VIRTUAL SYMPOSIUM on SOLID-STATE ORGANIC CHEMISTRY

Wednesday, May 27, 2020
Thursday May 28, 2020

MERCK

Molecular Design Institute
NEW YORK UNIVERSITY

Message from the Organizing Committee

Welcome to the Virtual Symposium on Solid-State Organic Chemistry! We are ecstatic that you can join us. It is your participation and contributions that have made this event a unique and exciting science get-together. We're living in a time where the word "get-together" is almost taboo, and as such, it has become difficult for the scientific community to unite in the collaborative spirit that is so engrained in our identity. Scientific meetings such as BACG 2020, MOSSCS, Crystal Engineering GRC and the 5th David Grant Symposium have been postponed or cancelled as most individuals are working remotely and unable to share their latest findings with the rest of the scientific community. The global pandemic has catapulted us into a new reality, a virtual reality, and though it comes with challenges, it also provides an opportunity to adapt to a new way of learning and thinking. Change is a means of fostering innovative and creative ideas, and at the heart of it, that is what science is all about. We are proud to host VS^{3}OC, our first ever virtual symposium and a platform to share the research progresses we've made in the field of solid-state organic chemistry. Thank you to all our speakers and to all participants tuning in!

List of Participating Institutions

Ying Diao, University of Illinois, Urbana Champaign

Lara Estroff, Cornell University

Bart Kahr, New York University

Alfred Lee, Merck & Co., Inc

Vilmali Lopez-Mejias, University of Puerto Rico - Rio Piedras

Len MacGillivray, University of Iowa

Calvin Sun, University of Minnesota

Jennifer Swift, Georgetown University

Lynne Taylor, Purdue University

Mike Ward, New York University

Lian Yu, University of Wisconsin

Scientific Program

Day 1 (S1) – Wednesday, May 27

13:00 **Alfred Lee**, Merck & Co., Opening Remarks

13:10 **Scott Schultz**, Merck & Co., Plenary Talk
(Not so) Virtual Tales of the Solid State in the Pharmaceutical Development of Small Molecule Drug Candidates

13:50 **Xiaolong Zhu**, New York University
Manipulating Solid Forms of Contact Insecticides for Infectious Disease Prevention

14:20 **José R. Hernández**, University of Puerto Rico
Polymorphism in Crystalline Solid Dispersions

14:50 **Break**

15:00 **Zhenxuan Chen**, University of Wisconsin-Madison
Organic glasses with tunable liquid-crystalline order through kinetic arrest of end-over-end rotation

15:30 **Tu Van Duong**, Purdue University
Reversible single-crystal-to-single-crystal polymorphic phase transition of the antifungal drug posaconazole at exceptionally high temperature

16:00 **Daniel Davies**, University of Illinois, Urbana Champaign
Understanding the Origins of Polymorphic Transition Mechanisms in an N-type Organic Semiconductor

16:30 **Gonzalo Campillo-Alvarado**, University of Iowa
Crystalline Boron Sponges: From Photochemical Design to Petrochemical Applications

17:00 **Mike Ward**, New York University, Closing Remarks

Day 2 (S2) – Thursday, May 28

13:00 **Alfred Lee**, Merck & Co., Opening Remarks

13:10 **Jennifer Swift**, Georgetown University, Plenary Talk
New Approaches to Probe Molecular Hydrate Properties and Transformations

13:50 **Shencheng Ge**, Merck & Co.
Magnetic Levitation in Chemistry, Materials Science, and Biochemistry

14:20 **Taylor Watts**, Georgetown University
Dynamic behavior of a channel hydrate system with tailored lattice substitutions

14:50 **Break**

15:00 **Noalle Fellah**, New York University
Benzamide and Beyond: Exploring the Solid-State Landscape of Small Molecules

15:30 **Gerrit Vreeman**, University of Minnesota
Can we make tablets for elastic crystals?

16:00 **Amnon Ortoll-Bloch**, Cornell University
Measuring temperature-dependent crystal growth kinetics of hybrid organic–inorganic perovskites using in situ atomic force microscopy

16:30 **Mike Ward**, New York University, Closing Remarks

Presentation Abstracts

S1. (Not so) Virtual Tales of the Solid State in the Pharmaceutical Development of Small Molecule Drug Candidates

C. Scott Schultz

Merck & Co., Inc., Merck Research Laboratories

Molecular and Materials Characterization, Rahway, New Jersey, 07065 USA

email: scott_shultz@merck.com

This talk will provide a materials science perspective and associated case studies highlighting the types of interesting scientific opportunities and challenges encountered in chemical process research and development in the pharmaceutical industry. It will also highlight critical aspects of understanding molecular composition of solid phases for developing robust and scalable chemical processes to support our core mission of positively impacting the course of human health.

S1. Manipulating Solid Forms of Contact Insecticides for Infectious Disease Prevention

Xiaolong Zhu
New York University
Molecular Design Institute
email: xz1668@nyu.edu

Malaria control is under threat by the development of vector resistance to pyrethroid insecticides, which has prompted calls for a return to the notorious crystalline contact insecticide DDT. A faster acting difluoro congener, DFDT, was developed in Germany during World War II, but in 1945 Allied inspectors dismissed its superior performance and reduced toxicity to mammals. It vanished from public health considerations. Herein, we report the discovery of amorphous and crystalline forms of DFDT and a mono-fluorinated chiral congener, MFDT. These solid forms were evaluated against mosquito vectors for malaria and Zika. Contact insecticides are transmitted to the insect when its feet contact the solid surface of the insecticide, resulting in absorption of the active agent. Crystalline DFDT and MFDT were much faster killers than DDT, and their amorphous forms were even faster. The speed of action, which destroys vectors before they can become infective, depends inversely on the thermodynamic stability of the solid form. These observations suggest that manipulation of the solid-state chemistry of contact insecticides, demonstrated here for DFDT and MFDT, is a viable strategy for mitigating insect-borne diseases, with an accompanying benefit of reducing environmental impact.

S1. Polymorphism in Crystalline Solid Dispersions

José R. Hernández
University of Puerto Rico – Río Pedras Campus
Molecular Sciences Research Center
email: josehernandez40@upr.edu

Solid dispersions embed active pharmaceutical ingredients (APIs) in polymeric carriers to improve their solubility. Three solid dispersion preparation techniques are typically employed: solvent evaporation, solvent-fusion, and fusion methods. Although these are also widely recommended as preparative methods for phase diagram determination, few examples exist concerning their effect on the resulting polymorph once the solid dispersion is formed. Furthermore, the fusion method is also employed in continuous manufacturing techniques such as hot melt extrusion (HME). The inadvertent occurrence of polymorphic phase transformations of APIs during HME processes has been claimed to limit the application of this technique. Hence, the control of polymorphism would need to be addressed for HME to be successfully implemented as an alternative solid dosage formulation strategy in continuous manufacturing processes. In this study, the influence of these three methods on the polymorphic form obtained in crystalline solid dispersions (CSDs) composed of flufenamic acid (FFA) and polyethylene glycol (PEG) was investigated. The results reveal that the solvent evaporation and solvent-fusion methods lead to FFA III. In contrast, the fusion method leads to concomitant polymorphs (mainly FFA I and III) in the CSDs. To avoid concomitant polymorphism in CSDs prepared by the fusion method, design spaces where the polymer is molten, and the API remains in the crystalline state were further applied. These results demonstrate that FFA can be processed during a temperature-simulated HME. At temperatures above the transition point of FFA forms III and I (42 °C), the induction time of the polymorphic phase

transformation (FFA form III to form I) is longer than the average reported residence time in conventional HME processes (~5 min). Moreover, it was demonstrated that a thorough understanding of the thermodynamic and kinetic design space for the FFA-PEG system leads to polymorphic control in the produced CSDs. Collectively, these results demonstrate that preparative methods have a significant influence on the phase diagrams determined (average relative deviation, ARD ≤ 8%), which are often used to justify the thermodynamic design space of manufacturing processes. Likewise, these results help to gain fundamental understanding of the processing needs of CSDs, which will lead to a broader application of HME for drug products containing polymorphic APIs, representing about 80% of all APIs.

S1. Organic glasses with tunable liquid-crystalline order through kinetic arrest of end-over-end rotation

Zhenxuan Chen
University of Wisconsin Madison
email: zchen492@wisc.edu

Liquid crystals (LCs) and glasses are two important classes of materials, with LCs offering easy tunability of molecular packing by external stimuli and glasses providing liquid-like spatial uniformity and crystal-like mechanical strength. Here we report that it is possible to create organic glasses with tunable LC order by controlling glass-forming conditions such as cooling rate. For rod-like mesogens itraconazole and saperconazole, smectic LC order trapped in the glass is determined by the kinetic arrest of the end-over-end rotation at a given cooling rate. Synchrotron X-ray scattering measured using a simultaneous SAXS/WAXS setup reveals identical intramolecular structures in glasses with different LC order, but widely different molecular packing. Density modulation is observed along the smectic LC director for at least several micrometers, while the order perpendicular to the LC director has a shorter range of several nanometers. The structure of the glass is highly dependent on cooling rate. Together these results indicate a general principle for controlling LC order in organic glasses for electronic and pharmaceutical applications. Given that current theories treat LC transitions as instantaneous and thermodynamically controlled, our results motivate further development in which kinetics plays an important role in LC transitions.

S1. Reversible single-crystal-to-single-crystal polymorphic phase transition of the antifungal drug posaconazole at exceptionally high temperature

Tu Van Duong
Purdue University
email: vduong@purdue.edu

The antifungal drug posaconazole (PCZ) exists in various polymorphic forms; The Form I polymorph is the thermodynamically stable form at room temperature. The differential scanning calorimetry (DSC) thermogram of Form I shows a melting peak at approximately 170°C and an endothermic event at *ca*. 135°C. This event is either ignored or commonly interpreted as a nematic-like phase transition or the melting of an impurity without adequate supporting data. Variable temperature powder X-ray diffraction (XRD) showed that PCZ exhibited distinct X-ray diffractograms below and above 135°C, suggesting that this event might correspond to a solid-state polymorphic transition. DSC data further supported the interpretation that the endothermic event was related to a reversible enantiotropic phase transformation. In order to gain further insights into this phase transition phenomena, single crystals of PCZ were grown and subjected to variable temperature single crystal XRD, which confirmed the polymorphic transition of PCZ upon heating, with crystal system and space group being unchanged; β angle as well as a, b axis and cell volume profoundly decreased whereas the c axis and density increased. This transition to a denser high temperature phase is surprising as the density rule would suggest that the high temperature form in an enantiotropic system exhibits a lower density than the thermodynamically stable form. Above 135°C, hydroxyl groups were not hydrogen bonded to neighboring molecules, *i.e*. the H-bond to nitrogen was broken during the phase transition. As a consequence, the distance between PCZ molecules shortened upon heating to above the transition point, eliminating the void space in the crystal lattice. This explains why a, b axis and cell volume

decreased whereas density increased. The endothermic enthalpy of *ca*. 7.2 J/g observed in DSC thermogram corresponds to the energy required to disrupt hydrogen bonds. The change in the crystal structure of PCZ upon polymorphic transition was accompanied by substantial shifts of –OH, -C-N-, and –C=N- vibrations in Fourier-transform infrared spectroscopy spectra.

S1. Understanding the Origins of Polymorphic Transition Mechanisms in an N-type Organic Semiconductor

Daniel Davies
University of Illinois
email: dwdavie2@illinois.edu

Cooperativity has long been used by living systems to circumvent energetic and entropic barriers to yield highly efficient molecular processes. Cooperative structure transition involves simultaneous, concerted displacement and rotation of molecules in a crystalline material, in stark contrast to the typical nucleation and growth mechanism occurring in a molecule-by-molecule fashion that often disrupt the material structural integrity. Cooperative transitions have acquired much attention in the research community for its low transition barrier, ultrafast kinetics, and structural reversibility. On the other hand, cooperative transition is rarely observed in molecular crystals and its molecular origin is not well understood. In 2-dimensional quinoidal terthiophene (2DQTT-o-B), a high-performance n-type semiconductor our research has shown prolific diversity in polymorphism and transition behavior resulting in 5 obtainable polymorphs showing large variations in electronic and optical behaviors. Along with the diversity of structure, both a cooperative and nucleation and growth transition has been reported simultaneously in the same system through 2 different thermally activated phase transitions. In situ microscopy, single crystal and grazing incidence X-ray diffraction, and Raman spectroscopy suggest a reorientation the alkyl side chains results in a cooperative transition behavior. While in stark contrast, we find the nucleation and growth mechanism occurs through a combination of side chain melting and increased core interactions resulting from a sudden increase in biradical nature of 2DQTT-o-B and is confirmed through in situ electron paramagnetic resonance. This is the first time, to our knowledge, that biradical interactions result in a structural change.

Through studying these fundamental mechanisms, we may establish design rules to rationally control polymorphic behavior for novel (opto)electronic applications.

S1. Crystalline Boron Sponges: From Photochemical Design to Petrochemical Applications

Gonzalo Campillo-Alvarado
University of Iowa
email: gonzalo-campillo-alvarado@uiowa.edu

Organoboron compounds are among the most versatile and valuable reagents in organic chemistry. Within this class of molecules, boronic acids and derivatives have attracted broad attention in the field of supramolecular chemistry and crystal engineering owing to the ability to participate in reversible covalent and non-covalent interactions.

In this presentation, we introduce the B←N interaction in boronic esters to direct [2+2]-photodimerizations in the solid state. Specifically, self-assembly of boronic esters with pyridines generate B←N adducts that organize into π-stacks that undergo [2+2] photodimerizations in the solid-state upon UV irradiation. The resulting photoproducts have a bis-tweezer geometry that facilitates sponge-like confinement of aromatic molecules and haloforms. The high selectivity of the bis-tweezer hosts enables the separation of thiophene from benzene, a challenging process in petrochemistry.

S2. New Approaches to Probe Molecular Hydrate Properties and Transformations

Jennifer Swift
Georgetown University
email: jas2@georgetown.edu

This talk will describe two recent computational and experimental approaches used by the Swift group to examine molecular hydrates. First, we will describe how data informatics can be used to identify trends in compounds that crystallize in both hydrate and anhydrate forms. Second, we will describe how time-resolved synchrotron X-ray diffraction aids our understanding of solid state mechanisms in model systems by elucidating the molecular motions that occur during dehydration.

S2. Magnetic Levitation in Chemistry, Materials Science, and Biochemistry

Shencheng Ge

Merck & Co., Inc., Merck Research Laboratories

Department of Analytical Research and Development, West Point, PA 19486 USA

email: shencheng.ge@merck.com

All matter has density. The uses of density to characterize matter date back as early as ~250 BC when Archimedes was believed to have solved "The Puzzle of The King's Crown". Today, measurements of density are used to separate and characterize a range of materials, and their chemical and/or physical changes in time and space. This presentation will describe a density-based technique—Magnetic Levitation ("MagLev")—developed and used to solve problems in the fields of chemistry, materials science, and biochemistry. MagLev has two principal characteristics—simplicity, and applicability to a wide range of materials—that make it useful for a number of applications. For example, separation and characterization of materials (e.g., separations of crystal polymorphs, and also powdered materials), monitoring of chemical reactions on solid supports, quality control of manufactured parts, separation of different types of biological cells, bioanalyses (e.g., label-free bioassays), and many others. Its simplicity and breadth of applications also enable its use in low-resource settings (for example, in evaluating water/food quality, identifying counterfeit drugs, and diagnosing disease.

S2. Dynamic behavior of a channel hydrate system with tailored lattice substitutions

Taylor Watts
Georgetown University
email: tw554@georgetown.edu

A large fraction of organic molecules can crystallize as hydrates, including all four of the DNA nucleobases. Hydrated (H) and anhydrous (A) phases exhibit different physical properties. Here we examine the properties of thymine hydrate (TH) and isomorphous solid solutions of TH prepared with 5-aminouracil (AUr). Using neutron backscattering spectroscopy (NIST Center for Neutron Research) and thermal analysis methods, we are able to observe and quantify significant differences in the local environment of diffusive water and the thermal stability of these hydrate phases. Complementary time-resolved synchrotron PXRD studies (Advanced Photon Source, 17- BM) make it possible to monitor both subtle and dramatic structural changes that occur during the solid-state dehydration processes under controlled environmental conditions. This work serves to illustrate how the reaction kinetics and dehydrated products can be rationally tuned by altering the chemical purity of the precursor hydrate phase.

S2. Benzamide and Beyond: Exploring the Solid-State Landscape of Small Molecules

Noalle Fellah
New York University
Molecular Design Institute
email: nf983@nyu.edu

Polymorphism in solid-state materials is a double-edged sword. Differences in molecular packing can lead to new functional materials. Conversely, overlooking the unanticipated appearance of a new crystal of a commercial compound can be costly. Therefore, characterizing the phase behavior of polymorphs, the factors influencing their occurrence and the discovery of new forms is paramount. In this talk, I will discuss the polymorphic behavior of benzamide and its analogues. Benzamide is a simple derivative of benzoic acid and a common intermediate of pharmaceutical compounds. We first present a new, highly disordered polymorph of benzamide, discovered by melt crystallization concurrently with its crystallization under nanoconfinement. Its crystallographic complexity is elucidated by pairing powder X-ray diffraction analysis with crystal structure simulation. We further explore the crystal landscape of aromatic amides by considering the crystallization behavior of isonicotinamide (INA) and nicotinamide (NA). NA and INA exhibit markedly different growth behavior, despite their structural similarity. We aim to deepen the understanding of solid form properties and uncover nuances in crystallization behavior that can eventually guide process and product design.

S2. Can we make tablets for elastic crystals?

Gerrit Vreeman
University of Minnesota
Pharmaceutical Materials Science and Engineering Laboratories
College of Pharmacy
email: vreem012@umn.edu

Crystal mechanical properties play a central role in powder compaction.1 In accordance with the bonding area-bonding strength (BABS) model, adequate crystal plasticity is necessary to form a high bonding area (BA) between particles in a tablet through permanent plastic deformation.1 Plastically deforming crystals keep their deformed shape and maintain a large bonding area (BA) after compaction, which is highly beneficial for tablet formation.1 The emerging class of elastic crystals, however, are expected to experience a large elastic recovery after compression, which would have a deleterious effect on tabletability due to a low conserved BA between adjacent particles.1–3 However, no systematic studies have been performed on the tableting properties of elastic crystals.2

Although elasticity is detrimental to tablet formation, the 2-dimensionally elastic caffeine:4chloro-3-nitrobenzoic acid methanol solvate (CCM)4 surprisingly exhibited exceptionally good tabletability, even better than some of the best plastically deforming crystals.5,6 This indicates that a high BA must have been formed and conserved between particles in the compact as a result of significant plastic deformation. A low in-die elastic recovery and high degree of plasticity was observed for CCM, indicating a large, highly conserved BA after decompression. Analysis of CCM bonding strength (BS), derived from compactibility plots, also revealed a moderate bonding strength.

The seemingly contradictory observation between exceptional single crystal elasticity in 3-point bending and high powder plasticity during compression can be explained by the activation of the (010) slip plane along the slip direction during compression, which remains dormant during uniaxial 3-point bending. This is a result of the high, pseudo– hydraulic stress condition introduced during compression. To confirm the decoupling between qualitative bending behaviors and powder compression properties, CCM was desolvated to form an isostructural crystalline material (CCMd), which is structurally similar to that of CCM but exhibits brittle fracture during 3-point bending. Despite their differences in mechanical behavior by qualitative 3-point bending, CCMd exhibited bulk powder compaction properties similar to that of CCM. This shows that powder compaction properties are inherently linked to crystal structure but are decoupled from mechanical response during 3-point bending

S2. Measuring temperature-dependent crystal growth kinetics of hybrid organic–inorganic perovskites using *in situ* atomic force microscopy

Amnon Ortoll-Bloch
Cornell University
email: ago26@cornell.edu

Hybrid organic–inorganic perovskites (HOIPs), such as $CH_3NH_3PbBr_3$, have attracted much attention for use in inexpensive, high-performance solar cells. Researchers have established that HOIPs exhibit inverse-temperature solubility (*i.e.*, lower solubility at higher temperature) in certain organic solvents, proposing that, for crystallization to proceed, heating is required to dissolve colloidal aggregates and dissociate lead–solvent complexes. As an additive for HOIP crystallization, formic acid (FAH) lowers the onset temperature for crystallization, perhaps by promoting the dissolution of colloidal particles. It is not known, however, if FAH changes the thermodynamics (*i.e.*, solubility) or kinetics (*i.e.*, growth rates) of HOIP growth. Such insight is essential for growing both large single crystals as well as technologically more relevant HOIP thin films with well-controlled morphologies and electronic properties. Our current work focuses on investigating the kinetics and molecular-level mechanistic details of HOIP single-crystal growth as a function of temperature and FAH concentration. We have used *in situ* fluid-cell atomic force microscopy (AFM) to monitor $CH_3NH_3PbBr_3$ growth in dimethylformamide (DMF). We have demonstrated the capabilities of *in situ* AFM to find spiral growth hillocks on $CH_3NH_3PbBr_3$ crystal surfaces and measure step dynamics as a function of temperature, supersaturation, and FAH concentration. To the best of our knowledge, these AFM measurements are the first-of-its-kind data for observing step flow and growth via screw dislocations on single crystal HOIPs. Our temperature-dependent step velocity measurements indicate that FAH changes both the kinetic growth coefficient (β) and the thermodynamic solubility of $MAPbBr_3$ in DMF. Our findings suggest that

optimization of FAH concentration could help tune growth rates to control crystal size and morphology. These synthesis optimizations are vital to improve the performance of HOIP devices based on both single crystals and thin films.