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Temperature dependent terahertz pulsed spectroscopy of carbamazepine

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Abstract

In this study for the first time temperature dependent terahertz pulsed spectroscopy was performed on a pharmaceutical drug. The polymorphic conversion process of carbamazepine form III to I was studied at varying temperatures. Furthermore, the solid-state transformation at isothermal conditions below the melting point of carbamazepine was investigated. The ability to study solid-state reactions with terahertz pulsed spectroscopy could be demonstrated.

Keywords: Terahertz pulsed spectroscopy; Carbamazepine; Polymorphic conversion

1. Introduction

Carbamazepine (CBZ) is a dibenzazepine derivative (Fig. 1) and is principally used in the treatment of epilepsy and other neurological disorders [1]. CBZ is polymorphic and is known to exist in four anhydrous forms, as a dihydrate and also as other solvates. Of the anhydrous forms, a polymorph with a primitive monoclinic crystal structure is most commonly referred to as form III [2–6], and a triclinic polymorph is usually referred to as form I [6,7]. Forms I and III both exist as dimers with cyclic hydrogen bonding between the $CONH_2$ groups [2,3,6].

Forms I and III are enantiotropic, with form III being the stable form at room temperature and form I being stable at high temperatures [4]. Several studies have investigated the thermally induced conversion between forms I and III [6,8,9]. The solid-state conversion from form III to I that occurs below the melting temperature of form III has been suggested to occur via a solid–vapour–solid mechanism [8]. However, the mechanism and kinetics of this conversion still require clarification [9].

The terahertz region of the electromagnetic spectrum spans the frequency range between the mid-infrared and the millimetre/microwave. Its relatively unexplored central part (0.05–4 THz or 1.7–133 cm^{-1}) comprises frequencies lower than those corresponding to most internal vibrations of isolated molecules. Instead a terahertz absorption spectrum contains information on motions associated with coherent, delocalized movements of large numbers of atoms and molecules. The newly developed technique of terahertz pulsed spectroscopy (TPS) has been demonstrated to be a powerful tool for studying these low-frequency vibrational modes [10–12]. A major advantage of TPS is that the amplitude and phase of the transient electric field is measured, and not simply the intensity of the terahertz radiation. The coherent detection scheme not only yields terahertz spectra with excellent signal-to-noise ratio and high dynamic range, but also allows both absorption coefficients and spectral refractive indices to be obtained without the need for the Kramers–Kronig dispersion relationship [10]. Owing to these advantages, TPS is being increasingly used in studying low-frequency vibra-

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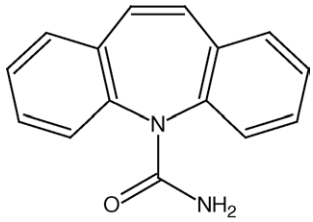

Fig. 1. Chemical structure of carbamazepine.

tional modes for a wide variety of samples including chemical, biological, pharmaceutical and security-related materials [13–20].

Since TPS is particularly sensitive to the intermolecular bonding of materials it is well suited to the study of polymorphism, and CBZ forms I and III have recently been found to have large spectroscopic differences in the terahertz regime [17]. In this study, the temperature-induced reversible transition between CBZ forms I and III is investigated using TPS. The spectral changes associated with the polymorphic transition are analysed to provide more information on the conversion mechanism.

2. Experimental

2.1. Materials

Carbamazepine (5H-dibenz[*b*,*f*]azepine-5-carboxamide) was obtained from Sigma–Aldrich (Poole, UK). The commercial product was supplied as polymorph III (*P*-monoclinic) and used without further purification. The triclinic form I was obtained by heating form III to 443 K for 2 h, as described by McMahon et al. [5] and Lefebvre et al. [21].

2.2. Sample preparation

Using a die press (Specac, Orpington, UK), 200 mg of the pure material (form I or III) was pressed directly with 1 t load for 3 min into a pellet of 13 mm diameter. Previous studies have shown that this compression is not sufficient to induce a polymorphic change in the sample [17].

2.3. Temperature dependent terahertz pulsed spectroscopy

The sample pellets were held in a brass ring with a circular aperture of 8 mm and inserted into a heatable transmission cell (Specac) with no windows. The sample temperature was controlled by a 3000 series high stability temperature controller (Specac). Temperature was calibrated using compounds of known melting point. The sample pellet temperature was changed at a rate of approximately 2 K min^{-1}. TPS spectra were recorded with a TPI spectra 1000 spectrometer (TeraView, Cambridge, UK) using an instrument resolution of 2 cm^{-1} over the range of 2–95 cm^{-1} as previously described [22]. To remove atmospheric water vapour, the sample chamber was purged with dry nitrogen prior to and throughout the experiment. Spectra were recorded by co-adding 1800 scans taking 1 min. Each sample spectrum was referenced against a spectrum of an empty sample holder, with nitrogen purging. Sample and reference spectra were calculated by a fast Fourier transformation (FFT) of the time-domain waveform. Zerofilling with a factor of two was carried out as well as applying Blackman–Harris three-term apodization. Absorbance spectra were calculated from the sample and reference spectra. Measurements and spectrum processing were carried out using OPUS 4.2 (Bruker Optik, Ettlingen, Germany).

To investigate the solid–solid conversion process of CBZ form III to I in more detail, a sample of CBZ was heated at a rate of 25 K min^{-1} to 438 K and then kept at isothermal conditions. Sample spectra were recorded by co-adding 900 scans for 30 s every 5 min during the whole conversion process. The conversion was assumed to be completed when no spectral changes could be observed for more than 30 min. The complete conversion to form I was confirmed by differential scanning calorimetry (DSC).

2.4. Differential scanning calorimetry

DSC was performed using a TA Q1000 (TA Instruments, New Castle, USA) differential scanning calorimeter. The

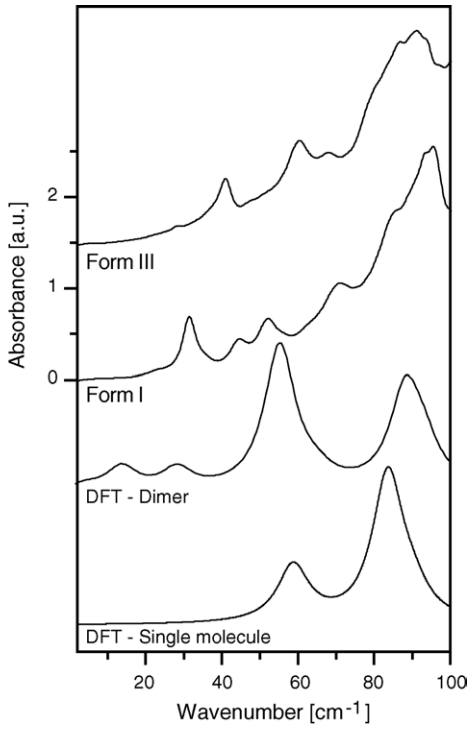

Fig. 2. Experimental terahertz absorption spectra of CBZ forms I and III. DFT predicted vibrational spectra of CBZ for the dimer structure and the single molecule. Plots are offset in absorbance for clarity.

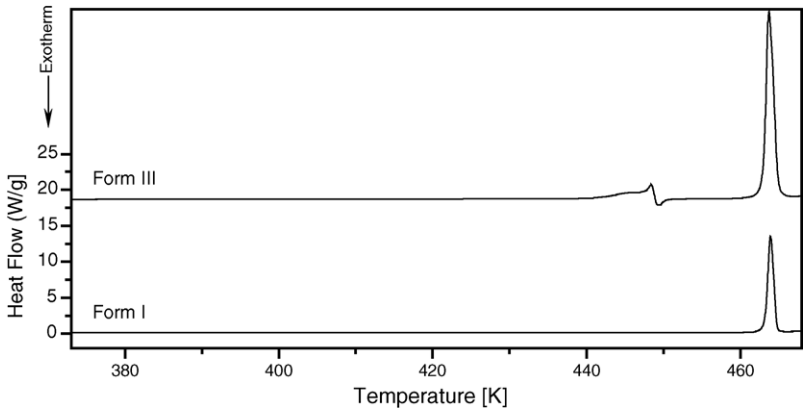

Fig. 3. DSC traces of CBZ forms I and III.

instrument was calibrated using indium standards. Between 1 and 2 mg/sample of CBZ forms I and III were weighed into aluminium pans and sealed. Under a helium gas purge, the samples were equilibrated at 293 K, and then heated up to 483 K at a ramp rate of 10 °C min^{-1}.

3. Results and discussion

The terahertz absorption spectrum for CBZ form III at room temperature (293 K) shows distinct spectral features with peaks at 29, 42 and 61 cm^{-1} (Fig. 2). There is a shoul-

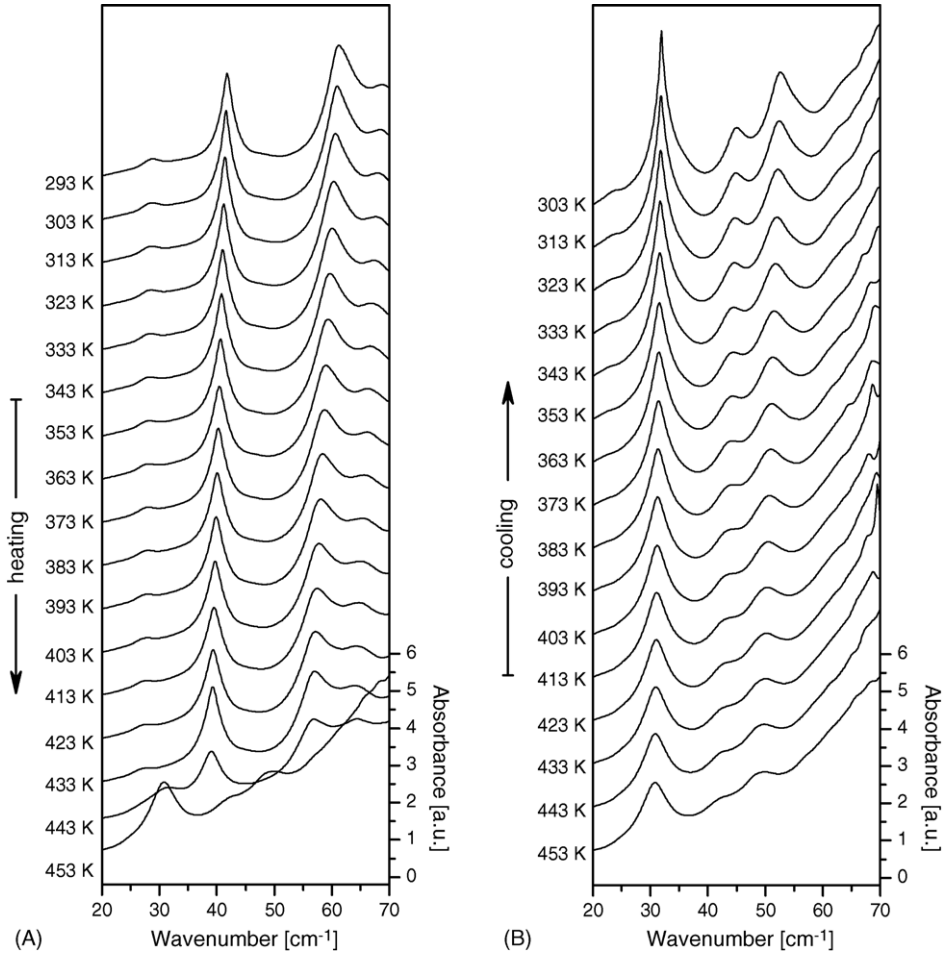

Fig. 4. Terahertz absorption spectra of CBZ form III during the temperature dependent measurements. The plots are offset in absorbance for clarity. (A) Heating from 293 to 453 K, transformation of form III to I takes place. (B) Cooling the transformed sample of CBZ form I from 453 to 303 K.

der at 69 cm^{-1} on the 61 cm^{-1} peak. The peak at 42 cm^{-1} is sharper than the other spectral features. In contrast the spectrum of CBZ form I exhibits a sharp peak at 32 cm^{-1} with a weak shoulder at 24 cm^{-1} and two further peaks at 45 and 52 cm^{-1}. Fig. 2 shows a comparison between the absorption spectrum of CBZ forms I and III and CBZ form I appears to show none of the features of form III in the range between 2 and 70 cm^{-1}. The spectral features observed in both CBZ III and I spectra around 90 cm^{-1} are very broad. The features are reproducible but, due to the characteristics of the radiation source, the signal-to-noise ratio in this spectral range is not high enough to enable a good quality spectral signal in a short acquisition time. We, therefore, do not include the spectral range above 70 cm^{-1} in the subsequent figures.

At least two transformation processes have been reported for CBZ form III conversion to form I upon heating. In the DSC trace of CBZ form III (Fig. 3) a melting event is recorded at temperatures above 433 K. At higher temperatures, this melting event is followed by a recrystallization to form I [6]. According to the literature, the other transformation process is via a solid–solid transformation without melting. This process is reported for temperatures between 403 and 433 K [23,24]. In the DSC trace (Fig. 3), at a heating rate of 10 °C min^{-1}, this event can be observed as a gradual endothermal inflection of the baseline. As the conversion is occurring at a slower rate than the temperature ramp rate, most of the form III has not converted at 433 K. Therefore, the melting event at 443 K is still very prominent. The extent of the solid-state transformation in the DSC trace depends very much on the temperature ramp rate as shown earlier by Behme and Brooke [8].

Upon heating CBZ form III in the TPS temperature dependent measurements, between 293 to 433 K all the spectral features show a red-shift, peak broadening and decrease in intensity (see Fig. 4A). Further heating up to 453 K leads to melting of CBZ form III followed by recrystallization to form I as reported previously (Fig. 3). At 443 K, an intermediate spectrum with peaks corresponding to both forms III and I is observed. The spectral features of form III at 39 and 57 cm^{-1} lose significant intensity at this temperature and the spectral feature of form I initially at 32 cm^{-1} red-shifts towards 31 cm^{-1}. At 453 K, the conversion from CBZ form III to I is complete and only form I spectral features are recorded as shown in Fig. 5. In this figure, the baseline is subtracted for greater clarity. Cooling form I from 453 to 303 K produces a blue-shift, the peaks sharpen and increase in intensity (see Fig. 4B).

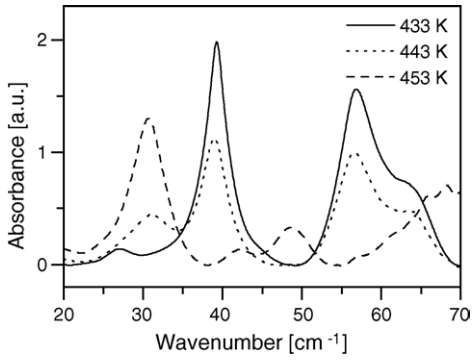

Fig. 5. Terahertz absorption spectra of the conversion process of CBZ form III to I at different temperatures. 433 K solid line, 443 K dotted line, 453 K dashed line (spectra are baseline corrected for better clarity).

The data from the isothermal experiment at 438 K gives more information about the solid–solid conversion process. It shows that the feature of form I at 31 cm^{-1} gradually increases in intensity as the transformation progresses (Fig. 6). Initially the peak shifts position to a lower wavenumber. After 40 min at 438 K, the red-shift stops and the peak position is unchanged for the rest of the conversion process (Fig. 7A). In contrast the form III peak initially at 39 cm^{-1}

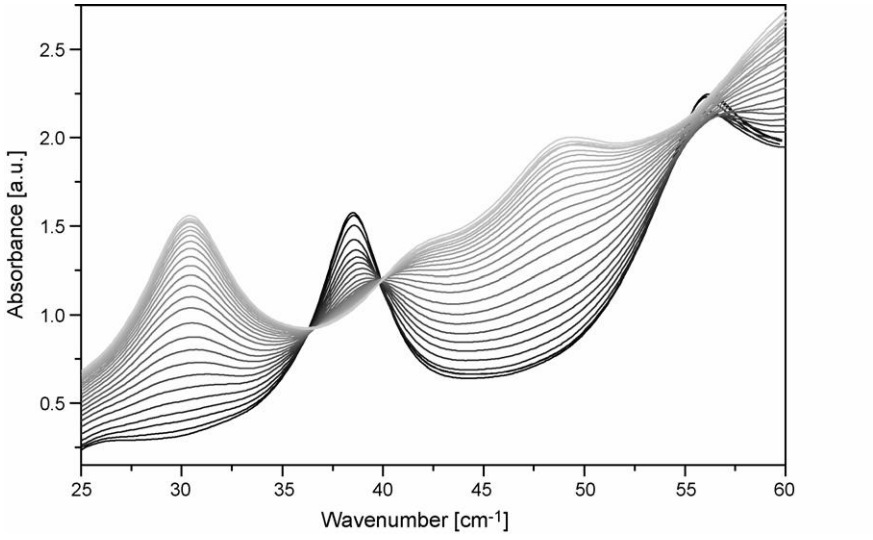

Fig. 6. TPS spectra of the isothermal solid–solid transformation from CBZ form III (black) to I (light grey) at 438 K. The spectra were taken in 5 min intervals until complete conversion.

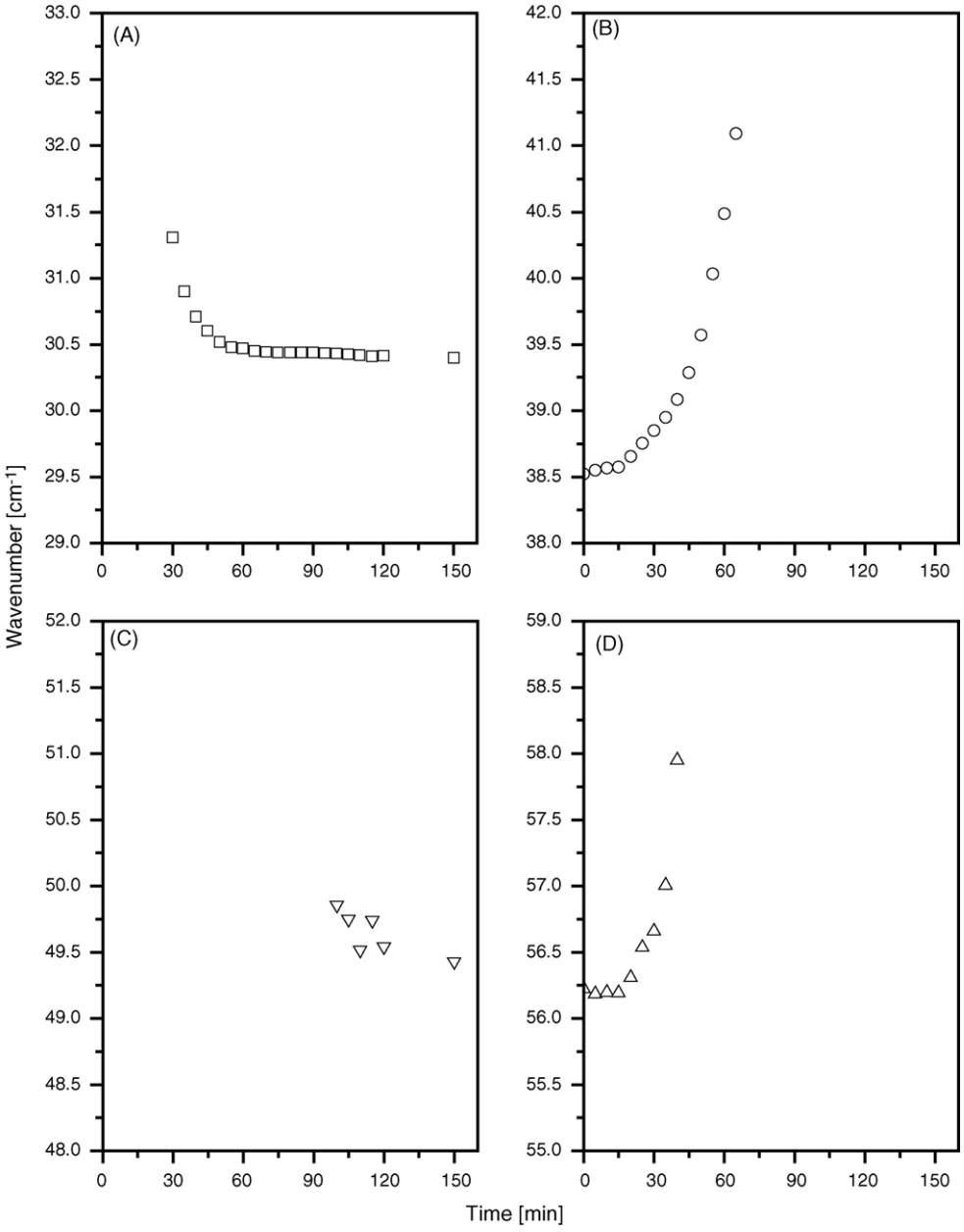

Fig. 7. Peak position of the four major spectral features of CBZ I and III vs. equilibration time at 448 K isothermal heating of CBZ form III. (A) Form I feature red-shifting after 30 min as it appears at the beginning of the conversion process. (B) Form III feature blue-shifting as it is disappearing after 65 min. (C) Form I feature appearing late in the process after 100 min and red-shifting. (D) Form III feature blue-shifting and diminishing in intensity after 40 min.

is blue-shifted and reduces in intensity, disappearing after 65 min (Fig. 7B). The spectral feature of form I at 52 cm^{-1} appears after 100 min at 438 K red-shifted at 50 cm^{-1}. Until completion of the conversion process after 150 min a slight red-shift can be observed (Fig. 7C). Again in contrast to the form I peak shifting behaviour, the form III peak at 57 cm^{-1} blue-shifts until it disappears after 40 min (Fig. 7D).

The sequence in the appearance and disappearance of the spectral features of forms III and I during the conversion process indicates that the mechanism involves more than a single step. Both form III spectral features diminish from the beginning of the process onwards. One of the form I features only appears very late in the process whereas the other feature appears at the beginning of the transformation. Furthermore, it is interesting to note that the decaying peaks of form III both blue-shift at different rates whereas the emerging peaks of form I both red-shift during the conversion. The dynamics of these shifts may give clues to the processes behind the conversion once the spectral features can be assigned to specific structural information.

It is possible to model CBZ using density functional theory (DFT) and this has been proven reliable as a theoretical model to predict vibrational spectral information. In particular, a study Chen et al. [25] has shown that within certain

limitations it is possible to use DFT calculations on the single molecule to predict some features in the terahertz spectral region of 2,4-dinitrotoluene and identify phonon modes from intermolecular vibrations. Density functional calculations have been carried out on a single molecule of CBZ and the hydrogen bonded dimer and the predicted spectra in the mid-IR region have been reported and discussed [26]. The predicted spectral data for the low frequency terahertz region may also be examined. The simulated spectra are shown in Fig. 2. Here, the lowest frequency vibration of the single molecule is predicted at 59 cm^{-1}. In the calculation, this vibration originates from a flexing mode of the aromatic ring system as depicted in Fig. 1. It is shifted to lower frequency in the dimer calculation (55 cm^{-1}). In the experimental spectra of the polymorphs at room temperature, bands are observed at 52 and 60 cm^{-1}, which may be attributable to this mode but more sophisticated calculations would be necessary to confirm this. Compared to the monomer calculations for the dimer a number of lower frequency modes with very weak intensity are observed below 30 cm^{-1}. However, in the experimental spectra, the dominant features below 60 cm^{-1} lie at 41 and 31 cm^{-1} for polymorphs I and III, respectively. These bands are of similar intensity to the higher wavenumber band and it seems unlikely from the DFT calculations that these modes originate from intramolecular vibrations. We attribute these to phonon modes involving the crystal lattice. Certainly the calculations presented must be rated as first attempts to correlate the spectral information obtained by the experiment to structural characteristics of the investigated system. For all the calculations, a temperature of 0 K is assumed with the system in the quantum mechanical ground state. More advanced algorithms would attribute much better for intermolecular interactions by including periodic boundary conditions in the calculation of solid-state vibrational spectra. Further promising approaches include the Car-Parrinello molecular dynamics (CPMD) simulations, Vienna ab initio simulation package (VASP) calculations or the use of DMOL3 software amongst others [28]. However, these calculations require far more computational power. In addition TPS spectra at low temperatures rather than at room temperature must be acquired to correlate the calculations with the experimental data. This work is in progress.

As Grzesiak et al. have reported, CBZ forms III and I both show an asymmetric unit cell. In form III, the unit cell consists of four molecules, of which one is in its asymmetric unit. For form I, eight molecules form the unit cell with four in its asymmetric unit. In all forms, hydrogen-bonded anti-carboxamide dimers are formed [6]. The molecular conformation and the strong hydrogen bonding scheme in CBZ remains the same for all its polymorphic forms. All differences in the crystal polymorphs arise solely from the different packing structure of the carboxamide dimer units [6,27]. This suggests that the spectral changes observed during the isothermal conversion process directly refer to shifting phonon modes. As the dimers change their relative arrangement during the transformation the lattice structure gets displaced resulting in a realignment of the unit cell from *P*-monoclinic in form III to triclinic in form I. The blue-shifts and red-shifts that occur in the terahertz spectra at different points during the conversion are most likely directly related to the expansion and contraction of the unit cell as the CBZ dimers realign.

Absorption spectra in the wavenumber range between 10 and 100 cm^{-1} could be acquired using a conventional far IR spectrometer. However, due to the weak blackbody radiation sources and more time-consuming and elaborate detection schemes studies using such instruments would be considerably more difficult to perform. Using this setup, slow transformation steps can be studied [29]. The ability to acquire high quality spectra in very short time without the need of cryogen cooled detectors makes TPS an ideal candidate to investigate fast processes in this spectral range. Compared to conventional far IR spectroscopy, the wavenumber range covered by TPS is smaller. Development is in progress to extend the spectral range accessible to TPS. As we have shown in this study, the spectral range accessible by TPS at present is sufficiently broad to study the polymorphic conversion of CBZ form III to I. We have further unpublished data that clearly shows that these studies are not limited to CBZ.

4. Conclusion

Using TPS, it is possible to study the mechanism of a polymorphic transition. TPS has the potential to follow rapid changes in the crystalline forms of organic materials. Kinetics experiments will be carried out to confirm the applicability of this technique to study solid-state reactions. However, so far too little is known to assign the recorded phonon modes and hydrogen-bond-stretching vibrations to specific molecular structures or lattice systems in a concluding way. More knowledge about the nature of the phonon modes observed is needed to explain the mechanism underlying the process in better detail.

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