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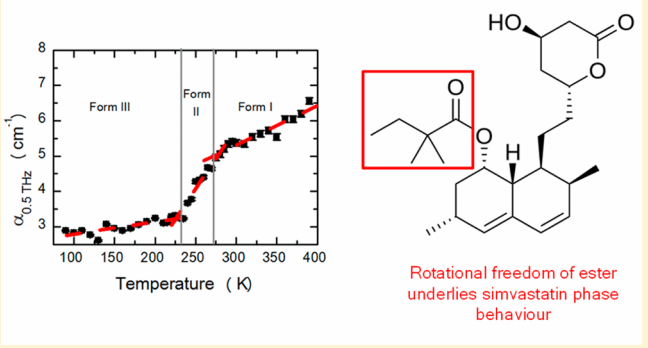
Probing Phase Transitions in Simvastatin with Terahertz Time-Domain Spectroscopy

Nicholas Y. Tan and J. Axel Zeitler*

Department of Chemical Engineering and Biotechnology, University of Cambridge, Pembroke Street, Cambridge CB2 3RA, United Kingdom

Supporting Information

ABSTRACT: Simvastatin is known to exist in at least three polymorphic forms. The nature of polymorphism in simvastatin is ambiguous, as the crystal structures of the polymorphs do not show any significant change in crystal packing or molecular conformation. We utilize terahertz time-domain spectroscopy to characterize each of the polymorphs and probe the phase transitions in the range of 0.2−3.0 THz and for temperatures ranging from 90 to 390 K. In form III, vibrational modes are observed at 1.0, 1.25, and 1.7 THz. For form I, we find that the spectrum is dominated by a baseline corresponding to libration−vibration motions coupled to the dielectric relaxations, which is characteristic of a disordered hydrogen bonding material but with additional broad vibrational modes at 0.8 and 1.4 THz. In addition, the baseline shifts with temperature similar to that observed in disordered materials. This background absorption exhibits pronounced changes around the phase transition temperatures at 232 and 272 K. The results are in agreement with molecular dynamics simulations, which indicate that changes in the rotational freedom of the ester tail in the molecule govern the polymorphism in simvastatin.



KEYWORDS: *simvastatin, disordered crystal, phase transition, terahertz, spectroscopy*

INTRODUCTION

Polymorphism is the ability of a compound to exist in different crystalline states and has been extensively studied over the last century.[1−3] While there is no single definition of polymorphism, the most commonly agreed upon one was given by McCrone,[4] which states that a polymorph is a "solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state". From this definition, it can be reasoned that there are two basic sources of polymorphism:[1−3] differences in intermolecular packing in the crystal lattice and differences in the intramolecular conformation of the molecules within the lattice, which includes enantiomers and tautomers. Polymorphism is of great importance in the pharmaceutical industry as polymorphs often exhibit different physical properties, which can directly influence the manufacturing, stability, formulation, and bioavailability of these compounds.[3,5]

In certain compounds, the identification of polymorphs is complicated by the presence of disorder within the crystal.[6,7] This disorder can be either orientational, where molecules have different orientations in the lattice, or positional, where one or more atoms occupy multiple sites in the lattice.[6] Given that disorder in crystals affects the energetics of the crystal lattice, it is unsurprising that it also affects the physiochemical properties of compound. Therefore, the study of disorder is also of great importance to the pharmaceutical industry.

Statins are a group of drugs which lower plasma cholesterol levels through the inhibition of HMG-CoA reductase, the enzyme responsible for cholesterol production in the liver.[8] Simvastatin (Figure 1) is a major member of the statin family that is widely used to treat hypercholesterolemia.[8] Now sold as a generic after patents expired in 2006, it is listed on the World Health Organisation's list of essential medicines,[9] which records all drugs needed in a basic healthcare system based on their efficacy, safety, and cost. Simvastatin is administered in the

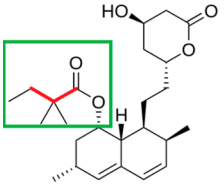


Figure 1. Molecular structure of simvastatin. Ester tail is highlighted by the green box, and dihedral angle D1 is indicated by the red lines.

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lactone form (Figure 1), which is inactive and must be hydrolyzed to form the biologically active ingredient after hepatic first-pass metabolism.[8] However, the compound is highly insoluble in water, which limits its efficacy as a drug.[10]

In simvastatin, three crystal forms have been identified thus far[11,12] and DSC experiments have shown clear crystal phase transitions at 232 and 272 K.[12,13] Of the three crystal forms, form I has been characterized by single-crystal X-ray diffraction[11] and exists between 272 K and the melting point at 408−411 K; forms II and III have been characterized by powder X-ray diffraction,[12] with form II stable from 232−272 K and form III stable below 232 K. Forms I and II have been assigned as orthorhombic ($P2_12_12_1$, $Z'/Z = 1/4$), while form III has been assigned as monoclinic ($P2_1$, $Z'/Z = 2/4$). Recent single-crystal X-ray diffraction studies have suggested the reassignment of form III to orthorhombic ($P2_12_12_1$, $Z'/Z = 1/4$).[13] The X-ray diffraction studies indicate that the structures of the polymorphs are very similar and do not involve any rearrangement of the crystalline lattice, instead only differing in the degree of disorder in the ester tail of the molecule.[11,12] Additional solid-state ^{13}C NMR data provide evidence that the three polymorphic forms differ in the rotational freedom of the ester tail:[11] it is rotationally restricted in form III, becoming increasingly free as the temperature is increased through form II, and fully free to rotate in form I. Despite the clinical importance of simvastatin, relatively few studies have been performed to investigate the nature of polymorphism in the compound. While DSC measurements show clear phase transitions,[12,13] X-ray analysis reveals only slight structural differences between the three crystal forms, hence the nature of polymorphism still remains ambiguous and complicated by the high molecular disorder in the compound.

Terahertz time-domain spectroscopy (THz-TDS) has been used to study the chemical and electrical properties a variety of systems, ranging from molecular crystals,[7,14−20] amorphous glasses,[21−23] liquids,[20] and proteins.[20] Because of the low energy of electromagnetic radiation at terahertz frequencies (1 THz = 4.1 meV), it is able to probe low frequency intermolecular modes as well as hydrogen bonding relaxation dynamics in condensed matter. The technique also benefits from being nondestructive, allowing for measurements to be done over a wide range of temperatures for a single sample.

Given the technique's high sensitivity to intermolecular interactions, it can be used to study vibrational motions within crystal lattices, which include lattice phonon vibrations and intramolecular librations. Because these vibrational motions are heavily influenced by the arrangements and orientations of individual molecules within the crystal lattice, THz-TDS has demonstrated great utility in the study of polymorphs, being able to differentiate polymorphs arising from both changes in lattice packing[18,19] as well as changes in molecular conformation.[7,15]

In addition, THz-TDS has been found to be capable of probing disorder in a variety of systems.[7,14,16,24] Crystalline benzoic acid exhibits disorder in the crystal, despite being a rigid molecule, due to the presence of two possible configurations of the hydrogen atoms in each dimer pair.[25] Li et al. found that THz-TDS was able to distinguish between the two possible dimer configurations despite the subtle difference between the two.[19] Apart from crystalline materials, THz-TDS has been extensively used to study the dynamics of disordered amorphous solids.[21−23,26−29] Šibík et al. demonstrated that in hydrogen-bonded amorphous organic solids, both the primary and secondary dielectric relaxation as well as the libration−vibration motions exhibit strong temperature dependence at terahertz frequencies and that these processes decouple at the glass transition temperature (T_g) and 0.67 T_g respectively.[21−23]

With the utility of THz-TDS in studying both vibrational motions in crystal lattices and the dynamics of disorder in amorphous solids, we expect that a THz-TDS study of simvastatin will be able to provide additional information about the nature of polymorphism exhibited by the compound.

MATERIALS AND METHODS

Simvastatin (≥99%) was obtained from Dalian Melian Biotech Co. (Dalian, China) and used without further purification. The identity and amount of impurities as provided by the manufacturer are lovastatin and epilovastatin (0.31%), anhydro simvastatin (0.16%), simvastatin dimer (0.14%), methylene simvastatin (0.09%), acetyl simvastatin (0.09%), and simvastatin hydroxyacid (0.08%). Powder X-ray diffraction pattern, as well as ^1H (500 MHz, $CDCl_3$ and ^{13}C (125 MHz, $CDCl_3$) NMR spectra are in good agreement with previous reports[12,13] (see Supporting Information). Differential scanning calorimetry (DSC) was performed and indicated onset temperatures of the phase transitions to be 230.9 and 270.7 K, approximately 1 K lower than was found by Hušák et al.,[12] and a melting point of 411.8 K, which is in good agreement with previously reported values[13] (see Supporting Information).

Samples for THz-TDS were prepared by mixing simvastatin and high-density polyethylene (HDPE) and compressed under 2.5 tons load (corresponding to a pressure of 1.85 MPa) for 5 min to obtain pellets 13 mm in diameter and approximately 2 mm thick, containing 40 mg of simvastatin and 200 mg of HDPE. Given the high molecular flexibility of polyethylene and the low percentage of simvastatin in the sample, we expect most of the compressive force to be transferred onto polyethylene rather than simvastatin and hence not induce any unwanted phase transitions in simvastatin. An additional pellet of 200 mg of pure HDPE was compressed under the same conditions to serve as a reference.

Terahertz Time-Domain Spectroscopy. Subpicosecond coherent pulses of broadband terahertz radiation were generated by photoexcitation of a DC biased semi-insulating GaAs substrate with 12 fs pulses of a NIR laser (Femtosource, Femtosource cM1, Vienna, Austria) as described previously.[24] The terahertz pulses were focused onto the sample, and transmitted pulses were detected via electro-optical sampling with a ZnTe crystal. The time-domain spectra were collected by employing a moving mirror as an optical delay.

Variable temperature THz-TDS measurements were performed under vacuum using a modified continuous flow liquid nitrogen cooled cryostat (ST-100 FTIR, Janis Research, Wilmington, MA, USA), and the temperature was controlled with a temperature controller (Lakeshore model 331, Westerville, OH, USA). The sample and reference pellets were mounted on a copper coldfinger using copper plates with 9 mm apertures. Samples were cooled to 90 K over 30 min and left to equilibrate for approximately 15 min before starting measurements. Spectra were acquired over a temperature range of 90−390 K with 10 K intervals from 90−210 K and above 290 K, and 5 K intervals from 210−290 K, the region where the 2 phase transitions occur. The time-domain terahertz waveforms were obtained for both sample and reference at all temperature points, and the terahertz absorption coefficients and refractive indices were extracted for the 0.2−3 THz frequency range.

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RESULTS AND DISCUSSION

Terahertz Spectra. Figure 2 shows the absorption coefficients (α) at three temperatures that are representative

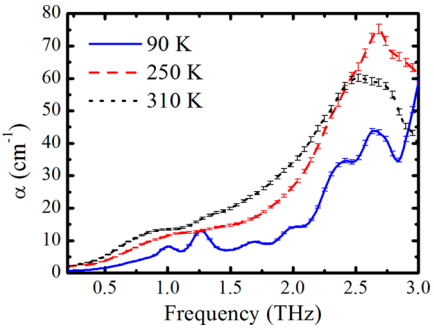

Figure 2. Absorption coefficient of simvastatin at 90 (blue), 250 (red), and 310 K (black). Error bars represent standard errors reflecting both the uncertainty in sample thickness and the noise estimate based on the averaging of 120 time-domain waveforms.

of forms III (90 K), II (250 K), and I (310 K), and Figure 3 shows the evolution of the spectra in the temperature regions where each polymorph exists as well as the phase transition temperatures.

In the absorption spectra from 90 to 200 K, four spectral features are observed at 1.0, 1.3, 1.7, and 2.0 THz. In form III, the entire simvastatin molecule is essentially rigid, with the ester tail lacking rotational mobility.[12] Because the molecules are fixed within the crystal lattice in this form, features arising from concerted lattice phonon motions can be observed in the spectra.

As the temperature is raised from 90 K, the features broaden due to an increase in the number of populated excited vibrational states and an increase in the rotational mobility of the ester tail. The features also red-shift to lower frequencies with increasing temperature, a phenomenon commonly observed in the terahertz spectra of solids.[7,16,30] From 215 to 235 K, the features become less pronounced, even though the absolute absorption remains relatively similar. This could be due to either an increase in the rate of peak broadening or an increase in the amount of background absorption. Both are indicative of an increase in the disorder of the system.

In the ^{13}C NMR studies performed by Hušák et al., it is argued that below 232 K, there is a splitting of the NMR signals which indicate the presence of two distinct conformations in the crystal, with neither conformation being energetically preferred.[12] In principle, the existence of two positional configurations can be determined by THz-TDS: in the case of benzoic acid, where temperature dependent positional disorder is well documented from neutron diffraction experiments, it was previously shown that the terahertz spectrum was an average of the spectra of both configurations weighted by their energies.[14] Features observed in terahertz spectra are complex, and it is well established that there is no simple principle for assigning peaks to specific vibrational modes.[31] Therefore, density functional theory (DFT) calculations under periodic boundary conditions are typically performed and used in conjunction with the experimental spectra to determine the vibrational motions underpinning the observed spectra.[14−17,24,30,31] However, because of the large size of the simvastatin unit cell[11] (2292 Å^3 vs 595 Å^3 for benzoic acid), and the fact that computational time scales with the cube of the volume of the unit cell in popular computational plane wave methods such as CASTEP, a DFT calculation under periodic conditions, is not practicable at present due to the resources available to us.

From 230 to 270 K, simvastatin exists in form II, where the rotational freedom of the ester tail increases with temperature.[11,12] From Figure 3, it is observed that the main features found in form III are no longer pronounced. As the temperature is raised from 230 to 270 K, the remaining feature at 1.2 THz gradually disappears, while a broad peak at 0.8 THz emerges. Additionally, the absorption at frequencies above 1.2 THz increase more quickly than the absorption below 1.2 THz and the spectra begin to resemble those of liquids, with a monotonously increasing absorption with frequency.

At the form II → I phase transition temperature, no change in spectral features is observed. However, the amplitude of absorption shows a greater increase between 270 and 275 K. Above 275 K, the spectra increase monotonously with frequency and are essentially featureless apart from two broad features centered at 0.8 and 1.4 THz. At these temperatures, the

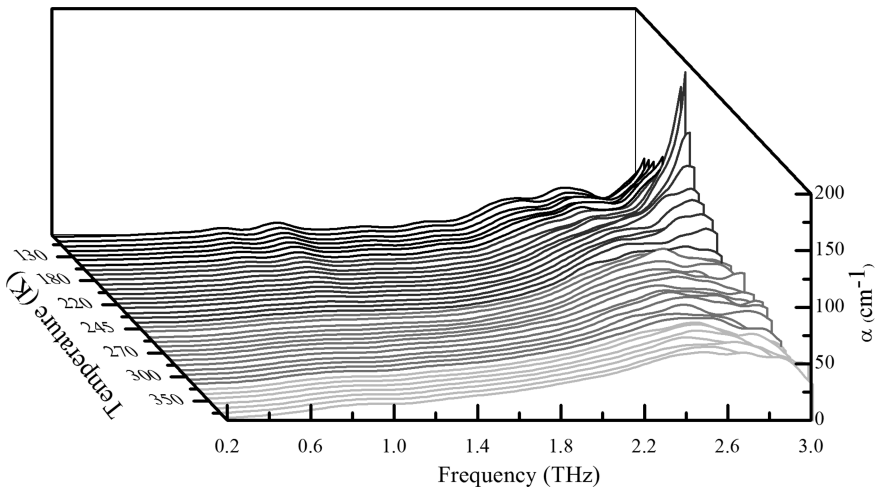

Figure 3. Waterfall plot showing terahertz absorption spectra of simvastatin from 90 to 390 K. The temperature increment between spectra is 10 K from 80 to 210 K and 290 to 390 K, and 5 K from 210 to 290 K. 2D plots of the spectra are available in the Supporting Information (Figure S5).

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Mol. Pharmaceutics 2015, 12, 810−815

ester tail of simvastatin has complete rotational freedom.[11,12] As such, it is capable of undergoing a reorientational process analogous to Debye relaxation in liquids after an external electric field is applied. This is also similar to the terahertz spectrum of succinonitrile in its plastic crystal (PC) phase, where the molecule is freely rotating around the central carbon−carbon bond.[16] The broad features are likely due to the fact that the remainder of the simvastatin molecule remains rigid across all three forms despite the rotational motions of the ester tail.[13] Such a feature is not observed in succinonitrile's PC phase because the entire molecule is involved in the rotational movement.[16]

While there are some observable changes that occur around the two phase transition temperatures, this is not accompanied by any sharp emergence or disappearance of spectral features. Such behavior is in contrast to that reported in most other polymorphic compounds to date such as carbamazepine, sulfathiazol, and paracetamol,[18,19,23,32] where there are distinct and rapid changes in the spectral features at the phase transition temperatures due to rearrangements of the crystal lattice, and therefore significant differences in the lattice phonon modes. The lack of such changes in distinct spectral features is in agreement with X-ray structures of the three forms of simvastatin where no major changes in the crystal lattice are observed between the different forms,[11,12] with all three structures exhibiting an infinite 1-D chain along the *b*-axis formed by hydrogen bonding between the carbonyl of the ester and the hydroxyl group on the lactone.[13] In addition, when spectra of simvastatin are taken upon cooling after a first heating cycle around the two phase transition temperatures (220−240 K and 260−280 K), the spectra are similar, within experimental error, to those acquired on heating. This is in agreement with the lack of hysteresis observed at the phase transition temperatures by Hušak et al.[12]

Spectral Background. In addition to the vibrational features observed in the spectra of simvastatin, further analysis reveals a background in the temperature-dependent spectra that rises with both frequency and temperature.

Frequency Dependence. It has been established in both far-infrared (FIR)[29] and terahertz spectroscopy experiments[21−23] that the absorption coefficients and refractive indices of amorphous solids are related to frequency by $n(\nu)\alpha(\nu) = A + C(\nu - \nu_0)^q$, where A and ν_0 account for the absorption offset and low frequency cutoff in the spectra respectively, and the exponent q is $\lesssim 2$. Such absorption behavior has been interpreted to be caused by the disorder-induced coupling of the radiation to a density of low-frequency Debye modes and is therefore related to the disorder in the system.[26]

Figure 4 shows the $n\alpha$ plot for simvastatin at 310 K and the fitted curve with the power law described above. The fit was performed with the data for $\nu < 0.4$ THz and $1.5 < \nu < 2.2$ THz to minimize any interference from the vibrational modes, and A and ν_0 were fixed to their experimental values. The extrapolated baseline fits well with the power law ($R^2 = 0.998$) and gives a fitted exponent of 2. This provides strong evidence that the background absorption is indeed related to the disordered component of the molecule.

Temperature Dependence. In amorphous glasses of alcohols and pharmaceutical compounds, the terahertz absorption has also been found to exhibit temperature dependence. In these systems, the absorption is associated with the vibrational density of states (VDOS) originating from libration−vibration motions as well as α and β relaxation processes.[21−23] When measuring the spectra from temperatures well below the glass transition, T_g, the terahertz absorption increases with temperature and the rate of increase changes as the β and α relaxation begin to contribute at 0.67 T_g and T_g, respectively. These dielectric relaxation processes are reflective of the molecular mobility in these systems, and the terahertz absorption of amorphous systems can be used to determine relative levels of disorder and the rate of change of molecular mobility.

Figure 5 shows the temperature dependence of the absorption coefficient at 0.5 and 1.8 THz.

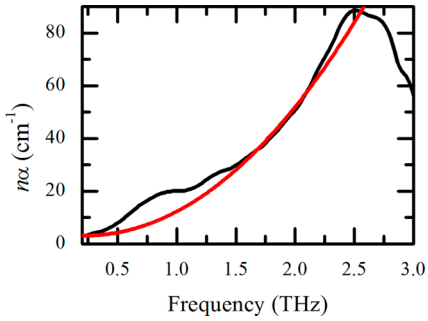

Figure 4. Plot of $n\alpha$ against frequency for simvastatin at 310 K. Black line is the experimental spectrum. Red line is the best-fit curve to $A + C(\nu - \nu_0)^q$ for experimental data extrapolated for $\nu < 0.4$ THz and $1.5 < \nu < 2.2$ THz. A and ν_0 were fixed to the experimental values of 3.1 cm^{-1} and 0.2 THz, respectively.

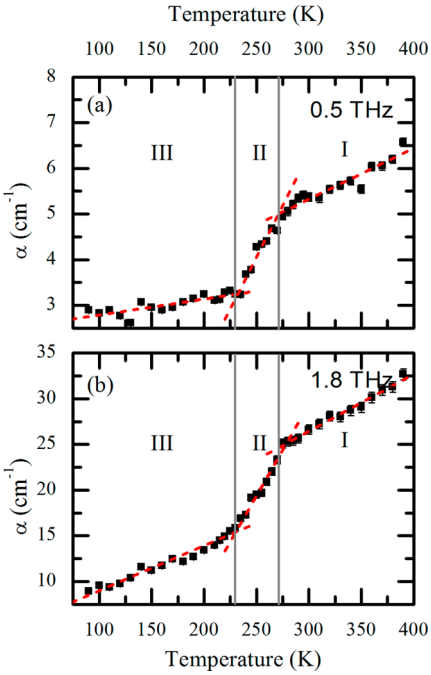

Figure 5. Plots of absorption over the 90−390 K temperature range. Red dashed lines represent best fit linear plots. (a) Absorption coefficient at 0.5 THz, (b) absorption coefficient at 1.8 THz. Gray vertical lines indicate the DSC derived phase transition temperatures of 230.9 and 270.7 K and separate the different polymorphic forms indicated by III, II, and I. Error bars represent standard errors reflecting both the uncertainty in sample thickness and the noise estimate based on the averaging data obtained from measurements of three samples, with 120 waveforms obtained at each temperature point per sample.

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Mol. Pharmaceutics 2015, 12, 810−815

These frequencies were chosen as they are removed from the spectral features across all temperature points and are therefore not affected by shifts in the features. The plots show an overall increase in absorption with increasing temperature, and they also resolve into three distinctly different regions where the absorption increases at different rates with temperature: there is minimal increase in absorption with temperature below 235 K, a rapid rise between 230 and 280 K, and again a slow increase beyond 280 K. When the intersection points of the best fit lines at both frequencies are averaged, they indicate the phase transition temperatures to be 231.4 and 274.6 K, which are close to the phase transition temperatures measured by DSC at 230.9 and 270.7 K (see Supporting Information). This further highlights the fact that the phase transitions in simvastatin are related to changes in the molecular mobility of the system. The close agreement of the terahertz and DSC data also shows suggests that there were no pressure induced changes in polymorphism when simvastatin was pressed into pellets for the terahertz experiments. From previous X-ray and solid-state NMR experiments, the only part of the molecule that exhibits significant temperature dependent changes in mobility is the ester tail.[11,12] Therefore, we conclude that this must be the major contributor to the changes in the terahertz absorption.

Simões et al. have recently presented a method for performing molecular dynamics (MD) simulations on simvastatin which allowed them to determine the volumetric and energetic properties of the system, and also the probability distribution of a dihedral angle, D1 (Figure 1), in the ester tail.[33] This method was later extended to calculate the probability distribution of D1 across a range of temperatures from 80 to 370 K.[13] The authors found that the MD simulations supported the presence of two phase transitions, at 220 ± 13 K and 260 ± 20 K. The results showed that below 220 K (form III), the ester tails have highly restricted rotation, only vibrating about a single D1 value; between 220 and 260 K (form II), there is a large increase in the rotational freedom of the ester tail, with D1 being able to be found over a range of 220°; above 260 K (form I), the ester tail is effectively freely rotating, and D1 can be found over the entire 360° range.

When the D1 probability distribution obtained from the MD simulations is compared with the terahertz absorption data shown in Figure 5, a much clearer picture of the simvastatin phase transition starts to emerge; below 230 K, simvastatin exists in form III, where the ester tail is highly rotationally restricted, resulting in low terahertz absorption. As the temperature is increased from 80 to 230 K, the rotational mobility remains low; hence the terahertz absorption does not increase significantly. While the X-ray diffraction studies of the form III structure suggests the presence of multiple frozen conformations of the ester tail, this is not reflected in the terahertz baseline absorption as the terahertz absorption measures dynamic disorder. Between 230 and 270 K, in form II, the ester tail experiences the most rapid rise in rotational freedom with temperature. This leads to the increase of the terahertz absorption at the highest rate, in agreement with the MD simulations of the D1 probability distribution. Finally, above 270 K, simvastatin exists in form I. In this form, the ester tail is freely rotating, therefore an increase in temperature results in a lower rise in rotational mobility than a corresponding increase in form II. The absolute terahertz absorption of form I is naturally greater than form II and III because the disorder is the highest due to the rotational freedom around D1.

CONCLUSIONS

The terahertz spectra of simvastatin were acquired between 0.2 and 3.0 THz and over a temperature range of 90 to 390 K, allowing all three known phases of the compound to be studied. These variable temperature THz-TDS studies provided direct evidence that the polymorphism in simvastatin is caused by rotational disorder in the ester tail. They also demonstrated the utility of the technique in studying disordered crystals, as it provides information about both the vibrational modes in the crystal and the dynamics of the disordered component.

While several vibrational features were observed, it was not possible to determine the vibrational motions underlying those features using computational means due to the large size of the unit cell. However, a qualitative analysis of the changes in the features across the three polymorphs was still able to provide information regarding differences between the polymorphs. The spectra showed no significant emergence or disappearance of vibrational features at both phase transition temperatures, corroborating X-ray diffraction studies that observed no major changes in the crystal packing across the polymorphs. Instead, subtle changes in absorption intensity and peak width are found which are related to variations in disorder within the crystal lattices.

A frequency and temperature dependent background component was also observed in the spectra. This background component was found to be related to frequency via a power law often used to describe amorphous systems and is dominant in the form I spectra. When plotted against temperature, the background absorption exhibited major changes at the two phase transition temperatures. This suggests that the THz spectra of disordered crystals contain additional information regarding the dynamic disorder in the crystals within the background absorption. The temperature dependent trends in background absorption were also in agreement with molecular dynamics simulations of the rotational freedom of the ester tail of the molecule.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectrum of simvastatin. ^{13}C spectrum of simvastatin. Experimental and calculated powder x-ray diffraction patterns for simvastatin. DSC measured curve obtained for a simvastatin sample of 2.893 mg mass in a heating/cooling cycle at a rate of 10 K min^{-1}. DSC measured curve obtained for a sample of 2.893 mg mass in a heating cycle at a rate of 10 K min^{-1}. Terahertz absorption spectra of simvastatin at varying temperatures from 90 to 390 K. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jaz22@cam.ac.uk.

Notes

The authors declare no competing financial interest.

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