BEST-CSP | COST Action CA22107

Bringing Experiment and Simulation Together in Crystal Structure Prediction

From molecules to materials:

2nd Workshop on Benchmarking Solid State Properties

Book of Abstracts

10-11 September 2025 | Bologna, Italy

Organizing committee:

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Contact E-mail: workshop1@best-csp.eu

Time	Wednesday 10/09	Title
8:00 am	REGISTRATION	
9:00 am	OPENING	
	Session Chairs:	**Michal Fulem, Joao Baptista**
9:15 am	KEYNOTE LECTURE: **Susan Reutzel Edens**	From digital design to the experimental realization of crystal polymorphs
10:00 am	Daria Szewczyk	Exploring Organic Crystalline Polymorphism through Heat Capacity Studies: Benzophenone, Picolinamide, Pyrazinamide, and Triethylenetetramine
10:15 am	Vera L.S. Freitas	When Intramolecular Hydrogen Bonds Undermine Crystal Cohesion: A Thermodynamic Perspective
10:30 am	Ricardo Castro	Discovery and Characterization of a Late-Appearing Polymorph of Famciclovir
10:45 am	Jonas Nyman	Blind test
11:00 am	COFFEE BREAK	
	Session Chairs:	**Anders Madsen, Inês Feliciano**
11:30 am	KEYNOTE LECTURE: **Mohamed Aouane**	Novel Materials: Opportunities with Neutron Scattering
12:15 pm	Ivor Loncaric	Modeling Molecular Crystals with Machine Learning Interatomic Potentials
12:30 pm	Vojtech Stejfa	From experiments to standard: reference data for sublimation properties
12:45 pm	Clara Gomes Mafalda Sarraguca	Women in STEM: Past, Present and Future
1:00 pm	LUNCH BREAK	
	Session Chairs:	**Sowmya Indrakumar, Luca Russo**
2:30 pm	KEYNOTE LECTURE: **Graeme Day**	Digital Navigation of Chemical-Crystal Space for Functional Materials Discovery
3:15 pm	Jacco van de Streek	Disorder, “correlated disorder”, energy and free energy
3:30 pm	Ctirad Cervinka	Coupled-clusters theory meets ab initio thermodynamic simulations for molecular liquids
3:45 pm	Demeter Tzeli	Computational Investigation of photophysical processes of chemosensors
4:00 pm	Pol Benitez	MLIPs for Crystal Prediction and Thermodynamic Phase Diagrams
4:15 pm	Lucia Gigli	Large-scale chemical and crystal packing space explora6on for HOF-based porous materials
4:30 pm	Zhuocen Yang	Relative Stability Evaluation of Polymorphic Systems via Pseudo-Supercritical Path Method using Different Force Fields
4:45 pm	COFFEE BREAK	
5:00 pm	POSTER SESSION	
6:30 pm	END of poster session	

Time	Thursday 11/09	Title
9:00 am	Management Committee Meeting	Management committee members only
10:00 am	Working Group Meetings	All participants
11:00 am	COFFEE BREAK	
11:30 am	Working Group Meetings	All participants
1:00 pm	LUNCH BREAK	
	Session Chairs:	**Helena Butkiewicz, Will Wood**
2:00 pm	KEYNOTE LECTURE: **Alberto de la Roza**	Design and benchmarking of methods for energy ranking in crystal structure prediction
2:45 pm	Natalia Correia	Exploring Crystal Polymorphism in Simvastatin: Insights from Dielectric Relaxation Spectroscopy
3:00 pm	Martin Dracinsky	NMR Crystallography of Molecular Solids with Strong Hydrogen Bonds
3:15 pm	Vassil Ivanov	Step Bunching and Meandering Dynamics: A pathway to surface morphology control
3:30 pm	Marta Dudek	NMR crystallography of organic solids at high magnetic fields
3:45 pm	Cheng-long Stephan	Stabilizing the Unstable: Using Additives to Control Metastable Polymorphs and Extend Their Lifetime
4:00 pm	COFFEE BREAK	
4:30 pm	Round Table Discussion	
5:45 pm	CLOSING REMARKS	
6:00 pm	Core Group Meeting	Core Group Members Only

Abstracts

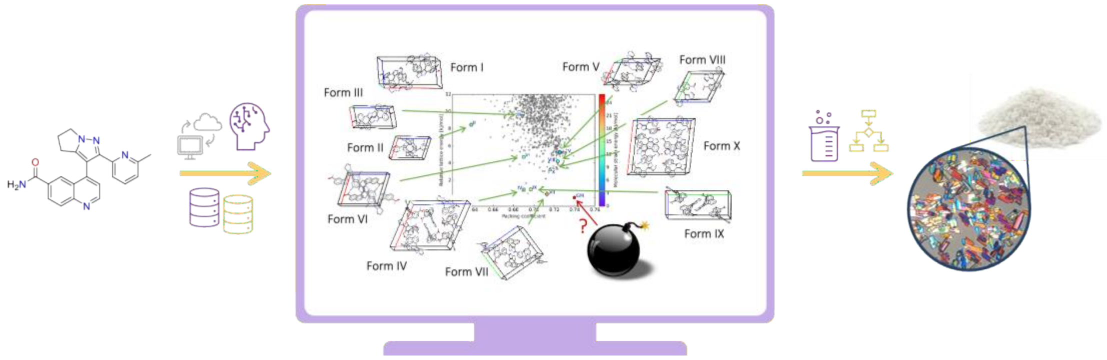
Keynote Lectures

From Digital Design to the Experimental Realization of Crystal Polymorphs

Susan M. Reutzel-Edens
SuRE Pharma Consulting, LLC, 7163 Whitestown Parkway, Zionsville, IN 46077

susan@surepharmaconsulting.com

The pharmaceutical industry has embraced rapidly developing computational methods for predicting crystal structures to augment their experimental solid form screening efforts, all in the hope of shortening development timelines, reducing costs, and mitigating the risk of late appearing polymorphs that once spurred the ritonavir crisis. Although crystal structure prediction (CSP) methods have been increasingly applied to large, flexible molecules with good success [1,2], and recent advances in predicting crystal form stability under real-world conditions have redefined the state-of-the-art in crystal modeling [3], the 7th Blind Test of CSP [4,5] has revealed a number of challenges that remain in both the computational assessment and experimental confirmation of crystal polymorphism. The interplay between experiment and computation proved essential in the Blind Test as it often does in practice, with each approach pushing the other to achieve higher accuracy and speed. In this presentation, the triumphs and challenges of applying CSP on real-world systems are highlighted. The need for not only faster, more accurate CSP and free energy calculations, but also improved experimental strategies for selecting target structures during crystal nucleation and definitively characterizing structures of imperfect, sometimes messy crystals, are also discussed. Predicting a hypothetical crystal structure falls short of experimentally realizing a crystal polymorph, but with continued progress on the computational *and* experimental fronts, the prospects are bright for CSP to be solidified as the first key step in digitally designing crystallization processes. [6]



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Digital Navigation of Chemical-Crystal Space for Functional Materials Discovery

Graeme M. Day[1]
School of Chemistry and Chemical Engineering, University of Southampton, Southampton,
United Kingdom

g.m.day@soton.ac.uk

The talk will explore the application of crystal structure prediction (CSP) methods to the inverse design of crystalline molecular materials with targeted properties. There has been impressive recent progress in computational methods for predicting crystal structures from first principles, making use of efficient methods for exploring energy landscapes coupled with accurate evaluations of the stability of computer-generated crystal structures [1]. Given these advances, there is a current focus on how to make the best use of CSP to identify the most promising molecules to deliver a desired property. Our goal is to build a computational framework that integrates structure prediction, property prediction and methods to explore the chemical space of possible molecules [2]. Examples from the area of porous materials will demonstrate how computation-led research has resulted in the discovery of unusual materials with extraordinary properties. [3, 4] We are also developing how these computational methods will interact with automation in the materials chemistry lab, where promising molecules are screened to realise predicted structures [5, 6], with a long-term aim of closed- loop materials discovery.

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Design and benchmarking of methods for energy ranking in crystal structure prediction

Alberto Otero-de-la-Roza[1], Nuria Vides García[1], Ernesto J. Blancas Jiménez[1]

Departamento de Química Física y Analítica, Facultad de Química, MALTA Consolider Team, Universidad de Oviedo, Oviedo 33006, Spain

oteroalberto@uniovi.es

The accurate and efficient calculation of free energies in molecular crystals is key to the prediction of their phase stability and thermodynamic and transport properties. Relative free energies between molecular crystal forms is essential for crystal structure prediction (CSP). Methods based on dispersion-corrected density functional in combination with the quasiharmonic approximation, are currently the most accurate methods for the free energy prediction. However, these techniques are also computationally expensive, which severely limits their applicability to molecular CSP, and inexpensive alternatives such as classical force fields, density-functional tight binding or machine learning potentials are currently being developed. The use of cheap free energy methods comes with an accuracy penalty, and therefore their development requires benchmarking using high-quality free energy data. In this talk, I give an overview of our work on developing DFT-based free energy methods for modeling molecular crystals [1]. The state of the art regarding the calculation of vibrational free energy contributions is discussed, as well as recent developments regarding the importance of anharmonicity and the limits of the quasiharmonic approximation [2]. Lastly, we describe past and present work in our group on the development of high-quality benchmark data for molecular crystal free energies based on sublimation enthalpies, enantiomeric excess and solubility data [3,4].

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Novel Materials: Opportunities with Neutron Scattering

Mo Aouane[1],

European Spallation Source ERIC – Lund, Sweden

mohamed.aouane@ess.eu

Neutron scattering is a powerful, non-destructive technique for exploring the atomic structure and dynamics of materials. Within this field, neutron spectroscopy provides unparalleled capabilities to probe molecular motions, collective dynamics, and magnetic excitations, delivering insights that are often unattainable with other scattering methods. By accessing these unique properties, neutron spectroscopy enables researchers to understand complex phenomena in novel materials with exceptional clarity.

This talk will showcase the opportunities that neutron spectroscopy offers to the materials discovery community, especially in benchmarking and validating advanced computational models of new materials. We will explore the diverse range of instruments available across major neutron facilities in Europe, with particular emphasis on the cutting-edge capabilities at the European Spallation Source (ESS). Through practical examples, attendees will gain an overview of the transformative experiments possible with neutron spectroscopy and how they can drive innovation in the development of next-generation materials.

Oral Presentations

Exploring Organic Crystalline Polymorphism through Heat Capacity Studies: Benzophenone, Picolinamide, Pyrazinamide, and Triethylenetetramine

Daria Szewczyk

Institute of Low Temperature and Structure Research PAS, Okólna 2, 50-422 Wrocław,
Poland

d.szewczyk@intibs.pl

Organic crystalline polymorphism plays a pivotal role in determining the physicochemical properties of molecular solids, with profound implications for pharmaceuticals, materials science, and thermodynamic modelling. In this study, we present a comparative analysis of the polymorphic behaviour of four structurally diverse organic compounds—benzophenone, picolinamide, pyrazinamide, and triethylenetetramine—through detailed heat capacity measurements.

Using thermal relaxation method implemented in the heat capacity option of the commercial Physical Property Measurement System from Quantum Design, we investigate the temperature-dependent heat capacities of each compound across their known polymorphic forms. The results reveal distinct thermal signatures associated with phase transitions, conformational rearrangements, and lattice dynamics. Benzophenone, a model aromatic ketone, exhibits subtle polymorphic transitions linked to molecular packing efficiency. Picolinamide and pyrazinamide, both nitrogen-containing heterocycles with pharmaceutical relevance, demonstrate pronounced polymorphic variability with implications for solubility and stability. Triethylenetetramine, a flexible polyamine, showcases unique thermal behaviour due to its conformational freedom and hydrogen bonding network.

Our findings contribute to a deeper understanding of the thermodynamic landscape of organic polymorphs and underscore the utility of heat capacity studies in characterizing solid-state transformations. This work highlights the interplay between molecular structure, crystal packing, and thermal properties, offering insights for the rational design of functional materials and drug formulations.

When Intramolecular Hydrogen Bonds Undermine Crystal Cohesion: A Thermodynamic Perspective

Vera L. S. Freitas

Research Centre in Chemistry of the University of Porto (CIQUP), Rua do Campo
Alegre, P-4169-007 Porto, Portugal

research@verafreitas.org

Intramolecular hydrogen bonding (IMHB) is a key factor in defining molecular conformation and, by extension, the solid-state organization of organic compounds. While IMHB often confers conformational stability, it can reduce the availability of donor and acceptor groups for intermolecular hydrogen bonding, thereby weakening crystal cohesion. This competition influences crystal packing, the manifestation of conformational or packing polymorphism, and key thermodynamic parameters such as vapor pressure and phase transition enthalpies [1-3].

Building on recent insights into how IMHB governs inclusion behavior and polymorphic preferences [4], this study examines *o*-acetamidobenzamide, picolinamide, danthron, and leucoquinizarin as case studies to explore how strong IMHB impacts cohesive energy and crystal thermodynamics. Both experimental data and theoretical calculations are used to quantify the energetic consequences of this intramolecular-intermolecular competition.

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Discovery and Characterization of a Late-Appearing Polymorph of Famciclovir

Luciano C. R. Rais[1]*, João A. Baptista*[2]*, M. Fátima M. Piedade*[3,4]*, M. Ermelinda S. Eusébio*[2]*, Éder T. G. Cavaleiro*[1]*,*
Ricardo A. E. Castro[2,5]

[1]Instituto de Química de São Carlos, Universidade de São Paulo, 13566-590 São Carlos, Brazil
[2]Centro de Química de Coimbra, Institute of Molecular Sciences, Departamento de Química, Faculdade de Ciências, Universidade de Coimbra, 3004-535 Coimbra, Portugal
[3]Centro de Química Estrutural, Institute of Molecular Sciences, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal [4]Centro de Química Estrutural, Institute of Molecular Sciences, Departamento de Engenharia Química, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal [5]Faculdade de Farmácia, Universidade de Coimbra, 3000-548 Coimbra, Portugal

rcastro@ff.uc.pt

Famciclovir (FCV), Figure 1, is a prodrug used in the treatment of hepatitis B virus, varicella- zoster virus, and herpes simplex virus types 1 and 2.[1] A previous study revealed the existence of four polymorphs[2] and a hydrate form[2,3]. The crystal structures have only been solved for form I[2] and the monohydrate[3].

In this work, a detailed investigation of forms I and II of famciclovir was carried out. The commercially available FCV was determined, in this investigation, to be crystalline form I. Crystallization experiments from different solvents were carried out and reproducible conditions to obtain polymorph II disclosed. Moreover, single crystals of form II could be grown and its crystal structure solved for the first time. The infrared spectra of both polymorphs were compared and interpreted with the assistance of the simulated spectrum of the conformer in one of the crystal structures. This was obtained using Gaussian software (version 6.0.16), after optimization, using the def2-TZVP basis set and the B3LYP density functional.

The thermal behaviour of both polymorphs was investigated by differential scanning calorimetry (DSC) and the solubilities of each form in ethanol obtained both by the gravimetric method and the polythermal method. The relative thermodynamic stability of both polymorphs was assessed, an enantiotropic system, both from the DSC measurements and the solubility data. Challenges of both methodologies are presented and discussed.

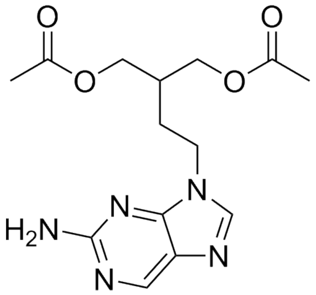

Figure 1: Famciclovir – [2-(acetyloxymethyl)-4-(2-aminopurin-9-yl)butyl] acetate

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Modeling Molecular Crystals with Machine Learning Interatomic Potentials

Ivor Lončarić[1]

Ruđer Bošković Institute, Zagreb, Croatia

ivor.loncaric@irb.hr

Molecular crystals are a common and important class of crystalline materials. However, modelling molecular crystals based on first principles (eg. with density functional theory) is often difficult due to the size of a typical unit cell. Therefore, high-throughput calculations for the discovery of useful properties are rare. In this presentation, I will show how machine- learned interatomic potentials can enable accurate and fast calculations of mechanical and thermal properties of molecular crystals enabling an understanding of experimental observations as well as high-throughput search for materials with the desired properties [1,2,3]. In principle, to train machine learning potential one would need to create a sufficiently large database of molecular crystals calculated with the desired accuracy. This is also a very challenging task and we will show how to partially avoid this step using transfer learning and existing databases of small systems.

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From experiment to standard: Reference data for sublimation properties

Vojtěch Štejfa[1], *Jiří Šnajdr*[1], *Květoslav Růžička*[1], *Michal Fulem*[1]

[1] Department of Physical Chemistry, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic

stejfav@vscht.cz

This talk will highlight the long-term contributions of the Applied Thermodynamics Group at UCT Prague to the development of highly reliable reference values for sublimation pressures and enthalpies. Key aspects of establishing trustworthy thermodynamic correlations of not only sublimation pressures will be explored, including:

- State-of-the-art experimental equipment for vapour pressure measurements at UCT Prague.
- Common approximations introduced to vapour pressure data treatment and correlations.
- The use of multi-property regression (SimCor) [1] enhancing the reliability of the recommended reference values.
- The benefit of treating sublimation and vaporization properties together.

The concepts will be illustrated through recent case studies emphasizing both established methodologies and challenges encountered in the process.

The sublimation properties are highly relevant for the Action, although possibilities for their determination are considerably limited throughout the Action community. First of all, sublimation enthalpy is the best experimental counterpart for the theoretically obtained lattice energies. Secondly, since direct observation of phase transformations is often hindered by kinetic barriers, sublimation pressure measurements are one of the few alternative approaches for assessing equilibrium conditions between the crystal forms providing that they are determinable for both of them.

The talk will also summarize the contributions of our group to the systematic description of thermodynamic properties of the compounds selected for the first period of the Action: sulfamerazine, picolinamide, *R*-phenylpiracetam, and 4-hydroxyacetophenone. While heat capacities of all eight considered polymorphs could be determined with a low uncertainty, static vapour pressure measurements could be performed only in few cases. The applicability of the static method is strongly restricted by the low volatility of the compounds combined with their low meting temperatures and thermal decomposition in liquid phase.

References

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Disorder, “correlated disorder”, energy and free energy

Jacco van de Streek[1]

[1]Avant-garde Materials Simulation, Alte Str. 2, Merzhausen, Germany

jacco.vandestreek@avmatsim.eu

Diffraction experiments see a space and time average of a crystal structure, but a proper evaluation of the temperature-dependent crystal free energy requires the computational crystallographer to deconvolute this space-time average into an ensemble of “unit cells”, each of which individually is fully ordered; in this ensemble, neighbouring “unit cells” are no longer necessarily the same, i.e. the periodicity is locally broken. Apart from the fundamental difference in dealing with disorder by experimentalists as averages and by theoreticians as individual, ordered unit cells, some of the more puzzling disorder cases are dealt with differently by different authors even within the same field. On top of this confusion, we (re)discovered a type of correlated disorder that is not disorder at all and that has to be identified by the computational crystallographer in order to evaluate certain crystal structures and their free energies correctly; this identification can be very difficult.

In this presentation I will give an overview of some of the more common and some of the more important disorder cases, especially in the context of crystal structures selected for the BEST-CSP project, and I will explain how to calculate their crystal free energies.

Coupled-clusters theory meets ab initio thermodynamic simulations for molecular liquids

Ctirad Červinka [1]

Department of Physical Chemistry, University of Chemistry and Technology Prague Technická 5, CZ-166 28
Prague 6, Czech Republic

ctirad.cervinka@vscht.cz

Delicate interplay of non-covalent interactions (NCI) governs the properties and phase behavior of molecular materials, being unprecedentedly rich already for the simplest molecules, such as water. Existing first-principles methods enable to model properties and polymorphism of molecular solids at least qualitatively [1]. However, those methods still frequently fail to yield at least semi-quantitative predictions [2], and are completely inapplicable for modelling properties of liquids or the solid-liquid equilibrium. Immense computational complexity inherently related to large-scale ab initio simulations of liquids and glasses has impeded this field of research for long [3]. Current work presents a newly developed fragment-based ab initio Monte Carlo approach for highly accurate predictions of structural and thermodynamic properties of amorphous molecular materials that require minimum empiric inputs [4]. A sophisticated nested Monte Carlo sampling that combines multiple potentials is a key feature enabling to reach a high computational accuracy at a reasonable computational cost. State-of-the-art methods for modeling non-covalent interactions, based on the coupled-clusters theory are incorporated in the presented Monte Carlo simulation workflow. Such ab initio simulations offer an unprecedented predictive accuracy, not only for bulk liquid densities, but also response properties such as thermal expansivity, compressibility or heat capacity of liquids. A suitable composite combination of force fields, semi-empiric quantum-chemical methods [5] and fragment-based ab initio many- body expansion [6] for the individual nested Monte Carlo layers represents a unique development, greatly advancing the state-of-the-art for first-principles molecular simulations of amorphous materials. Adoption of the many-body expansion of the cohesive energy and modern low-scaling formulations the coupled-clusters theory prove to be viable, indeed imparting the coupled-clusters accuracy to the amorphous realm of molecular liquids and glasses. Validation of the methodology is presented for three small model systems, but future development for material design of pharmaceuticals or organic semiconductors is expected. Financial support from the Czech Science Foundation (23-05476M) is acknowledged. Computational resources were supplied under the project e-INFRA CZ (ID:90254).

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Computational Investigation of photophysical processes of chemosensors

Demeter Tzeli[1,2], *Eleftherios Papamichalis,*[1] *Christina E. Tzeliou* [2]

[1] Department of Chemistry, National and Kapodistrian University of Athens, Greece
[2] Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, Greece

tzeli@chem.uoa.gr

The development of luminescence-based chemosensors which exemplify selectivity, sensitivity, and applicability is hot research area[1]. Up to now supramolecular luminescent sensors have solved significant problems in a variety of research areas, for instance in food and agricultural safety,[2] in biological imaging,[3] medical diagnostics,[4] national security,[5] and environment[6].

Theoretically, the accurate calculation of the electronic structure, absorption, and fluorescence spectra of luminescence-based chemosensors candidate and the prediction of the most promising ones is not a routine task.[7,8] Their physisorption and/or chemisorption on 2D materials can affect their spectra and the electronic properties of the 2D materials.

In this presentation, the photophysical properties of selected chemosensors of Ca^{2+}, Na^{+}, Hg^{2+}, Zn^{2+}, and Sn^{2+} will be discussed and analyzed. Key factors for the accurate prediction of the absorption and fluorescence spectra of chemosensors will be analyzed,[7-8] while structural characteristics of molecules that can make ideal molecules as sensors will be discussed.[7-10] Finally, the physisorption and/or chemisorption of metallic porphyrin complexes on 2D-MoS_2 will be presented, Figure 1.

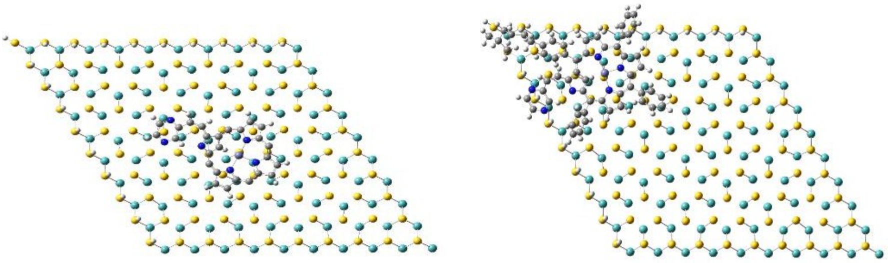

Figure 1. N-Confused porphyrin physiosorbed and linked in 2D-MoS_2.

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MLIPs for Crystal Prediction and Thermodynamic Phase Diagrams

Pol Benítez[1], *Claudio Cazorla*[1]

[1]Department of Physics, Universitat Politècnica de Catalunya, Barcelona, Spain

pol.benitez@upc.edu

We present a computational framework that leverages machine-learned interatomic potentials (MLIPs) to accelerate and expand the scope of crystal structure prediction (CSP) and phase diagram construction under varying pressure and temperature conditions. Our code enables efficient exploration of the potential energy surface (PES) using random search algorithms, supporting both inorganic and molecular crystals, with or without applied pressure. By replacing density functional theory (DFT) in early-stage sampling with MLIPs, we achieve a dramatic speed-up in structure generation, relaxation, and stability screening while maintaining high fidelity to DFT-level accuracy. The CSP framework also integrates diffraction analysis tools to support experimental phase identification.

In addition to CSP, our workflow automates the construction of pressure–temperature (pT) phase diagrams. This includes MLIP-based phonon calculations, thermal expansion, and free energy evaluation, tasks that are typically computationally prohibitive using DFT alone.

We demonstrate the approach on HfO_2, a system known for its rich polymorphism. We compare MLIP and DFT results to validate structural predictions and thermodynamic trends, illustrating how MLIPs enable comprehensive phase space mapping with reduced computational cost.

This work underscores the potential of MLIPs to make high-throughput structural and thermodynamic exploration feasible and accessible for a broad class of materials systems.

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Large-scale chemical and crystal packing space exploration for HOF-based porous materials

Lucia Gigli[1], *Joshua Dickman*[1], *Jay Johal1*, *Qiang Zhu*[2], *Thomas Fellowes*[2], *Filip Szczypinski*[2], *Andrew I. Cooper*[2], *Graeme M. Day*[1]

[1]University of Southampton (UK), [2]University of Liverpool (UK)

Functional materials impact most aspects of our lives, but their design at the microscopic scale cannot be approached with the engineering rules that would be used in planning and constructing macroscopic objects. The ADAM (Autonomous Discovery of Advanced Materials) project aims at changing the way to discover functional molecular crystals by coupling a computational engine for the evolutionary exploration of chemical space using Crystal Structure Prediction (CSP) and Machine Learning, with an experimental engine for autonomous synthesis and characterization using robo- chemists. Although the ADAM project has a much broader scope, we here focus on a computational screening strategy for porous molecular materials based on hydrogen bonding groups from known Hydrogen-Bonded Organic Frameworks (HOFs).

Porous packing is a property that cannot be predicted purely based on molecular structure, so requires CSP on all candidate molecules. This contribution will discuss how this is now possible for candidate libraries of thousands of molecules.

Relative Stability Evaluation of Polymorphic Systems via Pseudo-Supercritical Path Method using Different Force Fields

Zhuocen Yang[1], *Yizu Zhang*[1], *Zhuhong Li*[1], *Yunfei Zhou*[1], *Liwen Fang*[1], *Shigang Ruan*[1],
R. Alex Mayo[2], *Guangxu Sun*[1]

[1]XtalPi Inc. (Shenzhen Jingtai Technology Co., Ltd.), International Biomedical Industrial Park (Phase II) 3F, 2 Hongliu Rd, Futian District, Shenzhen, China, 518038

[2]XtalPi Inc., 100 Chestnut Street, Suite 300, Somerville, MA 02143, United State of America

zhuocen.yang@xtalpi.com

Pseudo-supercritical Path (PSCP) method has been used to evaluate the relative Gibbs free energy difference between different forms of polymorphic systems [1-2]. This molecular dynamic (MD) based simulation is expected to provide a better simulation of dynamic behaviour at higher temperatures, although it requires force fields with reasonable accuracy to obtain reliable results. Moreover, the selection of the force field will affect the stability of the geometry of different polymorphs during the MD simulation, which may lead to unrealistic polymorphic transitions or simulation failure. In this study, we present an evaluation of the relative stability relationship of multiple polymorphic systems using the PSCP method. The performance of the PSCP method with different force fields is compared and cross-validated, and the errors are benchmarked against experimental observations.

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Exploring Crystal Polymorphism in Simvastatin: Insights from Dielectric Relaxation Spectroscopy

Natália T. Correia[1], *Maria T. Viciosa[1], Frederic Affouard[1]*

[1]Univ. Lille, CNRS, INRAE, Centrale Lille, UMR 8207, UMET, Unité Matériaux et Transformations, F-59650
Villeneuve d'Ascq, France

natalia.correia@univ-lille.fr

To gain a comprehensive understanding of the behaviour of single- and multi-component crystalline and amorphous systems, researchers employ a suite of analytical techniques, including X-ray diffraction, infrared and Raman spectroscopy, solid-state nuclear magnetic resonance, and calorimetric analysis. While these methods are well-established, Dielectric Relaxation Spectroscopy (DRS) presents a powerful yet underutilised alternative in materials science and pharmaceutical research. DRS excels at probing molecular mobility and phase transitions across a broad temperature and frequency range (10^{-3} Hz to 1 GHz), making it particularly suited for characterising amorphous and semi-crystalline disordered states.

In this study, we investigate molecular dynamics and phase transformations using DRS in conjunction with Molecular Dynamics simulations, focusing on simvastatin, a widely prescribed cholesterol-lowering agent. Our analysis highlights the intricate interplay between molecular structure, intermolecular interactions, and dynamic processes. These findings advance the physicochemical understanding of disordered pharmaceutical solids and underscore the potential of DRS as a complementary tool for exploring polymorphism and formulation stability.

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This project has received funding from the Interreg 2 Seas programme 2014-2020 co-funded by the European Regional Development Fund under subsidy contract 2S01-059_IMODE.

NMR Crystallography of Molecular Solids with Strong Hydrogen Bonds

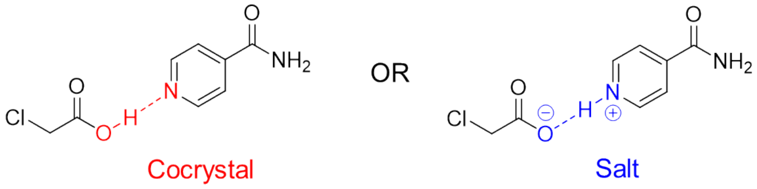
Martin Dračínský[1], Jakub Štoček[1], Jan Blahut[1]

Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague,
Czech Republic

dracinsky@uochb.cas.cz

Solid-state NMR (ssNMR) spectroscopy has emerged as a powerful and versatile tool for probing the structure, dynamics, and interactions of molecules in the solid phase. The progress of ssNMR methods has led to the development of NMR crystallography, which combines experimental ssNMR data with theoretical simulations to obtain otherwise inaccessible insights into the structure and dynamics of solid materials.

We will discuss several recent examples of NMR-crystallography studies, such as investigation of temperature-induced salt-to-cocrystal transformation of pharmaceutical solids [1-3]. We will also discuss the importance of nuclear quantum effects for the structure of solids with short hydrogen bonds.



Acknowledgement

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Step Bunching and Meandering Dynamics: A pathway to surface morphology control

Vassil Ivanov[1], *Vesselin Tonchev*[2]

[1]Faculty of Mathematics and Informatics and [2]Faculty of Physics Sofia University, “St. Kliment Ohridski”, Sofia, Bulgaria

vvasilevi@fmi.uni-sofia.bg

Step bunching on DC-heated Si(111) vicinal surfaces was first reported more than 30 years ago by Latyshev et.al.[1] Since then, major advances in the field have been achieved and step bunching has been observed in a wide range of material systems (experimental conditions): GaN(001)[2], W(110)[3,4], Al_2O_3(0001)[4], $MgAl_2O_4$(100)[5]. More recently Murata et al.[6] reported step bunching at the interface of a crystal and its melt - ice and supercooled water. Another general direction of bunching studies is dominating the discourse at present - that of applications[7,8].

What has been paradigmatic in the field, especially from theoretical point of view, is that step bunching and the meandering of the steps are two separate, incompatible processes [9] with alternative prerequisites, that occur at different conditions during which the growth (or sublimation) is carried out.

In the present work we start from a model initially formulated as a mean-field model of impurity driven step-bunching introduced by Kandel and Weeks[13,14]. It was later analyzed theoretically by Connel [15]. This model originally assumed that the step velocity depends only on the width of the front terrace, which is a mean-field formulation and requires careful derivation of the velocity function. Thus, we depart from this assumption and extend the model to a more general one of step bunching:

$$\frac{\partial u_i}{\partial t} = \gamma \frac{\partial^2 u_i}{\partial x^2} + f(u_{i-k}, \ldots, u_i, \ldots u_{i+l}), \qquad i = 1, 2, 3 \ldots N$$

Where N is the number of steps on the surface, γ is the step line tension and x is the coordinate tangential to the step edge. This system of PDEs is general enough to accommodate a wide range of velocity functions f(…), s.t. we can revisit all previous extended BCF-type ODE-based models of step-dynamics extending them in 2+1D.

As a first step, we use for the velocity function a simplistic minimal model, the so-called MM2 [16], known to show the B1-type of step bunching characterized by a single length scale (e.g. the number of steps in the bunch), to obtain the PDE system:

$$\frac{\partial u_i}{\partial t} = \gamma \frac{\partial^2 u_i}{\partial x^2} - k_a\left(\Delta u_i^{-r} - \Delta u_{i+1}^{-r}\right) + k_r\left(\Delta u_i^{-m} - \Delta u_{i+1}^{-m}\right)$$

Using the tools of dimensional analysis we show existence conditions for meandering, straight-step bunching and bunching of meandered steps for the case of MM2. This approach further provides us with a template to revisit all 1+1D ODE-based models from past literature.

Such an understanding of surface dynamics provides a pathway for better controlling the crystal growth process and obtaining functional surfaces with desired properties. Further, such a model that exhibits rich morphologies from simple pre-conditions allows us to develop monitoring schemes of the growth process *in sillico* which can later be integrated directly in AFM/STM analysis software.

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NMR crystallography of organic solids at high magnetic fields

Marta K. Dudek[1], Przemysław Nowak[1,2], Piotr Paluch, Agata Jeziorna, Dorota Krasowska

[1]Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland
[2]BioMedChem Doctoral School of University of Lodz and Institutes of PAS in Lodz, Matejki 21/23, 90-237 Łódź, Poland

marta.dudek@cbmm.lodz.pl

NMR crystallography, combining solid-state NMR, powder X-ray diffraction and theoretical calculations offers a real possibility of solving a crystal structure of a molecule when single crystal X-ray diffraction cannot be used (for example because the crystals large enough could not be obtained). It is not, however, a straight-forward techique, not least because of the fact that solid-state NMR spectra are often quite crowded and difficult to assign, even when advanced 2D techniques are applied [1, 2]. As a result it can be immensely difficult to build a reliable structural model from the experimental data, which can be further refined through calculations. This contribution will show the application of NMR crystallography to solve several structural puzzels. In particular, it will be shown how this method can be used to establish a tautomeric form present in a crystal of meloxicam:pyrazine cocrystal, especially through the use of ^{1}H-^{1}H BaBa spectrum registered at 1GHz NMR spectrometer (Fig.1, left), and to unambiguously differentiate between salts and cocrystals in meloxicam:imidazol binary systems employing ^{1}H-^{14}N T-HMQC experiment (Fig 1, right).

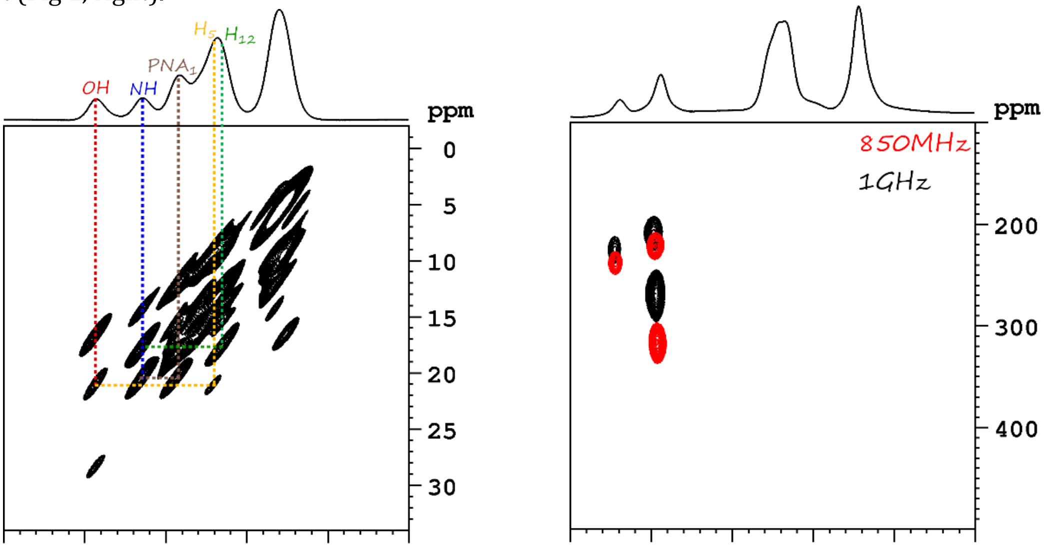

Figure 1. ^{1}H-^{1}H DQ-SQ Back-to-Back spectrum of meloxicam:pyrazine system (left) registered at 1GHz spectrometer and an overlay of two ^{1}H-^{14}N T-HMQC spectra registered at 1GHz and 850 MHz for meloxicam:imidazole system (right).

Acknowledgements
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Stabilizing the Unstable: Using Additives to Control Metastable Polymorphs and Extend Their Lifetime

Cheng-long Stephan[1], Gabin Gbabode[1], Ivo B. Rietveld[1]

[1]*Univ Rouen Normandie, Normandie Univ, SMS , UR 3233, F-76000 Rouen, France.*

cheng-long.stephan@univ-rouen.fr

A major problem exists for active pharmaceutical ingredients (APIs) is polymorphism. Represented by a difference in the organisation of the molecules inside the unit cell of a crystal, polymorphism affect the quality, safety and efficacy of the final drug product.[1–3] Several ways are commonly used for the manufacturing of a specific polymorphic phase during crystallization, including temperature control, seeding, choice of solvent and pH control.[4] However, these APIs depend on thermodynamic and possess one stable form and multiple metastable form.[5] The stable form is the preferred one for a pharmaceutical development based on thermodynamic considerations, despite the risk of poor solubility, and thus bioavailability.[6]

Pyrazinamide, featured in the W.H.O. list of essential drugs as an antituberculosis medicine,[7] and in the BEST-CSP Cost Action CA22107 benchmark,[8] displays four polymorphic forms (alpha: α, beta: β, delta: δ, and gamma: γ). The γ phase described as having the highest intrinsic dissolution rate at 1 hour under ambient conditions[6], is of interest to improve pyrazinamide solubility. However, this metastable form tends to convert into the stable form α within 7 to 14 days.[9,10] While crystallizing γ form using urea derivatives as additives, its lifetime is increased to 1 year.[9] This presentation highlights how additives can be used to control and extend the lifetime of the metastable γ form of pyrazinamide in the presence of either 1,3-diethylurea or 1,3-dimethylurea.

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Poster Presentations

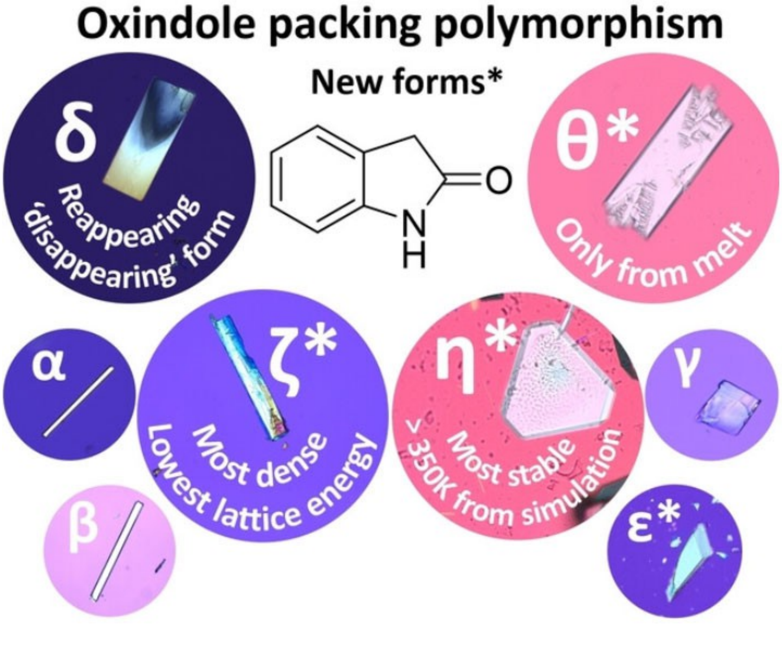
Unprecedented Packing Polymorphism of Oxindole Inspired by Crystal Structure Prediction

Alfred Lee, Emily Wu, Andrew Kelly, Luca Iuzzolino and Xiaolong Zhu

Analytical Research & Development, MSD Rahway, New
Jersey, 07065 United States

alfred.lee@merck.com

Crystal polymorphism, characterized by different packing arrangements of the same compound, strongly ties to the physical properties of a molecule. Determining the polymorphic landscape is complex and time-consuming, with the number of experimentally observed polymorphs varying widely from molecule to molecule. Furthermore, disappearing polymorphs, the phenomenon whereby experimentally observed forms cannot be reproduced, pose a significant challenge for the pharmaceutical industry. Herein, we focused on oxindole (OX), a small rigid molecule with four known polymorphs, including a reported disappearing form. Using crystal structure prediction (CSP), we assessed OX solid-state landscape and thermodynamic stability by comparing predicted structures with experimentally known forms. We then performed melt and solution crystallization in bulk and nanoconfinement to validate our predictions. These experiments successfully reproduced the known forms and led to the discovery of four novel polymorphs. Our approach provided insights into reconstructing disappearing polymorphs and building more comprehensive polymorph landscapes. These results also establish a new record of packing polymorphism for rigid molecules, surpassing the previous understanding of the polymorphic diversity of such molecules.[1]



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The Effect of Molecular Characteristics on Solvate Formation of Structurally Related Bisphenol Compounds

J. A. Baptista[1], J. Canotilho[1,2], R. A. E. Castro[1,2], E. Fantechi[3], L. Chelazzi[3], S. Ciattini[3],
M. T. S. Rosado[1], M. E. S. Eusébio[1]

[1]University of Coimbra, CQC/IMS, Department of Chemistry, 3004-535 Coimbra, Portugal
[2]University of Coimbra, Faculty of Pharmacy, 3000-548 Coimbra, Portugal
[3]Università degli Studi di Firenze Centro di Cristallografia Strutturale, Firenze 50019, Italy

jabaptista@qui.uc.pt

Crystallization from solutions remains a fundamental technique in the pharmaceutical sciences, particularly for the final stages of active pharmaceutical ingredient (API) synthesis and purification. This process plays a pivotal role in determining critical attributes such as crystal size, morphology, particle size distribution, and the solid form obtained [1]. Systematic solid form screening is essential, as it can lead to the discovery of new polymorphic or solvate forms, some of which may emerge during late-stage development or even after a drug product has been approved and marketed.

A previous study on the crystallization behaviour of the antihyperlipidemic drug probucol (PROB), Figure 1a, under a range of conditions—including several solvent systems—led to the discovery of new polymorphic forms [2], nearly 30 years after the last crystal structures were reported [3]. In addition, several novel solvate forms were identified and characterized.

PROB is a very flexible molecule, however, despite containing two hydroxyl groups, their accessibility is significantly restricted due to the steric hindrance imposed by the adjacent tert-butyl substituents. In this study, two structurally related bisphenol compounds, tetramethyl bisphenol A (TM-BPA, Figure 1b) and 4,4′-methylenebis(2,6-di-tert-butylphenol) (TB-BPF, Figure 1c), were selected for investigation due to their structural resemblance to PROB. While both compounds share key structural motifs with PROB, they exhibit reduced conformational flexibility. Additionally, the hydroxyl groups in TM-BPA are more readily accessible for hydrogen bonding, greatly influencing its crystallization behaviour when compared to PROB and TB-BPF.

By conducting a solid-state screening of these three bisphenol compounds under identical experimental conditions and comparing their crystal structures, intermolecular interactions, and thermal behaviour, this study aims to provide insights into the role of molecular features in directing solvate formation with a common solvent among structurally related molecules.

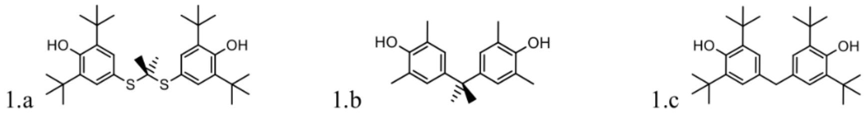
1.a 1.b 1.c

Figure 1. Molecular structures of: 1.a. PROB; 1.b. TM-BPA; 1.c. TB-BPF.

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Cocrystallization of Phenylpiracetam with Optically Active Compounds

Artjoms Jermakovs, Marks Urbāns, Artis Kons, Agris Bērziņš

Department of Chemistry, Faculty of Medicine and Life Sciences, University of Latvia, Jelgavas iela 1, Riga, Latvia

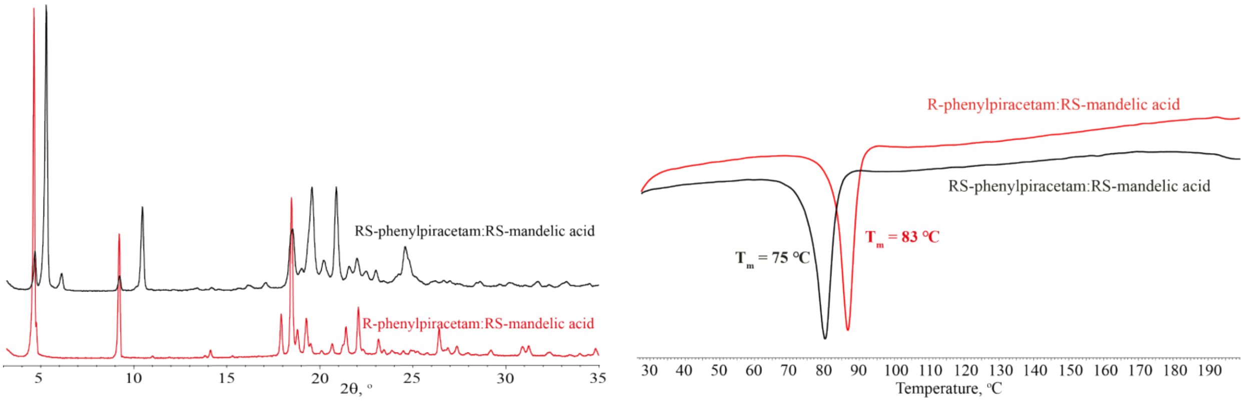
agris.berzins@lu.lv

Optical activity of the active pharmaceutical ingredients is an important factor affecting the properties of drugs. One enantiomer often produces the desired effect, while the opposite enantiomer may be less efficient, inactive or even toxic. It has been demonstrated that cocrystallization is an efficient technique for chiral resolution, not only providing an enantiopure compound but additionally allowing to improv solubility and bioavailability of the drug [1-2].

In this study, phenylpiracetam was used as a model compound to investigate the cocrystal formation of enantiopure and racemic phenylpiracetam. Phenylpiracetam is a nootropic drug, with R-enantiomer having stronger effect in the human body if compared to the S-enantiomer [3].

The cocrystallization of R-phenylpiracetam and RS-phenylpiracetam with optically active pharmaceutically acceptable coformers was explored under different conditions by performing liquid- assisted grinding and crystallization from different solvents. Solid forms obtained in the crystallization were characterized by powder X-ray diffraction (PXRD). The melting points of the new cocrystals were determined by differential scanning calorimetry (DSC) and crystal structure of part of the newly obtained cocrystals was determined using single crystal X-ray diffraction.

R-phenylpiracetam was found to form cocrystals with itaconic acid, oxalic acid, maleic acid and L- malic acid forming different types of intermolecular interactions. Both R-phenylpiracetam and RS- phenylpiracetam showed the potential for cocrystal formation with RS-mandelic (see Figure 1) acid and tartaric acid.



(a) (b)

Figure 1. (a) PXRD of the new cocrystals with RS-mandelic acid, (b) DSC of the new cocrystals with RS-mandelic acid.

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Phenylpiracetam: Solid Solutions and Attempts at Chiral Resolution

Laura Contini,[1] *Yihua Jiang*,[2] *Tom Leyssens*,[2] *Doris E. Braun*,[3] *Fabrizia Grepioni*,[1]

[1]Molecular Crystal Engineering Laboratory, Department of Chemistry "Giacomo Ciamician", University of Bologna, Via Gobetti 85, 40129, Bologna (Italy);
[2]Institute of Condensed Matter and Nanosciences, UCLouvain, Place Louis Pasteur 1, 1348 Louvain-la-Neuve (Belgium);
[3]University of Innsbruck, Institute of Pharmacy, Pharmaceutical Technology, Innrain 52c, A- 6020 Innsbruck (Austria).

Laura.contini3@unibo.it

Phenylpiracetam (PPA) is an API belonging to the racetam family, a class of nootropic compounds known for their cognitive-enhancing properties used in the treatment of neurological disorders such as cognitive impairment and restless leg syndrome. [1] Despite its therapeutic potential, the crystallographic behaviour of phenylpiracetam is remarkably complex. Enantiopure PPA is known to crystallize in two enantiotropically related polymorphs, Form A and Form B (stable and metastable at room temperature, respectively). Additionally, miscibility of the phenylpiracetam enantiomers in the solid state is possible over a wide compositional range, hindering the chiral resolution of (RS)-PPA. [2]

This work aims to investigate whether solid solution formation, an intrinsic feature of PPA hindering chiral resolution, can be circumvented through crystal engineering strategies. First, cocrystallization with chiral coformers was attempted but, despite testing over 150 chiral coformers, no racemic conglomerate was isolated. Then, given that co-crystallization with inorganic salts has proven successful for the chiral resolution of other racetam derivatives, [3- 5] we extended our investigation to metal salts. Co-crystallization with $ZnCl_2$, $ZnBr_2$ and $CaCl_2$ led to the formation of several novel PPA complexes, which were structurally characterized. However, these structures still exhibited features of enantiomeric solid solution formation. To further elucidate the structural landscape of PPA and rationalize its strong tendency to form enantiomeric solid solutions, computational studies were carried out. Conformational analysis highlighted the conformational flexibility of the PPA molecule around the chiral centre, suggesting that its ability to adopt multiple low-energy conformations may contribute to the formation of substitutionally disordered solids.

These results suggest that enantiomeric solid solution formation is a recurring feature accompanying PPA crystallization, posing a challenge for its chiral resolution in the solid state. Further studies with different molecular systems and salts are ongoing to assess whether this trend is general or system specific.

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A Tangled Web of Solvates: Unravelling the Solid-State Forms of Daprodustat

Aleksandra J. Dyba[1,2], *Thomas Gelbrich*[1,2], *Doris E. Braun*[1,2]

[1]Institute of Pharmacy, University of Innsbruck, Austria. [2]Christian Doppler Laboratory for Advanced Crystal Engineering Strategies in Drug Development, Institute of Pharmacy, University of Innsbruck, Austria.

aleksandra.dyba@uibk.ac.at, doris.braun@uibk.ac.at

Daprodustat exhibits a rich solid-state landscape, as documented in patent literature, comprising multiple polymorphs, many solvates, (ionic) cocrystals, as well as amorphous solid dispersions [1-7]. Understanding and controlling this polymorphic and solvate diversity is essential for the development of stable and manufacturable solid forms.

A systematic screening was conducted using 40 diverse solvents. Crystallization methods included solvent evaporation, slurry conversion, cooling crystallization, antisolvent addition, and vapour diffusion. The resulting solid forms were characterized using powder X-ray diffraction, infrared spectroscopy, and thermoanalytical techniques. The crystal structures of three solvates and one anhydrate were resolved.

All previously reported daprodustat solvates were successfully reproduced. Additionally, two novel solvates were identified and characterized. The enol form of daprodustat is present in all structurally characterized solid forms. The acicular morphology of each of these crystals coincides with the presence of a single type of columnar arrangement of molecules along the shortest crystallographic axis. In addition, the THF solvate contains a layer arrangement of daprodustat molecules which is also found in the isostructural *i*-PrOH and 2-BuOH solvates.

Overall, this study reveals key trends governing the solvate formation in the daprodustat system. Solvents with both H-bonding donor and acceptor sites and flexible or cyclic features promote solvate formation. Aprotic polar solvents generally outperformed esters, ketones, and hydrocarbons. Intermediates were detected along the desolvation pathways of the solvate forms. The observed transformations, instability of certain solvates, and formation of intermediates reflect a highly dynamic solid-state system. These findings highlight the intricate phase behaviour of daprodustat and the challenges associated with its characterization and control.

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Informatics meets energetics: combining crystal structure prediction and knowledge of the crystal landscape

Emma Hawking[1]

[1] The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK

ehawking@ccdc.cam.ac.uk

The significance of polymorphism in pharmaceuticals necessitates careful selection of a solid form to ensure thermodynamic or kinetic stability throughout drug manufacturing and production. Despite extensive polymorph screening methods, finding a more stable polymorph remains a risk, therefore experimental workflows are supplemented by computational methods such as Crystal Structure Prediction (CSP) and informatics-based risk assessments to derisk emerging of new solid forms. CSP has evolved to become integral in pharmaceutical materials science workflows to investigate the solid form landscape. However, the landscapes of predicted crystal packing arrangements are complex, with contributions from hydrogen bonding, molecular conformation and weak intermolecular interactions. Therefore, it can be challenging to for crystal engineers to understand the contribution of individual factors to the overall relative energy of structures. The Cambridge Structural Database (CSD), comprising over 1.3 million experimentally determined crystal structures, serves as a comprehensive resource for understanding the vast diversity of intramolecular geometries and intermolecular interactions [1]. This dataset provides valuable insights into the structural factors that influence solid- state properties. Solid Form Informatics leverages this wealth of crystallographic data to analyse and contextualize the various contributors to polymorphism and understand the risk of emerging forms.

Analysis of CSP landscapes has been conducted using the tools from informatics-based risk assessments. This has focused on generating and mining structural data from CSP landscapes, as well as the CSD, to de-risk solid forms. This combined approach offers a comprehensive understanding of the solid form, highlighting the intricate interplay between hydrogen bonding, molecular conformation and weak intermolecular interactions, and demonstrates how CSP can be leveraged alongside structural data to understand contributing factors to low and high energy polymorphs. This analysis has been utilised to show how structural landscapes can show competing and co-occurring interactions and rationalise why molecules may prefer to deviate from the major populations of CSD distributions. This has enabled rationalization of the factors contributing to the thermodynamic stability of small molecule crystal structures, helping to de-risk pharmaceutical development.

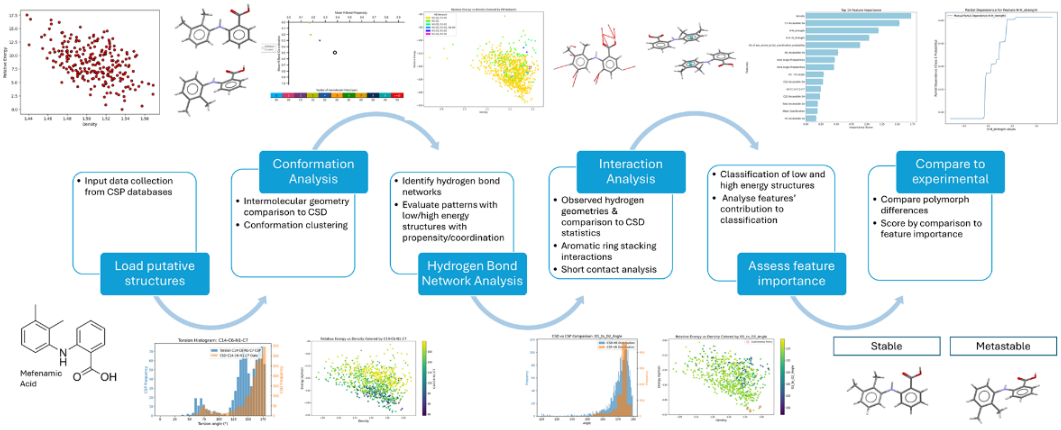

Fig. 1. Informatics meets energetics workflow leveraging CSD data to rationalize experimental stability.

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Structure and Energetics of NIC$_a$:DA Co-crystals (NIC = nicotinamide; DA = Fumaric Acid, Maleic Acid, Succinic Acid)

<u>I.O. Feliciano</u>, C.E.S. Bernardes, M.F.M. da Piedade, M.E. Minas da Piedade

[1]Centro de Química Estrutural, Institute of Molecular Sciences, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

idfeliciano@fc.ul.pt

Multicomponent crystallization has become a prominent strategy in crystal engineering to obtain active pharmaceutical ingredients (APIs) with physicochemical properties tuned for optimal performance. Key aspects within this scope, which are also strongly aligned with the BEST-CSP objectives, are the assessment of the multicomponent crystals (MC) stability relative to decomposition into their precursors and how this stability depends on the nature of the co-formers and the MC stoichiometry. The study of families of structurally related MCs is very helpful in this context, to provide insights into how systematic changes in molecular structures influence stability.

In this study the thermodynamic stability of bicomponent crystals composed of nicotinamide, NIC, and fumaric acid, FA, maleic acid, MA, or succinic acid, SA, (Fig. 1) was carried out. The materials were synthesized by mechanochemistry and structurally characterized by powder and single crystal X-ray diffraction. Differential scanning calorimetry experiments provided information on thermal behavior. Finally, the thermodynamic stability of MC relative to decomposition into the individual precursors was characterized by determining $\Delta_r G^o_m$, $\Delta_r H^o_m$ and $T\Delta_r S^o_m$ for the dissociation process (DA = FA, MA, SA; a = 1 or 2)

$$\mathrm{NIC}_a:\mathrm{DA(cr)} \rightarrow a\mathrm{NIC(cr)} + \mathrm{DA(cr)}$$

bicomponent crystals studied were stable relative to the corresponding individual precursors and this stability is enthalpically driven, i.e. by cohesion energy.

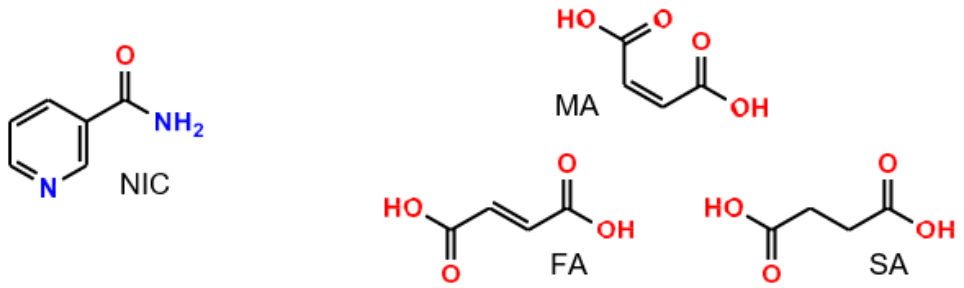

Fig.1 Molecular structure of the precursors studied in this work.

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Impact of geometrical confinement on the polymorphism of biclotymol

Gabin Gbabode[1], Clementmanohar Arava[1], Artur Shevchuk[1], Sandrine Morin-Grognet[2]

[1] Normandie Univ, Laboratoire SMS – EA3233, Univ Rouen, 76821 Mont Saint Aignan, France. 2 Normandie univ,
Laboratoire PBS – UMR CNRS 6270, IUT
d'Evreux, 27004 Evreux, France
gabin.gbabode@univ-rouen.fr

Controlling polymorphism is crucial in many applied fields exploiting organic materials such as pharmaceutics[1] or organic electronics[2] to name a few. Each polymorphic form possesses its own physical and chemical properties and also its own stability behaviour depending on the external conditions.[3] Furthermore, the most stable polymorph is not necessarily the one with the most suitable properties as exemplified by drugs for which metastable polymorphs are inherently more soluble than the most stable form[4] thus yielding to potential drug products with enhanced bioavailability.[1] It is therefore important to find robust procedures that not only ensures the crystallization of metastable polymorphs but also allows their preservation for a long period of time. Crystallization in confined geometry (e.g. thin films or insertion in nanoporous particles) might be a promising route to achieve this goal.[5,6]

In the present communication, we use solution-based deposition techniques such as spin- coating and drop-casting to fabricate thin films of biclotymol, an active pharmaceutical ingredient used as an antiseptic for Ear Nose and Throat infections.[7] This molecule was chosen as it is known to possess two polymorphic forms, named forms I and II, related by a monotropic relationship, form I being the most stable polymorph.[7] Form II can only be obtained by crystallization from the amorphous solid but converts back to form I in a few days. It appears that drop-casted films exhibit form I in all the concentration range investigated i.e. from 1.9 mg/mL to 38.3 mg/mL and for all solvents used (acetone, ethanol, methanol and DMSO). However, when the polycrystalline films are submitted to a suitable thermal treatment, form II is reproducibly obtained and no conversion to form I is observed up to 12 weeks at least. In the case of spin-coated films, which are around one order of magnitude less thick than the drop-casted ones (hundreds of nm for the former compared to the micron scale for the latter) amorphous films are always obtained. However, crystallization and the type of polymorph occurs more or less rapidly with time depending on the solution concentration i.e., from ~1 week for 38.3 mg/mL to >3 months for very low concentrations (with some variation depending on the solvent and the environmental conditions). It was found that below a certain solution concentration (9.6 mg/mL typically), only form II crystals grow on the substrate from the amorphous solid while above this threshold concentration form I films are only observed. Furthermore, no reconversion to form I has been observed in the low concentration films up to now (8 months storage at ambient conditions).

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Benchmarking composite quasi-harmonic models of polymorphism of Benzophenone and Sulfamerazine

Reynaldo Geronia II, *Ctirad Červinka*

Department of Physical Chemistry, University of Chemistry and Technology Prague,
Technická 5, Prague 6 166 28, Czech Republic

geroniar@vscht.cz

Density functional theory (DFT) remains widely used for property prediction despite the high computational requirements of its periodic implementations. To deal with increasingly complex systems, cruder algorithms such as density functional tight binding (DFTB) have been developed. One implementation, DFTB+, exploits parallelism and matrix algebra to accelerate calculations by up to two orders of magnitude [1]. At the same time, the approximations themselves can cause property prediction to fail due to the semi-empirical nature of such models.

In this work, we explore the use of DFT-D3 and DFTB-D3, both individually and simultaneously, to predict thermodynamic properties and polymorphism of benzophenone and sulfamerazine within the quasi-harmonic approximation (QHA). We examine how the DFTB- only QHA, which itself is burdened by unacceptable errors, benefits from a composite treatment that consists of shifting DFTB outputs to match DFT signals [2]. In particular, in the context of QHA, DFTB is used to model the dependence of the crystal's static and dynamic degrees of freedom on its volume, whereas the costly DFT calculations are run only for a single crystal volume. We also investigate whether the calculated discrepancies between individual QHA levels depend on temperature and polymorphism. To address the latter, comparisons are made for α- and β-benzophenone. Finally, the utility of the hybrid approach is demonstrated through the $Pna2_1$ polymorph of sulfamerazine, where a volume-dependent description of DFT energies is otherwise too costly to obtain.

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Computational and crystallographic insights into H-Bonding driven by anion···anion interactions in new salts of fumaric and maleic acids

Mahdi Jemai[1,2], Miquel Barceló Oliver[3], Houda Marouani[2], Thierry Roisnel[4], Rafel Prohens[1] and Antonio Frontera[3]

(1) Laboratory of Organic Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av.Joan XXIII 27-31, 08028-Barcelona, Spain

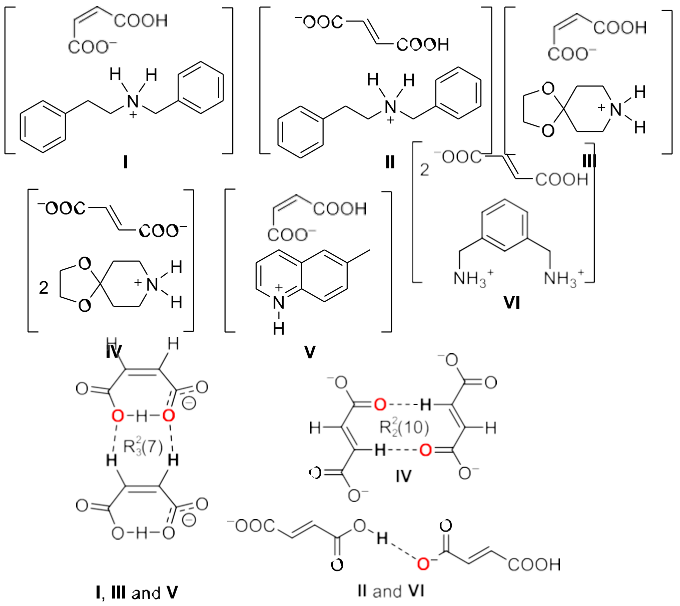
(2) Laboratory of Material Chemistry, LR13ES08, Faculty of Sciences of Bizerte, University of Carthage, 7021 Bizerte, Tunisia

(3) Department of Chemistry, University of Balearic Islands,07122 Palma de Mallorca, Spain

(4) Université de Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes), UMR 6226, F-35000 Rennes, France

jmmahdim56@alumnes.ub.edu

Understanding non-covalent interactions, particularly hydrogen bonds between anions, is critical for advancing in the predictive accuracy of solid-state properties. This study presents the synthesis and comprehensive structural characterization of novel ammonium salts of fumaric and maleic acids via single-crystal X-ray diffraction. Detailed analysis reveals extensive networks of hydrogen bonds, including anion···anion contacts. To elucidate the nature and strength of these interactions, we applied density functional theory (DFT), molecular electrostatic potential mapping, and quantum theory of atoms in molecules (QTAIM). Our study is a new example of how hydrogen bonding can overcome Coulombic repulsion to stabilize organized anionic frameworks within the crystal lattice.



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Unconventional methods of crystallizing meloxicam crystals and cocrystals with pyrazole

Agata Jeziorna,[1] Przemysław Nowak[1,2], Marta K. Dudek[1]

[1]Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland
[2]BioMedChem Doctoral School of University of Lodz and Institutes of PAS in Lodz, Matejki 21/23, 90-237 Łódź, Poland

agata.jeziorna@cbmm.lodz.pl

Meloxicam (MLX) belongs to non-steroidal anti-inflammatory agents. It is sold in it's the most thermodynamically stable crystal form, designated as MLX-I. There are also three other crystal forms of MLX, identified on the basis of their PXRD patterns, MLX-II, MLX-III and MLX-V [1]. The published procedure for their crystallization turned out to be unrepeatable, and this prompted us to use CSP calculations to indicate possible crystallization pathways for MLX. The obtained crystal structure energy landscape of MLX featured mainly crystal structures stabilized by the NH···O S dimers (motif A), present also in MLX-I, but we also noticed the presence of low energy and low density crystal forms stabilized by the NH···N dimers (motif B). This led to the design of a series of desolvation and/or decocrystallization experiments, which could lead to low density polymorphs, in the presence of crystallization additives able to disrupt the most prevailing hydrogen bonds. As a result, MLX-II, III and V were crystallized in their pure forms, in addition to a discovery of several new solvates and two polymorphic cocrystals with pyrazole (POL) [2].

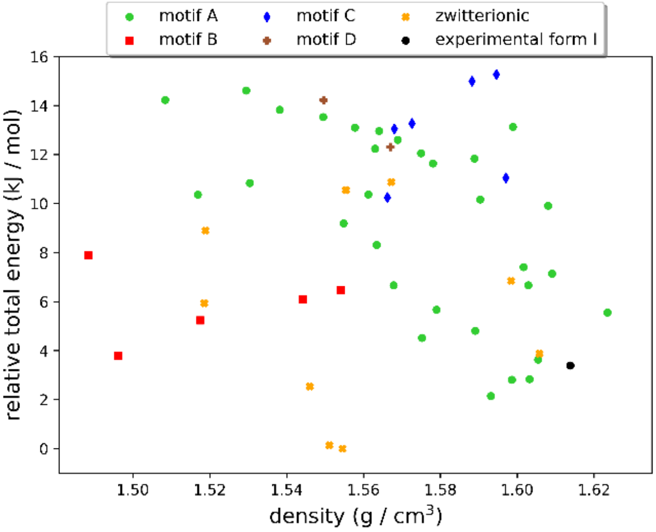

Figure 1. The CSP crystal energy landscape of MLX.

In this work we showcase experimental procedures leading to the elusive forms of MLX, as well as stable binary systems of MLX:POL, including classic crystallization from solution, but also through mechanochemical neat and liquid-assisted grinding, slurry and melting.

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Exploring Solid-State Landscapes: Advances In Pharmaceutical Polymorphism Of Phenprocoumon

Yihua Jiang[1], Laura Contini[2]

[1]Institute of Condensed Matter and Nanosciences,Université catholique de Louvain
[2]Department of Chemistry, University of Bologna, Via Francesco Selmi 2, Bologna

yihua.jiang@uclouvain.be, laura.contini3@unibo.it

Background:
Pharmaceutical polymorphism plays a critical role in determining the physical and chemical properties of drug substances. Different polymorphs can exhibit significant variations in solubility, bioavailability, stability, and manufacturability, which directly impact drug efficacy, safety, and regulatory approval[1-3]. As such, identifying, characterizing, and controlling polymorphic forms is essential throughout the drug development process, from early discovery to commercial production. This study focuses on the solid-state behavior of Phenprocoumon, a widely used anticoagulant drug, exploring its polymorphic landscape through a combination of analytical techniques. The findings contribute to a deeper understanding of solid-state transitions and provide insights into the selection of optimal crystal forms for formulation development.
Methods:
Through a combination of powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and meticulous data analysis, we successfully identified four previously unreported polymorphic forms of phenprocoumon. Single crystal X-ray diffraction and powder structure resolution techniques enabled us to determine the crystal structures of three of these forms.
Results:
Five polymorphic forms of phenprocoumon were identified and characterized. Among them, three forms were structurally resolved, exhibiting distinct packing motifs and thermal behaviors. The differences in their melting points, enthalpies, and PXRD patterns clearly confirmed their unique crystalline nature.
Conclusion:
This study reveals the rich polymorphic landscape of phenprocoumon and underscores the necessity of comprehensive solid-state screening during drug development. Our findings not only expand the crystallographic database for this widely used anticoagulant drug but also enhance the understanding of thermal transitions in polymorphisms, thereby guiding future polymorphism screening efforts.

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Many-body errors of theoretical methods

Jiří Klimeš[1], Khanh Ngoc Pham[1], Marcin Modrzejewski[2], and Sirous Yourdkhani –

11 Department of Chemical Physics and Optics, Faculty of Mathematics and Physics, Charles University, Ke Karlovu 3, Prague, CZ
2 Faculty of Chemistry, University of Warsaw, Pasteura 1, PL

jiri.klimes@matfyz.cuni.cz

Density functional theory (DFT) is often used to predict binding energies of molecular solids. And one can consider it successful as, with dispersion corrections, the errors are around several percent. However, comparing to a single number, the binding energy, can be deceiving as good results can be due to error cancellations. A more detailed information about the accuracy of different DFT approaches and other methods can be obtained via many-body expansion (MBE). Within MBE the binding energy is divided into contributions of dimers, trimers, and larger clusters. For small molecules reference quality contributions can be obtained using quantum chemical methods. We use MBE to show that the trimer and tetramer contributions have large errors at the level of DFT [1]. Within the context of crystal structure prediction (CSP), it is often hoped that these many-body errors are similar for different polymorphs and that they cancel when calculating energy differences between the polymorphs. However, it is not clear to what extent is this assumption true. In Fig. 1 we illustrate that for two structures of acetylene, the errors of the PBE functional are significant even for the four body contributions. Situation is likely worse for hydrogen bonded systems where the three- and four- body contributions can represent a large contribution to the total binding energy [2]. Finally, we will present comparison of binding energies obtained using different programmes to assess the errors due to the use of pseudopotentials or the projector-augmented method.

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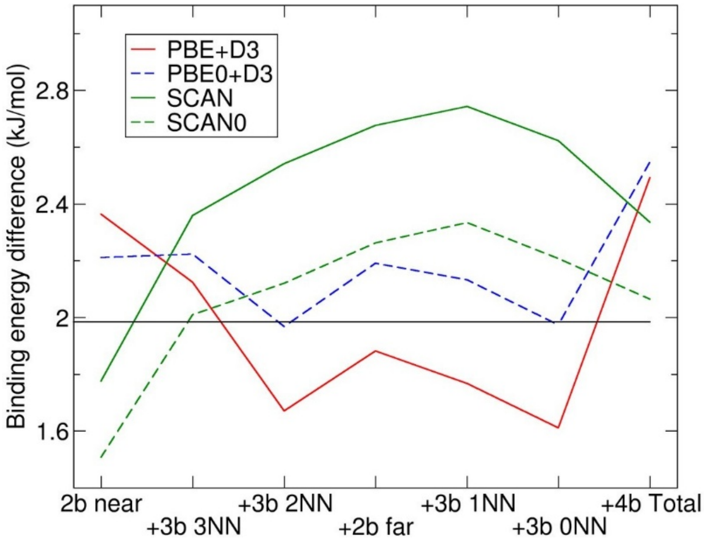

Figure 1: Convergence of the energy difference between cubic and orthorhombic acetylene structures for different DFT methods as a function of included many-body contributions. The "mb" means "m"- body contributions and "nNN" means clusters with "n" nearest neighbour molecules [1].

Energetic Characterization of 3-Hydroxy-2-methyl-4-pyrone: Supporting Thermochemical Conversion of Biomass

Ana Luísa R. Silva, Maria D.M.C. Ribeiro da Silva

Centro de Investigação em Química (CIQUP), Institute of Molecular Sciences (IMS),
Department of Chemistry and Biochemistry, Faculty of Sciences of University of Porto,
Rua do Campo Alegre, P-4169-007 Porto, Portugal

analuisa.rs@fc.up.pt

The thermochemical processes of biomass conversion are based on the concept of breaking down the feedstock into smaller building block molecules from which new chemicals can be generated [1]. Bio-oil is one of the products whose refining can produce highly valuable chemicals and biofuels. Many studies have been carried out in this field, namely concerning reactor design, products formation, and its upgrading. A significant input of accurate thermodynamic data is required for model compounds to overcome the industrial challenges related to the reaction mechanisms leading to advanced biofuels. These data enable the evaluation of the species reactivity and the exploration of various sustainable pathways towards biofuel synthesis.

In this context, our Research Group has been involved in a comprehensive experimental and theoretical study of biomass-derived compounds [2], specifically pyrone derivatives.

In this work, the energy of combustion and enthalpy of sublimation, as well as the enthalpy of fusion of 3-hydroxy-2-methyl-4-pyrone were measured using calorimetric techniques. Subsequently, the respective standard molar enthalpies of formation, in the crystalline and gaseous phases, were derived. Complementarily, based on quantum chemical calculations, the standard molar enthalpy of formation was calculated and compared with the experimental one. Finally, the study of conversion reactions (ring-opening and deoxygenation) of a model compound of biomass-derived 2-pyrones was also performed, calculating the Gibbs energies of the reactants, intermediates, and products in reactions.

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Bridging Materials Informatics and Crystal Structure Prediction: The EuMINe COST Action Perspective

Francesco Mercuri[1]

DAIMON Lab, CNR-ISMN Bologna, Italy - EuMINe COST Action Chair

francesco.mercuri@cnr.it

The European Materials Informatics Network (EuMINe, COST Action CA22143)[1] is a pan-European initiative focused on accelerating innovation in materials development through data-centric and AI-driven approaches. EuMINe fosters collaboration across computational modelling, data infrastructures, and materials design, aiming to bridge the gap between digital tools and real-world applications. The activities of EuMINe, aligned with FAIR data principles and standardisation, support the creation of interoperable frameworks and workflows that complement experimental research. With over 250 participants from 35 countries, EuMINe promotes community-driven solutions for predictive modelling, digital infrastructures, and knowledge exchange. These shared objectives naturally resonate with BEST-CSP's mission to integrate simulation and experiment in crystal structure prediction. EuMINe's networking activities and open approach offer valuable synergies for joint initiatives in materials data interoperability, digital workflows, and cross-disciplinary training.

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Voltammetry determination of selected herbicides using novel Pd decorated multiphase electrode

Jelena Milićević[1], *Marija Prekajski Đorđević*[1], *Željko Radovanović*[2], *Branko Matović*[1], *Aleksandra Dimitrijević*[1],
Marjan Ranđelović[3]

[1] Vinča Institute of Nuclear Sciences, National Institute of the Republic of Serbia, University of Belgrade, Mike Petrovića Alasa 12-14, 11351 Vinča, Belgrade, Republic of Serbia
[2]Innovation Center of the Faculty of Technology and Metallurgy, Karnegijeva 4, 11120 Belgrade, University of Belgrade, Serbia
[3]Department of Chemistry, Faculty of Sciences and Mathematics, University of Niš, Višegradska 33, 18106 Niš, Serbia

jdjordjevic@vinca.rs

Due to the adverse health effects and toxicity of the pesticide dicamba (DIC) and 2,4-D, the continuous monitoring of this pesticide in the environment is an issue that is receiving increasing scientific attention[1]. With the aim of establishing a simple, rapid, economical, and reliable method for monitoring the pesticides DIC and 2,4-D in aqueous solution, the one-step synthesis and characterisation of a palladium (Pd)-decorated multiphase composite (TiN/Ti1.886O3/MgTiO3/Mg2TiO4), denoted as Pd@MPC, as an electrochemical sensor using Differential Pulse Stripping Voltammetry (DPSV) was carried out. This study investigates Field Emission Scanning Electron Microscopy (FESEM) and Energy-Dispersive X-ray spectroscopy (EDX) which confirm the XRD results. The observed granular morphology indicates a high surface area, which is crucial for the electrocatalytic performance, while the smooth surface of the Pd-decorated composite indicates a uniform distribution of Pd nanoparticles. This uniformity plays a key role in improving the electrochemical detection of pesticides such as dicamba (DIC) and 2,4-D by facilitating the kinetics of electron transfer, increasing the number of active catalytic sites and improving the overall electrochemical response. EDX analysis confirms the successful incorporation of Pd with a relatively high content (8.1%), which further enhances the catalytic efficiency in oxidation reactions.

The electrochemical performance was evaluated using the Pd@MPC/GC electrode in a $K_4[Fe(CN)_6]$ redox system and showed superior electrocatalytic activity compared to a commercially available glassy carbon electrode. The composite was tested as a voltametric sensor for the determination of DIC and 2,4 D pesticides. The oxidation peaks for DIC and 2,4-D were observed at +0.9 V and +1.3 V against SCE, respectively. The results emphasise the strong influence of pH on the signal-to-noise ratio, with optimal analytical performance achieved at a pH 2.0 and a detection limit of 3.03 ng/mL. These results confirm that Pd@MPC is a promising material for high-performance electrochemical sensors, offering a unique combination of structural stability, conductivity and catalytic activity.

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Structural and Optical Characterization of $FeGaInS_4$ Layered Crystals

Zeynab Addayeva[1], Mustafa Muradov[1], Vaqif Salmanov[1]

Baku State University

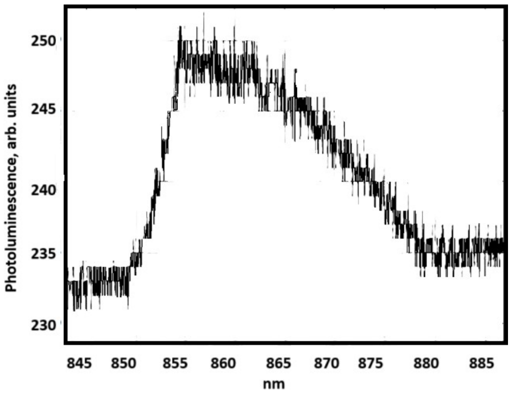
zeynab.addayeva@bsu.edu.az

$FeGaInS_4$ layered crystals were synthesized using the Bridgman technique, and their crystal structure was investigated via powder X-ray diffraction (XRD). $FeGaInS_4$ is a quaternary complex metal chalcogenide that belongs to the class of layered, quartz-like A–B– C–X_4 type compounds. The material crystallizes in the rhombohedral system and adopts the R3m (No. 160) space group, according to the International Union of Crystallography (IUCr) classification. The refined lattice parameters (a = b = 5.406 Å, c = 10.708 Å) confirm the presence of a highly symmetric and anisotropic layered crystal structure [1].

Within the structure, Fe, Ga, and In atoms occupy different coordination environments and form tetrahedral bonds with sulfur (S) anions, resulting in a complex three- dimensional network. These bonding interactions directly influence the material's electronic structure and related functional properties, including electrical conductivity, optical absorption, dielectric response, and thermal stability.

Due to its anisotropic layered architecture, $FeGaInS_4$ exhibits natural cleavage along specific crystallographic directions. This property renders it suitable for exfoliation into few- layer or monolayer nanosheets, making it a promising candidate for the fabrication of two- dimensional (2D) materials and high-performance composite systems[2].

Photoluminescence and absorption spectroscopy measurements, conducted using a Nd:YAG laser source (photon energy $\hbar\omega = 2.34$ eV), revealed that the optical band gap of $FeGaInS_4$ is approximately 1.46 eV.



Considering its structural and optical characteristics, $FeGaInS_4$ was employed as a layered filler within a polyvinyl alcohol (PVA) matrix to fabricate nanocomposites, whose dielectric properties were systematically evaluated.

The results revealed that external stimuli such as temperature and γ-irradiation can modulate the interfacial interaction between the polymer matrix and the layered filler. These effects enhance the mobility of the polymer chains, facilitating their intercalation into the interlayer spaces of the filler. Consequently, the interphase region expands, leading to significant improvements in the dielectric and physical properties of the resulting nanocomposite material.

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Accuracy Over Precision: Building a Reliable Affinity Database for Protein–Ligand Interactions

Marius Gedgaudas, Vaida Paketurytė-Latvė, Darius Lingė, Asta Zubrienė,
Lina Baranauskienė, Daumantas Matulis, Vytautas Petrauskas

Department of Biothermodynamics and Drug Design, Institute of Biotechnology, Life Sciences Center, Vilnius University, Sauletekio 7, 10257 Vilnius, Lithuania

vytautas.petrauskas@bti.vu.lt

Accurate determination of protein-ligand binding affinity is critical for understanding molecular recognition and enabling rational drug design. However, affinity values (expressed as Gibbs free energy or dissociation constant, K_d) obtained from different experimental techniques often diverge, raising concerns about reliability despite high internal reproducibility.

Although biophysical techniques such as isothermal titration calorimetry (ITC), thermal shift assay (TSA), surface plasmon resonance (SPR), and enzyme inhibition assays are widely used, individual methods often prioritize precision over accuracy. This can yield highly reproducible but potentially misleading affinity values. Our study shows that even precise ITC experiments may vary by more than 1.5-fold in repeated trials, while incorporating TSA increases observed variability in K_d to 2-fold. This apparent imprecision reflects underlying systematic uncertainties – not experimental failure. Such discrepancies underscore the importance of orthogonal validation: integrating results from multiple, complementary techniques provides more reliable and accurate binding parameters by mitigating method-specific biases.

To explore this concept, we analyzed over 600 synthetic inhibitors targeting carbonic anhydrase isoforms. Their binding interactions, ranging from micromolar to picomolar affinity, were quantified using a combination of biophysical techniques. These measurements were complemented by 149 high-resolution X-ray crystal structures of protein-ligand complexes, revealing key structural determinants of binding affinity and selectivity. All results were curated in the Protein-Ligand Binding Database (PLBD) – a resource designed to support quantitative modeling of protein-ligand recognition. PLBD integrates thermodynamic, kinetic, and structural data under standardized conditions, making it well-suited for machine learning applications in drug discovery. By combining rigorous experimental methods with robust data curation, PLBD enables more meaningful correlations between molecular structure and binding energetics.

Our work emphasizes that precision alone is not a guarantee of truth – a dataset can be reproducible yet systematically wrong. What ultimately matters is accuracy, and achieving it requires validating affinity measurements using multiple orthogonal techniques rather than relying on a single method. These principles drive the development of the PLBD – a resource aimed at improving how affinity data are measured, reported, and reused in drug discovery and beyond.

Stability of a New Monomethyl Fumarate Nicotinamide Co-Crystal from Solubility and Calorimetric Measurements

M. F. M. Piedade, R. Mané, R. G. Simões, M. E. Minas da Piedade

Centro de Química Estrutural, Institute of Molecular Sciences, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal.

mdpiedade@fc.ul.pt

Fumaric acid and alkyl fumarates have demonstrated a wide spectrum of potential or effective therapeutic applications. Monomethyl fumarate (MMF), the compound of interest here, was FDA-approved in April 2020 (tradename Bafiertam) as an oral medicine for treatment of relapsing forms of multiple sclerosis[1] and it is also being considered for the treatment of Parkinson disease type conditions.[2]

As observed for about 90% of drugs under development, MMF has poor aqueous solubility.[3] Because this normally has a strong negative impact on bioavailability, in this work co- crystallization was explored to improve solubility. Using nicotinamide (NIC) as co-former, a new MMF:NIC co-crystal of 1:1 stoichiometry was obtained by mechanochemistry. The material was characterized in terms of structure by single-crystal X-ray diffraction (Figure 1) and in terms of thermal behavior by differential scanning calorimetry. Solubility determinations in water showed a considerable enhancement in mole fraction solubility when the co-crystal was compared with pure MMF. Moreover, these results when combined with enthalpy of solution measurements allowed the quntitative assessment of the co-crystal solubility based on the $\Delta_r G_m^0$, $\Delta_r H_m^0$ and $T\Delta_r S_m^0$ changes associated with its decomposition into the precursors.

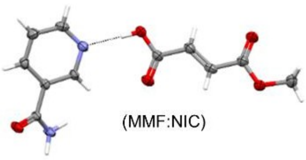

Figure 1. Molecular structure of the monomethyl fumarate-nicotinamide co-crystal

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Synthesis, characterization and biological evaluation of a tyrosinase inhibitor with antimelanoma potential

Edyta Pindelska[1]*, Zbigniew Majka*[1]*, Hanna Naklicka*[2]*, Izabela Madura*[3]

[1]Faculty of Pharmacy, Medical University of Warsaw, Banacha 1, 02-093 Warsaw, Poland, [2]Scientific Circle "Crystals" at Department of Pharmaceutical Chemistry and Biomaterials, Faculty of Pharmacy, Medical University of Warsaw, Banacha 1, 02-093 Warsaw, Poland, [3]Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw,
Poland edyta.pindelska@wum.edu.pl

4,4'-(sulfanediyldimethanediyl)diphenol [IT] was first identified and isolated from *Gastrodia elata* Blume [1]. Isolating IT from plant material is not very efficient. The IT content of material from different crops is variable. The most efficient method for obtaining IT is chemical synthesis. IT is the most potent tyrosinase inhibitor known [2]. Tyrosinase is an enzyme involved in pigment synthesis in pigment cells - melanocytes. Melanoma cells also produce melanin.

The purpose of this study is to optimize synthesis conditions, physicochemical and structural characterization, and determine the sensitivity of various melanoma cell lines to IT.

The synthesis of IT was performed by Bunte salts as intermediates. In order to simplify the synthesis, the indirectly formed Bunte salts were not isolated. 4-Hydroxybenzyl alcohol and sodium thiosulphate were placed in the flask. Acid solutions were added dropwise to the resulting suspension and heated by maintaining the temperature in the 60-80°C range. Formic, acetic, propionic, citric and hydrochloric acids were used as acids. The drained product was washed several times with water and left to dry in air. The structure of IT was determined using X-ray (SCXRD and PXRD) and spectroscopies (FTIR and NMR) methods. The IT content of the crude reaction product was determined by HPLC. The effect of IT on the viability of MNT1 was assessed using MTS assay.

The findings of this study suggest that citric acid, when employed in the IT synthesis reaction, yields superior outcomes in comparison to acetic acid. As demonstrated in the extant literature, the optimal yield is achieved through the utilization of acetic acid. The results of the cellular investigation indicate that melanoma cells are sensitive to the presence of IT.

The findings suggest that IT synthesis is more efficient in the presence of acids of higher potency than acetic acid. GOLD molecular docking analysis was applied to investigate the binding interactions of IT molecule with mushroom tyrosinase to elucidate the possible molecular mechanism. The results of the structural studies will facilitate the design of other tyrosinase inhibitors for the treatment of melanoma.

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Refining the Crystal Structure Prediction Landscape by Incorporating Intramolecular Energy Corrections

Sowmya Indrakumar[1], *Sten Nilsson Lill*[1], *Anders Broo*[1]

AstraZeneca, BioPharmaceuticals R&D, Pharmaceutical Sciences

Pepparedsleden 1, SE-431 83 Mölndal, Sweden

Sowmya.indrakumar@astrazeneca.com

Crystal structure prediction (CSP) is a powerful computational approach that enables the exploration of possible crystal forms, the assessment of polymorphism risk, and the prediction of material properties for drug-like molecules. This information is critical for solid form selection, risk assessment, and ultimately, successful pharmaceutical development.

Within AstraZeneca, an established in-house transferable force field (AZ-FF) is utilized for CSP, as described in [1,2]. AZ-FF is based on the well-known general purpose OPLS-aa force field, with key modifications to enhance its suitability for pharmaceutical solids. The workflow begins with generating three-dimensional coordinates from a 2D sketch or SMILES string, followed by quantum mechanical geometry optimization. Force field parameters for bonded interactions are largely taken from OPLS-aa, while equilibrium bond distances and certain angles are refined using quantum mechanically optimized geometries. Additionally, van der Waals and hydrogen bond parameters are tuned to improve solid-state predictions. This parameterization allows AZ-FF to be directly applied to new drug-like molecules, bypassing the need for molecule-specific force field development, and supports efficient and accurate prediction of crystal packing and polymorphism across diverse chemical entities.

To further improve predictive accuracy, the CSP landscapes are refined through advanced intramolecular energy corrections using revDSD and HF-DFT methods [3,4]. These approaches incorporate substantial Hartree–Fock exact exchange with DFT correlation and MP2-like corrections, which together enhance both intra- and intermolecular interaction descriptions, provide a robust treatment of dispersion forces, and significantly reduce electron density delocalization errors typically found in GGA and hybrid DFT functionals, particularly in π-conjugated systems.

This integration leads to markedly improved agreement between computational and experimental results, enables more precise polymorph ranking, and deepens our understanding of polymorphism. Such advancements are crucial for guiding form selection decisions and addressing challenges in drug development and materials science.

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Spray-Drying of a Metastable Polymorph: Influence of Additives on Particle Size, Solid- State Properties, and Stability

Cheng-long Stephan[1], *Gabin Gbabode*[1], *Ivo B. Rietveld*[1]

[1]Univ Rouen Normandie, Normandie Univ, SMS , UR 3233, F-76000 Rouen, France.

cheng-long.stephan@univ-rouen.fr

Active pharmaceutical ingredients (APIs) can exist in different crystalline forms creating issues related to the quality, safety and efficacy of the final drug product.[1–3] Several ways are commonly used for the manufacturing of a specific polymorphic phase in crystallisation processes, including temperature control, seeding, choice of solvent or even pH control.[4]

Featured in the W.H.O. list of essential drugs as an antituberculosis medicine,[5] and in the BEST-CSP Cost Action CA22107 benchmark,[6] pyrazinamide displays four polymorphic forms (alpha: α, beta: β, delta: δ, and gamma: γ). The γ phase described as having the highest intrinsic dissolution rate at 1 hour under ambient conditions[6], is of interest to improve pyrazinamide solubility. However, this metastable form[8] is tending to convert into the stable form α within 7 to 14 days.[9,10]

This work investigates the use of urea derivatives as additives to control the crystallization of pyrazinamide and extend the lifetime of the metastable γ form. Three samples were prepared using spray-drying. One containing pyrazinamide, and the two others pyrazinamide with respectively 1,3-diethylurea or 1,3-dimethylurea. Solid-state characterization (XRPD, FT-IR, POM) was carried out right after the crystallization confirms the presence of the γ phase in each sample. ICH stability studies with three different conditions (accelerated, long term and non-ICH long term dry) were carried on the powder, revealing distinct behaviours. The ability of the additive to “stabilize” the metastable polymorphs will be discussed. The morphology and the particle size have also been explored, showing variations depending on the additive used. Finally, FT-IR measurements have been used to study the interaction between pyrazinamide and the additives.

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Ethylmethylimidazolium-based ionic liquids: A crystal structure prediction study

Petr Touš[1], *Ctirad Červinka*[1], *Graeme M. Day*[2]

[1]Department of Physical Chemistry, University of Chemistry and Technology, Prague, Technická 5, CZ-166 28 Prague 6, Czech Republic,[2]School of Chemistry and Chemical Engineering, University of Southampton, University Road, Southampton, SO17 1BJ, United Kingdom

petr.tous@vscht.cz, cervinka.ctirad@vscht.cz, g.m.day@soton.ac.uk

Ionic liquids represent an important and relatively novel group of materials. Essentially, they are compounds comprised of two charged species, with the cation being often organic in nature. The name of ‘liquid’ comes from their melting points being (sometimes well) below 373.15 K. Thanks to their low volatility and ability to act as solvents of organic molecules, they have prospect applications as solvents with a negligible environmental impact. This has sparked massive interest in their phase behavior, both in the liquid phase and the crystal phase. During one such study, it was discovered that [emIm][EtSO4] does not seem to crystallize in a periodic lattice, whereas a similar ionic liquid, [emIm][MeSO3], does crystallize and exhibits polymorphism [1], even though its crystallization is difficult to reproduce. Upon subsequent computational studies, it was discovered that there seems to be little to no reason for the crystallization to not occur from the intermolecular interaction point of view [2]. Therefore, we decided to study these compounds using methods of crystal structure prediction: Using the system of [emIm][MeSO3] and its known crystal structure to test and validate our approach and [emIm][EtSO4] as our target system, seeing if any viable crystal structures can be created from these two molecules.

For the methodology itself, since the molecules are small and should behave as effectively rigid from the crystal lattice point of view, we decided to utilize the program mol-CSPy [3], a quasi- random crystal structure generation algorithm. Using this workflow, we arrived at a set of plausible structures, which we subjected to several further calculations based on DFT-D methods increasing in computational complexity and applied to a continuously refined set of structures. These calculations entailed both re-optimizations of the crystal lattice and vibrational analysis, which allowed us to evaluate the thermodynamic properties of these prospect crystals, most importantly the free energy as a ranking criterion.

The results show that the quasi-random methodology is able to generate the experimental structure of [emIm][MeSO3] and the subsequent DFT-D free energy assessment indeed puts it as the most stable structure, thus reproducing the known experimental phase behavior of this phase. Furthermore, a set of structures was identified which can represent some of the polymorphs which are known to exist but whose crystal structure is as of yet unknown. Based on these validated methods, the [emIm][EtSO4] results suggest that there is likely a plethora of structures with a similar thermodynamic stability but varied crystal structures, suggesting that vitrification of this compound is far more likely upon cooling of its melt than crystallization. This poster presents the results of work which began with a short-term scientific mission, financed with help of the BEST-CSP COST Action, conducted in the summer of 2024 and continues to this day.

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From Prediction to Attempted Realisation: Mapping the Polymorph Landscape of Sulfamerazine and Sulfadiazine

William P. Wood[1], *Sarah L. Price*[1], *Dr Matteo Salvalaglio*[2], *Doris E. Braun*[3], *Dejan-Krešimir Bučar*[1], *Rui Guo*[4], *Rajni M. Bhardwaj*[4]

[1]Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK, [2]Thomas Young Centre and Department of Chemical Engineering, University College London, London WC1E 7JE, U.K., [3]Institute of Pharmacy, University of Innsbruck, Innrain 52c, 6020 Innsbruck, Austria, [4]Pfizer Research & Development, Pharmaceutical Sciences, Pfizer Inc, Groton, CT 06340, United States

uccawpw@ucl.ac.uk

Crystal Structure Prediction (CSP) is increasingly employed to complement experimental form screening in the pharmaceutical industry, aiming to mitigate risks in the drug development process [1,2]. However, a significant challenge with CSP is the tendency for overprediction, resulting in the prediction of many more structures than are likely to be found experimentally [3], which can complicate the process of identifying potential forms that might be found by further experimentation. In this study, we conducted a CSP search on two chemically similar pharmaceutical molecules, sulfadiazine (SDZ) and sulfamerazine (SMZ), which exhibit different solid-form behaviours. Throughout this study, SDZ has one known polymorph, while SMZ now has five. We utilised CSP and further ab initio methods, including harmonic phonon free energy estimates, to investigate the reasons behind these observed differences. Additionally, we applied a molecular dynamics (MD) based workflow [4] to rationally reduce the number of predicted structures by modelling the effect of temperature on static CSP_0 crystal structures. From our computational investigation, we were able to predict a new and recently published fourth form of SMZ [5].

To validate our computational predictions, we employed non-classical crystallisation techniques, such as templating by sublimation, to try to discover new polymorphs of either molecule. During this process, we identified a novel solid solution of SDZ and SMZ and were able to identify a novel fifth form of SMZ that our experiments show is the new most stable form at high temperature. Furthermore, we collected experimental data on the transition between the SMZ forms I and II to contribute to the BEST-CSP benchmark.

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Mechanochemical synthesis of essential oil cocrystals

Sundermann Remie, Andrea Dalio, Michele Prencipe, Alessia Bacchi, Paolo P. Mazzeo

Department of chemical, life sciences and environmental sustainability; University of Parma, Parma, Italy

remiematthieu.sundermann@unipr.it

The Industrial scale use of most conventional pesticides, insecticides and bactericides are unsustainable for ecosystems, users and consumers. Essential oils (EOs) have been demonstrated to possess antibacterial, antiviral, antifungal and insecticide effects [1] . However, their ability to evaporate or sublime quickly makes them more prone to be used in the perfume industry than anywhere else for now. By including them in co-crystal structures or host-guest arrangements in MOFs or HOFs, synthesized in bulk by mechanochemistry, the stabilization of EOs increases the timeframe of action by several orders of magnitudes from several days to weeks of effective action [2] .

We developed cocrystal structures for example between thymol and isonicotinamide or niacin or isonicotonitrile, and carvacrol and isonicotinamide or 8-aminochinoline. We subsequently demonstrated that our carvacrol cocrystals with isonicotinamide released carvacrol constantly over a timeframes greater than 2 weeks at room temperature. This highlights the successful modulation of the release profile of EOs into the environment, thus opening the possibility to exploit their properties in agricultural or food related uses.

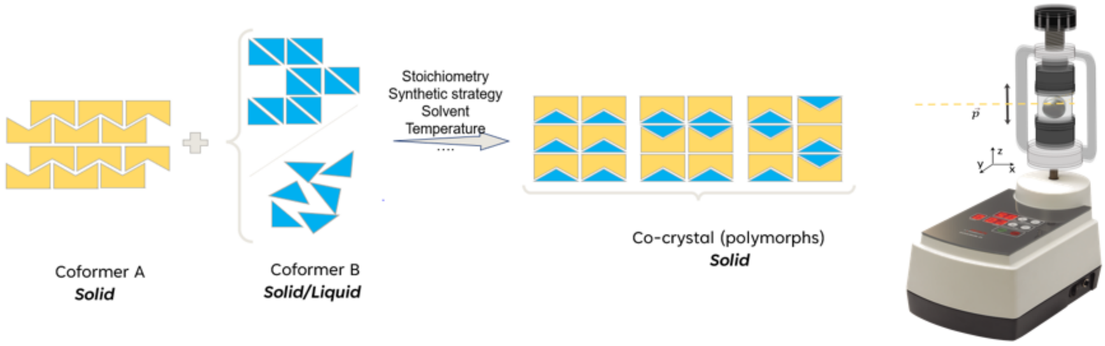

Figure 1. Process of mechanochemical synthesis of cocrystals.

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Resolution of Phenprocoumon by diastereoisomeric salts formation with chiral bases

Sokhna SOUARE[1], *Yihua JIANG* [2]

Catholic University of Louvain, Belgium Suaresonya@gmail.com,

Yihua.Jiang@uclouvain.be

Due to the antagonistic effects that enantiomers of a racemic compound can have, their separation becomes more than necessary. This study explores the method of chiral resolution by diastereoisomeric salt formation, a technique based on the reaction of a racemic mixture with a chiral agent to precipitate salts with different physicochemical properties such as solubility. Based on these differences, an efficient separation can therefore be carried out by selective crystallization. The experimental study was conducted on phenprocoumon with the chiral bases Quinine and Quinidine. The results yielded salts of R-phen + Qn_2 and S-phen + Qdn which, upon acidification, demonstrated enantiomeric excess (ee) values of 100% for R and S respectively, as confirmed by HPLC analysis. This method proved to be adapted to the system studied and highlighted the influence of the ratio, solvent and temperature used in the efficiency of chiral resolution.

Crystal structure and physicochemical properties of Cu(II) azo pyridone dye complex

Jelena Lađarević[1], Lidija Radovanović[2], Aleksandra Mašulović[2], Bojan Božić[3], Nemanja Trišović[1], Jelena Rogan[1], Dušan Mijin[1]

[1]Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, Belgrade,Serbia
[2]Innovation Centre of the Faculty of Technology and Metallurgy in Belgrade Ltd, Karnegijeva 4, Belgrade, Serbia
[3]Institute of Physiology and Biochemistry "Ivan Đaja", Faculty of Biology, University of Belgrade, Studentski trg 16, Belgrade, Serbia

jmirkovic@tmf.bg.ac.rs

The design of new biologically active compounds through coordination of heterocyclic azo dyes with transition metals represents an important research direction, since complexation often enhances or modifies the pharmacological potential of the ligands [1]. Transition metal complexes of azo dyes have been reported to exhibit antimicrobial, anti-inflammatory, antioxidant, and antitumor activities [2], in addition to their well-established application in dyeing, optics, and recording media. Within this group, azo pyridone dyes are recognized as promising chelating agents, where the azo-hydrazone tautomerism governs the coordination process. In the reaction of 5-(4-chlorophenylazo)-1-ethyl-3-cyano-6-hydroxy-4-methyl-2- pyridone (HL) with $Cu(CH_3COO)_2 \cdot H_2O$ in *N*,*N*-dimethylformamide (DMF) at room temperature, a complex $[CuL_2(DMF)] \cdot DMF$ was prepared [3]. The complex was characterized by UV–Vis and ATR–FTIR spectroscopy, simultaneous TG/DSC, and single- crystal X-ray diffraction. The asymmetric unit of the complex comprises one Cu(II) atom, two chelate ligands (L), one coordinated and one noncoordinated DMF molecule (Figure 1). The Cu(II) atom adopts a square-pyramidal geometry, defined by two N and two O donor atoms from the ligands and one O atom from the solvent. The crystal packing is stabilized by weak noncovalent interactions, including C–H⋯O/N, π–π stacking, C–H⋯π contacts, and Cl⋯Cl interactions.

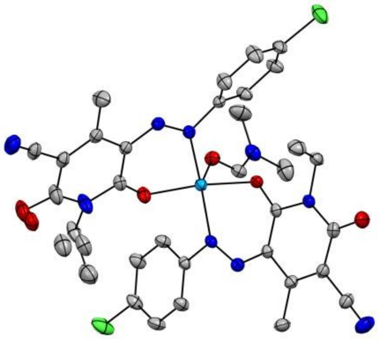

Figure 1. ORTEP diagram of the asymmetric unit of Cu(II) complex showing 30% thermal ellipsoids (grey – C, blue – N, red – O, green – Cl, turquoise - Cu). Noncoordinated molecule of DMF and H atoms are not presented for the sake of clarity.

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Characterization of Polymorphic Landscapes in Molecular Crystals

Natalia Goncharova, Alexander List, Johannes Hoja, and A. Daniel Boese

Department of Chemistry, University of Graz, Austria

In this poster, we present our latest results for the COST action CA22107 (BEST-CSP): When computing molecular crystals, the workhorse of density functional theory is often limited to generalized gradient approximation (GGA) functionals including dispersion corrections. Hybrid functionals, on the other hand, are often out of reach, as the computation of intermolecular interactions require diffuse functions [1], numerical or plane-wave basis sets. Especially in the latter two cases, the computational cost of hybrid functionals is often prohibitive. For this purpose, we utilize a multimer embedding approach [2], where multimer energies up to trimers, calculated with PBE0+MBD, are embedded into a GGA functional (PBE+MBD).

As this method is computationally rather fast, we broaden our investigation beyond zero-point structures and to account for the volumetric change of a unit cell with temperature (thermal expansion), also utilizing the quasi-harmonic approximation (QHA), as done in previous contributions. [3,4] Therefore, the equilibrium unit cell volume and free energy corresponding to certain temperature are obtained with Murnaghan equation of state fits utilizing several unit cell volumes.

This allows us to track the impact of thermodynamic conditions on the relative stabilities of polymorphs and to generate phase diagrams for the molecules investigated in the COST action. Here, we will compare our results for a range of molecular crystals to the experimental data, also obtaining some statistics.

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Organic Luminescent Cocrystal Based on Benzimidazole: Crystallization, Characterization of Physical Properties and Computational Study

Christina Kolokytha [1,2], *Demeter Tzeli* [1,2], *Nektarios N. Lathiotakis* [2], *Rajaboopathi Mani* [3], *Ivo B. Rietveld* [4]

[1] Laboratory of Physical Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Greece
[2] Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, Athens, Greece
[3] Key Laboratory of Emergent Materials, SRM Institute of Science and Technology, Kattankulathur 603203, Chengalpattu Dt, Tamil Nadu, India.
[4] Laboratoire SMS, Universite of Rouen, Normandy, France kolokythac28@chem.uoa.gr, *kolokc@eie.gr*

Benzimidazole derivatives have attracted increasing attention in the design of cocrystals due to their ability to form non-covalent interactions, such as hydrogen bonding, van der Waals forces, and π–π stacking, which can result in materials with unique luminescent properties.[1, 2] A remarkable feature of these systems is the retention of luminescence both in solution and in the solid state. Herein, we aim to gain expertise in the experimental characterization of structural and optical properties using techniques such as high-temperature X-ray diffraction (HT-XRD), FTIR spectroscopy, and Differential Scanning Calorimetry (DSC). Moreover, a theoretical study will be carried out using Density Functional Theory (DFT) and Time- Dependent Density Functional Theory (TD-DFT).[3,4] These calculations will provide insight into the structural features and optoelectronic properties of the optimized cocrystals, as well as guidance for the rational design of new fluorescent materials. The combined experimental and theoretical approach is expected to elucidate how intermolecular interactions influence the arrangement of fluorescent molecules in both solution and the solid state.

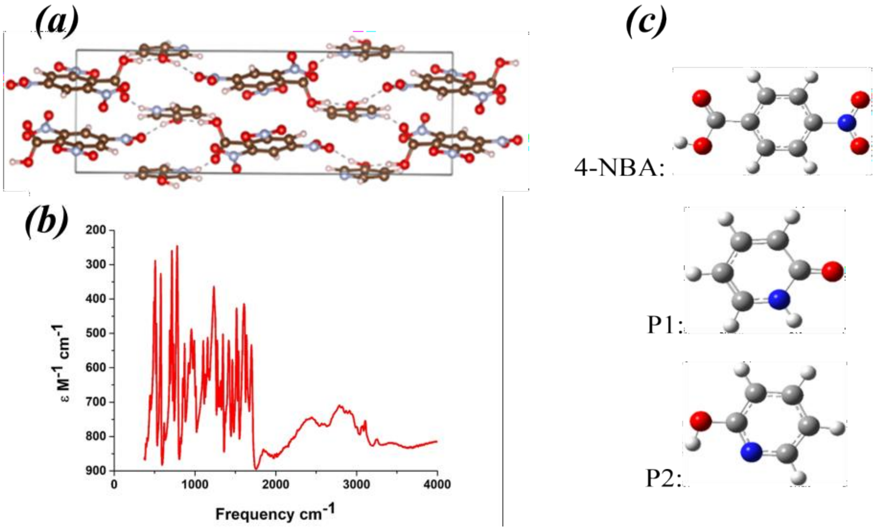

Figure 1. *(a) Calculated structure for cocrystal, (b) experimental FTIR spectra for cocrystal and (c) calculated structures for monomers of cocrystal (4-nitrobenzoic acid (4-NBA) and two tautomers of 2-pyridone (P1 and P2)).*

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Hierarchy of sigmoid growth models - towards justification of sigmoid treatment of nucleation data

Aleksandar Cvetkovski (1), Vassil V. Ivanov (2), V.Tonchev (3)

1. Faculty of medical sciences, Goce Delcev University, Stip 2000, No.10-A P.O. Box 201 North Macedonia

2. Faculty of Mathematics and Informatics and 3Faculty of Physics, Sofia University,

1164 Sofia, Bulgaria

aleksandart.cvetkovski@ugd.edu.mk

In the poster we provide a brief introduction to the general problem of fitting the nucleation data – the so called N-t curves, with an hierarchy of sigmoid growth models [1] (HSGM). The special focus of such a treatment is to be on the principal mechanisms of nucleation that could give raise to a positive feedback as demonstrated in the supelinear regime (before the inflection point) of N-t curves.

In the introductory part, we continue the mothodological development of the HSGM by identifying a novel quantitative criterium for "sigmoidness" based on the idea of catastrophe. Here we will use examples of population dynamics.

In the course of implementing the HSGM-approach we revisit several typical datasets reporting sigmoid data [2] and more. A novel tool used in the course of this revisit is the so called Multiple Fitting of a Single Dataset (MFSDS) as first proposed in [3]. Here we also make further refinements of the approach by including datasets generated by the Richards model and Cellular Automata.

In collaboration with: Daniela Tsekova and Feyzim Hodzhaoglu

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Thermodynamic Characterization of the SMZ_II → SMZ_I Phase Transition Using NoMoRe Refinement

H. Butkiewicz[1], A. A. Hoser[1]

[1] Faculty of Chemistry, University of Warsaw, Warsaw, Poland

b.helena@uw.edu.pl

This contribution presents a computational study of the SMZ_II → SMZ_I phase transition in sulfamethazine, combining experimental data, periodic DFT calculations and normal mode refinement (NoMoRe). The low-frequency vibrational modes of both polymorphs were refined against single-crystal X-ray diffraction data, enabling estimation of thermodynamic parameters such as vibrational contributions to free energy and heat capacities. The transition temperature was evaluated by comparing the Gibbs free energies of the two forms as a function of temperature. To improve accuracy while reducing computational cost, a hybrid approach was employed: vibrational frequencies were computed or refined at the B3LYP-D3/6-31G(d,p) level, while electronic energies were obtained using HFsol3c or B3LYP-D3/VTZP. Depending on the combination of methods and refinement, the predicted transition temperature ranged between 440 and 660 K (Fig. 1). Although the refined frequencies offered only moderate improvement due to the lack of multi-temperature diffraction data, the results provide insight into the thermodynamic stability and entropy contributions of the polymorphs. Further work will involve refinement of different number of vibrational modes and calculations with an extended basis set to increase predictive accuracy.

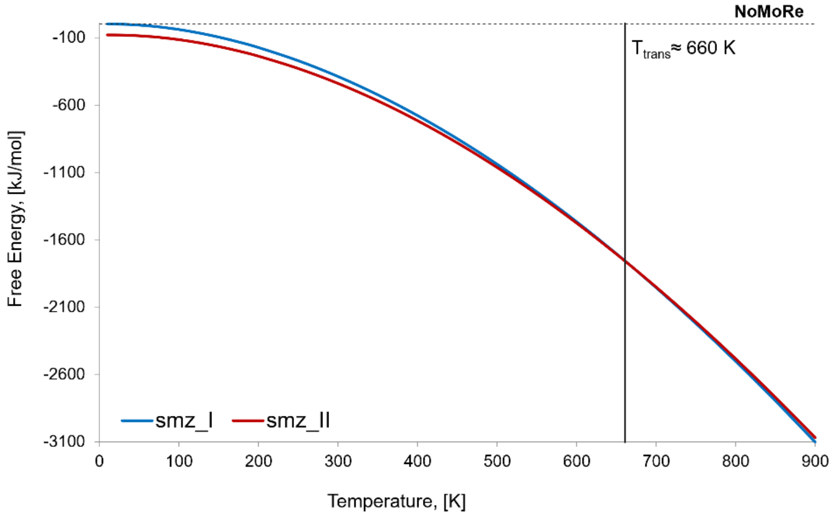

FIGURE 1. FREE ENERGY OF THE TWO POLYMORPHS AS A FUNCTION OF TEMPERATURE, AS COMBINED WITH NOMORE REFINEMENT; COMBINATIONS OF TWO LEVELS OF THEORY: B3LYP-D3/6-31G(D,P) FOR FREQUENCY CALCULATIONS AND AHL-VTZP BASIS SET FOR ELECTRONIC ENERGY.

Multi-level coupled-cluster description of crystal lattice energies

Krystyna Syty1, Marcin Modrzejewski1

1 Faculty of Chemistry, University of Warsaw, 02-093 Warsaw, Pasteura 1, Poland

K.syty@student.uw.edu.pl

The many-body expansion (MBE) of the lattice energy offers a route to an ab initio description of molecular solids based on systematic wave-function approximations. However, MBE can only be practical if one can deal with the daunting number of n-body contributions. To this end, we employ a multi-level approach. CCSD(T) is only required for the first and second coordination shells. At longer distances and for the three-body interactions, RPA with third-order corrections [1] is sufficient. The extremely long-range and beyond three-body interactions appear to be driven by the mean field and can be efficiently accounted for at the Hartree-Fock level with periodic boundary conditions.

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Tailoring Supramolecular Assemblies of Drug-like Spirohydantoin Derivatives

Anita Lazić[1], Lidija Radovanović[1], Jelena Rogan[2], Olivier Jeannin[3], Franck Camerel[3], Sergi Burguera[4], Antonio Frontera[4], Nemanja Trišović[2]

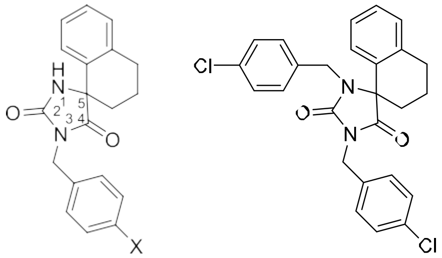
[1]Innovation Centre of the Faculty of Technology and Metallurgy, Karnegijeva 4, 11120 Belgrade, Serbia; [2]University of Belgrade, Faculty of Technology and Metallurgy, Karnegijeva 4, 11120 Belgrade, Serbia; [3]Institut des Sciences Chimiques de Rennes, CNRS UMR 6226, Université de Rennes, Rennes, France; [4]Departament de Química, Universitat de les Illes Balears, Crta de Valldemossa Km 7.5, 07122 Palma de Mallorca, Baleares, Spain

ntrisovic@tmf.bg.ac.rs

To expand biologically relevant chemical space of hydantoin derivatives, we designed and synthesized a series of molecules built around this scaffold with a tetralin moiety in a spiro arrangement and a 4-substituted benzyl group (Figure 1). Such a molecular design enabled us to study the influence how conformational flexibility and substitution patterns influence intermolecular interactions and supramolecular organization.

Single-crystal X-ray diffraction revealed that these structures are primarily stabilized by N–H···O hydrogen bonds, forming either discrete $R_2^2(8)$ dimers or infinite chain motifs. However, medium to weak interactions proved to be decisive in constructing extended supramolecular architectures, especially in the case where these hydrogen bonds were absent. Computational analyses provided complementary insights: interaction energy calculations and molecular electrostatic potential (MEP) surface mapping clarified the hierarchy of hydrogen bonds involving different acceptor sites.

Overall, this study highlights the role of substituent effects and electronic properties in shaping the supramolecular assemblies and solid-state structures. These insights not only advance crystal engineering strategies but also highlight the versatility of hydantoin derivatives as promising building blocks for materials science and pharmaceutical applications.



1, X = H
2, X = CH_3
3, X = Cl
5, X = NO_2
6, X = CN

4

Figure 1. Chemical structures of the investigated compounds.

Crystal structure of a new 2,2'-dipyridylamine polymorph

Lidija Radovanović[1], Nemanja Trišović[2], Jelena Rogan[2]

[1]Innovation Centre of the Faculty of Technology and Metallurgy Ltd. in Belgrade, Karnegijeva 4, 11000 Belgrade, Serbia; [2]University of Belgrade, Faculty of Technology and Metallurgy, Karnegijeva 4, 11000 Belgrade, Serbia

lradovanovic@tmf.bg.ac.rs

2,2'-Dipyridylamine (dipya) is an organic charge transfer base that can exist in a variety of protonation states, allowing it to adopt one of nine coordination modes [1]. This molecule has attracted attention as a ligand in coordination chemistry due to the inherent flexibility of the amine N atom and its ability to stabilize transition metal complexes [2, 3]. The chemistry of dipya is characterized by the diverse geometries around the amine N atom, as well as the enhanced acidity of the amine H atom occurring as a result of complex formation [1]. Dipya possesses two rotational degrees of freedom around the N–C bonds, thus serving as a model with which to study structural differences and phase transitions. To date, three distinct polymorphs of dipya have been identified: namely, triclinic (P1), monoclinic (P21/c) and orthorombic (Pccn), with melting points of 366, 364 and 360 K, respectively [4–6]. Recently, a fourth modification of dipya was discovered. Colourless single crystals of a new monoclinic polymorph were prepared by slow evaporation method at room temperature. Single crystal X- ray analysis revealed that the asymmetric unit consists of two dipya moieties linked by strong N–H···N hydrogen bonds into a dimer (Figure 1a). The main structural feature is a supramolecular tape formed by N/C–H···N interactions along c axis, while weak C–H···N and C–H···π interactions were observed between the tapes resulting in the formation of supramolecular 3D network (Figure 1b).

Crystallographic data: C10H9N3, Mr = 171.2, monoclinic, P21/n, a = 11.714(2),

b = 12.424(3), c = 12.200(2) Å, β = 94.21(3) °, V = 1770.9(6) Å3, Z = 8, R1 = 0.0422,
wR2 = 0.1096, S = 1.026 for 236 parameters and 3228 reflections.

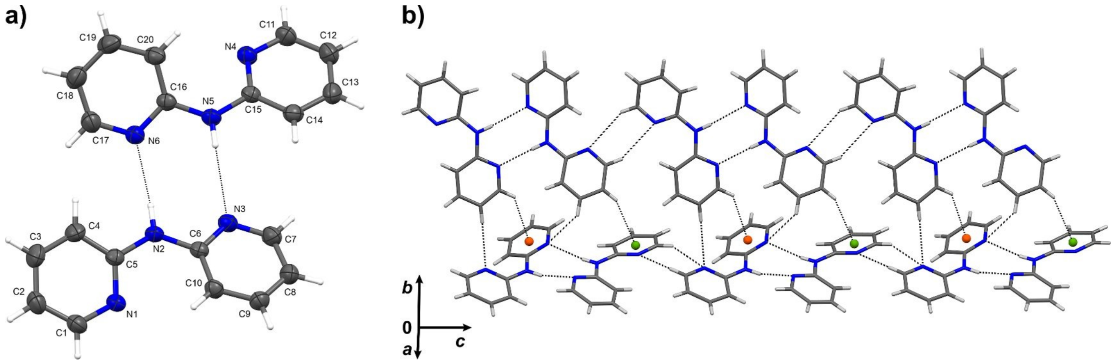


Figure 1. a) ORTEP diagram of a new polymorph showing 30% displacement ellipsoids. H atoms are presented as small spheres of arbitrary radii. The intramolecular N–H···N hydrogen bonds are shown as dotted lines; b) Supramolecular 3D networking of dipya *via* N/C–H···N and C–H···*π* interactions (green *C*g1: C1–C5/N1, orange *C*g2: C16–C20/N6).

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Kink Crystal Position: The gateway into the crystal

Vesselin Tonchev[1] *and Vassil Ivanov*[2]

[1]Faculty of Physics and 2Faculty of Mathematics and Informatics, Sofia University, 5 James Bourchier Blvd., 1164 Sofia, Bulgaria

tonchev@phys.uni-sofia.com

Here we present the current development of the Cellular Automaton (CA) approach to crystal growth, aggregation, nucleation and instabilities on **atomistic scale**.

First, we enlist the types of attachments to the growing structure in 2D, 2+1D and 3D, as introduced generally with an accent on three types of them – attachment to (A2) only one particle from the growing structure, A21 [1], leading when taken alone to **aggregation**, and A2 crystal plane (A2P) as a version of the A21, A2 step from the crystal surface (A2S), , and the most important one – the attachment to a kink crystal position (A2K) [2] that is essential along the **crystallization** route. Attention is paid to the role of the kink position as the only primary position in which the attaching unit is having half of the bonds in each direction grouped in such a way to form concavity from the crystal side. A2K not only brings a unit from the ambience into the crystal **-** it forms there the same number of bonds in the crystal volume, but also perpetuates the crystal symmetry along the increasing scales – from the microscopic to the macroscopic [3].

We further show how to implement these attachments as rules in different mutual ratios in a Cellular Automaton [4,5]. To complement the code, we add a realistic diffusion field around the growing structure, where the update is, inevitably, serial, and the number of such updates per diffusing particle (on average) *n*DS could vary thus permitting to study the diffusion limited, *n*DS = 1, and *less-diffusion limited*, *n*DS =100 and more, versions of a concrete growth phenomenon as defined by the concrete *mix* of growth rules. Here we illustrate these with the clear types of growth – **aggregation**, where only A21 is sufficient, and crystallization, where A2P and A2S complement (in small portions) the A2K. A step aside permits us to study in the same context the **nucleation**. We also provide an intriguing case study – crystal growth between 2D and 3D – while keeping a constant base of the simulation box with area M x M, we increase systematically the height of the box *h* from 0 to M in several steps. We use our

aDg model to fit the obtained “transformation ratio vs. time” dependencies and comment on the results. The consequences and opportunities of using our approach in the context of the COST action are drawn at the end in brief.

In collaboration with: Hristina Popova, Magdalena Zaluska-Kotur, Marta Chabowska, Noriko Akutsu, Yoshihiro Kangawa and Alexey Redkov.

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