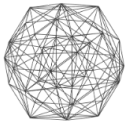
VIRTUAL SYMPOSIUM ON SOLID-STATE ORGANIC CHEMISTRY

Tuesday, May 24, 2022
Wednesday, May 25, 2022



Molecular Design Institute
NEW YORK UNIVERSITY

Message from the Organizing Committee

Welcome to the 3rd Annual Virtual Symposium on Solid-State Organic Chemistry! The NYU Molecular Design Institute and Merck & Co. are proud to team up once more to bring you this exciting, two-day virtual symposium spanning research groups all across the globe. Though we may be emerging from the pandemic, VS^3OC provides a platform for faculty, students, postdocs, industrial research scientists, and national lab investigators to convene informally and stay connected without burdening travel budgets and busy calendars.

The global pandemic catapulted us into a new reality, a virtual reality, but with all its challenges, it also provided 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. Merck & Co., and NYU teamed up in May 2020 to organize a virtual symposium in the area of organic solid-state chemistry whereby graduate students and postdocs were invited to share their research with their peers from other institutions. This marked the inception of VS^3OC, an event we held once more in May 2021, and continued in spirit with the spin-off Bimonthly Symposium on Solid-State Organic Chemistry (BOSSs), a series of virtual bi-monthly mini-meetings. We are delighted to be able to continue this tradition as we gear up for the Third Annual 2022 VS^3OC, featuring two exciting days of talks and insight to the expansive pot of organic solid-state research happening globally.

We are ecstatic that you can join us! Thank you to all our speakers and all participants tuning in! It is your participation and contributions that have made this event a unique and exciting science get-together.

List of Participating Institutions / Research Groups

Takuji Adachi, University of Geneva

Shuang Chen, AbbVie Inc.

Michael Hall, University of Newcastle / Indicatrix Co.

Travis Holman, Georgetown University

Kristin Hutchins, Texas Tech University

Qi Jiang, Boehringer Ingelheim

Alfred Lee, Merck & Co., Inc

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

Len MacGillivray, University of Iowa

Krishna Rajan, SUNY Buffalo

Torsten Stelzer, University of Puerto Rico - Rio Piedras

Jennifer Swift, Georgetown University

Mark Tuckerman, New York University

Rein Ulijn, Hunter College CUNY

Michael Ward, New York University

Lian Yu, University of Wisconsin

List of Career Panelists and Affiliations

Session Moderator: **Justin Newman**, Merck & Co.

Noalle Fellah
Senior Scientist
Pfizer Inc.

Clara Hartmanshenn
Senior Scientist
Merck & Co.

Maya Lipert
Principal Research Scientist
AbbVie Inc.

Fredrik Nordstrom
Senior Research Fellow
Boehringer Ingelheim

James Ormes
Associate Principal Scientist
Merck & Co.

Scientific Program

Day 1 (S1) – Tuesday, May 24, 2022 Zoom: https://nyu.zoom.us/j/97495578780

13:00 **Michael Ward,** New York University, Opening Remarks
Session Moderator: Chunhua (Tony) Hu, New York University

13:10 **Michael Hall,** University of Newcastle / Indicatrix Co. (Plenary Talk)
High throughput encapsulated nanodroplet crystallization (ENaCt) of small organic molecules

13:40 **Andrew Kelly,** Georgetown University
"Click"-Like η6-Metalation/Demetalation of Aryl Iodides as a Means of Turning "ON/OFF" Halogen Bond Donor Functionality

14:10 **Qi Jiang**, Boehringer Ingelheim
Multicomponent Crystals in Pharmaceutical Applications: From Solid State to Therapeutics

14:40 **Changan Li**, University of Iowa
Molecules Generated in Crystals: Cubane-like Cages and Rapid Functional Group Diversifications

15:10 **Break**

Session Moderator: Allie Dillon, New York University

15:20 **Kristin Hutchins,** Texas Tech University (Plenary Talk)
Using Mixed Environments and Dynamic Behaviors to Tune Solid-State Materials

15:50 **Yuhui Li,** University of Wisconsin
PolyAmorphism of D-mannitol: A low-density second amorphous phase with mesoscopic order

16:20 **Shuang Chen,** AbbVie Inc.,
Overcoming Bioavailability Challenges of HCV Drug Dasabuvir through a Salt of Very Weak Acid for Oral Delivery

16:50 **Michael Ward**, New York University, Closing Remarks

Day 2 (S2) – Wednesday, May 25, 2022

13:00	**Alfred Lee**, Merck & Co., Opening Remarks
13:10	**Takuji Adachi**, Université de Genève (Plenary Talk) *In situ optical spectroscopy of crystallization: One crystal nucleation at a time*
13:40	**Arpan Mukherjee,** SUNY Buffalo *Applicability of Machine Learning using Hirshfeld surfaces as chemical representations*
14:10	**Richard Hong,** New York University / AbbVie Inc., *Molecular Crystals on a Humid Summer Afternoon – Probing the Effects of Entropy and Hydration From Atomistic Insights to Industrial Implications*
14:50	**Break**
	Session Moderator: Justin Newman, Merck & Co.,
15:20	**Rein Ulijn,** Hunter College CUNY (Plenary Talk) *Supramolecular Peptide Crystals*
15:50	**José Hernández Espinell,** University of Puerto Rico *Solvent-mediated Polymorphic Transformations in Molten Polymers: The Account of Acetaminophen*
16:20	**Megan Fleming,** Georgetown University *Cytosine Monohydrate under thermal and mechanical stress*
16:50	**Alfred Lee**, Merck & Co., Closing Remarks
17:00	**Career Panel hosted by Merck & Co.,** (https://nyu.zoom.us/j/96701829809)

Presentation Abstracts

S1. *High throughput encapsulated nanodroplet crystallization (ENaCt) of small organic molecules*

Michael Hall

University of Newcastle / Indicatrix Co.

Senior Lecturer in Organic and Biological Chemistry

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The major bottleneck in the analysis of small molecules by single crystal X-ray diffraction is accessing suitable single crystals. Classical methods require large quantities of analyte and considerable laboratory time to find suitable crystallization conditions. We have recently described our Encapsulated Nanodroplet Crystallisation technology (ENaCt) which allows 100's of individual crystallization experiments to be undertaken simultaneously, with only a few milligrams of analyte (Chem, 2020, 1755-1765). We have successfully applied this approach to a wide range of organic soluble small molecules, including APIs, challenging crystallizations and highly polymorphic molecules (e.g. ROY). Continuing developments in the area of ENaCt is helping to accelerate both industrial and academic research through reliable, early access to full structural and solid state analysis of small organic molecules of interest.

S1. *"Click"-Like η6-Metalation/Demetalation of Aryl Iodides as a Means of Turning "ON/OFF" Halogen Bond Donor Functionality*

Andrew Kelly

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η^6-Metalated aryl halides—particularly the aryl iodides—are recognized for the first time as a class of effective halogen bond (XB) donors and the fully reversible, click-like η^6-metalation/demetalation of aryl iodides by cyclopentadienylruthenium ($[(h^5\text{-}C_5H_5)Ru^{II}]^+$) moieties is shown to be a convenient means of turning ON/OFF (*i.e.*, amplifying/*suppressing*) XB donor functionality. As an illustration, $[CpRu(MeCN)_3][PF_6]$ is shown to react effectively quantitatively with iodobenzene and the diiodobenzenes (ArI_n, n = 1, 2) at room temperature in acetone to yield $[CpRu(\eta^6\text{-}ArI_n)][PF_6]$ sandwich compounds. Photochemically-induced demetalation in CH_3CN, using violet LEDs (405 nm), quantitatively reverts these sandwich compounds to their ArI_n and $[CpRu(MeCN)_3][PF_6]$ starting materials, without C-I bond homolysis. Analysis of the crystal structures of $[CpRu(\eta^6\text{-}ArX_n)]^+$ salts reveals that the η^6-metalated aryl iodide cations are effective, charge-assisted XB donors that are functionally analogous to widely studied *N*-alkyl substituted (or protonated) iodopyridinium XB donors. XB-induced association of the weakest of these XB donors, $[CpRu(C_6H_5I)]^+$, with diazobicyclo[2.2.2]octane (DABCO) in relatively polar acetone solvent is established by NMR spectroscopy. $[CpRu(C_6H_5I)][BPh_4]$ and $[CpRu(1,4\text{-}C_6H_4I_2)][BPh_4]$ co-crystallize with DABCO and the structure of $[CpRu(1,4\text{-}C_6H_4I_2)][BPh_4]\cdot DABCO\cdot Et_2O$ is reported. DFT

calculations support amplification of the positive electrostatic potential of the Ar-I sigma hole and XB donor functionality or aryl iodides upon $[CpRu]^+$-functionalization.

S1. *Multicomponent Crystals in Pharmaceutical Applications: From Solid State to Therapeutics*

Qi Jiang

Boehringer Ingelheim

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Pharmaceutical multicomponent crystals (MCCs) including salts and co-crystals of active pharmaceutical ingredients (APIs) are an active focus of research to improve various physicochemical properties of drugs. The concept of modifying the physicochemical properties of a drug molecule by forming a pharmaceutical cocrystal has generated immense interest due to its multidrug therapy. In this work, we demonstrate that the pharmaceutical Artesunate (AS), a derivative of Artemisinin (ART), forms a 1: 1 salt with two cinchona alkaloids: Quinine (QN) and Cinchonidine (CND), representing a first report of MCCs combining two major types of antimalarial drugs. The AS-QN and AS-CND MCCs exhibit stereochemical selectivity for different cinchona alkaloids. The crystal structure of AS-CND, determined by single crystal X-ray diffraction (SCXRD), reveals the unique hydrogen bonding network between one AS molecule and two adjacent CND molecules. 13C and 15N solid-state NMR (SSNMR) spectra confirm formation of the MCCs and identify proton transfer from the AS to QN or CND molecules, indicating both AS-QN and AS-CND are salts. Aqueous solubility testing in different pH values shows the solubility enhancement of both AS-QN and AS-CND salts relative to the independent components. Overall, the new salts are novel candidates for therapeutic antimalarial drugs.

S1. *Molecules Generated in Crystals: Cubane-like Cages and Rapid Functional Group Diversifications*

Changan Li

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Crystals used to be considered as the "graveyard" of chemistry due to the fact that molecules in crystals are closely packed within the lattices and are restricted from participating in any transformative activities. However, recent developments in crystal engineering have revealed organic solid state to be a highly attractive medium (i.e. degree of organization, solvent-free) to direct the formation of covalent bonds and construct molecules. In this context, we have developed a strategy of using small-molecule templates to participate in hydrogen-bond-driven self-assembly to direct the formation of carbon-carbon single (C-C) bonds in solids via intermolecular [2+2] photodimerizations. While experiencing significant successes, there is a growing need to generate complex cyclobutanes in the form of three-dimensional cubanes as well as a method to rapidly diversify the photoproduct. Here we describe the solid-state construction of a highly-symmetric cubane-like tetraacid cage by UV-irradiating a binary cocrystal of two different cyclic dienes. A method to rapidly diversify molecules formed in organic crystals will also be introduced with aryl nitriles that serve a dual role as both hydrogen-bond-acceptors and modifiable organic groups.

S1. *Using Mixed Environments and Dynamic Behaviors to Tune Solid-State Materials*

Kristin Hutchins

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Thermal expansion (TE) is the response of a material to a change in temperature. Materials that undergo well-controlled TE are useful in high precision instruments, sensors, and aerospace applications. TE behavior of a solid largely depends on the type of bonds that comprise it. Along a given direction, the expansion will depend on the bonds that lie along that direction. For example, having only strong bonds, in cases such as inorganic or network solids, leads to minimal TE. On the other hand, having weaker, noncovalent interactions leads to larger TE. Here, we describe our efforts to design organic solids that undergo molecular motion in response to temperature as a platform for achieving large TE. We will discuss the use of mixed cocrystals as a platform for fine-tuning TE behaviors in organic solids. Finally, we will discuss our efforts in engineering anisotropic and switchable TE behaviors.

S1. *PolyAmorphism of D-mannitol: A low-density second amorphous phase with mesoscopic order*

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Polyamorphism, the existence of two amorphous phases of the same substance separated by a first-order transition, is an important and often controversial phenomenon. The polyamorphism of D-mannitol has been described as "the most recent (and perhaps the cleanest) example". We show that the normal liquid of D-mannitol transforms to a low-density amorphous phase (LDA) that exhibits low-angle X-ray scattering peaks indicative of mesoscopic order. Notably, the peak at 0.24 Å-1 (corresponding to a real-space periodicity of 3 nm) is absent from any crystalline phase and disappears upon crystallization. In the LDA, the non-polar hydrocarbon groups are farther apart from each other, consistent with reduced density, while the hydrogen-bond network undergoes significant reorganization from the second coordination shells and beyond. The LDA has weak smectic order as seen in the crystal structures but the new 3 nm density modulation is completely devoid of any crystalline counterpart. This new length scale could be associated with the locally favored structures or the densely nucleated LDA domains in the normal liquid.

S1. *Overcoming Bioavailability Challenges of HCV Drug Dasabuvir through a Salt of Very Weak Acid for Oral Delivery*

Shuang Chen

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Senior Principal Research Scientist

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Dasabuvir is a non-nucleoside polymerase inhibitor for the treatment of hepatitis C virus (HCV) infection. It is an extremely weak diacidic drug (pKa = 8.2 and 9.2) and a prolific solvate former. Due to its exceedingly low aqueous solubility (≤ 0.127 µg/mL at pH 1 – 6.8, dose number of 1.31 × 104), crystalline dasabuvir free acid exhibited poor oral bioavailability in animal PK assessment. While salt formation has been widely used to enhance solubility and dissolution rate of solids, this approach has rarely been applied to develop oral solid dosage forms for acidic drugs as weak as dasabuvir due to concerns of rapid disproportionation and crystallization of free acid. In this presentation, we highlight our efforts in identifying dasabuvir monosodium monohydrate as drug substance that is stable, manufacturable, and significantly enhances dissolution and oral absorption of this poorly soluble drug. The oral delivery of dasabuvir through salt approach has enabled the commercialization of triple combination direct acting antiviral HCV regimen Viekira Pak. The methodologies and solutions identified in targeted studies to overcome technical challenges (i.e., incorporation of polymers to inhibit crystallization and disproportionation and species mapping to enable salt manufacturing process, etc.) can be applied to other insoluble compounds.

S2. *In situ optical spectroscopy of crystallization: One crystal nucleation at a time*

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Establishing the microscopic picture of crystal nucleation could lead to better understanding and control of crystallization process including polymorphism. Stochastic and heterogeneous nature of crystallization has been a major challenge to observe the nucleation event experimentally. While recent literature observed the presence of amorphous or featureless prenucleation aggregates before crystal nucleation, how the structural order emerges from these "amorphous" aggregates remains a question.

We developed a method called Single Crystal Nucleation Spectroscopy (SCNS) which spectroscopically probes crystallization process one crystal nucleation at a time. A single focused laser beam serves a dual role as to spatially confine a crystal nucleation and to generate Raman spectrum during the nucleation process. We achieved measuring Raman spectral evolution of a single glycine crystal formation in aqueous solution with 46 ms time resolution at room temperature. The spectral analysis by a non-supervised spectral decomposition technique uncovered the Raman spectrum of pre-nucleation aggregates as well as its critical role as an intermediate species in the dynamics. The comparison with simulated spectra from glycine solutions suggests that glycine forms hydrogen-bonded linear networks as likely precursors of crystallization. This work provides a strong impetus for accelerating the investigation of crystal nucleation by optical spectroscopy.

S2. *Applicability of Machine Learning using Hirshfeld surfaces as chemical representations*

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There is an increasing research interest in using Hirshfeld surfaces as chemical representations. Hirshfeld surfaces are 3D polytopes that encode rich information about the packing modes and intermolecular interactions of a crystal structure. Calculating Hirshfeld surfaces is computationally inexpensive and is less memory-intensive regardless of the type of chemistry. In this work, we have shown Hirshfeld surfaces as a suitable descriptor for applications of Machine Learning (ML) algorithms that address different scientific questions pertaining to inorganic crystals. Specific cases of predicting geometric and thermodynamic properties for perovskite crystals are used to demonstrate the capacity of Hirshfeld surfaces in predicting DFT properties with extremely high accuracy. It is demonstrated how different ML algorithms work upon different mathematical transformations of the 3D polytopes and what features of the Hirshfeld surfaces these algorithms look at while making their predictions.

S2. *Molecular Crystals on a Humid Summer Afternoon – Probing the Effects of Entropy and Hydration From Atomistic Insights to Industrial Implications*

Richard Hong

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Reversible solid phase changes, mediated by either temperature or water, can often occur in many molecular crystals at both ambient and process-relevant conditions. Such transformations can often have significant implications for the properties of the crystalline solid. As such, predicting these transformations and understanding their resulting structures is of great importance.

In the first part of this talk, I will present an example of how we have utilized molecular simulations to elucidate the mechanisms behind the enantiotropic transformation between the orthorhombic and monoclinic versions of paracetamol Form III. Through standard molecular dynamics in addition to Crystal Adiabatic Free Energy Dynamics, an MD-based enhanced sampling approach for crystalline systems, we have extracted both the free energy landscape and critical insights into the underlying entropy mediated mechanism of this transformation.

In the second part of my talk, I will discuss how both entropy and hydration can affect the solid-state properties, and developability of a hydrated commercial HCV drug. By combining detailed experimental and computational techniques, we show from an assessment of its respective hydration and dehydration behavior, unique hybridized

non-stoichiometric/stoichiometric features of its hydrates. The implications of these features on their solid-state properties and required manufacturing controls are then discussed.

S2. *Supramolecular Peptide Crystals*

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The talk will explore the use of computation [1] and experimental methods to explore how to program supramolecular order and disorder through side chain interactions in short peptides, and how the conformations adopted by these peptides can be exploited to regulate self-assembly and crystallization [2]. Based on these insights, we are developing a class of supramolecular materials that change their properties in response to specific chemical stimuli via induced fit supramolecular recognition, and consequent non-linear amplification resulting in deformation of their macroscopic structure. These supramolecular materials are composed of designed short peptides that self-assemble to form porous supramolecular crystal lattices that are composed of periodic stiff/ordered and reconfigurable/disordered domains, that show dramatic and reversible changes in H-bond patterns upon variation of humidity [3].

1. P.W.J.M. Frederix, et al., Nature Chem., 2015, 7, 30-37.

2. A. Lampel, et al. Science, 2017, 356, 1064.

3. R. Piotrowska, et al., Nature Materials, 2021, 20, 403-409.

S2. *Solvent-mediated Polymorphic Transformations in Molten Polymers: The Account of Acetaminophen*

José Hernández Espinell

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Solvent-mediated polymorphic transformations (SMPTs) employing non-conventional solvents (polymer melts) is an underexplored research topic that limits the application of polymer-based formulation processes. Acetaminophen (ACM), a widely studied active pharmaceutical ingredient (API), is known to present SMPTs spontaneously (< 30 s) in conventional solvents such as ethanol. *In situ* Raman spectroscopy was employed to monitor the induction time for the SMPT of ACM II to I in polyethylene glycol (PEG) melts of different molecular weights (M_w, 4 000, 10 000, 20 000, 35 000 g/mol). The results presented here demonstrate that the induction time for the SMPT of ACM II to I in PEG melts is driven by its diffusivity through the polymer melts. Compared to conventional solvents (i.e., ethanol) the mass transfer (diffusion coefficient, *D*) in melts is significantly hindered ($D_{ethanol}$ = 4.84x10^{-9} m^2/s > D_{PEGs} = 5.32 x 10^{-11} – 8.36 x 10^{-14} m^2/s). Ultimately, the study proves that the induction time for the SMPT can be tuned by understanding the dispersant's physicochemical properties (i.e., η), and thus, the *D* of the solute in the dispersant. This allows to kinetically access and stabilize metastable forms or delay their transformations under given process conditions.

S2. *Cytosine Monohydrate under thermal and mechanical stress*

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A large percentage of molecular compounds—materials ranging from explosives to pharmaceuticals—can crystallize in different hydration states. The relative stability of hydrated and anhydrous crystal forms depends to some extent on the environment (e.g. temperature, pressure, relative humidity). A wide range of environmental conditions can be encountered in the manufacturing and tableting processes, and these changes can potentially lead to dehydration or other solid state crystal transformations. Through our investigations on cytosine monohydrate (CM), a model hydrate of DNA nucleobase, we aim to better understand how mechanical and thermal stresses alter material structure and properties. Here we show that CM crystals prepared with select quantifiable dopants which include in low concentrations (< 2.0% wt) exhibit markedly different thermal properties than the pure crystals. Nanoindentation experiments performed on CM single crystals at CINT-LANL yielded elastic modulus and hardness values, and post-indent atomic force microscopy images revealed highly anisotropic pile up along specific crystallographic directions. With a better understanding of the deformation mechanisms in this system in hand, the next phase of this work will involve defect engineering as a means to rationally tune the mechanical and thermal properties of the system.