light chopped at 1 kHz was focused and irradiated on a THz emitter consisting of a dipole antenna with a 10 μm-gap space fabricated on low-temperature grown GaAs (LT-GaAs) layer and attached on a hemispherical Si-lens, on which the antenna was biased at 10 V to generate a transient current in the pico-second order. A THz-pulse generated on the emitter was radiated through the Si-lens, then focused normally incident to the sample using two off-axis parabolic metal mirrors. After passing through the sample, the THz-pulse was introduced to the detector with the same antenna configuration of the emitter by two off-axis parabolic mirrors and a hemispherical Si-lens. When the THz-pulse was introduced to the antenna in the detector, the probe laser light was simultaneously irradiated to detect the pulse by a sampling technique, where time-delay of the probe light was controlled by a retro-reflector and a micro-step stage controller with a step distance of 1 μm. The sampling data were recorded in a PC after signal-amplification, lock-in

noise reduction, and A/D conversion. The recorded pulse data was processed by a discrete Fourier transform (DFT) after a Gaussian-window was superposed on the pulse data to remove aliasing. Temperature in the THz-TDS system was carefully controlled at 20°C.

Commercially available pure lactose α-D(+)-lactose monohydrate [$L_\alpha \cdot H_2O$: O − β-galactopyranosyl-(1 → 4)-α-D-glucopyranose monohydrate ($C_{12}H_{22}O_{11} \cdot H_2O$)] powder (≥99% total lactose basis, ≤0.05% glucose Sigma-Aldrich, St. Louis, Missouri) was used to prepare a lactose solution and for seeding. The anomer (L_β: anhydrous β-D(+)-lactose) content in the $L_\alpha \cdot H_2O$ powder was about 4% in the commercial specifications. Lactose particles were extracted from lactose supersaturated solution (1 g-lactose powder/3 cc-water) and the size was controlled by the extract period, where ultra-pure water with the resistivity above 18.2 MΩ cm was used as a solvent. The crystallization was enhanced by seeding 10 mg-$L_\alpha \cdot H_2O$ powder added into the solution at 20°C with stirring (300 rpm), and then the extracted lactose was dried at 60°C for three days in an incubator after removal of the residual solution. The extracted lactose powders consist of the crystallized particles, which are then filled and lightly compressed in a metal aperture of 0.7 mm-thickness with a hole of 6 mm-diameter. A THz-wave was normally incident to the lactose-sample placed with the aperture in the THz-TDS system. The weight of the lactose-powder used for the THz-TDS was measured by an electronic weight-scale.

3 Result and Discussions

3.1 *THz-Absorption Feature of Lactose Powder*

Figure 1 shows the THz-spectra in the THz-TDS system without a lactose-sample, and the inset shows the THz-pulse and Gaussian-window superimposed on the pulse before DFT. Periodic fluctuation was observed in the THz-spectra (plain line) but successfully removed by using the Gaussian-window (bold-line). If the THz-pulse was sufficiently intense, the fluctuation due to aliasing was negligible, but the pulse-edge in relatively weak signal passed through samples should be taken into account for the precise analysis.

A typical prelimary absorption spectrum of the $L_\alpha \cdot H_2O$ powder consists of several narrow-bands and a broad-band as shown in Fig. 2, where the experimentally obtained data were shown by filled-circles with a fit (dash-line), by the deconvoluted spectra (solid-lines), and broad-band (dot-line). The spectral deconvolution was successfully achieved by Lorentzian as previously shown for the lowest lying spectrum[8] after removal of a broad-band by a polynomial cubic function. The narrow-bands with peaks at 17.1 cm^{-1} (0.53 THz) and 45.6 cm^{-1} (1.37 THz) can be recognized as the fingerprint of $L_\alpha \cdot H_2O$,[9,10] which were denoted as α_1 and α_2, respectively. The absorptions derived from $L_\alpha \cdot H_2O$ are recognized to be associated to lactose molecular-rotations in the crystal as indicated by first principle calculations.[10] A weak absorption with a peak at 39.7 cm^{-1} (1.19 THz) denoted as β_1 can be suggested to be derived from L_β because the absorption was dominant in L_β powder.[4]

3.2 *Crystallization Behavior of Lactose in Supersaturated Solution*

Figure 3 shows a photograph of crystallized lactose-particles observed by a Nomarski differential interference microscope, where the lactose was crystallized for (a) 24, (b) 72, and (c) 120 h and then dispersed in ethanol by ultra-sonic vibration for 20 s after being dried in an incubator. It has been recognized that lactose in the supersaturated solution around room-temperature can be mainly crystallized into $L_\alpha \cdot H_2O$ by seeding of the $L_\alpha \cdot H_2O$ powder. The crystallization behavior is also dependent on this condition because the β-lactose present in the aqueous solution selectively blocks the growth of the (020) face, which results in growth along the b direction (not the $-b$ direction) and the Tomahawk shape as shown in Fig. 4.[11,12] Further, it was demonstrated by a dimethyl sulfoxide-lactose system with controlled β-lactose content in the solution that the Tomahawk shape is extended along the $-b$ direction, reducing the growth along the c direction with increasing β-lactose

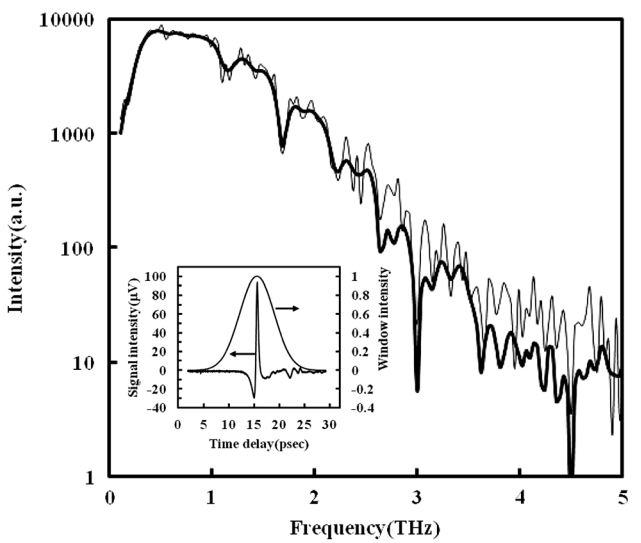

Fig. 1 Fourier transformed THz-spectra from the THz-pulse without Gaussian window (plain-line) and superposed Gaussian window (bold-line). The inset shows the THz-pulse and Gaussian window.

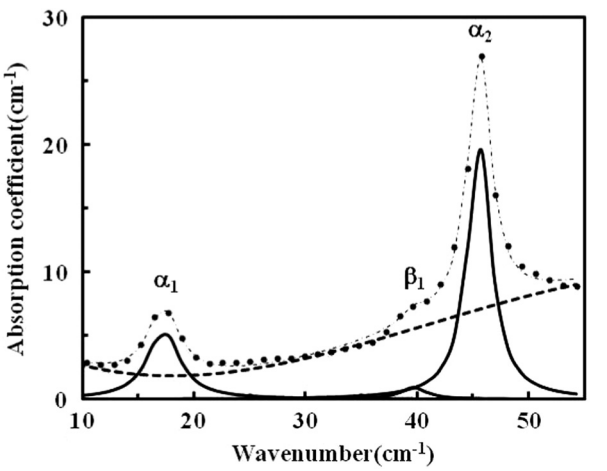

Fig. 2 Absorption spectrum of preliminary used α-lactose powder, where experimentally obtained data, broad band background, deconvoluted spectra and the fit are shown by filled-circle, bold dash-line, solid-line, and plain dash-line, respectively. Absorptions due to α-lactose monohydrate and anhydrous β-lactose are denoted as "α_1," "α_2," and "β_1," respectively.

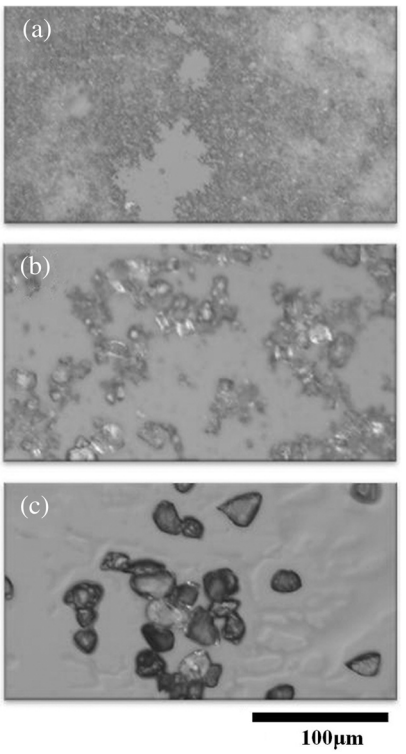

Fig. 3 Nomarski photographs of extracted lactose from the supersaturated solution for (a) 24, (b) 72, and (c) 120 h.

content in the lactose solution.[12] Since β-lactose is present above 60% in aqueous lactose solutions around room-temperature by the mutarotation in equilibrium,[13] the crystal is enlarged to the $-b$ direction as shown in Fig. 4. In this article, the crystal size was determined along the b axis in the anisotropic shape, and the average crystal size was uniquely increased with the crystallized period as shown in Fig. 5.

3.3 *Dependence of THz-Absorption Feature on Crystallized Lactose Particle Size*

Figure 6 shows the absorption spectra (solid-line) of lactose consisting of crystallized lactose particles with an average size of 4.3, 14.7, and 27.6 μm, where the lactose crystals were extracted for 24, 72, and 120 h from the lactose solution, respectively. The inset shows deconvoluted spectra of the absorptions due to $L_\alpha \cdot H_2O$ crystal, in which the

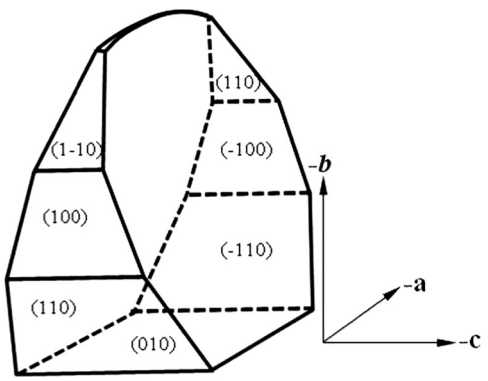

Fig. 4 Miller indicates of Tomahawk shaped α-lactose monohydrate crystal.[12]

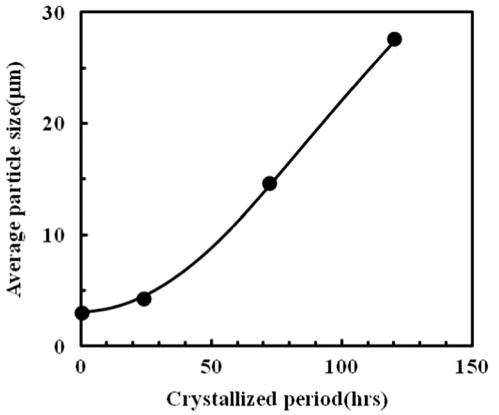

Fig. 5 Dependence of average crystallized particle size of α-lactose monohydrate on the crystallized period, where the crystal size was estimated along the b-axis.

absorption of anhydrous L_α was removed. It was mentioned that the broad-band was numerically removed by a polynomial cubic function, and the absorption coefficient is normalized by the weight of the lactose sample because the density of lactose was different in aperture for each sample. As expected from the particle shape, lactose was mainly crystallized into $L_\alpha \cdot H_2O$ because the spectra were dominated by the absorptions due to $L_\alpha \cdot H_2O$ (α_1 and α_2). Anhydrous L_β was also crystallized. It was probably formed on the $L_\alpha \cdot H_2O$ crystal in the drying process, but the content in the extracted lactose was within 4%. The absorption features of α_1 and α_2 were dependent on the particle size as shown in the inset of Fig. 6. Details on the integrated absorption intensity and the full-width at half-maximum (FWHM) for the average particle size are shown in Fig. 7, in which the results on the average particle size of 3 μm is for the preliminarily used $L_\alpha \cdot H_2O$ powder. The α_1 line width (filled-square) was independent of the particle size. A significantly narrow absorption spectrum of α_1 with a FWHM of about 1.3 cm^{-1} has been reported by using a photomixer and continuous-wave, however, the obtained THz-TDS was broader than

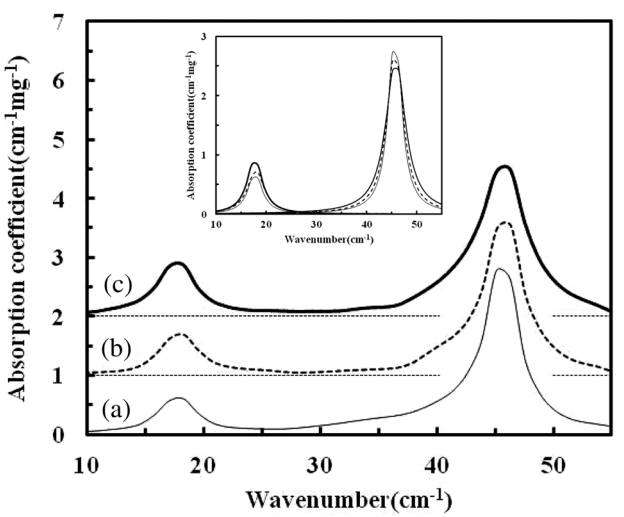

Fig. 6 Absorption spectra of extracted lactose from the supersaturated solution with the average size of (a) 4.3, (b) 14.7, and (c) 27.6 μm. The inset shows the deconvoluted α-lactose monohydrate spectra.

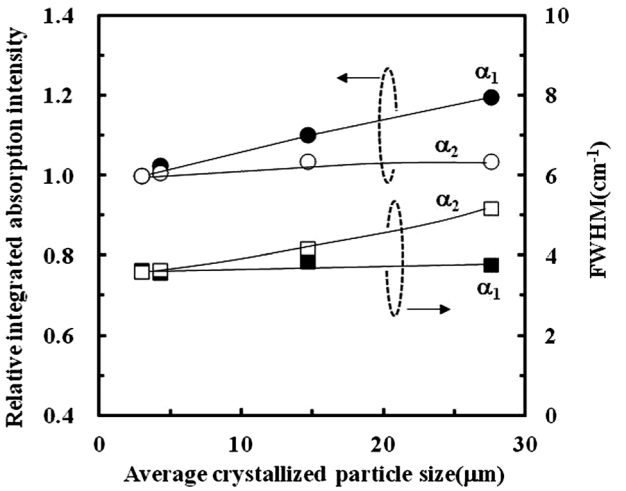

Fig. 7 Variation of relative integrated absorption intensity of α_1 and α_2 (filled circles and open circles) and full-width at half-maximum of α_1 and α_2 (filled squares and open squares) for average crystallized particle size of α-lactose monohydrate.

that,[8] which is because of the resolution of the spectroscopy methods. Since the FWHM of 3.7 cm^{-1} obtained in this work was smaller than that of 4.91 cm^{-1} as demonstrated by THz-TDS,[8] but much broader compared to the native feature with an FWHM less than 1.3 cm^{-1}, it is considered that the spectrum width was not apparently changed in the results under the resolution limit of the THz-TDS system. Previously, the significantly sharp feature of α_1 was discussed by the solid-state density functional theory and assigned to externally hindered rotational modes in the crystal *b*-axis, not to the internal modes.[14] In such modes, the absorption intensity can be expected to increase with the crystal size much less than the wavelength of the incident THz-electromagnetic wave as shown in Fig. 7 (closed circles). On the other hand, the absorption of α_2 was broader than that of α_1 and the line width increased with the particle size (open-squares). However, the integrated intensity of α_2 (filled-squares) was scarcely increased with the particle size,

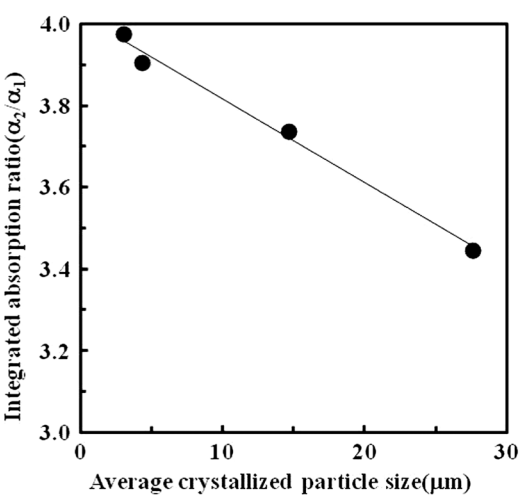

Fig. 8 Dependence of integrated absorption ratio of α_2/α_1 on average crystallized particle size of α-lactose monohydrate.

but the dependence was very small compared to α_1. The vibration mode of α_2 was identified as molecular-rotation in a lactose active mode by the first principles calculation.[10] The significant difference of α_2 feature is possibly due to the absorption is due to the internal vibrations associated with intermolecular hydrogen-bonding. The significant difference of α_1 and α_2 intensities resulted in assignment of the particle size. Figure 8 shows the intensity ratio of α_2/α_1 for the average particle size. A ratio as high as 3.98 was linearly decreased with the particles' size and to 3.45 for the size of 27.6 μm, where the correlative square-factor was 99.2% on the least squares method. As a result, if the particles are contained inside samples, the average particle size can be nondestructively evaluated by the ratio of α_2/α_1 obtained by THz-TDS.

4 Conclusions

THz-TDS was applied to evaluate the average particle size of crystallized α-lactose monohydrate. The dependence of THz-absorption on the particle size below 30 μm was different for the two spectra, with peaks at 17.5 cm^{-1} (0.53 THz) and 45.6 cm^{-1} (1.37 THz). The integrated absorption intensity ratio, which is linearly dependent on the particle size, was able to assign the average particle size. The results in this work showed a THz-absorption feature in organic crystal that incorporates hydrogen-bonding was dependent on the crystal size which was far smaller compared to the wavelength of the incident THz-wave and can present a new concept focused on the absorption intensities to evaluate the crystal size of organic crystal.

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