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Low-frequency vibrational properties of crystalline and glassy indomethacin probed by terahertz time-domain spectroscopy and low-frequency Raman scattering

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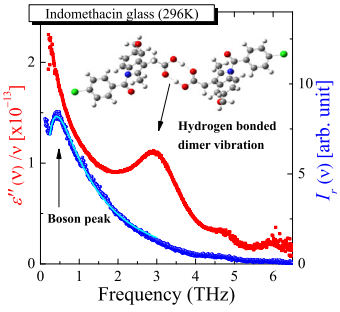
HIGHLIGHTS

- Vibrational properties of pharmaceutical indomethacin were investigated.
- The dielectric spectra of glassy and crystalline state were compared with Raman spectra.
- Remarkable differences were observed between the dielectric and Raman spectra.
- Low-frequency Raman scattering spectra clearly showed the boson peak.

GRAPHICAL ABSTRACT



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ABSTRACT

In order to clarify the intermolecular vibrations, the low-frequency modes of the glassy and crystalline states of model pharmaceutical indomethacin have been studied using broadband terahertz time-domain spectroscopy and low-frequency Raman scattering. In the crystalline γ-form, the center of symmetry was suggested by the observation of the exclusion principle of the infrared (IR) and Raman selection rules in the frequency range between 0.2 and 6.5 THz. In addition, a boson peak of the glassy state was observed in both IR and Raman spectra and their frequency showed apparent discrepancy. The intermediate correlation length of the glassy structure was estimated to be about 2.5 nm. The existence of hydrogen bonded cyclic dimers in a glassy state was suggested by the observation of the infrared active intermolecular vibrational mode of the hydrogen bonded cyclic dimers as a broad peak at 3.0 THz in the IR spectrum.

Introduction

Indomethacin (IMC) [1-(p-chlorobenzoyl)-5-methoxy-2-methy lindole-3-acetic acid] is one of the non-steroidal anti-inflammatory drugs used for the treatment of fever, pain, and swelling. The molecular structure of IMC is shown in inset of Fig. 1(a). IMC easily undergoes a liquid-glass transition at the glass transition temperature, T_g = 315 K upon cooling from the melt. It then exhibits physical properties similar to typical structural glasses [1–5].

Currently, in the pharmaceutical research, there is a growing interest in the development of amorphous (glassy) pharmaceuticals, because they often show a better solubility than the crystalline counterpart [6]. As a model system of the glassy pharmaceuticals, IMC is of particular interest. However, one concern is the instability of the glassy state originating from the disordered structure and the

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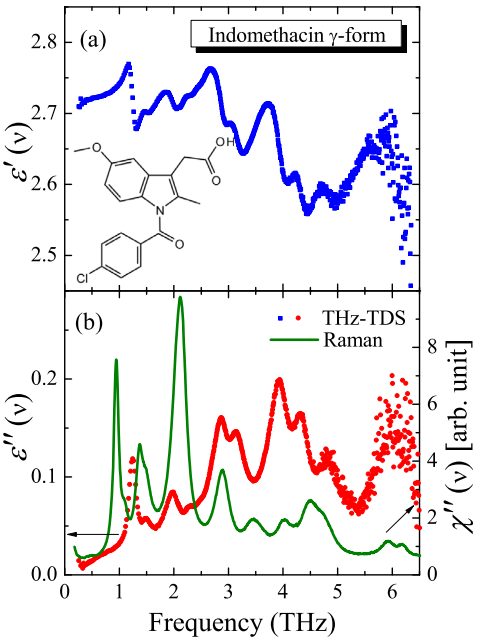

Fig. 1. (a) Real part $\varepsilon'(\nu)$ (squares) and (b) imaginary part $\varepsilon''(\nu)$ (circles) of complex dielectric constant and Raman susceptibility $\chi''(\nu)$ (solid line) spectra of γ-IMC in the frequency range between 0.2 THz and 6.5 THz at 296 K. The inset in (a) shows the molecular structure of IMC.

aging effect. Therefore, it is crucial to make clarify the molecular dynamics in the glassy states of the pharmaceutical system for obtaining a predictable stability [1,2]. In addition, these kinds of studies will provide new insights into understanding the universality in the dynamics of glass transitions on complex molecules.

The molecular dynamics of glass-forming liquids have been observed by the use of conventional dielectric, infrared (IR), and light scattering spectroscopies. Also, these kinds of measurements have been used for the crystalline and glassy IMC [1–5,7–9]. In particular, several spectroscopic studies of crystalline and glassy (amorphous) IMCs have already been reported [3–5,7–9]. In several articles, the IR and Raman spectra of quench-cooled glassy IMCs were reported based on the density functional theory (DFT) calculations. By comparing the vibrational spectra, it was suggested that IMC molecules predominantly exist as hydrogen bonded cyclic dimers [8,9]. However, the exact nature of the interactions between molecules in the glassy state is still unknown. One common feature in the dynamics of glass-forming materials appears in the gigahertz and terahertz frequency range. The inelastic scattering spectra of glasses have generally shown a universal low-frequency response called the "boson peak" in the region below 3.0 THz [10,11]. In specific heat measurements, the excess contribution, which represents the boson peak, was found at low temperatures [12]. However, in pharmaceuticals, the boson peaks have never been satisfactorily understood.

To study the molecular interactions and dynamics, we have applied the terahertz time-domain spectroscopy (THz-TDS), typically covering that frequencies range from 0.1 to 4.0 THz. The selection rules are different between the THz-TDS and Raman scattering, and usually considered as complementary, especially for centrosymmetric materials. Moreover, complex dielectric constants of some molecular liquids, such as water and the lower alcohols, were reported by THz-TDS [13–15]. According to these studies, the relaxation process and intermolecular stretching mode were observed. The dynamics of organic glass forming materials, such as polymers, poly-alcohols, sugars, and pharmaceutics, were investigated in the frequency of 0.2–3.0 THz using THz-TDS [16–20]. It is expected that the low-energy excitations of glassy materials such as a boson peak, intermolecular vibrations, and fast relaxation processes, can be studied by THz-TDS [21].

The purpose of the present study is to give new insights into the understanding of crystalline and glassy IMCs in the THz regions by obtaining far-IR and Raman spectra for the same material. The direct comparison of both spectra can provide us an improved analysis of the vibrational spectra and especially structural interpretation of the glassy IMC.

Experimental

IMC ($C_{19}H_{16}ClNO_4$; T_m = 434 K and T_g = 315 K) crystalline powder with 99% purity was purchased from Sigma–Aldrich. The commercial product was supplied as the crystalline γ-form (γ-IMC) and used without further purification. The glassy state of IMC was prepared by melt-quenching of the crystalline powder γ-IMC from 438 K which is slightly higher than the melting point, to 296 K under normal atmospheric conditions. The identity of the different indomethacin forms was established using differential scanning calorimetry and X-ray diffraction experiments. In order to accurately determine the complex dielectric constants $\varepsilon^*(\nu) = \varepsilon'(\nu) - i\varepsilon''(\nu)$ in THz-TDS measurements, the pure samples were used without mixing other solid powders, such as polyethylene. The crystalline and glassy samples were formed into pellet or thin plates with a thickness between 0.4 and 2.5 mm.

Two different THz-TDS systems were applied to cover the broad frequency range from 0.2 to 6.5 THz. The broadband THz transmission spectra were measured from 0.5 to 6.5 THz using the THz-TDS system (TAS7500SU, Advantest Corp.) with a high-speed asynchronous optical sampling technique in which two femtosecond lasers were used instead of the mechanical delay stage [21–23]. The low-frequency THz transmission spectra were also measured in the frequency range from 0.2 to 4.0 THz using another THz-TDS system (RT-10000, Tochigi Nikon Corp.) with low temperature-grown GaAs photoconductive antennas for both the emitter and detector [24,25]. In the data analysis, we smoothly connected the absolute value of the complex dielectric constants of the same sample with different thickness as based on of the low-frequency data of the thick samples. All samples were measured at room temperature (296 K) and the glassy sample with a thickness of 2.5 mm was measured at 12 K by the RT-10000 with using a He flow cryostat.

The depolarized low-frequency Raman scattering spectra were measured in the frequency range from 0.15 to 6.5 THz, under a scattering angle θ = 180°, using a single frequency green-YAG laser at the wavelength 532 nm. A double-grating spectrometer (U1000, Horiba-Jobin-Yvon) with a resolution of 0.05 THz was used. The crystalline sample was measured without an analyzer.

Results and discussion

The crystalline state

Fig. 1(a and b) show the complex dielectric constant, $\varepsilon^*(\nu) = \varepsilon'(\nu) - i\varepsilon''(\nu)$ of the crystalline γ-IMC in the frequency range of 0.2–6.5 THz at 296 K. Determination of the complex dielectric constant makes it possible to extract, as examples, the complex phonon-polariton dispersion [26] and the longitudinal optical (LO) phonon frequency from an energy loss function $\mathrm{Im}[-1/\varepsilon^*]$. In organic materials such as pharmaceuticals, a dielectric constant is generally small and their phonon-polariton dispersion shows almost a linear dispersion. In addition, the LO frequency is almost close to the transverse optical (TO) phonon frequency due to the small oscillator strength, and there is only a little LO-TO splitting.