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PROBING ELECTRICAL AND MECHANICAL PROPERTIES OF NANOSCALE MATERIALS USING ATOMIC FORCE MICROSCOPY

by

R-A-Thilini Perera Rupasinghe

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

December 2015

Thesis Supervisor: Associate Professor Alexei V. Tivanski

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Graduate College The University of Iowa Iowa City, Iowa

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 December 2015 graduation.

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To, Lahiru, for your constant encouragement and support during this journey

&

To, my motherland Sri Lanka, the place which I truly belong to...

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ABSTRACT

Studying physical properties of nanoscale materials has gained a significant attention owing to their applications in the fields such as electronics, medicine, pharmaceutical industry, and materials science. However, owing to size constraints, number of techniques that measures physical properties of materials at nanoscale with a high accuracy and sensitivity is limited. In this context, development of atomic force microscopy (AFM) based techniques to measure physical properties of nanomaterials has led to significant advancements across the disciplines including chemistry, engineering, biology, material science and physics. AFM has recently been utilized in the quantification of physical-chemical properties such as electrical, mechanical, magnetic, electrochemical, binding interaction and morphology, which are enormously important in establishing structure-property relationship.

The overarching objective of the investigations discussed here is to gain quantitative insights into the factors that control electrical and mechanical properties of nano-dimensional organic materials and thereby, potentially, establishing reliable structure-property relationships particularly for organic molecular solids which has not been explored enough. Such understanding is important in developing novel materials with controllable properties for molecular level device fabrication, material science applications and pharmaceutical materials with desirable mechanical stability. First, we have studied electrical properties of novel silver based organic complex in which, the directionality of coordination bonding in the context of crystal engineering has been used to achieve materials with structurally and electrically favorable arrangement of molecules for an enhanced electrical conductivity. This system have exhibited an exceptionally high conductivity compared to other silver based organic complexes available in literature. Further, an enhancement in conductivity was also observed herein, upon photodimerization and the development of such materials are important in nanoelectronics.

Next, mechanical properties of a wide variety of nanocrystals is discussed here. In particular. an inverse correlation between the Young's modulus and atomic/molecular polarizability has been demonstrated for members of a series of macro- and nano-dimensional organic cocrystals composed of either resorcinol (res) or 4,6-di-X-res (X = Cl, Br, I) (as the template) and *trans*-1,2-bis(4-pyridyl)ethylene (4,4'-bpe) where cocrystals with highly-polarizable atoms result in softer solids. Moreover, similar correlation has been observed with a series of salicylic acid based cocrystals wherein, the cocrystal former was systematically modified. In order to understand the effect of preparation method towards the mechanical properties of nanocrystalline materials, herein we have studied mechanical properties of single component and two component nanocrystals. Similar mechanical properties have been observed with crystals despite their preparation methods. Furthermore, size dependent mechanical properties of active pharmaceutical ingredient, aspirin, has also been studied here. According to results reduction in size (from millimetre to nanometer) results in crystals that are approximately four fold softer.

Overall, work discussed here highlights the versatility of AFM as a reliable technique in the electrical, mechanical, and dimensional characterization of nanoscale materials with a high precision and thereby, gaining further understanding on factors that controls these processes at nanoscale.

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PUBLIC ABSTRACT

Nanoscale materials are on the order of one billionth of a meter in size and have attracted a significant attention over last few decades. These materials are vastly used in applications in the fields of electronics, medicine, material science, consumer products, pharmaceuticals, owing to their unique properties as a consequence of smaller size. It has been found that nanoscale materials exhibit properties that differ from their bulk counterpart. Hence, it is important to study their properties such as electrical, mechanical, magnetic and thermal properties to gain an understanding on their behaviour.

However, owing to size limitations, traditional testing methods used in the characterization of bulk materials cannot be used in the nanoscale. In this context, atomic force microscopy (AFM) is a versatile technique that can be used to study electrical, mechanical, dimensional and magnetic properties of nanomaterials. AFM has the ability to image even single atoms with a high resolution and a high accuracy. Therefore, today it is widely used in the characterization of nanomaterials. Research described herein, involve electrical and mechanical characterization of organic nanoscale materials including semiconductors, pharmaceutical materials, cocrystals etc to develop new relationships between the structure and properties. It is important in developing materials with predictable properties.

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CHAPTER 1

INTRODUCTION

1.1 Atomic Force Microscopy (AFM)

Atomic Force Microscopy (AFM) is a versatile technique used in the characterization of a broad spectrum of materials such as semiconductors, nanocrystals, biological materials, pharmaceuticals, polymers etc.¹⁻⁵ AFM uniquely offers unprecedented spatial resolution imaging owing to its high force sensing capability and nanometer scale position accuracy. ^{6,7} Thus, AFM has gained a great interest across the disciplines having applications in chemistry, physics, material science, engineering and biology.⁶ Recently, it has been utilized in the direct quantification of various properties of material such as electrical,² mechanical,^{3,8} dimensional, magnetic,^{9,10} electrochemical,¹¹ surface tension,¹² protein folding¹³ and binding interactions.^{7,14}

AFM was first invented in 1986 by Gerd Binnig, Calvin Quate and Christoph Gerber to overcome the limitations of its ancestor, scanning tunnelling microscopy (STM).^{5,7,15} STM utilizes a sharp metal tip which is raster scanned over the surface to obtain an image and has the ability to reach atomic level resolution. Hence, it led to a great encroachment in science over the other microscopic techniques such as light or electron microscopy.¹⁶ Even though STM was a versatile tool, it suffered from limitations where atomic level resolution could only be attained with conducting samples under vacuum and controlled conditions.¹⁶ Further, STM was not capable of

monitoring the force experienced by the samples. Hence, to overcome these limitations, AFM, which has the capability to achieve atomic level resolution even with nonconductive samples was developed.¹⁵ AFM can be operated under ambient conditions in air and liquid medium while measuring forces with a pN sensitivity.⁵⁻⁷ AFM also has the advantage where a wide variety of samples including soft materials such as cells and flexible polymers, hard materials such as ceramics or metal particles, conductive or nonconductive material can be imaged.⁵ Further, in recent years, AFM has been utilized to obtain images of even single atoms or molecules within a chemical structure.^{17,18} Apart from its use as an ingenious imaging tool, AFM has different spectroscopic modes which measures electrical, mechanical and magnetic properties of materials at nanoscale.

1.2 Basics of AFM

Fundamentally AFM is used to examine surface morphology of materials as well as to measure interaction forces between the tip and a sample. This is done by scanning a very sharp probe over a sample surface. AFM is different compared to other imaging techniques as AFM physically interacts with the sample with this sharp probe while imaging.

AFM consists of a sharp probe (~nm dimension) attached to a cantilever which is positioned over the sample, laser, detector and feedback electronics, photodiode, and a piezoelectric scanner as shown in Figure 1.1. The force between the probe and the sample is measured with a force sensor and the output of the force sensor is then sent to the feedback controller which drives the piezoelectric scanner.



Figure 1.1: Schematic representation of the main components of an atomic force microscope

Generally, a fixed distance or a fixed force between the probe and the sample is maintained by the feedback controller by moving the piezoelectric scanner in z direction, depending upon the interaction force between the probe and the surface.⁵ Additionally, there is a laser beam (Figure 1.1) which is focused on the back of the cantilever which reflects off its surface onto the position sensitive photodiode (PSPD). Depending on the interaction between the probe and the surface, the deflection of the cantilever changes and that is measured by the PSPD. Changes in the deflection is then converted into force by Hooke's law, allowing the quantification of forces in pico newton (pN) resolution.

Basically, AFM has two most common operating modes; namely contact mode and the intermittent mode (or tapping mode or Ac mode). Each mode is used for different applications and has its own advantages and disadvantages. In contact mode, the AFM probe is in continuous contact with the sample while in tapping mode, the probe comes into contact with the surface at pre-defined time intervals. In particular, when contact mode is used, the cantilever is moved along the surface while maintaining a constant force, or cantilever deflection. The cantilever is displaced in the z-direction using the piezoelectric device to maintain a constant force while lineby-line topographic images are collected. However, contact mode imaging exerts high local pressures and stresses, which can damage samples. Therefore, it is recommended for hard samples such as nanocrystals, ceramics, metals etc.⁵ On the other hand, in tapping mode, the cantilever is excited into oscillations near its resonant frequency. The instrument then maintains constant oscillation amplitudes and taps along the surface at given time intervals. Any height variation on the sample is detected by the displacement in the z dimension. Generally, tapping mode is suitable for soft materials such as biological cells and flexible films as it causes less damage to sample upon imaging compared to the contact mode.⁵

A typical force-displacement curve, which measures the interaction force between the tip and the sample as a function of vertical displacements (displacement in the z-direction) is shown in Figure 1.2. Initially the tip is far away from the surface (1) and no interaction force is experienced by the tip. Then tip starts to move towards the surface and comes into contact with the surface at point 2. Tip moves towards the sample until a pre-defined force is achieved, 10 nN in this case (3). Then the process is repeated in the reverse direction where the tip moves away from the surface. The interaction force between the tip and sample is shown in step 4. At point 5, tip overcomes the force which holds it at the surface and the tip breaks away from the surface, retracting back to its initial position 1. This process enables force spectroscopy and allows the direct quantification of interaction strength between the probe and the sample.⁵ In addition, force-displacement curves are used in the mechanical characterization of materials where the Young's modulus is extracted from force-displacement curves.³

Overall, AFM visualizes and measures nanoscale features of materials with an unprecedented accuracy and spatial sensitivity. Furthermore, it has many other unique characteristics such as precise motion control, excellent fabrication technology and built-in atomic scale sensitivity.⁵



Figure 1.2 : Representative force-displacement curve used in force spectroscopy showing AFM probe moving towards (red) and away (blue) from surface. 1-6 demonstrates typical steps in a force-displacement curve

1.3 Electrical Characterization of Materials using AFM

One of the unique applications of AFM is its ability to measure electrical properties of nanoscale materials with high accuracy. Due to size constraints, traditional methods in measuring electrical properties of materials cannot be applied in the nanoscale. In this context, AFM based electrical characterization is of enormous importance as it has the capability to visualize different features of nanomaterials while measuring electrical properties.

Specific technique which measures electrical properties using AFM is, conductive probe AFM (CP-AFM). Recently, this has extensively been used in the electrical characterization of nanowires¹⁹, thin films or monolayers²⁰, nanocrystals², graphene sheets²¹ etc. CP-AFM has the unique ability to measure force, current, and bias, simultaneously and independently and it allows the direct quantification of electrical properties.

Briefly, in CP-AFM, a sharp conductive probe is used to electrically connect to nanostructures on a conductive substrate.²² Then a voltage is applied between two electrodes (conductive probe and the substrate) and resulting current is recorded as a function of applied voltage. Resistance of the sample is calculated using Ohm's law (from the inverse slope of current *vs* voltage plot) and converted into resistivity or conductivity. Importantly, CP-AFM has the ability to measure local electrical properties and at the same time imaging is not limited to conductive samples like with STM. ^{20,22} CP-AFM uses force feedback for the control of tip-sample separation and hence, the vertical position of the tip is decoupled from electrical measurements,

which is of enormous importance in obtaining precise vertical position of an unknown sample.²²

1.4 Mechanical Characterization of Nanomaterials using AFM

Another important application of AFM is its unique capability to measure mechanical properties of nanoscale materials. As described in section 1.3, size constraints limits the use of traditional methods in quantifying properties at the nanoscale. AFM based nanoindentation technique has been used in the mechanical characterization of nanocrystals², thin films, semiconductors², nanowires²³, polymers²⁴, biological materials²⁵, pharmaceutical crystals²⁶ etc. This technique allows direct quantification of mechanical properties of small volume materials in the form of Young's moduli with high accuracy.

Specifically, the AFM tip is used to indent a sample of interest and force *vs* displacement curves are collected while indentation takes place. Then, force *vs* displacement is converted to force *vs* tip sample separation and the Young's modulus of the sample is calculated using well-known Hertzian contact model.³ Compared to other depth sensing instruments, AFM is advantageous as it allows us to relate the morphology (obtained from high resolution imaging capability of AFM) to local mechanical properties, which is not possible with other instruments.²⁷

1.5 Significance of Electrical and Mechanical Characterization of Nanomaterials

Mechanical, dimensional, and electrical characterization of nanoscale materials is important in understanding their structure-property relationships. Establishing reliable structure-property relationship of materials is essential for the potential design of novel materials with tunable mechanical, electronic, optical, and chemical properties.²⁸ For example, in organic solids, understanding of physical and intermolecular phenomenon in the context of crystal engineering and thereby, establishing relationships between structure and electrical properties is essential in order to design novel organic solids with improved electrical properties. This type of understanding can further be tailored into molecular level device fabrication, material science applications and other applications in molecular electronics.²⁹ Further, in pharmaceutical industry, establishing reliable structure - property relationships are important in achieving active pharmaceutical ingredients (APIs) with better tabletability, improved pharmaco-kinetic properties, and higher stability.³⁰

In particular, investigating dimensional, electrical, and mechanical properties of organic molecular crystals and thereby, establishing reliable structure - property relationships has no yet been explored enough, despite their extensive applications in several fields.³¹ Hence, the scope of this dissertation examines application of AFM to investigate physical properties of different organic molecular solids, primarily focusing on their electrical and mechanical properties. Through these studies, we hope to gain a better insight into the behaviour of materials in the nanoscale and thereby, understand the factors that controls properties at nanoscale for the potential design of materials with tunable properties.

CHAPTER 2

NANOCRYSTLS OF A METAL-ORGANIC COMPLEX EXHIBIT REMARKABLY HIGH CONDUCTIVITY THAT INCREASES IN A SINGLE-CRYSTAL-TO-SINGLE-CRYSTAL TRANSFORMATION¹

2.1 Introduction

Crystal engineering is under increasing development³² with emerging applications in areas such as reactivity,³³ porosity,³⁴ and magnetism.³⁵ In this context, the design of organic semiconductor materials using principles of crystal engineering remains in early stages.³⁶ Applications of functional organic semiconductors include flexible electronics, smart cards, and solar panels among others.³⁷ A current challenge in the field lies in achieving face-to-face π -stacking of candidate semiconductor molecules. Crystal engineering offers an opportunity to design semiconductor materials with structurally- and electrically-favorable arrangements of molecules.³⁸ The relevance of extending concepts of crystal engineering to nanoscale electronics is also particularly important since electronic materials of nanoscale dimensions are promising to fabricate solar cells³⁹ and optoelectronic devices.⁴⁰ Furthermore, nanocrystalline materials can uniquely offer long-range order, well-defined molecular packing, and fewer structural defects, making them desirable for studies to understand intrinsic electronic behavior.^{41,42}

¹ Adapted from *Nanocrystals of Metal-Organic Complex Exhibit Remarkably High Conductivity that Increases in a Single-Crystal-to-Single-Crystal Transformation*, Hutchins, K.M.; Rupasinghe, T.P.; Ditzler, L.R., *etal. Journal of the American Chemical Society* **2014**, *136 (19)*, 6778-6781. Copyright (2014) American Chemical Society.

Whereas purely organic π -rich molecules (e.g. pentacene) have been pursued as building blocks of semiconductor materials, the integration of metal atoms into such materials with favorable electrical conductivity is at a nascent stage.^{38,43} The directionality of coordination bonds supported by transition-metal-ions can be exploited to achieve face-to-face stacking⁴⁴ that leads to favorable enhancement of conductivity.^{45,46} In this context, a transition metal-organic complex of a relatively high conductivity is [Ag₂(ophen)₂] (where: ophen = [1,10]phenanthrolin-2-one). The solid consists of chelated Ag(I) ions that stack face-to-face and afford a solid with a conductivity of 14 S·cm⁻¹.³⁸

A major tenet of crystal engineering is that supramolecular synthons provide reliable means to achieve and tune properties of molecular solids. For solids based on Ag(I) ions, both the Ag···Ag interaction and Ag-N(pyridyl) bond⁴⁷ are ubiquitous in the crystal engineering of metal-organic complexes and materials, yet have remained unexplored to control properties of semiconductor materials. The synthons have, however, been employed to enforce π -stacking of olefins that undergo single-crystalto-single-crystal (SCSC) [2+2] photodimerizations, which suggests an opportunity to develop crystalline materials that exhibit both enhanced conductivity and reactivity.^{48,49} Such solids would be attractive as components for photo activated molecular switches,⁵⁰ 3D data storage media,⁵¹ and nanoscale photomechanical actuators.^{52,53}

Here, we report the Ag-based metal-organic solid $[Ag_2(4-stilbz)4][CF_3SO_3]_2$ (1) (where: 4-stilbz = trans-1-(4-pyridyl)-2-(phenyl)ethylene) that exhibits remarkably high electrical conductivity of 20.8 ± 1.3 S·cm⁻¹. The solid is sustained by

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Ag····N(pyridine) bonds that organize 4-stilbz into a face-to-face π -stacked geometry. The olefin undergoes a SCSC [2+2] photodimerization to give [Ag₂(4-pyr-ph $cb)2[CF_3SO_3]_2$ (2) 4-pyr-ph-cb rctt-1,2-bis(4-pyridyl)-3,4-(where: =bis(phenyl)cyclobutane) (Figure 2.1) that results in over a 40% increase in electrical conductivity to 37.0 ± 4.1 S·cm⁻¹ as determined by conductive probe atomic force microscopy (CP-AFM). The SCSC reaction generates a 1D coordination polymer that is accompanied by the formation of Ag...C(phenyl) forces and a blue shift in fluorescence. Density of states (DOS) calculations support the origin of increase in conductivity to be ascribed to increased contribution of the Ag(I) metal ions at the top edge of the valence band in 2 relative to 1. To our knowledge, an increase in conductivity of a solid that results from a [2+2] photodimerization has not been reported. We also demonstrate comparable effects in isostructural [Ag2(4stilbz)₄][CO₂CF₃]₂ that SCSC photoproduct 3 generates [Ag₂(4-pyr-phcb)₂][CO₂CF₃]₂ **4**.⁵⁴ Further, efforts were utilized to prepare thin films of solid **1**, which was challenging but tremendously important in the context of possible applications in electronics and device fabrication.



Figure 2.1: Silver coordination compound of interest, [Ag₂(4-stilbz)4][CF₃SO₃]₂ photoreacts to yield [Ag₂(4-pyr-ph-cb)2][CF₃SO₃]₂ via a SCSC transformation. (Anions omitted for clarity)

2.2 Experimental

2.2.1 Synthesis of Silver Coordination Complexes

First, 4-stilbz (= trans-1-(4-pyridyl)-2-(phenyl)ethylene) was prepared as follows. A round bottom flask was charged with bromobenzene (10 g, 0.063 mol), 4vinylpyridine (6.695 g, 0.063 mol), PdCl2(PPh3)2 (1.26 g, 2.8 mol %), and potassium carbonate (12.5 g, 0.09 mol) in 100 mL DMF. The solution was refluxed overnight. The solution was cooled and poured over \approx 500 mL of ice. The precipitate was filtered and purified via sublimation to afford white crystals 5.78 g (50.1 %).

Complex [Ag₂(4-stilbz)₄][CF₃SO₃]₂ was prepared by dissolving 30 mg of 4stilbz and 21.45 mg of AgCF₃SO₃ (Sigma Aldrich) separately in minimal ethanol. The compounds were simultaneously injected into 200 mL of hexanes and exposed to ultrasonic irradiation for two minutes.^{55,56} The solid was filtered and coordination complex formation was confirmed *via* powder X-ray diffraction. For the photoreacted sample, **2**, powdered sample of complex [Ag₂(4-stilbz)₄][CF₃SO₃]₂ was exposed to broadband UV irradiation using a medium pressure Hg lamp for 30 hours. ¹H NMR data was collected to ensure complete photodimerization.⁵⁴

Complex $[Ag_2(4-stilbz)_4][CO_2CF_3]_2$ was prepared by dissolving 25 mg of 4stilbz and 15.2 mg of AgCO_2CF_3 (Sigma Aldrich) in minimal ethanol. The compounds were simultaneously injected into 200 mL of hexanes and exposed to ultrasonic irradiation for two minutes.⁵⁴ The solid was filtered and coordination complex formation was confirmed *via* powder X-ray diffraction. For photoreacted sample, **4**, the powdered sample of complex $[Ag_2(4-stilbz)_4][CO_2CF_3]_2$ was exposed to broadband UV irradiation using a medium pressure Hg lamp for 20 hours. ¹H NMR data was collected to ensure complete photodimerization.

2.2.2 Substrate Preparation

The sample substrates were formed by thermally depositing Au on mica (V-I grade, SPI Supplies, Westchester, PA) substrates. Au modified mica substrates were fixed to a glass slide using epoxy (Epotek 377, Epoxy Technology, Billerica, MA). Crystals were then suspended in hexanes using 1 milligram of crystals per 0.5 millilitre of hexanes and sonicated for 30 seconds to evenly disperse the material. The crystal suspension was then added to the Au substrate drop wise. Samples were air dried for 20 minutes until the solvent was evaporated and immediately used for measurements using conductive probe atomic force microscopy. In nanoindentation experiments, samples were prepared under the same conditions and crystals were deposited on mica substrates.

2.2.3 Conductive Probe AFM Measurements (CP AFM)

Topographic height imaging and *I-V* measurements were performed using a commercially available atomic force microscope (MFP 3D, Asylum Research, Santa Barbara, CA) with a conducting probe module (ORCA, Asylum Research, Santa Barbara, CA). CP-AFM measurements were collected at room temperature. Samples were first imaged using AC mode imaging to determine crystal morphology. All imaging and measurements were collected using a diamond coated tip (NANOSENSORS, Switzerland) with an average radius of curvature of 150 ± 50 nm and average spring constant between 0.02 - 0.77 N/m. Actual spring constants were

determined using built-in thermal noise method. Crystal showing average morphology with heights between 30 and 200 nm were used for *I-V* measurements. All *I-V* measurements were performed in air. For these experiments force was held constant for all measurements at 50 nN. This force was found to be sufficient for a stable contact to obtain reproducible electrical measurements. The bias was swept over various ranges, depending on the crystal thickness. For a thinner crystal a smaller bias range must be used to prevent saturation of the detector. High electrical current and bias can lead to sample deformations, therefore all crystal were imaged after measurements. Only crystals showing no sample deformation and morphology matching the initial image were used for the data analysis. Electrical measurements were performed on 11 different crystals of **1**, 13 crystals of **2**, 12 crystals of **3** and 11 crystals of **4** using 3 different AFM tips for each sample.

2.2.4 Nanoindentation Measurements

AFM nanoindentation measurements were collected at room temperature using silicon probes (Mikromasch, San Jose, CA, CSC37) with a nominal spring constant of 0.35 N/m and a typical tip radius of curvature of 10 nm. Actual spring constants were determined using built-in thermal noise method. Topographic images were collected using intermittent contact mode both before and after indentation experiments to compare crystal morphology. Force-displacement curves were recorded in an organic solvent, n- tetradecane (Sigma), which served to minimize capillary adhesion between the probe and the surface. In a single force-displacement curve the AFM probe approaches the crystal and contacts the crystal face applying 10 nN, and subsequently, retracts from the surface recording the force as a function of vertical displacement
from the sample. The applied force of 10 nN gave reproducible results without damaging the crystal surface.⁵⁷ A total of 10 sample locations were collected per crystal recording 10 measurements per location to insure reproducibility. Similar measurements on the substrate were performed to calibrate the deflection sensitivity of the AFM instrument to convert the force-displacement curve to force versus tip-sample separation plot. In these experiments, ~30 different crystals and 2 tips were used for each crystal sample. All force-displacement plots used showed no deviation between the approach and the retract data; the indentation can then be assumed purely elastic.⁵⁸

2.3 Results and discussion

2.3.1. Initial Conductivity Measurements of Millimeter-sized Crystals and Pellets

Initial experiments were performed on millimeter-sized plate-shaped single crystals of **1**, grown *via* slow evaporation, using a two-point probe technique able to measure resistances of *ca* 2000 k Ω .³⁸ In a typical experiment, two contacts were made on opposite sides of a crystal. All attempts to measure current, however, resulted in no measureable response, with the crystals repeatedly cleaving. We ascribe the inability to detect current to the crystals being extremely fragile, which likely results in an accumulation of cleavage planes that disrupt and shear the 1D stacked arrays.⁵⁴ We also performed conductivity measurements on pressed pellets of **1** using the same two-point probe method as above, but were unable to observe a measureable response.

2.3.2 Structure and Characterization of Silver Coordination Compounds

Owing to the cleavage of millimeter-sized single crystals during two point probe approach, we next extended our study to measure electrical properties of nanocrystals of silver coordination compounds *via* CP-AFM. To form nanocrystals of **1**, we employed sonochemistry. That sonochemistry affords crystals of nanoscale dimensions has been realized in inorganic-based solids⁵⁹ and organic co-crystals.⁵⁶ Crystal data for [Ag₂(4-pyr-ph-cb)₂][CF₃SO₃]₂: crystal size 0.36 x 0.11 x 0.05 mm³, monoclinic, space group C2, a = 21.768(4) Å, b = 13.498(3) Å, c = 17.570(4) Å, $\alpha,\gamma =$ 90°, $\beta = 98.24(3)$ °, V = 5109.2(2) Å³, MoK α radiation ($\lambda = 0.7107$ Å) for Z = 4 and R = 0.1291 for I >2 σ (I).

The components of **1** are sustained by a combination of argentophilic forces $(Ag(1)\cdots Ag(1) \text{ distance: } 3.50 \text{ Å})$ and Ag-N(pyridine) bonds (N(1) 2.153(5), N(2) 2.144(5) Å) (Figure 2.2). The carbon-carbon double (C=C) bonds lie criss-crossed and separated by 3.90 Å. With exception to the nature of the coordinating anions (Ag(1)-O(1) 2.63(7) Å), metrics related to the packing of 1 are virtually identical to 3 (including disorder of the anion).⁵⁴ The isostructural packing is defined by 1D quadruple face-to-face π -stacked arrays. The olefin of **1**, in contrast to **3**, however, lacks disorder. The anions lie orthogonal to the olefins, with the -CF₃ group pointing away from the metal and in a plane parallel to the pyridyl moieties.

The geometry of the stacked olefins of **1** is suitable for a solid-state [2+2] photodimerization.⁶⁰ Single crystals and powdered crystalline samples of **1** were, thus, exposed to broadband UV irradiation for a period of 30 h.⁵⁴ Visual inspection of the single crystals demonstrated the shapes, morphologies, and transparent appearance to

be retained upon exposure to the UV radiation. ¹H NMR spectroscopy revealed the disappearance of 4-stilbz and formation of 4-pyr-ph-cb stereoselectively and in 100% yield. The photodimerization likely involved pedal motion of the C=C units in the solid.^{61,62} Moreover, a single-crystal X-ray analysis confirmed the reaction of **1** to occur via a SCSC transformation to give **2**. In the solid, the resulting cyclobutane ligand lies disordered such that 4-pyr-ph-cb occupies two orientations [site occupancies: 0.538(9) and 0.462(9)] and the anion is also heavily disordered. Similar to the SCSC reaction of **3** to **4**,⁵⁴ the photoreaction was accompanied by repositioning of the Ag(I) ions (Ag···Ag 5.05 Å), rotation of the counter triflate anions, and generation of Ag···C(phenyl) forces (Ag(1)···C(50) 2.79 Å, Ag(2)···C(11) 2.75 Å) (Fig. 2) to give a 1D coordination polymer (Figure 2.3).



Figure 2.2: X-ray crystal structure of 1 showing labelling of atoms in dinuclear assembly. Selected interatomic distances (Å) and angles (°): Ag(1)-N(1): 2.153(5), Ag(1)-N(2): 2.144(5), Ag(1)-O(1): 2.63(7), C(6)...C(19): 3.80, C(6)...C(20): 3.85, C(7)...C(19): 4.09, C(7)...C(20): 4.27; O(1)-Ag(1)-N(1): 89(2), N(1)-Ag(1)-N(2): 171.9(3), O(1)-Ag(1)-N(2): 99(2). Highest occupancy shown for disordered anions



Figure 2.3: Generation of Ag...C(phenyl) forces and 1D coordination polymer upon SCSC photodimerization of 1 to 2. Highest occupancies shown for all disordered atoms

2.3.3 Mechanical Properties of Nanocrystals using AFM based Nanoindentation

The force *versus* tip-sample separation data were used to determine the Young's modulus of a crystal by fitting the nanoindentation plots to the Hertzian model, which assumes elastic contact.

$$F^{2/3} = C - \left(\frac{4\sqrt{R}}{3(1-\nu^2)}E\right)^{\frac{2}{3}}\Delta$$
 2.1

Where, *F* is the loading force, *R* is the tip radius of curvature, Δ is the tip–sample separation, *E* is the Young's modulus, *C* is a constant and v is the Poisson's ratio of the crystal. Based on the Equation 2.1, a plot of the force to the 2/3 power versus the tip-sample separation should be linear in the contact region. The Young's modulus of the sample can then be calculated from the linear slope of the $F^{2/3}$ versus Δ dependence in the contact region and using known or reported values of the tip radius of curvature and the Poisson's ratio(R= 10 nm and v = 0.3).⁵⁷ Only force displacement curves with an adhesion force less than 0.5 nN and those with overlapping approach and retract data were used in this study.

Young's modulus for **1** and **2** were found to be 505 ± 85 MPa and 305 ± 50 MPa, respectively (Figure 2.4 (a,b)). This corresponds to a 40% decrease in the stiffness following photodimerization. The Young's modulus of complexes **3** and **4** were found to be 350 ± 80 MPa and 200 ± 40 MPa, respectively (Figure 2.4 (c,d)).



Figure 2.4: Distributions of the Young's modulus values for $[Ag_2(4-stilbz)_4][CF_3SO_3]_2$ (a) and $[Ag_2(4-pyr-ph-cb)_2][CF_3SO_3]_2$ (b), $[Ag_2(4-stilbz)_4][CO_2CF_3]_2$ (c) and $[Ag_2(4-pyr-ph-cb)_2][CO_2CF_3]_2$ (d)

2.3.4 Electrical Properties of Nanocrystals

Given the fragility of the millimeter-sized crystals, we examined nanometersized crystals of **1** using CP-AFM. The technique has been used to characterize electrical properties of organic crystals and polymers.⁶³⁻⁶⁶ The method allows measurements of conductivities on multi-nanometer length scales, which are considered indicative of intrinsic conductivity of a solid.^{49,57}

Initially AFM height images of nanocrystals were collected and the AFM imaging revealed the presence of nano-sized crystals that generally ranged from 30 to 200 nm. (Figure 2.5(a)) Current-voltage (*I-V*) measurements were next collected on individual nanocrystals of **1** in air under 50 nN of force, which provided stable electrical contacts between each crystal and tip (Figure 2.5 (b)). Individual crystals were deposited on the Au substrate in a dropwise fashion from hexane suspensions. Resistances for each nanocrystal were determined using the linear Ohmic region of the *I-V* curve within \pm 0.05 V (Figure 2.5(b)). The bias range was fitted using Ohm's Law to determine resistance (*R*) and the resistivity (ρ) then obtained using Equation 2.2

$$\rho = \frac{Ra}{l}$$
 2.2

where *l* is crystal height and *a* is contact area between the probe and sample. Crystal heights were determined directly using AFM height images.⁶³ The contact area was determined using the Hertzian elastic contact model as shown below.^{57,58}

The Hertzian elastic contact model assumes a sphere of radius r indenting a perfectly elastic surface, the contact area can be determined.^{58,67} According to the model, the mechanical contact radius a between a spherical tip of radius r penetrating into a uniform elastic film may be estimated as,

$$a^2 = \left(\frac{Fr}{K}\right)^{\frac{2}{3}}$$
 2.3

where F is the loading force and K is an effective modulus equaling,

$$K = \frac{4}{3} \left[\frac{1 - v_{ip}^2}{E_{iip}} + \frac{1 - v_s^2}{E_s} \right]^{-1}$$
 2.4

and E_s , v_s , E_{Tip} , and v_{Tip} are the Young's modulus and the Poisson's ratio of the sample and the AFM tip, respectively. The Poisson ratio for most materials is between 0.25 and 0.5,^{67,58,68} and thus assuming $v_t \approx v_s \approx 0.33$, an effective modulus can be approximated as $K=1.5E_tE_s/(E_t+E_s)$. The elastic modulus of the diamond tip is 1220 GPa.⁶⁹ The E_s for similar materials was found using nanoindentation techniques.⁶⁹ With the known tip radius of curvature of 150 ± 50 nm, contact areas for [Ag₂(4stilbz)₄][CF₃SO₃]₂, [Ag₂(4-pyr-ph-cb)₂][CF₃SO₃]₂, [Ag₂(4-stilbz)₄][CO₂CF₃]₂, and [Ag₂(4-pyr-ph-cb)₂][CO₂CF₃]₂ were found to be 1450 ± 150 nm², 2025± 200 nm², 1850 ± 40 nm² and 2690 ± 120 nm², respectively.



Figure 2.5: Complex 1: (a) representative AFM height image, (b) *I-V* curve (height ~70 nm), and (c) distribution of resistivities (Gaussian fit by red line)

A Gaussian fit to distribution of resistivities (Figure 2.5(c)) yielded a mean resistivity of $(4.8 \pm 0.3)^{*10^{-2}} \Omega \cdot \text{cm}$ for **1**, which corresponds to an electrical conductivity of $20.8 \pm 1.3 \text{ S} \cdot \text{cm}^{-1}$. The conductivity is outstanding for a metal-organic solid, being significantly higher than that of $[\text{Ag}_2(\text{ophen})_2]$.³⁸,⁷⁰ We attribute the high conductivity to the face-to-face π - π interactions of the stilbazoles, which are assisted by the Ag···Ag forces.

We next examined effects of the photodimerization on the conductivity of the solid.^{71,72} The elastic modulus and electrical conductivity of photodimerized **2** were, thus, measured using CP-AFM (Figure 2.6). An AFM image revealed crystals of similar heights and morphologies to nanocrystalline **1** (Figure 2.6 (a)), while PXRD was consistent with the crystallinity of the powder being maintained after photodimerization Using the Young's modulus calculated from AFM base nanoindentation, the contact area was determined to be $2025 \pm 200 \text{ nm}^{2,32}$ which corresponds to a resistivity of $(2.7 \pm 0.3)*10^{-2} \Omega \cdot \text{cm}$ and electrical conductivity of 37.0 $\pm 4.1 \text{ S} \cdot \text{cm}^{-1}$. Hence, in the SCSC cycloaddition of **1** to **2**, the solid underwent an approximate 40% increase in conductivity.



Figure 2.6: Complex 2: (a) representative AFM height image, (b) *I-V* curve (height ~75 nm), (c) distribution of resistivities (Gaussian fit by solid red line, dashed red line shows the response of 1)

2.3.5 In-situ Conductive Probe AFM Measurements

The electrical response of an individual nanocrystal as a function of UV light exposure was also measured *in situ* using CP-AFM. The measurement revealed an average resistivity before photoreaction to be $(4.7 \pm 0.3)^{*10^{-2}} \Omega$ ·cm. Exposures to UV light were performed from the side of the AFM tip, which allowed the AFM measurements to be performed in real time during the photodimerization. Four sequential UV exposures were applied, up to a total of 135 sec, and after each exposure the nanocrystal was reimaged and the resistivity was determined (Figure 2.7 (b)). Whereas the crystal remained intact with no obvious changes in size or shape (Figure 2.7 (a)), a steady decrease in the resistivity up to 32% was observed, which is consistent with the ensemble-averaged response (40%). The *in situ* experiment unambiguously supports the ensemble-averaged determination that the nanocrystals become more conductive after photoreaction.



Figure 2.7: (a) In situ AFM measurements: AFM height image of nanocrystal before (left) and after (right) UV exposure for 135 s. (b) Decrease in averaged resistivity of nanocrystal of 2 versus UV exposure time (blue lines: ensemble-averaged responses, black dashed line provided as eye guide for visualization)

2.3.6 Understanding the Increase in Conductivity upon Photoreaction

Theoretical calculations were utilized to gain further insight into the current observation. Here in, experimentally obtained structures were treated quantum chemically to subject the current systems to Density of states (DOS) calculations using Periodic *ab initio* solid state program suite CRYSTAL'09.

According to the results of density functional theory (DTF) calculations, the increase in conductivity can be attributed to a combination of effects. A quantum chemical analysis of the crystal data of 2 to calculate density of states (DOS) revealed the highest-occupied crystalline orbital (HOCO) energies to be located close to the work function of the Au substrate, while the lowest-unoccupied crystalline orbital (LUCO) levels are at significantly higher energies (Figure 2.8). Hence, the HOCO is considered to play a dominant role in facilitating charge transport in the solid.⁷³ The calculations also reveal a 20% higher contribution from the Ag(I) ions at the top edge of the valence band of 2 compared to 1. Contributions from the coordinated olefins were also diminished upon photoreaction (Figure 2.8). Moreover, provided the conductivity proceeds via charge hopping, 74,75 the diffused orbital shell of the Ag(I) ions can be expected to have enhanced efficient charge carrier mobility in the solid. The newly-formed and strained cyclobutane rings and $Ag \cdots C(phenyl)$ forces that generate the 1D coordination polymer may also act as efficient electron donors in the photodimerized solid.^{76,77}



Figure 2.8: DOS for compounds: a) 1, b) 2, c) 3, and d) 4. 4-stilbz includes contributions from the aromatic rings, Ag is contribution from Ag(I), CH is contribution from the olefins in 1 and 3, cb is contribution from the cyclobutane ring in 2 and 4, and CF₃SO₃/CO₂CF₃ are contributions from the respective anion. Embedded tables show the percent contribution from each component at the top edge of the valence band

Moreover, we noted that there is no evidence of photoreduction of Ag(I) in the SCSC transformation. In particular, the crystals remain transparent during the photoreaction and PXRD shows no peaks from Ag. UV-Vis spectroscopy also shows no characteristic absorption band for photoreduced Ag(I) particles ^{78,79} Hence, the conductivity is considered to be intrinsic of the metal-organic solid.

Solid-state fluorescence of conductive materials is relevant to design solids as light emitting diodes and electronic displays.⁴⁹ In this context, the solid-state fluorescence of **1** revealed an emission band centered at 398 nm, which is attributed to 4-stilbz.⁸⁰ Photoreacted **2** displayed an emission band with two peaks at 360 and 396 nm.⁸¹⁻⁸³ The SCSC reaction was, thus, accompanied by a blue shift in fluorescence, which is in line with a loss of conjugation of 4-stilbz.⁸⁴

To gain added insight into the change in conductivity, nanocrystals of isostructural **3** and **4** were generated.⁵⁴ The resistivity of 3 was determined to be 0.86 $\pm 0.47 \ \Omega \cdot cm$, which corresponds to a conductivity of $1.17 \pm 0.41 \ S \cdot cm$ -1. Moreover, the resistivity of photodimerized 4 was $0.67 \pm 0.58 \ \Omega \cdot cm$, which corresponds to a conductivity of $1.50 \pm 0.84 \ S \cdot cm$ -1. Hence, as with 1 and 2, a significant increase in electrical conductivity (~30%) was realized in the SCSC reaction of **3** to **4**. The increase in conductivity was also reflected in DOS calculations, which revealed a 15% higher contribution of the Ag(I) ions to the edge of the valence band of **4**.

2.3.7 Preparation of Thin Films of Silver Coordination Complexes

Preparation of a uniform thin film relies on the development of suitable experimental conditions, including reactant concentrations, solvent system and spin coater speed and time. By trial and error, it was found that 10.0 mg of 4-stilbz and 6.1 mg of AgCO₂CF₃ in 200 μ L of acetonitrile (99 %, Fisher scientific, USA) with a spin time of 1 minute rotating at 1000 rpm yields a thin film on both glass and gold. However, initially some regions with pits were observed (Figure 2.9 (a)) and to overcome this, substrate was heated to ~70 °C, prior to spin coating. This resulted in an evenly distributed thin film and AFM height images were collected using silicon probes to see the uniformity (Figure 2.9 (b)). Thickness of the thin film was measured by making a scratch on the film followed by imaging using AFM and observed to be ~100 nm. However, no conductivity was observed with prepared thin film which can be attributed to the possible interactions between N of pyridine and Au which is unfavourable for formation of metal coordination complex on the surface.



Figure 2.9: AFM images of (a) unevenly distributed thin film and (b) evenly distributed thin film on gold after annealing

2.4 Conclusions

In conclusion, herein Ag(I) is used to form a π -stacked metal-organic solid that exhibits remarkably high electrical conductivity. The solid undergoes a single-crystalto-single-crystal [2+2] photodimerization to generate a 1D coordination polymer with over 40% higher conductivity. The Ag(I) complex represents the first example of an increase in conductivity that results from a [2+2] photodimerization. Density of states calculations show a higher contribution from Ag(I) ions to the valence band in the photodimerized solid, supporting the increase in conductivity. The observed increase in conductivity is evidenced in an isostructural solid as well. In addition to expanding the approach to additional photoactive materials, we are turning to apply concepts of crystal engineering to achieve and alter electrical properties of additional classes of metal-organic solid-state materials.

CHAPTER 3

MECHANICAL PROPERTIES OF A SERIES OF MACRO- AND NANO-DIMENSIONAL ORGANIC COCRYSTALS CORRELATE WITH POLARIZABILITY

3.1 Introduction

Studies on the mechanical properties of organic crystalline solids have gained significant attention owing to potential applications in fields such as pharmaceutics, electronics, gas storage, biophysics, explosives, and device fabrication.⁸⁵⁻⁸⁹ Mechanical property characterization is essential, for example, to achieve materials with increased tabletability in pharmaceutics and to understand structural changes (e.g., phase transitions).⁹⁰ For device fabrication, especially in flexible electronics, knowledge of mechanical properties is important to establish and optimize operational limits.⁹¹ Understandings of mechanical properties can also provide insights into relative strengths of intermolecular interactions in solids (e.g., hydrogen bonds), which can serve to link size-dependent structural properties (e.g., elasticity) that span atomic to macroscopic levels.⁹²

In this context, polarizability is a property of a chemical system that describes the tendency of charge distribution to be distorted in response to an external electric field. At the atomic level, polarizability increases as volume occupied by electrons increases, although much less is known regarding polarizabilities of molecules, assemblies of molecules, and those of corresponding bulk material solids. There is emerging evidence that polarizability can be *inversely* related to the stiffness of a material as measured by its Young's modulus.⁹³⁻⁹⁶ An inverse relationship between stiffness and atomic or molecular polarizability has been observed for metals, oxides, covalent crystals and polymers.^{9, 96-99} A linear relationship between molecular polarizability and compressibility, which is inversely proportional to Young's modulus, has also been demonstrated in halomethanes.⁹³ A linear relationship has also been noted between Young's modulus and binding energy within graphene nanoribbon materials, which was attributed to the decrease in the molecular polarazability.⁹⁴ No such relationship has been discussed in the context of organic crystalline solids. Moreover, given that elastic properties of nano-sized materials may differ considerably from larger and extended particles,³ it will be of paramount importance to determine relationships between polarizability and mechanical properties to facilitate the rational design, or crystal engineering,^{91,92} of novel multi-component solids with controllable and useful physical-chemical properties.

Herein, we present Young's modulus and polarizability measurements on a series of macro- and nano-dimensional organic cocrystals composed of either resorcinol (res) or 4,6-di-X-res (X = Cl, Br, I) and trans-1,2-bis(4-pyridyl)ethylene (4,4'-bpe) (Figure 3.1). From AFM nanoindentation measurements,^{8,100-103} we show that both macro- and nano-sized cocrystals display a decrease in Young's modulus when the size of the substituent is increased from parent res (H) to Cl to Br to I. A correlation between the Young's modulus and polarizability is demonstrated through both measurements and DFT calculations. Terahertz (THz) time domain spectroscopy (TDS) is also used to directly measure the polarizabilities of the solids and, in doing so, verify the AFM measurements.

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Figure 3.1: Schematic representation of the mechanical properties of (res)· (4,4 bpe) and (4,6-di-X-res)·(4,4'-bpe) (X = Cl, Br, I)

3.2 Experimental

Current study involves macro- and nano-dimensional cocrystals of (res)·(4,4'-bpe) **1**, (4,6-di-Cl-res)·(4,4'-bpe) **2**, (4,6-di-Br-res)·(4,4'-bpe) **3** and (4,6-di-I-res)·(4,4'-bpe) **4**.

3.2.1 Synthesis and Characterization of Macro-sized Cocrystals

Macro (millimeter)- dimensional crystals of (res)·(4,4'-bpe) and (4,6-di-X-res)·(4,4'-bpe) were grown via slow solvent evaporation.¹⁰⁴ Specifically, 4,4'-bpe (40 mg, 0.22 mmol) and the res template (0.22 mmol) were separately dissolved in EtOH (15 ml total). The solutions were combined and filtered through a cotton plug. The solution was left to evaporate over a period of 1-3 days to afford crystals suitable for single-crystal X-ray diffraction.

3.2.2 Synthesis and Characterization of Nano-sized Cocrystals

Nano- dimensional crystals of (res)·(4,4'-bpe) and (4,6-di-X-res)·(4,4'-bpe) were obtained *via* sonochemistry.¹⁰⁵ Both 4,4'-bpe (50 mg, 0.27 mmol) and the res template (0.27 mmol) were separately dissolved in minimal EtOH. The solutions were filtered through a Millex syringe filter (PVDF, 0.2 μ m, 13mm) directly into 200 mL of cold hexanes (ca. 0 °C) while exposed to low-intensity ultrasonic radiation (ultrasonic cleaning bath Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W). The resulting suspension was sonicated for 1-2 min, filtered, dried at room temperature, and analysed *via* PXRD using a Siemens D5000 X-ray diffractometer using CuKa1 radiation (λ = 1.54056 Å) (scan type: locked coupled; scan mode: continuous; step size: 0.02°; scan time: 2s/step)

3.2.3 AFM based Nanoindentation

Nano- dimensional crystalline samples were suspended in hexanes at 0.5 mg/mL and then deposited on a freshly cleaved atomically flat mica substrate (V-I grade, SPI Supplies, Westchester, PA). Millimeter-sized (macro-dimensional) crystals were also directly placed on a freshly cleaved mica substrate and measurements were conducted using a closed Fluid cell (Fluid cell lite, Asylum Research, Santa Barbara, CA). All AFM studies were conducted using a Molecular Force Probe 3D AFM (Asylum Research, Santa Barbara, CA). AFM height images and nanoindentation measurements were collected at room temperature using silicon probes (Mikromasch, San Jose, CA, CSC37) with a nominal spring constant of 0.35 N/m and a typical tip radius of curvature of 10 nm. The tip radius of curvature was verified using scanning electron microscopy and was found to be approximately 10 nm, as expected. Actual spring constants were determined using built-in thermal noise method.¹⁰⁶ Topographic images were collected using intermittent contact mode (AC mode) or contact mode at a typical scan rate of 1 Hz.

Force-displacement curves were recorded at 1 Hz in an organic solvent (olefin free n-tetradecane) that served to minimize the adhesion force between the probe and the surface. Each force-displacement curve was collected during AFM probe motion towards and away from the sample. The probe started motion toward the sample from the height of approximately 200 nm above the surface that continued until the predetermined force of 10 nN was reached. Then the motion was reversed bringing the probe to approximately the initial height above the surface.

The maximum force of 10 nN was used as no sign of mechanical damage on a crystal surface was observed under such conditions after a series of repeated forcedisplacement measurements. To ensure the reproducibility of the measurements, typically 10 to 15 repeated force measurements were collected at each crystal (15 nanocrystals of 1, 25 of 2, 18 of 3 and 13 of 4 and ~ 100 positions on each macro crystal) location. In addition, force plots were collected on the substrate approximately 100-150 nm away from the corresponding crystal position. Measurements on the substrate were used to calibrate the deflection sensitivity of the AFM instrument to convert the force-displacement curve to force *versus* tip-sample separation plot.¹⁰⁷ Overall, 10 different AFM probes were used for the nanoindentation measurements.

The force *versus* tip-sample separation data were used to estimate the Young's modulus of a crystal by fitting the nanoindentation plots to a rearranged form of the Hertzian model which assumes elastic contact.¹⁰⁷⁻¹¹⁰ Since practically all force-displacement plots showed no deviation between the approach and the retract data, the indentation can be assumed purely elastic thus facilitating the use of the Hertzian elastic model. The substrate-induced effects on the measured Young's modulus values were negligible under our experimental conditions since a typical height of a nanocrystal (ranging from 50 to 200 nm) is more than one order of magnitude larger than typical indentation depths of 3.5 nm.

3.2.4 Polarizability Measurements- Theoretical Calculations

Polarizability of each cocrystal system was computed via the RB3LYP method of Density Functional Theory (DFT) using the 6.31 G* basis set using Spartan 10 software.^{111,112} Unfortunately, these theoretical calculations were unable to incorporate a term for size of the particle thereby limiting values to qualitative findings and therefore, we extended our measurements to Terahertz time domain spectroscopy (THz-TDS) to obtain experimental polarizability values.

3.2.5 Polarizability Measurements- Terahertz (THz) time-domain Spectroscopy

THz-TDS is a rapidly-developing technique that uses electromagnetic radiation (0.3 to 4.0 THz) to provide information related to vibrations in crystalline solids, intermolecular interactions in liquids, and rotational transitions in gases.¹¹³⁻¹¹⁵ Further, the coherent nature of THz spectroscopy permits a direct measure of polarizability as related to dielectric properties. Dielectric constants were, thus, determined for **1-4** from 10 to 20 cm⁻¹. The constants were determined within 4-5 min by measuring the delay in a THz pulse transmitted across a pressed pellet composed of 5% cocrystal embedded within a matrix of polytetrafluoroethylene. Average values from measurements over several pellet preparations were used to calculate polarizability using the Clausius-Mossotti relationship.^{116,117} Given the nature of the dielectric measurements, the resulting polarizability values correspond to ensemble measurements over a population of crystals randomly oriented with respect to the optical axis of the THz pulse, thereby representing a bulk property of **1-4**.

3.3 Results and Discussion

3.3.1 Structural Details of Cocrystals

Single-crystal X-ray experiments reveal each solid to exhibit a closed hydrogen-bonded tetramer of molecules sustained by four O-H····N hydrogen bonds (O···N separations (Å): O(1)···N(1) 2.71(1), O(2)···N(2) 2.76(1) **3**; O(1)···N(1) 2.77(1), O(2)···N(2) 2.69(1) **4**) (Figure 3.2). Cocrystals **1**, **3**, and **4** are isostructural, crystallizing in the triclinic space group $P\bar{I}$, while **2** lies in the monoclinic space group $P2_1/n$.

The tetramers in each cocrystal self-assemble to form offset layers. The tetramers of **1** interact in the crystallographic (042) plane *via* face-to-face π - π forces (C···C: 3.44 Å) of the olefins (Figure 3.2 a). The layers stack offset along the *b*-axis and interact *via* C-H(pyridine)····O(res) (C···O: 3.33, 3.56 Å) and C-H(pyridine)···· π (res) forces (C···C: 3.68 Å). Tetramers of **2** interact in the crystallographic (103) plane *via* Cl···Cl forces (3.55 Å). The Cl···Cl interactions are classified as Type II ($|\theta_1-\theta_2| = 36^\circ$),¹¹⁸ which define halogen bonds between the res molecules (Figure 3.2 b). The layers also stack along the *c*-axis *via* C-H(pyridine)···· π (res) forces (C···C: 3.63 Å). For **3** and **4**, the tetramers interact in a layer *via* O···Br (3.16 Å, **3**) and O···I (3.22, **4**) forces, respectively (Figure 3.2 c,d). While the O···Br and O···I distances are shorter than the van der Waals distances, the interactions are Type I ($|\theta_1-\theta_2| 2^\circ$ (**3**) and 2^o (**4**)), which is consistent with strong effects of close packing.¹¹⁸⁻¹²⁰ The layers stack offset, interacting *via* C-H(pyridine)···· π (res) forces (C···C: 3.63 Å **4**).



Figure 3.2: X-ray structures: (a) 1, (b) 2, (c) 3, and (d) 4 highlighting layered packing of assemblies. AFM planes probed for macro-sized crystals highlighted in Red. Offset layers highlighted in gray

3.3.2 AFM Height Images of Macro-dimensional Cocrystals

AFM height images of top and bottom crystal planes of each macrodimensional cocrystals used in the study are shown in Figure 3.3. Cleavage planes were present in the faces of cocrystals **1-4**. The height variation for the cleavage planes typically ranges between 5-100 nm and likely originates from the inhomogeneous distribution of the crystal growth centers and unequal growth rates of the crystals.



Figure 3.3: Representative AFM height images of (A) (001) face and (B) (00-1) face of **1**, (C) (10-1) face and (D) (-101) face of **2**, (E) (010) face and (F) (0-10) face of **3**, (G) (010) face and (H) (0-10) face of **4**

3.3.3 AFM Height Images of Nano-dimensional Cocrystals

Morphology and the sizes of nano-dimensional cocrystals were studied using AFM 3-D height images. Cocrystals of 1-4 exhibited similar morphologies with a prism like shapes with bases ~ between 150 nm to 1 μ m and heights between 30-200 nm.



Figure 3.4: Representative AFM height images of (a) cocrystal **1**, (b) cocrystal **2**, (c) cocrystal **3**, and (d) cocrystal **4**

3.3.4 AFM Nanoindentation Analysis of Cocrystals

Characterizations of Young's moduli for both macro- and nano-dimensional samples of **1-4** were carried out using AFM nanoindentation. The macro-sized cocrystals of **1-4** exhibited prism morphologies with bases ca. 0.30×0.05 mm and heights of ca. 0.05 mm. Top and bottom crystal faces that correspond to the crystallographic (001) and (00-1) planes of **1**, (10-1) and (-101) planes of **2**, and (0-10) and (010) planes for **3** and **4** were directly probed by AFM. The planes probed for **1** correspond to the long-axis of a hydrogen-bonded tetramer within a layer, extending along the c-axis (Figure 3.2 a). The planes for **3** and **4** bisect neighbouring layers that sit along the b-axis (Figure 3.2 c,d). The nano-sized cocrystals were of bases ca. $0.8 \times 0.8 \ \mu m$ and heights of ca 50-200 nm and their measurements are expected to yield an orientation averaged response and, thus, are considered more reflective of bulk properties.³

The Young's modulus (stiffness) of macro- and nano-sized cocrystals were studied using AFM nanoindentation technique.^{107,121-124} The force versus tip-sample separation data were used to determine the Young's modulus of a cocrystal using the rearranged form of the Hertzian model,

$$F^{2/3} = C - \left(\frac{4\sqrt{R}}{3(1-v^2)}E\right)^{\frac{2}{3}}\Delta$$
 3.1

where *F* is the loading force, *R* is the tip radius of curvature, Δ is the tip–sample separation, *E* is the Young's modulus, *C* is a constant and σ is the Poisson's ratio of the

crystal. This rearranged form eliminates the necessity of knowing the exact contact position between the tip and the sample.¹²⁵ Based on the Equation 3.1, a plot of the force to the 2/3 power *versus* the tip-sample separation should be linear in the contact region. The Young's modulus of the sample can then be calculated from the linear slope of the $F^{2/3}$ versus Δ dependence in the contact region and using known or reported values of the tip radius of curvature and the Poisson's ratio. As the Hertzian model assumes purely elastic contact without adhesion interactions, force curves with the adhesion force greater than 0.5 nN were not used in the data analysis. Additionally, force plots were also not considered when variation was observed between the approach and retract data because such deviation represents inelastic effects.^{107,123} Both criteria resulted in a removal of less than 3% of the total number of individual force indentation measurements used in the analysis. Representative plots for force to the power 2/3 versus tip-sample separation for macro-dimensional cocrystals of 1-4 (top plane) are shown in Figure 3.5. As expected, a linear relationship was observed in the contact region (negative tip-sample separation region) for all samples, which confirms the applicability of the Hertzian contact model in the form of Equation 3.1. The fitted lines are shown in Figure 3.5 in solid lines with R^2 values of 0.96 for 1, 0.98 for 2, 0.97 for 3 and 0.96 for 4. The Young's modulus of each sample was calculated using the slope obtained from the linear fit. The AFM tip radius of curvature and Poisson's ratio was estimated to be 10 nm (SEM measurements) and 0.3 (typical Poisson's ratio value for organic materials), respectively.



Figure 3.5: Representative plots for force to the power of 2/3 versus tip-sample separation for macro-dimensional cocrystals of (1), (2), (3) and (4) (top plane data only). Solid lines represent the linear fits using Equation 3.1

3.3.5 Mechanical Properties of Nano- and Macro- dimensional Cocrystals

The histograms of extracted Young's modulus for nano and macro- dimensional cocrystals are shown in Figure 3.6 and summarized in Table 3.1 According to the results of macro-dimensional cocrystals, two conclusions can be drawn. First, the top faces for cocrystals **2** and **4** show 10-20% higher Young's modulus values relative to the bottom, while the Young's modulus for the top face of **1** is ~20% lower than that for the bottom. (Top planes correspond to the initial phase of crystal growth while bottom planes towards the end). The differences may reflect the presence of either hydrogen-bond-donor or -acceptor groups at the individual crystal surfaces (*i.e.* either res or 4,4'-bpe at face).^{3,126}

More importantly, the AFM measurements of the cocrystals in both dimensions show a general dependence of the Young's modulus on the nature of the res substituent. Specifically, cocrystals of 1 (H) exhibited the highest Young's modulus values, followed by 2 (Cl), 3 (Br), and 4 (I). Further, the nano-sized X-substituted cocrystals also displayed a size-dependent increase in stiffness compared to the macro-sized solids (33% for 2, 120% for 3, and 95% for 4). However, for the cocrystal 1 which has the unsubstituted resorcinol template, macro-dimensional cocrystals exhibited higher Young's modulus compared to its' nano-dimensional cocrystals.
SAMPLE	YM (MPa)	α (Å ³)
1-macro	$1600 \pm 350 (00-1)$ $1250 \pm 350 (001)$	88.5 ± 1.6
2-macro	$270 \pm 25 (10-1)$ $235 \pm 25 (-101)$	93.1 ± 0.7
3-macro	$120 \pm 15 (0-10)$ $95 \pm 10 (010)$	98.3 ± 0.6
4-macro	$54 \pm 3 (0-10)$ $40 \pm 2 (010)$	104.1 ± 1.4
1-nano	570 ± 200	87.6 ± 1.4
2-nano	370 ± 140	89.6 ± 1.0
3-nano	275± 140	97.5 ± 1.7
4-nano	160 ± 50	102.2 ± 1.3

Table 3.1 Young's modulus (YM) and polarizability (α) measurements (crystallographic plane in parentheses)



Figure 3.6: Histograms of Young's modulus for macro- (left) and nano-sized (right) **1-4** (Gaussian fits as red lines). For macro crystals, top plane data in blue bars, bottom plane in green bars

3.3.6 Relationship between the Atomic Polarizability and the Young's Modulus

A systematic decrease in Young's modulus was observed with increasing atomic polarizability from H to Cl to Br to I (H = 0.67, Cl = 2.18, Br = 3.05, I = 4.7 Å³).⁹³ The decrease in stiffness was on the order of 55% from H to Cl, 25% from Cl to Br and 42 % from Br to I in macro-dimension. The nano-sized cocrystals also displayed a similar decrease in Young's modulus with increasing atomic polarizability from H to Cl to Br to I (Figure 3.7). The decrease in stiffness was on the order of 55% from H to Cl, 25% from Cl to Br and 42 % from Br to I for nano-sized cocrystals.

This observed relationship is particularly noteworthy for isostructural **1**, **3** and **4**, where the change across the series can be directly attributed to the identity of the H and halogen atoms. In order to gain further insight into this observation, inverse Young's modulus *vs* atomic polarizability was plotted as shown in Figure 3.7 where an excellent agreement between inverse Young's modulus and atomic polarizability was observed with R^2 values (weighted linear fit) of 0.85 (macro) and 0.93 (nano).



Figure 3.7: Inverse Young's modulus vs atomic polarizability for **1-4** (weighted fit macro R²=0.85, nano R²=0.93). Top plane data has been used for the macro samples

3.3.7 The Relationship between Molecular Polarizability and the Young's Modulus

After observing above relationship between the Young's modulus and the atomic polarizability, we next turned into molecular polarizabilities. First, attempts were utilized to calculate the polarizability of cocrystal assemblies using theoretical approach where polarizability of each cocrystal system was computed via the RB3LYP method of Density Functional Theory using the 6.31 G* basis set.^{111,112} The calculated polarizability was 89.55, 94.40, 95.90 and 98.16 Å³ for **1**, **2**, **3**, and **4**, respectively. As expected, the largest polarizability was indicated for cocrystal **4** which has the largest of the three halogens (I). Unfortunately, these theoretical calculations were unable to incorporate a term for the size dependence of cocrystals thereby limiting values to qualitative findings.

Hence, we next utilized THz-TD Spectroscopy to obtain experimental polarizability values for cocrystals and these measured polarizability values are summarized in Table 3.1. Similar to theoretical polarizabilities, the largest polarizability was indicated for cocrystal **4** whereas the lowest was observed for cocrystal **1**, which is consist of unsubstituted res. In general, the measured polarizability values were comparable to benzoic acid, sucrose, and thymine as determined from THz-TDS measurements on single crystals at 10 K (Table 3.1).¹²⁷ Moreover, the polarizabilities from the THz-TDS measurements display a clear correlation (weighted fit macro R^2 =0.93, nano R^2 =0.93) with inverse Young's modulus (95% confidence limit) (Figure 3.8) Hence, the polarizabilities of the solids increase with increasing size of the res substituent, which corresponds to the decrease in stiffness consistent with the expected inverse relationship.

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While the correlation between Young's modulus and atomic polarizability in 1-4 may seem surprising given the highly anisotropic nature of organic crystals, two features of the crystal structures of 1-4 are noteworthy in relation to the mechanical data. First, the four-component assemblies of each cocrystal assemble to form layers. That the components form layers across the series is likely a consequence of the isosteric relationship between the res derivatives. Atoms with comparable volumes are considered isosteric, while molecules that differ only in substitution of isosteres at a specific position are generally expected to form similar crystal structures.¹²⁸ Even the anomalous behaviour of 2 in forming Type II halogen bonds^{118,129} is unable to circumvent a tendency of the hydrogen-bonded assemblies to form a layered structure. Moreover, the structural similarities of 1-4 allow the data from the AFM measurements to be directly compared between the solids. Second, the interactions between the four-component assembles involve numerous weak and dispersive forces,¹³⁰ with the interactions involving the halogen atoms in **2-4** being considerably weak. Indeed, the $O \cdots X$ interactions in 3 and 4, which are generally considered stronger than those of Cl···Cl forces in 2^{119} fall within the definition of a weaker Type I halogen interaction wherein organization in the solid state arises owing to strong contributions of close packing.¹¹⁸ Thus, in the absence of any particularly strong interassembly forces¹³⁰ yet with layering pervading across the series, the general increase in softness and polarizability from 1 (H) to 4 (I) can be ascribed to the atomic compositions of the res components.



Figure 3.8: Inverse Young's modulus *vs* polarizability from THz-TDS for 1-4 (weighted fit macro R^2 =0.93, nano R^2 =0.93). Mechanical data for macro-sized crystals are for top plane

Further, plots of inverse Young's modulus *versus* atomic polarizability and THz-TDS-measured polarizability are shown in Figure 3.9 utilizing Young's moduli for macro-sized crystals corresponding to bottom face (00-1) of **1** (1600 \pm 350 GPa), (-101) of **2** (235 \pm 25 GPa), (010) of **3** (95 \pm 10 GPa) and (010) of **4** (40 \pm 2 GPa). Similar to analogous data presented in the text body (Figure 3b), a clear correlation was observed with R²=0.93 for a weighted linear fit.



Figure 3.9: Plots of (**a**) inverse Young's modulus vs atomic polarizability (weighted $R^2 = 0.86$) and (**b**) inverse Young's modulus vs polarizability from THz-TDS spectroscopy for macro-sized **1-4** using bottom plane data (weighted $R^2 = 0.93$)

3.4 Conclusions

Here in, we have demonstrated that a bulk mechanical property in the form of Young's modulus for a series of organic cocrystals is correlated to atomic polarizability. The inverse relationship has been verified using THz-TDS, which establishes the analytical technique as a rapid and convenient method to obtain polarizability data related to atomic, molecular, and supramolecular structure. Given the now demonstrated relationship between chemical structure and physical properties, we expect present and future findings to establish atomic-to-bulk correlations that enable the rational design of a variety of multicomponent materials with desired mechanical and chemical properties.

CHAPTER 4

MECHANICAL PROPERTIES OF ORGANIC NANOCRYSTALLINE SOLIDS PREPARED VIA DIFFERENT SYNTHETIC METHODS

4.1 Introduction

Nanocrystalline materials have been shown to exhibit electrical,¹³¹ mechanical,¹³² thermal¹³³ and magnetic¹³³ properties that differ from their bulk counterparts.¹³⁴ As a consequence, nano-dimensional solids have been utilized in technological applications as well as basic scientific research, which aims to provide insight into the structure-property relationship at the nanoscale.¹³² In particular, organic nanocrystalline materials have attracted significant attention in recent years owing to their applications in the fields of pharmaceutics, materials science, electronics and medicine.^{2,55,135,136} Several approaches have been utilized to prepare organic nanocrystalline solids including chemical methods, sonochemical synthesis, grinding, mechanochemistry, etc.¹³⁷

Application of ultrasonic irradiation (sonochemistry) for the synthesis of organic nanocrystalline materials is a rapidly developing area of research.¹³⁸ Although its' exact mechanism of action has not yet been fully understood, it is generally considered that sonochemistry results in materials with improved properties such as narrow size distribution, morphologies etc.^{55,139} In sonocrystallization, the effect of ultrasound doesn't come from the direct interactions between ultrasound and molecules owing to the fact that the acoustic wavelengths are much larger than

molecular dimensions.^{136,137} Instead, the acoustic cavitation; the formation, growth and implosive collapse of bubbles in a liquid resulting from high intensity ultrasound, leads to the chemical effects associated with sonochemistry.^{136,137,140} This acoustic cavitation results in extreme reaction conditions such as high temperatures of ~ 5000 K, Pressures of 105 kPa and large heating and cooling rates greater than 105 K/s.139 Further, it has been demonstrated in literature that sonochemistry can dramatically affect the properties of crystalline materials such as narrow size distributions, unique particle size and morphology.^{137,141-143} The synthesis of materials with specific sizes and narrow size distributions is extremely important in materials science and the pharmaceutical industry. Specifically, the preparation of active pharmaceutical ingredients (APIs) can directly affect the bioavailability and dissolution rates.^{141,144} Furthermore, sonochemical approaches uniquely offer improved reproducibility, control of polymorphism and reduction of critical reaction conditions and long induction time in the nanocrystalline materials production processes.^{139,141,145}. Also, it allows the crystallization of materials which are normally resistant to crystallization.^{138,139} Therefore, the utilization of ultrasonic irradiation in the synthesis of nanocrystalline materials is considered to be a versatile and extensive synthetic tool.^{136,137}

Despite the enormous interest in sonochemical approaches, the fragmentation of molecular crystals under ultrasonic irradiation (sonofragmentation) to yield nanocrystalline materials remains relatively unexplored.¹³⁹ It is generally considered that the interparticle collisions are the origin of sonofragmentation. However, according to recent work by Suslick and co-workers¹⁴¹, the mechanism of crystal breakage in the case of molecular crystals is different compared to metallic systems where interaction between shockwaves and crystals are the main contributors. Further this shift has been attributed to the unique properties observed in molecular crystals. We wanted to gain further insight into this observation.

Moreover, it can be claimed that the physical properties of nanocrystalline materials can be dependent on the synthetic method.^{136,137,145} Thus, choosing the appropriate synthetic method for the preparation of nano-dimensional crystalline materials has been the key for the successful design of novel materials with preferable electronic, mechanical, chemical and thermal properties. To test this hypothesis, here we study the mechanical properties of a nanocrystalline single component system, aspirin and a multi component system (cocrystal system) to investigate whether their mechanical properties depends on the synthetic route.

In this study, we first present the mechanical properties of a single component nanocrystalline system, aspirin (1), which is a widely used active pharmaceutical ingredient (API) and the nano-sized aspirin crystals are prepared using three different methods, sonocrystallization, sonofragmentation, and grinding to determine whether the mechanical properties are dependent on the synthetic method (Figure 4.2). We further extend this study to a two component cocrystal system of (4,6-di-Cl-res)·(4,4'-bpe)¹⁴³ (2) where nano-sized cocrystals are prepared using four different preparation methods, sonocrystallization, sonofragmentation, grinding and mechanochemistry. Briefly, two of the preparation methods utilized here involve ultrasound radiation where in sonocrystallization, our system of interest is injected to an anti-solvent in the presence of ultrasound radiation while in sonofragmentation, macro-sized crystal is

subjected to ultrasound radiation to yield nanocrystals after crystal fragmentation. Next two methods involve application of mechanical energy to yield nanocrystals *via* grinding of a macro-sized crystal or grinding of initial components, i.e. mechanochemistry.

From atomic force microscopy (AFM) nanoindentation measurements, we show that the mechanical properties are independent of the synthetic route for both single component system, aspirin and two component system, $(4,6-di-Cl-res)\cdot(4,4'-bpe)$. These mechanical measurements are further supported by polarizability measurements obtained from terahertz (THz) time domain spectroscopy (TDS).



Figure 4.1: Structures of interest, (a) single component system, aspirin (1) and (b) two component system, (4,6-di-Cl-res)·(4,4'-bpe) (2)



Figure 4.2: Summary of mechanical properties of nanocrystals prepared *via* different methods

4.2. Experimental

4.2.1 Synthesis of Aspirin Nanocrystals via Three Different Methods

Acetylsalicylic acid (aspirin) was purchased from Sigma Aldrich and used without further purification. For Sonocrystallization, aspirin (200 mg, 1.1 mmol) was dissolved in minimal acetone. The solution was rapidly injected directly into 175 mL of cold hexanes while exposed to low-intensity ultrasonic radiation (ultrasonic cleaning bath Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W). The resulting suspension was sonicated for 1-2 min, filtered, dried at room temperature, and analysed via powder X-ray diffraction (PXRD). In order to prepare nanocrystals via sonofragmentation, millimeter-sized crystals of aspirin were first grown via slow solvent evaporation in a concentrated solution of acetone. These millimeter-sized crystals were placed in 5 mL of hexanes and exposed to low-intensity ultrasonic radiation (ultrasonic cleaning bath Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W) for 10 min. The resulting suspension was filtered, dried at room temperature, and analysed via PXRD. In the preparation via grinding, millimeter-sized crystals of aspirin (grown via slow solvent as mentioned above) were placed in an agate mortar and pestle and ground to a powder (approximately 20 sec of grinding). The powder was analysed via PXRD.

4.2.2 Synthesis of Cocrystals of (4,6-di-Cl-res)·(4,4'-bpe) via Different Methods

We first attempted to utilize a reprecipitation method to obtain nano-sized cocrystals of **2**. Thus, 40 mg of 4,4'-bpe and 39.3 mg of 4,6-di-Cl-res were separately dissolved in minimal EtOH. The solutions were filtered through a Millex syringe filter

directly into 200 mL of stirring hexanes. The resulting suspension was stirred for two min, filtered, and dried at room temperature. A powder X-ray diffraction (PXRD) pattern of the crystalline powder, however, did not match the simulated pattern of the cocrystal, thus, reprecipitation is unsuccessful for obtaining nanocrystalline cocrystals of **2**. A similar observation has been seen in literature for nano-sized cocrystals of (resorcinol)·(4,4'-bpe) as well, where reprecipitation fails to yield nano-sized crystals.⁵⁵

For the synthesis of cocrystals the starting materials, (4,4'-bpe) and (4,6-di-Clres) were purchased from Sigma Aldrich and used without further purification. For sonocrystallization, both 4,4'-bpe (50 mg, 0.27 mmol) and 4,6-di-Cl-res (0.27 mmol) were separately dissolved in minimal EtOH. The solutions were filtered through a Millex syringe filter (PVDF, 0.2 μ m, 13mm) directly into 200 mL of cold hexanes (ca. 0 °C) while being exposed to low-intensity ultrasonic radiation (ultrasonic cleaning bath Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W). The resulting suspension was sonicated for 1-2 min, filtered, dried at room temperature, and analysed via PXRD.

In sonofragmentation method, millimeter-sized crystals of (4,6-di-Cl-res)·(4,4'bpe) were grown *via* slow solvent evaporation in EtOH.¹⁴³ Then these millimeter-sized crystals were placed in 5 mL of hexanes and exposed to low-intensity ultrasonic radiation (ultrasonic cleaning bath Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W) for 10 min. The resulting suspension was filtered, dried at room temperature, and analysed *via* PXRD. In grinding, millimeter-sized crystals of (4,6-di-Cl-res)·(4,4'-bpe) grown *via* slow solvent evaporation were placed in an agate mortar and pestle and ground to a powder (approximately 20 sec of grinding). The powder was analysed *via* PXRD. For mechanochemical method, both 4,4'-bpe (100 mg, 0.55 mmol) and 4,6-di-Cl-res (98 mg, 0.55 mmol) were placed in an agate mortar and pestle and ground together for 45 minutes to form the co-crystalline phase. The powder was analysed *via* PXRD.

4.2.3 Characterization using Powder X-Ray Diffraction

PXRD data were obtained on a Siemens D5000 X-ray diffractometer using CuK α 1 radiation (λ = 1.54056 Å) (scan type: locked coupled; scan mode: continuous; step size: 0.02°; scan time: 2s/step). The samples were mounted on glass slides.

4.2.4 AFM based Nanoindentation

Nano- dimensional crystalline samples were suspended in hexanes at 0.5 mg/mL and then deposited on a freshly cleaved atomically flat mica substrate (V-I grade, SPI Supplies, Westchester, PA). All AFM studies were conducted using a Molecular Force Probe 3D AFM (Asylum Research, Santa Barbara, CA). AFM height images and nanoindentation measurements were collected at room temperature using silicon probes (Mikromasch, San Jose, CA, CSC37) with a nominal spring constant of 0.35 N/m and a typical tip radius of curvature of 10 nm. The tip radius of curvature was verified using scanning electron microscopy and was found to be approximately 10 nm, as expected. Actual spring constants were determined using built-in thermal noise method.¹⁰⁶ Topographic images were collected using intermittent contact mode (AC mode) or contact mode at a typical scan rate of 1 Hz.

Force-displacement curves were recorded at 1 Hz in an organic solvent (olefin free n-tetradecane) that served to minimize the adhesion force between the probe and the surface. Each force-displacement curve was collected during AFM probe motion towards and away from the sample. The probe started motion toward the sample from the height of approximately 200 nm above the surface that continued until the predetermined force of 10 nN was reached. Then the motion was reversed bringing the probe to approximately the initial height above the surface.

The maximum force of 10 nN was used as no sign of mechanical damage on a crystal surface was observed under such conditions after a series of repeated forcedisplacement measurements. To ensure the reproducibility of the measurements, typically 10 to 15 repeated force measurements were collected at each crystal location. (for aspirin, 11 crystals of sonocrystallization, 12 of sonofragmentation, and 11 of sonocrystallization, grinding and for cocrystals, 13 crystals of 11 of sonofragmentation, 12 of grinding and 15 of mechanochemistry) In addition, force plots were collected on the substrate approximately 100-150 nm away from the corresponding crystal position. Measurements on the substrate were used to calibrate the deflection sensitivity of the AFM instrument to convert the force-displacement curve to force versus tip-sample separation plot.¹⁰⁷ Overall, 5 different AFM probes were used for the nanoindentation measurements.

The force versus tip-sample separation data were used to estimate the Young's modulus of a crystal by fitting the nanoindentation plots to a rearranged form of the Hertzian model, which assumes elastic contact.¹⁰⁷⁻¹¹⁰ Since practically all force-displacement plots showed no deviation between the approach and the retract data, the

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indentation can be assumed purely elastic thus facilitating the use of the Hertzian elastic model. The substrate-induced effects on the measured Young's modulus values were negligible under our experimental conditions since a typical height of a nanocrystal (ranging from 30 to 150 nm) is more than one order of magnitude larger than typical indentation depths of 3.5 nm.

4.3 Results and Discussion

4.3.1 AFM Height Images of Aspirin Crystals and Cocrystals

Size and the morphology of crystals prepared v*ia* different methods were determined using AFM height images (Figure 4.3). Aspirin crystals prepared *via* sonocrystallization, sonofragmentation and grinding showed similar shapes with heights ranging from 25 to 200 nm and bases from 400 to 1000 nm. Moreover, cocrystals of **2** prepared *via* sonocrystallization, sonofragmentation, grinding and mechanochemistry also showed similar morphologies (Figure 4.4) Heights of cocrystals ranged from 30- 200 nm and bases of 400 to 1000 nm.

This observation results in an important conclusion about the application of ultrasound radiation for the synthesis of nanocrystallization materials, where different mechanisms of preparation has led to crystals of similar sizes and shapes in the single component as well as multi component systems. According to literature, similar morphologies and sizes have been observed with different types of crystals such as lactose¹⁴⁶, inorganic nanoparticles¹⁴⁷, despite of their preparation method.



Figure 4.3: AFM height images of crystals of **1**, prepared via three different methods (a) Sonocrystallization (b) Sonofragmentation (c) Grinding



Figure 4.4: AFM height images of cocrystals of 2, prepared via four different methods,
AFM height images of crystals of 1, prepared via three different methods
(a) Sonocrystallization
(b) Sonofragmentation
(c) Grinding
(d) Mechanochemistry

4.3.2 PXRD Patterns of Nanocrystals Prepared via Different Methods

PXRD patterns of nanocrystals of **1** and **2** are shown in Figure 4.5 and 4.6. Aspirin nanocrystals prepared *via* three methods showed similar PXRD patterns with prominent peaks around 8, 15, 23 and 27, 2 θ values. Further, these also matched well with simulated PXRD pattern and assuring the purity and the crystallinity of the prepared nanocrystals of aspirin.

Correspondingly, cocrystals of **2** prepared via four different methods showed similar PXRD patterns with prominent peaks around 20, 25 and 30, 20 values. Also, these patterns matched with the simulated PXRD pattern as well and hence, can be concluded that they are similar in structure.



Figure 4.5: Comparison of PXRD patterns of aspirin nanocrystals prepared *via* three different methods



Figure 4.6: Comparison of PXRD patterns of nanococrystals of **2** prepared *via* four different methods

4.3.3 Calculation of Crystal Sizes using PXRD

The size of the nanocrystals from the bulk powder was calculated using the broadening in the PXRD peaks. The Scherrer Equation (4.1) was used for the calculation:

$$L = \frac{\kappa \lambda}{\beta \cos \theta} \tag{4.1}$$

where L is the mean size of the crystallites, K is the shape factor, λ is the X-ray wavelength, β is the line broadening at half of the maximum intensity in radians (after subtracting the instrumental line broadening), and θ is the angle.¹⁴⁸

A shape factor of 0.9,¹⁴⁹ wavelength of 0.15406 nm (CuK α 1), and peaks at 32.6° (2 θ), 29.6° (2 θ) were used respectively for the calculation of aspirin (1) and cocrystals (2). The β value for the peak is equal to 0.23307° and the instrumental line broadening was 0.05° . The crystal sizes extracted from this calculations are presented in Table 4.1. As can be seen, nanocrystals of aspirin prepared in three different methods have shown similar sizes ranging from 42 to 50 nm. Similarly, cocrystals of 2 also showed comparable sizes (in the same order) despite their preparation method. This was further confirmed by the size calculated using AFM single crystal imaging.

4.3.4 Nanoindentation Analysis

AFM-based nanoindentation was utilized to obtain the Young's moduli of the nanocrystals obtained from these different preparation methods. Repeated forcedisplacement curves were recorded on nanocrystals at room temperature using a molecular probe force 3D AFM (Asylum Research, Santa Barbara, CA). The Young's moduli of nanococrystals were obtained using a rearranged form of well-known Hertzian contact model using force- displacement curves as described in Chapter 3.¹⁵⁰

Histograms for extracted Young's moduli for nanocrystals of **1** and **2** are shown in Figure 4.7, 4.8 and summarized in Table 4.1. Importantly, nanocrystals have shown similar mechanical properties despite of their preparation method. Moreover, they showed similar morphologies as revealed by the AFM height images. Another important observation here is that the nanocrystals of single component system, aspirin is harder than the nano-dimensional crystals of the two component system.



Figure 4.7: Histograms of Young's moduli of aspirin nanocrystals (1) prepared *via* (a) Sonochemistry (b) Sonofragmentation (c) Grinding



Figure 4.8: Histograms of Young's moduli of cocrystals (2) prepared *via* (a) Sonochemistry (b) Sonofragmentation (c) Grinding and (d) Mechanochemistry

Sample	Young's modulus (MPa)	Polarizability (Å3)	Size by XRD* (nm)	
Aspirin nanocrystals				
Sonocrystallization	700 ± 200	22.6 ± 0.1	50	
Sonofragmentation	650 ± 150	21.6 ± 0.2	40	
Grinding	600 ± 150	22.1 ± 0.6	50	
(4,6-di-Cl-res)·(4,4'-bpe) cocrystals				
Sonocrystallization	370 ± 140	89.64 ± 0.96	50	
Sonofragmentation	370 ± 150	93.1 ± 1.9	90	
Grinding	330 ± 120	93.06 ± 0.65	65	
Mechanochemistry	350 ± 100	93.5 ± 0.5	25	

Table 4.1 Summary of the Young's modulus, polarizability and calculated crystal sizes of nanocrystals of aspirin and cocrystals

*Accuracy is on the order of magnitude and should only be viewed as semi- quantitative.

4.3.5 Polarizability Measurements

Polarizability of the nanocrystals were determined by THz-TD spectroscopy which is a rapidly-developing technique that uses electromagnetic radiation (0.3 to 4.0 THz) The coherent nature of THz spectroscopy permits a direct measure of polarizability as related to dielectric properties. Dielectric constants were, thus, determined for crystals of **1** and **2** from 10 to 20 cm⁻¹ as described in Chapter 3. Polarizability of the samples were calculated using the Clausius-Mossotti relationship.^{116,117} Given the nature of the dielectric measurements, the resulting polarizability values correspond to ensemble measurements over a population of crystals randomly oriented with respect to the optical axis of the THz pulse, thereby representing a bulk property of nanocrystals. And, resulting polarizability values are presented in Table 4.1 column 3.

As can be seen, polarizability value of nanocrystals show comparable values and thus, further supports our observation of similar mechanical properties, despite the preparation method. However, sonocrystallized sample (A) of cocrystals, **2** have shown deviations compared to other samples of **2** and this can be attributed to the variations of spectral features within our range of interest.

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4.4 Conclusions

involve Synthetic methods used here application of ultrasound (sonocrystallization and sonofragmentatiom) and application of mechanical energy (grinding and mechanochemistry). Our results show that the Young's moduli of nanocrystals are comparable upon application of either ultrasound or mechanical energy. Hence, it can be concluded that although mechanical energy and ultrasound radiation have different mechanisms of crystal generation, they result in crystals with similar mechanical properties and structures. According to the literature, there has been a significant attention on understanding how ultrasound radiation affects crystal properties such as well-defined morphology, narrow size distributions enhanced purity and high crystallinity^{139,151}. And, there's not much attention that has been devoted to study on how physical and chemical properties can be affected by the application of ultrasound radiation in the synthesis of nanocrystalline materials. In this context, our observation is of enormous importance as it provides us the opportunity to gain an insight into synthetic method-property relationship in the case of molecular crystals.

This also results in another important inference about the use of ultrasound radiation in the synthesis of nanomaterials where it can now be used to synthesize a wide variety of nanostructured materials with controlled morphologies, structures and compositions without affecting mechanical properties. Further, the greatest advantage of using ultrasonic radiation is that with slight modifications in reaction conditions and precursors, it allows the convenient synthesis of materials (ex: nanocomposites, functionalized graphene etc) which are otherwise difficult to prepare. Hence, current observation of preparation method independent mechanical properties, is tremendously useful in different fields such as the pharmaceutical industry, material science etc. Previously in our studies we have utilized sonochemical approaches to study mechanical properties in order to establish reliable structure-property relationships, under the assumption that the differences in mechanical properties of nanocrystalline materials are due to structural differences and are independent of the preparation method.¹⁵⁰ These observations validate our previous assumption as well.

Further, a similar observation has been reported in literature describing magnetic properties of Ni Zn ferrite nanoparticles synthesized *via* two different routes, a chemical method (polyol method) and a sonochemical method.¹⁴⁷ In that study, sonochemistry has yielded nanoparticles with narrow size distributions, high crystallinity and uniform shapes compared to the chemical method. However, nanoparticles have displayed similar trends in magnetic behaviour irrespective of the synthetic method, which has been attributed to the similar particles size and composition of Ni Zn ferrite nanoparticles.

Overall, here we have shown that the mechanical properties of nanodimensional cocrystals $(4,6-di-Cl-res) \cdot (4,4'-bpe)$ and single-component system aspirin is independent of the synthetic route. This is supported through THz-TDS polarizability measurements. Findings of this study will be of enormous importance in the design of novel materials with preferable mechanical properties.

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CHAPTER 5

MECHANICAL PROPERTIES OF PHARMACEUTICAL MATERIALS: SIZE DEPENDANT MECHANICAL PROPERTIES OF ASPIRIN

5.1 Introduction

In recent years, an enormous amount of attention has been devoted to the mechanical property characterization of pharmaceutical materials as it is of paramount importance in practical as well as in scientific aspects.^{92,152,153} In particular, the mechanical behaviour of APIs is important in the production of tablets where their mechanical stability is a critical factor in the milling, grinding and compression processes in industrial scale.^{92,154} For example, it is generally considered that soft crystals become 'pastelike' upon grinding and make them resistant to milling.¹⁵⁵ Moreover, understanding the polymorphs of APIs with better mechanical stabilities makes production of tablets economically viable.⁹² On the other hand, in scientific aspects, mechanical characterization is useful in establishing reliable structure-property relationships of APIs and thereby, leading to APIs with predictable properties.

Despite the wide range of studies on mechanical characterization, of organic solids, little attention has been placed on the mechanical properties of single crystals of APIs while most of the attention has been devoted for compact powders.¹⁵² In this context, studying mechanical properties of single crystals of API, aspirin is of enormous importance. Aspirin is a commonly used analgesic and can exist in two

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polymorphs (Form I and II), although the X-ray structure of Form II has only recently been described.¹⁵⁶ Form II has been demonstrated to be metastable, and converts to Form I under ambient conditions or through mechanical grinding.¹⁵⁷ The crystal packing of both polymorphs is dominated by centrosymmetric carboxylic acid dimers, while the packing of adjacent dimers involves acetyl groups engaged in centrosymmetric dimers (Form I)¹⁵⁸ or catemeric hydrogen bonds (Form II).¹⁵⁶ High quality tablets of aspirin can be readily generated through direct compression,^{159,160} and use of smaller aspirin particles for tablet formation has been shown to increase the tablet strength.¹⁶¹

Hence, herein we have studied mechanical properties of macro-dimensional and nano-dimensional single crystals of aspirin using AFM based nanoindentation technique. Macro-dimensional crystals of aspirin were prepared through slow evaporation while sonochemistry was utilized to prepare crystals in the nanodimension. We show that decreasing the size of aspirin crystals from millimeter to nanometer-scale dimensions results in an order of magnitude decrease in crystal stiffness from approximately 3 GPa to 700 MPa as determined using atomic force microscopy (AFM) nanoindentation method.

5.2. Experimental

5.2.1 Synthesis of Macro-dimensional Aspirin Crystals

Acetylsalicylic acid (aspirin) was purchased from Acros Organics and used without further purification. Macro-sized crystals of aspirin were grown *via* slow solvent evaporation in a concentrated solution of acetone.¹⁶²

5.2.2 Synthesis of Nano-dimensional Aspirin Crystals

Nano-sized crystals of aspirin were obtained *via* sonochemistry. Aspirin (200 mg, 1.1 mmol) was dissolved in minimal acetone. The solution was rapidly injected directly into 175 mL of cold hexanes while exposed to low-intensity ultrasonic radiation (ultrasonic cleaning bath Branson 2510R-DTM, frequency: 42 kHz, 6% at 100 W). The resulting suspension was sonicated for 1-2 min, filtered, dried at room temperature, and analysed *via* powder X-ray diffraction.

5.2.3 AFM based Nanoindentation Measurements

Millimeter-sized crystals were directly placed on a freshly cleaved mica substrate and measurements were conducted using a closed Fluid cell (Fluid cell lite, Asylum Research, Santa Barbara, CA). Nano-sized crystalline samples were suspended in hexanes at 1.0 mg/mL and then deposited on a freshly cleaved atomically flat mica substrate (V-I grade, SPI Supplies, Westchester, PA). All AFM studies were conducted using a Molecular Force Probe 3D AFM (Asylum Research, Santa Barbara, CA). AFM height images and nanoindentation measurements were collected at room temperature using silicon probes (Mikromasch, San Jose, CA,

CSC37) with a nominal spring constant of 0.35 N/m and a typical tip radius of curvature of 10 nm. The tip radius of curvature was verified using scanning electron microscopy and was found to be approximately 10 nm, as expected. Actual spring constants were determined using built-in thermal noise method.¹⁰⁶ Topographic images were collected using intermittent contact mode (AC mode) or contact mode at a typical scan rate of 1 Hz. Force-displacement curves were recorded at 1 Hz in an organic solvent (olefin free n-tetradecane) and each curve was collected during AFM probe motion towards and away from the sample. The maximum force of 10 nN was used as no sign of mechanical damage on a crystal surface was observed under such conditions after a series of repeated force-displacement measurements. As described in previous chapters, to ensure the reproducibility of the measurements, typically 10 to 15 repeated force measurements were collected at each crystal location of nano-sized samples while force measurements were collected at ~10 different locations on the each face of the millimeter-sized crystals. In addition, force plots were collected on the substrate approximately 100-150 nm away from the corresponding crystal The force versus tip-sample separation data were used to estimate the position. Young's modulus of a crystal by fitting the nanoindentation plots to a rearranged form of the Hertzian model, which assumes elastic contact as described in previous chapters.8,107-110

5.3 Results and Discussion

5.3.1 PXRD Measurements

PXRD data were obtained on a Siemens D5000 X-ray diffractometer using CuK α 1 radiation ($\lambda = 1.54056$ Å) (scan type: locked coupled; scan mode: continuous; step size: 0.02°; scan time: 2 s/step). The samples were mounted on glass slides.

Crystallinity and the purity of synthesised macro- and nano-dimensional crystals were confirmed by PXRD patterns where experimental patterns matched perfectly with the simulated (Figure 5.1).



Figure 5.1: PXRD data of macro-, nano-dimensional and simulated pattern from X-ray data

5.3.2 Single Crystal X-ray Diffraction Indexing

Single-crystal indexing was performed using a Nonius Kappa CCD singlecrystal X-ray diffractometer at room temperature using MoK α radiation ($\lambda = 0.71073$ Å). According to X-ray crystals data, top and bottom crystal faces probed in the AFM experiments were corresponding to the crystallographic (100) and (-100) planes (Figure 5.2).



Figure 5.2: Indexed faces of aspirin crystal



Figure 5.3: X-ray structure of aspirin. AFM planes probed for macro-sized crystals highlighted in red

5.3.3 Size Calculations of Nanocrystals using PXRD Data

The size of the nanocrystals was calculated using the broadening in the PXRD peaks obtained from the bulk powder. The Scherrer Equation (5.1) was used for the calculation:

$$L = \frac{\kappa \lambda}{\beta \cos \theta}$$
 5.1

where L is the mean size of the crystallites, K is the shape factor, λ is the X-ray wavelength, β is the line broadening at half of the maximum intensity in radians (after subtracting the instrumental line broadening), and θ is the angle.¹⁴⁸

A shape factor of 0.9,¹⁴⁹ wavelength of 0.15406 nm (CuK α 1), and the peak at 32.6° (2 θ) (see Fig. S2) were used for the calculation. The β value for the peak is equal to 0.23307° and the instrumental line broadening was 0.05° . The calculation yielded a crystallite size of 50 nm.

5.3.4 AFM Height Images of Aspirin Crystals

AFM height images of macro- and nano-dimensional aspirin crystals were collected using a Molecular Force Probe 3D AFM (Asylum Research, Santa Barbara, CA). Macro- dimensional crystals exhibited prism morphologies with base sizes on the order of 3.3 x 1.5 mm and heights of 0.5 mm. Top and bottom crystal faces corresponding to the crystallographic (100) and (-100) planes, respectively, were probed by AFM (Figure 5.4). Cleavage planes were present on the faces of macro crystals. The height variation for the cleavage planes typically ranges between 1-5 nm and likely originates from the inhomogeneous distribution of the crystal growth centers and unequal growth rates of the crystals.

Nano-dimensional cocrystals showed semi-spherical shapes with heights ranging from 30-150 nm and bases from 50-1000 nm (Figure 5.5). AFM imaging exhibited an average crystal volume equivalent diameter of 150 ± 100 nm for nanocrystals. This is comparable with the crystal size determined from PXRD.



Figure 5.4: (a) AFM image of (100) face of macro-dimensional crystal, (b) representative AFM height image of nano-dimensional crystal

5.3.5 Analysis of Mechanical Properties of Aspirin Crystals

The Young's modulus (stiffness) of millimeter- and nano-sized Aspirin crystals were studied using AFM nanoindentation technique.^{107,121-124} The force *versus* tip-sample separation data were used to determine the Young's modulus of a cocrystal using the rearranged form of the Hertzian model as described in Chapter 3.³

Representative plots for force to the power 2/3 *versus* tip-sample separation for millimeter-sized and nano-meter sized crystals are shown in Figure 5.6. As expected, a linear relationship was observed in the contact region (negative tip-sample separation region) for both samples, which confirms the applicability of the Hertzian contact model in the form of Equation 3.1. The fitted lines are shown in Figure 5.5 in solid lines with R² values of 0.94 for nano-sized sample and 0.97 for the millimeter-sized sample. The Young's modulus of each sample was calculated using the slope obtained from the linear fit. The AFM tip radius of curvature and Poisson's ratio was estimated to be 10 nm (SEM measurements) and 0.3 (typical Poisson's ratio value for organic materials), respectively.³



Figure 5.5: Representative plots for force to the power of 2/3 versus tip-sample separation for millimeter-sized (macro) and nanometer-sized samples. Solid lines represent the linear fits (R^2 = 0.94 for the nano-sized and 0.97 for the macro-sized samples)

Histograms of Young's moduli for macro- and nano-dimensional aspirin crystals are shown in Figure 5.7. Average Young's modulus values (mean \pm standard deviation) were determined to be 2.9 \pm 0.9 GPa for the (100) plane and 3.0 \pm 0.5 GPa for the (-100) plane. The Young's moduli for these planes have been studied previously, with reported values that range between 1.3 and 9.5 GPa ^{157,163-165} and our experimental values lie within the previously reported range.

The corresponding average Young's modulus (mean ± 1 standard deviation) for nano-dimensional crystals was 700 \pm 200 MPa, (Figure 5.7. b) and compares to an average value of 2.9 \pm 0.8 GPa obtained for the macro-dimensional crystals (Figure 5.7 a). These measurements indicate over a four-fold reduction in the Young's modulus for the nano-dimensional crystals as compared to macro-sized crystals.

Further, THz-TD Spectroscopy, which is a widely used technique in the polarizability characterization of organic materials, was utilized to obtain polarizability of macro- and nano-dimensional crystals of aspirin. Polarizability was calculated using the well-known Clausius-Mossotti relationship.^{116,117} from the dielectric constants determined by measuring the delay in a THz pulse transmitted across a pressed pellet composed of 5% aspirin embedded within a matrix of polytetrafluoroethylene. The polarizability of the macro-dimensional aspirin crystals was determined to be (22.1 ± 0.6) Å³. This observed lower polarizability further validates higher Young's modulus of aspirin crystals.

This observed decrease in Young's modulus upon size reduction of aspirin crystals can be attributed to the increase in surface energy and relaxation in the nanoscale, and thereby altering the elastic properties of the crystal.^{166,167}



Figure 5.6: (a) Histogram of Young's modulus for macro-dimensional crystal (100 and - 100 plane data), and (b) histogram of Young's modulus for nano-dimensional crystal. Gaussian fits are shown in red for both (a) and (b)

Conclusions

Here we have demonstrated that aspirin single crystals exhibit size-dependent mechanical properties. A reduction in size results in crystals that are approximately four fold softer. However, the factors which control these observed changes in mechanical properties are yet be fully understood. Hence, we are expanding our studies to other pharmaceutically-relevant compounds as the means to establish strategies to design crystals with targeted physical properties. This approach can have implications in optimizing pharmaceutical properties and preparation methods of APIs

CHAPTER 6

MECHANICAL PROPERTIES OF SALICYLIC ACID BASED COCRYSTALS WITH SYSTEMATIC MODIFICATIONS TO THE COCRYSTAL FORMER

6.1 Introduction

Establishing reliable structure – property relationship of materials is the key for potential design of novel materials with desirable and tunable electronic, optical, magnetic and physical properties.^{92,168,169} Further, such relationships can be tailored into molecular level device fabrication, active pharmaceutical ingredients with desired properties and various material science applications.^{169,170} Such materials with tunable and desired properties can be achieved by changing the way atoms within a structure interact with each other, or by adding or replacing different functional groups or atoms attached to the molecule.¹⁶⁹ For example, allotropes of carbon, diamond and graphite provide an insight as to how properties can vary with the type of interactions present. Diamond, having an extended 3-dimensional tetrahedrally bound structure is one of the hardest materials known, while graphite is extremely soft due to the presence of weak van der Waals interactions that holds graphite layers together. In this context, understanding the role of intermolecular interactions and gaining an insight into structure - solid state properties of materials especially in the nanoscale, is challenging, but crucial.

In chapter 3, a direct correlation between the Young's modulus and atomic polarizability was discussed for members of a series of cocrystals based on systematic

changes to one cocrystal component. Specifically, a hydrogen atom present in the template of the cocrystal (shown in red circle in Figure 6.1) was modified with halogens (X=Cl, Br, I) which leads to an increase in the polarizability of the cocrystals system where atomic polarizability increases from Cl to Br to I. A decrease in the Young's modulus of cocrystals was observed with modifying the template with more polarizable atoms. Hence, establishing a reliable structure- property relationship between atomic/ molecular polarizability and Young's modulus.

Unfortunately, not much attention has been devoted in studying such structureproperty relationships of nanoscale organic solids. Therefore, the actual mechanisms and factors that control mechanical properties at nanoscale are yet to be understood. Hence, we wanted to gain further insight into this. Accordingly, herein mechanical properties of a similar cocrystal system was studied with systematic changes to the cocrystal former, CCF of the system instead of the template (Figure 6.2). The cocrystal system of interest utilizes salicylic acid (SA) and bipyridine based CCFs as the cocrystal former with systematic modifications to the covalent spacer (bridge between the two pyridines) as shown in Figure 6.2. In particular, current study involves macro-dimensional cocrystals of salicylic acid and 1, 4,4'-bipyridine 1,2-bis(4-pyridyl)ethane (SA)·(BPEth), (SA)·(BIPY), 2, and 3, 1,2-di(4pyridyl)ethylene (SA) \cdot (BPE). Single-crystal X-ray experiments revealed each solid to exhibit two component closed hydrogen-bonded trimer of molecules sustained by two O-H···N hydrogen bonds. Current study provides further pathway to explore structure- property relationships of nanoscale organic solids, for the potential design of materials with predictable properties.



Figure 6.1: Cocrystal system with systematic modifications to the template, described in Chapter 3



Figure 6.2: Cocrystal system with systematic modifications to the bipyridine cocrystal former, CCF

6.2. Experimental

6.2.1 Synthesis of Salicylic Acid Cocrystals

4,4'-bipyridine (BIPY), 1,2-di(4-pyridyl)ethylene (BPE), and 1,2-bis(4pyridyl)ethane (BPEth) were purchased from Sigma Aldrich and used without further purification. Salicylic acid was purchased from Fischer Scientific and was also used without further purification.

Macro-sized crystals of $2(SA) \cdot (BIPY)$, $2(SA) \cdot (BPE)$, and $2(SA) \cdot (BPEth)$ were synthesized by dissolving SA and the appropriate bipyridine co-crystal former in EtOH (2:1 molar ratio, respectively). Slow solvent evaporation over a period of two days yielded single crystals suitable for X-ray diffraction.

6.2.2 Characterization of Salicylic Acid Cocrystals

The diffraction data and crystal indexing were measured on a Nonius Kappa CCD single-crystal X-ray diffractometer at room temperature using MoK α radiation ($\lambda = 0.71073$ Å). Structure solution and refinement were accomplished using SHELXS-97 and SHELXL-97, respectively.¹⁷¹ All non-hydrogen atoms were refined anisotropically. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained positions. Hydrogen atoms associated with oxygen atoms were calculated in an optimal hydrogen bonding geometry.

6.2.3 AFM nanoindentation Measurements

Millimeter-sized crystals were directly placed on a freshly cleaved mica substrate and measurements were conducted using a closed Fluid cell (Fluid cell lite,

Asylum Research, Santa Barbara, CA). All AFM studies were conducted using a Molecular Force Probe 3D AFM (Asylum Research, Santa Barbara, CA). AFM height images and nanoindentation measurements were collected at room temperature using silicon probes (Mikromasch, San Jose, CA, CSC37) with a nominal spring constant of 0.35 N/m and a typical tip radius of curvature of 10 nm. The tip radius of curvature was verified using scanning electron microscopy and was found to be approximately 10 nm, as expected. Actual spring constants were determined using built-in thermal noise method.¹⁰⁶ Topographic images were collected using intermittent contact mode (AC mode) or contact mode at a typical scan rate of 1 Hz. Force-displacement curves were recorded at 1 Hz in an organic solvent (olefin free n-tetradecane) and each curve was collected during AFM probe motion towards and away from the sample. The maximum force of 10 nN was used as no sign of mechanical damage on a crystal surface was observed under such conditions after a series of repeated forcedisplacement measurements. As described in previous chapters, to ensure the reproducibility of the measurements, typically 10 to 15 repeated force measurements were collected at ~10 different locations on the each face of the millimeter-sized crystals. In addition, force plots were collected on the substrate approximately 100-150 nm away from the corresponding crystal position. The force versus tip-sample separation data were used to estimate the Young's modulus of a crystal by fitting the nanoindentation plots to a rearranged form of the Hertzian model, which assumes elastic contact as described in previous chapters.^{8,107-110}

6.3 Results and Discussion

6.3.1 Structural Details of Cocrystals

Single-crystal X-ray experiments revealed each crystalline solid to exhibit a closed hydrogen bonded trimer. The trimer is sustained by two O-H…N hydrogen bonds (O…N separations (Å): O(1)…N(2) 2.6257(2) **1**; O…N 2.552(2) **2**; O(1)…N(1) 2.56597(18) **3**). In addition, salicylic molecules exhibit one O-H…O intramolecular hydrogen bond (O…O separations (Å): O(3)…O(2) 2.685(2) **1**; O(3)…O(2) 2.5443(17) **2**; O(3)…O(2) 2.55135(19) **3**). Cocrystal **1** crystallized in the triclinic space group Pī, while **2** and **3** crystallize in the monoclinic space groups P2₁/n and P2₁/c, respectively.

The trimers in each cocrystal self-assemble to form offset layers. Trimers interact with adjacent layers *via* C-H(SA)-O contacts (C(12)···O(1): 3.46 Å) and C-H(pyridine)-O contacts (C(4)···O(3): 3.42 Å). The trimers of **1** interact *via* offset π (SA)- π (pyridine) forces (centroid···centroid: 3.91 Å). Trimers of **2** assemble to form offset layers along the *b*-axis *via* offset π (SA)- π (pyridine) (centroid···centroid: 3.76 Å). Adjacent layers interact via C-H(pyridine)-O contacts (C(11)···O(3): 3.41 Å) along the *a*-axis. Trimers arrange into a 2D herringbone along the *c*-axis (ca. 64.5°) network *via* edge-to-face C-H(SA)- π (SA) forces (centroid···centroid: 5.07 Å) and C-H(SA)-O contacts (C(5)···O(1): 3.40 Å). Trimers of **3** assemble into offset layers along the *b*-axis *via* π (pyridine)- π (alkene) (centroid···centroid: 3.489 Å) and π (SA)-O forces (centroid···O(2): 3.43 Å). Adjacent hydrogen bonded layers crisscross perpendicularly (ca. 90°) and interact *via* C-H(alkene)-O contacts (C(6)···O(3): 3.31 Å) and C-H(SA)-O contacts (C(10)···O(1): 3.34 Å).



Figure 6.3: X-ray structures: (a) **1**, (b) **2** and (c) **3**, highlighting layered packing of assemblies. AFM planes probed for macro-sized crystals highlighted in red

6.3.2 AFM height images of Macro-dimensional Cocrystals

AFM height images of top and bottom crystal planes of each macrodimensional cocrystals used in the study are shown in Figure 6.4. Cleavage planes were present in the faces of cocrystals **1-3**. The height variation for the cleavage planes typically ranges between 5-100 nm and likely originates from the inhomogeneous distribution of the crystal growth centers and unequal growth rates of the crystals.



Figure 6.4: Representative AFM height images of (A) (100) face and (B) (-100) face of 1, (C) (001) face and (D) (00-1) face of 2, (E) (001) face and (F) (00-1) face of 3

6.3.3 Mechanical Properties of Cocrystals

The histograms of the Young's modulus for macro- dimensional cocrystals are shown in Figure 6.5. The Young's modulus of (100) plane of cocrystal **1** was found to be (1.3 ± 0.6) GPa while that of (-100) plane was (1.4 ± 0.6) GPa. (001) plane of cocrystal **2** exhibited a Young's modulus of (450 ± 200) MPa and (00-1) plane, a value of (410 ± 75) MPa. For cocrystal **3**, average Young's moduli of (230 ± 50) and (225 ± 50) MPa was observed for (00-1) and (001) planes, respectively.

Cocrystal **1** exhibited the highest Young's modulus while cocrystal **3** showed the lowest Young's modulus value. Interestingly, cocrystal **1** was ~5 fold harder than cocrystal **3**. The percent decrease in Young's modulus was 65 % from **1** to **2** and 50 % from **2** to **3**. Moreover, cocrystal **1** is among the hardest organic cocrystals that have been studied previously in our group, where the reported highest so far was (res)·(4,4'bpe) cocrystals discussed in Chapter 3 with an average Young's modulus of (1.2 ± 0.3) for 001 plane and (1.6 ± 0.3) for 00-1 plane.



Figure 6.5: Histograms showing Young's modulus of cocrystals. (a) 100 (b) -100 plane of cocrystal 1, (c) 001 (d) 00-1 plane of cocrystal 2 and (e) 00-1 (f) 001 planes of cocrystal 3. Red line shows the Gaussian fit

6.3.3 Connection between Polarizability and the Young's Modulus

We next utilized THz-TD Spectroscopy to obtain experimental polarizability values for cocrystals and these measured polarizability values are (67.1 ± 0.8) for **1**, (81.7 ± 0.6) for **2** and (86.8 ± 0.5) for **3**. The largest polarizability was indicated for cocrystal **3** whereas the lowest was observed for cocrystal **1**. C=C bond presents in the cocrystal **3** makes it more polarizable owing to its higher delocalized electron density compared to other two systems. In particular, higher 'p' character of sp² hybridization in C=C bond leads to a higher delocalization of electrons. And polarizability, the ability of the molecule to be polarized is larger in highly delocalized systems.

Inverse Young's modulus vs polarizability plot for SA based cocrystals is shown in Figure 6.6. An excellent linear relationship was observed with a R² value of 0.92. Hence, the polarizabilities of the solids increase with introducing electron delocalized systems to the CCF, which corresponds to the decrease in stiffness consistent with the expected inverse relationship. Moreover, this is in line with what we observed in Chapter 3 and further supports our idea that polarizability plays a key role in determining the mechanical response.



Figure 6.6 : Inverse Young's modulus vs polarizability from THz-TDS for 1-3 (weighted fit macro $R^2=0.92$) Data for macro-sized crystals for top plane

6.4 Conclusions

Herein, we have studied mechanical properties of a series of salicylic acid based two component system, with systematic modifications to the cocrystal former. A decrease in the Young's modulus was observed when CCF was modified from 4,4'bipyridine (N-N) to 1,2-di(4-pyridyl)ethylene (N-C-C-N), to 1,2-bis(4-pyridyl)ethane (N-C=C-N). Cocrystal systems **2** and **3** are isostructural and hence, observed difference in the mechanical properties can be attributed to the differences in their polarizabilities owing to the variations in electron delocalization of C-C (single bonds) and C=C (double bonds). In order to gain more insight into this, we are currently investigating mechanical properties of nano-dimensional cocrystals of **1-3**.

CHAPTER 7

CONCLUSIONS AND FUTURE DIRECTIONS

The scope of the material discussed herein has been focused on characterizing physical properties of nanoscale materials to gain an insight into their structureproperty relationships in order to develop novel materials with tunable electrical and mechanical properties. Understanding the factors that control these properties in the nanoscale is challenging, but is of enormous importance. Moreover, due to size constraints, traditional testing methods cannot be used in the nanoscale. In this context, utilization of highly sensitive techniques such as AFM is indispensable.

The work described in Chapter 2 focuses on studying the electrical properties of a novel silver based metal organic complex which undergoes a photoreaction in solid state. In this complex, Ag(I) was used to form the π -stacked metal-organic solid and it exhibits remarkably high electrical conductivity, which is among the highest reported for silver based metal-organic complexes. Moreover, a 40 % increase in conductivity upon photodimerization was also observed, where this represents the first example of an increase in conductivity that results from a [2+2] photodimerization. This increase in conductivity has been attributed to higher contribution from Ag(I) ions to the valence band in the photodimerized solid. Further, newly-formed and strained cyclobutane rings and Ag···C(phenyl) forces upon photodimerization also act as efficient electron donors in the photodimerized solid and lead to a reliable relationship between electrical properties and the crystal structure.

Chapter 3 investigates mechanical properties of a series of cocrystals based on systematic changes to one co-crystal component. In particular, these cocrystals are composed of (di-x-res) (x= H, Cl, Br, I) and (4,4'-bpe) and display a decrease in the Young's modulus when the size of the substituent is increased from parent res (H) to Cl to Br to I. This observed decrease in the Young's modulus has been attributed to the difference in polarizability due to different halogens present, where lowest Young's modulus was observed with cocrystal with highly polarizable I. Thus, this results in a direct relationship between the polarizability, and mechanical property of organic cocrystals where Young's modulus is inversely proportional to the polarizability. Such relationship has been demonstrated in literature for metals, oxides, and inorganic materials. However, this was the first ever demonstration of this inverse relationship in the context of organic molecular solids. Moreover in this study, time domain spectroscopy over terahertz frequencies (THz-TDS) was used for the first time to directly measure the polarizability of macro- and nano-sized organic solids. Overall, this study has led to a novel structure-property relationship between polarizability and mechanical property where highly-polarizable atoms result in softer solids.

In Chapter 4, mechanical properties of single component (aspirin) and two component ($(4,6-di-Cl-res) \cdot (4,4'-bpe)$ systems prepared *via* different synthetic routes has been studied. Basically synthetic methods discussed here incorporate either mechanical energy (grinding and mechanochemistry) or ultrasound radiation (sonochemistry and sonocrystallization) to generate nanocrystals. Despite their preparation method, nanocrystals showed similar mechanical properties in the case of single component as well as two component systems. This is important in the context

of sonochemistry, as it can now be used to synthesize a wide variety of nanostructured materials with controlled morphologies, structures, and compositions without affecting the mechanical properties. Moreover, this leads to the conclusion that although mechanical energy and ultrasound radiation have different mechanisms of crystal formation, they result in crystals with similar structures.

Chapter 5 discusses mechanical properties of pharmaceutically important material, aspirin in nano- and macro- dimensions. Here we have demonstrated that aspirin single crystals exhibit size-dependent mechanical properties. A reduction in size (from millimetre to nanometer) results in crystals that are approximately four fold softer. However, the factors which control these observed changes in mechanical properties are yet be fully understood and further investigations are in progress to gain more insight into this observation.

Work described in Chapter 6 provides further understanding on structureproperty relationships described in Chapter 3. Herein, components of a cocrystal systems has been changed with systematic changes to the covalent spacer of the cocrystal former (CCF), where in Chapter 3, the template was systematically modified. Again, introducing C=C bonds resulted in an increase in polarizability as measured by THz-TDS and softer materials (lower Young's modulus value compared to C-C) which further provided evidence for the inverse relationship between polarizability and the Young's modulus demonstrated in Chapter 3. This is also important as it provides us the opportunity to systematically modify components (either the template or the cocrystal former) of cocrystal systems to achieve materials with preferable mechanical properties.

Overall, the current thesis focuses on electrical and mechanical characterization of organic nanoscale materials in order to establish reliable structure-property relationships for the potential design of materials with controllable properties. Further, understanding the factors that control these properties at the nanoscale is crucial and hence, is of enormous importance in molecular level device fabrication, electronics, pharmaceutical industry and material science applications. Overall, goals of the current thesis have been achieved by developing materials with high electrical conductivity using the directionality of transition metals in the context of crystal engineering to generate interactions that are favourable for enhanced conductivity, establishing direct correlation between polarizability and the Young's modulus for multi component system, investigating size dependant mechanical properties of APIs and finally understanding the effect of ultrasound radiation in the mechanical properties of nanocrystalline materials. Through these studies and future endeavours, we are trying to gain additional understanding on structure-property relationships of materials at the nanoscale and thereby, understand the factors that control these properties. As organic nanocrystalline materials have not been explored extensively compared to their inorganic solids, studying electrical and mechanical properties of similar systems and thereby, gaining comprehensive understanding would be of enormous importance in future directions.

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