The 78th Annual Pittsburgh Diffraction Conference
SSRL - SLAC National Accelerator Lab
September 19-21, 2021

PDC 2021 BOOKLET

Conference Organizers:

Silvia Russi, Aina Cohen, Wah Chiu

Session Chairs:

Leighton Coates, Darya Marchany, Kevin Stone, Sarah Bowman, Jennifer Bridwell, Apurva Mehta, Cora Lind-Kovacs, Blaine Mooers, Tzanko Doukov

Poster Session Organizer:

Clyde Smith

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PROGRAM

Sunday 19 September

- **15:00 - 16:00 Welcome Social & Sponsor Exhibits**

- **16:00 - 17:00 Diffraction Games (Game Night Sponsored by DECTRIS Ldt.)**

Monday 20 September

- **8:00 - 12:00 Parallel Session 1: Metals in Biology**
  Chairs: Sarah Bowman and Jennifer Bridwell

  Metals play critical roles in biology, conferring unique reactivity, enabling challenging chemistry and redox reactions, and functioning as structural scaffolds. It has been estimated that 30-50% of all proteins bind a metal or metal cofactor. Synchrotron-based techniques enable experiments that measure and monitor metal active site geometry and protein structure, as well as permitting elemental analysis to probe exactly what metals are present in a sample. This workshop brings together many different research areas linked by the common theme and use of SLAC facilities including the use of spectroscopic, X-ray crystallography, XFEL, and cryo-EM methods to study metalloprotein structure and function.

  - 8:00-8:20 Introduction to session and Metalloprotein Design Principles for Site-Selective Hydroxylation, Jennifer Bridwell-Rabb (University of Michigan)

  - 8:20-8:50 Observing Extradiol Dioxygenase in Action Through a Crystalline Lens, Aimin Liu (University of Texas at San Antonio)

  - 8:50-9:20 Sam Webb (SLAC/SSRL)

  - 9:20-9:30 Coffee Break

  - 9:30-10:00 Ingrid Pickering (University of Saskatchewan)

- 10:00-10:20 Using Spectroscopy for the Pre-Characterization of Enzyme Reactions in Microcrystals for Effective Mix-and-Inject Experiments at X-ray Free-Electron Lasers, Kara Zielinski (Cornell University)

- 10:20-1030 Coffee Break

- 10:30-11:00 Structural Insights into the Transcriptional Regulation by WhiB-Like Proteins, Limei Zhang (University of Nebraska-Lincoln)

- 11:00-11:30 The Great Metallocofactors of Biology, Catherine Drennan (MIT)

- 11:30-12:00 Richard Neutze (University of Gothenburg)

- **8:00 - 12:00 Parallel Session 2: Scientific Opportunities for Remote Access to User Facilities**
  Chair: Kevin Stone

  Constraints imposed by the global pandemic have spurred the development of remote access tools to enable user science when users are unable to travel. While not all experiments are conducive to remote operations, some types of measurement have become easier and better than before. In this workshop, we will review the advances that have been made for remote access to beamlines at SSRL and the impact these have had on user science. We will also cover how continued development of remote access and automation tools can impact the way that users do science at SSRL well into the future.

  - 8:00-8:20 Welcome and Introduction, Kevin Stone (SSRL)

  - 8:20-8:50 Sarah Hesse (SLAC)

  - 8:50-9:20 TBD

  - 9:20-9:50 Alex Wallace (LCLS)

  - 9:50-10:10 Coffee Break

- 10:10-10:40 Automation and Remote Access to Room and Elevated Temperatures Experiments at the SSRL Structural Biology Beamlines, Silvia Russi (SSRL)

- 10:40-11:10 Automation and Robotic Sample Changes for Materials Science Scattering Beamlines at SSRL, Kevin Stone (SSRL)

- 11:10-12:00 Discussion

- **12:00 - 13:00** **SSRL Virtual Tour**
  Tour Guides: Clyde Smith and Sam Webb

- **13:00 - 14:30** **Plenary Session of the Pittsburgh Diffraction Conference**
  Chair: Silvia Russi

  - 13:00-14:00 Keynote talk: Force-dependent allosteric regulation of molecular assemblies in cell-cell adhesion, William Weis (Stanford University)

  - 14:00-14:30 Young Investigator talk: Deep neural language modeling enables structurally and functionally active protein generation, Eric Greene (UCSF)

- **14:30 - 16:00** **Parallel Session 1: Metals in Biology (cont.)**
  Chairs: Sarah Bowman and Jennifer Bridwell

  - This second part of the Metals in Biology workshop will include time for discussion around different research areas linked by the common theme and use of SLAC facilities. Please join this popular workshop to learn the latest and spark new ideas and collaborations.

- **14:30 - 16:00** **Parallel Session 2: Diffraction and Material Research**
  Chair: Apurva Mehta

  Topics in this session involved the study of crystal structure though application of X-ray diffraction, X-ray spectroscopy and neutron diffraction at users' facilities.

  - 14:30-15:00 Kevin Stone (SSRL)

- 15:00-15:30 The Diffraction Suite at ORNL's world leading neutron sources: High flux Isotope Reactor(HFIR) and Spallation Neutron Source (SNS), Clarina Dela Cruz (ORNL)

- 15:30-16:00 Studying Metal Organic Framework Formation using Scattering Techniques, Gino Giri (University of Virginia)

- **16:00 - 18:00** **Poster Session & Sponsor Exhibits**

Tuesday 21 September

- **8:00 - 12:00** **Parallel Session 1: Computational Methods in Structural Sciences**
  Chairs: Blaine Mooers and Tzanko Doukov

  This workshop covers all computational methods (Bayesian, maximum likelihood, optimization, machine learning, deep learning, and so on) in data processing, structure determination, structure refinement, and structure analysis in structural biology. This is a sequel to our popular workshop at the 2020 SSRL/LCLS Users Meeting "Machine learning in the structural sciences". We have broadened the scope of the algorithms to be more inclusive, and we narrowed the focus to structural biology to better reflect the interests of the audience that participated last yest. We plan to have a new line-up of speakers and aim to have speakers from the fields of X-ray crystallography, SAXS, cryo-EM, and micro electron diffraction.

  - 8:00-8:05 Introduction, Blaine Mooers (University of Oklahoma)

  - 8:05-8:30 Electron crystallography for X-ray crystallographers, Tim Gruene (Universität Wien)

  - 8:30-8:55 ISOLDE: Bringing macromolecular model building to life, Tristan Croll (Cambridge University)

  - 8:55-9:20 Advances in heterogeneous cryo-EM reconstruction with cryoDRGN, Ellen Zhong (MIT)

  - 9:20-9:45 Vagabond: torsion angle-based refinement for structural biology, Helen Ginn (Diamond Light Source)

- 9:45-9:55 Coffee Break
- 9:55-10:20 Simulations and refinement strategies for biomolecular crystals, David Case (Rutgers University)
- 10:20-10:45 Flexible tools for scaling, merging, and analyzing your diffraction data, Doeke Hekstra (Harvard University)
- 10:45-11:10 Efficient evaluation of structural dynamics and mechanisms of function using network models, Ivet Bahar (University of Pittsburgh)
- 11:10-11:35 New computational approaches for interpreting small and wide angle scattering data, Lois Pollack (Cornell University)
- 11:35-12:00 SAXS: ISOLDE: Bringing macromolecular model building to life, Steven Meisberger (Cornell University)

- **8:00 - 12:00** **Parallel Session 2: Complimentary Techniques in Structural Biology**
  Chairs: Leighton Coates and Darya Marchany

  The application of complimentary techniques in structural biology promote scientific discovery by bringing about a deeper understanding of the relationship between protein structure and function. Presentations in this workshop will cover scientific findings resulting from the use single crystal neutron and X-ray diffraction, NMR and powder diffraction at cryogenic and room temperatures.

  - 8:00- 8:30 Direct Detection of Coupled Proton and Electron Transfers in Human Mitochondrial Manganese Superoxide Dismutase, Gloria Borgstahl (University of Nebraska)
  - 8:30-9:00 Site Mixing and Complex Magnetic Structures of Topological Insulators MnSb2Te4 and MnBi2Te4, Yaohua Liu (ORNL)
  - 9:00-9:30 Searching for Lattice Site Ordering in Combinatorial High Throughput Heusler Materials, Nathan Scott Johnson (Stanford University)

- 9:30-10.00 Coffee Break

- 10:00-10:30 Crystal structure of the SARS-CoV-2 NSP3 macrodomain determined using neutron diffraction, Galen Corey (UCSF)

- 10:30-11:00 Synergistic Use of X-ray and NMR Improves Structural Biology, Fatema Bhinderwala (University of Pittsburgh)

- 11:00-11:30 Room temperature X-ray crystallography reveals insights into directed evolution and protein design, Michael Thompson (UC Merced)

- **12:00 - 13:00** **LCLS Virtual Tour**
  Tour Guides: Aina Cohen and Meng Liang

- **13:00 - 16:00** **Parallel Session 1: CryoEM of macromolecules and cells**
  Chair: Wah Chiu

  CryoEM RNA and protein-nucleic acid complex. RNA structure is challenging for either NMR or X-ray crystallography. The advances in cryoEM have made possible for solving RNA structure at 2-4 Å resolution. The speakers have used our SLAC cryoEM facilities or data from structures solved at SLAC.

  - Alfonso Mondragon (Northwestern University)

  - Integration of biochemical and structural data to investigate stabilizing triplex-forming elements in RNA, Seyed Torabi (Yale University)

  - Accelerating RNA structure determination with cryo-EM and DRRAFTER computational modeling, Kalli Kappel (MIT Board Institute)

  - Cryo-EM reveals multiple states in splicing reaction of Tetrahymena intron, Zhaoming Su (Sichuan University)

  - Determination of small RNA-only 3D structures by Cryo-EM, Kaiming Zhang (National Natural Science Foundation of China NSFC)

- **13:00 - 16:00** **Parallel Session 2: Materials and Catalysis Research**
  Chairs: Kevin Stone and Cora Lind-Kovacs

Solutions to many of the challenges facing us today need discovery of new functional materials. Recent results that involve the application of X-ray diffraction to applied materials research will be presented.

- 13:00-13:25 Quantification of heterogeneous, irreversible lithium plating in extreme fast charging of lithium-ion batteries using X-ray diffraction, Chuntian Chao (BNL)
- 13:25-13:50 Yi Cui (Stanford University)
- 13:50-14:15 Guided discovery and exploration of Mn-based magnetocaloric materials, Joya Cooley (California State University, Fullerton)
- 14:15-14:35 Coffee Break
- 14:35-15:00 New capabilities and upcoming opportunities for structural analysis at the APS, Uta Ruett (APS)
- 15:00-15:25 Roopali Kukreja (UC Davis)
- 15:25-15:50 High Pressure Deformation of Al7075 Alloy, Abhinav Parakh (Stanford University)

- **16:00 - 17:00 Poster awards and PDC business meeting (Chairs: Silvia Russi and Leighton Coates)**

POSTER ABSTRACTS

SB-01 Tackling lysosomal storage diseases by enzyme fold stabilization

Agnieszka Bogucka[(1)], Tracey M. Gloster[(1)]

(1) University of St. Andrews, UK

N-acetylglucosamine 6-sulfatase (GNS) catalyses the hydrolysis of sulfate in heparan sulfate (HS) and keratan sulfate (KS). In Sanfilippo D syndrome (MPS IIID), caused by autosomal recessive mutations in the GNS gene, undegraded N-acetylglucosamine 6-sulfate is retained and accumulated in primarily the central nervous system (CNS). These are usually missense mutations that cause changes in single amino acids and occur outside of the enzyme's active site. These mutations disrupt the enzyme's native folding in the endoplasmic reticulum (ER) and affect its efficiency, thermodynamic stability, and lysosomal trafficking. This faulty enzyme folding leads to enzyme retention in the ER, aggregation, retro-translocation into the cytosol and degradation by ER-associated degradation (ERAD). However, it has been shown that these misfolded enzymes otherwise retain either full or partial catalytic activity.

Currently, the treatments used for lysosomal storage disorders (LSDs) are mostly focused on increasing the cellular activity or level of the defective enzyme to decrease cellular levels of accumulated substrate. These treatments involve enzyme replacement which is not successful with LSDs affecting the CNS, such as MPS IIID, due to the inability of these large protein molecules to cross the blood–brain barrier (BBB).

However, a threshold enzyme activity of approximately 10% was shown to be sufficient to prevent lysosomal storage in many of these diseases and activity of 3-5% is often enough to delay or slow down the progression of the disease. This retention of residual activity could be used if enzymes were to be able to get through the lysosomal trafficking out of ER and Golgi and into the lysosomes. Development of pharmacological chaperone therapies (PCT), where small-molecule ligands are used to selectively bind and stabilize mutant enzymes could potentially increase lysosomal trafficking, sulfatase cellular levels and activity.

To find these pharmacological chaperones, XChem fragment screening at Diamond Light Source has been performed to identify potential small molecules which bind to sites on GNS. It is hoped this will be the starting point to develop a molecular chaperone that would selectively bind to GNS, stabilize its fold and allow it to exit from the ER, be post-translationally modified (e.g. glycosylation) and trafficked into to the lysosomes. In the lysosome, the chaperone would be either displaced from the active site of the enzyme by the excess natural substrate, dissociate, or stay bound to an allosteric site.

This approach has the potential to overcome some of the limitations encountered by existing therapies, since molecular chaperones show good oral bioavailability, broad tissue distribution to key cell types and tissues, and have the ability to diffuse across blood-brain-barrier.

SB-02 Neutron diffraction directly determines protonation states in SARS-CoV-2 main protease

Daniel W. Kneller[1, 2], Leighton Coates[1, 2], Andrey Kovalevsky[1, 2]

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(2) National Virtual Biotechnology Laboratory, Washington DC, USA

SARS-CoV-2, the virus that causes COVID-19, introduced the ongoing worldwide economic and public health calamity. The viral cysteine protease enzyme (Mpro) serves as the 'heart' of viral replication and thus has been a major target for structure-guided drug design of small-molecule inhibitors. Historic strategies derive atomic scale understanding of enzymes from cryogenically preserved samples using X-ray diffraction that are hindered by cryo-artifacts and the inability to determine protonation states. Neutrons provide an ideal probe to directly visualize protonation states of ionizable residues at near-physiological temperatures. The macromolecular neutron diffraction capabilities at Oak Ridge National Laboratory are providing unique contributions to the pandemic response through direct protonation state determination of key residues in the Mpro active site.

The neutron crystal structure of ligand-free Mpro provided direct observation of protonation states in any cysteine protease enzyme for the first time. The atypical catalytic Cysteine-Histidine dyad exists in the zwitterionic state at rest, pre-organized for immediate catalysis. A follow-up neutron crystal structure of deuterated Mpro in complex with a covalent inhibitor witnessed the maintenance of a net +1 electric charge of the active site through remodeling of the active site electrostatics. A third neutron structure of Mpro bound to a non-covalent inhibitor reveals the net +1 charge can also be achieved through a completely different re-combination of protonation states. Neutron crystallography of Mpro showcases the importance of accurate experimental models for mechanistic, in silico, and drug design research to better understand pathogens at the atomic level. All results are immediately shared with the scientific community in order to contribute real-time insights to create novel antiviral therapeutics to fight COVID-19.

SB-03 Structural and functional characterization of ATPase domain of Rv3870 of M. tuberculosis ESX-1 system

Arkita Bandyopadhyay(1), Ajay Kumar Saxena(1)

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Successful pathogenesis by Mycobacteria requires evasion of host immune system and survive within the macrophage. For this purpose virulence factors which needs to be secreted out of the bacterial cytosol to impair phagosomal acidification, inhibition of phagoslysosome formation and escape into the host cytosol. For secretion of molecules Mycobacteria uses Type VII secretion system, a ~1500kDa protein complex containing a transmembrane channel, membrane associated and cytosolic ATPases. The five different ESX components in M. tuberculosis are involved in varied class of physiological functions including virulence factor transport and are collectively called the Type VII secretion system (T7SS). ESX-1 is involved in virulence factor transport. Rv3870 and Rv3871 are two of the eight major components of ESX-1 and are responsible for the translocation of ESAT-6/CFP-10 complex and both are in the ASCE group of AAA+ ATPases. Rv3871 is a cytosolic ATPase associated with the cytosolic domain of the membrane anchored ATPase Rv3870.

The diderm mycolate Mycobacterium tuberculosis is a member of MTBC (Mycobacterium tuberculosis complex) which includes Mycobacterium tuberculosis, Mycobacterium canettii, Mycobacterium africanum, Mycobacterium microti, Mycobacterium bovis, Mycobacterium caprae and Mycobacterium pinnipedii. Not all members of MTBC are pathogenic to humans; some causes infection in other species as well. In M. tuberculosis several types of export machineries have been identified like Sec, Tat, ABC transporters and ESX secretion system. Not all are involved in virulence. Each ESX secretion system has five different components termed as ESX Conserved Components A to E (EccA to E). The ESX-1 secretion system is involved in secretion of virulence factors like ESAT-6, CFP-10, EspA, EspC, and EspB. The ESX-1 secretion system have both membrane bound and cytosolic components. The EccA1 of ESX -1 is a cytosolic ATPase and the rest are membrane associated. The EccC1 complex of M. tuberculosis exists as two different proteins denoted as Rv3870 (EccCa1) which is a membrane protein with cytosolic ATPase domain which forms a complex with Rv3871 (EccCb1). The ESAT-6/CFP-10 1:1 heterodimer interacts with EccCb1 for secretion. Only in case of ESX-1out of five ESX systems the EccC component is divided in two different polypeptide chains.

The M. tuberculosis ESX-1 locus extends from rv3864 to rv3883c. Within this region the Region of Difference (RD1) lies expending from rv3871 to rv3879c. RD1 is one of the distinguishing features that separate pathogenic M. tuberculosis with the vaccine strains like BCG (Bacillus Calmette-Guerin) of M.bovis and M. microti. The virulence factor and some T7SS genes fall within the RD1 locus and others are located neighboring regions of RD1 and within the ESX-1 locus. Rv3870 is located outside the RD1 region and translated into a 747 amino acid long (Mw~ 80.9 kDa) polypeptide with two transmembrane domain followed by a DUF domain (Domain of Unknown Function) and a single ATPase domain. Like the two ATPase domains of its cytosolic partner Rv3871, Rv3870 ATPase domain also belong to the FtsK/SpoIIIE family of P-loop NTPases which reside in the ASCE (Additional Strand Conserved Glutamate) of AAA+ ATPase. The ATPase activity of this group of proteins renders to the 'Arginine finger' which upon oligomerization participates in forming active assembly.

The research objective focuses on the biochemical, biophysical and structural characterization of Rv3870 ATPase domain. The domain was cloned, expressed and purified as a cytosolic fraction using standard recombinant protein purification protocol and was used for various characterization. Biochemical characterization involves ATPase assay by radioactive and colorimetric method to determine the kinetic parameters of enzymatic catalysis so that we can compare its kinetic efficiency with other proteins of its

class characterized till date. In case of calorimetric ATPase assay the importance of different residues which are involved in ATP hydrolysis are elucidated by site directed mutagenesis and then comparing the catalytic parameters of the mutants with the wild type enzyme. Biophysical characterization involves circular dichroism to understand the secondary structure content of the enzyme and as well as the thermal denaturation profile of it. Crystallization trials were done in different chemical environments but it still remains an obstacle to obtain a good quality crystal to determine structure. Recent advancements in CryoEM bypass the time taking procedure of protein crystal formation in order to determine structure of the macromolecules. By using single particle CryoEM/tomography one can reach good resolution without distorting the sample in solution, and it will be very useful to determine the low resolution structure of large proteins alone or in complex but was unable to obtain good quality data. SAXS, which is also a useful tool to bypass the obstacle to get the protein in crystallized form, was used to determine the oligomeric state of this protein in solution. Alongside modeling, comparative structure and dynamics simulation analysis, sequence alignment of Rv3870 ATPase domain was also done. These data explains the structure and mechanism of ATPase domain of Rv3870 enzyme, which will help significantly in designing virulence inhibitor development against M. tuberculosis.

SB-04 Killing superbugs: Screening drugs against FDTS

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Antibiotic development is of great importance as bacteria develop more resistance to the current drugs. A good target for antibiotics is involved in vital cellular processes and will not impact human processes. In this case X-ray crystallography and activity studies were used to discover a new enzyme to target. An important building block of DNA called thymidylate is made by an enzyme called Thymidylate synthase in humans. In many bacteria, thymidylate is made by the very different Folate Dependent Thymidylate Synthase (FDTS). Since the enzymes are very different and involved in a vital process, DNA synthesis, FDTS is a good target. Once the target is identified, the mechanism is investigated, and drug screening can begin.

Using a library of FDA approved drugs, virtual docking studies revealed three hits out of 248 molecules when docked to Thermotoga maritima FDTS. Roxadustat, used to treat renal anemia, Tanshinone I, an anti-tumor drug, and tanshinone IIA, used to treat cardiovascular and inflammatory diseases were all identifies as possible antibiotics. Interestingly, tanshinones were known to have antimycobacterial properties, though the mechanisms are unclear. Structural differences between T. maritima and Mycobacterium tuberculosis FDTS prevented the strong interactions seen in the former when the hits were docked in the latter.

SB-05 Toward Elucidating the mechanism of lytic polysaccharide monooxygenases: Chemical insights from X-ray and neutron crystallography

Flora Meilleur[(1)], Gabriela Schroder[(1)]

(1) North Carolina State University and Oak Ridge National Laboratory

Lytic polysaccharide monooxygenases (LPMOs) are copper-center enzymes involved in the oxidative cleavage of the glycosidic bond. LPMOs are responsible for chain disruption of crystalline cellulose, thereby increasing the accessibility of the carbohydrate substrate to cellulases for hydrolytic depolymerization. The enhanced cellulose conversion of biomass due to addition of LPMOs makes them valuable for the generation of biofuels. The LPMO active site is located on the planar enzyme–cellulose binding surface in which a single copper ion is coordinated in a 'histidine-brace' motif composed of a N-terminal histidine and a second conserved histidine residue in the equatorial plane, with a coordinating tyrosine residue in the axial position. The LPMO reaction is initiated by the addition of a reductant and oxygen to ultimately form an unknown activated copper–oxygen species responsible for polysaccharide substrate hydrogen atom abstraction. Previous work in our group on LPMO9D from Neurospora crassa has provided insight into the binding and activation of oxygen at the LPMO active site as well as the role of the protonation state of a second-shell residue His 157 in oxygen-prebinding (O'Dell et al., 2017). The metallocenter of LPMO makes it highly susceptible to radiation damage, particularly photoreduction and radiolysis due to X-ray beam exposure. Neutron protein crystallography provides a non-destructive technique for structural characterization while also allowing the determination of the positions of light atoms such as hydrogen and deuterium which are central to understanding protein chemistry. Neutron cryo-crystallography permits trapping of catalytic intermediates, thereby providing insight into protonation states and chemical nature of otherwise short-lived species in the reaction mechanism. To this end, we collected a cryo-neutron diffraction dataset on an ascorbate-reduced LPMO9D crystal to characterize the reaction mechanism intermediates (Schröder et al., 2021). A second neutron diffraction dataset was collected at room temperature on a LPMO9D crystal exposed to low pH conditions to probe protonation states under acidic conditions.

1. O'Dell, W. B., Agarwal, P. K. & Meilleur, F. (2017). Angew. Chemie - Int. Ed. 56, 767–770.

2. Schröder, G. C., O'Dell, W. B., Swartz, P. D. & Meilleur, F. (2021). Acta Crystallogr. Sect. F Struct. Biol. Commun. 77, 128–133.

SB-06 A conserved arginine residue is critical for stabilizing the N2 FeS cluster in mitochondrial complex I

Mikhail A. Hameedi[(1)], Daniel N. Grba[(1)], Katherine H. Richardson[(2),(3)], Andrew J. Y. Jones[(1)], Wei Song[(2)] , Maxie M. Roessler[(2),(3)] , John J. Wright[(1),(2),*], Judy Hirst[(1)]

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Respiratory complex I (NADH:ubiquinone oxidoreductase) is the first enzyme of the mitochondrial electron-transport chain. Structurally, complex I is a 1 MDa complex located in the inner mitochondrial membrane (IMM). Functionally, it captures the free energy released by NADH oxidation and ubiquinone reduction to translocate protons across the energy-transducing IMM, thereby driving ATP synthesis during oxidative phosphorylation. In complex. I, the cofactor which transfers electrons directly to ubiquinone is the N2 iron-sulfur cluster. N2 is located in the NUCM/NDUFS2 subunit of complex I. A nearby arginine residue in NUCM, R121, forms part of the second coordination sphere of N2. R121 is known to be post-translationally dimethylated, but its functional and structural significance is unknown.

Here, we show that mutation of this arginine residue to methionine (R121M) and lysine (R121K) abolishes the ubiquinone-reductase activity, concomitant with disappearance of the N2 signature from the electron paramagnetic resonance (EPR) spectrum. Analysis of the cryo-EM structure of NDUFS2-R121M complex I at 3.7 Å resolution identified the absence of the cubane N2 cluster as the cause of the dysfunction, within an otherwise intact enzyme. The mutation further induced localized disorder in nearby elements of the quinone-binding site, consistent with the close connections between the cluster and substrate-binding regions. Our results demonstrate that R121 is required for the formation and/or stability of the N2 cluster and highlight the importance of structural analyses for mechanistic interpretation of biochemical and spectroscopic data on complex I variants.

SB-07 MSKC: A Stanford Biofacility at the Crossroad Between Medicine, Engineering, and Chemistry

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The Macromolecular Structure Knowledge Center (MSKC) at Stanford is a joint initiative of the Stanford ChEM-H Institute, the School of Engineering, and SLAC National Accelerator Laboratory, providing state-of-the-art equipment and expertise for the production, purification, and structural characterization of biological macromolecules and their complexes with ligands, inhibitors, and partner proteins.
The MSKC is a hybrid shared research facility and teaching laboratory where scientists of all academic levels – whether students, post-docs, or PIs – can find a place to incubate their structural biology ideas and carry them to fruition. The MSKC has been particularly useful for new junior faculty members by providing shared instrumentation and workspace as they establish their lab operations. Its user base comes from a wide variety of Stanford Schools (Engineering, Medicine, Humanities and Sciences) and Departments (Chemical Engineering, Chemistry, Bioengineering, Ophthalmology, Pathology, Biochemistry, Systems Biology), and beyond (SLAC Structural Biology, private industry).
Since its inauguration in 2016, several core projects are underway at MSKC – from protein expression and purification to full structural determination. Instrument automation and streamlined access to major SLAC facilities expands MSKC's ability to support high-level structural biology projects for the Stanford research community and beyond.

SB-08 3D printed Gas dynamic virtual nozzles to synchronize droplets with the XFEL (X-Ray Free Electron) pulses

Reza Nazari[(1)(2)], Adil Ansari[(1)(2)], Konstantinos Karpos[(1)], Judicael Tombo[(1)], Sahba Zaare[(1)], Roberto Alvarez[(1)(3)], John C.H. Spence[(1)], Uwe Weierstall[(1)], Ronald J. Adrian[(2)], Richard A. Kirian[(1)]

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Continuous liquid microjets have been widely used in time-resolved solution scattering (TR-SS) experiments at X-Ray Free Electron Lasers (XFELs) to deliver samples to the intense focus of the x-ray beam. When conducting experiments at XFELs with pulse repetition rates on the order of100 Hz, these continuous jets waste the vast majority of injected sample between shots, which is a major problem particularly in cases of irreversible reactions that do not allow for sample recycling. This is a major problem for expensive or difficult-to-produce samples and as such, triggering periodic droplets or jets under vacuum is a highly desired improvement for solution scattering experiments. Here we develop and test 3D-printed gas dynamic virtual nozzles (GDVNs) that are designed to produce periodic droplets that may be synchronized with XFEL pulses.

SB-09 Plugging a transporter with a nanobody: Structural and biochemical studies of a Transporter-VHH complex and its implications on the transporter's dynamics

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(1) Molecular Biophysics Unit, Indian Institute of Science, Bengaluru (India)

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Members of the Major Facilitator Superfamily are peculiar in existing with nearly the same structural fold, despite high sequential divergence. Many of these membrane protein transporters in bacteria have now repurposed to act as antibacterial efflux pumps, and blocking them could provide a much needed approach to counter emergence of multidrug resistance in such pathogens. Our work describes the structure solution of one such transporter called NorC, found in Staphylococcus aureus, in complex with a single domain antibody fragment that absolves solvent accessibility to NorC's vestibule.

NorC is known to provide resistance against antibiotics of the fluoroquinolone class, and due to low sequence similarity with any known homolog, predicting its exact function and mechanism without structural information was difficult. All initial crystallization attempts in its apo state yielded mere spherulites. We used VHH fragments from camels to chaperone them into crystallization. Fortunately, a VHH, called ICab, with it's highly unusual architecture, not only co-crystallized with NorC, but while doing so, blocked potential substrate accessibility and changed NorC's conformational landscape through it, providing a proof of concept of using VHH fragments to block such transporters.

MS-01 Evoking the 18-n rule: Chemical Pressure-driven Structural Transitions along the REAl3 (RE = Sc, Y, Lanthanides) Series

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Atomic packing and electronic structure are key factors in the determination of a compound's structure type, but the extent and nature of their roles is highly variable or unresolved among different systems of interest. A series of group III and rare earth tri-aluminides (REAl3) adopt structures with stacking patterns ranging from a cubic close packing variant (AuCu3 type) and to one that exhibits hexagonal close packing (Ni3Sn type) and upon inspection, fall under the 18-n bonding scheme. The percentage of the hcp stacking in the structures correlates with the size of the rare earth atom, yet initial forays into the electronic structure indicate the Ni3Sn variants are electron-poor relative to the expected 18-n scheme. In this presentation, we will show how the 18-n view of the REAl3 series is the basis for a more nuanced understanding of the bonding within the structural series. Through DFT-Chemical Pressure analysis, we show that the AuCu3 type is suitable for RE atoms with a range of sizes, though the Ni3Sn type relieves tensions in for larger RE atoms by expanding its coordination environment and reducing contacts in its columns of Al octahedra. While the ScAl3 type falls neatly into the 18-n model with 12 e-/Sc, YAl3 breaks the 18-n rule by transferring valence electrons into partially filled states. These results show how atomic packing competes with and influences electronic structure.

MS-02 Solving the magnetic structure of EuCd2As2 and its implications for Weyl Physics

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Recently, a decades old prediction of the relativistic wave equation which suggests the existence of an exotic chiral (Weyl) particle has found experimental reality in a class of materials which combine a Dirac band crossing with either broken inversion or time-reversal symmetry – the so-called Weyl semi-metals. However, in most such materials the desired physics is often obscured by myriad Weyl points which give rise to higher order interactions muddying clear signatures of the Weyl physics. One route to avoid this downfall is to find a material with only a single Dirac point which is then split by time-reversal symmetry breaking begetting the minimal number of Weyl points. One such candidate material (EuCd2As2) has gained significant interest for its nearly ideal band structure which symmetry analysis has indicated can be tuned to various topological phases depending on the realized magnetic structure. Yet, the solution of the magnetic structure has been stymied by the presence of strongly neutron absorbing Eu and Cd. Here we will discuss the results of combined neutron diffraction, density functional theory and transport measurements on isotopic 153Eu116Cd2As2, elucidating its magnetic structure and suggesting an ideal situation to study Weyl physics in this material.

MS-03 Understanding reactivity in modular intermetallics: Chemical Pressure (CP) driven epitaxy between domain interfaces in YNi3

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The extensive structural diversity of intermetallic compounds points to the wealth of exciting possibilities that this class of compounds can lend to the design of new and interesting materials with desirable properties. However, the development of fundamental principles for understanding the structure-property relationships of these materials as well as design principles for the targeted synthesis of these compounds are essential for us to access the full potential of intermetallics. Towards this goal, a common theme arising in the literature for this class of materials suggests that increasingly complex intermetallic structures can be interpreted in terms of smaller, more simple building blocks. One example can be seen in the YNi3 phase where CaCu5- and MgCu2-type domains are found to intergrow, forming the layered NbBe3 structure type. Here, we will demonstrate how this interaction can be rationalized as a Chemical Pressure (CP) driven epitaxy between these domain interfaces. DFT-Chemical Pressure analysis reveals that packing tensions inherent to the YNi5 parent structure serves as the major driving force towards intergrowth, meanwhile the lattice and CP compatibility of YNi2 serves as an indicator of its favorability as a potential intergrowth partner. Indeed, we do see substantial CP relief within the YNi5-like layers upon adopting the intergrowth structure as interlayer Y-Y contacts are shortened along directions of negative CP – referred to here as an 'induced fit' model according to CP-derived matching rules used to describe such reactivity in modular structures. Through this analysis, we aim to establish guiding principles through which new modular materials with multifunctional properties can be theoretically anticipated and experimentally realized.

MS-04 Structure determination from laboratory X-ray powder diffraction data of (S)-dapoxetine hydrochloride

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Dapoxetine (DAP) is a potent selective serotonin reuptake inhibitor (SSRI) used for the treatment of premature ejaculation (PE), the most prevalent sexual dysfunction in men. Its hydrochloride form (DAPHCl, figure 1a), marketed under the name PriligyTM, has been approved for the treatment of PE in over 50 countries worldwide. A search in the Cambridge Structural Database (CSD) did not show previous reports of the crystal structure of dapoxetine or of any closely related phases. Also, a search in the PDF-4/Organics database produced no results. After searching for “dapoxetine” in the Google Patents site many entries are encountered. Some of them refer to the preparation of various crystal forms of anhydrous and hydrated DAPHCl phases. In only one of the patents [1] information about the unit cell parameters of a DAPHCl phase is provided. This phase crystallizes in an orthorhombic unit cell. In this contribution, the structure of (S)-Dapoxetine hydrochloride is reported, determined from laboratory X-ray powder diffraction data with DASH [2] and refined by the Rietveld method (figure 1b) with TOPAS-Academic [3]. This compound crystallizes in an orthorhombic cell, space group P212121. The final unit-cell parameters are a = 6.3300(6), b = 10.6830(10), c = 28.215(2) Å, V = 1908.0(3) Å3, Z = 4. The refinement converged to Rp =0.0526, Rwp = 0.0714, and GoF = 2.697. It must be noted that the cell parameters obtained are similar to the values reported by Guobin et al. [1], indicating that it corresponds to the phase patented by those authors. The asymmetric unit is shown in figure 1c. The crystal structure of DAPHCl is a complex 3D arrangement of hydrogen bonds, π···π, and C–H···π interactions. The chloride ions form layers parallel to the ab plane and are connected by dapoxetinium moieties by N–H···Cl and C–H···Cl hydrogen bonds. These layers stack along the c-axis, connected by π···π and C–H···π interactions (figure 1d). Hirshfeld surface analysis performed with CrystalExplorer21 [4] shows that the strongest interaction corresponds to the N-H···Cl contact, followed by π···π and H···π interactions. From fingerprint plots, it can be seen that H···H interactions contribute 59.7% while H···C/C···H interactions represent 28.6%, and H···Cl/Cl···H an 8.8%. Energy frameworks calculations, also carried out with CrystalExplorer21, show that the stabilization energies involving Dapoxetine moieties extend in a zig-zag fashion along the b-axis. A detailed discussion of the structure will be presented in this work.

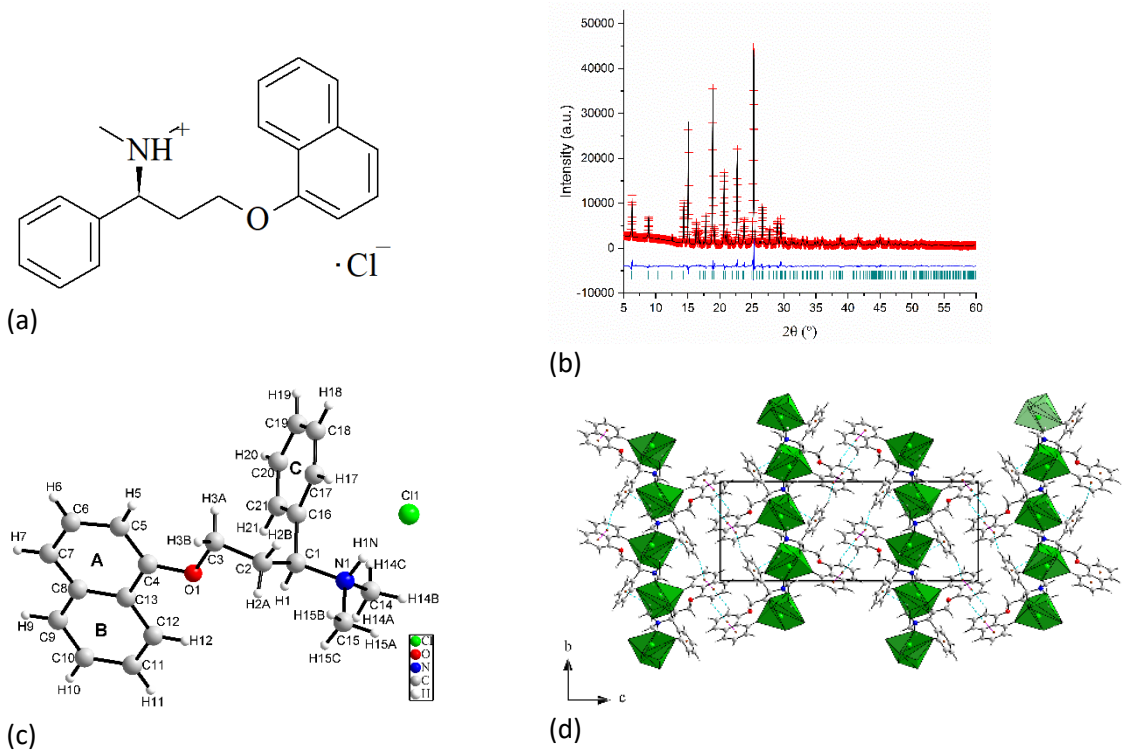

Figure 1. (a) Chemical diagram, (b) Rietveld refinement plot, (c) asymmetric unit, and (d) crystal packing viewed along the a-axis for DAPHCl.

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MS-05 Structural and luminescent properties of rare earth doped KSrVO4 nano powders prepared by low cost combustion route

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In this study, we have developed Nd3+ doped KSrVO4 synthesized via low cost combustion synthesis route. Herein, we report the variation in the lattice parameters and confirmed the orthorhombic phase for the as-synthesized undoped and KSr(1-x)VO4: xNd3+ (x = 0.0025 – 0.03) phosphor investigated by powder XRD system. The morphology was procured via SEM and TEM and the elemental analysis was carried out with EDAX. UV-Vis spectroscopy showed the variations in the band gap energy values. The Photoluminescence (PL) spectra shows three sharp peaks in the emission spectra located at 424 nm, 486 nm and 507 nm in the visible spectra. As a function of Nd3+ concentration, it was observed that 0.05 mol% Nd3+ doped nanophosphors exhibit the strongest emission intensity. Concentration quenching is induced mainly due to the energy transfer among nearby neighboring ions. The enhanced emission intensity of the phosphor with doping suggests that it may be used in display applications.

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[2] S. Kobayashi, Y. Ikuhara, T. Mizoguchi, Lattice expansion and local lattice distortion in Nb- and La-doped SrTiO3 single crystals investigated by x-ray diffraction and first-principles calculations. Phys. Rev. B. 98(13) (2018) 134114.

MS-06 Preliminary Study by Powder X-Ray Diffraction, Crystal Structure and Framework Energy of 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin

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Porphyrins are versatile macrocycles; their photophysical properties are interesting to develop electronic and medical applications [1]. These compounds have special physical and chemical properties (e.g., photostability, phototoxicity, and singlet oxygen production by irradiation with visible light). Furthermore, these macromolecules are considered benchmarks in biological sciences as potential photosensitizing agents in anticancer, antiviral, antifungal, antibacterial, and antiparasitic photodynamic therapy [2]. The 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (THPP) was synthesized and characterized (Figure 1). The NMR study showed the presence of propionic acid in the compound. Two phases were identified, Phase 1 indexing suggests the following crystallographic parameters: triclinic system and space group P$\bar{1}$ (Nº 2) with parameters a=11,8379(9) Å, b=12,3415(9) Å, c=14,8003(1) Å, □=85,394 (1)°, β=85,291(3)°, γ=80,752(2)°, V=2122,02 Å3 and Z=2; Phase 2 crystallizes in a unit cell triclinic P$\bar{1}$ (Nº 2) with parameters a=12,2271(1) Å, b=12,8689(5) Å, c=14,9077(9) Å, □=97,836 (3)°, β=93,219(1)°, γ=94,393(1)°, V=2311,74 Å3 and Z=2. The presence of two phases was corroborated by adjustment by algorithm Le Bail using the Fullprof program, and the intensities corresponding to each of them were extracted. A preliminary study of the structural resolution was carried out with EXPO2014 program using phase 2 obtained by powder X-ray diffraction. The crystal structure of THPP has been solved and refined using X-ray powder diffraction data and optimized using Density Functional Theory (DFT) techniques.

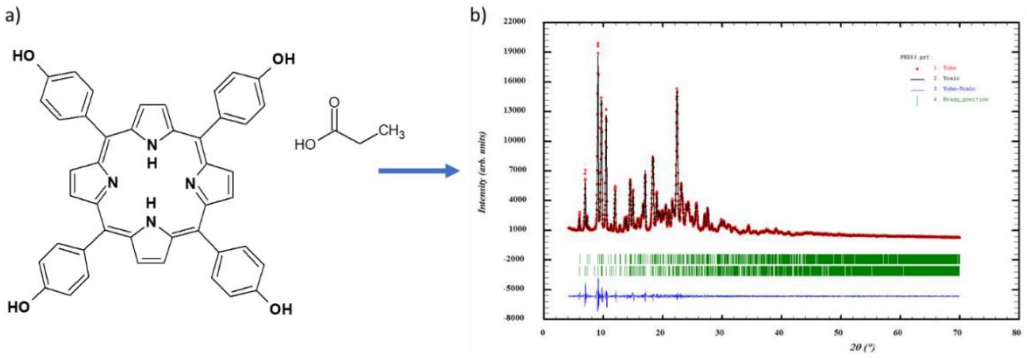

Figure 1. (a) Molecular structure of 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin with propionic acid. (b) Adjustment Le Bail of THPP. The red dots represent the observed pattern, the black line is the calculated pattern, and the green lines represents Bragg position of two phases. The blue curve at the bottom represents the difference between the calculated and the observed pattern, plotted on the same vertical scale as the other patterns

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MS-07 Crystal structure and solubility study of two copper-enalaprilat complexes

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Enalapril maleate is the prodrug of diacid enalaprilat (Enal) used in the treatment of arterial hypertension. Enal is the active form, but it is poorly absorbed in the gastrointestinal tract, reducing its bioavailability and the inhibition effect. For this reason, enalapril maleate is used to improve the dynamics of enalaprilat liberation, absorption, distribution, metabolism, and elimination, therefore optimizing its bioavailability [1,2]. An alternative method to improve the physicochemical properties and bioavailability of antihypertensive drugs is the synthesis of complexes with metal ions such as copper. The formation of Cu (II) complexes of enalaprilat (Enal) arises as an option to improve the stability, action, and pharmacokinetics of this drug [3]. In this work, two Cu-Enal complexes with chemical formulas [Cu2(Enal)2(H2O)]•4H2O•NO3 (I) and [Cu2(Enal)2(H2O)]•3H2O•C2H5OH•NO3 (II) were obtained. Complex I crystallizes in an orthorhombic unit cell with space group P212121 and parameters a = 10.8925(3) Å; b = 15.1087(5) Å, c = 26.2900(7) Å and V = 4326.6(2) Å3, Z = 4, while II crystallizes in a similar orthorhombic cell with space group P212121 and cell parameters a = 10.9483(1) Å; b = 15.1534(1) Å, c = 26.9954(1) Å and V = 4478.64(5) Å3, Z = 4. The asymmetric units of I and II show that two enalaprilat molecules coordinate to two copper atoms (Figures 1a and 1b). Both structures can be described in terms of dimers of the complexes that are connected through an enalaprilat moiety. The most notable difference between the two structures is the substitution of a molecule of water in complex II by a molecule of ethanol. The copper atoms in both complexes have square-based pyramid coordination with tetragonal elongation, and the top of the pyramid shows trigonal distortion with respect to the base plane. Figure 1c shows the superposition of both complexes, where small differences are observed in the conformational arrangement of the aromatic rings and in the pyrrolidine fragment in both complexes. Solubility tests show that complexes I and II have higher solubility, 0.02999 g/ml and 0.05339 g/ml, respectively, compared to enalapril maleate (0.01507 g/ml) and diacid enalaprilat 0.01387 g/ml.

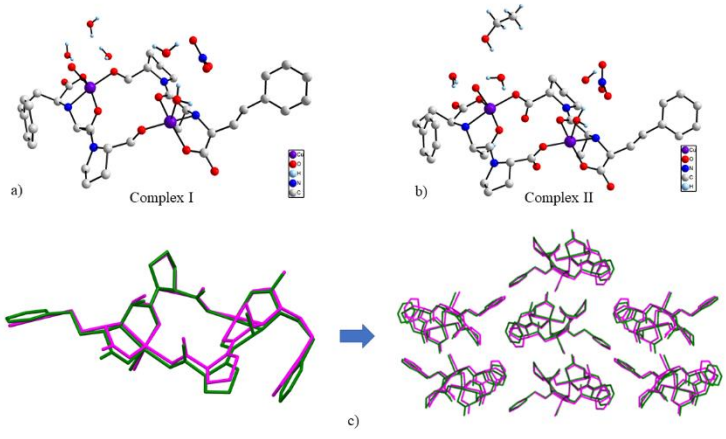

Figure 1. (a) Asymmetric unit of complex I, (b) asymmetric unit of complex II and (c) superposition of both complexes (complex I in magenta and II in green).

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MS-08 Mathematics of Two-Dimensional X-Ray Diffraction

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(1) Bruker AXS

The 2D diffraction pattern contains the scattering intensity distribution as a function of two orthogonal angles. One is the Bragg angle 2θ and the other is the azimuthal angle about the incident x-ray beam, denoted by γ. A 2D diffraction pattern can be analyzed directly or by data reduction to the intensity distribution along γ or 2θ. The data integration can reduce the 2D pattern into a diffraction profile analogs to the conventional diffraction pattern so that many existing algorithms and software can be used for the data evaluation. However, the materials structure information associated to the intensity distribution along γ direction is lost through γ-integration. The intensity distribution and 2θ variation along γ are associated to the orientation distribution, stress, crystallite size and size distribution.

Single crystal and random powder represent two extreme cases of the diffraction samples. The Laue equations are suitable to interpret the diffraction pattern from single crystal. The Bragg law is more conveniently used for the diffraction pattern from a random powder. For most other samples and applications, the diffraction vector approach has been proved to be the genuine theory to interpret and evaluate the 2D diffraction data. The unit diffraction vector representing any feature in a 2D pattern measured in the laboratory coordinates can be transformed to the sample coordinates. A flow chart from the introduction of diffraction vector as a function of 2θ and γ, transformation of unit diffraction vector from laboratory coordinates into sample coordinates, and fundamental equations for stress, texture, and reciprocal mapping are displayed in the poster.

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MS-09 Synthesis, characterization and pharmacological viability study of 1-(1-p-tolyamino) ethyl)pyrrolidin-2-one and 1-(1-p-hloramino)ethyl)pyrrolidin-2-one

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The fragment 2-oxo-1-pyrrolidine is present in a wide variety of compounds with biological and pharmacological activity. Being the most important, the drugs of the racetam family, widely used for central nervous system disorders such as cognition/memory, epilepsy and seizures, neurodegenerative diseases, stroke/ischemia, stress and anxiety due to their function as modulators of brain functions [1]. The synthesis of 1-(1-p-tolyamino)ethyl)pyrrolidin-2-one (compound A) and 1-(1-p-chloramino)ethyl)pyrrolidin-2-one (compound B) (Figure 1) have been reported in protic medium with the use of Bronsted acid as catalysts such as sodium bisulfate [2], acetic acid [3] and iodine [4]. However, the authors found only one report in the Cambridge Structural Data-base (CSD) of the homologue substituted with a chlorine atom in the benzene ring (Refcode: IWULIW) [4], although a crystallographic discussion was not carried out, on the other hand, in the PDF-4/Organic powder database, no report related to this structure was found.

In the present work, the synthesis of A and B was carried out using NH4-P zeolite as catalyst, the products were isolated and purified, and the obtained solids were characterized by powder X-ray diffraction. The solids were recrystallized obtaining crystals which were measured by single crystal X-ray diffraction, the compound A crystallizes in a monoclinic system and space group P21/c with cell parameters a=11.589(1) Å, b=9.4056(7) Å, c=12.6135(8) Å, β=117.061(6)° and V=1224.37(17)Å3 and the compound B crystallizes in a monoclinic system and space group P21/c with cell parameters a=11.649(2) Å, b=9.5147(2) Å, c=12.4269(3) Å, β=116.997(3)° and V=1187.4(2) Å3. The cell parameters and packaging for compound B are different from those reported in the CSD (a=11.180(3) Å, b=9.4995(18) Å, c=12.049(3) Å, β=111.894(5)° and V=1187.4(2) Å3), thus, compound B obtained after crystallization is a polymorph of the reported. The powder pattern of compound B is the same as the calculated pattern of the report, showing that the polymorph is generated during the recrystallization. A comparison of the intermolecular and intramolecular interactions and lattice energies of compounds A and B was performed using the CrystalExplorer program.

A pharmacological feasibility prediction was performed with the virtual programs SwissADME and Osiris, finding a high potential as drugs with pharmacological kinetics at the blood-brain barrier.

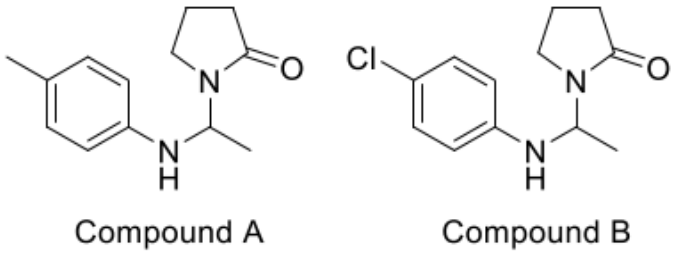

Figure 1. Synthesized compounds.

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MS-10 Crystal Structure, Hirshfeld surface analysis and solubility of Fexofenadine hydrochloride trihydrate

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Solubility is one of the most important properties in drugs that are administered orally, for this reason, improving this property is an objective in the pharmaceutical industry and for this there are different methodologies such as the formation of sales, co crystals, complexes, solvates and hydrates [1, 2]. Fexofenadine (Figure 1a), is a third-generation antihistamine, a selective antagonist of histamine H1 receptors, and is marketed as the chloride salt (FXCl) for oral administration [3]. There are patent reports of various polymorphs of fexofenadine chloride, however, the structure of the material has not been determined. In FXCl crystallization tests, a crystalline material was obtained that presented a different powder pattern to that obtained by FXCl (Figure 1b) and those reported. The TGA-DSC thermal analysis showed the loss of three water molecules. This contribution shows the formation and structural determination by powder and single crystal X-ray diffraction of fexofenadine chloride trihydrate (FXCl3H). FXCl3H indexes in a monoclinic crystal system with space group P21/c and cell parameters a = 11.5980 Å, b = 21.0405 Å, c = 25.9095 Å, β = 92.466 °, V = 6316.78 Å3 and Z= 4. The compound crystallizes with the chemical formula 2(C32H39NO4)•6(H2O)•Cl and the asymmetric unit is made up of two independent molecules where one is in zwitterion form (Figure 1c). The structure shows disorder in some fragments and in the water molecules. Crystal packing is governed by hydrogen bond, where the molecules form dimers that extend along the c axis. The solubility study carried out at 37 °C and pH = 3 show that FXCl is more soluble than FXCl3H (166,66 mg/l and 130,35 mg/l respectively). In addition, the Hirshfeld surface analysis and energy frameworks are shown in this contribution.

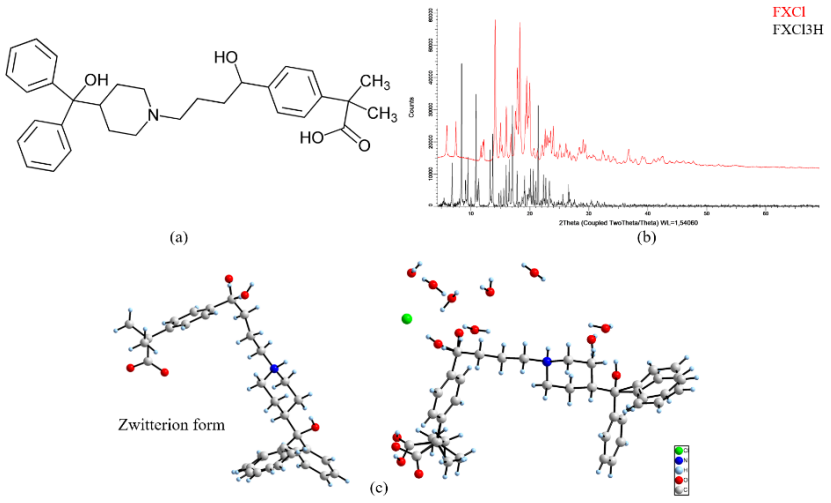

Figure 1. (a) Chemical diagram, (b) powder diffraction patterns of FXCl y FXCl3H, and (c) Asymmetric unit of FXCl3H.

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MS-11 Biogeochemical reactivity of floodplain interfaces

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(2) Stanford Earth, Stanford University

(3) Desert Research Institute

Groundwater flowing through riparian floodplains travels across major sedimentary interfaces, driven by monsoonal rain, meltwater, plant evapotranspiration, drought, and beaver activity. Groundwaters with different compositions mix across these interfaces, giving rise to particularly intense microbial activity and geochemical reactions that profoundly influence nutrient and contaminant cycling. These reactions and export of their products to adjacent streams are mediated by intricate coupling between groundwater flow and the ensuing microbial-geochemical processes interacting across these interfaces. In spite of their importance, our understanding of subsurface interfaces as nexuses for coupling between these hydrological and biogeochemical processes is poor. We are studying this process coupling across soil-gravel bed interfaces and across interfaces surrounding clay-rich sediment lenses, both ubiquitous across the intermountain West. We found that groundwater flowing out of beaver-constructed ponds flows downward, stimulating microbial C, S, Fe, and N cycling, spreading sulfidic conditions into underlying coarse cobble-gravel alluvium, and causing downward export of micronutrients and contaminants out of the metal- and nutrient-rich floodplain soils. These reaction products can be transported into adjacent streams and impact the larger watershed. In a similar fashion, clay-rich anoxic sediment lenses export microbial cells, organic carbon, HS^-, and Fe(II), promoting establishment of reducing conditions in surrounding aquifers.