

New Insights into the Solid-State Transition Mechanism in Carbamazepine Polymorphs by Time-Resolved Terahertz Spectroscopy

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Abstract—Preprint, the communication has been published in ChemPhysChem 8(13):1924-1927 (doi:10.1002/cphc.200700261).

Polymorphism of molecular crystals is a phenomenon in solid-state chemistry where a compound is able to exhibit more than one crystal structure. It is of wide importance in an industrial context as key physicochemical properties, such as solubility, are strongly dependent on the crystal structure. [1] Carbamazepine (CBZ, 5H-dibenz[*b,f*]azepine-5-carboxamide), a drug used for the treatment of epilepsy is known to exhibit at least four anhydrous polymorphic modifications. [2] At room temperature the P-monoclinic modification (form III) is the thermodynamically most stable of the four polymorphs. It converts to the triclinic form I by melting and subsequent crystallization upon heating. In addition, at temperatures below the melting point of form III a solid-state conversion occurs which was reported to follow a two step mechanism via the gas phase. [3] The study of the mechanism was solely based on the phenomenological observations by hot stage microscopy. However, this two step process was neither detected nor considered in previous structural or spectroscopic studies of the conversion kinetics. [4]–[6] Here, we present a study that for the first time shows the ability to resolve the mechanism spectroscopically and take it into account for the kinetics of the phase transition.

Terahertz pulsed spectroscopy (TPS) is very sensitive to subtle differences in structure by directly probing the lattice dynamics of molecular crystals in the far-infrared. [7] Earlier work demonstrated that form I and III of CBZ show distinct spectral features in the terahertz range between 2 and 130 cm^{-1} and that these differences can be used to monitor the phase transition between the two forms. [8] The assignment of spectral features in the terahertz range is still subject to scientific debate and several approaches are currently discussed. [9] For the fairly rigid molecule of CBZ, that forms dimers in all its polymorphic modifications, we have made some tentative assignments based on force-field lattice dynamics calculations. [9]

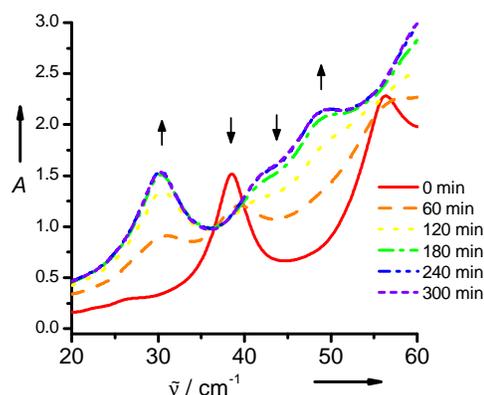


Fig. 1. *In situ* terahertz spectra of CBZ form III converting to form I at isothermal conditions (433 K). The arrows indicate the decrease of spectral features from form III and the increase in intensity of form I spectral features during the conversion process.

Using TPS we investigated the enantiotropic solid-state phase transition between the two polymorphs below the melting point of form III. It was possible to detect distinct spectral features for the different solid-state modifications rather than just shifts in peak position or change in intensity ratios as was the case in Raman spectroscopy. During the transition no spectral features are detected that are not present in one of the two polymorphs. At 433 K form III exhibits a very distinct peak at 39 cm^{-1} while form I has a pronounced peak at 30 cm^{-1} (Figure 1).

In order to investigate the conversion mechanism the peak area of those two features can be followed over time at isothermal conditions. Alternatively, a simple principal component analysis (PCA) was performed where the loadings on the first principal component represented form III while the second loading vector represented form I. [10] The scores of the loadings over time directly represent the change in polymor-

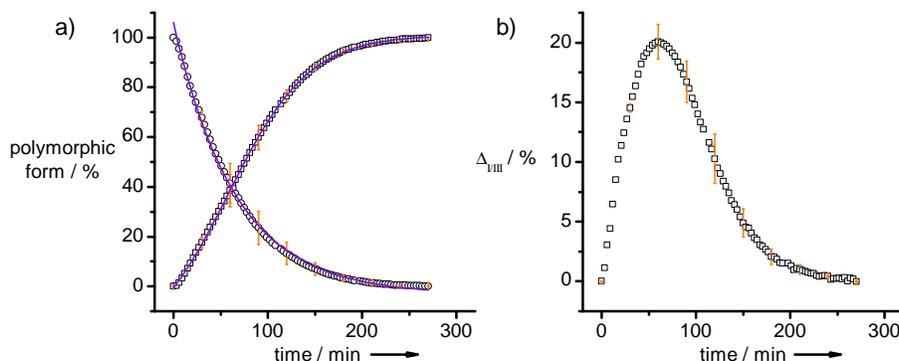


Fig. 2. Conversion of CBZ form III to I at 433 K. For clarity not all error bars are shown. a) The decrease in form III (squares) follows an exponential decay function (solid line) while the formation of form I (circles) occurs at a slower rate following Boltzmann sigmoidal (solid line). b) Amount of CBZ in the gas phase during the conversion process.

phic form during the conversion process. For the terahertz experiments the results from both techniques, integration of the peak areas and PCA analysis, were similar. Since in the Raman spectra it was not possible to determine the polymorphic conversion based on the integration over a single peak the PCA method was chosen for the analysis of all spectroscopic experiments.

The analysis of the terahertz spectra reveals the two step mechanism of the solid-state conversion (Figure 2): the spectral features of form III decrease faster than the spectral features of form I appear. This finding is in agreement with the previously suggested mechanism of the conversion: sublimation of form III and subsequent condensation of form I. While CBZ is in the gas phase it does not exhibit any spectral features as the rotational transitions of CBZ are at different energies and are not detected by TPS. However, the amount of CBZ in the gas phase during the transformation process can be determined indirectly from the sum of form III and I as quantified from their terahertz spectra. During the conversion process this sum does not add up to 100%. It can be assumed that the difference is due to CBZ in the gas or amorphous solid phase (Figure 2b). In principle CBZ could condense - at least partially - in the amorphous phase and only crystallize in a subsequent second step. However, the baseline in the spectrum of the fully crystalline form I is always slightly higher than that of form III [8] and no pronounced increase in the overall baseline absorbance, typical for the presence of amorphous phase, [11] can be observed during the conversion. In addition, spectral signatures of form I can be detected at very early stages of the phase transformation process indicating that nuclei of form I are formed within the sample or on the surface of the sample disc where the condensation takes place. In the presence of nuclei of form I and temperatures of 428 and 438 K the formation of form I is thermodynamically and kinetically more favorable than condensation in the amorphous phase. [12]

Throughout the experiment the temperature of the sample

is kept above the temperature at which sublimation of CBZ occurs, hence both adsorption/condensation of CBZ molecules from the gas phase onto the solid surface and further sublimation of CBZ molecules occur simultaneously. Initially, only form III sublimates as no form I is present in the sample. As the process progresses form I is condensing exclusively while both forms continue to sublimate. The overall process is irreversible and eventually yields in the crystallization of pure form I.

During the conversion process very fine needle-like crystals of form I start building up on the surface of the sample pellet and eventually cover the whole surface of the sample pellet with a fluffy layer. This effect is more pronounced at higher temperatures where the sublimated CBZ can form larger crystal aggregates on the surface of the sample pellet due to the higher sublimation rate. It is important to note that this layer of crystals does not interfere with the terahertz measurement as the spectral acquisition is performed in transmission and the particle size of the formed crystals is much smaller than the wavelength of the terahertz radiation and thus no scattering artifacts are observed.

The sublimation step exhibits exponential decay while the condensation kinetics of form I from the gas phase can be described using the Boltzmann sigmoidal fit (Equation 1, Figure 2a).

$$x_I = \ln \left(\frac{A_1 - A_2}{y - A_2} - 1 \right) dx + x_0 \quad (1)$$

with $A_1 = 1$ and $A_2 = 0$

The irreversible nature of the conversion mechanism, yielding a condensate of pure form I, explains the exponential decrease in form III rather than linear kinetics as observed for the sublimation process itself. As soon as no form III is remaining in the sample equilibrium is reached and continuing sublimation of form I is observed (Figure 3a and b, marked as t_{428K} , t_{433K} and t_{438K} for the three temperatures).

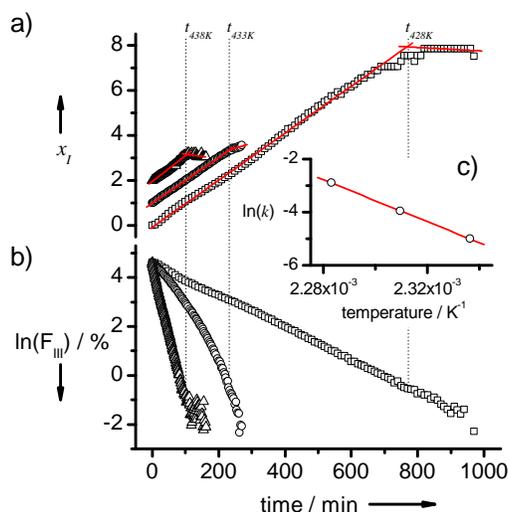


Fig. 3. Fit of the conversion kinetics at 428 K (squares), 433 K (circles) and 438 K (triangles). a) Form III - first-order exponential decay. t_{428K} , t_{433K} and t_{438K} mark the end-point of the conversion process. b) Form I - Boltzmann sigmoidal fit, x_I refers to Equation 1. The plots at different temperatures are offset vertically by 1. c) Arrhenius plot for the sublimation of form III.

From the Arrhenius plot the activation energy for the sublimation of form III is determined as 327 kJmol^{-1} (Figure 3c). As the activation energy has been determined using only three temperatures the accuracy of the actual values might be limited.

In order to confirm our findings from TPS we repeated the experiment at 433 K with Raman spectroscopy. The Raman spectra allowed to distinguish between the two polymorphic modifications yet the spectra exhibit no unique spectral features for each form. While Raman spectroscopy could be used for the *in situ* analysis of the overall conversion kinetics, it did not allow the discrimination between the two steps of the conversion mechanism. The overall conversion kinetics observed by Raman spectroscopy was identical to the results from TPS.

The activation energy of the sublimation kinetics recorded by TPS and Raman spectroscopy is in agreement with earlier reports of the overall conversion process using Raman spectroscopy where a faster conversion was reported (activation energy $344\text{-}368 \text{ kJmol}^{-1}$). [6] Here, complete transformation was measured after less than 150 min at 413 K and less than 50 min at 423 K. The conversion process was described to be almost linear, even though exponential fitting models were evaluated, and did not follow exponential decay kinetics. Considerably faster kinetics were also reported by X-ray powder diffraction (XRPD). [4] In this study the conversion process was even faster. After 40 min over half of form III was already converted to form I at 413 K. It is interesting to note that in this study 40% residual intensity of form III peaks in the diffractogram at 'complete conversion' were detected and no data was presented for isothermal holding times longer than 100 min. The activation energy for the conversion was reported to be 229 kJmol^{-1} . In contrast to our experiments

the first study [6] measured the conversion process in a sealed sample cell. In the second study [4] it is not clear whether the sample was sealed. Using a glass cover slide to seal the sample cup during heating we were able to reproduce the results from O'Brien *et al.* [4] (Figure 4a).

Condensation of the sublimate occurred to the glass cover through which the scattered light was acquired. Due to the limited penetration depth of the scattered photons we conclude that the study of O'Brien *et al.* was measuring the sublimation of form I to the cover sheet rather than the phase transition in the bulk of the sample. This hypothesis is confirmed by our determination of the sublimation rate of CBZ by TGA which was found to be constant for both polymorphic forms and strongly dependent on the particle size and experimental temperature (Figure 4b).

The solid-state transformation mechanism of CBZ as described here is only possible because sublimation occurs below the melting temperature of the lower melting polymorphic modification. However, from careful variable temperature optical microscopy it is evident that such sublimation processes are very common in pharmaceutical organic molecular crystals. [3] The results from our study suggest that these mechanisms might indeed be overlooked by using vibrational spectroscopy at higher wavenumbers. Furthermore, our findings underline that under isothermal conditions different conversion mechanisms are observed compared to non-isothermal conditions and, thus, the results question the transferability of kinetic data acquired in such an experiment to non-isothermal processes. In the light of these results and the early reports from Kuhnert-Brandsttter, [3] it might need to be considered whether the numerous studies of solid-state conversion mechanisms and kinetics based on mid-infrared and Raman spectroscopy have to be revisited. Terahertz spectroscopy, with

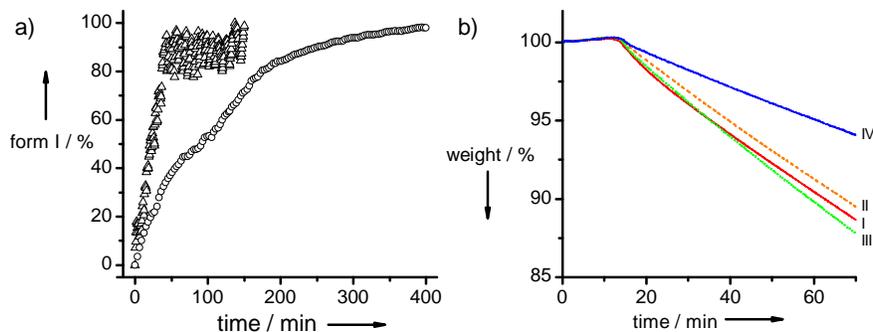


Fig. 4. a) Measured conversion kinetics by Raman spectroscopy at 433 K with open sample pan (triangles) and sealed sample pan (circles). b) Thermogravimetric analysis of the weight loss during sublimation of CBZ at different particle size fractions (I < 63 μm , II 63-180 μm , III 180-250 μm , IV > 250 μm).

its ability to measure the low frequency phonon modes and intermolecular hydrogen bonding modes in the far-infrared spectral range, which directly represent the lattice dynamics and hence the crystal structure, has proven to be a very useful to resolve such mechanisms.

EXPERIMENTAL SECTION

Carbamazepine form III was obtained from Aldrich and used as received. The experiments were performed at isothermal conditions at 428, 433 and 438 K ($T_{m(III)}$ 447 K). Transmission terahertz spectra were acquired *in situ* with 30 second time resolution (Temperature control to ± 1 K, spectral resolution 1.3 cm^{-1}) on a TPS spectra1000V spectrometer (TeraView, Cambridge, UK) as reported previously. [8]b The spectra were recorded from discs containing 250 mg pure form III. For each spectrum 900 scans were co-added. All measurements were performed in duplicate. Thermogravimetric analysis (TGA) was used to study the sublimation of CBZ at isothermal conditions. Between 2 and 4 mg sample material was heated at a rate of 10 Kmin^{-1} to 433 K and the weight loss over time was recorded (TGA Q50, TA Instruments, New Castle, DE, USA). To validate the results obtained by TPS the solid-state transition was also studied by Raman spectroscopy (excitation wavelength 785 nm, excitation power 500 mW, spectral range $\tilde{\nu} = 200\text{-}1700$ cm^{-1}) from a 20 mg powder sample in an open aluminium sample cup using a Raman spectrometer (Control Development, South Bend, IN, USA).

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- [12] Further evidence for the preferred condensation of the crystalline phase under such conditions is the macroscopic observation that CBZ condenses in its amorphous yellow phase on the actively cooled part (288 K) of the temperature cell and as crystalline form I on the hot surfaces of the heating element.