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Investigation of solid-state reaction by terahertz time-domain spectroscopy

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Abstract Terahertz time-domain spectroscopy (THz-TDS) was utilized to investigate the solid-state reaction between L(+)-Tartaric acid and sodium hydrogen carbonate. Solid sodium hydrogen L(+)-tartrate monohydrate was synthesized efficiently by mechanical grinding, which is particularly sustainable and environmentally benign. Distinct THz absorptions were observed for pure reactants and the proposed product. The reaction process could be clearly visualized by THz spectral patterns of the reaction mixtures at different grinding time. The observed results were further confirmed by synchrotron radiation X-ray powder diffraction (SRXRPD) and Fourier transform infrared (FT-IR) spectroscopy. The study demonstrates that THz-TDS is an effective novel tool to monitor solid-state reactions in pharmaceutical industry.

Key words Terahertz time-domain spectroscopy (THz-TDS), Solid-state reaction, Tartaric acid, Grinding

1 Introduction

Terahertz time-domain spectroscopy (THz-TDS) has received considerable attention for its increasingly important applications in analytical chemistry, biology, medical sciences, non- destructive evaluation, and quality control of food and agricultural products[1-5]. Compared with traditional infrared spectroscopic techniques, THz-TDS is advantageous, for solid materials analysis particularly. Near- and mid- infrared spectroscopy mainly gives information on intramolecular vibrations, whereas THz radiation can probe intermolecular vibrations or crystalline phonon vibrations which originate directly from the crystal structure. Many organic materials have characteristic THz fingerprints[2]. In addition, THz radiation does not cause any thermal strain or phase change in the sample due to its low energy, so it is nondestructive and safe.

THz-TDS has many useful applications in investigating crystallinity[6,7], polymorphism[8,9], and monitoring transitions between polymorphs[10-12]. Until recently, THz-TDS technique was tentatively used to study solid- state reactions activated by grinding, such as cocrystal[13,14] and complex[15–17] formations. These attempts highlight the great possibility of THz-TDS as a powerful and alternative technique in examining solid-state reactions.

Solid-state reactions, known as mechanochemical reactions induced by grinding or milling, have great potential applications in Green Chemistry, which is free from solvents[18,19]. Tartaric acids and tartrates are important additive in pharmaceuticals, foods, and chemical industries. Also, tartrates (e.g. alkali metal tartrates) possess electrical, magnetic and optical properties[20]. Mechanochemical reaction between L(+)-tartaric acid (L-TA) and sodium hydrogen carbonate (SHC) at the 1:1 stoichiometry produces cleanly sodium hydrogen L(+)-tartrate monohydrate (STM) with quantitative yield[21]. The reaction has a potential of industrial scale production.

In this work, we used THz-TDS to monitor this reaction process. Solid-state analytical techniques of synchrotron radiation X-ray powder diffraction (SRXRPD) and Fourier transform infrared (FT-IR) spectroscopy were used to support the investigation.

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2 Experimental

2.1 Materials

L(+)-tartaric acid (L-TA, 99+%) was purchased from Acros Organics. Sodium hydrogen carbonate (SHC, ≥99.5%) and potassium bromide (KBr, ≥99%) were obtained from Sinopharm Chemical Reagent Co., Ltd. Sodium hydrogen L(+)-tartrate monohydrate (STM, ≥98%) and polyethylene powder (particle size 53~75 µm) were purchased from Sigma-Aldrich. All chemicals were used without further purification.

2.2 Sample preparation

The mechanochemical reactions were performed by grinding together the equimolar amount of L-TA and SHC at room temperature using a planetary ball mill with a rotation rate of 600 rpm and a revolution rate of 300 rpm (QM-3SP, gear type, Nanjing University Instrument Plant). A measured amount of products produced in the solid-state reaction at different milling time were taken out for further analysis.

2.3 Terahertz time-domain spectroscopy

A standard THz-TDS apparatus for transmission measurements and the corresponding experimental data analysis method have been described in detail in previous reports[22,23]. The model-locked Ti: sapphire laser system provided 100 fs pulses at a center wavelength of 800 nm with average power of 600 mW and a repetition rate of 80 MHz. The laser beam was split into a pump beam and a probe beam, so as to generate and detect THz radiation, respectively. The amplitude dynamic range was larger than 1000, and the spectral resolution was better than 40 GHz. Spectra were taken on pellets prepared by compressing 30 mg of powder sample and 150 mg of polyethylene transparent to THz radiation. The sample and polyethylene were thoroughly mixed using a mortar and pestle. The mixture was made into pellets of Φ13 mm×1.5 mm under 5 MPa using an oil press. All the measurements were done at room temperature and the entire path of THz beam was purged with dry nitrogen to reduce the absorption of water vapor.

2.4 SRXRPD

The XRD patterns were obtained at room temperature on XRD station of beamline BL14B1 at Shanghai Synchrotron Radiation Facility (SSRF). The incident beam was based on bending magnet and monochromatized by Si(111) double crystals to a 1.2398-Å wavelength. The size of the focal spot was about 0.5 mm. The end station was equipped with a Huber 5021 diffractometer. NaI scintillation detector was used for data collection. The sample was loaded into the cavity (1 cm×1cm×0.5 mm) of a glass sample holder with the sample surface being coplanar with the holder surface. The data were recorded at a step size of 0.02°(2θ) with an exposure time of 0.4 s.

2.5 FT-IR spectroscopy

The powder samples were manually mixed with dry KBr using a mortar and pestle and made into pellets. FT-IR spectroscopy measurements were taken on a Nicolet Avatar 370 spectrometer with a resolution of 4 cm^{-1}. Spectra were collected in the range of 4000−675 cm^{-1} for 32 scans.

3 Results and discussion

Figure 1 shows the measured absorption coefficient and the refractive index of L-TA, SHC, and the proposed reaction product STM in the frequency range between 0.3 THz and 2.4 THz. The collective data below 0.3 THz were not considered due to the multiple reflections of probe pulses inside the sample pellets.

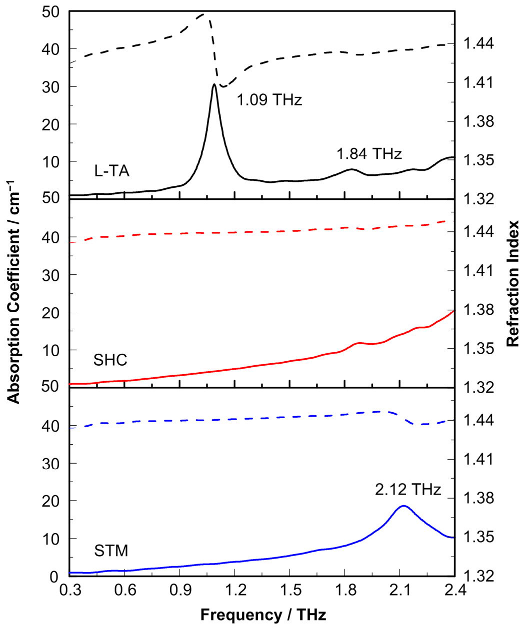

Fig.1 Measured absorption coefficient (solid line) and refractive index (dash line) of L-TA, SHC, and STM.

The absorption spectra for the reactants and product differ obviously. L-TA exhibits a prominent peak at 1.09 THz and a low intensity peak at 1.84 THz, STM shows a medium peak at 2.12 THz, and SHC has no peak and appears with monotonously increasing absorption intensity at high frequencies. It indicates that THz spectroscopy is sensitive to different chemical compounds. The absorption features are confirmed by the observation of characteristic changes in the refractive index.

THz spectra mainly reflect the intermolecular vibrations and phonon frequency[24]. In THz spectra of retinal isomers[3], carbamazepine[8], anhydrous and monohydrated caffeine and theophylline[25], the low-frequency vibration features were mainly associated with collective vibration modes of molecules held together by hydrogen bonded networks. Chiral tartaric acid crystal has low symmetry, and the molecules are linked to each other by hydrogen bonds[26]. There also exists hydrogen bonds between tartrate molecules[27]. Therefore, the observed THz characteristic absorption features appearing in L-TA and STM probably originate from the collective vibration modes of hydrogen bonding interactions in the crystal structures.

The solid-state reaction was performed by grinding together the 1:1 stoichiometry of L-TA and SHC at room temperature. THz spectra of reaction mixtures at different grinding time are shown in Fig.2. Upon grinding, the absorption profiles of mixtures changed along time. The characteristic absorption peak at 1.09 THz deceased throughout the reaction time, indicating the reactant L-TA was consumed and the stoichiometric organic solid-state reaction took place. It is noticeable that the absorption of L-TA, SHC and STM at high frequencies all contributes well to the absorption profiles for the reaction mixtures. The decreasing peak at 1.84 THz was recognizable at the initial stage of the reaction, and the peak at 2.12 THz became visible and increased gradually after 4 min, suggesting that the growing product might have accumulated to a certain amount. The decreasing absorption at 1.09 THz reached the minimum and the increasing absorption at 2.12 THz reached the maximum at a certain time, indicating that the reaction approached completion.

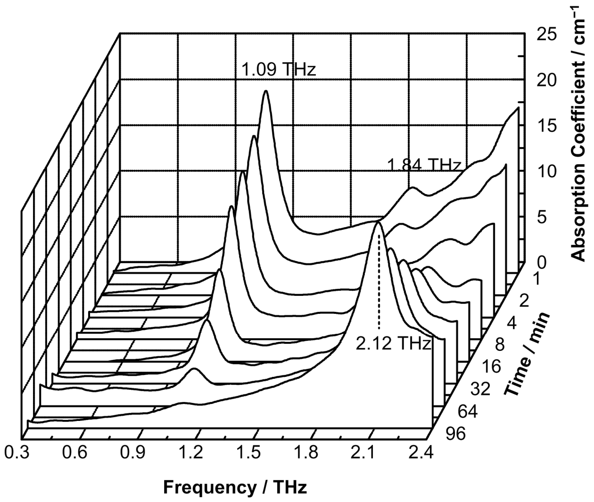

Fig.2 Terahertz spectra of the reaction process of L-TA and SHC by grinding.

THz-TDS, due to its unique ability to probe the intermolecular interactions, may elucidate further information about the crystal-to-crystal transformation process. Fig.3 shows the change of THz absorption at 1.09 THz along the grinding time. The spectral band at 1.09 THz decreased dramatically in the initial stage and flattened out gradually after 64 min, suggesting that the mechanochemical reaction proceeded smoothly and slowed down gradually.

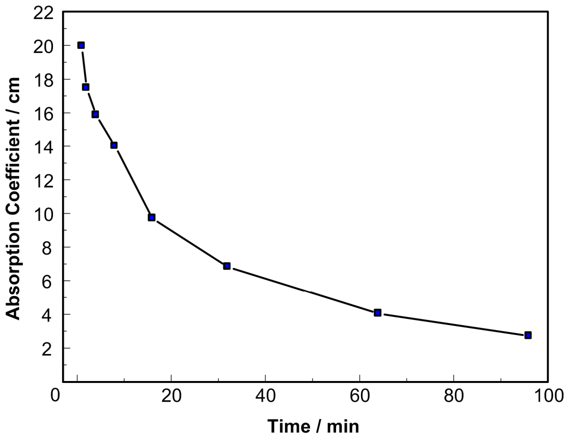

Fig.3 Changes of THz absorption at 1.09 THz along the grinding time.

The mechanochemical grinding can overcome the strong intermolecular forces within the reactant crystals and activate the tartrate construction, and the process can be enhanced by providing fresh reactive surfaces and mixing the solid reaction mixture. As the reaction proceeded, the formation of product layers and the molecular rearrangement within the crystalline products hindered the diffusion of reactants, and therefore slowed down the reaction. It appears that much of the tartrate formation occurs within the first 64 minutes, suggesting that the accumulation of mechanical activation effects may play an important role in the synthesis of tartrate. At 96 min, the absorption reached the minimum and remained almost unchanged even after further grinding, demonstrating that the reaction was nearly completed. This was in agreement with results observed by using SRXRPD and FT-IR spectroscopy.

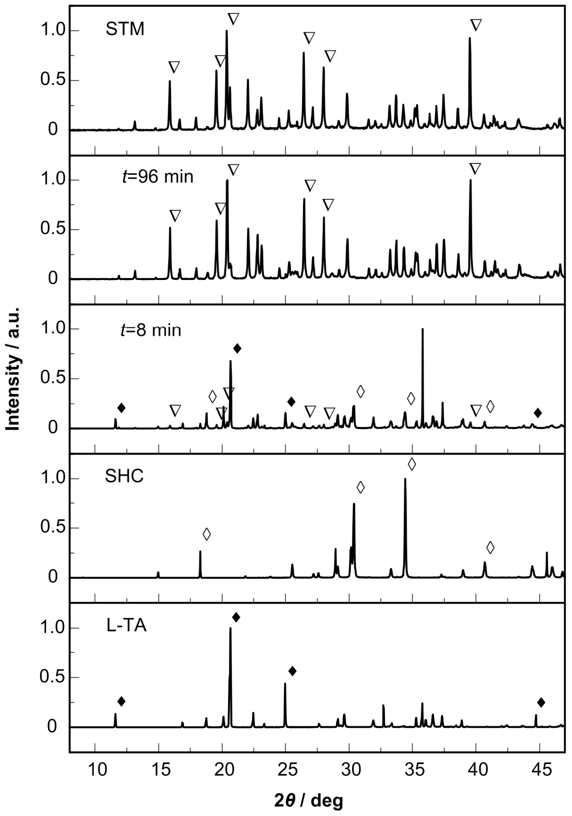

Fig.4 Synchrotron based XRPD patterns of pure L-TA, SHC, STM and the reaction mixtures ground for 8 min and 96 min. Peaks were assigned as those of L-TA (solid diamonds), SHC (open diamonds) and STM (open down-pointing triangles).

SRXRPD gives additional evidence concerning the tartrate formation progress and the identity of the reaction product formed. Fig.4 shows the diffraction patterns of pure L-TA, SHC and STM, and of the reaction mixtures of L-TA and SHC ground for 8 min and 96 min respectively. To make a comparison with the standard PDF cards, all the 2θ values obtained on the BL14B1-XRD station at a wavelength of 1.2398 Å were converted to 2θ values corresponding to the wavelength of 1.5406 Å according to Bragg's law $n\lambda=2d\sin\theta$. The intensity values were normalized based on the strongest peak heights. All the XRD patterns of the pure components were in good agreement with corresponding PDF cards, and peaks were assigned as those of L-TA (◆), SHC (◇) and STM (▽). Peaks corresponding to pure L-TA and SHC decreased with the grinding time, and in parallel to this, peaks corresponding to the proposed reaction product STM increased. After co-grinding the L-TA and SHC mixture for 96 min, the resulting diffraction pattern of the reaction mixture matches that of STM, suggesting the solid-state reaction might be completed.

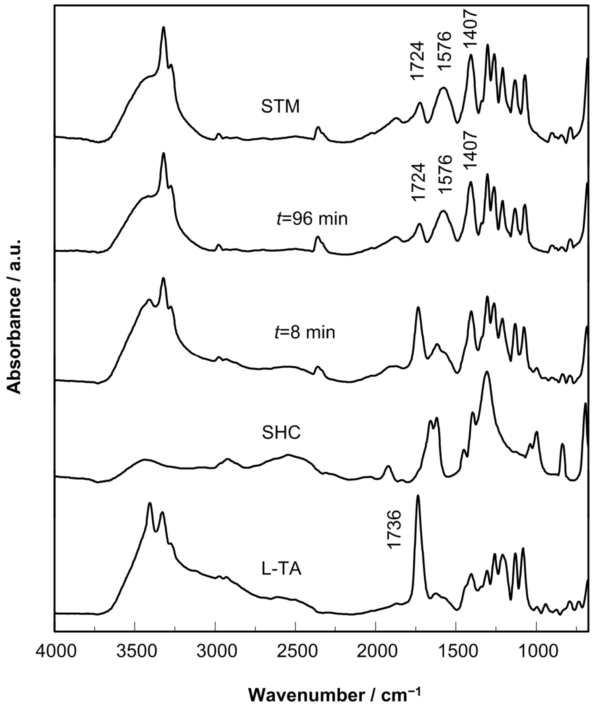

Fig.5 FT-IR spectra of pure L-TA, SHC, STM and reaction mixtures ground for 8 and 96 min.

FT-IR spectroscopy is capable of providing intramolecular information of changes in functional groups during the mechanochemical reaction. Fig.5 shows the typical IR spectra of pure L-TA, SHC and STM, and of the reaction mixtures ground for 8 min and 96 min, respectively, in the region of 675–4000 cm^{-1}. The L-TA spectrum shows a strong peak at 1736 cm^{-1}, which is indicative of free carboxyl groups. The decreased peak in the spectrum of reaction mixture at 8 min suggests the consuming of L-TA. At 96 min, the spectrum exhibits two peaks at 1576 and 1407 cm^{-1}, which are assigned to the asymmetric and symmetric stretching vibrations of carbonyl groups in the carboxylate product. Because of the new chemical environment, the absorption band of carboxyl group red shifts to 1724 cm^{-1}, presumably from hydrogen bonding with one or more of the water molecules. The great similarity between the spectra of reaction mixture at 96 min and STM confirms the identity of the product again and demonstrates that the reaction nearly draws to completion.

4 Conclusion

Solid STM was cleanly synthesized with high efficiency by mechanical co-grinding of L-TA and SHC, which is particularly sustainable and environmentally benign. The reaction has potential for practical and industrial application. The pure reactants and the proposed reaction product were well distinguished via THz spectroscopy. The characteristic absorption features observed in L-TA and STM were suggested to originate from the collective vibration modes of hydrogen bonding interactions in the crystal structures. The absorption features in the frequency region of 0.3–2.4 THz were utilized to monitor the dynamic process of crystal-to-crystal transformation. The mechanochemical reaction proceeded smoothly upon grinding and slowed down gradually. After grinding for 96 min, the reaction approached completion. The results were further confirmed by using SRXRPD and FT-IR spectroscopy. The study demonstrates that THz-TDS is a powerful new tool to investigate the dynamic process of solid-state reactions and it has potential to find wide variety of applications in chemical and pharmaceutical research and industry.

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