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Terahertz time domain spectroscopy (THz-TDS) for solid state analysis

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TERAHERTZ TIME DOMAIN SPECTROSCOPY (THz- TDS) FOR SOLID STATE ANALYSIS

by

B. M. Bimali S. Bandaranayake

A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Chemistry in the Graduate College of The University of Iowa

May 2016

Thesis Supervisor: Professor Mark A. Arnold

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CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

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has been approved by the Examining Committee for the thesis requirement for the Doctor of Philosophy degree in Chemistry at the May 2016 graduation.

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To my loving family, with love.....

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ABSTRACT

Terahertz time-domain spectroscopy (THz-TDS) probes inter-molecular interactions within solid materials. THz-TDS covers the spectral region of 0.1-3 THz or 5-100 cm⁻¹ which is a low energy and non-ionizing region of the electromagnetic spectrum. Spectra are collected in a time-domain configuration where a coherent broad-band pulse of THz electromagnetic radiation passes through a sample and gated-detection is used to monitor the electric-field vector of the transmitted THz radiation. This methodology permits a direct measure of the time-of-flight of THz radiation through the sample and, as a result, provides a direct means to measure interactions between the propagating THz electromagnetic wave and the sample material. Time of interaction between the THz wave and the sample gives a measure of the optical and electronic properties of the material and attenuation of the propagating THz wave gives information pertaining to both absorption and scattering properties of the sample. The analytical utility of these features of THz-TDS is explored in this dissertation.

Cocrystals represent a novel class of supra-molecular materials composed of two or more inorganic or organic units (molecules, ions or atoms) configured within a crystalline structure. The components interact by hydrogen bonding, π - π stacking or weak Vander Waals interactions to create ordered structures with unique chemical and physical properties. The potential of such unique properties has spurred efforts to design cocrystal materials specifically direct toward long-standing problems within the fields of pharmaceutics and electronics. Research findings presented in this dissertation demonstrate the potential of THz-TDS as an analytical tool for characterizing fundamental chemical and physical properties of cocrystal materials, thereby providing the means to advance the rational design of cocrystal materials for selected applications.

The analytical utility of THz-TDS is established through a series of transmission measurements through samples composed of the cocrystal of interest embedded within a polymeric matrix. Both high-density polyethylene and polytetrafluoroethylene are used to form compressed pellets containing cocrystals for analysis. Initial efforts demonstrate quantitation of cocrystalline materials within such pellets through a Beer-Lambert relationship where the magnitude of selected absorption bands is related to the amount of a cocrystal within a given pellet. In addition, time-domain THz spectra are used to determine the refractive index of sample pellets and this information is shown to provide dielectric spectra at THz frequencies for the cocrystal components of the sample pellets. The so-called LLL model is applied to generate accurate dielectric information for the cocrystal component of these pellets on the basis of volume fraction. The ability to measure the polarizability of cocrystals is also demonstrated by applying the Clausius-Mossitti relationship between polarizability and dielectric spectra.

The utility of the established analytical features of THz-TDS is demonstrated in a series of preliminary experiments designed to: 1) follow the single-crystal-single-crystal (SCSC) [2+2] photodimerization reaction of 2(5-cyano-resorcinol)·2(trans-1,2-bis(4-pyridyl)ethylene) to produce rctt-tetrakis (4-pyridyl) cyclobutane; 2) establish the relationship between polarizability and hardness for a series of cocrystals; and 3) determine differences in polarization of cocrystals produced by different synthetic methods. Results support the following conclusions: 1) kinetics of SCSC reactions can be followed through dielectric measurements, but concentration measurements are confounded by unique

spectroscopic features observed for partially reacted cocrystals; 2) polarizability at THz frequencies are inversely related to hardness of the tested cocrystals; 3) differences are observed in the polarizability of macro versus nano size cocrystals; and 4) polarizability of these cocrystals is independent of synthesis method.

PUBLIC ABSTRACT

The utility of terahertz time-domain spectroscopy (THz-TDS) is established as a unique analytical tool for characterizing chemical and physical properties of designed organic cocrystals. This spectroscopic methodology uses low energy electromagnetic radiation at terahertz frequencies to provide information related to the concentration, dielectric properties and polarizability of cocrystalline materials. The low energy nature of this approach makes it well suited for the noninvasive characterization of innovative materials. The features of THz-TDS established from this research can enhance the rational design of novel materials with applications in the pharmaceutical and electronics industries.

THz-TDS methods are developed for the quantification of concentration, refractive index, dielectric properties, and polarizability of unique crystalline materials. This crystalline materials are cocrystals, which are composed of two organic molecules that assemble into unique configurations within the crystal lattice. Such configurations determines the properties of these cocrystals. Results are provided that establish the ability of the THz-TDS method to: 1) follow a rare single-crystal-single-crystal photochemical reaction, 2) investigate the relationship between polarizability and hardness of cocrystal structures, 3) examine the impact of synthesis method on cocrystal polarizability, and 4) explore differences in polarizability of macro-size and nano-size cocrystals.

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CHAPTER 1

INTRODUCTION

1.1 THz spectroscopy

Terahertz time domain spectroscopy (THz-TDS) was introduced several decays ago by using a single-cycle pulse of far-IR radiation.^{1,2} This technique has found extensive applications in a variety of fields including gas phase samples^{3,4} and biomedical imaging.^{1,5} This spectroscopic technique probes rotational transitions of gas phase molecules, intermolecular interactions of liquid phase molecules and crystalline vibrations of solid phase molecules.^{6,7} THz spectroscopy is capable of providing real time information which can be valuable for measurements in the pharmaceutical and polymer industries.⁸ THz-TDS offers promise for process analytical technology in the pharmaceutical industry where the quality of products can be analyzed throughout the manufacturing process starting with raw materials and ending with the blending processes to produce the final product. Real time monitoring throughout a process offers the potential to optimize production quality. In addition, THz-TDS can be perform through a host of materials such as polymers, paper, cloth, and leather, thereby expanding its analytical utility for applications in the pharmaceutical industries as well as in security screening processes.^{1,7,9,10}

1.2 THz radiation

THz-TDS covers the spectral region commonly referred to as the far-infrared region. Electromagnetic (EM) radiation over the frequencies ranging from several gigahertz (GHz) to several terahertz (THz) ^{7,11} is consider the THz region of the EM spectrum. As illustrated in Figure 1-1, this THz region is positioned between the microwave and infrared regions.¹² Radiation at THz frequencies is non- ionized and low energy, thereby making THz-TDS attractive as a nondestructive technique.



Figure 1-1. Map of electromagnetic radiation indicating the relative position of

THz spectroscopy.

1.3 THz spectrometer

THz-TDS is performed by generating a coherent pulse of EM radiation at THz frequencies, passing this radiation through the sample of interest and detecting the transmitted radiation in a time dependent manner. Figure 1-2 presents a schematic diagram of a typical THz-TDS experiment. This schematic illustrates the positioning and function of the key elements involved in the time-domain measurement. The following sections provide descriptions of these major elements, including the THz emitter, sample compartment, and detection system.



Figure 1-2. Schematic diagram of the THz time domain spectroscopy experiment.

1.3.1 THz Emitter

A coherent pulse of THz radiation can be created from a femto-second pulse of a near infrared laser. Ti:sapphire lasers are commonly used for this purpose and produce a broad band of coherent THz radiation. The broad band nature of this radiation makes it well suited for solid-phase measurements where spectral bands are relatively broad compared to gas-phase spectra. The 1000D TeraView spectrometer used for the experiments described in this dissertation is equipped with a Ti:sapphire (Ti:Al₂O₃) laser producing a near infrared pulse over a period less than 100 fs at a wavelength of 800 nm.

Alternatively, continuous wave (CW)¹³ sources are available. Such sources typically give poorer analytical performance (lower signal-to-noise ratios) but are nicely suited for imaging applications, because they produce a narrower band of radiation. A family of CW sources are report with molecular gases like CO₂,¹⁴ semiconductor lasers,^{15,16} p-doped germanium lasers,¹⁷ lead lasers, quantum-cascade lasers,^{18,19} and quantum dot lasers (QDL).^{7,20}

Figure 1-3 presents a schematic diagram of a pulsed THz source where the incident near infrared femto-second pulse produced by a Ti:sapphire laser is split into a probe and pump beam. The pump beam strikes a polarized semiconducting emitter material and the resulting excitation creates electron-hole pairs. The mobile electrons are accelerated in the polarizing field and this acceleration of a charge electron results in the creation of a coherent band of EM radiation. The frequency of this EM radiation covers the THz frequency region.^{21,22}



Figure 1-3. Schematic diagram of the THz emitter.

1.3.2 Sample compartment

As illustrated in Figure 1-2, the THz radiation is directed into the sample compartment where it interacts with the sample. Although Figure 1-2 shows a transmission experiment, alternative configurations can be used for reflectance or attenuated total internal reflectance (ATR) measurements. After interaction with the sample, the resulting THz radiation is directed to the detection optics.

1.3.3 THz detections

Two types of detectors are commonly used for THz-TDS. In both cases, the probe beam generated from the near infrared pulsed laser is used in a time-gated manner for detection. For photo-conductive (PC) detection, a semiconductor material is used; whereas an electro-optic (EO) element is used in the other detection method.

For PC detection, the probe beam and the transmitted THz radiation simultaneously illuminate a semiconducting element, as depicted in Figure 1-4. The higher energy probe beam generates electron-hole pairs in the semiconducting PC material. The mobile electrons are accelerated by the oscillating electric field vector of the THz radiation. The result is a measureable current between the antenna electrodes of the detector assembly and its magnitude is proportional to the strength of the THz beam. The Teraview 1000D spectrometer used in this study is equipped with a PC detection system. The semiconducting material used in the Teraview 1000D spectrometer is GaAs with 1.5eV band gap at room temperature.²³ Electrical field strength is measured as a function of time and produces a time-domain spectrum that can be transformed into a frequency domain spectrum by the common Fourier transformation function.

For EO detection, the probe and THz beams travel simultaneously through an electro-optic (EO) crystal lattice. The THz beam changes the birefringence of the EO crystal lattice, thereby changing phases of the propagating near infrared probe beam. The degree of phase retardation of the near infrared probe beam is proportional to the strength of the THz radiation incident upon the EO crystal.⁷ The retardation of the near infrared phase is determined by using a series of optical components such as quarter wave plate, Wollaston prism two-photo diodes.⁷ The transmitted near infrared beam from the EO crystal passes through the quarter wave plate, which converts this linearly polarized near infrared radiation to circularly polarized radiation which is a combination of two linear polarized waves. These two waves are $90^{\circ}, \frac{1}{4}\lambda$, or $\frac{1}{2}\lambda$ radians out-of-phase. The components of the circular polarized wave passing through the Wollaston polarizer are separated into two orthogonal plane polarized rays and then each strikes a different photodiodes.²² The relative amplitude of the two orthogonal polarized waves is proportional to the strength of the THz wave.



Figure 1-4. Schematic diagram of the PC detection system used for THz-TDS.

1.4 Spectral analysis using THz-TDS

1.4.1 THz-time domain spectra

Figure 1-5 provides an example of time-domain spectra collected over THz frequencies with the TeraView 1000D spectrometer. The time axis corresponds to the position of the delay line in the path of the pump beam used for PC detection. The signal corresponds to the magnitude of the THz electrical field vector after passing through the sample compartment. The blue time-domain spectrum in Figure 1-5 corresponds to the signal obtained with air in the sample compartment while the green spectrum corresponds to a sample in the optical path. The delay in time between the two main peaks (sample versus air) is a measure of the time the THz radiation is delayed by the sample relative to air. The magnitude of this peak will be impacted by absorption or scattering events. Peaks prior to the main peak reflect instrumental noise.

The relatively small peak highlighted in the red box in Figure 1-5 is called an etalon and is the result of internal reflections within the sample. As the THz wave passes through the sample, a fraction is reflected back into the sample at the sample-air interface based on differences in the refractive index of each medium. This portion of the reflected wave is again reflected at the second sample-air interface and eventually departs the sample to the detection optics. This etalon wave is delayed relative to the main peak by passing twice through the sample. As a result, the location of the etalon peak along the time axis depends on both the thickness and refractive index of the sample. The shape of the etalon peak is similar to the main peak, but its magnitude is substantially less.

The etalon feature creates Fabry-Perot interference fringes in the corresponding frequency-domain spectrum and these oscillations can confound absorption information in such spectra. These fringes can be eliminated by removing the etalon from the time-domain spectrum before transforming to the frequency domain. One way to accomplish this is to increase the thickness of the sample so the etalon shifts outside the collected time domain spectrum. Depending on its composition, samples can be too thick and result in low signals and poor signal-to-noise. Alternatively, the time- domain spectrum can be truncated before the etalon feature and filled with zeros to enable a proper Fourier transformation calculation.^{24,25} Limitations of this approach are: 1) a reduction in resolution of the corresponding frequency-domain spectrum and 2) the potential to distort measured band shapes. In the work presented here, time-domain spectra are typically truncated prior to the etalon feature and the removed points are filled with values that linearly track from the value at the truncation point to zero at the end of the time axis required for the Fourier transformation. The Matlab code for this etalon removal process was written by Dr. Ryan Smith, while in the Arnold research group at the University of Iowa.



Figure 1-5. Example THz time-domain spectra of air and solid samples.

1.4.2 THz Frequency-domain spectra/Single beam spectra

Applying the Fourier transform to the time-domain spectra in Figure 1-5 produces the frequency-domain spectra shown in Figure 1-6. The intensity or radiant power reaching the detector is plotted as a function of optical frequency or wavenumber for both singlebeam spectra.

The quality of the final spectrum can be enhanced by apodization where the timedomain spectrum is multiplied by a weighting function designed to reduce high frequency noise. Common apodization functions include triangular, Hap-Genzel, Hamming, Nortonbeer week, medium and strong, Blackman-Harris 3-term and 4-term, and boxcar.⁷ Apodization functions can provide smoother spectra by reducing noise but are susceptible to distortion of spectral shapes. A boxcar function is the simplest function and retains spectral features at high frequencies.

Zero-filling is commonly used to provide smoother spectra. In this method, zeros are artificially added to the end of the time domain spectrum to extend to the next 2^N time points required for the Fourier transformation calculation. This process extrapolates between spectral points, thereby providing smoother spectral features. This process is similar to the zero-filling process mentioned above to remove etalon effects and the corresponding fringe pattern in frequency-domain spectra.


Figure 1-6. Log-single beam spectra for the air reference and sample (5-CN-res·4,4'bpe) THz-time domain spectra presented in Figure 1-5.

1.4.3 Absorbance calculation

An absorbance spectrum can be obtained as the negative logarithm ratio of a sample single- beam spectrum to a reference single beam spectrum, as shown in Equation 1-1.

$$Absorbance = -log \left[\frac{I_{sample}}{I_{reference}} \right]$$
 Equation 1-1

Examples of such spectra are presented in Figure 1-7 for solid samples of 5-CNresorcinol bpe embedded within a polymer matrix of polytetrafluoroethylene (PTFE). In both cases, sample single-beam spectra are ratioed to a single-beam spectrum of air. The blue spectrum is obtained from direct processing of the raw time-domain spectrum; whereas the red spectrum corresponds to results after removing the etalon effect by truncation, applying one level of zero filling and implementing a boxcar apodization function prior to generating the single-beam spectrum. The impact of these pre-processing functions is evident, particularly at low frequencies.



Figure 1-7. Absorbance spectrum of 5-CN-res·4, 4'- bpe showing absorbance spectra without signal preprocessing (blue) and absorbance spectra after signal preprocessing (red).

1.5 THz applications

A wide array of applications are reported for THz spectroscopy, particularly in the characterization of polymorphs²⁶ and enantiomers²⁷ in the pharmaceutical industry.²⁸ Different polymorphs give rise to different crystal structures giving rise to unique absorption features over the THz spectral range.²⁹ Distinction of polymorphs and enantiomer is superior with THz spectroscopy over common spectroscopic methods, such as mid-infrared spectroscopy, near infrared spectroscopy, and Raman scattering spectroscopy which are centered on functional groups as opposed to inter-molecular interactions.

Spectroscopic, imagining, and dielectric applications of THz spectroscopy are discussed below.

1.5.1 Spectroscopic Applications

Absorption spectroscopy over THz frequencies can be used for both qualitative and quantitative analysis. The position of absorption bands can be used to identify chemical components and the magnitude of absorbance can be related to concentration according to the Beer-Lambert law. Such methods are reported for applications in the pharmaceutical,³⁰ polymer³¹ and semiconducting industries,^{32,33} biomedicine³⁴ and biomolecules,³⁵ and in the analysis of solid materials.³⁶⁻⁴⁰ THz spectroscopic techniques are reported for identifying impurities in samples common to the polymer industry,^{10,12} pharmaceutics,⁴¹ and food industry.⁴²⁻⁴⁵

The attenuated total reflectance (ATR) measurement geometry is reported for many applications of THz-TDS.^{46,47} This approach is particularly effective when the quantity of sample is limited or when the sample is strongly absorbing, highly scattering or too thick for acceptable transmission measurements. For the ATR measurement, the sample is positioned against an ATR crystal and irradiated by an evanescent wave extending from the crystal to the sample. The penetration depth of the evanescent wave depends on the refractive index difference between the sample and ATR crystal, the angle of the incident beam angle and the strength of the incident radiation. ATR spectroscopy is less effective when the refractive index of the sample is higher than that of the ATR crystal and the sample is heterogeneous in composition.

1.5.2 Imaging Applications

Imaging by THz-TDS is a popular area of research, particularly for noninvasively imagining works of art and other historical artefacts.⁴⁸ This methodology involves illuminating the object of interest and measuring the time delay in a returned signal corresponding to reflected THz radiation. Reflection occurs at each interface composed of materials with different refractive indices.

THz imaging, or T-Ray imaging,⁴⁹ is being investigated as a replacement for Xray imaging because of the non-ionizing nature of the low energy THz radiation. The low energy nature of THz imaging makes it well suited for medical⁵⁰ and security screening applications. Medical applications of THz imaging are reported for the detection of cancerous tissues^{20,51-53} and in the identification of initial stages of dental cavities.⁵⁴ THz imaging is demonstrated to be well-suited for skin cancer detection⁵⁵ owing to its limited penetration depth and strong sensitivity to water present in the layers of skin.⁵⁶ THz imaging is also reported for identification of cancer cells within breast biopsy samples and the ability to reveal edges of tumors during surgical procedures.⁵¹

THz pulsed imaging is reported for measuring thickness and homogeneity of tablet coatings.^{29,57,58} Such imaging can be done quickly, thereby enabling real-time, quality control during manufacturing. Improved coating quality can enhance dissolution consistency of active pharmaceutical ingredients (API) and enhance storage or shelf-life of the product.

As noted before, THz radiation is transparent to leather, cloth, paper, and plastics but is strongly reflected by other materials such as metals,⁵⁹ and polar substances.⁶⁰ These properties make THz imaging well-suited for security applications. The spatial resolution for THz imaging is 1 mm which is sufficient to view most concealed weapons. THz imaging has also been investigated for detection of explosives, drugs, and weapons.^{49,59,61,62} Explosive materials such as TNT, RDX and HMX have been imaged.⁵⁹

1.5.3 Dielectric Measurements

Dielectric properties of a material relate to its ability to store charge. This fundamental property has implications for the application of materials for an array of applications. The dielectric properties of materials are frequency dependent and are mostly characterized at frequencies below THz, especially in the megahertz to gigahertz frequency range. Many methods are available to quantify the dielectric constant of materials over these low frequency ranges. An example is the dielectric constant measurement of pulverized minerals over the frequency range of 1.0- 22 GHz.⁶³

The coherent nature of THz radiation makes it well-suited for dielectric measurements using a free-space geometry.⁶⁴ When THz radiation propagates through a sample, the phase of the transmitted radiation changes according to the refractive index of the material.⁶⁵ As a result, the time-domain spectrum provided by THz-TDS provides a direct measure of the refractive index of a material. At THz frequencies, the dielectric constant is simply the square of the refractive index, thereby providing a straight forward measurement of the dielectric constant for materials.

The dielectric constant study of inorganic and organic materials over THz frequencies is an active field of research.⁶⁶ THz dielectric constants are reported of biological samples.⁶⁷ Polymer materials, including low density polyethylene, polypropylene and polyamide, have been characterized by combining these polymers with inorganic materials such as magnesium hydroxide, calcium carbonate, silicon and silicon dioxide. In general, polymers are nearly transparent to THz radiation but their material properties change when mixed with additives, thereby providing a means for further characterization.⁶⁸ in addition, the dielectric properties of the epoxy polymer SU-8, which is a common photo-resistant used in the fabrication of microelectronic structures, are reported over THz frequencies.⁶⁹

Transition metals are known to possess magnificent magnetic, electronic and optical properties which are important for electronic and semiconductor applications.⁷⁰ The dielectric and conductivity properties of films of NiCo₂O₄ are examined by THz-TDS at temperatures of 10, 200 and 300K. The metallic character of these films was maintained at

lower temperatures and waned as the temperature increased.⁷⁰ In addition, the dielectric constant is reported for superconducting Rb₂Fe₄Se₅ single crystals at THz frequencies.⁷¹

THz-TDS is also reported for the measurement of refractive index of glass, polymer and oil samples. The dielectric properties of various glass materials, such as quarts, silica, Pyrex and BK7, are reported over THz frequencies.⁷² Tellus R5, Tellus 46, HVI160 (C20 - C50), and HVI 650 (> C25) are types of oils for which dielectric properties are reported at THz frequencies and it was found that the refractive index of high density polyethylene (HDPE) is similar to that of oil (n=1.45).⁷²

1.6 Polarizability of materials

Polarizability is a measure of the distortion of charge within a material in response to an external electric field. The net polarization of the solid material is the combination of electronic, ionic, and dipole orientation polarizations and the magnitude of the polarizability is frequency dependent.⁷³ Polarizability is related to practical properties of materials. For example, materials with higher polarizability possess enhanced solubility in polar solvents as well as higher conductivity. Polarizability is also related to the dielectric properties of materials as characterized by the Clausius-Mossotti relationship.⁷³

Methods are established for measuring the polarizability of different materials, such as inorganic compounds, polymers, liquid crystals, and organic materials over frequencies ranging from kHz to GHz. Few studies are reported, however, for characterization of materials over THz frequencies. Computationally, polarizabilities have been estimated for polyethylene crystals from dielectric information⁷⁴ and electronic polarizability of organic crystals has been reported from *ab initio* calculations.⁷⁵

THz polarizability measurements are reported over a range of 0.1-3.5 THz at 5K. These measurements involved orient millimeter size crystals of sucrose relative to the incident THz wave. The electric field vector of the propagating THz wave serves as a source of varying applied electric field. Magnitude of the measured polarizability depended on this orientation. Higher polarizabilities were obtained when the polarizability vector of the crystal aligned with the applied field and significantly lower polarizability was measured when the applied electric field vector was perpendicular to the polarizability vector within the crystal structure.⁷⁶ While numerous reports describe measurements on millimeter dimensional crystals, the work presented in Chapter 4 advances this field by detailing polarizability measurements for smaller dimensional organic crystals.

1.7 Cocrystals

Cocrystals are single-phase crystalline materials composed of two or more atoms, molecules or ionic compounds in a specific stoichiometric ratio and with unique properties.⁷⁷ Figure 1-8 presents a general description of the basic structure of a cocrystal and its principal components. These components include the cocrystal formers (CCF) and the cocrystal assemblies (CCA). CCF's are the active reactant and the CCA's, or templates, help to establish the proper orientation and distance between cocrystal formers in order to modify material properties and reactivity. Modes of interaction between these components, CCF and CCA, include hydrogen bonding, π - π stacking and weak Van der Waal forces.⁷⁸



Figure 1-8. Cocrystal formation using cocrystal former (CCF) and assembly (CCA).

This is an example of the cocrystal 2(5-CN-res)·2(4,4'-bpe).

Several types of cocrystal preparation methods are commonly used, such as solution crystallization,⁷⁹ grinding (mechanochemistry),⁷⁹ and sonochemistry. Size of the cocrystals can be strongly affected by the method of preparation. Solution crystallization is the traditional method and produces large millimeter size crystals. During the solution crystallization process, the CCF and CCA are dissolved separately in solvents and mixed together followed by slow evaporation of the solvent. Drawbacks of solution crystallization include: 1) formation of undesired kinetically controlled polymorphs; 2) finding a suitable solvent for both components; and 3) use of large volumes of solvent. Sonochemistry methods involve passing ultrasonic radiation through the solution with CCA and CCF components during crystal formation. This method produces cocrystals of micrometer and nanometer dimensions. Solid-state grinding is known as mechanochemistry⁸⁰ and involves either wet grinding (kneading) and dry grinding (neat) of solid CCA and CCF crystals.⁸¹ During wet grinding, a minimal amount of solvent is introduced in order to enhance the solid-state crystallization kinetics and the formation of desired polymorphs. No solvent is used for dry grinding. Mechanochemistry avoids generating excess waste solvent and enhances reaction productivity. Drawbacks of grinding processes are: 1) crystals can be too small for subsequent PXRD analysis; 2) purification of the cocrystal product from the CCA and CCF components can be difficult; and 3) grinding can reduce crystallinity of the product.79

Sonochemistry methods are popular because cocrystals of micrometer and nanometer dimensions have been shown to possess unique properties compared to their millimeter counterparts, such as magnetic properties.⁸² These smaller crystal sizes are also conducive to single-crystal-to-single-crystal (SCSC) reactions. Such reactions involve

chemical transformations within the crystal, essentially forming new chemical species while maintaining the physical structure of the crystal. Photodimerization reactions are reported to undergo SCSC reactions for certain cocrystal compositions. Millimeter size cocrystals of the same composition tend to cracked under the stress of the chemical transformation.⁸³

Cocrystals are nonionic complexes with interesting physicochemical properties, such as solubility, stability, and dissolution rate as well as mechanical properties like compressibility, and tablettability. These properties are of central importance for small molecule pharmaceutics and are modified by CCF's. The physicochemical, mechanical and bioactivity of active pharmaceutical ingredients can be enhanced by cocrystallization.⁸⁴

Several studies are reported where cocrystal structures are used to improve quality and bioactivity of active pharmaceutical ingredients (API). The pharmaceutical cocrystals have been prepared by mixing API with a one CCF. The anticancer drug, lenalidomine has a low oral bioactivity due to its poor solubility in water. Cocrystals of lenalidomine and urea provide enhanced bioactivity by increasing solubility in water.⁸⁵ Likewise, the anticonvulsant drug carbamazepine has low solubility in water and cocrystals with saccharin improves solubility⁸⁶ significantly.

Selectivity and efficiency can be enhanced significantly through cocrystal chemistry. Examples include the following solid-state reactions: 1) [2+2] photodimerization; 2) diacetylene and triacetylene polymerization; and 3) Diels-Alder reactions.⁸¹ Such reactions in the solid-state have potential applications for data storage at the molecular level.

Cocrystals can have properties of interest in the semiconductor industry.⁸⁷ Face-toface stacking within the cocrystal assembly can enhance the semiconductor properties of these crystals,⁸⁸ especially in the case of overlapping π -orbitals and the ability to enhance the rate of charge transfer chemistry. Semiconductor building blocks such as resorcinol and its derivatives (5-methylresorcinol and 5-iodoresorcinol) have been used to form with semiconductor cocrystals formers, such as 2,5 –bis(4-pyridineethylenyl)thiophene and 9, 10-bis(4-pyridyllethylenyle)anthracene.⁸⁸

Atomic force microscopy (AFM) is a novel technique for characterizing the surface properties of cocrystalline materials.⁸⁹ AFM techniques have been shown to image in solid and biological samples,⁹⁰ hardness measurements, and polymer characterization.⁹¹ This technique can be used to characterize nano-size samples with nanometer resolution.⁹²

1.8 Dissertation summary

The overall objective of the work described in this dissertation is to advance the analytical utility of THz-TDS for solid samples. Measurements of concentration, dielectric constant, and polarizability are detailed.

Chapter 2 examines the potential of THz-TDS to follow the [2+2] photodimerization reaction of cocrystals composed of 2(5-CN-res)·2(4, 4'-bpe) to produce rctt-tetrakis (4-pyridyl) cyclobutane. This is a SCSC reaction that involves the formation of a cyclobutane ring by adding across oriented olefins in the bpe (CCF). Differences in intermolecular interactions within the crystal structure between the reactant and photochemical product give rise to differences in the THz spectrum. The work in Chapter

2 explores the potential to quantify reactant and product separately and use this information to learn about the kinetics of this reaction.

The coherent nature of THz-TDS is used to measure refractive index and dielectric properties of crystalline materials in Chapter 3. Advances in electronics demands methods for assessing dielectric properties of solids at THz frequencies. In Chapter 3, a novel method for measuring dielectric constants of solid materials at THz frequencies is developed and verified. In this method, the sample of interest is embedded within a polymer matrix and pressed into a pellet. Dielectric constants of the pellets are obtained from its time-domain THz spectrum and the dielectric constant of the material of interest is extracted by modeling the dielectric properties of the pellet composition. This method is verified through a set of measurements on solid materials with known dielectric constants at 1 THz.

Polarizability measurements at THz frequencies are developed in Chapter 4 for crystals and cocrystals. This method is an extension of the dielectric constant measurements and relies on the Clausius-Mossotti relationship between dielectric and polarizability properties of materials. Polarizability measurements are made on an array of crystalline and cocrystal materials. These measured values are compared to polarizabilities calculated for each material as the sum of the polarizability values for each atom in the molecule. Although a strong correlation is observed between these measured and calculated values, systematic differences are noted and postulated to be related to intermolecular or inter-assembly interactions within the crystals.

In Chapter 5, an inverse relationship is disclosed between the polarizability at THz frequencies and hardness of a set of cocrystals. In this experiment, a set of cocrystals

composed of di-X-resorcinol·bpe are prepared, where X is H, Cl, Br, and I. Hardness of these crystals is measured as the Young's modulus as determined by a nano-indentation Atomic Force Microscopic technique. Results indicate an inverse relationship between these properties (polarizability and hardness) which is consistent with other types of solid materials.

The relationship between polarizability and hardness is extended in Chapters 6 and 7. Chapter 6 examines the impact on synthesis methods on polarizability and hardness of crystals of acetylsalicylic acid and cocrystals of 4,6-dichloro-resorcinol·bpe. Results are discussed for crystals created by sonocrystallization, sonofragmentation, and mechanochemisrty techniques. In Chapter 7, polarizability and hardness are measured for a set of cocrystals with different compositions and, as such, different molecular assemblies. The effect of changes in the chemical structure of the forming component (CCF) is investigated for both macro- and nano-dimensional cocrystals.

CHAPTER 2

THz-TDS CHARACTERIZATION OF SINGLE-CRYSTAL-TO-SINGLE-CRYSTAL COCRYSTAL REACTIONS

2.1 Introduction

As discussed in Chapter 1, THz absorptions in the gas and liquid phases are mainly related to rotational transitions, and intermolecular interactions, respectively.⁷ In solids, absorptions arise from intermolecular interactions, hydrogen-bonding stretches and phonon vibrations or lattice vibrations.^{28,80,93-96} Amorphous materials result in mixed intermolecular vibrational modes which create broad absorptions. In contrast, crystalline materials produce narrow absorption features which distinguish crystalline from amorphous solids.⁹⁷

Cocrystals are homogeneous crystalline materials, of organic or inorganic origin, composed of two or more molecular assemblies joined by hydrogen bonding, π - π stacking or weak Vander-Waals interactions.^{78,98} Different cocrystal structures can provide unique properties of value in pharmaceutical,⁹⁹⁻¹⁰¹ electrical,¹⁰² and electronic industries.¹⁰³ For this reason, the engineering of innovative cocrystal structures, and their characterization, is an active area of research.

When functional groups are oriented correctly within the crystal structure, chemical reactions are possible. Figure 2-1 shows one such reaction involving a [2+2] photodimerization reaction of two proximity olefin groups. This particular [2+2]

photodimerization reaction is an example of a rare single-crystal-to-single-crystal (SCSC) reaction where crystallinity is retained before and after the reaction. Such reactions have applications in material and pharmaceutical sciences⁸² and can enable reactions not possible in liquid phases.¹⁰⁴ Several requirements have been established for [2+2] photodimerization reactions to occur. First, the olefin groups must be parallel to each other and, second, the olefin groups must be in close proximity.¹⁰⁴ According to experimental results reported by Schmidt, the distance between the two olefin groups must be less than 4.2 Å and greater than 3.5 Å for the reaction to proceed.¹⁰⁵

The objective of this study is to explore the utility of THz-TDS to examine the SCSC reaction shown in Figure 2-1. Changes in the crystal lattice in response to the reaction are expected to result in different THz absorption bands for the reactant and products of this reaction. The photodimerization reaction of 2(5-CN-res)·2(4, 4'-bpe) to produce rctt-tetrakis (4-pyridyl) cyclobutane¹⁰⁴ (See Figure 2-1) was selected because it is known to proceed in a SCSC fashion.

The reactant, 2(5-CN-res)·2(4, 4'-bpe) cocrystal, contains two 4,4'-bpe and two 5-CN-res units assembled in a tetrameric species with 4,4'-bpe as the CCF and 5-CN-res as the CCA, as described in Chapter 1. X-ray crystallographic data show the distance between the two olefin groups is 3.82 Å and are positioned face-to-face, as necessary for a successful [2+2] photodimerization reaction. The reaction product contains a highly strained cyclobutane ring.





Figure 2-1. [2+2] photodimerization SCSC reaction involving (a) 2(5-CN-res)·2(4, 4'-bpe), and (b) rctt-tetrakis (4-pyridyl) cyclobutane.

2.2 Sample preparation

2.2.1 Synthesis of 2(5-CN-res)·2 (4, 4'-bpe)

2(5-CN-res)·2(4, 4'-bpe) was prepared in Professor MacGillivray's laboratories by cocrystallization of 3,5-dihydroxybenzonitrile (5-cyano resorcinol/ 5-CN-res) and trans-1,2-bis (4-pyridyl) ethylene (4, 4'-bpe), where the former was purchased in 98% purity from Alfa Aesar and the latter was purchased from Sigma Aldrich. Two solutions were prepared in a minimum amount of warm acetonitrile. One solution was composed of 107.8 mg of 4, 4'-bpe and the other of 79.6 mg of 5-CN-res. Each solution was filtered separately with cotton wool in glass pipettes. These solutions were mixed to form the cocrystals and the resulting mixture was allowed to stand for 5 minutes to ensure the completion of the cocrystallization process. Cocrystals were vacuum filtered using a Buchner funnel with Whatman filter paper. Cocrystals were dried using molecular sieves for 3 minutes. Purity of the preparation was determined by comparing the powder x-ray diffraction (PXRD) pattern for these cocrystals to the corresponding simulated pattern for the compound. Proton nuclear magnetic resonance (¹HNMR) spectroscopy was also used to verify the structure of the single crystals. The resulting PXRD patterns are presented in Figure 2-2. The same pattern for the measured and simulated PXRD signals ensures formation of reactant cocrystals.



Figure 2-2. Powder X-ray diffraction (PXRD) pattern for prepared and modeled for

2(5 CN-res)·2(4, 4'-bpe).

2.2.2 Preparation of rctt-tetrakis (4-pyridyl) cyclobutane

4,4'-tpcb was prepared, also in Professor MacGillivray's laboratory by the [2+2] photodymerization of 2(5-CN-res)·2(4,4'-bpe), as shown in Figure 2-1. For this reaction, approximately 50 mg of the prepared 2(5-CN-res)·2(4,4'-bpe) was pressed between two quartz plates and irradiated with light generated by a UV - mercury lamp that supplied energy between 200-800 nm. This lamp was powered at 450 Watts and the sample was irradiated continuously for approximately four days. The reaction product was collected and analyzed by nuclear magnetic resonance (H¹ NMR) spectroscopy. All ¹H NMR and PXRD data for this project were collected by the Dr. Jelena Stojakovic from Professor MacGillivray's laboratory.

The degree of the photodimerized reaction was determined by integration of NMR peaks associated with reactant (Figure 2-3) and product (Figure 3-3). As shown in Figure 2-3, the hydrogen attached to oxygen (H_c), showed a single peak at ~10 ppm. The hydrogen at position "d" (H_d) in Figure 2-3, gave a doublet at ~ 8.6 ppm due to the coupling effect by the hydrogen in adjacent carbon at position "e". Similarly, the hydrogen at position "e" (H_e) gave a doublet due to the coupling effect of H_d. The olefin hydrogen (H_f) gave a singlet at ~7.5 ppm. As shown in Figure 2-4, the singlet at ~7.5 ppm due to the presence of olefin hydrogen H_f disappeared and appeared as a new singlet at ~4.25 ppm due to the presence of the presence of the hydrogen (H_j). The peak due to the presence of H_d at ~8.6 ppm in 4,4'-bpe moved to H_g position at ~8.35 ppm in 4,4'-tpcb due to the environment change around that hydrogen. The percent conversion of 2(5-CN-res)-2(4,4'-bpe) of the photo dimerization reaction was determined by the peak height ratios of H_d and H_g as shown in Equation 2-1:

% Conversion =
$$\frac{Peak \ height \ of \ H_d}{Peak \ height \ of \ H_d + Peak \ height \ of \ H_g} \times 100$$
 Equation 2-1

It was found that the 5-CN-res in 2(5-CN-res) $\cdot 2(4,4'$ -bpe) was in the *syn, syn* conformation which positioned the 4,4'-bpe units in the face-to-face geometry (Figure 2-1). According to the PXRD data, the distance between the two olefin bonds is 3.82 Å. These parameters enable the [2+2] photodimerization reaction to proceed.



Figure 2-3. ¹H NMR of spectrum and structure of reactant - 2(5-CN-res)·2(4, 4'bpe)/ 4,4'-bpe.



Figure 2-4. ¹H NMR of spectrum and structure of rctt-tetrakis (4-pyridyl) cyclobutane/ 4, 4'-tpcb.

2.3 Sample analysis using THz spectroscopy

2.3.1 Pellet preparation

Pellets were prepared by mixing 5% w/w of sample with polytetrafluoroethylene, PTFE (purchased from Micro Powder Inc., particle size 9-13 μ m, with a density of 2.2 g/cm³). Mixtures of reactant and product were prepared by mixing target masses of the two cocrystals with PTFE by using a spatula followed by vortexing for one hour. Pellets were then prepared by placing ~580 mg of the mixture into a 13-mm diameter stainless steel die positioned in a Specac hydraulic press (GS15011). A vacuum pump was connected to the die housing to remove air from the powder sample. After two minutes of vacuum, pellets were made by applying five tons of pressure for five minutes, while continuing to run the vacuum pump. Pellets were removed from the die and placed in a desiccator for two days prior to collecting the THz spectra. This period permitted physical dimensions of the pellet to relax and stabilize.¹⁰⁶ Mass of each pellet was recorded and dimensions were measured with calipers after this two-day relaxation period.

2.3.2 Spectral collection

The TeraView 1000D THz spectrometer (TeraView Limited, Cambridge, UK) was used to collect all THz time-domain spectra. Samples were placed in the sample compartment and purged with dry air for 5 minutes to remove ambient water. Spectra were collected over one minute while the pellet was rotated in the optical path at a rate of 1 revolution per minute. This rotation was done to reduce the impact of heterogeneity within the pellet structure. Spectra were collected as time-domain spectra with sufficient points to provide a resolution of 1.2 cm⁻¹ over the spectral range of 0.15-3.0 THz or 5-100 cm⁻¹. Reference spectra were collected after purging an empty sample compartment. Over the one minute data collection period, 1800 time-domain spectra were collected and averaged to provide the analytical data. Eight sample pellets with different masses were prepared for these experiments. For each sample, three trials and three back-to-back THz spectra were collected for analysis.

2.4 Results and discussion

2.4.1 Spectral analysis

The corresponding reference and sample time-domain spectra were collected for reactant $(2(5-CN-res)\cdot 2(4, 4'-bpe))/4$, 4'-bpe and the photodimerized product (rctt-tetrakis (4-pyridyl) cyclobutane/4, 4'-tpcb). Figure 2-5 shows time-domain spectra for a sample of 4, 4'-bpe and air. The position of the main peak in the time-domain spectrum is delayed for the sample because of the slower velocity of the THz wave through the sample. The height of the signal represents the strength of the transmitted electrical field vector which depends on the strength of the incident beam and losses due to absorption, scattering, and reflection while interacting with the sample pellet.

Figure 2-6 shows the corresponding single-beam spectra after Fourier processing the time-domain spectra shown in Figure 2-5. These single beam spectra are plotted on a semi-log scale to illustrate the wide dynamic range for the measured intensity. Lower signal-to-noise ratios are evident at high frequencies (e.g., > 100 cm⁻¹) as the intensity drops.

2.4.1.1 Etalon effect removal

The etalon effect is caused by internal reflections within the sample pellet and can cause interference fringes in the frequency-domain spectrum. The small feature within the box in Figure 2-5 is the etalon. As described in Chapter 1, the effect of the etalon can be removed by truncating the time-domain spectrum prior to the etalon and filling the missing time data with zeros or a linear function to zero. In this study a linear function was used to fill missing data.

Figure 2-7 shows absorbance spectra obtained as the negative log ratio of the single beam spectra for sample and air shown in Figure 2-6. Two absorbance spectra are presented in Figure 2-7 showing results before (blue) and after (red) removing the etalon from the time-domain sample spectrum. Elimination of interference fringes is evident.



Figure 2-5. Time-domain spectra of air (blue) and sample (green) where the red box highlights the etalon.



Figure 2-6. Single-beam spectra of air and sample from the THz time-domain spectra presented in Figure 2-5.



Figure 2-7. Absorbance spectra of 4, 4'-bpe before (blue) and after (red) truncating the time-domain spectrum to remove the etalon before Fourier processing.

2.4.1.2 Absorbance Spectra

Absorbance spectra are presented in Figure 2-8 for the reactant and photodimerized product. Differences in the lattice structure of these cocrystals results in noticeable differences in the position, shape, and magnitude of the resulting absorption bands.⁹⁴

As noted above, samples were prepared by embedding a known weight percent of the cocrystal in a PTFE polymer matrix. PTFE was selected because it creates pellets of low porosity and PTFE possesses minimal absorptions over the THz frequency range. Although the spectral features of PTFE are small, they were removed by subtraction of a weighted standard PTFE spectrum, where the weighting corresponded to the mass of PTFE in the pellet. The mass-normalized standard spectrum for PTFE was established by collecting replicate THz- absorbance spectra for a series of PTFE pellets prepared from different masses. Each spectrum was divided by the mass of PTFE in milligrams (Equation 2-2). All mass normalized spectra were averaged to give the standard spectrum used in all subsequent analyses. This mass-normalized standard spectrum of PTFE is presented in Figure 2-9.

Mass normalized absorbance_{PTFE} =
$$\frac{Absorbance_{ptfe} (a.u.)}{pellet mass_{ptfe} (mg)}$$
 Equation 2-2

The absorbance for the cocrystalline samples were corrected for PTFE absorptions by using Equation 2-3:

$$Cocrystal \ abs = Abs \ (sample \ pellet) - \left[(Abs \ mass - normptfe \) \times mass \ _{ptfe} \right]$$

Equation 2-3

where *Abs* (*sample pellet*) is the absorbance spectrum of the sample pellet, *Abs mass-norm*_{*ptfe*} is the mass-normalized PTFE standard spectrum, and mass_{*ptfe*} is the mass of PTFE in the mixture pellet.

Figure 2-10 shows spectra for the reactant with and without removing the absorbance contribution from the PTFE matrix. The solid lines represent the absorbance of pure cocrystals, which have lower absorbance values compared to the mixture pellet.



Figure 2-8. Absorbance spectra of reactant (blue) and product (red). Peak 1 (blue), Peak 1 (red) and Peak 2 (red) were considered for calibration purposes for measurements of the reactant and product concentrations, respectively.



Figure 2-9. Mass-normalized absorption spectrum of PTFE.



Figure 2-10. Absorbance spectra of cocrystal 4, 4'-bpe before (dotted lines) and after (solid lines) removing mass-normalized PTFE spectrum.

2.4.1.3 Digital filtering

Digital filtering was used to reduce the slope and offsets in the spectral baseline after removing the mass-normalized PTFE spectrum. A digital Fourier filter was used to discriminate spectral features on the basis of spectral shapes. The following types of filters can be used depending on the shape and frequency range of interest: 1) low-pass Gaussian cutoff filter; 2) high-pass Gaussian cutoff filter; and 3) bandpass filter. A high-pass Gaussian cutoff filter was used in this case to reduce broad features associated with baseline variations.

Figure 2-11 present a series of reactant spectra before (dotted lines) and after (solid lines) implementing the digital Fourier filter. In this case a Gaussian shaped filter function defined by a mean of 5 cm⁻¹/ 0.15THz and standard deviation of \pm 3 cm⁻¹ was used. The optimum value was obtained by visually comparing the digital filtered spectra with the actual absorbance spectra. Results in Figure 2-11 illustrate the effectiveness of this filtering process to reduce slopes in the baseline. Offsets remain, however.


Figure 2-11. Absorbance spectra of reactant before (dotted line) and after (solid line) digital filtering. Sample composition increased from light blue to red.

2.4.1.4 Baseline offset correction

Scattering significantly impacts the spectral baseline, particularly at the higher THz frequencies.¹⁰⁷⁻¹⁰⁹ Scattering in THz spectra is caused principally by refractive index mismatch between the sample crystals and the surrounding pellet medium (PTFE in this case).¹⁰⁸ Requirements for Rayleigh, Debye, and Mie scattering are presented in Table 2-1.¹¹⁰

Type of scattering	Refractive index requirement	Size requirements
Rayleigh	$ (\eta_{r}-1) << 1$	$d_s\!<\!0.05\;\lambda$
Debye	$ (\eta_r\text{-}1) \approx 0.1$	$0.05 \ \lambda < d_s < \lambda$
Mie	$ (\eta_r-1) >> 0$	$d_s > \lambda$

Table 2-1. Requirements for the different types of scattering, were η_r is refractive index of the material relative to the medium.

Dimensions of the particles used in this study range from 10 to 100 μ m, while the wavelength of the THz radiation ranges from 100 to 2000 μ m. According to the criteria listed in Table 2-1, Debye scattering is prominent for these measurements.

The remaining baseline offset was removed by the fitting a segment of the spectrum void of absorption features with a linear function. This function was applied across the spectral range of interest (20.8-24 and 55.5-56 cm⁻¹ for 4,4'-bpe and 14-17.5 and 54-58 cm⁻¹ for 4, 4'-tpcb spectra). The spectra presented in Figure 2-12 illustrate the effectiveness of this offset correction method.



Figure 2-12. Absorbance spectra of 4, 4'-bpe before (dotted line) after (solid line) baseline correction.

2.4.2 Quantitation

Quantification was evaluated by relating area under specific absorption bands for different masses of cocrystals in the PTFE pellets. Areas were determined by fitting the measured absorption bands to an appropriate function and determining the area under this band. Figures 2-13 a and b specify the spectral regions examined for the reactant and product, respectively. The reactant band corresponds to a single absorption band centered at 35.96 cm⁻¹ and the product band corresponds to two overlapping absorptions where one is centered at 33.33 cm⁻¹ and the other constitutes a shoulder around 44.24 cm⁻¹.



(b)

Figure 2-13. Absorption bands considered for quantitative analysis of (a) reactant 4,4'-bpe, and (b) product 4,4'-tpcb.

These spectral bands were fit with Lorentzian, Gaussian, and Voigt functions, where the Voigt function is a weighted mixture of Lorentzian and Gaussian functions. The goodness of fit was determined from the sum squared error (SSE) according to Equation 2-6:

$$SSE = \sum (Abs_{actual} - Abs_{fit})^2$$
 Equation 2-6

Minimum SSE values are plotted in Figure 2-14 for each of the fitting functions for a set of samples representing the reactant. The Lorentzian to Gaussian ratio used in the Voigt fit was 0.5. According to the data in Figure 2-14, the Voigt function resulted in the lowest differences and best fits.

Voigt functions with different Gaussian to Lorentzian ratios were examined for both reactant (4,4'-bpe) and product (4,4'-tpcb). The minimum SSE values were determined for fits to each spectral type (reactant and product) as a function of the Gaussian to Lorentzian ratio (L/G) and the findings are presented in Figures 2-15 and 2-16. According to these figures, the best L/G ratio for reactant and product were 0.69 and 0.3, respectively.

Figure 2-17 present the measured and fitted absorption bands for the reactant. These fits are presented over 20-60 cm⁻¹ and correspond to the optimum Voigt function with L/G of 0.69. The fit residuals are plotted at the bottom of these fits. Likewise, results of the optimized Voigt fits are plotted in Figure 2-18 for the reaction product (4,4'-tpcb). This second fitted data is plotted over 20-60 cm⁻¹ with L/G at 0.3 and fit residuals are plotted at the bottom of the graph. The average and standard deviations of the fit residuals are 0.3 \pm 0.07, and 0.002 \pm 0.002 for reactant and product, respectively.

Using the Voigt fits specified above, peak areas were determined using one peak for the reactant and two overlapping peaks for the product, as shown in Figure 2-13. Figure 2-19 shows the linear relationship between these areas and the mass of cocrystal in the sample pellet. Linear regression analyses indicate r^2 -values of 0.997 and 0.998 for reactant (4,4'-bpe), and product (4,4'-tpcb), respectively. Such strong linear correlations supports a Beer-Lambert type relationship for each component over these spectral ranges. Slopes presented in Figure 2-19 indicate a slight positive offset for the reactant with a *y*- intercept of 0.23 ± 0.07.

Overall, the results presented in Figure 2-19 confirmed that both reactant and product follow the Beer-Lambert law and each can be quantified from the area under the fitted absorption bands.



Figure 2-14. Comparison of the sum squared error for Lorentzian, Gaussian and Voigt fits to the absorbance spectra collected for the 4,4'-bpe sample (before reaction).



Figure 2-15. Comparison of the minimum SSE values for different L/G ratios for the measured absorption band of 4,4'-bpe.



Figure 2-16. Comparison of the minimum SSE values for different L/G ratios for two peaks in 4,4'- tpcb.



Figure 2-17. Comparison of the measured absorbance bands (solid line) with the Voigt fit with L/G ratio of 0.69 (dotted line), and the residuals (dashed line) for reactant (4,4-bpe).



Figure 2-18. Comparison of the absorbance band (solid line), Voigt fit with L/ G ratio of 0.3 (dotted line), and the residuals from the absorbance band and the fit (dashed line) for reaction product (4,4'-tpcb).



Figure 2-19. Correlation between the cocrystal mass and peak area for reactant (4,4'bpe) (blue), and product (4,4'-tpcb) (red), respectively. Error bars represent standard deviation between trials.

2.4.3 Feasibility of following SCSC reaction

In order to evaluate the ability to follow the [2+2] photodimerization SCSC reaction of 5-CN-res·4,4'-bpe to form 5-CN-tpcb, a series of samples were prepared by photoreacting 5-CN-res·4,4'-bpe cocrystals to different stages of completeness. The percent completion to 5-CN-tpcb was determined for each sample by ¹HNMR data and calculated using Equation 2-1. THz time-domain spectra were collected for each sample by mixing with PTFE and the resulting absorbance spectra were analyzed.

The concentrations of reactant and product in each sample pellets were measured by fitting the mixture spectrum to Voigt functions and calculating the area for each component. These initial attempts failed to provide a meaningful relationship between the measured areas and extent of the SCSC reaction.

Figure 2-20 shows absorbance spectra for the reactant and product standards. The spectrum measured for one of the partially reacted samples is superimposed on these standard spectra. This partially reacted mixture corresponded to 56% reaction completion according to the ¹HNMR measurement. Comparison of these spectra leads to the conclusion that the mixture spectrum does not appear to be the sum of the individual components. Indeed, Figure 2-21 shows an overlay of this mixture spectrum along with a spectrum of a mixture prepared by mixing 44% of the reactant and 56% of product in order to simulate the reaction mixture sample. The spectra for the prepared mixture and the reaction mixture do no match and this lack of match is responsible for the inability to quantify these two components and follow the reaction kinetics.

The discovery that the THz spectra for the mixture is not the sum of the individual components is interesting. This observation suggests that samples prepared by reaction

possess different intermolecular or phonon vibrations than samples composed of a physical mixture of the two types of cocrystals.



Figure 2-20. Absorbance spectra of reactant (5-CN-res·4,4'-bpe), product (rctt-tetrakis (4-pyridyl) cyclobutane) and partially photodimerized product (56%).



Figure 2-21. Absorbance spectra of reactant (5-CN-res·4,4'-bpe), product (5-CN-res·tpcb), partially photodimerized product (56%), and mechanically prepared sample (56%).

The material presented in Chapter 4 will demonstrate measurement of dielectric spectra for crystals embedded within PTFE pellets. The dielectric loss term accounts for losses due to absorption and scattering processes.¹¹¹ Figure 2-22 shows the dielectric spectrum for the reaction product (5-CN-tpcb) superimposed on its absorption spectrum. The magnitude of the dielectric changes sharply at the absorption bands as expected due to dispersion processes. The peak identified in Figure 2-22 corresponds to a band centered at 14 cm⁻¹ which appears to be related to the product with no overlapping spectral features associated with the reactant, as shown in Figure 2-20. Given the potential selectivity of this band, an attempt was made to quantify the extent of the SCSC reaction on the basis of the difference in the dielectric constant associated with this absorption band.

Figure 2-23 shows a linear relationship between the extent of the reaction and the difference in the dielectric constant at 14 cm⁻¹. The r^2 term is 0.88 which suggests a significant correlation between these parameters. These findings suggests that quantitation is possible for following the reaction kinetics for this SCSC reaction.



Figure 2-22. Comparison of the absorbance spectrum (blue) and the measured dielectric spectrum (red) of reaction product.



Figure 2-23. Comparison of the percent reaction with the dielectric constant change at 14 cm⁻¹ using 5-CN-res·bpe samples, 5-CN-res·tpcb and partially photo reacted samples. Error bars represent the standard deviation between trials.

2.5 Conclusion

This study focused on the reaction kinetics for the cocrystal SCSC reaction and explored the use of THz-TDS to follow such a reaction. SCSC reactions are the reactions that involve crystals where its crystallinity is preserved during the reaction process.

Results show that the reactants and products can be quantified individually in a Beer-Lambert type relationship between concentration and absorbance. However, reaction kinetics study of the SCSC photodimerization failed when using these absorbance bands. The simulated absorbance spectra of reactant and product mixtures (physical mixtures) had different absorbance spectra than samples from the reaction process. This observation gave an interesting finding that *inter*-molecular interactions associated in reaction process samples are different from that of physical mixtures. Selective quantitation of the reaction product of the photodimerized reaction was demonstrated by considering the dielectric constant loss at 14 cm⁻¹. This result illustrates the potential of THz TDS for following reaction kinetics for this SCSC.

CHAPTER 3

TERAHERTZ TIME-DOMAIN SPECTROSCOPY FOR MEASURING ELECTRICAL PROPERTIES OF MATERIALS

3.1 Introduction

Modern electronics for the telecommunication, medical, and security industries demand materials compatible with operational frequencies above 300 GHz.¹¹² The search for such high performance materials has generated the need for methods to measure the dielectric properties of materials at THz frequencies.⁶⁵ The work presented in this chapter establishes the analytical feasibility of measuring the dielectric constant of submillimeter size particles of crystalline materials by THz time-domain spectroscopy.

The dielectric constant measures the electrical property of a material related to its permittivity (ε) or ability to polarize in the presence of an applied electric field. Materials with a permanent dipole moment or materials with an induced dipole moment have significant permittivity values in the presence of an applied electric field.⁷³ The dielectric constant corresponds to the permittivity of a material relative to that of a vacuum. Equation 3-1 shows the relationship between relative permittivity (ε_r), or dielectric constant, and permittivity of the material in question (ε_c) and of vacuum (ε_0).

$$\varepsilon_r = \frac{\varepsilon_c}{\varepsilon_0} = \frac{Q_c}{Q_0} = \frac{C_c}{C_0}$$
 Equation 3-1

here, Q_c and Q_o correspond to the charge separation measured across two parallel electrodes separated by the material of interest and vacuum, respectively, and C_c and C_o

correspond to the respective capacitance values. The capacity of a parallel capacitor with free space as an insulator depends on the plate area (A) and the distance between the two parallel plates (d), and ε_0 is the absolute permittivity as shown in Equation 3-2.⁷³

$$C = \frac{\varepsilon_0 * A}{d}$$
 Equation 3-2

According to Figure 3-1, when a constant voltage is applied across the parallel plates in vacuum, the charge separation between the two plates is Q_0 . When a non-conducting material is inserted between the plates, the corresponding charge separation is Q_c . Once established, this charge separation is constant while the voltage remains constant.



Figure 3-1. Dielectric constant of non-conducting material in the presence of an applied electric field.

In the presence of an applied dc current, charged elements within the material reorient in response to the applied field. Under these conditions, the measured permittivity is termed the static relative permittivity (ε_s) or the static dielectric constant.¹¹³ In the presence of an oscillating applied electric field, the charged species within the material must dynamically reorient to the applied filed. If the oscillating frequency of the applied field is faster than the time required for charge reorientation within the material, the magnitude of the charge separation within the material will be reduced and the measured permittivity will be less than the value in a constant applied electric field. As a result, the dielectric constant is a frequency dependent factor.⁷³

Dielectric properties of materials are commonly determined from pure substances over megahertz to gigahertz frequencies.¹¹⁴ The focus of this chapter is the measurement of dielectric properties of small dimensional samples of materials at THz frequencies. For the work presented in this chapter, materials with known dielectric constant are embedded within an inert polymer matrix and the dielectric constant of the material is determined from THz time-domain spectroscopy. Accuracy of this spectroscopic approach is judged by comparing values determined by this method relative to values reported in the literature for the same materials and over THz frequencies.

3.2 Experimental methods

3.2.1 Materials

The following materials were used as obtained from the supplier without further purification. The following materials were used: High Density Polyethylene (HDPE-Aldrich, ultra-high molecular weight, CAS 9002-88-4, density 0.94 g/cm³, particle size 53-

75 μm), Polytetrafluoroethylene (PTFE- FLUO 625F, Micro Powders, Inc, density 2.2 g/cm³, particle size 9-13 μm), Mg(OH)₂ (Fisher Scientific, FW-58.33 g/mol, CAS 1309-42-8, density 2.36 g/cm³), Al₂O₃ (γ-Alumina, Degussa, CAS 1344-28-1, density 3.27 g/cm³), ZnO (Alfa Aesar, Nano tek, vapor oxidized ZnO, CAS 1314-13-12, density 5.6 g/cm³), and SiO₂ (Degussa, AEROSIL OX 50, CAS 112945-52-5, density 2.2 g/cm³).

3.2.2 Procedure and methods

A series of sample pellets were prepared from homogenous mixtures of the test compound in particles of the polymer. A set mass of the mixture was transferred to the die within the press and a pressure of five tons was applied to form the pellet. This pressure was applied continuously for five minutes in the presence of a vacuum, as described in Chapter 2.

Dielectric constants were determined from time-domain THz spectra collected by transmitting THz radiation through a pellet composed of the material of interest embedded within a matrix of either high density polyethylene (HDPE) or polytetrafluoroethylene (PTFE).

The refractive index of the mixture pellet was measured directly from the corresponding time-domain spectrum by Equation 3-3¹¹⁵

$$n = 1 + \frac{c(\varphi_s - \varphi_R)}{2\pi v d}$$
 Equation 3-3

where, *n* and c represent refractive index of the material and speed of light, respectively; φ_s and φ_R are the recorded phases of the THz radiation after passing through the sample and reference media, respectively; *v* represents the frequency of the applied electrical field vector, and d is the thickness of the sample pellet. The dielectric constant of the mixture sample was determined using Equation 3-4

$$\varepsilon_r = n^2 - k^2$$
 Equation 3-4

where, ε_r is the dielectric constant or the relative permittivity, *n* represents the refractive index of the material, and k is the extinction coefficient.¹¹⁶

Extinction coefficient k is related to the power absorption coefficient (α)¹¹⁷ and measures attenuation of the transmitted electromagnetic radiation (EMR) by absorptivity and scattering effects according to Equation 3-5.^{73,111,117}

$$k = \frac{c\alpha}{2\omega}$$
 Equation 3-5

where c, α , and ω (2 πv) are the speed of light, absorption coefficient and the angular frequency, respectively.

The absorption coefficient (α) at frequency v can be calculated according to Equation 3-6.¹¹⁵

$$\alpha(\upsilon) = -\frac{2}{d_{sample}} ln \left[\frac{E_{sample} (\upsilon)}{T * E_{reference} (\upsilon)} \right]$$
 Equation 3-6

where $E_{sample}(v)$ and $E_{reference}(v)$ are the electrical field strength at frequency v for the sample and reference materials, respectively, d is the thickness of the sample pellet, and T is the fraction of power transmitted through the air-sample interface. The value of T can be calculated by Equation 3-7.¹¹⁵

$$T = 1 - \left(\frac{n_{average} - 1}{n_{average} + 1}\right)^2$$
 Equation 3-7

where $n_{average}$ is the average refractive index of the materials over the spectral region of interest.

Absorption loss terms for HDPE and PTFE were determined to be negligible compared to their refractive index values. Therefore the relative permittivity equation was simplified and the dielectric constant was taken as $\varepsilon_r = n^2$ throughout the remainder of this dissertation.¹¹⁸

Dielectric constant measurements requires knowing the thickness of the sample, as indicated in Equation 3-3. For this reason, the pellets of HDPE and PTFE are allowed to relax upon removal from the dye press for at least 48 hours in a desiccator before measurements.¹⁰⁶

3.3 Method development and optimization

The stability of pellets composed of PTFE and HDPE was examined to ensure collection of representative spectra. In this study, a series of pellets composed of either pure PTFE or HDPE was prepared with different masses ranging from 200-800 mg for PTFE and 150-450 mg for HDPE. Thickness, diameter and mass were measured for each pellet over a period of five days, while storing pellets in a desiccator between measurements to minimize water adsorption. Figures 3-2 and 3-3 summarize the thickness measurements for PTFE and HDPE, respectively. These data indicate stable pellet dimensions were obtained by the second day post pellet formation. For this reason, all spectra were collected after at least two days maintained under desiccation, unless stated otherwise.

In addition to pellet dimensions, the dielectric properties of the pellets were measured over time post pellet formation. The proper pellet thickness was used for these dielectric measurements and the averaged dielectric constant value determined between 0.3-1.2 THz (10-40 cm⁻¹) is plotted in Figures 3-4 and 3-5 for PTFE and HDPE, respectively, as a function of time post pellet formation. As was found for pellet dimensions, a constant dielectric constant is obtained two days post pellet formation. Polymer structure prior to full relaxation impacts the dielectric properties of the pellet, thereby demanding a two day equilibration period.



Figure 3-2. Relative percent difference of PTFE thickness variation with time.



Figure 3-3. Relative percent difference of HDPE thickness variation with time.



Figure 3-4. Variation of measured dielectric constant of PTFE with time.



Figure 3-5. Variation of the measured dielectric constant of HDPE with time.

Initial results demonstrated that a confounding sinusoidal pattern on the dielectric spectrum of pellet samples is caused by an etalon effect which is caused by the internal reflections as described in previous chapters. This effect can be removed by truncating the time-domain spectra before the etalon and adding zeros to fill the space of the time-domain spectra before Fourier transformation, as explained in Chapter 1. The phase difference between the sample and reference spectra have been calculated using the Fourier transformed spectra which have been used for the refractive index calculation using Equation 3-3 above. The dielectric constant of the material has been calculated as described in Section 3.2.2.

3.4 Dielectric constant measurements of analytes embedded within polymer pellet mixtures

Pressed pellets are composed of the polymer binder, either HDPE or PTFE in these experiments, the analyte of interest, and air. The air is trapped between particles of the polymer and analytes when packed and pressed. The amount of air is given by the porosity of the pressed pellet. As the THz electromagnetic (EM) radiation passes through a pressed pellet, interactions with each of these three components contributes to the measured phase shift and, hence, the composite refractive index and dielectric constant.

A model first proposed by Looyenga and colleagues, termed the LLL model,¹¹⁹ was investigated here as a means to distinguish the dielectric constant for the analyte of interest in the presence of polymer and air. The LLL model assumes the composite dielectric constant is composed of the sum of the individual dielectric constants according to their relative volume fractions within the matrix or pellet. Equation 3-8 gives the corresponding function:

$$\varepsilon_{mix}^{1/3} = v_s \varepsilon_s^{1/3} + v_p \varepsilon_p^{1/3} + v_{air} \varepsilon_{air}^{1/3}$$
 Equation 3-8

where, ε_s , ε_p , ε_{air} are the relative permittivity or dielectric constants of sample, polymer, and air, respectively, and v_s, v_p, v_{air} represent the volume fraction of sample, polymer and air, respectively.

The volume fraction of each component was calculated according to the method of Nelson et al.¹²⁰ Here, the volume fraction was determined by taking the ratio between the sample and pellet volumes. The pellet volume was determined by the physical dimensions of the pellets. The sample volume of each component was determined from the mass of the sample in the pellet and its density. The sample mass in the pellet was calculated by assuming a homogeneous distribution of the sample within the pellet. The volume fraction of air was determined by assuming the summation of all volume fractions equals one.

Accordingly, the dielectric constant for the analyte of interest (ε_s) can be determined from the measured dielectric constant of the mixture pellets as well as known dielectric constants for the polymer binder and air as shown in Equation 3-9.¹¹⁹ Equation 3-8 can be extended to additional components as necessary to model more complicated mixtures.

$$\varepsilon_{s} = \left[\frac{\varepsilon_{mix}^{1/3} - \left(v_{p}\varepsilon_{p}^{1/3} + v_{air} \ \varepsilon_{air}^{1/3}\right)}{v_{s}}\right]^{3}$$
Equation 3-9
$$\varepsilon_{s} = \left[\frac{\varepsilon_{mix}^{1/3} - \left(v_{air} \ \varepsilon_{air}^{1/3}\right)}{v_{s}}\right]^{3}$$
Equation 3-10

The LLL model assumes no significant interactions between the pellet components that would impact the dielectric properties of the pellet. This model also assumes a homogeneous chemical distribution within the pellet. In addition, particle shape was not taken in to account during the model derivation. Therefore this model is applicable for irregular shaped particle mixtures.¹¹⁶

3.5 LLL model validation

The LLL model has been validated at megahertz and gigahertz frequencies,^{65,121} but must be assessed at THz frequencies. In order to validate this model for determining dielectric constants at THz frequencies, measurements were made using components for which literature values have been reported. These literature values were determined from pure samples of the particular substance by established techniques.^{65,122} Table 3-1 summarizes both the value determined by the proposed method based on the LLL model as well as literature values reported for the test compounds.^{65,117,121,122} Measured values for the dielectric constant presented in the Table 3-1 correspond to average values determined over the 10-40 cm⁻¹ spectral region. The measured dielectric constant values were compatible with the literature values with maximum percent difference of 10.2%.

A correlation plot is presented in Figure 3-6 showing the correlation between measured and reported values with r^2 -value of 0.978.

As expected, dielectric constants for HDPE and PTFE are low with values of 2.328 ± 0.006 and 2.084 ± 0.004 , respectively and errors represent the sample standard deviation. The nonpolar nature of these polymers results in limited interaction between the induced dipole moments and the electric field vector of the THz EM waves. The replacement of
hydrogen with fluorine in PTFE increases the molar volume hence decrease the free space volume, thereby lowering both polarizability and dielectric constant of PTFE relative to HDPE.

Material	Measured dielectric constant ^a	Reference dielectric constant ^b	% Relative error	Reference method
PTFE	2.084 ± 0.004	2.088117	0.19%	THz-TDS at 1THz
HDPE	2.328 ± 0.006	2.35365,117	1.1%	THz-TDS at 1THz
HDPE ^c	2.34 ± 0.01	2.35365,117	0.55%	THz-TDS at 1 THz
Mg(OH)2	7.4 ± 0.1	7.09 ¹²²	4.4%	Mg(OH) ₂ in LLDPE ^d pellets at 1THz
SiO ₂	4.1 ± 0.1	4.45 ⁶⁵	7.9%	Crystals at 80GHz -1.8 THz
ZnO	8.1 ± 0.3	7.9^{65}	2.5%	Crystals at 80 GHz-1.8 THz
Al ₂ O ₃	8.46 ± 0.07	9.42 ¹²¹	10.2%	Ceramic pieces at 100 GHz- 1THz

- a Determined by proposed method average \pm one standard deviation over 10-40cm⁻¹ spectral range
- b Reference for reference value provided in parenthesis
- c HDPE- Dielectric constant measured using pellets of HDPE in PTFE
- d LLDPE- Linear Low density polyethylene
- Table 3-1. Comparison of measured and reference values for dielectric constants of different materials.



Figure 3-6. Correlation of measured versus reference value showing ideal correlation as solid line.

3.5.1 Dielectric constants of HDPE pellets

Pellets prepared with only HDPE are porous mixtures composed of HDPE and air. The LLL model was tested further by determining the dielectric constant for a series of HDPE pellets composed of different porosities. In this study, a series of HDPE pellets were prepared with different masses of HDPE, thereby resulting in pellets of different thicknesses and different amount of trapped air. The dielectric constant for the pellet was then calculated using Equation 3-8 with using 2.353 as the dielectric constant for HDPE, 1 as the dielectric constant for air ($\varepsilon_{air}=1$), and the relative volumes obtained from the dimensions of the pellets and a density for HDPE of 0.941 g/cm³. The dielectric constant was measured from the time-domain spectrum obtained for each pellet by using Equation 3-3 as described above.

Figure 3-7 shows the correlation between the measured (THz-TDS) and calculated (LLL model) dielectric constants for HDPE pellets with different relative volumes of air and Figure 3-8 presents the residuals. The maximum percent relative error in the LLL model was 0.47%.



Figure 3-7. Comparison of measured and calculated dielectric constants of HDPE pellets.



Figure 3-8. Residuals of measured and calculated dielectric constants of HDPE pellets.

3.5.2 Dielectric constant comparison of mixture pellets of HDPE in PTFE

Accuracy of the LLL model was assessed by comparing measured and calculated dielectric constants for a series of pellets composed of mixtures of HDPE, PTFE, and air. Calculated values were from Equation 3-8 based on known dielectric constants for pure PTFE and HDPE¹¹² and using 1 as the dielectric constant for air. The volume fraction of each components was determined as described in Section 3.4. A strong correlation between measured and calculated values is presented in Figure 3-9 with r^2 -value of 0.995.



Figure 3-9. Comparison of measured and calculated dielectric constants of HDPE in PTFE mixture pellets.

3.5.3 Dielectric constant of inorganic materials embedded in polymer matrix

A series of pellets of Mg(OH)₂ embedded in the HDPE polymer matrix was prepared with concentrations of Mg(OH)₂ ranging from 0-90% and the dielectric constant determined for each pellet. Measured values are compared to calculated values in Figure 3-10 where the calculated dielectric constant of each pellet was obtained by the LLL model with literature values for the dielectric constants of Mg(OH)₂,¹²² and HDPE.¹¹² Again, the dielectric constant of air was taken as one.

The points in Figure 3-10 illustrate how values from the LLL model track the measured values up to a concentration of 60%, after which the LLL model begins to fail. One possibility for failure is a breakdown in the LLL model. The LLL model is based on a Taylor approximation which might deviate at the higher dielectric values created by higher percentages of Mg(OH)₂ in these pellets. Alternatively, the actual Mg(OH)₂ used to form pellets might be slightly different compared to that used in establishing the reference dielectric constant used in these calculations. Certainly, the morphology of Mg(OH)₂ is known to vary as a function of percentage in polymer mixtures.¹²³



Figure 3-10. Comparison of measured and calculated dielectric constants of Mg(OH)₂ in HDPE mixture pellets.

Similar to the measurements of Mg(OH)₂ pellets described above, a series of SiO₂ pellets was prepared in PTFE were the concentration of SiO₂ varied from 0 to 50%. Figure 3-11 illustrates the relationship betweeen the measured and calculated dielectric constants for the SiO₂/PTFE pellets. Again, the LLL model provides accurate values over this range of SiO₂ concentrations with r^2 -value of 0.79 and % averaged difference of 7.9.



Figure 3-11. Comparison of measured and calculated dielectric constants of SiO₂ in PTFE mixture pellets.

Pellets composed of ZnO in PTFE were prepared over a concentration range of 0 – 90 % ZnO. Figure 3-12 compares measure and calculated dielectric constants from the LLL model. The strong correlation demonstrates further the accuracy of this model for this metal oxide with r^2 -value of 0.998 and % average difference of 2.5.



Figure 3-12. Comparison of measured and calculated dielectric constants of ZnO in PTFE mixture pellets.

Three mixture pellets of Al_2O_3 (0%, 5%, and 10%) were prepared in PTFE. The measured dielectric constant of these mixture pellets matched the calculated dielectric values. The Figure 3-13 shows the relationship between the measured and calculated dielectric constants of Al_2O_3 mixute pellets in PTFE polymer matrix.



Figure 3-13. Comparison of measured and calculated dielectric constants of Al₂O₃ in PTFE mixture pellets.

3.6 Effect of particle size

Literature reports demonstrate that the size of the polymer particles used to prepare pellets can impact THz frequency-domain spectra. In general, an increase in particle size creates an increasing curvature in the spectral baseline, presumably caused by the effects of scattering within the pellet.⁷

The impact of the polymer particle size on dielectric measurements was established for a series of HDPE pellets prepared with different average particle sizes for the HDPE stock. Pellets were prepared with HDPE particle size ranges of 50 -100 μ m, 100-200 μ m, 200-300 μ m, and > 300 μ m. For each particle size range, five sets of pellets were prepared with different masses of HDPE. As noted before, each pellet was prepared by applying 5 tons of pressure for 5 minutes while applying vacuum, using the hydrolic press (Specac). The THz time-domain spectrum was collected for each pellet from which the refractive index as well as dielectric constant were obtained as described before. Etalons were removed by truncating the time-domain spectrum just before the etalon feature followed by zero-filling.

Figure 3-14 presents raw THz dielectric spectra collected for the HDPE pellets prepared with different particle sizes. Variations in the spectra are evident and generally demonstrate a decrease in the composite dielectric constant with an increase in particle size. This finding is consistent with higher porosity for the pellet with larger particle size of the polymer.

Dielectric constants of pure HDPE were determined from these raw spectra according to the LLL model with a dielectric constant of one for air. The average dielectric constant for HDPE determined from each of these different particle size pellets is presented as a bar plot in Figure 3-15 and the values are tabulated in Table 3-2. As before, the average is taken over the 10-40 cm⁻¹ spectral region. Although a slight trend is evident in the average values, a *t*-test analysis indicates no significant difference in these averages at the 95% confidence level. Residual spectra are presented in Figures 3-16 to 3-20. These spectra highlight the non-random nature of these residuals, thereby revealing a systematic bias in the measurement caused by variations in scattering properties of the pellets. Nevertheless, the overall percent relative error is only 1.2 % compared to the literature value of 2.353 for HDPE when values are averaged over the 10-40 cm⁻¹ spectral range.



Figure 3-14. Measured dielectric constants of HDPE pellets with different particle sizes (HDPE and air). Blue, red, green and purple lines correspond to particle size ranges of 50-100, 100-200, 200-300, and $> 300 \ \mu m$ respectively.



Figure 3-15. Comparison of the dielectric constants of pure HDPE with different particle sizes. Here, 50-100 μ m (red), 100-200 μ m (green), 200-300 μ m (dark blue), and >300 μ m (light blue). Error bars represent the sample standard deviation.

HDPE Sample	Mean dielectric constant (10- 40 cm ⁻¹) region	t-cal	t-recorded at 95% confidence interval and *df=8
50 – 100 μm	2.334 ± 0.006	2.069	2.306
100 – 200 μm	2.350 ± 0.005	1.010	2.306
200– 300 µm	2.357 ± 0.007		
>300 µm	2.360 ± 0.003	0.276	2.306

*df- degree of freedom

Table 3-2. The averaged dielectric constant of HDPE with different particle sizes. Standard deviation of measured values represent the sample standard deviation.



Figure 3-16. Residuals of measured dielectric constant of HDPE 50-100 μm particles.



Figure 3-17. Residuals of measured dielectric constants of HDPE 100-200 μm particles.



Figure 3-18. Residuals of measured dielectric constants of HDPE 200-300 μm particles.



Figure 3-19. Residuals of measured dielectric constants of HDPE greater than 300 μ m particles.



Figure 3-20. Comparison of the residuals of measured dielectric constants of pure HDPE with different particle sizes. Here, black, red, green and blue solid lines represent variation in residuals for pellets prepared by 50-100, 100-200, 200-300, and > 300 μm size particles.

The permittivity, or dielectric constant, depends on the free space or how easily molecules can move⁷³ within the sample matrix. Polymers, such as HDPE, consist of long aliphatic chains with sufficient flexible to maximize packing, thereby minimizing free space within the pellet structure and minimizing permittivity. Likewise, dielectric loss is low owing to minimal absorptivity over THz frequencies. Scattering properties of the sample also contribute to dielectric loss and can be minimized for HDPE by decreasing particle size which increases packing density of the polymer of the material within the pellet and lowers scattering.

3.7 Conclusion

The coherent nature of THz radiation offers the possibility to measure optical properties of a material directly from its time-domain spectrum. This chapter explores the analytical utility of measuring permittivity of samples embedded within pellets composed of an inert polymer and air. The attractiveness of this measurement configuration is the ability to determine permittivity properties of crystals too small to probe individually. A critical aspect of such measurements is the ability to extract permittivity information for the analyte of interest from time-domain spectral data collected from the composite pellet.

A LLL model demonstrated previously for dielectric measurements over megahertz and gigahertz frequencies is examined here as a means to determine dielectric values over THz frequencies for mixture samples. In this LLL model, the dielectric constant for the sample is taken as the sum of the dielectric constant of its chemical components according to the volume fraction of each component. Utility of the LLL model is validated by comparing dielectric constants obtained from this model to values reported in the literature for a series of test compounds, including HDPE, PTFE, Mg(OH)₂, SiO₂, ZnO, and Al₂O₃. In all cases, the LLL model applied to THz time-domain spectra of pellets provided accurate values for the dielectric constants. Results also confirm that the dielectric properties over THz frequencies are lower for PTFE compared to HDPE as a result of a decrease in free volume within the polymer structure realized by replacing hydrogens with fluorine. Lastly, THz dielectric values are shown to be insensitive to particle size for HDPE, consistent with minimal dielectric loss owing to flexibility of the polymer chain.

CHAPTER 4

POLARIZABILITY MEASUREMENTS AT TERAHERTZ FREQUENCIES

4.1 Introduction

Polarizability is a measure of the tendency of charge distribution to be distorted in the presence of an external electric field. As described in Kasap, polarizability of materials can be derived from electronic, ionic or orientation polarization of atoms, ions or molecules.⁷³ Electronic polarization corresponds to distortion of electrons within the atom, ion, or molecular bond.⁷³ Ionic polarization involves distortion of cationic and anionic components of ionic materials and orientation polarizability reflects changes in charge distribution upon changes in alignment of polar regimes within a material.

As a fundamental property of matter, polarizability represents a key parameter in the characterization of materials⁷³ as well as a diagnostic tool in material science.¹²⁴ An example is the use of polarizability to assess structural symmetry within crystalline materials where low-symmetry crystals are known to display higher polarizability owing to charge-induced dipole moments.¹²⁵ Polarizability can also be used to identify defects in high-symmetry crystalline materials,^{126,127} thereby guiding the production of nonlinear optical (NLO) materials.

Polarizability over THz frequencies provides a measure of inter-molecular interactions within materials.¹²⁸ Such measurements have been shown to be valuable in the study of liquid crystals and their applications in the electronics industry.¹²⁹ Dissolution

kinetics of pharmaceutical crystals are also related to intermolecular properties that can be probed by polarizability measurements at THz frequencies.¹³⁰

As EM radiation passes through a material, the electric field vector represents an oscillating, externally applied electric field. The existence of polar or ionic regions with the material that are free to modulate in response to this oscillating electric field slows the propagating EM wave and results in a high dielectric constant. Intuitively, a material with higher polarizability at the frequency of the propagating EM wave will likewise possess higher dielectric properties at this frequency. The Clausius-Mossotti equation expresses this relationship¹¹⁵

$$P = \left[\frac{\varepsilon - 1}{\varepsilon + 2}\right] * \left(\frac{3}{4\pi}\right) * \left(\frac{M}{\rho}\right) * \left(\frac{1}{N_A}\right)$$
 Equation 4-1

where P is the polarizability, ε is the dielectric constant of the sample material, N_A is the Avogadro constant, M is the molecular mass of the analyte and ρ is the density of the material. For the pellet measurements used here, the compressed density is used according to Equation 4-2,¹⁰⁶

$$\rho_{sample=\frac{1}{\left[t_{pellet} - \left(\frac{m_{PTFE}}{\rho_{PTFE} * \pi r^{2}}\right)\right]} * \left[\frac{m_{sample}}{\pi r^{2}}\right]}$$
Equation 4-2

where m_{sample} , and m_{PTFE} are the analyte mass and PTFE mass in the pellet, respectively, ρ_{PTFE} and ρ_{sample} are the compressed densities of PTFE and analyte, respectively, t_{pellet} is the pellet thickness, and r is the pellet radius.

Polarizability of organic crystals have been calculated computationally with single crystals positioned in a particular orientation using 2,5-dichloroanilinium picrate crystal.¹³¹

Such measurements require relatively large crystals with dimensions of at least a millimeter. Unfortunately, millimeter size crystals can be difficult to produce for many organics and cocrystal structures, thereby creating the need for a more versatile analytical methadologies.

In this chapter, the Clausius-Mossotti relationship is used to determine polarizability for a set of organic crystals from dielectric constants obtained from time-domain THz spectra. The method is evaluated for crystals with sub-millimeter dimensions, specifically crystals with sizes of tens of microns to hundreds of nanometers. Polarizability values are obtained from crystals embedded within an inert polymer matrix of PTFE. This approach is validated by comparing measured polarizability values at THz frequencies to values calculated on the basis of the additive law of atomic polarizability.⁷³

4.2 Experimental methods

4.2.1 Collection of dielectric spectra

Samples were prepared as pellets in PTFE as described in Chapter 3. The corresponding time-domain spectrum was collected for each sample pellet with the Teraview 1000D spectrometer as described in Chapter 3. Each time-domain spectrum was truncated just before the etalon feature and the removed points are filled with values that linearly track from the value at the truncation point to zero at the end of the time axis required for the Fourier transformation prior to calculating the dielectric constant of the mixture pellet. The LLL model validated in Chapter 3 was used to obtain the dielectric constant for the crystals in question considering the relative volume fraction within the PTFE matrix and a dielectric constant of PTFE over the region of interest.

4.3 Cocrystals

Cocrystals are homogeneous crystalline materials, of organic or inorganic origin, composed of two or more molecular assemblies joined by hydrogen bonding, π - π stacking or weak Vander-Waals interactions.^{78,98} The following sections provide a summary of the cocrystal structures examined here.

4.3.1 Summary of cocrystals

Figure 4-1 represent a general assembly of an organic cocrystal. Such cocrystals are generally composed of an assembly (or template molecule) and a former molecule as identified in Figure 4-1. The assembly molecule helps to orient the former molecule to generate a supramolecular assembly of molecules that involves orientation and positioning of the molecules in a specific structure. Inter-molecular interactions are associated with hydrogen-bonding, π - π stacking or weak Vander-Waals interactions. Hydrogen-bonding is the principal intermolecular force associated with the cocrystal structures studied in this chapter.



Figure 4-1. General assembly of a cocrystal structure.

This chapter contains the study of different cocrystal formers (CCF), cocrystal assemblies (CCA) and cocrystals. The examined cocrystals, and crystals of the corresponding CCF and CCA molecules, are listed in Table 4-1.

Cocrystal Assembly (CCA) molecules				
	Resorcinol (res)			
	4,6 di-Chloro-resorcinol (di-Cl-res)			
	4,6 di-Bromo-resorcinol (di-Br-res)			
	4,6 di-Iodo-resorinol (di-I-res)			
	Acetylsalicylic acid (Aspirin)			
	Salicylic acid (SA)			
Cocrystal Former (CCF) molecules				
	trans-1, 2-bis (4-pyridyl) ethylene (4, 4'-bpe)			
	4,4'- bipyridine (bipy)			
	1,2- bis (4-pyridyl) ethane (bpeth)			
Cocrystals				
	Res·bpe			
	di-Cl-res·bpe			
	di-Br-res·bpe			
	di-I-res·bpe			
	SA·bipy			
	SA·bpeth			
	SA·bpe			

Table 4-1. Examined crystals and cocrystals.

CCAs were prepared by recrystallization of stock materials by Dr. Kristin Hutchins from Professor MacGillivray's group. The cocrystals of the resorcinol derivatives were prepared according the description in Chapter 5, cocrystals of salicylic acid were prepared as described in Chapter 7, and crystal preparations of acetylsalicylic acid and SA are described in Chapter 6 and 7. Cocrystal purity was determined by PXRD and ¹HNMR as described in the corresponding chapters. Macro samples were obtained by crushing crystals from slow evaporation while nano-size materials were obtained by sonochemistry or seeding processes as described in the appropriate chapters.

4.3.2 Crystal structures

Crystal structures were determined by PXRD and ¹HNMR methods as described in Chapter 2. Chemical structures and crystal structures determined by PXRD are presented in Figures 4-2 to 4-10 for each of the compounds listed in Table 4-1, except for the bipy and bpeth CCF compounds, for which crystal structures are not available. The following points are noteworthy from the crystal structures presented in these figures: 1) π - π interactions are important between the olefin functionality of the stacked bpe forming groups; 2) crystal structures for the di-X-res bpe cocrystals are isostructural when X is hydrogen, bromine, or iodine, as detailed in Chapter 5 a different crystal structure is obtained for the di-Cl-res bpe cocrystals resulting in different inter-molecular interactions; 4) significant hydrogen-bonding is evident within the crystal structures of salicylic acid and acetylsalicylic acid; and 5) the salicylic acid cocrystals are not isostructural but do involve hydrogen bonding with the respective CCF.


Figure 4-2. Chemical structure of resorcinol.



Figure 4-3. Chemical structure of di-X-res crystal structure, yellow X= (Cl, Br, I), red oxygen, and light gray hydrogen atoms, respectively.



(b)

Figure 4-4. Crystal structure (a) and crystal lattice structure (b) of acetylsalicylic acid where red atoms represent oxygen and light gray atoms represent hydrogen.



(a)



(b)

Figure 4-5. Crystal structure (a) and crystal lattice structure (b) of salicylic acid where red atoms represent oxygen and light gray atoms represent hydrogen.



(b)

Figure 4-6. Crystal structure (a) and crystal lattice structure (b) of bpe where blue atoms represent nitrogen and light gray atoms represent the hydrogen.



Figure 4-7. Crystal structure (a) and crystal lattice structure (b) of di-X-res·bpe, where yellow –X (H, Cl, Br, I), blue- nitrogen, red- oxygen, and light gray- hydrogen atoms represent, respectively.



(b)

Figure 4-8. Crystal structure (a) and crystal lattice structure (b) of SA·bipy where red- oxygen, blue-nitrogen atoms.



(b)

Figure 4-9. Crystal structure (a) and crystal lattice structure (b) of SA·bpeth where red and blue represent oxygen and nitrogen atoms, respectively.



(a)



(b)

Figure 4-10. Crystal structure (a) and crystal lattice structure (b) of SA·bpe where red and blue represent oxygen and nitrogen atoms, respectively.

4.4 Dielectric spectra of analyte samples

Dielectric spectra are presented below for both the individual CCF and CCA crystals as well as for the corresponding cocrystals listed in Table 4-1. Each spectrum shows the dielectric constant obtained for the crystals of note over the full THz spectral range (5-100 cm⁻¹).

The dielectric spectra presented in Figure 4-11 correspond to individual crystals of bpe and the di-X-res structures where (X=H, Cl, Br, I). Measured dielectric constants for the resorcinol derivatives reveal an increase in order of the size of the halogen substituent in the 4,6 positions on the resorcinol ring. The non-substituted resorcinol does not follow this pattern because its dielectric constant falls between the di-chloro and di-bromo derivatives. The unique crystal structure for the di-Cl derivative compared to the other, which are isostructural, might be responsible for this variation in the trend.

Figure 4-12 provides dielectric spectra for cocrystals composed of the di-X-res-bpe structures. Different spectra are presented for the macro- and nano-size cocrystal preparations in Figures 4-12 a and b, respectively. Again, differences in the magnitude of the dielectric properties are noted for each substituent within the resorcinol CCA derivatives. These differences are discussed in more discussion in Chapter 5.

Dielectric spectra are provided in Figure 4-13 for both macro- and nano-size crystals from the salicylic acid and acetylsalicylic acid preparations. Similar spectra are evident for the macro and nano dimensional crystals. The small differences may be due to structural-induced differences in crystal packing.

Dielectric spectra measured for the macro- and nano-preparations of salicylic acid cocrystals with three different CCA molecules (bpe, bipy, and bpeth) are shown Figure 4-14. The slope in dielectric spectra of macro and nano dimensional SA-bpeth samples may be due to scattering.¹¹¹ The sample shape and the scatter orientation may be responsible for the scattering in the macro and nano samples.



Figure 4-11. Measured dielectric spectra of organic crystalline materials.



Figure 4-12a. Dielectric spectra of macro dimensional organic cocrystalline materials.



Figure 4-12b. Dielectric constant of nano dimensional organic cocrystalline materials.



Figure 4-13. Dielectric spectra of nano and macro dimensional acetylsalicylic acid and salicylic acid crystals.



Figure 4-14. Dielectric spectra of macro and nano salicylic acid cocrystals with different CCFs.

4.5 Polarizability values of CCFs, CCAs and cocrystals

Polarizability (P) of cocrystals were calculated using the derived equation from Clausius-Mossotti relationship as shown in Equation 4-1.¹¹⁵

4.5.1 Polarizability spectra of analyte samples over the THz region

The corresponding polarizability spectra are presented in Figures 4-15 through 4-18. The Clausius-Mossotti relationship is used to calculate polarizability for each crystal sample from the corresponding dielectric spectrum. Equation 4-9 is used for these calculations with compressed density provided for each crystal-containing pellet. Compressed density of pellets is described in more the Chapter 5.

Several noteworthy points can be made from analysis of these polarizability spectra: 1) polarizability increases from X=H to Cl to Br to I for the di-X-res·bpe cocrystals; 2) this trend is conserved for the macro- and nano-size cocrystal preparations, as has been reported;¹³² 3) polarizabilities are similar in magnitude for acetylsalicylic acid and salicylic acid and are much lower than those obtained for the di-X-res·bpe cocrystals; and 4) differences in polarizability for the various salicylic acid cocrystals prepared with bipy, bpeth, and bpe represent differences in hydrogen-bonding and electron conjugation within the cocrystal structure. More analysis of the salicylic acid cocrystals is provided in Chapter

7.



Figure 4-15. Polarizabilities spectra of 4, 4'-bpe, resorcinol, 4, 6-dichloro-resocinol (4, 6-diCl-res), 4, 6-diBr-res, and 4, 6-diI-res.



Figure 4-16a. Polarizabilities spectra of macro sized cocrystals of res·bpe, di-Clres·bpe, di-Br·bpe, and di-I-res·bpe.



Figure 4-16b. Polarizabilities spectra of nano sized cocrystals of res·bpe, di-Cl-res·bpe, di-Br·bpe, and di-I-res·bpe.



Figure 4-17. Polarizability spectra of macro and nano dimensional acetylsalicylic acid, and salicylic acid.



Figure 4-18. Polarizability spectra of macro and nano dimensional salicylic acid cocrystals with different CCFs.

4.5.2 Polarizability values over the THz region

The average was calculated for the polarizability of each crystalline sample by calculating the average measured values over the 10-20 cm⁻¹ spectral range. This range was selected because polarizabilities tend to be relatively constant over this range for all compounds tested. The average values are tabulated in Table 4-2 where the reported values corresponds to the average \pm one standard deviation. The standard deviation represents the sample standard deviation.

Sample	Measured polarizability (Å ³)		
Res	14.6 ± 0.4		
Вре	25.01 ± 0.04		
di-Cl-Res	18.3 ± 0.6		
di-Br-Res	21.6 ± 0.1		
di-I-Res	25.3 ± 0.4		
m-Res-bpe	88.5 ± 1.6		
n-Res-bpe	87.6 ± 1.4		
m-di-Cl-res-bpe	93.1 ± 0.7		
n-di-Cl-res-bpe	89.6 ± 1.4		
m-di-Br-res-bpe	98.3 ± 0.6		
n-di-Br-res-bpe	97.5 ± 1.7		
m-di-I-res-bpe	104.1 ± 1.4		
n-di-I-res-bpe	102.2 ± 1.3		
m-di-I-res-tpcb	87.43 ± 0.03		
m-SA	23.30 ± 0.1		
n-SA	17.86 ± 0.05		
m-SA-bpe	86.75 ± 0.5		
n-SA-bpe	86.73 ± 0.3		
m-SA-bpeth	81.00 ± 1		
n-SA-bpeth	79.00 ± 1		
m-SA-bipy	66.00 ± 1		
n-SA-bipy	59.40 ± 0.2		
m-aspirin	22.1 ± 0.6		
n-aspirin	22.6 ± 1.3		

Table 4-2. Summarized polarizabilities of CCAs, CCFs, single crystals and

cocrystals. m, and n defines the macro and nano dimensional samples respectively.

4.6 Comparison of measured polarizability values to calculated values

4.6.1 Polarizability calculations

The following section explores the relevance of polarizability measurements over THz frequencies for the crystalline materials discussed in this chapter. Specifically, a comparison is made between the measured polarizability and that calculated as the sum of atomic polarizabilities for each crystal assembly.

For this investigation, the calculated polarizabilities corresponded to the simple addition of atomic polarizability values for each species, where the atomic polarizabilities were obtained from literature (*NIST.gov database*). The atomic polarizabilities used in these calculations are listed in Table 4-3. As a sample calculation, the calculated polarizability for bpe (H₁₀C₁₂N₂) corresponds to: 2×1.1 (N) + 12×1.76 (C) + 10×0.667 (H) = 29.22 Å³ (atomic polarizability values obtained from Table 4-3).

4.6.2 Comparison of calculated and measured polarizability values

Table 4-4 summarizes the calculated and measured values for polarizability of the different crystalline materials. In addition to the actual values, this table includes the absolute difference as well as the relative percent difference in these two values. The maximum percent relative difference is approximately 22% for the salicylic acid·bpe cocrystals. Figure 4-19 shows a correlation plot of the measured versus calculate polarizability values across all crystal samples. The ideal unity line is plotted in Figure 4-19, which highlights the strength of this correlation. The r^2 -value for this plot is 0.95.

4.6.3 Discussion

Clearly, the data plotted in Figure 4-20 illustrate a strong correlation between polarizability values measured at THz frequencies and the sum of atomic polarizabilities. Because the atomic polarizabilities are obtained from gas phase measurements, the principal component of the THz polarizability measurements does not include either *intra* or *inter* molecular interactions. Still, difference between the measured and calculated values might represent secondary effects associated with *intra* or *inter*-molecular interactions associated with crystal structures. Sensitivity to polymorphs and hydration are yet to be determined.

Atom	Literature Polarizability (Å ³)		
Cl	2.18		
Br	3.05		
Ι	4.7		
С	1.76		
Ν	1.1		
Н	0.667		
0	0.802		

Table 4-3. The literature polarizability values from NIST.gov data base

(http://cccbdb.nist.gov/polcalccomp2.asp).

Sample	Measured/ /Å ³	Calculated $/\text{\AA}^3$	Difference /Å ³	Relative percent difference/ %
Res	14.60	16.17	-1.56	10.71
Bpe	25.01	29.99	-4.98	19.89
m-Res-bpe	88.49	92.31	-3.82	4.32
n-Res-bpe	87.64	92.31	-4.67	5.33
di-Cl-Res	18.34	19.19	-0.86	4.67
di-Br-Res	21.64	20.93	0.71	3.29
di-I-Res	25.25	24.23	1.02	4.03
m-di-Cl-res-bpe	93.06	98.36	-5.30	5.70
n-di-Cl-res-bpe	89.64	98.36	-8.72	9.73
m-di-Br-res-bpe	98.25	101.84	-3.59	3.66
n-di-Br-res-bpe	97.49	101.84	-4.35	4.47
m-di-I-res-bpe	104.08	108.44	-4.36	4.19
n-di-I-res-bpe	102.23	108.44	-6.21	6.08
m-di-Cl-res-tpcb	87.43	98.36	-10.93	12.51
m-SA	23.30	18.73	4.57	19.62
n-SA	17.86	18.73	-0.87	4.86
m-SA-bpe	86.75	67.45	19.30	22.25
n-SA-bpe	86.73	67.45	19.29	22.24
m-SA-bpeth	81.00	68.78	12.22	15.09
n-SA-bpeth	79.00	68.78	10.22	12.94
m-SA-bipy	66.00	62.59	3.41	5.16
n-SA-bipy	59.40	62.59	-3.19	5.37
m-aspirin	22.1	24.38	-2.28	10.33
n-aspirin	22.6	24.38	-1.78	7.89

Table 4-4. Measured and calculated polarizabilities of organic materials.



Figure 4-19. Correlation of measured and calculated polarizabilities for organic crystalline materials, where dashed gray line is the ideal correlation $(r^2=0.95)$. Error bars represent the sample standard deviation.

4.7 Conclusion

The polarizability of macro- and nano-dimensional organic crystals and cocrystals are measured at THz frequencies. Measured dielectric spectra of pure analytes are coupled with the Clausius-Mossotti relationship to calculate polarizability for a set of crystals and cocrystals across the 5-100 cm⁻¹ spectral range. In addition, polarizability is calculated for each crystal on the basis of the law of additivity of atomic polarizabilities. A strong correlation is demonstrated between the calculated and measured polarizability values across all materials tested. Differences in these values are speculated to be related to *inter*- and *intra*-molecular interactions within the crystalline structures.

CHAPTER 5

RELATIONSHIP BETWEEN POLARIZABILITY AND HARDNESS OF ORGANIC COCRYSTALS

5.1 Introduction

The field of crystal engineering strives to develop crystalline materials with customized properties for selected applications.¹³³ Established relationships between chemical composition, molecular structure and mechanical properties¹³⁴ can facilitate the rational design of materials for targeted applications in pharmaceutics,^{78,99,135} electronics,¹³⁶ explosives,¹³⁷ sensors,¹³⁸ and other advanced technologies.¹³² Recent studies demonstrate a correlation between polarizability and stiffness for various materials, including metals, oxides, covalent crystals and polymers. In these reports, polarizability is inversely related to Young's modulus, or hardness, of the tested materials.¹³²

The purpose of the research described in this chapter is to expand the relationship noted above by correlating polarizability to the corresponding Young's modulus values for a family of organic cocrystals, where organic cocrystals are nonionic supra-molecular complexes as described in Chapter 1. The series of cocrystals examined in this study include resorcinol or 4,6-dihaloresorcinol coupled with trans-1,2-bis(4-pyridyl)ethylene (bpe), where the halogen is either Cl, Br, or I. Figure 5-1 shows the tetrameric molecular assembly for this class of cocrystals. In this chapter, polarizability is measured at THz frequencies by the method detailed and validated in Chapter 4 and Young's modulus is measured by a nano-indentation technique of atomic force microscopy (AFM).⁸² Both measurements are made on macro- and nano-dimensional preparations of each cocrystal.

This study is part of a collaboration between the research programs headed by Professors Tivanski, MacGillivray, and Arnold within the Department of Chemistry at the University of Iowa. Polarization measurements at THz frequencies is the component of this collaboration most relevant to this chapter. Additional details are available in a publication and its corresponding supplemental information.¹³²

5.2 Experimental

5.2.1 Preparation of cocrystals

The macro- and nano-dimensional cocrystals of the molecular assemblies shown in Figure 5-1 were prepared in Professor Len MacGillivray's research group in the Department of Chemistry at the University of Iowa.

5.2.1.1 Macro-dimensional cocrystals

Each 4,6-diX-res cocrystal assembly (CCA) molecule, where X represents H, Cl, Br, or I, was mixed with bpe by dissolving each component in a minimum volume of ethanol. Solutions were filtered using cotton plugs and mixed together. Millimeter sized crystals were obtained by slow evaporation over one to three days. The percent purity of the cocrystals was determined by PXRD and ¹HNMR spectroscopy.

5.2.1.2 Nano-dimensional cocrystals

Nano-size crystals of res-bpe and diX-res-bpe were obtained by exposing the crystals to ultrasonic radiation. For this sonochemical synthesis, individual solutions of 4,6-diX-res, where X represents H, Cl, Br or I and bpe were prepared by dissolving each component in a minimum volume of ethanol. These solutions were injected directly into a volume of hexane maintained at 0 °C via a Millex syringe filter (PVDF, 0.2 µm, 13mm) while a low-intensity ultrasonic radiation (ultrasonic cleaning bath Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W) was applied. The resulting product was filtered and dried in room temperature and the purity was determined by PXRD. Structure of both the macro-and nano-preparations were verified by comparison to simulated PXRD spectra from single crystal X-ray diffraction data.



X= H, Cl, Br, I

Figure 5-1. Tetrameric supra-molecular assembly of resorcinol-trans-(1,2-bis)(4pyridyl)ethylene (res·bpe), 4,6-dichloro-res·bpe (diCl-res·bpe), 4,6dibromo-res·bpe (diBr-res·bpe), and 4,6-diiodo-res·bpe (diI-res·bpe).

5.2.2 PXRD analysis

PXRD crystal structures are presented in Figure 5-2 for both macro- and nano-size diCl-res·bpe, diBr-res·bpe, diI-res·bpe, and res·bpe cocrystals. Macro sized cocrystals were obtained by crushing millimeter sized cocrystals using a mortar and pestle prior to the PXRD analysis. Nano dimensional cocrystals were obtained by sonochemical synthesis as described above. Again, the PXRD patterns used for comparison corresponded to X-ray diffraction patterns of single cocrystals. The purity and conformation of each cocrystal preparation were determined by comparing the single cocrystal pattern with the PXRD patterns. ¹H NMR spectral analysis was also used to confirm each structure, as explained in Chapter 2.

5.2.3 Young's modulus measurements

Young's modulus measurements were obtained by nano-indentation with atomic force microscopic (AFM) and were completed by Dr. Thilini Rupasinghe in Professor Alexei Tivanski's research group in the Department of Chemistry at the University of Iowa.

All AFM measurements were conducted with a Molecular Force Probe 3D AFM instrument (Asylum Research, Santa Barbara, CA) with tip diameters of approximately 10 nm. Measurements with macro-dimensional cocrystals were performed on millimeter size cocrystals positioned on a freshly cleaved surface of a mica substrate. For measurements on nano-dimensional samples, cocrystals were suspended in hexane (0.5 mg/mL) and deposited onto a freshly cleaved mica substrate. Results from measurements on approximately 25 individual cocrystals were averaged to provide sound estimates of the population distribution for these samples.

The loading force (F) was measured as a function of tip-sample separation (Δ).⁸² The Young's modulus (YM) of cocrystal samples was determined by the linear slope of the plot of loading force vs. tip-sample separation. Histograms were obtained by plotting number of counts vs. YM values and the average was determined from fitting each histogram to a Gaussian distribution.

5.2.4 Polarizability measurements using THz-TDS

Each sample was prepared as a pellet composed of 5 weight-percent (wt-%) of the cocrystal embedded within a matrix of polytetrafluoroethylene (PTFE). The PTFE was purchased from Micro Powders Inc. (Tarrytown, NY) as a powder with an average particle size of 9-13 µm. Mixtures were prepared by combining 30 mg of the cocrystal and 550 mg of PTFE, stirring with a spatula and vortexing for 60 minutes. Pellets were prepared by placing approximately 580 mg of the mixture into a 13-mm diameter stainless steel die positioned in a Specac hydraulic press (GS15011). A vacuum line was connected to the die housing to remove air from the powdered mixture within the die. After pumping for 2 minutes, pellets were made by applying five tons of pressure for five minutes, while continuing to run the vacuum pump. After preparation, pellets were removed from the die and placed in a desiccator for two days prior to collecting THz spectra. While in the desiccator, pellets remained dry while the physical dimensions were allowed to relax fully following the compression process. Mass of each pellet was recorded and dimensions were measured with calipers after this two-day relaxation period.

A TeraView TPS Spectra 1000D TDS-THz spectrometer (TeraView Limited, Cambridge, UK) was used to collect time-domain spectra from which refractive index and dielectric measurements were obtained over the 5-100 cm⁻¹ spectral range (0.15- 3.0 THz). Air reference data were collected after purging the sample compartment with dry air for five minutes to remove ambient water. Refractive index and dielectric constant data were obtained for each sample by positioning the pellet of interest into a custom made sample holder that rotated the pellet at a frequency of one revolution per minute. Rotation of the sample in the optical beam served to average out heterogeneities within the pellet preparation. Prior to data collection, the sample compartment was purged for five minutes with dry air.

Refractive index was determined from the phase shift of the electric field vector of the THz electromagnetic (EM) radiation. The coherent nature of the EM radiation produced by the THz source⁶⁴ coupled with the rapid temporal response of the detection optics enables direct measurement of the oscillating electric field of the detected radiation. As the EM THz radiation propagates through the sample, it is delayed according to the refractive index of the sample. The phase difference measured between the sample and air can be used to determine the refractive index of the sample pellet as described in Chapter 3. For the data presented here, time-domain spectra were truncated prior to the etalon followed by zero-filling. The refractive index was obtained from Equation 3-3 and the corresponding dielectric constant of the pellet was determined from Equation 3-4.

The LLL model, introduced in Chapter 3, was used to extract dielectric information for cocrystals embedded within pellets. It was determined that cocrystal-PTFE pellets used in these measurements can be treated as a simple binary mixture composed of only cocrystal and PTFE. Although, pellets produced by compression can trap air thereby creating a ternary system for the purpose of determining the dielectric constant from the
LLL model, the presence of air in the cocrystal-PTFE pellets was determined to be negligible from porosity measurements based on the volume dimensions of relaxed crystals.¹⁰⁶

Polarizability of cocrystals were calculated on the basis of the Clausius-Mossotti relationship¹¹⁵ as described in Chapter 4.

5.3 Crystal structure of cocrystal preparations

Crystal structures of the molecular assemblies for the cocrystals investigated here are presented in Figure 5-2. The X-ray crystallographic data highlight show the resorcinol and bpe molecules assemble through hydrogen-bonding between O-H···N. Cocrystal assemblies with H, Br, and I in the 4,6-positions on the resorcinol ring are isostructural, whereas the di-Cl-res bpe cocrystals have a different, more complex crystal packing. The di-H, di-Br, and di-I cocrystals are aligned in the crystallographic plane to create face-toface interactions between the olefin groups on the bpe units. The di-Cl-res bpe cocrystals consist of type 2 interactions between Cl···Cl which defines as halogen molecules in the two resorcinol units in the two layers.¹³² Apart from that, assemblies stack along the *c-axis via* C-H···*π* interactions of pyridine and resorcinol, respectively, with a C···C distance of 3.63Å. Cocrystal assemblies of X= Br, and I in Figures 5-2 c and d, show interactions between layers *via* O···Br (3.16 Å) and O···I (3.22 Å).



Figure 5-2. X-ray structures of (a) res·bpe, (b) di-Cl-res·bpe, (c) di-Br-res·bpe, and(d) di-I-res·bpe. The packing assemblies are highlighted in gray. Redlines represent the millimeter size crystals probed planes in AFMmeasurements. Offset layers have been highlighted in gray.

5.4 Nano-indentation Young's modulus results obtained for cocrystals

Young's modulus results are summarized in Table 5-1 as determined from the AFM nano-indentation technique. Such AFM probe measurements are sensitive to the surface chemistry and can, therefore, be sensitive to the crystal plane probed during the measurement. The crystallographic planes specified in Table 5-1 were determined from the X-ray crystallography data and differences in the measured Young's modulus values are noted for different planes of the same cocrystal composition. Overall, Young's modulus values decrease systematically from the res-bpe, di-Cl-res-bpe, di-Br-res-bpe, and di-I-res-bpe cocrystals, indicating the following trend in cocrystal hardness:

where res bpe is hardest and di-I-res bpe is softest. The same trend is observed for both the macro- and nano-dimensional cocrystals.

An interesting finding is the difference in the absolute magnitude of Young's modulus values for macro- versus nano-dimensional cocrystals for the same chemical composition. For the res-bpe cocrystals, the Young's modulus is smaller for the nano-dimensional cocrystals, whereas the Young's modulus is larger for the nano-dimensional cocrystals compared to the macro preparations for the di-Cl-res-bpe, di-Br-res-bpe, and di-I-res-bpe cocrystals. These findings indicate nano-cocrystals for halogen-containing cocrystals are harder than their macro-dimensional counterparts, while the opposite is true for the res-bpe cocrystals. These differences in crystal hardness might reflect differences in the nano-dimensional surface chemistry in comparison to the macro-cocrystals. A major difference in these measurements relates to the ability to probe specific crystal planes with the macro-size crystals in contrast to the nano-size crystals for which the samples are too

small to specify the crystal plane being probed. In this regard, Young's modulus values for the nano-dimensional cocrystals correspond to values obtained across a distribution of crystal planes. Young's modulus values listed in Table 5-1 for the different crystal planes of the macro-size preparation demonstrate significant differences between these planes. Overall, cocrystal hardness depends on substituents in the 4,6-positions of the resorcinol ring of these tetrameric supra-molecular assemblies.¹³²

Sample	Young's modulus (YM)/ MPa	
	Macro*	Nano
Res·bpe	$\begin{array}{c} 1600 \pm 350 \ (00\text{-}1) \\ 1250 \pm 350 \ (001) \end{array}$	570 ± 200
di-Cl-res·bpe	270 ± 25 (10-1) 235 ± 25 (-101)	370 ± 140
di-Br-res·bpe	$120 \pm 15 (0-10)$ $95 \pm 10 (010)$	275± 140
di-I-res·bpe	$54 \pm 3 (0-10)$ $40 \pm 2 (010)$	160 ± 50

Table 5-1. Young's modulus values for cocrystal assemblies obtained by AFM nano-indentation.

*Values in parantheses correspond to the crystal plane used for the measurement.

5.5 Polarizability spectra of cocrystal preparations

Polarizability was measured over THz frequencies for the series of cocrystals under investigation by using the Clausius-Mossotti relationship described in Chapter 4. For measurements on macro-size cocrystals, the crystals were crushed before mixing with PTFE and forming pellets for the THz time-domain measurements. The nano-size crystals, on the other hand, were mixed with PTFE without alteration (no crushing) and pellets were prepared as described above (Section 5.2.4).

Absorption and polarizability spectra are presented together in Figure 5-3 for a representative sample of the macro-size res bpe cocrystals. Three absorption bands and a sloping baseline are the key elements of this spectrum. These absorption bands are centered at 49.7, 75.4, and 84.5 cm⁻¹. Polarizability is relatively flat at low frequencies with values averaging 88.5 ± 1.6 Å³ over the 10-20 cm⁻¹ range. As the polarizability is derived from refractive index of the sample, large changes are noted in polarizability corresponding to the absorption bands owing to resonant interactions between the EM radiation and crystal structure. Inter-molecular interactions are probed at THz frequencies, giving unique insight into cocrystal structure.

Polarizability spectra are presented in Figure 5-4 for both macro- and nanodimensional crystalline preparations of the four tetrameric cocrystal assemblies. Unique resonant dispersion features are observed, each associated with an absorption band (not shown). Comparing all these spectra, the spectral region between 10 and 20 cm⁻¹ is relative flat and, therefore, polarizability values were averaged over this spectral range and reported for each sample type.



Figure 5-3. Polarizability spectra (blue) and absorptivity spectra (red) for res·bpe cocrystals.



Figure 5-4. Polarizability spectra of macro and nano-preparations of res·bpe and dihaloresorcinol·bpe cocrystals.

5.6 Correlation between polarizability and Young's modulus

The relationship between polarizability and Young's modulus is presented in Figure 5-5 by plotting the reciprocal of the Young's modulus versus polarizability for both the macro- and nano-preparations. Error bars represent \pm one standard deviation for the two types of measurements.

In general, the Young's modulus is inversely related to polarizability for both the macro- and nano-dimensional samples. This finding is consistent with previous reports for other materials.^{139,140} A linear regression analysis for macro- and nano-dimensional cocrystals reveals a significant linear relationship between the reciprocal of Young's modulus and polarizability with correlation coefficients of 93% for weighted fits for both macro- and nano-size cocrystal preparations ($r^2 = 0.93$ for macro-samples and $r^2 = 0.93$ for nano-samples).



Figure 5-5. Relationship between polarizability and the inverse hardness of tested cocrystals. Error bars represent the sample standard deviation.

As presented in Figure 4-18, polarizability of organic crystals at THz frequencies is related to the sum of its substituent atomic polarizabilities. As the atomic composition of the four cocrystals differs only by the atoms located at the 4,6 positions of the resorcinol ring, a relationship is expected between polarizability of the cocrystals composed of tetrameric assemblies and polarizability of the atoms in the 4,6 positions on the resorcinol ring. Figure 5-6 shows this expected relationship for the cocrystals investigated here. As the atomic polarizability increases with atomic radius, the polarizability of the cocrystals increases.

It is interesting to point out that the measured polarizability for each cocrystal corresponds to the tetrameric form. While the empirical formula for these cocrystals represent a 1:1 mole ratio of the resorcinol and bpe units, the measured polarizability does not match this empirical formula, but a molecular formula representing the tetrameric formulation. Figure 5-7 shows a plot of measured versus calculated polarizability for each of the cocrystals investigated in this chapter. These points represent a subset of those in the bigger plot presented in Figure 4-19. Measured values are systematically lower compared to the calculated values based on the 2:2 mole ratio. The difference (calculated – measured) is similar for each of the cocrystal types (res·bpe = 4.7, di-Cl-res·bpe = 8.7, di-Br-res·bpe = 4.4, and di-I-res·bpe = 6.2 Å^3) and might represent the impact of *inter*-molecular or *inter*-assembly interactions within the cocrystal structure that can be probed at these THz frequencies.



Figure 5-6. Polarizability of cocrystals as a function of atomic polarizabilities of substituent in the 4,6 positions of the resorcinol ring of the tested res bpe cocrystal materials. Error bars represent the sample standard deviation.



Figure 5-7. Comparison of measured and calculated polarizability values for macro and nano di-X-res·bpe (X=H, Cl, Br, I) samples. The solid line represents the ideal unity fit between these two parameters. Error bars represent the sample standard deviation.

5.7 Conclusion

The mechanical and chemical properties of cocrystalline materials have been studied using AFM and THz time-domain spectroscopy. Polarizability is a chemical property of a material which depends on electron mobility in response to an applied electric field as well as the crystal packing. A series of diX-res bpe (X=H, Cl, Br, I) cocrystal samples have been examined over THz optical frequencies. An inverse relationship was established between the material hardness (YM) and polarizability of these cocrystal supramolecular assemblies. Atomic polarizabilities increase with atomic radius (H < Cl <Br < I) of the substituents in the 4,6 positions of the resorcinol ring. This finding is consistent with an increase in atomic polarizability of these substituents and the ease of electron cloud distortions in the presence of the applied electric field vector of the EM radiation. The opposite trend is observed in terms of hardness of these cocrystals, as the measured Young's modulus decreases from H > Cl > Br > I. It is important to note that the measured polarizability for these cocrystals is less than calculated values based on the additivity law of atomic polarizability. Such differences might reflect inter-molecular or inter-assembly interactions that are ignored in the additivity of atomic polarizabilities. The potential to probe such interactions within the crystal structures by THz time-domain spectroscopy is an exciting advance.

CHAPTER 6

IMPACT OF SAMPLE PREPARATION METHOD ON POLARIZABILITY AND HARDNESS PROPERTIES OF COCRYSTALS

6.1 Introduction

Nanoscience is a central component for the creation of the next generation of advanced materials for electronic, catalysis, energy, cosmetics, and biological and clinical sciences.¹⁴¹⁻¹⁴³ Several methods are available to prepare nano-dimensional organic cocrystals, including sonocrystallization, sonofragmentation, and mechanical grinding. The sono-chemical methods are recognized as the most popular, especially within the pharmaceutical industry. The popularity of such methods is based on narrow particle size distributions, reproducible crystallizations, low impurities, and control over polymorphism.^{144,145} Sonocrystallization methods are known to result in production of nanocrystals with highly crystalline, and monodisperse particles with uniform shape distribution¹⁴⁶, but its exact mechanism has not been fully understood.

Published accounts indicate that the method used to prepare nano-materials can impact their physical and chemical properties. An example is the sonofragmentation method can improve crystallinity and purity relative to other methods of producing nano size organic crystals.¹⁴⁷ In other cases, no effect of preparation method has been found. An example is the preparation of inorganic crystals of Ni or Zn. In this study, two different methods were compared; one a chemical polyol process and the other a sonocrystalliztion

method.¹⁴⁸ The preparation method had no effect on the magnetic properties of these materials.

Sonocrystallization is a commonly used method for generating nano-dimensional crystals. In this method, ultrasonic radiation is passed through the solution during the crystallization process. Direct interactions between the crystals and sonic radiation is not thought to impact crystallization formation.^{141,149} Energy associated with the growth and collapse of sonic cavities is more likely involved in the formation of nano-size crystals.^{141,149,150} The impact on the process of forming cocrystals is likewise poorly understood.¹⁴⁶ Some have proposed that nano dimensional cocrystals are related to inter particle collisions induced by the sonic radiation. Suslick and co-workers found that crystal breaking occurred through interactions between shockwaves and crystal and such interactions are different compared to those observed for metallic systems.¹⁴⁴ As a result of these observations and uncertainty in the crystallization mechanism in the presence of sonic energy, exploring crystalline characteristic of nano-dimensional cocrystals from different preparation methods became an interest of this study.

In this chapter, different preparation methods are compared for the synthesis of acetylsalicylic acid crystals and cocrystals of di-Cl-res·bpe. Products from sonocrystallization, sonofragmentation, mechanical grinding and mechanochemistry are compared in terms of their polarizability and hardness properties.

6.2 Sample preparation

6.2.1 Crystal and cocrystal preparation

Figures 6-1 and 6-2 show the chemical structure and crystal structures for the test compounds used in this study; acetylsalicylic acid crystals and cocrystals of di-Cl-res-bpe. The three methods used to prepare nano-size crystals of acetylsalicylic acid are sonocrystallization, sonofragmentation, and mechanical grinding. For the grinding method, physical grinding was used to reduce millimeter size crystals to nanometer size crystals. Four methods were used to prepare nano dimensional di-Cl-res-bpe cocrystals and include sonocrystallization, sonofragmentation, grinding, and mechanochemistry. Two common mechanochemistry methods are wet and dry processing, where the grinding of two or more components is performed in either a wet and dry medium. In this study, dry grinding is examined.

Crystals of acetylsalicylic acid and di-Cl-res·bpe were prepared in Professor MacGillivrays laboratory in the Department of Chemistry at the University of Iowa.

6.2.1.1 Acetylsalicylic acid nano-crystals

The sonocrystallization synthesis was performed in the following manner. A solution of commercial acetylsalicylic acid was prepared by dissolving the acid in a minimal volume of acetone. This solution was injected into chilled hexane under low-intensity ultrasonic irradiation provided by a commercial ultrasonic cleaning bath (Branson 2510R-DTM, frequency: 42 kHz, 6% at 100W). The resulting suspension was sonicated for 1-2 minutes followed by filtration and drying under room temperature.

The sonofragmented nanocrystals of acetylsalicylic acid were prepared from millimeter size crystals. Millimeter size crystals were prepared by slow solvent evaporation of acetylsalicylic acid in ethanol. Once isolated and dried, a quantity of the millimeter size crystals was suspended in 5 mL of hexane to which a low intensity ultrasound radiation was applied for 10 minutes. The ultrasonic radiation was provided by a commercial ultrasonic cleaning bath (Branson 2510R-DTM, frequency: 42 kHz, 6% at 100W).

Nanocrystals of acetylsalicylic acid were also prepared by mechanical grinding. In this case, the millimeter size crystals described above were placed in a mortar and a pestle was used to grind these crystals for approximately 20 minutes which as sufficient to reduce the size of these crystals to the nanometer domain.

6.2.1.2 Di-Cl-res·bpe nano-cocryatals

Nano-cocrystals of di-Cl-res bpe were prepared by the methods described below starting with di-Cl-res and bpe purchased from Sigma Aldrich. These compounds were used as received, without further purification.

Sonochemistry synthesis was carried out by preparing separate solutions of di-Clres and bpe. The first was composed of 0.27 mmol of di-Cl-res dissolved in a minimum volume of ethanol and the second was composed of 0.27 mmol of bpe dissolved in a minimum volume of ethanol. Each solution was filtered through a Millex syringe filter (PVDF, 0.2μ m, 13mm) directly into 200 mL of cold hexane (0°C) while being exposed to a low-intensity of ultrasonic radiation provided by a standard laboratory ultrasonic cleaning bath (Branson 2510R-DTM, frequency: 42 kHz, 6% at 100W). Millimeter size di-Cl-res·bpe cocrystals were prepared for the sonofragmentation and grinding methods described below. These initial cocrystals were prepared by dissolving 39.3 mg of di-Cl-res and 40 mg of bpe separately into minimal volumes of ethanol followed by slow evaporation.

Sonofragmentation preparation was performed starting with millimeter size cocrystals, as described above. These cocrystals were suspended in 5 mL of hexane and exposed to low-intensity ultrasonic radiation (Branson 2510R-DTM, frequency: 42 kHz, 6% at 100W) for 10 min. The resulting cocrystals were removed from the solvent and dried at room temperature.

Grinding production of nano size cocrystals involved grinding millimeter size di-Cl-res·bpe cocrystals with in a mortar and pestle for approximately 20 sec.

Mechanochemical synthesis was accomplished by combining 0.55 mmoles of di-Cl-res (98 mg) and 0.55 mmoles of bpe (100 mg) in a mortar and grinding for 45 min.

Structure and purity of all the preparations described above were determined by PXRD analysis. PXRD data were obtained from a Siemens D5000 X-ray diffractometer using CuK α 1 radiation (λ =1.54056 Å). Parameters were set as follows: scan type: locked coupled, scan mode: continuous, step size: 0.02Å, scan time: 2s/ step. Samples were mounted in a glass slide. Figure 6-3 represents the PXRD patterns of nano di-Cl-res-bpe samples obtained by the different methods along with the simulated pattern obtained by single crystal analysis. Crystal structures were found to be identical for the acetylsalicylic acid and di-Cl-res-bpe crystals described above.



(a)



(b)

Figure 6-1. Acetylsalicylic acid crystal structure (a) and crystal lattice (b), where red atoms indicate oxygen and light gray atoms indicate hydrogen.



(a)



(b)

Figure 6-2. di-Cl-res·bpe crystal structure (a) and crystal lattice (b), where red atoms indicate oxygen where light gray atoms indicate hydrogen, blue atoms indicate nitrogen, and green atoms indicate chlorines.



Figure 6-3. PXRD for the di-Cl-res·bpe cocrystalline material prepared by different

preparation methods.

6.3 Sample analysis

6.3.1 AFM analysis

Crystal hardness was determined by Young's modulus values obtained by nanoindentation methods using atomic force microscopy (AFM), as described in Chapter 5. These measurements were performed in Professor Tivanski's group in the Department of Chemistry at the University of Iowa. Young's modulus values are listed in Table 6-1 for each compound and each preparation method.

6.3.2 THz-TDS analysis

Time-domain THz spectra were collected on sample pellets prepared in PTFE. As described in detail in previous chapters, THz spectra were collected while rotating the sample pellet in the optical path to reduce the impact of pellet heterogeneity. Pellets were prepared by pressing under 5 tons of pressure and allowing the pressed pellets to relax over a period of two days while stored in a desiccator.

Dielectric spectra were obtained by calculating the dielectric constant at each spectral resolution element over the 5-100 cm⁻¹ spectral range. The LLL model described in Chapter 3 was used to extract dielectric values for the crystalline sample. Polarizability of sample was then calculate using the dielectric constant coupled with the Clausius-Mossotti relationship introduced and validated in Chapter 4.

Figures 6-4 and 6-5 present polarizability spectra obtained for the nano-crystalline preparations of acetylsalicylic acid and di-Cl-res·bpe. The average polarizability measured over the 10-20 cm⁻¹ spectral range is listed in Table 6-1 for each compound and each

preparation method. The standard deviations of polarizability and Young's modulus values represent the sample standard deviation.



Figure 6-4. Polarizability spectra for acetylsalicylic acid nano-crystals prepared by different methods.



Figure 6-5. Polarizability spectra for nano-cocrystals of di-Cl-res bpe prepared by different methods.

Sample	YM value (MPa)	Polarizability (A ^{°3})	
Acetylsalicylic acid crystals			
crushed	600 ± 150	22.1 ±0.6	
sonocrystallization	700 ± 200	22.6 ± 0.6	
sonofragmentation	650 ± 150	21.6 ± 0.2	
di-Cl-res·bpe cocystals			
crushed	330 ± 120	93.06 ± 0.65	
sonocrystallization	370 ± 140	89.64 ± 0.96	
sonofragmentation	$\overline{370 \pm 150}$	93.1 ± 1.9	
mechanochemistry	350 ± 100	93.5 ± 0.5	

Table 6-1. Comparison of Young's modulus (hardness) and polarizability of single crystal and cocrystal systems.

*Polarizability values correspond to the average value over the 10-20 cm⁻¹ spectral region. Standard deviation represent the sample standard deviation.

Comparison of the Young's modulus and polarizability values for the acetylsalicylic acid crystal preparations indicates no statistical difference at the 95% confidence level. Student *t*-tests were performed in both cases.

Similarly for the di-Cl-res bpe cocrystals, no significant differences are indicated for the Young's modulus values for the four sample preparation methods. For the polarization measurements, however, results for cocrystals prepared by the sonocrystallization method are statistically different from the others at the 95% confidence level. In this case, the measured polarizability is significantly lower than the other values. Inspection of Figure 6-5 reveals the shape of the polarizability spectrum is consistent with the di-Cl-res bpe cocrystal structure, only values over the measurement frequencies (10-20 cm⁻¹) are shifted lower compared to the others.

One possible explanation for the lower polarizability values for the sonocrystallization methods is chemical contamination of these crystals compared to the other preparations. The PXRD method used to characterize purity and structure is limited to detection of impurities down to 5% of the sample. One would imagine that impurities would lower polarizability on the basis of the additive effect of dielectric measurements in the LLL model. Similarly, it is reasonable that the polarizability measurement would be more sensitive to impurities compared to the nano-indentation AFM measurement because these AFM measurements are sensitive to the surface of the crystals, whereas the THz-TDS measurements of dielectric and polarizability probe the bulk properties of these crystals.

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6.4 Conclusion

Three methods are compared for the synthesis of crystals of acetylsalicylic acid and four methods are compared for the synthesis of cocrystals of di-Cl-res-bpe. These methods span the scope of both sono-chemical and mechanical methods for the production of nano-dimensional crystals of organic materials. Differences in the physical and chemical properties of crystals prepared by these methods were determined. Young's modulus gave a measure of crystal hardness and polarizability gave a measure of the extent to which charge density within the crystal structure can be distorted in the presence of an external applied electric field. Measured values are compared by Student *t*-test statistics at the 95% confidence level.

Results reveal no differences in either hardness or polarizabilty for acetylsalicylic acid nano-crystals prepared by sonocrystallization, sonofragmentation, and mechanical grinding. For di-Cl-res·bpe nano-cocrystals, no statistical difference was found in the measurement Young's moduli across the different preparation methods. A significant difference was obtained for polarizability values measured for di-Cl-res·bpe nano-cocrystals prepared by sonocrystallization in comparison to nano-cocrystals produced by sonofragmentation, mechanical grinding and mechanochemistry. The possibility that impurities are responsible for this difference is discussed.

CHAPTER 7

DIELECTRIC, POLARIZABILITY AND HARDNES PROPERTIES OF SALICYLIC ACID BASED COCRYSTALS WITH A SERIES OF COCRYSTAL FORMERS

7.1 Introduction

Polarizability and Young's modulus measurements are described in Chapter 5 for a series of cocrystals based on trans-1,2-bis(4-pyridyl)ethylene (bpe) as the cocrystal former (CCF) and different resorcinol derivatives as the cocrystal assembly (CCA). The approach presented in Chapter 5 involves keeping the same CCF molecule (bpe) while the chemical structure of the CCA molecule is varied in a systematic manner. In the case of the results presented in Chapter 5, the examined CCA's included resorcinol and 4,6dihaloresorcinol derivatives where the halogen varies from chlorine to bromine to iodine. This experimental designed enabled examination of the polarizability and hardness for a series of cocrystals with a systematic variation of the atom in the 4 and 6 positions on the resorcinol ring. Polarizability and hardness were found to vary systematically for these cocrystals and the properties of polarizability and hardness were found to be inversely related to each other.¹³²

In this chapter, properties are measured for a series of cocrystals were the CCA is constant and the CCF is varied. In this case, salicylic acid (SA) is the CCA combined with the following CCF molecules: 4, 4'-bipyridine (bipy), 1, 2, bis (4-pyridyl) ethane (bpeth) and 1, 2-di (4-pyridyl) ethylene (bpe). Structure for the resulting cocrystals are presented in Figure 7-1. This set of CCF molecules provides chemical variation in the linkage between the two pyridine rings that hydrogen bond to the salicylic acid CCA molecules. These linkages vary the distance and degree of conjugation between these pyridine rings.



Figure 7-1. Salicylic acid cocrystals with CCF's of 1, 2, bis (4-pyridyl) ethane (bpeth), 1, 2-di (4-pyridyl) ethylene (bpe), and 4, 4'-bipyridine (bipy).

7.2 Sample preparation and analysis

Synthesis and PXRD analysis were carried out in Professor Leonard MacGillvray's research laboratory in the Department of Chemistry at the University of Iowa. Nanoindentation measurements of Young's modulus were performed in Professor Alexei Tivanski's research group in the Department of Chemistry at the University of Iowa.

7.2.1 Preparation of salicylic acid crystals and cocrystals

Salicylic acid (SA) was purchased from Fisher Scientific and used as received. Millimeter size crystals of SA were prepared by slow solvent evaporation from a solution of SA in 30% methanol in H₂O. This procedure gives the P2₁/a polymorph. Nano-size crystals of SA were obtained by sonochemistry where 2.2 mmoles of SA (300 mg) was dissolved in a minimum volume of ethanol. This solution was rapidly injected into a 100 mL volume of cold hexanes while exposed to a low-intensity of ultrasonic radiation provided by an ultrasonic cleaning bath (Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W). The resulting crystal suspension was sonicated for 1-2 min and approximately 20 mL of solvent was removed under air. The resulting crystalline material was filtered and dried at room temperature.

4,4'-bipyridine (bipy), 1,2,-bis(4-pyridyl) ethane (bpeth) and 1,2-di(4-pyridyl) ethylene (bpe) were purchased from Sigma Aldrich and were used without further purification.

Macro size cocrystals of each CCFs were synthesized by preparing a solution containing SA and the CCF of interest in a minimum volume of ethanol. This solution was prepared such that the CCA-to-CCF mole ratio was 2:1. Slow solvent evaporation was permitted over two days. A single crystal suitable for the X-ray diffraction analysis was selected for each product.

Nano size cocrystals were prepared by using sonochemistry with crystal seeding. In the absence of a seed crystal, sonochemical synthesis resulted in solids with PXRD patterns that did not match the simulated patterns from the single-crystal X-ray diffraction data. Attempts to find a suitable solvent were not successful. Only by seeding was it possible to produce nano-dimensional cocrystals that match the X-ray analysis.

The following procedure was used to generate nano-size SA cocrystals. Approximately 10 mg of the appropriate macro-size cocrystals was crushed using an agate mortar and pestle and the crushed material was suspended in 150 mL of cold hexanes. SA and the appropriate bipyridine CCF were dissolved in separate minimum volumes of ethanol with a mole ratio of 2:1. These solutions were rapidly injected directly into a cold hexanes solution containing the seed while being exposed to low-intensity ultrasonic radiation generated by an ultrasonic cleaning bath (Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W). The resulting suspension was sonicated for 5 min, filtered, dried at room temperature, and analyzed by PXRD.

7.2.2 Analysis of salicylic acid crystals and SA cocrystals

Structure and purity of all the preparations described above were determined by PXRD analysis. PXRD data were obtained from a Siemens D5000 X-ray diffractometer using CuK α 1 radiation (λ =1.54056 Å). Parameters were set as follows: scan type: locked coupled, scan mode: continuous, step size: 0.02Å, scan time: 2s/ step. Samples were

mounted in a glass slide as described in Chapter 6. PXRD patterns for both nano and macro preparations were consistent with the simulated single crystal data, thereby confirming these structures.

Figures 7-2, 3, 4, and 5 present the chemical and crystal structures of SA crystals as well as, SA·bipy, SA·bpeth, and SA·bpe cocrystals respectively. The PXRD patterns of SA, SA·bipy, SA·bpeth, and SA·bpe are shown in Figures 7-6, 7, 8, and 9.

7.2.3 AFM measurements

The Young's modulus measurements of both macro and nano size crystals were performed as described in Chapters 5 and 6. All AFM measurements used the Molecular Force Probe 3D AFM system (Asylum Research, Santa Barbara, CA). AFM measurements were obtained from at least 15 crystals and the average values are reported. For macro dimensional crystals, Young's modulus values were measured on a specific crystallographic plane.

7.2.4 THz-TDS measurements

As detailed in previous chapters, crystals were embedded within polymer pellets for THz-TDS measurements. Pellets were prepared with 2.5 - 5 weight percent of the crystals in PTFE. Pellets were formed with 5 tons of pressure and freshly formed pellets were allowed to relax under desiccation. THz time-domain spectra were collected for each sample after purging the sample compartment with dry air for 5 minutes. Dielectric values were obtained from the time-domain spectra by using the LLL model described in Chapter 3 and polarizability values were determined using the Clausius-Mossotti relationship presented in Chapter 4.




Figure 7-2. Crystal (a) and crystal lattice structures (b) of salicylic acid where the red color represents oxygen atoms.





Figure 7-3. Crystal (a) and crystal lattice structure (b) of SA·bipy where red and blue colors represent oxygen and nitrogen atoms, respectively.





Figure 7-4. Crystal (a) and crystal lattice structure (b) of SA·bpeth where red and blue colors represent oxygen and nitrogen atoms, respectively.





Figure 7-5. Crystal (a) and crystal lattice structure (b) of SA·bpe where red and blue colors represent oxygen and nitrogen atoms, respectively.



Figure 7-6. PXRD diffractograms of macro and nano dimensional salicylic acid crystals simulated from single crystal X-ray diffraction data.



Figure 7-7. PXRD diffractograms of SA·bipy showing pattern simulated from single crystal X-ray diffraction data, and for macro and nano-dimensional cocrystals.



Figure 7-8. PXRD diffractograms of SA bpeth showing pattern simulated from

single crystal X-ray diffraction data as well as patterns for macro and nano-dimensional cocrystals.



Figure 7-9. PXRD diffractograms of SA·bpe showing patterns simulated from single crystal X-ray diffraction data as well as for macro and nano-dimensional cocrystals.

7.3 Results

7.3.1 Crystal structures

Crystal structures and packing patterns are presented in Figures 7-2, 3, 4, and 5 for the SA, SA·bipy, SA·bpeth, and SA·bpe crystals, respectively. The crystallographic data indicate different crystal packing for the cocrystals. The following points are noteworthy: 1) these cocrystals are not isostructural; and 2) the distance between the olefin rings in the SA-bpe cocrystals is 4.88 Å, which is too far for [2+2] photodimerization. Figure 7-6 presents the PXRD patterns and Figures 7-7, 8 and 9 present the PXRD patterns for salicylic acid crystals and SA cocrystals respectively. PXRD patterns for both nano and macro preparations were consistent with the simulated single crystal data, thereby confirming these structures.

7.3.2 Dielectric and polarizability THz spectra

The measured dielectric spectra are presented in Figure 7-10 for the SA-based cocrystals and the corresponding polarizability spectra are shown in Figure 7-11. In both cases, spectra are provided for the macro and nano preparations over the 5-100 cm⁻¹ spectral range. Reported polarizability values for each material were taken as the average over the 10-20 cm¹ spectral range where spectral variations in polarizability are minimal.

7.3.3 Crystal hardness and polarizability

Measured values of polarizability and Young's modulus for SA crystals as well as the three different SA-containing cocrystals are tabulated in Table 7-1. Inspection of results for the macro size cocrystals indicates that polarizability and Young's modulus (hardness) are inversely correlated. Polarizability increases in the order of $SA < SA \cdot bipy < SA \cdot bpeth$ < $SA \cdot bpe$ while the opposite trend is noted for Young's modulus values. This finding is consistent with the results presented in Chapter 5.

Comparison of macro and nano dimensional crystals and cocrystals reveals mixed results. Polarizability values for macro and nano preparations of SA and SA·bipy cocrystals are significantly different at the 95% confidence level comparing macro versus nano preparations. Polarizability values for the macro vs. nano preparations of SA·bpeth and SA·bpe materials, on the other hand, are not statistically different at the 95% confidence level. Large differences are indicated for Young's modulus results between the two preparations, particularly for SA and SA·bipy; whereas differences are much less for SA·bpeth and SA·bpe cocrystals. The lack of consistency in measurement difference between macro and nano preparations defies explanation on a dimensionality argument and calls into question the importance of differences in the crystal packing or presence of impurities within these preparations.

Comparison of polarizability values for SA·bipy and SA·bpeth might reflect the impact of extending the size of the linker between the pyridine rings. An increase in flexibility would be expected for the extra methylene group in the bpeth linkage, which could reasonably be associated with higher polarizability.¹²⁹ The double bond within the bpe linker of the SA-bpe cocrystals enhances electron delocalization within the CCF molecule which can be responsible for higher polarizability.



Figure 7-10. Dielectric spectra of macro and nano dimensional SA-cocrystalline materials.



Figure 7-11. Polarizability of macro and nano dimensional SA-cocrystalline materials.

	Macro		Nano	
Sample	Polarizability (Å ³)	YM (MPa)	Polarizability (Å ³)	YM (MPa)
SA single crystal	23.3 ± 0.1	1100 ± 300 (-1-10) 1000 ± 300 (110)	17.86 ± 0.05	375 ± 80
SA·bipy	66 ± 1	$1300 \pm 600 (100)$ $1400 \pm 600 (-100)$	59.4 ± 0.2	450 ± 150
SA·bpeth	81 ± 1	450 ± 200 (001) 410 ± 75 (00-1)	79 ± 1	350 ± 200
SA·bpe	86.8 ± 0.5	$230 \pm 50 (00-1)$ $225 \pm 50 (001)$	86.7 ± 0.3	200 ± 100

Table 7-1. Polarizability and Young's modulus for macro and nano dimensional SAcocrystalline materials. Standard deviation represents the sample standard deviation.

7.4 Conclusion

Crystals of SA and cocrystals of SA coupled with a series of CCF's (bipy, bpeth, and pbe) are examined in terms of Young's modulus and polarizability, where the polarizability measurement is performed over THz frequencies with noninvasive THz-TDS. Polarizability is significantly higher for the SA-cocrystals compared to SA crystals, which is consistent for other comparisons presented in Chapters 4 and 5. Polarizability increases in order of SA < SA·bipy < SA·bpeth < SA·bpe and the opposite trend is observed for the corresponding Young's modulus values. This inverse relationship is consistent with the principal findings presented in Chapter 5 for a different set of cocrystals. A relationship between macro and nano preparation of these SA-cocrystals is not evident with confounding results for the tested cocrystals. Finally, the limited number of samples tested indicates that increases in flexibility or electron delocalization within the CCA portion of the cocrystals can increase polarizability and hardness of these materials. Results from additional cocrystal types and assessment of cocrystal purity are warranted in order to characterize these preliminary conclusions more fully.

CHAPTER 8

CONCLUSION

As described in Chapter 1, terahertz time domain spectroscopy (THz-TDS) uses a single-cycle pulse of far-IR radiation.^{1.2} It has various applications in gas phase sample analysis^{3,4} as well as biomedical imaging.^{1,5} Apart from that, it probes crystalline vibrations of solid phase molecules.^{6,7} The coherent nature of THz radiation makes it well-suited for dielectric measurements using a free-space geometry,, which is another advantage of this technique.⁶⁴ When THz radiation propagates through a sample, the phase of the transmitted radiation changes according to the refractive index of the material.⁶⁵ As a result, the time-domain spectrum provided by THz-TDS provides a direct measure of the refractive index of a material. At THz frequencies, the dielectric constant is simply the square of the refractive index, thereby providing a straight forward measurement of the dielectric constant for materials. Thus, THz spectroscopy is capable of providing real time information which can be valuable for measurements in pharmaceutical, semiconducting, and polymer industries.⁸

Cocrystalline materials are crystalline materials which have various applications in pharmaceutical and semiconducting industries. ^{84,87} Cocrystals are single-phase crystalline materials composed of two or more atoms, molecules or ionic compounds in a specific stoichiometric ratio and with unique properties.⁷⁷ Cocrystals are composed of cocrystal assemblies (CCA) and cocrystal formers (CCF). The characteristics of cocrystals varies with CCAs and CCFs. The anticancer drug, lenalidomine has a low oral bioactivity due to its poor solubility in water. Cocrystals of lenalidomine and urea provide enhanced

bioactivity by increasing solubility in water.⁸⁵ Likewise, the anticonvulsant drug carbamazepine has low solubility in water and cocrystals with saccharin improves solubility⁸⁶ significantly. According to the observations mentioned above, it has been found that bio-reactivity can be enhanced through the formation of cocrystals. For this reason, it is very important to study the solubility and tablet forming ability of organic cocrystalline materials. Though many research studies have been done under MHz and GHz frequencies,¹²² very few studies have been done at THz frequencies. As described in Chapter 1, it is important to characterize material characteristics over THz frequencies due to an increase in applications for materials over this frequency range.⁶⁵

Single crystal single crystal (SCSC) reactions are a special case of a chemical reactions taking place within a crystal where the crystallinity of the substrate is retained during and after the reaction. Such reactions have possible applications for data storage, semiconductors, and pharmaceutics. The kinetics of such reactions are difficult to measure owing to the unique environment of the reaction, e.g., within a single crystal. The ability of THz-TDS to probe lattice and phonon vibrations of crystalline materials in a nondestructive manner makes it well suited to examine reaction kinetics of SCSC reactions. Results presented in Chapter 2 illustrate the feasibility of this approach. The work presented here illustrate that reactants and products of a SCSC reaction can be quantified individually in a Beer-Lambert type relationship. Despite uniqueness in the THz spectral features for reactants and products, collection of THz spectra of crystals with different degrees of reaction completeness indicated the corresponding mixture spectrum was not the simple sum of the two individual spectra (reactant and product). This observation gave an interesting finding that *inter*-molecular interactions associated in reaction process

samples are different from that of the binary mixtures of reactant and product. The component of the partially reacted crystal spectrum that is different than the binary mixture of reactant and product spectra represents a unique chemical structure within the crystal during the reaction. Such information is uniquely available within THz spectra. Still, the potential of using THz spectroscopy to follow SCSC reactions is demonstrated by following features corresponding to the dielectric-loss of the material at 14 cm⁻¹.

Dielectric constant and relative permittivity represent fundamental properties of a material that can be obtained directly from the time-domain THz spectrum. Chapter 3 explores the analytical utility of measuring permittivity of small dimensional samples embedded within pellets composed of an inert polymer and air. Such a measurement configuration is attractive in that it permits measurement of these critical parameters of crystals and cocrystals that are too small to measure individually. The LLL model, developed by Landu, Lifshits and Looyenga, has been demonstrated by others for the measurement of dielectric constants of analytes in mixture samples over both megahertz and gigahertz frequencies.¹²¹ Chapter 3 details the extension of the LLL model to mixtures of solids over THz frequencies. The LLL models the dielectric property of a mixture as the sum of the dielectric constants of its chemical components according to the volume fraction of each component. The validity of the LLL model is established in Chapter 3 by comparing dielectric constants obtained from this model to values reported in the literature for a series of test compounds, including HDPE,^{65,112} PTFE,¹¹² Mg(OH)₂,¹²² SiO₂,⁶⁵ ZnO,⁶⁵ and Al₂O₃.¹²¹ Dielectric constants obtained from THz time domain spectra were comparable with literature values. Results from this work confirm that the dielectric properties over THz frequencies are lower for PTFE compared to HDPE as a result of a decrease in free

volume within the polymer structure realized by replacing hydrogens with fluorine. Finally it was found that dielectric measurements are insensitive to particle size for HDPE, consistent with minimal dielectric loss owing to flexibility of the polymer chain.

Polarizability is a measure of the tendency of charge distribution to be distorted in the presence of an external electric field. As a fundamental property of matter, polarizability represents a key parameter in the characterization of materials⁷³ as well as a diagnostic tool in material science.¹²⁴ An example is the use of polarizability to assess structural symmetry within crystalline materials where low-symmetry crystals are known to display higher polarizability owing to charge-induced dipole moments.¹²⁵ Polarizability can also be used to identify defects in high-symmetry crystalline materials,^{126,127} thereby guiding the production of nonlinear optical (NLO) materials. Polarizability over THz frequencies provides a measure of inter-molecular interactions within materials.¹²⁸ Such measurements have been shown to be valuable in the study of liquid crystals and their applications in the electronics industry.¹²⁹ Dissolution kinetics of pharmaceutical crystals are also related to intermolecular properties that can be probed by polarizability measurements at THz frequencies.¹³⁰

Polarizability is a new direction in the use of THz-TDS to characterize organic crystals and cocrystals.¹³² In Chapter 4, the Clausius-Mossotti relationship is used to determine polarizability from the dielectric properties of organic crystals and cocrystals. Specifically, polarizability is measured for a series of CCAs, CCFs, and cocrystals over THz frequencies. The average polarizability was calculated for each crystalline sample over the 10-20 cm⁻¹ THz range. A comparison is made between the measured polarizability and that calculated as the sum of atomic polarizabilities for each crystal assembly. Results

show a strong correlation between the measured and calculated polarizability with r^2 value of 0.95. Deviations between the measured and calculated values are noted and thought to contain information related to molecular and intermolecular interactions. Values used for the atomic polarizabilities correspond to gas-phase measurements, the principal component of the THz polarizability measurements does not include either *intra* or *inter* molecular interactions. Other than that, difference between the measured and calculated values might represent secondary effects associated with *intra* or *inter*-molecular interactions associated with crystal structures which were not considered in the calculations. Sensitivity to polymorphs and hydration are yet to be determined.

Crystal engineering helps to develop materials with different properties according to the applications¹³³ in pharmaceutics,^{78,99,135} electronics,¹³⁶ explosives,¹³⁷ sensors,¹³⁸ and other advanced technologies.¹³² The properties of crystals such as chemical and mechanical, depends on both chemical composition and molecular structure.¹³⁴ Few studies demonstrate a correlation between polarizability and stiffness for various materials, including metals, oxides, covalent crystals and polymers. In these reports, polarizability is inversely related to Young's modulus, or hardness, of the tested materials.¹³²

The chemical relationship between polarizability and hardness or stiffness of cocrystals is explored in Chapter 5. Measurement of THz polarizability, as described in Chapter 4, are compared to measurements of cocrystal hardness as Young's modulus by the methods of nano-indentation atomic force microscopy (AFM).⁸² Results for a series of macro- and nano-dimensional diX-res·bpe (X=H, Cl, Br, I) cocrystal samples illustrates an inverse relationship between material hardness (YM) and polarizability for this set of cocrystal supramolecular assemblies. Within these findings, it is shown that the measured

THz polarizability increases with the atomic radius (H < Cl < Br < I) of the substituents in the 4,6 positions of the resorcinol ring. This finding is consistent with an increase in atomic polarizability of these substituents and the ease of electron cloud distortions in the presence of the applied electric field vector of the electromagnetic radiation. The opposite trend is observed in terms of hardness of these cocrystals. It is noteworthy that the measured THz polarizability for these cocrystals is less than the sum of the atomic polarizabilities. As noted above, such differences might reflect *inter*-molecular or *inter*-assembly interactions. The potential to examine inter-molecular or inter-assembly interactions represents an exciting advance for material science.

Nano-dimensional crystalline materials can be obtained by different preparation methods, including grinding, sonocrystallization, and sonofragmentation. The popularity of these methods is based on narrow size distributions, reproducible crystallizations, low impurities, and control over polymorphism.^{144,145} Published accounts indicate that the method used to prepare nano-materials can impact the physical and chemical properties of these crystals. In other reports, no effect of preparation method has been found. An example is the preparation of inorganic crystals of Ni or Zn. In this study, two different methods were compared; one a chemical polyol process and the other a sonocrystallization method.¹⁴⁸ The preparation method had no effect on the magnetic properties of these materials. Sonocrystallization is a common method used to generate nano-size crystals based on the impact of growth and collapse of acoustic cavities.^{141,149}.^{141,149,150} This research study mainly focused on the chemical and mechanical changes of cocrystals materials from different preparation methods, including sonocrystallization.

Three methods are compared for the synthesis of crystals of acetylsalicylic acid and four methods are compared for the synthesis of cocrystals of di-Cl-res·bpe. Differences in the physical and chemical properties of crystals prepared by these methods were determined. Results reveal no differences in either the hardness or polarizability for acetylsalicylic acid nano-crystals prepared by sonocrystallization, sonofragmentation, and mechanical grinding. For di-Cl-res·bpe nano-cocrystals, no statistical difference was found in the measurement Young's moduli across the different preparation methods. According to these observations it is confirmed that the physical properties such as Young's modulus is independent of the preparation method. A significant difference has been observed for polarizability values measured for di-Cl-res·bpe nano-cocrystals produced by sonofragmentation, mechanical grinding and mechanochemistry. Impurities trapped in crystals could be responsible for such differences.

Changes in the mechanical and chemical properties of cocrystals with different CCFs and CCAs were examined. Findings illustrate that polarizability increases with the formation of cocrystals while material hardness decreases. Moreover, polarizability increases with the number of bonds between the two pyridyl groups. As the number of bonds increases the flexibility enhances electron mobility resulting an increase in polarizability and decrease in Young's modulus. Lastly, results show that π -electron delocalization increase the polarizability while decreasing hardness of the crystals. According to all observations it was confirmed that polarizability and material hardness are inversely related.

Combined, the research reported in this dissertation illustrates the power of THz-TDS for characterizing cocrystal materials. This new analytical tool can provide fundamental material properties in a rapid and nondestructive manner.

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