

Monitoring polymorphic conversion processes with terahertz pulsed spectroscopy

Summary

Terahertz pulsed spectroscopy is used to study the polymorphic conversion process of carbamazepine form III to form I.

Introduction

Carbamazepine (CBZ) is a dibenzazine derivative and is principally used in the treatment of epilepsy and other neurological disorders. CBZ is polymorphic and is known to exist in four anhydrous forms, as a dihydrate and also as other solvates. Of the anhydrous forms, the polymorph with a primitive monoclinic crystal structure is most commonly referred to as Form III. The triclinic polymorph is usually referred to as form I. Forms I and III both form dimers by cyclic hydrogen bonding between the CONH₂ groups. Forms I and III are enantiotropic, with form III being the stable form at room temperature and form I being stable at high temperatures. The solid-state conversion from form III to form I that occurs below the melting temperature of form III has been suggested to occur via a solid-vapour-solid mechanism.

Terahertz Pulsed Spectroscopy (TPS) is particularly sensitive to the intermolecular bonding of materials and therefore is ideally suited to the study of polymorphism. In this study the temperature induced transition between CBZ forms I and III is investigated using TPS. The spectral changes associated with the polymorphic transitions are analysed to reveal information about the conversion mechanism.

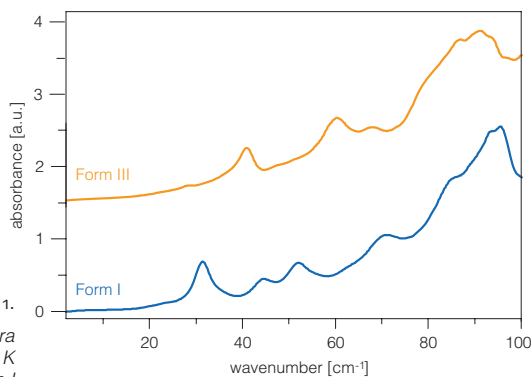


Figure 1. Terahertz absorption spectra (ambient temperature - 293 K) terahertz spectra for CBZ form I and III.

Terahertz Pulsed Spectroscopy

Transmission spectra from 2 cm⁻¹ to 95cm⁻¹ at 0.1 cm⁻¹ spectral resolution were collected using a TeraView TPS spectra 1000 terahertz spectrometer. To remove spectral contribution associated with atmospheric moisture the sample chamber was purged with dry nitrogen (10 l/min) prior to and throughout the experiment. Each sample spectrum was referenced against a spectrum of an empty sample holder, with nitrogen purging. For each rapid-scan spectrum within one minute the average of 1800 co-added scans was recorded.

The sample pellets were held in a brass ring with a circular aperture of 8mm and inserted into a heatable transmission cell with no windows. Temperature was calibrated using compounds of known melting point. The sample pellet temperature was changed at a rate of approximately 2K·min⁻¹.

Results and discussion

Figure 1 shows room temperature (293 K) terahertz spectra for CBZ form I and III. The terahertz absorption spectrum for CBZ form III shows distinct spectral features with peaks at 29 cm⁻¹, 42 cm⁻¹ and 61 cm⁻¹. 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 cm⁻¹ and 52 cm⁻¹. CBZ form I appears to show none of the features of form III in the range between 2 cm⁻¹ and 70 cm⁻¹.

At least two transformation processes have been reported for CBZ form III conversion to form I upon heating. One of the processes is a melt of form III at 445K followed by the recrystallization of the melt to form I at higher temperatures. The second process is a solid-solid transformation below the melting point of

form III. This process is reported for temperatures between 403 K and 433 K.

Upon heating CBZ form III in the TPS temperature dependent measurements,

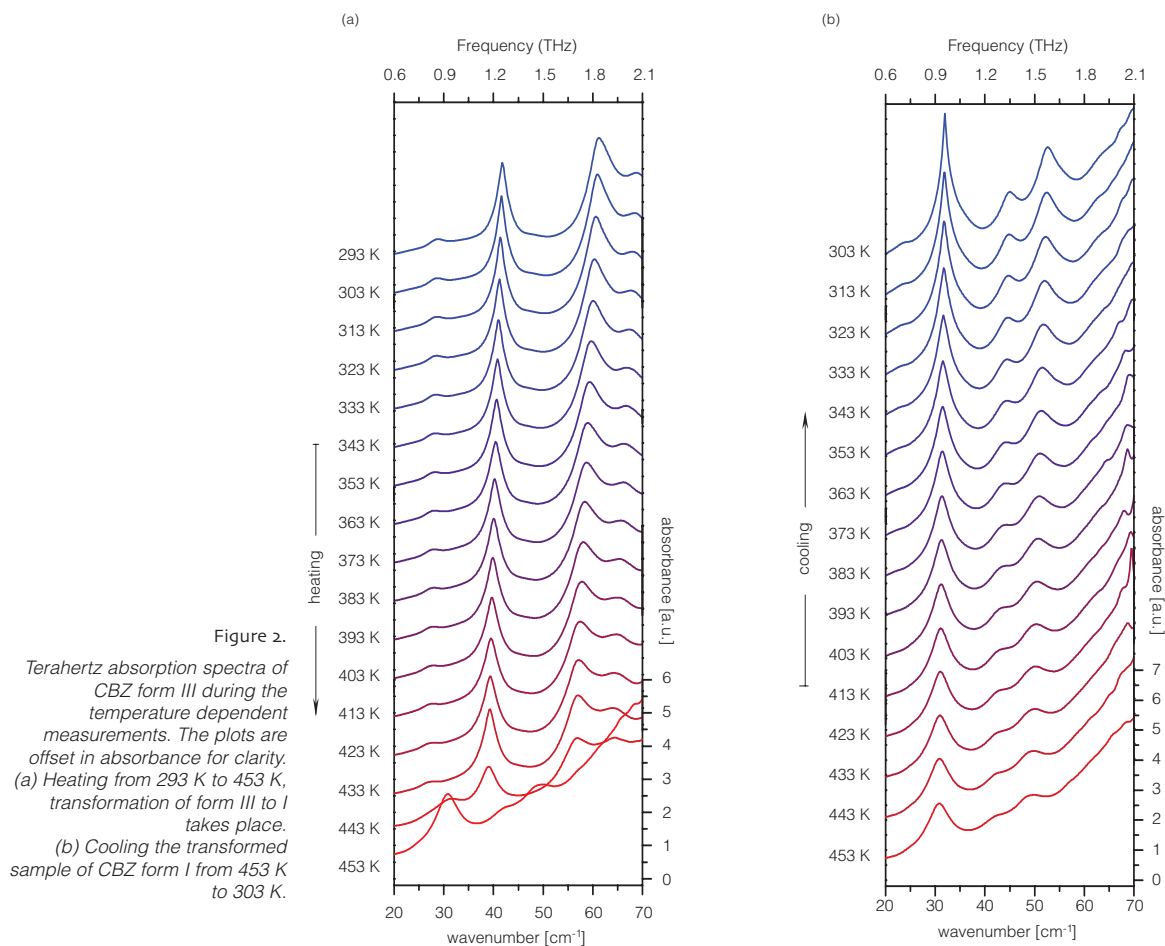


Figure 2.

Terahertz absorption spectra of CBZ form III during the temperature dependent measurements. The plots are offset in absorbance for clarity.

(a) Heating from 293 K to 453 K, transformation of form III to I takes place.
 (b) Cooling the transformed sample of CBZ form I from 453 K to 303 K.

between 293 K to 433 K all the spectral features show a red-shift, peak broadening and decrease in intensity, shown in figure 2. Further heating up to 453 K leads to melting of CBZ form III followed by recrystallization to form I. At 443 K an intermediate spectrum with peaks corresponding to both form III and form I is observed. The spectral features of form III at 39 cm^{-1} 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 form I is complete and only form I spectral features are recorded as shown in Figure 2a. In this figure the baseline is subtracted for greater clarity. Cooling form I from 453 K to 303 K produces a blue-shift, the

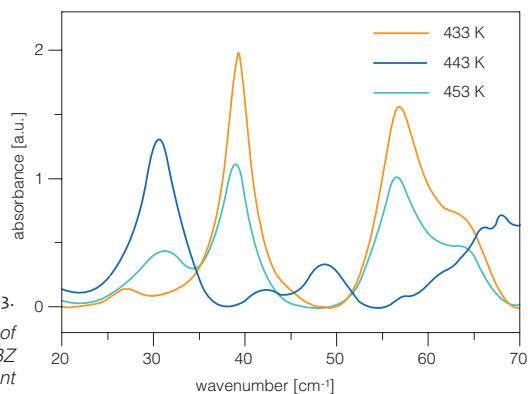


Figure 3.

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.

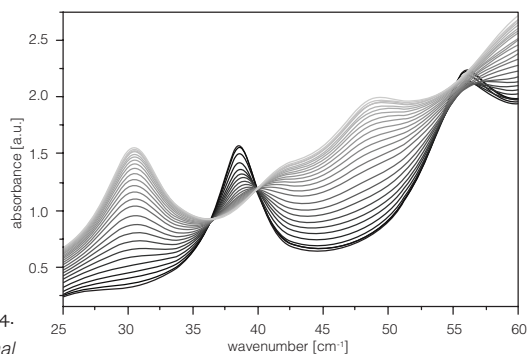


Figure 4.

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

peaks sharpen and increase in intensity (see Figure 2b).

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 (Figure 4). 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. In contrast the form III peak initially at 39 cm^{-1} is blue-shifted and reduces in intensity, disappearing after 65 min. 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. 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.

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 has been reported, CBZ form III and I both show an asymmetric unit cell of hydrogen-bonded anti-carboxamide dimers. In form III four molecules form the unit cell with one in its asymmetric unit whereas in form I the cell consists of eight molecules with four in the asymmetric unit. 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. 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.

Conclusions

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. To assign the recorded phonon modes and hydrogen-bond-stretching vibrations to specific molecular structures or lattice systems requires additional knowledge about the nature of the phonon modes.



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